Some Aspects of Chemistry of Oxygenated Heterocycles and Use of Chiral 1,3-Diols in Asymmetric Synthesis

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Submitted by

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Dedicated
To
My Parents, Brothers and Sister

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled "**Some Aspects of Chemistry of Oxygenated Heterocycles and Use of Chiral 1,3-Diols in Asymmetric Synthesis**" is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India under the guidance of Professor Anil K. Saikia.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

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CERTIFICATE

This is to certify that Mr. **Paramartha Gogoi** has been working under my supervision since July 2009 as a regular registered Ph. D. student. I am forwarding his thesis entitled "**Some Aspects of Chemistry of Oxygenated Heterocycles and Use of Chiral 1,3-Diols in Asymmetric Synthesis**" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

19th November, 2014
IIT Guwahati

Prof. Anil K. Saikia
Supervisor

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Paramartha Gogoi

LIST OF ABBREVIATIONS

Ac	acetyl	*m*-CPBA	meta-chloroperbenzoic acid
BINOL	Binanpthol	M. P.	melting point
Bn	benzyl	MS	molecular sieves
Bu	butyl	MsOH	Methanesulfonic acid
Boc	*tert*-butoxy carbonyl	m/z	mass to charge ratio
CCDC	cambridge crystallographic data centre	NMO	*N*-methylmorpholine *N*-oxide
CHP	Cumene hydroperoxide	NMR	nuclear magnetic resonance
CSA	camphorsulfonic acid	NOESY	nuclear overhauser enhancement spectroscopy
Cy	cyclohexyl	ORTEP	oak ridge thermal ellipsoid plot
DCE	1,2-dichloroethane	Ph	phenyl
DCM	dichloromethane	ppm	parts per million
DET	Diethyl-tartarate	Pr	propyl
DFT	Density Function Theory	*p*-TSA	*p*-toluenesulfonic acid
DMF	*N*, *N*-dimethylformamide	rt	room temperature
DTBP	Di-tertiary butyl phenol	TBHP	*tert*- butyl hydroperoxide
de	diastereomeric excess	TBS	tributylsilyl
dr	diastereomeric ratio	TFA	trifluoroacetic acid
ee	enantiomeric excess	Tf	trifluoromethanesulfonyl
HRMS	high resolution mass spectrometry	THF	tetrahydrofuran
HPLC	high-performance liquid chromatography	TLC	thin layer chromatography
IR	infrared	TMS	trimethylsilyl
LA	Lewis acid	Ts	*p*-toluenesulfonyl

Abbreviations for intensities of ^{1}H-NMR signals

s	singlet	t	triplet
d	doublet	q	quartet
dd	doublet of doublet	m	multiplet
ddd	doublet of doublet of doublet	brs	broad signal
dddd	doublet of doublet of doublet of doublet	Hz	Hertz
dt	doublet of triplet	MHz	Mega-Hertz

Abstract

The contents of this thesis have been divided into two parts based on the results of experimental work performed during the complete course of the research period. Part I consists of four chapters. Chapter 1 deals with an introduction to substituted tetrahydropyran and tetrahydrofuran ring containing natural products and previous approaches for their synthesis. In chapter 2 diastereoselective synthesis of 4-iodotetrahydropyrans is described. Chapter 3 presents the diastereoselective synthesis of substituted 3-aroyltetrahydrofurans *via* Prins cyclization of enol ethers. Chapter 4 deals with the Beckmann rearrangement of 3-aroyltetrahydrofurans. Part II consists of two chapters. Chapter 1 presents an overview of important aspects of chiral 1,3-diols and chiral sulfoxides and their synthesis using different approaches. Chapter 2 describes the synthesis and resolution of racemic 1,3-diol ligands and their application in enantioselective sulfoxidation of alkyl aryl sulfides.

Part I

Chapter 1: Some Aspects of the Synthesis of Five and Six Membered Oxygen Heterocycles

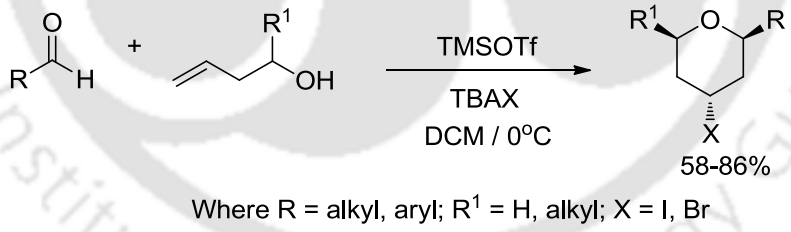
Five and six membered oxygen heterocycles occur widely in nature. Tetrahydropyrans are structural features of many biologically active natural products such as polyether antibiotics, marine toxins, and pheromones. Over recent years thousands of tetrahydropyran containing compounds have been entered into preclinical and clinical trials. Similarly a wide variety of interesting biologically active molecules contain substituted tetrahydrofuran subunits. For example, the annonaceous acetogenins are a large family of natural products with a diverse range of biological activities including antitumor, antihelmic, antimalarial, antimicrobial, and antiprotozoal. Substituted tetrahydrofurans are also found in polyether antibiotics, lignans, and C-glycosides.

To build this class of heterocycles many strategies have been developed over the years. The most widely used methods in natural product synthesis are the Prins, intramolecular oxonium-ene cyclisation reactions, hetero-Diels-Alder cyclization, the intramolecular Michael additions and ring-closing metathesis. Other strategies include electrophile-induced cyclizations of nonactivated alkenes and Lewis acid-promoted cyclizations of epoxy alcohols. Among these methods stated here Prins cyclization has attracted much attention towards the synthesis of natural products. Since, these cyclization reactions themselves proceed largely through a chair-

like transition state that allows for control of stereoisomers in the course of the reaction. This organization of the reaction allows to set four relative stereogenic centers in one step. We have attempted to utilize Prins cyclization stratergy for the synthesis of five and six membered oxygen heterocycles.

Chapter 2: Axial-selectivity in Prins-Cyclization Reaction: Synthesis of 4-Iodotetrahydropyrans

The main advantage of Prins cyclization is its all-*cis* selectivity. Recently, several groups have reported the highly selective synthesis of all-*cis* 4-substituted tetrahydropyrans with good yields. Among these, 4-halotetrahydropyrans are important in organic synthesis, because it can be transformed into other substituted tetrahydropyrans. Generally 4-halotetrahydropyrans are prepared by Lewis acid mediated reaction, and the Lewis acids used are $SnCl_4$, $SnBr_4$, TMSBr, $TiCl_4$, $TiBr_4$, TiF_4, $InCl_3$, $AlCl_3$, $FeCl_3$, $ZrCl_4$, $BF_3{\cdot}OEt_2$, etc. The halo functions in all these reactions are placed in equatorial positions. This is in accordance to the Alder's model. There are limited methods for the synthesis of axial-4-halotetrahydropyrans. Here we have developed an axial selective Prins-cyclization reaction for the synthesis of 4-iodotetrahydropyrans from homoallylic alcohols and aldehydes promoted by TMSOTf and tetrabutyl ammonium iodide/bromide. The reaction is generalized as shown in *Scheme 1*.



Scheme 1: *Synthesis of 4-halotetrahydropyans and the scope of the reaction*

The stereoselectivity and stereochemistry of the compounds were determined from crude ^1H NMR and single crystal X-ray analysis. The axial position of the halide group at 4-position was determined by comparison with equatorial products. It is known that reaction of aldehydes with homoallylic alcohols in the presence of iodine gives equatorial iodinated products. It was observed that the equatorial proton of 2-(4-bromophenyl)-4-iodotetrahydro-*2H*-pyran, attached to the axial iodide resonates at 4.91 ppm and in the case of axial proton of equatorially substituted iodide resonates at 4.38 ppm (*Figure 1*), this is in agreement with the fact that the equatorial proton resonates at lower field than the axial proton.

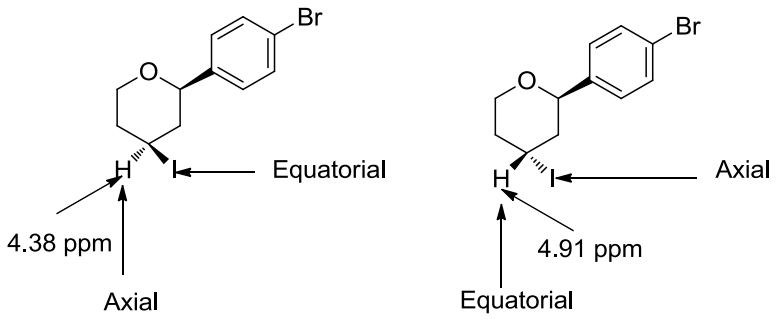
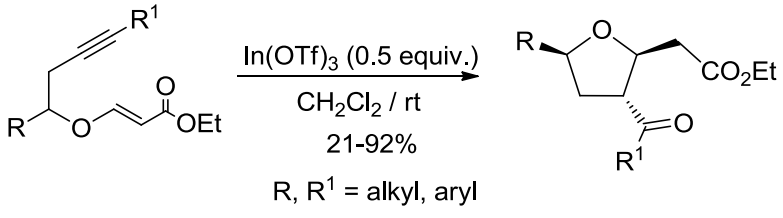


Figure 1: *Chemical shift values (ppm) of axial and equatorial protons of 2-(4-bromophenyl)-4-iodotetrahydro-2H-pyran*

In conclusion, we have developed an axial-selective Prins-cyclization reaction with high diastereoselectivity and good yields. The 4-axial halosubstituted products would be an important synthetic intermediate for the synthesis of 4-equatorial substituted tetrahydropyrans by substitution reactions.

Chapter 3: Diastereoselective Synthesis of Substituted Tetrahydrofurans *via* Prins Cyclization of Enol Ethers

The synthesis of tetrahydrofurans, because of their importance in many biological processes, has attracted particular attention from the organic synthetic chemist. Therefore an abundant literature deals with numerous approaches to the synthesis of mono- or poly-THF skeletons. Prins cyclization is an important reaction for the synthesis of tetrahydropyrans and tetrahydrofurans because of its diastereoselectivity. Although the preparation of these heterocycles through C-C bond-forming Prins cyclization is becoming increasingly important, Pure Prins-type cyclization has rarely been used for the synthesis of tetrahydrofurans, though Prins-type cylcization followed by pinacol rearrangement gives tetrahydrofurans. In the present work an attempt was made to cyclize enol ethers having alkyne group. After screening of various Lewis and Brønstad acids it Indium triflate was found to be the best reagent for cyclization which afforded the substituted tetrahydrofurans in good yield and excellent stereoselectivity (*Scheme 2*).



Scheme 2: *Synthesis of substituted tetrahydrfurans*

The reaction is diastereoselective, only a single diastereomer was obtained from each reaction, which was determined by crude ^{1}H NMR. The stereochemistry of the cyclized products were determined by nOe experiments and single-crystal X-ray analysis (*Figure 2*).

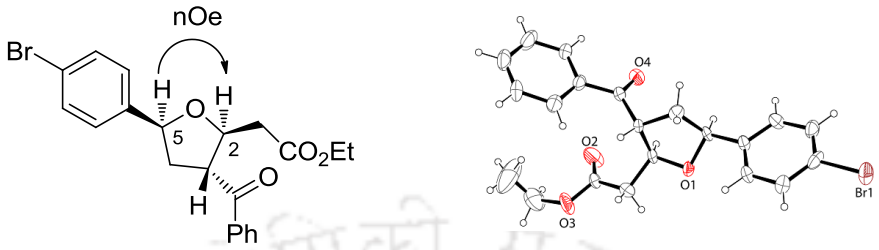
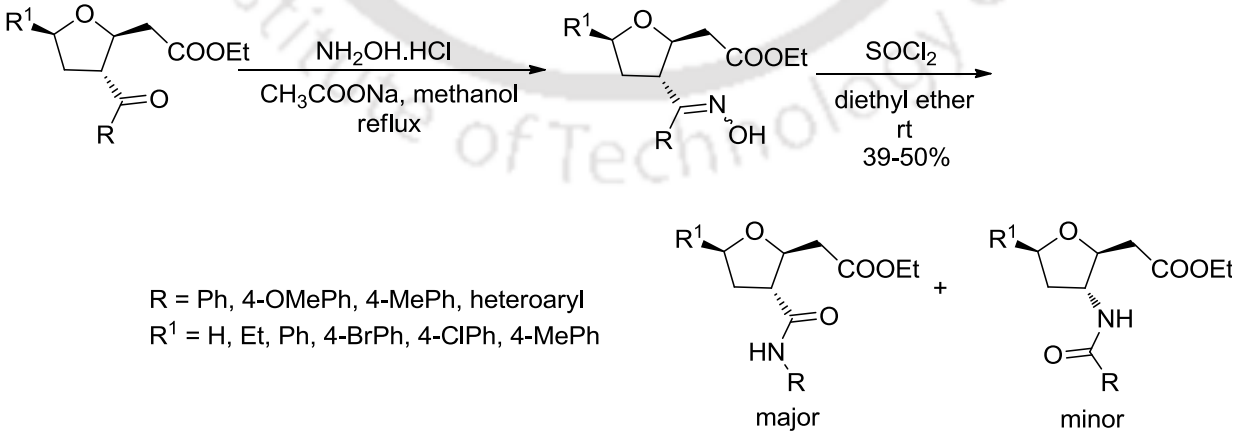


Figure 2. *Correlation between NOE and X-ray crystallographic structure of Ethyl 2-(-3-benzoyl-5-(4-bromophenyl)tetrahydrofuran-2-yl)acetate*

In conclusion, we have developed a mild and efficient method for the synthesis of substituted tetrahydrofurans *via* Prins cyclization reaction from enol ethers in good yields. The method is highly diastereoselective and gives only cis- 2,5-diastereomers.

Chapters 4: Beckmenn rearrangement of 3-aroyltetrahydrofuran: synthesis of *N*-aryltetrahydrofuran-3-carboxamides

In chapter 3 we have described the diastereoselective synthesis of substituted tetrahydrofurans *via* Prins cyclization reaction from enol ethers. In order to provide the synthetic application of these 3-aroyl tetrahydrofurans, Beckmann rearrangement reaction was studied (*Scheme 3*). The substituted tetrahydrofurans were first converted to oxime derivatives containing both anti and syn isomer as inseparable mixture.



Scheme 3: *Beckmen rearrangement of 3-aroyltetrahydrofuran*

Thionyl chloride treatment of those oximes gave the Beckmann products at room temperature. It was observed that Beckmann rearrangement of 3-benzoyltetrahydrofuran (R = Ph, R^{1} = H)

resulted in an inseparable mixture of *N*-phenyltetrahydrofuran-3-carboxamide and *N*-(tetrahydrofuran-3-yl)benzamide with a ratio of 9:1 in 50% overall yield. On the other hand other tetrahydrofurans gave only *N*-aryltetrahydrofuran-3-carboxamides as a single isomer. The exclusive formation of aryl migrated products indicates that the aryl group is a better migrating group than the tetrahydrofuran ring.

In conclusion we have studied the thionyl chloride-mediated Beckmann rearrangement of 3-aroyl-tetrahydrofurans. *N*-aryltetrahydrofuran-3-carboxamides were obtained almost exclusively from the *E*/*Z* mixture of oximes in moderate yields. The preferential formation of aryl migrated products indicates that aryl group is a better migrating group than the tetrahydrofuran ring.

Part II

Chapter 1. Review on Asymmetric Synthesis of 1,3-Diols and Chiral Sulfoxides

Optically active 1,3-diols are very important compounds in asymmetric synthesis, since they represent chiral building blocks for many polyketide-derived natural products, and have frequently been used as valuable intermediates in the synthesis of drugs and natural products with important biological activity. Such diols have shown promise as chiral ligands and more frequently as chiral auxiliaries. Unlike 1,2 and 1,4 diols, 1,3-diols are less frequently encountered as chiral ligand. It is important that the diol is conformationally rigid for it to be an effective chiral auxiliary / ligand. Chiral 1,3-diols can be obtained *via* the following three methods: (a) diastereoselective reduction of chiral hydroxy ketones (b) enantioselective reduction of *β*-diketones (c) diastereoselective reduction of *β*-diketones followed by resolution of the resulting diol.

Sulfoxides are found in a variety of natural products and pharmaceuticals. They have also been employed as chiral auxiliaries in a range of reaction classes, and as chiral ligands. Sulfur is well-suited to the role of an agent for transfer of chirality for several reasons. The faces of a sulfoxide are highly differentiated due to the large steric difference between its substituents, which range from an electron lone pair to large alkyl groups. Both sulfur and oxygen have lone pairs of electrons available to coordinate to Lewis acidic functionality, often promoting highly ordered transition states. Finally, sulfur can readily form covalent bonds, including to heteroatoms, and can be cleaved under relatively mild conditions. These properties have inspired considerable investigation into the synthetic applications of sulfoxides.

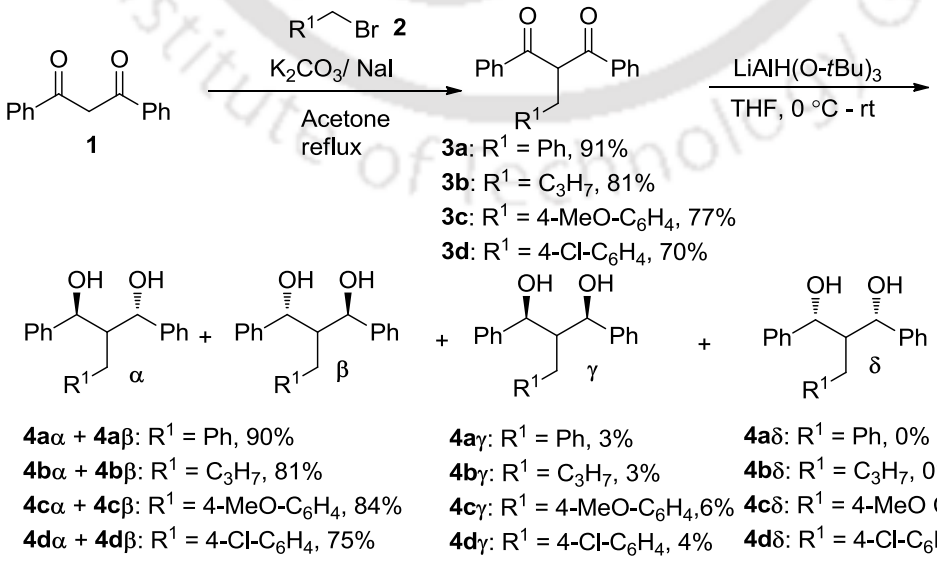
A diverse array of techniques for the synthesis of enantiomerically enriched sulfoxides has been developed. These methods generally fall into two categories: chiral auxiliary directed functionalizations and catalytic enantioselective oxidations. The most straightforward route to enantiomerically enriched sulfoxides involves preparation and substitution of a pure diastereomer using a chiral reagent. This method consists of the synthesis of a sulfinylating agent with an electrophilic sulfur of known configuration, followed by reaction with an organometallic reagent. Chiral auxiliary methodologies produce relatively simple sulfoxides with very high enantiomeric purity. These products are ideally suited for use as chiral ligands or chiral auxiliaries.

Catalytic enantioselective oxidations involve asymmetric oxidation of prochiral sulfides catalyzed by metal complexes with enantiomerically pure chelating lingands. C_2-symmetricbidendate diols, C_3-symmetric triethanol amines, tridendate Schiff bases, and tetradendate salen-type ligands, have been commonly used, typically in combination with d0 metal ions: Ti(IV) and V(V) and less frequently with Mn(III), Fe(III), and Al(III) .

Chapter 2. Synthesis of a new chiral 1,3-diol ligand with a benzyl backbone and application in asymmetric sulfoxidation of alkyl aryl sulfides.

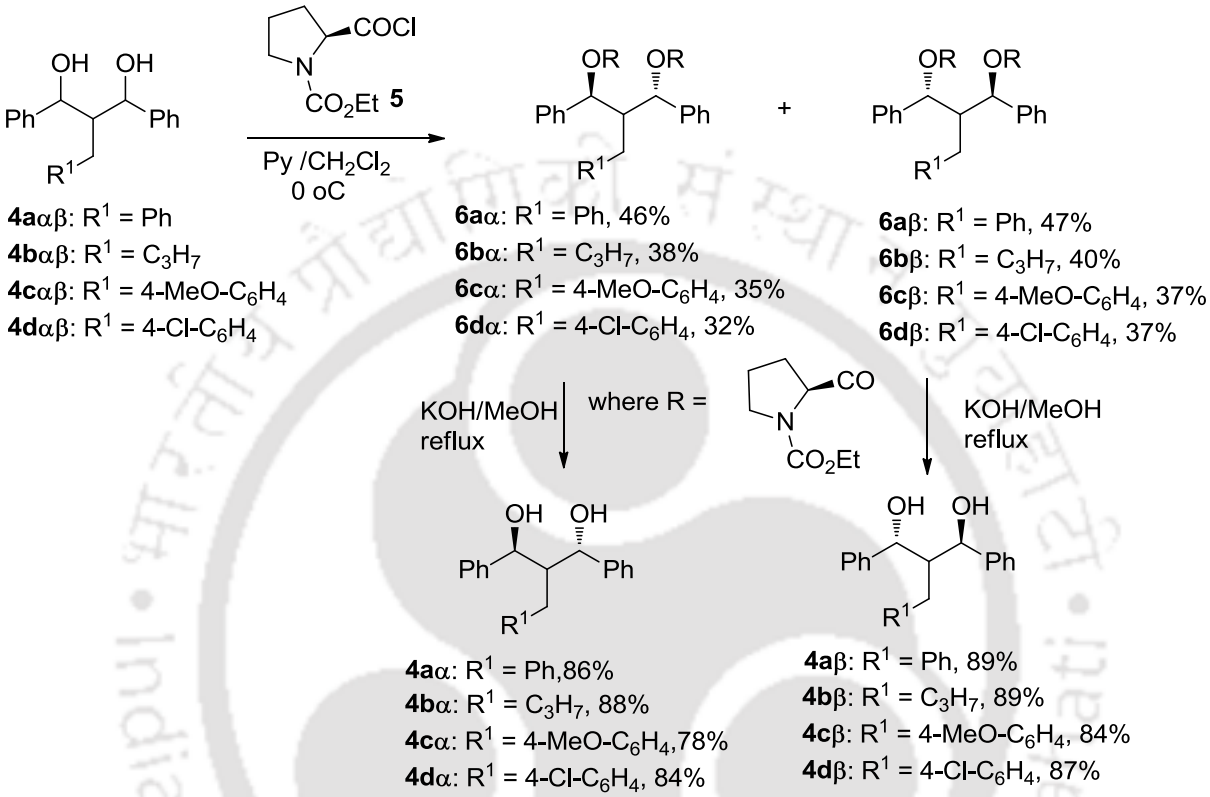
Section A: Synthesis and resolution of 1,3-diols

Our synthetic route involved the diastereoselective reduction of *β*-diketones **3** by $LiAlH(O\text{-}tBu)_3$, followed by resolution of the racemic mixture containing the anti diols.



Scheme 4: *Diastereoselective reduction of β-diketones*

After successful synthesis of the (±)-**4αβ**, the diols were resolved into its chiral components **4α** and **4β** by converting them to their diastereomeric esters **6α** and **6β** using *N*-ethoxycarbonyl-L-proline derivative **5**, and subsequent hydrolysis by methanolic solution of potassium hydroxide. (*Scheme 5*).



Scheme 5: *Resolution of the racemic mixtures*

The absolute configuration of the diols was determined by X-ray crystallographic analysis. The absolute stereochemistry of **(+)-4aα** was found to be (*S*,*S*). The ORTEP diagram shows that there are two molecules in the asymmetric unit.

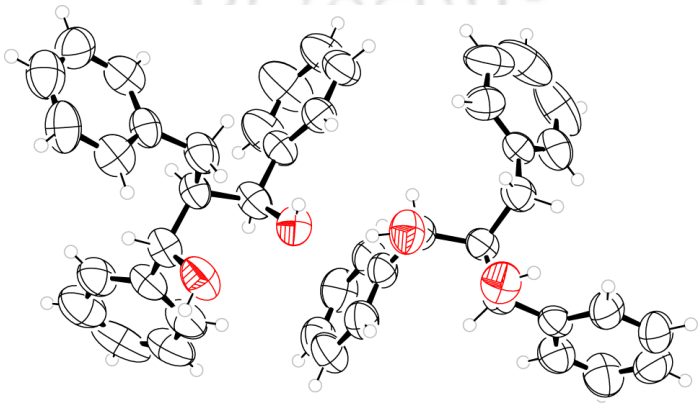
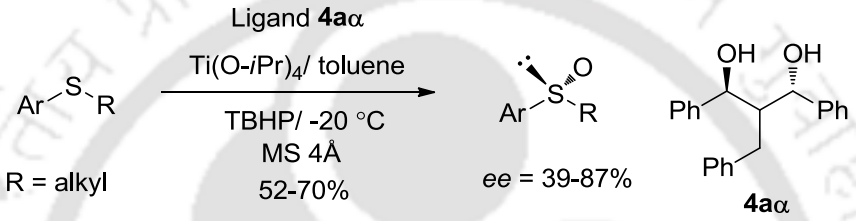


Figure 3: *ORTEP diagram of compound **4aα***

Section B: Enantioselective oxidation of alkyl aryl sulfides using 1,3-diols as chiral ligand

After the synthesis and resolution to chiral 1,3-diols **4aα-4dα** and **4aβ-4dβ,** the diols were examined as chiral ligands for titanium catalyzed oxidation of sulfides to sulfoxides, using TBHP as oxidant. After screening of the diol ligands the ligands **4aα** and **4aβ** having a benzyl backbone are found to be the best ligand for enantioselectivity. Various alkyl aryl sulfides were allowed to react under optimized reaction conditions (*Scheme 6*). Sulfoxides were obtained in good yields and in moderate to good enantioselectivities.



Scheme 6: *Synthesis of chiral sulfoxide from sulfides*

In conclusion we have investigated a new chiral ligand, 1,3-diol for the oxidation of prochiral sulfide using titanium peroxo complex as oxidant. The new catalytic system provided chiral sulfoxides in moderate to good *ee* values.

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Part I

CHAPTER 1

Introduction

1.1. Importance of tetrahydropyrans and tetrahydrofurans

Five and six membered oxygen heterocycles occur widely in nature.[1] Tetrahydropyrans are structural features of many biologically active natural products such as polyether antibiotics, marine toxins, and pheromones.[2] Over recent years thousands of tetrahydropyran containing compounds have been entered into preclinical and clinical trials.[3] Tetrahydropyran containing macrocycle, (–)-kendomycin (**1**) has a diverse and fascinating pharmacological profile and exhibits potent antagonism of the endothelin receptor agonism.[4] Catechols (**2**) and (**3**) isolated from extracts of *Plectranthus sylvestris* (labiatae), a plant found in the woody hills in east Africa are potent antioxidants and possess anti-inflamatory properties.[5] (-)-centrolobine (**4)** was isolated

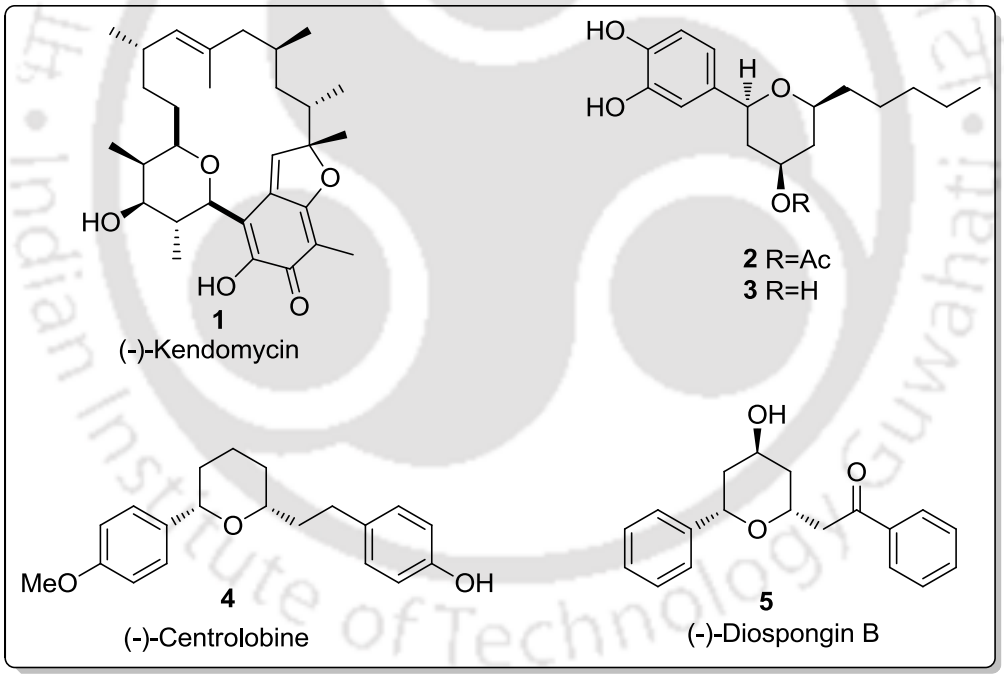


Figure 1.1.1*.Important natural products containing tetrahydropyran as a core unit.*

from the heart-wood of the tree *Centrolobiumtomentosum*, whereas its enantiomer (+)-centrolobine occurs in the closely related species *Centrolobiumrobustum*. Both enantiomers have antibiotic and anti-fungal activity.[6] The 2,3,6-trisubstitutedtetrahydropyran, (-)-diospongin B (**5**), isolated from the rhizomes of *Dioscoreaspongiosa* exhibits antiosteoporotic acitivity.[7]

A wide variety of interesting biologically active molecules contain substituted tetrahydrofuran subunits.[8] For example, the annonaceousacetogenins are a large family of natural products

containing multiple tetrahydrofuran units. They exhibit diverse range of biological activities such as antitumor, antihelmic, antimalarial, antimicrobial, and antiprotozoal.[9] Substituted tetrahydrofurans are also found in polyether antibiotics,[10] lignans,[11] and C-glycosides.[12] The 16 membered macrodiolide pamamycin-607 (**6**) was isolated from *Streptomyces albonigerand S. aurantiacus.* It shows potent activity against gram-positive bacteria as well as against phytopathogenic fungi.[13] The biologically active alkaloid muscarine (**7**) is the major toxic principle found in the well-known mushroom *Amanita muscaria* (Fly agaric).[14] Muscurine acts as a selective agonist of the neurotransmitter acetylcholine on smooth muscles of the gastrointestinal tract, eye exocrine glands and heart.[15]

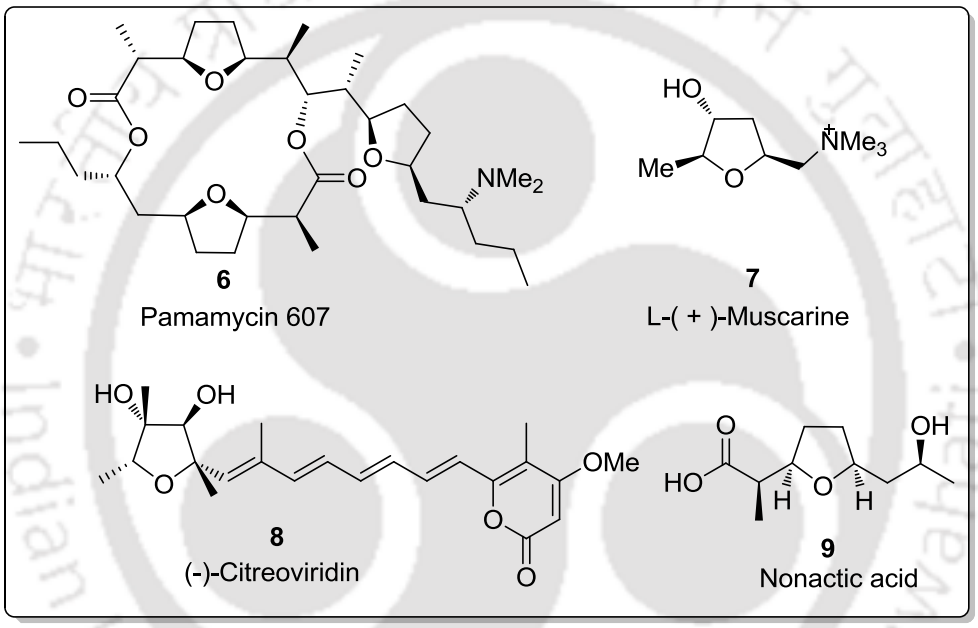


Figure 1.1.2*.Important natural products containing tetrahydropyran as a core unit.*

The mycotoxin citreoviridine (**8**), isolated from *Penicillum citreoviride,* is a potent inhibitor of the soluble mitochondrial ATPase.[16] Nonactin, an ionophoric macrolide antibiotic, has been shown to possess antitumor activity both against mammalian cell lines *in vitro* and against Crocker sarcoma 180 in studies with mice. The potential biological importance of nonactin is because of its ability to bind alkali metal cations, particularly potassium.[17] It was isolated from a variety of Streptomyces cultures, and consists of two subunits of (+)-nonactic acid (**9**) and two subunits of (-)-nonactic acid arranged in an alternating order.

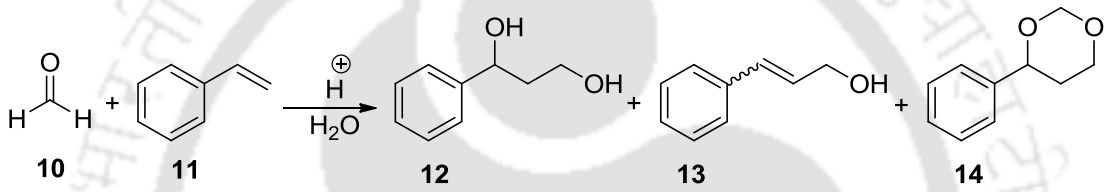
1.2. General approaches for the synthesis of tetrahydropyrans

To construct this class of heterocycles many strategies have been developed over the years. The most widely used methods in natural product synthesis are the Prins,[18] intramolecular oxonium-ene cyclization reactions,[19] hetero-Diels–Alder cyclization,[20] the intramolecular Michael

additions[21] and ring-closing metathesis.[22] Other strategies include electrophile-induced cyclizations of nonactivated alkenes and Lewis acid promoted cyclizations of epoxy alcohols. Among these methods stated here Prins cyclization has attracted much attention towards the synthesis of natural products.[23] We have attempted to highlight Prins cyclization stratergy for the synthesis of five and six membered oxygen heterocycles.

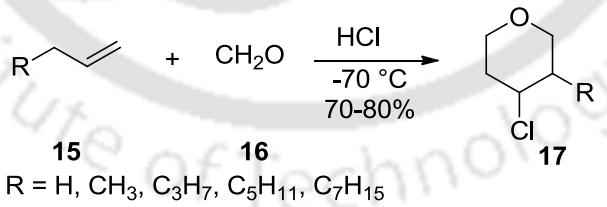
1.2.1. The Prins cyclization

The Prins reaction is one of the fundamental methods for C-C bond formation, first reported by H. J. Prins in the year 1919.[24] Basically, it is the addition of aldehydes or ketones to alkenes in the presence of acid. In his initial studies, H. J. Prins performed the reaction of formaldehyde **10** and styrene **11** using water as solvent. The outcome of the reaction was a mixture of 1,3-butanediol **12**, unsaturated alcohol **13** and 1,3-dioxane **14** (*Scheme 1.2.1.1*).



Scheme 1.2.1.1

Later the reaction was developed by Stapp for the synthesis of tetrahydropyran derivatives **17**.[25] The Stapp's reaction involves the condensation of aliphatic terminal olefins **15** with paraformaldehyde **16** and hydrochloric acid in anhydrous media ***(****Scheme 1.2.1.2).* The investigators observed the formation of 4-chloro tetrahydrofuran.

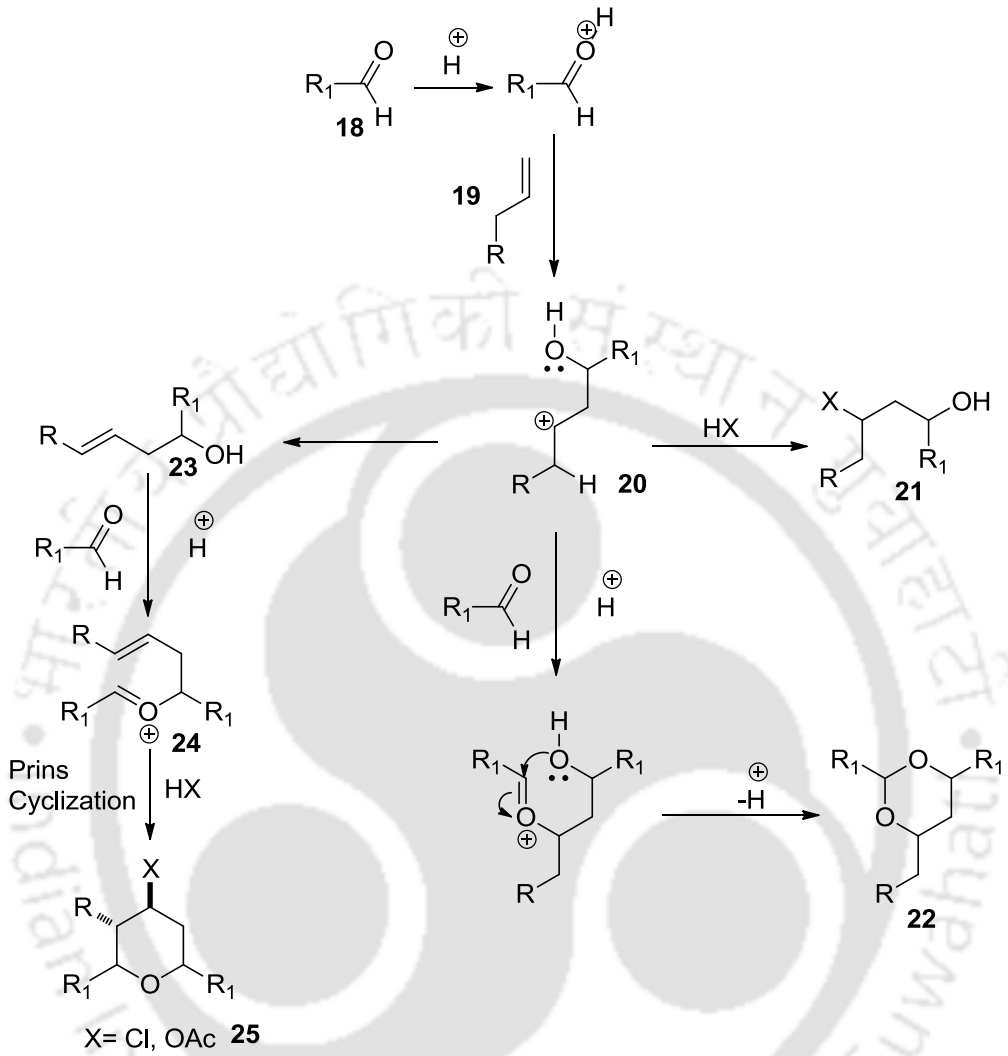


Scheme 1.2.1.2

1.2.2. Mechanism of Prins reaction

The general mechanism is shown in *Scheme 1.2.2.1*. The alkene **19** reacts with carbonyl compounds **18** in the presence of acid catalyst to generate the key intermediate *β*-hydroxy carbocation **20**. This intermediate can either react with a nucleophile such as chloride, water or acetate to give **21**, or adds to a second molecule of aldehyde to give the dioxane **22**, or loses a proton to give homoallylic alcohol **23**. The in situ generated homoallylic alcohol further reacts with another molecule of aldehyde in the acidic medium to generate the oxocarbenium ion **24**,

which after Prins cyclization and subsequent addition of nucleophile gives the tetrahydropyran derivative **25** .[26]

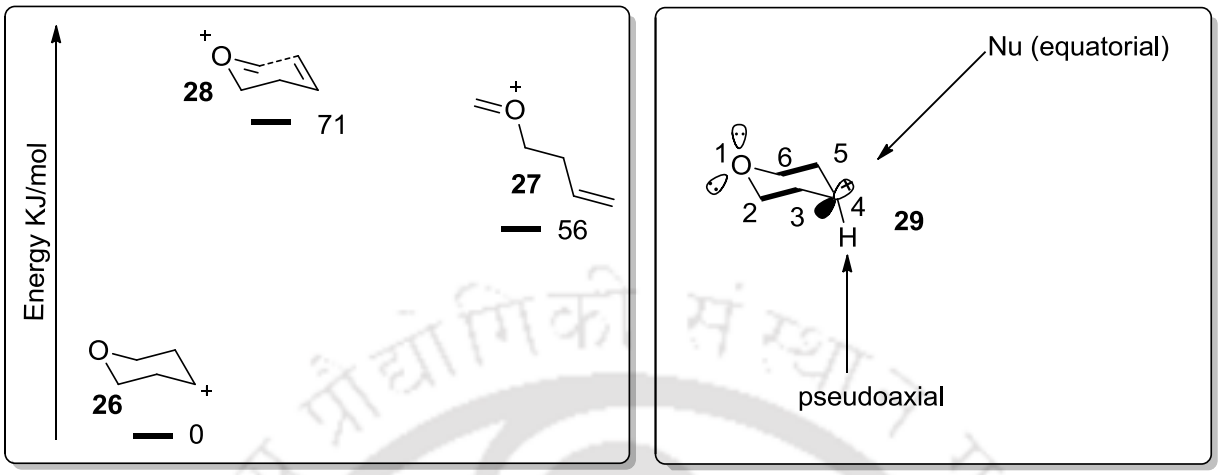


Scheme 1.2.2.1

1.2.3. Stereoselectivity in Prins cyclization

The Prins cyclization has attracted attention from synthetic chemists because the stereochemistry of substituted products is well-controlled in favor of equatorial trapping of cyclic carbocation by the nucleophiles. Alder has performed the DFT calculations on different possible reaction intermediates, and rationalized the diastereoselectivity through a chairlike transition state.[27] Carbocation **26** in its chair conformation is more stable by 56 kJ/ mol than cation **27** in its most stable staggered conformation, which reveals that the reaction proceeds through a chair like transition state very close to **28**. According to DFT calculations, carbocation in its chair conformation **29** is stabilized by stereoelectronic effects. The C2-C3 and C5-C6 σ* and σ orbital overlap both the equatorial lone pair of the oxygen atom and the vacant p orbital at C4. Optimal

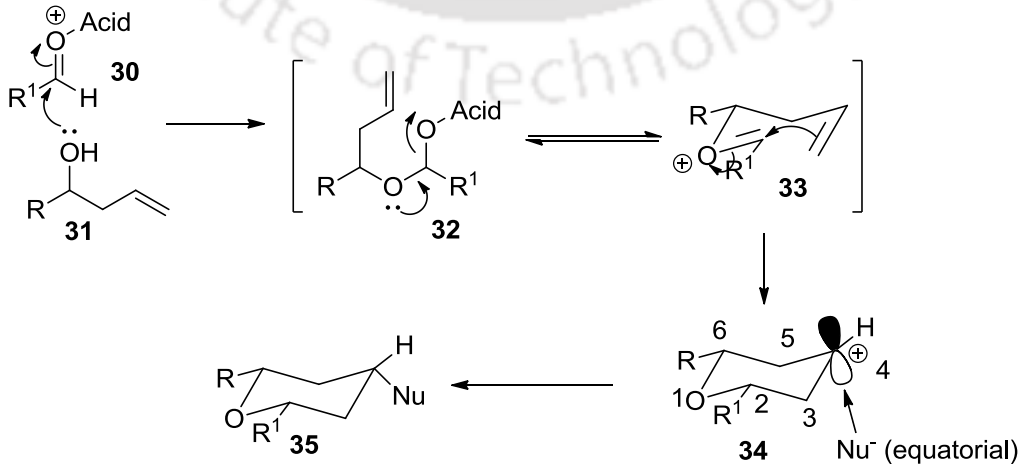
overlap is reached when the hydrogen atom at C4 is pseudo axial. This stabilization favors equatorial attack by the nucleophile.



Scheme 1.2.3.1

1.2.4. Scope of the Prins cyclization in tetrahydropyran synthesis

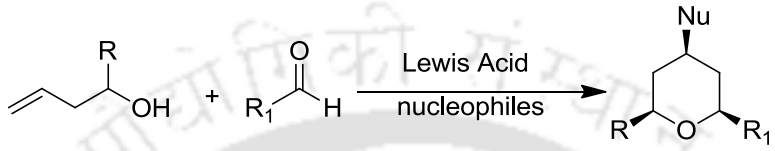
In general, oxa-Prins cyclization is the Lewis acid catalyzed/mediated reaction of an aldehyde and a homoallylic alcohol. The general mechanism is shown in *Scheme 1.2.4.1*. Reaction of aldehyde **30** and homoallylic alcohol **31** in the presence of Lewis acid generates an oxocarbenium ion **33** as key intermediate. The oxocarbenium ion undergoes 6-endo cyclization to give selectively a secondary tetrahydropyrynyl cation **34**, which is trapped by the nucleophile present in the reaction mixture to produce tetrahydropyran **35**. Thus, by varying the nature of nucleophile source present in the solution, it is possible to functionalize the C-4 of the tetrahydropyran with different functional groups (*Table 1.3.4.1*).[28]



Scheme 1.2.4.1. *Mechanism of Prins cyclization reaction*

Over the last five decades several halogenated Lewis acids have been used by different investigators where the tetrahydropyranyl cation is trapped by halide nucleophiles. Combination of Lewis acids and arenes has been utilized in tandem Prins-Friedel-Crafts reactions sequences to trap the tetrahydrpyrynylcation by aryl nucleophile, similarly tandem Prins-Ritter sequences have been used to trap by nitrile nucleophile. Trapping of the cations by hydroxide, acetate, azide, alkyne, and various sulfur nucleophiles have also been reported.

