Enantioselective Synthesis of Bioactive Molecules and Development of Synthetic Methodologies Involving *N*-Heterocyclic Carbene and Iodine Catalysis of Alkenes and Aldehydes

Thesis Submitted to the AcSIR for the Award of
The Degree of
DOCTOR OF PHILOSOPHY
In Chemical Sciences

By
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UNDER THE GUIDANCE OF
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June 2015

Dedicated To

Amma – Nanna

and Tammudu

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled ***"Enantioselective Synthesis of Bioactive molecules and Development of Synthetic Methodologies Involving N-Heterocyclic Carbene and Iodine catalysis of Alkenes and Aldehydes"*** which is being submitted to the ***AcSIR*** for the award of ***Doctor of Philosophy*** in ***Chemical Sciences*** by ***Mr. Rambabu Reddi*** was carried out by him under my supervision at the CSIR-National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

June 2015 **Dr. A. Sudalai**
Pune (Research Guide)

CSIR-NATIONAL CHEMICAL LABORATORY

DECLARATION

I hereby declare that the thesis entitled ***"Enantioselective Synthesis of Bioactive molecules and Development of Synthetic Methodologies Involving N-Heterocyclic Carbene and Iodine catalysis of Alkenes and Aldehydes"*** submitted to AcSIR for the award of degree of Doctor of Philosophy in Chemical Sciences, has not been submitted by me to any other university or institution. This work was carried out at the CSIR-National Chemical Laboratory, Pune, India.

June 2015
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CONTENTS

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Pradeep, Pavan, and M. Sc. Friends Naresh, Srinu, Shivaji, Pullaiah Naidu, Siva kumar, Sarita, Bhanu, etc. for their support and suggestions throughout my career.

Though my name appears in bold in the thesis, the backbone of it is the patience of my beloved parents and my dear brother Srinivas Reddi. Especially, I wish to thank my dear parents from the core of my heart who allowed me to take chemistry as my profession without any hesitation.

My parents, my best friends, the core of my being, Forever I am grateful to you. I would like you to know that I appreciate everything you've done for me. My dear great bearable Mother and Father, Thank you evenmore for providing me a loving and caring home. Without your unending support I never would have made it through this process or any of the tough times in my life. You have made countless sacrifices for me, and have provided me with steady guidance and encouragement. Thank you, both Amma and Nanna.

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

R. Rambabu

ABBREVATIONS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Boc	*N*-*tert*-Butoxycarbonyl
$(Boc)_2O$	Di*tert*-butyl dicarbonate
n-Bu	*n*-Butyl
n-BuLi	*n*-Butyl lithium
t-Bu	*tert*-Butyl
Cbz	Benzyloxy carbonyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	Diisobutyl aluminium hydride
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DMAP	*N,N*-dimethyl-4-aminopyridine
dr	Diastereomeric ratio
ee	Enantiomeric excess
Et	Ethyl
g	Grams
h	Hours
HCl	Hydrochloric acid
HPLC	High pressure liquid chromatography
H_2SO_4	Sulfuric acid
HNO_3	Nitric acid
imid.	Imidazole
IR	Infra red
IBX	2-Iodoxybenzoic acid
K_2CO_3	Potassium carbonate
KOH	Potassium hydroxide
$LiAlH_4$	Lithium aluminum hydride
LiHMDS	Lithium hexamethyldisilazide
M+	Molecular ion
MOM	Methoxymethyl
min	Minutes
mg	Miligram
mL	Milliliter
mp	Melting point
MS	Mass spectrum
Ms	Mesyl
$NaBH_4$	Sodium borohydride

$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulfate
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NMO	*N*-Methyl morpholine *N*-oxide
PCC	Pyridinium chlorochromate
Pd/C	Palladium on activated charcoal
PDC	Pyridinium dichromate
$Pd(OH)_2$	Palladium hydroxide
Ph	Phenyl
p-Ts	*p*-Tosyl
p-TSA	*p*-Toluene sulfonic acid
PhNO	Nitrosobenzene
Py	Pyridine
TBS	*tert*-Butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethyl-1-piperidinyl)oxyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
TFA	Trifluoroacetic acid

GENERAL REMARKS

1. All solvents were distilled and dried before use.

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

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

4. Column Chromatography was performed over silica gel (230-400 mesh).

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

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

7. ^{1}H and ^{13}C NMR spectra were recorded on Brucker FT AC-200 MHz, Brucker Avance 500 MHz and JEOL ECX 400 instruments using TMS as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, dd = doublet of doublet, dt = doublet of triplet and ddd = doublet of doublet of doublet.

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

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

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

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

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

13. All the *N*-heterocyclic carbene catalysts were procured from Aldrich and used as such without further purification.

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

ABSTRACT

Enantioselective Synthesis of Bioactive Molecules and Development of Synthetic Methodologies Involving *N*-Heterocyclic Carbene and Iodine Catalysis of Alkenes and Aldehydes

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Research Guide: Dr. A. Sudalai

The thesis entitled "**Enantioselective Synthesis of Bioactive Molecules and Development of Synthetic Methodologies Involving *N*-Heterocyclic Carbene and Iodine catalysis of Alkenes and Aldehydes"**is divided into four chapters.The title of the thesis clearly reflects the objective, which is to synthesize enantiomerically pure bioactive molecules, drugs and to interface synthetic organic chemistry for the development of new methodologies. **Chapter 1**describes NHC catalyzed oxidative coupling of aromatic aldehydes with tributyl tin chloride and allylic C-H bonds for the synthesis of organotin(IV) carboxylates and allylic esters respectively.**Chapter 2** presents the synthesis of α,β-epoxy ketones and α-acyloxy carbonylcompounds using NHC catalyzed oxidative coupling of aldehydes with alkenes, epoxides and α-bromoacetophenones.**Chapter 3**deals with iodine catalyzedoxo-acyloxylation of alkenes with carboxylic acids and its application in the asymmetric synthesis of Reboxitine. **Chapter 4** presents thestudies towards the synthesis of neopeltolide macrolactone, DAB-1 and zoledronic acid.

Introduction

The reversal of the classical reactivity (umpolung) using *N*-heterocyclic carbenes (NHC) opens up new synthetic pathways like benzoin condensation, Stetter reaction, homo enolate and enolate reactivity and various other oxidation reactions.[1] The present work deals with NHC catalyzed synthesis of organotin(IV) carboxylates **3a-p** and allylic esters **5a-j** from aromatic aldehydes. These compounds show anti-tumour, antimicrobial, anti-fungaland cytotoxic activity. Further, allylic/benzylic esters **5** are useful in industrial and fine-chemical processes. In addition, the synthesis of α,β-epoxyketones**9a-m** and α-acyloxycarbonyls**8a-v**, which are versatile building blocks and synthetic intermediates in natural product synthesis, is also presented. Its application to synthesis of (+)-neopeltolide intermediate (**32**) has been developed. (+)-Neopeltolide is a naturally-occurring macrolide, which inhibits the proliferation of several cancer cell lines, with a minimum inhibitory concentration value of 0.62 μgmL^{-1}.[3] I_2-catalyzed synthesis of mono protected diols**11**, which are common motifs in many natural products and sugars has been developed.[4] This methodology has been successfully applied to the formal synthesis of (S,S)-reboxetine[5] intermediate (**15**), a selective noradrenaline reuptake inhibitor (NaRI) and the first new antidepressant drug. In addition to this, total synthesis of 1,4-dideoxy-1,4-imido-D-arabinitol (DAB-1) (**41**), a glycosidase inhibitor of HIV replication and zoledronic acid (**45**), a potent osteoporosis drug are also presented. These bioactive molecules have become popular synthetic targets due to their challenging structures.

Statement of Problem

Since these molecules possess interesting biological activities, the need for efficient methods for their synthesis from commercially available materials is of current interest.

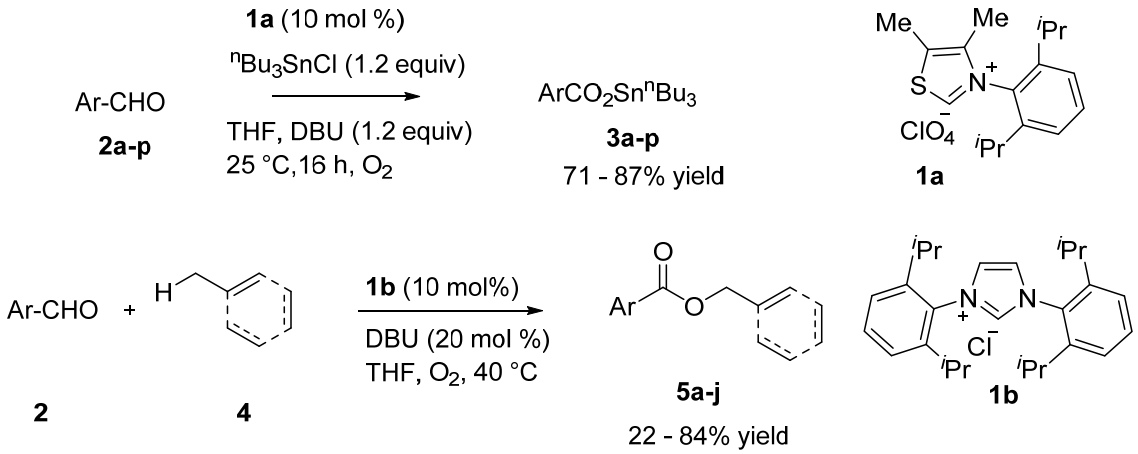
The reported synthesis of these highly bioactive molecules suffer from disadvantages such as lengthy reaction sequences including the protection and deprotection of various functional groups, use of chiral auxiliaries and expensive organometallic reagents, etc.

Methodology used

Some of the biologically important molecules have been synthesized and their structures characterized by the advanced analytical and spectroscopic techniques such as high field NMR (^{1}H &^{13}C), FT-IR, LC-MS and HRMS. The optical purity of chiral intermediates and final drug molecules are determined from chiral HPLC analysis (**Fig. 1**) and comparing their specific rotation with those reported in the literature.

Chapter-1

NHC catalyzed oxidative stannylation of aromatic aldehydes **2** with $^{n}Bu_3SnCl$ to thecorresponding organotin(IV) carboxylates[6]**3a-p** has been achieved in high yields (up to 87%) that utilizes atmospheric O_2 as the sole oxidant under basic condition. The uniqueness of the reaction lies in the direct conversion of aldehydes to the corresponding organotin(IV) carboxylates *via*stannylation of carboxylic acids, generated from the reaction of a Breslow intermediate with O_2.In continuation of this work, we have described NHCcatalyzed oxidative cross dehydrogenative coupling of aromatic aldehydes **2** with benzylic/allylic C-H bonds **4** leading to the synthesis of allylic/benzylic esters **5a-j** in high yields, employing NHC catalysts (10 mol %), DBU as base under O_2 atmosphere (**Scheme 1**).



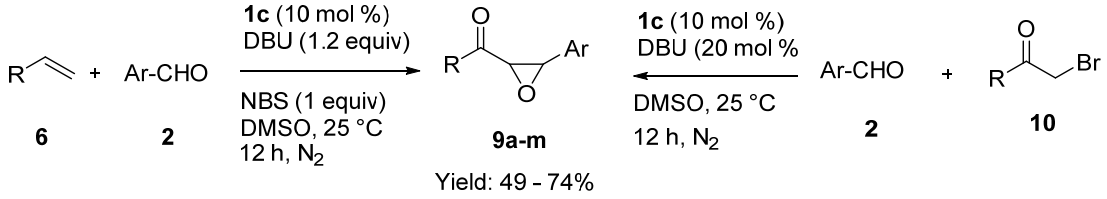
Scheme 1: *N*-Heterocyclic carbene catalyzed oxidative coupling of aromatic aldehydes with $^{n}Bu_3SnCl$ and allylic/benzylic C-H bonds

Chapter 2

In this chapter, *N*-Heterocyclic Carbene (NHC)-catalyzed reaction of alkenes **6** or epoxides **7**with aromatic aldehydes**2** providing for a high yield synthesis of α-acyloxy ketones and esters**8a-v** has been described. This unprecedented regioselective oxidative process employs NBS and Et_3N in stochiometric amounts and O_2 (1 atm) as oxidant at ambient condition in DMSO as solvent.

Scheme 2: NHC catalyzed oxidative coupling of aldehydes with alkenes/epoxidesfor synthesis of α-acyloxy ketones

Thus, *under complete N_2 atmosphere*, terminal alkenes **6** react with aromatic aldehydes in presence of NHC catalyst (10 mol %) and *N*-bromosuccinamide under basic condition in DMSO to give α,β-epoxyketones**9a-m** in moderate to good yields (49-74%)(**Scheme 3**).

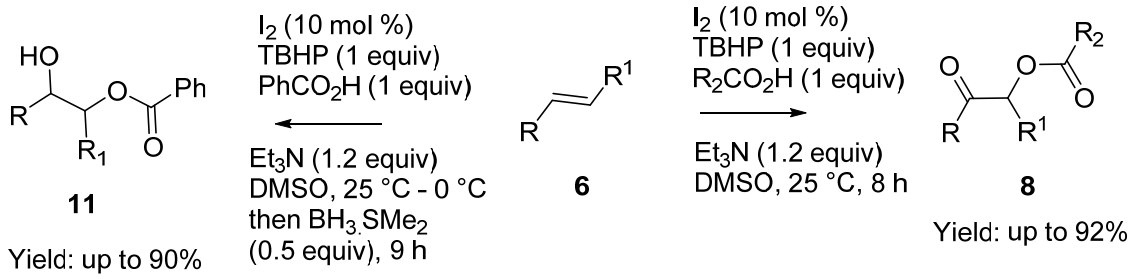


Scheme 3: NHC catalyzed oxidative coupling of aldehydes with alkenes/α-bromoacetophenones for synthesis of α-acyloxy ketones

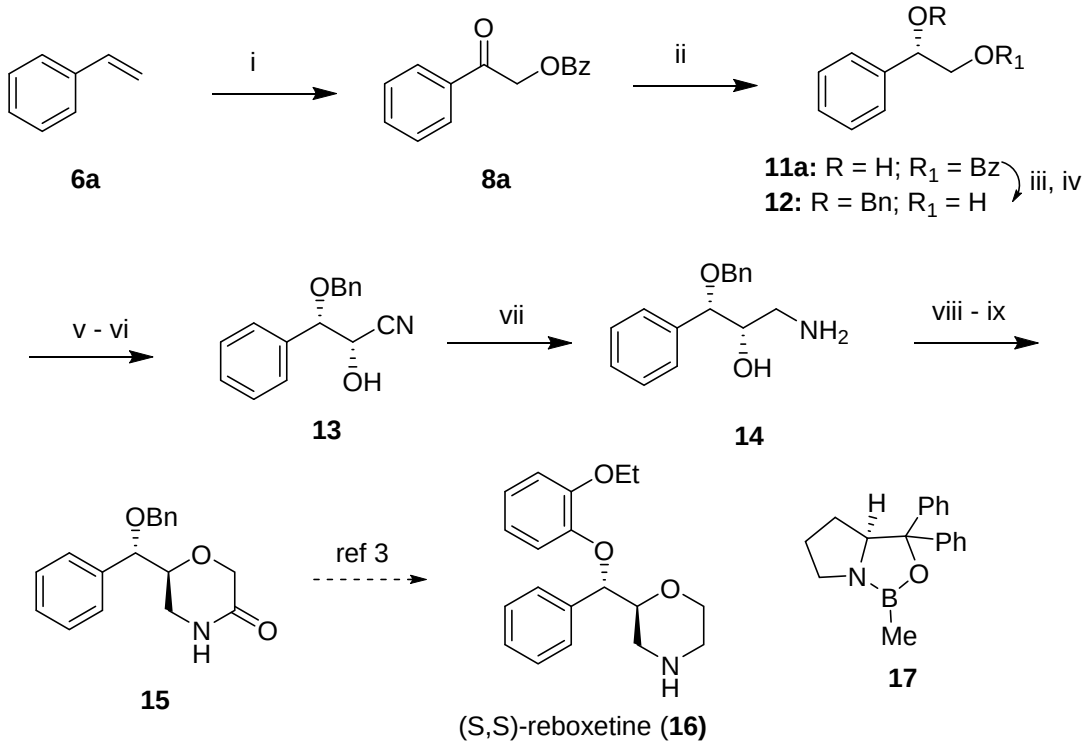
Further, first NHC catalyzedDarzens reaction has been developed by coupling α-bromoketone**10** with aldehydes **2**under basic condition. This reaction expected to proceeds through the formation of ketodeoxy-Breslow intermediate, which was isolated and characterized.

Chapter 3

I_2-catalyzed oxo-acyloxylation of alkenes **6**with carboxylic acids providing for the high yield synthesis of α-acyloxyketones**8** has been developed. This unprecedented regioselective oxidative process employs TBHP and Et_3N in stoichiometric amounts under metal-free conditions in DMSO as solvent. Additionally, I_2-catalysis allows the direct hydroxy-acyloxylation of alkenes with the sequential addition of $BH_3{\cdot}SMe_2$ leading to monoprotecteddiol derivatives in excellent yields.(**Scheme 4**).Based on oxo-acyloxylation strategy, formal synthesis (S,S)-Reboxetinehasbeen achieved in 9 steps using CBS reduction and diastereoselectivecyanation reactions are key steps (**Scheme 5**).



Scheme 4: I_2-catalyzed oxo- and hydroxyacyloxylation of alkenes and enol ethers

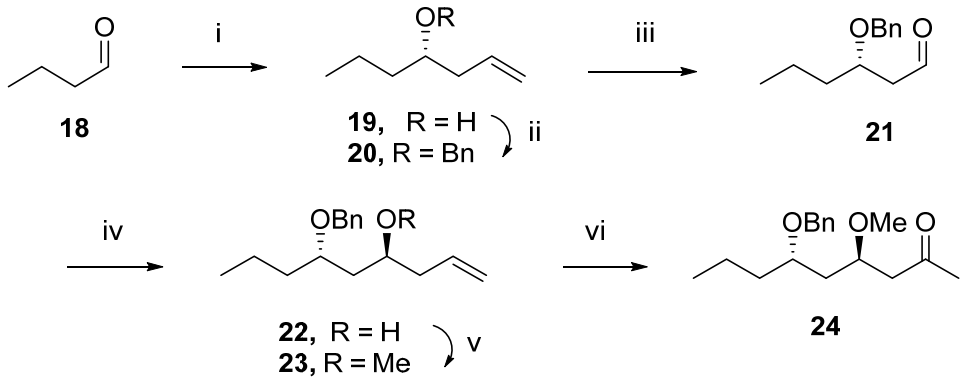


Scheme 5: (i) I_2 (10 mol %), TBHP (1 equiv), $PhCO_2H$ (1 equiv), Et_3N (1.2 equiv), DMSO, 25 °C, 8 h, 84%; (ii) **17**(5 mol%), BH_3.THF (0.5 equiv), THF, 0°C, 0.5 h, 90%, 94% ee; (iii) BnBr, NaH, DMF, 0 °C 3 h; (iv) K_2CO_3, MeOH, 84% (over 2 steps); (v) IBX (1.2 equiv), DMSO, 25 °C, 3h; (vi) TMSCN (1.1 equiv), $MgBr_2.Et_2O$ (1 equiv), CH_2Cl_2, 0 °C, 2 h, 82 % (over 2 steps); (vii) $LiAlH_4$, THF, 0 °C, 4 h, 82%; (viii) $ClCH_2CO_2Cl$, Et_3N, CH_2Cl_2, -10 °C; (ix) KO^tBu, ^tBuOH, 3 h, CH_2Cl_2, 25 °C (80%).

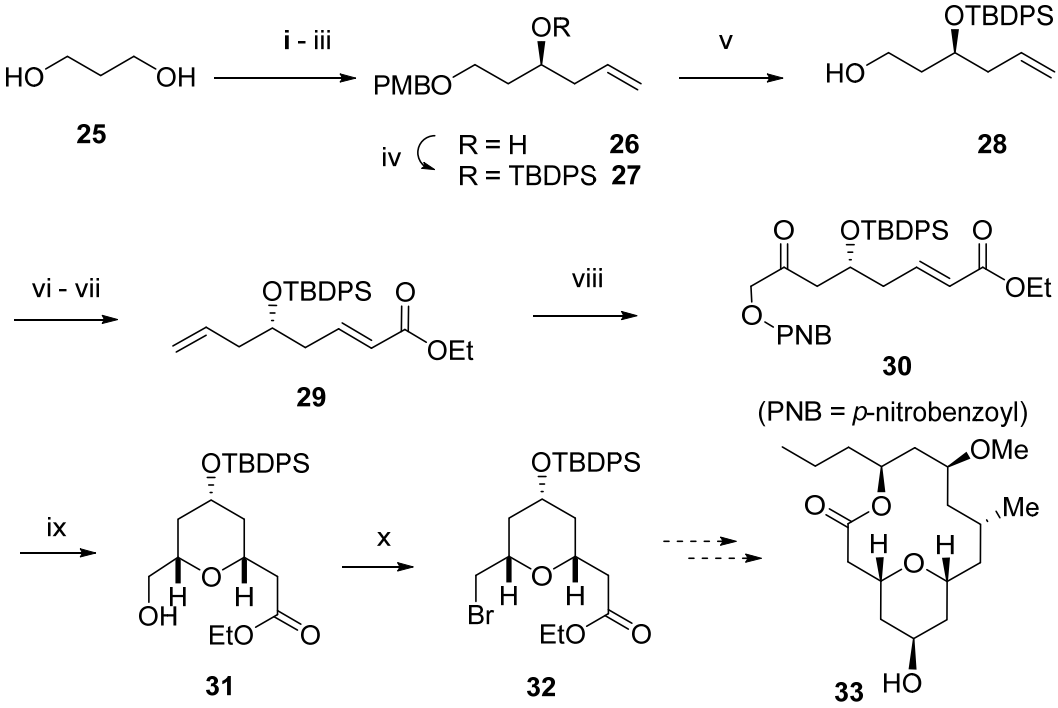
Chapter 4

This section describes studies towards the synthesis of (+)-neopeltolide macrolactone **33**. Chiral ketone**24**has been prepared starting from butyraldehyde(**18**) using asymmetric Keck allylation and Lewis acid catalysed diastereoselectiveallylationas key steps

(Scheme 6), while bromo compound **32** has been prepared starting from 1,3 propane diolusing NHC catalyzedoxo-acyloxylationand reductive oxa-Michel addition of1,6 dienoate**23 (Scheme 7)** .



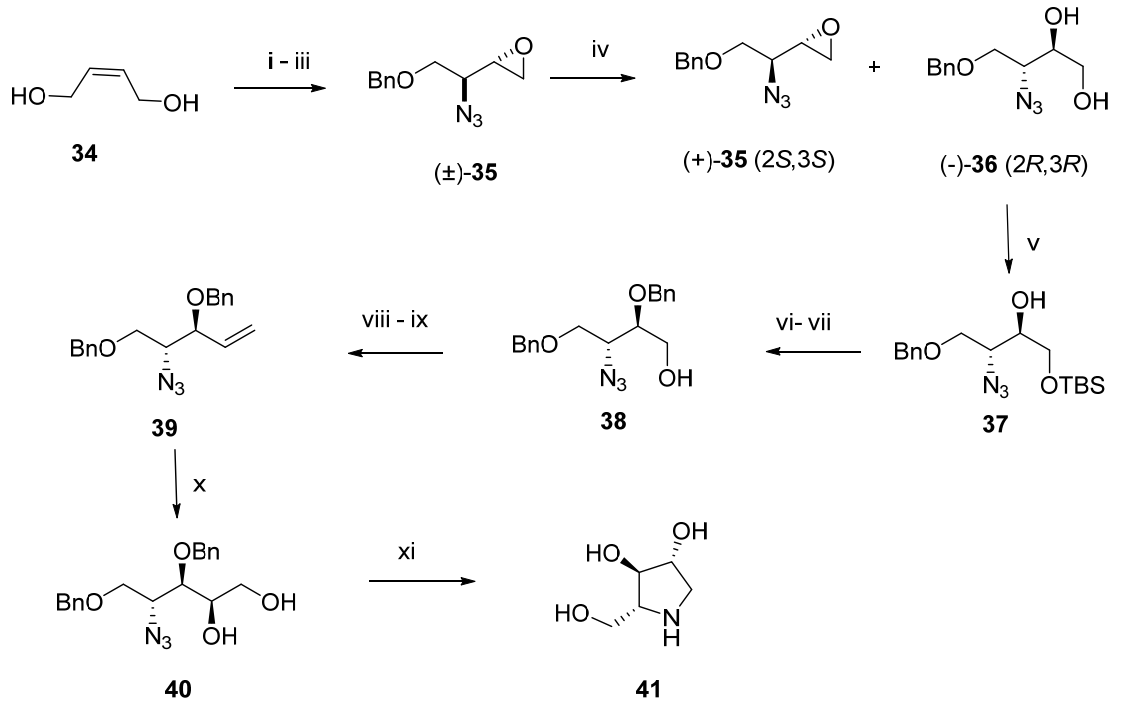
Scheme 6: (i) (*S*,*S*)-BINOL, 4 Å MS, $Ti(OiPr)_4$, allyltri-*n*-butyltin, CH_2Cl_2,-78 to -20 °C, 24 h, 82%; (ii) BnBr, NaH, DMF, 0°C, 4h (iii) (a) K_2OsO_4, NMO acetone:H_2O (4:1), 3 h; (b) $NaIO_4$, CH_2Cl_2, 0.5 h, rt, 87% (over 2 steps); (iv) allyltri-*n*-butyltin, $MgBr_2.Et_2O$, CH_2Cl_2, 0 °C, 8 h, 1:99 dr, 86%; (v) MeI (1.1 equiv), NaH (1.5 equiv), DMF, 0° C, 91%; (vi) $PdCl_2$ (2 mol %), CuI (10 mol %), DMF:H_2O (1:1), O_2 (1 atm), 81%.



Scheme 7: (i) PMBCl (1.1 equiv), NaH (1.5 equiv), DMF, 0-25 °C, 3 h, 88%; (ii) PCC, CH_2Cl_2, 25 °C, 4 h, 94%; (iii) (S,S)-BINOL, 4 Å MS, $Ti(OiPr)_4$, allyltri-*n*-butyltin, CH_2Cl_2, -78 to -20 °C, 24 h, 84%, 96% ee; (iv) TBDPSCl (1.1 equiv),

imidazole (3 equiv), CH_2Cl_2, 25 °C, 3 h, 86% ;(v) DDQ (3 equiv), CH_2Cl_2, 25 °C, 4 h, 84% ;(vi) IBX, DMSO, 25 °C, 89%; (vii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 92% ; (viii) NHC cat. **1c** (10 mol %), Et_3N (1.2 equiv), NBS (1 equiv), DMSO, 25° C, O_2 (1 atm), 16 h, 72% ; (ix) $NaBH_4$ (4 equiv), LiI (10 equiv), MeOH, -20°C, 3 h, 72 %; (xi) PPh_3, CBr_4, imidazole, CH_2Cl_2, 82%.

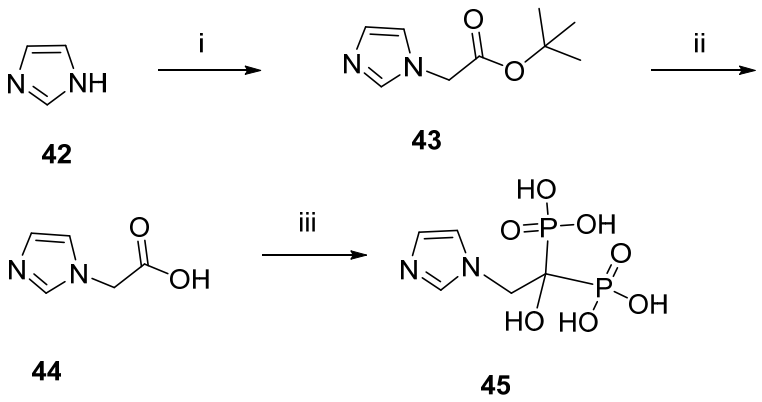
Further,total synthesis of DAB-1 has been achieved in 11 linear steps starting from *cis*-butenediol (**28**) using Co(Salen) catalyzed hydrolytic kinetic resolution of anti-azido epoxide **30,** diatereoselectivedihydroxylation and reductive cyclization of diolazidodiol**34.**



Scheme 8: Reagents and conditions: (i) NBS (1.1 equiv), NaN_3 (2 equiv), CH_3CN:H_2O (3:1), 0 °C, 4 h, 89%; (ii)NaOH powder, THF, 0 °C, 1 h, 84%; (iii) BnBr (1.1 equiv), NaH (1.5 equiv), DMF, 0 to 25 °C, 92%; (iv) (*S,S)*-salen-cobalt(III)OAc (1 mol %), H_2O (0.5 equiv), 0 °C, 14 h, **35**: 48% and **36**: 50%. (v) TBSCl (1.1 equiv), imidazole (1.5 equiv), CH_2Cl_2, 25 °C, 92%; (vi) BnBr (1.1 equiv), NaH (1.5 equiv), DMF, 0 °C to 25 °C; (vii) CSA (10 mol %), CH_2Cl_2:MeOH (1:1), 84% (over 2 steps); (viii) PCC, CH_2Cl_2, 4 A ° MS, 25 °C; (ix) CH_3PPh_3I (1.1 equiv), *n*-BuLi (1.5 equiv), THF, 0 - 25 °C, 81% (over 2 steps) (x) K_2OsO_4 (1 mol %), NMO (3 equiv), acetone:H_2O (4:1), 88%; (xi) (a) Bu_3SnO (2 equiv), *p*-TsCl (1.1 equiv), Et_3N (2 equiv), DMAP (10 mol %), CH_2Cl_2, 0 - 25 °C; (b)10% Pd/C, 6N HCl, MeOH, H_2 (1 atm), 25 ^oC, 12 h, 90 %.

The osteoporosis drug zoledronic acid (**45**) was prepared from carboxylic acid **44,** which

was preparedby alkylation followed by basic hydrolysis of imidazole (**42**). The biphosphorylation of imidazole carboxylic acid **44**using phosphoric acid gave the desired zoledronic acid (**45**) in 90% yield (**Scheme 9**).



Scheme 9: (i) $BrCH_2CO_2{}^tBu$ (1.1 equiv), K_2CO_3 (1 equiv), CH_2Cl_2, 40 °C, 90%; (ii) NaOH (2 equiv), MeOH:H_2O (1:1), 94%; (iii) H_3PO_4 (2 equiv), $POCl_3$ (2 equiv), PhCl, 100 °C, 5 h then 6 N HCl, 100 °C, 12 h, 85%.

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Signature of Ph.D. Supervisor **Signature of the Candidate**

(Dr. A. Sudalai) **(RambabuReddi)**

CHAPTER I

N-Heterocyclic Carbene Catalyzed Oxidative Coupling of Aromatic Aldehydes with $^{n}Bu_3SnCl$ and allylic C-H Bonds

1. *N*-Heterocyclic Carbene Catalyzed Oxidative Stannylation of Aldehydes: a Facile Entry to Organotin(IV) Carboxylates; **Rambabu N. Reddi**, Pushpa V. Malekar, Arumugam Sudalai. *Tetrahedron. Lett.*, **2013**, *54*, 2679.

2. *N*-Heterocyclic Carbene Catalyzed Oxidative Cross Dehydrogenative Coupling of Aldehydes and Allylic/Benzylic C-H bonds; **Rambabu N. Reddi**, Arumugam Sudalai; (manuscript under preparation).

Section I

N-Heterocyclic Carbene Catalyzed Oxidative Stannylation of Aromatic Aldehydes: A Facile Entry to Organotin(IV) Carboxylates

1.1.1 *N*-Heterocyclic Carbene Catalysis: Literature

In the last two decades, *N*-heterocyclic carbenes (NHC) have emerged as an important and prevailing class of organocatalysts with remarkable applications in a variety of synthetic transformations and are receiving much attention as proline, because of their unique electronic properties. **Fig. 1** shows the presence of a carbene moiety stabilized by two adjacent π-donating atoms in NHC. The unsaturation in the backbone makes this an aromatic system, so that the carbene *p*-orbital is available to act as a π-acid. The ability of NHCs to act as both electron donors and acceptors permits them to serve as organocatalysts in a variety of coupling reactions.[1]

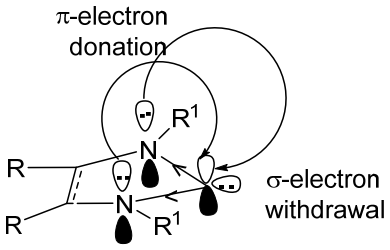


Fig. 1: Stabilization of *N*-heterocyclic carbenes

NHC can provide catalytic access to acyl anion equivalents, an umpolung strategy in which organic molecules react in an inverse manner compared to their innate polarity-driven reactivity.[2]

In the beginning, thiazolium salt derived NHCs (**1a-c**) were the most popular class of NHC in organocatalytic transformations, such as intermolecular cross-benzoin condensation reported by Stetter in the 1970s.[3,4] Since then, imidazolium (**1d-f**) and triazolium (**1h** & **1i**)[5]-derived NHCs have become more prominent organocatalysts,

with each of them having preferred fields of application,[6] where as only a very few examples have been reported of imidazolinylidenes (**1g**) acting as organocatalysts.[7] However, the sulfur atom renders thiazolylidenes to be a unique class of NHCs: Whereas the steric demand of the *N*-substituent can be varied over a wide range, sulfur does not even have a substituent, rendering the carbene environment highly unsymmetrical (**Fig. 2**). In addition, the electronic properties and carbene stabilization are also greatly influenced by the very small π character of the carbene C–S bond, which may be responsible for the specific reactivity of this class of NHCs.[8]

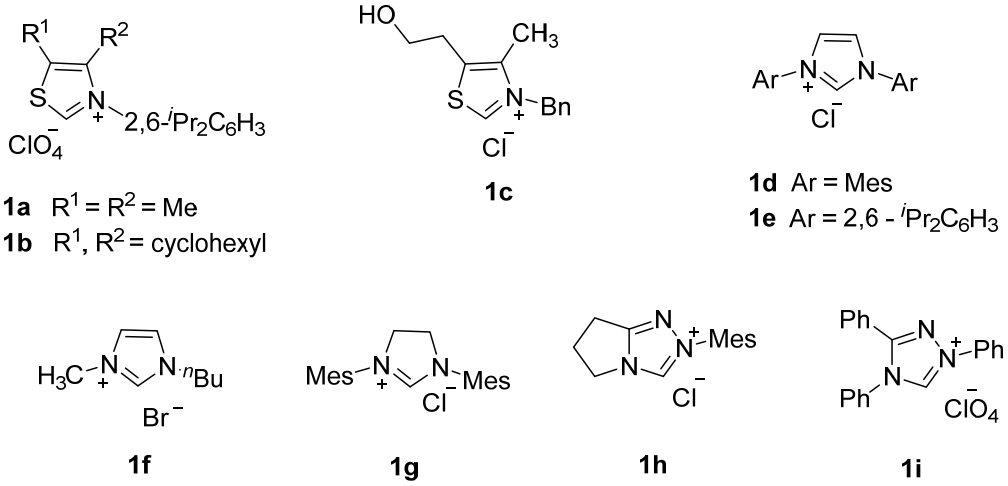


Fig. 2: Some of the *N*-heterocyclic carbene precatalysts

The majority of organocatalyzed transformations that are proceeding through umpolung are catalyzed by NHCs. They have a various of modes of activation for a given substrate, like (i) acyl anion,[9] (ii) hydroacylation,[10] (iii) homoenolate,[11] and (iv) rebound catalysis[12] in which it forms four important intermediates namely (i) Breslow intermediate, (ii) enolate, (iii) homoenolate, (iv) acylazolium and α,β-unsaturated acylazolium (**Fig. 3**). The most prominent intermediate in NHC catalysis is Breslow intermediate. It is assumed that the NHC precatalyst **1** is deprotonated in the reaction

mixture to afford a nucleophilic carbene **I**. Addition to an aldehyde **2** followed by proton transfer affords an enamine type intermediate, referred to as the

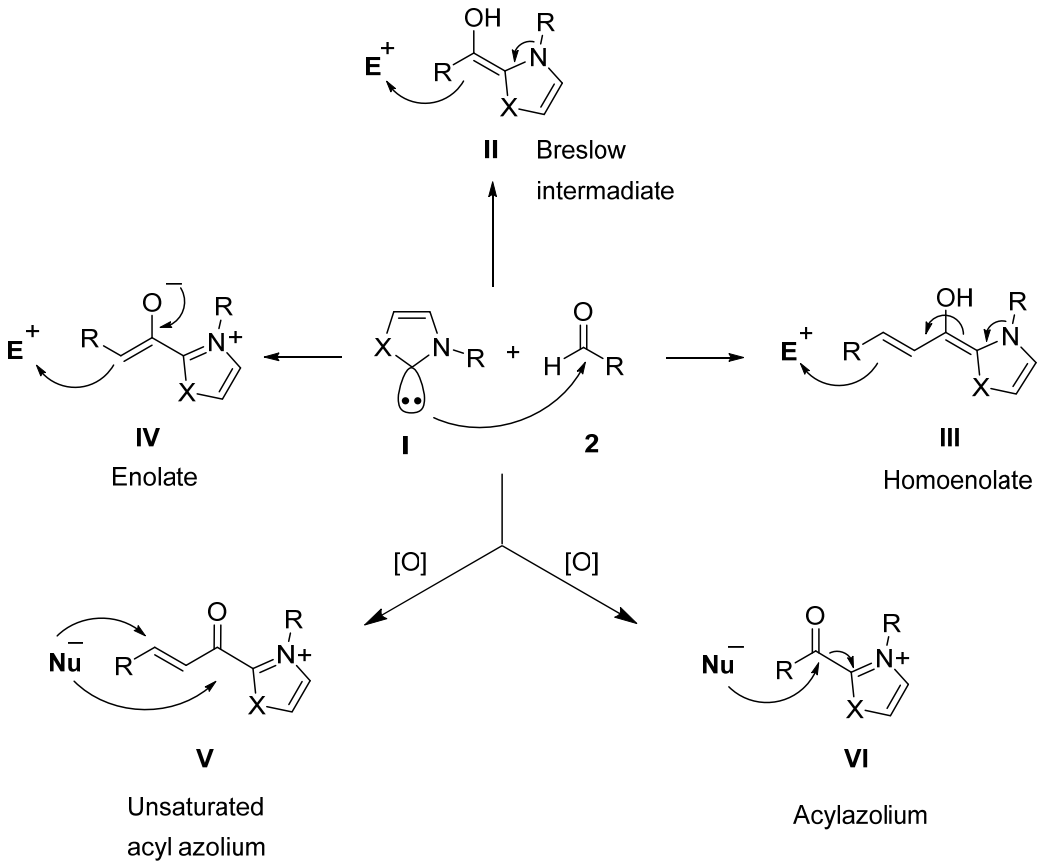


Fig. 3: Intermediates in NHC-organocatalysis

Breslow intermediate **II**,[13] in which the originally electrophilic carbon atom of the aldehyde has gained nucleophilic character. This acyl anion equivalent now can attack on various electrophilic carbons. When Breslow intermediate attacks on (i) aldehyde provides α-hydroxy ketones (benzoin condensation),[14] (ii) Michael acceptor provides 1,4-dicarbonyl compounds (Stetter reaction)[15] and (iii) simple alkenes provide ketones (hydroacylation reaction). In 2004, Glorius[16] and Bode[17] independently reported that analogous to the formation of Breslow intermediates from aldehydes and NHCs, 'extended Breslow intermediates' can be generated from α,β-unsaturated aldehydes. This intermediate **III**, due to the extended conjugation, exhibits significant

nucleophilic reactivity at the β-position and is appropriately called a homoenolate (**Fig 3**). Formation of a new bond with an electrophile at the β-position affords an enol intermediate **IV,** which can react with other electrophiles. In addition, NHC catalyzed oxidative reactions involves acylazolium ion intermediates (**V** & **VI**) has been reported under the name of oxidative NHC catalysis (a sub-area of NHC catalysis).

Oxidative NHC Catalysis[18]

Oxidative NHC-catalyzed reactions rely on the oxidation of the initially formed nucleophilic NHC-aldehyde adduct **II** (Breslow intermediate). The oxidation event can either result in the formation of an electrophilic acyl azolium ion **VI** *via* transfer of two electrons to the oxidant (path A: oxidation) or alternatively can afford a peroxy anion species **VII** by oxygen atom transfer from the oxidant (path B: oxygenation).

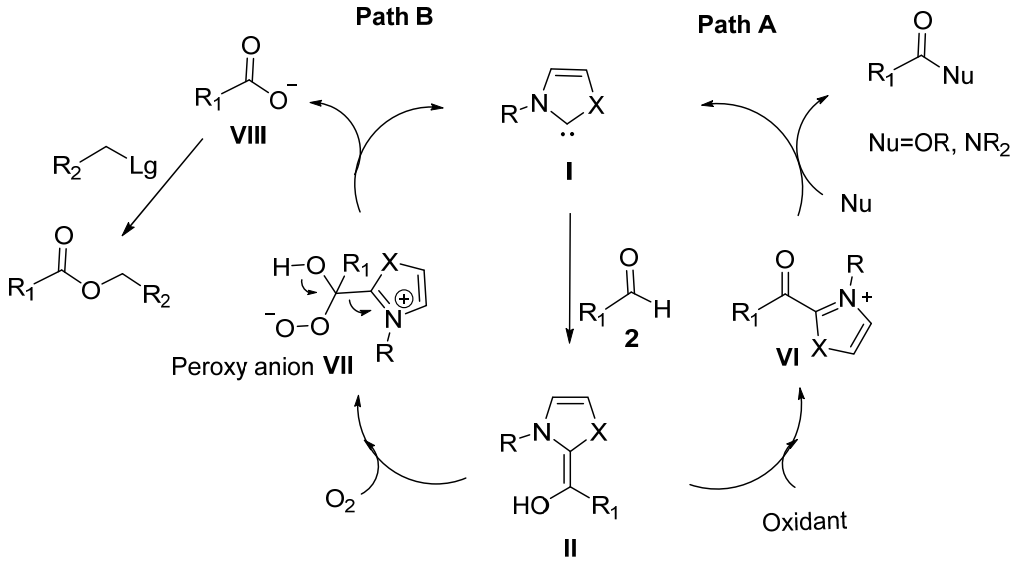


Fig. 4: Oxidative acylation of nucleophiles (path A); oxygenative acylation of electrophiles (path B)

The C2-substituents of both resultant azolium ions now differ in nature and reactivity: Path A sets the stage for a nucleophilic substitution at the carbonyl group with

elimination of the azolium ion. The overall acylation through path A thus involves sequential nucleophilic addition, oxidation, and nucleophilic substitution, the two former of which are umpolung events (**Fig.4**). This net hydride substitution at the aldehydes bears a conceptual relationship to nucleophile-catalyzed trans-esterification reactions, but exploits a different oxidation state of the starting material (aldehyde vs. ester). On the other hand, oxygenation of the formal Breslow intermediate **II**, that is, the transfer of an oxygen atom (path B) was postulated to proceed *via* zwitterionic peroxide. The spin-allowed oxygenation with molecular oxygen could also involve an intermediate dioxetane species. This oxygenative pathway funnels into a carboxylation event with a suitable electrophile. Here, the overall reaction sequence also involves two umpolung steps. The latter (oxygenation) step transposes the site of reactivity from the carbonyl group to the oxygen atom, which harbors nucleophilic character to react with various *C*-electrophiles to form the corresponding esters.[19]

Based on this concept, various oxidative reactions have been reported for C-C, C-O and C-N bond formation. Particularly, the direct esterification of aldehydes was well-documented with alcohols as nucleophiles under different oxidative conditions.[20] These reactions employ boronic acids[21] under aerobic conditions. Recently, a useful preparative procedure for the oxidative esterification[22] of aldehydes under aerobic oxidative condition with alcohols has been reported. Nevertheless, NHC catalyzed oxidative metallation reactions using metal electrophiles has not been reported.

1.1.2 Organotin(IV) carboxylates: Introduction

The direct transformation of aldehydes to the corresponding organotin(IV) carboxylates **4** with $^{n}Bu_3SnCl$ under mild conditions is interesting due to their potent pharmacological properties. It is well-known that organotin carboxylates **4** have versatile molecular structures both in solids and solutions, such as monomers, dimers,

tetramers, oligomeric ladders and hexameric drums, etc.[23] It has also been demonstrated that other structural types are formed due to the presence of additional coordinating sites (S, N or O, etc) along with a carboxylate moiety (**Fig 5**).

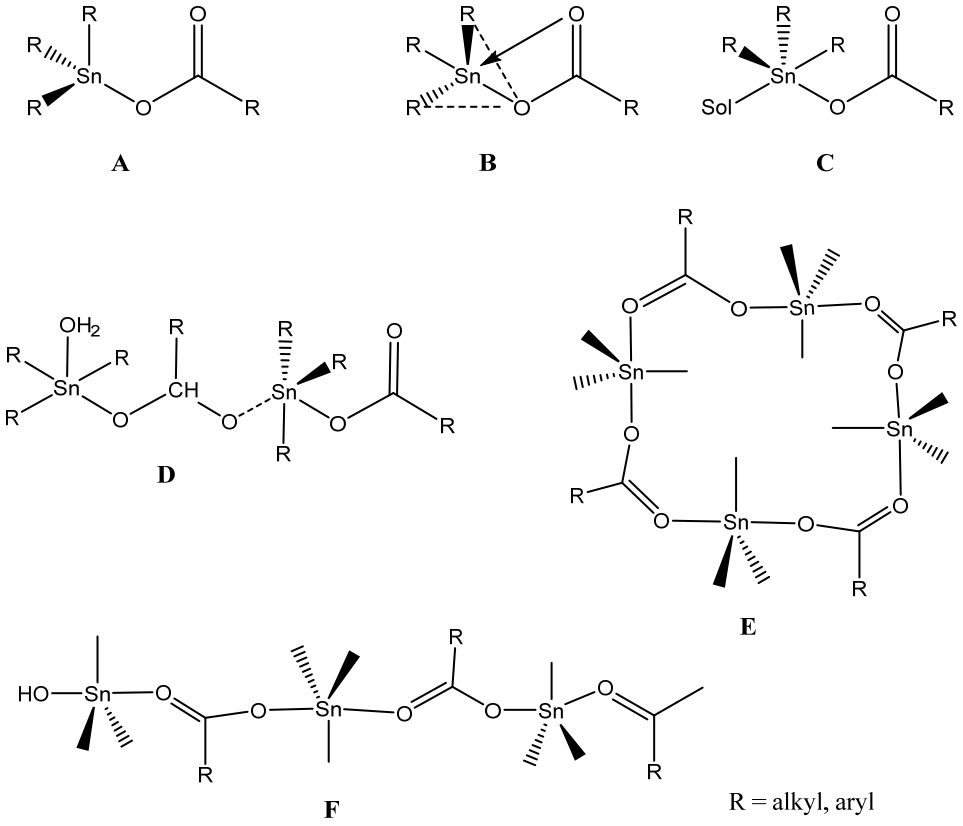


Fig. 5: The various structural forms of triorganotin carboxylates. (A) and (B) represent the discrete forms; (C) is a discrete form with a solvent molecule coordination; (D) is a dimeric form; (E) macrocyclic form; (F) polymeric form.

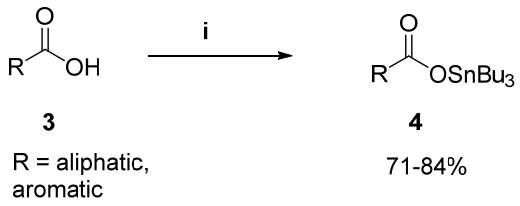
Organotin carboxylates act as potential pharmaceuticals such as anti-tumour,[24] antimicrobial,[25] anti-fungal[26] and cytotoxic activity.[27] They are also used as fungicides,[28] pesticides,[29] antifouling coating materials,[30] preservatives for wood,[31] acaricides[32] and homogeneous catalysts[33] in industry. There are no methods available in the literature for the synthesis of carboxylic acid stannanes directly from aldehydes using tributyltin chloride.

1.1.3 Review of Literature

In the literature, synthesis of organotin(IV) carboxylates **4** has been reported from the corresponding carboxylic acids and their salts. Some of the recent developments on this transformation are discussed below.

Basu's approach (2000)[27]

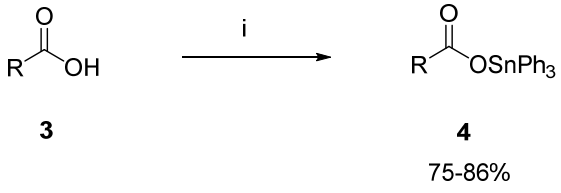
In Basu Baul approach, carboxylic acids **3** in the presence of *bis*-tributyltinoxide undergo stannylation to give the corresponding organotin(IV) carboxylates **4** under reflux condition in toluene as a solvent (**Scheme 1**).



Scheme 1: (i) $(Bu_3Sn)_2O$, toluene, reflux, 6 h.

Mahmudov's approach (2002)[34]

In Mahmudov approach, aromatic or aliphatic carboxylic acids were treated with triphenyltin chloride to give the corresponding acid stannanes in 75-86% yields (**Scheme 2**).

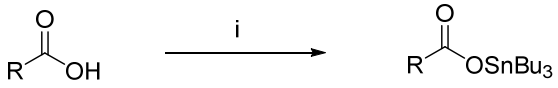


Scheme 2: (i) Ph_3SnCl, toluene, reflux, 4 h.

Akrivos's approach (2003)[29]

In Akrivo's approach, the direct stannylation of carboxylic acids with $^tBu_3SnCl$ was carried out using toluene as a solvent under reflux conditions. A variety of carboxylic

acids **3** were converted to their corresponding organotincarboxylates **4**. Further, a variety of aliphatic acids were also converted to the corresponding acid stannanes in good yields under the same reaction conditions (**Scheme 3**).



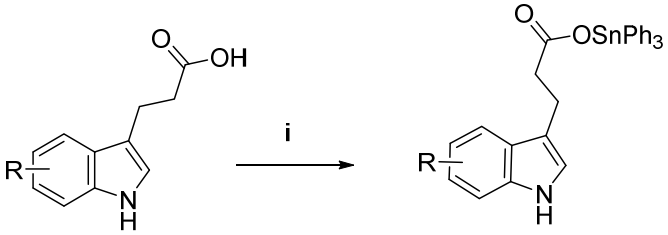
3 **4**

54-71%

Scheme 3: (i) Bu_3SnCl, toluene, reflux, 4 h.

Chilwal's approach (2007)[35]

In Chilwal approach, indole-3-propionic acid stannanes **6** have been synthesized by the reactions of the corresponding triphenyltin (IV) hydroxide with respect to indole-3-butyric acid (IBH) or indole-3-propionic acid (IPH) **5** in the desired molar ratios of 1:2/1:1 (**Scheme 4**).



5 **6**

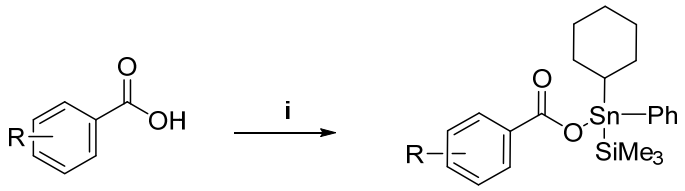
62-78%

Scheme 4: (i) Ph_3SnOH, CH_3CN, reflux, 8 h

Gong's approach (2011)[36]

Gong *et al.* have developed a highly efficient, mild, and simple protocol for stannylation of carboxylic acids **3** to the corresponding organotin carboxylates **7** utilizing (cyclohexyliodo(phenyl)stannyl)trimethylsilane as the stannylating agent.

These reactions may prove to be valuable alternatives to traditional metal-mediated oxidations (**Scheme 5**).



3 **7**

58-81%

Scheme 5: (i) TMSSnI(Ph)(Cy), toluene, reflux, 9 h.

1.1.4 Present Work

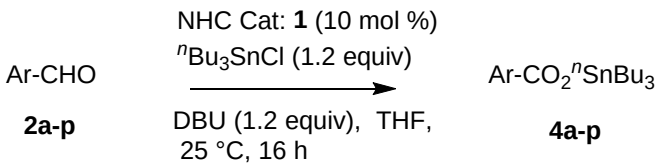
1.1.4.1 Objective

A few reports for the transformation of carboxylic acids to the corresponding organotin carboxylates using various stannylating agents have been reported. However, there are certain drawbacks associated with them such as (i) harsh reaction conditions; (ii) metals as biproducts; (iii) often low yields. In this regard, an organocatalytic additive-free mild protocol for oxidative stannylation of aldehydes is highly desirable. This section describes the first NHC-catalyzed direct stannylation of aromatic aldehydes **2a-p** with a tributyltin chloride under aerobic condition using catalytic amount of DBU to give the corresponding organotin (IV) carboxylates **4a-p**.

1.1.4.2 Results and Discussion

It may be noted that, there is no report available for NHC catalyzed oxidative metallation of aldehydes **2** with metal halides as electrophiles. In this section, we report a new efficient and practical method for the 'one-step' conversion of aldehydes directly into the corresponding organotin(IV) carboxylates using *N*-heterocyclic carbenes as catalysts (**Scheme 6**). We envisaged that molecular O_2 should be an ideal

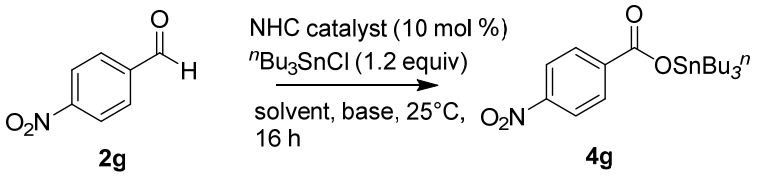
oxidant for this purpose based on its nature of reactivity, low cost, and environment-friendly characteristics.



Scheme 6: Oxidative stannylation of aromatic aldehydes using NHC catalysis

Initially, we have chosen 4-nitrobenzaldehyde **2g** as a test substrate for the oxidative stannylation using tributyltin chloride (1.2 equiv) as tin source, NHC precatalyst **1a** (10 mol %) and DBU (1.2 equiv) as base in CH_3CN, which produced tri-*n*-butyltin 4-nitrobenzoate **4g** in 55% yield (**Table-1**, entry 1). We conducted several experiments to improve the yield and found that THF was the best choice (90%) while other solvents (DMF, CH_2Cl_2) gave only moderate yield of **4g**. Use of other inorganic bases (K_2CO_3, $KOBu^t$ and NaH) resulted in a sluggish reaction with poor yields. DBU was thus chosen as the base for further optimization (**Table 1**, entry 2). Among the NHC precatalysts[18] screened, thiazolium (**1b** and **1c)** -based precatalysts afforded **4g** in 41% and 75% yields respectively while the imidazolium (**1d** & **1e**) and triazolium (**1h** & **1i**) - based precatalysts also gave only moderate yields (54%).

Table 1: Oxidative stannylaltion of 4-nitrobenzaldehyde: Optimization studies[a]



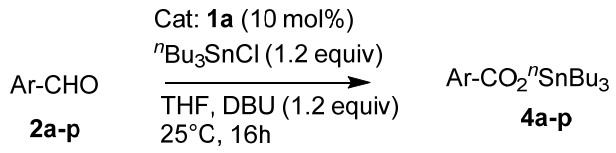
2g **4g**

s.no.	catalyst	solvent	base	yield of **4g** (%)[b]
1	**1a**	CH_3CN	DBU	55
		THF	DBU	90
		DMF	DBU	35
		CH_2Cl_2	DBU	5
2	**1a**	THF	K_2CO_3	40
		THF	KO^tBu	35
		THF	NaH	20
3	**1b**	THF	DBU	41
4	**1c**	THF	DBU	75
5	**1d**	THF	DBU	40
6	**1e**	THF	DBU	33
7	**1h**	THF	DBU	54
8	**1i**	THF	DBU	20

a: Reaction conditions: 4-nitrobenzaldehyde (1 equiv), *n*-tributyltin chloride (1.2 equiv), NHC catalyst (10 mol%), base (1.2 equiv), under O_2 atmosphere; 25 °C, 16 h; b: isolated yields after column chromatographic purification.

With this optimized condition in hand, we examined the substrate scope of the reaction. Various aldehydes were then subjected to oxidative stannylation; the results of which are presented in **Table 2**. Aromatic aldehydes, having electron-withdrawing and releasing groups at various positions on the aromatic ring were reacted to give the corresponding organotin(IV) carboxylates (**Table 2**) in excellent yields. Also, heteroaromatic aldehydes underwent this oxidative stannylation efficiently to give the corresponding organotin(IV) carboxylates in 82% and 87% yields respectively.

Table 2: Oxidative stannylaltion of aromatic aldehydes: Substrate Scope[a]



s.no.	substrate, Ar (**2a-p**)	product (**4a-p**)	yield (%)[b]
1	benzaldehyde	**4a**	40
2	*m*-tolualdehyde	**4b**	76
3	4-OMe-benzaldehyde	**4c**	79
4	3,4-(-OCH_2O-)benzaldehyde	**4d**	81
5	salicylaldehyde	**4e**	74
6	3-NH_2-benzaldehyde	**4f**	71
7	4-NO_2- benzaldehyde	**4g**	90
8	2-NO_2- benzaldehyde	**4h**	85
9	4-Br- benzaldehyde	**4i**	70
10	4-CN- benzaldehyde	**4j**	87
11	3-pyridine carboxaldehyde	**4k**	82
12	furfural	**4l**	87
13	cinnamaldehyde	**4m**	22 (84)[c]
14	4-Br-cinnamaldehyde	**4n**	79[c]
15	3,4 – $(OMe)_2$-cinnamaldehyde	**4o**	72[c]
16	1-Br-3,4-dihydronaphthaldehyde	**4p**	74[c]

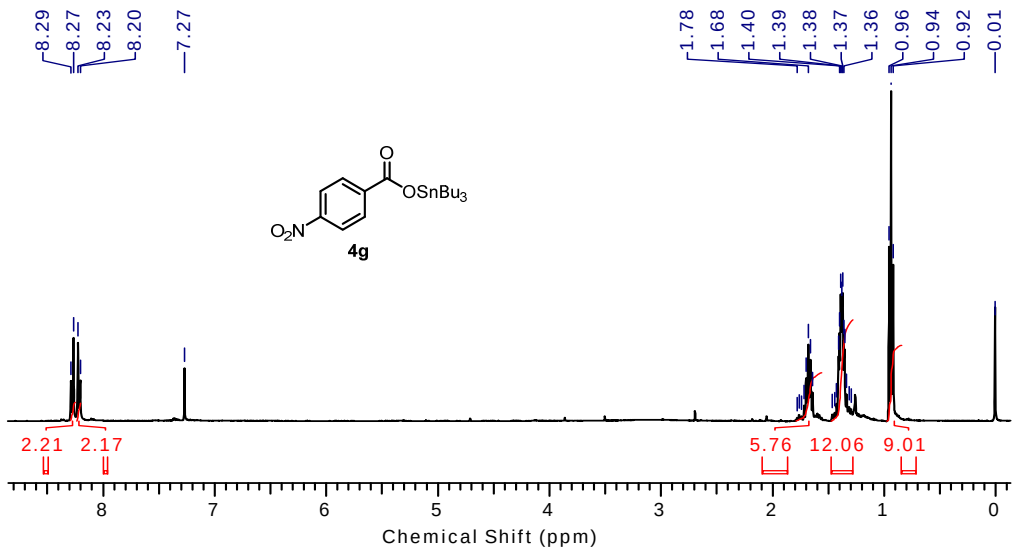
a: Reaction conditions: aldehyde (5 mmol), *n*-tributyltin chloride (6 mmol), NHC catalyst **1a** (10 mol %), DBU (6 mmol), under O_2 atmosphere; 25 °C, 16 h; b: isolated yield after column chromatographic purification; c: NHC catalyst **1d** was used.

In the case of α, β-unsaturated aldehydes, the oxidative stannylation under the above optimized condition gave **4m** (entry 13, **Table 2**) in low yield (22%). However, replacing NHC catalyst **1a** with **1d** gave the corresponding α, β-unsaturated acid stannane in 84% yield. Thus, with **1d** as precatalyst, α,β-unsaturated aldehydes (entries 14-16) underwent this reaction successfully to give excellent yields of the

corresponding organotin(IV) carboxylates (**4n-p**). However, aliphatic aldehydes failed to undergo this catalytic transformation.

The structure of tri-*n*-butyltin carboxylates **4a-p** was specifically ascertained on the basis of spectroscopic techniques. Generally, these compounds show a characteristic peak in ^{13}C NMR for carbonyl group around δ155-174 and IR absorption peak around 1630-1670.

Example 1: The ^{1}H NMR spectrum of tri-*n*-butyltin(IV) 4-nitrobenzoate (**4g**) showed three typical peaks at δ 0.94 (t, *J* = 7.2 Hz, 9H), 1.36-1.38 (m, 12H) and 1.39-1.78 (m, 5H) corresponding to the proton of tributyl group attached to tin metal, while other signals at δ 8.21 (d, *J* = 8.6 Hz, 2H) and 8.28 (d, *J* = 8.6 Hz, 2H) correspond to aromatic protons. Its ^{13}C NMR spectrum showed a characteristic carbon signal at δ 169.1 attributed to carbonyl carbon (**C**=O). Its HRMS spectrum displayed a molecular ion peak at m/e value of [M+Na] 480.1153 which confirms the presence of tri-*n*-butyltin(IV) 4-nitrobenzoate (**Fig. 6**).



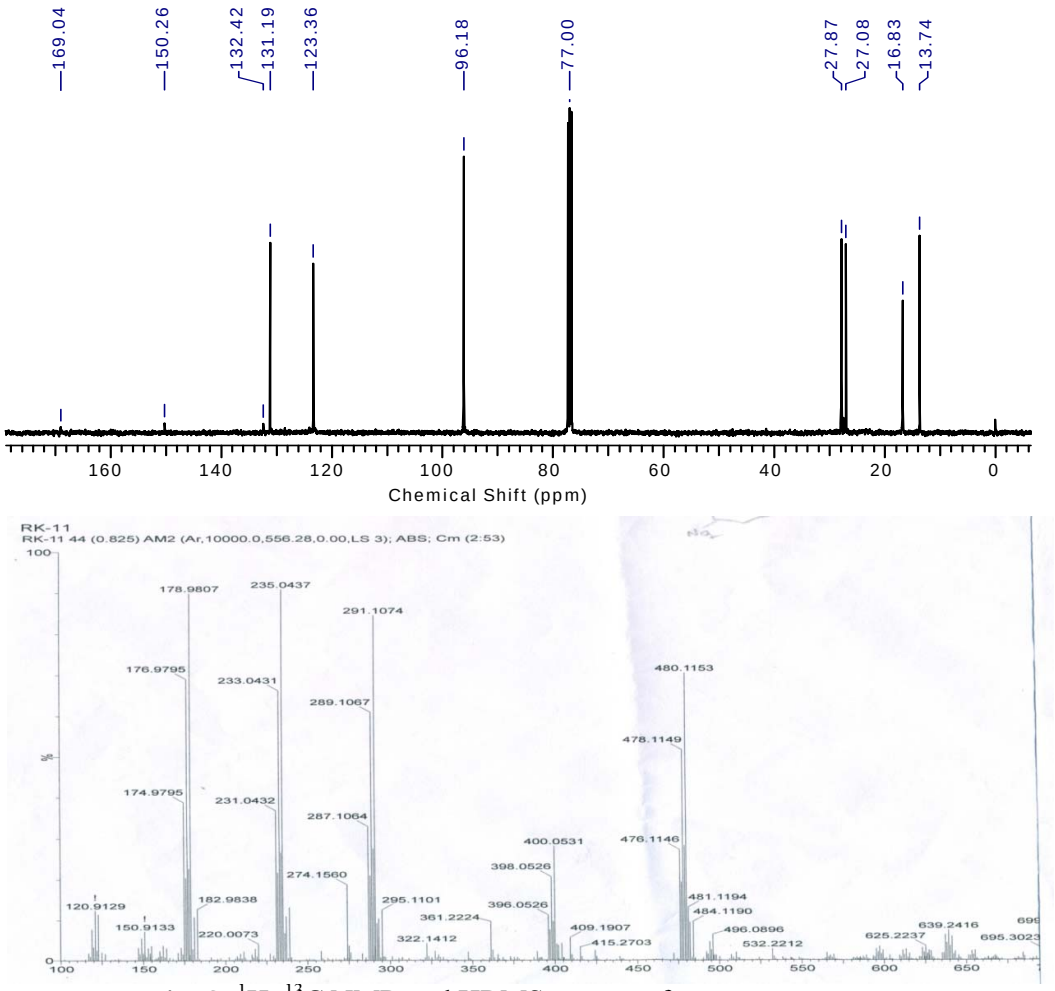


Fig. 6: ^{1}H, ^{13}C NMR and HRMS spectra of **4g**

Example 2: The ^{1}H NMR spectrum of tri-*n*-butyltin(IV) furan-2-carboxylate (**4l**) showed three typical peaks at δ 0.89 (t, J = 7.1 Hz, 9H), 1.32-1.38 (m, 12H) and δ 1.59-1.71 (m, 6H) corresponding to the protons of tributyl group attached to tin metal, while other signals at δ 6.48 (dd, J = 3.3 Hz, J = 1.6 Hz, 1H), 7.11 (d, J = 3.4 Hz, 1H) and 7.53 (s, 1H) correspond to aromatic protons. Its ^{13}C NMR spectrum showed a characteristic carbon signal at δ 163.3 attributed to carbonyl carbon (**C**=O) (**Fig. 7**).

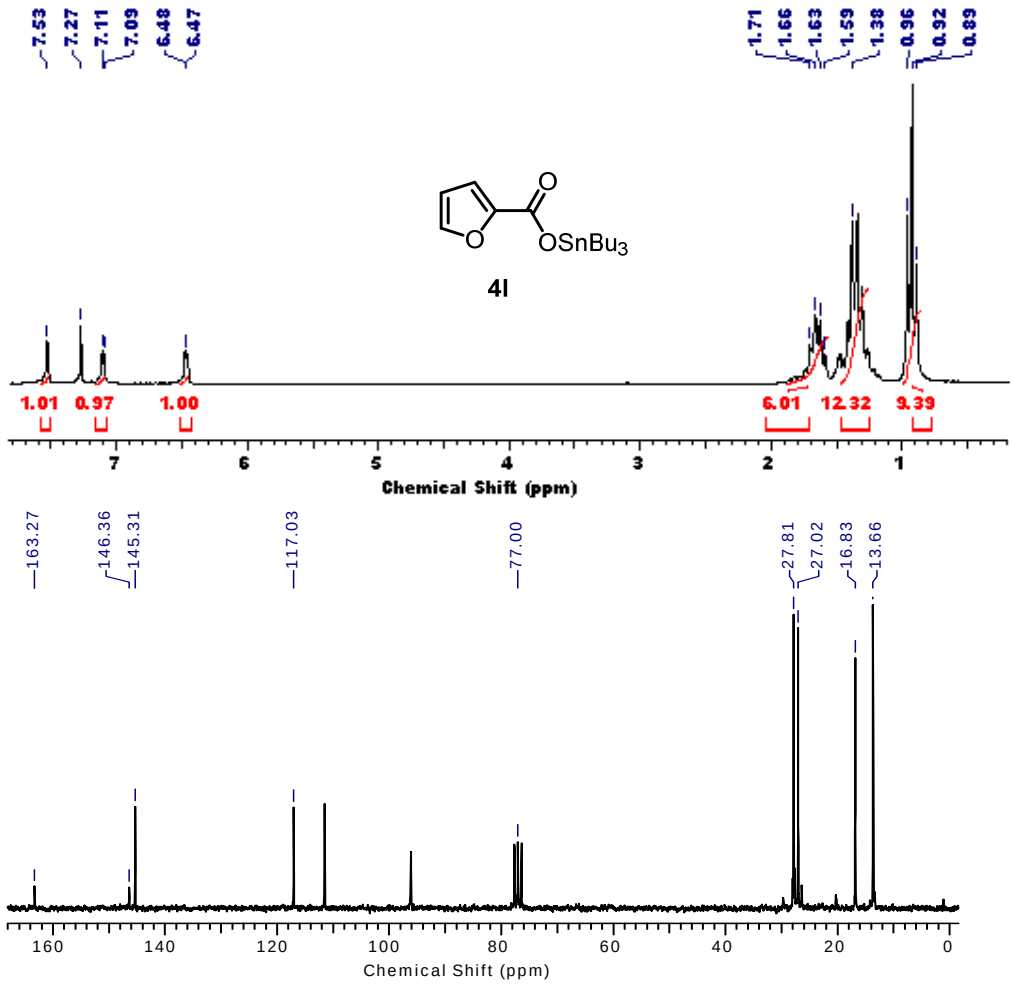
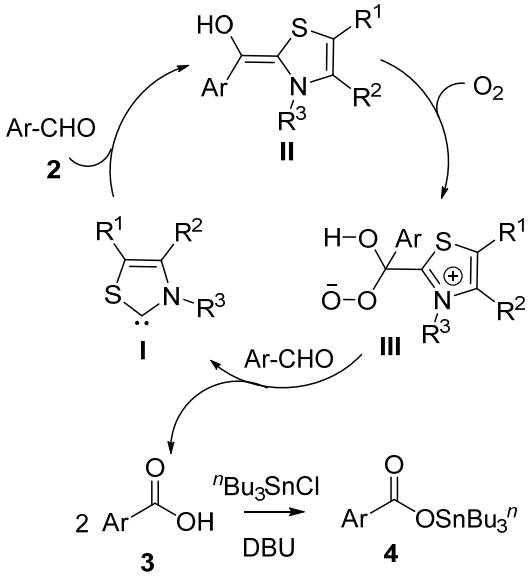


Fig. 7: ^{1}H and ^{13}C NMR spectra of **4l**

In order to gain insight into the mechanistic details of the reaction, the following experiments were conducted. (i) For aldehyde **4g,** no stannylation took place under N_2 atmosphere; suggesting the necessity of O_2 atmosphere. (ii) When *4*-nitrobenzaldehyde was treated with NHC catalyst under basic condition, 4-nitrobenzoic acid was isolated in the absence of tributyltin(IV) chloride under O_2 atmosphere. (iii) Treatment of *4*-nitrobenzoic acid (**3g**) and tributyltin(IV) chloride gave organotin(IV) carboxylates under the reaction conditions; suggesting the carboxylic acid (**3**) as the intermediate.

Based on the above results and literature precedence,[19] a probable mechanistic pathway is shown in Scheme 7. The Breslow intermediate **II**, upon reaction with O_2 gives the peroxy anion **III**,[18] which then reacts with another molecule of aldehyde to afford carboxylic acid **3** *in situ*; the stannylation of which with tri-*n*-butyltin chloride produces tri-*n*-butyltin carboxylates (**4**).



Scheme 7: Proposed mechanistic pathway for oxidative stannylation of aldehydes.

1.1.5 Conclusion

In conclusion, we have developed an efficient catalytic process for the preparation of organotin(IV) carboxylates (40-90%) using *N*-heterocyclic carbene catalyzed oxidative metallation of aldehydes under aerobic conditions. This methodology provides for the use of metal electrophiles in NHC catalyzed reactions.

1.1.6 Experimental Section

General experimental procedure for oxidative stannylation of aromatic aldehydes

To a stirred solution of *N*-heterocyclic carbene precursor (10 mol %), DBU (6 mmol) and aldehyde (5 mmol) in anhydrous THF (5 ml), tri-*n*-butyltin chloride (6 mmol) was added under an O_2 atmosphere. The reaction mixture was then stirred at 25 °C for 16 h. After completion of the reaction (monitored by TLC), the reaction mixture was then concentrated, followed by the addition of H_2O (50 mL). It was extracted with EtOAc (3 x 50 ml) and the combined organic layers dried over anhydrous Na_2SO_4. Removal of solvent gave organotin carboxylates, which were purified by column chromatography over silica gel using pet ether/EtOAc (1/19) as eluent to obtain pure tri-*n*-butyltin(IV) carboxylates in high purity.

Tri-*n*-butyltin(IV) benzoate (4a)

Yield: 40%, colorless liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 716, 1333, 1463, 1646, 2854, 2871, 2923, 2957; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.3 Hz, 9H), 1.41–1.34 (m, 12H), 1.66–1.68 (m, 6H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 8.07 (d, *J* = 7.3 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.7, 16.5, 27.0, 27.8, 128.0, 130.2, 132.2,171.4; **MS (ESI)**: $[M+Na]^+$ calcd for $C_{19}H_{32}NaO_2Sn$: 435.13; found: 435.10.

Tri-*n*-butyltin(IV) 3-methyl benzoate (4b)

Yield: 76%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 753, 1216, 1331, 1587, 1606, 1644, 2923, 2956; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.2 Hz, 9H), 1.29-1.39 (m, 12H), 1.63-1.71 (m, 6H), 2.40 (s, 3H), 7.28-7.31 (m, 2H),7.84-7.87 (m, 2H),; **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.6, 16.5, 21.2, 27.0, 27.8, 127.3, 128.0, 130.7, 131.2, 133.1, 137.6, 171.7; **MS (ESI)**: $[M+Na]^+$ calcd for $C_{20}H_{34}NaO_2Sn$: 449.14; found

: 449.11.

Tri-*n*-butyltin(IV) 4-methoxy benzoate (4c)

Yield: 79%, colorless liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 1029, 1166, 1253, 1306, 1336, 1605, 1640, 1684, 2853, 2923, 2956; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.91 (t, *J* = 7.3 Hz, 9H), 1.22-1.37 (m, 12H), 3.85 (s, 3H), 1.61-1.81 (m, 6H), 6.91 (d, *J* = 8.7 Hz, 2H), 8.03 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.7, 16.5, 27.0, 27.9, 55.2, 113.3, 127.8, 132.2, 160.8, 171.2; **MS (ESI)**: $[M+Na]^+$ calcd for $C_{20}H_{34}NaO_3Sn$: 465.14; found: 465.16.

Tri-*n*-butyltin(IV) 3, 4-(-OCH_2O-) benzoate (4d)

Yield: 81%, colorless gum ; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 1039, 1257, 1374, 1488, 1655, 2956; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.2 Hz, 9H), 1.27-1.41 (m, 12H), 6.02 (s, 2H), 1.61-1.71 (m, 6H), 6.79 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 1.5 Hz, 1H), 7.64 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.6, 16.6, 26.9, 27.8, 101.4, 107.6, 110.2, 125.6, 126.8, 147.3, 150.9, 170.7; **Analysis**: $C_{20}H_{32}O_4Sn$ requires C 52.77, H 7.09; found: C 52.61, H 7.23 %.

Tri-*n*-butyltin(IV) 2-hydroxybenzoate (4e)

Yield: 74%, colorless solid, mp: 67-68 ^oC; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 757, 1253, 1386, 1598, 1635, 3441; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.1 Hz, 9H), 1.33-1.43 (m, 12H), 1.64-1.64 (m, 6H), 5.15 (bs, 1H), 6.84-6.95 (m, 2H), 7.34-7.44 (m, 1H), 7.85 (dd, *J* = 7.8 Hz, 1.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.7, 17.0, 27.0, 27.8, 117.1, 118.5, 128.4, 131.2, 134.8, 161.7, 174.4; **Analysis**: $C_{19}H_{32}O_3Sn$ requires C 53.42, H 7.55; found: C 53.60, H 7.35 %.

Tri-*n*-butyltin(IV) 3-amino benzoate (4f)

Yield: 71%, colorless liquid, **IR** ($CHCl_3$, cm^{-1}): ν_{max} 1340, 1459, 1618, 1637, 2853, 2870, 2923, 3432; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.1 Hz, 9H), 1.28-1.38

(m, 12H), 1.61-1.69 (m, 6H), 3.73 (s, 2H), 6.82 (m, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.36 (m, 1H), 7.44 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (100 MHz, CD_3COCD_3): δ 13.9, 18.6, 27.4, 28.6, 116.1, 118.8, 118.9, 129.4, 133.3, 149.1, 170.2; **Analysis**: $C_{19}H_{33}NO_2Sn$ requires C 53.55, H 7.80, N 3.29; found: C 53.41, H 7.61 N 3.18 %.

Tri-*n*-butyltin(IV) 4-nitrobenzoate (4g)

Yield: 90%, colorless gum; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 722, 1331, 1527, 1603, 1651, 2923, 2956; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.3 Hz , 9H), 1.36-1.40 (m, 12H), 1.68-1.78 (m, 6H), 8.21 (d, *J* = 8.5 Hz, 2H), 8.28 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR:** (100 MHz, $CDCl_3$): δ 13.7, 16.8, 27.0, 27.8, 123.3, 131.1, 132.4, 150.2, 169.0; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{19}H_{31}NNaO_4{}^{120}Sn$: 480.1173; found: 480. 1153.

Tri-*n*-butyltin(IV) 2-nitrobenzoate (4h)

Yield: 85%, colorless gum ; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 756, 1348, 1532, 1653, 2924, 2956; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.3 Hz, 9H), 1.34-1.39 (m, 12H), 1.65-1.71 (m, 6H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 6.8 Hz, 1H), 7.76 (t, *J* = 6.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.6, 16.7, 27.0, 27.7, 123.3, 129.5, 130.0, 130.7, 132.1, 148.7, 169.5; **MS (ESI)**: $[M+Na]^+$ calcd for $C_{19}H_{31}NNaO_4Sn$: 480.11; found: 480.43**.**

Tri-*n*-butyltin(IV) 4-bromobenzoate (4i)

Yield: 70%, colorless gum; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 766, 1012, 1126, 1327, 1588, 1643, 2923, 2956; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.3 Hz, 9H), 1.33-1.40 (m, 12H), 1.63-1.65 (m, 6H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.89 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): 13.7, 16.6, 27.1, 27.9, 127.0, 131.09, 131.3, 131.8, 170.5; **MS (ESI)**: $[M+Na]^+$ calcd for $C_{19}H_{31}BrNaO_2Sn$: 513.05; found: 513.14**.**

Tri-*n*-butyltin(IV) 4-cyanobenzoate (4j)

Yield: 87%, colorless liquid, IR ($CHCl_3$, cm^{-1}): ν_{max} 865, 1126, 1334, 1463, 1653,

2230, 2924, 2956; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.3 Hz, 9H), 1.33-1.39 (m, 12H), 1.64-1.73 (m, 6H), 7.70 (d, *J* = 8.2 Hz, 2H), 8.13 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.6, 16.7, 27.0, 27.8, 115.5, 118.1, 130.6, 131.8, 136.1, 169.4; **Analysis**: $C_{20}H_{31}NO_2Sn$ requires C 55.07, H 7.16, N 3.21; found C 55.21, H 7.36 N 3.12 %.

Tri-*n*-butyltin(IV) pyridine-3-carboxylate (4k)

Yield: 89%, colorless solid, mp:152-153 ^oC, **IR** ($CHCl_3$, cm^{-1}): ν_{max} 753, 1076, 1342, 1463, 1591, 1650, 2854, 2870, 2923, 2956; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.2 Hz, 9H), 1.24-1.41 (m, 12H), 1.57-1.68 (m, 6H), 7.27-7.38 (ddd, *J* = 0.63 Hz, 4.8 Hz, 7.8 Hz, 1H), 8.27 (dt, *J* = 7.8 Hz, 2.0 Hz, 1H), 8.71 (d, *J* = 1.8 Hz, 4.9 Hz, 1H), 9.21 (dd, *J* = 0.6 Hz, 2.0 Hz, 1H) ; **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.5, 16.8, 26.9, 27.8, 122.9, 128.2, 137.5, 151.3, 152.0, 169.5; **MS (ESI):** $[M+Na]^+$ calcd for $C_{18}H_{31}NNaO_2Sn$: 436.12; found: 436.16

Tri-*n*-butyltin(IV) furan-2-carboxylate (4l)

Yield: 87%, colorless liquid; **IR** ($CHCl_3$): ν_{max} 1011, 1364, 1389, 1409, 1549, 1579, 1600, 2853, 2921, 2954; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.1 Hz, 9H), 1.25-1.48 (m, 12H), 1.85-1.58 (m, 6H), 6.48 (dd, *J* = 3.3 Hz, 1.6 Hz, 1H), 7.11 (d, *J* = 3.4 Hz, 1H), 7.53 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.6, 16.8, 27.0, 27.8, 111.5, 117.0, 145.3, 146.3, 163.2; **Analysis:** $C_{17}H_{30}O_3Sn$ requires C 50.90, H 7.54 found C 50.78, H 7.39 %; **MS (ESI)**: $[M+Na]^+$ calcd for $C_{17}H_{30}NaO_3Sn$: 425.11; found: 425.44.