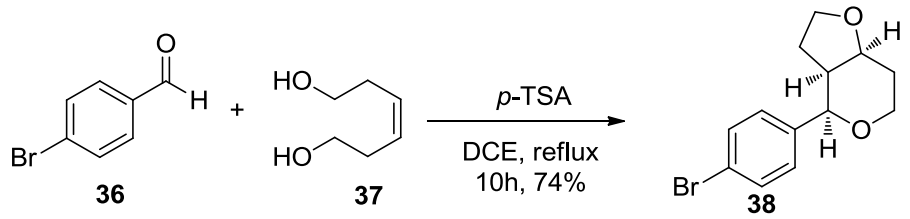
Table1.2.4.1. *Scope of the Prins cyclization with various nucleophiles*



Lewis Acid/ Nucleophile	Nu
TiF_4, $NEt_4{\cdot}5HF$, $BF_3{\cdot}OEt_2$	F
HCl, $TiCl_4$, $SnCl_4$, $AlCl_3$, $InCl_3$, $ZnCl_2$, $SbCl_5$, $ZrCl_4$, $NbCl_5$, $In(OTf)_3$/TMSCl	Cl
$SnBr_4$, $TiBr_4$, $InBr_3$, $FeBr_3$	Br
I_2, TMSCl/NaI, $CeCl_3{\cdot}7H_2O$/LiI, TMSCl/NaI	I
CF_3COOH, Montmorillonite KSF, $O_3ReOSiPh_3$, $Sc(OTf)_3$, Amberlyst 15, Amberlite® IR-120, $Ce(OTf)_3.H_2O$/IL/PhCOOH	OH
$BF_3{\cdot}OEt_2$/AcOH, TsOH/AcOH, TESOTf/TMSOAc/AcOH	OAc
TFA/NaN_3	N_3
$In(OTf)_3/NH_4SCN$	SCN
$BF_3{\cdot}OEt_2/CH_3CN$, PMA/CH_3CN, $CeCl_3{\cdot}7H_2O$-AcCl/CH_3CN	$NHCOCH_3$
$BF_3{\cdot}OEt_2$/Arene	Ar
$BF_3{\cdot}OEt_2$/CuI/ Ph—≡—H	$PhCOCH_2$

1.2.5. Intramolecular Prins cyclization

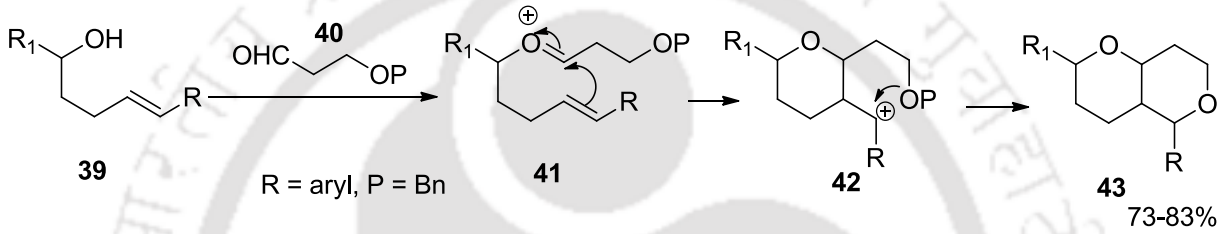
The tetrahydropyranyl cation generated after Prins cyclization can be trapped by internal nucleophiles which results ultimately the formation of bicyclic systems. Yadav and coworkers reported the coupling of *(Z)*-hex-3-ene-1,6-diol **37** with a series of aldehydes **36** by means of p-toluenesulfonic acid-catalyzed intramolecular-Prins-cyclization to provide the corresponding hexahydro-2*H* furo[3,2-*c*]pyran derivatives **38** in good yields with complete *cis*-selectivity ***(****Scheme 1.2.5.1)*. On the other hand, the reaction of (*E*)-hex-3-ene-1,6-diol with aliphatic aldehydes gave *trans*-fused bicyclic furopyrans.[29]



Scheme 1.2.5.1

1.2.6. Prins cyclization of *γ, δ*-unsaturated alcohols

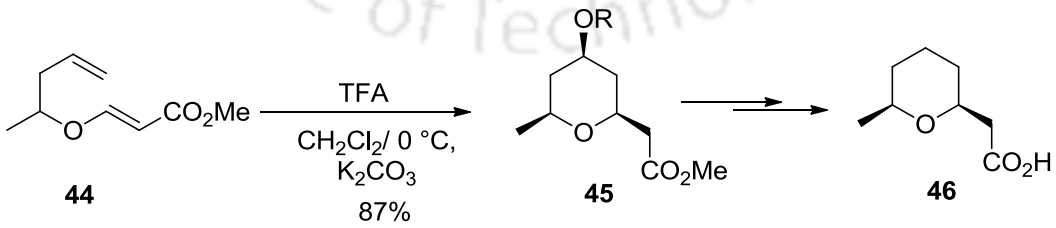
Bunt and co-workers developed a Prins cyclization method involving *γ,δ*-unsaturated alcohols **39** and aldehydes **40** having a tethered nucleophile.[30] This cascade process gave bicyclic products, 2,8-dioxa[4.4.0]bicyclodecanes **43**, with concomitant generation of three new stereocenters.



Scheme 1.2.6.1

1.2.7. Enol ethers in Prins cyclization

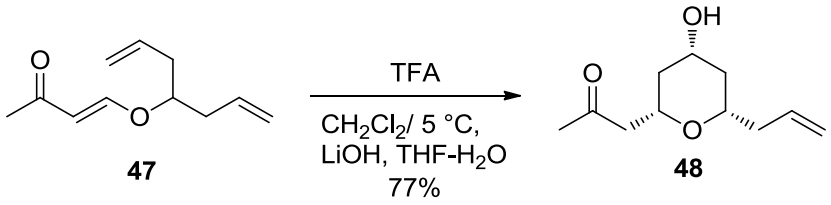
One variation of the Prins cyclization that has been reported is the use of enol ethers as the source of the oxocarbenium ion. Fráter and Nussbaumer utilized this methodology for the synthesis of the natural products (±)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid **46** by TFA promoted cyclization of enol ether **44 (***Scheme 1.2.7.1)***.**[31] The stereochemical outcome of the cyclization of **44** was explained by chair like transition state in which the ester functionality and methyl group occupied quasi-equatorial positions and the addition of electrophile (oxocarbenium ion) and nucleophile (trifluoroacetate) occurred largely in an anti-fashion.



Scheme 1.2.7.1

Another example of using enol ether as the source of the oxocarbenium ion intermediate was reported by Kozmin for the synthesis of 4-hydroxy tetrahydropyrans.[32] The cyclization of **47** was promoted by trifluoroacetic acid. The resulting trifluoroacetate was hydrolyzed using LiOH to

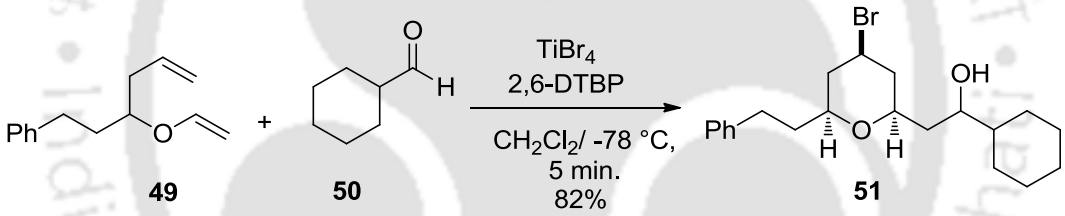
afford the all *cis*-tetrahydropyran **48** in high yield. The observed stereochemistry in the product was consistent with Fráter's explanation. The reaction proved to be efficient in the construction of the three stereogenic centers and only one isomer was observed.



Scheme 1.2.7.2

1.2.8. Mukaiyama Aldol-Prins cyclization in tetrahydropyran synthesis

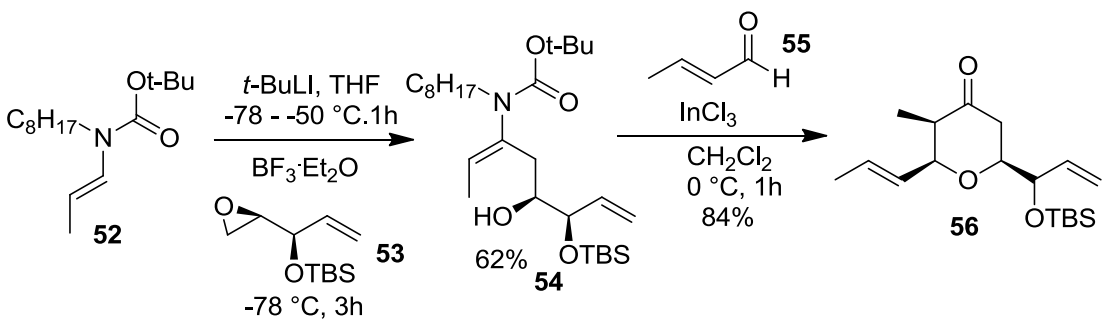
Rychnovsky and co-workers developed a new version of Mukaiyama aldol-Prins (MAP) cyclization. Unsaturated enol ethers such as **49** were allowed to react with aldehydes **50** in the presence of $TiBr_4$ to give 4-bromotetrahydropyran products **51** (*Scheme 1.2.8.1*).[33]



Scheme 1.2.8.1

1.2.9. Prins cyclizations of enecarbamates

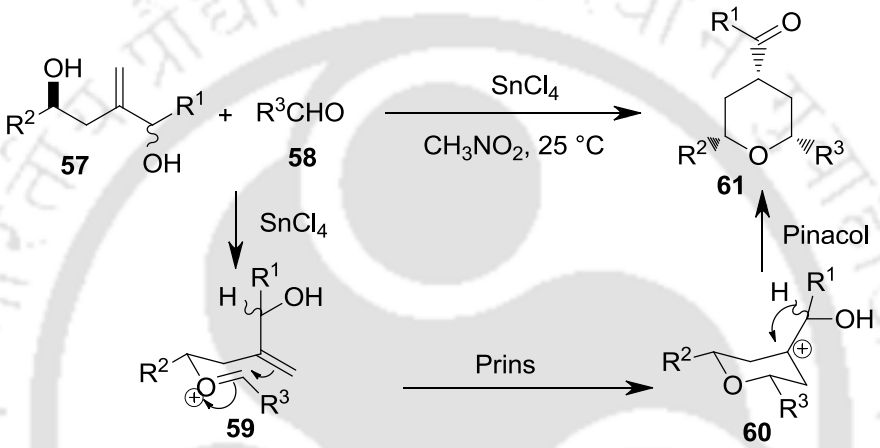
Enecarbamates are shown to be excellent terminating groups for Prins cyclizations. Funk and coworkers developed a diastereoselective synthesis of 2,3,6-trisubstituted tetrahydropyran-4-ones *via* Prins cyclizations of enecarbamates (*Scheme 1.2.9.1*).[34]



Scheme 1.2.9.1

1.3. Prins-pinacol rearrangement in tetrahydropyran synthesis

Prins-pinacol reactions are employed to construct a wide variety of oxygen heterocycles. Overman and co-workers reported a convenient synthesis of tetrahydropyrans by acid promoted condensation of 2-methylene-1,4-diols **57** with aldehydes **58** in a reaction sequence whose central step is pinacol terminated Prins cyclization.[35] Preferential formation of oxocarbenium ion **59** occurs by condensation of **57** and **58** in the presence of acid catalyst. Prins cyclization of **59** would generate cation **60**, followed by preferential axial hydride shift would complete the reaction (*Scheme 1.3.1*).



Scheme 1.3.1

1.4. General approaches for the synthesis of tetrahydropyrans

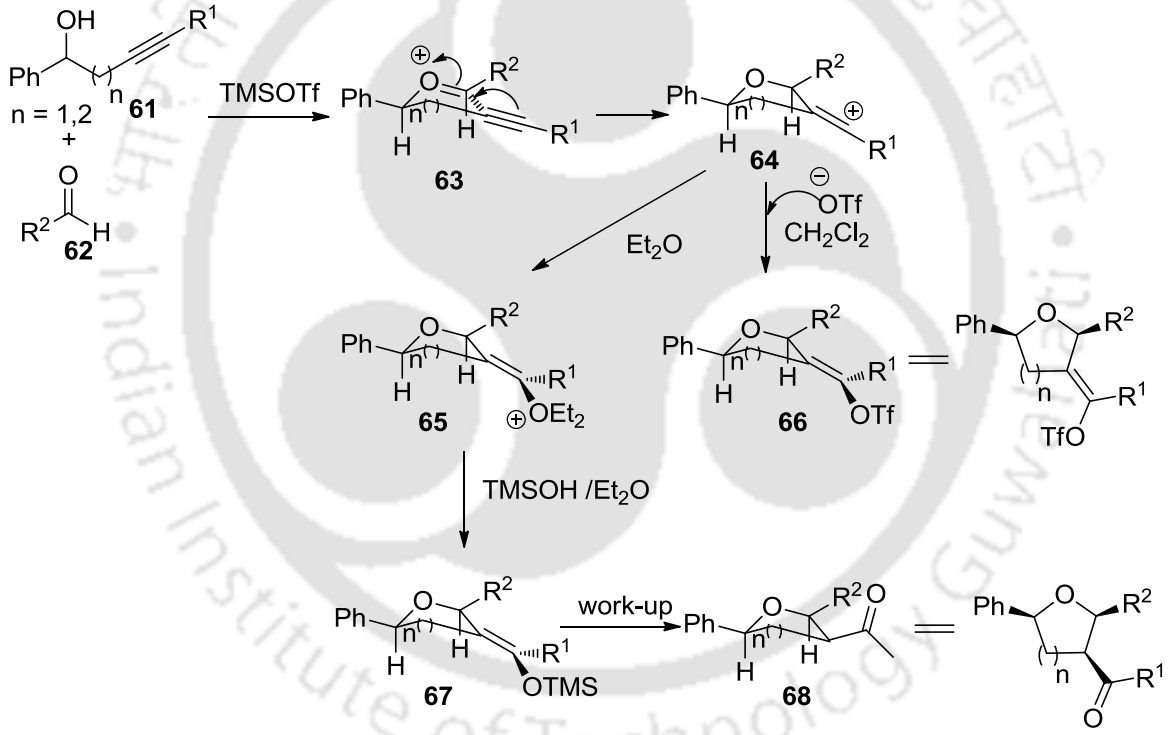
Due to the importance of tetrahydrofurans, huge amount of effort has been devoted toward the development of methods for the stereoselective construction of these heterocyclic ring systems having different substitution. Some of the commonly used methods include intramolecular nucleophilic substitutions,[36] intramolecular cyclization of 4-alkenols,[37] 3-alkenols,[38] oxidative cyclization of 1,5-dienes,[39] [3+2]cycloaddition and annulation reactions,[40] metal-catalyzed cycloisomerization,[41] olefin metathesis,[42] radical cyclizations,[43] ring expansion of oxetanes,[44] Prins cyclization,[45] etc. This part of thesis mainly deals with the synthesis of tetrahydrofurans involving Prins cyclization.

1.4.1. Prins cyclization in tetrahydrofuran synthesis

Although Prins-cyclization has emerged as a powerful C-O and C-C bond-forming technique in the synthesis of tetrahydropyran rings, reports of pure Prins-cyclization in the synthesis of tetrahydrofurans are very rare. However Prins cyclizations terminated by a pinacol

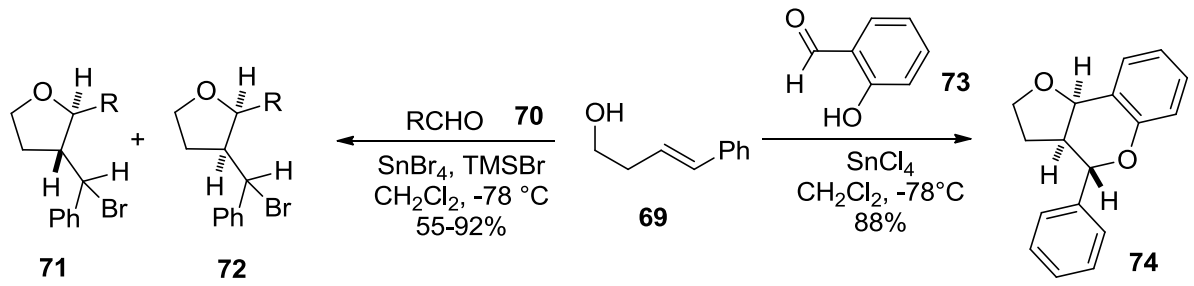
rearrangement have been widely used to construct a wide variety of polysubstituted tetrahydrofurans.

Cho and co-workers utilized Lewis acid promoted Prins-type cyclization of terminally substituted alkynyl alcohols **61**with various aldehydes **62** to synthesize *cis*-2,5-tetrahydrofurans and *cis*-2,6-tetrahydropyrans *(Scheme 1.4.1.1)*.[45b,45c] The 5- and 6-exocyclic vinyl cations **64** generated as a result of Prins-type cyclization was trapped as a vinyl triflate in CH_2Cl_2 to give 3-furanylidenes and 3-pyranylidenes **66**. Those 3-furanylidenes and 3-pyranylidenes underwent hydrolysis to give the corresponding 3-acyl-substituted products having *all-cis*-configured isomers, such as 2,3,5-trisubstituted tetrahydrofurans and 2,3,6-trisubstituted tetrahydropyrans. On the other hand, in ethereal solution the reaction directly gave the corresponding 3-acyl-substituted products **68**.



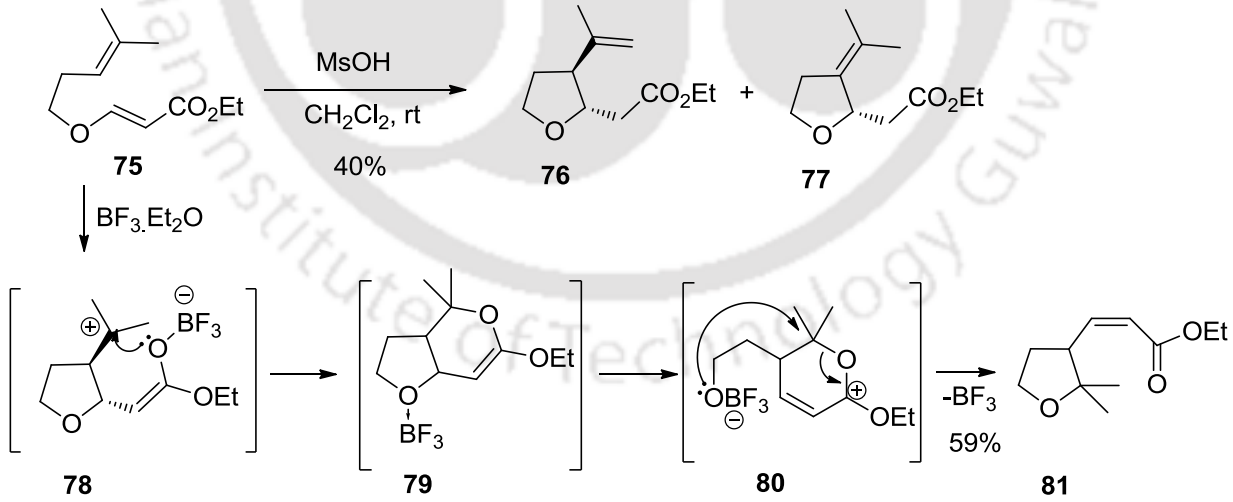
Scheme 1.4.1.1

A diastereoselective synthesis of 2,3-disubstituted tetrahydrofurans was developed by White and coworkers where $SnBr_4$ promoted oxonium-Prins cyclization of (*E*)-4-phenylbut-3-en-1-ol **69** and aldehyde **70** was used.[46] In the absence of an internal nucleophile, the benzyl carbocation intermediates generated after Prins-cyclization were trapped by bromide to give 2,3-*cis*- and 2,3-*trans*-configured products **71**/**72**. On the other hand, trapping of the carbocation intermediates by a proximate internal nucleophile led to the formation of bicyclic products **74** *(Scheme 1.4.1.2)*.



Scheme 1.4.1.2

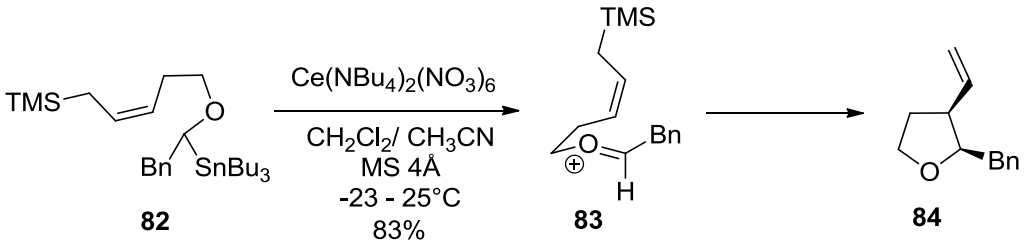
Kraft and co-workers reported the Prins-type cyclization of the 3-(4-methylpent-3-enyloxy)acrylate **75** under different Lewis acidic conditions (*Scheme 1.4.1.3*).[47] They observed the formation of a 1:1 mixture of tetrahydrofurans **76** and **77**, when a solution of the enol ether in CH_2Cl_2 was treated with a catalytic amount of MsOH at room temperature. But employing an excess of boron trifluorideetherate instead of MsOH, the Prins-type cyclization of **75** led to the formation of the (tetrahydrofuranyl)acrylate **81**, which was isolated in 59% yield. They proposed a mechanism, where a zwitterionic boron ester enolate **78** was formed by the reaction with boron trifluoride. This underwent cyclization to give the tetrahydro-4*H*-furo [3,2-c]pyran **79**, and cleavage of the allylictetrahydrofuranyl ether bond led to **80**. Intramolecular nucleophilic attack by the boron trifluoride alcoholate to the geminally dimethyl-substituted C-atom resulted finally in the formation of the (tetrahydrofuranyl)acrylate **81** with extrusion of boron trifluoride.



Scheme 1.4.1.3

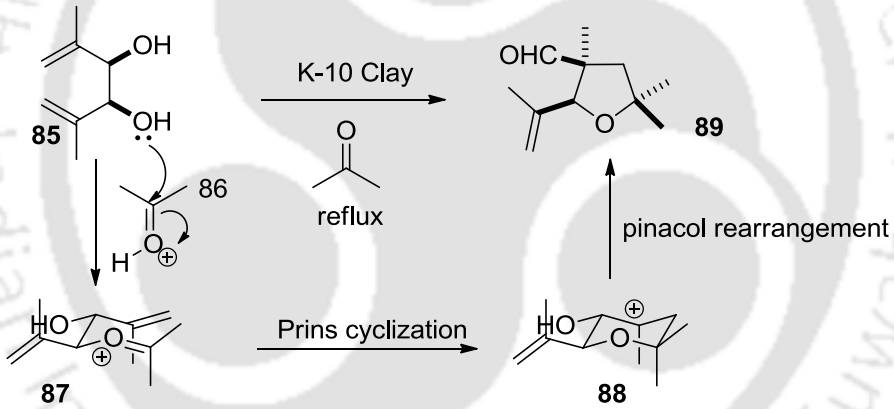
Chen and co-workers devised an oxidative Prins cyclization method for the synthesis of substituted tetrahydropyrans and tetrahydrofurans.[48] Allylsilane-tethered α-stannyl ethers were used as precursors to generate oxocarbenium ions under oxidative condition. Thus, treatment of *Z*-allylsilane derivative with $Ce(NBu_4)_2(NO_3)_6$ generated the intermediate oxocarbenium ion,

which underwent Prins cyclization with the pendant allylsilane to afford 2,3-*cis*-disubstituted tetrahydrofuran as a single diastereomer (*Scheme 1.4.1.4*).



Scheme 1.4.1.4

Mousset and co-workers discovered Pinacol terminated Prins cyclization in an attempt to make the acetonide of *meso* allylic diol **85** by condensation with acetone **86** in the presence of an acidic clay catalyst,[49] these authors instead observed the formation of tetrahydrofuran **89** in high yield.



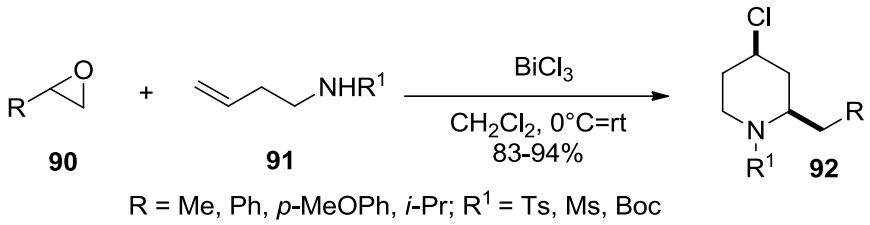
Scheme 1.4.1.5

They proposed the mechanism as generation of an oxocarbenium ion **87** by the condensation of allylic diol and acetone that underwent Prins cyclization via chair conformer, resulting hydroxypyranyl α-hydroxycarbenium ion **88**. Pinacol rearrangement of the carbenium ion ultimately generated the tetrahydrofuran **89** *(Scheme 1.4.1.5).* In this cascade process, two C-C bonds, one C-O bond, and two new stereocenters were created with complete stereoselectivity.

1.5. Aza-Prins cyclization

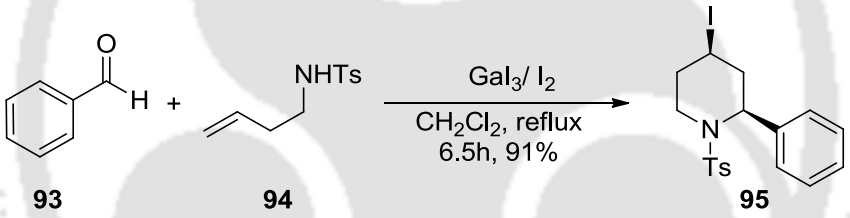
In aza-Prins cyclization homoallyl amines are used as counterpart of homoallyl alcohol in oxa-Prins cyclization. Aza-Prins cyclization leads to the formation of piperidines. Yadav and co-workers reported a rapid and efficient $BiCl_3$ promoted stereoselective synthesis of *trans*-2,4-

disubstituted piperidine derivatives **92** by aza-Prins cyclization of *N*-protected homoallylamines **90** and epoxides **91***(Scheme 1.5.1).*[50]



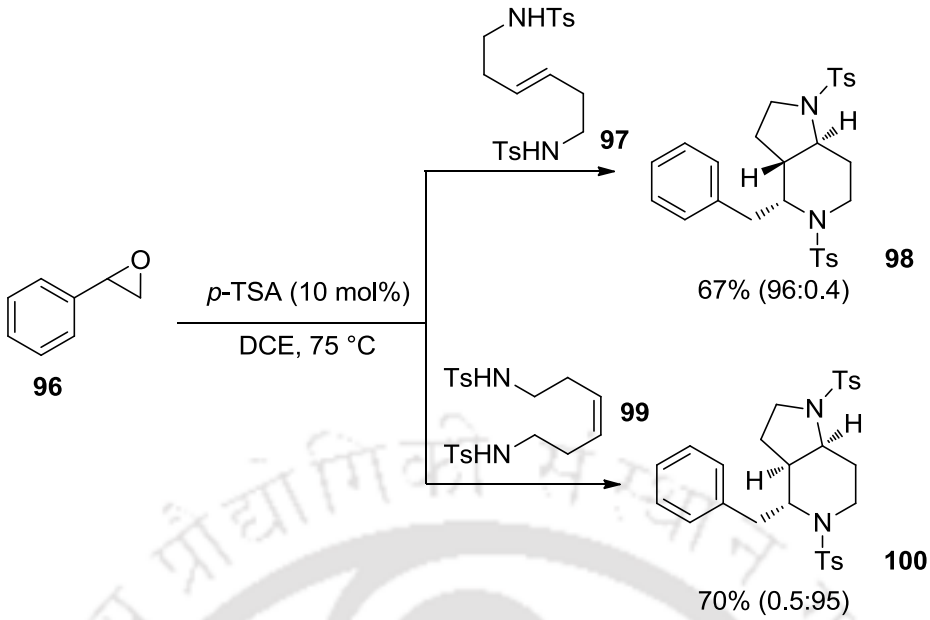
Scheme 1.5.1

In a similar way Yadav's group utilized GaI_3 catalyzed aza-Prins cyclization of aldehydes and *N*-tosylhomoallylamines for the synthesis of 4-iodopiperidines. Thus, the reaction of benzaldehyde with *N*-tosylhomoallylamine in the presence of 10 mol% of GaI_3 and stoichiometric amount of molecular iodine at ambient temperature gave the 4-iodo-2-phenylpiperidine in 91% yield with *cis*-selectivity.[51]



Scheme 1.5.2

Yadav and co-workers further developed Brønsted acid catalyzed intramolecular aza-Prins cyclization for the synthesis of fused aza-bicyclic systems.[52] Thus, reaction of *(E)*-hex-3-ene-1,6-ditosylamide **97** and styrene oxide **96** in the presence of 10 mol% *p*-TSA in 1,2-dichloroethane at 75 °C afforded the corresponding 1,5-ditosyl-octahydro-1*H*-pyrrolidino[3,2-*c*]pyridines **98** in good yields with high *trans*-selectivity, whereas the reaction of *(Z)*-hex-3-ene-1,6-ditosylamide **99** afforded *cis*-fused octahydro-1*H*-pyrrolidino[3,2-*c*]pyridines **100** predominantly (*Scheme1.5.3*).

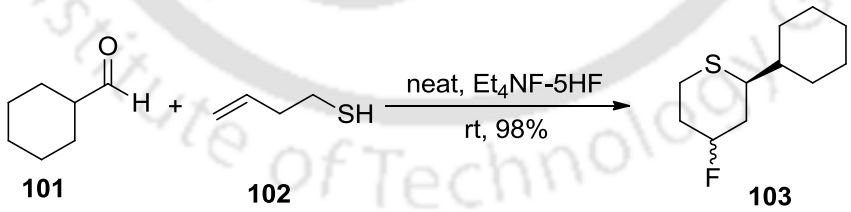


Scheme 1.5.3

1.6. Thia-Prins cyclization

Thia-Prins cyclization involves Lewis acid catalyzed reaction of homoallyl thiols and aldehydes. Recently, these types of reaction have received considerable attention and showed significant progress in tetrahydrothiopyran synthesis.

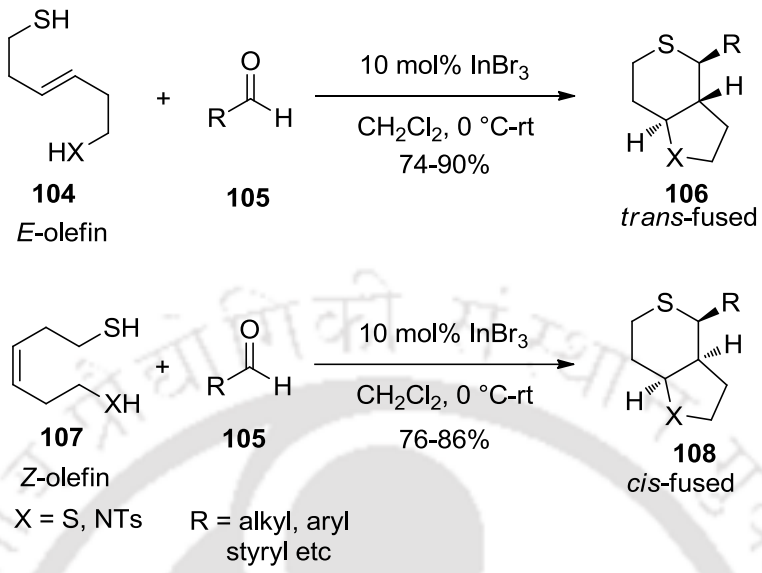
Kishi *et al*. have studied thia-Prins cyclization of various aldehydes and homoallylthiol in ionic liquid HF salt to obtain 4-fluorothiacyclohexanes in excellent yields.[53] Although, *cis*-products were obtained selectively (higher than 92%), formation of small amount of *trans*-products were also observed (*Scheme1.6.1*).



Scheme 1.6.1

A novel thia-Prins bicyclization approach was developed by Yadav and coworkers for the stereoselective synthesis of dithia- and azathia-bicycles.[54] Coupling of homoallylic mercaptans such as hex-3-ene-1,6-dithiol and *N*-(6-mercaptohex-3-enyl)-4-methylbenzenesulfonamide **104** with various aldehydes **105** using 10 mol% $InBr_3$ in dichloromethane gave hexahydro-*2H*-thieno[3,2-*c*]thiopyran derivatives and octahydrothiopyrano[4,3-*b*]pyrrole **106** derivatives, respectively, with high stereoselectivity. *Trans*-fused products **106** were obtained from *E*-

homoallyllic mercaptans whereas *Z*-homoallylic mercaptans afforded *cis*-fused products **108** (*Scheme1.6.2*).



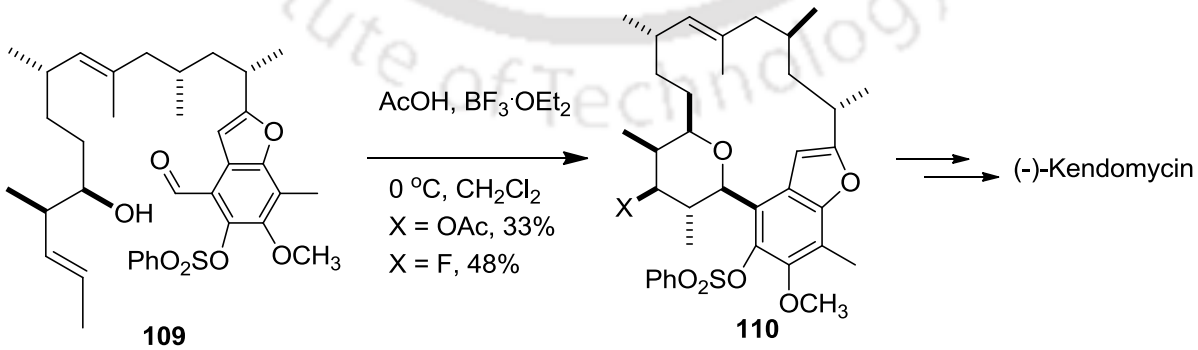
Scheme 1.6.2

1.7. Applications of Prins cyclization towards natural product synthesis

The Prins cyclization is a potentially powerfull method for the synthesis of oxygen heterocycles. A number of research groups have been investigating Prins cyclization reactions towards the synthesis of natural products.

Synthesis of Kendomycin

(–)-Kendomycin is an antitumor macrolide antibiotic isolated from the bacteria *Streptomyces violaceoruber*. It exhibits potent antagonism of the endothelin receptor agonism.[4]



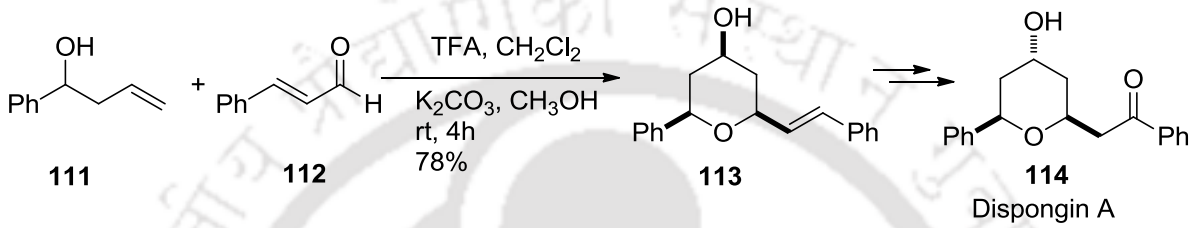
Scheme 1.7.1

In an approach towards the formal synthesis of this macrolide, Rychnovsky *et al.* utilized a $BF_3{\cdot}Et_2O$ mediated intramolecular macro Prins cyclization of **109** containing an electron-rich

benzaldehyde and a homoallylic alcohol moiety within the framework (*Scheme 1.7.1*).[22] For the electron rich benzaldehyde, the use of acetic acid is necessary to suppress the side reactions.

Synthesis of diospongin A

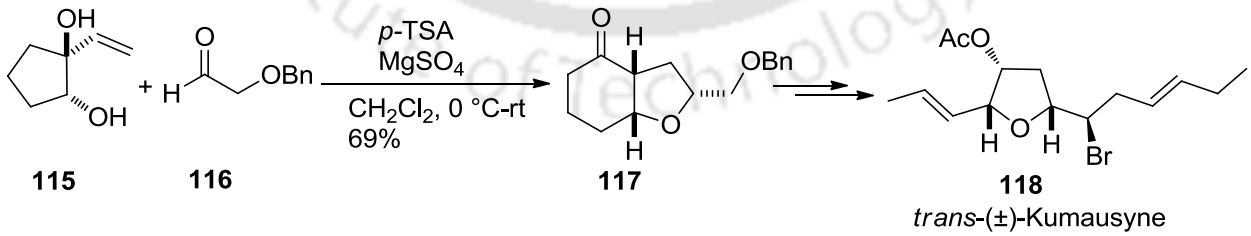
Dispongin A (**114**) exhibits antiosteoporotic acitivity. Piva and coworkers developed a concise and efficient total synthesis of dispongin A using Prins cyclization and kinetic resolution.[55] It enabled control of the relative configuration of the three stereogenic centres contained in the natural product.



Scheme 1.7.2

Total synthesis of (±) kumausyne

Kumausynes are secondary metabolites produced by red algae of the genus *Laurencia*. Overman and coworkers developed a total synthesis of (±) kumausyne (**118**) consisting 13 steps with > 5% yield.[56] The central step is the convenient formation of (±)-hydrobenzofuranone **117** on large scale, and with complete stereocontrol, by Prins-pinacol sequence involving 1-vinyl cyclopentanediol **115** and *α*-(benyloxy)acetaldehyde **116** as starting material. Starting with the chiral, nonracemic (*1S,2R*) diol, (-)-hydrobenzofuranone was obtained in good enantiomeric purity.



Scheme 1.7.3

Conclusion

The Prins cyclization is a powerful and versatile tool for the synthesis of functionalized tetrahydropyran and tetrahydrofuran skeletons that are commonly encountered in a wide range of biologically active natural products. Involvement of cyclic transition state makes Prins-cyclization methodologies to be high diastereoselective. Furthermore the cationic intermediates

formed during the course of the reactions can be trapped by various nucleophiles either by intramolecular fashion or by intermolecular fashion. Due to the high stereoselective nature, versatility, simple reaction precursors, and mild reaction conditions, it has been a key strategic process in the total synthesis of heterocyclic and carbocyclic natural products.

1.8. References

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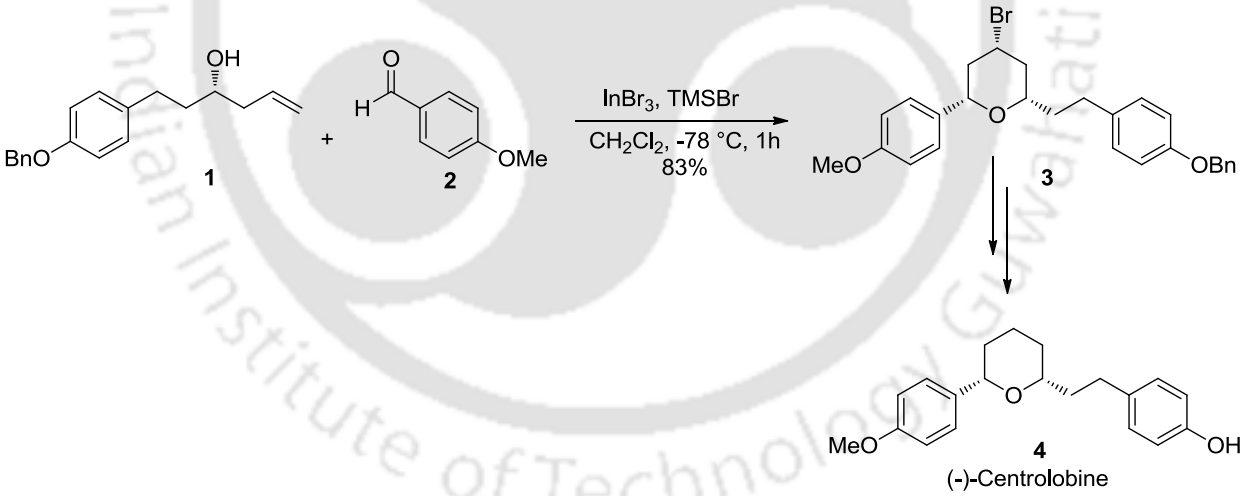
CHAPTER 2

Axial Selectivity in Prins-Cyclization: Synthesis of 4-Iodotetrahydropyrans

2.1. Importance and applications of 4-halotetrahydropyrans

Tetrahydropyran unit is found in many natural and biologically active compounds.[1] 4-halotetrahydropyrans are synthetically attractive because they can be transformed into other substituted tetrahydropyrans by functionalization of the halo function.[2] Therefore, 4-halo tetrahydropyrans have been used as key intermediates in organic synthesis. For example, in the Loh's methodology for the total synthesis of (-)-centrolobine **4** involves the 4-bromo tetrahydropyran **3** as the key intermediate (*Scheme 2.1.1*).[2b] Certain 4-halotetrahydropyrans and their mixtures are effectively employed as plasticizers and extrusion aids for polyvinyl fluoride.[3]



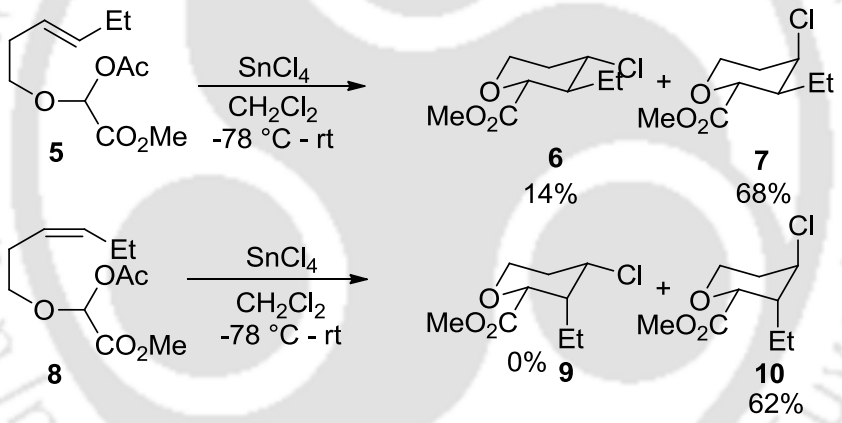
Scheme 2.1.1. *Total synthesis of (-)-centrolobine*

2.2. Literature methods for the synthesis of 4-halotetrahydropyrans

Since tetrahydropyrans are frequently encountered in nature, there has been much interest in the development of methods for the stereoselective synthesis of these units. Over the years many strategies have been developed for the synthesis of substituted tetrahydropyrans, among which the Prins-Cyclization reaction has been most widely used because of its

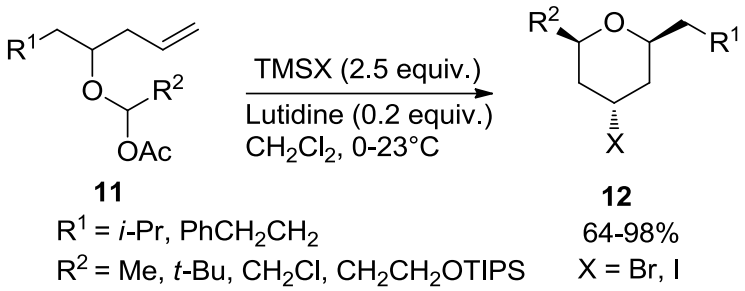
distereoselectivity.[4] Generally, 4-halo tetrahydropyrans are prepared using Lewis acids such as $SnCl_4$,[5] $SnBr_4$,[6] TMSBr,[3a-c] $TiCl_4$,[7] $TiBr_4$,[8] TiF_4,[9] $InCl_3$,[10] $AlCl_3$,[11] $FeCl_3$,[4b] $ZrCl_4$,[12] $BF_3{\cdot}OEt_2$,[13] $NbCl_4$,[14] $BiCl_3$,[15] TMSI,[16] $CeCl_3$[17]and others.[18] The halo function in all these reactions is placed in equatorial position. This is in accordance to the Alder's model.[19] There are limited methods for the synthesis of 4-axial halotetrahydropyrans. There are a few methods where axial-4-halo substituted tetrahydropyrans are side products or 1:1 mixture with equatorial products.[13, 18b]

Lolkema *et al.* reacted methyl 2-acetoxy-2-(3-alken-l-oxy)acetates with different chain substitution as precursors to generate α-ester oxocarbenium ions. They observed that the $SnCl_4$-induced cyclization of the acetales, in most cases gives tetrahydropyran derivatives containing an equatorial methoxycarbonyl function at C-2 and an axial chlorine atom at C-4.[20] Thus the acetales **5** and **8** after cyclization yielded axial 4-chlorotetrahydropyran derivatives (**7** and **10**) as the major isomer (*Scheme 2.2.1*).



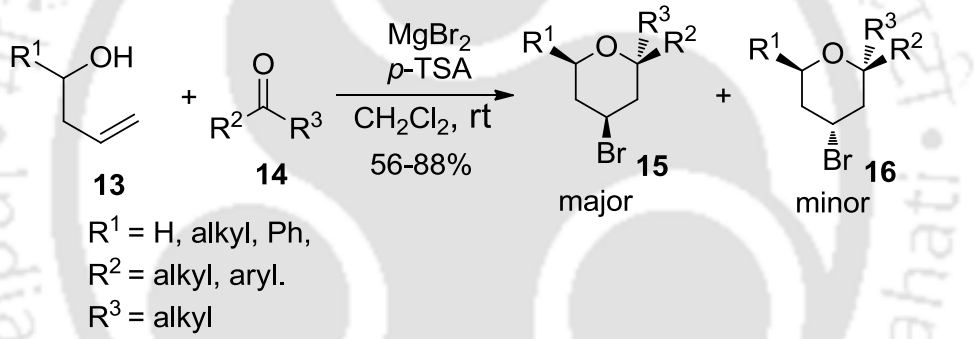
Scheme 2.2.1

Rychnovosky and co-workers reported an axial selective Prins-cyclization of α-bromo ethers or α-iodo ethers promoted by TMSX (X = Br, I) in high diastereoselectivity and very good yields, for the synthesis of axial 4-bromo or 4-iodotetrahydropyran derivatives (*Scheme 2.2.2).*[21] The actual precursors of the reaction were α-acetoxy ethers **11** which underwent halide exchange under the reaction condition to generate α-halo ethers.



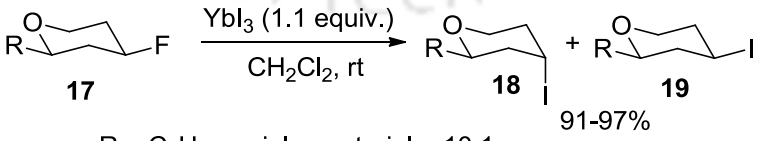
Scheme 2.2.2

Borkar *et al*. developed a methodology where the combination of $MgBr_2$ and *p*-TSA was used for the Prins-cyclization of homoallylic alcohols **13** and aldehydes **14**.[22] The outcome of the reaction in all the cases was a diastereomeric mixture of both equatorial and axial 4-bromo tetrahydropyrans, where the axial isomer **16** was obtained as minor isomer *(Scheme 2.2.3)*.



Scheme 2.2.3

Alternatively, axial 4-iodotetrahydropyrans can be synthesized from their equatorial isomers by iodide substitution. Hilmersson and co-workers reported a methodology for substitution of unactivated alkyl fluorides with iodide by means of YbI_3.[23] They applied the methodology to



R = C_5H_{11}, axial:equatorial = 10:1

R = *p*-F-C_6H_4, axial:equatorial = 5:1

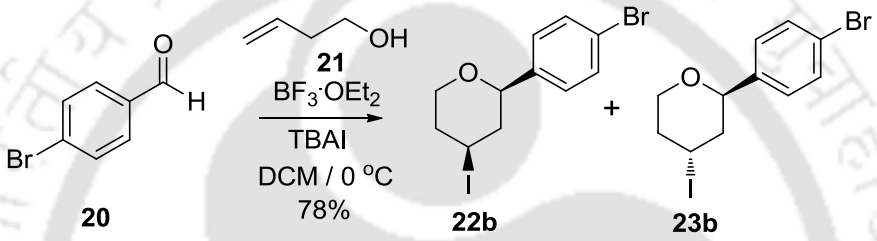
R = *p*-Br-C_6H_4, axial:equatorial = 4:1

Scheme 2.2.4

the equatorial 4-fluoro tetrahydropyrans **17** and observed the formation of axial 4-iodo tetrahydropyrans **18** as a major diastereomers with moderate to good selectivity.

2.3. Present work

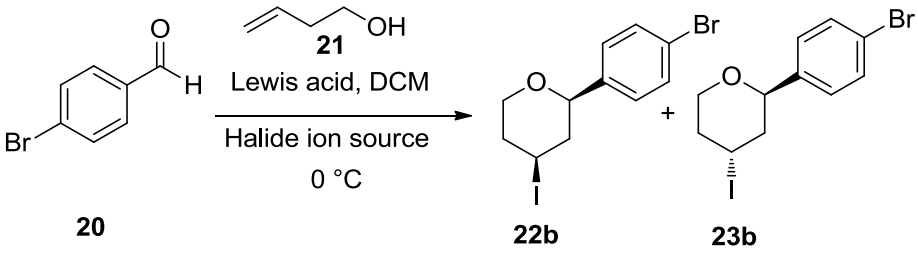
In continuation of our interest in tetrahydropyran synthesis,[24] we were in search of a halogenating agent, other than Lewis acid, for the synthesis of 4-halotetrahydropyrans. Considering tetrabutyl ammonium iodide (TBAI) as such type of iodinating agent, we started our investigation by treating 4-bromobenzaldehyde **20** and homoallylic alcohol **21** with tetrabutylammonium iodide in Prins-cyclization condition (*Scheme 2.3.1*).



Scheme 2.3.1

To our surprise, a diastereomeric mixture (**22b** and **23b**) with an equatorial to axial ratio of 1:2 was obtained in 78% overall yield (*Scheme 2.3.1*). The result is in contrast to the usual Prins-cyclization reaction. This result encouraged us to explore the reaction under different Lewis acidic conditions and with various iodinating agents. The results are summarized in *Table 2.3.1*. Reaction of 4-bromobenzaldehyde and homoallylic alcohol with $BF_3{\cdot}OEt_2$/NaI and TMSCl/NaI resulted a 1:1 mixture of axial and equatorial isomers with 46% and 91% yield, respectively. The reaction with TMSI along with catalytic amount of 2,6-lutidine gave 3:2 mixture of equatorial and axial products which was in contrast to the results reported by Rychnovosky.[21] On the other hand, $BF_3{\cdot}OEt_2$/TBAI and TMSCl/TBAI gave mixtures with ratios of 1:2.5 and 1:2 in 78% and 62% yield, respectively. It was observed that systems like $InCl_3$/TBAI, $Sc(OTf)_3$/TBAI, and $In(OTf)_3$/TBAI were not suitable for this reaction. The reaction with one equivalent of TMSOTf produced a single diastereomer **23b** with 76% yield, which was confirmed by ^{1}H NMR of crude product. The same reaction with catalytic amount of TMSOTf gave only 18% yield.

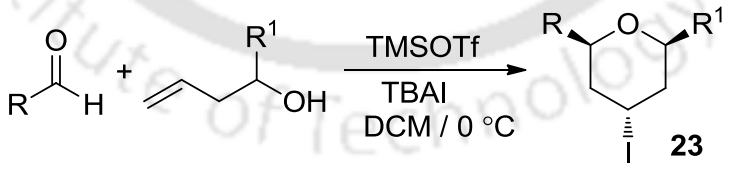
Table 2.3.1. Prins-cyclization in different conditions



Entry	Lewis acid (equiv.)	Iodide ion source	Ratio[b] of **22b**:**23b**	Yield(%)[a]
1	$BF_3{\cdot}Et_2O$ (1)	NaI	1:1	46
2	$BF_3{\cdot}Et_2O$ (1)	TBAI	1:2.5	78
3	TMSI (1) / 2,6-Lutidine	_	3:2	82
4	TMSCl (1)	NaI	1:1	91
5	TMSCl (1)	TBAI	1:2	62
6	$InCl_3$ (1)	TBAI	NR	_
7	$Sc(OTf)_3$ (1)	TBAI	NR	_
8	$In(OTf)_3$ (1)	TBAI	NR	_
9	TMSOTf (0.1)	TBAI	0:1	13
10	TMSOTf (1)	TBAI	0:1	76
11	TMSOTf (1)	I_2	1:1	50

[a]Yields refer to isolated yield. The compounds are characterized by IR, ^{1}H and ^{13}C NMR, and mass spectrometry. [b]Diastereomeric ratios were determined by ^{1}H NMR. NR= No reaction.

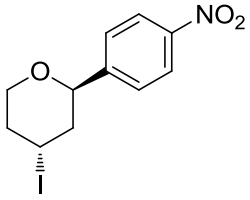
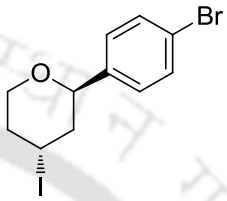
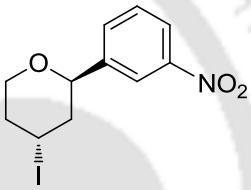
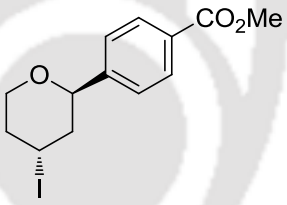
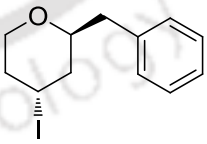
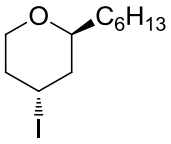
Replacement of TBAI with iodine (entry 11) also gave mixture (1:1) of products. Thus 1.0 equivalent of TMSOTf and TBAI as iodide ion source are found to be the most effective. The reaction is generalized as shown in *Scheme 2.3.2*.



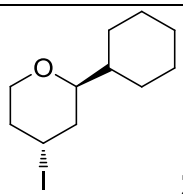
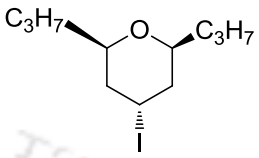
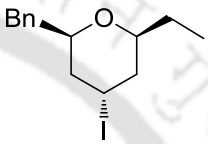
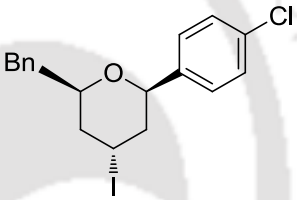
Scheme 2.3.2

The scope of the reaction was further studied with varieties of aldehydes and homoallylic alcohols under the same reaction conditions (*Table 2.3.2*). Both aliphatic and aromatic aldehydes gave axial-selective products with high yields and diastereoselectivity.

Table 2.3.2. *Synthesis of axial-4-bromo- and iodotetrahydropyran*

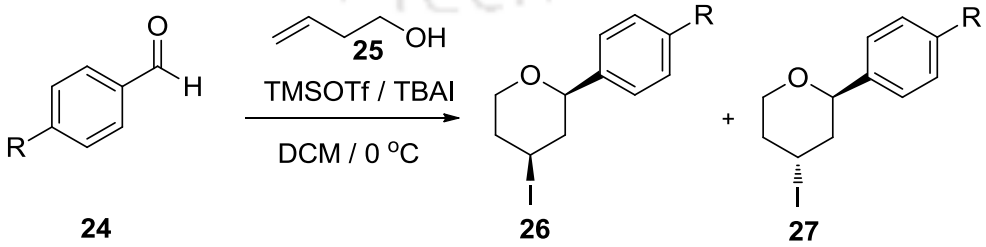
Entry	Aldehyde (R)	Alcohol (R^1)	Time/h	Product **23**	Yield[a]
a	4-NO_2-C_6H_4	H	0.5	 **23a**	78
b	4-Br-C_6H_4	H	0.5	 **23b**	76
c	3-NO_2-C_6H_4	H	0.5	 **23c**	76
d	4-MeO_2C-C_6H_4	H	0.5	 **23d**	85
e	C_6H_5-CH_2	H	0.5	 **23e**	78
f	*n*-C_6H_{13}	H	0.5	 **23f**	83

Continued……..

Entry	Aldehyde (R)	Alcohol (R^1)	Time/h	Product	Yield[a]
g	*cyclo*-C_6H_{11}	H	0.5	 **23g**	82
h	*n*-C_3H_7	*n*-C_3H_7	2.0	 **23h**	80
i	*n*-C_2H_5	C_6H_5-CH_2	2.0	 **23i**	74
j	4-Cl-C_6H_4	C_6H_5-CH_2	2.0	 **23j**	86

[a]Yields refer to isolated yield. The compounds are characterized by IR, ^{1}H and ^{13}C NMR, and mass spectroscopy

It was observed that simple aromatic aldehydes, benzaldehyde and aldehydes having electron donating substituents on an aromatic ring, such as 4-methoxybenzaldehyde gave equatorial and axial diastereomers **26** and **27** with a ratio of 1:1 and 1:2, respectively (*Scheme 2.3.3*). This is due to the stabilization of oxocarbenium ion by phenyl and methoxy groups, which leads to oxonia-Cope rearrangement.



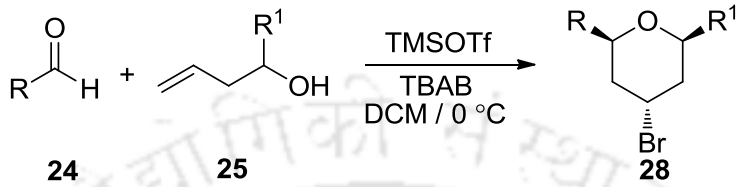
when R = H; **26a**:**27a** = 1:1; 74%

when R = OMe; **26b**:**27b** =1:2; 80%

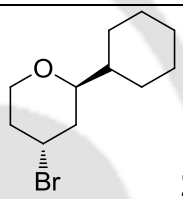
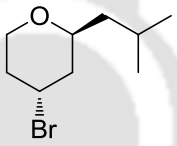
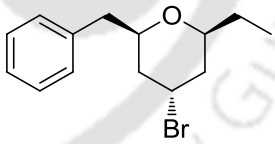
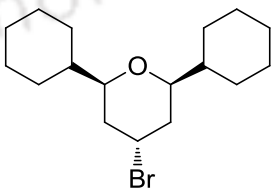
Scheme 2.3.3

The TMSOTf mediated cyclization was also studied with brominating agent, tetrabutyl ammonium bromide (TBAB), which yielded axial-4-bromotetrahydropyrans **28** (*Table 2.3.3*). The longer reaction time and lower yields of the 4-bromotetrahydropyrans is attributed to the less reactivity of TBAB compared to that of TBAI.

Table 2.3.3.*Reaction with TBAB*



24 **25** **28**

Entry	Aldehyde (R)	Alcohol (R^1)	Time/h	Product **28**	Yield (%)[a]
a	*cyclo*-C_6H_{11}	H	2	 **28a**	65
b	$(CH_3)_2CHCH_2$	H	2	 **28b**	70
c	*n*-C_2H_5	C_6H_5-CH_2	2	 **28c**	58
d	*cyclo*-C_6H_{11}	*cyclo*-C_6H_{11}	2	 **28d**	60

[a]Yields refer to isolated yield. The compounds are characterized by IR, ^{1}H and ^{13}C NMR, and mass spectroscopy

The stereoselectivity and stereochemistry of the compounds were determined from crude ^{1}H NMR and single crystal X-ray crystallographic analysis (*Figure 2.3.1*).[25]

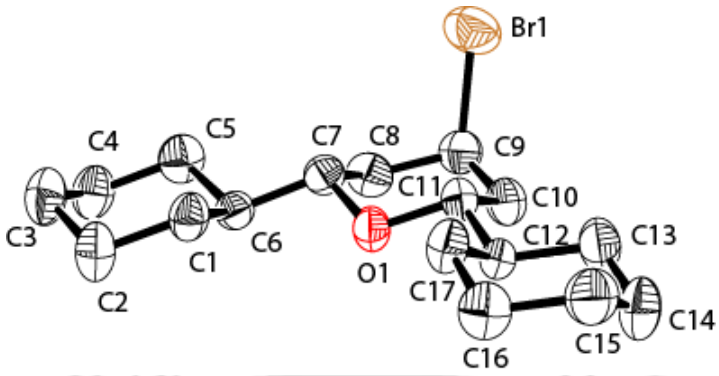


Figure 2.3.1. *ORTEP diagram of 4-bromo-2,6-dicyclohexyl-tetrahydro-2H-pyran (**28d**)*

The axial position of the halide group at 4-position was determined by comparison with equatorial products. It is known that reaction of aldehydes with homoallylic alcohols in presence of iodine gives equatorial iodinated products.[18c] It was observed that the equatorial proton of **23b** attached to the axial iodide resonates at 4.91 ppm and in the case of axial proton of equatorially substituted iodide (compound **22b**) resonates at 4.38 ppm (*Figure 2.3.2*). This is in agreement with the fact that the equatorial proton resonates at lower field than the axial proton.[18c]

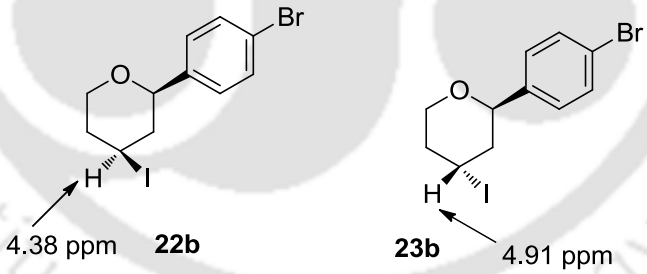
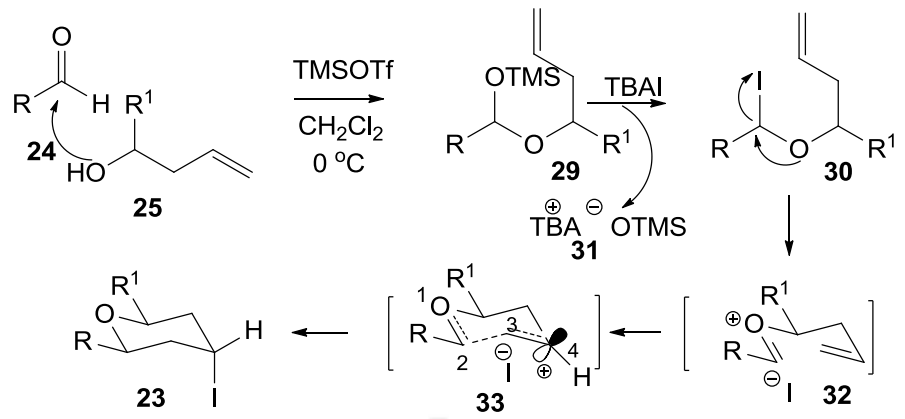


Figure 2.3.2.*Chemical shift values (ppm) of axial and equatorial protons of **22b** and **23b***

A mechanistic proposal for the axial-selective Prins-cyclization is shown in *Scheme 2.3.4.* The reaction of aldehyde **24** with alcohol **25** in presence of TMSOTf gives acetal **29,** which after reaction with TBAI gives species **30**. The species **30** decomposes to provide oxocarbenium ion **32**, which then, forms an intimate ion pair **33** with iodide ion. Prins-cyclization of favored chair conformation **33** and simultaneous addition of proximate iodide ion produces the desired axial product **23**.



Scheme 2.3.4: *Proposed mechanism of the reaction*

Conclusion

In conclusion, we have developed an axial-selective Prins-cyclization reaction with high diastereoselectivity and good yields. The 4-axial halosubstituted products would be an important synthetic intermediate for the synthesis of 4-equatorial substituted tetrahydropyrans by substitution reactions.

2.4. Experimental Section

2.4.1. Instrumentation and Characterization

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. The solvents were of commercial grade and purified according to established procedures. Organic extracts were dried with anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-10 mesh size) was used for coloumn chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm).

Melting points were recorded with a Büchi B-540 melting point apparatus.^{1}H NMR spectra were recorded in $CDCl_3$ on 600 and 400 MHz NMR spectrometer using TMS as internal standard. The ^{13}C NMR spectra were recorded at 150 and 100 MHz using $CDCl_3$ as internal standard. IR spectra were recorded on FT-IR spectrometer. The HRMS data were measured with Waters QTOF-Premier, LC Ms/Ms system. The crystal data were collected with Brukar Smart Apex-II CCD diffractrometer using graphite monochromatic $Mock_{\alpha}$ radiation (λ = 0.71073Å) at 298 K.

2.4.2. General procedure for the synthesis of compounds 23a-23j and 28a-28d. To an ice-cold solution of homoallyl alcohol (1.2 equiv.), aldehyde (1.0 equiv.) and tetrabutylammonium halide (1.2 equiv) in anhydrous CH_2Cl_2 (3 mL) under nitrogen atmosphere was added TMSOTf (1.2 equiv) through a syringe. Then the reaction mixture was stirred at the same temperature for a specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. The reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution; the product was extracted with CH_2Cl_2, and then washed with brine solution. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the title compounds.

2.5. References and Notes

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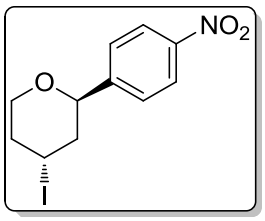
25. Thecrystallographic data for compound **28d** has been deposited with the Cambridge Crystallographic Data Centre as supplimentary publication No. CCDC 792987.

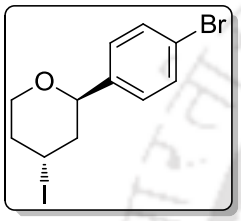
2.6. Characterization Data

4-Iodo-2-(4-nitrophenyl)tetrahydro-*2H*-pyran (23a).



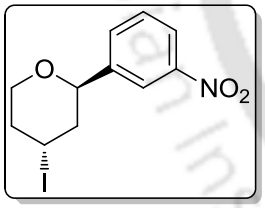
White solid, M.P: 103-105 ^{o}C; (125mg, 76% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80 (dddd, *J* =11.2, 10.8, 4.0 and 3.6 Hz, 1 H), 1.97-2.10 (m, 2 H), 2.24 (m, 1 H), 4.09(m, 2 H), 4.92-4.97 (m, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 8.20 (*J* = 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.4, 35.0, 43.1, 64.9, 74.9, 123.9, 126.7, 147.5, 149.4; IR: 2922, 2858, 1519, 1346, 1070, 1048, 848, 747 cm^{-1}. HRMS (APCI) *m/z* calcd for $C_{11}H_{12}INO_3$ $(M+H)^+$ 333.9940, found 333.9957.

2-(4-Bromophenyl)-4-iodotetrahydro-*2H*-pyran (23b)



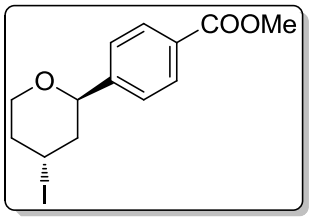
Colorless solid; M. P.: 74-76 ^{o}C; (139 mg, 76% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82 (dddd, *J* = 10.8, 10.8, 3.6 and 3.6 Hz, 1 H), 1.95-2.15 (m, 2 H), 2.10 (dm, J = 14.4 Hz, 1 H), 4.00-4.11(m, 2 H), 4.80 (dm, *J* = 10.8 Hz, 1 H), 4.90-4.93 (m, H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.46 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.1, 35.2, 43.0, 64.9, 75.2, 121.6, 127.9, 131.7, 141.0; IR: 2919, 2857, 1458, 1245, 1069, 1047, 818, 797 cm^{-1}. HRMS (APCI) *m/z* calcd for $C_{11}H_{12}BrIO$ $(M+H)^+$ 366.9194, found 366.9185.

4-Iodo-2-(3-nitrophenyl)tetrahydro-*2H*-pyran (23c)



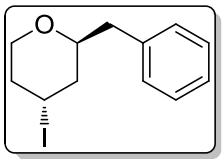
Brown color solid; M. P.: 82-84 ^{o}C; (124 mg, 75% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.84 (dddd, *J* = 10.8, 10.4, 4.0 and 3.6 Hz, 1 H), 1.96-2.03 (m, 2 H), 2.24 (m, 1 H), 4.08-4.11 (m, 2 H), 4.90-4.97 (m, 2 H), 7.52 (t, *J* = 7.6 Hz, 1 H), 7.67 (d, *J* = 7.6 Hz, 1 H), 8.13 (dt, *J* = 8.0 and 1.2 Hz, 1 H), 8.24 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.5, 35.0, 43.0, 64.9, 74.7, 121.1, 122.7, 129.5, 132.1, 144.2, 148.5; IR: 2917, 2859, 1530, 1348, 1070, 1048, 736, 708 cm^{-1}. HRMS (APCI) *m/z* calcd for $C_{11}H_{12}INO_3$ $(M+H)^+$ 332.9940, found 332.9953.

Methyl 4-(4-iodotetrahydro-*2H*-pyran-2-yl)benzoate (23d)



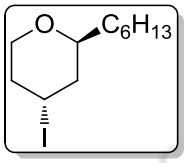
Colorless solid, M. P.: 93-95 ^{o}C; (147 mg, 85% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.83 (dddd, *J* = 11.2, 10.8, 3.6 and 3.2 Hz, 1 H), 1.95-2.05 (m, 2 H), 2.22 (m, 1 H), 3.91 (s, 3 H), 4.07-4.10 (m, 2 H), 4.89-4.96 (m, 2 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.46 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.0, 35.1, 43.0, 52.3, 64.9, 75.4, 125.9, 129.5, 129.9, 147.1, 167.1; IR: 2925, 1716, 1638, 1273, 1099, 1068, 1046, 964 cm^{-1}. HRMS (APCI) *m/z* calcd for $C_{13}H_{15}IO_3$ $(M+H)^+$ 347.0144, found 347.0156.

2-Benzyl-4-iodotetrahydro-*2H*-pyran (23e)



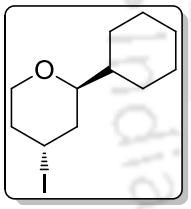
Yellowish oil; (118 mg, 78% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (dddd, *J* = 11.2, 10.4, 3.6 and 2.8 Hz, 1 H), 1.81-1.89 (m, 2 H), 1.97 (m, 1 H), 2.70 (dd, *J* = 14.0, and 6.0 Hz, 1 H), 2.90 (dd, *J* = 14.0, and 7.2 Hz, 1 H), 3.82-3.89 (m, 2 H), 4.04 (ddd, *J* = 12.0, 7.2, and 6.0 Hz, 1 H), 4.82(brm, 1 H), 7.19-7.24 (m, 3 H), 7.27-7.31 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.8, 35.5, 40.7, 42.0, 64.6, 74.3, 126.5, 128.5, 129.5, 138.3; IR: 2951, 2855, 1428, 1252, 1181, 1064, 1047, 751, 700 cm^{-1}. HRMS (APCI) *m/z* calcd for $C_{12}H_{15}IO$ $(M+H)^+$ 303.0246, found 303.0231.

2-Hexyl-4-iodotetrahydro-*2H*-pyran (23f):



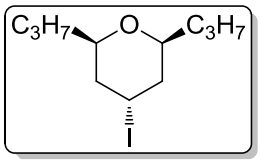
Colorless oil; (123 mg, 83% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.2 Hz, 3 H), 1.20-1.35 (m, 8 H), 1.37-1.44 (m, 2 H), 1.55 (dddd, *J* = 10.8, 10.0, 4.4 and 3.6 Hz, 1 H), 1.80-1.89 (m, 2 H), 1.98 (m, 1 H), 3.70-3.79 (m, 1 H), 3.82-3.89 (m, 2 H), 4.85(brm, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.7, 25.5, 29.5, 31.3, 31.9, 35.7 (2C), 41.2, 64.4, 73.7; IR: 2927, 2856, 1458, 1245, 1183, 1069, 855, 724 cm^{-1}. HRMS (APCI) *m/z* calcd for $C_{11}H_{21}IO$ $(M+H)^+$ 297.0715, found 297.0729.

2-Cyclohexyl-4-iodotetrahydro-*2H*-pyran (23g):



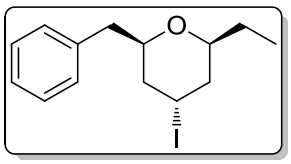
Pale yellow oil; (118 mg, 81% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94-1.05 (m, 2 H), 1.10-1.28 (m, 3 H), 1.34-1.44 (m, 1 H), 1.58 (dddd, *J* = 10.8, 10.0, 4.0 and 3.2 Hz, 1 H), 1.61-1.66 (m, 2 H), 1.70-1.77 (m, 2 H), 1.80-1.88 (m, 3 H), 1.99 (m, 1 H), 3.50 (ddd, *J* = 10.4, 2.4 and 2.0 Hz, 1 H), 3.81-3.91 (m, 2 H), 4.88 (quin, *J* = 2.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2, 26.3, 26.7, 28.9, 29.1, 32.0, 35.8, 38.2, 42.4, 64.6, 77.9, IR: 2924, 2852, 1449, 1243, 1188, 1070, 1054, 810 cm^{-1}. HRMS (APCI) *m/z* calcd for $C_{11}H_{19}IO$: $(M+H)^+$ 295.0559, found 295.0552.

4-Iodo-2,6-dipropyltetrahydro-*2H*-pyran (23h):



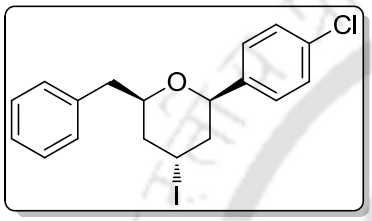
Pale yellow oil; (118 mg, 80% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, *J* = 7.2 Hz, 6 H), 1.28-1.60 (m, 10 H), 1.94 (dd, *J* = 14.8 and 2.4 Hz, 2 H), 3.74 (ddd, *J* = 10.4, 4.4 and 2.0 Hz, 2 H), 4.84 (quin, *J* = 2.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 19.0, 32.0, 37.8, 41.1, 73.4; IR: 2957, 2871, 1638, 1465, 1223, 1186, 1081, 1064, 820 cm^{-1}. HRMS (APCI) *m/z* calcd for $C_{11}H_{21}IO$ $(M+H)^+$ 297.0715, found 297.0722.

2-Benzyl-6-ethyl-4-iodotetrahydro-*2H*-pyran (**23i**):



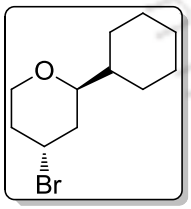
Pale yellow oil; (122 mg, 74% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.2 Hz, 3 H), 1.37-1.53 (m, 2 H), 1.58 (ddd, *J* = 14.0, 7.6 and 4.8 Hz, 1 H), 1.92-2.00 (m, 2 H), 2.69 (dd, *J* = 13.6, and 5.6 Hz, 1 H), 2.95 (dd, *J* = 13.6, and 3.2 Hz, 1 H), 3.67-3.72 (m, 2 H), 4.00-4.07 (m, 1 H), 4.82 (quin, *J* = 2.8 Hz, 1 H), 7.19-7.29 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.1, 28.6, 31.3, 40.4, 40.5, 42.1, 74.3, 75.0, 126.4, 128.3, 129.6, 138.6; IR: 2962, 2879, 1634, 1454, 1207, 1075, 1063, 752, 699 cm^{-1}. HRMS (APCI) *m/z* calcd for $C_{14}H_{19}IO$ $(M+H)^+$ 331.0559, found 331.0545.

2-Benzyl-6-(4-chlorophenyl)-4-iodotetrahydro-*2H*-pyran (**23j**):



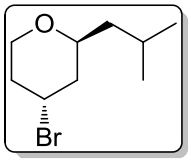
Colorless oil; (178 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (dddd, *J* =10.8, 10.4, 4.4 and 3.6 Hz, 1 H), 1.68 (dddd, *J* =11.2, 10.8, 4.0 and 3.2 Hz, 1 H), 2.00 (dd, *J* = 14.8 and 2.0 Hz, 1 H), 2.18 (dd, *J* = 14.8 and 2.0 Hz, 1 H), 2.83 (dd, *J* = 13.6 and 5.6 Hz, 1 H), 3.02 (dd, *J* = 14.0 and 6.4 Hz, 1 H), 4.22-4.28 (m, 1 H), 4.80-4.90 (m, 2 H), 7.20-7.33 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.1, 39.7, 42.0, 42.7, 74.7, 74.9, 126.5, 127.4, 128.4, 128.6, 129.7, 133.2, 138.1, 140.7; IR: 2922, 2854, 1492, 1065, 816, 699 cm^{-1}. HRMS (APCI) *m/z* calcd for $C_{18}H_{18}ClIO$ $(M+H)^+$ 413.0169, found 413.0188.

4-Bromo-2-cyclohexyltetrahydro-*2H*-pyran (**28a**):



Pale yellow oil; (80 mg, 65% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95-1.06 (m, 2 H), 1.09-1.29 (m, 4 H), 1.32-1.41 (m, 1 H), 1.58 -1.69 (m, 2 H), 1.71-1.76 (m, 2 H), 1.80 (dddd, *J* = 11.2, 10.8, 3.6 and 3.2 Hz, 1 H), 1.87 (m 1 H), 1.99 (m, 1 H), 2.03-2.12 (m, 1 H), 3.56 (ddd, *J* = 8.8, 7.2 and 1.6 Hz, 1 H), 3.83-3.96 (m, 2 H), 4.75 (quin, *J* = 2.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3, 26.4, 26.7, 28.8, 29.0, 34.7, 37.2, 42.6, 51.3, 63.3, 76.5; IR: 2924, 2853, 1449, 1224, 1191, 1072, 1029, 809 cm^{-1}. HRMS (APCI) *m/z* calcd for $C_{11}H_{19}BrO$ $(M+H)^+$ 247.0698, found 247.0692.

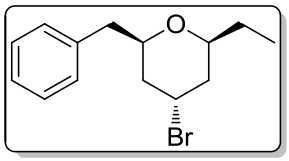
4-Bromo-2-isobutyltetrahydro-*2H*-pyran (**28b**):



Colorless oil; (78 mg, 70% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (d, *J* = 6.4 Hz, 6 H), 1.09-1.16 (m, 1 H), 1.40-1.48 (m, 1 H), 1.68–1.77 (m, 2 H), 1.81-1.96 (m, 2 H), 2.01-2.10 (m, 1 H), 3.79-3.94 (m, 3 H), 4.68 (quin, *J* = 2.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 23.3, 24.4, 34.5, 40.5, 44.9, 50.8, 63.1,

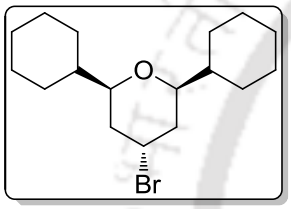
70.5; IR: 2956, 2867,1459, 1235, 1189, 1068, 1020, 790 cm^{-1}. HRMS (APCI) *m/z* calcd for $C_9H_{17}BrO$ $(M+H)^+$ 221.0541, found 221.0552.

2-Benzyl-4-bromo-6-ethyltetrahydro-*2H*-pyran (**28c**):



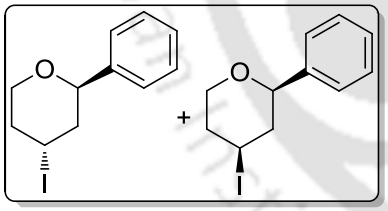
Pale yellow oil; (82 mg, 58% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.6 Hz, 3 H), 1.45 (q, *J* = 7.6 Hz, 1 H), 1.54 (q, *J* = 7.2 Hz, 1 H), 1.69 (dddd, *J* = 11.2, 10.8, 3.6 and 3.2 Hz, 2 H), 1.95 (m, 2 H), 2.94 (dd, *J* = 14.0 and 6.0 Hz, 1 H), 2.66 (dd, *J* = 14.0 and 6.8 Hz, 1 H), 3.73 (ddd, *J* = 11.6, 6.8 and 4.8 Hz, 1 H), 4.08 (ddd, *J* = 11.2, 6.8 and 5.2 Hz, 1 H), 4.71 (quin, *J* = 2.8 Hz, 1 H), 7.18-7.30 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.1, 28.8, 39.4 (2C), 42.2, 51.1, 73.0, 73.6, 126.3, 128.3, 129.6, 138.5; IR: 2962, 2864,1454, 1242, 1189, 1076, 1031, 752, 700 cm^{-1}. HRMS (APCI) *m/z* calcd for $C_{14}H_{19}BrO$ $(M+H)^+$ 283.0698, found 283.0704.

4-Bromo-2,6-dicyclohexyltetrahydro-*2H*-pyran (**28d**):



Colorless solid, M. P.: 62-64 ^{o}C; (98 mg, 60% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92-1.05 (m, 4 H), 1.10-1.28 (m, 6 H), 1.30-1.39 (m, 2 H), 1.58-1.79 (m, 10 H), 1.95-2.07 (m, 4 H), 3.47-3.52 (m, 2 H), 4.79 (quin, *J* = 2.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2, 26.3, 26.8, 29.0, 29.3, 37.5, 42.8, 52.4, 76.7; IR: 2924, 2851,1445, 1262, 1094, 1063, 741, 718 cm^{-1}. HRMS (APCI) *m/z* calcd for $C_{17}H_{29}BrO$ $(M+H)^+$ 329.1480, found 329.1465.

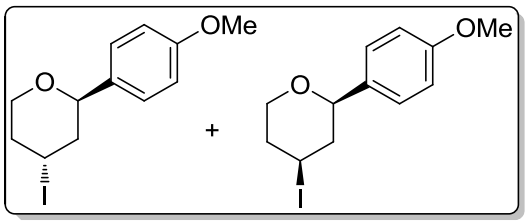
4-Iodo-2-phenyltetrahydro-*2H*-pyrans (**26a** & **27a**)*:*



Pale yellow oil; (107 mg, 74% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89 (dddd, *J* =10.8, 10.8, 4.0 and 3.6 Hz, 1 H), 1.97 (ddd, *J* =11.2, 4.0, and 3.6 Hz, 1 H), 2.16-2.28 (m, 1 H), 2.30-2.40 (m, 1 H), 2.56 (ddd, *J* = 13.2, 2.0 and 2.0 Hz, 0.5 H), 3.59 (ddd, *J* = 11.6, 10.8, and 3.2 Hz, 0.5 H), 4.00 (dddd, *J* = 11.6, 9.2, 3.6 and 2.0 Hz, 0.5 H), 4.02-4.11 (ddd, *J* = 14.4, 12.0 and 5.2 Hz, 0.5 H), 4.32 (dd, *J* = 11.2, and 2.0 Hz, 0.5 H), 4.40 (dddd, *J* = 11.6, 10.4, 4.8 and 4.4 Hz, 0.5 H), 4.83 (dd, *J* = 10.8, and 2.0 Hz, 0.5 H), 4.93 (quin., *J* = 3.2 Hz, 0.5 H), 7.25-7.35 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 30.6, 35.3, 39.7, 42.9, 47.7, 64.9, 69.6, 75.8, 81.4, 125.9, 126.1, 127.8, 128.0, 128.6; IR: 2954, 2853, 1451, 1245, 1069, 1044, 752, 698 cm^{-1}. HRMS (APCI) *m/z* calcd for $C_{11}H_{13}IO$ $(M+H)^+$ 289.0089, found 289.0074.

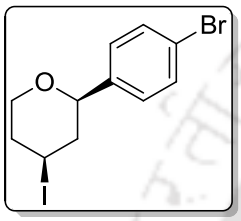
4-Iodo-2-(4-methoxyphenyl)tetrahydro-*2H*-pyran (**26b** & **27b**)*:*

Pale yellow oil; (128 mg, 80% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89 (dddd, *J* =11.2, 10.4, 4.4 and 3.2 Hz, 1 H), 1.94-1.99 (m, 1 H), 2.16-2.26 (m, 1 H), 2.28-2.40 (m, 1 H), 2.52 (ddd, *J* = 13.2, 2.4 and 2.0 Hz, 0.5 H), 3.58 (ddd, *J* = 12.0, 10.8, and 3.2 Hz, 0.5 H), 3.79 (s, 3



H), 4.00 (dddd, *J* = 11.6, 11.2, 3.2 and 2.8 Hz, 0.5 H), 4.02-4.11 (ddd, *J* = 14.4, 12.0 and 4.4 Hz, 0.5 H), 4.27 (dd, *J* = 11.2, and 2.0 Hz, 0.5 H), 4.40 (dddd, *J* = 12.4, 12.0, 5.6 and 4.4 Hz, 0.5 H), 4.83 (dd, *J* = 10.8, and 2.0 Hz, 0.5 H), 4.93 (quin., *J* = 3.2 Hz, 0.5 H), 6.87 (d, *J* = 8.8 H, 2 H), 7.24 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 30.8, 35.2, 39.7, 42.7, 47.6, 55.4, 64.9, 69.6, 75.4, 81.0, 113.9, 127.2, 127.5, 133.5, 134.0, 159.2, 159.3; IR: 2954, 2850, 1462, 1247, 1071, 1035, 828 cm^{-1}. HRMS (APCI) *m/z* calcd for $C_{12}H_{15}IO_2$ $(M+H)^+$ 319.015, found 319.0204.

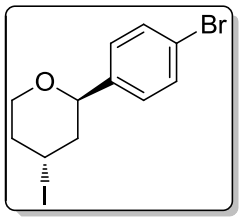
2-(4-Bromophenyl)-4-iodotetrahydro-*2H*-pyran (22b):

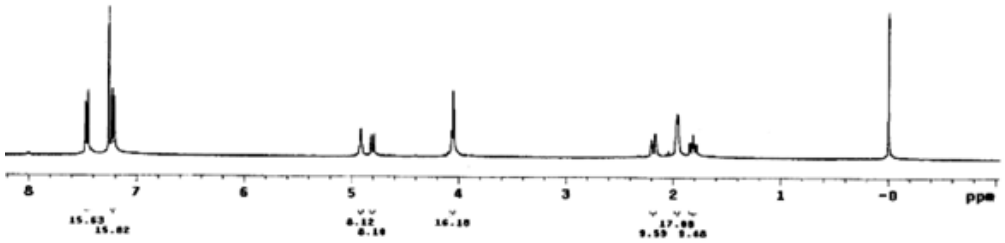


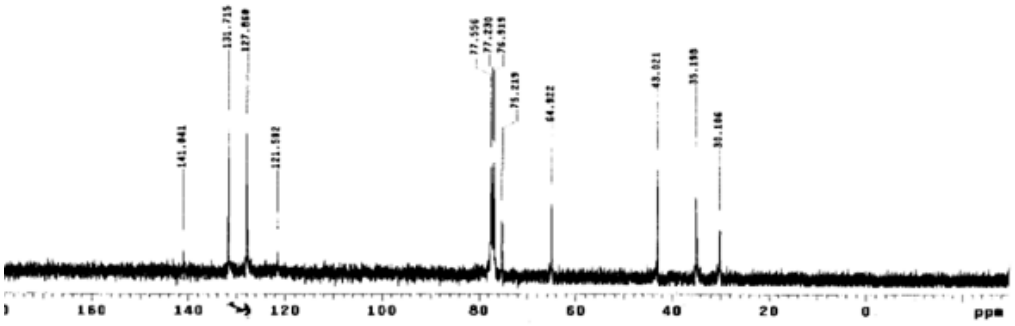
Colorless solid; M. P.: 82-84 ^{o}C; (70 mg, 38% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.19 (dd, *J* = 12.8 and 11.2 Hz, 1 H), 2.30-2.36 (m, 2 H), 2.53 (dddd, *J* = 12.8, 2.4, 2.0 and 1.6 Hz, 1 H), 3.55-3.62 (m, 1 H), 4.00 (dddd, *J* = 11.2, 3.6, 3.2 and 2.8 Hz, 1 H), 4.29 (dd, *J* = 10.8 and 2.0 Hz, 1 H), 4.34-4.42 (m, 1 H), 7.20 (d, *J* = 8.8 Hz, 2 H), 7.46 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.9, 39.6, 47.6, 69.6, 80.7, 121.8, 127.6, 131.8, 140.4; IR: 2928, 2854, 1489, 1231, 1068, 1042, 817 628 cm^{-1}.HRMS (APCI) *m/z* calcd for $C_{11}H_{12}BrIO$ $(M+H)^+$ 366.9194, found 366.9187.

2.7. Selected Spectra of tetrahydropyrans

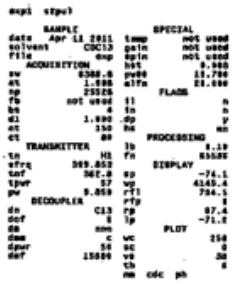
^{1}H and ^{13}C spectra of 2-(4-bromophenyl)-4-iodotetrahydro-*2H*-pyran (23b)

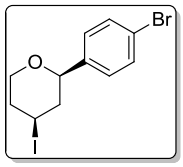


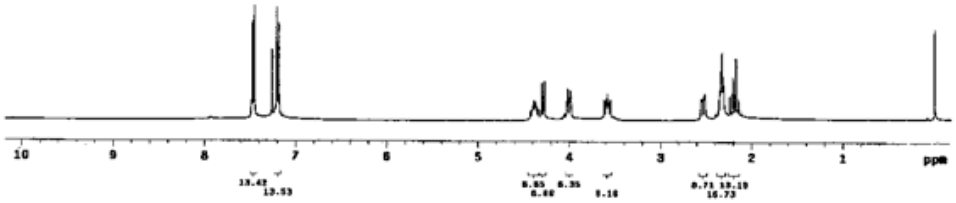


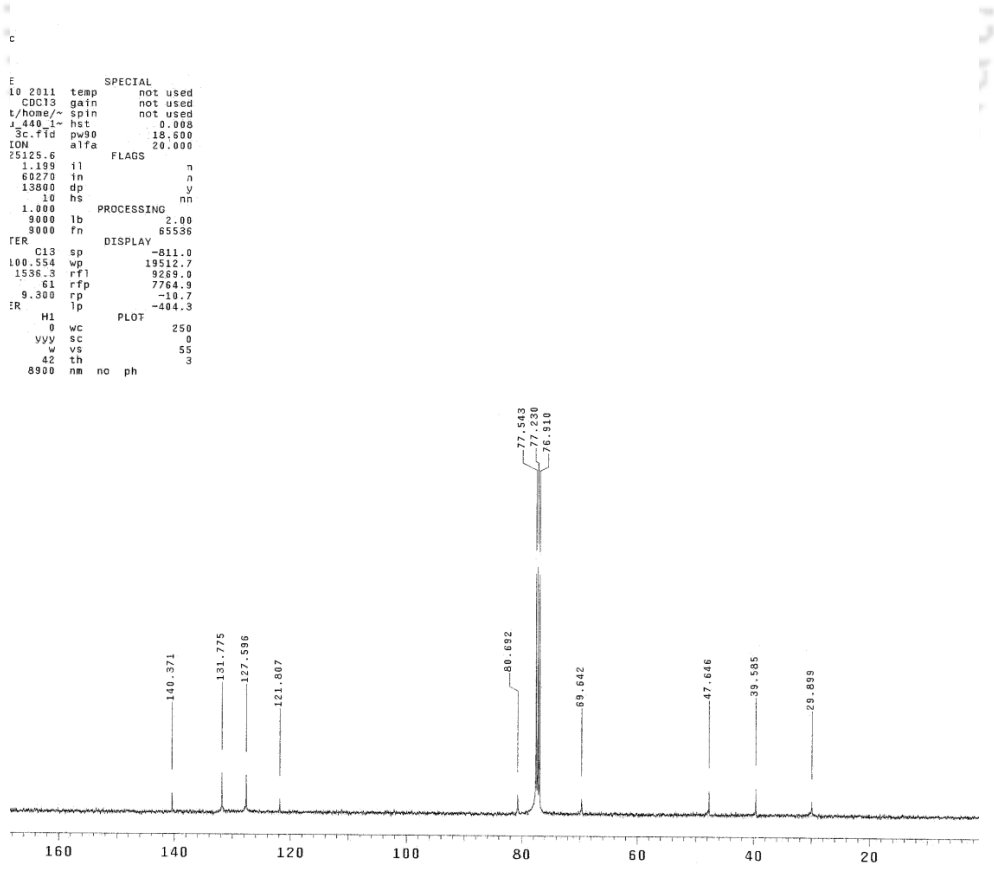


^{1}H and ^{13}C spectra of 2-(4-bromophenyl)-4-iodotetrahydro-*2H*-pyran (22b)

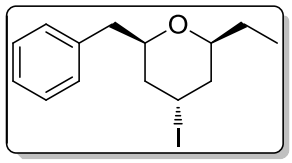


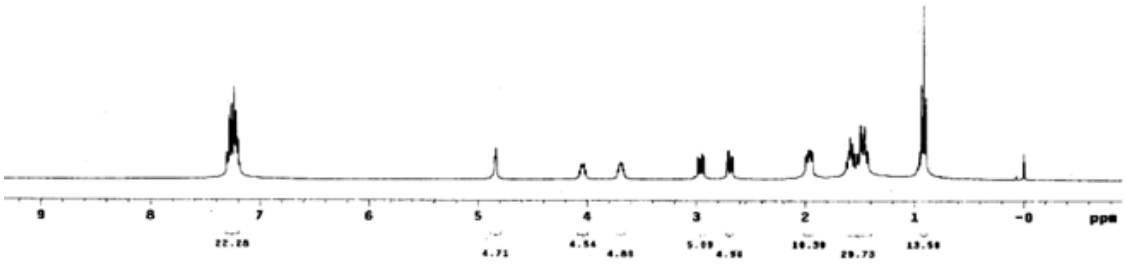


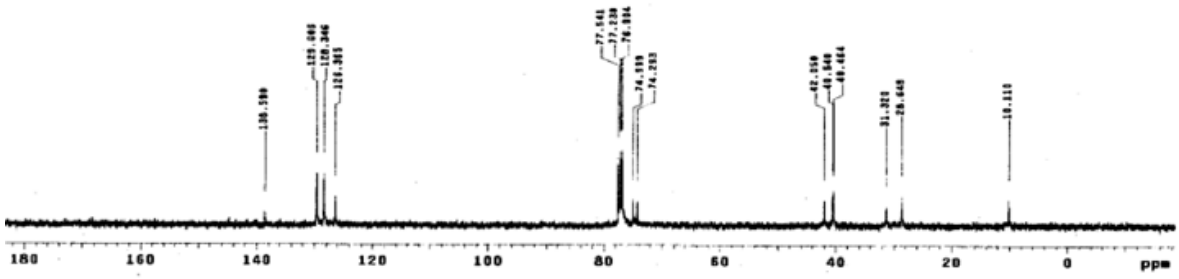




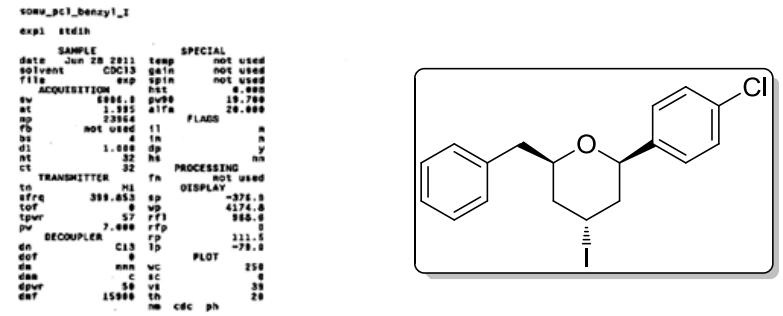
^{1}H and ^{13}C spectra of 2-benzyl-6-ethyl-4-iodotetrahydro-*2H*-pyran (23i)