Tri-*n*-butyltin (IV) *trans*-cinnamate (4m)

Yield: 84%, colorless solid, mp: 67-68 ^oC; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 1216, 1346, 1449, 1620, 1646, 2872, 2959; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.1 Hz, 9H), 1.39-1.22 (m, 12H), 1.43-1.69 (m, 6H), 6.46 (d, *J* = 15.9 Hz, 1H), 7.34-7.54 (m, 6H)

^{13}C NMR (50 MHz, $CDCl_3$): δ, 13.7, 16.7. 27.1, 27.9, 126.2, 128.4, 128.8, 130.5, 138.4, 140.2, 171.7 ; **MS (ESI)**: $[M+Na]^+$ calcd for $C_{21}H_{34}NaO_2Sn$: 461.14; found: 461.18.

Tri-*n*-butyltin(IV) 4-bromo *trans*-cinnamate (4n)

Yield: 89%, colorless solid, mp: 230-231 ^oC; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 766, 1012, 1068, 1126, 1169, 1327, 1396, 1588, 1643, 2854, 2870, 2956; **^{1}H NMR** (400 MHz, CD_3COCD_3); δ 0.87 (t, *J* = 7.3 Hz, 9H), 1.21-1.37 (m, 12H), 1.58-1.66 (m, 6H), 6.45 (d, *J* = 15.8 Hz, 1H), 7.47-7.54 (m, 5H) ; **^{13}C NMR** (50 MHz, CD_3COCD_3): 13.8, 18.1, 27.2, 28.3, 120.5, 124.1, 130.0, 132.4, 134.4, 142.7, 169.6; **MS (ESI)**: $[M+Na]^+$ calcd for $C_{21}H_{33}BrNaO_2Sn$: 539.05; found: 539.10.

Tri-*n*-butyltin(IV) 3, 4–dimethoxy-*trans*-cinnamate (4o)

Yield: 72%, colorless solid, mp: 224-225 ^oC; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 1025, 1139, 1262, 1513, 1639, 2922, 2954; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.2 Hz, 9H), 1.36-1.28 (m, 12H), 1.83-1.62 (m, 6H), 3.90 (s, 6H), 6.32 (d, *J* = 15.9 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 7.07 (m, 2H), 7.62 (d, *J* = 15.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): 13.7, 16.5, 27.0, 27.8, 55.8, 109.6, 110.9 , 122.7, 127.5, 145.2, 149.2, 151.1, 172.3; **Analysis:** $C_{23}H_{38}O_4Sn$ requires C 55.55, H 7.70; found C 55.77, H 7.48 %; **MS (ESI):** $[M+Na]^+$ calcd for $C_{23}H_{38}NaO_4Sn$: 521.16; found: 521.25.

Tri-*n*-butyltin(IV) 1-bromo-3, 4-dehydronaphthalate (4p)

Yield: 74%, colorless solid; mp: 242-243 ^oC ; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 759, 1318, 1341, 1463, 1639, 2852, 2923, 2956; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.2 Hz, 9H), 1.23-1.48 (m, 12H), 1.60-1.72 (m, 6H), 2.85 (t, *J* = 8.2 Hz, 2H), 2.87 (t, *J* = 8.21 Hz, 2H), 7.28-7.08 (m, 3H), 7.73-7.11 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): 13.7, 16.7, 22.7, 27.1, 27.8, 27.9, 114.2, 126.8, 127, 133.5, 136.7, 139.2, 174.9; **MS (ESI)**: $[M+Na]^+$ calcd for $C_{17}H_{30}NaO_3Sn$: 565.07; found: 565.12.

Section II

N-Heterocyclic Carbene Catalyzed Oxidative Cross Dehydrogenative Coupling of Aldehydes with Allylic sp^3 C-H Bonds

1.2.1 Cross Dehydrogenative Coupling

The selective oxidative cleavage of the sp^3 C–H bonds is of paramount interest to both academic and industrial research.[37] The two most common strategies adopted for the C–H bond activation processes rely on the concept of chelation assisted C–H bond functionalization[38] and cross dehydrogenative coupling (CDC).[39] CDC based methodologies are highly appreciable because it does not require substrate pre-functionalization. Further, being atom and step economic, these reactions are often air and moisture insensitive, and thereby can be performed in an aqueous environment or under air atmosphere (**Scheme 1**).[40]

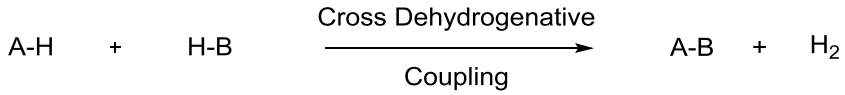


Fig. 8: Cross dehydrogenative coupling

The CDC approach has been mainly exploited towards the C–C bond formations,[41] but of late, the number of reports for C–O bond forming reactions are also increasing.[42] The CDC based protocols in the construction of a C–O bond have been achieved using transition metal catalysts such as Cu, Fe, Ru, Rh, Ir, and Pd in combination with various oxidants.[43] However, the disadvantages associated with these methodologies, owing to the use of expensive metal catalysts, elevated reaction temperature and the problems associated with the removal of metal residues limit their practical applicability. Therefore, increasing interest has been focused on metal free catalysts, particularly towards the formation of a C–O bond.[44]

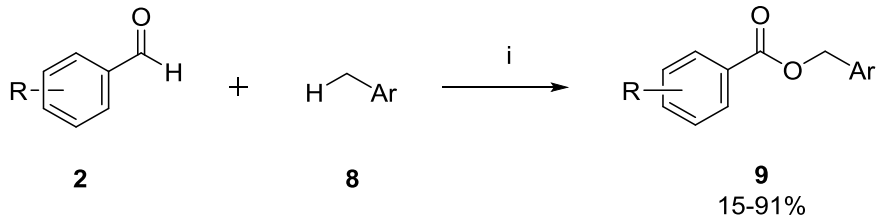
In C–O bond formation, the ester functionalities, particularly the benzylic/allylic esters, are common targets because of their applications in synthetic organic and medicinal chemistry.[45] Further, esterification processes are widespread in the industrial synthesis of a variety of end-products such as fragrances, monomers, plasticizers, etc, many of which are classified as high production volume (HPV) chemicals. In addition, applications to lower volume, high-value pharmaceutical and fine chemicals targets are prominent and often require more stringent coupling protocols to achieve the desired chemo- and stereoselectivity. Aromatic esters are also important and useful structural elements finding tremendous applications in wide range of fields encompassing solvents, lubricants, plasticizing agents, perfumes, pharmaceuticals, agrochemicals, *etc*.[46] The conventional methods for the synthesis of carboxylic esters from aldehydes involve oxidation of aldehydes to carboxylic acids followed by esterification with alcohols catalyzed by acids. In contrast, the direct method of conversion of aldehydes to carboxylic esters holds considerable promise in organic synthesis as it minimizes the number of steps.

1.2.2 Review of Literature

Literature search revealed that there are several methods available for the direct transformation of aldehydes into the corresponding esters. The direct transformation of aldehydes into esters has been achieved using a variety of reagents such as V_2O_5/H_2O_2,[47] oxone®,[48] pyridinium hydrobromide perbromide,[49] acetone cyano hydrins,[50] $(NaIO_4)$/LiBr,[51] I_2,[52] TBHP[53] and electrochemical methods.[54] Recently, *N*-Heterocyclic Carbene (NHC)-catalyzed oxidative esterification of aldehydes with alcohols, alkyl halides and boronic acids has also been reported. Some of the recent developments on this transformation using CDC are discussed below.

Wang's approach (2012)[55]

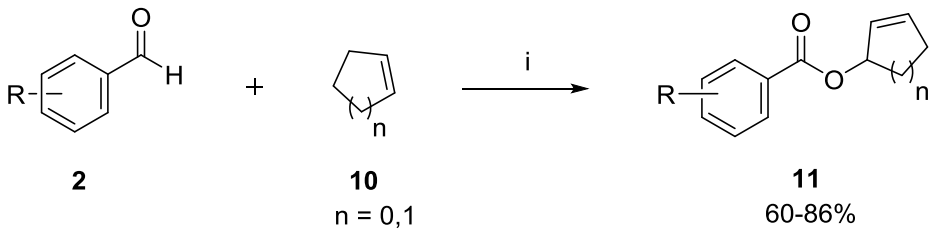
Wang *et al.* have developed tetrabutyl ammonium iodide (TBAI) catalyzed benzylic C–H acyloxylation of alkyl arenes with readily available aromatic aldehydes **2**. These reactions can occur under mild and clean reaction conditions using *tert*-butyl hydroperoxide (TBHP) as the green terminal oxidant (**Scheme 8**).



Scheme 8: (i) $^{n}Bu_4NI$ (20 mol %), TBHP (2 equiv), H_2O (4 mL), 80 °C, 12 h.

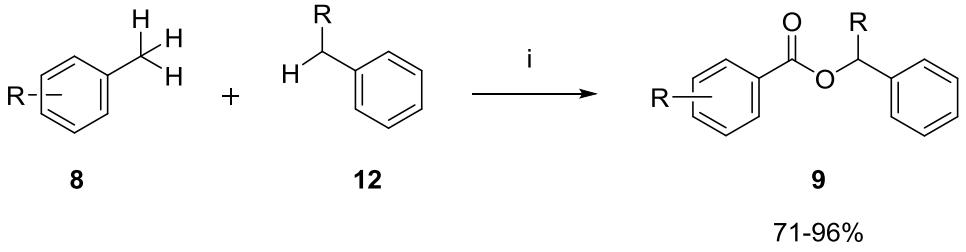
Patel's approach (2012)[56]

In Patel's approach, $Cu(OAc)_2$ was used as the catalyst in a cross dehydrogenative coupling (CDC) reaction for the synthesis of allylic esters **11** using aromatic aldehydes **2** and cyclo alkenes **10** as coupling partners (**Scheme 9**).



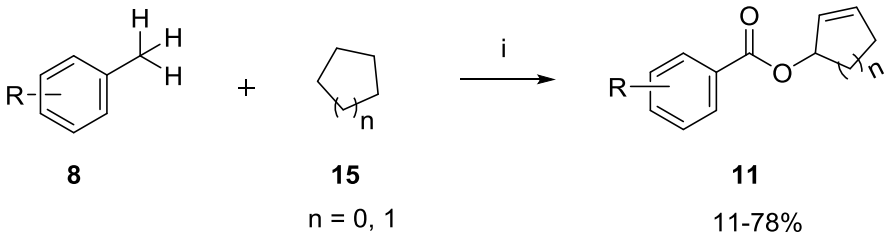
Scheme 9: (i) $Cu(OAc)_2.2H_2O$ (0.1 mmol), TBHP (5−6 M) (8 mmol), 100 °C.

In another approach in 2013,[57] Patel *et al.* have developed a metal free protocol for the synthesis of benzylic esters **9** *via* a cross dehydrogenative coupling involving alkylbenzene(s) **12** as a self- or as a cross-coupling partner(s) through the intermediacy of $ArCO_2H$ and the benzylic carbocation obtained from the other half of the alkylbenzene (**Scheme 10**).



Scheme 10: (i) TBAI (0.1 mmol), TBHP (5−6 M) (8 mmol), 80 °C.

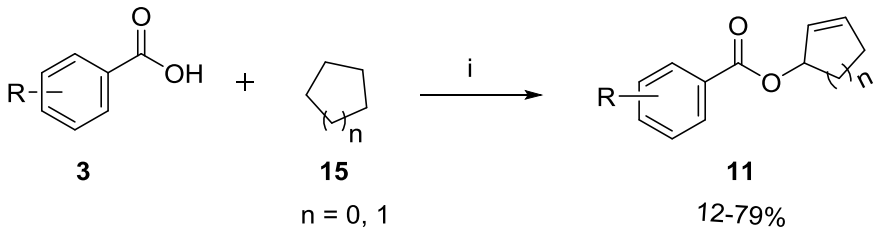
In yet another approach in 2014,[58] Patel *et al.* have developed a Cu-catalyzed CDC strategy for the synthesis of esters **11** from simple solvents. The reaction of methylarenes with cyclic ethers resulted in α-acyloxy ethers involving four sp^3 C−H cleavages, while treatment of methylarenes **8** with cycloalkanes led to the formation of allyl esters **11** at the expense of six consecutive sp^3 C−H bonds (**Scheme 11**).



Scheme 11: (i) $Cu(OAc)_2$ (0.2 mmol), TBHP (5-6 M) (8 mmol), 120 °C.

Hartwig's approach (2012)[59]

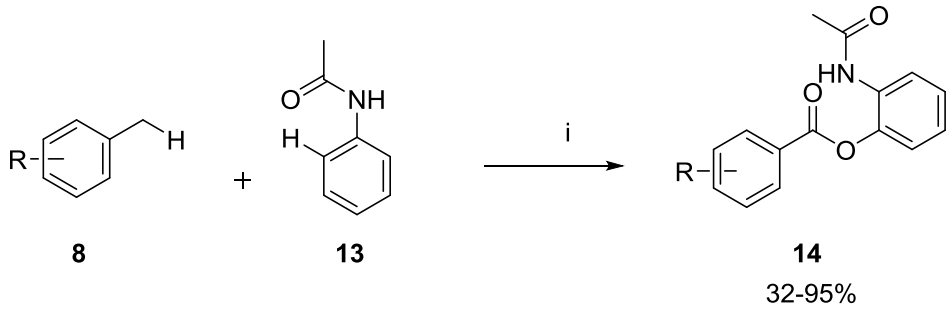
Hartwig *et al.* have described a copper catalyzed oxidative dehydrogenative carboxylation (ODC) of unactivated alkanes **15** with various substituted benzoic acids to produce the corresponding allylic esters **11** (**Scheme 12**).



Scheme 12: (i) $[(phen)Cu]_2(\mu 2\text{-}I)_2$ (2.5 mol %), *t*BuOO*t*Bu (2 equiv), 100 °C, benzene, 24 h.

Kwong's approach (2013)[60]

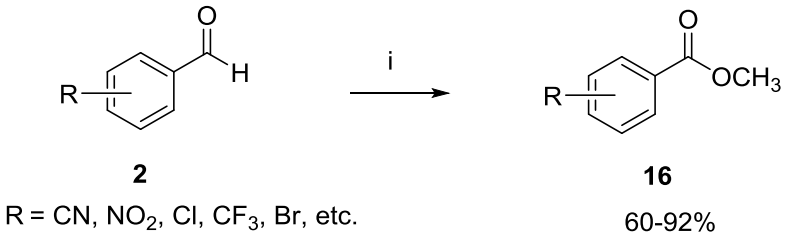
Kwong *et al.* have developed a novel palladium catalyzed cascade cross-coupling of acetanilide **13** and methylarenes **8** for the synthesis of *ortho*-acylacetanilides **14**. Toluene derivatives **8** can act as effective acyl precursors (upon sp^3C–H bond oxidation by a Pd/TBHP system) in the oxidative coupling between two C–H bonds (**Scheme 13**).



Scheme 13: (i) $Pd(OAc)_2$ (10 mol %), TBHP (5−6 M) (8 mmol), 80 °C, 24 h.

Sudalai's approach (2005), (2007)[50, 51]

Sudalai *et al.* have described a simple procedure for the conversion of electron-deficient aldehydes **2** into the corresponding esters **16** on reaction with methanol in excellent yields mediated by acetone cyanohydrin and base (**Scheme 14**).

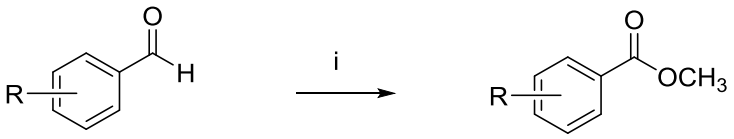


2 **16**

R = CN, NO_2, Cl, CF_3, Br, etc. 60-92%

Scheme 14: (i) acetone cyanohydrin (5 mmol), Et_3N, CH_3OH, 25 ^oC, 2 h.

In yet another approach, these authors have converted aromatic aldehydes **2** directly to the corresponding aromatic esters **16** in high yields on treatment with CH_3OH using sodium metaperiodate ($NaIO_4$)/LiBr as oxidant under acidic medium (**Scheme 15**).



2 **16**

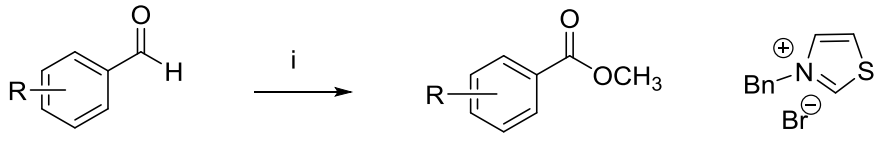
R = CN, NO_2, OH, CH_3, H, etc. 78-98%.

Scheme 15: (i) LiBr, $NaIO_4$, conc. H_2SO_4, CH_3OH, 25 ^oC, 18 h.

Some of the NHC catalyzed oxidative esterification of aldehydes

Connon's approach (2008)[61]

Connon *et al.* have developed a novel method of direct esterification of aldehydes with methnol using thiazolium NHC (**1j**) as a catalyst and azobenzene as an oxidant in THF. Aromatic aldehydes **2** were thus converted to their corresponding methyl esters **16** in moderate to good yields (**Scheme 16**).



2 **16** NHC (**1j**)

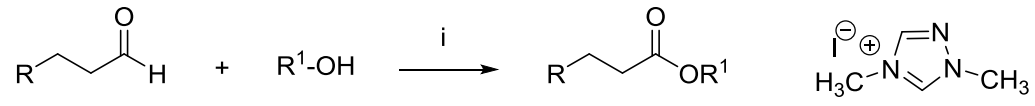
R = OCH_3, CH_3

Scheme 16: (i) NHC (**1j**) (5 mol %), PhN=NPh, CH_3OH, THF, Et_3N, 25 to

60 ^{o}C, 24-48 h, 16-97%.

Scheidt's approach (2008)[62]

Scheidt *et al.* have described NHC-catalyzed oxidation of unactivated aldehydes to the corresponding carboxylic esters. Thus, the reaction of unactivated aldehydes **17** with alcohols **18** in the presence of triazolium NHC catalyst (**1k**) and oxidant MnO_2 provided esters **19** in high yields (**Scheme 17**).



17 **18** **19** NHC (**1k**)

R = aryl, alkyl, heteroaryl

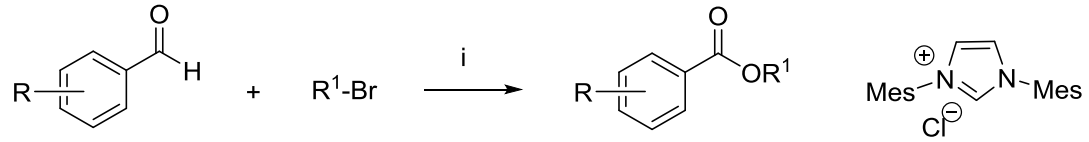
R^1 = CH_3, ^{i}Pr, etc.

56-98%

Scheme 17: (i) NHC (**1k**) (10 mol %), DBU, MnO_2, CH_2Cl_2, 25 ^{o}C, 0.5-3 h.

Xin's approach (2011)[19]

Xin *et al.* have developed an oxidative esterification reaction between aldehydes **2** and alkyl halides **20** catalyzed by imidazolium NHC (**1d**) and molecular oxygen as an oxidant in THF at 50 ^{o}C that gave carboxylic esters **21** in good yields (**Scheme 18**).



2 **20** **21** NHC (**1d**)

R = NO_2, CH_3, Cl, H, etc.

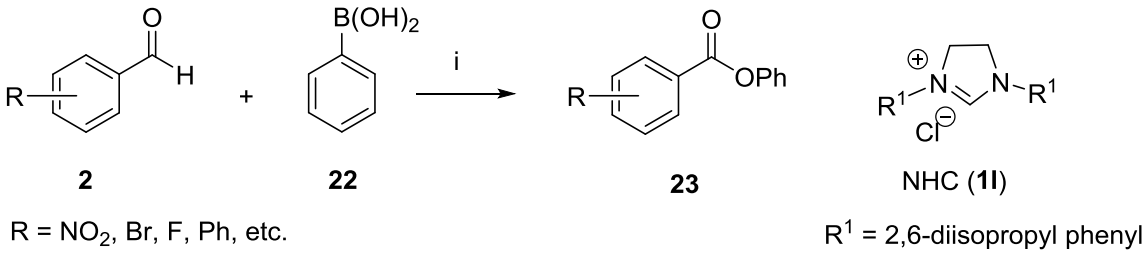
R^1 = ethyl, ^{i}Pr, etc.

Scheme 18: (i) NHC (**1d**) (10 mol %), DBU, O_2, THF, 50 ^{o}C, 24-72 h, 25-90%.

Arde's approach (2011)[63]

Arde *et al.* have developed a useful method of imidazolidine NHC (**1l**) catalyzed

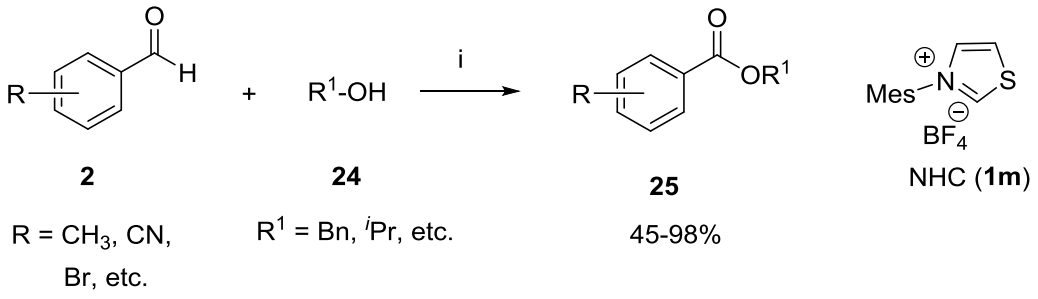
aerobic oxidation of aromatic aldehydes **2** with boronic acids **22**. Aromatic aldehydes **2** were thus converted into their corresponding esters **23** in good yields (**Scheme 19**).



Scheme 19: (i) NHC (**1l**) (10 mol %), Cs_2CO_3, O_2, toluene, 25 ^{o}C, 3-48 h, 25-99%.

Boydston's approach (2012)[54]

This methodology involves thiazolium NHC (**1m**) catalyzed anodic oxidation of aldehydes **2** to the corresponding carboxylic esters **25** on reaction with alcohols **24** (**Scheme 20**). The electrochemical approach assumes the formation of electroactive intermediates that react with alcohol to provide esters.



Scheme 20: (i) NHC (**1m**) (10 mol %), DBU, TBAB, CH_3CN, graphite anode, Pt cathode, +0.1V vs. $Ag/AgNO_3$, 2-56 h,.

1.2.3 Present Work

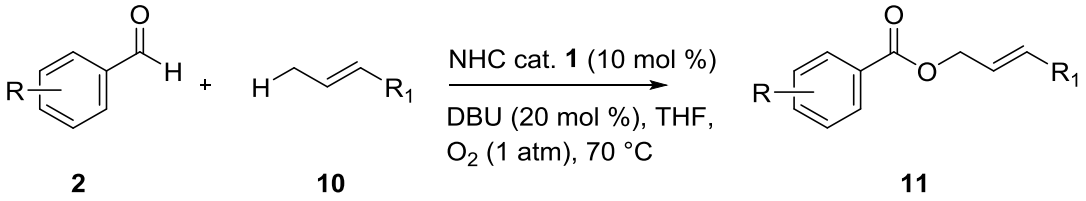
1.2.3.1 Objective

A few number of reports for oxidative CDC of aldehydes with allylic C-H bonds have been reported for the formation of the corresponding esters. Yet, there are certain drawbacks associated with them such as (i) heavy metals (Cu) and peroxides as oxidants; (ii) harsh reaction conditions; (iii) use of more than stoichiometric amounts of oxidants and (iv) effective for a limited range of substrates. In this regard, an organocatalytic additive-free mild protocol for oxidative CDC of aldehydes with

allylic/benzylic C-H bonds is highly desirable. This section describes NHC-catalyzed direct esterification of aromatic aldehydes **2** with a variety of allylic C-H bonds under aerobic condition.

1.2.3.2 Results and Discussion

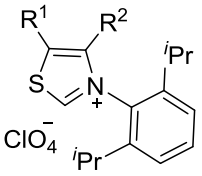
In continuation to our earlier studies on oxidative esterification and oxidative stannylation of aromatic aldehydes, herein, we present for the first time, NHC catalyzed cross-dehydrogenative coupling of aldehydes with allylic C-H bonds leading to the formation of the corresponding esters **11** (**Scheme 22**).



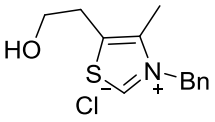
Scheme 22: NHC catalyzed cross-dehydrogenative coupling of aldehydes with allylic C-H bonds

Initially, we have chosen 4-nitrobenzaldehyde **2g** (1equiv) as a test substrate for the oxidative cross dehydrogenative coupling with β-methylstyrene **10a** (2 equiv) using NHC precatalyst **1a** (10 mol %) and DBU (20 mol %) as base in THF, which produced cinnamyl 4-nitrobenzoate **11d** in 26% yield (**Table-1**, entry 1). Among the NHC precatalysts screened, thiazolium -based precatalysts (**1b** and **1c**) afforded **11d** in 21 and 34 % yields respectively. Interestingly, imidazolium based precatalyst **1d** and **1e** are very effective which produced 76 and 84% yield of the corresponding allylic ester **11d,** while triazolium - based precatalysts **1h** and **1i** gave 18 and 12% yields respectively. Other solvents (DMF, CH_2Cl_2) and other inorganic bases (K_2CO_3, $KOBu^t$ and NaH) resulted in sluggish reaction with poor yields. Thus, **Table 1** enty 5 was chosen as best optimized condition.

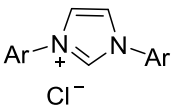
Table 1: Cross-dehydrogenative coupling of aromatic aldehydes with β-methyl styrene: Optimization conditions[a]



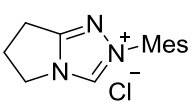
1a $R^1 = R^2 = Me$
1b R^1, R^2 = cyclohexyl



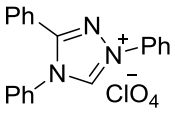
1c



1d Ar = Mes
1e Ar = 2,6 - $^{i}Pr_2C_6H_3$



1h



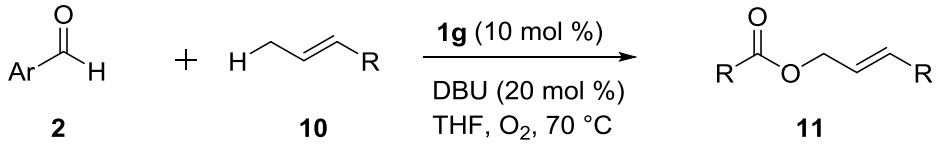
1i

s.no.	catalyst	solvent	base	yield (%)[b]
1	Thiazolium (**1a**)	THF	DBU	26
2	Thiazolium (**1b**)	THF	DBU	21
3	Thiazolium (**1c**)	THF	DBU	34
4	IMes (**1d**)	THF	DBU	76
5	Imidazolium (**1e**)	THF	DBU	84
6	Triazolium (**1h**)	THF	DBU	18
7	Triazolium (**1i**)	THF	DBU	12
8	Imidazolium (**1e**)	CH_3CN	DBU	45
9	Imidazolium (**1e**)	DMF	DBU	45
10	Imidazolium (**1e**)	THF	K_2CO_3	30
11	Imidazolium (**1e**)	THF	KO^{t}Bu	25

a: Reaction conditions: 4-nitrobenzaldehyde (1 equiv), β-methyl styrene (2 equiv), NHC catalyst (10 mol %), base (1.2 equiv), under O_2 atmosphere; 70 °C, 8 h; b: isolated yields after column chromatographic purification.

With the optimized condition in hand, we examined the substrate scope of the reaction. Various aromatic aldehydes were then subjected to oxidative CDC; the results of which are presented in **Table 2**. Aromatic aldehydes, having electron-withdrawing and -releasing groups at various positions on the aromatic ring were treated with β-methylstyrene (**10a**) in presence of NHC catalyst **1e** in 10 mol % and DBU (20 mol %) under O_2 (1 atm) to give the corresponding allylic esters **11a-g** (**Table 2**) in high yields (66-84%). Other aliphatic aldehydes failed to undergo this catalytic transformation. Further, various other alkenes with (α-sp^3 C-H bonds)

Table 2: NHC catalyzed oxidative coupling of alkenes with aldehydes: substrate scope[a]



s.no.	aromatic aldehyde (**2**)	alkene (**10**)	products (**11**)	yield (%)[b]
1	Benzaldehyde (**2a**)	β-Methylstyrene (**10a**)	**11a**	66
2	4-Br- Benzaldehyde (**2b**)	β-Methylstyrene	**11b**	69
3	3-Cl – Benzaldehyde (**2c**)	β-Methylstyrene	**11c**	71
4	4-NO_2- Benzaldehyde (**2g**)	β-Methylstyrene	**11d**	80
5	4- NO_2- Benzaldehyde (**2g**)	Crotononitrile (**10b**)	**11e**	84
6	4- NO_2- Benzaldehyde	Ethyl crotonoate (**10c**)	**11f**	71
7	4- NO_2- Benzaldehyde	Indene (**10d**)	**11g**	64
8	4- NO_2- Benzaldehyde	Toluene (**8a**)	**9a**	22

[a]Reaction conditions: alkene (1 mmol), aldehyde (1.1 mmol), NHC precatalysts **1g** (10 mol %), DBU (1.2 mmol), NBS (1 mmol); in DMSO, 25 °C, 22 h. [b]isolated yield after column chromatographic purification;

(**10b-d**) were treated with 4-NO_2-benzaldehyde under the optimized condition, the corresponding allylic esters **11e-g** were formed in good yields. Disappointingly, toluene (**8a)** gave the corresponding benzylic ester **9a** in low yield (22%).

The formation of all ester products were confirmed unambiguously from their corresponding ^{1}H, ^{13}C NMR and IR spectral data.

Example 1: The ^{1}H NMR spectrum of (E)-3-cyanoallyl 4-nitrobenzoate (**11e**) showed a typical signal at δ 4.86 (dd, *J* = 6.8 Hz, 1.37 Hz, 2H) corresponding to methelene protons (-O-C**H$_2$**-), while other signals at δ 6.19 (dd, *J* = 6.8 Hz, 13.7 Hz, 1H) and

6.48 (d, *J* = 1.37, 13.7 Hz, 1H) corresponding to olefinic protons. Its IR spectrum displayed two characteristic strong absorption frequencies at 1727 and 2229 cm^{-1} indicating the presence of ester carbonyl and cyano functional groups respectively (**Fig. 9**).

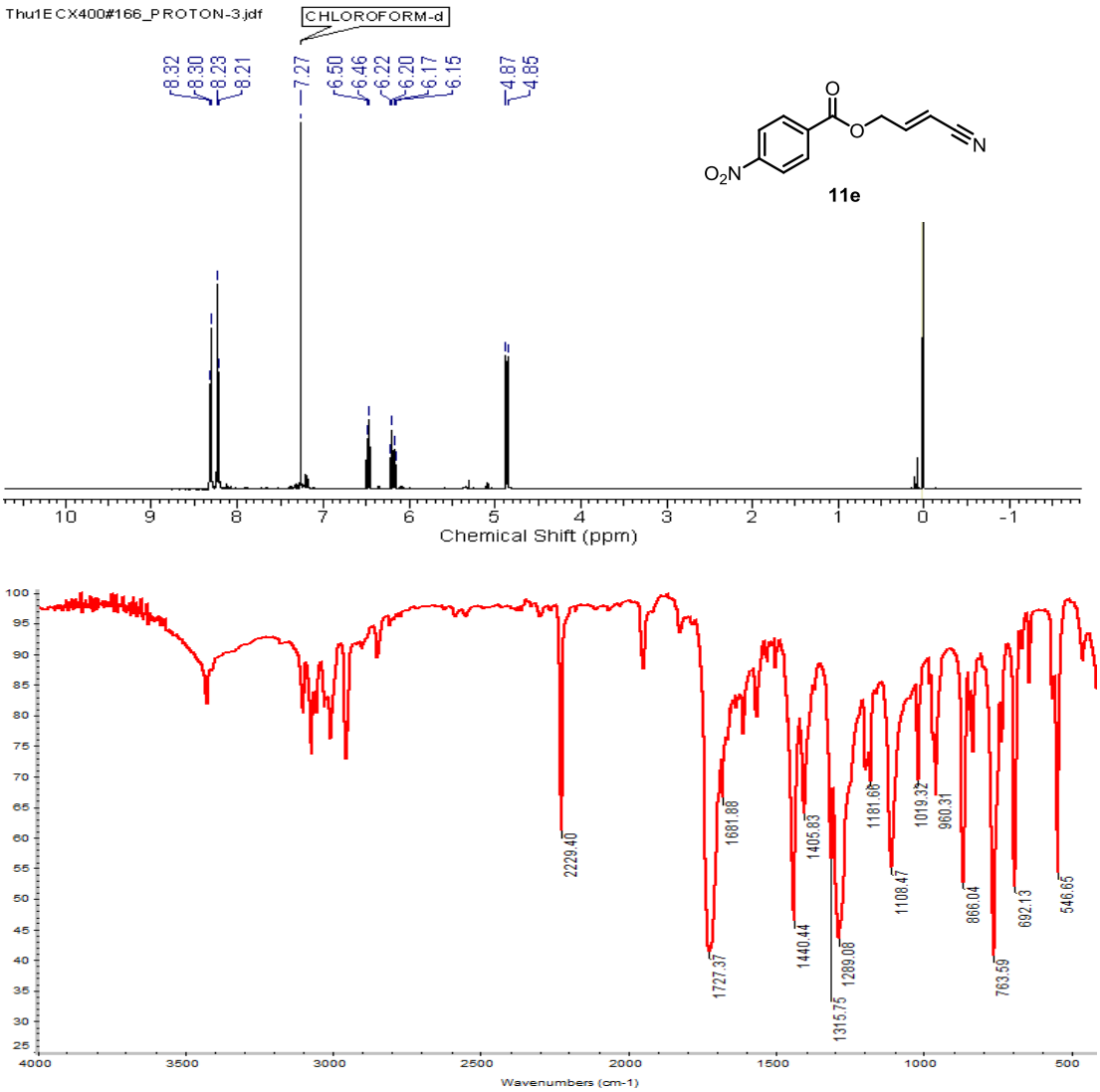


Fig. 9: ^{1}H NMR and IR spectra of **11e**

Example 2: The ^{1}H NMR spectrum of benzyl 4-nitrobenzoate (**9a**) showed a singlet proton signal at δ 5.40 (s, 2H) corresponding to benzylic methylene carbon, while its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 67.5 and 164.1 corresponding to benzylic carbon and ester carbonyl carbons respectively (**Fig. 10**).

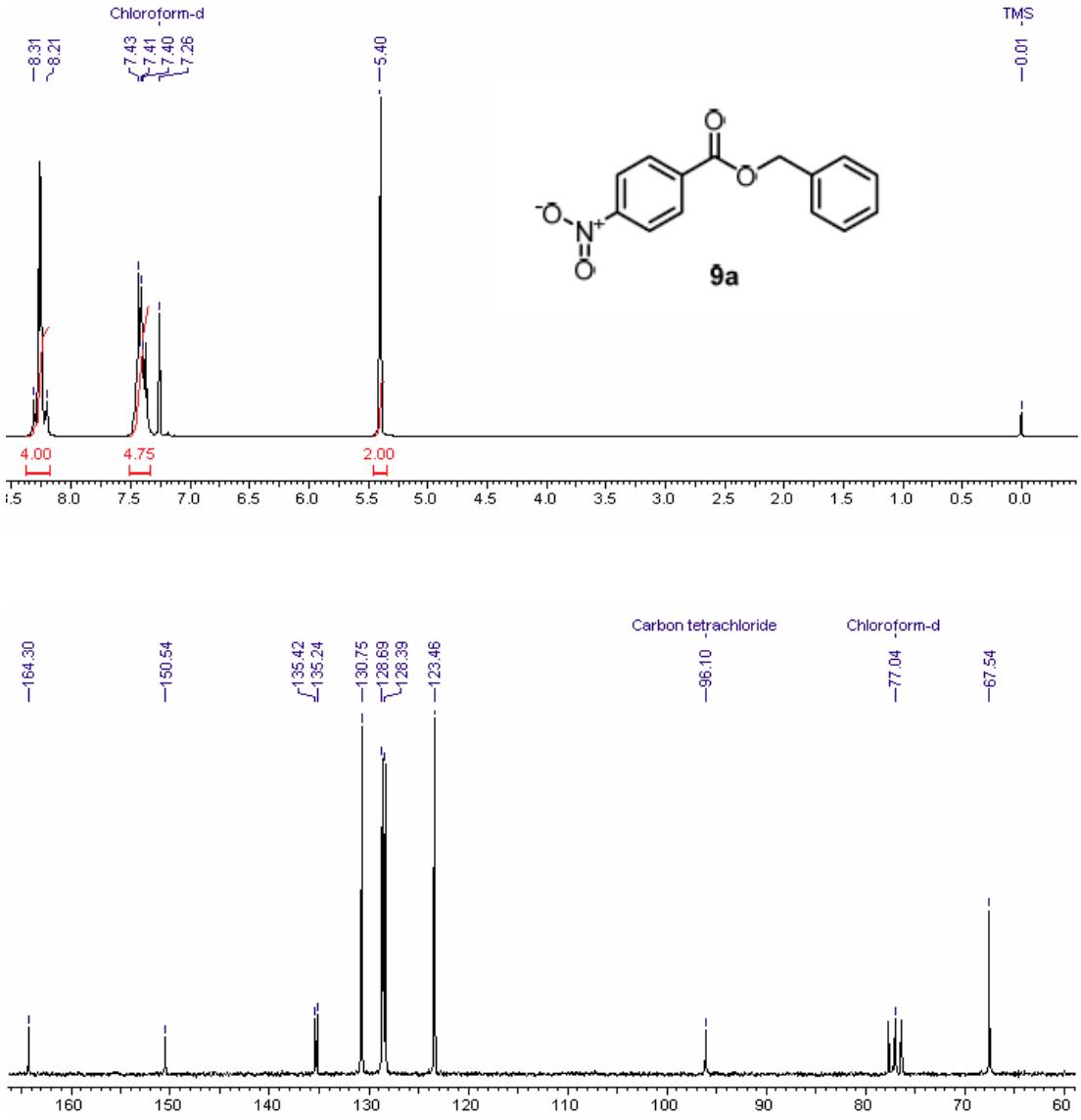
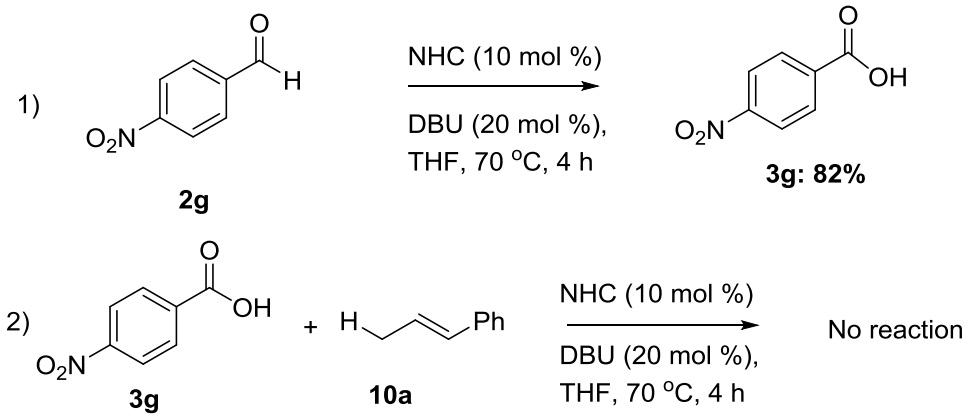


Fig. 10: ^{1}H and ^{13}C NMR spectra of **9a**

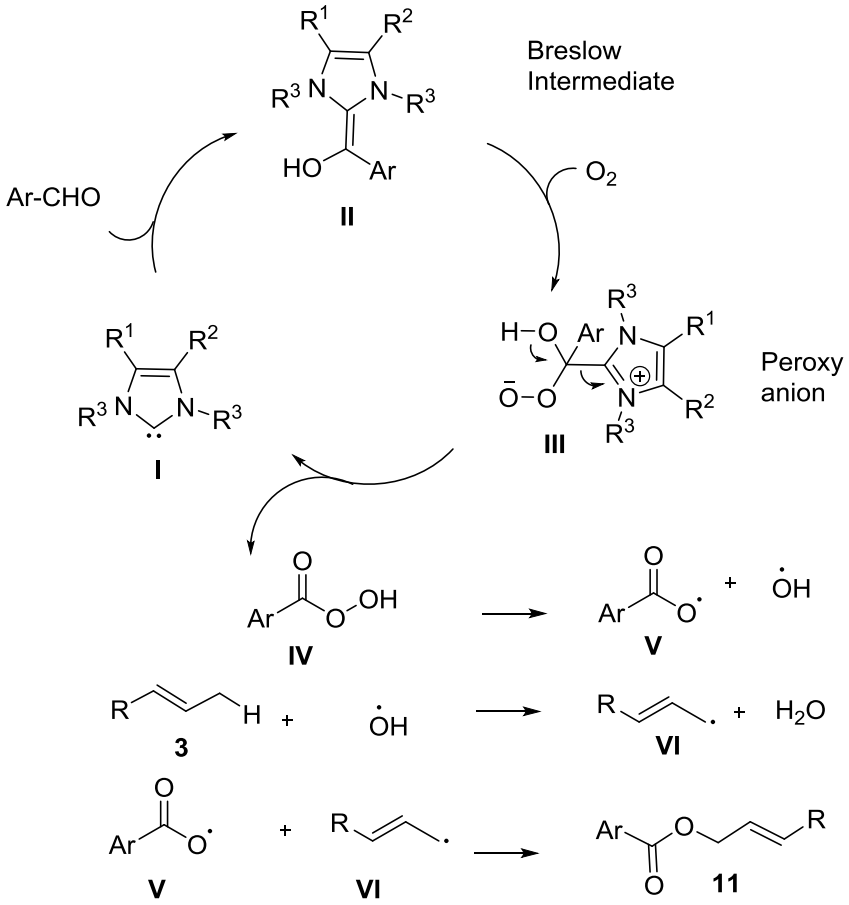
In order to gain insight into the mechanistic details of the reaction, the following experiments (see **Scheme 23**) were conducted: (i) In the absence of β-methylstyrene, 4-nitrobenzaldehyde gave the corresponding 4-nitrobenzoic acid (**3g**) in 82% yield under optimized condition. (ii) When 4-nitrobenzoic acid is treated with β-methylstyrene in presence of NHC catalyst (**1e**), allylic ester **11a** was not formed which confirms that carboxylic acid is probably not the key intermediate. (iii) When radical scavenger TEMPO (2 equiv) is used in the reaction yield of **11a** dropped to

5% which proveed that the reaction proceeds *via* radical pathway.



Scheme 23: Control experiments for mechanistic details

Based on the control experiments and literature reports,[19] a probable mechanistic pathway is shown in **Scheme 24**.



Scheme 24: Probable mechanism for oxidative cross dehydrogenative coupling

The Breslow intermediate **II** generated from aldehyde **2** and NHC catalyst **I,** upon reaction with O_2 gives the peroxy anion **III,**[17] which then furnish NHC catalyst with the generation of peracid **IV**. The generated peracid decomposes to give an acid radical **V** and hydroxyl radical. Hydroxy radical abstracts a hydrogen radical from allylic/benzylic position of the alkene and generate an allylic radical **VI**, which then recombines with acid radical **V** to afford allylic esters **11**.

1.2.4 Conclusion

In conclusion, we have developed an efficient catalytic process for the preparation of allylic/benzylic esters using *N*-heterocyclic carbene catalyzed oxidative CDC of aldehydes with allylic/benzylic C-H bonds. This methodology provides the use of NHC in cross dehydrogenative coupling reactions.

1.2.5 Experimental Section

General experimental procedure for esterification of aromatic aldehydes

To a flame-dried round bottom flask equipped with a magnetic stir bar was added imidazolium salt **1** (0.17 g, 10 mol %), DBU (0.15 mL, 20 mol %) and THF (10 mL) in that order. The contents were evacuated and covered with molecular O_2 in balloon. The resultant reaction mixture was kept stirring at 25 °C for 45 min. To this mixture was added aromatic aldehydes **2** (1 mmol) and alkene (2 mmol) successively. It was allowed to stir at 70 °C. After completion of the reaction (monitored by TLC), THF was evaporated, H_2O (20 mL) was added and the mixture extracted with EtOAc (3 x 20 ml). The combined organic layers were dried over anhyd. Na_2SO_4 concentrated to give crude ester, which was purified by silica gel-packed column chromatography to obtain pure esters, **11a-h**.

Cinnamyl benzoate (11a)

Yield: 66%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1440, 1534, 1681, 1727, 2893, 2953: **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.97 (d, *J* = 6.4 Hz, 2H) 6.43-6.36 (m, 1H), 6.70 (d, *J* = 16.0 Hz, 1H), 7.33-7.23 (m, 3H), 7.43-7.39 (m, 4H), 7.54-7.52 (m, 1H), 8.08 (d, *J* = 7.7, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 65.5, 123.4, 126.6, 128.2, 128.3, 128.6, 129.6, 130.2, 133.0, 134.2, 136.2, 166.3; **HRMS** (EI): calcd for $C_{16}H_{14}NaO_2$ $(M+Na)^+$: 261.0891; found 261.0875.

Cinnamyl 4-bromobenzoate (11b)

Yield: 69%; colorless gum: **IR** ($CHCl_3$, cm^{-1}): υ_{max} 566, 777, 1125, 1365, 1477, 1563, 1684, 1731, 2869: **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 4.95 (dd, *J* = 6.6, 1.4 Hz, 2H), 6.44-6.34 (m, 1H), 6.72 (d, *J* = 16.0 Hz, 1H), 7.42-7.26 (m, 5H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.92 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 65.0, 123.3, 126.6, 128.4, 128.3, 128.8, 129.2, 131.3, 131.9, 134.6, 136.2, 165.7. HRMS (EI) calcd for $C_{16}H_{13}BrO_2Na(M+Na)^+$: 316.0099; found 316.0091.

Cinnamyl 3-chlorobenzoate (11c)

Yield: 71%; colorless gum: **IR** ($CHCl_3$, cm^{-1}): υ_{max} 544, 723, 1128, 1415, 1510, 1578, 1681, 1727, 2229: **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 4.98 (dd, *J* = 6.8, 1.4 Hz, 2H), 6.43-6.35 (m, 1H), 6.74 (d, *J* = 16.0 Hz, 1H), 7.42-7.22 (m, 6H), 7.55-7.51 (m, 1H), 7.98-7.94 (m, 1H), 8.05 (m, 1H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 66.1, 123.0, 126.9, 128.1, 128.2, 128.8, 129.91, 129.7, 132.1, 133.2134.7, 134.9, 136.1, 165.6; **HRMS** (EI) calcd for $C_{16}H_{13}O_2ClNa$ $(M + Na)^+$: 295.0502; found 295.0514.

Cinnamyl 4-nitrobenzoate (11d)

Yield: 80%; colorless solid: **IR** ($CHCl_3$, cm^{-1}): υ_{max} 723, 1108, 1315, 1354, 1440, 1530, 1691, 1737, 2899, 2996: **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 5.02 (dd, *J* = 1.4, 6.8 Hz, 2H), 6.43-6.36 (m, 1H), 6.75 (d, *J* = 16.0 Hz, 1H), 7.38-7.25 (m, 3H), 7.45-7.39

(m, 2H), 8.30-8.20 (m, 4H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 66.6, 122.4, 123.6, 126.6, 128.5, 128.8, 130.8, 135.3, 135.5, 136.0, 150.6, 164.5; HRMS (EI) calcd for $C_{16}H_{13}NO_4$ $(M + Na)^+$: 306.0742;, found 306.0749.

(E)-3-cyanoallyl 4-nitrobenzoate (11e)

Yield: 84%; colorless solid, **IR** ($CHCl_3$, cm^{-1}): υ_{max} 546, 763, 1108, 1315, 1440, 1681, 1727, 2229: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.79-4.90 (m, 2H), 6.19 (dt, *J* = 13.74, 6.87 Hz, 1H), 6.40-6.55 (m, 1H), 8.14-8.27 (m, 2H), 8.27- 8.38 (m, 2H): **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 65.5, 101.2, 117.9, 125.6, 131.1, 137.1, 148.1, 151.6, 169.9; **HRMS** (EI) calcd for $C_{11}H_9N_2O_4$ $(M + H)^+$: 233.0562;, found 233.0566.

(E)-4-Ethoxy-4-oxobut-2-en-1-yl 4-nitrobenzoate (11f)

Yield: 71%; Yellow colored solid: **IR** ($CHCl_3$, cm^{-1}): υ_{max} 755, 1217, 1246, 1300, 1438, 1496, 1662, 2940, 298, 3021. **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.13 (t, J = 7.2 Hz, 3H), 3.74 (s, 3H), 4.05 (q, *J* = 7.2 Hz, 2H), 4.81 (dd, *J* = 2.1, 4.2 Hz, 2H), 6.06 (td, *J* = 2.1, 15.6 Hz, 1H), 6.80-6.94 (m, 3H), 7.25-7.35 (m, 1H), 7.65-7.71 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.7, 55.3, 55.9, 62.3, 111.5, 119.6, 121.5, 131.3, 133.4, 141,0, 144.5, 158.7, 164.8, 165.3: **HRMS** (EI) calcd for $C_{13}H_{14}NO_6$: 280.0821; $(M + H)^+$, found 280.0820.

1*H*-Inden-1-yl 4-nitrobenzoate (11g)

Yield: 64%; Yellow colored solid: **IR** ($CHCl_3$, cm^{-1}): υ_{max} 755, 1217, 1246, 1300, 1438, 1496, 1662, 2940, 298, 3021; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.42-6.53 (m, 2H), 6.72-6.89 (m, 1H), 7.32-7.41 (m, 4H), 8.20-8.33 (m, 4H); **HRMS** (EI) calcd for $C_{16}H_{11}NO_4$: 282.0766; $(M + H)^+$, found 282.0764.

Benzyl 4-nitrobenzoate (9a)

Yield: 22%; colorless solid; mp: 82-84 ºC ;**IR** ($CHCl_3$, cm^{-1}): υ_{max} 743, 1103, 1286, 1348, 1523, 1713; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.40 (s, 2H), 7.37-7.46 (m, 5H),

8.21-8.31 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 67.5, 123.5, 128.4, 128.6, 128.7, 130.7, 135.2, 135.4, 150.5, 164.3; **Analysis**: $C_{14}H_{11}NO_4$ requires C, 65.37; H, 4.31; N, 5.44; found: C, 65.23; H, 4.21; N, 5.31%.

1.2.6 References

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CHAPTER II

N-Heterocyclic Catalyzed Oxidative Coupling of Aldehydes with Alkenes, Epoxides and α-Bromoacetophenones

1. *N*-Heterocyclic Carbene Catalyzed Regioselective Oxo-acyloxylation of Alkenes with Aromatic Aldehydes: a High Yield Synthesis of α-Acyloxy Ketones and Esters; **Rambabu N. Reddi**, Pushpa V. Malekar, Arumugam Sudalai; *Org. Biomol. Chem.*, **2013**, *11*, 6477.

2. *N*-Heterocyclic Carbene Catalyzed Oxidatative Coupling of Alkenes/α-Bromoacetophenones with Aldehydes: a Facile Access to α,β-Epoxy-ketones and Esters; **Rambabu N. Reddi**, Pragati Kishore Prasad, Arumugam Sudalai; (*Angew. Chem.accepted, DOI: 10.1002/anie.201507363*).

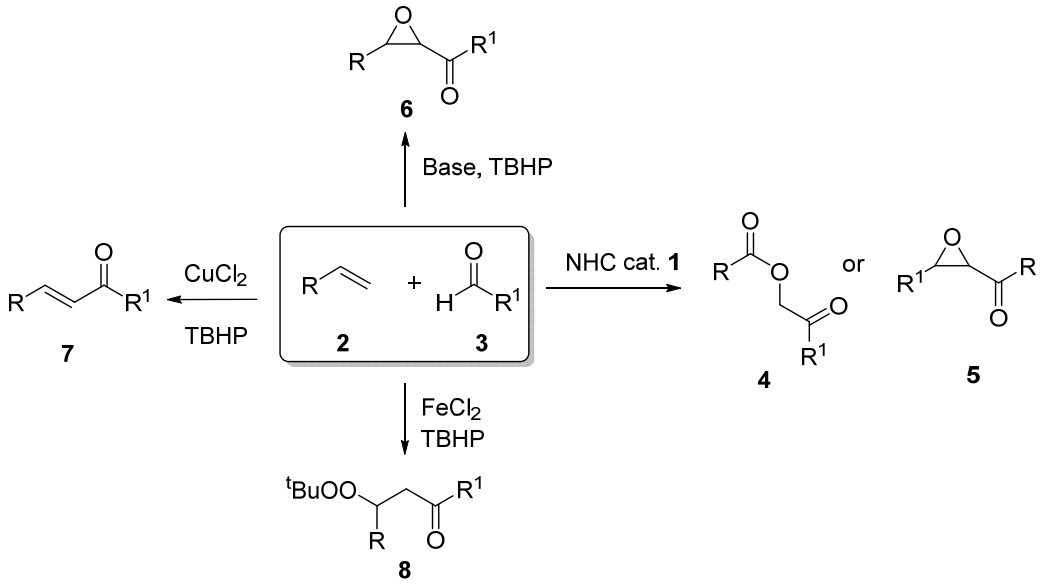
3. *N-Heterocyclic Carbene Catalyzed Regioselective Oxidative Ring Opening of Epoxides with Aromatic Aldehydes: A Facile Entry to α-Acyloxy Ketones* **Rambabu N. Reddi**, Arjun Gontala, Pragati Kishore Prasad, Arumugam Sudalai; (*Asian J. Org. Chem. just accepted*).

Section I

N-Heterocyclic Carbene Catalyzed Regioselective Oxo-acyloxylation of Alkenes/Epoxides with Aromatic Aldehydes: A High Yield Synthesis of α-Acyloxy Carbonyl Compounds

2.1.1 Introduction

The direct oxidative coupling of aldehydes **3** with alkenes **2** is a highly attractive and sustainable strategy for the synthesis of functionalized ketones, as neither the aldehyde nor the alkene needs to be prefunctionalized. Despite remarkable advances in the oxidative coupling field, approaches for the coupling of alkenes with the aldehydes are rare and limited (**Scheme 1**).[1]

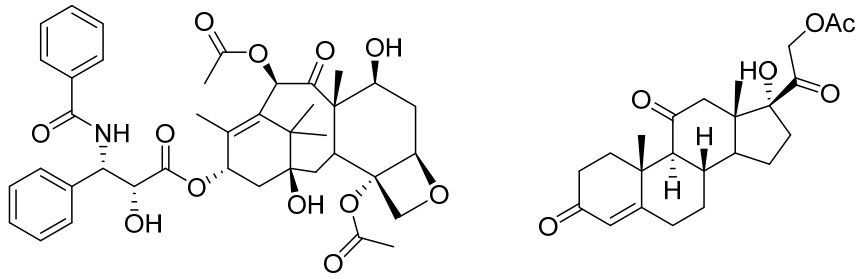


Scheme 1: Oxidative coupling reactions of alkenes and aldehydes

The recent methods mainly focused on coupling with the aldehyde C(sp^2)-H bonds with C(sp^2)-H bond of alkene using the $[(Cp^*RhCl_2)_2]/C_5H_2Ph_4/Cu(OAc)_2$ or the $CuCl_2$/*tert*-butyl hydroperoxide (TBHP) system for synthesizing α,β,-unsaturated

ketones.[2] Further, β-peroxy ketones were prepared by oxidative coupling of alkenes and aldehydes using $FeCl_2$/TBHP as oxidative system.[3] Recently, transition metal free catalyzed direct oxidative coupling of alkenes with aldehydes using TBHP as oxidant for the synthesis of α,β–epoxyketones has also been reported.[4,5] However, these methods employ excess amount of aldehydes and TBHP than alkenes at high temperature and hence, complementary methods for oxidative coupling of aldehydes with alkenes is highly desirable.

α-Acyloxy ketones and esters are significant building blocks present in a variety of biologically interesting natural products, pharmaceuticals and synthetic intermediates of broad utility (**Fig. 1**).[6] Further, these compounds can be transformed to mono protected diols (by reduction of carbonyl group), protected amino alcohols (by reductive amination of ketone moity), acyloins (by hydrolysis of acyloxy group).



Taxol **9** Cortisone **10**

Fig. 1: Interesting natural products having α-acyloxy ketone moity

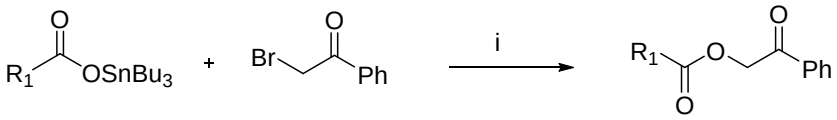
2.1.2 Review of Literature

In the literature, α-acyloxy ketones are prepared either by the substitution of α–halo carbonyl compounds as well as insertion reaction of α-diazoketones[7] with alkaline carboxylates or the direct oxidative coupling of ketones with toxic heavy metal oxidants (e.g. $Pb(OAc)_4$, $Tl(OAc)_3$, $Mn(OAc)_3$, etc).[8] Recently, hypervalent iodine catalyzed oxidative coupling of ketones with carboxylic acids has been reported to give α-acyloxy ketones. More atom economic method was reported by the addition of

carboxylic acids on to alkynes using Ru catalysis. These developments are discussed below.

Balasubramanian's approach (1985)[9]

Balasubramanian *et al.* have developed a facile and convenient method for the synthesis of phenacyl esters **13** using organostannyl carboxylates **11** and phenacyl bromides **12** in the presence of quaternary ammonium salts. In the absence of the quaternary ammonium salt the yields are poor and the reaction is incomplete (**Scheme 2**).



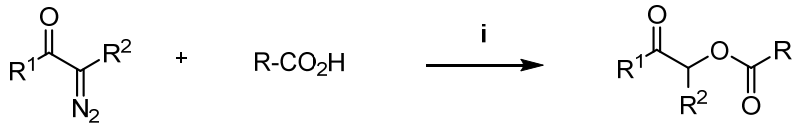
11 **12** **13**

R_1 = alkyl 50-80%

Scheme 2: (i) $Bu_4N^+Br^-$, benzene, 25 °C, 1 h.

Ohfune's approach (1998)[7]

Ohfune *et al.* have developed an efficient insertion reaction of α-diazoketones **14** in to various carboxylic acids using $Cu(acac)_2$ as catalyst. Treatment of diazo compound **14** with carboxylic acid **15** (1.2 equiv) in the presence of $Cu(acac)_2$, (0.1 equiv) at room temperature afforded the corresponding ketoester **16** in good yields. Various kinds of functional groups were tolerated (**Scheme 3**).



14 **15** **16**

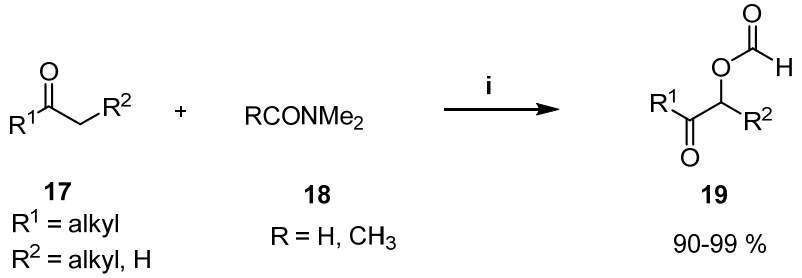
R^1 = alkyl (1.2 equiv) 40-84 %

R^2 = alkyl, H R = alkyl

Scheme 3: (i) $Cu(acac)_2$, toluene, 25 °C, 1 h.

Lee's approach (2001)[8f]

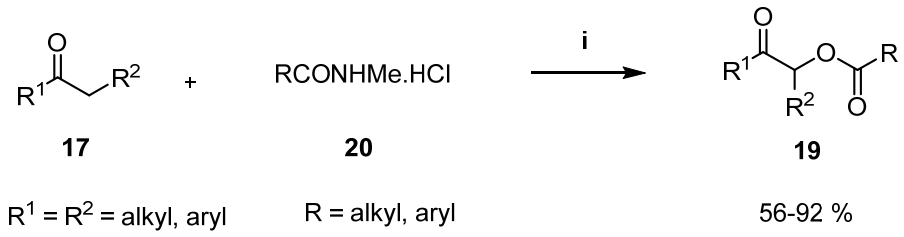
In Lee's protocol, treatment of ketones **17** with thallium (III) triflate (formed by the reaction of thallium acetate and trifloromethane sulfonic acid) in amide **18** solvents at 60 °C for 30 min followed by addition of small amounts of H_2O cleanly provided the corresponding α-acyloxy ketones **19** (**Scheme 4**).



Scheme 4: (i) Thallium(III) acetate, CF_3SO_3H, DMF, 60 °C, 0.5 h then H_2O.

Tomkinson's approach (2005)[8g]

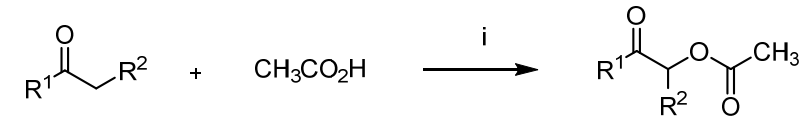
Tomkinson *et al*. have developed a simple, one-pot method for α-acyloxylation of carbonyl compounds that proceeds at room temperature in the presence of both moisture and air. Treatment of a variety of aldehydes and both cyclic and acyclic ketones **17** with *N*-methyl-*O*-benzoylhydroxylamine hydrochloride **20** provides the α-functionalized product **19** in 56−92% isolated yield. The transformation is tolerant of a wide range of functional groups and significantly, is regiospecific in the discrimination of secondary over primary centers in the case of nonsymmetrical substrates (**Scheme 5**).



Scheme 5: (i) DMSO, 25-50 °C.

Ochiai's approach (2005)[10]

For the first time, Ochiai *et al.* have developed iodobenzene-catalyzed α-oxidation of ketones **17**, in which diacyloxy(phenyl)-λ^3-iodanes generated *in situ* act as real oxidants of ketones and *m*-chloroperbenzoic acid serves as a terminal oxidant. It should be noted that use of water and $BF_3 \cdot Et_2O$ is crucial to the success of this α-acetoxylation (**Scheme 6**).



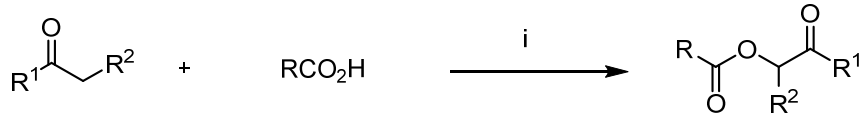
17 **21** **22**

$R^1 = R^2$ = alkyl, aryl 43-79 %

Scheme 6: (i) m-CPBA, PhI, H_2O, BF_3-Et_2O (3 equiv) 25-30 °C 20-48 h.

Ishihara's approach (2011)[11]

Ishihara *et al.* have developed both tetrabutyl ammonium iodide (TBAI) catalyzed intra- and intermolecular oxidative coupling of carbonyl compounds **17** with carboxylic acids **15** using either H_2O_2 or TBHP as a co-oxidant. A large number of substrates have been screened. However, aliphatic ketones produced very low yields of α-acyloxy ketones (**Scheme 7**).



17 **15** **19**

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

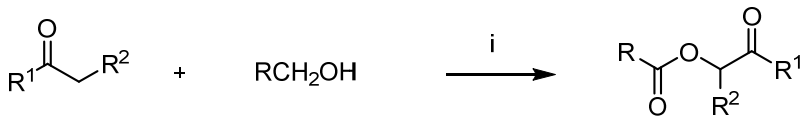
R = alkyl, aryl

40-90 %

Scheme 7: (i) $^n Bu_3NI$, TBHP or H_2O_2, 25-30 °C 20-48 h.

Cheng's approach (2014)[11a]

In this approach, Cheng *et al.* have reported Bu_4NI-catalyzed reaction of ketones **17** with benzylic alcohols **23**, leading to α-acyloxy carbonyl compounds in moderate to good yields. This metal-free procedure featured the employment of commercially available starting materials and TBHP as a clean oxidant with high atom economy (**Scheme 8**).



17 **23** **19**

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

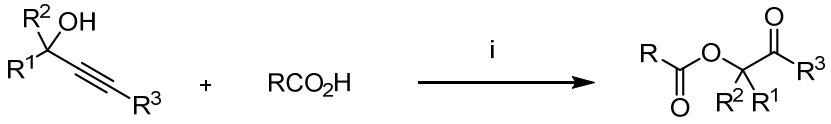
R = alkyl, aryl

33-90 %

Scheme 8: (i) $^nBu_3NI$, TBHP or H_2O_2, PhCN, air, 90 °C, 20-68 h.

Bauer's approach (2010)[5d]

Bauer's *et al.* has developed Rh-catalyzed novel protocol for the addition of carboxylic acids **15** on to propargyllic alcohols **25** for the synthesis of α-acyloxycarbonyl compounds **26**. The method is practical as no additives are required and the exclusion of oxygen and moisture is not needed (**Scheme 9**).



25 **15** **26**

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

R = alkyl, aryl

43-86 %

Scheme 9: (i) Ru cat. (1.5 mol %), cyclohexane, 90 °C, 8 h.

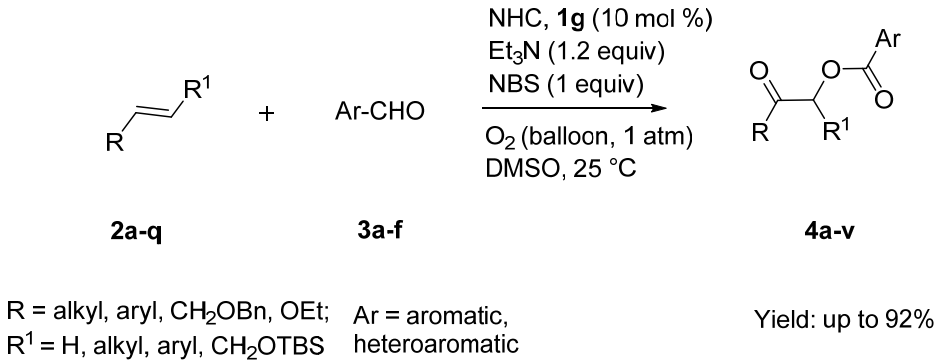
2.1.3 Present Work

2.1.3.1 Objective

As can be seen, a few reports for the synthesis of α-acyloxy carbonyl compounds have been reported. The drawbacks of the reported methods however include: (i) harsh reaction conditions; (ii) low chemo- and regio- selectivity; (iii) generation of large amounts of carboxylic acids as by-products; (iv) limitations in the substrate scope and (v) multistep reaction sequences. Thus, a new synthetic procedure which employs readily available starting materials and overcomes the above difficulties is still desirable for obtaining α-acyloxy ketones and esters.

2.1.3.2 Results and Discussion

It may be noted that, there is no report available for NHC catalyzed oxidative coupling of alkenes **2** with aldehydes **3** for the synthesis of α-acyloxyketones **4**. In this section, we report a new efficient and practical method for the coupling of alkenes **2a-q** and aldehydes **3a-f** directly into the corresponding α-acyloxyketones **4a-v** using *N*-heterocyclic carbenes as catalysts (**Scheme 10)**. We envisaged that molecular O_2 should be an ideal oxidant for this purpose based on its nature of reactivity, low cost, and environment-friendly characteristics.



Scheme 10: NHC catalyzed oxo-acyloxylation of alkenes with aromatic aldehydes

When styrene (5 mmol) was treated with a mixture containing *p*-nitrobenzaldehyde (5.5 mmol), NBS (5 mmol) and Et_3N (6 mmol) in the presence of NHC catalyst **1a** (10 mol %) at 25 °C in DMSO under O_2 (1 atm), the corresponding α-acyloxy ketone **4a** was obtained in 65% isolated yield with excellent regioselectivity (>99%) (T**able 1**).

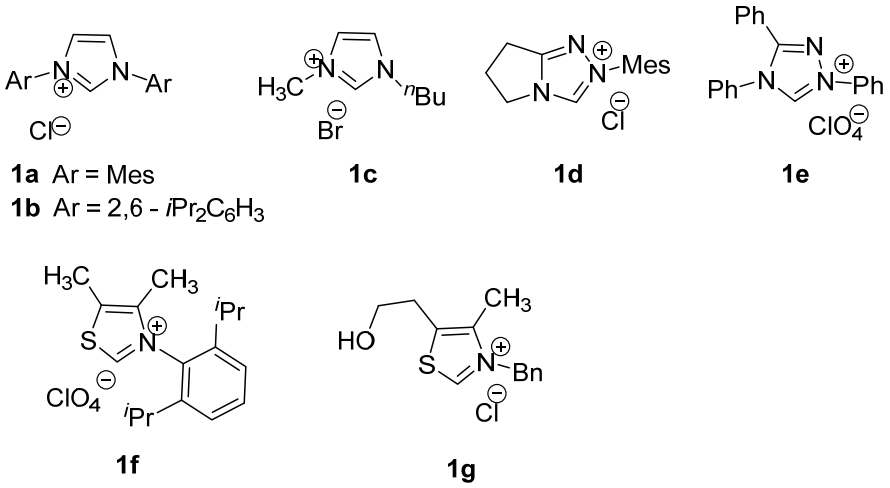


Fig. 2: NHC catalysts used for optimization study

With this interesting result, it was of interest to screen other NHC pre-catalysts (**Fig. 2**) for the yield improvement of the oxo-acyloxylation process. Among the NHC precatalysts screened, imidazolium-based precatalysts **1b** and **1c** afforded **4a** in 47% and 52% yields respectively, while the triazolium-based precatalysts **1d** and **1e** gave extremely low yields of **4a** (**Table 1**). Surprisingly, the thiozolium-based catalysts, **1f** and **1g** were found to be quite effective giving phenacyl ester **4a** in 78% and 92% yields respectively. Further, either decrease in amount of the catalyst or increase in the temperature had deleterious effect on the yield. Other halogen sources such as *N*-halosuccinimides (X = I, Cl) could also be employed giving **4a** in 81% and 46% yields respectively. Use of other bases (*e.g.* NaH, DBU, Cs_2CO_3 and $KOBu^t$) resulted

in a sluggish reaction with poor yields (entry 8-11), so also a mixture of solvent (THF and DMSO) was found to be less suitable (<15% yield).

Table 1: NHC catalyzed oxo-acyloxylation of styrene with 4-NO_2-benzaldehyde: optimization studies[a]

entry	NHC catalyst	base	solvent	yield of **4a** (%)[b]
1	**1a**	Et_3N	DMSO	65
2	**1b**	Et_3N	DMSO	47
3	**1c**	Et_3N	DMSO	52
4	**1d**	Et_3N	DMSO	14
5	**1e**	Et_3N	DMSO	8
6	**1f**	Et_3N	DMSO	78
7	**1g**	Et_3N	DMSO	92 (81)[c] (46)[d]
8	**1g**	NaH	DMSO	54
9	**1g**	DBU	DMSO	52
10	**1g**	Cs_2CO_3	DMSO	24
11	**1g**	$KOBu^t$	DMSO	16
12	**1g**	Et_3N	DMSO (5 eq) +THF	15

a:Reaction conditions: styrene (5 mmol), *p*-nitrobenzaldehyde (5.5 mmol), NHC precatalysts (**1a-g**) (10 mol %), base (6 mmol), NBS (5 mmol); all under O_2 (1 atm) in DMSO, 25 °C, 18 h; b; isolated yield after column chromatographic purification;c: NIS is used instead of NBS; d: NCS is used as halogen source.

With this optimized yield in hand, NHC catalytic system consisting of **1g** (10 mol %), NBS (1 equiv), Et_3N (1.2 equiv) in DMSO and O_2 (1 atm) was chosen for the substrate scope study. Accordingly, a variety of aromatic aldehydes, having substituents bromo, chloro, methyl, *etc* at various positions on the aromatic nucleus, were subjected to oxo-acyloxylation (**Table 2**) with styrene as substrate. For all the substrates studied, high yields of phenacylesters **4r-u** with excellent regioselectivities

were obtained, although its rate was found to be slow. Interestingly, pyridine-3-carboxaldehyde **3e** gave 73% yield of **4v** under the reaction conditions (entry 5).

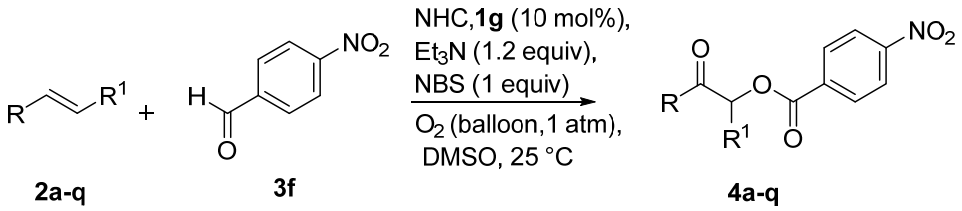
Table 2: NHC catalyzed oxo-acyloxylation of styrene with aromatic aldehydes[a]

entry	aromatic aldehydes (**3a-f**)	t (h)	α-acyloxy ketones (**4**)	
			products	yield (%)[b]
1	benzaldehyde (**3a**)	38	**4r**	68
2	m-tolualdehyde (**3b**)	28	**4s**	81
3	4-Br-benzaldehyde (**3c**)	22	**4t**	78
4	4-Cl-benzaldehyde (**3d**)	24	**4u**	75
5	3-pyridine carboxaldehyde (**3e**)	22	**4v**	73
6	4-NO_2-benzaldehyde (**3f**)	18	**4a**	92

[a] see footnote *a* under Table 1; [b]isolated yield after column chromatographic purification.

Further, several olefins with varied functional groups were then examined under the optimized reaction conditions. For instance, styrenic substrates with electron-releasing and electron-withdrawing groups on the aromatic nucleus (**2a-j**) underwent this oxidative process smoothly to afford exclusive formation of single regioisomers **4a-j** in excellent yields (**Table 3**). Also aliphatic alkenes (**2k-n**) produced good yields of acyloxy ketones **4k-n** (entry 11- 15) despite taking longer reaction times as compared to styrenic substrates. Notably, electron-rich olefins such as vinyl ethers (**2o-2q**) gave the corresponding α-acyloxy esters (**4o-4q**) in high yields (entry 16-19). However, electron-deficient olefins (e.g. α,β-unsaturated carbonyl compounds) failed to undergo this oxo-acyloxylation process under the optimized reaction conditions.

Table 3: NHC catalyzed oxidative functionalization of alkenes with 4-NO_2-benzaldehyde[a]



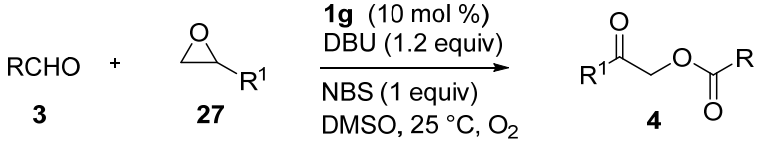
entry	alkenes (**2a-q**)	t (h)	products (**4a-q**)	yield (%)[b]
1	styrene (**2a**)	18	**4a**	92
2	4-CH_3-styrene (**2b**)	20	**4b**	77
3	4-Br- styrene (**2c**)	18	**4c**	71
4	4-F- styrene (**2d**)	22	**4d**	79
5	4-OAc- styrene (**2e**)	23	**4e**	82
6	3,4 –$(OMe)_2$ styrene (**2f**)	26	**4f**	74
7	indene (**2g**)	18	**4g**	72
8	stilbene (**2h**)	24	**4h**	81
9	Ph-CH=CH-CH_3 (**2i**)	26	**4i**	81
10	Ph-CH=CH-CH_2-OTBS (**2j**)	28	**4j**	92
11	benzyloxy-1-propene (**2k**)	27	**4k**	79
12	1-octene (**2l**)	32	**4l**	71
13	1-decene (**2m**)	29	**4m**	76
14	4-phenyl-1-butene (**2n**)	26	**4n**	74
15	ethoxyethene (**2o**)	30	**4o**	78[c]
16	dihydropyran (**2p**)	28	**4p**	69
17	Ph-CH=CH_2-O-CH_3 (**2q**)	21	**4q**	72

a:see footnote a under Table 1; b:isolated yield after column chromatographic purification; c: reaction was carried out at 0 °C.

During our mechanistic studies, we found that styrene epoxide (**27a**) reacts with 4-nitrobenzaldehyde (**3f**) in the presence of NHC catalyst **1g,** NBS (1 equiv) and DBU (1.2 equiv) under complete O_2 atmosphere, the corresponding α-acyloxy ketone **4a** was obtained in 82% yield. With this unexpected result, various epoxides **27** and

aldehydes **3** were screened and the results are summarized in **Table 4**. Several aromatic aldehydes **3** underwent this coupling to afford the corresponding α-acyloxy ketones **4** in high yields (71-76%) and regioselectivities (88-95%). Various styrene oxides having groups (Br, Cl, OMe) on aromatic ring were subjected to this oxidative coupling with *p*-nitrobenzaldehyde that gave the corresponding α-acyloxy ketones **4** in good to excellent yields. Moreover, aliphatic epoxides (**27f** & **27g)** gave the corresponding α-acyloxy ketones (**4l** & **4m)** in 67% yield.

Table 4: NHC catalyzed oxidative coupling of epoxides with aldehydes: Substrate scope



entry	R (**3**)	R^1 (**27**)	products	yield (%)[b]
1	Benzaldehyde (**3a**)	Ph (**27a**)	**4r**	71
2	4-Br-Benzaldehyde (**3c**)	Ph	**4t**	78
3	4-Cl-Benzaldehyde (**3d**)	Ph	**4u**	76
4	4-NO_2-Benzaldehyde (**3f**)	Ph	**4a**	82
5	4-NO_2-Benzaldehyde (**3f**)	4-Me- Ph (**27b**)	**4b**	75
6	4-NO_2-Benzaldehyde (**3f**)	4-Br-Ph (**27c**)	**4c**	81
7	4-NO_2-Benzaldehyde (**3f**)	4-OAc- Ph (**27d**)	**4e**	73
8	4-NO_2-Benzaldehyde (**3f**)	3,4-$(OMe)_2$ (**27e**)	**4f**	69
9	4-NO_2-Benzaldehyde (**3f**)	C_6H_{13}- (**27f**)	**4l**	81
10	4-NO_2-Benzaldehyde (**3f**)	C_8H_{17}- (**27g**)	**4m**	67

[a]Reaction conditions: epoxide (1 mmol), aldehyde (1.1 mmol), NHC precatalysts **1g** (10 mol %), DBU (1.2 mmol), NBS (1 mmol); in DMSO, 25 °C, 12 h, O_2 atm. [b]isolated yield after column chromatographic purification;

The structures of all the α-acyloxy carbonyl compounds **4** were established by their spectroscopic data.