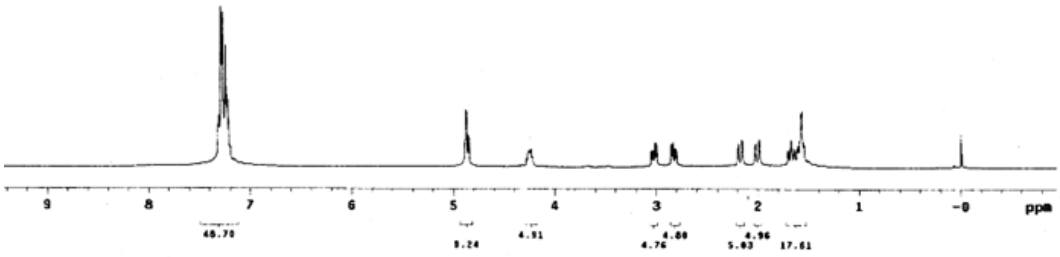


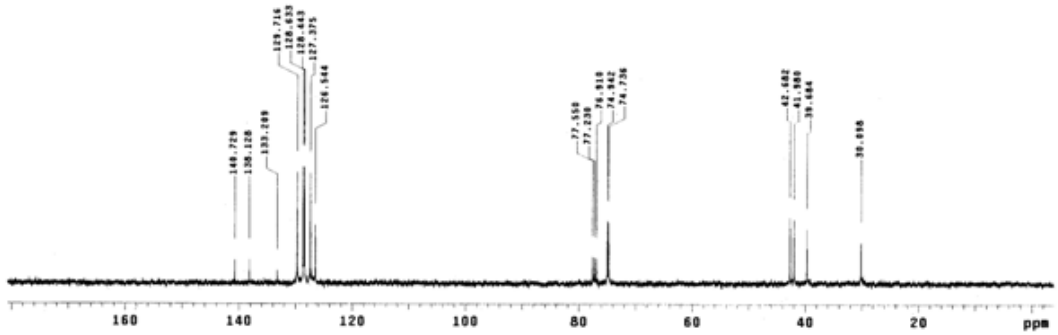




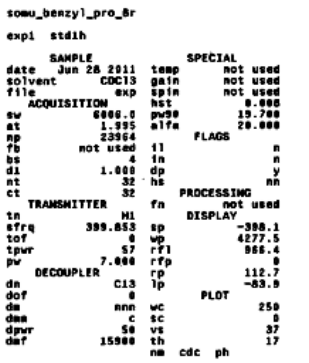
^{1}H and ^{13}C spectra of 2-benzyl-6-(4-chlorophenyl)-4-iodotetrahydro-*2H*-pyran (23j)

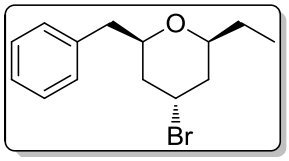


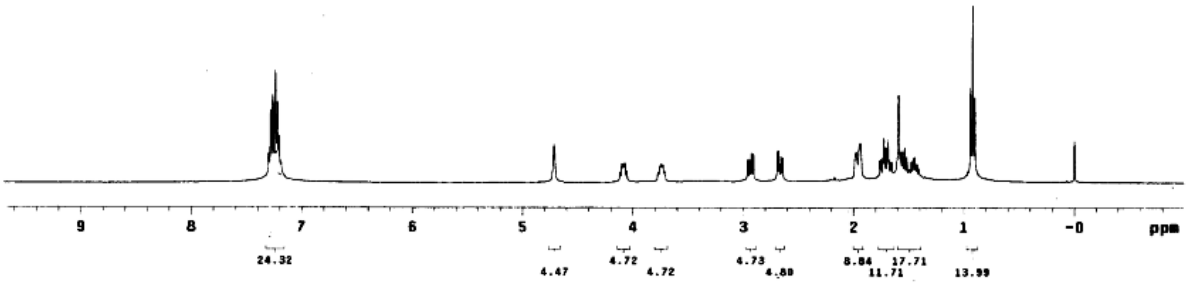


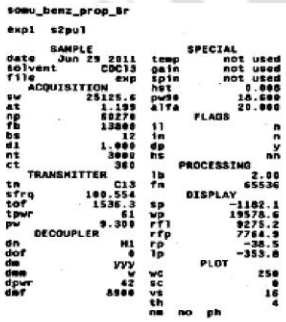


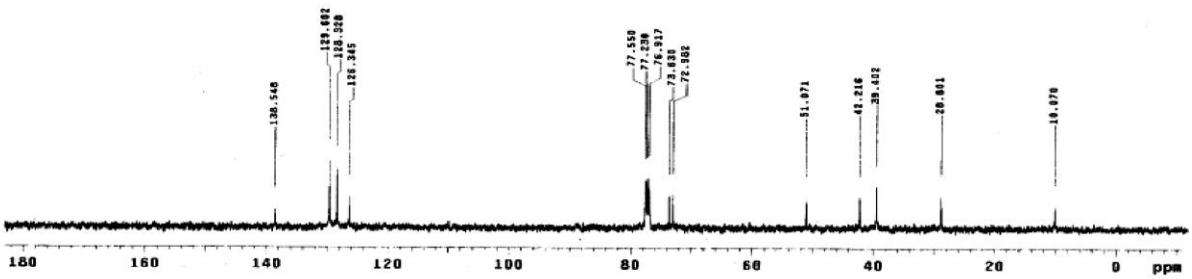
^{1}H and ^{13}C spectra of 2-Benzyl-4-bromo-6-ethyltetrahydro-*2H*-pyran (28c)



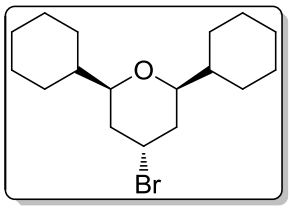


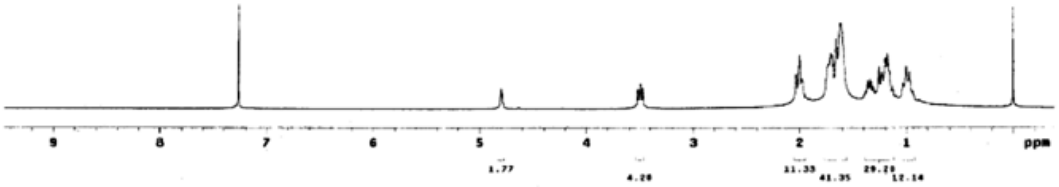


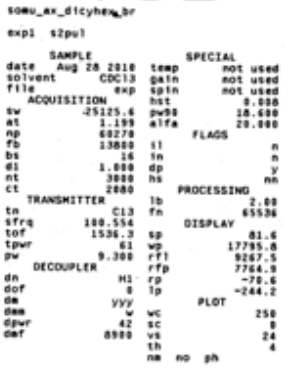


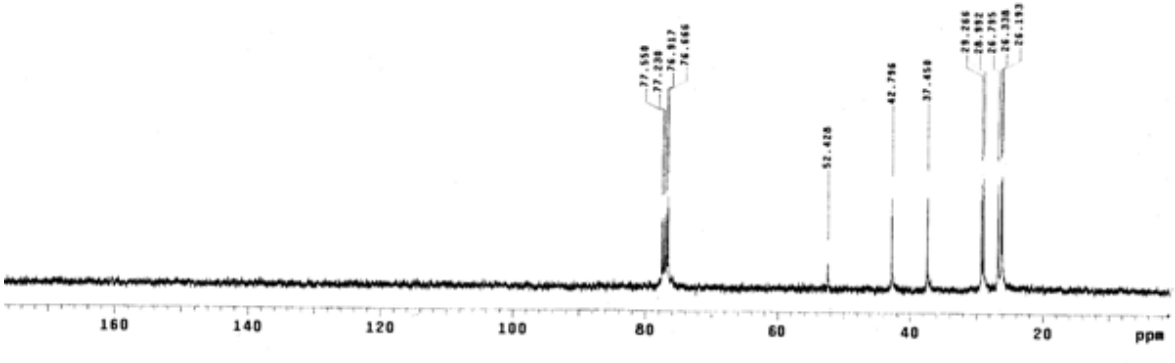


^{1}H and ^{13}C spectra of 4-bromo-2,6-dicyclohexyltetrahydro-*2H*-pyran (28d)









2.8. Crystal Parameters

The crystal parameters of compound **28d**

Parameters	**28d**-CCDC 792987
Formula	C_{17} H_{29} Br O
Formula weight	329.30
T/K	296(2)
Crystal system	Monoclinic
Space group	P2(1)/n
a/Å	5.3938(5)
b/Å	22.729(2)
c/Å	13.7330(15)
α/°	90.00
β/°	97.254(7)
γ/°	90.00
V/Å^3	1670.1(3)
Z	4
Abs. Coeff./mm^{-1}	2.454
Abs. Correction	Multi-Scan
GOF on F^2	0.847
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0443
	wR2 = 0.1200
R indices [all data]	*R1* = 0.1160
	wR2 = 0.1609

CHAPTER 3

Diastereoselective Synthesis of Substituted Tetrahydrofurans *via* Prins Cyclization of Enol Ethers

3.1. Importance and applications of tetrahydrofurans

Tetrahydrofuran units are essential part of many naturally occurring and biologically active molecules including the group of cytotoxic polyethers,[1] polyether antibiotics,[2] antitumor acetogenins,[3] lignans[4] etc. For example the marine natural product *trans*-kumausyne (**1**) is a secondary metabolite produced by red algae of genus *Laurencia*.[5] Pamamycins are sixteen membered macrodiolides containing two or three *cis* 2,5-disubstituted tetrahydrofuran units within the macrocyclic framework. They were isolated from *Streptomyces alboniger* and *S. aurantiacus*[6] and display autoregulatory, antibiotic, and anionophoric activities.[7] Pamamycin-607 (**2**) is especially interesting for its potent activity against gram-positive bacteria including multiple antibiotic resistant strains of *Mycobacterium tuberculosis* as well as against phytopathogenic fungi. The mycotoxin (-)-citreoviridine (**3**) isolated from *Penicillum citreoviride* is a potent inhibitor of the soluble mitochondrial ATPase.[8] The ionophoric macrolide antibiotic nonactin, possesses antitumor activity both against mammalian cell lines *in-vitro* and against Crocker sarcoma 180 in studies with mice.[9] It was isolated from a variety of streptomyces cultures, and consists of two subunits of (+)-nonactic acid and two subunits of (-)-nonactic acid arranged in an alternating order.

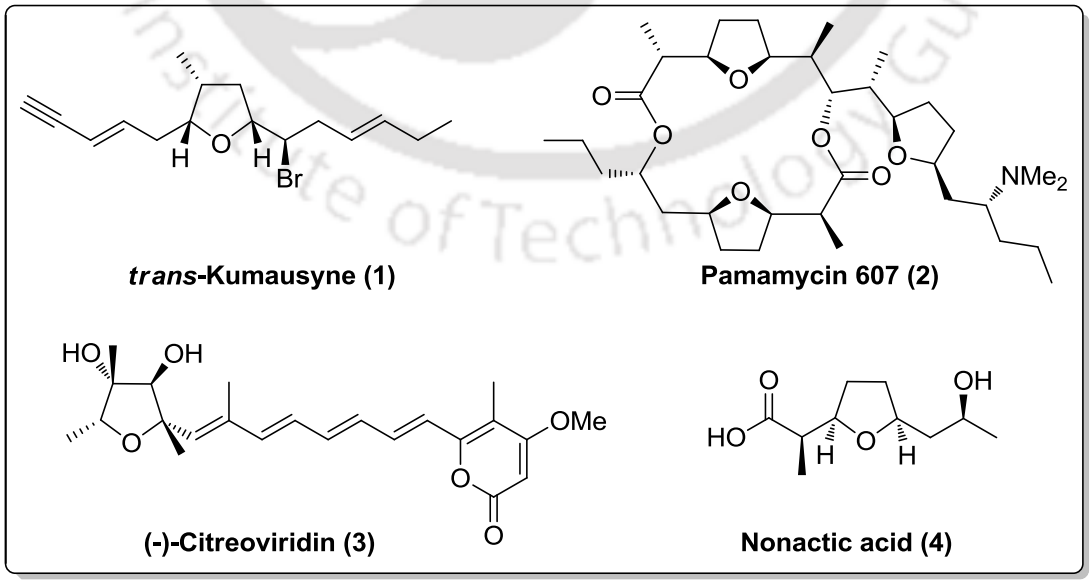
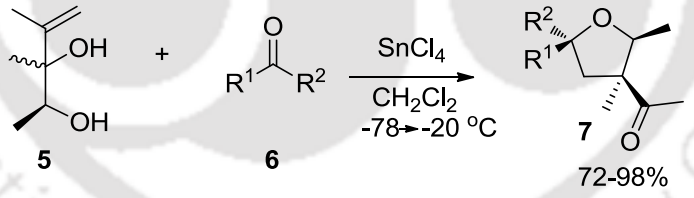


Figure 3.1.1. *Some important biological active molecule containing tetrahydrofuran as a substructure.*

3.2. An overview of relevant synthetic methods

The stereoselective synthesis of tetrahydrofurans (THF), because of their ubiquitous nature in many biological processes, has been the subject of extensive investigation. Therefore, an abundant literature deals with numerous synthetic strategies to construct mono- or poly-THF skeletons, namely, intramolecular cyclization of 4-alkenols,[10] 3-alkenols,[11] oxidative cyclization of 1,5 dienes,[12] [3+2] cycloaddition,[13] radical cyclization of alkoxy acrylates,[14] ring expansion of oxetanes,[15] Prins cyclization[17] etc. These methods have their own merits and demerits but some of them suffer from diastereoselectivity. Prins cyclization is an important reaction for the synthesis of tetrahydropyrans and tetrahydrofurans because of its diastereoselectivity.[10] Although there are many reported methods for the synthesis of di- and tetrahydropyrans *via* C-C bond-forming Prins cyclization,[16a-c] pure Prins-type cyclization has rarely been used for the synthesis of tetrahydrofurans,[17,18] though Prins-type cylcization followed by pinacol rearrangement gives tetrahydrofurans.[19]

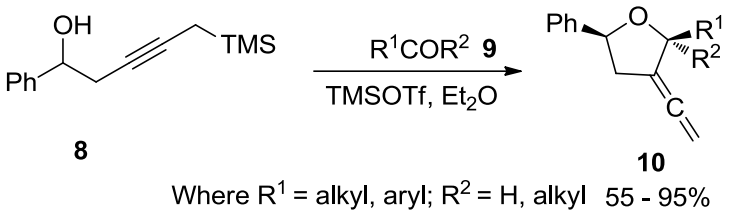
Wurtster and co-workers described a highly stereoselective method for the synthesis of 2,2-disubstituted 4-acyl tetrahydrofuran **7**, involving Prins-pinacol condensation of allylic diols **5** with unsymmetrical ketones **6** mediated by $SnCl_4$ *(Scheme 3.2.1)*. The reaction proceeds via the Prins cyclization of the acetal derived from the allylic diol and the ketone and subsequent pinacol rearrangement of the tetrahydropyranyl cation gives the tetrahydrofuran product.[19c]



R^1 = alkyl, cycloalkyl, aryl, $-CH_2OMe$, $-CH_2Br$. R^2 = alkyl

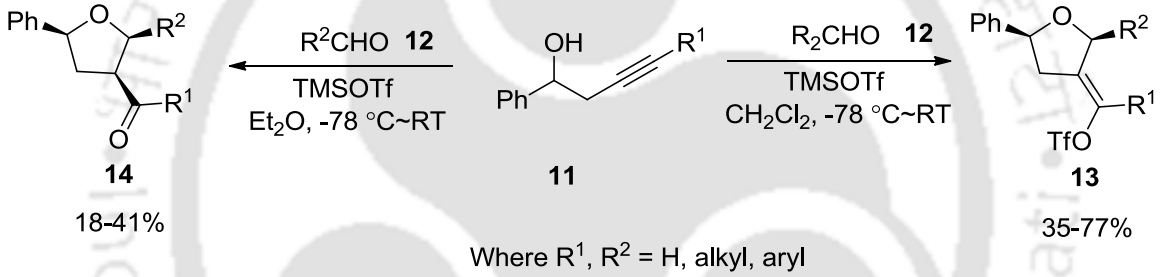
Scheme 3.2.1

Cho *et al.* reported a novel methodology for stereoselective synthesis of *cis*-disubstituted tetrahydrofurans **10** bearing an allenyl group at the 3-position *via* TMSOTf-mediated Prins-type cyclization of terminally substituted homopropargylic alcohols **8** and aldehydes **9** (*Scheme 3.2.2)*[17a]. In most cases, various aldehydes provided the corresponding product in moderate to good yields with excellent selectivity.



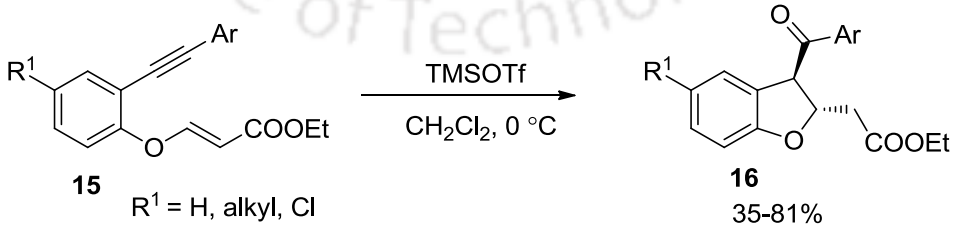
Scheme 3.2.2

Cho *et al.* further explored the methodology with homopropargyl alcohols **11** having alkyl and aryl substituent at the alkyne terminus. The reaction proceeded *via* the formation of oxocarbenium ion which underwent Prins-type cyclization giving exocyclic vinyl cation. The exocyclic vinyl cation was trapped as a vinyl triflate **13** when dichloromethane was used as a solvent, whereas in ethereal solution the vinyl cation underwent hydrolysis to give the all *cis*-2,3,5-trisubstituted ketone product **14** (*Scheme 3.2.3).*[17b-c]



Scheme 3.2.3

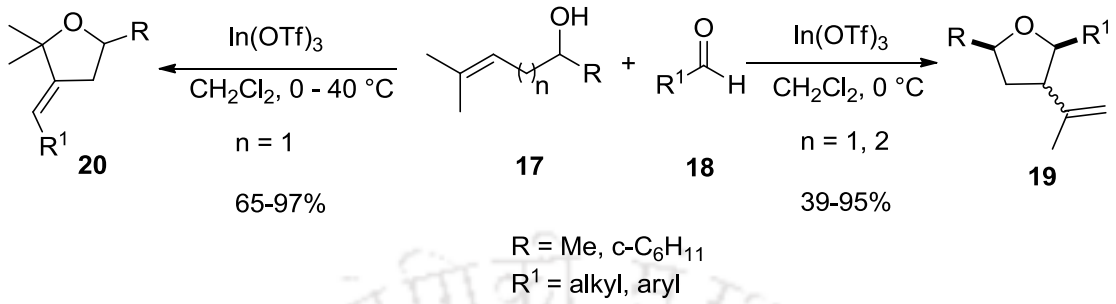
Gharpure reported a stereoselective method for the synthesis of *trans*-2,3-disubstituted dihydrobenzofuran derivatives **16** using TMSOTf-mediated intramolecular alkyne Prins type cyclization of **15** derived from *o*-alkynyl phenol at low temperature (*Scheme 3.2.4).*[18]



Scheme 3.2.4

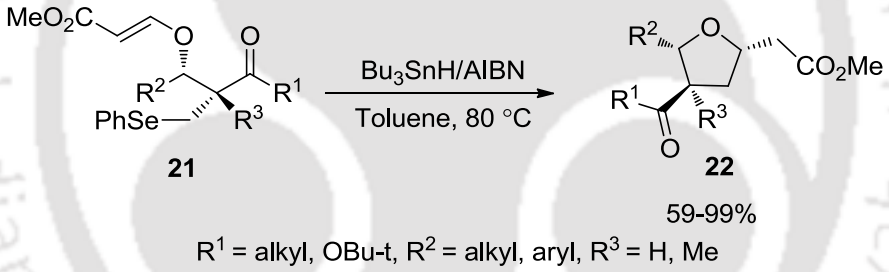
Loh and co-workers have developed a facile method for the synthesis of tetrahydrofurans and pyrans **19** from the reaction of aldehyde **18** and unsaturated alkenes having γ and δ hydroxy groups **17** promoted by $In(OTf)_3$ *via* intramolecular (3,5) oxonium-ene reaction at 0 ºC *(Scheme*

3.2.5). By increasing the reaction temperature from 0 to 40 ºC, they observed the formation of exocyclic isomer **20** as a major product.[20]



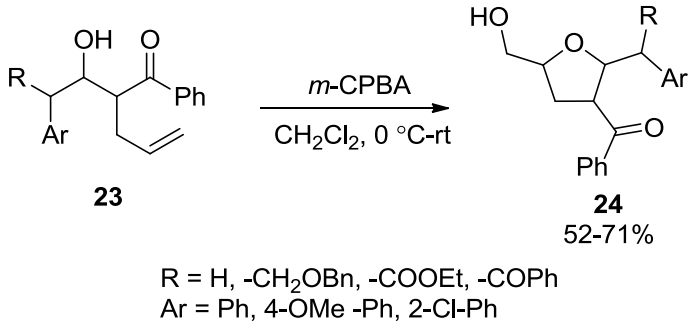
Scheme 3.2.5

Kamimura and co-workers have described a stereoselective procedure for the construction of multisubstituted tetrahydrofurans **22** utilizing the radical cyclization of alkoxyacrylate **21** mediated by Bu_3SnH/AIBN system at 80 ºC (*Scheme 3.2.6)*.[21]



Scheme 3.2.6

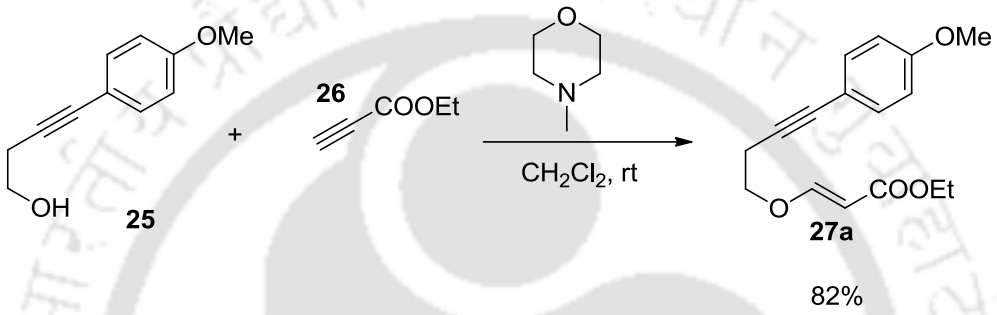
Yadav *et al.* have reported an oxidative ring closure methodology for the synthesis of 2-hydroxymethyl tetrahydrofurans **24** involving the *β*-hydroxyketone **23** as starting material using *m*-CPBA as oxidant *(Scheme 3.2.7)*.[22] However this methodology was found to be inferior when the diasteroselectivity of the product is considered.



Scheme 3.2.7

3.3. Present work

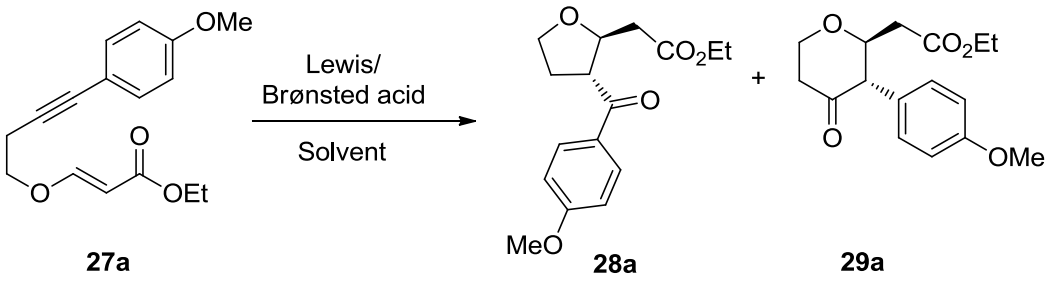
Recently, Saikia and co-workers developed a methodology for the synthesis of *cis*-2,6-dihydropyrans *via* Prins cyclization of enol ether.[23] Here enol ethers having terminal double bond was treated with trimethylsilyl trifluoromethanesulfonate (TMSOTf) to give *cis*-2,6-dihydropyrans *via* Prins cyclization reaction. Considering the earlier reports and the present work of our own group, an attempt was made to cyclize enol ethers having alkyne group. On that account enol ether **27a** was prepared from the homopropargylic alcohol **25** using Michael addition of alcohol to ethyl propiolate **26**.



Scheme 3.3.1

But on treatment with TMSOTf in dichloromethane at 0 °C to room temperature the reaction of enol ether **27a** ended with a black material. Several Lewis and Brønsted acids were screened and finally it was found that 0.2 equivalents of indium triflate ($In(OTf)_3$) in dichloromethane gave some product in 40% yield. The product was characterized as ethyl 2-(3-(4-methoxybenzoyl) tetrahydrofuran-2-yl) acetate **28a** by NMR spectroscopy and mass spectrometry (*Table 3.3.1*). The yield was increased by increasing the amount of $In(OTf)_3$ to 0.5 equivalents. Increasing the amount to 1.0 equivalent also resulted in same yield. It was observed that $Cu(OTf)_2$ and $BF_3{\cdot}Et_2O$ also resulted in the desired product but gave 28 and 35% yield, respectively. $Zn(OTf)_2$ was found to be unreactive. Brønsted acid TfOH gave two inseparable products tetrahydrofuran **28a** and tetrahydropyran **29a** in 42% overall yield with a ratio of 1:3. On the other hand, CSA was found to be inefficient for the reaction. Similarly, $BF_3{\cdot}Et_2O$ in benzene produced tetrahydrofuran **28a** and tetrahydropyran **29a** in 40% overall yield with a ratio of 1:1. $CeCl_3{\cdot}7H_2O$ was also found to be inefficient. The reaction with $FeCl_3$ was completed within two hours producing **28a** in 45% yield along with some decomposed products. $InCl_3$ gave **28a** in 28% and starting material **27a** was recovered in 50%.

Table 3.3.1.Optimization of the reaction

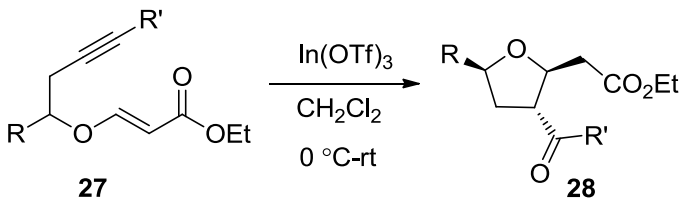


27a **28a** **29a**

Entry	Lewis/Brønsted acid (equiv.)	Time (h)	Solvent	% Yield[a] **28** & **29**
1	TMSOTf (1.1)	24	CH_2Cl_2	d
2	$In(OTf)_3$ (0.2)	24	CH_2Cl_2	40 (**28a**)
3	$In(OTf)_3$ (0.5)	12	CH_2Cl_2	60 (**28a**)
4	$In(OTf)_3$ (1.0)	12	CH_2Cl_2	60 (**28a**)
5	$BF_3{\cdot}Et_2O$ (1.1)	24	CH_2Cl_2	35 (**28a**)
6	$BF_3{\cdot}Et_2O$ (1.1)	24	Benzene	30 (**28a**+**29a**)[b]
7	TfOH (1.1)	24	CH_2Cl_2	42 (**28a**+**29a**)[b]
8	$CeCl_3.7H_2O$	24	CH_2Cl_2	n
9	$Cu(OTf)_2$ (0.2)	24	CH_2Cl_2	28 (**28a**)
10	$Zn(OTf)_2$ (1)	30	CH_2Cl_2	n
11	CSA (1)	10	CH_2Cl_2	N
12	$FeCl_3$ (1)	2	CH_2Cl_2	45 (**28a**)[e]
13	$InCl_3$ (1)	24	CH_2Cl_2	28 (**28a**)

[a]Yields refer to isolated yield. The compounds were characterized by IR, NMR and Mass spectrometry. [b]Ratio is determined by ^{1}H NMR. d = decomposed product. n = No reaction

The indium triflate-mediated Prins-cyclization reaction of alkyne enol ether is generalized as shown in (*Scheme 3.3.2*).

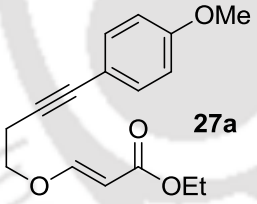
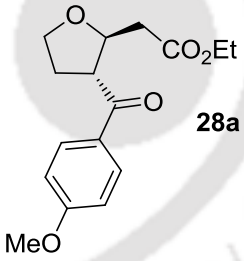
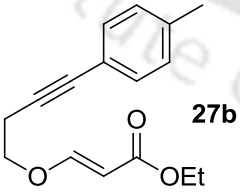
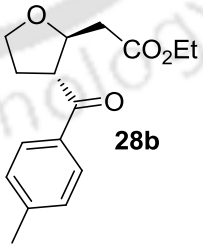
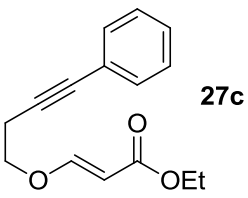
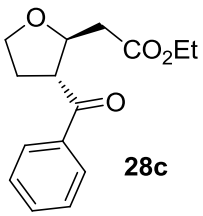


27 **28**

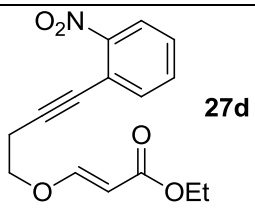
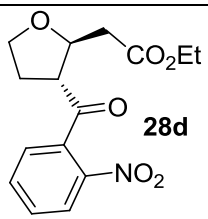
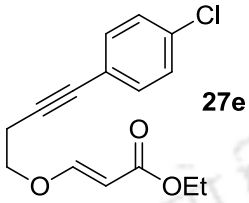
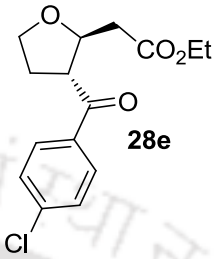
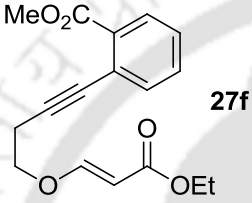
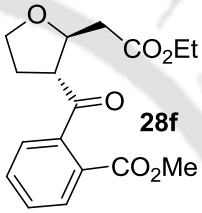
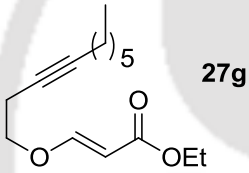
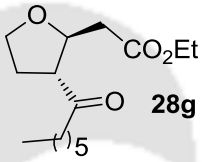
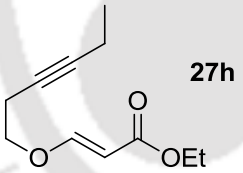
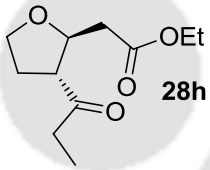
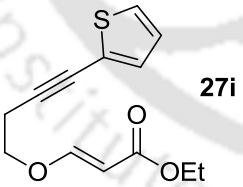
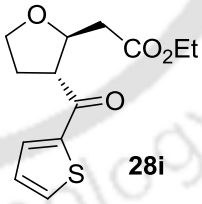
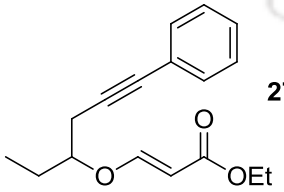
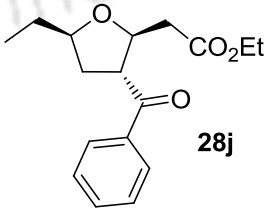
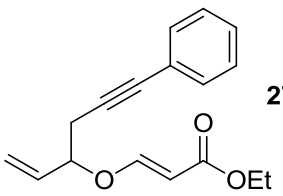
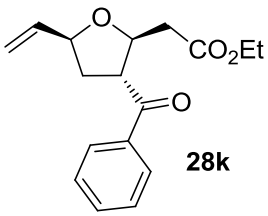
Scheme 3.3.2

In order to prove its general applicability, enol ethers **27b**-**27p** were synthesized similar to that of **27a** and subjected to optimized reaction condition (*Table 3.3.2*). It was observed from the *Table 3.3.2* that ethers having aromatic substituted alkyne side chains gave moderate to good yields. On the other hand, ethers with aliphatic substituted alkynes (entries 7-8) gave low yields. Electron withdrawing groups on the aromatic ring of the alkyne side chain play a role in the reactivity of the substrates. Electron withdrawing groups on the aromatic ring reduce the reactivity of the substrate **27e** (entry 5). Substrates **27d** and **27f** having strong electron withdrawing groups on aromatic ring, such as $-NO_2$ and -COOMe (entries 4 and 6) were decomposed under these reaction conditions. On the other hand, electron donating groups on aromatic ring enhance the reactivity (entries 2,3). This might be due to the better stabilization of carbocation **B** (*Scheme 3.3.3*) by electron rich aromatic ring and destabilization of the same carbocation by electron deficient aromatic ring. Aliphatic substituted substrates (entries 7-8) gave 21 and 30% yields, respectively, which indicate that carbocation **B** is less stabilized by alkyl groups than the electron rich aromatic groups at the alkyne terminus. It was observed that 1-substituted enol ethers (entries 10-16) gave tetrahydrofuran in good yields.

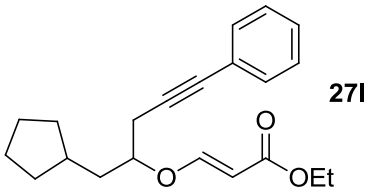
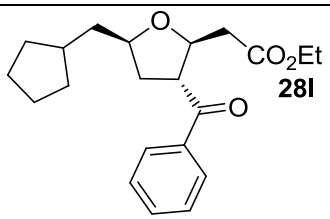
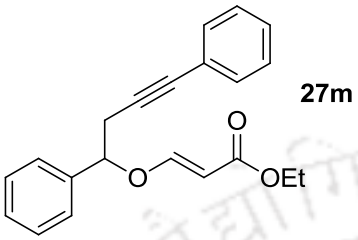
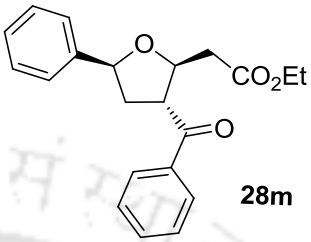
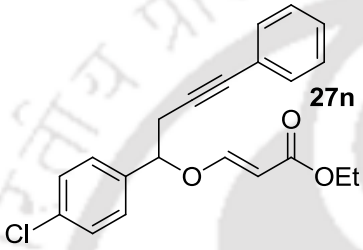
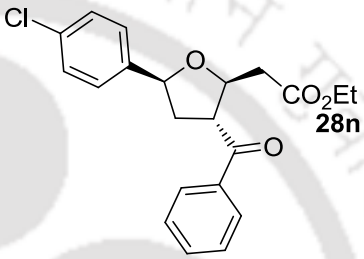
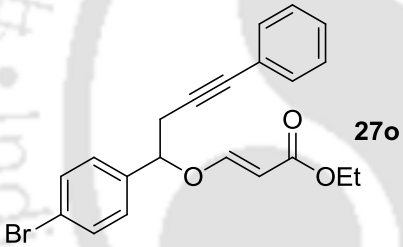
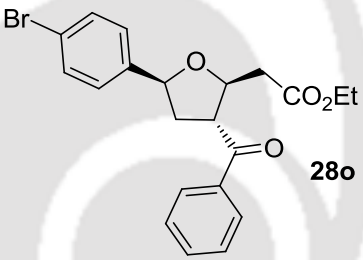
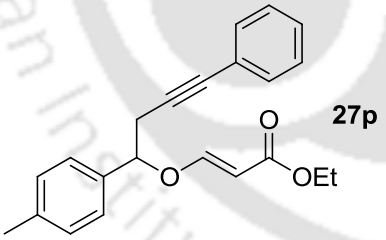
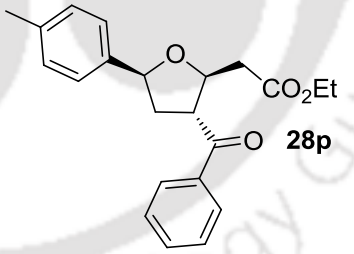
Table 3.3.2. Synthesis of substituted tetrahydrofuran

Entry	Acrylyl enol ether **27**	Product **28**	Yield (%)[a]
1	 **27a**	 **28a**	60
2	 **27b**	 **28b**	56
3	 **27c**	 **28c**	54

Continued……..

Entry	Acrylyl enol ether **27**	Product **28**	Yield (%)[a]
4	 **27d**	 **28d**	0[d]
5	 **27e**	 **28e**	45
6	 **27f**	 **28f**	0[d]
7	 **27g**	 **28g**	21
8	 **27h**	 **28h**	30
9	 **27i**	 **28i**	67
10	 **27j**	 **28j**	84
11	 **27k**	 **28k**	63

Continued……..

Entry	Acrylyl enol ether **27**	Product **28**	Yield (%)[a]
12	 **27l**	 **28l**	63
13	 **27m**	 **28m**	92
14	 **27n**	 **28n**	71
15	 **27o**	 **28o**	72
16	 **27p**	 **28p**	81

[a]Yield refers to isolated yield. The compounds are characterized by IR, ^{1}H, ^{13}C NMR and mass spectrometry. d = Decomposed product.

The stereochemistry of the product was determined by nOe of compound **28o**, which was further confirmed by X-ray crystallographic analysis.[24] There was a strong nOe between 2C-H and 5C-H protons, which indicates that substituents at 2 and 5 positions are *cis* to each other. The reaction is highly diastereoselective, which was determined from ^{1}H and ^{13}C NMR analysis of crude compound (*Figure 3.3.1).*

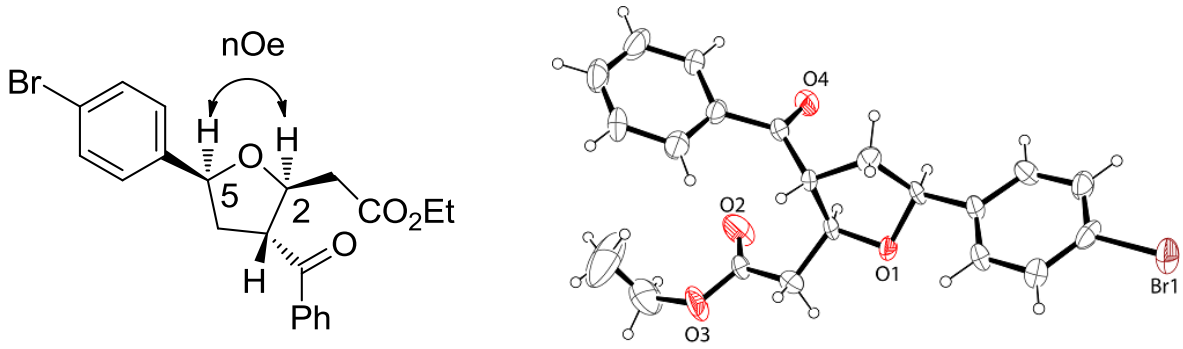
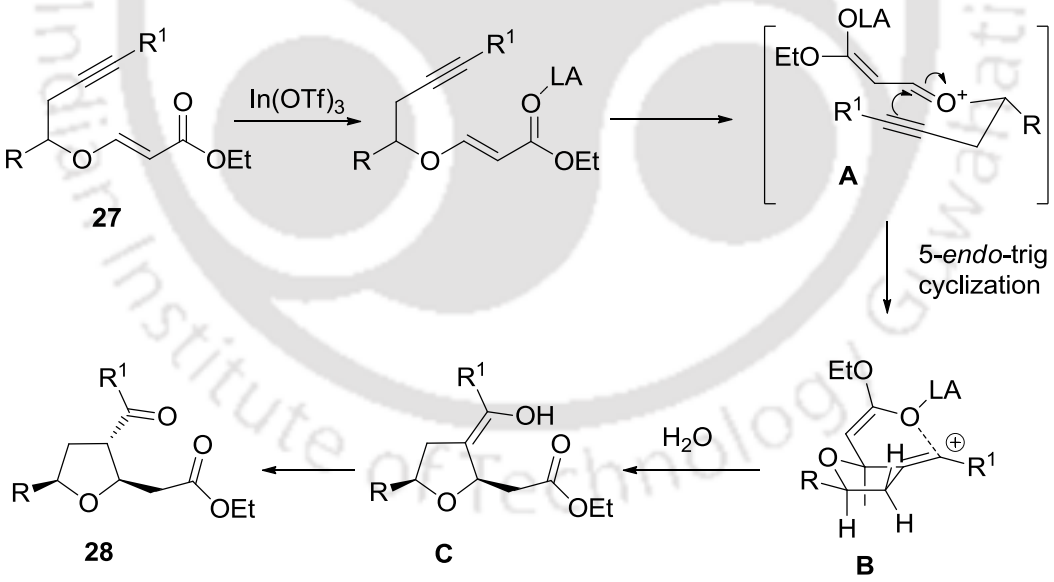


Figure 3.3.1. *nOe and ORTEP diagram of compound* ***28o***

The mechanism of the reaction can be explained as follows. The ester group of enol ether **27** is activated by $In(OTf)_3$ to form oxocarbenium ion **A**. The oxocarbenium ion **A** is then attacked by the alkyne group *via* a 5-*endo*-trig cyclization to give carbocation **B**. The formation of five membered ring is in contrast to Baldwin's rule,[25] but in the present situation formation of five membered ring is possible because of proper alignment of molecular orbital of alkyne group with the sp^2 hybridized carbonyl group.[26] The intermediate carbocation **B** is stabilized by enolate. The intermediate **B** is then trapped by water during the work up of the reaction to give enol **C**, which after rearrangement gives ketone **28** (*Scheme 3.3.3*).



Scheme 3.3.3. *Plausible mechanism of the reaction*

Conclusion:

In conclusion, we have developed a mild and efficient method for the synthesis of substituted tetrahydrofurans *via* Prins cyclization reaction from enol ethers in good yields. The method is highly diastereoselective and gives only *cis* 2,5-diastereomers.

3.4. Experimental section

3.4.1. Instrumentation and Characterization

As described in chapter 2 section 2.4.1

3.4.2. General Procedure for preparation of acrylyl enol ethers (27a-27p): To a solution of homopropargylic alcohol (2.0 mmol) in dichloromethane (3 mL), *N*-methyl morpholine (2 mmol) and ethyl propiolate (2.2 mmol) were added. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After completion of the reaction the solvent was removed on a rotary evaporator and diluted with water (5 mL). The product was extracted with ethyl acetate (3x10 mL), and the combined organic layers were washed with brine (3 mL) and finally dried over anhydrous Na_2SO_4. The solvent was removed under rotary evaporator and the crude product was purified on silica gel column chromatography using ethyl acetate and hexane as eluents.

3.4.3. General Procedure for the Synthesis of 2,3,5-trisubstituted tetrahydrofuran (28a-28p):

To a suspension of $In(OTf)_3$ (0.5 mmol) in dry dichloromethane (1 mL) at 0 °C, enol ether (1 mmol) in dry CH_2Cl_2 (2 mL) was added drop wise under nitrogen atmosphere. The reaction mixture was brought to room temperature. The reaction was continued for specified time and monitored by TLC. After disappearance of the starting material, the reaction mixture was treated with saturated sodium bicarbonate solution (5 mL). The product was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic layer was washed with brine. Organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using rotary evaporator to obtain the crude product. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane as eluents to afford the cyclic compounds **28**.

4.5. References and Notes

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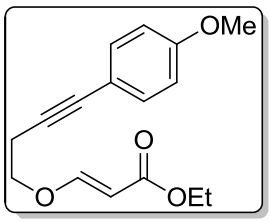
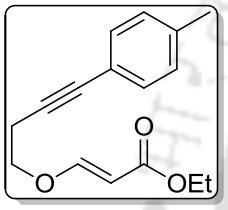
3.6. Characterization Data

(*E*)-Ethyl 3-((4-(4-methoxyphenyl)but-3-yn-1-yl)oxy)acrylate (27a):



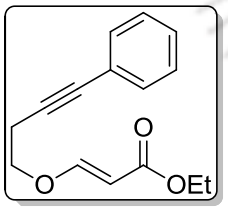
Colourless oil; R_f (hexane/ EtOAc 4:1) 0.66; yield 450 mg, 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.2 Hz, 3 H), 2.82 (t, *J* = 7.2 Hz, 2 H), 3.81 (s, 3 H), 4.03 (t, *J* = 7.2 Hz, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 5.26 (d, *J* = 12.4 Hz, 1 H), 6.82 (d, *J* = 9.2 Hz, 2 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.63 (d, *J* = 12.4 Hz, 1 H);^{13}CNMR(100 MHz,$CDCl_3$) δ 14.4, 20.3, 55.2, 59.8, 69.1, 82.3, 97.1, 104.2, 113.9, 115, 133.1, 159.4, 162.0, 167.5; IR (KBr, neat) 2986, 2839, 1708, 1627, 1259, 1136, 1038, 765 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{19}O_4$ $(M + H)^+$ 275.1278, found 275.1279.

***(E)*-Ethyl 3-((4-(*p*-tolyl)but-3-yn-1-yl)oxy)acrylate (27b):**



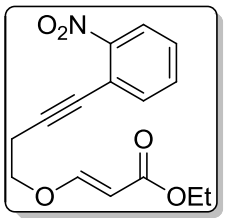
Colourless oil; R_f (hexane/ EtOAc 9:1) 0.63; yield 454 mg, 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3 H), 2.34 (s, 3 H), 2.82 (t, *J* = 7.2 Hz, 2 H), 4.03 (t, *J* = 7.2 Hz, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 5.26 (d, *J* = 12.4 Hz, 1 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.63 (d, *J* = 12.4 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 20.4, 21.6, 60.0, 69.2, 82.7, 84.1, 97.3, 120.2, 129.2, 131.7, 138.3, 162.1, 167.8. IR (KBr, neat) 2975, 2929, 1709, 1626, 1135, 1044, 818, 745 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{19}O_3$ $(M + H)^+$ 259.1329, found 259.1320.

***(E)*-Ethyl 3-((4-phenylbut-3-yn-1-yl)oxy)acrylate (27c):**



Colourless oil; R_f (hexane/ EtOAc 9:1) 0.61; yield 410 mg, 84%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.2 Hz, 3 H), 2.82 (t, *J* = 7.2 Hz, 2 H), 4.03 (t, *J* = 7.2 Hz, 2 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 5.26 (d, *J* = 12.6 Hz, 1 H), 7.28-7.30 (m, 3 H), 7.39-7.41 (m, 2 H), 7.62 (d, *J* = 12.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 20.5, 60.0, 69.2, 82.7, 85.0, 97.3, 123.3, 128.2, 128.4, 131.8, 162.1, 167.8. IR (KBr, neat) 2981, 2939, 1709, 1626, 1134, 1043, 817, 745 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{17}O_3$ $(M + H)^+$ 245.1172, found 245.1172.

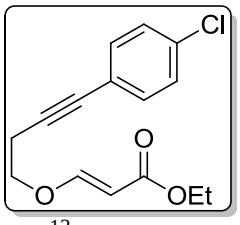
***(E)*-Ethyl 3-((4-(2-nitrophenyl)but-3-yn-1-yl)oxy)acrylate (27d):**



Colourless oil; R_f (hexane/ EtOAc 4:1) 0.54; yield 474 mg, 82%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3 H), 2.91 (t, *J* = 7.2 Hz, 2 H), 4.08 (t, *J* = 6.0 Hz, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 5.27 (d, *J* = 12.6 Hz, 1 H), 7.44 (t, *J* = 7.2 Hz, 1 H), 7.32 (d, *J* = 7.2 Hz, 1 H), 7.60 (d, *J* = 8.4 Hz, 1 H), 7.62 (d, *J* = 12.6 Hz, 1 H), 8.00 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.6, 20.9, 60.1,

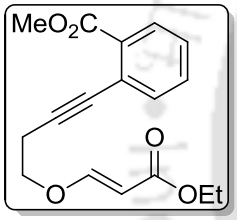
68.7, 78.0, 93.7, 97.6, 118.7, 124.7, 128.7, 132.9 (2C), 135.1, 162.0, 167.8; IR (KBr, neat) 2982, 2951, 1709, 1628, 1527, 1474, 1345, 1132, 1046, 476 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{16}NO_5$ $(M + H)^+$ 290.1023, found 290.1023.

***(E)*-Ethyl 3-((4-(4-chlorophenyl)but-3-yn-1-yl)oxy)acrylate (27e):**



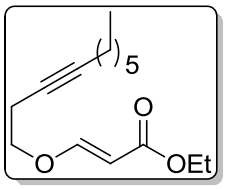
Colourless oil; R_f (hexane/ EtOAc 9:1) 0.57; yield 445 mg, 80%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3 H), 2.81 (t, *J* = 6.6 Hz, 2 H), 4.03 (t, *J* = 6.6 Hz, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 5.26 (d, *J* = 12.6 Hz, 1 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 7.62 (d, *J* = 12.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 20.4, 60.0, 69.0, 81.6, 86.1, 97.3, 121.7, 128.7, 133.0, 134.2, 162.0, 167.8. IR (KBr, neat) 2981, 2937, 1709, 1626, 1489, 1135, 1092, 828 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{16}ClO_3$ $(M + H)^+$ 279.0782, found 279.0810.

***(E)*-Methyl 2-(4-((3-ethoxy-3-oxoprop-1-en-1-yl)oxy)but-1-yn-1-yl)benzoate (27f):**



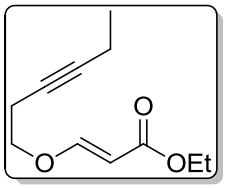
Colourless oil; R_f (hexane/ EtOAc 4:1) 0.60; yield 526 mg, 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.2 Hz, 3 H), 2.85 (t, *J* = 6.8 Hz, 2 H), 3.86 (s, 3 H), 4.03 (t, *J* = 6.8 Hz, 2 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 5.23 (d, *J* = 12.4 Hz, 1 H), 7.29 (t, *J* = 8.0 Hz, 1 H), 7.39 (t, *J* = 7.2 Hz, 1 H), 7.48 (d, *J* = 7.6 Hz, 1 H), 7.59 (d, *J* = 12.4 Hz, 1 H), 7.86 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 20.7, 52.2, 59.9, 69.0, 81.2, 90.3, 97.2, 123.7, 127.8, 130.3, 131.7, 132.0, 134.4, 162.0, 166.6, 167.7; IR (KBr, neat) 2982, 2952, 1732, 1714, 1626, 1328, 1129, 1044, 960, 760 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{19}O_5$ $(M + H)^+$ 303.1227, found 303.1247.

***(E)*-Ethyl 3-(dec-3-yn-1-yloxy)acrylate (27g):**



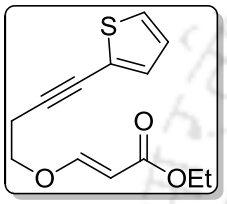
Colourless oil; R_f (hexane/ EtOAc 9:1) 0.76; yield 506 mg, 91%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.2 Hz, 3 H), 1.24-1.33 (m, 4 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.35-1.38 (m, 2 H), 1.44-1.49 (m, 2 H), 2.13-2.15 (m, 2 H), 2.54-2.58 (m, 2 H), 3.91 (t, *J* = 7.2 Hz, 2 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 5.21 (d, *J* = 12.6 Hz, 1 H), 7.58 (d, *J* = 12.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 14.6, 18.9, 19.8, 22.8, 28.7, 29.0, 31.5, 60.0, 69.7, 75.1, 82.9, 97.1, 162.2, 167.9; IR (KBr, neat) 2932, 2857, 1713, 1628, 1134, 1046, 824 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{25}O_3$ $(M + H)^+$ 253.1798, found 253.1800.

***(E)*-Ethyl 3-(hex-3-yn-1-yloxy)acrylate (27h):**



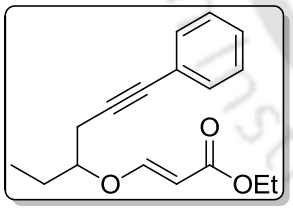
Colourless oil; R_f (hexane/ EtOAc 9:1) 0.50; yield 313 mg, 80%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.10 (t, *J* = 7.2 Hz, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 2.14-2.16 (m, 2 H), 2.53-2.56 (m, 2 H), 3.91 (t, *J* = 7.2 Hz, 2 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 5.21 (d, *J* = 12.6 Hz, 1 H), 7.58 (d, *J* = 12.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.6, 14.2, 14.3, 19.8, 61.5, 69.7, 81.7, 84.2, 97.2, 164.9, 167.9; IR (KBr, neat) 2978, 2850, 1716, 1625, 1242, 1181, 1025, 799 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{17}O_3$ $(M + H)^+$ 197.1172, found 197.1185.

***(E)*-Ethyl 3-((4-(thiophen-2-yl)but-3-yn-1-yl)oxy)acrylate (27i):**



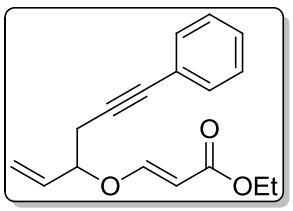
Colourless oil; R_f (hexane/ EtOAc 4:1) 0.60; yield 405 mg, 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.2 Hz, 3 H), 2.83 (t, *J* = 6.8 Hz, 2 H), 4.00 (t, *J* = 7.2 Hz, 2 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 5.25 (d, *J* = 12.4 Hz, 1 H), 6.93 (t, *J* = 4.8 Hz, 1 H), 7.15 (d, *J* = 4.0 Hz, 1 H), 7.20 (d, *J* = 4.8 Hz, 1 H), 7.61 (d, *J* = 12.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 20.6, 60.0, 68.7,75.8, 89.0, 97.3, 123.2, 126.8, 127.0, 131.9, 161.9, 167.7; IR (KBr, neat) 2981, 2905, 1710, 1625, 1328, 1132, 1045, 832, 703 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{15}O_3S$ $(M + H)^+$ 251.0736, found 251.0743.

***(E)*-Ethyl 3-((6-phenylhex-5-yn-3-yl)oxy)acrylate (27j):**



Colourless oil; R_f (hexane/ EtOAc 9:1) 0.56; yield 490 mg, 90%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.00 (t, *J* = 7.2 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.73-1.80 (m, 1 H), 1.82-1.87 (m, 1 H), 2.68 (dd, *J* = 17.4 and 6.6 Hz, 1 H), 2.73 (dd, *J* = 16.2 and 6.6 Hz, 1 H), 4.02-4.07 (m, 1 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 5.32 (d, *J* = 12.6 Hz, 1 H), 7.27-7.29 (m, 3 H), 7.38-7.40 (m, 2 H), 7.62 (d, *J* = 12.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) 9.6, 14.6, 25.3, 27.1, 60.0, 83.3 (2 C), 85.1, 97.8, 123.4, 128.2, 128.4, 131.8, 162.5, 168.3; IR (KBr, neat) 2975, 2936, 1708, 1640, 1491, 1135, 1048, 758 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{21}O_3$ $(M + H)^+$ 273.1485, found 273.1485.

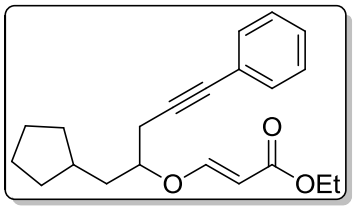
***(E)*-Ethyl 3-((6-phenylhex-1-en-5-yn-3-yl)oxy)acrylate (27k):**



Colourless oil; R_f (hexane/ EtOAc 9:1) 0.60; yield 475 mg, 88%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.2 Hz, 3 H), 2.76 (dd, *J* = 16.8 and 6.6 Hz, 1 H), 2.85 (dd, *J* = 16.8 and 6.6 Hz, 1 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 4.23 (q, *J* = 7.2 Hz, 1 H), 5.32-5.42 (m, 3 H), 5.88-5.95 (m, 1 H), 7.27-7.33 (m, 3 H), 7.38-7.41 (m, 2 H), 7.57 (d, *J* = 12.6 Hz, 1 H); ^{13}C NMR (150 MHz,

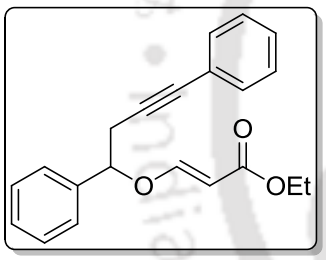
$CDCl_3$) δ 14.6, 26.5, 60.0, 81.8, 83.4, 84.6, 98.8, 119.2, 128.3, 128.5, 131.8, 132.0, 135.2, 161.3, 168.0; IR (KBr, neat) 2927, 2853,1707, 1644, 1475, 1134, 1044, 786 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{19}O_3$ $(M + H)^+$ 271.1329, found 271.1329.

***(E)*-Ethyl 3-((1-cyclopentyl-5-phenylpent-4-yn-2-yl)oxy)acrylate (27l):**



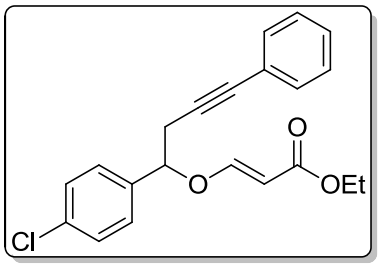
Colourless oil; R_f (hexane/ EtOAc 9:1) 0.60; yield 561 mg, 86%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23-1.31 (m, 4 H), 1.50-1.55 (m, 2 H), 1.63-1.70 (m, 2 H), 1.72-1.92 (m, 6 H), 2.64-2.77 (m, 2 H), 4.07-4.20 (m, 3 H), 5.32 (d, *J* = 12.0 Hz, 1 H), 7.27-7.30 (m, 3 H), 7.37-7.42 (m, 2 H), 7.63 (d, *J* = 12.0 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.6, 25.2, 25.3, 26.2, 32.7, 33.3, 36.6, 38.7, 40.5, 59.9, 83.1, 85.2, 97.8, 123.5, 128.2, 128.5, 131.8, 162.5, 168.2; IR (KBr, neat) 2953, 2863, 1709, 1642, 1371, 1131, 1045, 757 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{27}O_3$ $(M + H)^+$ 327.1955, found 327.1973.

***(E)*-Ethyl 3-((1,4-diphenylbut-3-yn-1-yl)oxy)acrylate (27m):**



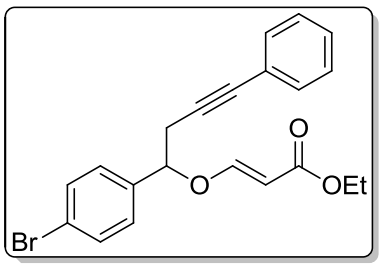
Colourless oil; R_f (hexane/ EtOAc 9:1) 0.51; yield 512 mg, 80%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.6 Hz, 3 H), 2.91 (dd, *J* = 16.8 and 5.6 Hz, 1 H), 3.05 (dd, *J* = 16.8 and 7.2 Hz, 1 H) 4.08-4.14 (m, 2 H), 5.08 (t, *J* = 6.8 Hz, 1 H), 5.27 (d, *J* = 12.8 Hz, 1 H), 7.26-7.29 (m, 3 H), 7.34-7.40 (m, 7 H), 7.58 (d, *J* = 12.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 29.0, 60.0, 82.7, 83.5, 85.0, 99.1, 123.3, 126.4, 128.2, 138.4, 128.9, 129.0, 131.8, 138.9, 161.3, 167.8; IR (KBr, neat) 2953, 2924, 1709, 1640, 1491, 1128, 1040, 830 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{21}O_3$ $(M + H)^+$ 321.1485, found 321.1486.

***(E)*-Ethyl 3-((1-(4-chlorophenyl)-4-phenylbut-3-yn-1-yl)oxy)acrylate (27n):**



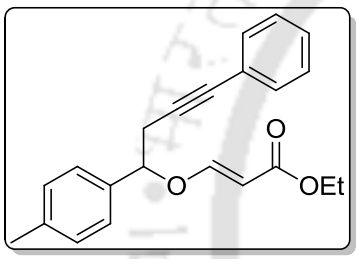
Colourless oil; R_f (hexane/ EtOAc 9:1) 0.44; yield 552 mg, 78%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.2 Hz, 3 H), 2.89 (dd, *J* = 16.8 and 6.6 Hz, 1 H), 3.02 (dd, *J* = 16.8 and 5.4 Hz, 1 H), 4.07-4.14 (m, 2 H), 5.06 (t, *J* = 6.6 Hz, 1 H), 5.24 (d, *J* = 12.6 Hz, 1 H), 7.25-7.40 (m, 9 H), 7.56 (d, *J* = 12.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 28.9, 60.1, 81.8, 83.9, 84.4, 99.5, 123.2, 127.9, 128.4, 128.5, 129.2, 131.8, 134.8, 137.4, 160.9, 167.6; IR (KBr, neat) 2924, 2854, 1709, 1644, 1492, 1133, 1092, 758 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{20}ClO_3$ $(M + H)^+$ 355.1095, found 355.1095.

(*E*)-Ethyl 3-((1-(4-bromophenyl)-4-phenylbut-3-yn-1-yl)oxy)acrylate (27o):



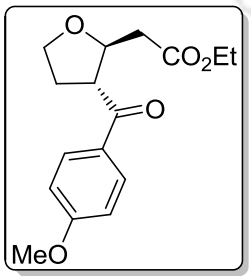
Colourless oil; R_f (hexane/ EtOAc 9:1) 0.40; yield 666 mg, 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.2 Hz, 3 H), 2.88 (dd, *J* = 16.8 and 6.4 Hz, 1 H), 3.02 (dd, *J* = 16.8 and 6.4 Hz, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 5.05 (t, *J* = 6.4 Hz, 1 H), 5.25 (d, *J* = 12.4 Hz, 1 H), 7.24-7.31 (m, 5 H), 7.32-7.35 (m, 2 H), 7.52-7.56 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 28.8, 60.1, 81.8, 83.9, 84.3, 99.5, 122.9, 123.2, 128.2, 128.4, 128.5, 131.8 (2C), 132.1 (2C), 137.9, 160.9, 167.6; IR (KBr, neat) 2956, 2853, 1708, 1643, 1131, 1044, 822, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{20}BrO_3$ $(M + H)^+$ 399.0590, found 399.0602.

(*E*)-Ethyl 3-((4-phenyl-1-(p-tolyl)but-3-yn-1-yl)oxy)acrylate (27p):



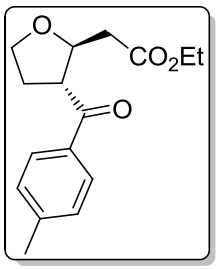
Colourless oil; R_f (hexane/ EtOAc 9:1) 0.50; yield 548 mg, 82%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.2 Hz, 3 H), 2.36 (s, 3 H), 2.88 (dd, *J* = 16.8 and 5.6 Hz, 1 H), 3.00 (dd, *J* = 16.8 and 7.6 Hz, 1 H), 4.05-4.15 (m, 2 H), 5.06 (t, *J* = 6.0 Hz, 1 H), 5.27 (d, *J* = 12.8 Hz, 1 H), 7.18-7.36 (m, 9 H), 7.58 (d, *J* = 12.8 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 21.4, 28.9, 60.0, 82.7, 83.4, 85.1, 99.0, 126.4, 128.2, 128.4, 129.6 (2C), 131.8, 135.9, 138.7, 161.4, 167.9; IR (KBr, neat) 2924, 2954, 1709, 1641, 1491, 1132, 1044, 758 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{23}O_3$ $(M + H)^+$ 335.1642, found 335.1644.

Ethyl 2-(3-(4-methoxybenzoyl)tetrahydrofuran-2-yl)acetate (28a):



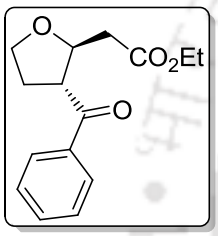
Colourless oil; R_f (hexane/ EtOAc 4:1) 0.40; Yield 176 mg, 60%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.18 (t, *J* = 7.2 Hz, 3 H), 2.13-2.18 (m, 1 H), 2.29-2.34 (m, 1 H), 2.60 (dd, *J* = 15.0 and 6.0 Hz, 1 H), 2.64 (dd, *J* = 15.0 and 6.6 Hz, 1 H), 3.78-3.86 (m, 1 H), 3.87 (s, 3 H), 3.91 (q, *J* = 7.8 Hz, 1 H), 4.00-4.06 (m, 1 H), 4.09 (q, *J* = 7.2 Hz, 2 H), 4.59 (q, *J* = 6.6 Hz, 1 H), 6.95 (d, *J* = 8.4 Hz, 2 H), 7.96 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 32.0, 39.7, 50.4, 55.7, 60.8, 68.1, 78.1, 114.1, 129.8, 131.0, 164.0, 170.9, 198.4; IR (KBr, neat) 2962, 2876, 1732, 1670, 1600, 1259, 1171, 1027, 840 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{21}O_5$ $(M + H)^+$ 293.1384 found 293.1392.

Ethyl 2-(3-(4-methylbenzoyl)tetrahydrofuran-2-yl)acetate (28b):



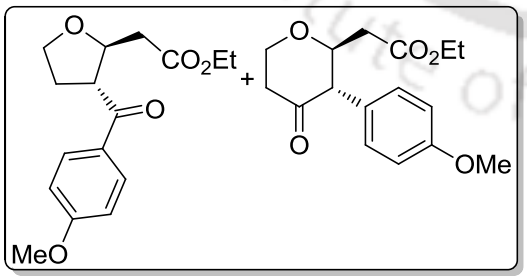
Colourless oil; R_f (hexane/ EtOAc 9:1) 0.30; Yield 155 mg, 56%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.18 (t, *J* = 7.2 Hz, 3 H), 2.13-2.17 (m, 1 H), 2.32-2.36 (m, 1 H), 2.42 (s, 3 H), 2.61 (dd,*J* = 15.0 and 6.0 Hz, 1 H), 2.66 (dd, *J* = 15.0 and 7.2 Hz, 1 H), 3.84-3.89 (m, 1 H), 3.91 (q, *J* = 7.8 Hz, 1 H), 4.00-4.05 (m, 1 H), 4.07 (q, *J* = 7.2 Hz, 2 H), 4.61 (q, *J* = 6.6 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 7.88 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 21.8, 31.9, 39.7, 50.7, 60.8, 68.0, 77.9, 128.8, 129.6, 134.2, 144.5, 170.8, 199.4; IR (KBr, neat) 2978, 2873, 1734, 1677, 1607, 1449, 1177, 1059, 1033, 774 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{21}O_4$ $(M + H)^+$ 277.1434 found 277.1429.

Ethyl 2-(3-benzoyltetrahydrofuran-2-yl)acetate (28c):



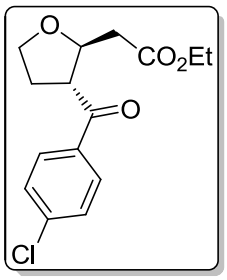
Colourless oil; R_f (hexane/ EtOAc 9:1) 0.30; Yield 142 mg, 54%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.18 (t, *J* = 7.2 Hz, 3 H), 2.12-2.18 (m, 1 H), 2.32-2.39 (m, 1 H), 2.61(dd, *J* = 15.0 and 6.0 Hz, 1 H), 2.68 (dd, *J* = 15.0 and 7.8 Hz, 1 H), 3.86-3.93 (m, 2 H), 4.01-4.04 (m, 1 H), 4.06 (q, *J* = 7.2 Hz, 2 H), 4.62 (q, *J* = 6.6 Hz, 1 H), 7.48 (t, *J* = 7.8 Hz, 2 H), 7.59 (t, *J* = 7.2 Hz, 1 H), 7.97 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) 14.3, 32.0, 39.7, 50.8, 60.8, 68.0, 77.9, 128.7, 129.0, 133.6, 136.7, 170.8, 199.9; IR (KBr, neat) 2979, 2875, 1733, 1678, 1448, 1058, 1028, 698 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{19}O_4$ $(M + H)^+$ 263.1278 found 263.1273.

Ethyl 2-(3-(4-methoxybenzoyl)tetrahydrofuran-2-yl)acetate (28a) and Ethyl 2-(3-(4-methoxy phenyl)-4-oxotetrahydro-2H-pyran-2-yl)acetate (29a):



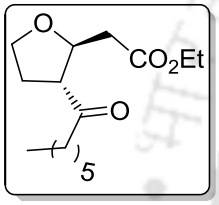
Colourless oil; R_f (hexane/ EtOAc 4:1) 0.40; Yield 122mg, 42%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.12 (t, *J* = 7.2 Hz, 3 H, pyran), 1.17 (t, *J* = 7.2 Hz, 3 H, furan), 2.08-2.12 (m, 1 H, pyran), 2.18 (dd, *J* = 16.2 and 5.4 Hz, 1 H, furan), 2.29-2.34 (m, 1 H, furan), 2.42 (dd,*J* = 15.6 and 9.0 Hz, 1 H, pyran), 2.46-2.50 (m, 1 H, pyran), 2.60 (dd,*J* = 15.0 and 6.0 Hz, 1 H, furan), 2.64 (dd, *J* = 15.0 and 6.6 Hz, 1 H, furan), 3.78-3.86 (m, 1 H, furan), 3.87 (s, 3 H, pyran and furan), 3.91 (q, *J* = 7.8 Hz, 1 H, furan), 3.97 (m, 2 H, pyran), (4.00-4.06 (m, 1 H, furan), 4.05 (q,*J* = 7.2 Hz, 2 H, pyran), 4.09 (q, *J* = 7.2 Hz, 2 H, furan), 4.11-4.15 (m, 1 H, pyran), 4.17 (q,*J* = 7.8 Hz, 1 H, pyran), 4.59 (q, *J* = 6.6 Hz, 1 H, furan), 4.70-4.75 (m, 1 H, pyran), 6.95 (d, *J* = 8.4 Hz, 2 H, pyran and furan), 7.96 (d, *J* = 8.4 Hz, 2 H, pyran and furan).

Ethyl 2-(3-(4-chlorobenzoyl)tetrahydrofuran-2-yl)acetate (28e):



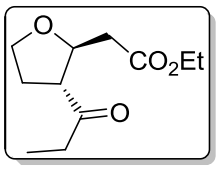
Colourless oil; R_f (hexane/ EtOAc 8:1) 0.30; Yield 133 mg, 45%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.2 Hz, 3 H), 2.12-2.16 (m, 1 H), 2.31-2.37 (m, 1 H), 2.61 (dd, *J* = 15.0 and 6.0 Hz, 1 H), 2.68 (dd, *J* = 15.0 and 6.6 Hz, 1 H), 3.80-3.87 (m, 1 H), 3.91 (q, *J* = 7.2 Hz, 1 H), 4.01-4.05 (m, 1 H), 4.07 (q, *J* = 7.2 Hz, 2 H), 4.61 (q, *J* = 6.6 Hz, 1 H), 7.47 (d, *J* = 7.8 Hz, 2 H), 7.91 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 31.9, 39.6, 50.8, 60.9, 68.0, 77.9, 128.8, 129.3, 130.1, 135.0, 170.8, 198.8; IR (KBr, neat) 2980, 2876, 1732, 1681,1589, 1488, 1171, 1092, 1059, 834 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{17}ClO_4$ $(M + H)^+$ 297.0888 found 297.0898.

Ethyl 2-(3-heptanoyltetrahydrofuran-2-yl)acetate (28g):



Colourless oil; R_f (hexane/ EtOAc 8:1) 0.30; Yield 57 mg, 21%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.6 Hz, 3 H), 1.22-1.32 (m, 9 H),1.58-1.60 (m, 2 H), 2.01-2.08 (m, 1 H), 2.14-2.21 (m, 1 H), 2.47 (t, *J* = 7.2 Hz, 2 H), 2.55 (dd, *J* = 15.0 and 6.0 Hz, 1 H), 2.62 (dd, *J* = 15.0 and 7.2 Hz, 1 H), 2.97-3.01 (m, 1 H), 3.85 (q, *J* = 7.2 Hz, 1 H), 3.90-3.94 (m, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.42 (q, *J* = 6.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 14.4, 22.7, 23.7, 29.1, 29.2, 29.6, 30.4, 31.8, 40.1, 55.9, 60.9, 67.9, 170.9, 210.3; IR (KBr, neat) 2954, 2856, 1732, 1711, 1629, 1172, 1062, 1032, 726 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{27}O_4$ $(M + H)^+$ 271.1904 found 271.1899.

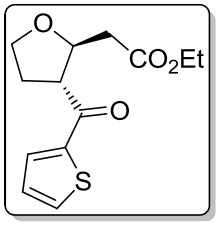
Ethyl 2-(3-propionyltetrahydrofuran-2-yl)acetate (28h):



Colourless oil; R_f (hexane/ EtOAc 8:1) 0.28; Yield 57 mg, 30%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, *J* = 6.8 Hz, 3 H), 1.25 (t, *J* = 6.8 Hz, 3 H), 2.02-2.30 (m, 1 H), 2.16-2.23 (m, 1 H), 2.51-2.58 (m, 3 H), 2.63 (dd, *J* = 15.2 and 6.8 Hz, 1 H), 2.97-3.03 (m, 1 H), 3.85 (dd, *J* = 15.2 and 8.4 Hz, 1 H), 3.92 (dd, *J* = 14.4 and 8.4 Hz, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.43 (q, *J* = 6.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8, 14.4, 30.5, 35.9, 40.1, 55.7, 60.9, 67.9, 77.6, 171.0, 210.7; IR (KBr, neat) 2980, 2849, 1739, 1693, 1172, 1094, 1030, 802 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{19}O_4$ $(M + H)^+$ 215.1278 found 215.1272.

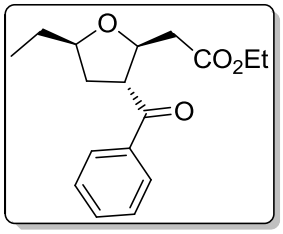
Ethyl 2-(3-(thiophene-2-carbonyl)tetrahydrofuran-2-yl)acetate (28i):

Colourless oil; R_f (hexane/ EtOAc 3:1) 0.40; Yield 180 mg, 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.2 Hz, 3 H), 2.24-2.37 (m, 2 H), 2.61-2.72 (m, 2 H), 3.75 (q, *J* = 6.8 Hz, 1 H), 3.96 (q, *J* = 7.2 Hz, 1 H), 4.00-4.10 (m, 3 H), 4.56 (q, *J* = 6.4 Hz, 1 H), 7.17 (t, *J* = 4.8 Hz, 1 H), 7.69



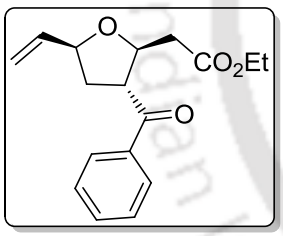
(t, *J* = 4.8 Hz, 1 H), 7.79 (d,*J* = 3.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ14.3, 32.1, 39.7, 52.2, 60.9, 68.2, 78.3, 128.5, 132.6, 134.7, 144.4, 170.7, 192.8;IR (KBr, neat) 2925, 2855, 1732, 1659, 1415, 1160, 1094, 729 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{17}O_4S$ $(M + H)^+$ 269.0842 found 269.0842.

Ethyl 2-(3-benzoyl-5-ethyltetrahydrofuran-2-yl)acetate (28j):



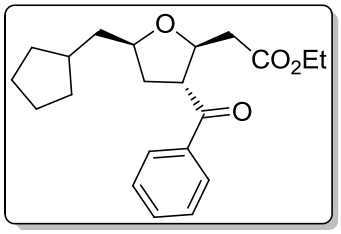
Colourless oil; R_f (hexane/ EtOAc 9:1) 0.40; Yield 244 mg, 84%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.2 Hz, 3 H), 1.13 (t, *J* = 7.2 Hz, 3 H), 1.49-1.54 (m, 1 H), 1.65-1.70 (m, 1 H), 1.94-1.99 (m, 1 H), 2.14-2.19 (m, 1 H), 2.61 (dd,*J* = 15.0 and 6.0 Hz, 1 H), 2.68 (dd, *J* = 15.0 and 6.0 Hz, 1 H), 3.89-3.96 (m, 2 H), 4.04 (q, *J* = 7.2 Hz, 2 H), 4.62 (q, *J* = 6.0 Hz, 1 H), 7.48 (t, *J* = 7.8 Hz, 2 H), 7.58 (d, *J* = 7.8 Hz, 1 H), 7.95 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.3, 14.3, 28.5, 36.9, 40.1, 50.7, 60.8, 77.5, 80.6, 128.6, 128.9, 133.5, 136.8, 170.9, 200.3; IR (KBr, neat) 2967, 2876, 1735, 1680, 1597, 1450, 1173, 1096, 1051, 700 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{23}O_4$ $(M + H)^+$ 291.1591 found 291.1568.

Ethyl 2-(3-benzoyl-5-vinyltetrahydrofuran-2-yl)acetate (28k):



Colourless oil; R_f (hexane/ EtOAc 9:1) 0.37; Yield 181 mg, 63%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.17 (t, *J* = 7.2 Hz, 3 H), 2.09-2.14 (m, 1 H), 2.27-2.32 (m, 1 H), 2.64 (dd, *J* = 15.0 and 6.6 Hz, 1 H), 2.72 (dd, *J* = 15.0 and 6.0 Hz, 1 H), 3.95-3.82 (m, 1 H), 4.05 (q, *J* = 7.2 Hz, 2 H), 4.50 (q, *J* = 6.6 Hz, 1 H), 4.68 (q, *J* = 6.6 Hz, 1 H), 5.15 (d, *J* = 10.8 Hz, 1 H), 5.29 (d, *J* = 16.2 Hz, 1 H), 5.83-5.90 (m, 1 H), 7.47-7.50 (m, 2 H), 7.58 (t,*J* = 7.8 Hz, 1 H), 7.95 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 37.7, 40.1, 50.8, 60.8, 77.9, 80.1, 116.6, 128.7, 129.0, 133.6, 136.7, 138.2, 170.8, 200.0; IR (KBr, neat) 2923, 2853, 1733, 1679, 1594, 1448, 1173, 1033, 1006, 692 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{21}O_4$ $(M + H)^+$ 289.1434found 289.1429.

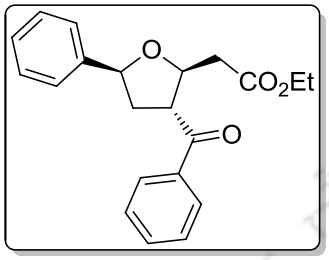
Ethyl 2-(3-benzoyl-5-(cyclopentylmethyl)tetrahydrofuran-2-yl)acetate (28l):



Colourless oil; R_f (hexane/ EtOAc 9:1) 0.50; Yield 217 mg, 63%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.15 (t, *J* = 7.2 Hz, 3 H), 1.45-1.50 (m, 4 H), 1.57-1.62 (m, 3 H), 1.69-1.85 (m, 4 H), 1.92-1.98 (m, 1 H), 2.15-2.19 (m, 1 H), 2.60 (dd, *J* = 15.0 and 6.6 Hz, 1 H), 2.68 (dd, *J* = 15.0 and 6.0 Hz, 1 H), 3.89-3.93 (m, 1 H), 4.00-4.07 (m, 3 H), 4.60 (q, *J* = 6.0 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 2 H), 7.57 (t, *J* = 7.2 Hz, 1 H), 7.95 (d,*J* = 7.8 Hz,

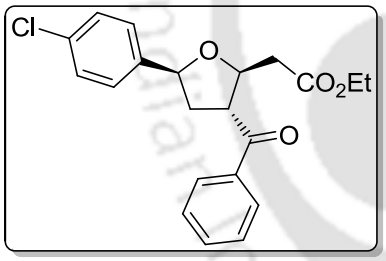
2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 25.1, 25.2, 33.1, 37.5, 37.9, 40.2, 42.1, 50.7, 60.7, 71.1, 77.5, 78.9, 128.7, 128.9, 133.5, 136.8, 170.9, 200.4; IR (KBr, neat) 2949, 2866, 1738, 1676, 1449, 1162, 1052, 709 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{29}O_4$ $(M + H)^+$ 345.2060 found 345.2076.

Ethyl 2-(3-benzoyl-5-phenyltetrahydrofuran-2-yl)acetate (28m):



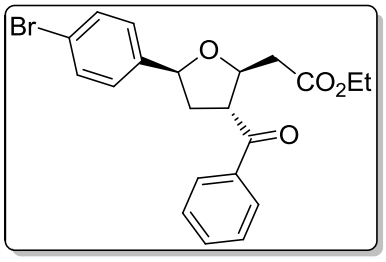
Colourless oil; R_f (hexane/ EtOAc 9:1) 0.37; Yield 311 mg, 92%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.2 Hz, 3 H), 2.25-2.31 (m, 1 H), 2.51-2.55 (m, 1 H), 2.76 (dd,*J* = 15.0 and 6.0 Hz, 1 H), 2.83 (dd, *J* = 15.0 and 5.4 Hz, 1 H), 4.06-4.11 (m, 3 H), 4.82 (q, *J* = 6.6 Hz, 1 H), 5.10 (dd, *J* = 7.8 and 7.8 Hz, 1 H), 7.26-7.28 (m, 1 H), 7.33-7.37 (m, 4 H), 7.48 (t, *J* = 7.8 Hz, 2 H), 7.56-7.60 (m, 1 H), 7.97 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 29.9, 39.9, 50.7, 60.9, 78.0, 80.7, 126.0, 127.9, 128.6, 128.7, 129.0, 133.7, 136.6, 141.8, 170.8, 200.1; IR (KBr, neat) 2921, 2852, 1731, 1679, 1614, 1448, 1130, 1060, 1031, 700 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{23}O_4$ $(M + H)^+$ 339.1591 found 339.1593.

Ethyl 2-(3-benzoyl-5-(4-chlorophenyl)tetrahydrofuran-2-yl)acetate (28n):



Colourless oil; R_f (hexane/ EtOAc 9:1) 0.32; Yield 264 mg, 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.2 Hz, 3 H), 2.15-2.26 (m, 1 H), 2.49-2.55 (m, 1 H), 2.75 (dd, *J* = 15.2 and 6.0 Hz, 1 H), 2.81 (dd, *J* = 15.2 and 6.0 Hz, 1 H), 4.02-4.12 (m, 3 H), 4.81 (q, *J* = 6.0 Hz, 1 H), 5.03 (dd, *J* = 8.4 and 6.8 Hz, 1 H), 7.27-7.33 (m, 4 H), 7.47-7.51 (m, 2 H), 7.56-7.62 (m, 1 H), 7.97 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 39.8 40.1, 50.5, 60.9, 78.1, 80.0, 127.4, 128.7, 128.8, 129.0, 133.5, 133.7, 136.5, 140.4, 170.7, 199.9; IR (KBr, neat) 2977, 2929, 1734, 1678, 1492, 1447, 1168, 1011, 823, 696 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{22}ClO_4$ $(M + H)^+$ 373.1201 found 373.1178.

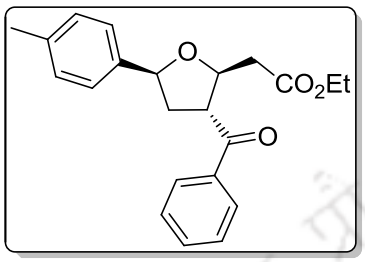
Ethyl 2-(3-benzoyl-5-(4-bromophenyl)tetrahydrofuran-2-yl)acetate (28o):



Colourlesssolid; M. P. 79-81 ^{o}C; R_f (hexane/ EtOAc 9:1) 0.30; Yield 300 mg, 72%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.2 Hz, 3 H), 2.16-2.23 (m, 1 H), 2.50-2.54 (m, 1 H), 2.75 (dd, *J* = 15.0 and 6.6 Hz, 1 H), 2.80 (dd, *J* = 15.0 and 6.0 Hz, 1 H), 4.06-4.10 (m, 3 H), 4.80 (q, *J* = 6.6 Hz, 1 H), 5.02 (dd, *J* = 7.8 and 7.8 Hz, 1 H), 7.24 (q, *J* = 8.4 Hz, 2 H), 7.45-7.50 (m, 4 H), 7.59 (t, *J* = 7.2 Hz, 1 H), 7.96 (d,

J = 7.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 39.6, 39.9, 50.3, 60.7, 77.9, 79.8, 121.4, 127.5, 128.5, 128.8, 131.5, 133.6, 136.3, 140.7, 170.5, 199.7; IR (KBr, neat) 2925, 2856, 1732, 1679, 1488, 1012, 816, 695 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{22}BrO_4$ $(M + H)^+$ 417.0696 found 417.0695 and 419.0682.

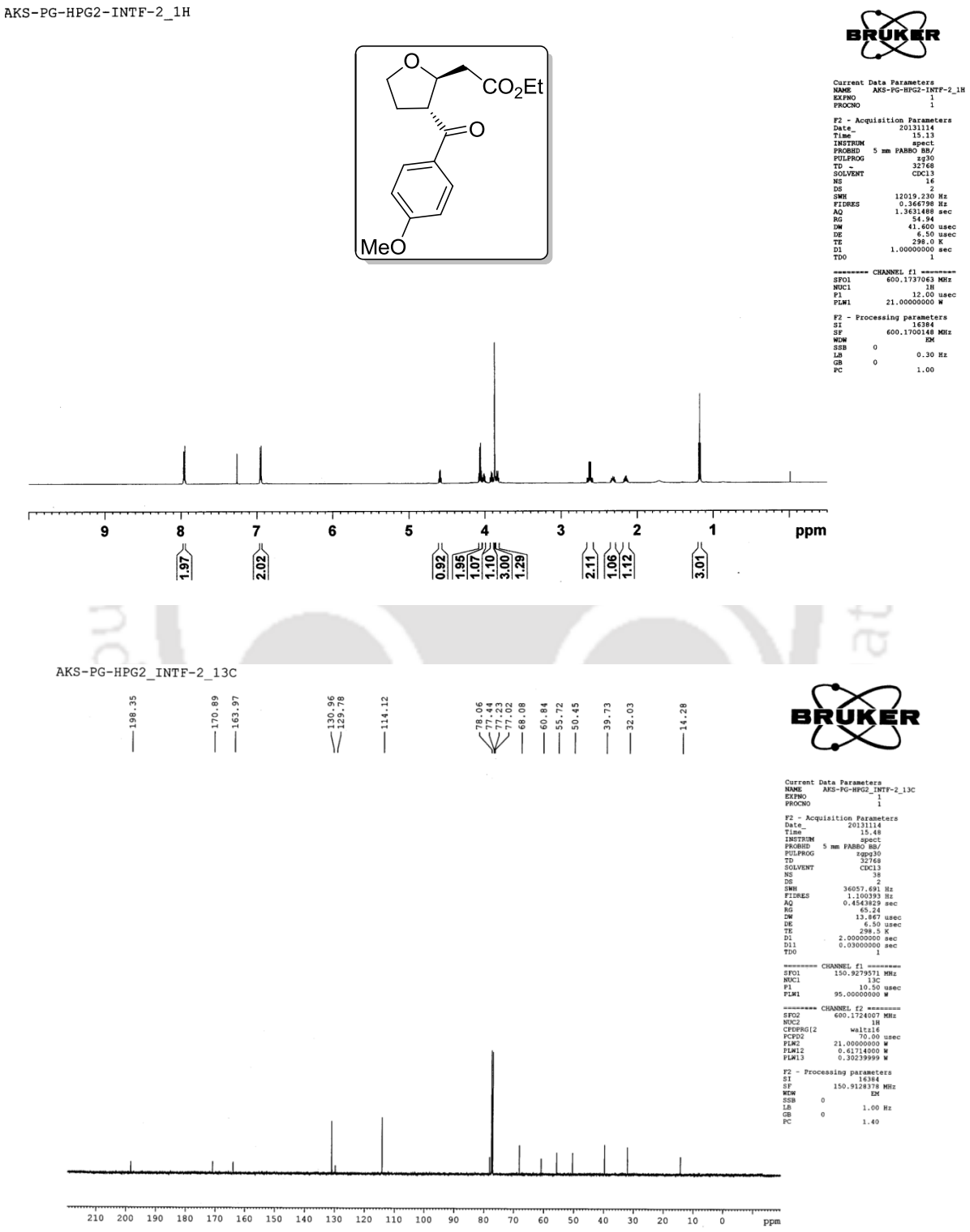
Ethyl 2-(3-benzoyl-5-(*p*-tolyl)tetrahydrofuran-2-yl)acetate (28p):



Colourless oil; R_f (hexane/ EtOAc 9:1) 0.36; Yield 285 mg, 81%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.17 (t, *J* = 7.2 Hz, 3 H), 2.24-2.30 (m, 1 H), 2.34 (s, 3 H), 2.47-2.52 (m, 1 H), 2.75 (dd, *J* = 15.0 and 6.0 Hz, 1 H), 2.82 (dd, *J* = 15.0 and 6.0 Hz, 1 H), 4.05-4.10 (m, 3 H), 4.80 (q, *J* = 6.0 Hz, 1 H), 5.03 (dd, *J* = 7.8 and 7.2 Hz, 1 H), 7.15 (d, *J* = 7.8 Hz, 2 H), 7.25 (d, *J* = 7.8 Hz, 2 H), 7.48 (t, *J* = 7.8 Hz, 2 H), 7.56-7.60 (m, 1 H), 7.96 (d, *J* = 7.8 Hz, 2 H); ^{13}CNMR(150 MHz, $CDCl_3$) δ 14.3, 21.4, 29.9, 40.0, 50.8, 60.9, 78.0, 80.6, 126.0, 128.7, 129.0, 129.3, 133.6, 136.7, 138.8, 170.8, 200.1; IR (KBr, neat) 2925, 2854, 1733, 1680, 1616, 1450, 1131, 1057, 1031, 813, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{25}O_4$ $(M + H)^+$ 353.1747 found 353.1748.