Example 1: The ^{1}H NMR spectrum of 2-(4-methylphenyl)-2-oxoethyl 4-nitrobenzoate (**4b**) showed three typical singlets at δ 2.46 (s, 3H) for methyl group (-C**H$_3$**), 5.62 (s, 2H) for (-CO-C**H$_2$**) and 8.33 (s, 4H) for protons on aromatic ring , while its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 190.6 attributed to carbonyl carbon (-**C**=O) and δ 66.9 (-CO-**C**H$_2$) due to methylene carbon (**Fig. 3**)

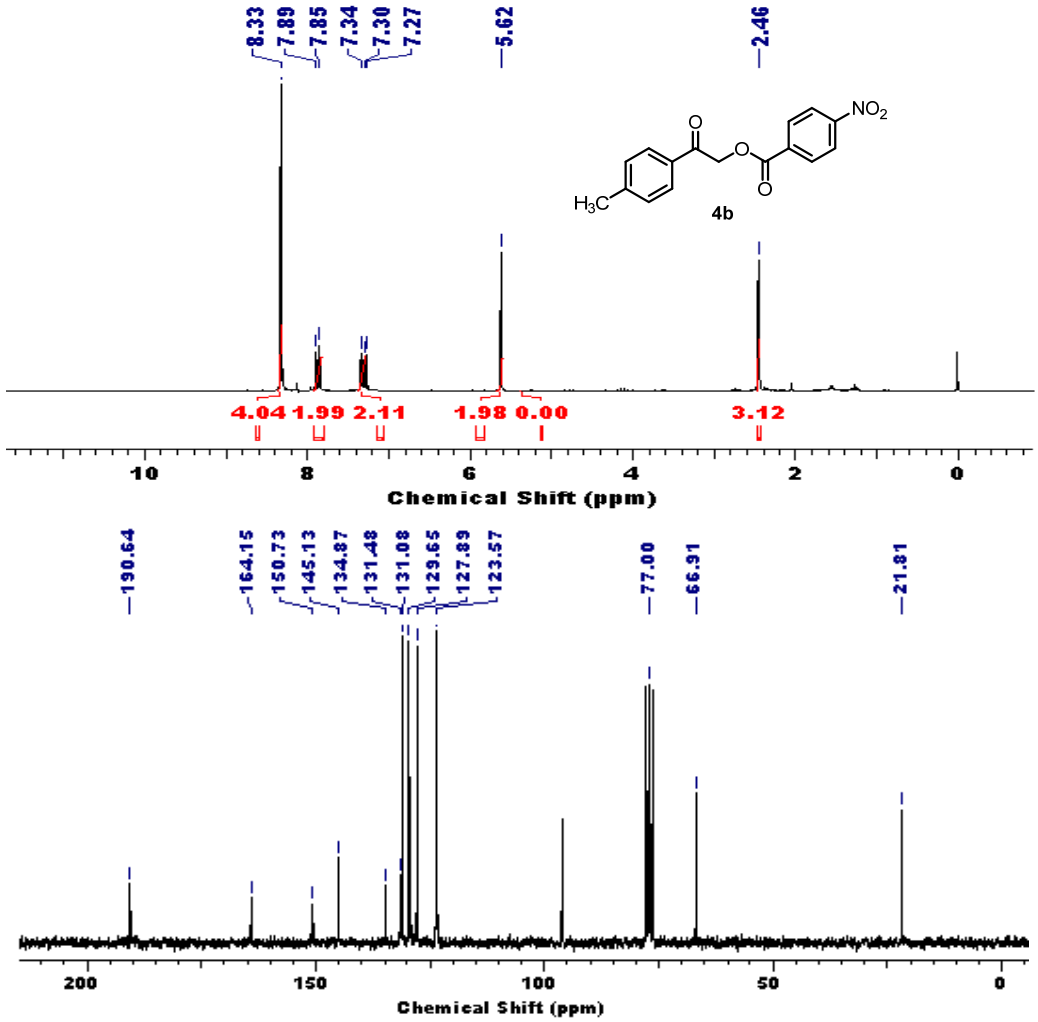


Fig. 3: ^{1}H and ^{13}C NMR spectra of **4b**

Example 2: The ^{1}H NMR spectrum of 2-oxo-2-phenylethyl 4-bromo benzoate (**4t**) showed two typical peaks at δ 5.57 (s, 2H) for methyl group (-C**H**$_2$) and 8.33 (m, 4H) for protons on aromatic ring, while its ^{13}C NMR spectrum showed a characteristic carbon signal at δ 191.4 attributed to carbonyl carbon (-**C**=O) and δ 66.4 (-CO-C**H**$_2$).

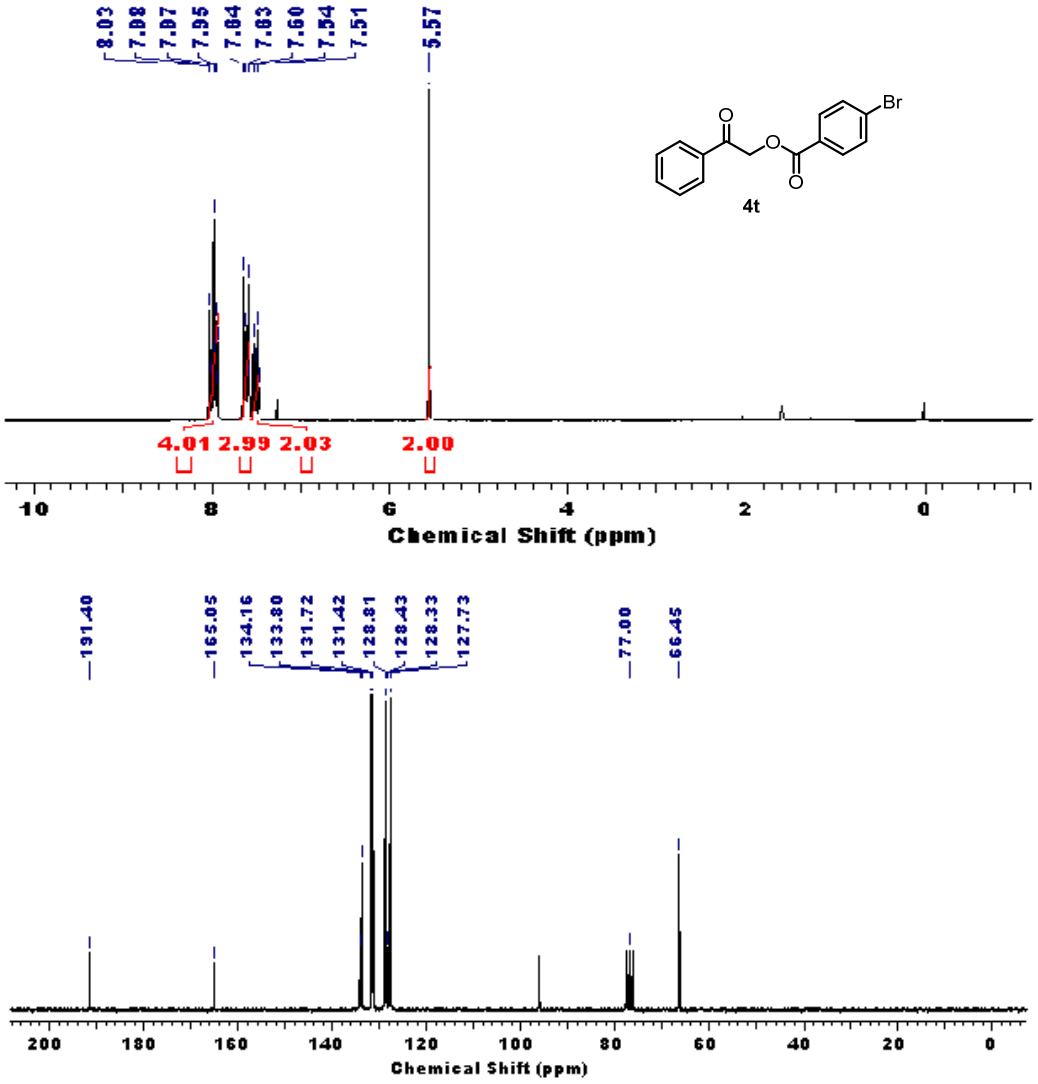
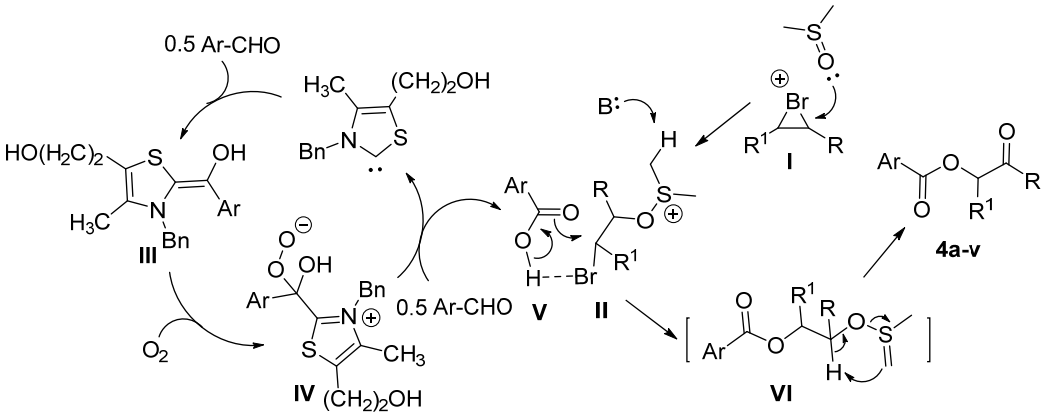


Fig. 4: ^{1}H and ^{13}C NMR spectra of **4t**

The following experiments were carried out to gain an insight into the mechanistic course of the reaction: (i) no styrene epoxide **27a** was observed during the course of the reaction; (ii) when the reaction was carried out under complete N_2 atmosphere, the

corresponding α,β-epoxy ketone **5** (where R = Ph and R^1 = 4-NO_2-Ph) was obtained in 58% yield and (iii) when styrene or epoxide was treated with *p*-nitrobenzoic acid, NBS and Et_3N in DMSO, phenacyl ester **4a** was indeed isolated in 74% yield.

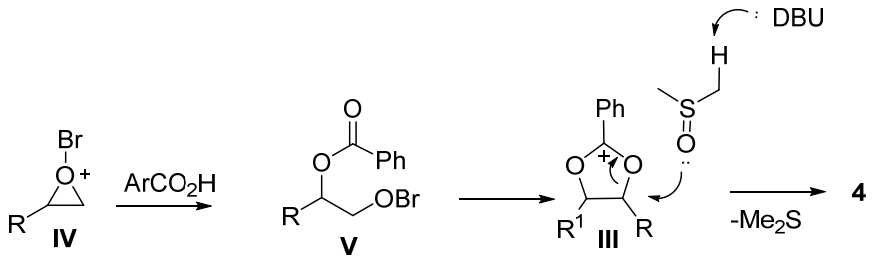
Based on the above experimental results coupled with literature information,[14] a probable mechanism is proposed in **Scheme 11**. Firstly, the bromonium ion **I**, generated from alkene and NBS, undergoes regioselective ring opening with DMSO giving β-bromodimethylalkoxysulfonium ion **II**. Further, in the catalytic cycle, 0.5 equiv of aldehyde reacts with NHC to generate the Breslow intermediate **III**, which upon reaction with molecular O_2 generates the peroxy anion **IV**. This is followed by reaction with another 0.5 equiv of aldehyde to afford 1 equiv of carboxylic acid **V** *in situ*. Displacement of bromide in **II** with carboxylic acid **V**, with simultaneous proton abstraction with base provides sulfur ylide **VI**, which eleminates Me_2S giving α-acyloxy carbonyl compounds **4a-v**.



Scheme 11: Mechanistic pathway for oxo-acyloxylation of alkenes

On the other hand, epoxides **27** were activated by NBS followed by ring opening with carboxylic acid (generated by the reaction of NHC catalyst with aromatic aldehyde)

to give intermediate species **V**, which forms cyclic intermediate **III** by anchimeric assistance shown by benzoate group. The intermediate species **III**, ring opening by DMSO followed by elimination of Me_2S, giving α-acyloxy carbonyl compounds **4a**-**v**.



Scheme 4: Proposed mechanism for oxidative acyloxylation of epoxides

2.1.4 Conclusion

In summary, we have described, for the first time, a novel organocatalytic process in which an oxo-acyloxylation of alkenes with aromatic aldehydes takes place leading to a facile synthesis of α-acyloxy carbonyl derivatives **4a**-**v** in high yields. The procedure employs NHC in catalytic amounts (10 mol %) in combination with NBS/DMSO/O_2 as oxidants. Further, reaction epoxides with aromatic aldehydes produced α-acyloxy carbonyl derivatives **4** under the similar conditions. The salient features of the methodology are: (1) metal-free synthesis, (2) milder reaction conditions, (3) functional group tolerance with broad substrate scope, and (4) high yields of products in highly protected form with excellent regioselectivity.

2.1.5 Experimental section

General experimental procedure:

To a stirred solution of alkene (5 mmol) in dry DMSO (35 mL), NBS (5 mmol), *N*-heterocyclic carbene precursor **1g** (10 mol %) and Et_3N (6 mmol), aromatic aldehyde (5.5 mmol) was added and the reaction mixture was then stirred at 25 °C under an O_2 atmosphere. After completion of the reaction as monitored by TLC, it was quenched with H_2O (50 mL) at 0 °C. It was then extracted with EtOAc (3 x 50 mL) followed by washing with brine (3x50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Removal of solvent gave the crude product, which was purified by column chromatography over silica gel using pet ether/EtOAc (9:1) as eluent to obtain α-acyloxy carbonyl compounds **4a-v** in high purity.

2-Oxo-2-phenylethyl 4-nitrobenzoate (4a)

Yield: 92%, colorless solid, mp: 123-124 °C ; **IR** (Nujol, cm^{-1}): υ_{max} 719, 1104, 1229, 1294, 1376, 1462, 1524, 1598, 1696, 1727, 275, 2840, 2923; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.64 (s, 2H), 7.51-7.55 (m, 2H), 7.63-7.65 (m, 1H), 7.97 (d, *J* = 8.5 Hz, 2H), 8.33 (s, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$) : δ 66.9, 123.4, 127.7, 128.9, 130.9, 133.8, 134.0, 134.7, 150.6, 164.0, 191.0: **HRMS (ESI)**: $[M+H]^+$ calcd for $C_{15}H_{11}NO_5$+H: 286.0715; found: 286.0726.

2-(4-Methylphenyl)-2-oxoethyl 4-nitrobenzoate (4b)

Yield: 77%, colorless solid, mp: 114-115 °C; **IR** (Nujol, cm^{-1}): υ_{max} 713, 1135, 1231, 1289, 1374, 1459, 1525, 1604, 1692, 1725, 2840, 2923; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.46 (s, 3H), 5.62 (s, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.87 (d, *J* = 8.1 Hz, 2H), 8.33 (s, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.8, 66.9, 123.5, 127.8, 129.6, 131.1, 131.5, 134.8, 145.1, 150.7, 164.1, 190.6; **HRMS (ESI)**: $[M+H]^+$ calcd for: $C_{16}H_{13}NO_5$+H : 300.0872; found: 300.0881.

2-(4-Bromophenyl)-2-oxoethyl 4-nitrobenzoate (4c)

Yield: 71%, colorless solid, mp: 117-118 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 717, 967, 1106, 1124, 1346, 1521, 1701, 1723, 2850, 2920; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.58 (s, 2H), 7.67 (m, J = 8.5 Hz, 2H), 7.83 (m, J = 8.5 Hz, 2H), 8.32 (s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) : δ 66.7, 123.6, 129.2, 129.5, 131.1, 132.4, 132.6, 134.6, 150.8, 164.0, 190.0; **HRMS (ESI)**: $[M+H]^+$ calcd for $C_{15}H_{10}BrNNaO_5$+H: 363.9820; found: 363.9834.

2-(4-Fluorophenyl)-2-oxoethyl 4-nitrobenzoate (4d)

Yield: 79%, colorless solid, mp:117-118 °C ; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 717, 871, 1131, 1155, 1231, 1320, 1521, 1595, 1698, 1722, 1746; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.59 (s, 2H), 7.21 (t, J = 8.6 Hz, 2H), 8.01 (dd, J = 8.6, J = 5.0 Hz, 2H), 8.32 (d, J = 2.7 Hz, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 66.7, 116.1, 116.4, 130.5, 130.5, 131.1, 134.6, 150.8, 164.0, 165.0, 167.5, 189.3; **HRMS (ESI)**: $[M+H]^+$ calcd for $C_{15}H_{10}FNO_5$+H: 304.0621; found: 304.0627.

2-(4-Acetoxyphenyl)-2-oxoethyl 4-nitrobenzoate (4e)

Yield: 82%, colorless solid, mp: 128-129 °C; **IR** (Nujol, cm^{-1}): υ_{max} 716, 1166, 1212, 1294, 1374, 1459, 1525, 1596, 1690, 1717, 1753, 2846, 2917; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.35 (s, 3H), 5.61 (s, 2H), 7.26 (d, J = 8.6 Hz, 2H), 8.01 (d, J = 8.6 Hz, 2H), 8.32 (s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.0, 66.7, 122.2, 123.5, 129.3, 131.0, 131.3, 134.6, 150.6, 155.0, 164.0, 168.4, 189.9; **HRMS (ESI)**: $[M+H]^+$ calcd for $C_{17}H_{13}NO_7$+H: 344.0770; found: 344.0778.

2-(3, 4 Dimethoxyphenyl)-2-oxoethyl 4-nitrobenzoate (4f)

Yield: 74%, colorless solid, mp: 162-163 °C; **IR** (Nujol, cm^{-1}): υ_{max} 720, 1021, 1131, 1255, 1376, 1460, 1524, 1684, 1725, 2855, 2925; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.95 (s, 3H), 3.98 (s, 3H), 5.60 (s, 2H), 6.92 (d, J = 8.3 Hz, 1H), 7.51-7.54 (m, 2H),

8.33 (s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 55.9, 56.0, 66.6, 110.0, 110.1, 122.1, 123.6, 127.1, 131.0, 134.9, 149.5, 150.8, 154.1, 164.1, 189.5; **HRMS (ESI)**: $[M+H]^+$ calcd for $C_{17}H_{15}NO_7$+H: 346.0922; found: 346.0927.

1-Oxo-2,3-dihydro-1H-inden-2-yl 4-nitrobenzoate (4g)

Yield: 72%, colorless solid, mp: 199-200 °C ; **IR** (Nujol, cm^{-1}): υ_{max} 713, 1122, 1273, 1349, 1374, 1522, 1604, 1709, 1722, 2846, 2923; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.23 (dd, *J* = 17.0, 4.9 Hz, 1H), 3.82 (dd, *J* = 17.0, 8.1 Hz, 1H), 5.70 (dd, *J* = 8.1, 4.9 Hz, 1H), 7.44-7.53 (m, 2H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 8.30 (s, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 33.4, 75.0, 123.6, 124.7, 126.7, 128.4, 131.1, 134.5, 134.7, 136.1, 150.1, 150.9, 164.1, 199.3; **HRMS (ESI)**: $[M+H]^+$ calcd for: $C_{16}H_{12}NO_5$+H: 298.0715; found: 298.0720.

2-Oxo-1,2-diphenylethyl 4-nitrobenzoate (4h)

Yield: 81%, colorless solid, mp: 114-115 °C; **IR** (Nujol, cm^{-1}): υ_{max} 762, 1097, 1288, 1341, 1374, 1462, 1522, 1692, 1720, 2851, 2923; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.13 (s, 1H), 7.41 - 7.58 (m, 8H), 7.99 (d, *J* = 7.2 Hz, 2H), 8.28 (s, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 78.7, 123.5, 128.7, 128.8, 129.3, 129.7, 131.1, 133.2, 133.6, 134.4, 134.8, 150.7, 164.0, 192.6: **HRMS (ESI)**: $[M+Na]^+$ calcd for: $C_{21}H_{15}NO_5$+Na: 384.0848; found: 384.0853.

1-Oxo-1-phenylpropan-2-yl 4-nitrobenzoate (4i)

Yield: 81%, colorless solid, mp: 119-120°C; **IR** (Nujol, cm^{-1}): υ_{max} 721, 965, 1122, 1270, 1374, 1462, 1522, 1599, 1692, 1725, 2851, 2923; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.72 (d, *J* = 6.9 Hz, 3H), 6.23 (q, *J* = 6.9 Hz, 1H), 7.52-7.63 (m, 3H), 7.97-8.01 (m, 2H), 8.29-8.30 (m, 4H) ; **^{13}C NMR** (100 MHz, $CDCl_3$); δ 17.2, 72.6, 123.4, 128.4, 128.8, 130.9, 133.7, 134.8, 150.6, 163.9, 195.5; **HRMS (ESI)**: $[M+H]^+$ calcd for: $C_{16}H_{13}NO_5$+H :300.0872; found: 300.0877.

3-((*tert*-Butyldimethylsilyl)oxy)-1-oxo-1-phenylpropan-2-yl 4-nitro benzoate (4j)

Yield: 92%, colorless solid, mp: 77-78 °C; **IR** (Nujol, cm^{-1}): υ_{max} 718, 839, 1270, 1371, 1459, 1530, 1695, 1733, 2851, 2917; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.00 (s, 3H), 0.02 (s, 3H), 0.82 (s, 9H), 4.18 (d, *J* = 5.1 Hz, 2H), 6.25 (t, *J* = 5.1 Hz, 1H), 7.47 - 7.62 (m, 3H), 8.00 - 8.04 (m, 2H), 8.29 - 8.30 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -5.4, 18.1, 25.6, 29.7, 62.9, 77.3, 123.5, 128.5, 128.7, 131.0, 133.7, 134.8, 135.2, 150.7, 163.9, 194.4; **HRMS (ESI)**: $[M+H]^+$ calcd for: $C_{22}H_{27}NO_6Si$+H: 430.1686; found: 430.1689.

3-(Benzyloxy)-2-oxopropyl 4-nitrobenzoate (4k)

Yield: 79%, colorless solid, mp: 83-84 °C; **IR** (Nujol, cm^{-1}): υ_{max} 718, 1083, 1283, 1374, 1459, 1517, 1722, 1739, 2851, 2823; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.21 (s, 2H), 4.64 (s, 2H), 5.23 (s, 2H), 7.37 (s, 5H), 8.28 (d, *J* = 4.3 Hz, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 67.8, 73.8, 73.9, 123.5, 127.9, 128.3, 128.6, 130.9, 134.6, 136.5, 150.7, 163.8, 200.8; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{17}H_{15}NO_6$+Na: 352.0796; found: 352.0801.

2-Oxooctyl 4-nitrobenzoate (4l)

Yield: 71%, colorless solid, mp: 75-76 °C: **IR** (Nujol, cm^{-1}): υ_{max} 717, 1121, 1272, 1352, 1377, 1463, 1536, 1543, 1722, 1733, 2854, 2923; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.87 - 0.93 (m, 3H), 1.26 - 1.31 (br. s, 6H), 1.67 - 1.70 (m, 2H), 2.49 (t, *J* = 7.3 Hz, 2H), 4.94 (s, 2H), 8.24 - 8.35 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 13.9, 22.4, 23.2, 28.7, 31.5, 38.7, 68.7, 123.5, 130.9, 134.6, 150.7, 163.8, 202.4: **HRMS (ESI)**: $[M+H]^+$ calcd for $C_{15}H_{19}NO_5$+H: 294.1341; found: 294.1347.

2-Oxodecyl 4-nitrobenzoate (4m)

Yield: 76%, colorless solid, mp: 76-77 °C; **IR** (Nujol, cm^{-1}): υ_{max} 713, 1119, 1270, 1374, 1459, 1541, 1610, 1717, 1736, 2857, 2928; **^{1}H NMR** (200 MHz, $CDCl_3$): δ

0.85 - 0.92 (m, 3H), 1.29 (br. s., 10H), 1.66 (t, *J* = 7.2 Hz, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 4.94 (s, 2H), 8.24 - 8.35 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 22.5, 23.2, 29.0, 29.0, 29.2, 31.7, 38.6, 68.6, 123.4, 130.8, 134.6, 150.6, 163.7, 202.2; **HRMS (ESI)**: $[M+H]^+$ calcd for $C_{17}H_{23}NO_5$+H: 322.1654; found: 322.1656.

2-Oxo-4-phenylbutyl 4-nitrobenzoate (4n)

Yield: 74%, colorless solid, Mp: 112-113 °C; **IR** (Nujol, cm^{-1}): υ_{max} 724, 1089, 1131, 1273, 1347, 1377, 1462, 1523, 1600, 1718, 1732, 2855, 2926; **^{1}H NMR** (200 MHz, $CDCl_3$) : δ 2.79 - 2.87 (m, 2H), 2.95 - 3.03 (m, 2H), 4.91 (s, 2H), 7.21 - 7.31 (m, 5H), 8.27 - 8.34 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 29.2, 40.4, 68.8, 123.6, 126.4, 128.2, 128.6, 131.0, 138.0, 140.2, 150.8, 163.9, 201.7; **HRMS (ESI)**: $[M+Na]^+$ calcd for: $C_{17}H_{15}NO_5$+Na: 336.0848; found: 336.0856.

2-Ethoxy-2-oxoethyl 4-nitrobenzoate (4o)

Yield: 78%, yellow liquid; **IR** (neat, cm^{-1}): υ_{max} 2926, 2983, 1759, 1738, 1732, 1608, 1531, 1349, 1285, 1213, 1121, 1018, 857, 718; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.1 Hz, 3H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.89 (s, 2H), 8.25 - 8.36 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 61.5, 123.5, 131.0, 134.5, 150.8, 163.9, 166.9; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{11}H_{11}NO_6$+Na: 276.0484; found: 276.0446.

2-Oxotetrahydro-2H-pyran-3-yl 4-nitrobenzoate (4p)

Yield: 69%, colorless solid, mp: 136-137 °C; **IR** (Nujol, cm^{-1}): υ_{max} 718, 1124, 1273, 1377, 1456, 1511, 1602, 1725, 1753, 2857, 2912; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.14-2.20 (m, 3H), 2.51-2.76 (m, 1H), 4.43-4.49 (m, 2H), 5.61-5.67 (m, 1H), 8.25-8.35 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.3, 24.8, 68.2, 68.2, 123.5, 131.0, 134.5, 150.7, 163.4, 168.1; **HRMS (ESI)**: $[M+H]^+$ calcd for $C_{12}H_{11}NO_6$+H: 266.0664; found: 266.0663.

2-(Methoxy)-2-oxo-1-phenylethyl 4-nitrobenzoate (4q)

Yield: 72%, yellow liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 718, 1101, 1167, 1269, 1346, 1368, 1508, 1527, 1606, 1731, 1760; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.80 (s, 3H), 6.20 (s, 1H), 7.47-7.48 (m, 3H), 7.59-7.60 (m, 2H), 8.32 (s, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 52.6, 75.4, 123.5, 127.7, 128.9, 129.5, 131.0, 133.3, 134.5, 150.8, 163.7, 168.5; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{16}H_{13}NO_6$+Na: 338.0641; found: 338.0649.

2-Oxo-2-phenylethyl benzoate (4r)

Yield: 68%, colorless solid, mp: 119-120 °C; **IR** (Nujol, cm^{-1}): υ_{max} 705, 1015, 1374, 1459, 1596, 1714, 1750, 2851, 2923; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.58 (s, 2H), 7.48-7.61 (m, 6H), 7.97-8.00 (m, 2H), 8.13-8.17 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 66.2, 127.6, 128.2, 128.73 , 129.8, 130.1, 133.1, 133.6, 134.1, 165.7, 191.6; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{15}H_{12}O_3$+Na: 263.0683; found: 263.0692.

2-Oxo-2-phenylethyl 3-methylbenzoate (4s)

Yield: 81%, colorless solid, mp: 94-95°C; **IR** (Nujol, cm^{-1}): υ_{max} 743, 814, 957, 1083, 1198, 1369, 1451, 1585, 1684, 1714, 2857, 2917; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.38 (s, 3H), 5.52 (s, 2H), 7.31-7.48 (m, 5H), 7.90 - 7.95 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.1, 66.2, 127.0, 127.6, 128.2 128.7, 129.2, 130.3, 133.6, 133.9, 134.1, 137.9, 165.8, 191.7; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{16}H_{14}O_3$+Na: 277.0840; found: 277.0848

2-Oxo-2-phenylethyl 4-bromobenzoate (4t)

Yield: 78%, colorless solid, mp: 84-85°C; **IR** (Nujol, cm^{-1}): υ_{max} 766, 1012, 1126, 1327, 1588, 1643, 1711, 1732, 2923, 2956; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.57 (s, 2H), 7.44-7.64 (m, 5H), 7.94-8.03 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 66.4, 127.7, 128.3, 128.4, 128.8, 131.4, 131.7, 133.8, 134.1, 165.0, 191.4: **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{15}H_{11}BrO_3$+Na: 340.9789; found: 340.9799.

2-Oxo-2-phenylethyl 4-chlorobenzoate (4u)

Yield: 75%, colorless solid, mp: 127-128 °C ; **IR** (Nujol, cm^{-1}): υ_{max} 753, 1091, 1226, 1273, 1376, 1456, 1595, 1697, 1726, 2724, 2857, 2926; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.58 (s, 2H) 7.44-7.56 (m, 5H), 7.97 (d, *J* = 7.3Hz, 2H) 8.07-8.11 (d, *J* = 7.3 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 66.5, 77.0, 127.8, 128.6, 128.8, 128.9, 131.3, 133.9, 134.2, 139.8, 165.0, 191.6; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{15}H_{11}ClO_3$+Na: 297.0294; found: 297.0294.

2-Oxo-2-phenylethyl nicotinate (4v)

Yield: 73%, colorless solid, mp: 64-65 °C**: IR** ($CHCl_3$, cm^{-1}): υ_{max} 753, 1076, 1342, 1463, 1591, 1650, 1695, 1726, 2854, 2870, 2923; **^{1}H NMR** (400 MHz, $CDCl_3$); δ 5.61 (s, 2H), 7.44 (dd, *J* = 7.6, 4.9 Hz, 1H) 7.50-7.54 (m, 2H), 7.62-7.64 (m, 1H), 7.97 (d, *J* = 7.5 Hz, 2H), 8.40 (d, *J* = 7.7 Hz, 1H), 8.82 (br. s, 1H), 9.33 (br. s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 66.6, 123.3, 125.6, 127.8, 128.9, 134.0, 134.1, 137.4, 151.2, 153.7, 164.6, 191.1; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{14}H_{11}NO_3$+Na: 264.0637; found: 264.0648.

2, 3-Epoxy-1-(4-nitrophenyl)-3-phenylpropan-1-one (5)

Yield: 56%, colorless solid, mp: 120-121 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 745, 1233, 1451, 1519, 1598, 1692, 2850, 2923; **^{1}H NMR** (200 MHz, $CDCl_3$); δ 4.21 (d, *J* = 1.7 Hz 1H), 4.25 (d, *J* = 1.7 Hz, 1H), 7.52-7.56 (m, 4H), 7.58 (m, 1H), 8.02 (d, *J* = 8.7 Hz, 2H), 8.29 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 57.9, 60.8, 124.1, 126.6, 128.4, 129.0, 134.3, 135.2, 142.7, 148.3, 191.9; **HRMS (ESI)**: $[M+H]^+$ calcd for $C_{15}H_{11}NO_4$+H: 270.0766; found: 270.0777.

Section II

N-Heterocyclic Carbene Catalyzed Oxidative Coupling of Styrenes/α-Bromo Acetophenones with Aldehydes for the Synthesis of α,β-Epoxy Ketones

2.2.1 Introduction

Racemic and optically active epoxy ketones are among the most versatile building blocks in organic synthesis.[16] These chiral multifunctionalized compounds have been extensively used in making valuable bioactive molecules and natural products in both synthetic organic laboratories and various chemical manufacturers, ranging from pharmaceutical to agriculture industries. Indeed, both the ketone and epoxide moieties can be further functionalised to provide interesting intermediates, useful for the synthesis of natural products or biologically active compounds. For example, stereoselective addition of various nucleophiles (hydride, organometallic reagents) to the ketone affords secondary or tertiary epoxy alcohols, which would be more difficult to obtain using other methodologies. Further manipulations can then furnish interesting polyhydroxyl compounds bearing several stereogenic centres. Many more transformations can be achieved on the ketone moiety, such as reductive amination, Baeyer–Villiger oxidation, Wittig olefination and Meerwein–Pondorf–Verley reduction–alkylation. On the other hand, the epoxide can also be opened by nucleophiles in a *syn*- or *anti*-stereoselective manner and both at the α– or β position depending on the conditions used. Reductive cleavage or reductive alkylation of the epoxide also provides useful synthetic intermediates.

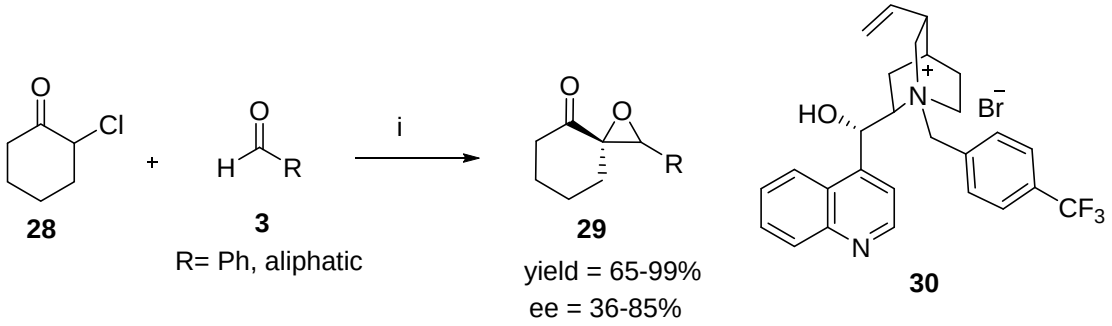
The conventional method for the preparation of α,β-epoxy ketones involves Darzens reaction of α-halo ketones with aldehydes under basic conditions or Lewis acid catalyzed epoxidation of chalcones using peroxides.

2.2.2 Review of Literature

Literature survey revealed that there are few methods available for the synthesis of α,β epoxyketones **5** some of which are described below.

Arai's approach (1999)[17]

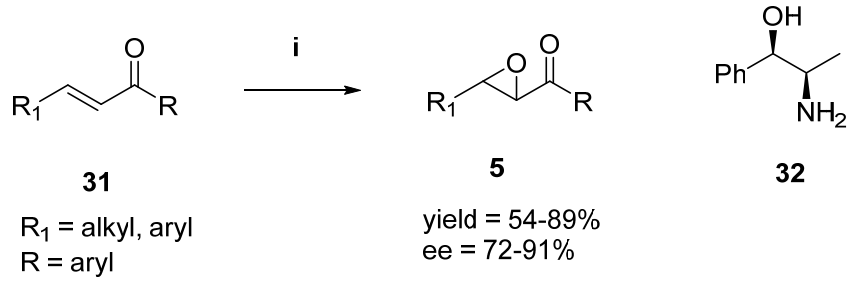
Arai *et al*. have developed an asymmetric Darzen's reaction promoted by a cinchonine derived chiral phase-transfer catalyst **30**. The desired epoxy ketones **29** were obtained by use of α-chloro acyclic and cyclic ketones **28** as substrates with moderate to high enantiomeric excesses under ambient conditions (**Scheme 13**).



Scheme 13: (i) Cat. **30** (10 mol %), LiOH/nBu$_2$O, 25 °C, 5 h.

Enders (1999)[18]

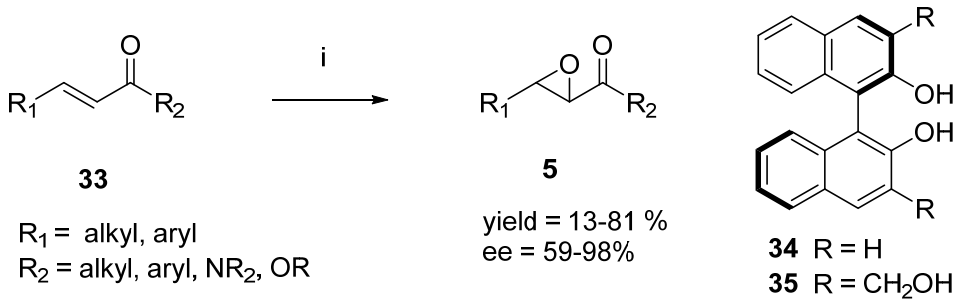
In 1996, Enders *et al*. disclosed that (*E*)-α,β-unsaturated ketones **31** can be epoxidised in asymmetric fashion using stoichiometric quantities of diethylzinc and a chiral alcohol **32**, under an oxygen atmosphere, to give *trans*-epoxides **5** (**Scheme 14**). Out of 35 optically active alcohols screened, (1*R*,2R)-*N*-methylpseudoephedrine (**32**) was chosen as the alcohol which gave the best enantioselectivities.



Scheme 14: Et_2Zn (1.2 equiv), O_2, **32** (2.4 equiv), THF, 25 °C.

Inanaga's approach (1999)[19]

Inanaga and coworkers have developed a new and efficient chiral catalyst system, lanthanum–chiral BINOL–tris(4-fluorophenyl)phosphine oxide–cumene hydroperoxide, for the epoxidation of α,β-unsaturated ketones **33** thus providing the corresponding α,β-epoxy ketoness **5** with good to excellent enantioselectivities (up to >98% ee) and yields (up to 81%) under ambient conditions (**Scheme 15**).

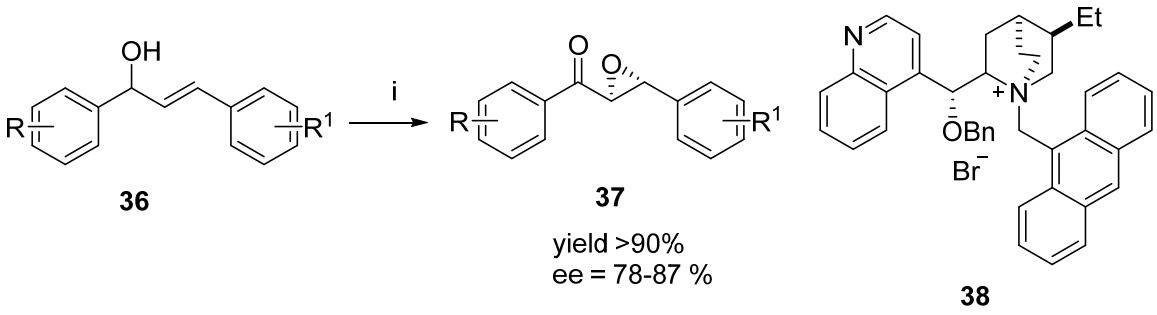


Scheme 15: $La(O\text{-}i\text{-}Pr)_3$ (5 mol %), (R)-BINOL(**34**/**35**) (5 mol %), $Ar_3P{=}O$ (15 mol %), MS 4A, THF, 25 °C

Lygo's approach (2002)[20]

Lygo *et al.* have used a chiral phase-transfer catalyst **38** in combination with sodium hypochlorite to achieve the enantioselective formation of α,β-epoxyketones **37** from allylic alcohols **36** (**Scheme 16**). In the presence of NaOCl and quinoline based chiral

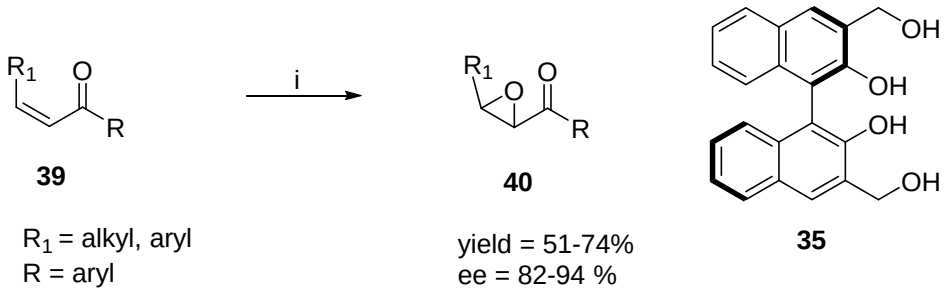
catalyst **38**, allylic alcohols **36** underwent oxidation and epoxidation to form corresponding chalcone epoxides **37** in high yields (up to 90%)



Scheme 16: (i) cat. **38** (1 mol %), 15% aq. NaOCl, toluene, 25 °C, 4-24 h.

Shibasaki approach (2005)[21]

Shibasaki *et al.* have shown that the unmodified Yb-catalyst is also effective for the epoxidation of (*Z*)-enones **39** to the corresponding *cis*-epoxides **40**. The transformation proceeds with good yields and high stereoselectivity for aliphatic enones **39**. In the case of aromatic enones **39**, the reaction is less effective owing to formation of substantial (up to 32%) amounts of the unwanted *trans*-epoxide (**Scheme 17**).

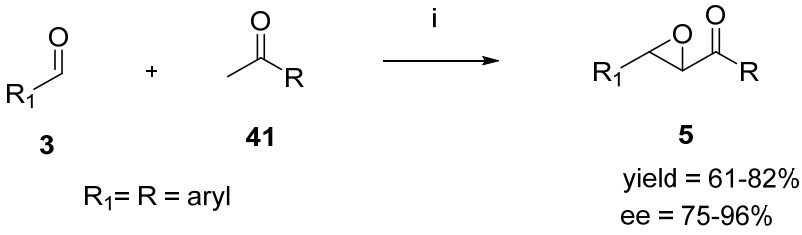


Scheme 17: Yb(O^iPr)$_3$ (5 mol %), **35** (10 mol %), TBHP (3 equiv), MS 4A°, THF, 25 °C

Liang approach (2007)[22]

Liang *et al.* have developed a novel Claisen–Schmidt condensation-epoxidation sequence of aldehydes **3** and ketones **41** to produce a series of chiral α,β-epoxy ketones **5** under

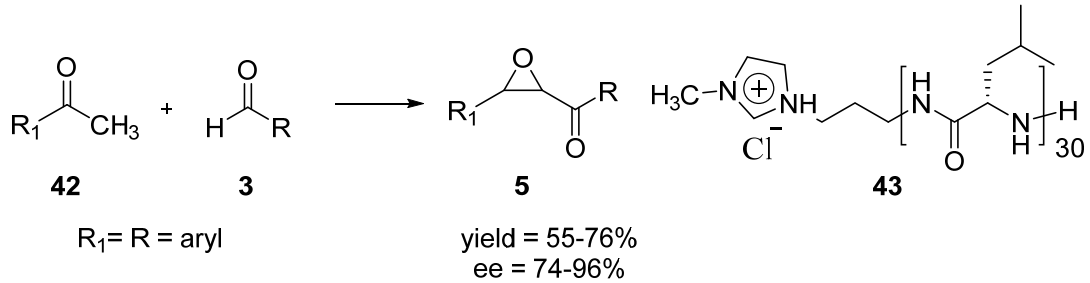
asymmetric phase-transfer catalytic conditions. The organocatalytic method reported here uses trichloroisocyanuric acid (TCCA) and chiral catalyst **38** for oxidation and asymmetric epoxidation of *in situ* formed α,β-unsaturated ketones (**Scheme 18**).



Sceheme 18: (i) (a) aq. 50 % KOH (5 mol %). (b) cat. **38** (1 mol %), TCCA, toluene, 25 °C, 24 h.

Yang approach (2011)[23]

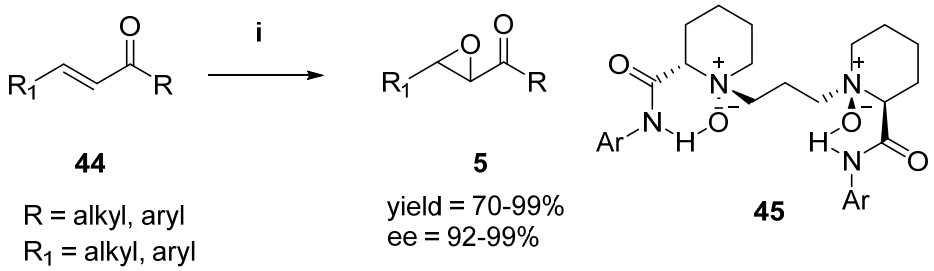
Liang has developed an efficient one-pot, two-step process for the production of chiral α,β-epoxy ketones **5** from aromatic aldehydes **3** and acetophenones **42** catalyzed by imidazolium-modified poly(L-leucine) **43**. Two effective reaction systems with complementary high enantioselectivities (up to 96% ee) or satisfactory yields (up to 76%) have been developed. Importantly, the poly(amino acid) catalyst **43** can be easily recovered and recycled for ten times without losing its catalytic efficiency in terms of both enantioselectivity and yield (**Scheme 19**). However this reaction has failed in case of aliphatic aldehydes and ketones.



Scheme 19: (i) 6 equiv of 10% KOH, H_2O, 5 °C; (ii) 1.5 equiv percarbonate, 0.2 equiv. Cat. **43**, toluene, H_2O, 0°C.

Feng approach (2012)[24]

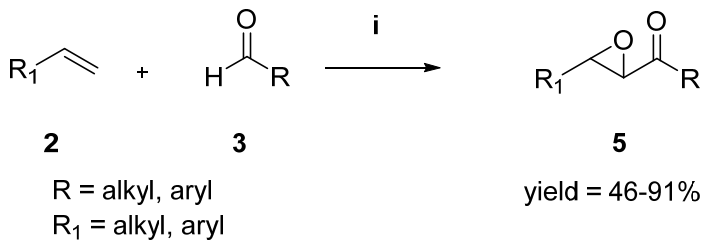
Feng *et al.* have developed a simple and efficient asymmetric epoxidation of α,β-unsaturated carbonyl compounds **44** using a chiral N,N'-dioxide–Sc(III) complex as catalyst. Various optically active epoxides **5** were prepared from the corresponding α,β-unsaturated ketones and α,β-unsaturated amides **44** under additive-free conditions (**Scheme 20**).



Scheme 20: (i) **45**-$Sc(OTf)_3$ (5 mol %), 30% aq. H_2O_2, THF, 35 °C, 24 h.

Li's approach (2014)[4]

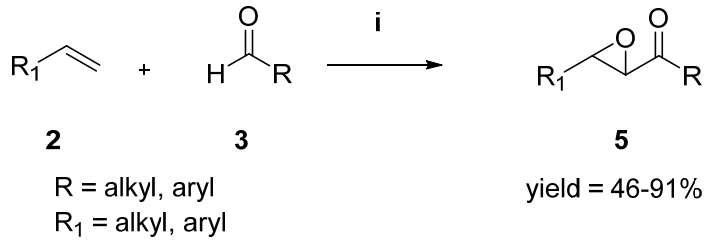
Li *et al.* have developed a new transition metal-free oxidative coupling of unactivated terminal alkenes **2** with aldehydes **3** using TBHP in the presence of 10 mol % of ^{t}BuOK, thereby realizing trifunctionalization of alkenes toward α,β-epoxy ketones **5**. This method is applicable to a wide range of aldehydes, including aryl and alkyl aldehydes, with excellent functional group tolerance; however aliphatic alkenes and aldehydes produced very low yields. (**Scheme 21**).



Scheme 21: (i) K^{t}OBu (10 mol %), TBHP (70% in water), THF, 100 °C, 24 h.

Lu's approach (2014)[5]

Lu *et al.* have developed a novel strategy for the synthesis of α,β–epoxy ketones **5**. This process allows the direct synthesis of epoxides from alkenes **2** and aldehydes **3** through C–H functionalization and C–C/C–O bond formation (**Scheme 22**). However, aliphatic alkenes and aldehydes failed to undergo this catalytic transformation.



Scheme 22: (i) K_2CO_3 (10 mol %), TBHP (70% in water), THF, 100 °C, 24 h.

2.2.3 Present Work

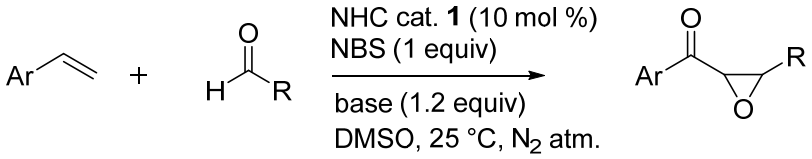
2.2.3.1 Objective

Although there are many methods available in the literature for the synthesis of α,β-epoxyketones, several of them suffer from certain drawbacks like low yields, cumbersome experimental procedures, use of expensive air and moisture sensitive or highly toxic catalysts. Hence, there arises a necessity to develop an efficient procedure for the synthesis of epoxy ketones from commercially available starting materials under ambient conditions.

2.2.4 Results and Discussion

We have reported NHC-catalyzed oxidative coupling of alkenes **2** (-C=C- bonds) and aldehydes **3** under oxygen atmosphere that led to the synthesis of substituted α-acyloxy carbonyl derivatives. Surprisingly, under N_2 atmosphere, the reaction took a different path affording α,β-epoxy ketones **5** in high yields. In this section, we describe NHC

catalyzed oxidative coupling of styrenes **2** and aldehydes **3** that afford the corresponding α,β-epoxy ketones **5** in good yields using NBS-DBU-DMSO as oxidative system in a highly regio- and diastereoselective manner, (**Scheme 23**).

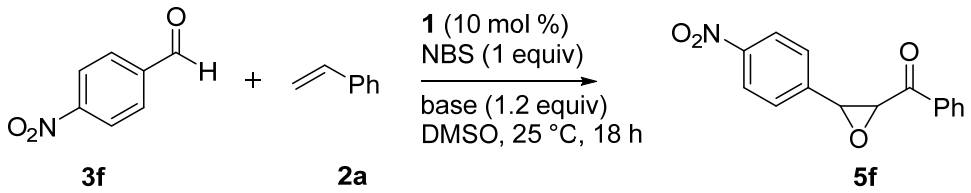


Scheme 23: NHC catalyzed oxidative coupling of alkene with aldehydes

To begin with, when styrene (**2a)** (1 mmol) was treated with a mixture containing *p*-nitrobenzaldehyde (**3f**) (1.1 mmol), NBS (1 mmol) and Et_3N (1.2 mmol) in the presence of NHC catalyst **1a** (10 mol %) at 25 °C in DMSO *under complete inert (N_2) atmosphere*, α,β-epoxy ketone **5f** was obtained in 56% isolated yield with excellent diastereomeric ratio (*trans:cis* = 98:2). It is unusual that the *ketone group* in **5f** is formed from the styrenic counterpart *via* benzylic oxidation while the *epoxide moiety* is obtained from the aldehydic coupling partner.

In order to improve the yield of epoxyketone **5f**, other NHC catalysts were examined (**Fig.2**). Among the catalysts screened, the thiozoium based catalysts **1f** and **1g** were found to be quite efficient for the oxidative coupling reaction (up to 66% yields) while the imidazolium based precatalysts (**1a-c**) gave only moderate yields (up to 45%) (**Table 1**; entry1-5). Other solvents such as THF, CH_3CN, CH_2Cl_2, 1,4-dioxane and DMF were found to be unsuitable for the reaction. Also, DBU was found to be an excellent base for the reaction (72% yield) while inorganic bases were only moderately active (up to 61%

Table 5: NHC catalyzed oxidative coupling of 4-nitrobenzaldehyde (**3f**) and styrene (**2a**): optimization studies[a]



3f **2a** **5f**

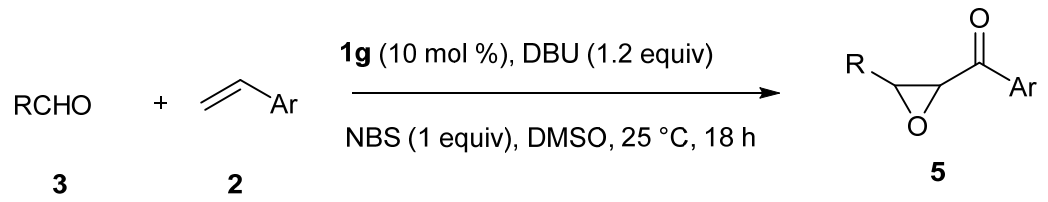
no	cat. **1** (10 mol %)	base	yield (%)[b] of **5f**
1	**1a**	Et_3N	56
2	**1b**	Et_3N	45
3	**1c**	Et_3N	37
4	**1f**	Et_3N	58
5	**1g**	Et_3N	66
6	**1g**	NaH	54
7	**1g**	Cs_2CO_3	24
8	**1g**	$KOBu^t$	61
9	**1g**	DBU	72 (51)[c] (15)[d]
10	**1g** (5 mol %)	DBU	41 (70)[e]

a:Reaction conditions: styrene (1 mmol), *p*-nitrobenzaldehyde (1.1 mmol), NHC precatalysts (**1**) (10 mol %), base (1.2 mmol), NBS (1 mmol) in DMSO, 25 °C, 18 h. b:isolated yield after column chromatographic purification. c:NIS was used instead of NBS. d:NCS was used as halogen source.e:20 mol % of catalyst **1g** was used.

yield) (entry 6-9). Other *N*-idoosuccinimides and *N*-chlorosuccinimides were also screened to give **5f** in 51% and 15% yields respectively (entry 9). Further, either lowering

of catalyst concentration or increase of reaction temperature did not significantly improve the yield (entry 10).

Table 6: NHC catalyzed oxidative coupling of styrenes **2** with aldehydes **3**: substrate scope



3 **2** **5**

no	aldehydes (**3**)	styrenes (**2**)	products	yield(%)[b,c]	mp (° C)
1	benzaldehyde (**3a**)	styrene (**2a**)	**5a**	61	89-90
2	4-Br-benzaldehyde (**3c**)	styrene	**5c**	58	86-88
3	4-Cl- benzaldehyde **(3d**)	styrene	**5d**	63	47-49
4	2- NO_2-benzaldehyde (**3e**)	styrene	**5e**	68	109-111
5	4-NO_2-benzaldehyde (**3f**)	styrene	**5f**	72	120-121
6	4-CN- benzaldehyde (**3g**)	styrene	**5g**	66	54-56
7	1-heptanal (**3h**)	styrene	**5h**	51	---
8	Isovaleraldehyde (**3i**)	styrene	**5i**	62	---
9	ethyl glyoxalate (**3j**)	styrene	**5j**	65	---
10	4- NO_2-benzaldehyde (**3k**)	4-Me-styrene (**2b**)	**5k**	64	122-123
11	4- NO_2-benzaldehyde (**3l**)	4-Br-styrene (**2c**)	**5l**	69	128-129

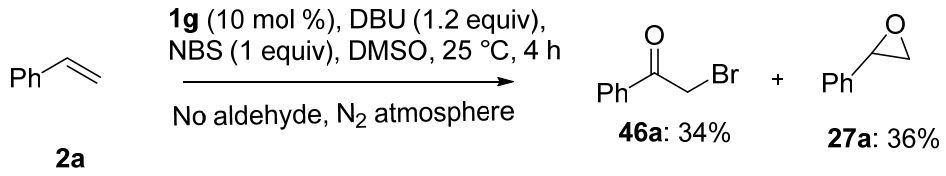
[a]Reaction conditions: styrenes (1 mmol), aldehyde (1.1 mmol), NHC precatalysts **1g** (10 mol %), DBU (1.2 mmol), NBS (1 mmol); in DMSO, 25 °C, 18 h. [b]isolated yield after column chromatographic purification;[c] diastereomeric ratios were found to be 95:5 in each case as determined by HPLC and ^{1}H NMR analysis.

With this optimized yield in hand, NHC catalytic system consisting of **1g** (10 mol %), NBS (1 equiv), DBU (1.2 equiv) in DMSO under inert N_2 atmosphere was chosen for the substrate scope study. Accordingly, a variety of aromatic aldehydes **3a-g**, having electron neutral (bromo, chloro, methyl, *etc.*), withdrawing (-NO_2) and donating (-O-CH_2-O-) groups at various positions on the aromatic nucleus, were subjected to oxidative coupling reaction (**Table 6**) with styrene. For all the substrates studied, moderate to good yields (56-72%) of epoxy ketones **5a-g** were obtained (**Table 6**; entry 1-6). Notably, aliphatic aldehydes such as heptanal (**3h)** and isovaleraldehyde (**3i**) afforded the corresponding epoxy ketones **5h** and **5i** in 51% and 62% yields, respectively (entry 7 & 8). Remarkably, ethyl glyoxalate (**3j**) gave ethyl 3-benzoyloxirane-2-carboxylate **5j** in moderate yield (65%) (entry 9).

Further, styrenic substrates, having Br and Me groups on the benzene nucleus were subjected to coupling with 4-nitrobenzaldehyde (**3f)** under the optimized condition, which gave good yields (64 and 69%) of the corresponding α,β-epoxy ketones **5k** and **5l** respectively (entry 11-13). However, other aliphatic terminal alkenes and disubstituted styrenes failed to undergo this catalytic transformation.

In order to probe into the reaction mechanism, the following control experiments were conducted (**Scheme 24**). (i) No reaction was observed in the absence of either NHC catalyst or NBS; hence, these reagents are essential in this coupling reaction. (ii) In the absence of aldehyde, with styrene (**2a**) as substrate, phenacyl bromide **46a** and styrene epoxide (**27a**) were formed in 34% and 36% yields, respectively. (iii) Further treatment of phenacyl bromide (**46a)** with *p*-nitrobenzaldehyde (**3f**), NHC catalyst **1g** and DBU

under N_2 atmosphere afforded the desired product **5f** in 78% yield; whereas styrene epoxide (**27a**) on reaction with 4-nitrobenzaldehyde (**3f**) under similar condition did not

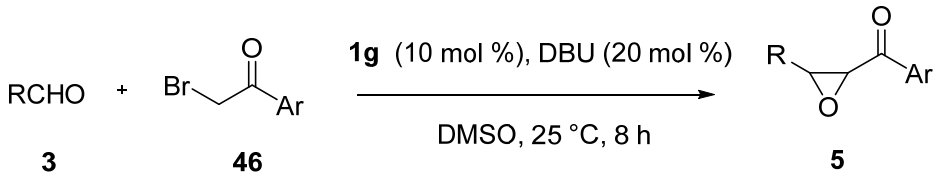


Scheme 24: Control experiments for illustration of mechanism

give the desired product **5f**. Hence, it is believed that the reaction proceeds through the formation of intermediate α-bromoketone which subsequently reacts with aldehyde: indeed a conventional Darzens reaction.

Consequently, it is of interest to explore the first NHC catalyzed Darzens reaction, which can overcome the disadvantages associated with its conventional reagent system (eg. strong basic conditions, use of sulphur compounds and phase-transfer reagents) and the results are presented in **Table 7**. Accordingly, various aromatic aldehydes having groups -Cl, -Br, -CN on aromatic nucleous (**3a-g**) were subjected to NHC catalyzed Darzens reaction with phenacyl bromide **46a** that afforded the corresponding α,β-epoxyketones (**5a-g**) in high yields (**Table 7**; entry 1-5). Also, heptanal **3h** gave the corresponding epoxy ketone **4h** in 68% yield. Further, substituted α-bromoacetophenones **46b** and **46c** gave **5k** and **5l** in 71 and 69% yields respectively (entry 7 & 8). Disappointingly, ethyl bromoacetate failed to undergo the Darzens reaction.

Table 7: NHC catalyzed oxidative coupling of α-bromoacetophenones with aldehydes: substrate scope



3 **46** **5**

no	aldehyde (**3**)	Ar (**46**)	products (**5**)	yield (%)[b]
1	benzaldehyde (**3a**)	Ph (**46a**)	**5a**	71
2	4-Br-benzaldehyde (**3c**)	Ph	**5c**	74
3	4-Cl-benzaldehyde (**3d**)	Ph	**5d**	75
4	4-NO_2-benzaldehyde (**3f**)	Ph	**5f**	78
5	4-CN-benzaldehyde (**3g**)	Ph	**5g**	72
6	1-heptanal (**3h**)	Ph	**5h**	68
7	4-NO_2-benzaldehyde (**3f**)	4-Me-Ph (**46b**)	**5k**	71
8	4-NO_2-benzaldehyde (**3f**)	4-Br-Ph (**46c**)	**5l**	69

[a]Reaction conditions: α-bromoacetophenones (1 mmol), aldehyde (1.1 mmol), NHC precatalysts **1e** (10 mol %), DBU (20 mol %), DMSO, 25 °C, 12 h, N_2 atm. [b]isolated yield after column chromatographic purification. [c]diastereomeric ratios were found to be >95:5 for all the case studied as determined by HPLC and ^{1}H NMR analysis.

The structures of the epoxyketones **5** were established by their spectroscopic (^{1}H NMR and ^{13}C NMR) and HRMS data.

Example 1: The ^{1}H NMR spectrum of (3-(4-cyanoophenyl)oxiran-2-yl)(phenyl)methanone (**5g**) showed two typical proton signals at 4.15 (d, J = 1.8 Hz, 1H) and 4.21 (d, J = 1.9 Hz, 1H) for hydrogens attached to epoxide, while its ^{13}C NMR spectrum showed four

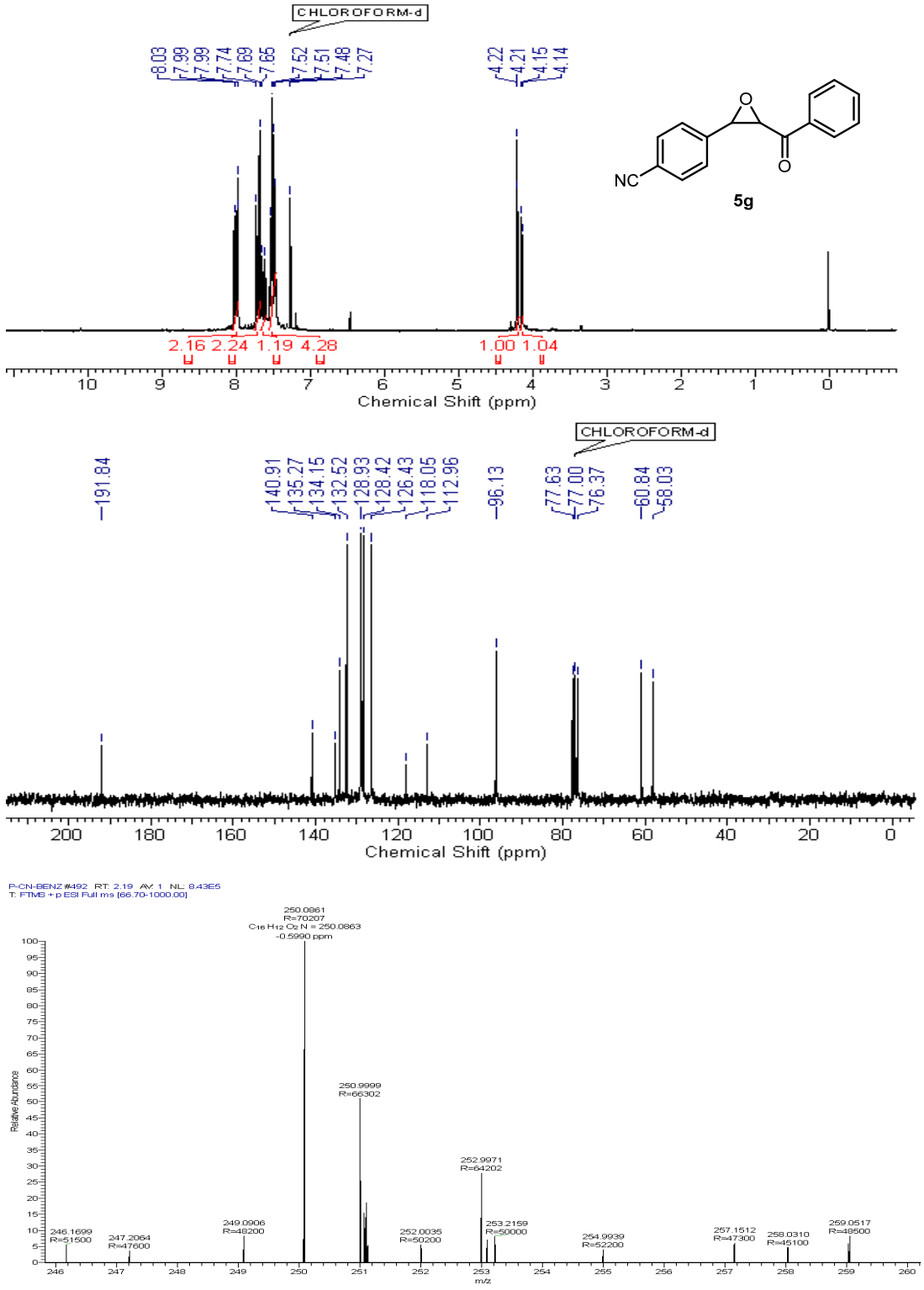


Fig. 5: ^{1}H, ^{13}C NMR and HRMS spectra of **5g**

characteristic carbon signals at δ 191.8 attributed to carbonyl carbon (-**C**=O), 112.8 corresponding to -CN group and 58 and 60 due to epoxide carbons respectively (**Fig 5**). Further, it is confirmed by its HRMS spectrum which showed its m/e value 250.0861 for the molecular formula $C_{16}H_{11}NO_2$+H.

Example 2: The ^{1}H NMR spectrum of ethyl 3-benzoyloxirane-2-carboxylate (**5j**) showed three typical peaks at 3.68 (d, J = 1.8 Hz, 1H) for -C**H** attached to epoxide group 4.31 (qd, J = 7.1, 0.9 Hz, 2H) for -C**H$_2$** and 4.42 (d, J = 1.8 Hz, 1H) for epoxide ring

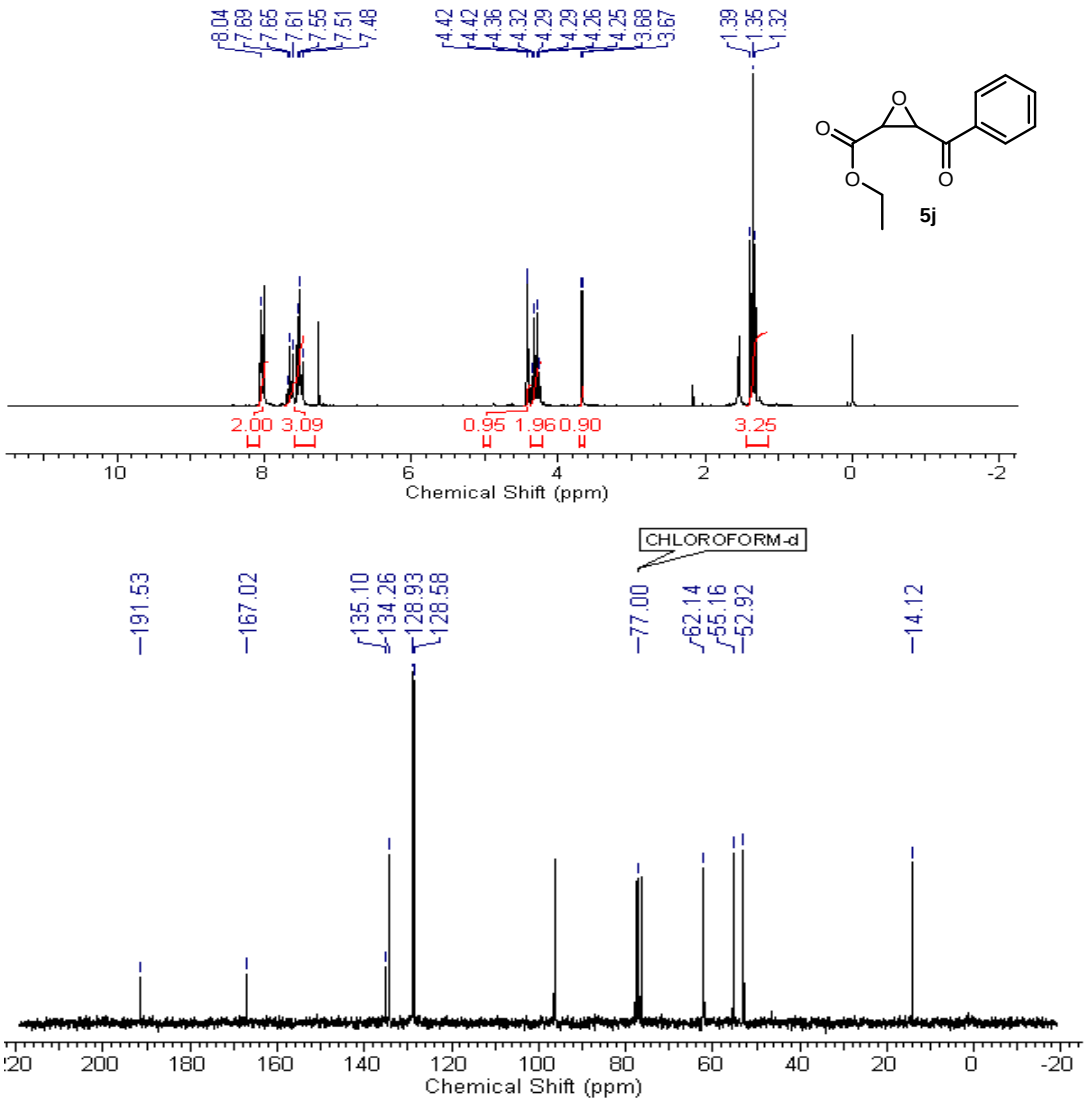
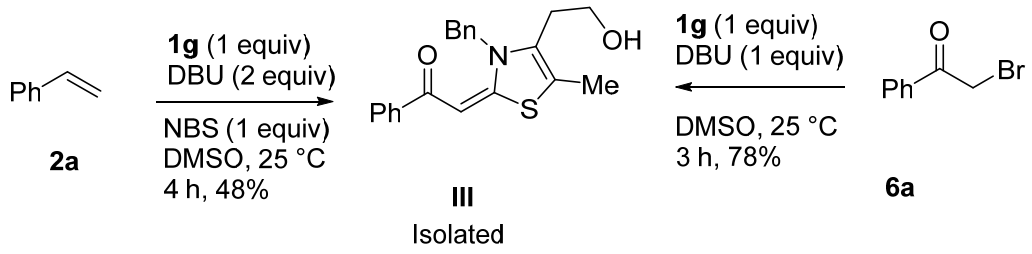


Fig. 6: ^{1}H and ^{13}C NMR spectra of **5j**

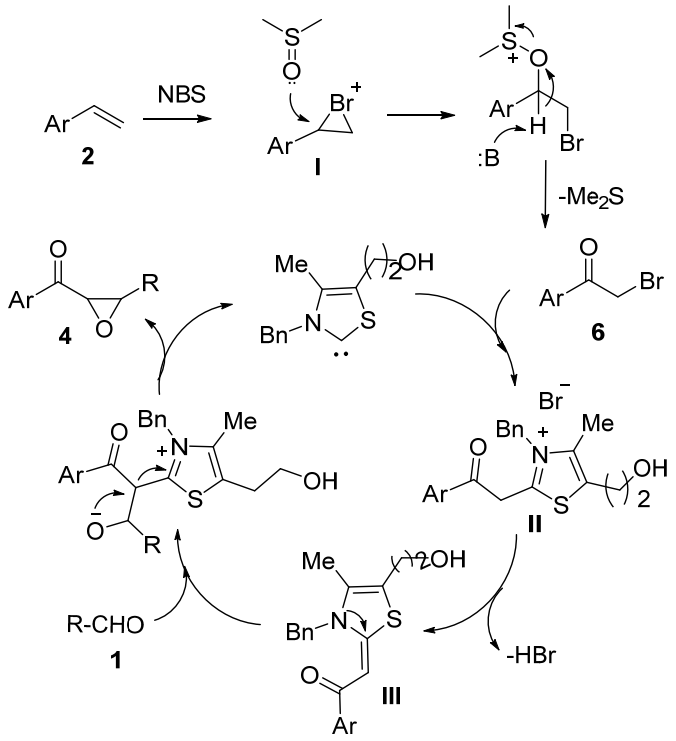
hydrogen, while its ^{13}C NMR spectrum showed two characteristic carbon signal at δ 191.4 and 167.0 attributed to carbonyl carbons (-**C**=O) (**Fig. 6**).

In order to explore the mechanism further, some stoichiometric experiments have been carried out (**Scheme 28**). When styrene was treated with 1 equiv of NHC catalyst **1g** in the absence of aldehyde under standard condition, ketodeoxy-Breslow intermediate (**II**) was isolated in 48% yield, which was also formed when phenacyl bromide was treated with NHC catalyst **1g** under basic condition both in the absence or presence of aldehyde **3f (**as confirmed by its HRMS spectrum: m/z 374.1186). This proves that, NHC preferably reacts with phenacyl bromide rather than its conventional reaction partners (aldehyde or alkene) under the optimized reaction condition. Furthermore, when intermediate **II** was treated with 4-nitrobenzaldehyde (**3f**) in DMSO, the corresponding epoxy ketone **4f** was isolated in 64% yield.



Scheme 28: Stoichiometric experiments to probe mechanism.

Based on the aforementioned results and previous reports,[25] a probable catalytic cycle for this NHC-catalyzed oxidative functionalization of styrenes is outlined in **Scheme 29**. Initially, styrene reacts with NBS to form bromonium ion **I**, which undergoes regioselective ring opening with DMSO followed by Me_2S elimination giving phenacyl bromide **6**. Further, NHC reacts with phenacyl bromide to form intermediate **II** which



Scheme 29: Probable mechanism for oxidative coupling of aldehydes with styrenes / α-bromoketones

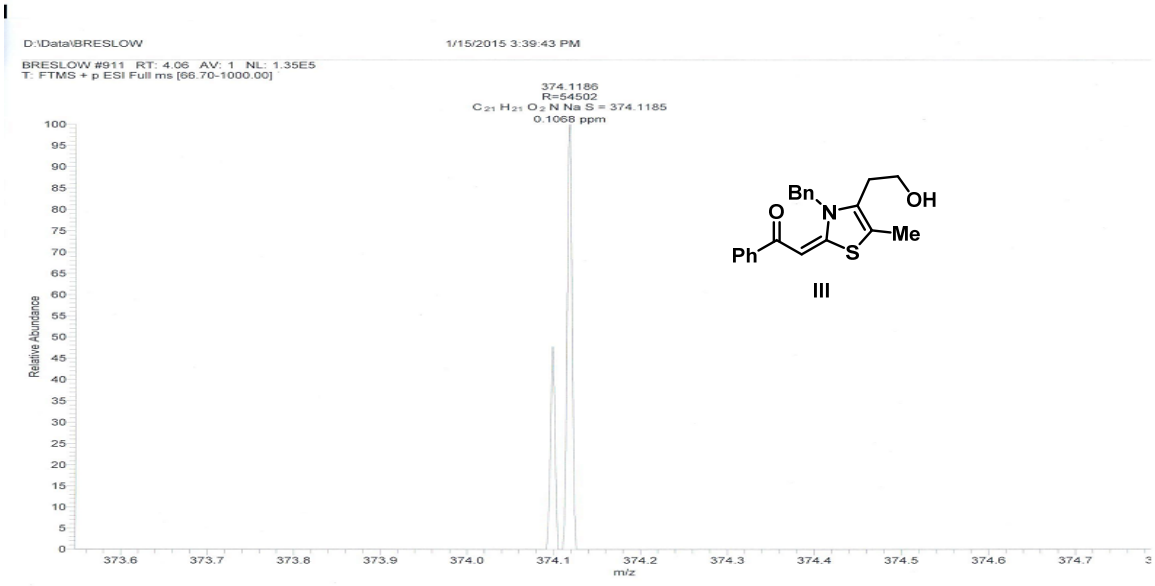


Fig 7: HRMS spectrum of ketodeoxy Breslow intermediate (**III**)

tautomerizes to give ketodeoxy-Breslow intermediate **III**. Finally, species **III** reacts with aldehyde followed by liberation of NHC catalyst furnishes the α,β-epoxy ketones **4**.

2.2.4 Conclusion

In summary, we have described, for the first time, a novel organocatalytic process in which an oxidative coupling of styrenes with aldehydes takes place leading to a facile synthesis of α,β-epoxy ketones **5a-m** in moderate to good yields with excellent dr (>95%). The procedure employs NHC in catalytic amounts (10 mol %) in combination with NBS-DBU-DMSO as oxidative system. An unconventional mechanistic course has been proposed based on isolated ketodeoxy-Breslow intermediate **III**. Further, α,β-epoxy ketones **5** were obtained by the reaction of α-bromoacetophenones **46** with aldehydes **3** (Darzens reaction) using NHC catalyst under mild basic condition. The salient features of the methodology are: (1) metal-free synthesis, (2) milder reaction conditions, (3) functional group tolerance and excellent regioselectivity.

2.2.5 Experimental section

General experimental procedure:

To a stirred solution of alkene (1 mmol) in degassed DMSO (8 mL), was added NBS (1 mmol), *N*-heterocyclic carbene precursor **1** (10 mol %), DBU (1.2 mmol) and aromatic aldehyde **3** (1.1 mmol) at 0 °C and the reaction mixture was then stirred at 25 °C under N_2 atmosphere. After completion of the reaction as monitored by TLC, it was quenched with H_2O (10 mL) at 0 °C. It was then extracted with EtOAc (3 x 20 mL) followed by washing with brine (3x20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Concentration of organic solvent under reduced pressure gave the

crude product, which was purified by column chromatography over silica gel using pet. ether /EtOAc (9:1) as eluent to obtain α,β-epoxyketone compounds **5a-m** in high purity.

Phenyl(3-phenyloxiran-2-yl)methanone (5a): Yield: 61%, colorless solid, mp: 88-90 ºC; **IR** (KBr, cm^{-1}): ν_{max} 1687, 1448, 1409, 1234, 756, 694; **^{1}H NMR** (200 MHz, $CDCl_3$); δ 4.07 (d, *J* = 1.8 Hz, 1H) 4.25 (d, *J* = 1.8 Hz, 1H) 7.36 - 7.40 (m, 5H) 7.48 - 7.52 (m, 2H) 7.57 - 7.66 (m, 1H) 7.99 - 8.04 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 59.2, 61.0, 125.8, 128.1, 128.4, 128.8, 128.8, 129.0, 133.9, 135.5, 192.8: **HRMS (ESI)**: $[M+Na]^+$ calcd for $[C_{15}H_{12}O_2+ H]^+$: 225.0910; found: 225.0909.

(3-(4-Bromophenyl)oxiran-2-yl)(phenyl)methanone (5c): Yield: 58%, colorless solid, mp: 86-88 °C; **IR** (KBr, cm^{-1}): ν_{max} 1663, 1438, 1297, 766; **^{1}H NMR** (200 MHz, $CDCl_3$); δ 4.05 (d, *J* = 1.8 Hz, 1H), 4.21 (d, *J* = 1.8 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.46 - 7.64 (m, 5H), 7.93 - 8.08 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 58.6, 61.0, 123.1, 127.4, 128.4, 128.9, 132.0, 134.0, 134.7, 135.5, 192.4: **HRMS (ESI)**: $[M+Na]^+$ calcd for $[C_{15}H_{11}BrO_2Na]^+$: 324.9835; found: 384.9835.

(3-(4-Chlorophenyl)oxiran-2-yl)(phenyl)methanone (5d): Yield: 63%, colorless solid; mp: 47-49 °C; **IR** (KBr, cm^{-1}): ν_{max} 789, 1022, 1228, 1687, 2883, 2936: **^{1}H NMR** (200 MHz, $CDCl_3$); δ 4.05 (d, *J* = 1.9 Hz, 1H), 4.21 (d, *J* = 1.8 Hz, 1H), 7.27 - 7.42 (m, 4H), 7.45 - 7.54 (m, 2H), 7.61 (d, *J* = 7.3 Hz, 1H), 7.93 - 8.07 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 58.0, 60.7, 127.9, 128.1, 128.5, 128.8, 131.5, 133.8, 134.5, 135.5, 191.4; **HRMS (ESI)**: $[M+Na]^+$ calcd for $[C_{15}H_{11}ClO_2+H]^+$: 259.0520; found: 259.0518.

(3-(4-Cyanoophenyl)oxiran-2-yl)(phenyl)methanone (5g): Yield: 66%, colorless solid; mp: 53-56 °C**; IR** (KBr, cm^{-1}): ν_{max} 763, 1322, 1428, 1689, 2143, 2883, 2936; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.15 (d, *J* = 1.8 Hz, 1H), 4.21 (d, *J* = 1.9 Hz, 1H), 7.47 - 7.56 (m,

4H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.68 - 7.75 (m, 2H), 7.96 - 8.06 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 58.0, 60.8, 76.4, 77.6, 96.1, 113.0, 118.0, 126.4, 128.4, 128.9, 132.5, 134.1, 135.3, 140.9, 191.8. **HRMS (ESI)**: $[M+Na]^+$ calcd for $[C_{16}H_{11}NO_2+H]^+$: 250.0863; found: 250.0861.

(3-(4-Nitrophenyl)oxiran-2-yl)(phenyl)methanone (5f): Yield: 72%, colorless solid; mp: 120-121 °C; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 745, 1233, 1451, 1519, 1598, 1692, 2850, 2923; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.21 (d, *J* = 1.7 Hz 1H), 4.25 (d, *J* = 1.7 Hz, 1H), 7.52 - 7.56 (m, 4H), 7.58 (m, 1H), 8.02 (d, *J* = 8.7 Hz, 2H), 8.29 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 57.9, 60.8, 124.1, 126.6, 128.4, 129.0, 134.3, 135.2, 142.7, 148.3, 191.9: **HRMS (ESI)**: $[M+Na]^+$ calcd for $[C_{15}H_{11}NO_4Na]^+$: 292.0580; found: 292.0577.