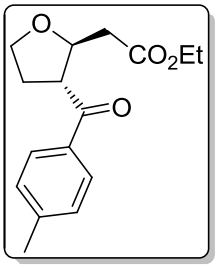
3.7. Selected spectra of Substituted Tetrahydrofurans

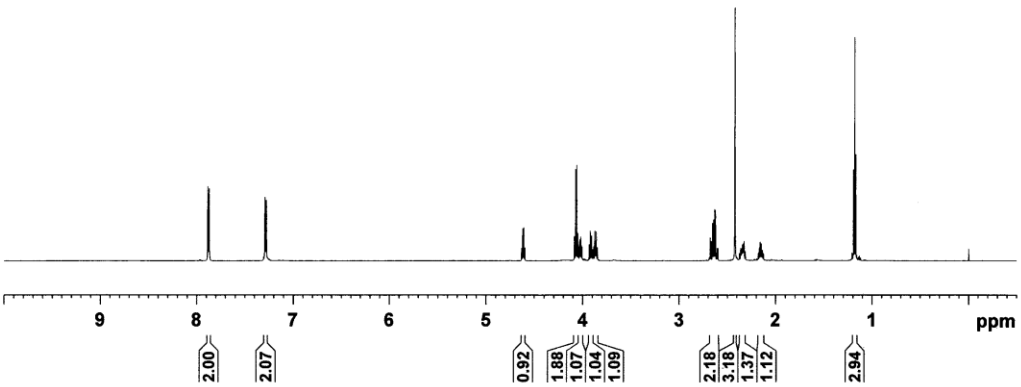
^{1}H and ^{13}C spectra of ethyl 2-(3-(4-methoxybenzoyl)tetrahydrofuran-2-yl)acetate (**28a**)



^{1}H and ^{13}C spectra of Ethyl 2-(3-(4-methylbenzoyl)tetrahydrofuran-2-yl)acetate (**28b**)

AKS_PG_HPG3_INTf_L_1H



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PROCNO                        1

F2 - Acquisition Parameters
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PULPROG                zg30
TD                    32768
SOLVENT               CDCl3
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DS                        2
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FIDRES             0.366798 Hz
AQ                 1.3631488 sec
RG                      22.18
DW                    41.600 usec
DE                     6.50 usec
TE                    297.2 K
D1                 1.00000000 sec
TD0                       1

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NUC1                       1H
P1                      12.00 usec
PLW1            21.00000000 W

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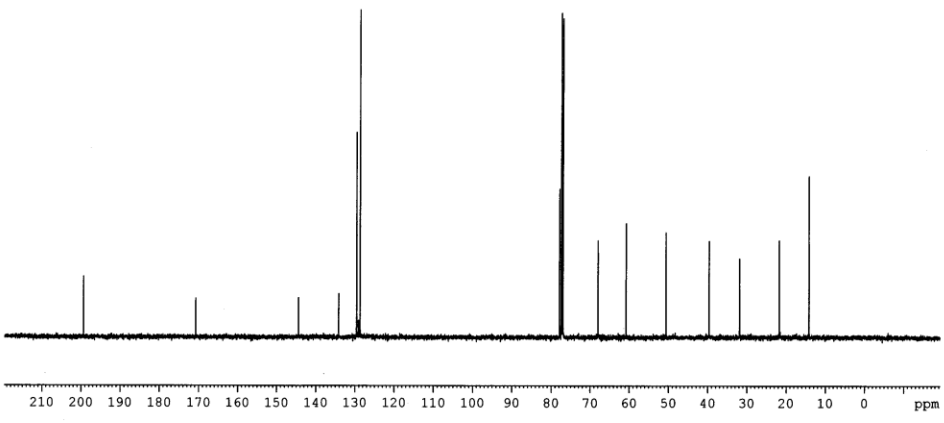


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DE                     6.50 usec
TE                    298.3 K
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D11                0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
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NUC1                      13C
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NUC2                       1H
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PCPD2                  70.00 usec
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PLW12            0.61714000 W
PLW13            0.30239999 W

F2 - Processing parameters
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WDW                          EM
SSB                       0
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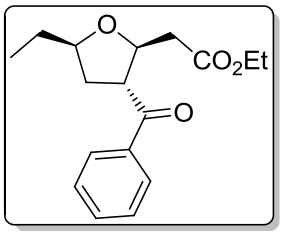
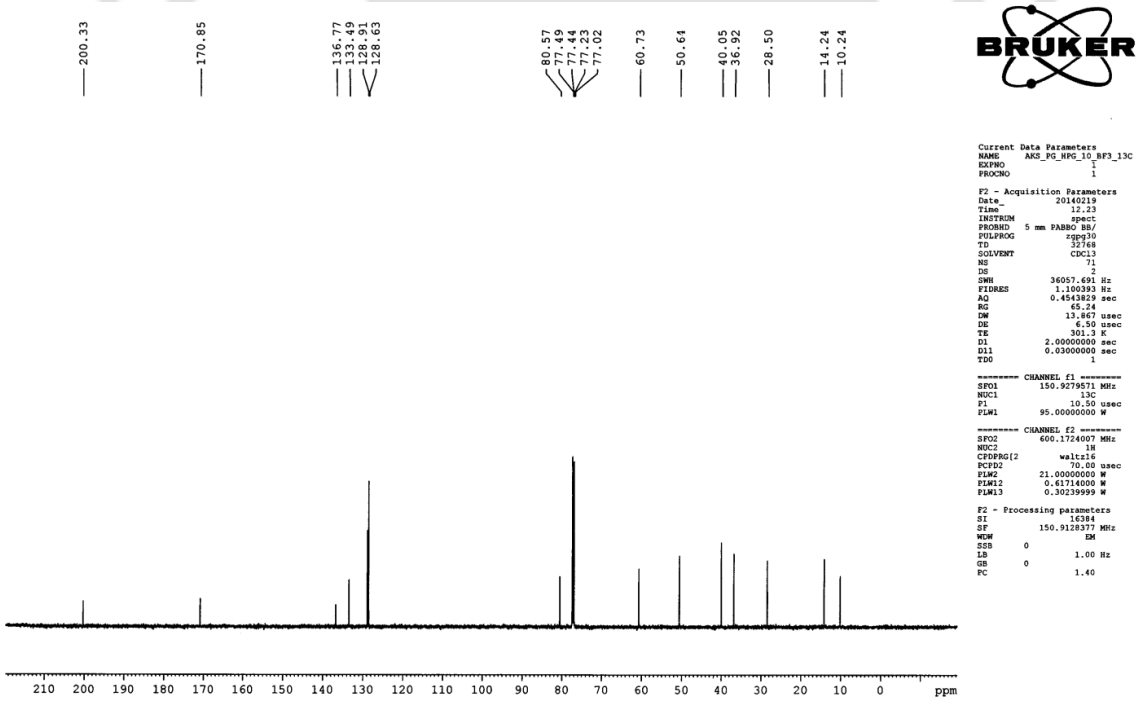
^{1}H and ^{13} Cspectra ofethyl 2-(3-benzoyl-5-ethyltetrahydrofuran-2-yl)acetate (**28j**)





^{1}H and ^{13} Cspectra of ethyl 2-(3-benzoyl-5-phenyltetrahydrofuran-2-yl)acetate (**28m**)

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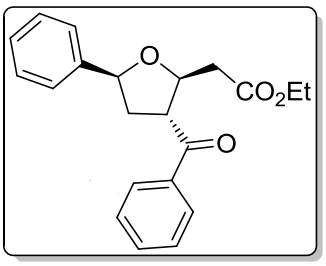

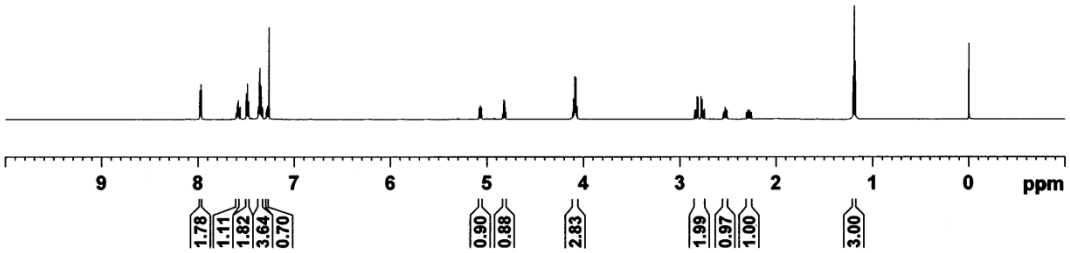


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TD                   32768
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FIDRES               0.366798 Hz
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RG                    99.36
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DE                    6.50 usec
TE                   298.9 K
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TD0                        1

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P1                       12.00 usec
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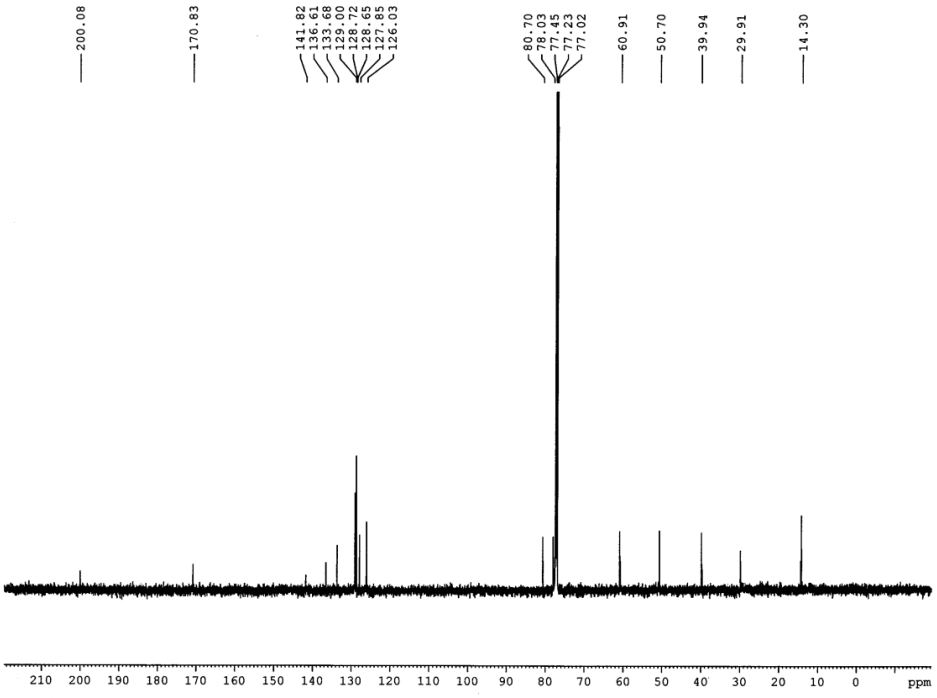


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DS                       2
SWH              36057.691 Hz
FIDRES               1.100393 Hz
AQ                0.4543829 sec
RG                    65.24
DW                   13.867 usec
DE                    6.50 usec
TE                   297.4 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                        1

======== CHANNEL f1 ========
SFO1             150.9279571 MHz
NUC1                       13C
P1                    10.50 usec
PLW1             95.00000000 W

======== CHANNEL f2 ========
SFO2             600.1724007 MHz
NUC2                       1H
CPDPRG[2              waltz16
PCPD2                 70.00 usec
PLW2             21.00000000 W
PLW12             0.61714000 W
PLW13             0.30239999 W

F2 - Processing parameters
SI                       16384
SF               150.9128348 MHz
WDW                         EM
SSB                      0
LB                    1.00 Hz
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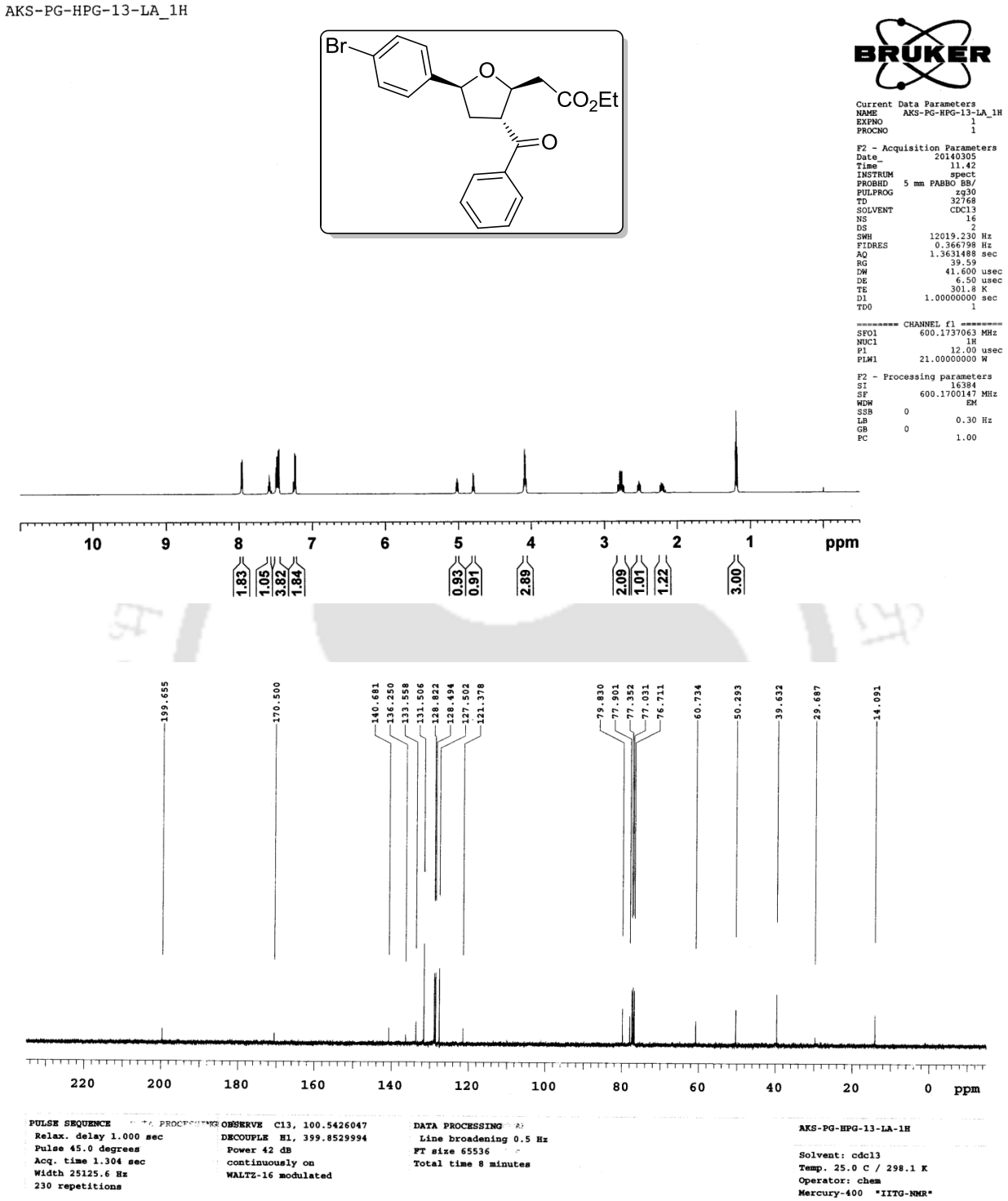
^{1}H and ^{13}C spectra ofethyl 2-(3-benzoyl-5-(4-bromophenyl)tetrahydrofuran-2-yl)acetate (**28o**)



3.8. Crystal parameters

Crystal parameters of compound 28o

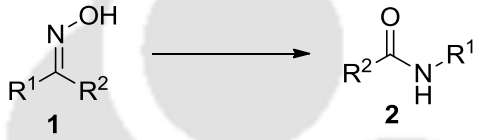
	CCDC 1005256
Formula	$C_{21}H_{21}Br_1O_4$
Formula weight	417.29
T/K	293(2)
Crystal system	Monoclinic
Space group	P 21/c
a/Å	16.043(2)
b/Å	5.0891(7)
c/Å	24.389(3)
α/°	90.00
β/°	101.335(9)
γ/°	90.00
V/Å3	1952.4(4)
Z	4
Abs. Coeff./mm^{-1}	2.128
Abs. Correction	Multi-scan
GOF on F^2	1.280
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0791
	w*R2* = 0.1835
R indices [all data]	*R1* = 0.2206
	w*R2* = 0.2315

CHAPTER 4

Beckmann Rearrangement of 3-Aroyl Tetrahydrofuran: Synthesis of *N*-Aryltetrahydrofuran-3-carboxamides

4.1. Introduction

The Beckmann rearrangement is an important reaction for the transformation of ketoximes into amides in the presence of an acid.[1] In 1886 Beckmann first carried out the conversion of an oxime into an amide, since then this reaction has been called after his name, the Beckmann rearrangement.

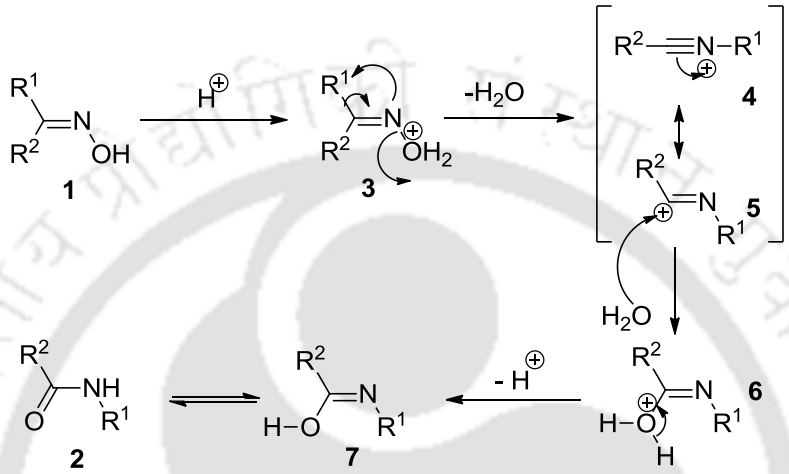


Scheme 4.1.1

The reaction generally requires high temperature and strongly acidic and dehydrating media such as phosphorus pentachloride, concentrated sulfuric acid, or the so-called 'Beckmann's mixture' which contains acetic acid, acetic anhydride and hydrogen chloride.[2] Since these reagents are not suitable for a large number of sensitive substrates, several attempts have been made to achieve the Beckmann rearrangement under significantly milder conditions. In these studies, thionyl chloride,[3] silica gel,[4] molybdenum trioxide on silica gel,[5] montmorillonite KSF,[6] bismuth(III) chloride,[7] 2,4,6-trichloro-1,3,5-triazine,[8] and gallium(III) triflate,[9] P_2O_5,[10] HSO_3Cl,[11] PCl_5,[12] metallic Lewis acids $[RhCl(cod)]_2$,[13] $RuCl_3$,[14] $HgCl_2$,[15] several liquid-phase catalysis systems, ethyl chloroformate/boron trifluoride etherate,[16] anhydrous oxalic acid,[17] bis(2-oxo-3-oxazolidinyl) phosphoric chloride,[18] and diethyl chlorophosphate[19] were used. Potential solid acid catalysts such as TS-1,[20] SAPO-11,[21] FSM-16,[22] ZSM-5,[23] ZSM-11,[24] TiO_2-ZrO_2,[25] and mordenite,[26] have been evaluated as substitutes for the traditionally employed reagents. Several lanthanide-containing catalysts have also been found to be effective for the rearrangement.[27,28] Recently, organocatalyst for the Beckmann rearrangement has attracted researcher's attention for its efficiency in catalytic activity and easy to handle during the rearrangement. Cyanuric chloride (CNC) is a highly efficient organocatalyst used for Beckmann rearrangement.[29]

4.2. Mechanism

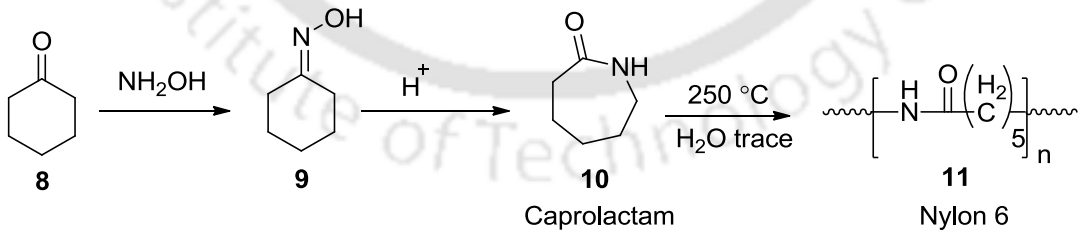
The general mechanism of Beckmann rearrangement is shown in *scheme 4.1.2*. Acid converts the oxime OH into a leaving group. The alkyl (or aryl) group *trans* to the leaving group then migrates to the nitrogen, with the release of a water molecule, resulting in a nitrilium ion **4** which rearranges to carbocation **5**. The water molecule then attacks the carbocation and after deprotonation and tautomerization results in the final amide product **2** (*Scheme 4.2.1*).[30]



Scheme 4.2.1

A general observation of this rearrangement is that the group in position *anti* to the leaving group migrates preferentially to the nitrogen atom in a concerted fashion.

The Beckmann rearrangement is well valorized in the industrial production of one of the important polyamides, nylon 6 (**11**).[31]

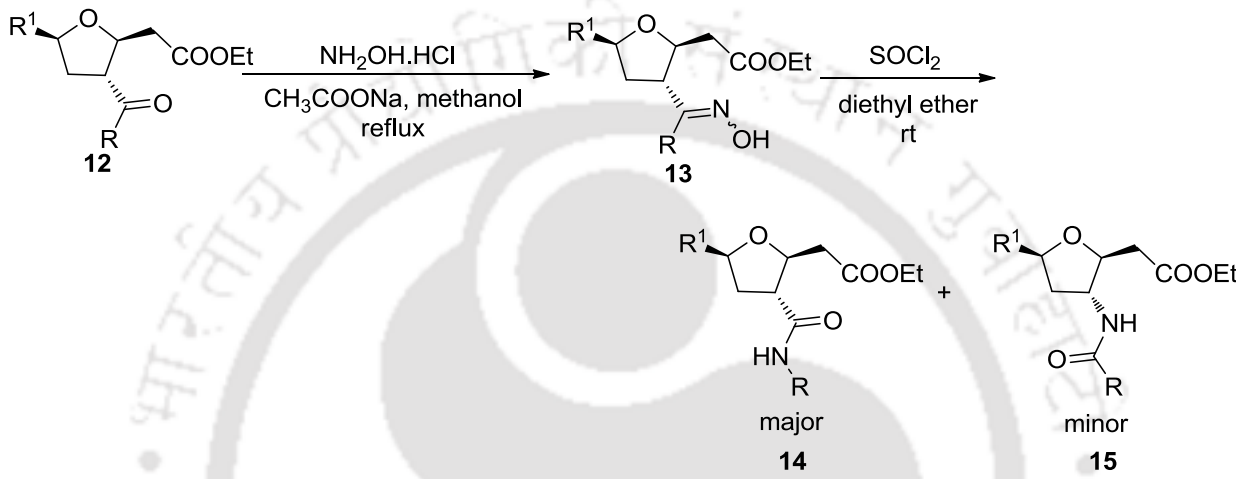


Scheme 4.2.2

4.3. Present work

In chapter 3 we have described the diastereoselective synthesis of substituted tetrahydrofurans *via* Prins cyclization reaction of enol ethers. In order to provide the synthetic application of these 3-aroyl tetrahydrofurans, Beckmann rearrangement reaction was studied (*Scheme 4.3.1*). The substituted tetrahydrofurans were first converted to oxime derivatives containing both *anti* and

syn isomer as inseparable mixture. Thionyl chloride treatment of those oximes gave the Beckmann products at room temperature. It was observed that Beckmann rearrangement of 3-benzoyl tetrahydrofuran **12a** resulted in an inseparable mixture of *N*-phenyltetrahydrofuran-3-carboxamide **14a** and *N*-(tetrahydrofuran-3-yl)benzamide **15a** with a ratio of 9:1 in 50% overall yield (*table 4.3.1*). On the other hand tetrahydrofurans **12b-i** gave only *N*-aryltetrahydrofuran-3-carboxamides as a single isomer. The exclusive formation of aryl migrated products indicates that the aryl group is a better migrating group than the tetrahydrofuran ring.



Scheme 4.3.1

Table 4.3.1. *Beckmann rearrangement of 3-aroyl tetrahydrofurans.*

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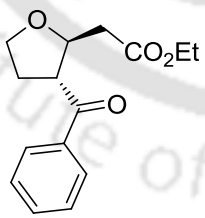
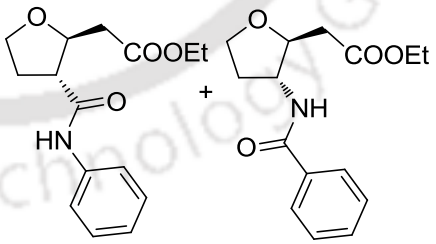
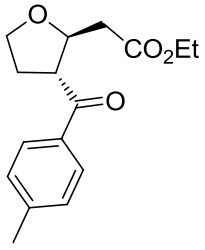
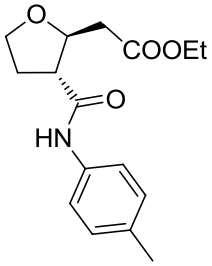
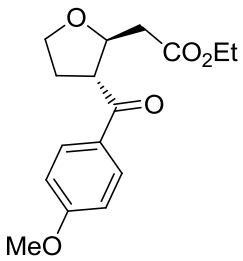
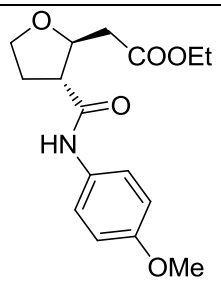
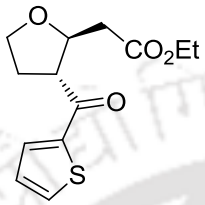
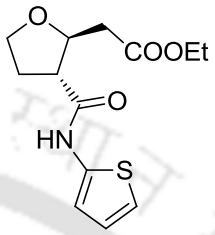
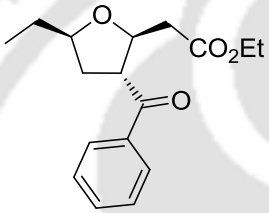
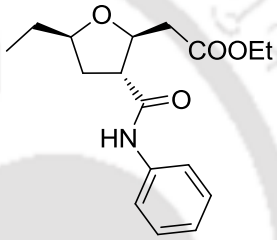
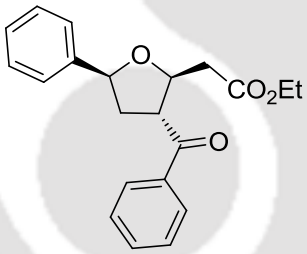
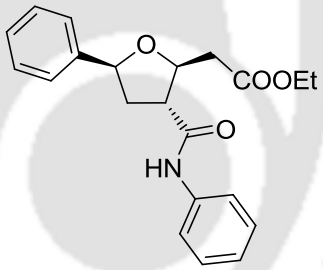
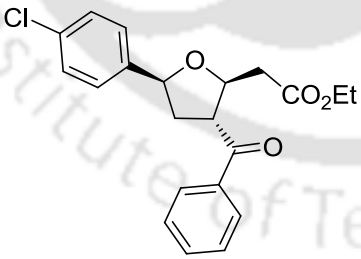
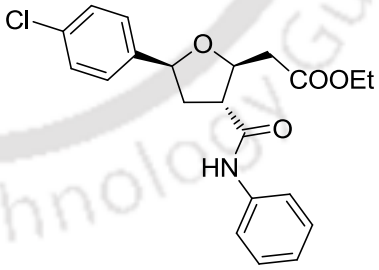
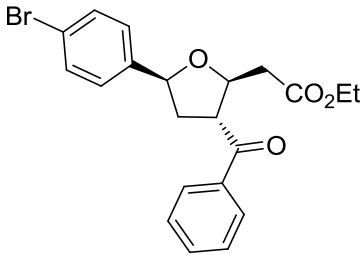
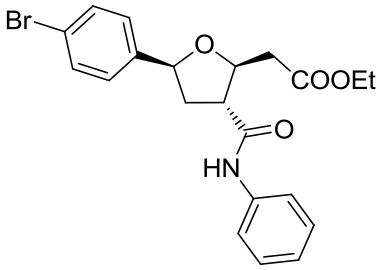
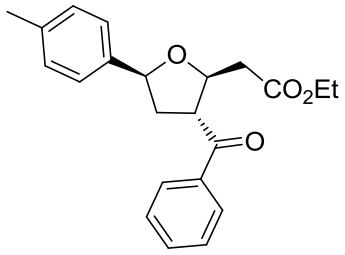
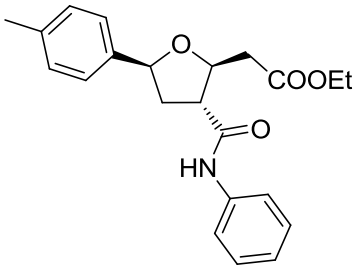
a			50 **14**:**15** = 9:1[b]
b			49

Continued……..

Entry	Reactant (**12**)	Product (**14** / **15**)	Yield(%)[a]
c			49
d			45
e			42
f			41
g			39
h			41

Continued……..

Entry	Reactant (**12**)	Product (**14** / **15**)	Yield(%)[a]
i			40

[a]Yield refers to isolated yield. The compounds are characterized by IR, ^{1}H, ^{13}C NMR and mass spectrometry. [b]Determined by ^{1}H NMR

Conclusion

In conclusion we have studied the thionyl chloride mediated Beckmann rearrangement of 3-aroyl tetrahydrofurans. *N*-aryltetrahydrofuran-3-carboxamides were obtained almost exclusively from the *E*/*Z* mixture of oximes in moderate yields. The preferential formation of aryl migrated products indicates that aryl group is a better migrating group than the tetrahydrofuran ring.

4.4. Experimental section

4.4.1. Instrumentation and Characterization

As described in chapter 2 section 2.4.1

4.4.2. General procedure for the Beckmann rearrangement.

A solution of tetrahydrofuran (1.1 mmol), hydroxylamine hydrochloride (1.1 mmol), and sodium acetate (1.1 mmol) in methanol (3 mL) was refluxed, and the reaction was monitored by TLC. After completion of the reaction, methanol was evaporated under vacuo and diluted with water, and the product was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuo. The crude *E*/*Z* oxime was dissolved in diethyl ether (1 mL) and treated with $SOCl_2$ (1.1 mmol), and the reaction was continued overnight. The solvent and residual $SOCl_2$ were removed under vacuo, and the product was purified by silica gel column chromatography using hexane:EtOAc as eluents.

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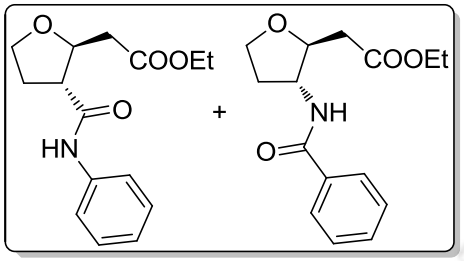
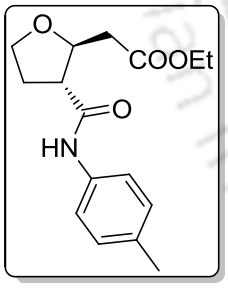
4.4. Characterization Data

Ethyl 2-(3-(Phenylcarbamoyl)tetrahydrofuran-2-yl)acetate (14a) and Ethyl 2-(3-Benzamido tetrahydrofuran-2-yl)acetate (15a)



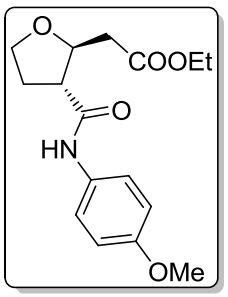
(14a:15a = 9:1). Semisolid, R_f (hexane/EtOAc, 4:1) 0.35; yield 69 mg, 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.2 Hz, 3 H, **14a** and **15a**), 1.99-2.08 (m, 1 H, **14a** and **15a**), 2.47-2.56 (m, 1 H, **14a** and **15a**), 2.63 (dd, *J* = 16.0 and 8.4 Hz, 1 H, **14a**), 2.70 (dd, *J* = 16.4 and 8.4 Hz, 1 H, **15a**), 2.76-2.84 (m, 1 H, **14a** and **15a**), 2.90-2.96 (m, 1 H, **14a** and **15a**), 3.88 (q, *J* = 7.6 Hz, 1 H, **14a** and **15a**), 3.92-3.90 (m, 1 H, **14a** and **15a**), 4.12 (q, *J* = 7.6 Hz, 2 H, **15a**), 4.19 (q, *J* = 7.2 Hz, 2 H, **14a**), 4.33 (t, *J* = 6.4 Hz, 1 H, **15a**), 4.38-4.46 (m, 1 H, **14a**), 7.09 (t, *J* = 7.2 Hz, 1 H, **14a** and **15a**), 7.29-7.34 (m, *J* = 7.2 Hz, 2 H, **14a**), 7.37-7.44 (m, 2 H, **15a**), 7.57 (d, *J* = 7.2 Hz, 2 H, **14a** and **15a**), 8.56 (brs, 1 H, **15a**), 8.70 (brs, 1 H, **14a**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 20.1, 29.1, 39.7, 40.0, 51.1, 61.4, 63.1, 68.5, 78.6, 78.7, 119.8, 124.2, 124.3, 128.3, 128.5, 129.1, 131.8, 138.5, 170.9, 172.6; IR (KBr, neat) 3319, 2980, 2885, 1731, 1666, 1600, 1539, 1443, 1311, 1163, 1067, 1028, 757 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}NO_4$ $(M+H)^+$ 278.1387, found 278.1396.

Ethyl 2-(3-(p-tolylcarbamoyl)tetrahydrofuran-2-yl)acetate (14b):



Semisolid, R_f (hexane/EtOAc, 4:1) 0.30; yield 71 mg, 49%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.6 Hz, 3 H), 2.01-2.08 (m, 1 H), 2.30 (s, 3 H), 2.49-2.60 (m, 1 H), 2.63 (dd, *J* = 14.0 and 8.8 Hz, 1 H), 2.78 (dd, *J* = 16.4 and 4.8 Hz, 1 H), 2.90-2.94 (m, 1 H), 3.87 (q, *J* = 7.6 Hz, 1 H), 3.93-3.99 (m, 1 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 4.37-4.42 (m, 1 H), 7.10 (d, *J* = 8 Hz, 2 H), 7.44 (d, *J* = 8 Hz, 2 H), 8.52 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.0, 29.1, 40.0, 51.1, 61.4, 68.5, 78.7, 119.8, 129.6, 133.8, 135.9, 170.7, 172.6; IR (KBr, neat) 3318, 2961, 2850, 1735, 1655, 1603, 1537, 1458, 1311, 1162, 1060, 1026, 736 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}NO_4$ $(M+H)^+$ 292.1543, found 292.1542.

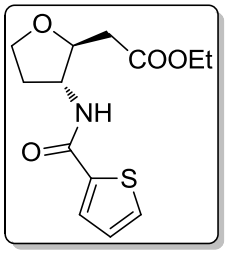
Ethyl 2-((2S,3R)-3-((4-methoxyphenyl)carbamoyl)tetrahydrofuran-2-yl)acetate (14c):



White solid, M. P.: 95-97 ◦C. R_f (hexane/EtOAc, 3:1) 0.35; yield 75 mg, 49%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3 H), 1.99-2.08 (m, 1 H), 2.47-2.54 (m, 1 H), 2.62 (dd, *J* = 16.0 and 8.4 Hz, 1 H), 2.78 (dd, *J* = 16.4 and 4.8 Hz, 1 H), 2.90-2.93 (m, 1 H), 3.78 (s, 3H), 3.87 (q, *J* = 7.6 Hz, 1 H), 3.94-3.99 (m, 1 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 4.37-4.41 (m, 1 H), 6.84 (d, *J* = 8.4 Hz, 2 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 8.46 (brs, 1 H); ^{13}C NMR (100

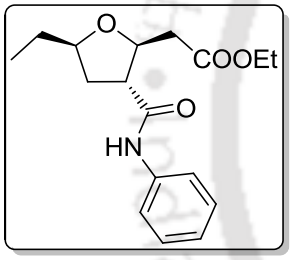
MHz, CDCl3) δ 14.3, 29.2, 40.0, 51.0, 55.7, 61.4, 68.5, 78.8, 114.3, 121.5, 121.7, 131.7, 170.6, 172.5; IR (KBr, neat) 3313, 2978, 2874, 1738, 1659, 1603, 1549, 1465, 1313, 1160, 1030, 737 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}NO_5$ $(M+H)^+$ 308.1492, found 308.1493.

Ethyl 2-(3-(thiophene-2-carboxamido)tetrahydrofuran-2-yl)acetate. (14d):



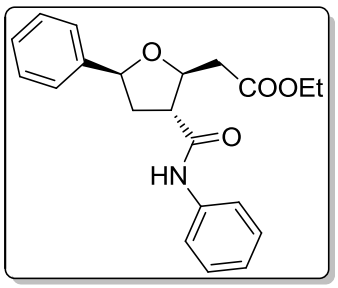
Semisolid, R_f (hexane/EtOAc, 4:1) 0.37; yield 64 mg, 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3 H), 2.01-2.08 (m, 1 H), 2.24-2.60 (m, 1 H), 2.63 (dd, *J* = 14.0 and 8.8 Hz, 1 H), 2.78 (dd, *J* = 16.4 and 4.8 Hz, 1 H), 2.96-3.01 (m, 1 H), 3.88 (q, *J* = 7.2 Hz, 1 H), 3.98-4.07 (m, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.34-4.39 (m, 1 H), 7.74 (d, *J* = 4.8 Hz, 1 H), 7.84 (d, *J* = 3.6 Hz, 1 H), 8.63 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 29.2, 40.0, 52.9, 61.5, 68.7, 78.9, 114.2, 117.8, 125.6, 142.4, 170.6, 172.8; IR (KBr, neat) 3319, 2980, 2885, 1731, 1666, 1600, 1539, 1443, 1311, 1163, 1067, 1028, 757 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{28}NO_4S$ $(M+H)^+$ 284.0951, found 284.0953.

Ethyl 2-(5-Ethyl-3-(phenylcarbamoyl)tetrahydrofuran-2-yl)-acetate (14e):



Semisolid, R_f (hexane/EtOAc, 4:1) 0.38; yield 64 mg, 42%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.2 Hz, 3 H), 1.13 (t, *J* = 7.2 Hz, 3 H), 1.58-1.68 (m, 1 H), 1.74-1.84 (m, 1 H), 2.02-2.10 (m, 1 H), 2.22-2.30 (m, 1 H), 2.66 (dd, *J* = 16.4 and 8.8 Hz, 1 H), 2.81 (dd, *J* = 16.4 and 5.6 Hz, 1 H), 3.18 (q, *J* = 7.6 Hz, 1 H), 3.74-3.82 (m, 1 H), 3.98-4.10 (m, 2 H), 4.34 (q, *J* = 7.2 Hz, 1 H), 7.07 (t, *J* = 7.6 Hz, 1 H), 7.28 (t, *J* = 8.0 Hz, 2 H), 7.47 (d, *J* = 8.0 Hz, 2 H), 7.60 (brs, 1 H); ^{13}C NMR (150 MHz, CDCl3) δ 10.6, 14.2, 28.3, 30.0, 34.9, 36.7, 49.7, 61.1, 80.8, 119.8, 124.5, 129.2, 138.1, 170.9, 172.5; IR (KBr, neat) 3444, 2925, 2856, 1731, 1666, 1600, 1540, 1443, 1311, 1177, 1034, 755 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{24}NO_4$ $(M+H)^+$ 306.1700, found 306.1709.

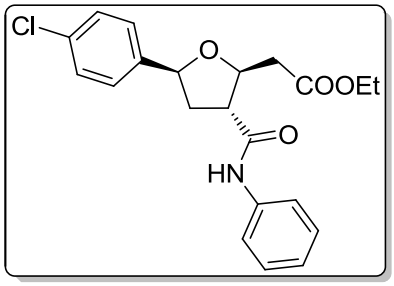
Ethyl 2-(5-phenyl-3-(phenylcarbamoyl)tetrahydrofuran-2-yl)acetate (14f):



White solid, M. P.: 101-102 ◦C. R_f (hexane/EtOAc 4:1) 0.33; yield 72 mg, 41%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.2 Hz, 3 H), 2.11-2.19 (m, 1 H), 2.32-2.39 (m, 1H), 2.74 (dd, *J* = 16.8 and 9.6 Hz, 1 H), 2.88 (dd, *J* = 17.6 and 5.6 Hz, 1 H), 3.08-3.12 (m, 1 H), 4.23 (q, *J* = 7.6 Hz, 2 H), 4.56-4.60 (m, 1H), 5.01 (dd, *J* = 8.8 and 6.0 Hz, 1 H), 7.11 (t, *J* = 7.2 Hz, 1 H), 7.24 (t, *J* = 7.6 Hz, 2 H), 7.34 (t, *J* = 7.6 Hz, 2 H), 7.46 (d, *J* = 8 Hz, 2 H), 7.59 (d, *J* = 8 Hz, 2 H), 8.88 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 29.9, 40.6, 51.3, 61.6, 79.0, 80.0, 119.7, 121.6, 124.3, 127.7, 129.2, 131.7, 138.6, 140.6, 170.8, 173.0; IR (KBr, neat) 3343, 2923, 2853, 1734, 1663, 1600, 1546,

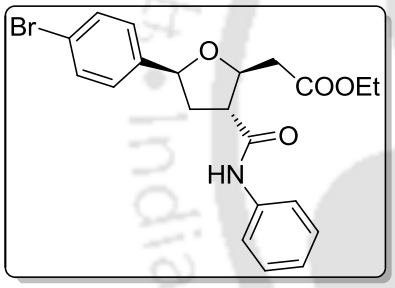
1443, 1310, 1175, 1011, 756, cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{24}NO_4$ $(M + H)^+$ 354.1700, found 354.1705.

Ethyl 2-(5-(4-chlorophenyl)-3-(phenylcarbamoyl)tetrahydrofuran-2-yl)acetate (14g):



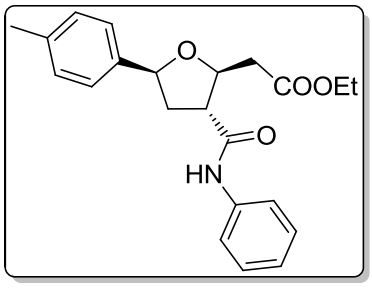
White solid, M. P.: 132-133 ◦C. R_f (hexane/EtOAc 4:1) 0.29; yield 75 mg, 39%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, *J* = 7.2 Hz, 3 H), 2.41-2.49 (m, 1 H), 2.54-2.61 (m, 1H), 2.75 (dd, *J* = 17.6 and 8.8 Hz, 1 H), 2.81 (dd, *J* = 17.6 and 4.4 Hz, 1 H), 3.36 (q, *J* = 7.2 Hz, 1 H), 4.09 (q, *J* = 7.6 Hz, 2 H), 4.53-4.60 (m, 1H), 4.83 (dd, *J* = 8.4 and 8.0 Hz, 1 H), 7.11 (t, J = 6.8 Hz, 1 H), 7.29-7.34 (m, 4 H), 7.44-7.82 (m, 4 H), 7.56 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 39.9, 40.2, 50.8, 61.1, 78.21, 80.2, 119.9, 124.3, 127.3, 129.0, 129.5, 133.8, 137.8, 140.5, 170.7, 172.8; IR (KBr, neat) 3324, 2923, 2855, 1730, 1665, 1600, 1541, 1446, 1308, 1175, 1010, 755, cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{23}ClNO_4$ $(M + H)^+$ 388.1310, found 388.1315.

Ethyl 2-(5-(4-bromophenyl)-3-(phenylcarbamoyl)tetrahydrofuran-2-yl)acetate (14h):



White solid, M. P.: 152-154 ◦C. R_f (hexane/EtOAc 4:1) 0.22; yield 88 mg, 41%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, *J* = 6.8 Hz, 3 H), 2.41-2.47 (m, 1 H), 2.54-2.61 (m, 1H), 2.79 (dd, *J* = 17.2 and 8.8 Hz, 1 H), 2.92 (dd, *J* = 16.4 and 4.0 Hz, 1 H), 3.35 (q, *J* = 6.8 Hz, 1 H), 4.09 (m, 2 H), 4.53-4.60 (m, 1H), 4.81 (t, *J* = 8.4 Hz, 1 H), 7.11 (t, *J* = 6.8 Hz, 1 H), 7.31 (t, *J* = 7.6 Hz, 2 H), 7.37 (d, *J* = 7.6 Hz, 2 H), 7.46-7.49 (m, 4H) 7.57 (brs, 1 H); ^{13}C NMR (100 MHz, CDCl3) δ 14.1, 39.8, 40.1, 50.7, 61.0, 78.2, 80.2, 119.7, 121.5, 124.4, 129.2, 133.7, 138.1, 140.8, 170.5, 172.8; IR (KBr, neat) 3322, 2927, 2857, 1731, 1669, 1601, 1542, 1447, 1308, 1174, 1020, 752, cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{23}BrNO_4$ $(M + H)^+$ 432.0805, found 432.0795.

Ethyl 2-(3-(phenylcarbamoyl)-5-(*p*-tolyl)tetrahydrofuran-2-yl)acetate (14i):

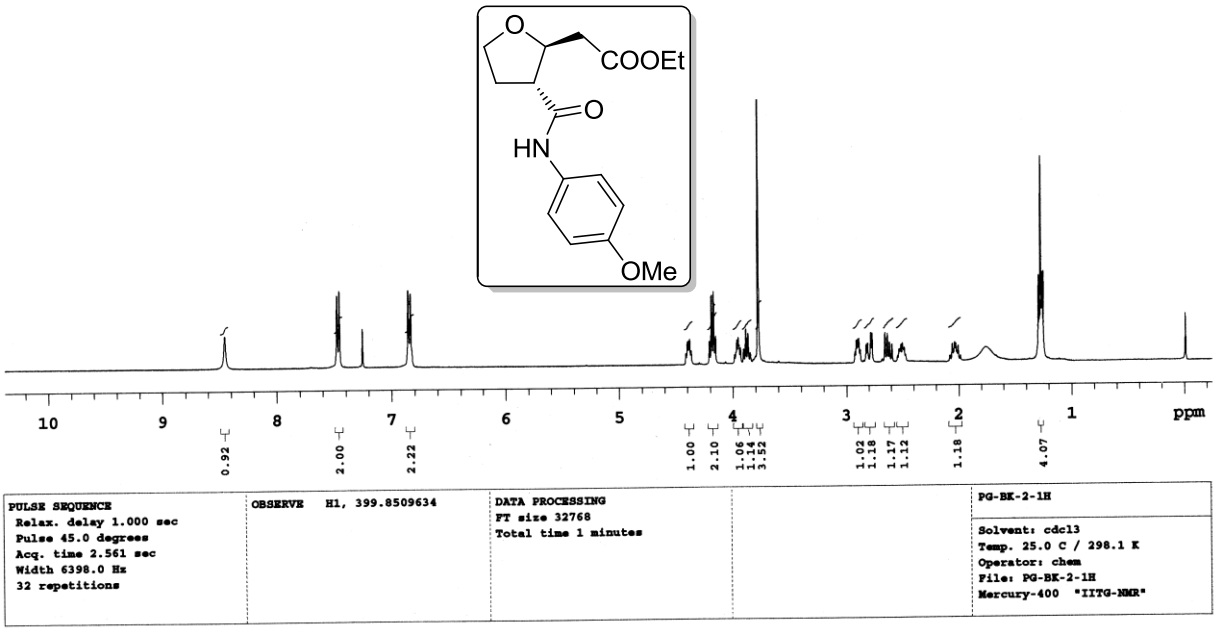


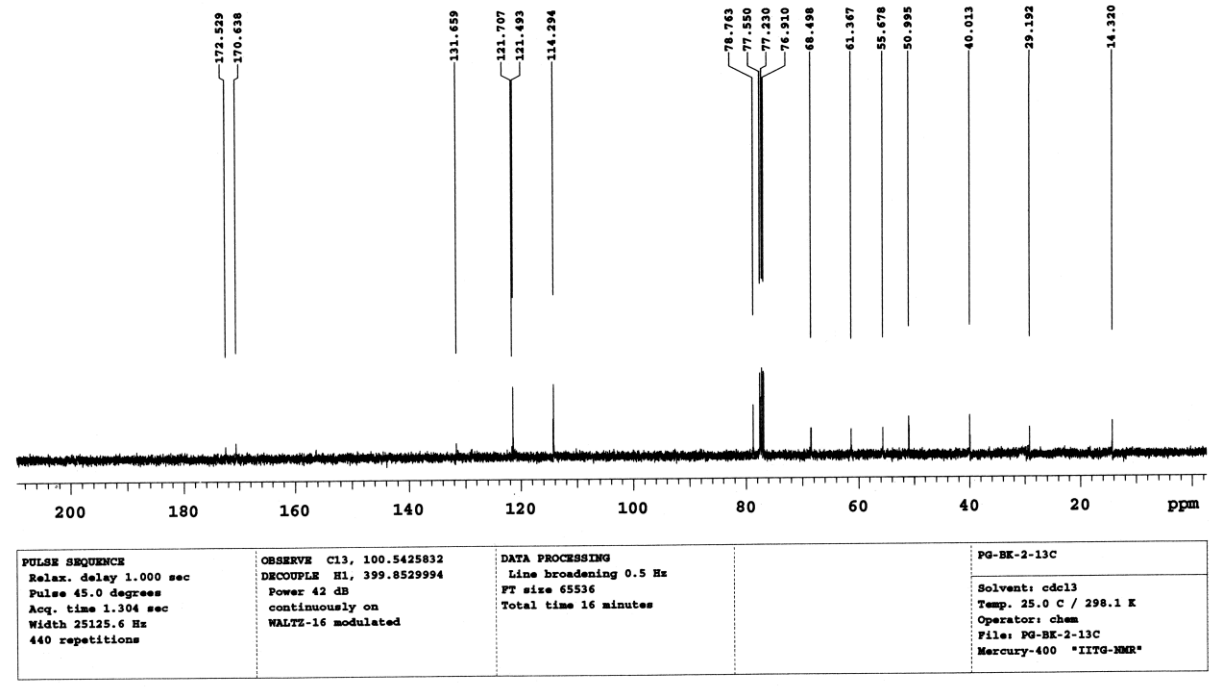
White solid, M. P.: 114-116 ◦C. R_f (hexane/EtOAc 4:1) 0.32; yield 72 mg, 41%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.2 Hz, 3 H), 2.22-2.28 (m, 1 H), 2.36(s, 3 H), 2.42-2.47 (m, 1H), 2.74 (dd, *J* = 15.0 and 6.0 Hz, 1 H), 2.84 (dd, *J* = 15.0 and 6.0 Hz, 1 H), 3.06-3.11 (m, 1 H), 4.21 (q, *J* = 7.6 Hz, 2 H), 4.53-4.57 (m, 1H), 4.89 (dd, *J* = 8.8 and 6.0 Hz, 1 H), 7.12 (t, *J* = 7.2 Hz, 1 H), 7.25 (d, *J* = 7.8 Hz, 2 H), 7.34 (d, *J* = 7.6 Hz, 2 H), 7.46 (t, *J* = 7.8 Hz, 2 H), 7.63 (d, *J* = 8 Hz, 2 H), 8.62 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.2, 29.9, 40.2, 51.4, 61.7, 79.1, 80.1, 119.5, 121.8, 124.2, 127.2, 129.8, 132.1, 138.8, 140.2, 170.6, 172.9; IR (KBr, neat) 3341, 2923,

2846, 1731, 1666, 1601, 1543, 1449, 1312, 1171, 1017, 753, cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{26}NO_4$ $(M + H)^+$ 368.1856, found 368.1848.

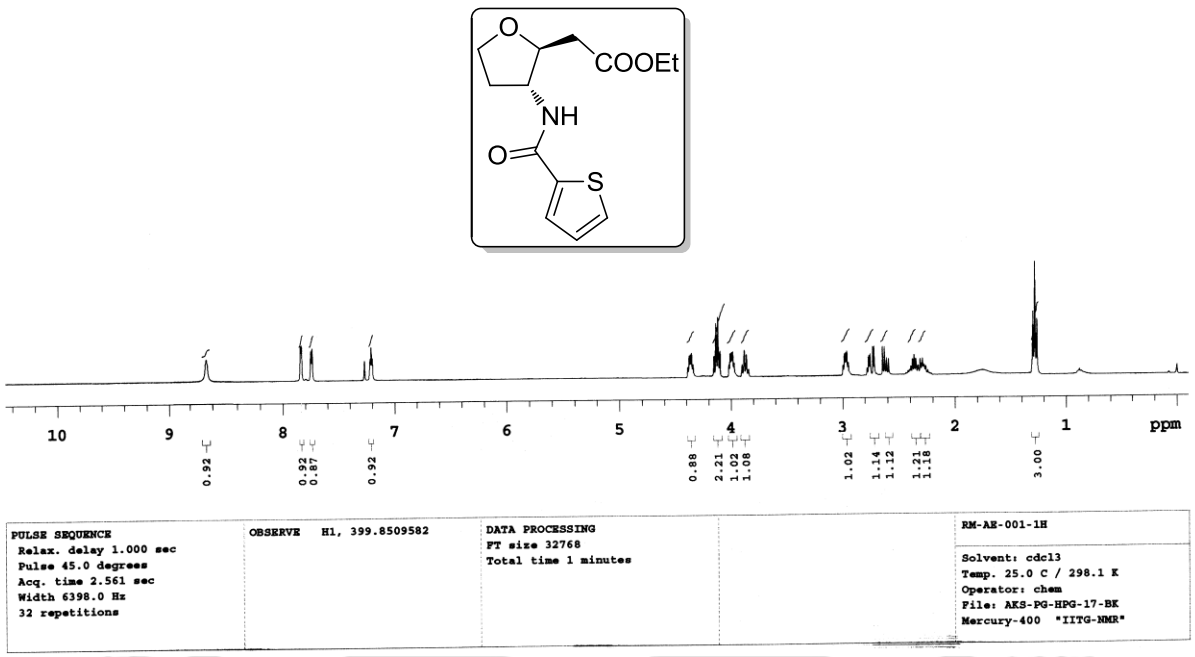
4.5. Selected spectra of *N*-aryltetrahydrofuran-3-carboxamides

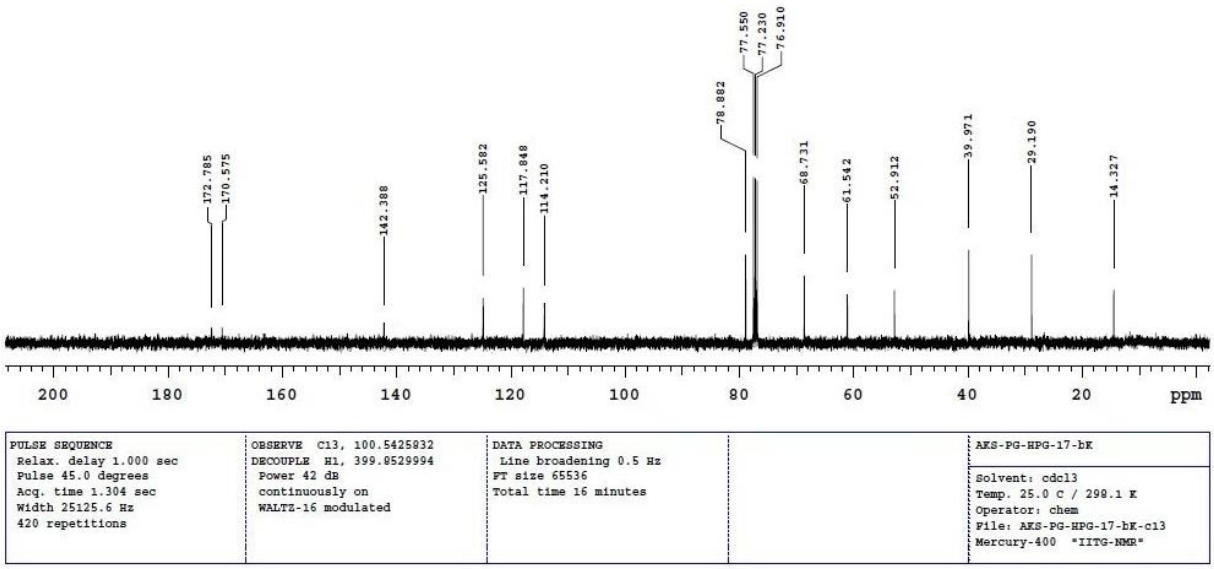
^{1}H and ^{13}C spectra of ethyl 2-(-3-((4-methoxyphenyl)carbamoyl)tetrahydrofuran-2-yl)acetate **(14c)**



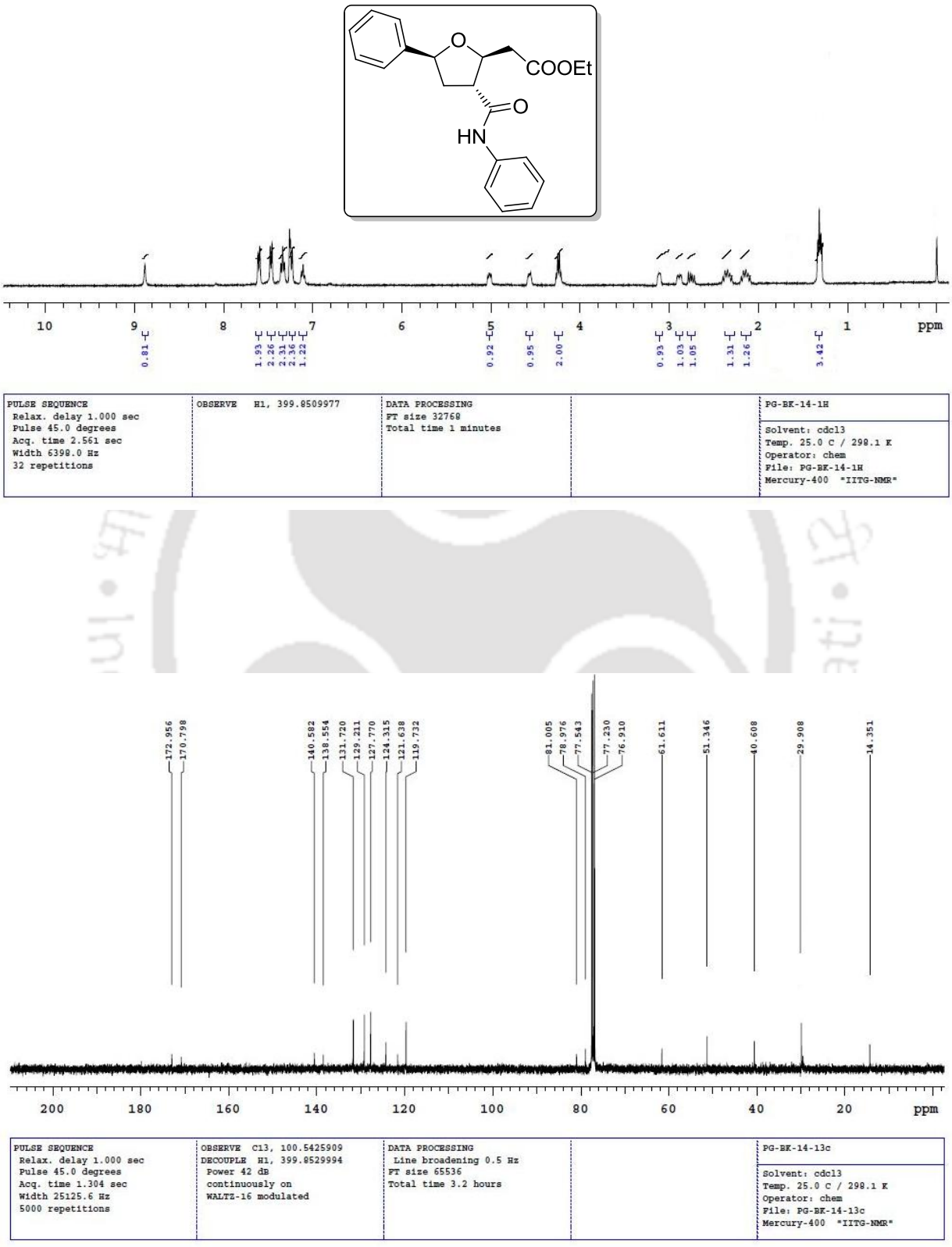


^{1}H and ^{13}C spectra of ethyl 2-(3-(thiophene-2-carboxamido)tetrahydrofuran-2-yl)acetate **(14d)**

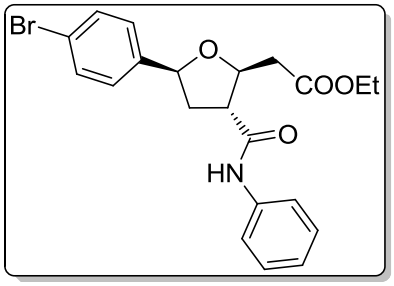


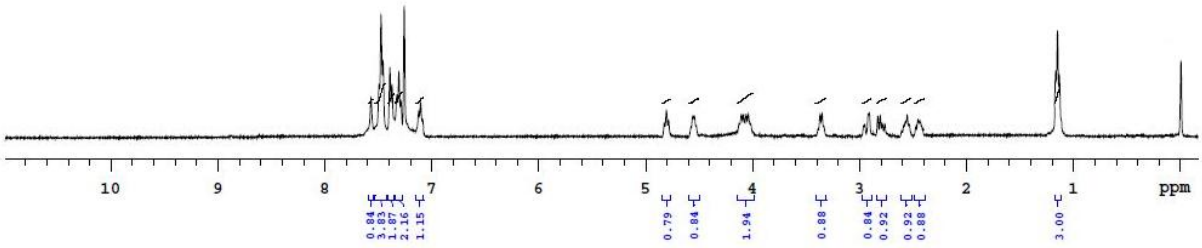


^{1}H and ^{13}C spectra of ethyl 2-(5-phenyl-3-(phenylcarbamoyl)tetrahydrofuran-2-yl)acetate **(14f)**

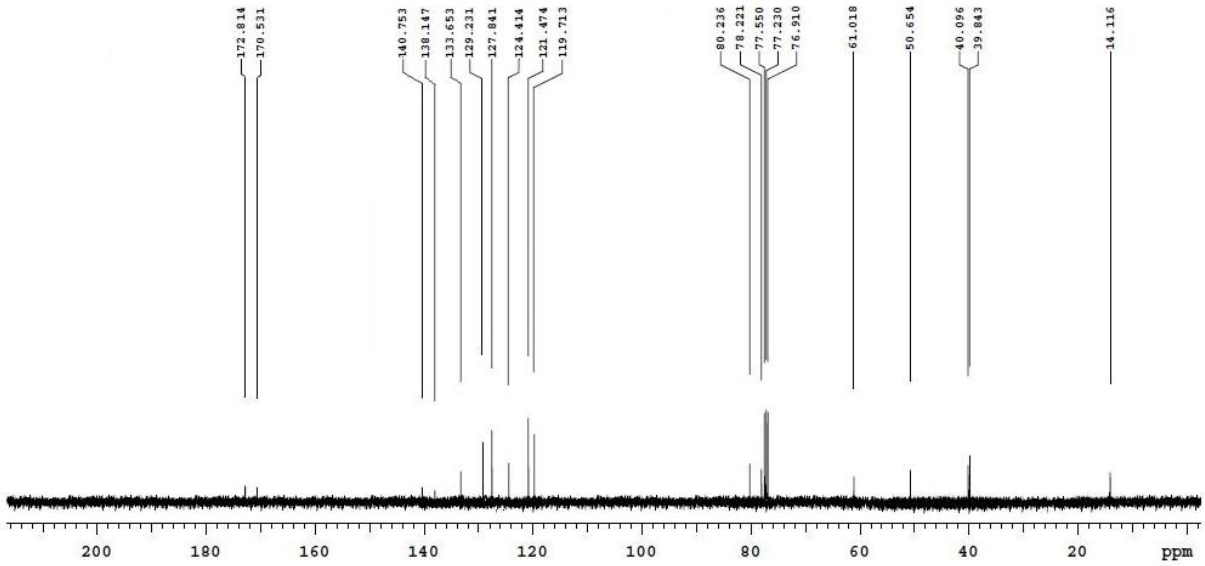


^{1}H and ^{13}C spectra of ethyl 2-(5-phenyl-3-(phenylcarbamoyl)tetrahydrofuran-2-yl)acetate **(14h)**





PULSE SEQUENCE Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 2.561 sec Width 6398.0 Hz 200 repetitions	OBSERVE H1, 399.8509985	DATA PROCESSING FT size 32768 Total time 11 minutes		PG-BK-13-1H Solvent: cdcl3 Temp. 25.0 C / 298.1 K Operator: chem File: PG-BK-13-1H Mercury-400 "IITG-NMR"



PULSE SEQUENCE Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 1.304 sec Width 25125.6 Hz 970 repetitions	OBSERVE C13, 100.5425047 DECOUPLE H1, 399.8529994 Power 42 dB continuously on WALTZ-16 modulated	DATA PROCESSING Line broadening 0.5 Hz FT size 65536 Total time 37 minutes		PG-BK-13-13C Solvent: cdcl3 Temp. 25.0 C / 298.1 K Operator: chem File: PG-BK-13-13C Mercury-400 "IITG-NMR"

Part II

CHAPTER 1

Review on Asymmetric Synthesis of 1,3-Diols and Chiral Sulfoxides

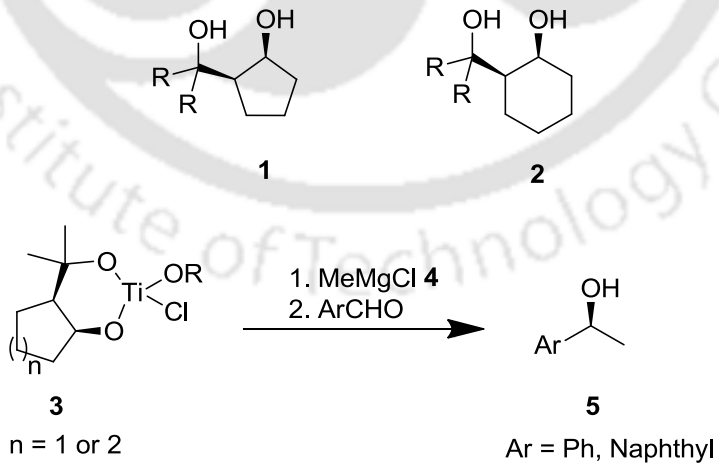
1.1. Importance and applications of chiral 1,3-diols

Optically active 1,3-diols are very important compounds in asymmetric synthesis, since they represent chiral building blocks for many polyketide-derived natural products, and have frequently been used as valuable intermediates in the synthesis of drugs and natural products with important biological activity.[1] Such diols have shown promise as chiral ligands[2] and more frequently as chiral auxiliaries.[3]

1.1.1. As chiral ligands

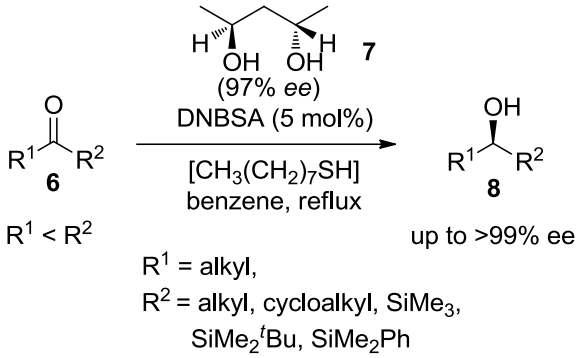
Unlike 1,2 and 1,4 diols, 1,3-diols are less frequently encountered as chiral ligand. A few C_2-symmetric chiral 1,3-diols are known in the literature, none have proved to be very good sources of chirality. It is important that the diol is conformationally rigid for it to be an effective chiral auxiliary / ligand.

Chiral 1,3-diols **1** & **2** were obtained from the yeast-reduction products of 2-oxocyclopentane- and 2-oxocyclohexane carboxylates and excess MeLi, BuLi or PhLi. These ligands form titanium complexes **3** with TiCl(*i*-PrO)$_3$ which are effective catalysts for enantioselective nucleophilic addition of MeMgCl **4** to benzaldehyde and 1-naphthaldehyde yielding 1-phenyl ethanol and 1-naphthyl ethanol, respectively in good enantioselectivities (*Scheme 1.1.1.1*).[2a]



Scheme 1.1.1.1

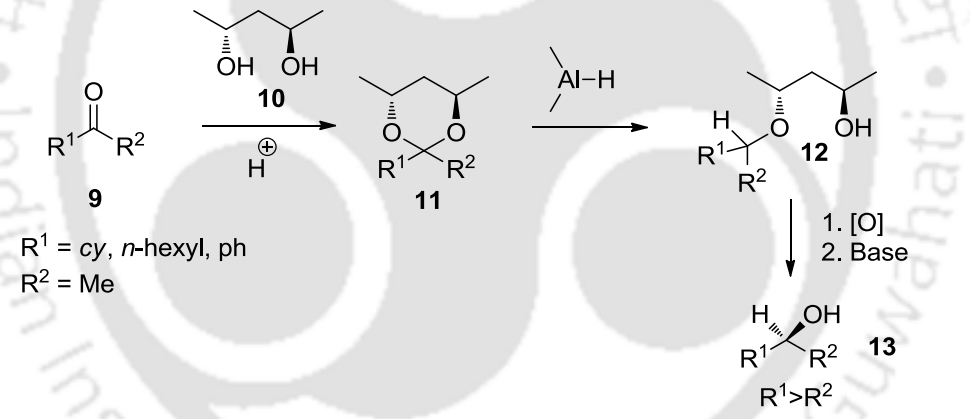
Recently Matsuo and coworkers have reported effective use of a chiral 1,3-diol ligand **7** for brønsted acid catalyzed asymmetric reduction of ketones **6** and acyl silanes (*Scheme 1.1.1.2*). The alcohols **8** were obtained with excellent enantioselectivity.[2b]



Scheme 1.1.1.2

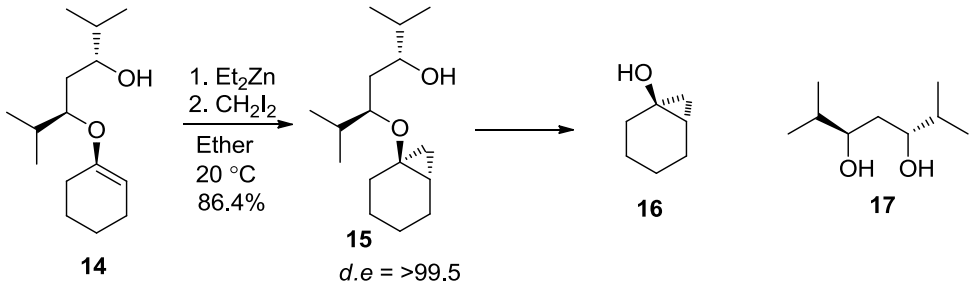
1.1.2. As chiral auxiliaries

(-)-(*R, R*)-2,4-pentanedioldiol **10** was found to be an excellent chiral auxilliary in the reductive cleavage of chiral acetals **11**, derived from ketones **9**, with hydride reagent to produce the optically active alcohols. The products **12** were formed diastereoselectively, and the removal of the chiral auxiliary afforded optically active alcohols **13** with *ee* upto 96%.[3a]



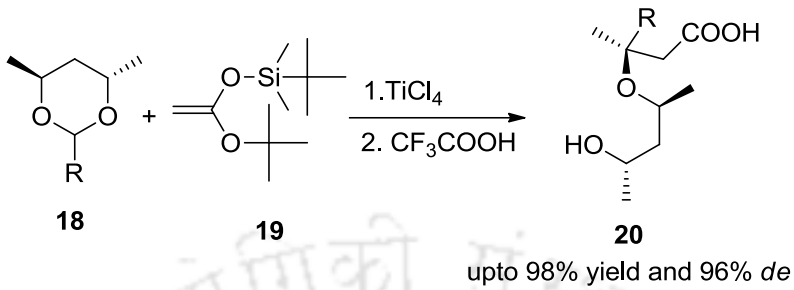
Scheme 1.1.2.1

Tai and co-workers used (*3S,5S*)-2,6-dimethyl-3,5-heptanediol **17** as chiral auxiliary for diastereo-differentiating Simmons-Smith reactions of enol ethers **14** derived from various ketones.[3b] The diastcrcomcric cxcess of these reactions reached to be >99%.



Scheme 1.1.2.2

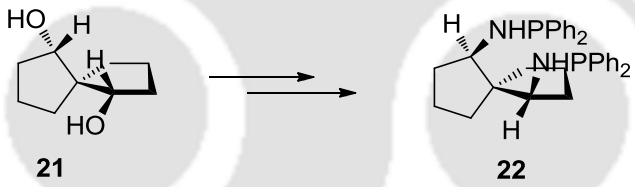
$TiCl_4$ catalyzed coupling of chiral acetals **18** derived from aldehydes and (*S*,*S*)-2,4-pentane diol with the silyl enol ether **19** provides excellent diastereoselection for the product **20** (*Scheme 1.1.1.3*).[3c] This procedure was followed towards the synthesis of (*R*)-(+)-*α*-lipoic acid.



Scheme 1.1.2.3

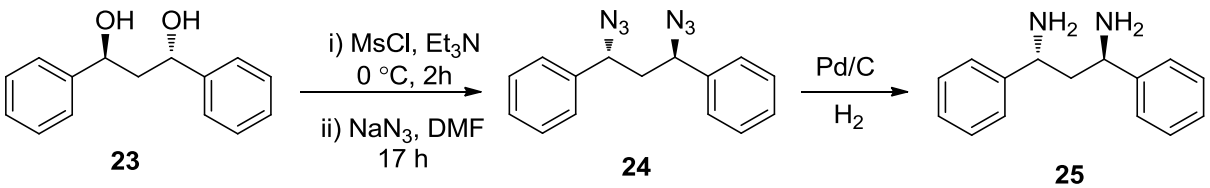
1.1.3. As intermediate in chiral synthesis

Chan and co-workers used rhodium complex of bisphosphinamidite ligand **22** for highly enantioselctive hydrogenation of methyl esters of 2-acetamidoacrylic acid and (*Z*)-2-acetamido-3-arylacrylic acid. The chiral bisphosphinamidite ligand **22** was prepared from the chiral diol **21** **(***Scheme 1.1.3.1*).[4a]



Scheme 1.1.3.1

Chiral 1,3 diols are known to act as precursors for chiral 1,3 diamine ligands. (1*R*,3*R*)-1,3-diphenylpropane-1,3-diamine **25** was used as ligand for Ru-catalyzed enantioselective hydrogenation of prochiral ketones. The synthetic route of the diamine ligand involved (1*S*,3*S*)-1,3-diphenylpropane-1,3-diol **23** as intermediate (*Scheme 1.1.3.2*).[4b]



Scheme 1.1.3.2

1.2. Synthesis of chiral 1,3 diols

Chiral 1,3-diols can be obtained *via* the following three methods:

(a) Diastereoselective reduction of chiral hydroxy ketones.

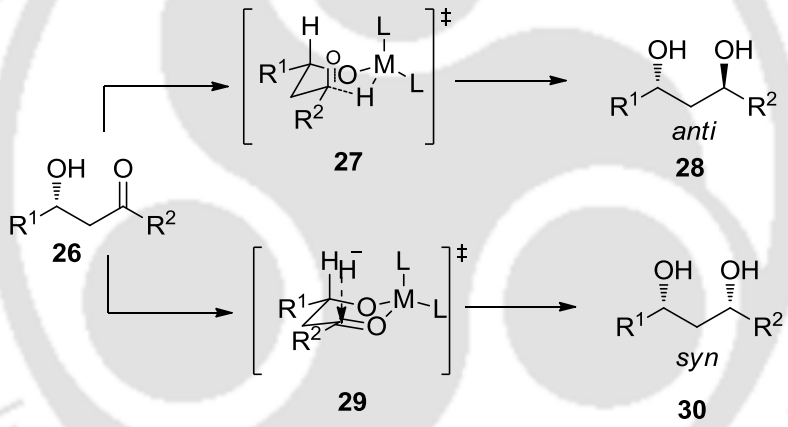
(b) Enantioselective reduction of *β*-diketones.

(c) Diastereoselective reduction of *β*-diketones followed by resolution of the resulting diols.

A brief description of these methods is given below.

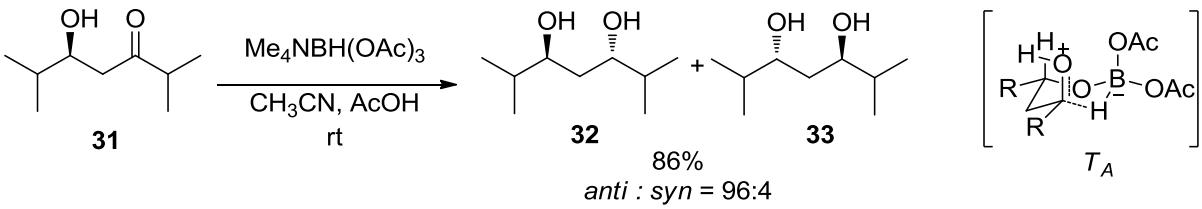
1.2.1. Diastereoselective reduction of chiral hydroxy ketones

This method involves hydroxyl directed reduction of the keto function by a suitable reducing agent. When the reducing agent possesses the capacity to bind to the hydroxyl function with intramolecular transfer of hydride, the *anti*-1,3-diol **28** is formed preferentially.[5a, 5b] On the other hand, when an additive is employed to preorganize the substrate prior to intermolecular hydride addition, the *syn* isomer **30** predominates.[5c, 5d, 5e]



Scheme 1.2.1.1

For example, Evans and coworkers used the mild reducing agent tetramethylammonium triacetoxyborohydride to reduce acyclic *β*-hydroxy ketones to their corresponding *anti* diols with high diastereoselectivity (*Scheme 1.2.1.2*).[5b]

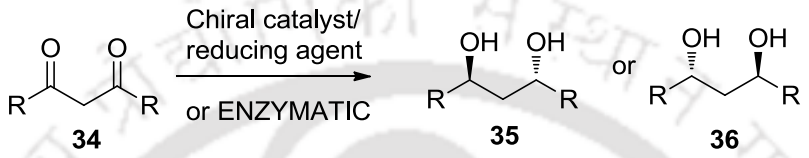


Scheme 1.2.1.2

The mechanism of these reductions involves an acid-promoted ligand exchange of acetate for substrate alcohol **31** by the triacetoxyborohydride anion. The resultant hydride intermediate, presumably an alkoxydiacetoxy borohydride, reduces proximal ketones by intramolecular hydride delivery.

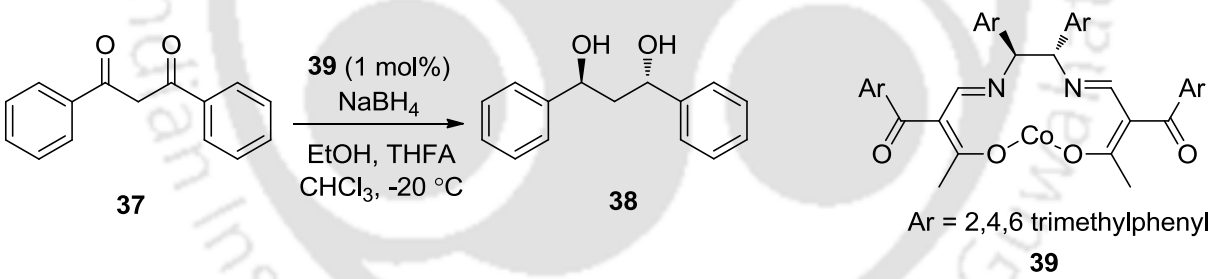
1.2.2. Enantioselective reduction of *β*-diketones

In this case the reduction can be achieved either by using the combination of a suitable chiral catalyst and a reducing agent or by enzymatically.[6]



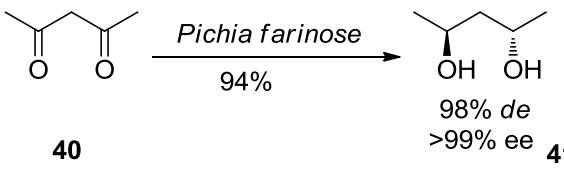
Scheme 1.2.2.1

Ohtsuka and co-workers prepared optically pure 1,3-diaryl-1,3-propanediols **38** from the corresponding 1,3-diketones **37** by enantioselective borohydride reduction in the presence of a catalytic amount of *β*-ketoiminato cobalt(II) complexes **39** (*Scheme 1.2.2.2*).[6a]



Scheme 1.2.2.2

Ikeda *et al.* reported a practical synthesis of optically pure (*R,R*)-2,4-pentanediol **41**. This highly efficient enzymatic method involves the reduction of acetylacetone **40** by *Pichia farinose* IAM 4682.[6c]



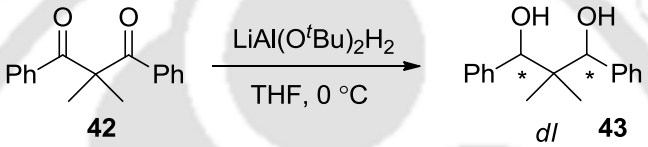
Scheme 1.2.2.2

Diastereoselective reduction of *β*-diketones followed by resolution of the resulting diols

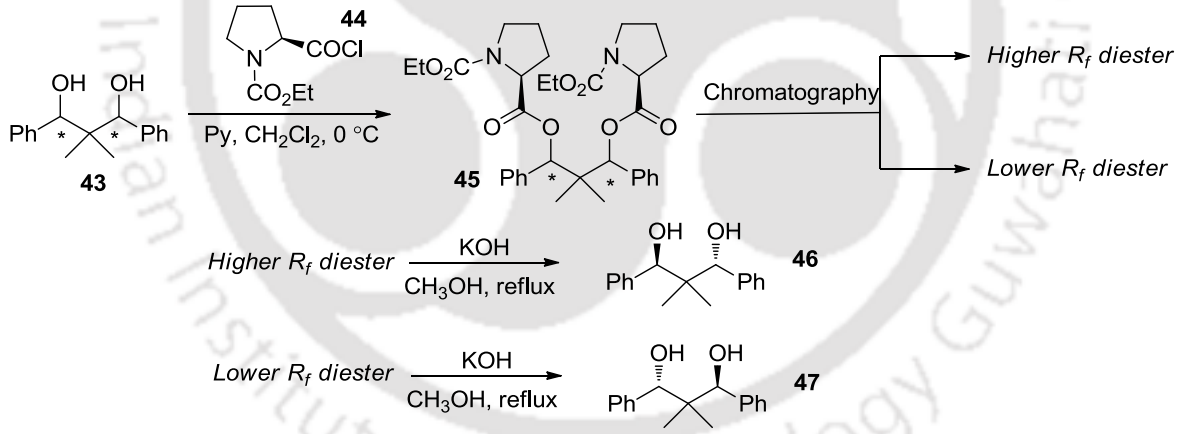
β-diketones can be diastereoselectively reduced to get predominantly a pair of enantiomers as a racemic mixture. The racemate can be resolved in to pure enantiomeric forms by using suitable resolution techniques. Several resolution techniques are available, including (a) Resolution by direct crystallization (b) Resolution through formation and separation of diastereomers (c) Crystallization-induced asymmetric transformations leading to total formation of the initial racemate into a single enantiomer.

Joshi and coworkers prepared (*R*,*R*) / (*S*,*S*)-2,2-dimethyl-1,3-diphenyl-1,3-propanediols **46** and **47** in enantiomerically pure form by diastereoselective reduction of the corresponding *β*-diketone

Diastereoselective reduction:



Resolution:



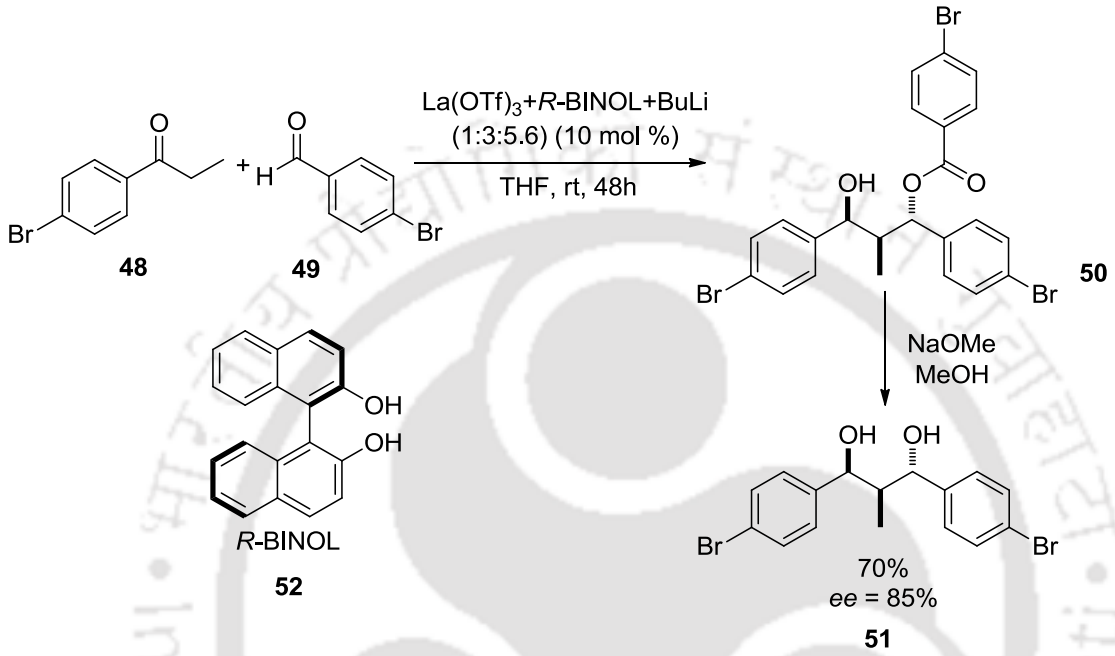
Scheme 1.2.3.1

42, followed by resolution of the resulting racemic diols **43**.[7] The racemic diols were converted to diastereomeric *N*-carbethoxy-L proline ester derivatives **45**, which after chromatographic separation and subsequent hydrolysis gave the pure enantiomers (*Scheme 1.2.3.1*).

1.2.3. Other synthetic transformations

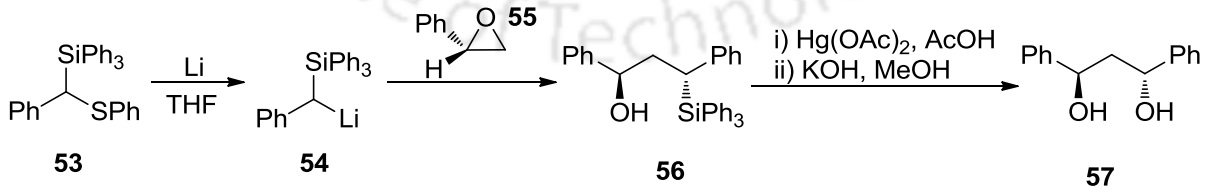
Enantioselective Aldol-Tishchenko reaction is widely employed to prepare chiral 1,3-diols.[8] A number of combinations of Lewis acids and chiral ligands have been used for the enantioselective direct tandem Aldol condensation-Evans-Tishchenko reduction of aldehydes and ketones. Shibasaki and coworkers developed mild and catalytic methods for the synthesis of

chiral 1,3-diols by enantioselective Aldol-Tishchenko reaction of aromatic aldehydes and ketones.[8c] Thus 1-(4-bromophenyl)propan-1-one **48** and 4-bromobenzaldehyde **49** were allowed to react under catalytic action of the system [$La(OTf)_3$+*R*-BINOL+BuLi], to provide the Tishchenko adduct **50**, which after hydrolysis gave (*1S,3S*)-1,3-Bis(4-bromophenyl)-2-methylpropane-1,3-diol **51** (*Scheme 1.2.4.1*).



Scheme 1.2.4.1

Corey *et al.* have described a synthetic route to obtain (*R,R*)-1,3-phenyl-1,3-propanediols. The racemic *α*-silyl organolithium **54** was allowed to react with (*R*)-styrene oxide **55** to produce the chiral *γ*-hydroxysilane **56** which afforded the (*R,R*)-chiral diol after treatment with mercuric acetate **57** (*Scheme 1.2.4.2*).[9]



Scheme 1.2.4.2

1.3. Importance and applications of chiral sulfoxides

Sulfoxides are found in a variety of natural products and pharmaceuticals. For example the drug armodafinil (**58**) is used for the treatment of sleep disorders and bipolar depression.[10] Esomeprazole (**59**) is a proton pump inhibitor[11] used in the treatment of dyspepsia, peptic ulcer

disease, and gastroesophageal reflux disease. Podolactone D (**60**) is one of the first terpenes known to contain a sulfoxide grouping, with plant growth inhibitory activity.[12] Fulvestrant (**61**) is an anti-oestrogen hormone antagonist, used to treat advanced breast cancer and metastatic breast cancer.[13]

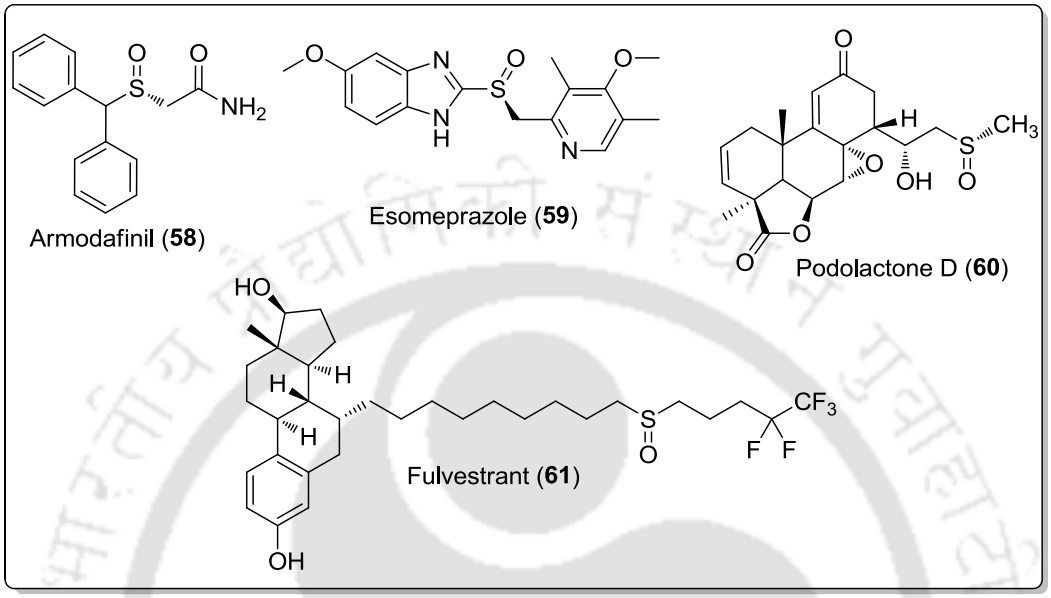


Figure 1.3.1*: Natural products and drugs molecules containing sulfoxide moiety.*

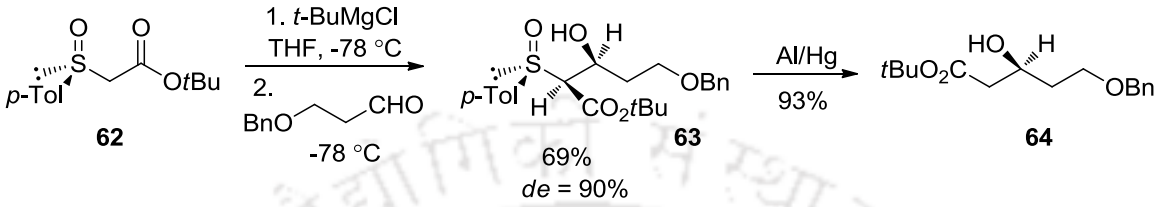
Chiral sulfoxides have been widely employed as chiral auxiliaries in a range of reaction classes,[14] and more recently as chiral ligands.[15] Sulfur is well-suited to the role of an agent for transfer of chirality for several reasons. The faces of a sulfoxide are highly differentiated due to the large steric and stereoelectronic difference between its substituents, which range from an electron lone pair to large alkyl groups, which are able to differentiate the diastereotopic faces of a proximale or even a remote reaction centre. Both sulfur and oxygen have lone pairs of electrons available to coordinate to Lewis acidic functionality, often promoting highly ordered transition states. Finally, sulfur can readily form covalent bonds, including to heteroatoms, and can be cleaved under relatively mild conditions. These properties have inspired considerable investigation into the synthetic applications of sulfoxides.

1.3.1. As chiral auxiliaries

Chiral sulfoxides belong to the class of chiral organosulfur compounds which are most widely used in asymmetric synthesis due to their ready availability and high asymmetric induction exerted by the chiral sulfinyl group. Moreover, the chiral sulfur groupings are easily removable under mild conditions by reductive or eliminative methods.[16] As a result a number of chiral sulfoxides have been utilised as chiral auxiliaries in a variety of stereoselective carbon-carbon

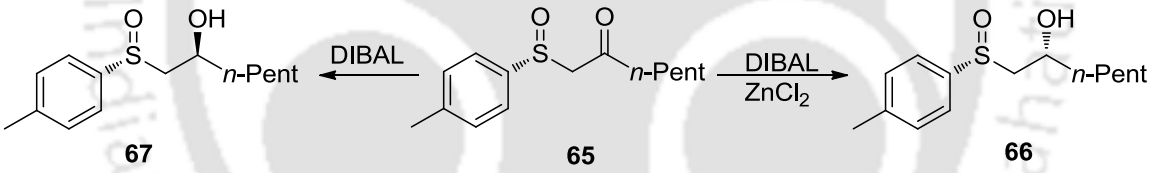
bond-forming reactions, such as Aldol reaction,[17] Diels-Alder reaction,[18] Michael additions,[19] asymmetric reductions[20] and asymmetric Heck reaction[21] as stereochemical controllers and in solid-phase asymmetric synthesis of amine and amino acid containing molecules.[22]

Solladié and co-workers employed chiral sulfoxide induced asymmetric aldol-type reaction to obtain chiral *β*-hydroxyesters **64** (*Scheme 1.3.1.1*).[17a]



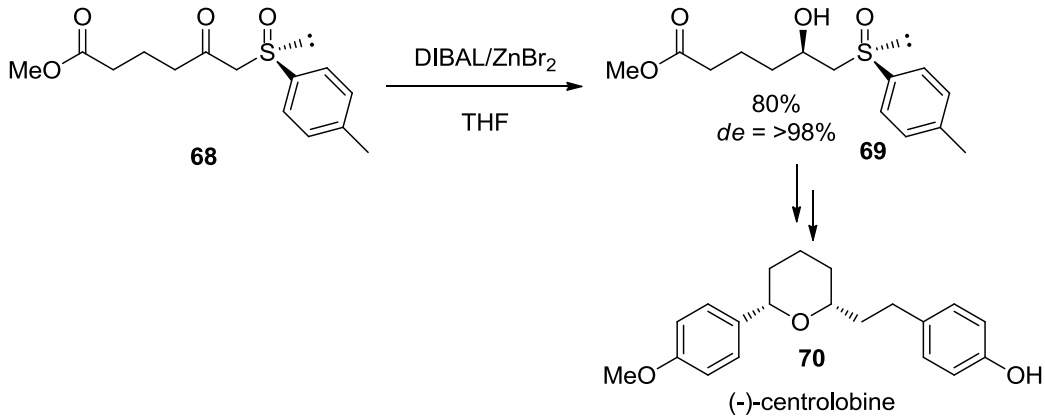
Scheme 1.3.1.1

The reduction of chiral *β*-ketosulfoxides has been the most extensively investigated and used reactions which ivolves the asymmetric induction by chiral sulfoxides.[20a] The stereochemical outcome in the reduction of either isomer of the *β*-ketosulfoxide can be controlled by the configuration of the sulfoxide, the reducing reagent and the absence or presence of a Lewis acid.



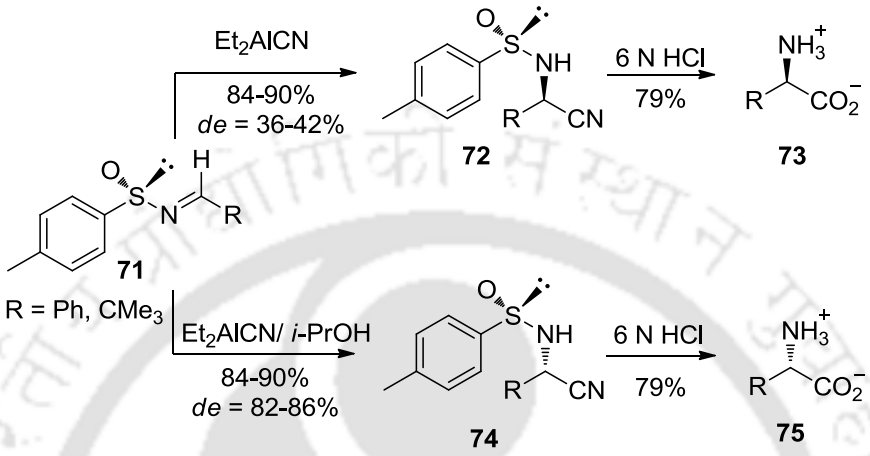
Scheme 1.3.1.2

This methodology was successfully applied by Carreno *et al.* for the enantioselective total synthesis of (-)-centrolobine **70** (*Scheme 1.3.1.3*).[23] Their strategy is based on the stereoselective reduction of a chiral *β*-ketosulfoxide **68** bearing an ester as the source of chirality.