(3-(2-Nitrophenyl)oxiran-2-yl)(phenyl)methanone (5e): Yield: 68%, colorless solid, mp: 109-111°C; IR (KBr, cm^{-1}): ν_{max} 774, 1227, 1332, 1574, 1686, 2893, 2933; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 4.19 (d, *J* = 2.0 Hz, 1H), 4.64 (d, *J* = 2.0 Hz, 1H), 7.46 - 7.66 (m, 4H), 7.72 - 7.80 (m, 2H), 7.97 - 8.09 (m, 2H), 8.23 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 57.5 , 59.6, 124.9, 127.4, 128.5, 128.8, 129.3, 132.7, 133.9, 134.5, 135.4, 147.6, 192.2; **HRMS (ESI)**: $[M+Na]^+$ calcd for $[C_{15}H_{11}NO_4Na]^+$: 292.0580; found: 292.0579.

(3-Hexyloxiran-2-yl)(phenyl)methanone (5h): Yield: 51%, colorless liquid; **IR** (KBr, cm^{-1}): ν_{max} 752, 1237, 1246, 1710, 2863, 2940; **^{1}H NMR** (200 MHz, $CDCl_3$); δ 0.74 - 0.98 (m, 5H), 1.09 - 1.38 (m, 10H), 1.47 (d, *J* = 5.9 Hz, 4H), 3.34 - 3.52 (m, 1H), 4.26 (d, *J* = 4.7 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.58 - 7.67 (m, 1H), 7.90 - 8.14 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.9, 22.4, 26.1, 27.5, 28.8, 31.5, 57.5, 58.8, 128.2, 128.8,

133.8, 135.8, 193.8; **HRMS (ESI)**: $[M+Na]^+$ calcd for $[C_{15}H_{20}O_2Na]^+$: 255.1356; found: 255.1351.

(3-Isobutyloxiran-2-yl)(phenyl)methanone (5i): Yield: 62%, colorless liquid; **IR** (KBr, cm^{-1}): ν_{max} 766, 1347, 1446, 1708, 2846, 2962; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (d, *J* = 6.7 Hz, 3H), 0.98 (d, 3H), 1.19 (d, *J* = 7.1 Hz, 1H), 1.39 (d, *J* = 6.8 Hz, 2H), 3.39 - 3.54 (m, 1H), 4.29 (d, *J* = 4.8 Hz, 1H), 7.42 - 7.69 (m, 3H), 8.03 (d, *J* = 6.9 Hz, 2H): **HRMS (ESI)**: $[M+Na]^+$ calcd for $[C_{13}H_{16}O_2Na]^+$: 227.1043; found: 227.1039.

Ethyl 3-benzoyloxirane-2-carboxylate (5j): Yield: 65%, colorless liquid; **IR** (KBr, cm^{-1}): ν_{max} 656, 744, 1256, 1354, 1712, 1732, 2888, 2960; **^{1}H NMR** (200 MHz, $CDCl_3$); δ 1.35 (t, *J* = 7.1 Hz, 3H), 3.68 (d, *J* = 1.8 Hz, 1H), 4.31 (qd, *J* = 7.1, 0.9 Hz, 2H), 4.42 (d, *J* = 1.8 Hz, 1H), 7.45 - 7.72 (m, 3H), 8.04 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 58.0, 60.8, 76.4, 77.6, 96.1, 113.0, 118.0, 126.4, 128.4, 128.9, 132.5, 134.1, 135.3, 140.9, 191.8; **HRMS (ESI)**: $[M+Na]^+$ calcd for $[C_{12}H_{12}O_4Na]^+$: 243.0628; found: 243.0627.

(3-(4-Nitrophenyl)oxiran-2-yl)(p-tolyl)methanone (5k): Yield: 64%, colorless solid; mp: 122-123 °C; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 740, 1243, 1354, 1456, 1529, 1556, 1698, 1715, 2850, 2923; **^{1}H NMR** (200 MHz, $CDCl_3$); δ 2.46 (s, 3H), 4.15 - 4.27 (m, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.56 (m, *J*=8.8 Hz, 2H), 7.92 (m, *J* = 8.3 Hz, 2H), 8.26 - 8.34 (m, 2H); **^{13}C NMR** (101 MHz,$CDCl_3$) δ 21.9, 57.9, 60.8, 124.1, 126.6, 128.6, 129.7, 132.9, 142.9, 145.4, 148.4, 191.3; **HRMS (ESI)**: $[M+Na]^+$ calcd for $[C_{16}H_{13}NO_4Na]^+$: 306.0737; found: 306.0732.

(4-Bromophenyl)(3-(4-nitrophenyl)oxiran-2-yl)methanone (5l): Yield: 69%, colorless solid, mp: 128-129 °C; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 777, 1244, 1340, 1652, 1519, 1561, 1598, 1692, 1720, 2850, 2923; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.43 - 4.63 (m, 2H), 7.50 (d, *J* =

8.6 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 2H), 8.13 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 57.5, 60.3, 123.5, 127.5 , 129.6, 129.7, 132.4, 139.9, 189.9; **HRMS (ESI)**: $[M+Na]^+$ calcd for $[C_{15}H_{10}BrNO_4Na]^+$: 369.9691; found: 369.9692.

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CHAPTER III

I_2 Catalyzed Oxo- and Hydroxy-acyloxylation of Alkenes with Carboxylic acids and Formal Synthesis of (S,S)-Reboxetine

1. I_2-Catalyzed Regioselective Oxo- and Hydroxy-acyloxylation of Alkenes and Enol Ethers: A Facile Access to α-Acyloxyketones, Esters, and Diol Derivatives **Rambabu N. Reddi**, Pragati Kishore Prasad, Arumugam Sudalai; *Org. Lett.* **2014**, *16*, 5674.

2. Oxidant Controlled Regio- and Stereodivergent Azidohydroxylation of Alkenes *via* I_2 Catalysis; Pragati Kishore Prasad, **Rambabu N. Reddi**, Arumugam Sudalai; *Chem. Commun*, **DOI:** 10.1039/C5CC02374B.

Section I

I_2-Catalyzed Regioselective Oxo- and Hydroxy-Acyloxylation of Alkenes and Enol ethers: A Facile Access to α-Acyloxyketones and Diol Derivatives

3.1.1 Introduction

In organic synthesis, molecular iodine has been used extensively in various reactions.[1] It can act as a mild oxidizing reagent to generate carbonyl compounds from alcohols[2] and has mild Lewis acidic properties; hence, it is often used as a catalyst in esterifications[3] and in protecting group chemistry.[4] The unique properties of this element, in particular in direct comparison with the other halogens, are summarized:

(1) Iodide anions are easily oxidized by inorganic and organic peroxides into molecular iodine (I_2) or the corresponding oxy acids (in particular hypoiodite $[IO]^-$, iodite $[IO_2]^-$ and iodate $[IO_3]^-$). The oxy acids themselves can also be interconverted by terminal oxidants or by disproportionation.

(2) Molecular iodine has the lowest homolytic dissociation energy among the non-radioactive halogens (151 kJ/mol), which makes one-electron-transfer processes attractive. This is one of two possible modes of activation for oxidation catalysis.

(3) After astatine, iodine has the lowest electronegativity (2.2) among the halogens. Therefore, it is much easier to generate the monocationic iodine species ('I^+') *in situ* than monocationic bromine or chlorine derivatives.

(4) Last but not least, I_2 and its salts have a low toxicity and are non-hazardous, in particular, compared to bromine and transition-metal-based oxidation catalysts. Thus,

they are ideal candidates as catalysts in environmentally benign processes. Based on these properties, two different reaction types can be formulated in iodine-mediated oxidative couplings: (a) A 'radical'-based oxidative coupling pathway, and (b) an '*in situ* iodination' based oxidative coupling pathway. This easy conversion of different oxidation states is mandatory in oxidation catalysis.

Even, stoichiometric iodine was used in many organic transformations, its catalytic version was developed in 1998 by Komatsu and co-workers. They have reported first iodine catalyzed aziridination of olefins using chloramine-T as the co-oxidant.[5] In recent times, I_2 catalysis, in combination with either aq. H_2O_2 or *tert*-butyl hydroperoxide as water soluble co-oxidants, has been increasingly explored as environmentally benign and inexpensive oxidation reagents in place of rare or toxic heavy metal oxidants. To the best of our knowledge, use of catalytic electrophilic iodine in combination with stochiometric co-oxidants is not known.

3.1.2 Review of Literature

Literature survey revealed that there are few methods available for the synthesis of α-acyloxyketones **2** and diol derivatives **3**. In section 1 of chapter 2, the literature methods for the synthesis of α-acyloxyketones and esters have been discussed. Some of the recent developments for the synthesis of diol derivatives have been discussed below.

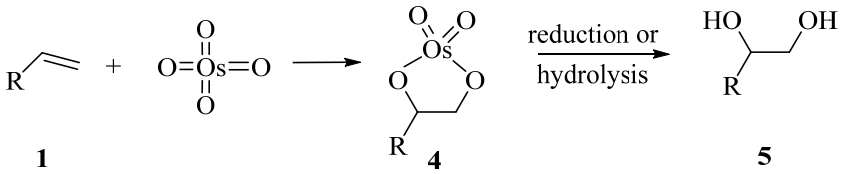
The dihydroxylation of alkenes is best method as it needs no prefunctionalization of starting materials. Based on the reagents used, the dihydroxylation methods can be divided into the following categories.

1. Metal oxide addition to olefin
2. Prevost-Woodward type reaction

The above types of dihydroxylation are briefly discussed below.

Metal oxide addition to olefin

OsO_4 catalyzes the *cis*-dihydroxylation of alkenes by hydrogen peroxide or related sources of oxygen atoms in the presence of water. In terms of mechanism, OsO_4 adds to alkenes to afford cyclic osmate esters **4** which undergo hydrolysis to give the *vic* diols 5 (**Scheme 1**).[6]



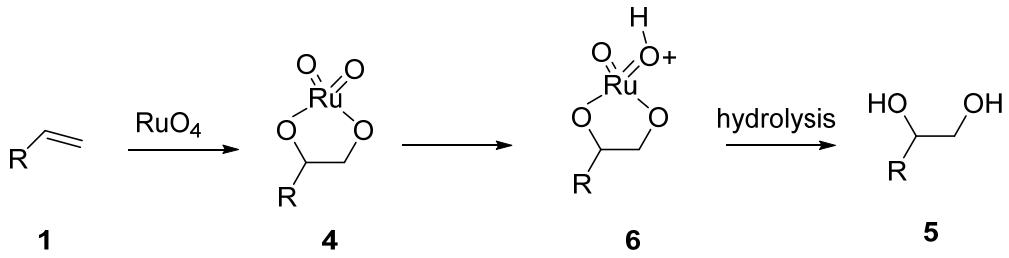
Scheme 1: OsO_4-catalyzed dihydroxylation of olefins

Lewis bases such as tertiary amines and pyridines were found to increase the rate of the reaction. This "ligand-acceleration" arises *via* the formation of adduct OsO_4-L, which adds more rapidly to the alkene. If the amine is chiral, then the dihydroxylation can proceed with enantioselectivity (see Sharpless asymmetric dihydroxylation).[6]

Since OsO_4 is toxic and expensive, it is used in catalytic amounts. The osmium catalyst is regenerated by oxidizing agents, such as H_2O_2, *N*-methylmorpholine *N*-oxide (NMO) and $K_3Fe(CN)_6$. These oxidizing reagents do not react with the alkenes on their own. Other sources of osmium tetroxide include potassium osmate(VI) dihydrate ($K_2OsO_4 \cdot 2H_2O$) and osmium (III) chloride hydrate ($OsCl_3.xH_2O$), which oxidize osmium (VI) to osmium (VIII) in the presence of above mentioned oxidants.

Despite its success, some problems still need to be solved. The oxidation is limited to electron-rich or mono-, di- and in some cases, trisubstituted olefins. Furthermore, the

osmium catalyst is toxic and very expensive. RuO_4, as a dihydroxylation catalyst, is most promising. In 1954, Djerassi introduced RuO_4 in organic chemistry. Since then, it has mainly been used for the degradation of unsaturated organic compounds. However, in ethyl acetate/acetonitrile/water a very fast dihydroxylation of olefins using 7 mol % of RuO_4 was observed (**Scheme 2**). Longer reaction times resulted in the formation of fission products. Thus, treatment of olefin **1** with catalytic $RuCl_3$, $NaIO_4$ as reoxidant in ethyl acetate/acetonitrile/water solvent system in the presence of acid produced the corresponding diols **5** in excellent yields. The reaction proceeds *via* the cyclic ruthenium ester **6**.[7]

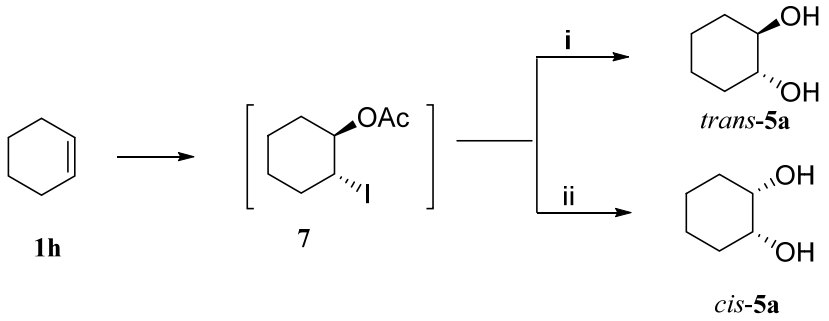


Scheme 2: RuO_4-catalyzed dihydroxylation of olefins

Prevost-Woodward type reaction

Prevost-Woodward reaction

The Prevost reaction[8] and its Woodward modification[9] are important methods for the preparation of *trans* and *cis* 1,2-diols respectively with excellent yields. These reactions involve the treatment of an alkene with iodine and silver(I) carboxylate. Both reactions are considered to proceed through *trans*-iodocarboxylate **7**, which by interaction of

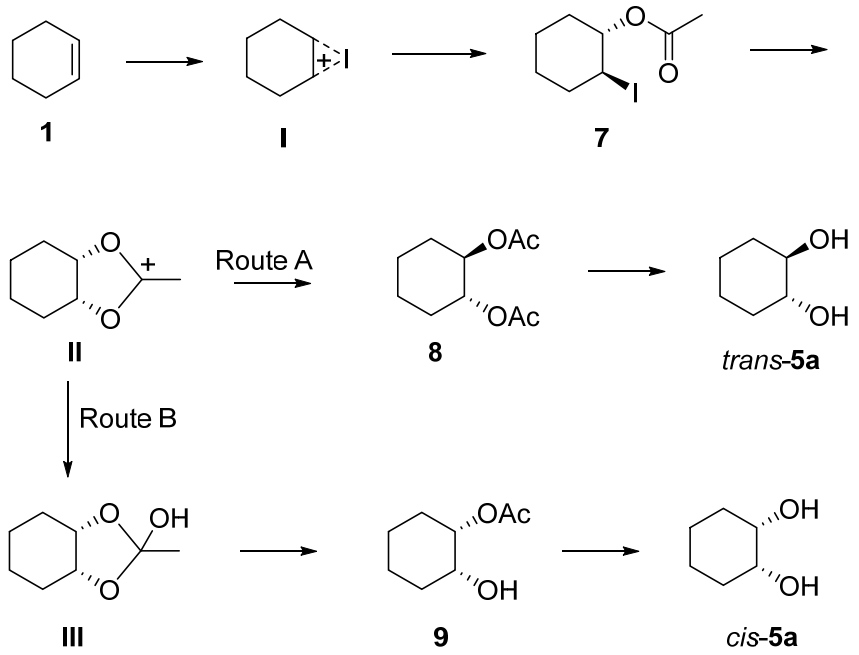


Scheme 3: (i) a) I_2, $PhCO_2Ag$ (2 equiv.), AcOH, 85 ºC; b) K_2CO_3, MeOH, 25 °C. (ii) a) I_2, $PhCO_2Ag$ (1 equiv.), AcOH, H_2O, 85 ºC; b) K_2CO_3, MeOH, 25 °C.

neighbouring acyloxy group and displacement with water or acetoxy group results in the formation of *syn* or *anti* diol derivatives depending upon the reaction conditions (**Scheme 3**). The alkaline hydrolysis of these diol derivatives gives the corresponding *trans* and *cis* diols **5a** respectively.

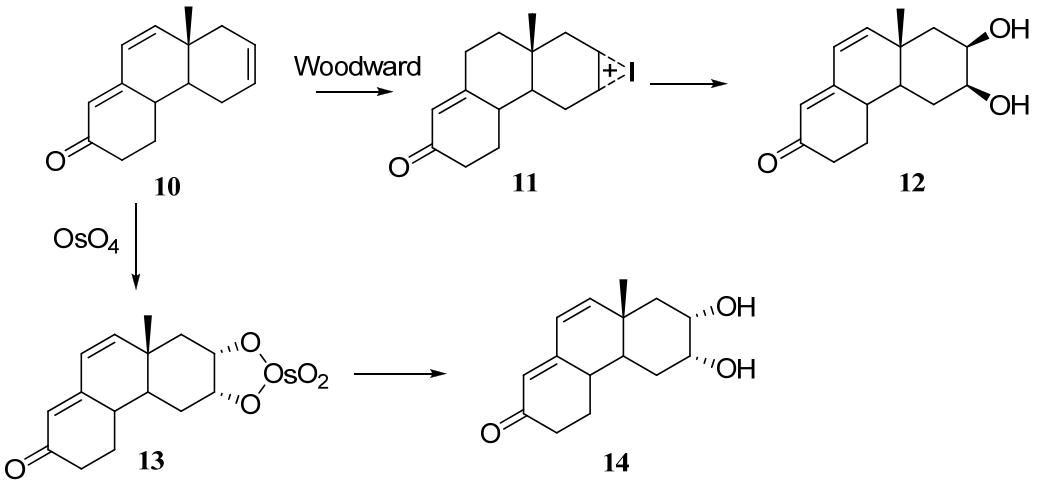
Mechanistically, in the first step of the reaction iodine adds to cyclohexene (**1h)** to form iodonium ion **I**, which is opened with nucleophilic silver(I) carboxylate to give *trans* 2-iodocyclohexyl acetate (**7, Scheme 4**). Iodo acetate **7** can be isolated in quantitative yield from the reaction by conducting the reaction at lower temperature and lesser equivalent of metal carboxylate. Neighboring group participation of the acetate group displaces the iodine to produce 1,3-dioxolan-2-ylium intermediate **II**. Under anhydrous condition (Prevost condition), acetate ion attacks the cyclic intermediate at C-4 position to furnish *trans*-diacetate (**8**, route **A**). On the other hand, in the presence of water (Woodward condition), the intermediate is attacked by the water molecule at C-2 position to produce hydroxy acetate (**9**) with *syn* stereochemistry (route **B**).

Woodward noted that his modification of the Prevost reaction offers the opposite facial selectivity as compared to oxidation with OsO_4 in the dihydroxylation of synthetic steroid



Scheme 4: Mechanism of Prevost-Woodward reaction

intermediate **10**. Here, the steric approach factors first direct the stereochemistry of the iodination which is followed by hydroxylation from the opposite face to furnish *cis* diol **12** whereas oxidation with OsO_4 leads to the isomeric *cis* diol **14** by direct attack of OsO_4 from the most accessible face *via* osmate ester **13** (**Scheme 5**).



Scheme 5: Comparison of facial selectivity between Woodward and OsO_4 dihydroxylations

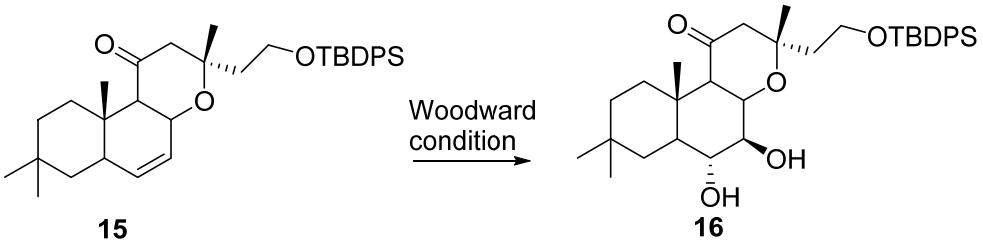
However, Prevost-Woodward reaction suffers from the following disadvantages;

i) Woodward reaction affords only low yields of *cis* diols with tri- or tetra substituted olefins.

ii) Highly activated aromatic rings like 2-allyl phenol undergo aromatic iodination to give 2-allyl 6-iodophenol.

iii) The deactivated olefins like alkyl cinnamates are less reactive or unreactive under this reaction condition.

iv) Often sterically hindered olefins fail to produce the desired diol derivatives. For example, the olefin **15** gave the corresponding *trans* 1,2-diol **16** even in the presence of water (Woodward condition). The reason for non-participation of water was discussed in terms of sterical hindrance that prevents nucleophilic attack of water to the acetoxonium ion (**Scheme 6**).[10]



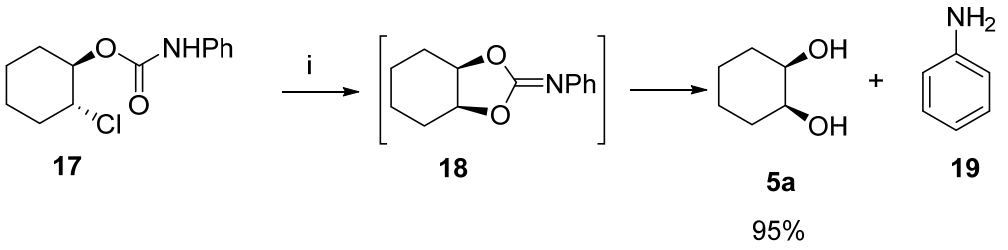
15 **16**

Scheme 6: Unprecedented Prevost reaction under Woodward condition

Since Prevost-Woodward reaction serves as a mild and efficient method to prepare diols, several modifications in the reagent system have been attempted. Several metal carboxylates like Cu, Bi, Hg (II) were employed as acetate sources and *N*-bromoacetamide, I_2, Br_2, *N*-bromosuccinamide were screened as halogen sources. Some of the modifications are briefly discussed below.

Fenton's approach (1970)[11]

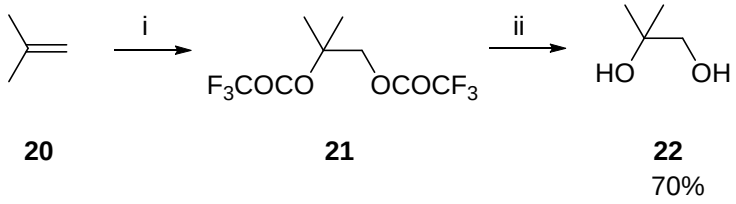
Fenton *et al.* found that when *trans* 2-*N*-phenylurethane cyclohexyl chloride (**17**) was heated in aqueous ethanol for 70 h in a sealed tube, *cis*-1,2-cyclohexane diol (**5a**) was formed in 95% *via* dioxane intermediate **18**. Aniline (**19**) was also separated as the by product (**Scheme 7**).



Scheme 7: (i) aq. EtOH, 90 ^{o}C, sealed tube, 70 h.

Buddrus' approach (1973)[12]

Buddru's *et al.* have found that iodine tris(trifluoroacetate) oxidizes olefins to diols. Thus, addition of olefin **20** to a solution of iodine tris(trifluoroacete) in pentane followed by hydrolysis resulted in the formation of *vic*-diol **22** in 50-70% yields *via* diacetate **21** (**Scheme 8**).

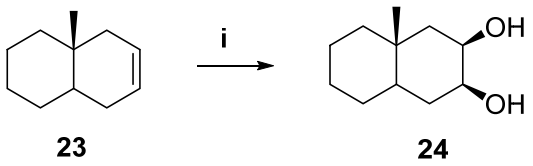


Scheme 8: (i) $I(OCOCF_3)$, pentane, 25 ^{o}C; ii) K_2CO_3, MeOH, 25 $^{\circ}$C, 5h.

Granger's approach (1976)[13]

N-Bromoacetamide (NBA) had also been employed as the halogen source to obtain bromoacetoxy derivative. When deccalin derivative **23** was treated with *N*-

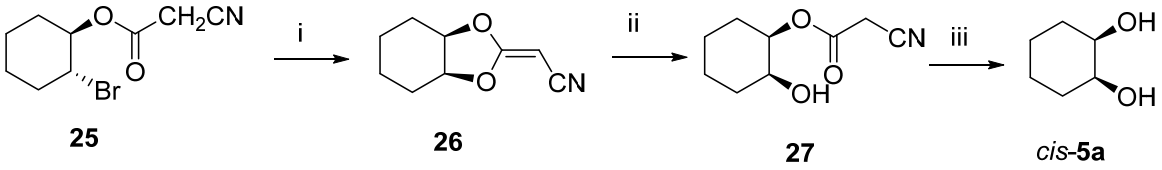
bromoacetamide (NBA) and silver(I) benzoate in wet acetic acid produced *syn* diol derivatives, which on hydrolysis produced *cis*-diol **24** (**Scheme 9**).



Scheme 9: (i) a) NBA, $PhCO_2Ag$ (1 equiv), AcOH, H_2O, 85 ºC; b) K_2CO_3, MeOH, 25 ^oC, 74%.

Corey's approach (1976)[14]

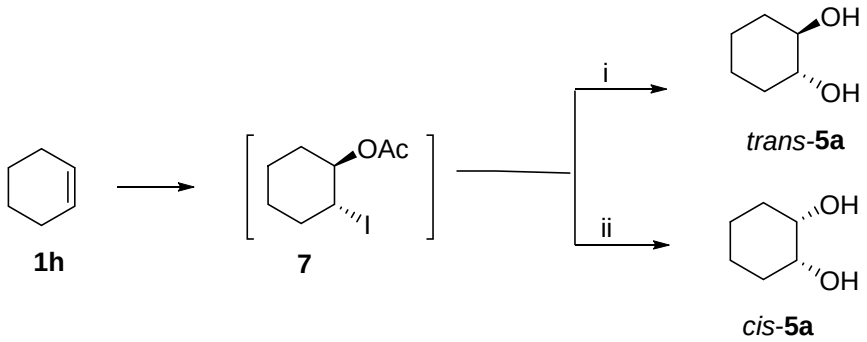
Corey *et al.* have reported an efficient method for the synthesis of *syn* diols that involves cyano acetic ester as the intermediate. Accordingly, reaction of the cyanoacetate ester **25** with excess of NaH generated the corresponding enolate, which underwent intramolecular nucleophilic displacement to form cyanoketone acetal **26**. Hydrolysis of **26** using 1N HCl produced the mono cyanoacetate **27**, which upon alkaline ester hydrolysis afforded *cis* diol **5a** (**Scheme 10**).



Scheme 10: (i) NaH (excess), THF, 0 ^oC; ii) 1N HCl, 25 ^oC; iii) aq. KOH, 80 ^oC, 79%.

Trainor's approach (1992)[15]

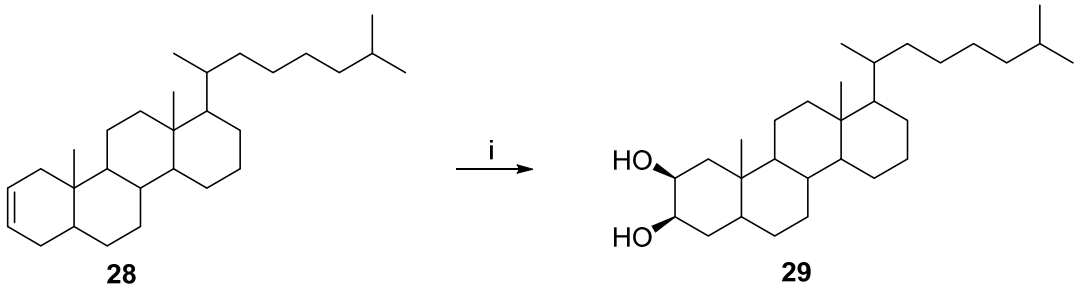
cis and *trans* Cyclohexane 1,2-diols (**5**) were prepared from cyclohexene (**1h**) by reaction with I_2 and bismuth(III) acetate in wet and dry acetic acid respectively. Reaction using lesser amounts of $Bi(OAc)_3$ under dry conditions gave the intermediate *i.e trans* 2-iodocyclohexyl acetate (**7**) (**Scheme 11**).



Scheme 11: (i) I_2, $Bi(OAc)_3$ (2 equiv), AcOH, 85 ºC; b) K_2CO_3, MeOH, 25 °C. (ii) (a) I_2, $Bi(OAc)_3$ (1 equiv.), AcOH, H_2O, 85 ºC; b) K_2CO_3, MeOH, 25 °C.

Welzel's approach (2000)[16]

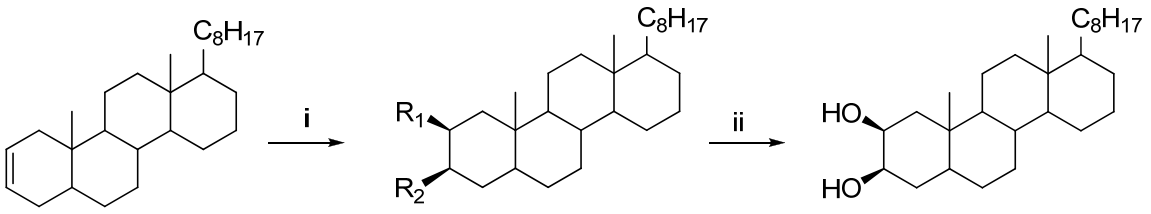
Welzel *et al.* replaced silver(I) benzoate or acetate with mercuric(II) acetate to get diol derivatives even in hindered cholestane. Cholestane **28** was treated with mercuric(II) acetate and iodine in wet acetic acid at 85 °C to get diol derivatives. The diol derivatives are further hydrolyzed under basic conditions to obtain the diol **29** (**Scheme 12**).



Scheme 12: i) a) I_2, $Hg(OAc)_2$ (1 equiv.), AcOH, H_2O, 85 ºC; b) aq. KOH, 50 °C.

Horiuch's approach (2006)[17]

Horiuch *et al.* have used copper(II) acetate as a better alternative to silver(I) benzoate. The reaction of cholest-2-ene (**30**) with iodine and copper(II) acetate in acetic acid under refluxing conditions yielded diol derivatives **31** and **32** which upon hydrolysis furnished diol **33** (**Scheme 13**).

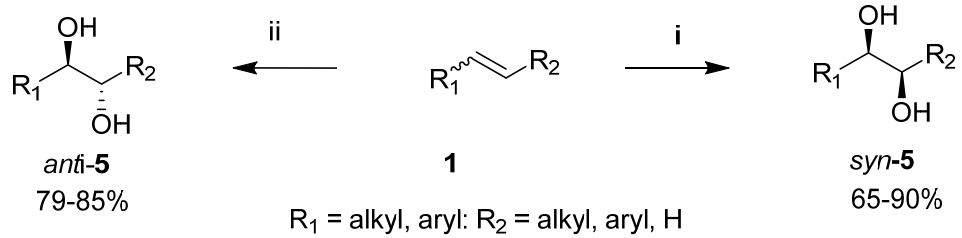


30 **31**, $R_1 = OH$; $R_2 = OCOCH_2I$ **33**
32, $R_1 = OCOCH_2I$; $R_2 = OH$

Scheme 13: (i) a) I_2, $Cu(OAc)_2$ (1 equiv), AcOH, H_2O, 85 ºC; ii) K_2CO_3, MeOH, 25 ^oC, 69-74%.

Sudalai's approach (2005)[18]

Sudalai *et al.* have reported a catalytic version for Woodward-Prevost dihydroxylation reaction. LiBr catalyzes efficiently the dihydroxylation of alkenes **1** to afford *syn* and *anti* diols with excellent diastereoselectivity depending upon the use of $NaIO_4$ (30 mol %) or $PhI(OAc)_2$ (1 equiv) respectively as the oxidants. The oxidation of non-benzylic halides has been achieved for the first time to afford the corresponding diols in excellent yields (**Scheme 14**).



anti-**5** 79-85% **1** *syn*-**5** 65-90%

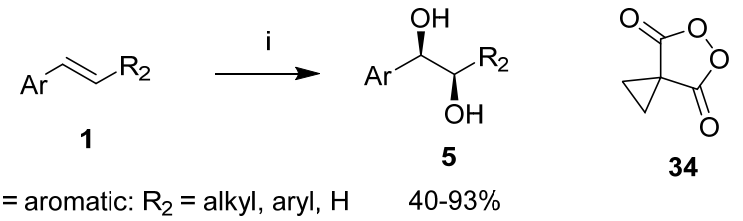
R_1 = alkyl, aryl: R_2 = alkyl, aryl, H

Scheme 14: (i) styrene, $NaIO_4$ (30 mol %), LiBr (20 mol %), AcOH, 95 °C, 18 h then K_2CO_3, MeOH, 25 °C, 24 h. (ii) styrene, $PhI(OAc)_2$ (1 equiv), LiBr (20 mol %), AcOH, 95 °C, 18 h then K_2CO_3, MeOH, 25 °C, 24 h.

Tomkinson's approach (2010)[19]

Tomkinsons *et al.* have developed cyclopropyl malonoyl peroxide (**34**), which can be prepared in a single step from the commercially available diacid, is an effective reagent for the dihydroxylation of alkenes **1**. Reaction of **34** with an alkene **1** in the presence of 1

equiv of water at 40 °C followed by alkaline hydrolysis leads to the corresponding diol **5** (40-93%). With 1,2-disubstituted alkenes, the reaction proceeds with *syn*-selectivity (3:1 to >50:1) (**Scheme 15**).

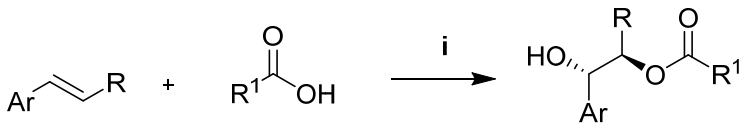


Scheme 15: (i) Melonyl peroxide (1.2 equiv), H_2O (1 equiv), $CHCl_3$, 40 °C, then aq. NaOH, 60 °C, 4 h.

In another approach (2012),[20] Tomkinson *et al,* have found the effect of fluorinated alcohols on the dihydroxylation of alkenes using cyclopropyl malonyl peroxide **34**. Addition of perfluoro-*tert*-butyl alcohol to a toluene solution (instead of $CHCl_3$) of alkene and peroxide increases the rate of product formation and stereoselectivity observed, providing a simple and effective method for acceleration of this important class of reaction. Basic hydrolysis of the crude reaction mixture provides access to *syn*-diol **5** in high yield and stereoselectivity.

Zhu's approach (2014)[21]

Zhu *et al.* has reported a new synthetic approach toward difunctionalization of alkenes under metal-free conditions. Various carboxylic acids and amines could react smoothly with alkenes to give dioxygenation and oxyamidation products, respectively. This organocatalytic process delivers 2-hydroxy alcohols directly from simple alkenes with high levels of regioselectivity. (**Scheme 16**).



1 **35** **3**

Ar = aryl: R = alkyl, aryl, H
R^1 = aryl, alkyl

40-93%

Scheme 16: (i) TBAI (10 mol %)), 70% aq. TBHP, *n*-hexane, 120 °C, 4 h.

3.1.3 Present Work

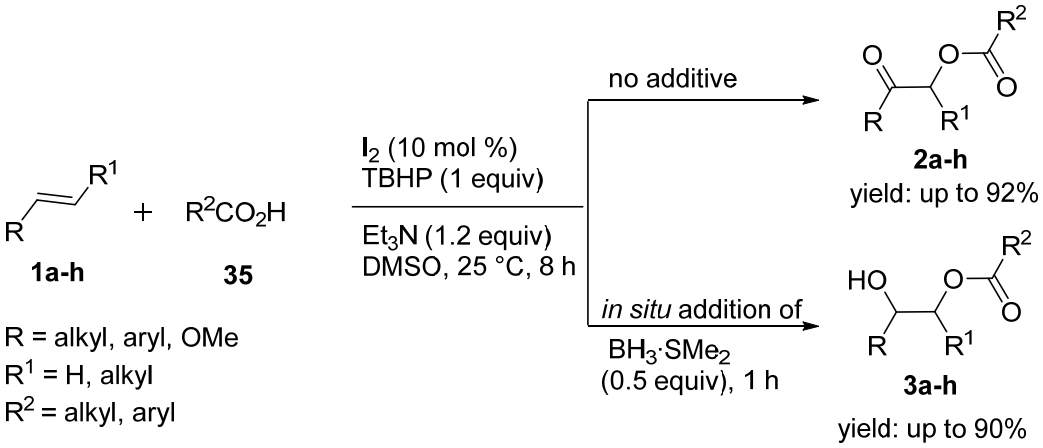
3.1.3.1 Objectivev

Although there are many methods available in the literature for the synthesis of diol derivatives, several of them suffer from certain drawbacks like low yields, cumbersome experimental procedures, use of expensive air and moisture sensitive or highly toxic catalysts. Hence, there arises a necessity to develop an efficient procedure for the synthesis of α-acyloxy ketones **2** and diol derivatives **3** from commercially available starting materials, under ambient conditions.

3.1.3.2 Results and Discussion

To the best of our knowledge, use of catalytic electrophilic iodine in combination with stoichiometric co-oxidants for functionalization of alkenes is not known. In this section, we describe for the first time, a catalytic modification of Woodward-Prevost oxidation for C-O bond formation using I_2/TBHP catalyzed oxo-acyloxylation of alkenes and enol ethers with carboxylic acids in DMSO as solvent and Et_3N as base, giving α-acyloxyketones (**2a**-**h**) in high yields and excellent regioselectivity (99%). In addition, one-pot "hydroxy-acyloxylation" has been described by sequential addition of $BH_3{\cdot}SMe_2$

in the reaction mixture that produces mono protected diol derivatives (**3a**-**h**) in excellent yields (**Scheme 17**).

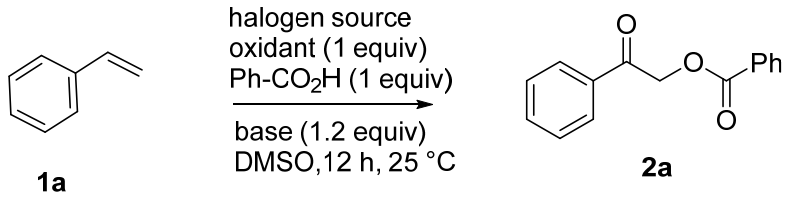


Scheme 17: I_2-catalyzed oxo- and hydroxy acyloxylation of alkenes.

Initially, when styrene (1 mmol) was treated with a mixture containing benzoic acid (1 mmol), NBS (1 mmol) and Et_3N (1.2 mmol) at 25 °C in DMSO, the corresponding α-benzyloxyketone **2a** was obtained in 89% isolated yield with excellent regioselectivity (>99%) (**Table 1**). When *stoichiometric* amount of I_2 was used as halogen source, **2a** (90% yield) was indeed obtained with perfect regioselectivity. Encouraged by the result, it was of interest to develop a *catalytic* version of this useful oxo-acyloxylation process**.**

Thus, a series of experiments were conducted employing I_2 in catalytic amounts (10 mol %) along with other stoichiometric oxidants like aq. H_2O_2, $NaIO_4$, Oxone or TBHP, which gave **2a** in 13, 15, 8 and 88% yields, respectively. With 5 mol % of I_2, a lowered yield of **2a** (53%) was however observed. Further modification in iodine source, base or solvent system (DMSO in combination with other solvents) did not show any significant improvement in the product yield (**Table 1**).

Table 1: I_2-catalyzed oxo-acyloxylation of styrene with carboxylic acids: optimization studies[a]



1a **2a**

s.no.	halogen (10 mol %)	oxidant (1 equiv)	base	yield of **2a**[b]
1	NBS[c]	-	Et_3N	89
2	I_2[c]	-	Et_3N	90
3	I_2	50% H_2O_2	Et_3N	13
4	I_2	$NaIO_4$	Et_3N	15
5	I_2	Oxone	Et_3N	8
6	NaI	TBHP	Et_3N	trace
7	$^nBu_4NI$	TBHP	Et_3N	11
8	I_2	TBHP	Et_3N	88 (53)[d] (89)[e]
9	I_2	TBHP	NaH	39
10	I_2	TBHP	KO^tBu	72
11	I_2	TBHP	DBU	67
12	I_2	TBHP	K_2CO_3	47

a:Reaction conditions: styrene (1 mmol), carboxylic acid (1 mmol), halogen source (10 mol %), base (1.2 mmol), TBHP (5-6 M in decane) (1 mmol); in 8 mL DMSO, 25 °C, 12 h; b:isolated yield after column chromatographic purification; c:1 equiv of halogen source was used; d:5 mol % of I_2 was used; e:20 mol % of I_2 was used.

The scope of the study was extended to substituted aromatics and alkenes; the results of which are subsequently displayed in **Table 2**. Several olefins with varied functional groups were found compatible in the reaction. Electron neutral (4-CH_3), electron-deficient and -rich groups on the aromatic nucleus were compatible and provided the

Table 2: I_2-catalyzed oxo- benzoyloxylation of alkenes with benzoic acid: substrate scope[a]

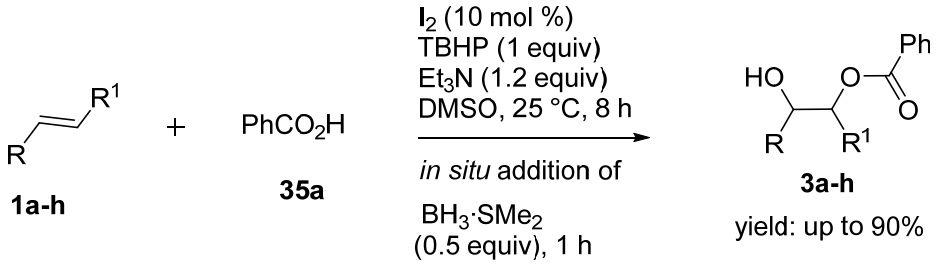
no.	alkene (**1**)	products	yields (%)[b]
1	styrene (**1a**)	**2a**	88
2	4-CH_3-styrene (**1b**)	**2b**	85
3	4-Br- styrene (**1c**)	**2c**	88
4	3,4 -$(OMe)_2$ styrene (**1d**)	**2d**	83
5	allyl acetate (**1e**)	**2e**	91
6	1-hexene (**1f**)	**2f**	88
7	1-octene (**1g**)	**2g**	92
8	cyclohexene (**1h**)	**2h**	82

a:see foot-note *a* under **Table 1**; b:isolated yields after column chromatographic purification.

corresponding products in excellent yields (81-86%). Similarly, aliphatic olefins were found compatible under the optimal conditions and provided (**2e-g**) in good yields (82–92%). Moreover, disubstituted alkenes (**1h**) underwent this oxo-acyloxylation smoothly providing the corresponding α-acyloxy ketone (**2h**) in high yields with excellent regioselectivity.

We envisioned that addition of $BH_3{\cdot}SMe_2$ to the reaction mixture would enable us to obtain the corresponding diol derivatives **3a-h** (**Table 3**). To our delight, we indeed found that several styrenes and aliphatic alkenes underwent this "oxo-acyloxylation-reduction" process smoothly affording diol derivatives **3a-h** in 81-90% yields and excellent chemoselectivity (99%). Remarkably, internal alkenes gave the desired products in good diastereomeric ratio (3:1) with high yields (**Table 1**, entry 8).

Table 3: I_2-catalyzed hydroxy benzoyloxylation of alkenes with benzoic acid: substrate scope[a]



s.no.	alkene (**1**)	products	yields (%)[b]
1	styrene (**1a**)	**3a**	86
2	4-CH_3-styrene (**1b**)	**3b**	84
3	4-Br- styrene (**1c**)	**3c**	86
4	3,4 -$(OMe)_2$ styrene (**1d**)	**3d**	81
5	allyl acetate (**1e**)	**3e**	89
6	1-hexene (**1f**)	**3f**	88
7	1-octene (**1g**)	**3g**	90
8	cyclohexene (**1h**)	**3h**	83 (3:1)[c]

[a]*in situ* addition of anhydrous Na_2SO_4 and $BH_3{\cdot}SMe_2$ (0.5 equiv) to conditions in foot-note *a,* in **Table 1**; [b]isolated yields after column chromatographic purification; [c]*anti:syn* ratio;

The structures of the compounds **2a-h** and **3a-h** were established based on the spectroscopic data.

Example 1: The ^{1}H NMR spectrum of 2-oxo-2-phenylethyl benzoate (**2a**) showed a typical singlet at δ 5.58 (s, 2H) for hydrogens of –O-C**H$_2$** group, while its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 191.6 attributed to carbonyl carbon -**C**=O and δ 66 for –O-**C**H_2 carbons (**Fig 1**).

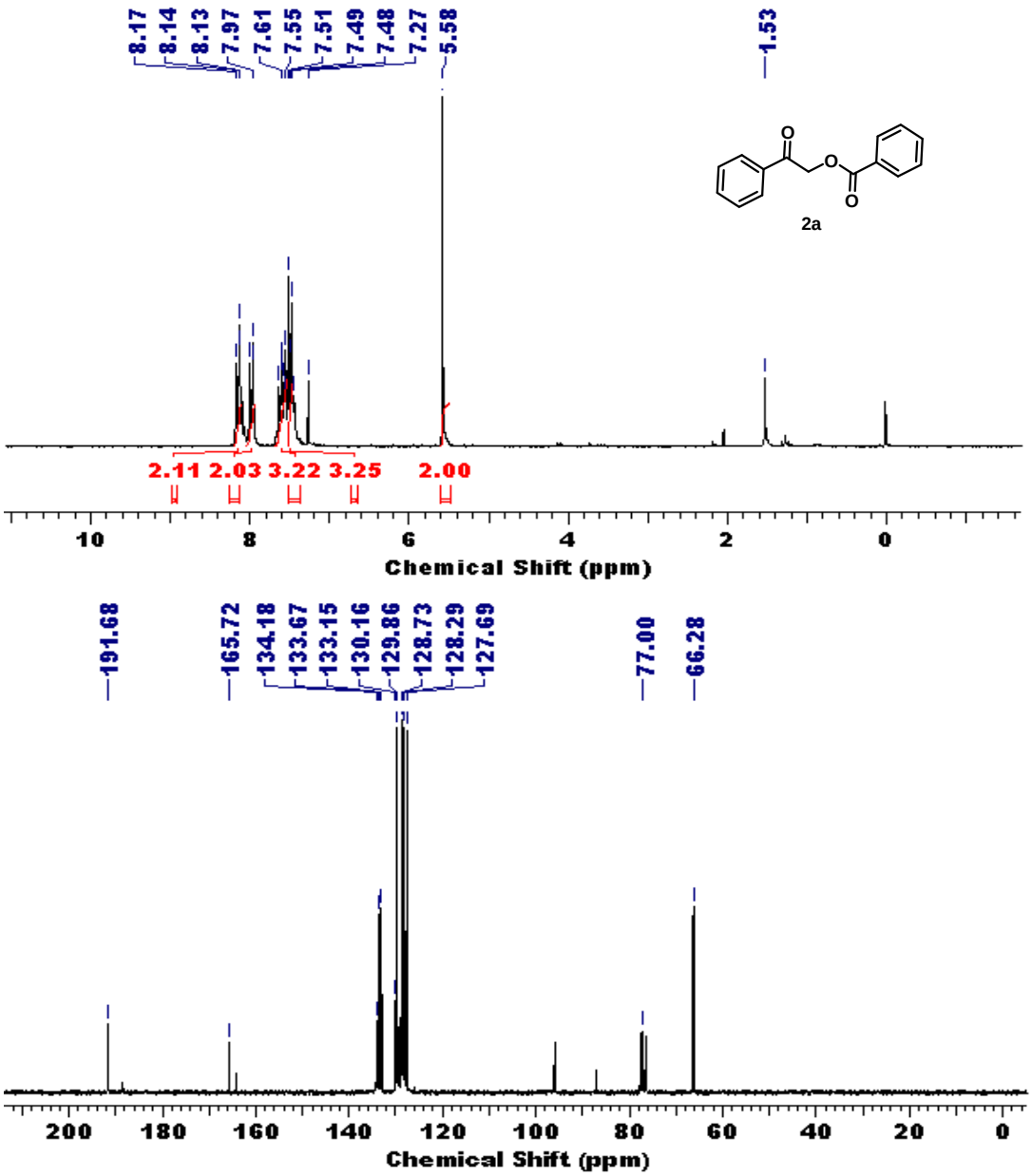


Fig. 1: ^{1}H and ^{13}C NMR spectra of **2a**

Example 2: The ^{1}H NMR spectrum of 2-hydroxyhexyl benzoate (**3g**) showed four typical proton signals at 2.09 (br. s., 1H) for –O**H** group, 3.97 (t, *J* = 9.0 Hz, 1H), for O-C**H** proton**,** 4.21 (dd, *J* = 11.4, 7.0 Hz, 1H) and 4.39 (dd, *J* = 11.4, 3.2 Hz, 1H) for diastreotopic protons of –OCH-C**H$_2$**- group, while its ^{13}C NMR spectrum showed three

characteristic carbon signals at δ 166.0 attributed to carbonyl carbon (-**C**=O) and δ 69.2 and 70.0 corresponding to —O**C**H-**C**H_2-carbons respectively (**Fig 2**).

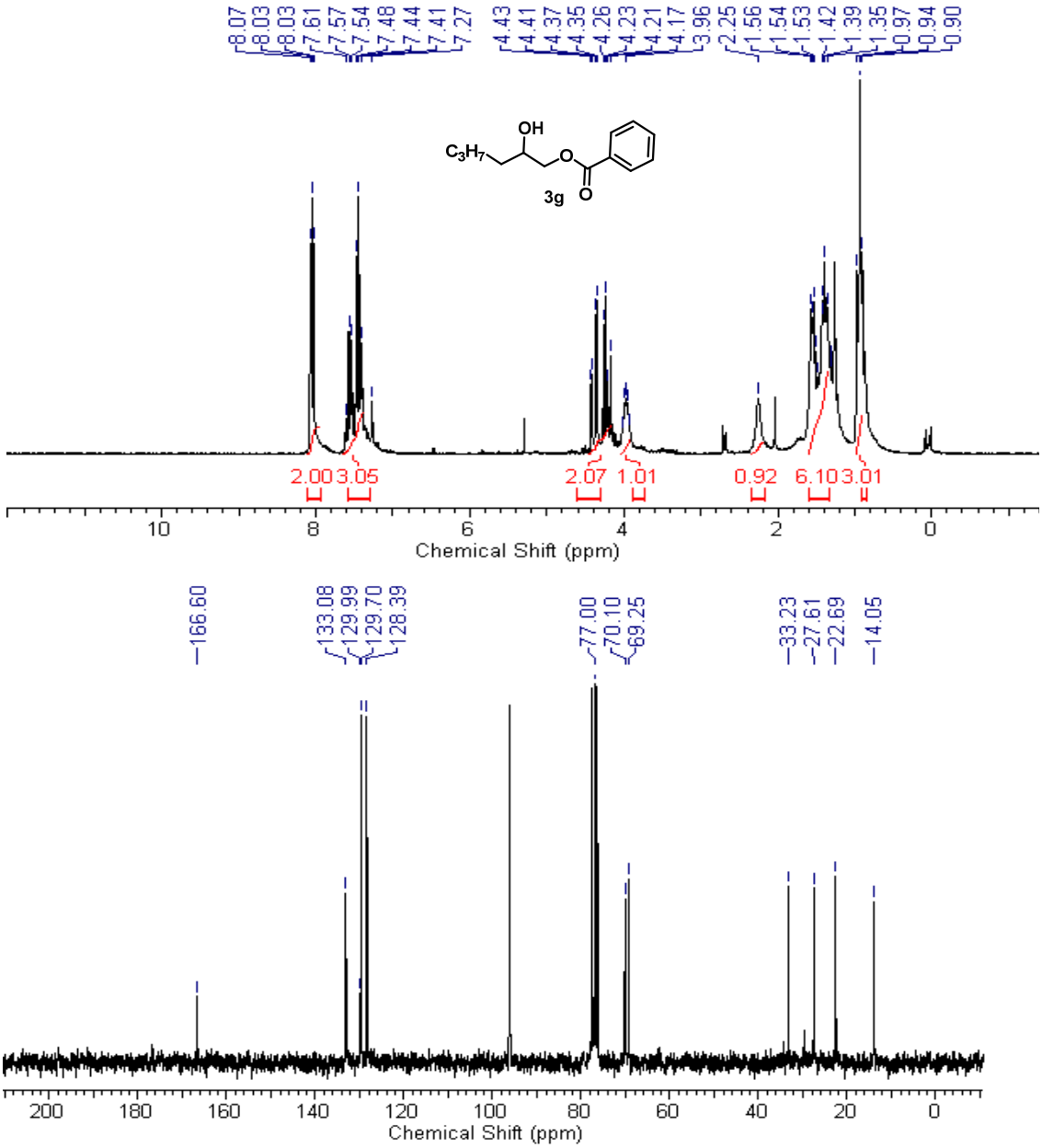
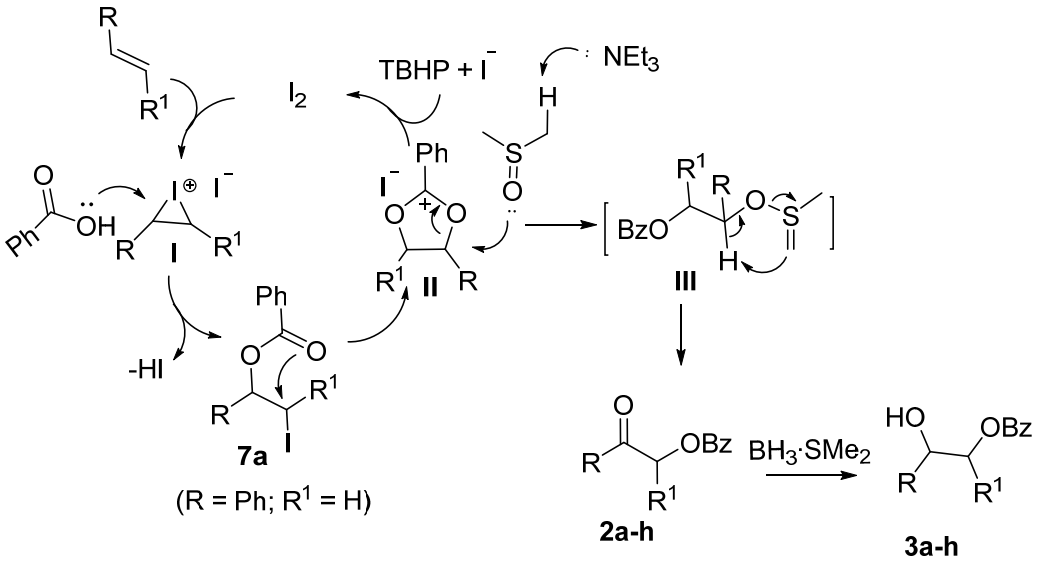


Fig. 2: ^{1}H and ^{13}C NMR spectra of **3g**

To gain some insight into the mechanism of the reaction, the following experiments were performed: (i) no reaction was observed in the absence of either benzoic acid or Et_3N; (ii) in the case of styrene, the iodo compound **7a** (where R = Ph, R_1 = H) was isolated (20%

yield after 2 h) and characterized completely (GC-MS, ^{1}H and ^{13}C NMR) which eliminates the role of hypervalent iodine in the mechanism; (iii) further treatment of **II** with DMSO and Et_3N afforded the desired product **2a** in 62% yield; (iv) **Table 1** (entry 2 and 8) suggests that TBHP can be used as a co-oxidant.

According to the aforementioned information and based on previous reports,[22] a plausible mechanism for this I_2-catalyzed oxidative functionalization of alkenes is outlined in **Scheme 18**.



Scheme 18: Probable catalytic cycle for oxo- and hydroxyl acyloxylation of alkenes

Initially, the substrate alkene reacts with I_2 to afford the iodonium ion intermediate **I**, which undergoes regioselective ring opening with benzoic acid giving the iodo compound **7a**. The proposed key intermediate species **II**, formed from **7a** by the anchimeric assistance shown by the benzoate group, reacts with DMSO in regioselective manner to give hydroxy ylide **III** with the liberation of iodide ion. Iodide ion is then reoxidized with TBHP to regenerate I_2 while elimination (-Me_2S) from **III** could then be

undertaken to provide the desired products **2a-h**, which on borane reduction gave diol derivatives **3a-h**.

3.1.4 Conclusion

In summary, we have demonstrated that the oxo- and hydroxy acyloxylation process of alkenes with carboxylic acids can be achieved using metal-free catalytic systems. This operationally simple and efficient method provides a new approach towards the synthesis of α-acyloxyketones (**2a-h**) and diol derivatives (**3a-h**) with a wide range of substrate scope. More importantly, this inexpensive catalyst-oxidant system provides for a single step, metal-free dihydroxylation process directly from alkenes, thereby complimenting OsO_4 catalyzed dihydroxylation of alkenes.

3.1.5 Experimental section

General experimental procedure for preparation of compounds 2a-h:

To a stirred solution of alkene (1 mmol) in dry DMSO (8 mL), I_2 (10 mol %), Et_3N (1.2 mmol), TBHP (1 mmol) and carboxylic acid (1.1 mmol) was added and the reaction mixture was then stirred at 25 °C under an N_2 atmosphere. After completion of the reaction (as monitored by TLC), it was quenched with H_2O (20 mL) at 0 °C. It was then extracted with EtOAc (3 x 20 mL) followed by washing with brine (3x20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Concentration of solvent under reduced pressure gave the crude product, which was then purified by column chromatography over silica gel using Pet. ether/EtOAc (9:1) as eluent to obtain α-acyloxy carbonyl compounds **2a-h** in high purity.

General experimental procedure for preparation of compounds 3a-h:

To a stirred solution of alkene (1 mmol) in dry DMSO (8 mL), I_2 (10 mol %), TBHP (1 mmol), Et_3N (1.2 mmol) and benzoic acid (1 mmol) were added and the resulting reaction mixture was then stirred at 25 °C under N_2 atmosphere. Once α-benzyloxy ketone (**2a-h**) was formed (monitored by TLC), Na_2SO_4 (10 mmol) and $BH_3.SMe_2$ (0.5 mmol) were added to the reaction mixture at 0° C. After completion of the reaction (monitored by TLC), it was quenched with ice and then H_2O at 0 °C. It was then extracted with EtOAc (3 x 20 mL) followed by washing with brine (3x20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure to give the crude product, which was then purified by column chromatography over silica gel using pet ether/EtOAc (8:2) as eluent to obtain diol derivative **3a-h** in high purity.

2-Oxo-2-phenylethyl benzoate (2a)

Yield: 88% (210 mg), colorless solid, mp: 119-120 °C; **IR** (Nujol, cm^{-1}): ν_{max} 705, 1015, 1374, 1459, 1596, 1714, 1750, 2851, 2923; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.58 (s, 2H), 7.48 - 7.61 (m, 6H), 7.97 - 8.13 (m, 2H), 8.14 - 8.17 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 66.2, 127.7, 128.2, 128.73, 129.9, 130.1, 133.1, 133.7, 134.2, 165.7, 191.7; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{15}H_{12}O_3$+Na: 263.0683; found: 263.0692.

2-Oxo-2-(p-tolyl)ethyl benzoate (2b)

Yield: 85% (216 mg), colorless solid, mp: 105-106 °C ; **IR** (Nujol, cm^{-1}): ν_{max} 713, 1135, 1231, 1289, 1459, 1604, 1698, 1732, 2840, 2923; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.47 (s, 3H), 5.57 (s, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.61 - 7.63 (m, 1H), 7.90 (d, *J* = 7.9 Hz, 2H), 8.17 (d, *J* = 7.3 Hz, 2H): **^{13}C NMR** (50 MHz, $CDCl_3$):

δ 21.8, 66.9, 123.5, 127.8, 129.6, 131.1, 131.5, 134.8, 145.1, 150.7, 164.1, 190.6; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{16}H_{14}O_3$+Na: 277.0840; found: 277.0848.

2-(4-Bromophenyl)-2-oxoethyl benzoate (**2c**)

Yield: 88% (280 mg), colorless solid, mp. 78-79°C; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 719, 967, 1115, 1124, 1701, 1723, 2848, 2930; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.52 (s, 2H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 8.7 Hz, 2H), 7.85 (d, *J* = 8.7 Hz, 2H), 8.09 - 8.18 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 66.2, 128.4, 128.6, 129.3, 129.9, 130.3, 132.2, 133.3, 165.7, 191.0: **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{15}H_{11}BrO_3$+Na: 340.9789; found: 340.9799.

2-(3,4-Dimethoxyphenyl)-2-oxoethyl benzoate (**2d**)

Yield: 83% (249 mg), colorless solid, mp: 121-123 °C**; IR** (Nujol, cm^{-1}): ν_{max} 720, 1031, 1161, 1255, 1460, 1685, 1725, 2857, 2925; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.91 (s, 3H), 3.94 (s, 3H), 5.51 (s, 2H), 6.87 (d, *J* = 7.9 Hz, 1H) 7.28 - 7.61 (m, 6H), 8.12 (d, *J* = 7.2 Hz, 2H): **^{13}C NMR** (100 MHz, $CDCl_3$): δ 55.8, 56.0, 66.0, 109.9, 110.0, 122.1, 127.3, 128.2, 129.4, 129.8, 133.0, 149.1, 153.7, 165.7, 190.2; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{17}H_{16}O_5$+Na: 323.0895; found: 323.0884.

3-Acetoxy-2-oxopropyl benzoate (2e)

Yield: 91% (214 mg), Colorless viscuss liquid ; **IR** (Nujol, cm^{-1}) ν_{max} 715, 1030, 1347, 1426, 1509, 1749, 1761, 2886, 2941: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.19 (s, 3H), 4.84 (s, 2H), 4.98 (s, 2H), 7.46 - 7.50 (m, 2H), 7.61 (t, *J* = 6.9 Hz, 1H), 8.09 (d, *J* = 8.7 Hz, 2H): **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.2, 66.2, 66.7, 128.5, 128.9, 129.9, 133.5, 165.5, 169.8, 197.6. **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{12}H_{12}O_5$+Na: 259.0582; found: 259.0576.

2-Oxohexyl benzoate (2f)

Yield: 88% (193 mg), Colorless liquid; **IR** (Nujol, cm^{-1}): ν_{max} 719, 1151, 1236, 1323, 1344, 1453, 1576, 1578, 1733, 1744, 2894, 2943; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.89 - 0.96 (t, 3H), 1.36 (dd, *J* = 15.0, 7.3 Hz, 2H), 1.60 - 1.67 (m, 2H), 2.49 (t, *J* = 7.3 Hz, 2H), 4.87 (s, 2H), 7.48 (d, *J* = 6.1 Hz, 2H), 7.55 - 7.62 (m, 1H), 8.09 (d, *J* = 7.0 Hz, 2H): **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.7, 22.1, 25.2, 38.4, 68.2, 128.3, 129.2, 129.7, 133.2, 165.6, 198.1, 203.6. **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{13}H_{16}O_3$+Na: 243.0997; found: 243.0965.

2-Oxooctyl benzoate (2g)

Yield: 92% (228 mg), Colorless liquid, **IR** (Nujol, cm^{-1}): ν_{max} 714, 1125, 1279, 1357, 1376, 1443, 1566, 1523, 1742, 1753, 2754, 2983: **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.86 - 0.93 (t, 3H), 1.30 (br. s., 7H), 1.62 - 1.69 (m, 2H), 2.50 (t, *J* = 7.3 Hz, 2H), 4.88 (s, 2H), 7.47 - 7.51 (m, 2H), 7.60 - 7.62 (m, 1 H), 8.08 - 8.13 (m, 2H): **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.0, 22.4, 23.2, 28.8, 31.5, 38.8, 68.3, 128.4, 129.8, 130.1, 133.3, 165.8, 203.9. **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{15}H_{20}O_3$+Na: 271.1310; found: 271.1321.

2-Oxocyclohexyl benzoate (2h)

Yield: 82% (178 mg), Colorless liquid; **IR** (Nujol, cm^{-1}): ν_{max} 785, 1115, 1394, 1419, 1556, 1734, 1760, 2891, 2933; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.71 – 1.97 (m, 6H), 2.43 - 2.54 (m, 3H), 5.35 - 5.43 (m, 1H), 7.40 - 7.47 (m, 2H), 7.52 - 7.56 (m, 1H), 8.06 - 8.10 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 23.6, 27.0 , 33.0, 40.5, 76.7, 128.1, 129.7, 132.9, 165.1, 203.6. **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{13}H_{14}O_3$+Na: 241.0841; found: 241.0847.

2-Hydroxy-2-phenylethyl benzoate (3a)

Yield: 86% (208 mg), colorless solid, mp: 65-67 °C; **IR** ($CDCl_3$, cm^{-1}): ν_{max} 744, 1155, 1494, 1556, 1736, 1754, 2891, 2933, 3133; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.67 (s, 1H), 4.42 - 4.51 (m, 1H), 4.52 - 4.55 (m, 1H), 4.69 (s, 1H), 5.09-5.12 (dd, *J* = 8.2, 3.2 Hz, 1H), 7.35 - 7.47 (m, 7H), 7.53 - 7.56 (m, 1H), 8.06 (d, *J* = 9.6 Hz, 2H): **^{13}C NMR** (100 MHz, $CDCl_3$): δ 69.7, 72.4, 126.2, 126.9, 128.1, 128.3, 128.5, 129.7, 133.1 , 140.0, 166.6; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{15}H_{14}O_3$+Na: 265.0835; found: 265.0839.

2-Hydroxy-2-(p-tolyl)ethyl benzoate (3b)

Yield: 84% (215 mg), colorless solid, mp: 79-80 °C; **IR** ($CDCl_3$, cm^{-1}): ν_{max} 1094, 1319, 1656, 1724, 1740, 2881, 2943, 3022; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.66 (br. s., 1H), 4.35 - 4.49 (m, 2H), 5.07 (dd, *J* = 8.0, 3.5 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.41 - 7.49 (m, 2H), 7.55 - 7.58 (m, 1H), 8.06 (d, *J* = 7.2 Hz, 2H): **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.2, 69.8, 72.4, 126.1, 128.4, 129.3, 129.8, 133.1, 137.1, 137.8, 166.6: **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{16}H_{16}O_3$+Na: 256.1099; found: 256.1094.

2-(4-Bromophenyl)-2-hydroxyethyl benzoate (3c)

Yield: 86% (275 mg), colorless solid, mp: 115-117 °C; **IR** ($CDCl_3$, cm^{-1}): ν_{max} 785, 1115, 1394, 1419, 1556, 1734, 1760, 2891, 2933, 3014; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.77 (br. s., 1H) 4.32 - 4.53 (m, 2H), 5.07 (dd, *J* = 7.8, 3.2 Hz, 1H), 7.31 - 7.36 (m, 2H), 7.42 - 7.50 (m, 4H), 7.59 - 7.63 (m, 1H), 8.03 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 69.5, 71.8, 122.0, 127.9, 128.4, 129.6, 131.6, 133.2, 139.0, 166.6; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{15}H_{13}BrO_3$+Na: 320.0048; found: 320.0056.

2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl benzoate (3d)

Yield: 81% (245 mg), colorless solid, mp: 129-130 °C; **IR** ($CDCl_3$, cm^{-1}): ν_{max} 775, 1175, 1374, 1479, 1656, 1744, 1762, 2881, 2916, 3242; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.65 - 2.67 (m, 1H), 3.89 (s, 6H), 4.41 - 4.52 (m, 2H), 5.03 - 5.07 (m, 1H), 6.83 - 6.87 (m, 1H), 6.95- 6.99 (m, 2H), 7.41 - 7.54 (m, 3H), 8.05 (d, *J* = 7.20 Hz, 2 H): **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.6, 55.7, 69.7, 71.8, 109.4, 111.1, 118.5, 128.3, 129.8, 133.0, 133.1, 148.6, 148.9, 166.5; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{17}H_{18}O_5$+Na: 271.0970; found: 271.0984.

2-Hydroxyhexyl benzoate (3e)

Yield: 88% (195 mg), colorless liquid; **IR** ($CDCl_3$, cm^{-1}): ν_{max} 762, 1144, 1355, 1436, 1676, 1735, 1756, 2864, 2976, 3162; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.94 (t, *J* = 6.9 Hz, 3H), 1.35 - 1.56 (m, 6H), 2.25 (br. s., 1H), 3.96 (m, 1H), 4.17 - 4.43 (m, 2H), 7.27 - 7.57 (m, 3H), 8.03 - 8.12 (m, 2 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 22.7, 27.6, 33.2, 69.2, 70.1, 128.4, 129.7, 130.0, 133.1, 166.6; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{13}H_{18}O_3$+Na: 245.1148; found: 245.1149.

2-hydroxyoctyl benzoate (3f)

Yield: 90% (225 mg), colorless liquid: **IR** ($CDCl_3$, cm^{-1}): ν_{max} 755, 1245, 1414, 1479, 1656, 1754, 1792, 2891, 2986, 3242 **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.86 - 0.91 (t, *J* = 7.3 Hz, 3H), 1.30 (br. s., 8H), 1.55 (br. s., 2 H) 2.09 (br. s., 1H), 3.97 (t, *J* = 9.03 Hz, 1H), 4.21 (dd, *J* = 11.4, 7.0 Hz, 1H), 4.39 (dd, *J* = 11.4, 3.2 Hz, 1H), 7.41 - 7.48 (m, 2H), 7.54 - 7.57 (m, 1H), 8.05 (dd, *J* = 8.3, 1.3 Hz, 2H): **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 22.5, 25.3, 29.2, 31.7, 33.4, 69.2, 70.0, 128.3, 129.6, 129.9, 133.1, 166.7: **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{15}H_{22}O_3$+Na: 273.1461; found: 273.1438.

3-Acetoxy-2-hydroxypropyl benzoate (3g)

Yield: 89% (212 mg), colorless liquid: **IR** ($CDCl_3$, cm^{-1}): ν_{max} 745, 1145, 1344, 1449, 1686, 1742, 1754, 2891, 2926, 3152; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.10 (s, 3H), 3.80-3.82 (m, 2H), 4.41-4.52 (m, 3H), 5.19-5.22 (t, 1H), 7.39 - 7.59 (m, 3H), 8.02 (d, *J* = 6.9, 2H); **^{13}C NMR** ($CDCl_3$): δ 20.2, 66.3, 66.7, 67.7, 128.5, 128.9, 129.9, 133.5, 165.5, 169.8; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{12}H_{14}O_5$+Na: 261.0738; found: 261.0741.

2-hydroxycyclohexyl benzoate (3h)

Yield: 83% (183 mg), colorless liquid; **IR** ($CDCl_3$, cm^{-1}): ν_{max} 745, 1275, 1354, 1419, 1556, 1739, 1764, 2891, 2926, 3022; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.39 - 1.47 (m, 3H), 1.67 - 1.76 (m, 4H), 1.96 (br. s., 1 H), 2.14 (d, *J* = 11.7 Hz, 2H), 3.67 - 3.98 (m, 1H), 4.83 - 5.23 (m, 1H), 7.40 - 7.56 (m, 3H), 8.05 (d, *J* = 7.2 Hz, 2H): **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.6, 23.8, 29.9, 32.9, 72.5, 78.5, 128.2, 129.6, 132.9, 166.6: **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{13}H_{16}O_3$+Na: 243.0992; found: 243.0998.

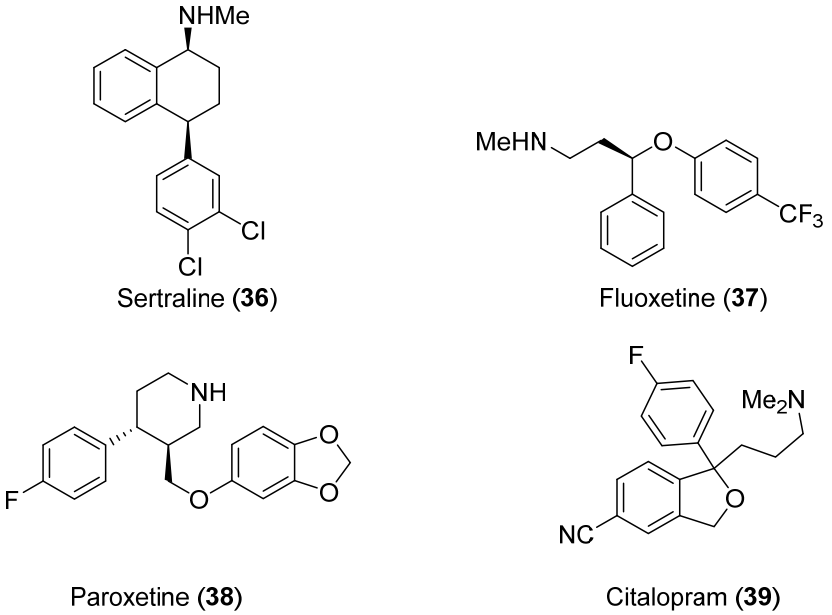
Section II

Enantioselective Formal Synthesis of (*S,S*)-Reboxetine using I_2-Catalyzed Oxoacyloxylation-CBS reduction Reaction

3.2.1 Introduction

Depression is a common and disabling disorder. The World Health Organization has ranked depression fourth in a list of the most urgent health problems world wide.[23] Depression has major effects on economic productivity, individual well being and social functioning, around the globe. It is a huge burden on individuals, families, and society. The lifetime risk for major depression has been estimated to be 7%-12% for men and 20-25 % for women.[24] Medical treatment for depression favors prescription of antidepressant drugs that work by increasing neurotransmission for one or more of the monoamines-serotonin, norepinephrine, or dopamine. Before 1980, antidepressant treatment consisted primarily of the tricyclics antidepressants (TCADs), monoamine oxidase inhibitors (MAOI), and lithium. The antidepressant properties of these medications are attributed to modulation of noradrenergic and serotonergic function, but they also have many side effects due to binding to multiple unrelated receptors. The tricyclics antagonize muscarinic, H1 histaminic, and A1 adrenergic receptors causing constipation, urinary retention, dry mouth, sedation, and postural hypotension. In addition to these; the monoamine oxidase inhibitors have the added risk of potentially severe hypertensive crisis due to pressor effects of dietary tyramine, which requires dietary restrictions. Both the tricyclics and the monoamine oxidase inhibitors can be lethal in overdose; the monoamine oxidase inhibitors interact dangerously with several over the counter and prescription drugs. In the late 1980's, an important class of antidepressant was introduced, the selective serotonin reuptake inhibitors (SSRIs), which includes sertraline (**36**), fluoxetine (**37**), paroxetine (**38**),

and citalopram (**39**) (**Fig. 3**). This class has become a mainstay of antidepressant treatment because of substantial advantages over the tricyclics and monoamine oxidase inhibitors in safety, tolerability and ease of dosing.



Sertraline (**36**) Fluoxetine (**37**)

Paroxetine (**38**) Citalopram (**39**)

Fig. 3: Selective serotonin reuptake inhibitors (SSRIs)

The SSRI's also have limitations, especially response failure in many of those most severely affected. Many patients experience side effects like gastrointestinal complaints, nervousness and agitation, sexual dysfunction and weight gain with long term use.[25] All these lead to difficulty in long term treatment and non-compliance. Hence, one of the most important goals in the pharmacological treatment of depression is to provide the patients with highly efficacious drugs that have few side effects, low or no toxicity and a high level of tolerability.

3.2.2 Reboxetine and pharmacology

Reboxetine (**40**) is a selective noradrenaline reuptake inhibitor (NaRI), the first drug of new antidepressant class introduced in 1997 (**Fig. 4**). It is α-aryloxybenzyl derivative of morpholine and its mesylate (*i.e.* methanesulfonate) salt is sold under

trade names including Edronax®, Norebox®, Prolift®, Solvex® or Vestra®. Reboxetine (**40**) is a selective inhibitor of noradrenaline reuptake. It inhibits noradrenaline reuptake *in vitro* to a similar extent to the tricyclic antidepressant desmethylimipramine. It does not affect dopamine or serotonin reuptake[5] and has low *in vivo* and *in vitro* affinity for adrenergic, cholinergic, histaminergic, dopaminergic and serotonergic receptors.[26]

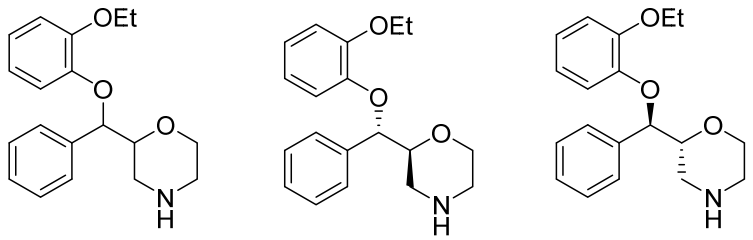


Fig. 4: Structures of reboxetine

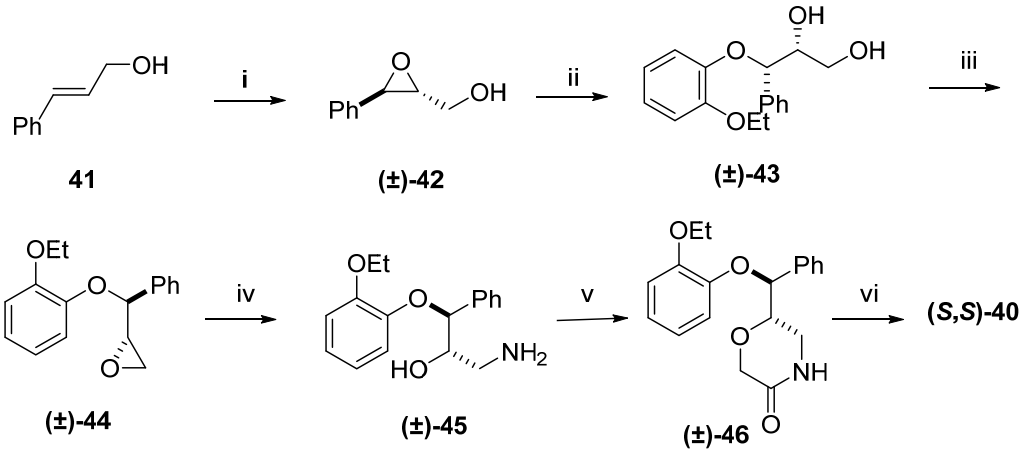
Due to selectivity of reboxetine (**40**) for norepinephrine, it is generally well tolerated with a benign side effect profile.[27] Against comparator antidepressants, reboxetine is at least as effective in the treatment of patients with major depressive disorder in the adult and the elderly population and offers a significant advantage over imipramine in the treatment of melancholic patients. It has a significantly improved adverse event profile compared with TCADs. In severely depressed patients, reboxetine (**40**) was significantly more effective than fluoxetine. Reboxetine (**40**), the first selective NaRI, with its selective mechanism of action, offering even better efficacy in certain patient groups and acceptable tolerability profile is a valuable addition to the existing armamentarium of drugs used for the treatment of depression.

3.2.3 Review of Literature

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

Melloni's approach (1985)[28]

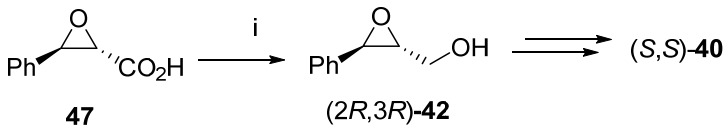
In Melloni's approach, cinnamyl alcohol (**41**) was subjected to diastreoselective epoxidation to give the (2*RS*,3*RS*) epoxide (±)-**42**. The epoxide (±)-**42** was then opened selectively at the benzylic position to give the diol (±)-**43** which was converted to the racemic epoxide (±)-**44**. The epoxide (±)-**44** was opened at primary position by NH_4OH to give the corresponding amino alcohol (±)-**45** (**Scheme 19**).



Scheme 19: (i) *m*-CPBA, CH_2Cl_2, 0 °C, 1 h, then 25 °C, 24 h, 94%; (ii) 2-ethoxyphenol, NaOH, H_2O, 70 °C, 2.5 h, 83%; (iii) (a) 4-nitrobenzoyl chloride, pyridine, -10 °C, 2 h, 61%; (b) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, 84%; (c) 2N NaOH, dioxane, 25 °C, 100%; (iv) 32% NH_4OH, MeOH, 6 h, 75%; (v) (a) $ClCH_2COCl$, Et_3N, CH_2Cl_2, -10 °C, 0.5 h, 98%; (b) *t*-BuOK, *t*-BuOH, 25 °C, 2 h, 86%; (vi) (a) Red-Al, toluene, 4 h, 72%; (b) L-(+)-mandelic acid, EtOH.

The amino alcohol (±)-**45** was treated first with chloroacetyl chloride and then with base to give the corresponding lactam (±)-**46**. Lactam (±)-**46** was reduced to the corresponding morpholine using Red-Al and the (*S*,*S*)-isomer was separated by resolution involving recrystallizing it with L-(+)-mandelic acid in ethanol to give (*S*,*S*)-reboxetine (**40**).

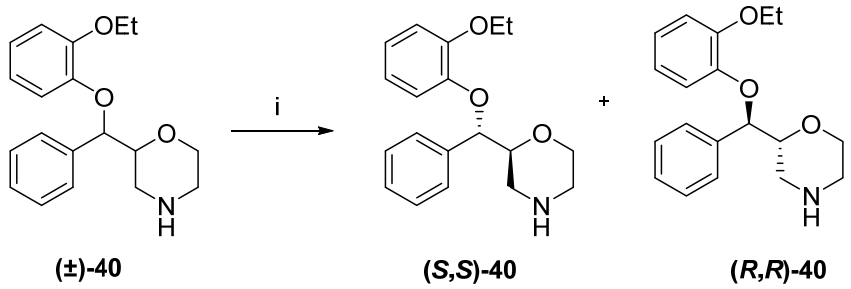
In another approach, Melloni *et al*. also carried out the synthesis of (*S*,*S*)-reboxetine (**40**) from the chiral (2*R*,3*R*)-epoxide **42,** obtained from chiral glycidic acid **47** (**Scheme 20**).



Scheme 20: (i) ethyl chlorocarbonate, Et_3N, CH_2Cl_2, 0 °C, 3 h, then $NaBH_4$, EtOH, 0 °C, 0.5 h, then 25 °C, 12 h, 31%.

Raggi's approach (2002)[29]

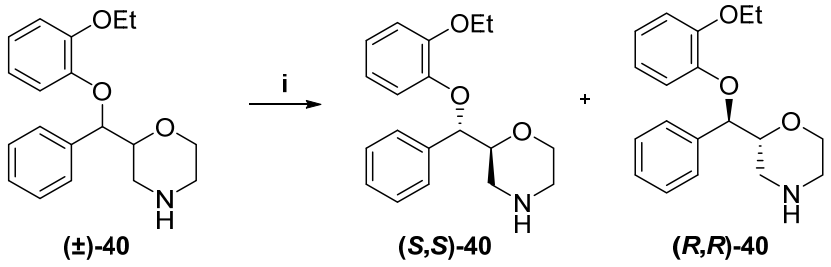
In this approach, Raggi *et al*. made use of capillary electrophoresis method to separate the enantiomers of racemic mixture of (*R*,*R*)-reboxetine and (*S*,*S*) reboxetine. Sulfobutyl ether-β-cyclodextrin was chosen as the chiral selector using an uncoated fused silica capillary (**Scheme 21**).



Scheme 21: (i) fused silica capillary (internal diameter 50 μm, total length 48.5 cm, effective length 40.0 cm), electrolyte pH 3.0, 100 mM phosphate buffer, 1.25 mM Sulfobutyl ether-β-cyclodextrin, 20 kV.

Öhman's approach (2002)[30]

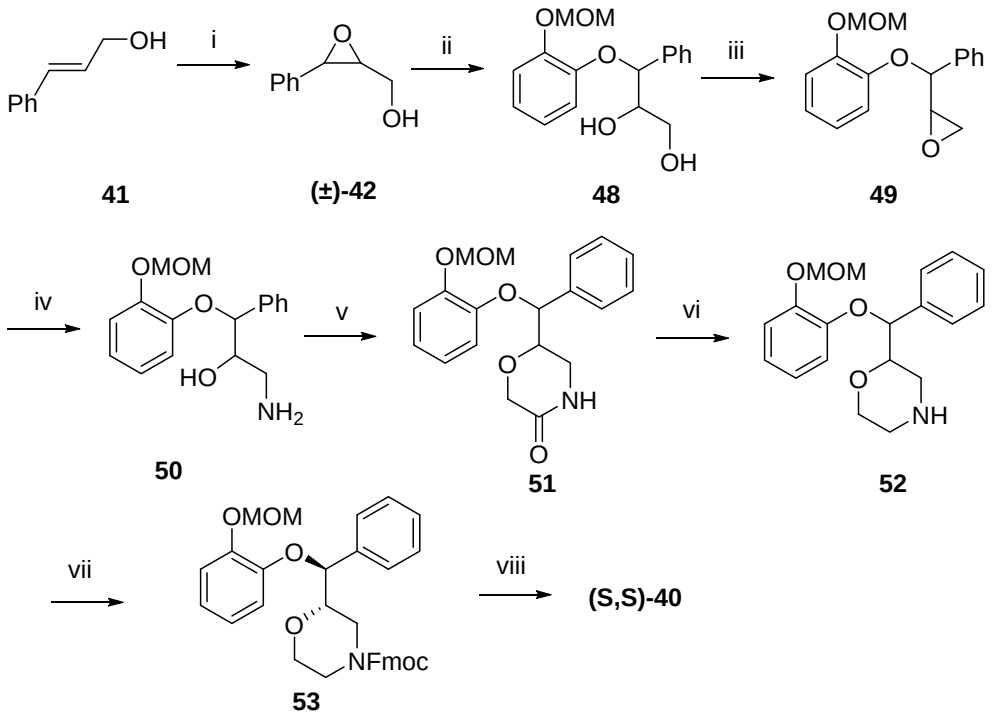
In this approach, the separation of the racemic mixture of reboxetine (±)-**40** was done using reversed-phase high-performance liquid chromatography using three different chiral columns*, i.e*. Chiral-AGP, ChiralGrom 2 or Chiral-CBH (**Scheme 22**).



Scheme 22: (i) separation *via* chiral HPLC method

Kumar's approach (2004)[31]

This approach is very much similar to the one reported by Melloni *et al*. involving the epoxidation of cinnamyl alcohol (**41**) and opening of epoxide **(±)-42** at benzylic position with mono MOM-protected catechol. Lactam **51**, obtained from **50** was reduced to the corresponding secondary amine **52**, which was resolved with (+)-mandelic acid and protected to give the corresponding chiral morpholine **53**. Morpholine **53**was converted to (*S*,*S*)-reboxetine (**40**) using simple transformations (**Scheme 23**).

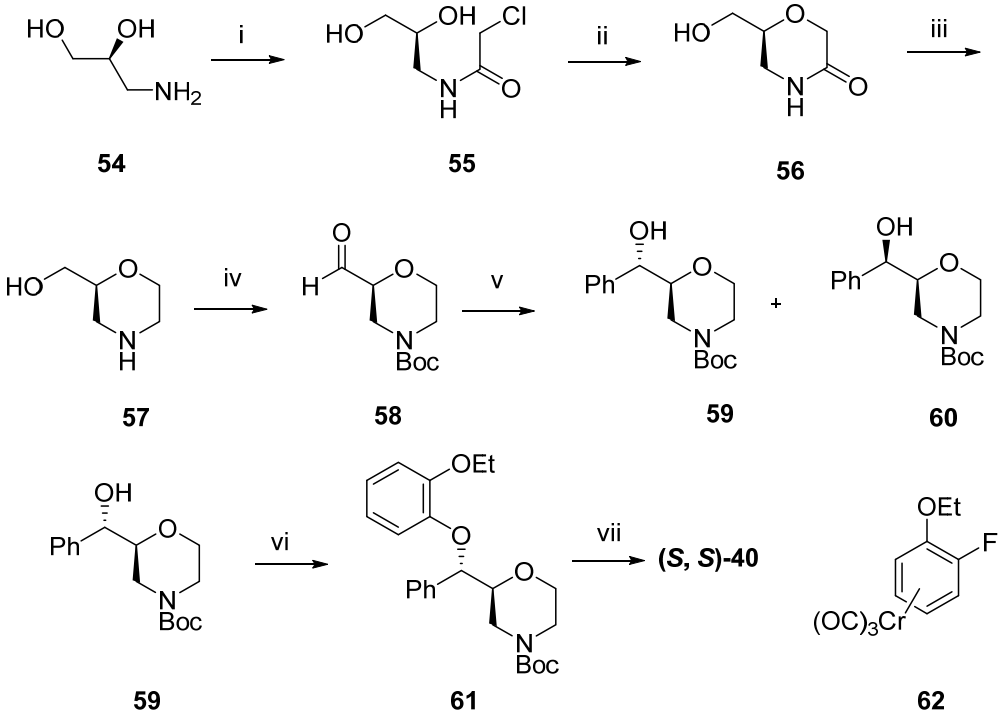


Scheme 23: (i) *m*-CPBA, CH_2Cl_2, 80%; (ii) 2-methoxymethoxyphenol, aq. NaOH, 64%; (iii) (a) 4-nitrobenzoyl chloride, pyridine, 65%; (b) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 90%; (c) 2N NaOH, 25 °C, 4 h, 95%; (iv) 30% NH_4OH, MeOH, 88%; (v) (a) $ClCH_2COCl$, Et_3N, CH_2Cl_2, (b) *t*-BuOK, *t*-BuOH, 64%; (vi) (a) Red-Al, toluene, 88%; (b) L-(+)-mandelic acid, EtOH; (vii) FMOC-Cl, Et_3N, Et_2O, 75%; (viii) (a) *p*TSA, MeOH, 94%, (b) TBAF.H_2O, THF, 87%, (c) $(Boc)_2O$, CH_2Cl_2, 87%, (d) *t*-BuOK, DMF, EtI, (e) TFA, 65%.

Tamagnan's approach (2005)[32]

Tamagnan's strategy was to build the chiral morpholine moiety first, before introducing the phenyl and aryloxy groups. Chiral aminoalcohol **54** was converted

to morpholinone **56** using simple transformations. Aldehyde **58** was obtained from morpholinone **56** in 2 steps of (i) amine protection with $(Boc)_2O$ (ii) alcohol oxidation with trichloroisocyanuric acid (TCIA) and TEMPO in EtOAc. Aldehyde **58** was treated with excess Ph_2Zn to give the diastereomers (2*S*,3*S*)-**59** and (2*S*,3*R*)-**60** in 60 and 19% yields respectively. Sodium alkoxide of **59** was reacted with arylchromium **62** to provide two chromium complexes, which led to **61** in 95% yields after oxidative dechromination with iodine. Finally, treatment of carbamate **61** with excess CF_3CO_2H provided (*S*,*S*)-reboxetine (**40**) in 98% yield (**Scheme 24**).

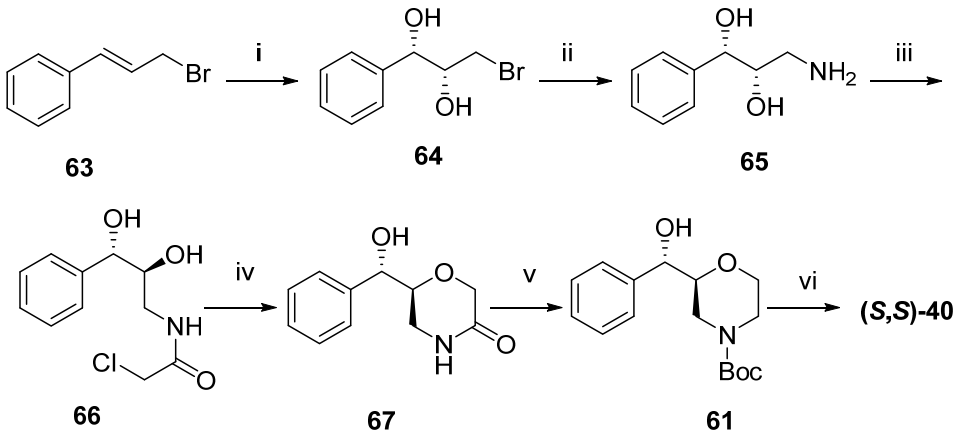


Scheme 24: (i) $ClCH_2COCl$, Et_3N, CH_3CN, MeOH, -10 °C to 25 °C, 16 h, 94%; (ii) *t*-BuOK, *t*-AmOH, 25 °C, 3 h, 92%; (iii) Red-Al, THF, 0 °C to 25 °C, 16 h, 85%; (iv) (a) $(Boc)_2O$, NaOH, CH_2Cl_2/H_2O, 0 °C to 25 °C, 4 h, 83%, (b) TEMPO, TCIA, $NaHCO_3$, EtOAc, -5 °C, 2 h, 89%; (v) Ph_2Zn, THF, -10 °C to 25 °C, 18 h, **59** (60 %), **60** (19%); (vi) (a) **62**, NaH, DMF, 25 °C, 2h, (b) I_2 in THF, 0 ^{0}C to 25 °C, 1 h, 95%; (vii) TFA, CH_2Cl_2, 0 °C to 25 °C, 1.5 h, 98%.

Srinivasan's approach (2006)[33]

Srinivasan *et al*. have made use of Sharpless asymmetric dihydroxylation approach for the asymmetric synthesis of (*S*,*S*)-**40**. *trans*-Cinnamyl bromide (**63**) on subjecting

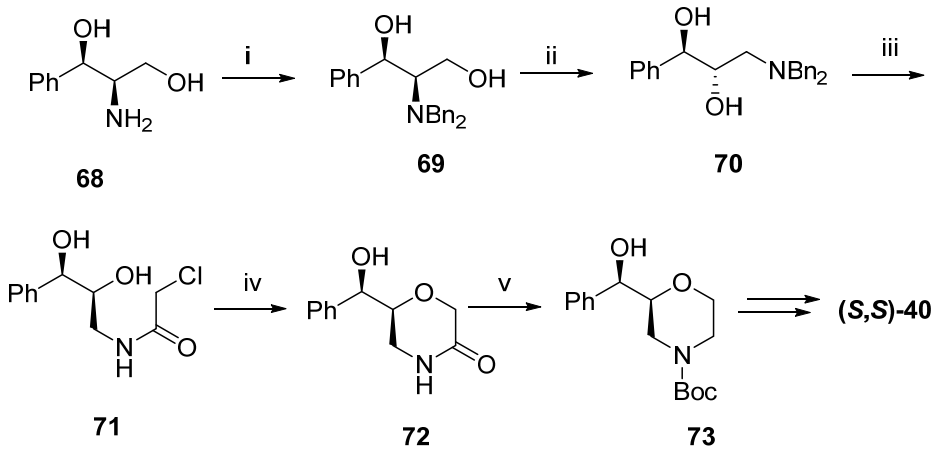
it to asymmetric dihydroxylation afforded diol **64**. Nucleophilic displacement of the bromo group with sodium azide furnished the azido alcohol, which was converted to amine **65** using 10% Pd/C and H_2. The free amine **65** was then treated with chloroacetyl chloride to furnish amide **66**, which was readily cyclized to compound **67**. This cyclic amide was reduced using Red-Al, to give the corresponding morpholine which was protected with $(Boc)_2O$ to afford **61**. The free hydroxyl group was coupled with chromium complex (**62**) and Boc protection was cleaved to give (*S,S*)-reboxetine (**40**) (**Scheme 25**).



Scheme 25: (i) $(DHQ)_2$-PHAL, OsO_4, $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, $MeSO_2NH_2$, H_2O-*t*-BuOH (1:1), 0 °C, 24 h, 84%; (ii) (a) NaN_3, DMF, 68 °C, 16 h, 80%, (b) 10% Pd/C, H_2 (1 atm), 25 °C, 12 h, 90%; (iii) $ClCOCH_2Cl$, Et_3N, CH_2Cl_2 at –10 °C to 25 °C, 6 h, 70%; (iv) *t*-BuOK, *t*-BuOH, 25 °C, 4 h, 80%; (v) (a) Red-Al, THF, 0 °C, 83%, (b) $(Boc)_2O$, NaOH, CH_2Cl_2–H_20, 0 °C to 25 °C, 5 h, 83%; (vi) (a) **62**, NaH, DMF, 25 °C, 2h, (b) I_2 in THF, 0 °C to 25 °C, 1 h, 95%, (c) TFA, CH_2Cl_2, 0 °C to 25 °C, 1.5 h, 98%.

Pardo's approach (2007)[34]

Pardo's *et al*. have made use of stereospecific rearrangement of *N,N*-dialkyl-*α*-amino alcohols in the presence of a catalytic amount of $(CF_3CO)_2O$ as the key step. Commercially available (-)-(1*R*,2*R*)-2-amino-1-phenyl-1,3-propanediol **68** was converted to the corresponding tertiary amine **69** by *N,N*-dibenzylation, which was precursor for

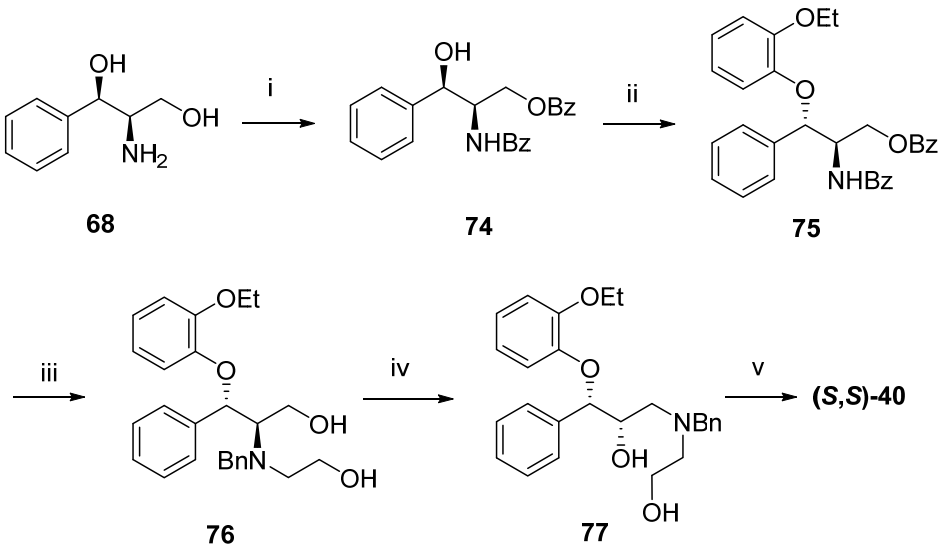


Scheme 26: (i) BnBr, K_2CO_3, MeCN, reflux, 8 h, 98%; (ii) (a) $(CF_3CO)_2O$, toluene, reflux, 5 h; (b) NaOH, 25 °C, 2 h, 78%; (iii) (a) $Pd(OH)_2$, H_2(1atm), MeOH, 25 °C, 26 h, 71%; (b) $ClCOCH_2Cl$, Et_3N, CH_2Cl_2/MeCN (9:1), 25 °C, 45 min., 89%; (iv) *t*-BuOK, *i*PrOH, 25 °C, 2 h, 62%; (v) (a) Red-Al, THF, reflux, 3 h; (b) $(Boc)_2O$, THF, 25 °C, 4 h, 67%.

the key step. Then **69** was treated with $(CF_3CO)_2O$ (0.4 equiv) in refluxing toluene for 5 h followed by a NaOH treatment to furnish the rearranged amino alcohol **70**. Amino alcohol **70** was converted to (*S*,*S*)-reboxetine (**40**) using literature reported reactions *via* simple transformations (**Scheme 26**).

In second approach, the aim was to introduce the phenyl and aryloxy groups first, before introducing the chiral morpholine moiety. Chiral aminodiol **68** was converted to benzoylated amino alcohol **74** in 3 steps of (i) amino alcohol protection with BzCl (ii) Mitsunobu reaction on the benzylic alcohol with 2-ethoxyphenol (iii) reduction of N/O benzoyl group with BH_3.THF. *N*,*N*-Dialkylamino alcohol **76** was obtained from amino alcohol **74** in two steps of *N*-alkylation using methyl bromoacetate followed by reduction of the crude material by $LiAlH_4$. *N*,*N*-Dialkylamino alcohol **76** was then subjected to the rearrangement by treatment with $(CF_3CO)_2O$ (under microwave irradiation), and rearranged aminodiol **77** was obtained in a modest yield of 36%.

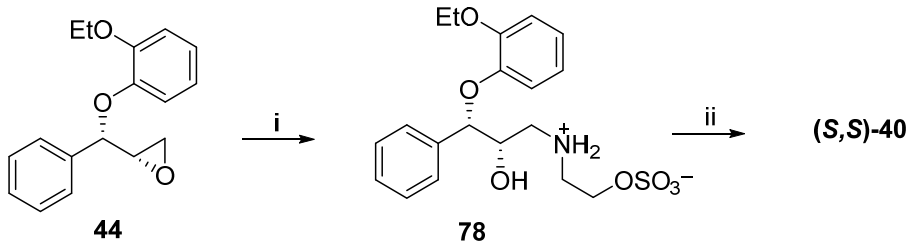
Amino diol **77** was converted to (*S*,*S*)-reboxetine (**40**) using literature reported reactions *via* simple transformations (**Scheme 27**).



Scheme 27: (i) BzCl, Et_3N, CH_2Cl_2, 25 °C, 24 h, 96%; (ii) PPh_3, 2-Ethoxyphenol, DIAD, THF, 25 °C, 2 h, 76%; (iii) (a) BH_3.THF, THF, reflux, 3 h, 92%; (b) $BrCH_2CO_2Me$, K_2CO_3, DMF, 25 °C, 7days; (c) $LiAlH_4$, THF, 25 °C, 2 h, 70%; (iv) $(CF_3CO)_2O$, THF, 120 °C, 18 h, MW, 36%; (vi) (a) TsCl, DMAP, Et_3N, CH_2Cl_2, 25 °C, 48 h; (b) NaOH, 25 °C, 24 h, 57%; (vii) *t*-BuOK, *i*PrOH, 25 °C, 2 h, 62%; (v) (a) Red-Al, THF, reflux, 3 h; (b) $(Boc)_2O$, THF, 25 °C, 4 h, 67%.

Assaf's approach (2010)[35]

In this approach, Assaf's *et al*. was able to convert a four-step morpholine synthesis into a more efficient two-step process. Synthesis of (*S*,*S*)-reboxetine (**40**) was achieved starting from the aryloxy epoxide **44** using two-step process *via* epoxide opening with 2-ethoxyphenol to afford amino alcohol **78** and base-mediated ring-closure using an a typical solid NaOH/THF/EtOH system. The combined transformations delivered (*S,S*)-reboxetine in more than 60% overall yield (**Scheme 28**).

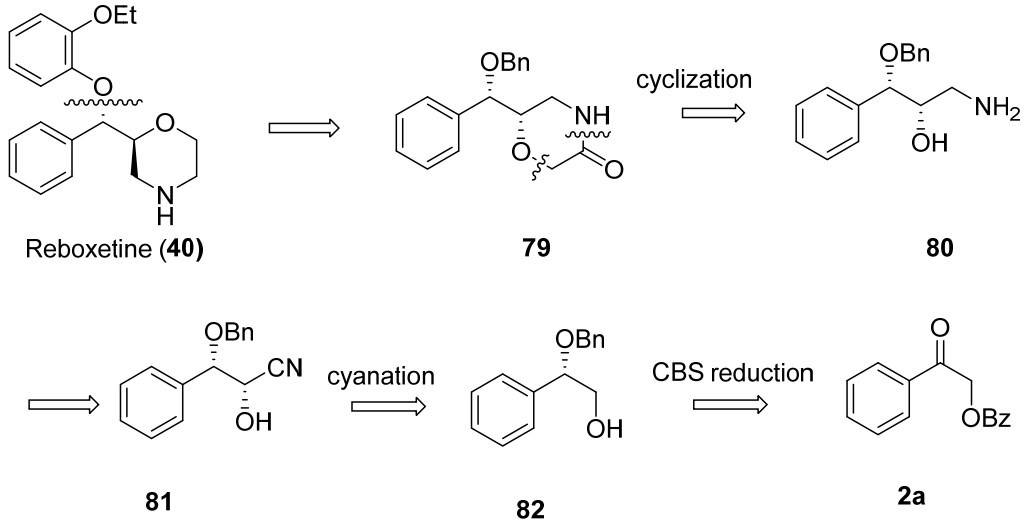


Scheme 28: (i) $H_2NCH_2CH_2OSO_3H$, DBU, PhMe, EtOH, 86%; (ii) NaOH, THF, EtOH, 78%.

3.2.4 Present Work

3.2.4.1 Objective

Among reboxetine enantiomers, (*S*,*S*)-reboxetine (**40**) exhibits the best affinity and selectivity for norepinephrine transporter. So far, the methods described in the literature for the synthesis of reboxetine (**40**) suffer from the following disadvantages: they involve separation of reboxetine enantiomers by classical resolution, capillary electrophoresis, or chiral HPLC and are specific to the reboxetine structure. In this section, we describe a new approach to the asymmetric synthesis of (*S*,*S*)-reboxetine (**40**) using sequential oxo-acyloxylation-CBS reduction as the key reaction. The retrosynthetic analysis for (*S*,*S*)-reboxetine (**40**) is presented in **Scheme 29**.

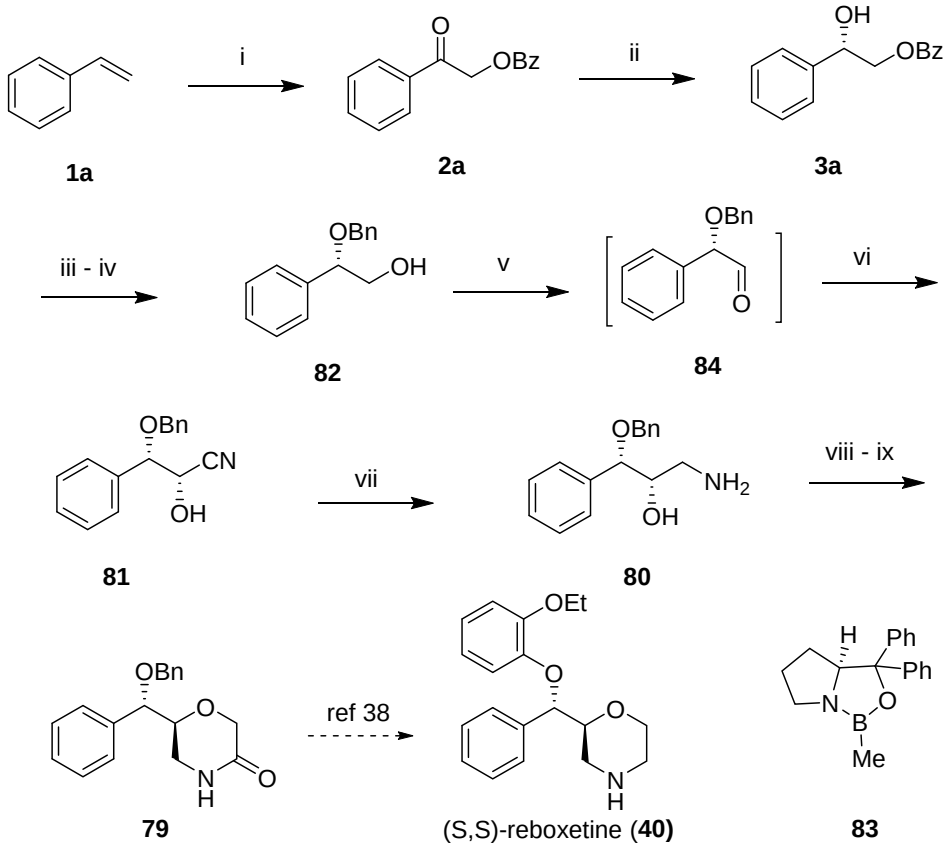


Scheme 29: Retrosynthetic analysis of (*S*,*S*)-reboxetine (**40**)

(*S*,*S*)-Reboxetine (**40**) can be obtained from the lactam **79,** which can be prepared from the corresponding key intermediate, amino alcohol **80**. This in turn can be obtained from chiral cyanohydrins **81.** The cyanodiol **81** could be prepared from **2a** by CBS-reduction and diastereoselective cyanation reaction.

3.2.4.2 Results and Discussion

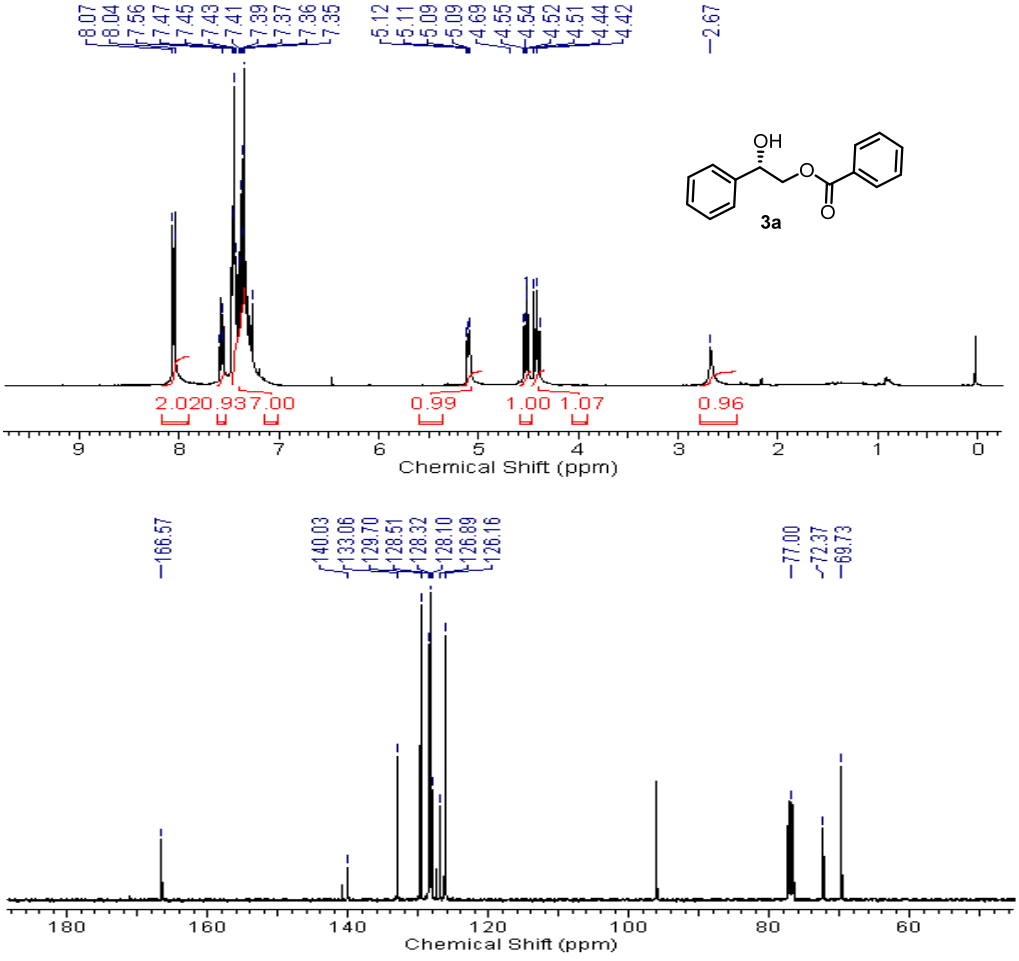
The complete synthetic sequence for the synthesis of key intermediate **79**, wherein I_2-catalyzed oxoacyloxylation-CBS reduction of styrene and Lewis acid mediated diastereoselective cyanation constitute the key steps, is presented in **Scheme 30**.

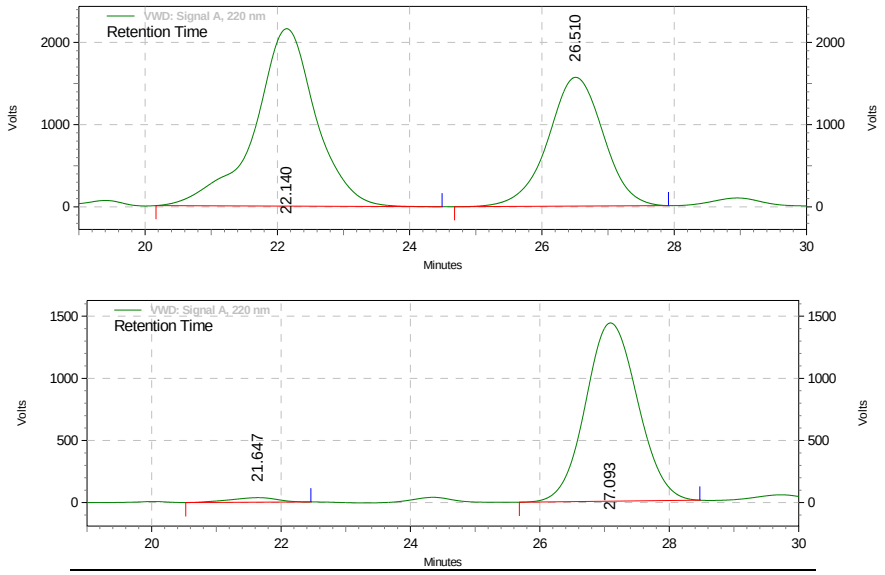


Scheme 30: (i) I_2 (10 mol %), TBHP (1 equiv), $PhCO_2H$ (1 equiv), Et_3N (1.2 equiv), DMSO, 25 °C, 8 h, 84%; (ii) **83** (5 mol%), BH_3.THF (0.5 equiv), THF, 0 °C, 0.5 h, 80%, 95% ee; (iii) BnBr, NaH, DMF, 0 °C 3 h; (iv) K_2CO_3, MeOH, 84% (over 2 steps); (v) IBX (1.2 equiv), DMSO, 25 °C, 3h; (vi) TMSCN (1.1 equiv), $MgBr_2.Et_2O$ (1 equiv), CH_2Cl_2, 0 °C, 2 h, 82 % (over 2 steps); (vii) $LiAlH_4$, THF, 0 °C, 4 h, 82%; (viii) $ClCH_2CO_2Cl$, Et_3N, CH_2Cl_2, -10 °C; (ix) KO*t*Bu, *t*-BuOH, 3 h, CH_2Cl_2, 25 °C (80%).

Accordingly, the formal synthesis of (*S*,*S*)-reboxetine **40** has started from styrene **1a,** which was transformed into benzoyl protected diol (+)-**3a** in two steps: (i) oxo-

acyloxylation; (ii) CBS reduction[36] to give diol derivative (+)-**3a** in 80% yield with 95% enantiomeric excess. The ^{1}H NMR spectrum of 2-hydroxy-2-phenylethyl benzoate (**3a**) showed four typical proton signals at δ 2.67 (br s, 1H), and 4.42-4.51 (m, 1H), 4.52-4.55 (m, 1H) corresponding to diastereotopic protons attached to the methylene carbon and a proton signal at 5.09-5.12 (dd, J = 8.2, 3.2 Hz, 1H) corresponding to methine proton attached to benzylic –OH group. Its ^{13}C NMR spectrum displayed characteristic carbon signals at δ 166.6 corresponding carbonyl group and at δ 69.7 and 72.3 corresponding to methelene and benzylic methine carbons respectively. The optical purity of **3a** was determined to be 95% ee from chiral HPLC analysis (Chiracel AD-H, *n*-hexane/*i*PrOH, 95:5, 0.5 mL/min) retention time 21.6 min (2.5%) and 27.1 min (97.5%)) (**Fig**.**4**).





Retention Time	Area	Area %	Height	Height %
21.647	30977944	2.25	614502	2.49
27.093	1348524270	97.75	24059261	97.51

Fig 4: ^{1}H, ^{13}C NMR spectra and HPLC chromatogram of **3a**

Benzyl protection of diol derivative **3a** using benzyl bromide and NaH at 0 °C followed by hydrolysis afforded the desired alcohol **82** in 90 % yield. The free hydroxyl group in **82** was then oxidized to aldehyde **84** under IBX condition *in situ*, which was subjected to the diastereoselective hydrocyanation (Ward's protocol)[37] using trimethylsilyl cyanide and $MgBr_2.OEt_2$ to give the corresponding cyanohydrins **81** in 82% yield over two steps. The diastereoselectivity (dr = 11:1) of cyanohydrin **81** was determined by its NMR spectra of the crude compound. The ^{1}H NMR spectrum of the cyanohydrin **81** showed two doublets at 4.33 (d, J = 12 Hz, 1H) and 5.58 (d, J = 6 Hz, 1H) corresponding to the benzyl and homobenzylic protons respectively. Its ^{13}C NMR spectrum showed carbon peaks at δ 114.67 corresponding to the nitrile carbon (**Fig. 5**). Also its IR spectrum showed characteristic absorption band at 2247 cm^{-1} corresponding to the CN stretching vibration.

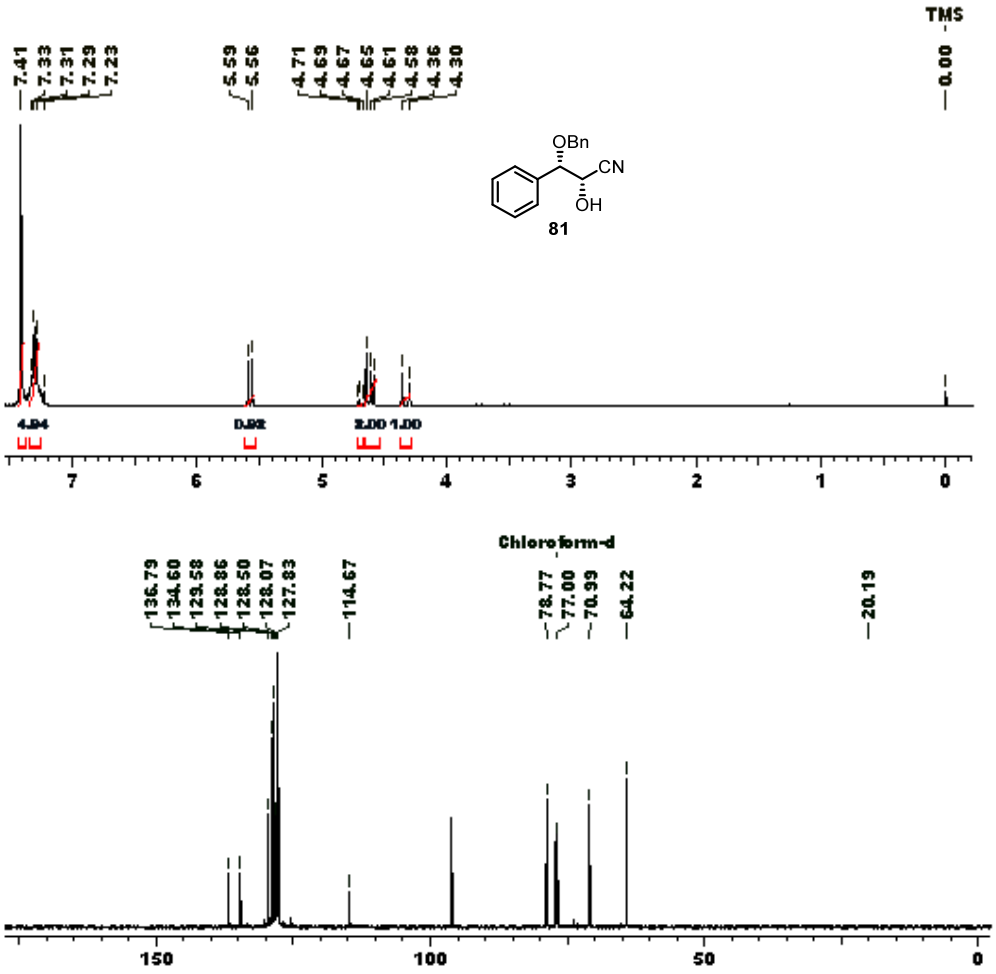


Fig. 5: ^{1}H and ^{13}C NMR spectra of **81**

The cyanohydrin **81** was reduced using $LiAlH_4$ in THF to give the corresponding amino alcohol **80** in 82% yield. The structure of aminodiol **80** was confirmed using spectroscopic data. The ^{1}H NMR spectrum of the aminoalcohol **80** showed typical proton signals at δ 4.16-4.22 (m, 2H) and 4.38-4.44 (m, 1H) corresponding to the homobenzylic and benzylic protons respectively. Its ^{13}C NMR spectrum showed carbon signals at δ 82.5 and 70.8 corresponding to the homobenzylic and benzylic carbons respectively. The other carbon signals at δ 41.6 corresponding to the methylene carbon ($-CH_2NH_2$) (**Fig. 6**).

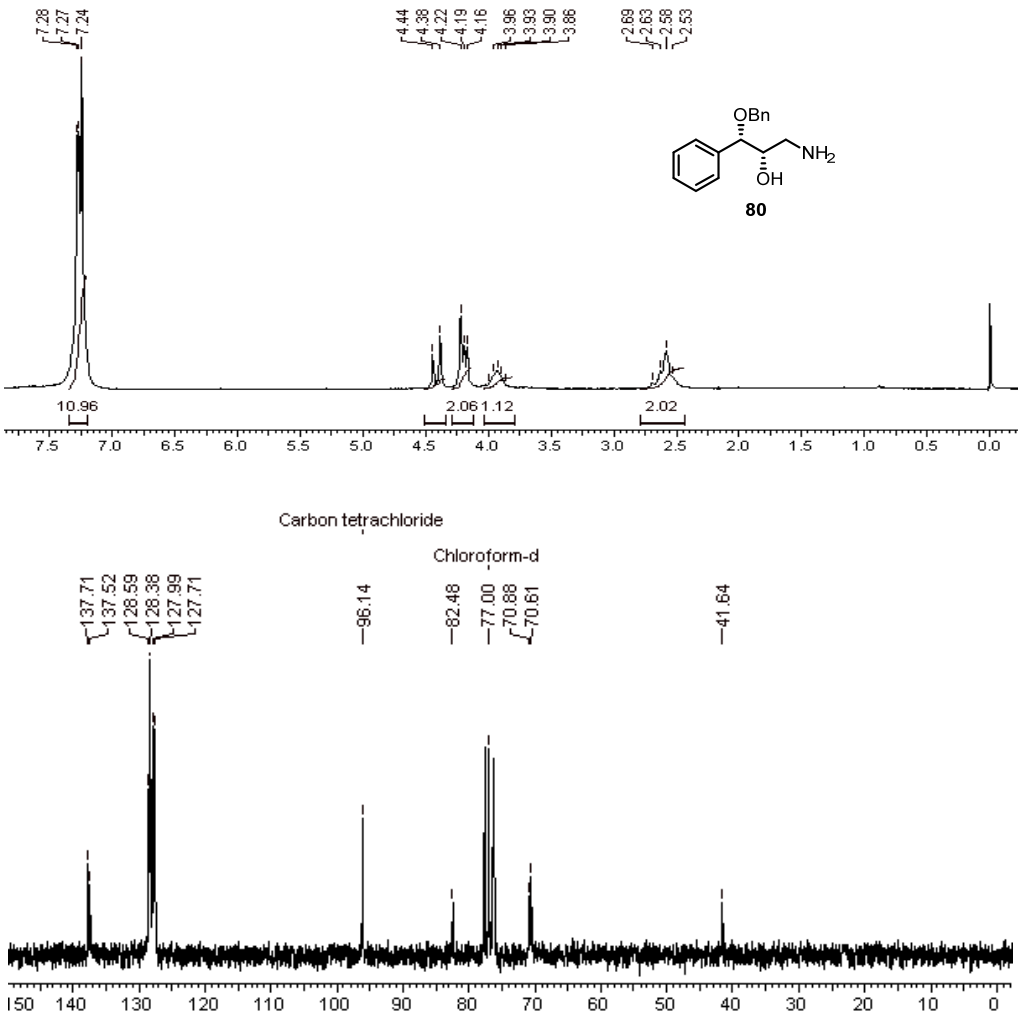


Fig. 6: ^{1}H and ^{13}C NMR spectra of **80**

The amino alcohol **80** was first reacted with chloroacetyl choride using Et_3N as the base at -10 °C to give the corresponding amide *in situ*, which was readily converted to the corresponding lactam **79** using *t*-BuOK as the base to give lactam **79** in 80% over two steps; $[\alpha]^{25}_{D}$: -30.41 (*c* 1.0, $CHCl_3$). The ^{1}H NMR spectrum of the lactam **79** showed proton signals at δ 2.80 (m, 1H) and 3.18 (t, *J* = 13.02 Hz, 1H) for two diastereotopic protons -CH**C**$\mathbf{H_2}$NHC=O- group, and 4.28 (m, 2H) (-O**C**$\mathbf{H_2}$C=ONH-) corresponding to the diastereotopic methylene protons present in the lactam moiety. Its ^{13}C NMR spectrum showed characteristic carbon signals at δ 42.9 (-CH**C**$\mathbf{H_2}$NHC=O-) and 67.5 (-O**C**$\mathbf{H_2}$C=ONH-) corresponding to methylene carbons

present in the lactam moiety. The amide carbonyl in the lactam moiety showed a characteristic carbon signals at δ 169.3 (**Fig. 7**). Its IR spectrum showed a characteristic strong absorption band at 1684 cm^{-1} confirming the presence of amide carbonyl.

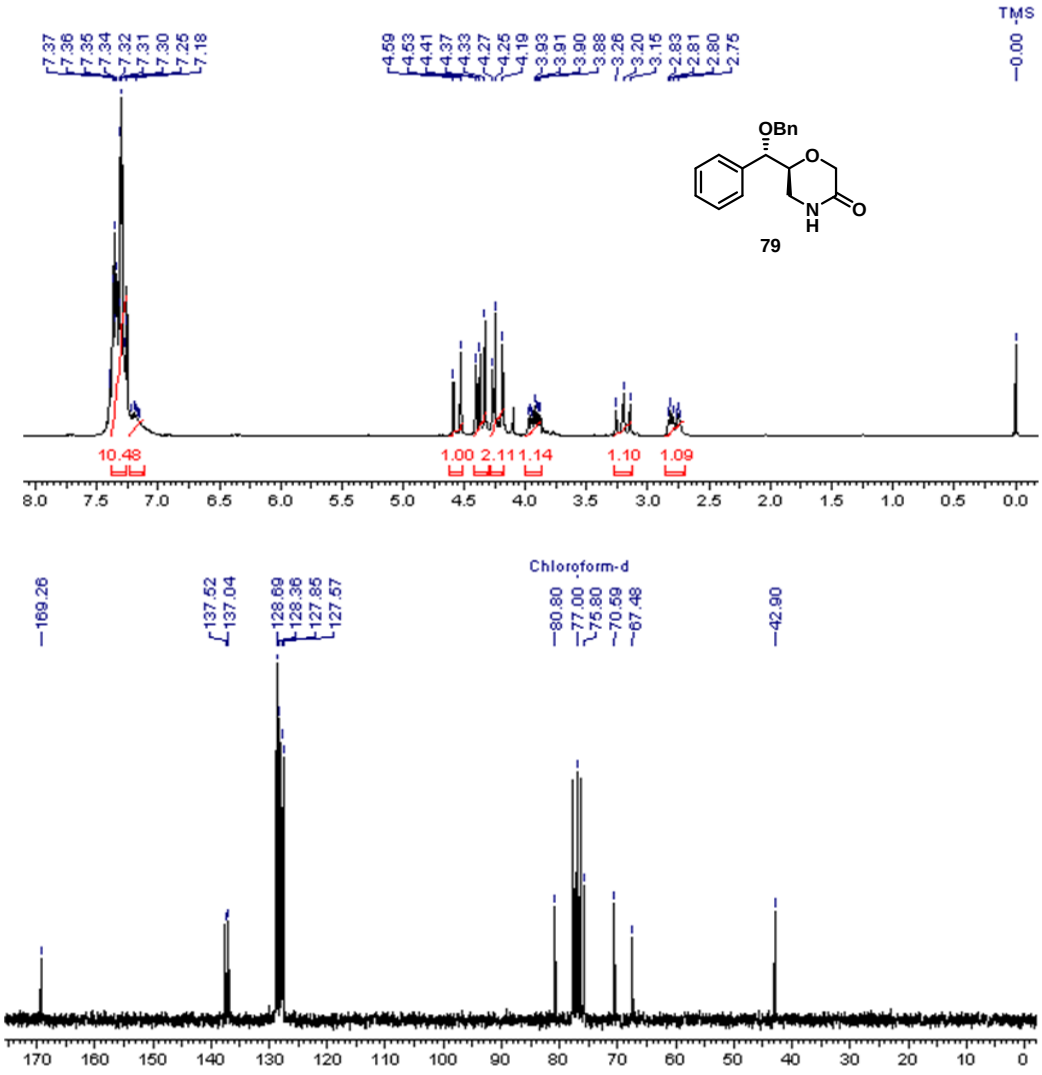


Fig. 7: ^{1}H and ^{13}C NMR spectra of **79**

Further, the synthesis of (*S*,*S*)-reboxetine, from the intermediate **79** has been reported in the literature.[38]

3.2.5 Conclusion

In conclusion, we have achieved the formal asymmetric synthesis of (*S*,*S*)-reboxetine

(**40**) using I_2-catalyzed oxoacyloxylation-CBS reduction and Lewis acid mediated diastereoselective cyanation constituting the key steps. The key intermediate **79** was prepared in 24% overall yield and 94% ee. The high yields obtained in this method render our approach a good alternative to the reported methods of its synthesis.

3.2.6 Experimental Section

2-Oxo-2-phenylethyl benzoate (2a)

To a stirred solution of styrene (2.0 g, 19.2 mmol) in dry DMSO (16 mL), I_2 (491 mg, 10 mol %), Et_3N (3.18 mL, 1.92 mmol), TBHP (3.5 mL,19.2 mmol) and benzoic acid (2.576 g, 21.1 mmol) was added and the reaction mixture was then stirred at 25 °C under an N_2 atmosphere. After completion of the reaction (as monitored by TLC), it was quenched with H_2O (30 mL) at 0 °C. It was then extracted with EtOAc (3 x 60 mL) followed by washing with brine (3 x 50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Concentration of solvent under reduced pressure gave the crude product, which was then purified by column chromatography over silica gel using Pet. ether/EtOAc (9:1) as eluent to obtain α-acyloxy ketone **2a** in 3.9 g (84% yield).

Yield: 84%, colorless solid, mp: 119-120 °C; **IR** (Nujol, cm^{-1}): ν_{max} 705, 1015, 1374, 1459, 1596, 1714, 1750, 2851, 2923; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.58 (s, 2H), 7.48-7.61 (m, 6H), 7.97-8.13 (m, 2H), 8.14-8.17 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 66.2, 127.7, 128.2, 128.73, 129.9, 130.1, 133.1, 133.7, 134.2, 165.7, 191.7; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{15}H_{12}O_3$+Na: 263.0683; found: 263.0692.

2-Hydroxy-2-phenylethyl benzoate (3a)

To a solution of catalyst (*R*)-Me-CBS (**83**) (193 mg, 5 mol %) in THF (15 mL) was added 1M BH_3.THF solution (14.4 mL, 14.5 mmol) and the mixture was stirred under N_2 atmosphere at -30 °C for 5 min. A solution of ketone **2a** (3.5 g, 14.5 mmol)

in THF (20 mL) was added dropwise. The reaction mixture was stirred until the ketone had disappeared on TLC (10 min). The reaction mixture was quenched with 2N HCl (4 mL), extracted with ether, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product, which upon column chromatographic purification with silica gel using pet ether: ethyl acetate (8:2) as eluent gave pure alcohol **3a** as colorless solid 2.8 g (80% yield).

Yield: 80%, colorless solid, $[\alpha]^{25}_{D}$: +30.2 (*c* 1, $CHCl_3$); mp: 65-67 °C; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 744, 1155, 1494, 1556, 1736, 1754, 2891, 2933, 3133; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.67 (s, 1H), 4.42-4.51 (m, 1H), 4.52-4.55 (m, 1H), 4.69 (s, 1H), 5.09-5.12 (dd, *J* = 8.2, 3.2 Hz, 1H), 7.35-7.47 (m, 7H), 7.53-7.56 (m, 1H), 8.06 (d, *J* = 9.6 Hz, 2H): **^{13}C NMR** (100 MHz, $CDCl_3$): δ 69.7, 72.4, 126.2, 126.9, 128.1, 128.3, 128.5, 129.7, 133.1, 140.0, 166.6; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{15}H_{14}O_3$+Na: 265.0835; found: 265.0839.

(*S*)-2-(Benzyloxy)-2-phenylethan-1-ol (82)

To a stirred solution of alcohol (2.6 g, 10.7 mmol) in anhydrous DMF was added NaH (644 mg, 16.5 mmol, 60% in mineral oil) at 0 °C. After stirring for 10 min, benzyl bromide (10.7 mmol, 1.27 mL) was added at 0 °C under N_2 atm. The reaction mixture was stirred at room temperature for 3 h under N_2 atm and quenched with H_2O (10 mL) at 0 °C. The aqueous layer was extracted with EtOAc (2 × 50 mL). The organic layer was washed with brine, dried over anhyd. Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to hydrolysis in K_2CO_3 (7 g, 51.5 mmol) in MeOH (40 mL) at 25 °C for 5 h. After completion of the reaction (monitored by TLC), MeOH was concentrated and then H_2O (30 mL) was added. The aqueous layer was extracted with EtOAc (3×45 mL). The organic layer was washed with brine, dried over Na_2SO_4,

and concentrated *in vacuo*. The residue was purified by flash column chromatography (Pet ether/EtOAc = 97/3) to afford **82** in 2.14 g (84% yield).

Yield: 84%, colorless gum, $[\alpha]^{25}_{D}$: +85.40 (*c* 1, EtOH); **IR** ($CHCl_3$, cm^{-1}): ν_{max} 1225, 1424, 1552, 1654, 2891, 2933, 3123; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.93 (br s, lH), 3.55 (dd, *J* = 3.7, 1.7 Hz, 1H), 3.68 (dd, *J* = 8.4, 11.7 Hz, lH), 4.38 (q, *J* = 7.3Hz, 2H), 4 46 (dd, *J* = 3.7, 8.1 Hz, lH), 7.27-7 34 (m, 1H); **^{13}C NMR** (50 MHz, $CDC1_3$) δ 67.0, 70.4, 82.1, 126.8. 127.5, 127.6, 127.9, 128.2, 128.3, 137.8, 138.4; **HRMS (ESI)**: $[M+Na]^+$ calcd for $C_{15}H_{16}O_2$+Na: 251.1048; found: 251.1046.

(2*S*, 3*S*)-3-(Benzyloxy)-2-hydroxy-3-phenylpropanenitrile (81)

To a stirred solution of benzyl ether **82** (2 g, 8.76 mmol) in DMSO (30 mL) was added IBX (2.93 g, 10.4 mmol), at 25 °C. After stirring for 4 h, water (30 mL) and ethyl acetate (60 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x30 mL). The combined organic layers were washed with water, brine, dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure to give the crude aldehyde **84** which was dissolved in CH_2Cl_2 (10 mL). To this solution, at 0 °C, was added freshly prepared magnesium bromide ethyl etherate $MgBr_2.OEt_2$ (11.15 g, 43.80 mmol) followed by the addition of timethylsilyl cyanide (TMSCN) (951.7 mg, 9.5 mmol). After stirring for 1.5 h, the reaction mixture was quenched by the sequential addition of trifluoroacetic acid (2.2 mL, 30 mmol) and water (30 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layer was washed with water, brine, dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure to give the crude cyanide, which was purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (5:95) to give pure cyanoacetate **81**.

Yield: 1.82 g (82%); gum; **$[\alpha]^{25}_{D}$**: +4.60 (*c* 0.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 702, 735, 837, 910, 1097, 1256, 1389, 1472, 1685, 2247, 2856, 2929, 2955, 3425; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.33 (d, *J* = 12.0 Hz, 1H), 4.61 (t, *J* = 6.1 Hz, 2H), 5.58 (d, *J* = 6.6 Hz, 1H), 7.23-7.33 (m, 5H), 7.41 (s, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 20.2, 64.2, 71.0, 78.8, 114.7, 127.8, 128.1, 128.5, 128.9, 129.6, 134.6, 136.8, 168.4; **Analysis: $C_{18}H_{17}NO_3$** requires C, 73.20; H, 5.80; N, 4.74%; found C, 73.29; H, 5.68; N, 4.82%.

(1*S*,2*S*)-3-Amino-1-(benzyloxy)-1-phenylpropan-2-ol (80)

To a stirred solution of cyanohydrin **82** (506 mg, 2 mmol) in diethyl ether (30 mL) was added $LiAlH_4$ (152 mg, 2 mmol) at 0 °C under N_2 atm. The mixture was stirred for 4 h. After completion of the reaction (as monitored by TLC), reaction mixture was filtered through a pad of celite and solvent was distilled off under reduced pressure to give the corresponding crude amino alcohol **80**, which was purified using column chromatography (Pet ether: EtOAc= 6:4).

Yield: 420 mg (82%); gum; **$[\alpha]^{25}_{D}$**: +18.4 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 735, 837, 910, 1097,1256, 1389, 1472, 1605, 1655, 2929, 3371, 3410, 3426; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.53-2.69 (m, 2H), 3.86-4.00 (m, 1H), 4.16-4.22 (m, 2H), 4.41 (d, *J* = 11.0 Hz, 1H) 7.24-7.28 (m, 10 H); **^{13}C NMR** (50 MHz, CDCl3): δ 41.6, 70.6, 70.9, 82.5, 127.7, 128.0, 128.4, 128.6, 137.5, 137.7; Analysis: $C_{16}H_{19}NO_2$ requires C,74.68; H, 7.44; N, 5.44; found C, 74.58; H, 7.39; N, 5.35%.

(S)-6-((S)-(Benzyloxy)(phenyl)methyl)morpholin-3-one (79)

To a stirred solution of amine diol **80** (257 mg, 1 mmol) and Et_3N (0.30 mL, 2.2 mmol) in CH_2Cl_2 (10 mL), was added drop-wise at –10 °C, a solution of chloroacetyl chloride (0.12 mL, 1.1 mmol) in CH_2Cl_2 (10 mL). After stirring for 0.5 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with water followed by saturated

brine. The combined organic phase was dried over anhyd. Na_2SO_4 and solvent distilled off under reduced pressure to give the crude product which was dissolved in *t*-BuOH (20 mL) and added to a stirred solution of KO^{t}Bu (236 mg, 2 mmol) in *t*-BuOH (6 mL). The reaction mixture was stirred for 3 h at 25 °C and quenched by the addition of water. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with water and brine, dried over anhyd. Na_2SO_4, the solvent distilled off under reduced pressure and crude product, which was purified by column chromatography over silica gel using EtOAc/Pet ether as eluent (25:75) to give the lactam **79** in 80% yield.

Yield: 80%; colorless gum; **$[\alpha]^{25}_D$** : +30.41 (c 1.0, $CHCl_3$); lit. [38] **$[\alpha]^{25}_D$**: -32.75 (*c* 1.0, $CHCl_3$).; **IR** ($CHCl_3$, cm^{-1}): 669, 700, 777, 860, 1029, 1105, 1251, 1362, 1462, 1541, 1684, 2856, 2885, 2927, 2954, 3219; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.79 (td, *J* = 12.0, 3.67 Hz, 1H,), 3.20 (t, *J* = 13.02 Hz, 1H), 3.88-3.98 (m, 1H), 4.19-4.27 (m, 2H), 4.33-4.41 (m, 2H), 4.77 (d, *J* = 12.6 Hz, 1H), 7.56 (br s, 1H), 7.28-7.40 (m, 10H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ 42.9, 67.5, 70.6, 75.8, 80.8, 127.5, 127.8, 128.4, 128.7, 137.0, 137.5, 169.3; **Analysis**: $C_{18}H_{19}NO_3$ requires C, 72.71; H, 6.44; N, 4.71; found C, 72.59; H, 6.39; N, 4.62%.

3.2.7 References

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CHAPTER IV

Studies towards the Synthesis of (+)-Neopeltolide and Total synthesis of DAB-1 and Zoledronic acid

1. Enantioselective Synthesis of 1,4-Dideoxy-1,4-imino-D-Arabinitol using Co (III)(salen)-catalyzed HKR of Two-Stereocentered *anti*-Azidoepoxide, **Rambabu N. Reddi**, Arumugam Sudalai; (manuscript under preparation)

Section 1

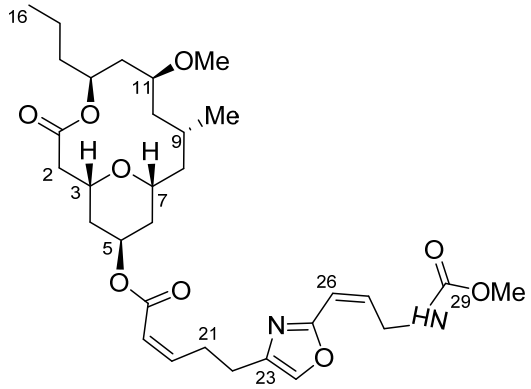
Studies Towards the Total Synthesis of (+)-Neopeltolide using NHC Catalysed Oxo-acyloxylation/Reductive Oxa-Michel Addition Strategy

4.1.1 Isolation, Structure and Pharmacology

Naturally occurring macrocycles such as cyclic peptides and polyketide macrolides represent a unique class of biologically- relevant small molecules. They display multiple functional groups with certain degrees of conformational flexibility along their macrocyclic backbone. Hence, they have a moreaccessible surface area compared with ordinary small organic molecules.[1] These characteristic features of macrocycles allow them to effectively interact with the extended shallow surface of target proteins and also make them potentially useful compounds for modulating protein–protein interactions.[2] Many naturally occurring or natural-product-derived macrocycles are known to have drug-like physicochemicaland pharmacokinetic properties, even though they violate the Lipinski rule of five.[3] Nonetheless, macrocycles have been less exploited as scaffolds in medicinal chemistry because of their complex structure, which contains multiple stereogenic centers. The significance of the relationship between chirality and biological activity of natural products and pharmaceuticals has long been recognized.[4, 5] Moreover, it has recently been argued that the molecular complexity arising from the presence of sp^3 hybridized carbon atoms and stereogenic centers (i.e., shape diversity[6]) may be important for the success of molecular probe development and drug discovery endeavors.[7, 8]

The isolation of neopeltolide (**1**) from the *Daedalopelta* sponge of the *Neopeltidae* family off the Jamaican coast[9] quickly sparked a significant research effort[10] that was based on the observation of extremely potent cytotoxic and antifungal activity for a

compound of moderate structural complexity (**Fig 1**). Wright and co-workers reported IC_{50} values of 0.56, 1.2, and 5.1 nM against P388 murine leukemia, A-549 human lung adenosarcomaand NCI-ADR-RES human ovarian sarcoma cell lines respectively. Cytostatic activity was postulated for two cell lines that contain p53 mutations. Flow cytometry experiments showed that neopeltolide arrests the cell cycle at the G1 stage. Neopeltolide also showed an MIC (minimum inhibitory concentration) of approximately 1 μM against the pathogenic fungus *Candida* albicans. The correct atomic connectivity for **1** was established by NMR analysis and the absolute and relative stereochemical assignments were determined unambiguously through total synthesis. The structural features of **1** include: a trisubstituted 2,6-cis tetrahydropyran moiety, within a 14-membered macrolide and 6-stereocenters (3*R*, 5*R*, 7*R*, 9*S*, 11*S*, 13*S*), besides the presence of an unsaturated oxazole-containing side chain at C5 on the tetrahydropyran ring.



1

Fig 1: Structure of (+)-Neopeltolide

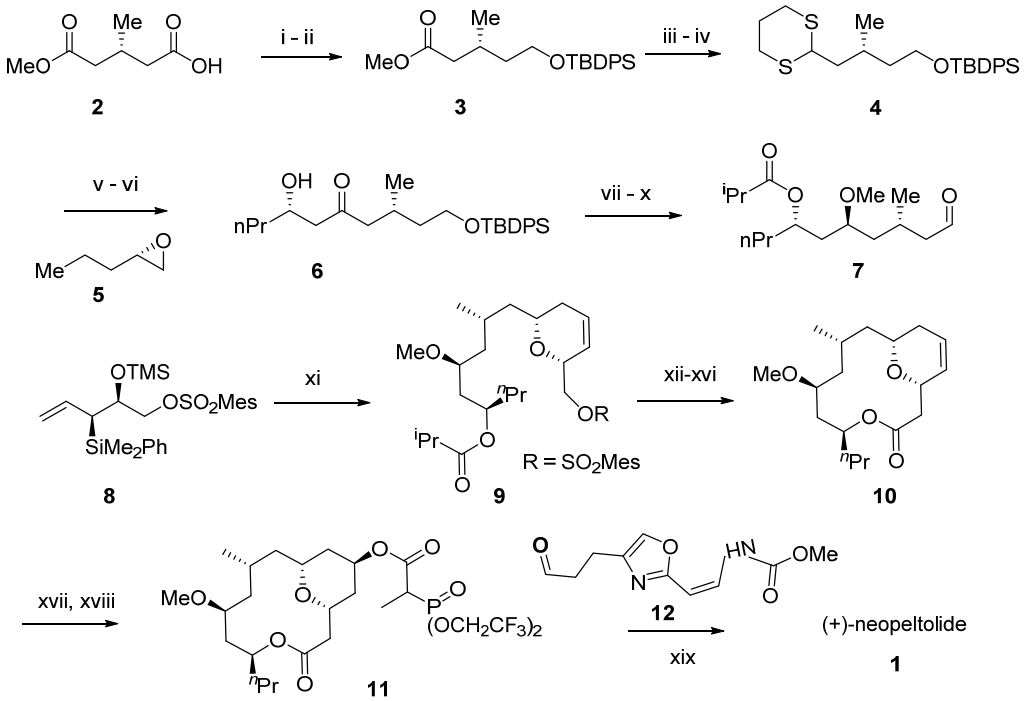
4.1.2 Review of Literature

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

Panek's approach (2007)[11]

In Panek'sapproach, synthesis of (+)-neopeltolide has begun from commercially available methyl (R)-(+)-3-methylglutarate (**2**). Chemoselective reduction of the carboxylic acid using $BH_3.SMe_2$ complex and subsequent protection as a TBDPS ether gave**3**.Reduction of TBDPS ether **3**followed by an iodine-catalyzed dithioacetalization of aldehyde to afford dithiane **4** in 68% overall yield. Coupling of dithiane **4** with epoxide **5** provided C7–C16 fragment**6** of neopeltolide. Removal of the dithioketal protecting group with $CaCO_3$/MeI and modified Evans–Tishchenko reduction (dr = 14:1) gave the *anti*-stereochemical relationshiprequired for the C11 and C13 centers, in addition to installing an isobutyrate protecting group, thereby differentiating the anti 1,3-diol. The remaining secondary alcohol was treated with Meerwein's reagent to give the C11 methyl ether. Deprotection of the silyl ether by using aqueous HF released the primary alcohol, which was immediately oxidized using Swern conditionto provide aldehyde **7**. Aldehyde **7** was combined with allylsilane **8** in a triflic acid promoted [4+2] annulation to access dihydropyran **9** in 75% yield and 10:1 diastereoselectivity. The sulfonate group of **9** was replaced with a nitrile moiety through an SN_2 displacement upon exposure to DIBAL-H, and the acyl protecting group was cleaved to restore the C13 alcohol. The nitrile functionality was converted to the corresponding carboxylic acid (*via* aldehyde) through Pinnick oxidation. Macrocyclization was affected through Yamaguchi esterification of the *seco* acid intermediate to form macrolide **10** in 44% yield. Selective oxymercuration of the pyran olefin yielded the axial C5 alcohol and Still–Gennari olefination was used to establish the *cis* enoate of the side chain. Acylation of alcohol with bis(2,2,2-trifluoroethyl)phosphonoacetic acid gave phosphonoacetate **11**, which was immediately deprotonated with KHMDS at -78 °C in THF in the presence of 18-

crown-6 ether; further treatment of the resulting anion with side-chain aldehyde **12** at -85 °C successfully provided a 7:1 mixture of (+)-neopeltolide **1** and the corresponding E olefin in 62% overall yield. This total synthesis was used for revision of structure of (+)-neopeltolide (**1**) (**Scheme 1**).

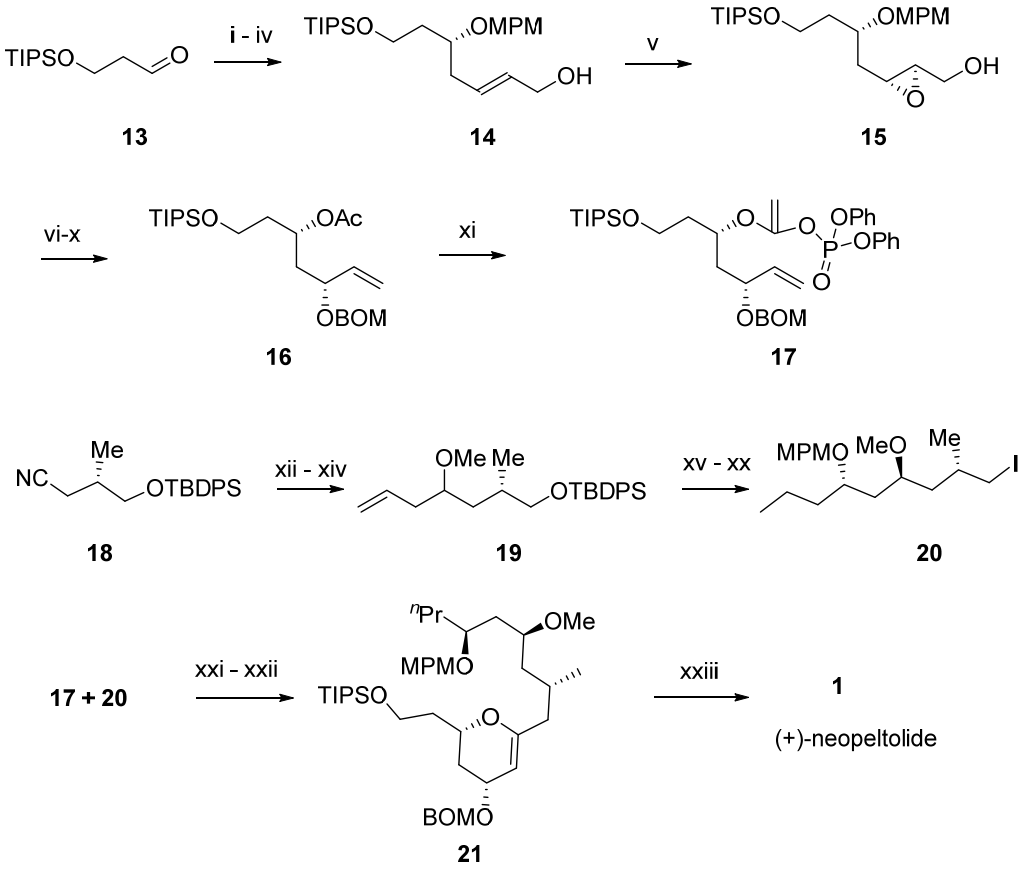


Scheme 1: (i) $BH_3 \cdot SMe_2$,THF, 0°C to RT; (ii) TBDPSCl, imidazole, DMF, 0 °C to RT, 80 % (over 2 steps); (iii) DIBAL-H, diethyl ether, -78 °C; (iv) 1,3-propanedithiol, I_2, $CHCl_3$, RT, 85% (over 2 steps); (v) *tert*-butyllithium, HMPA, THF, **5**, -78 °C, 68 %; (vi) $CaCO_3$,MeI, MeCN/H_2O, RT, 73%; (vii) $Zr(OtBu)_4$, ^{i}PrCHO, toluene, -78 °C; (viii) Me_3OBF_4, Proton Sponge, 4° molecular sieves, CH_2Cl_2, RT, 90% (over 2 steps); (ix) 49% HF in H_2O, MeCN, RT, 91%; (x) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78 °C to RT,89 %; (xi),TfOH,CH_2Cl_2/benzene (3:1),-78°C, 75% (d.r. 10:1); (xii) NaCN, DMF, 60 °C,84%; (xiii) DIBAL-H, diethyl ether, -78 °C, 96%; (xiv) DIBAL-H,CH_2Cl_2, -78°C,60%; (xv) $NaClO_2$,2-methyl-2-butene, $NaH_2PO_4 \cdot H_2O$, ^{t}BuOH,H_2O, 85%; (xvi) 2,4,6-trichlorobenzoyl chloride, toluene, DMAP, Et_3N, 44%; (xvii) $Hg(O_2CCF_3)_2$ then $NaBH_4$,THF:H_2O (1:1), 63% (d.r. > 20 :1); (xviii) $(CF_3CH_2O)_2P(O)CH_2CO_2H$, EDCI·HCl, HOBT·$H_2O$, CH_2Cl_2, 99 %; (xix) 18-crown-6, KHMDS, -78 °C, then **12**,85 °C, 62%.

Sasaki's approach (2007)[12]

In Fuwa's approach, the synthesis of enol phosphate **17** started with the asymmetric allylation of aldehydes **13** having 4 step sequences such as MPM protection, Grubbs

cross metathesis with methyl acrylate and reduction giving allylic alcohol **14**.Sharpless asymmetric epoxidation of allylic alcohol delivered epoxide **15** in 97% yield as a single diastereomer, which was elaborated to allylic alcohol **16** by an



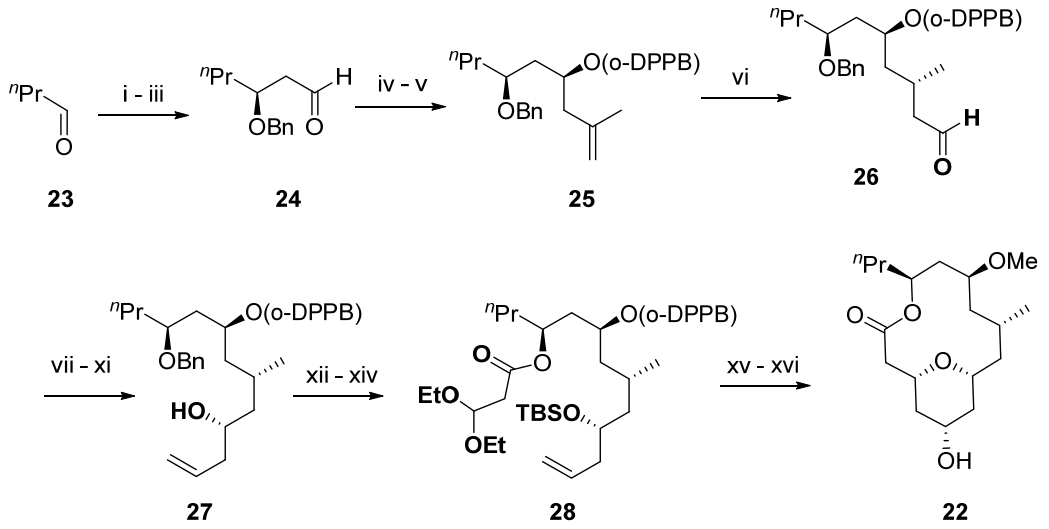
Scheme 2: (i) (+)-Ipc_2BOMe, allylMgBr, Et_2O, -78°C; then aqueous NaOH, H_2O_2, RT, 98%; (ii) MPMOC-(=NH)CCl_3, $La(OTf)_3$, toluene, RT; (iii) methyl acrylate, Grubbs IInd catalyst (3 mol%), CH_2Cl_2, 40°C, 58% (over 2 steps); (iv) DIBAL-H, CH_2Cl_2, -78 °C, 80%; (v) (-)-DET, $Ti(OiPr)_4$, tBuOOH, 4° M.S., CH_2Cl_2, -20 °C, 97%; (vi) I_2, PPh_3, imidazole, THF, RT; (vii) Zn, AcOH, EtOH, RT, 75% (over 2 steps); (viii) BOMCl, $^iPr_2NEt$, CH_2Cl_2, RT; ix) DDQ, CH_2Cl_2/pH 7 buffer, RT, 72% (over 2 steps); x) Ac_2O, Et_3N, DMAP, THF, RT, 99%; (xi) KHMDS, $(PhO)_2P(O)Cl$, THF/HMPA (1:1), -78 °C. (xii) DIBAL-H, CH_2Cl_2, -78 °C, 94%; (xiii) (+)-Ipc_2BOMe, allylMgBr, Et_2O, -78°C; then aqueous NaOH, H_2O_2, RT, 87%; (xiv) MeOTf, 2,6-di-tert-butylpyridine, CH_2Cl_2, RT, 88%; (xv)O_3, CH_2Cl_2,-78°C; then PPh_3, RT, 85%; (xvi) (-)-Ipc_2BOMe, allylMgBr, Et_2O, -78 °C; then aqueous NaOH, H_2O_2, RT, 96%; (xvii) H_2, Pd/C, EtOAc, RT, 100%; (xviii) MPMOC(=NH)CCl_3, $La(OTf)_3$, toluene, RT, 75%; (xix) TBAF, THF, 50°C, 87%; (xx) I_2, PPh_3, imidazole, THF, RT, 76%. (xxi)**17**, B-MeO-9-BBN, ^tBuLi, Et_2O/ THF (1:1), -78 °C to RT; then 3 M aqueous Cs_2CO_3, [$Pd(PPh_3)_4$] (10 mol %), **20**(1.5 equiv), DMF, RT; (xxii) Grubbs II catalyst (10 mol %), toluene (5 mm), 70 °C, 78% (over 2 steps); (xxiii) **12**, DIAD, PPh_3, benzene, RT, 61%.

iodination/reductive ring-openingsequence. Protection of **16** (BOMCl, $^{i}Pr_2NEt$), oxidative cleavage of the MPM ether, and subsequent acetylation gave acetate, which on enolization with KHMDS in the presence of $(PhO)_2P(O)Cl$ furnished enolphosphate **17**. On the other hand, the synthesis of iodide **20** commenced with the known nitrile **18**,which on DIBAL-H reduction,followed by asymmetric allylation and methyl protection afforded methylether **19**. The methyl ether **19** was subjected to: (a) ozonolysis of thedouble bond,(b) asymmetric allylation, (c) hydrogenation, (d) protection of the remaining hydroxy group as its MPM ether, (e) desilylation and (f) iodinationunder standard conditions that furnished iodide **20** as single diastereomer. The coupling of two advance fragments **17** and **20** followed by macrolactonization afforded the desired neopeltolide (**1)** (**Scheme 2**).

Lee's approach (2008)[13]

Lee *et al.* have made aldehyde **24** from *n*-butanal (**3**) by a reaction sequence involving anasymmetric crotyl transfer reaction, protection of thealcohol group with a benzyl group, and ozonolysis. Titanium (IV) chloride mediated methallylationproceeded stereoselectively to produce a homoallylic alcohol,from which ester **25** was obtained by esterification with 2-diphenylphosphinobenzoic acid. The substrate-directedhydroformylationproduced desiredaldehyde **26** in a 5:1 ratio which was preferentially transformedinto desired homoallylic alcohol **27** in a 5.5:1 ratio ofisomers by using Brown allylation. Intermediate **28** was prepared from **27** by asequence of reactions involving protecting the alcohol with a *tert*-butyldimethysilyl(TBS) group, cleaving the benzyl group by using2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), andesterifying with 3,3-diethoxypropanoic acid. Compound **28** was reacted with triethylsilyltrifluoromethanesulfonate(TESOTf) in acetic acid in the presence of trimethylsilyl acetate (TMSOAc) and subsequently

treated under basicconditions to yield bicyclic macrolactone **22**. Approximately10% racemizationwas observed by careful spectroscopicanalysis of **22 (Scheme 3)**.

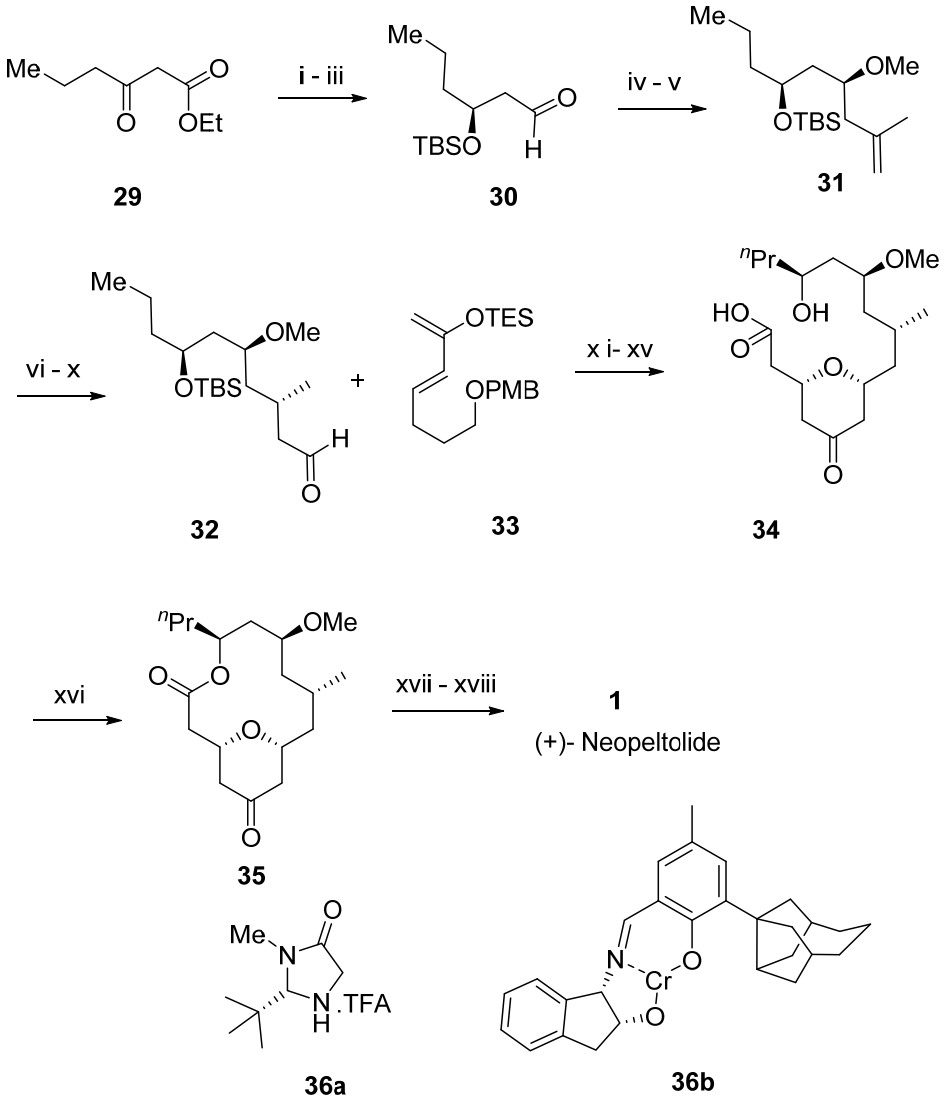


Scheme 3: (i) **4**, CSA, CH_2Cl_2 ; (ii) NaH, BnBr, TBAI, THF/DMF (5:1); (iii) O_3, CH_2Cl_2, -78 °C; Ph_3P 49% (over 3 steps); (iv) CH_2C- $(CH_3)CH_2TMS$, $TiCl_4$, CH_2Cl_2, -78°C; (v) **6**, DCC, DMAP, $CH_2Cl_2$78% (over 2 steps); (vi) $Rh(CO)_2(acac)$, $P(OPh)_3$, 40 bar H_2/CO (1:1), toluene, 30 °C, 65%; (vii) H_2SO_4, $HC(OMe)_3$, MeOH, 65%; (viii) KOH, EtOH, reflux; (ix) NaH, MeI,THF. (x) HCl, acetone; (xi) $CH_2CHCH_2B(dIpc)_2$, ether, -78 °C; H_2O_2, NaOH, 69%; (xii) TBSOTf, 2,6-lutidine, CH_2Cl_2 ; (xiii) DDQ, $ClCH_2CH_2Cl$, pH7 buffer;(xiv) $(EtO)_2CHCH_2CO_2H$, DCC, DMAP, CH_2Cl_2, 81%; (xv) TESOTf, TMSOAc, AcOH (0.01m), RT, 30 min; (xvi) K_2CO_3, MeOH, 47%.

Paterson's approach (2008)[14]

The synthesis of the required aldehyde **32** commenced with a Noyori asymmetric hydrogenationof the *β*-keto ester **29** using (S)-BINAP–Ru(II) catalyst and subsequent TBS ether formation and DIBAL-H reduction of the ester gave the enantiopure aldehyde **30**. A Brown methallylation **30** with the reagent derived from 2-methylpropene (^{n}BuLi, TMEDA, Et_2O) and (-)-Ipc_2BOMe gave alcohol, which was transformed(using methylation followed by ozonolysis) to aldehyde **32** by a series of transformations: (a) methylation (b) ozonolysis (c) HWE reaction (d) DIBAL-H reduction (e) oxidation and (f) chiral reduction. Thus, a Jacobsen asymmetric hetero Diels–Alderreaction between **32** and the readily available 2-siloxydiene **33** promoted

by the chiral tridentate chromium(III) catalyst **36b** gave correctly configured tetrahydropyran, which upon simple functional group transformations gave *seco* acid **34**. The seco acid **34** was subjected to Yamaguchi macrolactonization to give desired macrolactone **35**, which on simple reduction and Mistunobu reaction with **12** afforded the (+)-Neopeltolide **1** (**Scheme 4**).

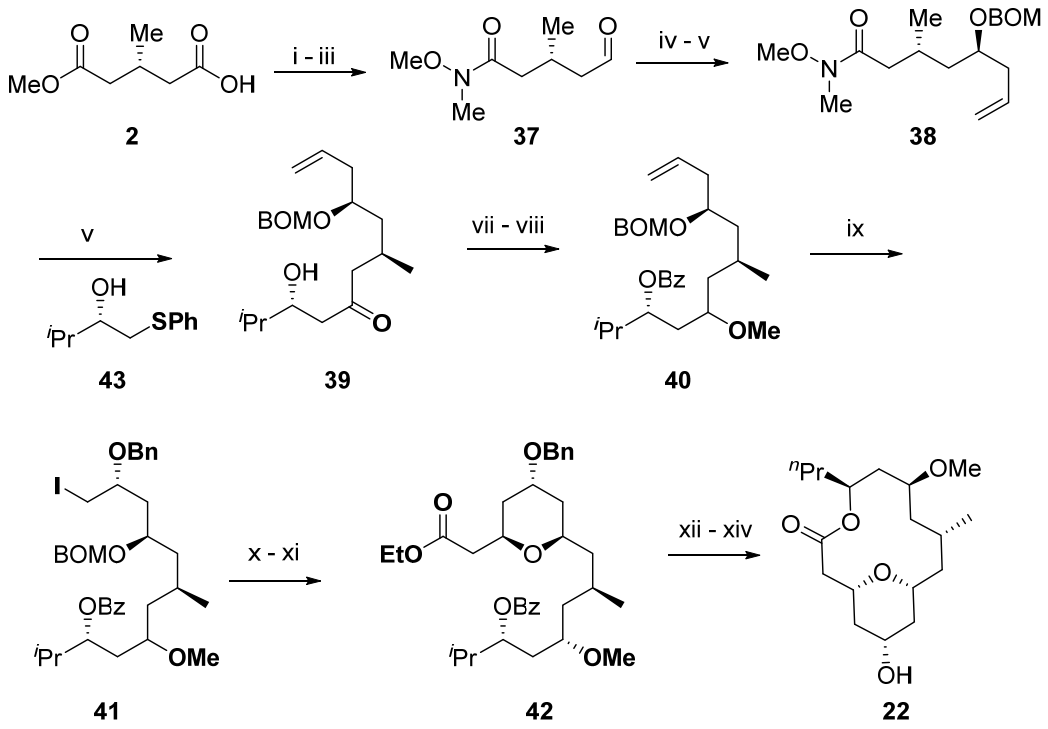


Scheme 4:(i) (S)-BINAP-Ru(II) complex, MeOH, H_2 (6 atm.), 100 °C, 92%; (ii) TBSCl, imid., DMF, 99%; (iii) DIBAL-H, -78 °C, 83%. (iv) Ipc_2B (-CH_2-$CH(CH_3)$=CH_2), Et_2O, -90 °C, 81% (94:6 dr); (v) NaH, MeI, THF, 95%; (vi) O_3; DMS, CH_2Cl_2;MeOH, 90%; (vii) trimethyl phosphonoacetate, NaH, THF, reflux, 16 h, 76% (E/Z 75:25; (viii) DIBAL-H, -78 °C, 84%; (ix) DMP, $NaHCO_3$, 99%; (x) **36a** (20 mol %), Hantzch ester, $CHCl_3$, -30°C, 72 h, 80% (76:24 dr); (xi)**36b** (10 mol %), 4A° MS, 8 d then acidified

$CHCl_3$, 78%; (xii) DDQ, CH_2Cl_2/pH 7 buffer (10:1), 99%; (xiii) DMP, $NaHCO_3$, CH_2Cl_2, 98%; (xiv) $NaClO_2$, 2-methyl-2-butene, $NaH_2PO_4 \cdot H_2O$, ^tBuOH,H_2O, 85 %; (xv)TBAF, THF, 91% (2 steps); (xvi) $Cl_3C_6H_2COCl$, NEt_3, THF, 1 h, 0 °C; DMAP, toluene, 80%; (xvii) $NaBH_4$, MeOH, 99%; (xviii) **12**, DIAD, PPh_3, C_6H_6, 53%

Taylor's approach (2008)[15]

Taylors *et al.* have developed a concise synthesis to neopeltolide macrolactone **22** whichbegan with chemoselective reduction of commercially available(*R*)-4-(methoxycarbonyl)-3-methylbutanoic acid **2** withborane dimethylsulfide complex to give alcohol,whichwas sequentially treated under Weinreb amidation andDess-Martin oxidation procedure to produce amide-aldehyde **37** in good yield. Asymmetricallylation (with Soderquist's chiralbicyclodecane-allylborane reagent)of **37** followed by BOM protection afforded BOM ether **38**. Hydroxylsulfide **43** on addition to Weinreb amide **38** according themethod of Rychnovsky cleanly produced hydroxyketone **39** in 92% yields without the necessity for protection at the C13 hydroxy group. The hydroxyl ketone was subjected to diastereoselective reduction followed by methyl protection of alcohol afforded methyl ether **40**. Treatment of homoallylic BOM ether **40** with iodine monochloride, uponaqueous workup, 1,3-*syn*-diol monoether **41** was liberated in 71% yield with excellent stereocontrol. The alternative tetrahydrofuran cyclization event of iodide **41** was highly competitive, upon optimization; the desired tetrahydropyran core was executed *via* radical cyclization with AIBN and *n*-Bu_3SnH in refluxing toluene. The ester moieties in **42** were deportected and upon Yamaguchi lactonization and benzyl deprotection, the desired (+)-neopeltolide macrolactone **22** was formed (**Scheme 5**).

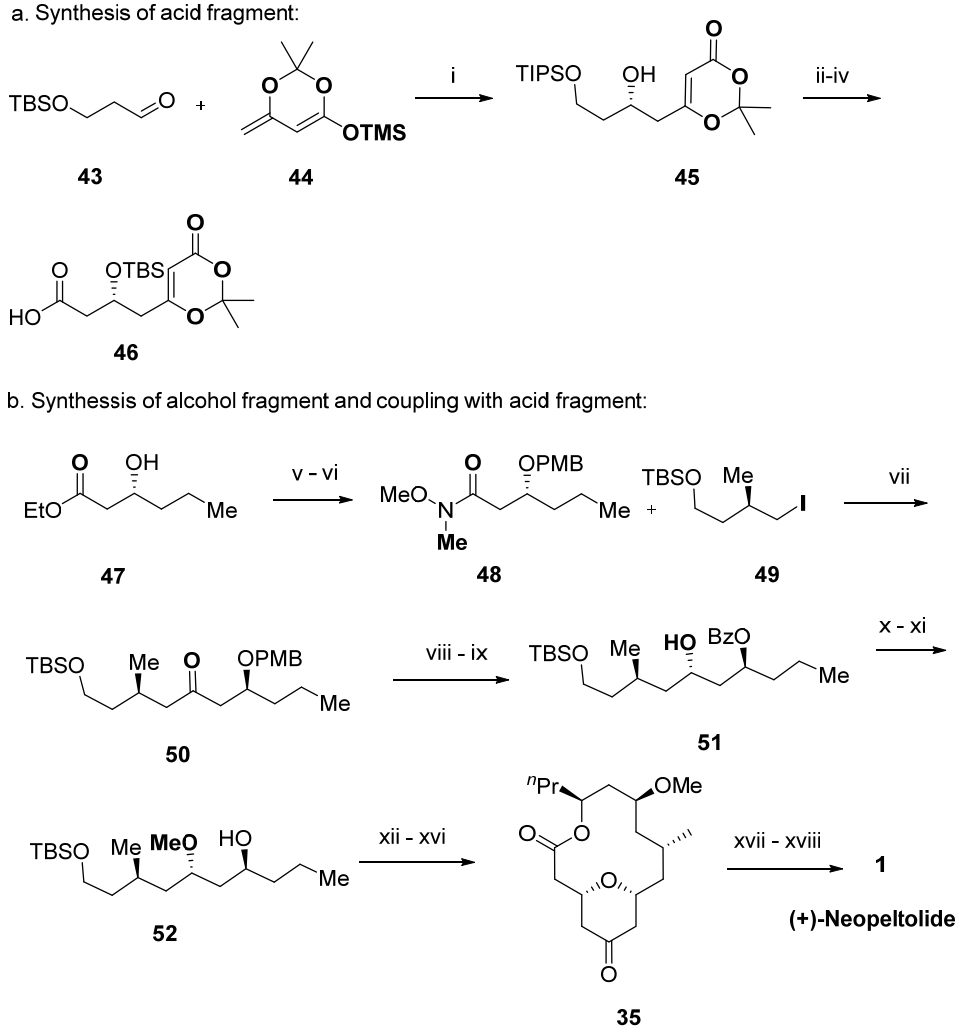


Scheme 5: (i) BH_3.DMS, THF, 0°C, 3 h; (ii) (OMe)$MeNH_2Cl$, i-PrMgCl, (87% over 2 steps) (iii) Dess-Martin reagent, $NaHCO_3$, CH_2Cl_2, 99%; (iv) Chiral bicyclodecane-allylborane, BF_3. OEt_2, 60%, (v) BOMCl, DIPEA, CH_2Cl_2, 0°C, 1 h; (vi) *n*-BuLi, LiDBB then**43**, THF, 2 h, 92%; (vii) SmI_2, PhCHO, THF, -10 °C, 15 min. 80%; (viii) MeO_2:BF_4, proton sponge, CH_2Cl_2,0 °C, 1 h, 99%; (ix) ICl, $Na_2S_2O_3$ (aq.), CH_2Cl_2, -78°C, 30 min., 71%; (x) ethyl propiolate, PBu_3, CH_2Cl_2, 25 °C, 30 min. 98% (xi) AIBN, *n*-BuSn-H, toluene, 25 °C, 5 h; (xii) KOH, MeOH, 95%; (xiii) TCBCl, TEA, DMAP, 87%; (xiv) H_2(1atm), Pd/C, 100%.

Scheidt's approach (2008)[16]

The synthesis of acid **46** began with the Ti(IV)-(*R*)-BINOL catalyzed aldol reaction between dienoxy silane **44** and the protected saturated aldehyde **43** to afford secondary alcohol **45** in 63% yield and 88% ee. The protection of the alcohol and subsequent two-step conversion of the primary silyl ether to the carboxylic acid furnished the dioxinone acid **46**. The synthesis of the targetalcohol commenced with the two-step conversion of hydroxy ester **47** to Weinreb amide **48**. The addition of the alkyl lithium derived from **49** to this amide afforded the extended ketone **50.** The removal of the PMB group and a selective Evans-Tischenko reduction generated

alcohol **51** with the requisite *anti* stereochemistry. A careful methylation of **51** and hydrolysis of the benzoate furnished the necessary alcohol **52**. The fragment coupling of **52** and **46** was accomplished usingYamaguchi's protocol. The removal of both silyl ethers proceeded smoothly with HF-pyridine, and the resulting diol underwent a selective oxidation of the

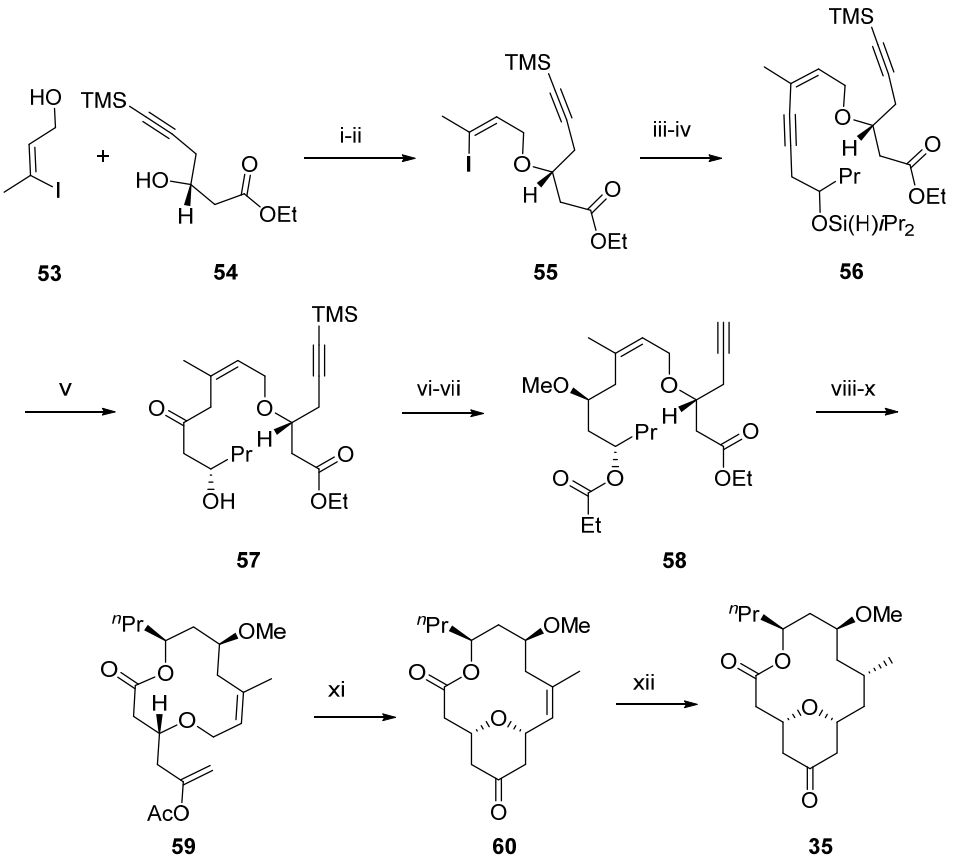


Scheme 6: (i) Ti(*i*-PrO)$_4$, (*R*)-BINOL, 4 Å sieves, CH_2Cl_2, 63%; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 91%; (iii) PPTs, EtOH, 83%; (iv) PDC, DMF, 97%; (v) HN(Me)OMeCl, *i*-PrMgBr, THF, 94%;(vi)PMB-OC(NH)CCl_3, PPTs, cyclohexane/CH_2Cl_2, 80%; (vii) *t*-BuLi, pentane/Et_2O, -78 °C, 90%; (viii) DDQ, pH 7 buffer, CH_2Cl_2, 84%; (ix) SmI_2, PhCHO, THF, 0 °C, 91%; (x) MeOTf, DTBMP, CH_2Cl_2, 88%; (xi) K_2CO_3, MeOH, 86%; (xii) 2,4,6-trichlorobenzoyl chloride, DMAP, THF; (xiii) HF, pyridine, THF, (xiv) TEMPO, $H_5C_6I(OAc)_2$, CH_2Cl_2, 69% (xv) $Sc(OTf)_3$, $CaSO_4$, MeCN, 25%; (xvi) DMSO, H_2O, 130 °C. (xvii) $NaBH_4$, MeOH, 0 °C, 75%; (xviii) DIAD, Ph_3P, **12**, benzene, 88%.

primary alcohol with TEMPO to generate acyclic aldehyde, which was subjected to scandium(III) triflate- promoted macrocyclizationto produce the fully elaborated 14-membered ring **35** in this single unprecedented step;thus confirming (+)-neopeltolide (**1**) structure unambiguously(**Scheme 6**).

Floreancig's approach (2009)[17]

Floreancig *et al*. have commenced their synthetic sequence with the conversionof **53** into its trichloroacetimidate, followed by etherificationwith **54** in the presence of TfOH to give **55** as aninseparable 7.3:1 mixture of alkene stereoisomers.Hept-1-yn-4-ol was converted into a diisopropylsilyl ether andcoupled to **55** to provide **56** in 69% overall yield as an inseparable 5.7:1 mixture of alkene stereoisomers. Regioselective alkyne hydration through a sequence of[Pt(DVDS)]-mediated hydrosilylation followed by oxidative cleavage of the intermediate vinylsilane and concomitant alkyne desilylation provided **57**. A stereoselective reduction of **57** with EtCHO and SmI_2 followed by methylation of the resulting hydroxy group, provided diester **58**. Cleavage of both esters and lactonization of the *seco*acid under Yamaguchi conditions provided macrolactone, which was subjected to ruthenium mediated addition of HOAc across the alkyne, providing an inseparable 5:1 mixture of enol acetat eregioisomers **59** in 82% yield. Exposure of **59** to DDQ in the presence of $LiClO_4$ and 2,6-dichloropyridine resulted in the formation of tetrahydropyrone **60** as a single stereoisomer in 58% yield. Indeed, when **60** was reduced with H_2 over Pd/C, **35** was obtained in 74% yield to complete the formal synthesis of (+)-neopeltolide (**1**)(**Scheme 7**).

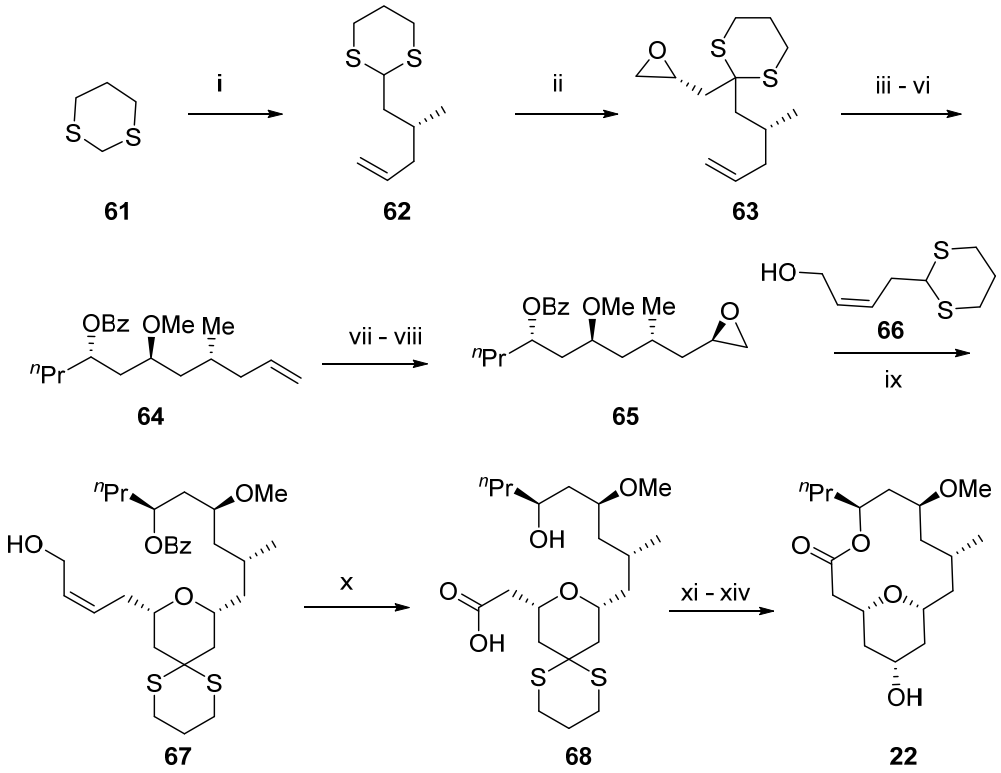


Scheme 7: (i) NaH, Cl_3CCN, Et_2O, 0 °C, 100%; (ii) TfOH, cyclohexane, 77%; (iii) $^{i}Pr_2Si(H)Cl$, imidazole, THF, 77%; (iv) hept-1-yn-4-ol, $[(Ph_3P)_2PdCl_2]$, CuI, iPr_2NH, 89%; (v) [Pt(DVDS)], THF, then H_2O_2, KF, Bu_4NF, $KHCO_3$, DMF, 40 °C, 57% (67% based on starting-material purity); (vi) EtCHO, SmI_2, THF, -10 °C, 77%; (vii) Me_3OBF_4, proton sponge, CH_2Cl_2, 0°C, 93%; (viii) LiOH, H_2O, MeOH, 45°C; (ix) Et_3N, 2,4,6-Cl_3BzCl, THF, then DMAP, toluene, 65°C, 72% (over 2 steps); (x) HOAc, Na_2CO_3, $[\{Ru(p\text{-cymene})Cl_2\}_2]$, (2-furyl)$_3$P, 1-decyne, toluene, 80 °C, 82%, 5:1 regioisomer, (xi) DDQ, 2,6-Cl_2Py, $LiClO_4$, DCE, 58% (65% based on starting-material purity); (xii) H_2, Pd/C, EtOH, 74%.

Hong's approach (2010)[18]

In Hong's approach, the synthesis of neopeltolide macrolactone **22** was started with the preparation of the chiral epoxide **61** which can be used for dithiane coupling. The coupling of **61** with (*R*)-5-iodo-4-methylpentene, followed by alkylation with (*R*)-(-)-epichlorohydrin and afforded **63**. The ring opening of epoxide **63**, deprotection of the 1,3-dithiane group, and Evans–Tischenko reduction of β-hydroxyketone, afforded the desired *anti*-1,3-diol, which upon methylation, asymmetric dihydroxylation and

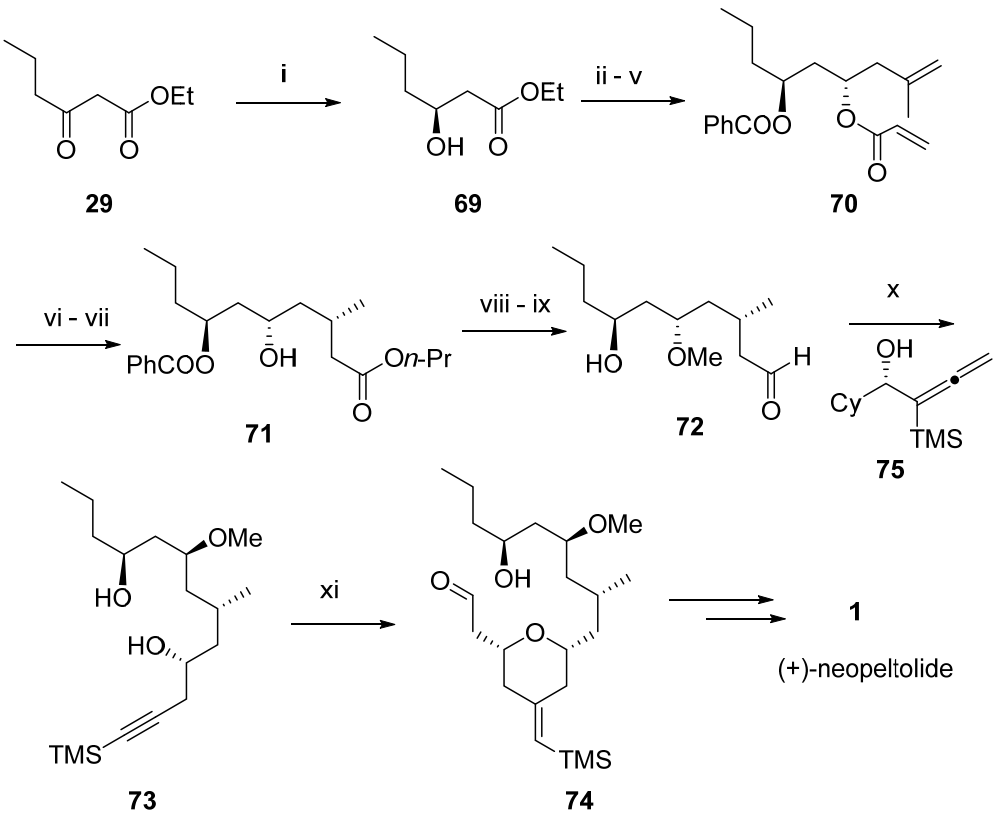
epoxide formation afforded epoxide **65** for the second 1,3-dithiane coupling. The coupling of **66** and **65** proceeded smoothly with accompanying deprotection of the benzoyl-protected hydroxyl group to set the stage for the key tandem allylic oxidation/oxa-Michael reaction. The allylic oxidation/oxa-Michael reaction/oxidation of **67** afforded the desired 2,6-*cis*-THP methyl ester, which under basic conditions, followed by a macrocyclization reaction gave the (+)-neopeltolide macrolactone **22** (**Scheme 8**).



Scheme 8: (i) *n*BuLi, THF, -78-10 °C, 1 h, then (*R*)-5-iodo-4-methylpentene, 78—40°C, 4 h, 79%;(ii) *n*BuLi, THF, 25 °C, 5 min, then (*R*)-epichlorohydrin, -78°C, 2 h, then 25°C, 12 h, 83%; (iii) EtMgBr, CuI, THF, -40-10°C, 3 h, 96%; (iv) MeI, $CaCO_3$, CH_3CN/H_2O (3:1), 25°C,14 h, 87%; (v) PhCHO, SmI_2, THF, 0 °C, 3 h, 87%; (vi) 1,8-bis(dimethylamino)naphthalene, $Me_3O{\cdot}BF_4$, CH_2Cl_2, 0–25°C, 2 h, 93%; (vii) AD mix-β, H_2O/*t*BuOH (1:1), 0 °C, 10h, 92%, α/β 3:1; (viii) NaH, *N*-p-toluenesulfonylimidazole, THF, 0–25 °C, 1 h, 92%; (ix) ^{t}BuLi, HMPA/THF (1:10), -78°C, 5 min, then 24, -78°C, 3 h, 75%; (x) MnO_2, CH_2Cl_2, 25°C, 3 h, then dimethyltriazolium iodide, MnO_2, DBU, MeOH, 4°MS, 25°C, 21 h, 78%; (xi) 0.1N LiOH, THF/ MeOH (3:1), 25 °C, 1 h, 99%; (xii) 2-methyl-6-nitrobenzoic anhydride, 4-dimethylaminopyridine, CH_2Cl_2, 24 h, 69%; (xiii) MeI, $CaCO_3$, CH_3CN/ H_2O (3:1), 25°C, 30 h, 89%; (xiv) $NaBH_4$, MeOH, 0°C, 1 h, 93%.

Roulland's approach (2011)[19]

Roulland *et al*. have commenced their synthesis by the ruthenium-catalyzed asymmetric hydrogenationof ketoester **29** providing alcohol **69,** which was transformed to diene **70** by a series of reactions (a) the Weinrebamide formation,(b) Grignard reaction with (2-methylallyl) magnesium chloride(c) Evans-Tishchenkoreaction (d) acylation. The diene **70** was subjected to ring closure metathesisusing second-generation Grubbs' catalyst and a simple Pd/Ccatalyzedhydrogenation that turned out to be totally diastereoselective to give *seco*-ester **71** (ratio: 1/2). Then, the

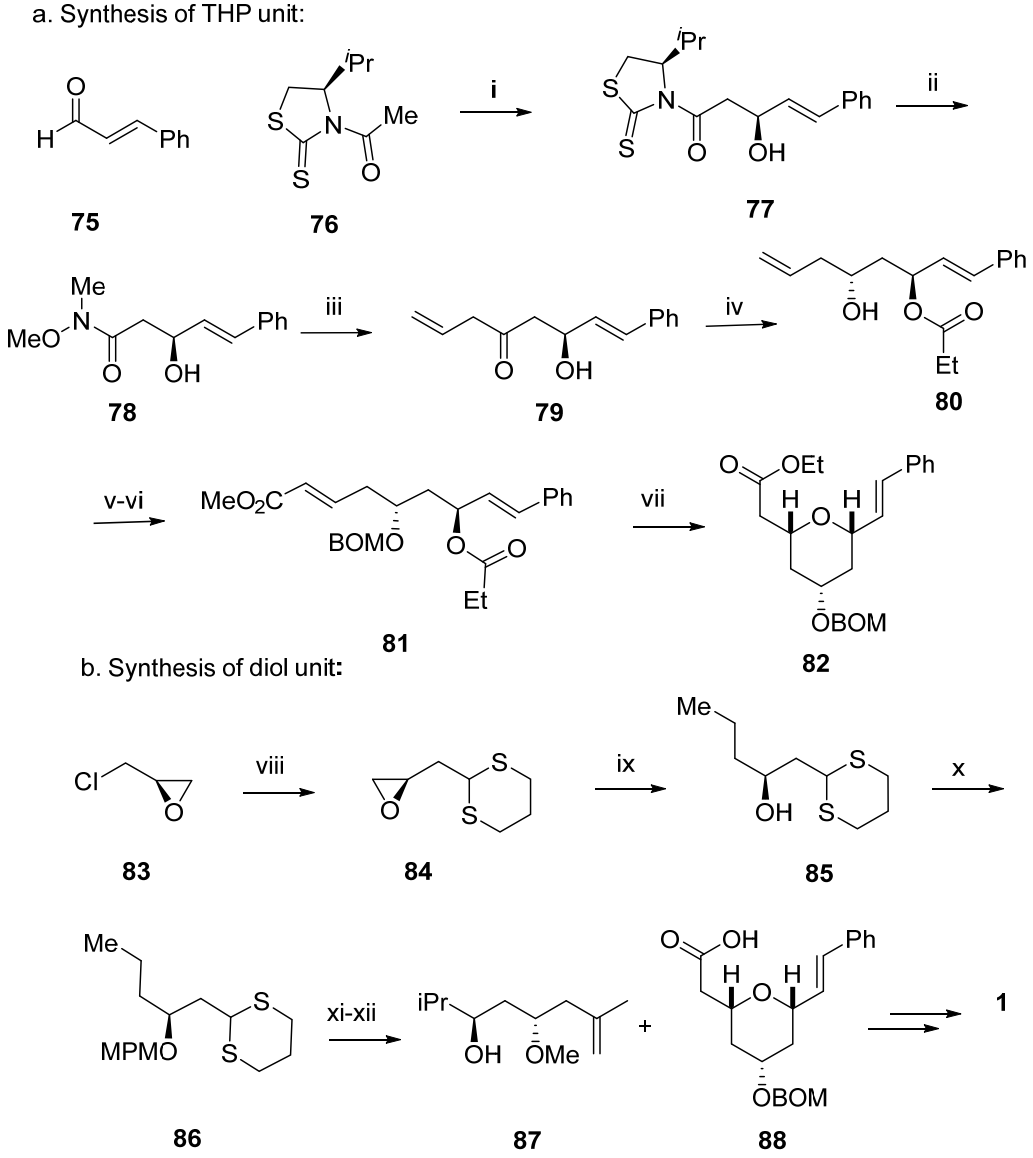


Scheme 9:(i) Ru cat., (0.25 mol %), (R)-(+)- SYNPHOS H_2 (4 bars), 50 °C, 87%, 99% ee; (ii) MeONHMe. HCl, $AlMe_3$/ THF, 25 °C, 100%; (iii) methallyl magnesium chloride, THF, -78 °C to 25 °C, 81%; (iv) PhCHO, SmI_2/ THF, -10 °C to 25 °C, 84%, >99:1; (v) *i*-$PrNEt_2$, acryloyl chloride, CH_2Cl_2, -10 to 25 °C, 97%; (vi) Grubbs 2nd cat. CH_2Cl_2, reflux, 86%; (vii) H_2(1 atm) Pd/C, *n*-PrOH, 25 °C, then PPTS, 60 %; (viii) Me_3OBF_4, Proton sponge, CH_2Cl_2, 25 °C, 93%; (ix) DIBAL-H, PhMe,-78 °C, 94%; (x) $InBr_3$, CH_2Cl_2, 25 °C, 77%; (xi) $CpRu(MeCN)_3PF_6$, AcOH (7 to 10%), Acetone , rt, 22% to 58 %.

secondary alcohol functionality was transformed into a methoxy group using the Meerwein'ssalt and a careful DIBAL-Haddition on diester at low temperature led to aldehyde**72** in 94% yield, while removing the benzoyl group inheritedfrom the Evans-Tishchenko step. In(III)-catalyzed propargylation reaction of trimethylsilylpropynyl group from the asymmetricallenyl alcohol **75** on aldehyde **72** leading to key homopropargylic alcohol **73**, which on simple functional group transformations produced (+)-neopeltolide **1**. Finally, the shortest andmost straightforward (16 steps from **29**, 6.2% overall yield) total synthesis of (+)-neopeltolide (**1**) was achieved (**Scheme 9**).

Fuwa's approach (2013)[20]

In Fuwa's approach, the synthesis of neopeltolide (**1**) commenced with the condensation of *trans*-cinnamaldehyde**75** with titanium enolate derived from chiral thiazolidinethione **76** under Nagao conditions to deliver alcohol **77** as an 11:1 mixture of diastereomers, from which the desired product was readily separated by flash column chromatography using silica gel. Direct amidation of **77** with MeONHMe·HCl and imidazole gave Weinreb amide **78**. The addition of allylmagnesium chloride to **78** providedα,β-unsaturated ketone **79**, which was subjected to Evans–Tishchenko 1,3-*anti*reduction (SmI_2, EtCHO) to yield alcohol **80** with greater than 20:1 diastereoselectivity. The olefin cross-metathesis of **80** with methyl acrylate under the influence of the Grubbs' second-generation catalyst (G-II) proceeded without incident to preferentially afforded α,β-unsaturated ester **81** over the corresponding RCM product. The protection of the C5 hydroxy group (BOMCl, iPr_2NEt) to gave BOM ether **81** in 68% yield (two steps). The methanolysis of the propionyl group using K_2CO_3 in methanol at room temperature and concomitant



Scheme 10: (i)$TiCl_4$, $^{i}Pr_2NEt$, CH_2Cl_2, -78°C, 84% (d.r. 11:1); (ii) MeONHMe.HCl, imidazole, CH_2Cl_2, 25°C, 94%; (iii) allylMgCl, THF, 0°C, 90%; (iv) SmI_2, EtCHO, THF, -10°C, quant. (d.r. >20:1); (v) Grubbs IInd generation catalyst, methyl acrylate, CH_2Cl_2, 25°C; (vi) BOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, 120°C (MW), 68% (2 steps); (vii)K_2CO_3, MeOH, 25°C; (viii) DBU, toluene, 100°C, 53% (2 steps)(d.r. >20:1); (ix) TMSOK, Et_2O, 25 °C, quant. (viii) 1,3-dithiane, *n*BuLi, THF, -78°C to 25°C, 90%; (ix) EtMgBr, CuI, THF, 0°C, 92%; (x) MPMCl, KO^{t}Bu, $^{n}Bu_4NI$, THF, 25°C, 92%; (xi) (a) methallyltr-ibutyltinchloride, $MgBr_2.OEt_2$, CH_2Cl_2, 0°C, 73% (d.r. 15:1) (b) MeI, NaH, DMF, 0°C-25°C; (c) DDQ, pH 7 buffer, CH_2Cl_2,0°C-25°C, 91% (2 steps).

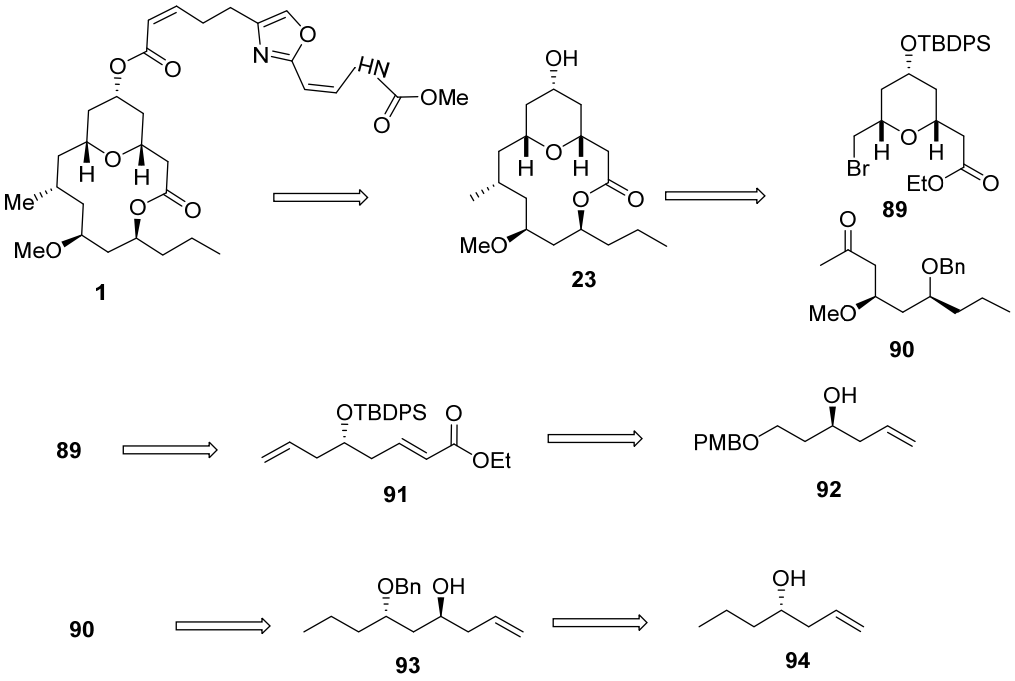
intramolecular oxa-conjugate cyclization provided tetrahydropyran **82**, albeit with lowdiastereoselectivity (*cis*/*trans* 2:1). Finally, the hydrolysis of the methyl ester **82**

afforded carboxylic acid **88** in quantitative yield. Alcohol fragment **87** could be conveniently prepared in a straightforward manner from commercially available (*R*)-epichlorohydrin **83**. The addition of 2- lithio-1,3-dithiane gave epoxide, which was treated with EtMgBr in the presence of CuI to provide alcohol **85**. The subsequent protection of the hydroxy group as its MPM ether **86** followed by removal of the dithiane furnished aldehyde, which was methallylated with methallyltrimethylsilane and $MgBr_2 \cdot OEt_2$ under chelate-control to afford homoallylic alcoholwith 15:1 diastereoselectivity. The methylation of the resultant hydroxy group and subsequent deprotection of the MPM group by using DDQ yielded alcohol **87.** Finally the coupling of **87** with **88** gave the desired neopeltolide macrolactone (**1**) (**Scheme 10**).

4.1.3 Present Work

4.1.3.1 Objective

Even though many synthetic methods are available for the synthesis of(+)-neopeltolide (**1**),[21] there are certain disadvantages associated with them such as longer reaction sequences, low overall yields, use of costly catalysts and exhaustive reaction conditions. In this section we present a higly convergent routetowards the synthesis of (+)-neopeltolide macrolactone **22**. The strategy employs simple Keck allylation, NHC catalyzed oxoacyloxylation andreductive oxa-Michel addition reactionsas key steps in the synthesis.A prerequisite for the efficient synthesis ofcomplex polyketide natural products is a high degree of stereo-controlto establish asymmetric carbon centers and tominimize oxygen functional group manipulations. With thisin mind, we planned our synthetic avenue toward **1** as summarizedin **Scheme 11**. As described below, we envisioned the attachment of the oxazole-containing side chain**12**to the macrolactone domain of **1** at thefinal stage ofthe total synthesis.

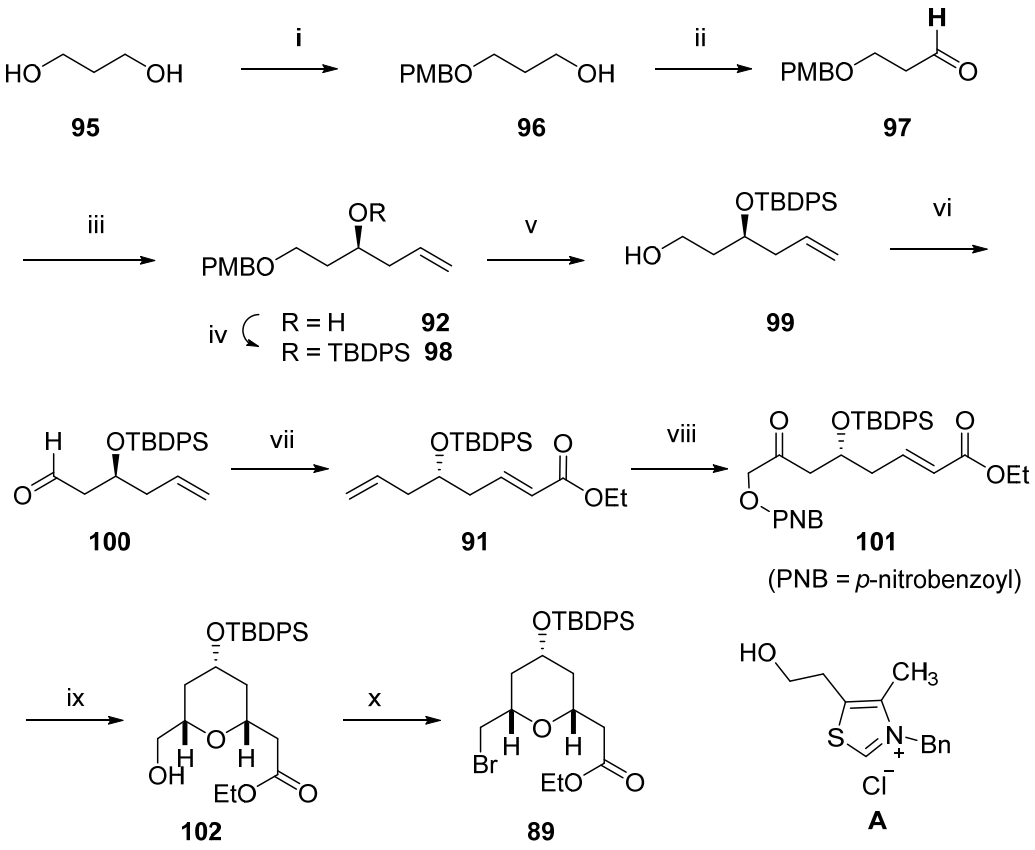


Scheme 11: Retrosynthetic analysis of (+)-neopeltolide (**1**)

The macrolactone domain **22** could be obtained from bromo ester **89** and ketone **90** by Witting reaction and macrolactonization. The bromoester **89** containing THP unit in turn can obtained by NHC catalyzed oxo-acyloxylation-reductive-oxa-Michael addition of diene ester **91**, which can be prepared from chiral homo allylic alcohol **92** by simple functional group transformations. On the other hand, ketone diol **90** could be obtained using methylation-Waker oxidation sequence of alcohol **93**, which in turn can be obtained in two steps from chiral homo allylic alcohol **94.**

4.1.3.2 Results and Discussion

The synthesis of key THP unit **89** (**Scheme 12)**commenced with monoprotection of 1,3 propane diol **95**, using PMBCl and NaH affording PMB ether**96**in 88% yield, which was oxidized to corresponding aldehydes **97** under PCC oxidation condition. Aldehyde **97** was then subjected to enantioselective keck allylation procedure[22] affording enantio- enriched homo allylic alcohol **92** in 84% yield and 96% ee.



Scheme 12: (i) PMBCl (1.1 equiv), NaH (1.5 equiv), DMF, 0-25 °C, 3h, 88%; (ii) PCC, CH_2Cl_2,25 °C, 4h, 94%; (iii) (*S,S*)-BINOL, 4 Å MS, $Ti(OiPr)_4$, allyltri-*n*-butyltin, CH_2Cl_2, -78 to -20 °C, 24 h, 84%, 96% ee; (iv) TBDPSCl (1.1 equiv), imidazole (3 equiv), CH_2Cl_2, 25 °C, 3h, 86% ;(v) DDQ (3 equiv), CH_2Cl_2, 25 °C, 4h, 84% ; (vi) IBX, DMSO, 25°C, 89%; (vii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 92% ; (viii) NHC cat. **A** (10 mol %), Et_3N (1.2 equiv), NBS (1 equiv),DMSO, 25° C, O_2 (1 atm), 16 h, 72% ; (ix) $NaBH_4$ (4 equiv), LiI (10 equiv), MeOH, -20°C, 3 h, 76 %; (xi) PPh_3, CBr_4,imidazole, CH_2Cl_2, 81%.

The homoallylic alcohol **92** was confirmed by its spectroscopic analysis. The ^{1}H NMR spectrum of **92** displayed four characteristic signals at δ 3.78 (s, 3H) due to OC**H**$_3$ protons, 3.83 (br. s., 1H) for –O**H** protons 5.04-5.12 (m, 2H) and 5.71-5.79 (m, 1H) corresponding to alkene protons while its **^{13}C NMR** spectrum showed four typical peaks at δ 35.6, 41.6, 67.9 and 72.5 corresponding to four methelene carbons (**Fig. 2**).

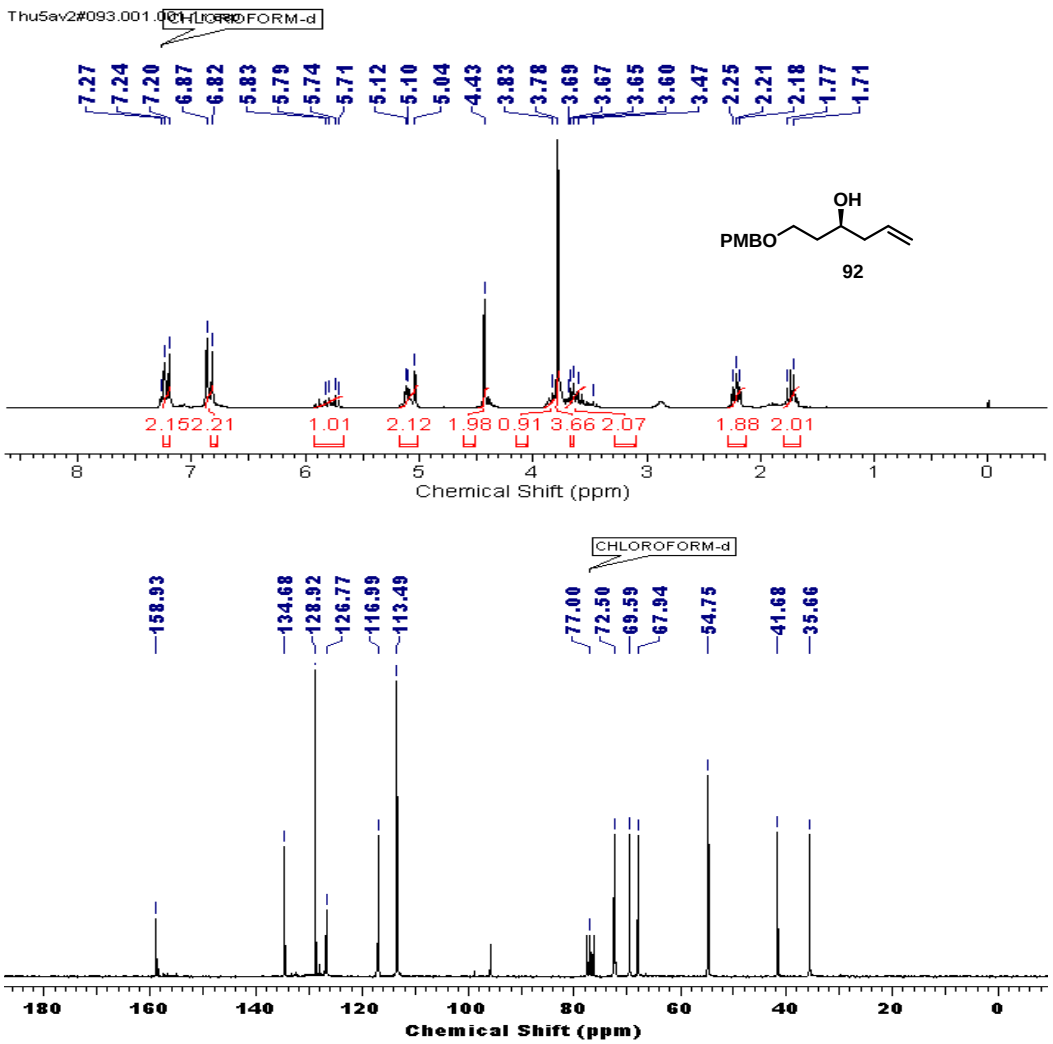


Fig 2: ^{1}H and ^{13}C NMR spectra of **92**

Alcohol **92** was protected as its TBDMS ether (TBDMSCl, imidazole at 0 °C) to give the corresponding protected alcohol **98** in 86% yields. The PMB group in **98** was deprotected using DDQ (3 equiv) to give primary alcohol **99** in 84% yield, which was further subjected to oxidation condition using IBX (1.2 equiv) in DMSO to give the corresponding aldehyde **100** in 89% yield.The ^{1}H NMR spectrum of **100** displayed two characteristic signals at δ1.07 (s, 9H) corresponding to *t*-Bu group and a triplet at

δ 9.69 (t, J = 2.3 Hz, 1H) for aldehydic proton, while its ^{13}C NMR spectrum showed a typical carbon signal at δ 201 attributed to aldehydic carbon (**Fig 3**).

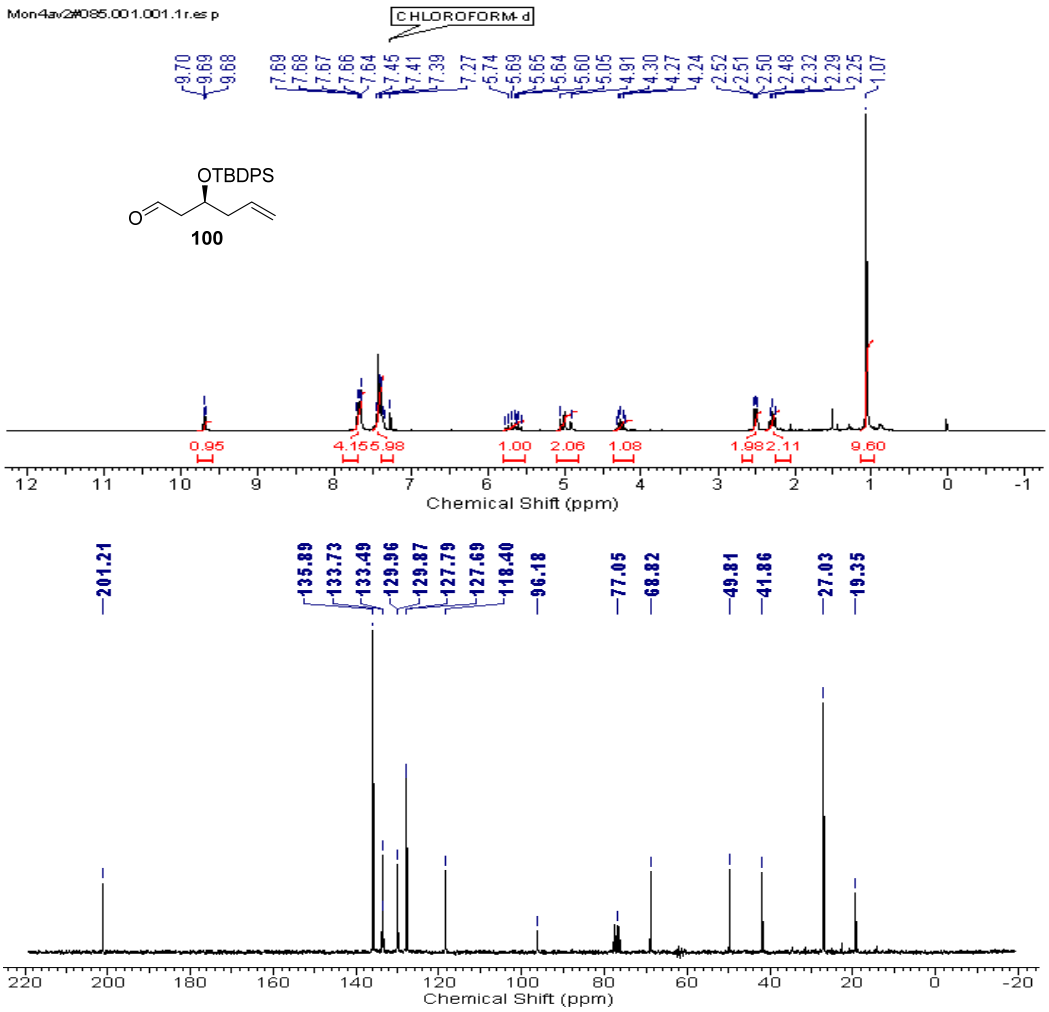


Fig 3: ^{1}H and ^{13}C NMR spectra of **100**

The aldehydes **100** was then subjected to Wittig olefination to form key precursor 1,6- dienic ester **91** in 92% yield. The ^{1}H NMR spectrum of 1,6 dienic ester **91** showed typical peaks at δ 4.82-5.08 (m, 2H), 5.52-5.82 (m, 2H) and 6.72 - 6.98 (m, 1H) corresponding to olefinic protons, while its ^{13}C NMR spectrum displayed a typical carbon signal at δ 166 corresponding to ester carbonyl moiety (**Fig 4**).

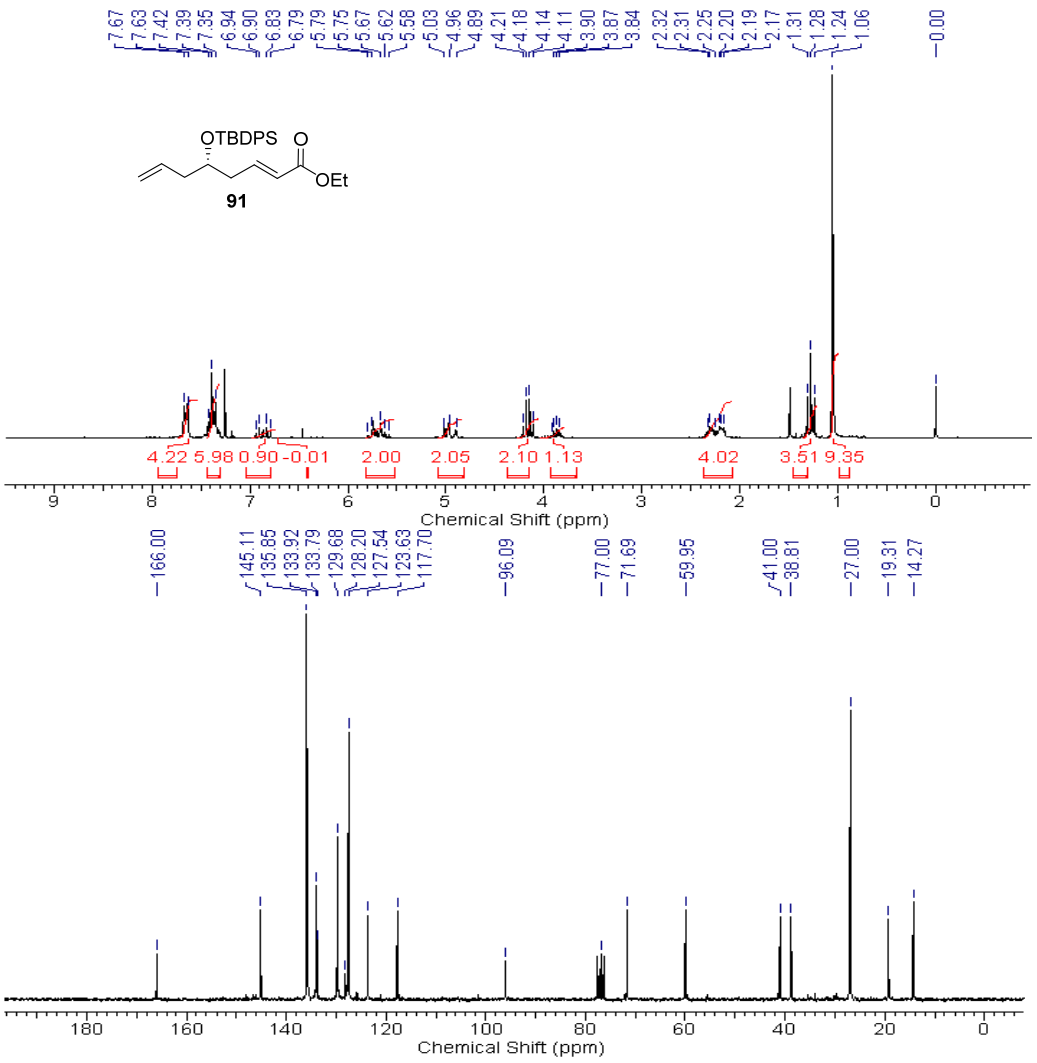


Fig 4: ^{1}H and ^{13}C NMR spectra of **91**

The 1,6-dienic ester**91**was subjected to NHC catalyzed oxo-acyloxylationreaction[23] using *p*-nitrobenzaldehyde (1 equiv), NBS (1 equiv) and Et_3N (1 equiv) in DMSO at 25 °C to give the corresponding α-acyloxy ketone **101** in 72% yield. The oxo-acyloxylation reaction occurred selectively at terminal olefin rather than electron deficient alkenes. The structure of α-acyloxy ketone **101** was confirmed by its spectroscopic analysis. The ^{1}H NMR spectrum of **101** showed two typical signals at

δ4.63- 4.89 (m, 2H) corresponding to –C**H**$_2$ adjacent to carbonyl group and a quadret at δ 8.1 - 8.4 (m, 4H) corresponding to 4-nitrobenzoate group (**Fig 5**).

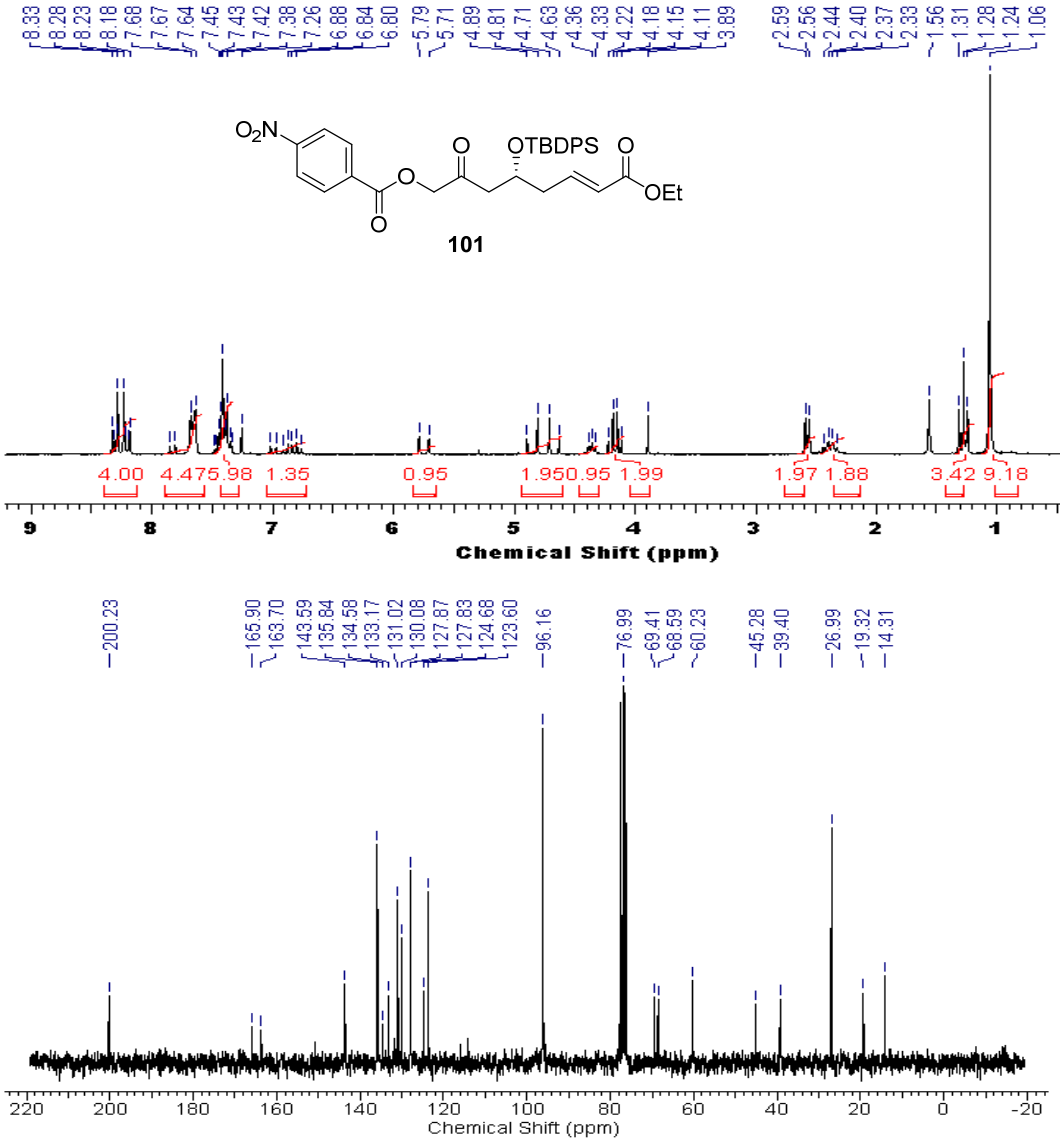
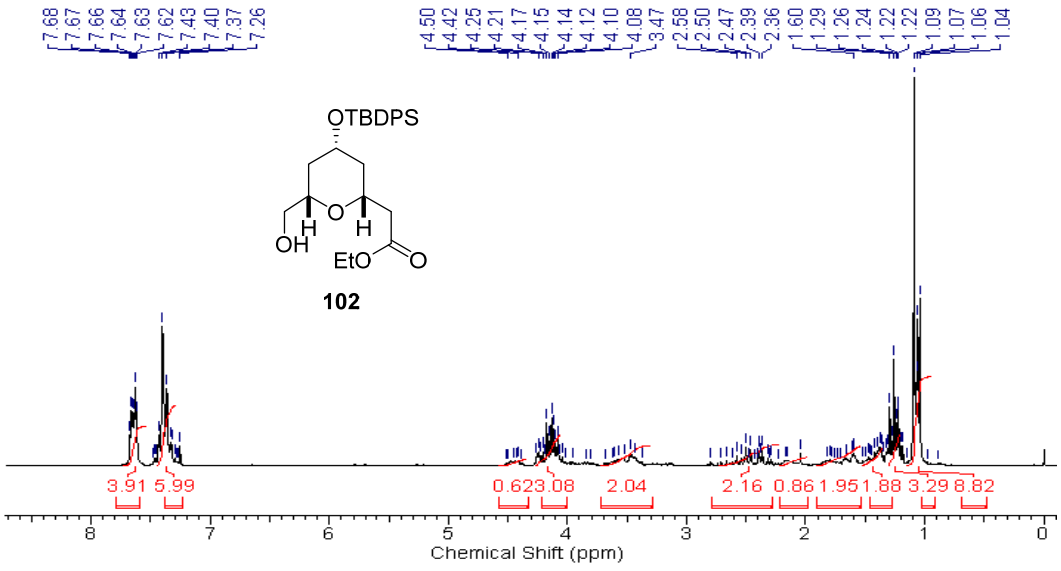
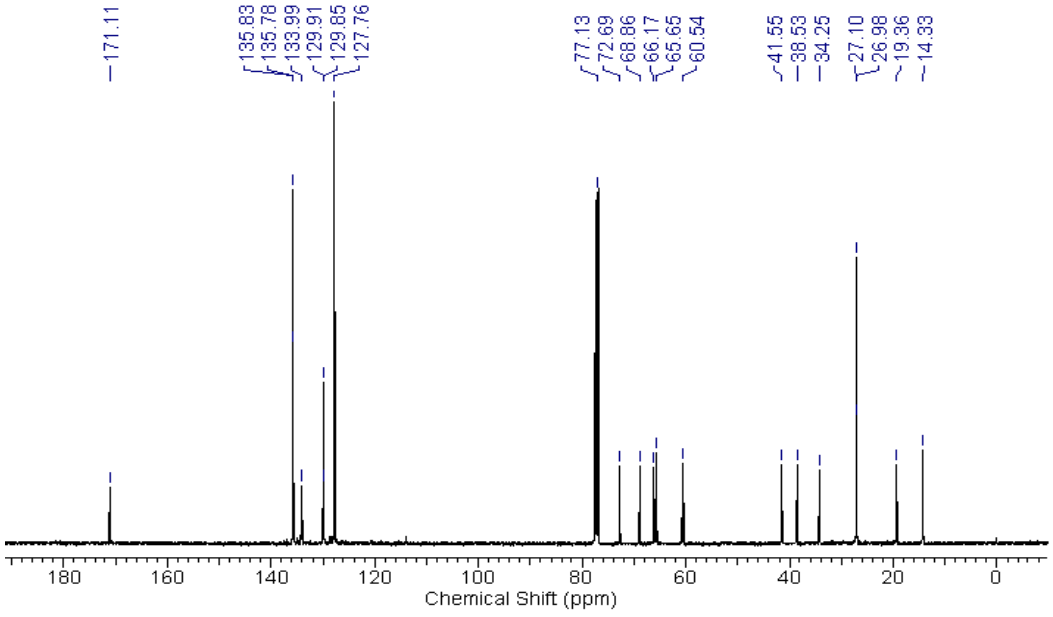


Fig 5: ^{1}H and ^{13}C NMR spectra of **101**

The ketone group in α-acyloxy ketone **101**was selectively reduced using $NaBH_4$-MeOH to give the corresponding alcohol with moderate diastereoselectivity 3:1 in favour of its *anti* isomer. With the addition of LiI (5 equiv) to the reaction mixtureincreased the diastereoselectivity[24] was however, increased to 8:1. Surprisingly, the hydroxy group was underwent oxa-Micheal addition-benzoate

deprotection to provide key THP unit **102**in 76% yield. The structure of **102** was confirmed by its ^{1}H NMR spectrum which showed typical proton signals at δ 2.2-2.7 (m, 2H) corresponding to –C**H$_2$** adjecent to ester moiety and δ 3.3-3.7 (m, 2H) corresponding to –C**H$_2$** attached to hydroxyl group while its ^{13}C NMRspectrum showed carbon signals atδ 60.5, 65.7, 66.2 corresponding to carbons attached to THP unit of oxygen atom.The relative stereochemistry was unambiguously confirmed by its NOESY spectrum.





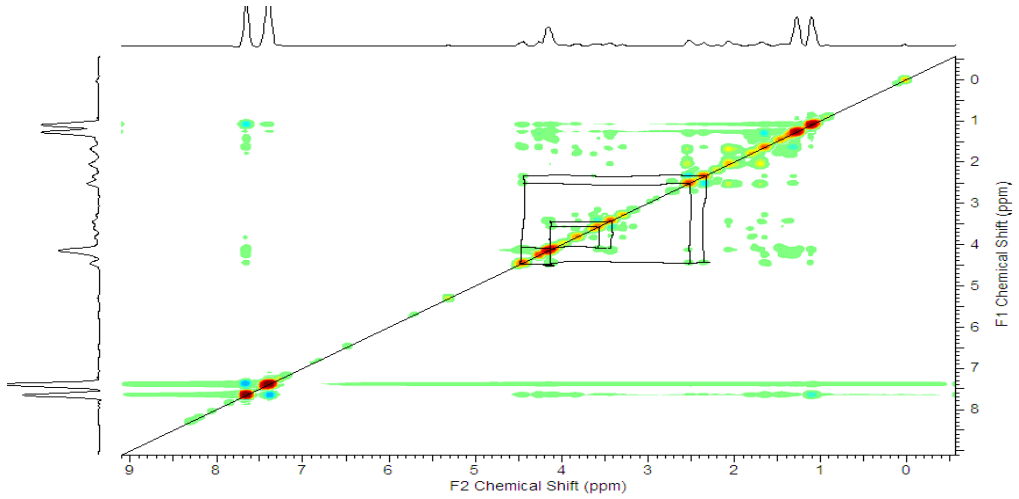
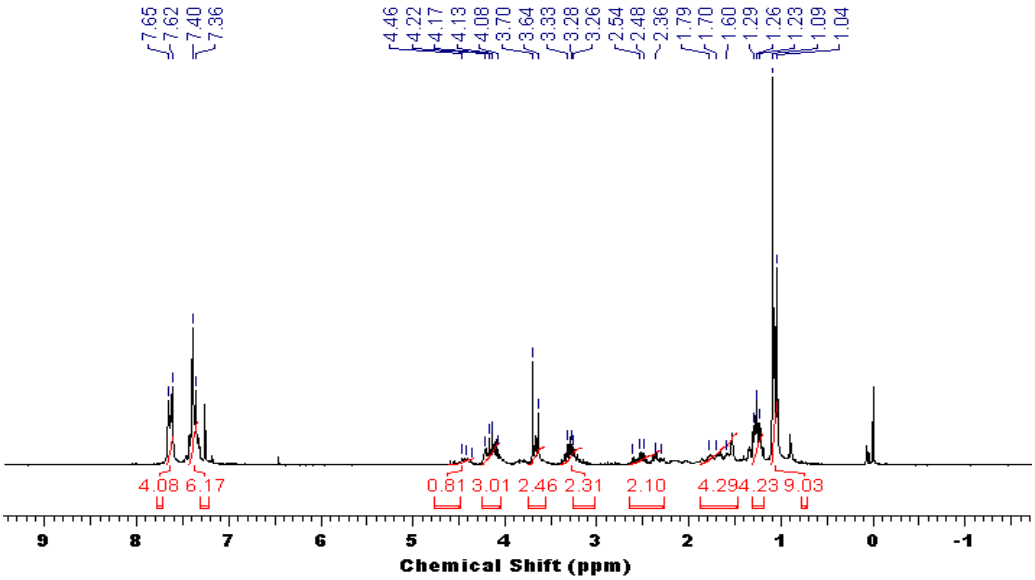


Fig.6: ^{1}H, ^{13}C NMRand NOESY spectra of **102**

The free primary hydroxyl group was converted to the corresponding bromide **89** in 81% yield using Appel conditions (CBr_4, PPh_3, THF, 25 °C).[23] The ^{1}H NMR spectrum of bromide **89** showed a multiplet at δ 3.26-3.33 (m, 2H) corresponding to –C**H$_2$** protons attached to bromine atom, while its ^{13}C NMR spectrum showed typical carbon signals at δ 171 corresponding to carbonyl group (**Fig 7**).



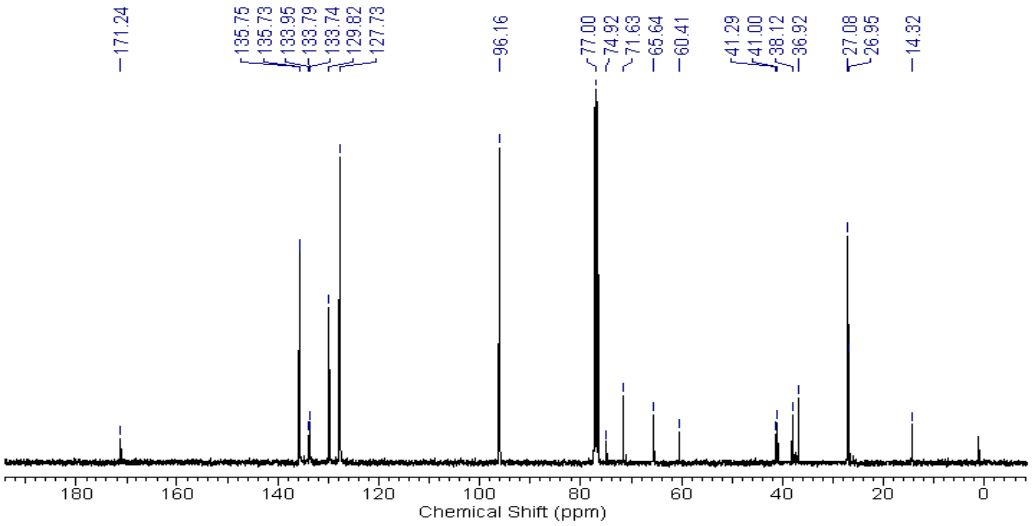
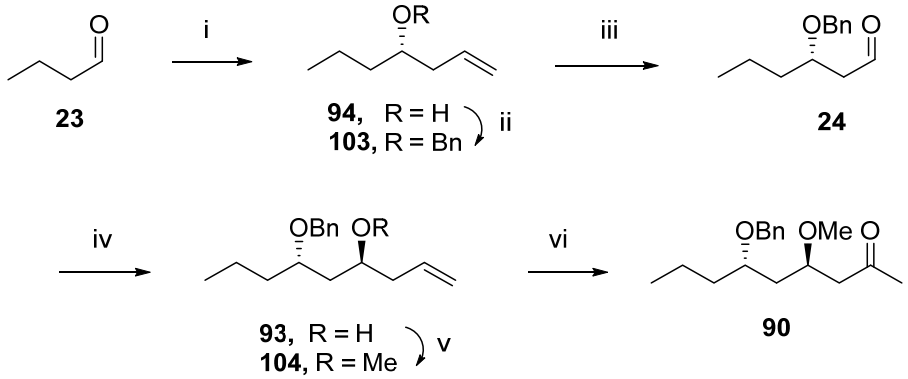


Fig 7: ^{1}H and ^{13}C NMR spectra of **89**

Synthesis of diol fragment 90

Next, the synthesis of ketone diol moiety **90** (**Scheme 13**)started with commercially available butyraldehye **23**, which upon Keck allylation [(*S*,*S*)-BINOL, $Ti(O^{i}Pr)_4$, allyl tri-*n*-butyltin in CH_2Cl_2] gave the corresponding homo allylic alcohol **94**in 74% yield and 94% ee.



Scheme 13: (i)(*S*,*S*)-BINOL, 4 Å MS, $Ti(OiPr)_4$, allyltri-n-butyltin, CH_2Cl_2,-78 to -20 °C, 24 h, 82% (ii) BnBr, NaH, DMF, 0° C, 4 h, 90% (iii) (a) K_2OsO_4, NMO acetone:H_2O (4:1), 3 h; (b) $NaIO_4$, CH_2Cl_2, 0.5 h, rt, 87% (over 2 steps); (iv) allyltri-*n*-butyltin, $MgBr_2.Et_2O$, CH_2Cl_2, 0 °C, 8 h, 1:99 dr, 86%; (v) MeI (1.1 equiv), NaH (1.5 equiv), DMF, 0° C, 91%; (vi) $PdCl_2$ (2 mol %), CuI (10 mol %), DMF:H_2O (1:1),O_2 (1 atm), 90%.

The ^{1}H NMR spectrum of homo allylic alcohol **94**showeda typical multiplet at δ 3.65 (m, 1H) corresponding to –C**H** attached to hydroxyl group and twoother multiplets at δ 5.13 (m, 2H) and 5.83 (m, 1H) correspondingto olefinic protons, while its^{13}C NMR spectrum showeda carbon signal at δ 70.3 corresponding to –**C**H attached tohydroxyl group (**Fig 8**).

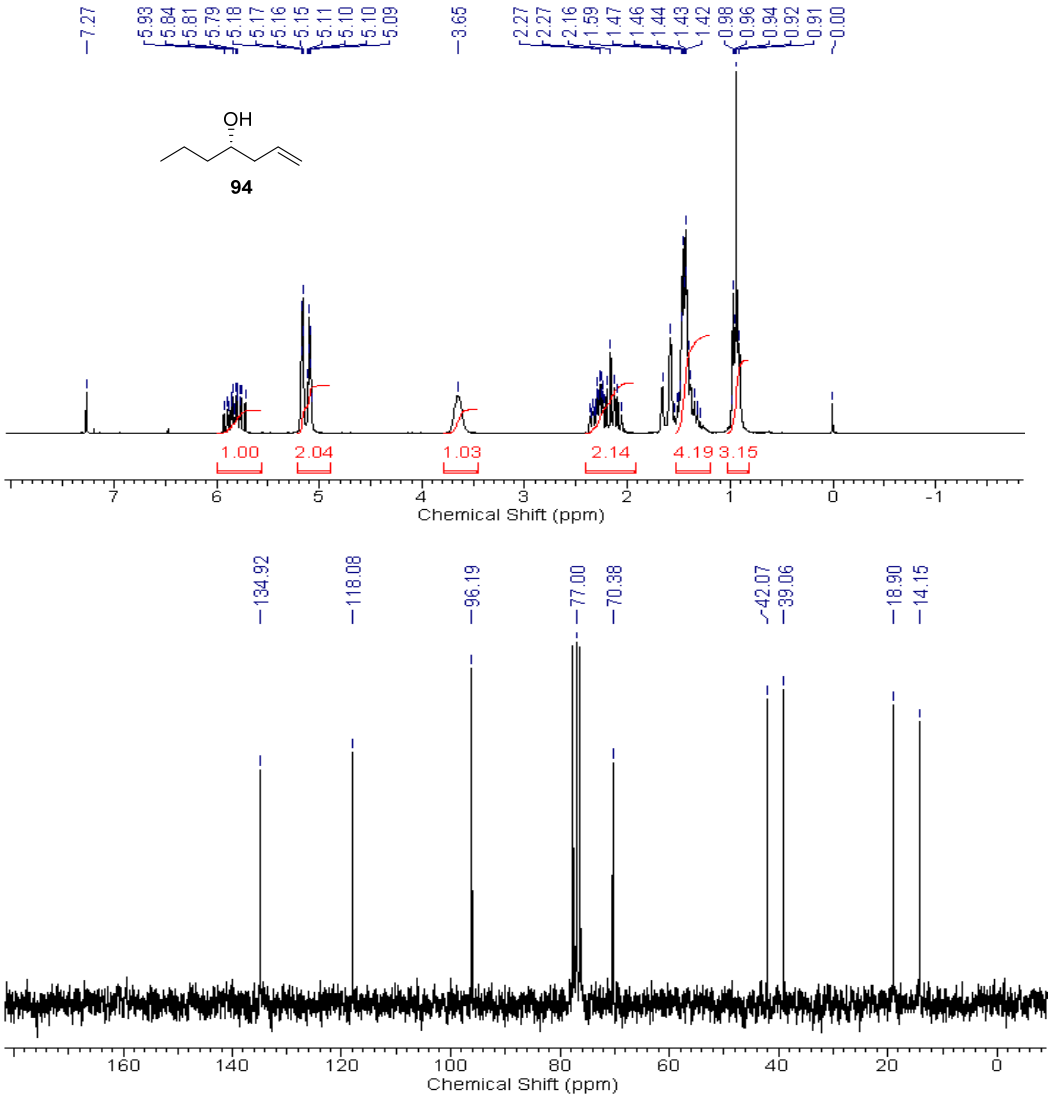


Fig 8: ^{1}H and ^{13}C NMR spectra of **94**

The alcohol**94**was protected as its benzyl ether using benzyl bromideandNaH andsubsequent dihydroxylation (OsO_4, *N*-morpholine oxide, acetone:H_2O) followed by oxidative cleavage of diol ($NaIO_4$, CH_2Cl_2) gave the corresponding aldehyde **24**in 81% yield.The The^{1}H NMRspectrum of aldehyde **24**showed a singlet at δ 4.55 (s, 2H) corresponding to benzylic protons and a triplet at δ 9.81 (t, J = 2.2 Hz, 1H) due to aldehydic hydrogen, while it^{13}C NMR spectrum showed a typical carbon signal atδ 201 corresponding to carbonyl group (**Fig 9**).

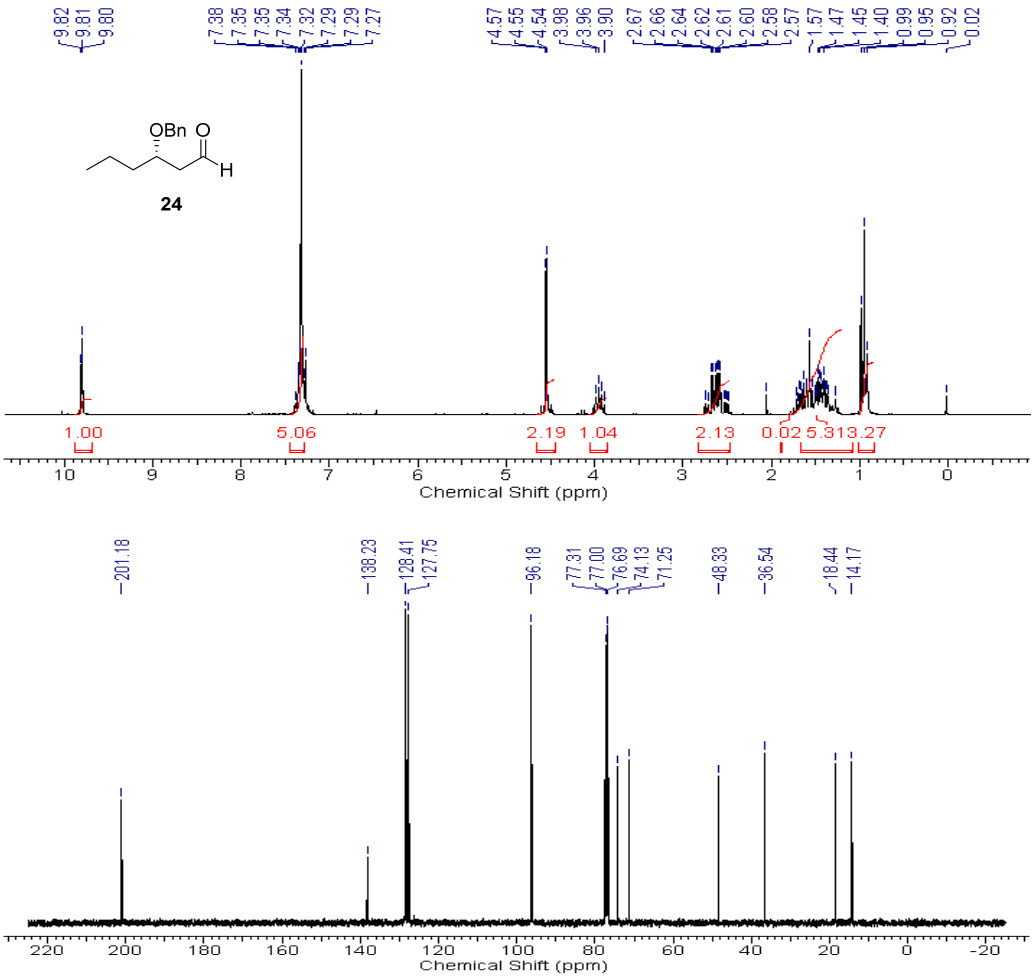


Fig 9:^{1}H and ^{13}C NMR spectra of **24**

Aldehyde **24** was subjected to Lewis acid catalyzed diastereoselective allylation[24] reaction using $MgBr_2.OEt_2$ and allyl tributyl tin, which gave homo allylic alcohol **93**

in 83% yield as a single diastereomer. The ^{1}H NMR spectrum of homo allylic alcohol **93** showed a typical proton signal at δ 2.21 (t, *J* = 6.8 Hz, 2H) corresponding to –C**H$_2$** allylic protons and two other multiplets at δ 5.02-5.18 (m, 2H) and 5.70-5.90 (m, 1H) corresponding olefinic protons. It ^{13}C NMR spectrum showed a characteristic carbon signal at δ 67.3 due to –**C**H attachedto hydroxyl group. The specific rotation of **93** **[α]$^{25}_{D}$**+52.8 (c 0.5, $CHCl_3$) Lit[26]: **[α]$^{25}_{D}$**+52.9 (c 0.55, $CHCl_3$)] is in well agreement with the literature value, which confirmed that the stereochemistry of the two hydroxyl groups are *anti* to each other (**Fig 10**).

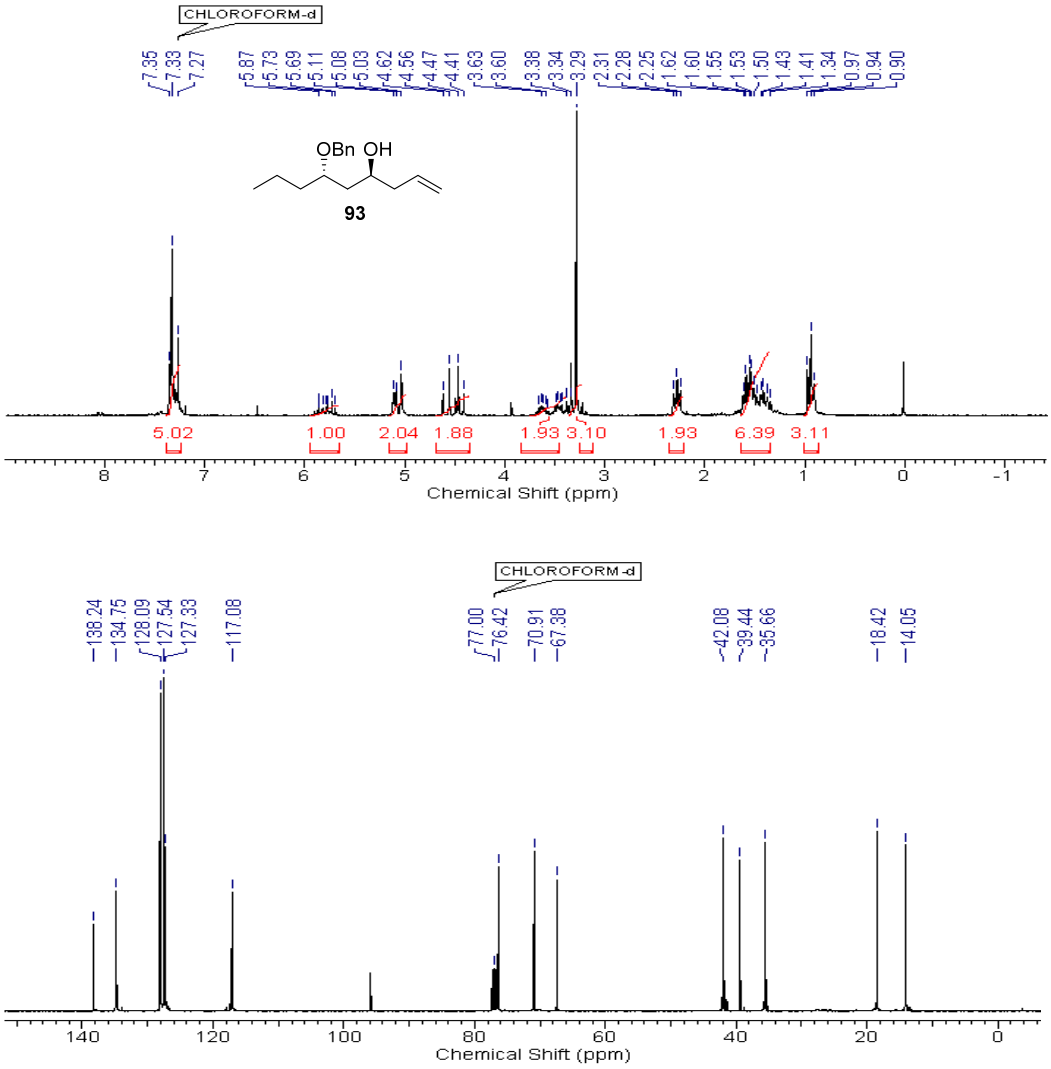


Fig 10: ^{1}H and ^{13}C NMR spectra of **93**

Methylation of homoallylic alcohol **93** using MeI and NaH gave the corresponding methyl ether **104**in 94% yield. The methyl ether **104**was confirmed by its ^{1}H NMRspectrum which showed a typical singlet atδ 3.29 (s, 3H) corresponding to methyl group while its ^{13}C NMR spectrum showed a typical carbon signals at δ 56.3 corresponding to -O**C**H_3 group (**Fig 11**).

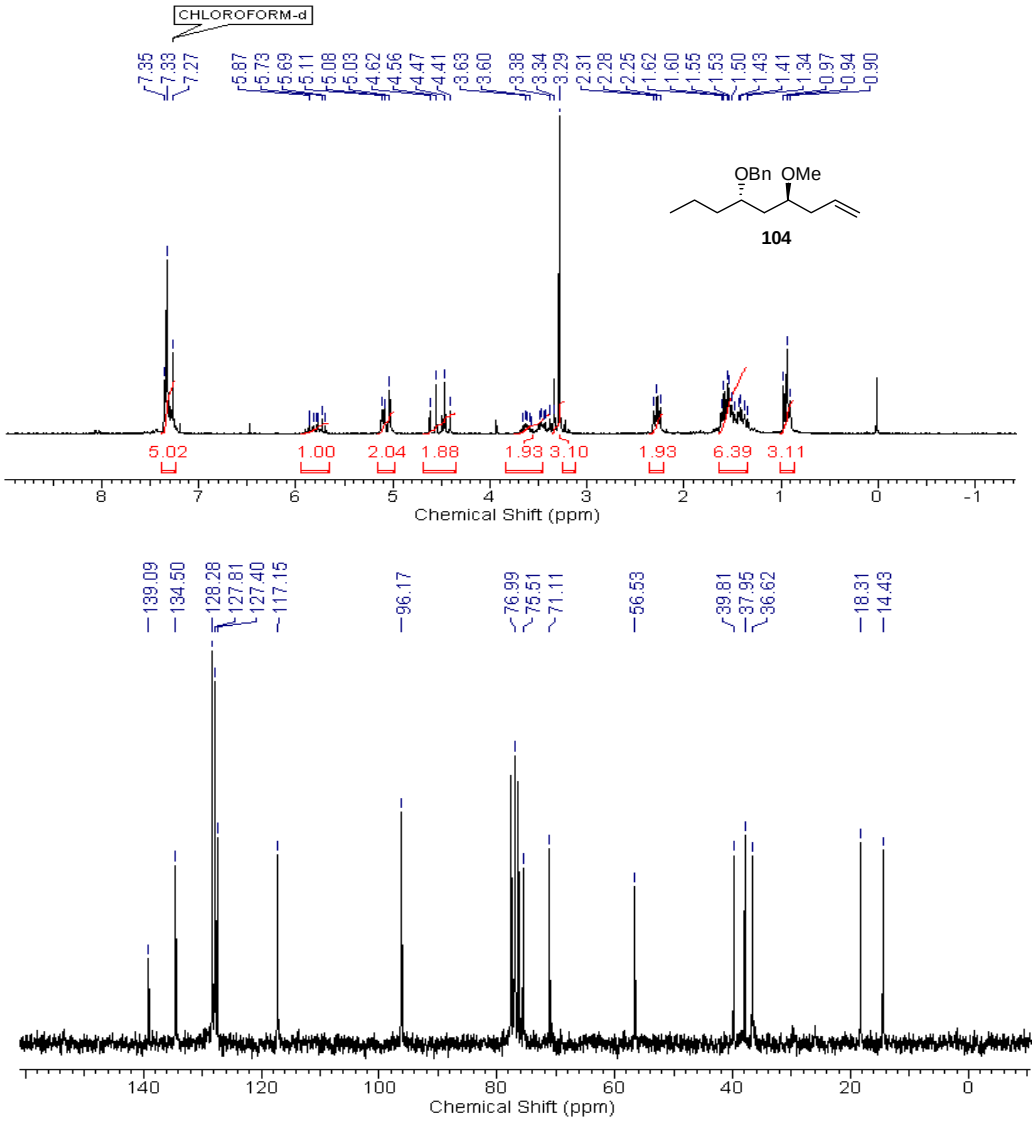


Fig 11: ^{1}H and ^{13}C NMR spectra of **104**

Alkene **104** was subjected to Wacker oxidation condition[25]using standard to procedure afford the key fragment **90** in 81% yield. The formation of ketone **90**was

confirmed by its spectroscopic data.The ^{1}H NMRspectrum of **90**showed a two singlets at δ2.09-2.18 (s, 3H) and δ3.19-3.30 (s, 3H) corresponding to methyl groups and a two doublets at 4.41 (d, *J* = 11.4 Hz, 1H), 4.58 (d, *J* = 11.4 Hz, 1H) for two benzylic protons while its ^{13}C NMR spectrum showed a typical carbonyl peak at δ 206.9 (**Fig 12**).

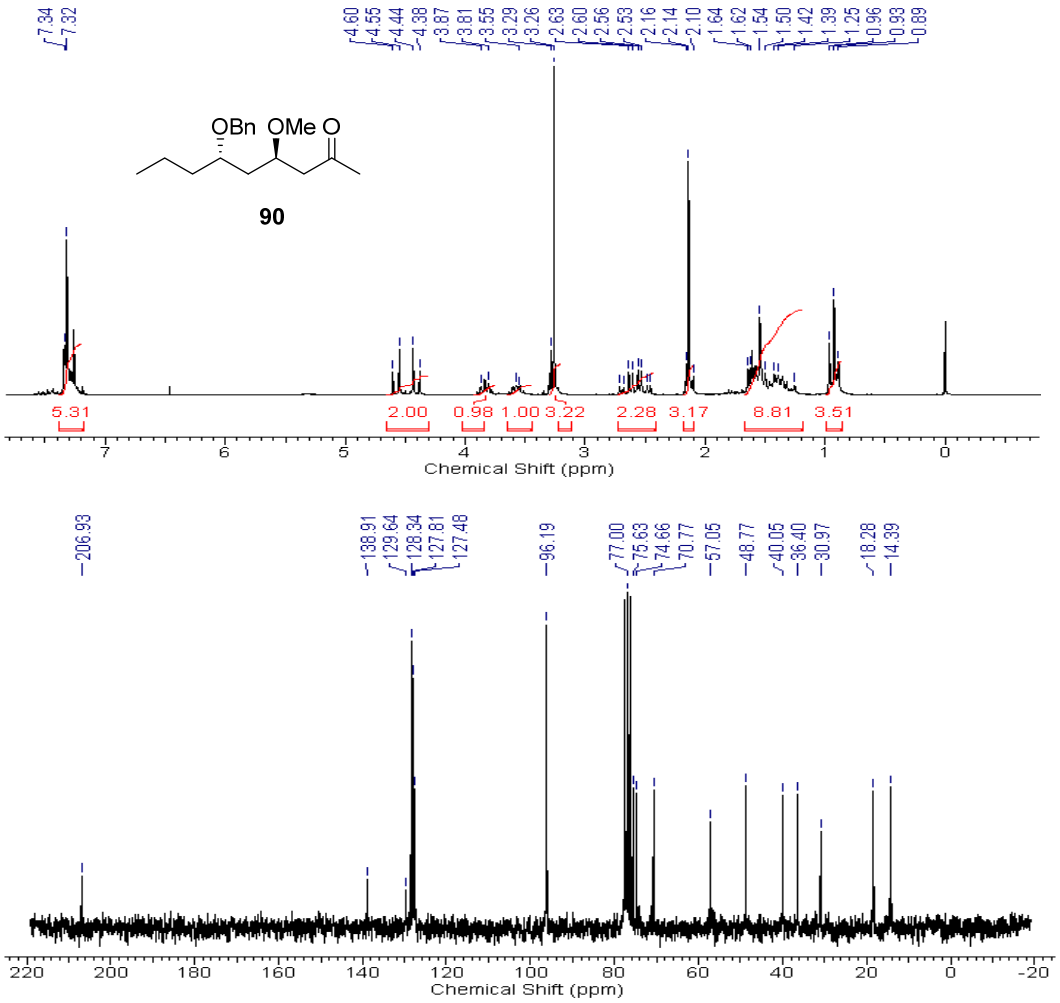
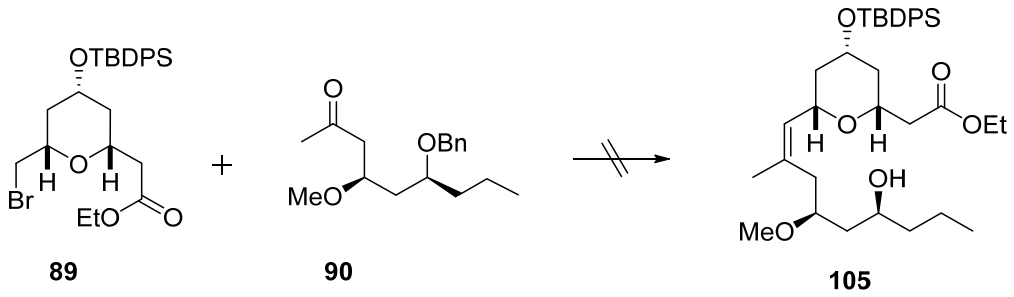


Fig 12: ^{1}H and ^{13}C NMR spectra of **90**

Finally, Wittig reaction between bromo compound **89** and ketone **90** has failed under different conditions. Particularly, the Wittig ylide was not generated with PPh_3 in toluene even after 3 days, then we have replaced the bromo compound with

corresponding iodo derivative, However the reaction has failed in this case also (**Scheme 14**).



89 **90** **105**

Scheme 14: Failed attempts.

4.1.5 Conclusion

In conclusion, we have completed a convergent synthesis towards (+)-neopeltolidein 10longer linear steps. Keck allylation, NHCcatalyzed oxo-acyloxylation/reductive oxa-Michael addition reactionfor the synthesis of key 2,6 disubstituted THP unitare the key steps of the synthetic studies.

4.1.6 Experimental Section

3-((4-Methoxybenzyl)oxy)propan-1-ol (96)

To a stirred solution of diol **95** (5.0 g, 65.7 mmol) in DMF (80 mL) was added sodium hydride (60% dispersed in oil) (2.62 g, 98.5 mmol) at 0 °C followed by the addition of 4-methoxybenzyl chloride (10.78mL, 78.8 mmol). After stirring for 1h, the reaction mixture was quenched by the addition of water (60 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with water, brine, dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure to give the crude product which was purified by column chromatography over silica gel using EtOAc/Pet.ether as eluent (5:95) to give pure benzyl ether **96** in 11.3 g (88%).

Yield: 11.3 g (88%); colorless liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max}1248, 1462, 1513, 1613, 3393; **^{1}H NMR** (200 MHz, $CDCl_3$): δ1.86-1.74 (m, 2H),2.52 (br s, 1H),3.56 (d, *J* = 7.0 Hz, 2H), 3.70 (d, *J* = 7.0 Hz, 2H), 3.79 (s, 3H), 4.41 (s, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H);**^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.2, 55.2, 61.5, 68.7, 72.8, 113.8, 129.2, 130.2, 159.2; Analysis calcd for $C_{11}H_{16}O_3$: C, 67.35; H, 8.16. Found: C, 67.45; H, 8.12%.

3-((4-Methoxybenzyl)oxy)propanal(97)

To a stirred solution of alcohol **96** (8 g, 40.77 mmol) in CH_2Cl_2 (80 ml) was added pyridinium chlorochromate (9.640 g, 44.84 mmol) at 25 °C and stirred for 2h. After completion of the reaction (monitored by TLC) the mixture was filtered and washed with CH_2Cl_2. The organic layer was dried (Na_2SO_4), and evaporated to give the crude aldehyde which was purified by column chromatorgraphy (Pet ether/AcOEt 9:1) that gave aldehyde **97** (7.44g, 94%) as a colorless viscous liquid**.**

Yield:7.44g (94%); colorless liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max}1472, 1523, 1643, 1712, 2893 : **^{1}H NMR** (500MHz, $CDCl_3$):δ 2.65 (t, *J*= 7.0 Hz, 2H), 3.74 (bs, 2H), 3.76 (s, 3H), 4.45 (s, 2H), 6.85 (d,*J*=8.5 Hz, 2H), 7.32 (d, *J*= 8.5 Hz, 2H), 9.73 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 44.0, 55.4, 63.7, 73.1, 114.0, 129.5, 130.1, 159.5, 201.3. Analysis calculated for: $C_{11}H_{14}O_3$is C, 68.02; H, 7.27;found C, 68.12; H, 7.34%.

(*S*)-1-((4-Methoxybenzyl)oxy)hex-5-en-3-ol (92)

A mixture of (+)-(*R*)-BINOL (1.0 g, 3.5 mmol) and Ti(^{i}PrO)$_4$ (1.0 g, 3.5 mmol) in CH_2Cl_2 (80 ml) in the presence of 4°A molecular sieves (5 g) was stirred under reflux. After 1 h, the reaction mixture was cooled to 25 °C, the previously prepared aldehydes **97** (6.79 g, 35 mmol) was added, and the resulting mixture was stirred for10 min. Then, the reaction mixture was cooled to -78 °C and allyltributylstannane (13 mL, 42 mmol) was added and stirring continued at -20°C for 36 h. After

completion of the reaction (TLC), it was quenched with sat. $NaHCO_3$ soln. (25 ml), stirred for an additional 30 min, and then extracted with CH_2Cl_2 (3 x 60 ml). The organic phase was dried, and concentrated and the residue purified by column chromatography (AcOEt / Pet ether = 2:8) (7.04 g, 84%).

Yield: 84% (7.04 g); colorless liquid. $[\alpha]^{25}_D$+3.24 (*c* 1, $CHCl_3$); Lit: [28]$[\alpha]^{25}_D$+3.26 (*c* 1, $CHCl_3$): **IR**(neat): ν_{max}3447, 3052, 2940, 2871, 1622, 1523, 1481, 1310, 1247, 1133: **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.71-1.74 (m, 2H), 2.22 (t, *J* = 6.7 Hz, 2H), 3.47-3.69 (m, 2H), 3.78 (s, 4H), 3.83 (br. s., 1H), 4.43 (s, 2H), 5.04-5.12 (m, 2H), 5.71-5.83(m, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H): **^{13}C NMR** (50 MHz,$CDCl_3$) δ 35.7, 41.7, 54.7, 67.9, 69.6, 72.5, 113.5, 117.0, 126.8, 128.9, 134.7, 158.9; **HRMS**:$C_{14}H_{20}NaO_3$+Na: 259.1310; found: 259.1318.

(*S*)-*tert*-Butyl((1-((4-methoxybenzyl)oxy)hex-5-en-3-yl)oxy)diphenylsilane (98)

To a stirred solution of alcohol **92** (6 g, 35.39 mmol) in CH_2Cl_2 (90 mL) was added TBDPSCl (9.72 g, 27.92 mmol) and Imidazole (4.843 g, 70.78 mmol) at 0 °C. The reaction mixture was stirred for 3 h at 25 °C. After completion of the reaction (as monitored by TLC), it was quenched with water (80 mL) and extracted with CH_2Cl_2 (3x 80). The organic layer was concentrated and the residue was purified by column chromatography (AcOEt/Pet ether = 1:9) to give the TBDPS ether **98** in 86% yield (10.36 g).

Yield: 86% (10.36 g); colorless liquid. $[\alpha]^{20}_D$ +13.5 (c 1.5, $CHCl_3$). **IR** (neat,cm^{-1}): ν_{max} 2851, 1613, 1515, 1249, 1094, 1073, 1027; **^{1}H NMR** (400 MHz,$CDCl_3$): δ 1.12(s, 9H)), 1.84 (q, *J* = 6.5 Hz, 2H), 2.34-2.18 (m, 2H), 3.58-3.46 (m, 2H), 3.84 (s,3H), 4.03 (m, 1H), 4.36 (d, *J* = 11.3 Hz, 1H), 4.36 (d, *J* = 11.3 Hz, 1H), 5.04-4.92(m, 2H), 5.77 (m, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.50-7.37 (m, 6H), 7.78-7.72 (m, 4H); **^{13}C NMR** (50 MHz,$CDCl_3$): δ 19.4, 27.1, 36.1, 41.6,

55.1, 66.5, 70.3, 72.4, 96.1, 113.6, 117.2, 127.5, 127.5, 129.1, 129.5, 130.6, 134.2, 134.4, 134.5, 135.9, 159.0; **HRMS** (ESI) calcd for $C_{30}H_{38}O_3Si$ [M + Na]+: 497.2482; found: 497.2481.

(*S*)-3-((*tert*-Butyldiphenylsilyl)oxy)hex-5-en-1-ol (99)

To a stirred solution of PMB ether **98** (5.0 g, 10.3 mmol) in CH_2Cl_2:H_2O (4:1) (50 mL) was added DDQ (4.67 g, 20.6 mmol) at 0 °C. After 30 min, the reaction mixture was warmed to room temperatureand further stirred for 3 h before it was diluted with CH_2Cl_2 and quenched with sat. aq. Na_2CO_3. The organic phase was separated, washed (sat. aq. Na_2CO_3),dried (Na_2SO_4), and concentrated to give the crude product which was purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (1:9) to give alcohol **99** in 3.13 g (84%).

Yield: 84% (3.13 g); colorless liquid; $[\alpha]^D_{24}$ = +26.5° (*c*0.5, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 506, 611, 739, 915, 1169, 1362, 1390, 1472, 1590, 1640, 3370; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.08 (s, 9H).1.67 (ddd, *J*=5.5, 11.2, 14.3 Hz, 2H), 1.88-1.78 (m, 2H), 2.19 (m, 1H), 2.30 (dt, *J* = 7.7, 14.1 Hz, 1H), 3.67 (dt, *J* = 5.5, 11.0 Hz, 1H), 3.77 (ddd, *J* = 4.9, 8.3, 11.0 Hz, 1H), 3.99 (m, 1H), 4.91 (m, 2H), 5.61 (ddt, *J* = 7.2, 10.2, 17.3 Hz, 1H), 7.48-7.37 (m, 6H), 7.71 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.3, 27.0, 37.5, 41.1, 59.7, 71.7, 117.3, 127.6, 127.7, 129.7, 129.8, 133.6, 133.9, 134.2, 135.9; **HRMS** (ESI): m/z calculated for $C_{22}H_{31}O_2Si$ $[M+H]^+$: 355.2088; found: 355.2086.

(*S*)-3-((*tert*-Butyldiphenylsilyl)oxy)hex-5-enal (100)

To a stirred solution of alcohol **99** (3 g, 8.46 mmol) in DMSO (50 ml) was added 2-iodoxybenzoic acid (2.84 g,10.15 mmol) in at 25 °C and stirred for 5 h. After completion of the reaction (monitored by TLC), the mixturewas filtered, diluted with H_2O (30 ml) and extracted with EtOAc (3x50 mL). The combined organic layerwas

washed with brine (3x 40 ml), dried (Na_2SO_4), and evaporated to give the crude aldehyde which waspurified by column chromatorgraphy (Pet ether/AcOEt 9 : 1) gave aldehyde **100** (2.65g, 89%) as a colorless liquid**.**

Yield: 89% (2.65 g); colorless liquid; $[\alpha]^{D}_{24}$ = +16.5° (*c*1, $CHCl_3$); **IR** (neat, cm^{-1}): ν_{max} 612, 701,822, 998, 1362, 1725, 3072; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.07 (s, 10 H), 2.29 (t, *J*=6.4 Hz, 2 H), 2.50 (dd, *J*=5.7, 2.3 Hz, 2H), 4.27 (quin, *J*=5.8 Hz, 1H), 4.91 (s, 1H), 5.05 (s, 2H), 5.51-5.80 (m, 1H), 7.35 - 7.50 (m, 6H), 7.67 (dt, *J*=7.4, 2.1 Hz, 4H), 9.69 (t, *J*=2.3 Hz, 1H);**^{13}C NMR** (50 MHz, $CDCl_3$) δ 19.3, 27.0, 41.9, 49.8, 68.8, 77.1, 96.2, 118.4, 127.7, 127.8, 129.9, 130.0, 133.5, 133.7, 135.9, 201.2; **HRMS** (ESI): m/z calcd for $C_{22}H_{28}O_2Si$+Na:375.1756; found:375.1754.

Ethyl (*S*, E)-5-((tert-butyldiphenylsilyl)oxy)octa-2,7-dienoate (91)

To a stirred solution of aldehyde **100** (2.5 g, 7.09 mmol) in CH_2Cl_2 (30 mL) was added (2-ethoxy-2-oxoethyl)triphenylphosphonium bromide ($PPh_3BrCHCO_2Et$) (3.03 g, 8.50 mmol) at 25 °C. The reaction mixture was stirred for 3 h at 25 °C. After completion of the reaction (as monitored by TLC), it was quenched with water (40 mL) and extracted with CH_2Cl_2 (3 x 40). The organic layer was concentrated and the residue was purified by column chromatography (AcOEt/Pet ether = 1:9) to give the dienoate in 92% yield (2.78 g).

Yield: 92% (2.78 g); colorless liquid; $[\alpha]^{25}_{D}$+19.24 (*c*1, $CHCl_3$); IR (neat, cm-1): ν_{max} 614, 4841, 919, 1342, 1545, 1581, 1739, 3072; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 4H), 2.07-2.37 (m, 4H), 3.78– 4.04 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.63–4.89 (m, 2H), 5.52-5.82 (m, 2H), 6.72-6.98 (m, 1H), 7.31-7.44 (m, 6H), 7.65 (d, *J* = 9.0 Hz, 4H); **^{13}C NMR** (50 MHz,$CDCl_3$) δ 14.3, 19.3, 27.0, 38.8, 41.0, 59.9, 71.7, 96.1, 117.7, 123.6, 127.5, 128.2, 129.7, 133.8, 133.9, 135.8, 145.1, 166.0. **HRMS** (ESI): m/z calcd for $C_{26}H_{34}O_3Si$+Na:422.2277; found:422.2279.

(*R*,E)-4-((*tert*-Butyldiphenylsilyl)oxy)-8-ethoxy-2,8-dioxooct-6-en-1-yl- 4-nitrobenzoate (101)

To a stirred solution of alkene **91** (2.5 g, 5.92 mmol) in dry DMSO (35 mL), NBS (5 mmol, 1.05 g), *N*-heterocyclic carbene precursor **A** (10 mol %, 0.151 g) and Et_3N (1 mL, 7.104 mmol), aromatic aldehyde (0.971 g, 6.15 mmol) was added and the reaction mixture was then stirred at 25 °C under an O_2 atmosphere. it was quenched with H_2O (40 mL) at 0 °C. It was then extracted with EtOAc (3 x 50 mL) followed by washing with brine (3x40 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Removal of solvent gave the crude product, which was purified by column chromatography over silica gel using pet ether/EtOAc (9:1) as eluent to obtain α-acyloxy ketone **101** in 72% yield (2.57 g).

Yield: 72% (2.78 g); yellow solid; mp: 124-126 °C; $[\alpha]^{25}_{D}$+22.24 (c 1, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 851, 924, 1354, 1531, 1712, 1726, 1738, 2893, 2932, 3072; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H), 2.33-2.44 (m, 2H), 2.57 (d, *J* = 5.9 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.36 (t, *J* = 5.7 Hz, 1H), 4.63-4.89 (m, 2H), 5.75 (d, *J* = 15.8 Hz, 1H), 6.80–6.88 (m, 1H), 7.38-7.45 (m, 6H), 7.64-7.68 (m, 4H), 8.18-8.33 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 14.3, 19.3, 27.0, 39.4, 45.3, 60.2, 68.6, 69.4, 77.0, 96.2, 123.6, 124.7, 127.8, 127.9, 130.1, 131.0, 133.2, 134.6, 135.8, 143.6, 163.7, 165.9, 200.2: **HRMS** (ESI): m/z calcd for $C_{33}H_{37}O_8Si$+Na:626.2186; found:626.2185.

Ethyl 2-((2*R*,4*R*,6*S*)-4-((tert-butyldiphenylsilyl)oxy)-6-(hydroxymethyl)tetra hydro-2H-pyran-2-yl)acetate (102)

To a stirred solution of α-acyloxy ketone **101** (2.5 g, 4 mmol) in MeOH was added LiI (5.32 g, 40 mmol) and $NaBH_4$ (0.76 g, 20 mmol) at -40 °C. The reaction mixture was allowed to stirr for 5 h at same temperature. After completion of the reaction as

monitored by TLC, MeOH was concentrated. The crude reaction mixture was dissolved in H_2O (30 mL) and extracted with EtOAc (3 x 30mL). The organic layer was concentrated to give the crude compound, which was purified by column chromatographic purification over silica gel using pet ether/EtOAc (8:2) as eluent to obtain tetrahedropyran derivative **102** in 76% yield (1.38 g).

Yield: 76% (1.38 g); colourless liquid; $[\alpha]^{25}_{D}$+28.24 (c 1, $CHCl_3$) mp: 124-126 °C; IR (neat, cm-1): ν_{max} 762, 941, 1310, 1541, 1732, 2883, 2942; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.94-1.15 (m, 9H), 1.19-1.30 (m, 3H), 1.33-1.53 (m, 2H), 1.54-1.91 (m, 2 H), 2.16 (d, *J* = 4.2 Hz, 1H), 2.22-2.73 (m, 2H), 3.29-3.71 (m, 2H), 4.05-4.27 (m, 3H), 4.33-4.58 (m, 1H), 7.29-7.45 (m, 6H), 7.65 (dt, *J* = 7.5, 2.1 Hz, 4H);**^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.3, 14.3, 19.4, 27.0, 27.0, 27.0, 27.1, 34.3, 38.5, 41.5, 60.5, 65.7, 66.2, 68.9, 72.7, 127.7, 127.8, 129.8, 129.9, 134.0, 135.8, 135.8, 171.1; **HRMS** (ESI): m/z calcd for $C_{26}H_{36}O_5Si$+Na:479.2230; found:479.2232.

Ethyl 2-((2*R*,4*R*,6*S*)-6-(bromomethyl)-4-((*tert*-butyldiphenylsilyl)oxy)tetrahydro-2H-pyran-2-yl)acetate (89)

To a stirred solution ofalcohol**102** (1 g, 2.08 mmol) in CH_2Cl_2 (40 mL) was added CBr_4 (0.760 g, 2.29 mmol) and PPh_3 (0.61 g, 2.29 mmol) at 0 °C. The reaction mixture was allowed to stirr for 3 h at room temperature. After completion of the reaction as monitored by TLC, it was quenched with water (30 mL) and extracted with CH_2Cl_2 (3 x 30). The organic layer was concentrated and the residue was purified by column chromatography (AcOEt/Pet ether = 1:9) to give the bromo compound **89** in 81% yield (0.88 g).

Yield: 81% (0.88 g); colourless liquid; **$[\alpha]^{25}_{D}$**+15.24 (c1, $CHCl_3$);**IR** (neat, cm^{-1}): ν_{max} 777, 952, 1314, 1733, 2893, 2932;**^{1}H NMR** (200 MHz,$CDCl_3$) δ 1.04-1.10 (m, 9H), 1.26 (t, *J* = 5.8 Hz, 4H), 1.48-1.88 (m, 4H), 2.32 (d, *J* = 12.9 Hz, 1H), 2.42-2.65 (m,

1H), 3.26-3.33 (m, 2H), 3.56-3.75 (m, 2H), 4.05-4.25 (m, 3H), 4.33-4.61 (m, 1H), 7.33-7.43 (m, 6H), 7.63 (d, *J* = 7.7 Hz, 4H): **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.3, 27.0, 27.0, 27.1, 36.9, 38.1, 41.0, 41.3, 60.4, 65.6, 71.6, 74.9, 96.2, 127.7, 129.8, 129.9, 133.7, 133.8, 134.0, 135.7, 135.7, 135.8, 171.2; **HRMS** (ESI): m/e calcd for $C_{26}H_{35}BrO_4Si$+Na: 541.1386; found: 541.1389.

(*S*)-Hept-1-en-4-ol (94)

To a mixture of (+)-(*R*)-BINOL (1 g, 3.5 mmol) and Ti(*i*PrO)$_4$ (1 g, 3.5 mmol) in CH_2Cl_2 (60 ml) in the presence of 4 °A molecular sieves (5 g) was stirred under reflux. After 1 h, the mixture was cooled to 25 °C thepreviously prepared aldehyde**97** (2.5 g, 35 mmol) was added, and the resulting mixture was stirred for 10 min. Then, the mixture was cooled to -78 °C and allyltributylstannane (13 mL, 42 mmol) was added and the stirring continued at -20°C for 36 h. After completion of the reaction (TLC), it was quenched with sat. $NaHCO_3$ soln. (25 ml), stirred for an additional 30 min, and then extracted with CH_2Cl_2 (3 x 60 ml). The organic phase was washed with H_2O (15 ml), dried, and concentrated and the residue purified by Column chromatography (AcOEt/Pet ether = 2: 8) (3.24 g, 82%).

Yield: 82% (3.24 g); colourless liquid; $[\alpha]^{25}_D$ -19. 0 (*c*1, $CHCl_3$) Lit:$^{27}[\alpha]^{25}_D$-19. 9 (*c*1, $CHCl_3$); **IR** (neat, cm^{-1}): ν_{max}732, 806, 978, 1094,1208, 1416, 1512, 1642, 3330; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.95 (m, 3H), 1.42 (m, 4H), 2.26 (m, 2H), 3.65 (br. s., 1H), 5.13 (m, 2H), 5.83 (m, 1H): **^{13}C NMR** (50 MHz, $CDCl_3$) δ 14.1, 18.9, 39.1, 42.1, 70.4, 96.2, 118.1, 134.9.

(*S*)- ((Hept-1-en-4-yloxy)methyl)benzene (103)

To a stirred solution of alcohol **94** (2.5 g, 26.27 mmol) in DMF (40 mL) was added sodium hydride (1.575 g, 39.41 mmol) at 0 °C followed by the addition of Benzyl bromide (3.5mL, 28.9 mmol). After stirring for 1 h, the reaction mixture was

quenched by the addition of water (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water, brine, dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure to give the crude product which was purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (5:95) to give pure benzyl ether **103** in 5.04 g(94%).

Yield: 5.04 g (94 %);colorless liquid;$[\alpha]^{25}_{D}$-17.24 (c 1, $CHCl_3$);**IR** ($CHCl_3$, cm^{-1}): ν_{max} 742, 812, 936, 1124,1512, 1652, 2893, 2946, 3330; **^{1}HNMR**($CDCl_3$, 200 MHz): 0.90 (t, *J* = 6.9, 3H), 1.60-1.09 (m, 4H), 2.36-2.30 (m, 2H), 3.50-3.41 (m, 1H), 4.49 (d, *J* = 11.4,1H), 4.58 (d, *J* = 11.4, 1H), 5.14-5.03 (m, 2H), 5.94-5.79 (m, 1H),7.39-7.26 (m, 5H); **HRMS** (ESI): m/e calcd for $C_{14}H_{20}O$+H:205.1592; found: 205.1599.

(*S*)-3-(Benzyloxy)hexanal (24)

To a stirred solution of alkene (3 g, 14.70 mmol) in acetone: H_2O (4:1) were added $K_2OsO_4.2H_2O$ (54 mg, 1 mol %) and *N*-methyl morpholine oxide (3.43 g, 29.4 mmol) at 25°C. The reaction was stirred for 4 h at room temperature. After completion of the reaction (as monitored by TLC), it was quenched with sat. $Na_2S_2O_3$ soln. (25 ml), stirred for an additional 30 min, and then acetone was concentrated. The aqueous layer was extracted with EtOAc (3x60 ml). The organic phase was washed with H_2O (15 ml), dried, and concentrated. The residue was dissolved in CH_2Cl_2 and $NaIO_4$ (silica gel supported in 25% $NaIO_4$) (25 g, 29.4 mmol) was added. The reaction mixture was stirred for 30 min. After completion, the reaction mixture was filtered and filtrate was concentrated to give crude product which was purified by column chromatography to give the aldehyde **24** in 82% yield(AcOEt/Pet ether = 2: 8) (2.70 g, 87%).

Yield: 2.70 g (87%);colorless liquid; $[\alpha]^{25}_{D}$-21.24 (c 1, $CHCl_3$);**IR** ($CHCl_3$, cm^{-1}): ν_{max} 712, 822, 1224, 1652,1708, 2896, 2936; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.83-1.02 (m, 3H), 1.19-1.78 (m, 6H), 2.47-2.83 (m, 2H), 3.86-4.05 (m, 1H), 4.44-4.66 (m, 2H), 7.28-7.46 (m, 5H), 9.81 (t, *J* = 2.2 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 14.2, 18.4, 36.5, 48.3, 71.3, 74.1, 76.7, 77.3, 96.2, 127.7, 127.8, 128.4, 138.2, 201.2.**HRMS** (ESI): m/e calcd for $C_{13}H_{19}O_2$+H:207.1385; found: 207.1389.

(4*S*,6*S*)-6-(Benzyloxy)non-1-en-4-ol (93)

To a stirred solution of magnesium bromide ethyl etherate $MgBr_2.OEt_2$ (12.05 g, 48.50 mmol) in CH_2Cl_2 was added allyltributystannane (3.53 g, 10.7 mmol). After stirring for 15 min, aldehydes **24** (2 g, 9.7 mmol) to the reaction mixture at the same temperature. Further, the reaction was allowed to stirr for 8 h at 0°C. After completion (as monitored by TLC), the reaction mixture was quenched with $NaHCO_3$ solution and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layer was washed with water, brine, dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure to give the crude product, whichwas purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (2:8) to give pure homoallylic alcohol**93** in 2.06 g (86%)**.**

Yield: 2.06 g (86%); colorless liquid; $[\alpha]^{25}_{D}$+52.7 (c1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): ν_{max}714, 822, 1244, 1662, 2883, 2946, 3341 : **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.90-0.96 (m, 3H), 1.29-1.41 (m, 2H), 1.53-1.72 (m, 4H), 2.21 (t, *J* = 6.8 Hz, 2H), 2.70 (d, *J* = 3.3 Hz, 1 H), 3.60-3.78 (m, 1H), 3.84-4.02 (m, 1H), 4.38-4.70 (m, 2H), 5.02-5.18 (m, 2H), 5.70-5.90 (m, 1H), 7.31 (s, 5H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 14.1, 18.4, 35.7, 39.4, 42.1, 67.4, 70.9, 76.4, 117.1, 127.3, 127.5, 128.1, 134.8, 138.2; **HRMS** (ESI): m/z calcd for $C_{16}H_{24}O_2$+Na:271.1674; found:271.1676.

((((4*S*,6*S*)-6-methoxynon-8-en-4-yl)oxy)methyl)benzene (104)

To a stirred solution of alcohol **93** (1 g, 4.03 mmol) in DMF (30 mL) was added sodium hydride (0.242 g, 6 mmol) at 0 °C followed by the addition of methyl iodide (0.3 mL, 4.8 mmol). After stirring for 1 h, the reaction mixture was quenched by the addition of ice at 0 °C. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water, brine, dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure to give the crude product which was purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (5:95) to give pure methyl ether **104** in 1.06g (91%).

Yield:1.06 g (91%); colorless liquid; $[\alpha]^{25}_{D}$+22.24 (*c*1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): ν_{max}777, 812, 1224, 1642, 2889, 2966, 3033; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.87-1.00 (m, 3H), 1.35-1.64 (m, 7H), 2.28 (t, *J*=6.3 Hz, 2H), 3.29 (s, 3H), 3.37-3.75 (m, 2H), 4.35-4.69 (m, 2H), 4.98-5.16 (m, 2H), 5.66-5.94 (m, 1H), 7.24-7.39 (m, 5H): **^{13}C NMR** (50 MHz, $CDCl_3$) δ 14.4, 18.3, 36.6, 38.0, 39.8, 56.5, 71.1, 75.5, 76.9 , 77.0, 96.2, 117.1, 127.4, 127.8, 128.3, 134.5, 139.1; **HRMS** (ESI): m/e calcd for $C_{17}H_{26}O_2$+Na: 285.1830; found: 285.1833.

(4*R*, 6*S*)-6-(Benzyloxy)-4-methoxynonan-2-one (90)

To a stirred solution of alkene **104** (0.5 g, 1.89 mmol) in DMF:H_2O (3:1) (30 mL) was added $PdCl_2$ (6.7 mg, 2 mol %) and CuCl (25.5 mg, 10 mol%) at 25 °C and allowed to stirr for 4 h under O_2 atmosphere (1 atm). After completion (as monitored by TLC),water was added to the reaction mixture. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL) and dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure to give the crude product which was purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (5:95) to give pure methyl ether **90** in 0.525g (90%).

Yield: 0.525 g (90%); colorless liquid; **IR** ($CHCl_3$, cm^{-1}): ν_{max}714, 1324, 1642, 1726, 2833, 2976, 3033; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.86-1.00 (m, 4H), 1.25 (s, 1H), 1.32-1.67 (m, 8H), 2.09-2.18 (m, 3H), 2.42-2.73 (m, 2H), 3.19-3.30 (m, 3H), 3.57 (d, *J*=5.6 Hz, 1H), 3.84 (d, *J*=13.1 Hz, 1H), 4.41 (d, *J*= 11.4 Hz, 1H), 4.58 (d, *J*=11.4 Hz, 1H), 7.18-7.39 (m, 5H): **^{13}C NMR** (50 MHz, $CDCl_3$) δ 14.4, 18.3, 31.0, 36.4, 40.0, 48.8, 57.0, 70.8, 74.7, 75.6, 96.2, 127.5, 127.8, 128.3, 129.6, 138.9, 206.9. **HRMS** (ESI): m/z calcd for $C_{17}H_{26}O_3$+Na:301.1780; found:301.1782.

Section II

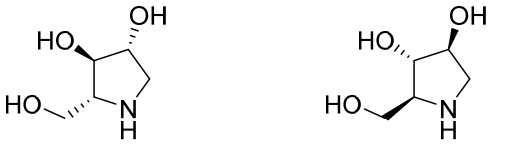
Enantioselective Synthesis of 1,4-Dideoxy-1,4-imino-D-Arabinitol using Co (III)(salen)-catalyzed HKR of Two-Stereocentered *anti*-Azidoepoxide

4.2.1 Introduction and pharmacology

Type-2 noninsulin dependent diabetes mellitus (NIDDM), a multifactorial disease accounts for 90–95% of all diabetes and affects about 150 million people globally. Over the last 10 years however, polyhydroxylated pyrrolidines and piperidines have inspired the design of novel potential glycosyltransferase inhibitors.[29,30] In particular, enhanced potency, as well as selectivity towards targeted enzymes, have been explored by simple *N*-substitution of these alkaloids and incorporation of key structural elements of either the natural glycosyl donor or acceptor. The field of therapeutic application of such compounds seems promisingly broad since they could, for example, be involved in treatment of fungal infections (chitine synthase inhibition), inflammatory processes or tumor growth (α-1,3-fucosyltransferase inhibition), glycosphingolipid storage disorders (ceramide glucosyltranferase inhibition), and xenotransplant rejection (α-1,3-glucosyltransferase inhibition). D-Arabinose presents indeed two advantageous characteristics: it is essential to the synthesis of the myco-bacterial cell wall, and it is not normally involved in the human host metabolism. The disruption of cell wall biosynthesis resulting from the inhibition of arabinosyltransferase has been recognised as the mode of action of important antibiotics. Interestingly, only few examples of imino sugar-derived arabinosyltransferase inhibitors have been reported.[31]

1,4-Dideoxy-1,4-imino-D-arabinitol **(**DAB-1**) (107)** is a naturally occurring pyrrolidine alkaloid found in *Arachniodes standishi* [32] and *Anqylocalyx*

boutiqueanus.[33] Both enantiomers of 1,4-dideoxy-1,4-iminoarabinitol (DAB-1 and LAB-1) are specific inhibitors of glycosidase and potential inhibitors of HIV replication (**Fig. 14**).



DAB-1 (**107**) LAB-1 (*ent*-**107**)

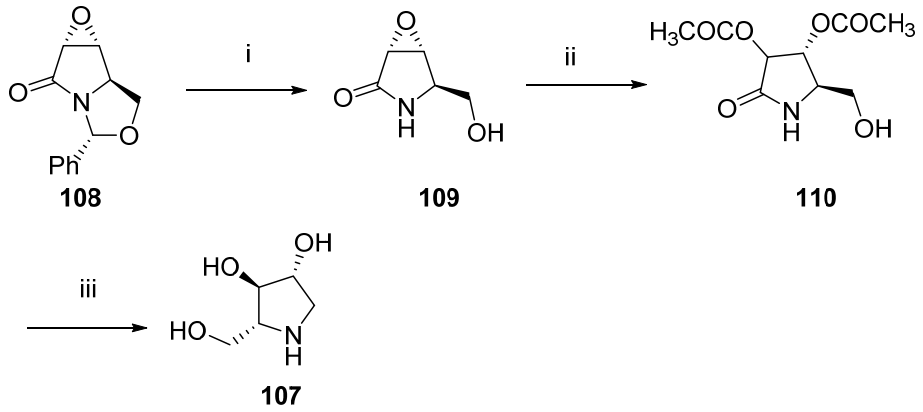
Fig 14: Structure of (+)-DAB-1 and (-)-LAB-1

4.2.2 Review of Literature

Literature search revealed that there are several reports available for the synthesis of (+)-DAB-1 (**107**), which are described below.

Langlois's approach (1994)[34]

Langlois's *et al.* have developed the synthesis of DAB-1 (**107**) starting from epoxy lactam **108,** which was prepared in 4 steps from commercially available (S)-pyroglutamic acid. The cleavage of oxazolidine unit in **108** afforded the lactam **109,** which was directly converted to its triacetate **110** in 43% yield. Reduction of lactam **110** using $LiAlH_4$ gave the desired DAB-1 (**107**) in 70% yield (**Scheme 15**).



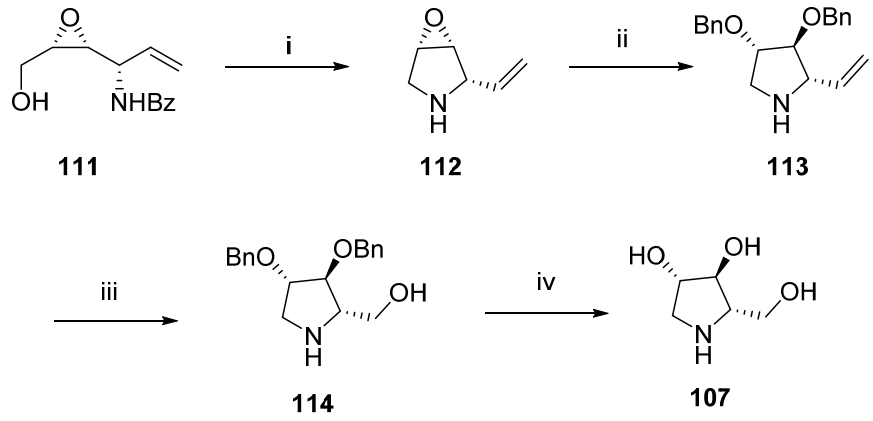
108 **109** **110**

107

Scheme 15: (i) CF_3CO_2H, THF: H_2O; (ii) (excess Ac_2O, pyridine, r.t., 24 h, 43% (over two steps) (iii) $LiAlH_4$, THF, reflux, 70%.

Genisson's approach (2003)[35]

Ge´nisson's *et al.* have achieved the synthesis of DAB-1 (**107**) starting from epoxyamine intermediate **111**, which was prepared from commercially available *cis*-1,4-butenediol in 4 steps (42% yield). The cyclization of epoxy amine **111** using PPh_3 and CCl_4 gave epoxy pyrrolidine **112** in 71% yield. The epoxy pyrrolidine **112** was subjected to epoxide ring opening using 3 M H_2SO_4 to give diol, which was subsequently protected as its benzyl ether **113** using benzyl bromide and NaH. Alcohol **114** was obtained (in 70% yield) from alkene **113** by a series of reactions involving dihydroxylation, oxidative cleavage of diol and reduction reactions. Finally, the benzyl deprotection of pyrrolidine **114** produced DAB-1(**107**) in 98% yield (**Scheme 16)**.

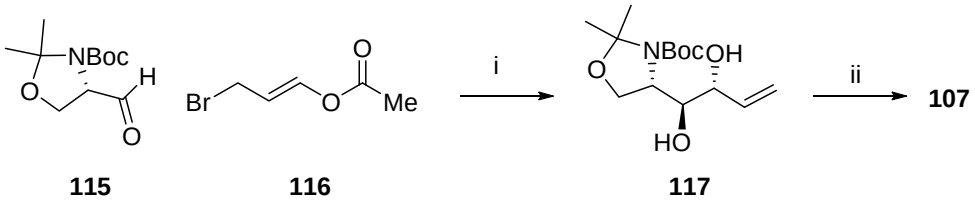


Scheme 16: (i) Ph_3P, CCl_4, Et_3N, DMF, RT, 71% (ii) (a) 3 M H_2SO_4/*p*-dioxane, reflux; (b): NaH, BnBr, Bu_4NI, THF, 80%; (iii) (a) OsO_4, NMO, acetone:H_2O, 25 °C, 4 h (b) $NaIO_4$ then $NaBH_4$, EtOH/H_2O, RT, 70%; (iv) Pd/C, 10 bar H_2, HCl, MeOH, 98%.

Trombini's approach (2003)[36]

In Trombini's approach, 3-bromopropenyl acetate **116** was added to Garner aldehyde **115** using Barbier allylation procedure, which produced diol **117** in 80% yield as a pure isomer. DAB-1 **107** was prepared from diol **117** in 30% yield by a four simple

steps involving (a) acetonide protection; (b) ozonolysis; (c) acetonide deprotection and (d) hydrogenation reactions (**Scheme 17)**.

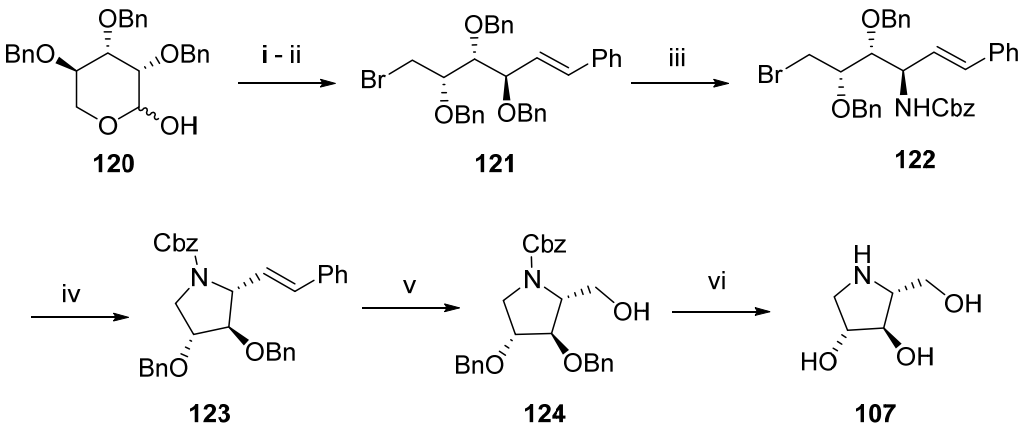


115 **116** **117**

Scheme 17: (i) **116,** In, THF, 80%; (ii) (a) 2,2-dimethoxypropane, Amberlyst® 15A°, CH_2Cl_2, 24 h, 70%; (b) O_3, CH_2Cl_2, −78 °C, 30 min then Me_2S, 12 h; (c) TFA/ H_2O 20:1, 30 min, 0 °C; (d) H_2/Pd, MeOH, 12 h, 45 psi, 30% (over 3 steps).

Jung's approach (2006)[37]

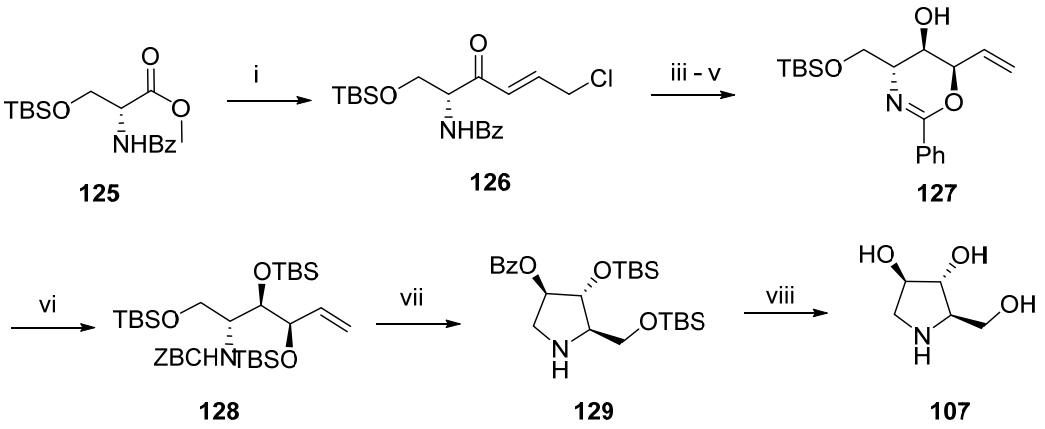
Jung *et al*. have developed the synthesis of **107** commencing from the benzyl protected lactol **120**. Wittig olefination of **120** with dimethylsulfoxide anion in THF at 45 °C afforded 3.1:1 mixture of *cis*/*trans* isomers of alkene and the free hydroxyl group was then converted to bromide **121** with carbon tetrabromide, triphenylphosphine, and triethylamine in 89% yield. The chlorosulfonyl isocyanate (CSI) reaction was carried out on cinnamyl tribenzyl ether **121** in toluene solution at 0 °C for 24 h, followed by desulfonylation using an aqueous solution of 25% sodium sulfite to give the allylic amine product **122** with a high diastereoselectivity (*syn*:*anti* 1:26, 96%) in 84% yield. Treatment of **122** with potassium *tert*-butoxide provided the pyrrolidine **123**. Ozonolysis of the double bond in **123** and subsequent reduction of the resulting aldehyde gave the alcohol **124**. Finally, benzyl and *N*-Cbz protecting groups of **124** were removed by palladium-catalyzed hydrogenolysis, which afforded DAB-1 (**107)** in 98% yield (**Scheme 19)**.



Scheme 19: (i) NaH, DMSO, $BnPPh_3Cl$, THF, 45° C, 94%; (ii) CBr_4, PPh_3, Et_3N, CH_2Cl_2, 0 °C, 89%; (iii) CSI, Na_2CO_3, toluene, 0 °C; (b) 25% Na_2CO_3, 84%; (iv) KO^tBu, THF, 0 °C, 95%; (v) O_3, MeOH: CH_2Cl_2 (1:1), -78°C, then $NaBH_4$, 0 °C, 85%; (vi) 10% Pd/C, H_2 (1 atm), 6N HCl, EtOH, 98%.

Ham's approach (2011)[38]

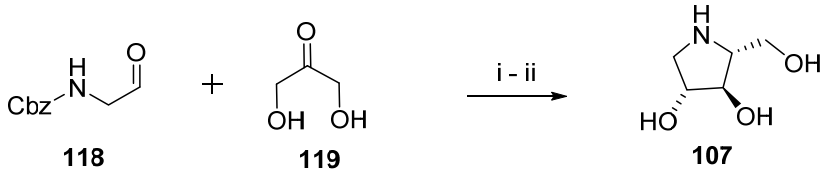
In Ham's approach, keto amine **126** was prepared in 63% yield from *N*-benzoyl-D-serine methyl ester **125** by two step sequence involving amidation using Weinreb amide and allylation using allylBu_3SnCl. Keto amine **126** was subjected to palladium(0)-catalyzed cyclization, which afforded oxazine **127** with high stereoselectivity. The oxazine **127** was treated with benzyl chloroformate in the presence of aqueous sodium bicarbonate to afford the carbamate **128**, which was converted to pyrrolidine **129** in 70% yield (single isomer) by two step sequence involving ozonolysis and hydrogenolysis reactions. Removal of benzoyl and silyl groups of **129** with sodium methoxide in MeOH followed by 6 N HCl yielded the DAB-1 salt, which was purified by ion-exchange chromatography through a DOWEX 50WX8-100(Hþ) to give DAB-1 (**107**) (**Scheme 20)**.



Scheme 20: (i) MeNHOMe-HCl, Me_3Al, CH_2Cl_2, 90%; (ii) allylBu_3SnCl, MeLi, THF, -78 °C, 70%; (iii) $LiAlH(O^tBu)_3$, EtOH, -78 °C , 85%; (iv) TBSCl, imidazole, CH_2Cl_2, 90%; (v) $Pd(PPh_3)_4$, NaH, *n*-Bu_4NI, THF, 65%; (vi) CbzCl, $NaHCO_3$, CH_2Cl_2, H_2O, 78%; (vii) O_3, MeOH, -78°C then $Pd(OH)_2/C$, H_2 (1 atm), MeOH, 70%; (viii) (a) NaOMe, MeOH; (b) 6 N HCl, MeOH.

Clapés's approach (2005)[39]

Clapes *et al.* have developed a straightforward chemo-enzymatic asymmetric stereodivergent synthesis of DAB-1 (**107)** starting from simple and achiral starting materials namely *N*-Cbz-glycinal (**118**) and dihydroxyacetone (**119**); this enzymatic aldol reaction followed by reduction gave DAB-1 (**107)** in 18% yields (**Scheme 18)**.

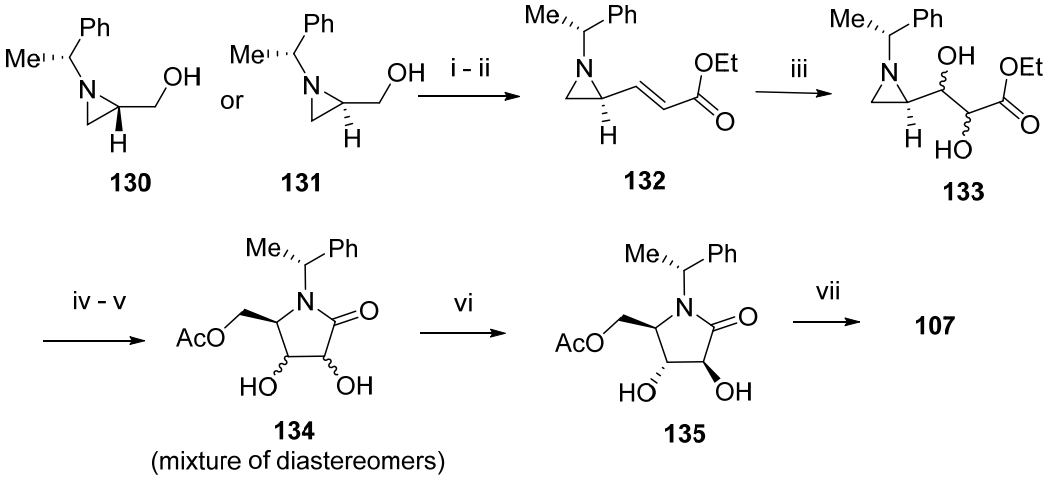


Scheme 18: (i) (a) D-Fructose-6-phosphate aldolase (FSA) mutant A129S/A165G; (b) H_2 (50 psi) Pd/C, 18%.

Sim's approach (2013)[40]

Sim's *et al.* have achieved the synthesis of DAB-1 (**107**) started with Swern oxidation of **130** and **131,** which gave the corresponding 1-methylbenzylaziridine-2-carboxaldehydes that were transformed to *trans*-3-aziridin-2-yl-acrylates **132** in 98:2

trans:cis ratios using Horner–Wadsworth–Emmons olefination with ethyl diethylphosphonoacetate. Dihydroxylation of **132** using OsO_4 in the presence of NMO afforded diastereomers **133** in 77% yield. The C-3 bonds present in the aziridine rings of (2*S*)-**133** and (2*R*)-**133** were regioselectively cleaved by treatment with AcOH in CH_2Cl_2, which produced the corresponding acyclic acetate ester product **133**. Lactam **134** was prepared in 85% yield by cyclization of **133** in the presence of AcOH at 50 °C. The facile recrystallization of **134** from ethanol at 0 °C afforded **135** in a pure form as colorless crystalline solid. Reduction of the amide and acetate groups in **135** was carried out using borane–dimethyl sulfide to generate the corresponding pyrrolidine, which was subjected to hydrogenolysis to form pure DAB-1 (**107)** in 91% yield **(Scheme 21)**.

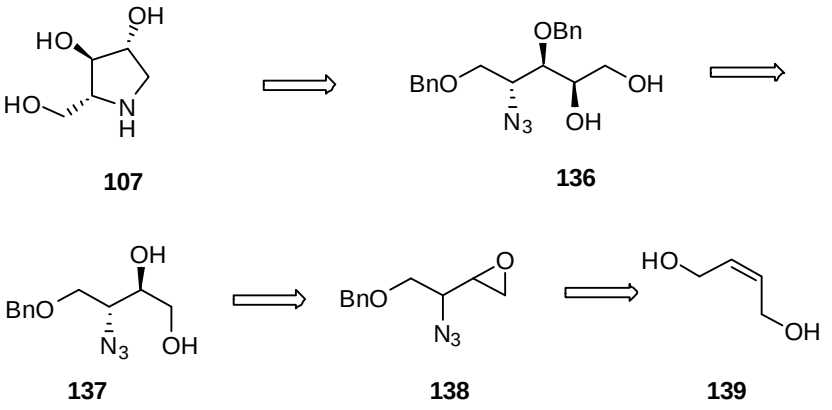


Scheme 21: (i) $COCl_2$, Et_3N, DMSO, CH_2Cl_2, -78 °C, 1 h, 70%; ii) triethyl phosphonoacetate, K_2CO_3, EtOH, RT, 8 h; (iii) OsO_4, NMO THF : H_2O = 3 : 1, RT, 12 h; (iv) AcOH, (0.3 M) CH_2Cl_2, RT, 18 h (v) toluene (0.03 M), 50 °C, 12 h, 85%; (vi) recrystallization, 52%; (vii) (a) BH_3.DMS, THF, 0 °C, 3 h, 95%; (b) $Pd(OH)_2$ (10 wt %), H_2 (1 atm), MeOH. RT, 3 h, 91%.

4.2.3 Present Work

4.2.3.1 Objective

So far, the methods described in literature for the synthesis of DAB-1 suffer from following disadvantages: longer reaction sequences, harsh reaction conditions, chiral pool approaches, use of chiral auxilaries and low overall yields. We became interested in providing a more practical method for the synthesis of (+)-DAB-1 (**107**). In this section, we describe the synthesis of (+)-DAB-1 (**107**) using Co-catalyzed hydrolytic kinetic resolution of two-stereocentered azido epoxide and Os-catalyzed diastereoselective dihydroxylation as the key reactions. With this in mind, we planned our synthetic avenue towards **107** as summarized in **Scheme 22**. Initially, we envisioned that the pyrrolidine formation at the final stage of the total synthesis could be achieved by reductive cyclization of azido diol **136**. The azido diol **136** can in turn be obtained from alcohol **137** by oxidation, Wittig reaction and diastereoselective dihydroxylation reactions. The key intermediate **137** can readily be obtained from azido epoxide **138** utilizing Co-catalyzed two-stereocentered hydrolytic kinetic resolution protocol. Azidoalcohol **138** can be prepared from *cis*-2-butene-1,4-diol (**139**) by azido bromination and epoxidation reactions.

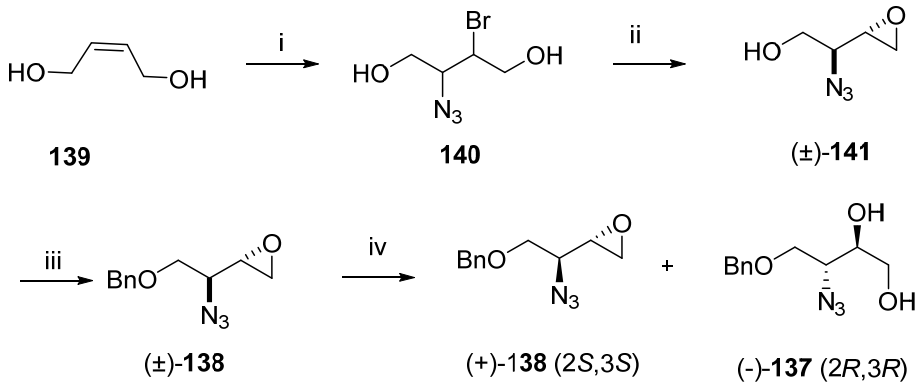


107 **136** **137** **138** **139**

Scheme 22: Retrosynthetic analysis of (+)-DAB-1 (**107**)

4.2.3.2 Results and Discussion

The complete synthetic sequence for the synthesis of key intermediate **137**, wherein Co(salen)-catalyzed hydrolytic kinetic resolution (HKR) of two-stereocentered azido epoxide **138**, a protocol developed in our lab, is presented in **Scheme 23**.



Scheme 23: Reagents and conditions: (i) NBS (1.1 equiv), NaN_3 (2 equiv), $CH_3CN:H_2O$ (3:1), 0 °C, 4 h, 89%; (ii) NaOH powder, THF, 0 °C, 1 h, 84%; (iii) BnBr (1.1 equiv), NaH (1.5 equiv), DMF, 0 to 25 °C, 92%; (iv) (*S,S)*-salen-cobalt(III)OAc (1 mol %), H_2O (0.5 equiv), 0 °C, 14 h, **138**: 48% and **137**: 50%.

Accordingly, the synthesis of DAB-1 (**107**) has commenced with commercially available *cis*-2-butene-1,4-diol (**139**), which on treatment with NBS in the presence of NaN_3 in $CH_3CN:H_2O$ (4:1) at 25 °C gave bromo azide **140** in 89% yield. The formation of azido bromide (±)-**140** was confirmed by ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectrum of **140** showed a typical proton signal at δ 4.12-4.20 (m, 1H) for methine (-C**H**-N_3) proton, while its ^{13}C NMR spectrum showed a typical carbon signal at δ 54.3 due to carbon attached to bromo group (**Fig. 15**).

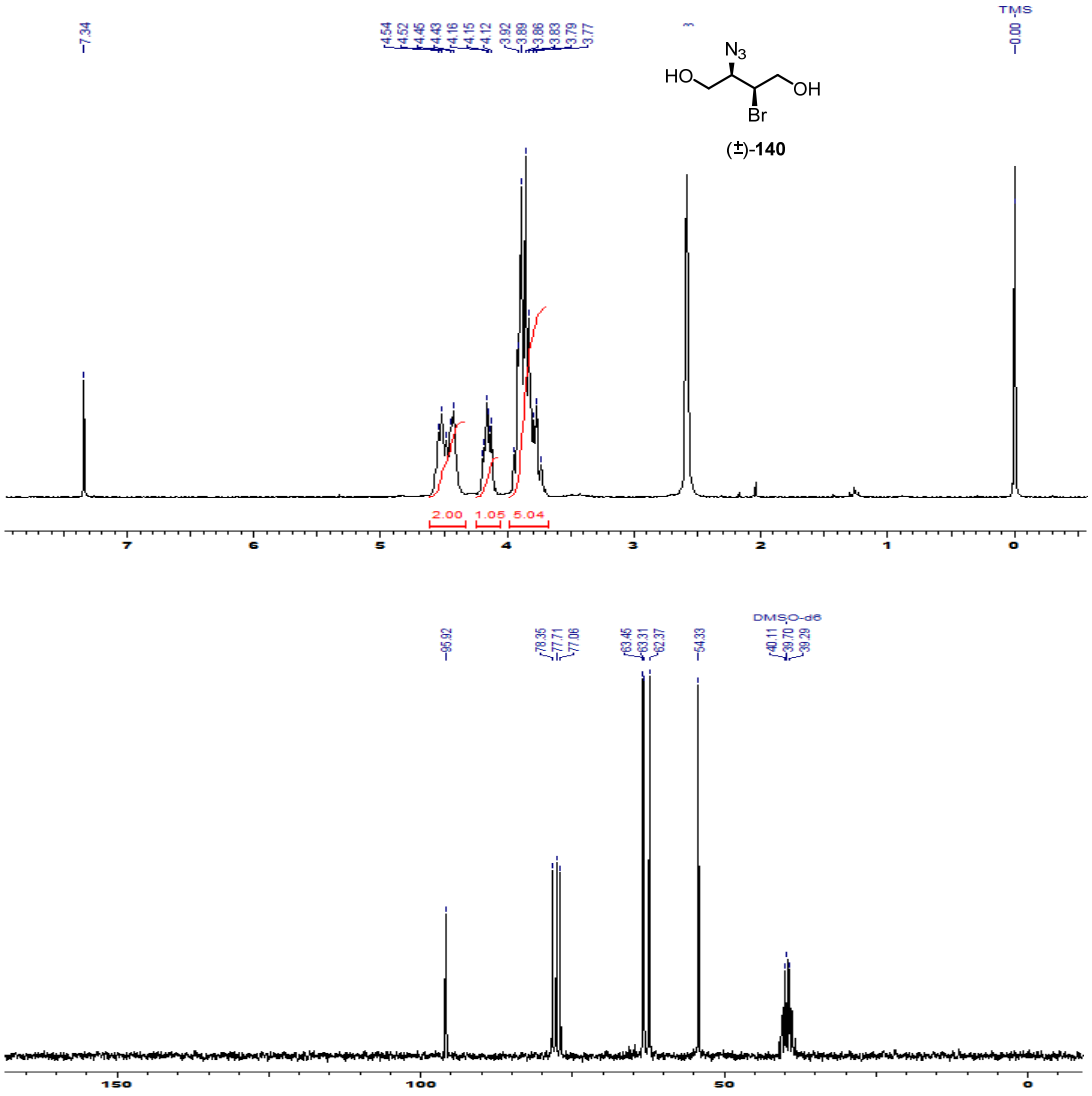


Fig.15: ^{1}H and ^{13}C NMR spectra of **(±)-140**

The bromo azide **140** was readily transformed into racemic *anti*-azido epoxide **141** (84% yield) under base treatment (NaOH, dry THF, 0 ^{o}C). The formation of epoxide was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of **144** showed proton signals at δ 2.82-2.90 (m, 2H) and δ 3.47-3.49 (m, 1H) for methylene and methine protons of epoxide ring respectively. Its ^{13}C NMR spectrum showed typical carbon signals at δ 44.8 and 50.6 corresponding to epoxide ring carbons (**Fig. 16**).

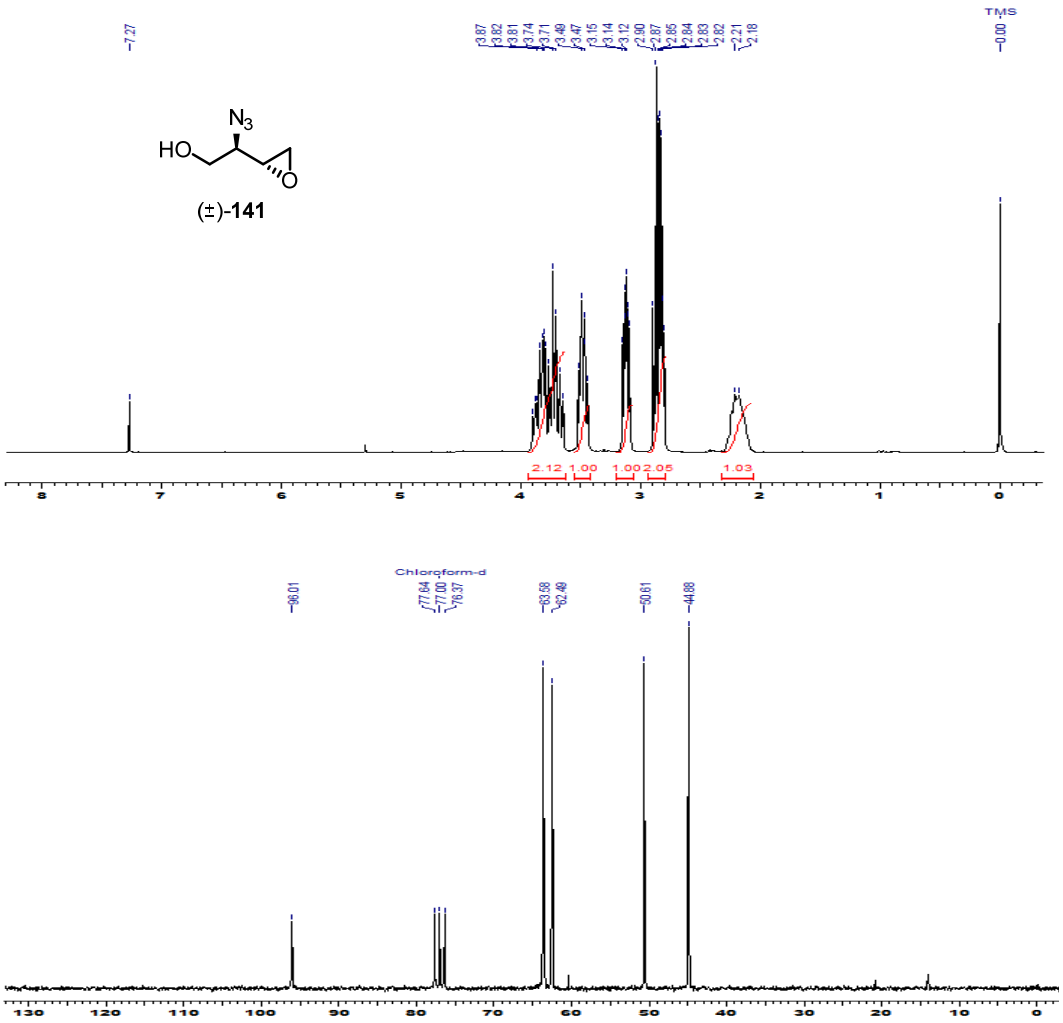


Fig. 16: ^{1}H and ^{13}C NMR spectra of **(±)-141**

The protection of primary hydroxyl group in azido epoxide **141** as its benzyl ether (BnBr, NaH, DMF, 0 ^{o}C) was achieved to give protected racemic azido epoxide (±)-**138** in 94% yield. The formation of compound **138** was confirmed by the appearance of a typical proton signal, in its ^{1}H NMR spectrum, at δ 7.33 (m, 5H) for aromatic protons of benzyl group. Its ^{13}C NMR spectrum showed a typical signal at δ 73.4 for benzylic carbon confirming benzyl protected azido epoxide **138** (**Fig. 17**).

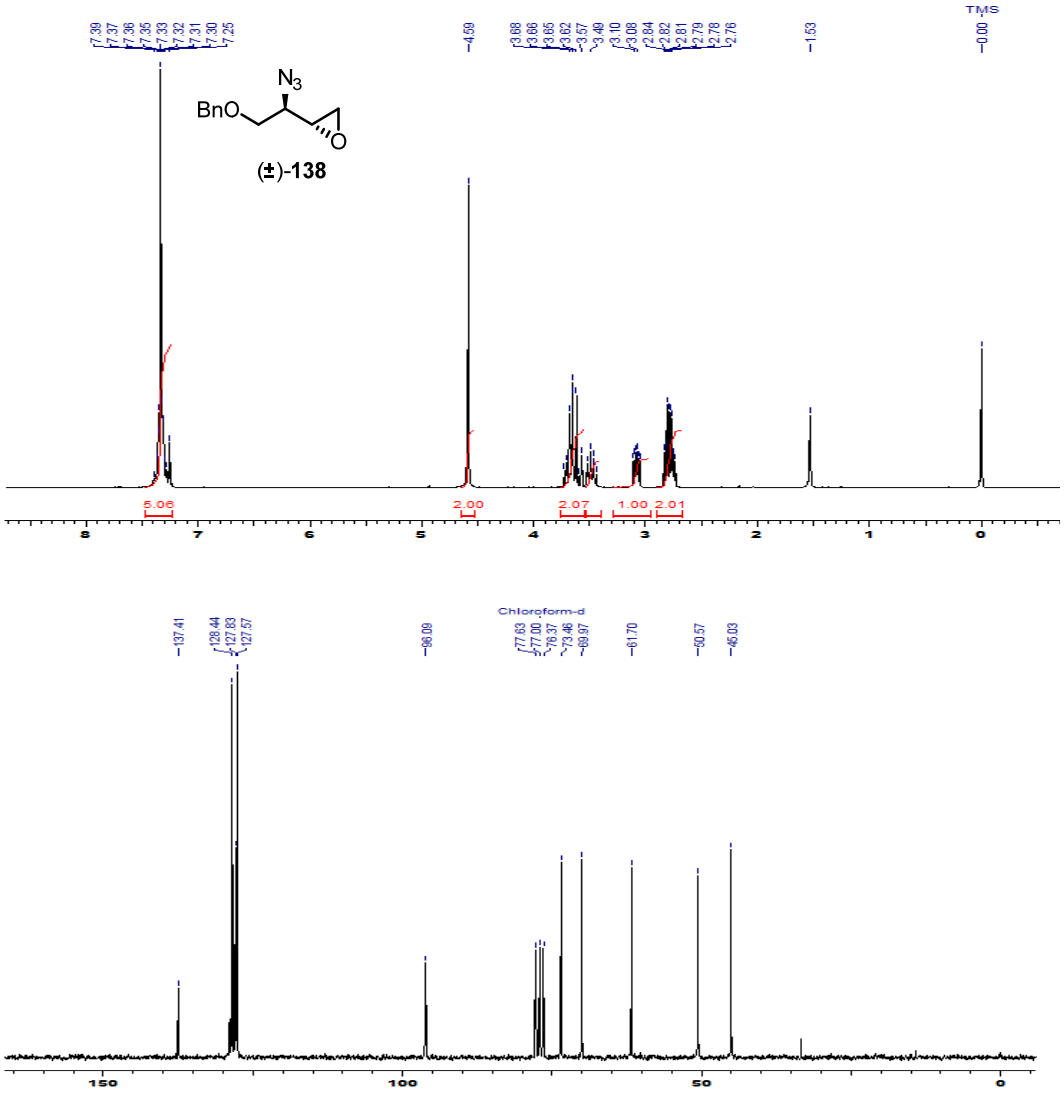


Fig. 17: ^{1}H and ^{13}C NMR spectra of (±)-**138**

The racemic azido epoxide **138** was then subjected to HKR with (*S*,*S*)-salen Co(III)OAc complex (0.5 mol %) and H_2O (0.49 equiv), which produced the corresponding diol **137** (48%, 99% ee) and chiral epoxide **138** (50%, 97% ee) in high optical purity (**Scheme 23**).[41] The diol (-)-**137** was, however, readily separated from epoxide (+)-**138** by a simple flash column chromatographic purification over silica gel. The enantiomeric excess of azido diol (-)-**137** was determined from chiral HPLC analysis; Chiralpak OD-H **(Fig. 18)**. The formation of azido diol (-)-**137** was confirmed by the appearance of a broad singlets, in its ^{1}H NMR spectrum, at δ 2.82

and δ 1.60 due to the hydroxy protons and a singlet at δ 4.56 due to benzylic protons. Its ^{13}C NMR spectrum showed characteristic signals at δ 63.3 and δ 71.3 for the methine and methylene carbons attached to hydroxyl groups respectively (**Fig. 19**).

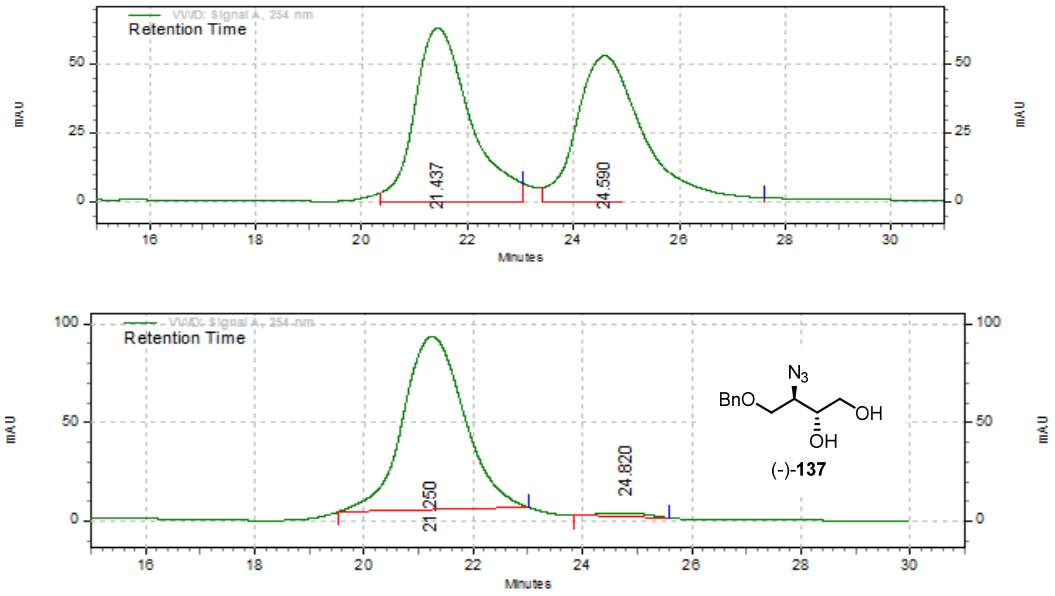
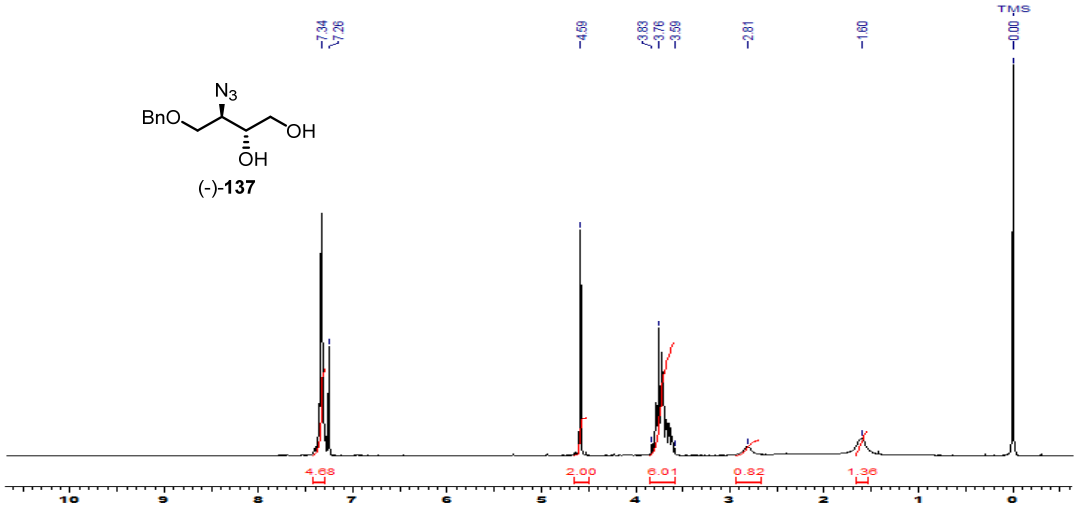


Fig. 18: HPLC chromatogram of (-)-**137,** 99% ee (Chiral OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm); Retention time: t_{major} = 21.50 (99.55%) and t_{minor} = 24.82 min. (0.45%)



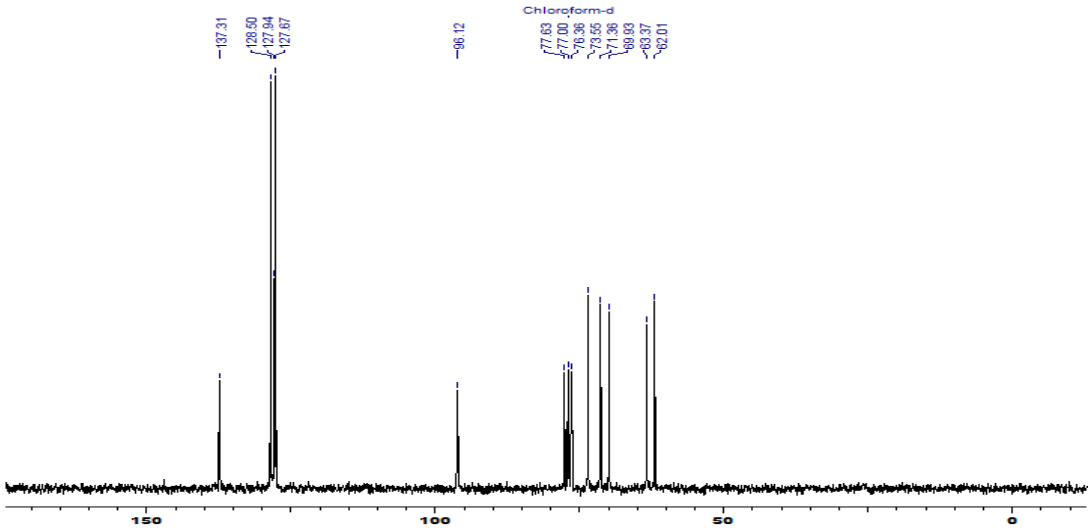
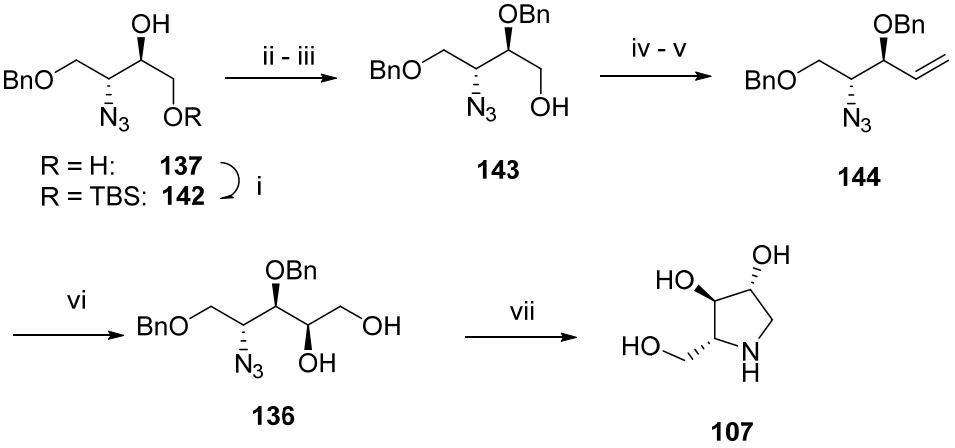


Fig. 19: ^{1}H and ^{13}C NMR spectra of (-)-**137**

The azidodiol **137** was then converted to DAB-1 (**107)** in seven simple steps, comprising of diastereoselective *syn*-dihydroxylation followed by reductive cyclization reaction as shown in **Scheme 24**.



Scheme 24: (i) TBSCl (1.1 equiv), imidazole (1.5 equiv), CH_2Cl_2, 25 °C, 92%; (ii) BnBr (1.1 equiv), NaH (1.5 equiv), DMF, 0 °C to 25 °C; (iii) CSA (10 mol %), CH_2Cl_2:MeOH (1:1), 84% (over 2 steps); (iv) PCC, CH_2Cl_2, 4 A ° MS, 25 °C; (v) CH_3PPh_3I (1.1 equiv), *n*-BuLi (1.5 equiv), THF, 0 - 25 °C, 81% (over 2 steps) (vi) K_2OsO_4 (1 mol %), NMO (3 equiv), acetone:H_2O (4:1), 88%; (vii) (a) Bu_3SnO (2 equiv), *p*-TsCl (1.1 equiv), Et_3N (2 equiv), DMAP (10 mol %), CH_2Cl_2, 0 - 25 °C; (b) 10% Pd/C, 6N HCl, MeOH, H_2 (1 atm), 25 °C, 12 h, 90 %.

The primary hydroxyl groups in azido diol (-)-**137** was protected as its silyl ether **142** in 92% yield. The ^{1}H NMR spectrum of **142** showed one doublet at □ 0.00 (d, J = 1.8 Hz, 6H) and a singlet 0.81 (s, 9H) corresponding to protons of TBS group and a singlet at 4.50 (s, 2H) corresponding to benzylic protons, while its ^{13}C NMR spectrum showed characteristic carbon signals at -5.4, 25.7 and 25.9 corresponding to carbons of TBS group **(Fig. 20)**.

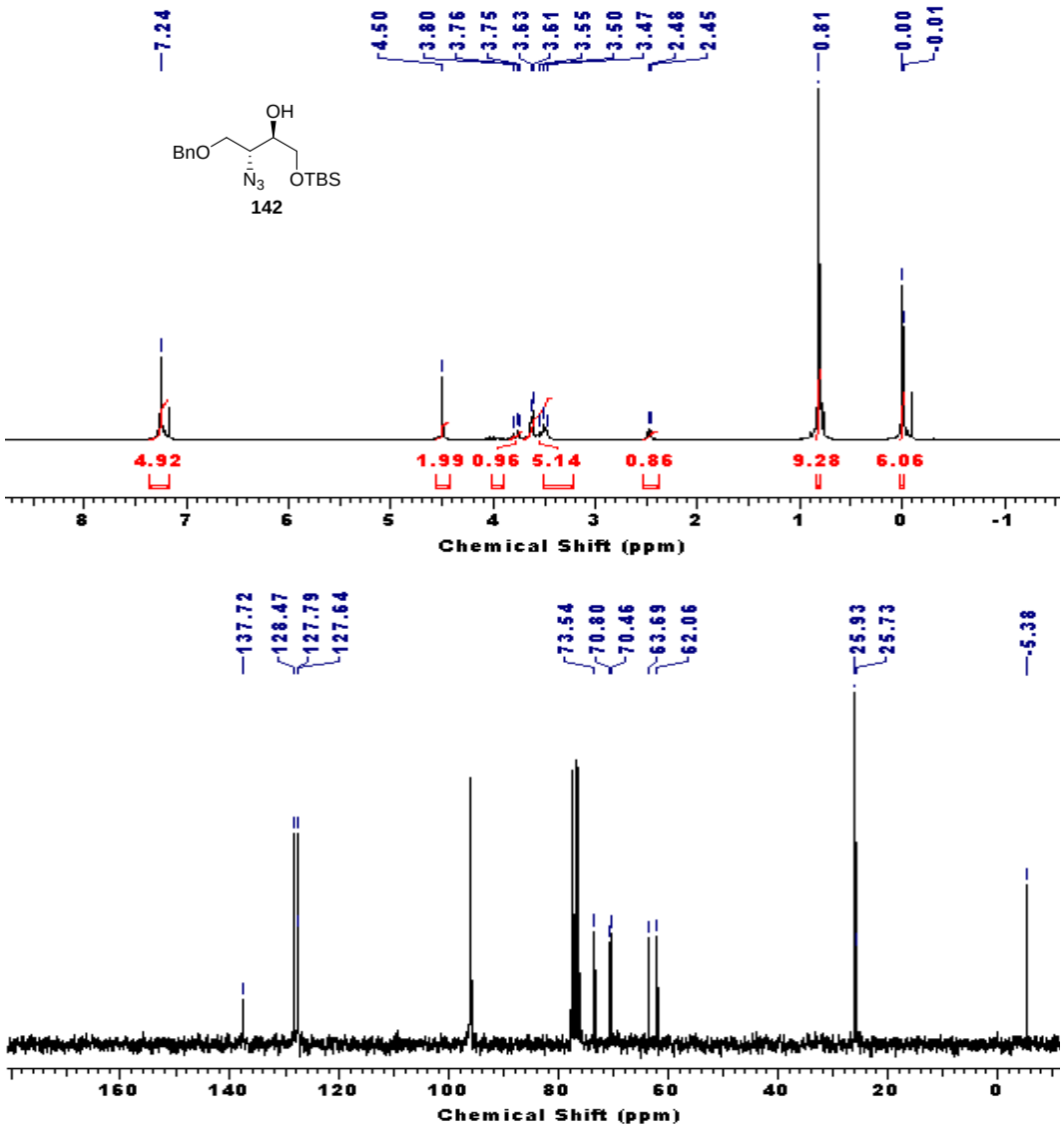


Fig. 20: ^{1}H and ^{13}C NMR spectra of **142**

The secondary hydroxyl group in **142** was then protected as its benzyl ether using BnBr and NaH at 0 °C in DMF. After work-up, the crude reaction mixture was used for selective deprotection (CSA, MeOH, 0 ^{o}C) of primary silyl ether that afforded alcohol **143** in 84% yield. The ^{1}H NMR spectrum of **143** showed a typical doublet at δ 4.56 (d, J = 6.1 Hz, 4H) corresponding to benzylic protons and while its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 73.1 and 78.2 corresponding to carbons at benzylic position **(Fig. 21)**.

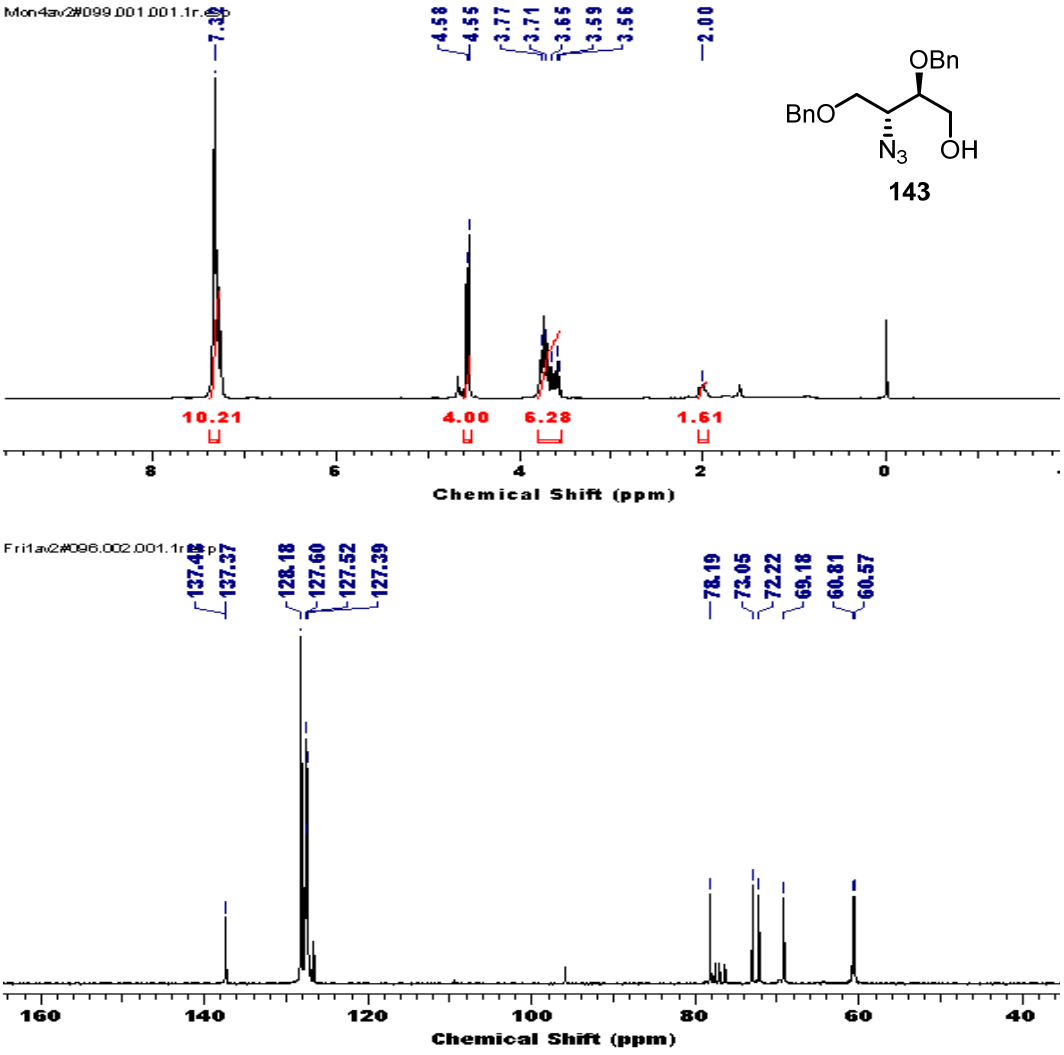


Fig. 21: ^{1}H and ^{13}C NMR spectra of **143**

Primary hydroxyl group in **143** was oxidized to aldehyde using pyridinium chlorochromate (PCC). The crude aldehyde was immediately subjected to one carbon homologation reaction, which afforded **144** in 81% yields over two steps. The ^{1}H NMR spectrum of **144** showed two typical multiplets at δ 5.27-5.47 (m, 2H) and 5.71-5.96 (m, 1H) corresponding to olefinic protons, while its ^{13}C NMR spectrum showed two carbon signals at δ 118.6 and 136.7 corresponding to olefinic carbons (**Fig. 22**).

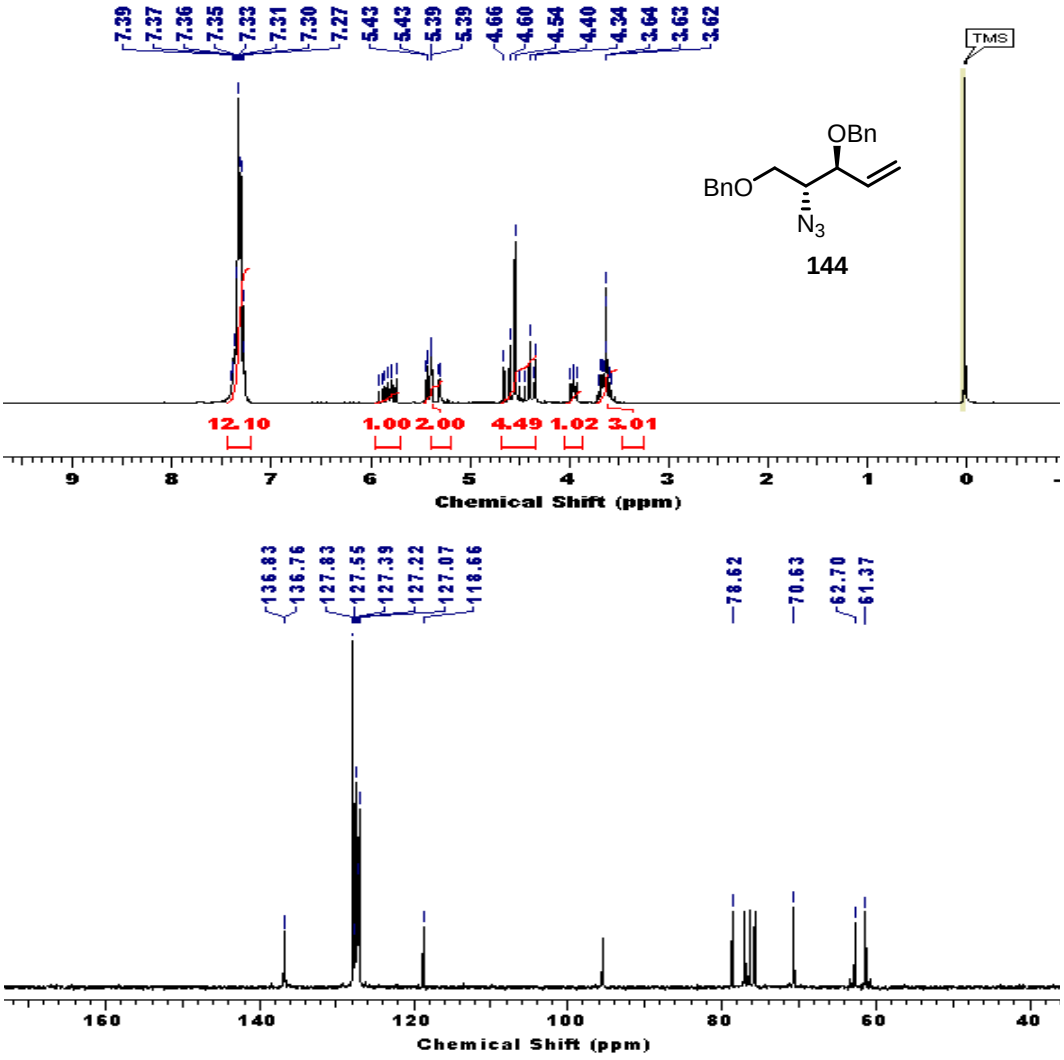
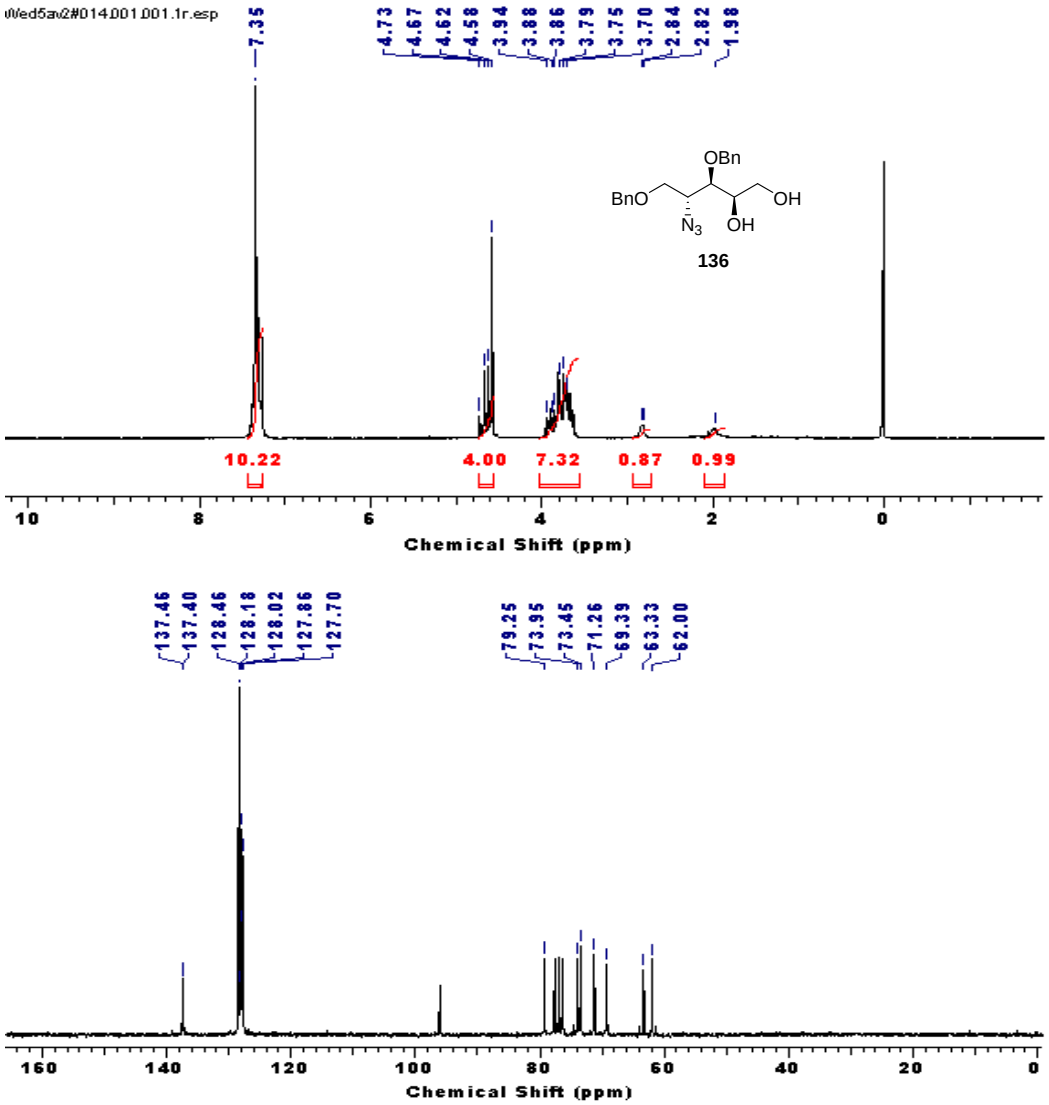


Fig. 22: ^{1}H and ^{13}C NMR spectra of **144**

The diastereoselective dihydroxylation of alkene **144** using potassium osmate and NMO gave corresponding diol **136** with diastereoselectivity (10:1 = *anti:syn*), which was separated using flash column chromatography.[46] The ^{1}H NMR spectrum of diol **136** showed two broad peaks at δ 1.98 (bs, 1H) and 2.83 (bs, 1H) corresponding to protons of hydroxyl groups and 4.58-4.73 (m, 4H) corresponding to benzylic protons. Its ^{13}C NMR spectrum showed two typical carbon signals at δ 79.2 and 73.9 corresponding to benzylic carbons **(Fig. 23)**.



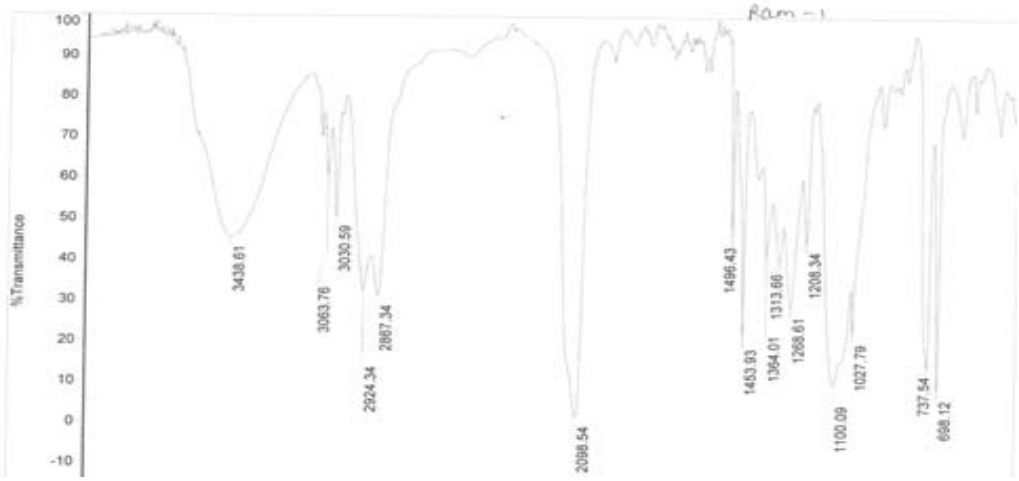


Fig. 23: ^{1}H, ^{13}C NMR and IR spectra of **136**

Finally, the primary hydroxyl group of diol **136** was selectively protected as its tosylate using Bu_2SnO and tosyl chloride. The crude tosylate was then subjected to hydrogenation reaction [10% Pd/C, H_2 (1 atm) MeOH] under strong acidic condition (6N HCl) for 24 h for the conversion of azide group to amine, nucleophilic displacement of tosyl group by amine and deprotection of benzyl groups, which all occurred simultaneously to afford our desired product DAB-1 in 90% yield. The formation of DAB-1 (**107**) was confirmed by its ^{1}H and ^{13}C NMR spectra. Its ^{1}H NMR spectrum showed multiplets at δ 3.03-3.09 (m, 1H), 3.23-3.39 (m, 2H) and 3.62-3.68 (m, 1H) for diastereotopic protons of two -C**H₂** groups, while its ^{13}C NMR spectrum showed two peaks at δ 50.5 and 60.5 corresponding to carbons of -**C**H_2 groups. The observed specific rotation value $[\alpha]^{25}_{D}$ +39.2 (*c* 0.5, D_2O) of DAB-1 (**107**) was in well agreement with the literature value.[45]

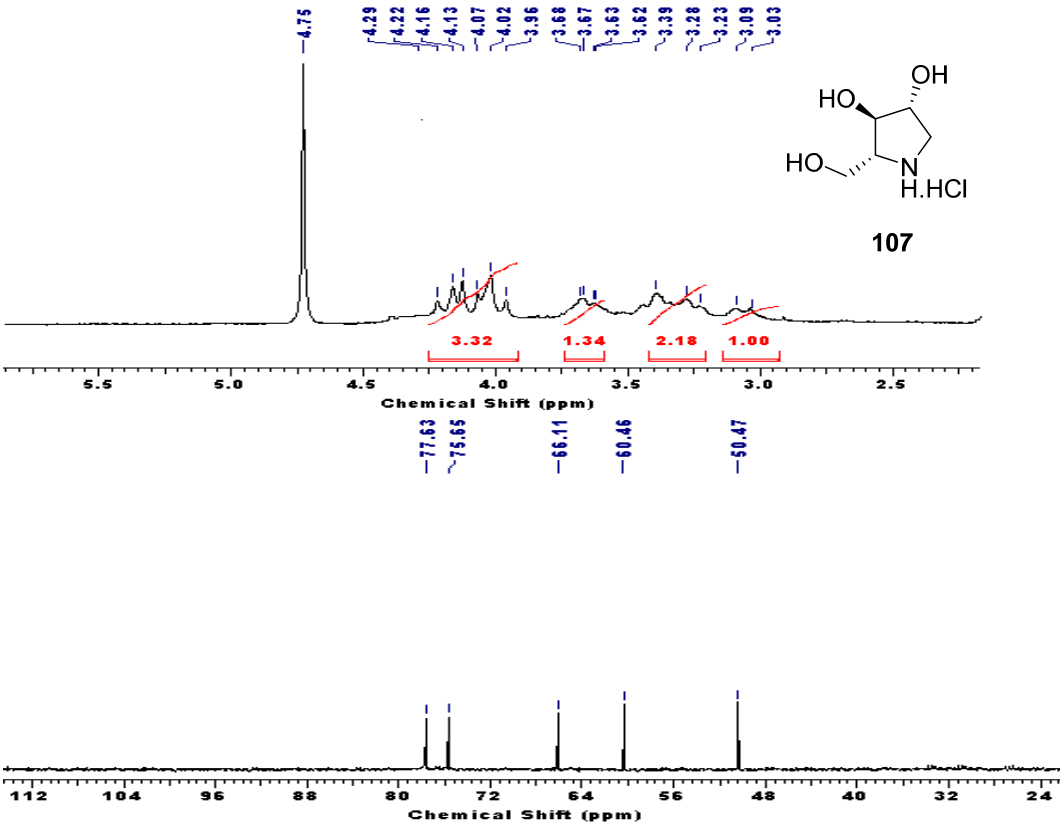


Fig. 24: ^{1}H and ^{13}C NMR spectra of **107**

4.2.4 Conclusion

In conclusion, this section has presented a short and practical enantioselective synthesis of DAB-1(**107**) with good overall yield (18.1%) and high optical purity (ee up to 99%). The key reaction employed was a two-stereocentered Co-catalyzed HKR of racemic azido epoxides. The other operationally simple reaction sequences include Wittig reaction, diastereoselective dihydroxylation and intramolecular reductive cyclization reactions. The synthetic strategy described herein has significant potential for further extension to other stereoisomers and related analogues of multifunctionalized pyrrolidine alkaloids owing to its flexible nature of the synthesis of racemic azido epoxides with different stereochemical combinations and with different substituents.

4.2.5 Experimental Section

2-Azido-3-bromobutane-1,4-diol (140)

A mixture of *cis*-2-butene-1,4-diol **139** (10 g, 113.63 mmol) and NaN_3 (14.77 g, 227.27 mmol) were taken in CH_3CN/H_2O (180:60 mL) and NBS (24.13 g, 136.36 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 (monitored by TLC), CH_3CN was evaporated and the reaction mixture was diluted with EtOAc (80 mL), and the aq. layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by column chromatography using petroleum ether: ethyl acetate (50:50) to afford pure product **140** as a colorless solid in 89% yield.

Yield: 89% (21.1 g) colorless solid, mp: 52 °C; **IR:** (neat, cm^{-1}): υ_{max} 1035, 1267, 2104, 3361; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 3.74-3.95 (m, 5H), 4.12-4.20 (m, 1H), 4.43-4.54 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+DMSO-d_6): δ 54.3, 62.4, 63.3, 63.4; **Anal**. Calcd for $C_4H_8BrN_3O_2$ requires C, 22.87; H, 3.84; N, 20.01; found C, 22.80; H, 3.82; N, 20.06%.

***rac*-2-Azido-2-(oxiran-2-yl)ethanol (141)**

Azido bromide **140** (8 g, 38.27 mmol) was taken in THF (50 mL) and NaOH powder (1.83 g, 45.93 mmol) was added slowly with stirring at 0 °C for 2 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with EtOAc (60 mL) and water (50 mL). The organic layer was further separated and the aq. layer extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give

crude product, which was then purified by column chromatography using petroleum ether: ethyl acetate (8:2) as eluents to afford **141** in 84% yield as colorless oil.

Yield: 84% (4.14 g) colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1264, 2104, 2931, 3383; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.18 (br s, 1H), 2.80-2.90 (m, 2H), 3.09-3.15 (m, 1H), 3.44-3.52 (m, 1H), 3.65-3.90 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 44.2, 49.9, 61.8, 62.9; **Anal**. Calcd for $C_4H_7N_3O_2$ requires C, 37.21; H, 5.46; N, 32.54; found C, 37.28; H, 5.56; N, 32.46%.

***rac*-2-(1-Azido-2-(benzyloxy)ethyl)oxirane (138)**

To suspension of sodium hydride (1.7 gm, 42.63 mmol) in DMF (50 mL), a solution of epoxy alcohol **141** (5 g, 38.75 mmol) in DMF (10 mL) was added. To this, BnBr (5 mL, 42.63 mmol) was added slowly and the stirring was continued for 2 h at -40 ^oC. After completion of reaction (monitored by TLC), it was quenched with saturated NH_4Cl and extracted with EtOAc (3 x 50 mL). The combined organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude product was purified by column chromatography over silica gel using petroleum ether: ethyl acetate (95:5) to give the product **138** in 94% yield.

Yield: 94% (7.97 g), colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1264, 1453, 2102, 2864; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.74-2.83 (m, 2H), 3.05-3.11 (m, 1H), 3.44-3.52 (m, 1H), 3.57-3.73 (m, 2H), 4.59 (s, 2H), 7.28-7.39 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 45.0, 50.5, 61.7, 69.9, 73.5, 127.6, 127.8, 128.4, 137.4; **Anal.** Calcd for $C_{11}H_{13}N_3O_2$ requires C, 60.26; H, 5.98; N, 19.17; found C, 60.24; H, 5.90; N, 19.20%.

HKR of 3-Azido-4-(benzyloxy)butane-1,2-diol (±)-138

To a solution of (*S*,*S*)-Co-*salen* (0.027 g, 0.5 mol %) in toluene (2 mL), AcOH (0.02 g, 0.36 mmol) was added. It was allowed to stir at 25 °C in open air for 30 min. During this time the color changed from orange-red to a dark brown, it was then dried

under vacuum. To this racemic azido epoxide (2 g, 9.13 mmol) and H_2O (0.08 mL, 4.47 mmol) was added at 0 °C. Then the reaction was allowed to stir for 12 h at 25 °C. After completion of reaction (monitored by TLC), the crude product was purified by column chromatography over silica gel to give chiral azido epoxide **(+)-138,** [solvent system; petroleum ether: ethyl acetate (95:5)] and chiral azido diol **(-)-137** [solvent system; petroleum ether: ethyl acetate (6:4)] in pure form.

(2*R*, 3*R*)-3-Azido-4-(benzyloxy)butane-1,2-diol (-)-137

Yield: 47% (1.01 g), colorless oil; $[\alpha]_D^{25}$ = -37.8 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1271, 1453, 2099, 2870, 2929, 3384; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.60 (br s, 1H), 2.81 (br s, 1H), 3.59-3.83 (m, 6H), 4.59 (s, 2H), 7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 62.0, 63.4, 69.9, 71.4, 73.5, 127.7, 127.9, 128.5, 137.3; **Anal**. Calcd for $C_{11}H_{15}N_3O_3$ requires C, 55.69; H, 6.37; N, 17.71; found C, 55.70; H, 6.48; N, 17.65%; **Optical purity**: 99% ee determined from HPLC analysis (Chiral OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm) Retention time: t_{major} = 21.25 and t_{minor} = 24.82 min.

(*S*)-2-((*S*)-1-Azido-2-(benzyloxy)ethyl)oxirane (+)-136

Yield: 50% (1 g), colorless oil; $[\alpha]_D^{25}$ = +29.3 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1264, 1453, 2102, 2864; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.74-2.83 (m, 2H), 3.05-3.11 (m, 1H), 3.44-3.52 (m, 1H), 3.57-3.73 (m, 2H), 4.59 (s, 2H), 7.28-7.39 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 45.0, 50.5, 61.7, 69.9, 73.4, 127.6, 127.8, 128.4, 137.4; **Anal**. Calcd for $C_{11}H_{13}N_3O_2$ requires C, 60.26; H, 5.98; N, 19.17; found C, 60.24; H, 5.90; N, 19.20%; **Optical purity**: 99% ee determined from HPLC analysis (Chiral OD-H column, *n*-hexane/ 2-propanol (95:5), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 13.51 and t_{major} = 16.20 min.

(2*R*,3*R*)-3-Azido-4-(benzyloxy)-1-((*tert*-butyldimethylsilyl)oxy)butan-2-ol (142)

To a stirred solution of azido diol **137** (2 g, 8.43 mmol) in CH_2Cl_2 (25 mL) was added TBSCl (1.07 g, 10.11 mmol) and imidazole (647 mg, 16.86 mmol) at 25 ºC. The resulting solution was stirred at same temperature for 3 h, then quenched with water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product. Column chromatographic purification with silica gel using petroleum ether: ethyl acetate (95:5) as eluent gave pure mono-TBS ether **142** as colorless oil in 92% yield (2.72 g).

Yield: 92%, colorless oil; $[\alpha]_D^{25}$ = +33.3 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1464, 1593, 2102, 2864, 3414; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.00 (d, *J* = 1.8 Hz, 6 H), 0.81 (s, 9H), 2.47 (d, *J* = 6.1 Hz, 1H), 3.40-3.69 (m, 5H), 3.71-3.83 (m, 1H), 4.50 (s, 2H), 7.24 (s, 5H): **^{13}C NMR** (125 MHz, $CDCl_3$): -5.4, 25.7, 25.9, 62.0, 63.7, 70.5, 70.8, 73.5, 127.6, 127.8, 128.5, 137.7; **HRMS** (ESIMS): calcd for $C_{17}H_{29}SiN_3O_3$+Na]$^+$ 374.1876, found 374.1875.

(2*R*,3*R*`)-3-Azido-2,4-bis(benzyloxy)butan-1-ol (143)

To a stirred solution of alcohol **142** (2.5 g, 7.11 mmol) in DMF (40 mL) was added sodium hydride (0.426 g, 10.66 mmol) at 0 °C followed by the addition of benzyl bromide (1 mL, 7.82 mmol). After stirring for 1 h, the reaction mixture was quenched by the addition of ice. The aqueous layer was exctracted with EtOAc (3 x50 mL) and the combined organic layers were washed with water, brine, dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure to give the crude benzyl ether. The crude product was dissolved in MeOH (30 mL) and camphorsulfonic acid (10 mol %, 0.165 mg) was added and the mixture stirred at room temperature. After completion of the reaction as monitored by TLC, MeOH was evaporated and water (30 mL) was added. The organic layer was separated and the aqueous layer was

extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water, brine, dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure to give the crude product, .which was purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (5:95) to give pure alcohol **143** in 1.95 g (84%).

Yield: 84 %, colorless oil; $[\alpha]_D^{25}$ = +26.3 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 745, 1364, 1553, 2100, 2864, 3342; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.00 (br.s, 2H), 3.54-3.81 (m, 7H), 4.56 (d, *J* = 6.1 Hz, 4H), 7.32 (s, 10H): **^{13}C NMR** (50 MHz, $CDCl_3$): δ 60.6, 60.8, 69.2, 72.2, 73.1, 78.2, 127.4, 127.5, 127.6, 128.2, 137.4, 137.4.; **HRMS** (ESIMS): calcd for $C_{18}H_{21}N_3O_3$ + Na]+ 350.1481, found 350.1489.

((((2*R*,3*S*)-2-Azidopent-4-ene-1,3-diyl)bis(oxy))bis(methylene))dibenzene (144)

To a stirred solution of alcohol **143** (1.0 g, 3.05 mmol) in CH_2Cl_2 (20 mL) was added PCC (0.78 g, 3.66 mmol) at 25 °C. The reaction mixture was allowed to stir at same temperature for 3 h. After completion (as monitored by TLC), the reaction mixture was filtered and water (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with water, brine and dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure to give the crude product. In a separate round bottomed flask one carbon Wittig salt (ICH_3PPh_3) (1.47 g, 3.66 mmol) in THF was added *n*-BuLi (390 mg, 6.1 mmol, 3.85 mL of 1.6 M solution in THF), at 0 °C, which gave yellow solution of Wittig ylide. The above crude aldehyde was added to this reaction mixture and allowed to stir at 25 °C for 8 h. After completion of the reaction, as monitored by TLC, the reaction mixture was quenched with ice followed by addition of water. The THF layer was concentrated and the resultant aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, solvent distilled off under reduced

pressure to give the crude product, which was purified by flash column chromatography over silica gel using EtOAc/Pet. ether as eluent (5:95) to give alkene **144** in 0.8 g (81%).

Yield: 81%, colorless oil; $[\alpha]_D^{25}$ = -22.3 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 760, 1259, 2102, 2864, 2937; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.50-3.72 (m, 3H), 3.96 (dd, *J* = 7.8, 5.1 Hz, 1H), 4.33-4.68 (m, 5H), 5.27-5.47 (m, 2H), 5.71-5.96 (m, 1H), 7.21-7.44 (m, 12H): **^{13}C NMR** (50 MHz, $CDCl_3$): δ 61.4, 62.7, 70.6, 78.6, 118.6, 127.0, 127.2, 127.4, 127.5, 136.7, 136.8. **HRMS** (ESIMS): calcd for $C_{19}H_{21}N_3O_2$+Na]$^+$ 323.1634, found 323.1639.

(2*R*,3*R*,4*R*)-4-Azido-3,5-bis(benzyloxy)pentane-1,2-diol (136)

To a stirred solution of alkene **144** (0.5 g, 1.55 mmol) in acetone:H_2O (4:1) (10 mL) was added $K_2OsO_4.2H_2O$ (6 mg, 1 mol %) and *N*-methylmorpholine oxide (0.362 g, 3.1 mmol) at 25 °C. The reaction was stirred for 4 h at room temperature. After completion of the reaction (as monitored by TLC), it was quenched with sat. $Na_2S_2O_3$ soln. (25 ml) and stirred for an additional 30 min. Acetone was evaporated and aqueous layer was extracted with EtOAc (3 x 30 mL). The organic phase was washed with H_2O (15 ml), dried, and concentrated. The crude product was purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (4:6) to give diol **136** in 0.484 g (88%).

Yield: 88%, colorless oil; $[\alpha]_D^{25}$ = -36.3 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 698, 737, 1100, 1453, 2098, 2924, 3438; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.98 (s, 1H), 2.83 (bs, 1H), 3.73-3.94 (m, 7H), 4.58-4.73(m, 4H), 7.35 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 62.0, 63.3, 69.4, 71.3, 73.4, 73.9, 79.2, 127.7, 127.9, 128.0, 128.2, 128.5,

137.4, 137.5; **HRMS** (ESIMS): calcd for $C_{19}H_{21}N_3O_2$+Na]$^+$ 323.1634, found 323.1639.

1,4-Dideoxy-1,4-imido-D-arabinitol (107)

To a stirred solution of diol **133** (0.3 g, 0.83 mmol) in MeOH (20 mL) was added a solution of aqueous 6 N HCl (4 mL) and 10% Pd/C (0.1 g, 0.1 mmol). The reaction mixture was allowed to stir under H_2 atmosphere (1 atm) for 36 h. The resulting mixture was filtered through a celite pad and concentrated in *vacuo*. The residue was purified by column chromatography eluting with CH_2Cl_2:MeOH (6:4) as eluent to afford 100 mg (90%) of 1,4-dideoxy-1,4-imino- D-arabinitol (**107**) as its hydrochloride salt, a colorless solid.

Yield: 90%, colorless solid; *R*f = 0.30 (CH_2Cl_2/MeOH/EtOH/30%NH_4OH 5:2:2:1); mp: 112-114 ^oC ; **[α]$^{25}_D$** +39.2 (*c* 0.5, D_2O); lit.[45][α]$^{25}_D$ +40.1 (*c* 0.5, D_2O); **^{1}H NMR** (500 MHz, D_2O) δ 3.03-3.09 (m, 1H), 3.23-3.39 (m, 2H), 3.62-3.68 (m, 1H,), 3.96-4.29 (m, 3H); **^{13}C NMR** (125 MHz, D_2O): δ 50.5, 60.5, 66.1, 75.6, 77.6; **HRMS** (ESIMS): calcd for $C_5H_{11}NO_3$+Na]$^+$ 156.0637, found 156.0639.

Section III

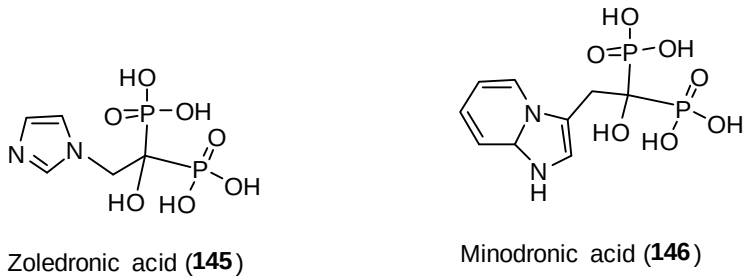
Process for the Synthesis of Zoledronic acid

4.3.1Pharmacology of Bisphosphonic acids: Zoledronic acid

Bisphosphonic acids and/or their salts are excellent antihypercalcemics and as such are rapidlyevolving as therapeutic agents for the treatment of a number of diseases which are characterizedby abnormal calcium metabolism.[43] Bisphosphonates, in particular, 1-hydroxy-2-(pyridinyl)ethylidene-1,1-bisphosphonicacid (risedronic acid), 1-hydroxy-3-(methylpentylamino),propylidenebisphosphonic acid (ibandronate 2d), 3-amino-1-hydroxy propylidenebisphosphonic acid (pamidronicacid), 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid(alendronate) are used for the treatment of Paget`s disease of bone and osteoporosis.

Zoledronic acid (**145**) is a third-generationbisphosphonate (or diphosphonate) derivative characterized bya side chain that includes an imidazole ring.[44] It inhibits osteoclastaction and bone resorption and is used to treat tumor-inducedhypercalcemia*i.e.* a disease condition characterized bythe high levels of calcium in the blood (normal range 9–10.5mg/dL or 2.2–2.6 mmol/L) usually caused by certain types ofcancer. Zoledronic acid (**145**) is also used along with the cancerchemotherapy to treat bone damage caused by multiplemyeloma (a type of cancer of plasma cells that are part of theimmune system cells in bone marrow and produce antibodies)or by cancer that began in another part of the body but hasspread to the bones. While the use of zoledronic acid canneither suppress nor stop cancer spreading, it can be used totreat bone disease in patients, who are suffering from cancer. Itworks by slowing bone breakdown and decreasing the amountof calcium released from the bones into the blood. It is commercially available in products sold

under the brand nameZometa™ in vials as a sterile powder or solution for intravenousinfusion. Minodronic acid is a third-generation bisphosphonate drug in the treatment of osteoporosis (**Fig. 25**).



Zoledronic acid (**145**) Minodronic acid (**146**)

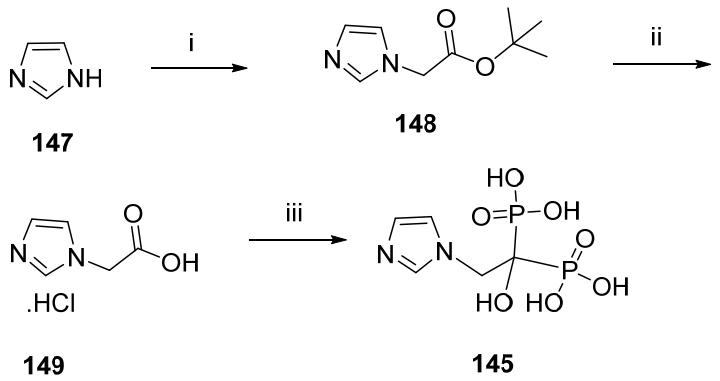
Fig25: Structure of zoledronic acid (**145**) and minodronic acid (**146**)

4.3.2 Review of Literature

Despite its high importance as a drug candidate, very less number of synthesisfor zoledronic acid (**145)**has been reported as described below.

Singh's approach (2003)[44]

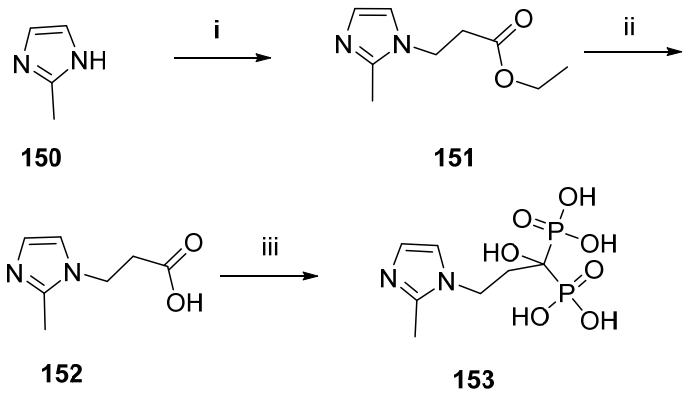
Santosh*et al.* have reported the synthesis of zoledronic acid (**145**)starting from commercially available imidazole **147**, which was alkylated with *tert*-butyl chloroacetateunder basic condition to give*tert*-butyl ester **148**in 75% yield.The *tert*-butyl ester **148**was then treated with$TiCl_4$ in CH_2Cl_2 at low temperature to facilitate thenon-aqueous cleavage of the*tert*-butyl ester moiety. Quenchingthe reaction mixture with *i*-PrOH provided the hydrochloridesalt **149**as a crystalline solid,whichwas converted tozoledronic acid (**145**) in 57% yield by reacting with H_3PO_3 and$POCl_3$ (**Scheme 25**).



Scheme 25: (i) *tert*-butyl chloroacetate, K_2CO_3, EtOAc, reflux, 10h, 75%; (ii) $TiCl_4$, CH_2Cl_2, -15 to 0 °C, 3 h; (iii) ^{i}PrOH, 10 °C to 25° C; (iv) H_3PO_3, $POCl_3$, PhCl, 57%.

Lin's approach (2006)[45]

Lin's*et al.* havedeveloped a general protocol for the synthesis of diphosphonic acids. Methyl imidazole **150**was subjected toalkylation reaction with ethyl 2-bromopropionate in CH_2Cl_2 to give ethyl 3-(1*H*-imidazol-1-yl)propanoate(**151)**, which was subsequently hydrolyzed under H_2O reflux condition to afford the corresponding acid **152**in 34% yield. The carboxylic acid group was finally converted to bisphosphonic acid **153**using H_3PO_3 and $POCl_3$in 65% yield.



Scheme26:(i) $Br(CH_2)_2CO_2Et$, CH_2Cl_2, RT; (ii) H_2O, HCl, 34% (over 2 steps) (iii) H_3PO_3, $POCl_3$, PhCl, 65%.

4.3.3 Present Work

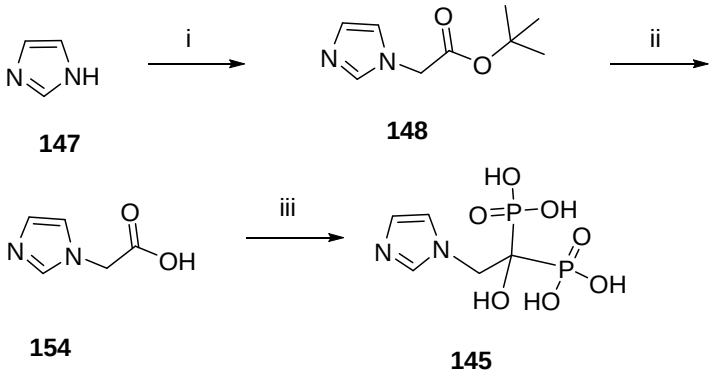
4.3.3.1 Objective

As can be seen from the above synthetic studies, the literature methods for the synthesis of zoledronic acid(**145**) suffered from following disadvantages. It is evident that all these processes required an additional step to produce the hydrochloride salt,thereby increasing the number of steps and hencelowering overall yields. Moreover, due to itshigh degree of water solubility isolation of compound **145**ofteninvolved evaporation of water instead of extraction of theaqueous solution by a common organic solvent. This section describes the synthesis of zoledronic acid (**145**) *via N*-alkylation imidazole and base hydrolysis of ester as

high yielding steps.

4.3.3.2 Results and Discussion

The complete synthetic sequence for zoledronic acid (**145**)wherein *N*-alkylation of imidazole, base hydrolysis of ester and bisphosporylation of carboxylic acid constituting the key steps is presented in **Scheme 27**.



Scheme 27:(i) $BrCH_2CO_2{}^tBu$ (1.1 equiv), K_2CO_3 (1 equiv), CH_2Cl_2, 40°C, 90%; (ii) NaOH (2equiv), MeOH:H_2O (1:1), 94%;(iii) H_3PO_4 (2 equiv), $POCl_3$ (2equiv), PhCl, 100 °C, 5 h then 6N HCl, 100°C, 12 h, 85%.

Accordingly, the synthesis of zoledronic acid (**145**)was undertaken starting from imidazole **147**, which was treated with *tert*-butyl bromo acetate and potassium

carbonateto give the corresponding *tert*-butyl ester **148**in 90% yield with high purity. The formation of *tert*-butyl ester **148**was unambiguously confirmed using its spectroscopic data. The ^{1}H NMR spectrumof **148**showed typical proton signals of *tert*-butyl ester**148** at δ 1.47 (s, 9H) and 4.57 (s, 2H) as two singlets corresponding to *tert*-butyl -(C**H$_3$**)$_3$ group and methylene (N-C**H$_2$**)group respectively. Its ^{13}C NMR spectrum displayed characteristic carbon signals at δ 27.8 and 166.2 corresponding to *tert*-butyl [-(**C**H$_3$)$_3$) group and carbonyl group respectively (**Fig. 26**). The ester group in **148** was then hydrolyzed to carboxylic acid **154**using NaOH (2 equiv) in MeOH:H_2O (1:1). The crude acid, obtained by the evaporation of solvent, was

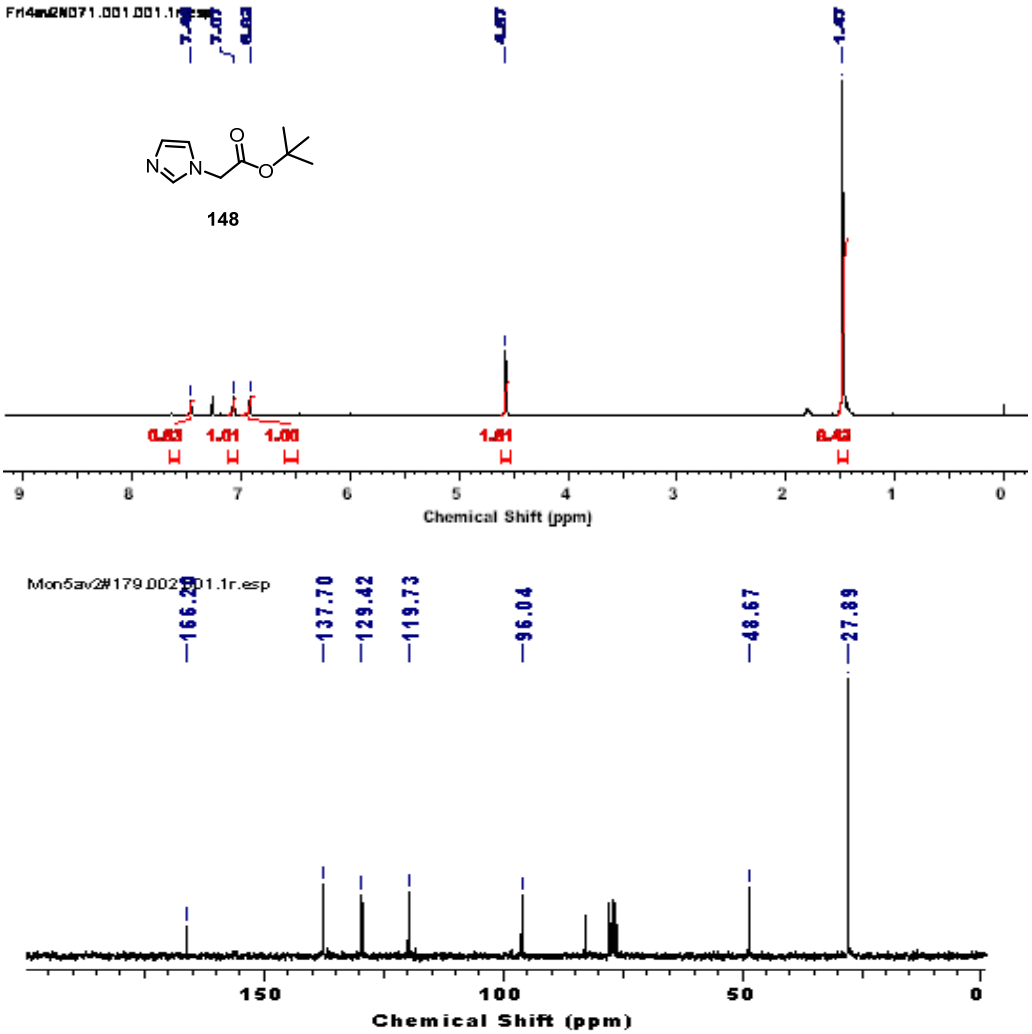
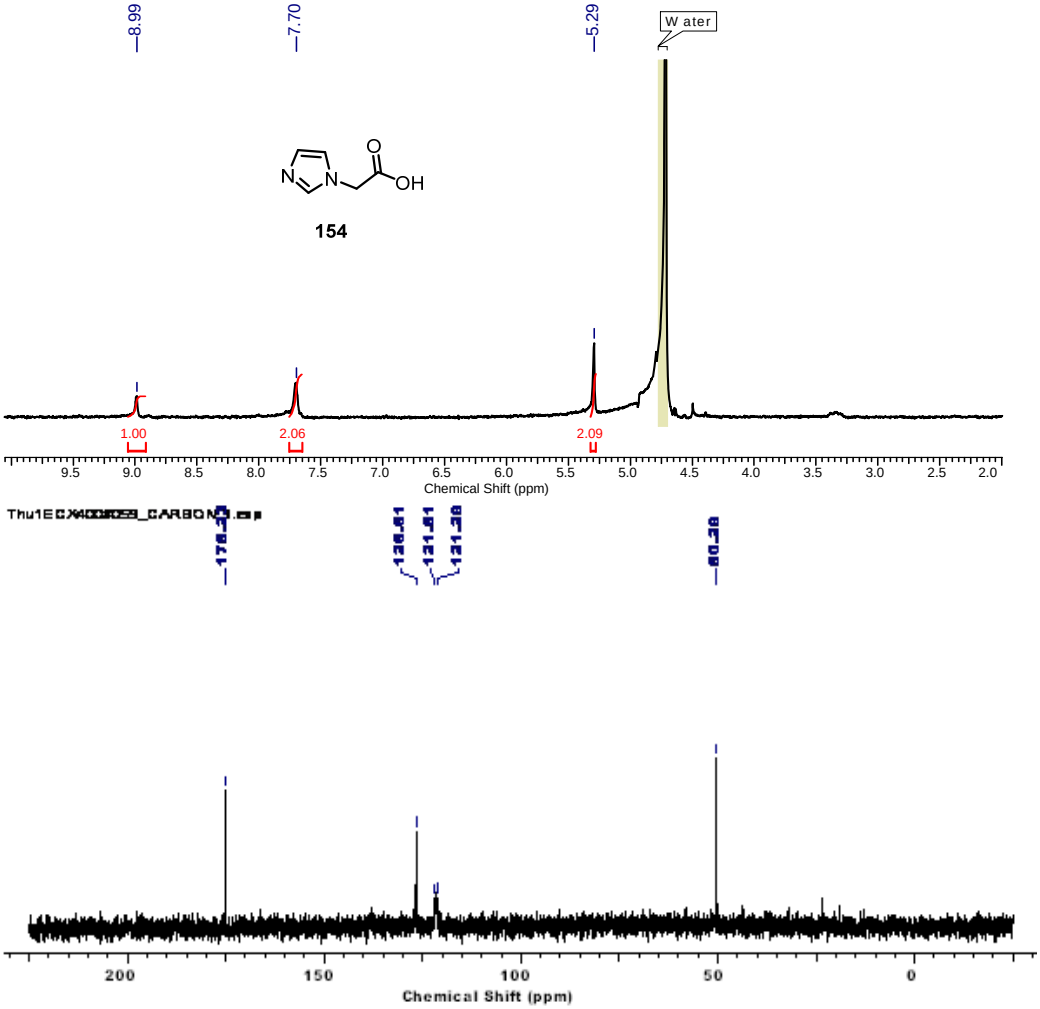


Fig. 26: ^{1}H and ^{13}C NMR spectra of **148**

recrystallized from EtOH to give 94% of carboxylic acid **154** in pure form.

In contrast to the previous reports, the present protocol we used base hydrolysis for the first time, which produced a very high yield of imidazole carboxylic acid **154**. The ^{1}H NMR spectrumof carboxylic acid**154**showed proton signals at δ 5.29 (s, 2H) assinglet corresponding to methelene group (N-C**H**$_2$).Its^{13}C NMR spectrum showedtwo characteristic carbon signals at δ 50.3 and 175.2corresponding to methylene group (N-C**H**$_2$) and carbonyl group respectively. The IR spectrum of **145** showed characteristic absorption bandsat 1708 and 3051 cm^{-1}corresponding to carboxylic acid group (**Fig. 27**).



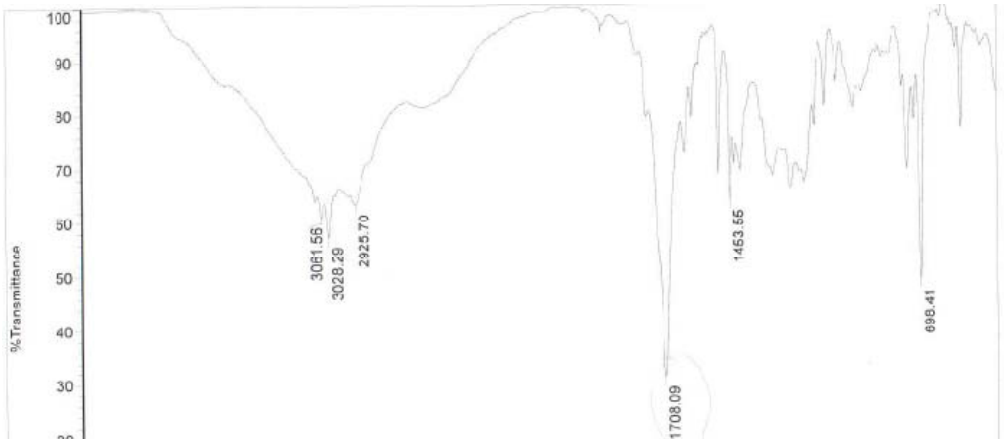
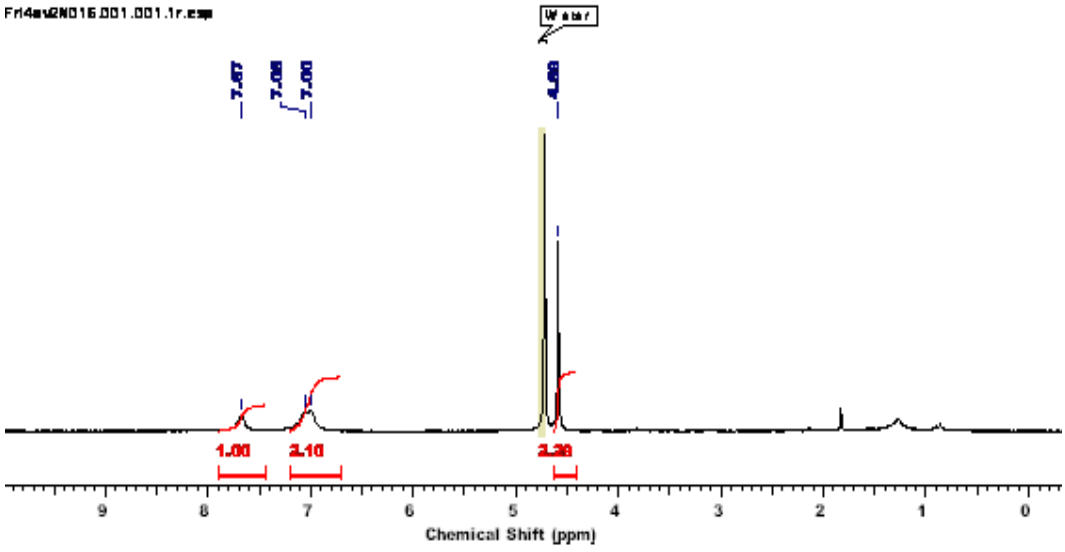


Fig. 27: $^{1}H,^{13}C$NMR and IR spectra of **147**

Finally, the carboxylic acid group in **147** was converted to zoledronic acid**145** on its treatment with H_3PO_4 (2.2 equiv) and $POCl_3$(2.2 equiv) under strong acidic condition.[50]The crude product wasrecrystalizedwith ethanol to give pure zoledronic acid in 85% yield.The ^{1}H NMR spectrumof zoledronic acid**145**showed the proton signal at δ 4.69 (s, 2H) as a singlet corresponding to methylene (N-C**H**$_2$)group while its ^{13}C NMR spectrum displayed characteristic carbon signals at δ 46.1 and 80.4corresponding to methylene group and quarternary carbons respectively. Its ^{31}P NMR showed a phosphorous peak at δ 3.87 corresponding to symmetrical phosphorous atom in zoledronic acid (**Fig. 28**).



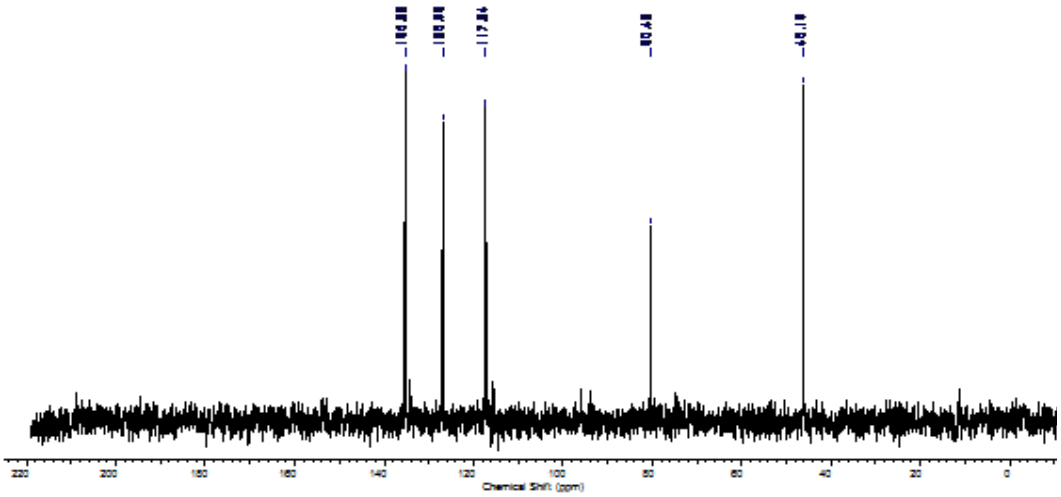


Fig. 28: ^{1}H and ^{13}C NMRspectra of **145**

4.3.4 Conclusion

To summarize, we have presented in this section a short and practical synthesis of zoledronic acid (**145**) with 71% overall yield. The key reactions employed were *N*-alkylation of imidazole and bisphosporylation of carboxylic acid. The synthetic strategy described herein has significant potential for further extension to other diphosphonic acids and related analogues of zoledronic acid owing to its flexible nature with varied substituents.

4.3.5 Experimental Section

tert-Butyl 2-(1*H*-imidazol-1-yl)acetate (148)

To a stirred solution of imidazole **147** (5 g, 72.37mmol) and*tert*-butyl bromoacetate (15.53 g, 79.61mmol) in CH_2Cl_2 (180 mL) was added K_2CO_3 (10.0 g, 72.3mmol) and allowed to stirrat 40°C for 5 h. The progress of reaction was monitored by TLC. After completion of the reaction, water (80 mL) was added.Aqueous layer was extracted with CH_2Cl_2(3 x 120 mL). The combined organic layers were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give pure product **148** as white solid in 90% yield (11.8 g).

Yield: 90% (11.8 g), colorless solid,mp: 111–113 °C; **IR** (nujol, cm^{-1}): υ_{max}583, 735, 820, 856,910, 1164, 1246, 1290, 1379, 1510, 1736, 2883, 2983, 3115, 3132; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.47 (s, 9H), 4.57 (s, 2H), 6.92 (s, 1H), 7.07 (s, 1H), 7.46 (s, 1H): **^{13}C NMR** (50 MHz, $CDCl_3$) δ 27.9, 48.7, 82.9, 119.7, 129.4, 137.7, 166.2;**Anal**. Calcd for $C_9H_{14}N_2O_2$ requires C, 59.32; H, 7.74; N, 15.37; found C, 59.4; H, 7.6; N, 15.4 %.

2-(1*H*-Imidazol-1-yl)acetic acid (154)

To a stirred solution of imidazole ester **148** (5 g, 27.44 mmol) in MeOH:H_2O (1:1) (80 mL) was added NaOH powder (1.20 g, 30.18 mmol) at 25°C. The reaction mixture was allowed to stirr for 5 h at the same temperature. After completion (monitored by TLC), the reaction mixture was neutralized with 1N HCl. The solvent was evaporated to give the crude product, which was purified by recrystallization using EtOHto give the pure carboxylic acid **154** in 3.25 g (94%).

Yield: 94% (11.8 g), colorless solid,mp: 190–192°C; **IR** (nujol, cm^{-1}): υ_{max}698, 1455,1708, 2925, 3026, 3061;**^{1}H NMR** (200 MHz, D_2O) δ5.29 (s, 2H), 7.70 (m, 2H), 8.99 (br. s., 1H): **^{13}C NMR** (100 MHz, D_2O) δ 50.3, 121.3, 121.8, 126.6,

175.2.**Anal**.Calcd for $C_5H_6N_2O_2$ requires C, 47.62; H, 4.80; N, 22.21; O, 25.37; found C, 47.5; H, 4.7; N, 22.3 %.

Zoledronic acid (145)

To a stirred solution of imidazol-1-yl-acetic acid (**154**)(2.0 g, 15.86 mmol) and phosphoric acid (3.42 g, 34.88 mmol) inchlorobenzene (40 mL) was added phosphorous oxychloride(5 mL, 17.44 mol) at 80–85 °C over a period of 5h then heatedto 90–95 °C for 2.5 h. The reaction mass was cooled to60–65 °C and water (40 mL) was added at the same temperature.The aqueous layer was separated and evaporated to give yellow solid which was dissolved in 6N HCl (10 mL) and refluxedfor 12 h. It was then cooled to room temperature and dilutedwith water (60 mL). The aqueous HCl was evoporatedand the crude product was dissolved in water. The reaction mixture was cooled to 0–5 °C and acetone was added slowly. The precipitated solid was filtered, washed with acetoneand then dried under vacuumat 60 °C for 12 h to afford the zoledronic acid (**145**) (3.6 g, 85% yield)as a white solid.

Yield: 85% (3.6 g), colorless solid,mp: 237-239°C(lit[48] 239 °C with decomposition); **IR** (nujol, cm^{-1}): υ_{max}530,820,925,1192,1263,1274, 1381, 1590, 1656, 1701, 2894, 2995, 3015, 3212, 3441; **^{1}H NMR** (200 MHz, D_2O) δ 4.59 (s, 2H), 6.70-7.20 (m, 2H), 7.67 (br. s., 1H): **^{13}C NMR** (100 MHz, D_2O) δ46.1, 80.4, 117.2, 126.9, 135.2; **^{31}P NMR** (400 MHz, D_2O) δ3.91; **HRMS** (ESIMS):calcd for $C_5H_{10}N_2NaO_7P_2$+Na]$^+$294.9861, found 294.9865.

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LIST OF PUBLICATIONS AND PATENTS

1. Oxidant Controlled Regio- and Stereodivergent Azidohydroxylation of Alkenes *via* I_2 Catalysis; Pragati Kishore Prasad, **Rambabu N. Reddi**, Arumugam Sudalai; *Chem. Commun,* **DOI:** 10.1039/C5CC02374B.
2. I_2-Catalyzed Regioselective Oxo- and Hydroxy-acyloxylation of Alkenes and Enol Ethers: A Facile Access to α-Acyloxyketones, Esters, and Diol Derivatives **Rambabu N. Reddi**, Pragati Kishore Prasad, Arumugam Sudalai; *Org. Lett.* **2014***, 16*, 5674.
3. *N*-Heterocyclic Carbene Catalyzed Regioselective Oxo-acyloxylation of Alkenes with Aromatic Aldehydes: a High Yield Synthesis of α-Acyloxy Ketones and Esters; **Rambabu N. Reddi**, Pushpa V. Malekar, Arumugam Sudalai; *Org. Biomol. Chem.*, **2013**, *11*, 6477.
4. *N*-Heterocyclic Carbene Catalyzed Oxidative Stannylation of Aldehydes: a Facile Entry to Organotin(IV) Carboxylates; **Rambabu N. Reddi**, Pushpa V. Malekar, Arumugam Sudalai. *Tetrahedron. Lett.,* **2013**, *54*, 2679.
5. *N*-Heterocyclic Carbene Catalyzed Oxidatative Coupling of Alkenes/α-Bromoacetophenones with Aldehydes: a Facile Access to α,β-Epoxy-ketones and Esters; **Rambabu N. Reddi**, Pragati Kishore Prasad, Arumugam Sudalai; (Communicated).
6 *N*-Heterocyclic Carbene Catalyzed Oxidative Cross Dehydrogenative Coupling of Aldehydes and Allylic/Benzylic C-H bonds; **Rambabu N. Reddi**, Arumugam Sudalai; (manuscript under preparation).
7 Enantioselective Synthesis of 1,4-Dideoxy-1,4-imino-D-Arabinitol using Co (III)(salen)-catalyzed HKR of Two-Stereocentered *anti*-Azidoepoxide, **Rambabu N. Reddi**, Arumugam Sudalai; (manuscript under preparation)
8 One step process for region selective synthesis of α acyloxy carbonyls: Rambabu Reddi, Pushpa Malekar, Sudalai. A (US patent filed, WO/2014/195972.