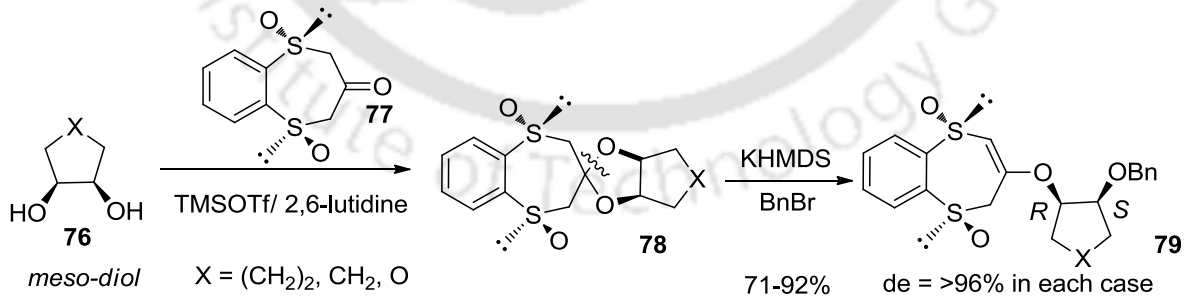
Scheme 1.3.1.3

Sulfinimines are being utilized as versatile chiral nitrogen intermediates for the preparation of a range of chiral amines, including α-branched and *α,α*-dibranched amines, *α*- and *β*-amino acids, aziridines and *α*- and *β*-amino phosphonic acids. Davis and co-workers reported a chiral sulfoxide induced asymmetric Strecker synthesis of *α*-amino acids **73**/**75** by diastereoselective addition of Et_2AlCN/*i*-PrOH to enantiopure sulfinimines **71** (*Scheme 1.3.1.4*).[24]



Scheme 1.3.1.4

C_2-symmetric bis-sulfoxides have proved to be efficient chiral auxiliaries for asymmetric desymmetrization of various diols such as meso-erythritol derivatives, or cyclic meso-1,2-diols. Maezaki *et al.* reported the use of *C_2*-symmetric bis-sulfoxide **77** as chiral auxiliary for asymmetric desymmetrization of cyclic meso-1,2-diols **76** *via* diastereoselective acetal fission (*Scheme 1.3.1.5*).[25]

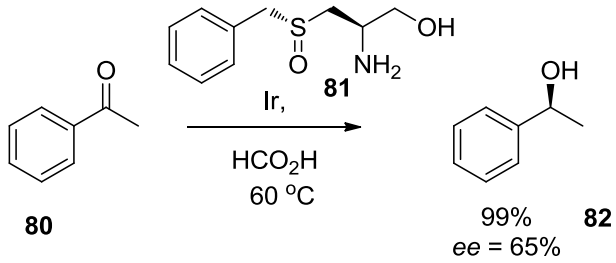


Scheme 1.3.1.5

1.3.2. As chiral ligands

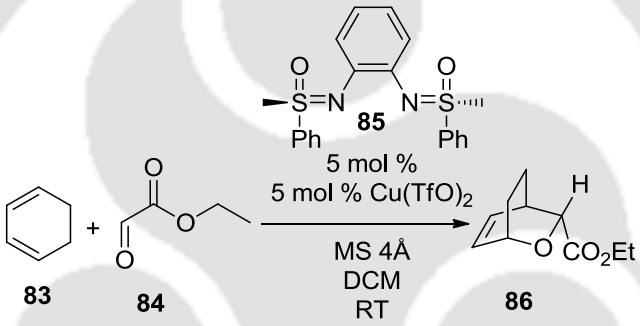
The application of chiral sulfoxides as ligands for transition metals has been less thoroughly explored than their use as chiral auxiliaries. Leeuwen and co-workers synthesized *R*-benzyl-(*R*)-cysteinol sulfoxide and *S*-benzyl-(*R*)-cysteinol sulfoxide **81** and used as ligands for iridium(I)-

catalyzed reduction of ketones (*Scheme 1.3.2.1*).[26] Thus acetophenone **80** was reduced to corresponding alcohol **82** in 99% yield and 65% *ee* by this method.



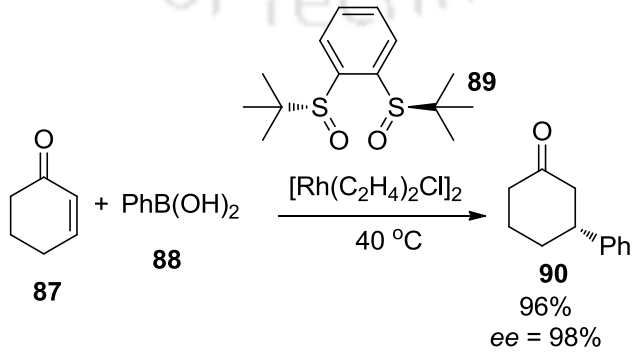
Scheme 1.3.2.1

Copper (II) complex of C_2-symmetric *bis*(sulfoximine) ligand **85** was used by Bolm and co-workers for catalytic enantioselective Diels-Alder reaction (*Scheme 1.3.2.2*).[27]



Scheme 1.3.2.2

Liao and co-workers synthesized a C_2-symmetric chiral bis-sulfoxide ligand **89** and for the rhodium-catalyzed asymmetric 1,4-addition of arylboronic reagents **88** to *α,β*-unsaturated substrates **87**,[28] which afforded the corresponding adducts **90** in good yields and excellent enantioselectivities (*Scheme 1.3.2.3*) .



Scheme 1.3.2.3

1.4. Synthesis of chiral sulfoxides

The synthesis of chiral sulfoxides has been the subject of constant interest over the past two decades. A diverse array of methods is presently available to obtain enantiomerically enriched sulfoxides. These methods generally fall into two categories:

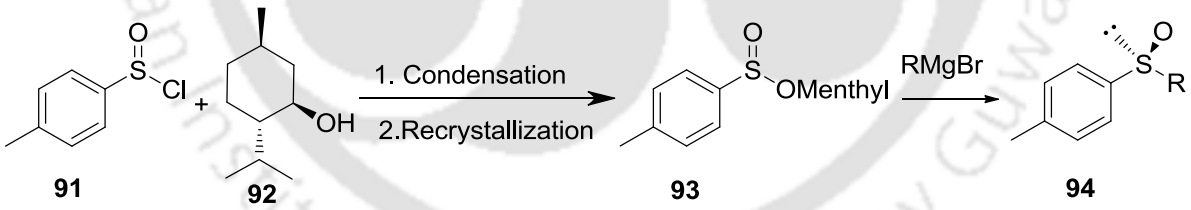
(a) Chiral auxiliary directed functionalizations

(b) Catalytic enantioselective oxidation

1.4.1. Chiral auxiliary-based method:

The most straightforward route to enantiomerically enriched sulfoxides involves preparation and substitution of a pure diastereomer using a chiral reagent. This method consists of the synthesis of a sulfinylating agent with an electrophilic sulfur of known configuration, followed by reaction with an organometallic reagent.

Andersen reported the first practical synthesis of chiral alkyl aryl sulfoxides, using optically pure menthol as chiral auxiliary (*Scheme 1.4.1.1*).[29] Substitution at the sulfur atom of commercially available (*S*)-menthyl *p*-toluenesulfinate **93** with an appropriate organometallic reagent , gave the sulfoxides **94** with excellent enantioselectivity, which is favoured since it has the advantage that the substitution takes place with 100% inversion of configuration. A wide variety of enantiomerically pure *p*-tolyl alkyl or aryl sulfoxides have been prepared by using various organometallic nucleophiles.

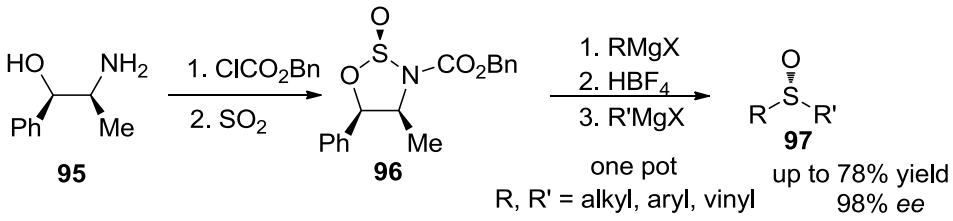


Scheme 1.4.1.1

The usefulness of this method is mainly due to the accessibility of the sulfinylating agent, which is obtained as a mixture of diastereomers, and can be separated by repeated recrystallizations. The enantiomerically pure sulfinate is then displaced by an organomagnesium halide with clean inversion at the sulfur center. However, this widely used method suffers from limitations. Efficient recrystallization of the menthol sulfinate is possible only if it contains an aryl substituent, so dialkyl sulfoxides are not accessible by this method.

Cyclic oxathiazolidines derivatives have also been employed to synthesize enantiorich chiral sulfoxides. José L. and co-workers described the use of cyclic oxathiazolidines **96** derived from

norephedrine **95** to obtain chiral sulfoxides **97** through two sequential nucleophilic attacks (*Scheme 1.4.1.2*).[30]



Scheme 1.4.1.2

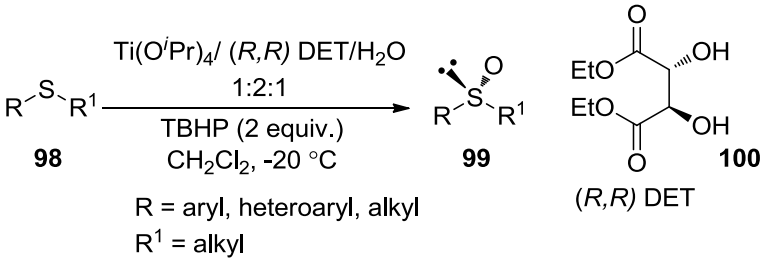
Sulfoxides obtained by chiral auxiliary based methodologies are relatively simple and having very high enantiomeric purity. These products are ideally suited for use as chiral ligands or chiral auxiliaries.

1.4.2. Catalytic enantioselective oxidation method

This method mainly involves asymmetric oxidation of prochiral sulfides catalyzed by metal complexes with enantiomerically pure chelating ligands. C_2-symmetric bidendate diols,[31] C_3-symmetric triethanol amines,[33] tridendate Schiff bases[34] and tetradendated salen-type ligands have been commonly used, typically in combination with d^0 metal ions: Ti(IV) , V(V) and less frequently with Mn(III), Fe(III), Al(III) . Non-metal catalyzed asymmetric sulfoxidations are also reported where chiral oxidizing agents, chiral organocatalysts, and enzymes have been used to induce chirality.

1.4.2.1. Metal catalyzed enantioselective sulfoxidations

The first major advance in metal catalyzed asymmetric sulfide oxidation was reported nearly simultaneously by Kagan[31a] and Modena[35] in 1984. Both are based on modifications to Sharpless titanium catalysed asymmetric epoxidation[36] reaction. Using (*R,R*) diethyl tartarate **100** as chiral ligand for titanium catalysed oxidation of prochiral sulfides Kagan and coworkers synthesized various sulfoxides **99** in moderate to good enentioselectivities (*Scheme 1.4.2.1.1*). They

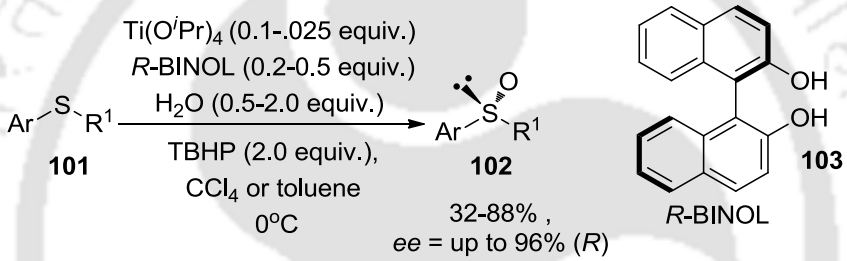


Scheme 1.4.2.1.1

discovered that addition of stoichiometric water to the catalyst was crucial to achieve enantioselectivity in the oxidation of sulfides. Yields and enantioselectivities were high for aryl alkyl sulfoxides and moderate for dialkyl sulfoxides.

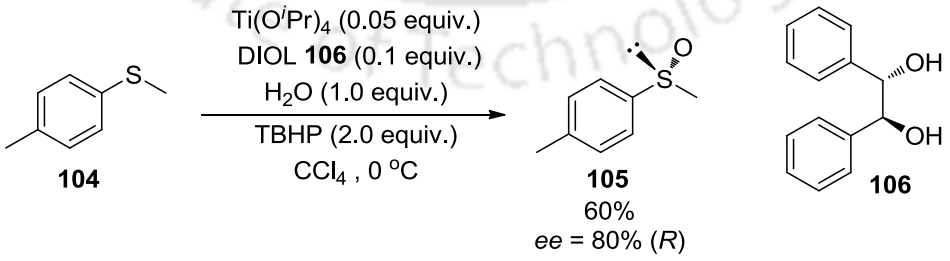
Modena and co-workers modified the Sharpless method by addition of excess diethyl tartrate. Yields and selectivities were nearly identical to those reported by Kagan, and experimental evidence suggested that the excess tartrate may in fact serve only to introduce an uncontrolled amount of water.

Uemura and co-workers reported advance titanium catalyzed oxidation of aryl alkyl sulfides **101** by substituting binaphthol **103** for tartrate **100** (*Scheme 1.4.2.1.2*).[31g, 37] This method is superior to that of Kagan and Modena when the catalyst loadings and enantioselectivities of the products are concerned.



Scheme 1.4.2.1.2

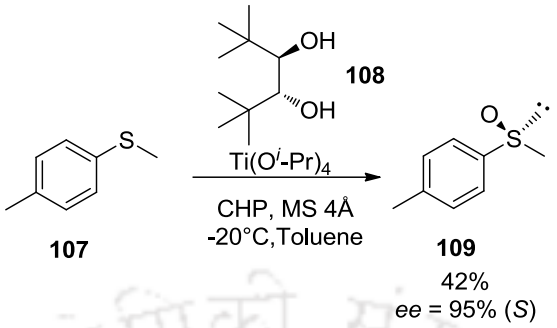
Superchi and Rosini used C_2-symmetric (1*S*,2*S*)-1,2-diphenylethane-1,2-diol **106** as chiral ligand. Their reaction conditions were similar to that of Umera.[38] Thus using TBHP as oxidant and carbon tetrachloride as solvent at 0 ^oC the sulfoxide **105** was obtained with 80% ee in 62% yield.



Scheme 1.4.2.1.3

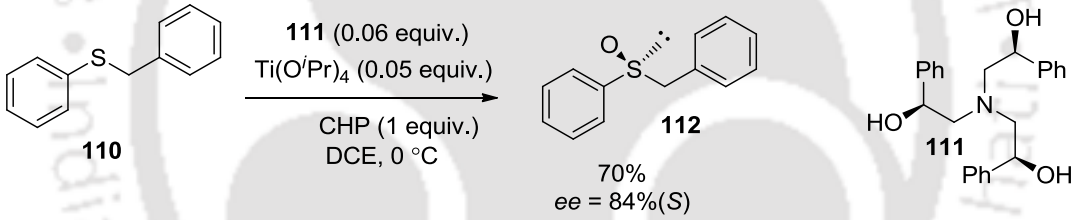
C_2-symmetric hexanediol **108** was used by Imamoto and co-workers as a chiral ligand in titanium catalyzed sulfide oxidation (*Scheme 1.4.2.1.4*).[39] Unlike Kagan and Umera's methods, the investigators used anhydrous conditions and observed that the oxidation proceeded with the

highest degree of enantiopurity when conducted in the presence of molecular sieves. Cumene hydroperoxide gave better result than TBHP.



Scheme 1.4.2.1.4

C_3-Symmetric chiral triethanolamine ligands have also been used for titanium catalysed enantioselective sulfoxidation.[40] Licini and Nugent investigated the use of **111** as ligand for titanium catalyzed sulfoxidation of alkyl aryl sulfides. The catalytic activity was good and the *ee* values were up to 84% (*Scheme 1.4.2.1.5*).



Scheme 1.4.2.1.5

Figure 1.4.2.1.1 shows some of the other chiral diol ligands used for titanium catalysed sulfoxidation.

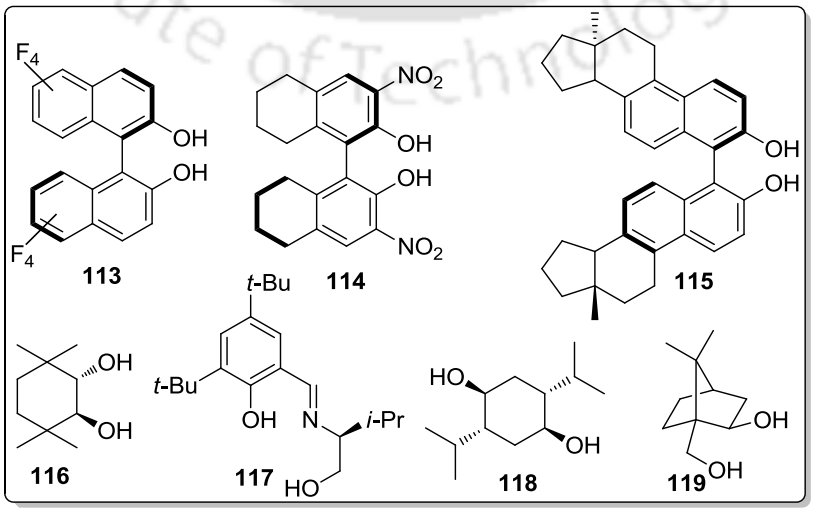
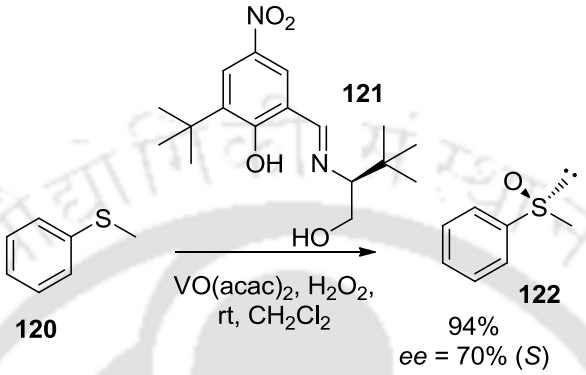


Figure 1.4.2.1.1. *Chiral diols used for titanium catalyzed sulfoxidation.*

After titanium, a number of vanadium complexes with chiral tridendate Schiff bases, and tetradendated salen-type ligands have been used successfully in asymmetric sulfide oxidation.

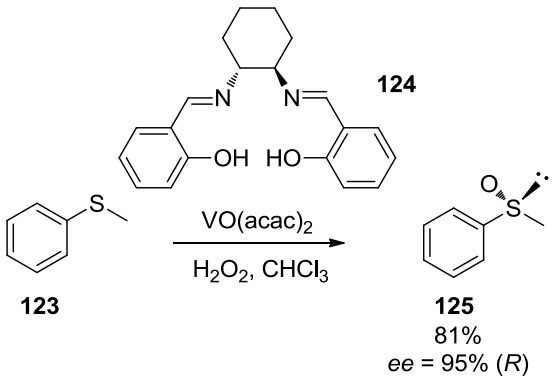
Bolm *et al.* achieved good levels of enantioselectivity in enantioselective sulfoxidation by using vanadium Schiff base complex formed in situ by the reaction of $VO(acac)_2$ and a Schiff base **121** (*Scheme 1.4.2.1.6*).[42]



Scheme 1.4.2.1.6

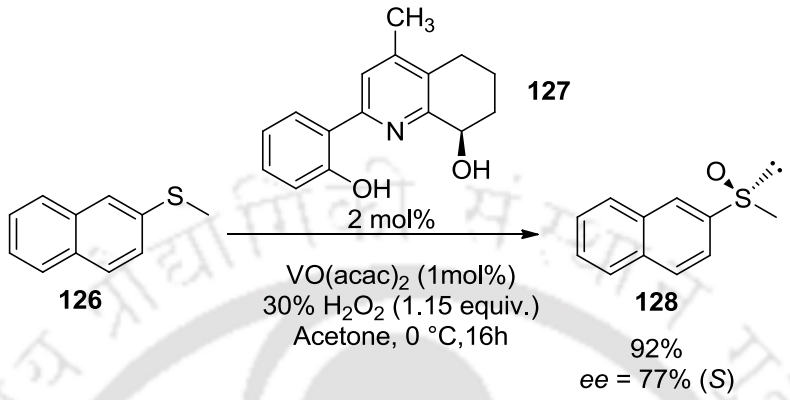
Aqueous hydrogen peroxide, a cheap and environmentally benign reagent was used as oxidant. Thus the use of atmospheric conditions was the most significant point, overcoming the extreme sensitivity associated with titanium catalyzed oxidations, and elliminataing the need for an inert atmosphere. Asymmetric oxidation occurred even in the presence of 0.1 mol% of the catalyst.

Sun *et al.* reported an efficient procedure for sulfide oxidation catalysed by a vanadium-salen complex under air (*Scheme 1.4.2.1.7*). The oxidant used was aquous hydrogen peroxide. After screening a number of salen ligands, ligand **124** was found to be the optimum ligand for this oxidation method.[43] Thus sulfoxide **125** was obtained from thoanisole **123** in very good yield (81%), and excellent enantioselectivity (*ee* = 95%). The investigators also found the catalytic system to be very impressive for kinetic resolution of racemic sulfoxides with hydrogen peroxide under air.



Scheme 1.4.2.1.7

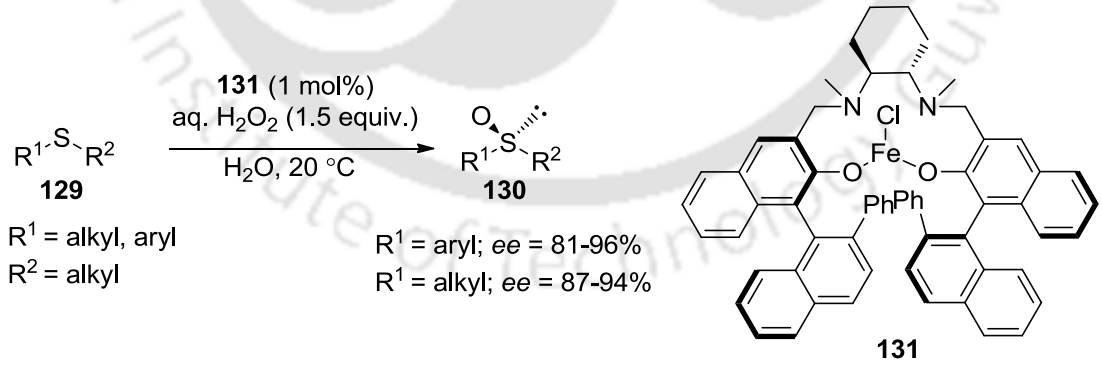
Liu *et al*. used a novel chiral NOO-tridentate ligand **127** bearing a rigid tetrahydroquinoline framework, for vanadium catalyzed enantioselective oxidation of aryl methyl sulfides (*Scheme 1.4.2.1.8*).[44] The oxidant was aquous H_2O_2. With this catalytic system (*S*)-2-(methylsulfinyl) naphthalene **128** was obtained from the sulfide **126** in 92% yield and 77% *ee*.



Scheme 1.4.2.1.8

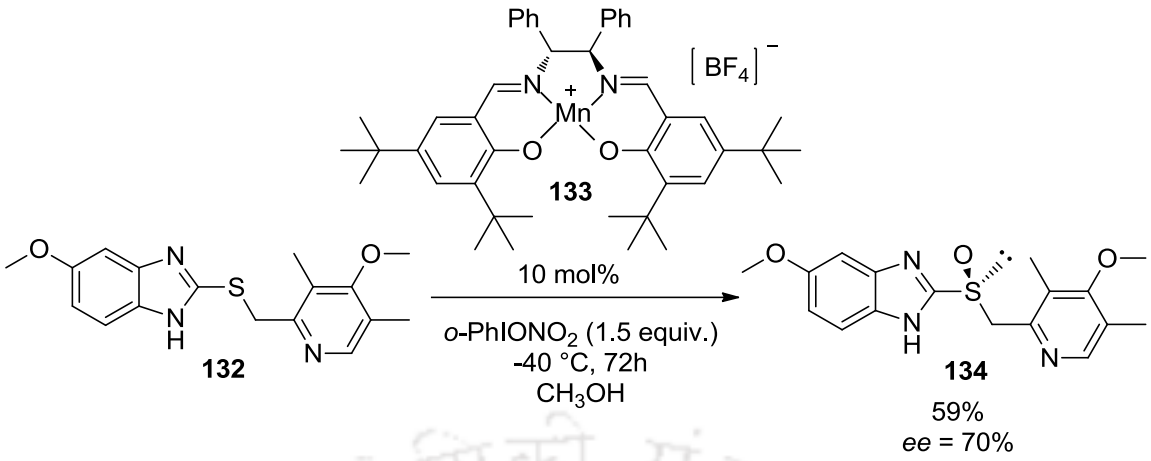
Chiral ligand-iron complexes have been successfully used in catalytic enantioselective sulfoxidation. Chiral salens, porphyrines are the most commonly used ligands among others.[45]

Katsuki and Egami used a novel chiral Fe (salen) complex **131** for asymmetric oxidation of alkyl aryl and methyl alkyl sulfides **129** using aquous hydrogen peroxide as oxidant (*Scheme 1.4.2.1.9*).[45c]



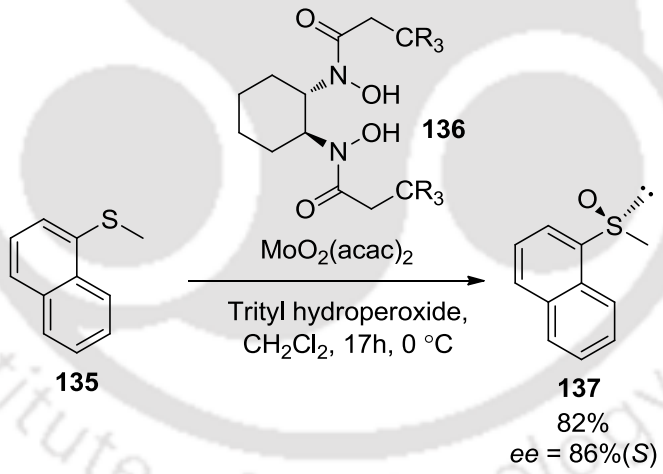
Scheme 1.4.2.1.9

Manganese-chiral schiff base complexes are also successfully used in enantioselective sulfide oxidation.[46] Recently, Choi *et al.* used a manganese-schiff base complex **133** to synthesize esomeprazole **134** in 59% yield and 70% *ee* (*Scheme 1.4.2.1.10*).[46b]



Scheme 1.4.2.1.10

Basak *et al.* reported a chiral bis-hydroxamic acid (BHA)-molybdenum complex catalyzed oxidation of sulfides and disulfides utilizing one equivalent of trityl hydroperoxide with yields up to 83% and *ee* up to 86% (*Scheme 1.4.2.1.11*). They synthesized the complex by stirring bis-hydroxamic acid **136** and $MoO_2(acac)_2$ at room temperature.[47] Thus (*S*)-1-(methylsulfinyl) naphthalene **137** was obtained from the corresponding sulfide **135** in 82% yield and 86% *ee*.



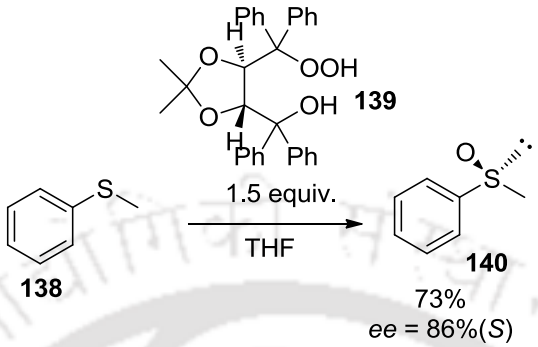
Scheme 1.4.2.1.11

Other less frequently reported metals are Al(III), Cu(II), W(VI), Zr(IV) etc with varous chiral schiff base derived ligands.[48]

1.4.2.2. Non-metal catalyzed enantioselective sulfoxidations

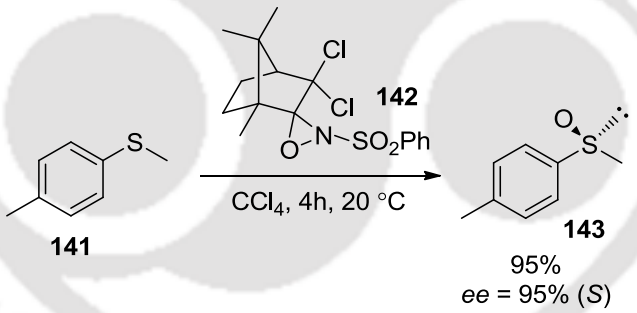
In non-metal catalyzed enantioselective sulfoxidation, enantioselectivity is controlled either by using chiral oxidants or by carrying out the oxidation in the presence of chiral catalysts. Generally used chiral oxidants are chiral peracids,[49] chiral hydroperoxides,[50] chiral oxaziridines,[51] chiral hypervalent iodo compounds[52] etc. Nonmetallic chiral catalysts used for this purpose includes chiral organocatalysts or biocatalysts.

Seebach and Aoki used a chiral hydroperoxide (TADOOH) **139** derived from H_2O_2 and tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) in asymmetric sulfide oxidation.[50] Using this hydroperoxide as oxidant, thioanisole **138** was oxidized in good yield and high enantiopurity (*Scheme 1.4.2.2.1*).



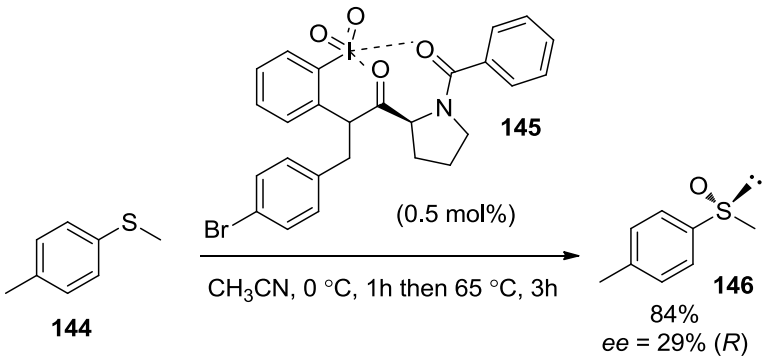
Scheme 1.4.2.2.1

Davis and co-workers found several *N*-sulfonyloxazaridines, derived from camphor, to be interesting reagents for enantioselective sulfoxidation.[53] The most successful catalyst discovered by this group is dichlorocamphorylsulfonyloxaziridine **142**. With this reagent methyl(*p*-tolyl)sulfane **141** provided the corresponding sulfoxide **143** in 95% *ee* (*Scheme 1.4.2.2.2*).



Scheme 1.4.2.2.2

Chiral hypervalent iodine reagents are known oxidize prochiral sulphides enantioselectively. Zhdankin and co-workers used a chiral benziodoxazine derivative **145**, developed from (*S*)-



Scheme 1.4.2.2.3

proline, in the enantioselective oxidation of sulfide, producing sulfoxide **146** in 84% yield and 29% *ee*.[52]

Enantioselective sulfoxidation by biological systems is a less popular method for preparing enantioriched sulfoxides. Oxidation is generally carried out using isolated enzymes or whole cell cultures. Holland *et al.* reported the oxidation of various sulfides to sulfoxides by the biocatalyst present in the fungus *Helminothosporium* sp. NRRL 4671 with very high enantioselectivity. Similarly *Mortierella isabellina* ATCC 42613 has also been successfully used to prepare highly enantioenriched sulfoxides.[54]

Conclusion

Chiral 1,3 diols have been shown to be good chiral auxiliary in a number of asymmetric reactions and have potential to act as chiral ligands in different organic transformations. Construction of conformationally rigid 1,3 diols is a great endeavour and better understanding in structure-reactivity-selectivity relationship of these chiral diols could open up an opportunity for designing new efficient and versatile ligands.

Enantiomerically pure sulfoxides are excellent stereocontrolling element in various asymmetric reactions. Also the utility of chiral sulfoxides in asymmetric syntheses of biologically interesting compounds is well documented. Over the past three decades considerable attention has been focused on developing routes to enantioenriched sulfoxides using a combination of metal catalyzed processes, biocatalysis and use of chiral auxiliaries. Among these catalytic enantioselective oxidation is highly desirable, and can be used to generate sulfoxides with excellent *ee* values. But it suffers from a lack of generality, and the catalyst must also be optimized and able to adjust to the structure of the sulfide.

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CHAPTER 2

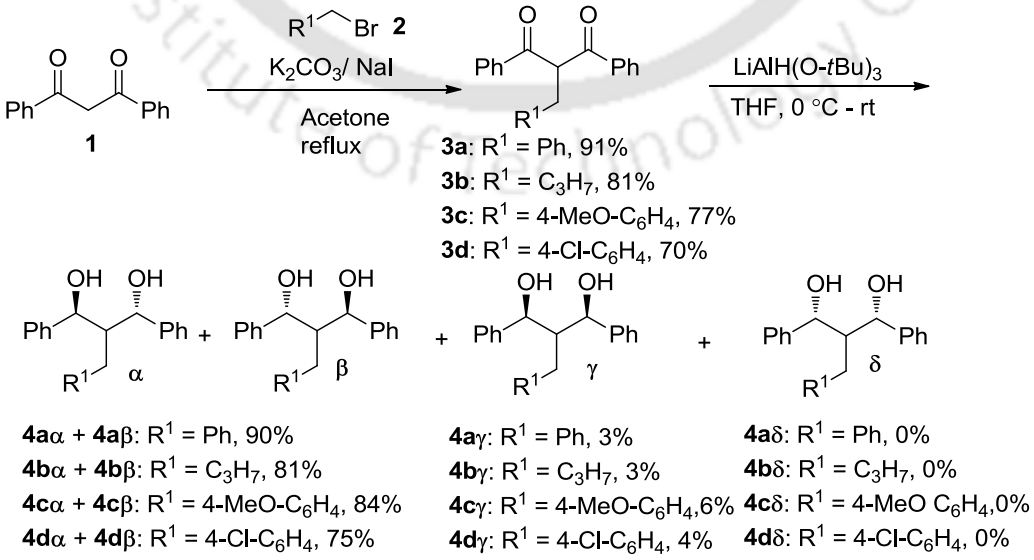
Synthesis of a New Chiral 1,3-Diol Ligand with a Benzyl Backbone and Application in Asymmetric Sulfoxidation of Alkyl Aryl Sulfides

Section A: Synthesis and resolution of 1,3-diols

1,3-Diol is a structural motif present in hundreds of natural products.[1] These diols have found applications as chiral auxiliaries[2] or rarely as chiral ligands[3] in various asymmetric transformations. Unlike 1,2- and 1,4-diols, number of successful 1,3-diols are limited in literature, because most of them lack sufficient conformational rigidity to be an effecetive chiral auxiliary/ligand. The design and synthesis of sterically constrained chiral 1,3-diols containing backbone rigidity, is an important endeavor. This part of work deals with diastereoselective synthesis of new 1,3-diols with a benzylic and alkyl backbone and resolution to their enantiomers by using chiral resolving agent.

2.1. Results and discussions

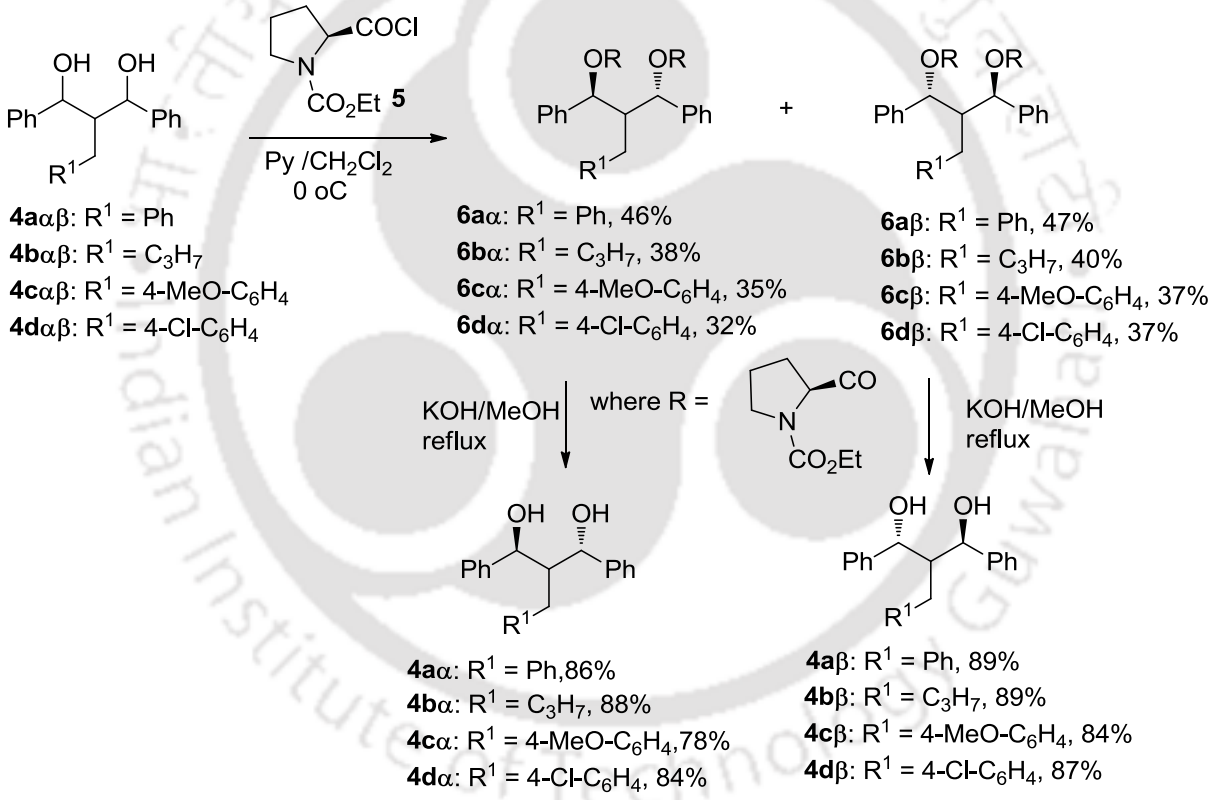
Our synthetic route involved the diastereoselective reduction of *β*-diketones **3** by $LiAlH(O\text{-}tBu)_3$, followed by resolution of the racemic mixture containing the anti diols. Diketones **3** were synthesized by the reaction of 1,3-diketone **1** with bromides **2** in the presence of K_2CO_3/NaI in



Scheme 2.1.1

acetone. The resulting diketones **3** were converted to 1,3-diols (±)-**4** according to Barluenga method,[4] which involed diastereoselective reduction of diketones by the bulky reducing agent $LiAlH(O\text{-}tBu)_3$ (*Scheme 2.1.1*). Out of four probable isomers **4α** and **4β** were obtained as major isolated products (75-90%). The isomers **4aγ, 4bγ, 4cγ** and **4dγ** were detected by ^1H NMR in minor amounts 3%, 3%, 6% and 4%, respectively. [4] On the other hand the isomers **4δ** were not detected by ^1H NMR.

After successful synthesis of the (±)-**4αβ**, the diols were resolved into its chiral components **4α** and **4β** by converting them to their diastereomeric esters **6α** and **6β** using *N*-ethoxycarbonyl-L-proline derivative **5**, and subsequent hydrolysis by methanolic solution of potassium hydroxide (*Scheme 2.1.2*).[5]



Scheme 2.1.1

The absolute configuration of the diols was determined by X-ray crystallographic analysis.[6] The absolute stereochemistry of **(+)-4aα** was found to be (*S,S*). The ORTEP diagram shows that there are two molecules in the asymmetric unit (*figure 2.1.1*).

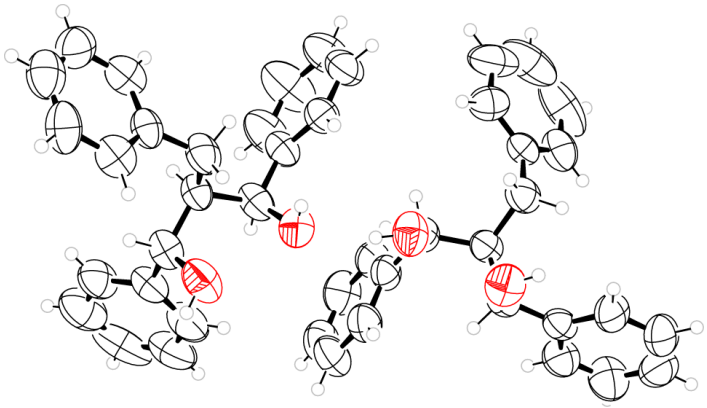


Figure 2.1.1: ORTEP diagram of compound **4aα**

Section B: Enantioselective oxidation of alkyl aryl sulfides using 1,3-diols as chiral ligand

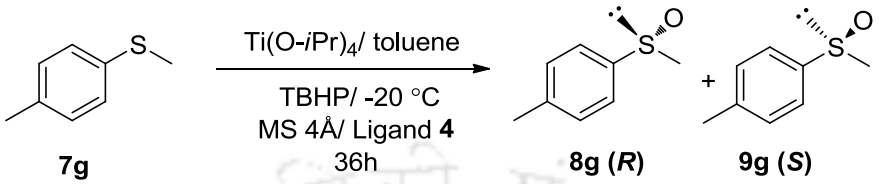
Over the years many approaches have been developed for the synthesis of chiral sulfoxides using metal complexes including initial reports of Kagan[7] and Modena.[8] Titanium peroxo complexes bearing C_2 symmetric chiral 1,2- and 1,4-diol ligands such as DEAT,[7,8] BINOL,[9] 1,2-diphenylethane-1,2-diol[10] etc. have been used for asymmetric sulfoxidation. Titanium peroxo complexes having C_3 symmetry have also been reported.[11] So far there is no reports of any metal catalyzed sulfoxidation where 1,3-diols are used as chiral controller. Present work demonstrates the use of a new chiral 1,3-diol for titanium catalyzed enantioselective sulfoxidation.

2.2. Results and discussions

After the synthesis and resolution to chiral 1,3-diols **4aα-4dα** and **4aβ-4dβ,** the diols were examined as chiral ligands for titanium catalyzed oxidation of sulfides to sulfoxides, using TBHP as oxidant. The results are summarized in *Table 2.2.1*. Thus the reaction of methyl (*p*-tolyl)sulfane with titanium isopropoxide and tertiary butyl hydroperoxide in presence of chiral 1,3-diols **4aα** and **4aβ** gave chiral methyl-4-(methylsulfinyl)benzene **8g** (*R*) and **9g** (*S*), respectively with 87% ee each (*Table 2.2.1*). On the other hand chiral 1,3-diol having a butyl backbone is found to be not effective in enantioselective oxidation of sulfide to sulfoxide under the same reaction conditions. The oxidation of methyl (*p*-tolyl)sulfane using chiral 1,3-diol **4bβ** gave only 24% *ee* of the corresponding *S*-isomer **9g** (*S*). Chiral diols with 4-methoxy- and 4-chloro-benzyl backbone gave sulfoxide **8g** (*R*) with 37% and 71% ee, respectively. This implies that the both rigidity and electronic effects of benzyl group are crucial in high enantioselectivity. Both electron-donating and electron-withdrawing substituent on the aromatic ring of the benzyl group decreases the enatioselectivity in comparison to the simple benzylic group. The chiral 1,3-

ligands **4aα** and **4aβ** having a benzyl backbone are found to be the best ligand for enantioselectivity.

Table 2.2.1. *Enatioselective oxidation of sulfides with chiral 1,3-diols.*

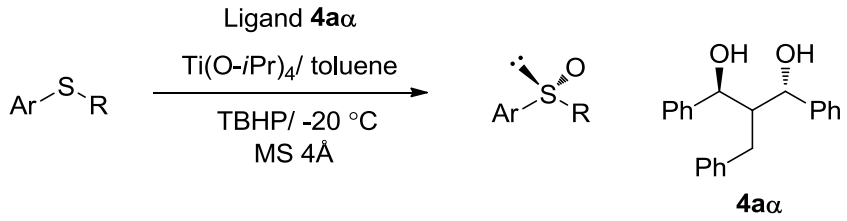


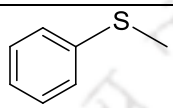
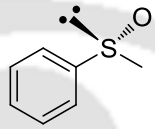
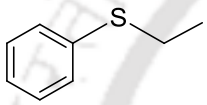
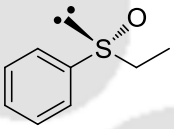
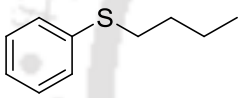
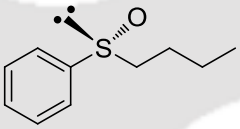
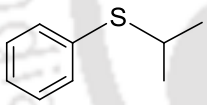
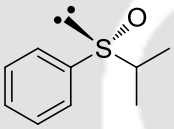
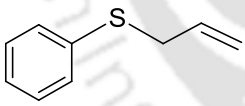
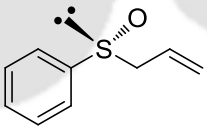
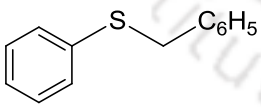
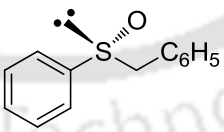
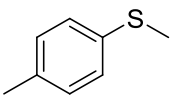
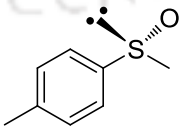
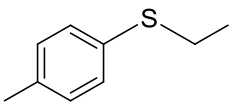
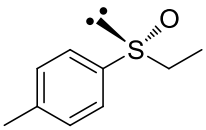
Entry	1,3 Diol (**4**)	Yield (%)[a]	% *ee*[b]	Products /Abs.Conf. [c]
1	**4aα**	60	87	**8g** (*R*)
2	**4cα**	59	37	**8g** (*R*)
3	**4dα**	57	71	**8g** (*R*)
4	**4aβ**	58	87	**9g** (*S*)
5	**4bβ**	45	24	**9g** (*S*)

[a]Yield refers to isolated yield of sulfoxides, the remaining is isolated as sulfone . [b]Determined by HPLC using Chiralcel OD-H column. [c]Determined by comparison of its sign of specific rotation with the literature data.

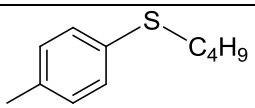
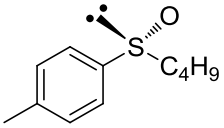
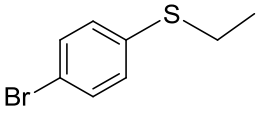
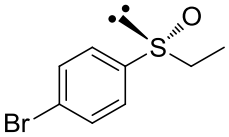
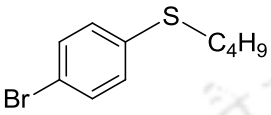
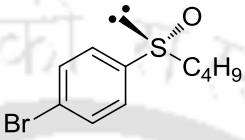
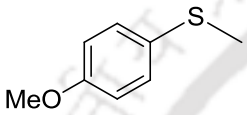
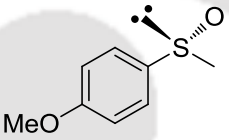
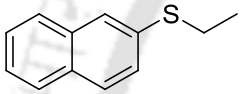
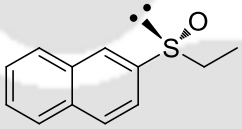
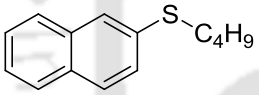
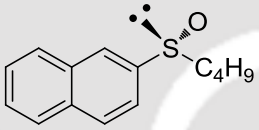
The utility of chiral 1,3-diol ligand **4aα** was extended to titanium catalyzed oxidation of various substrates as shown in *Table 2.2.2*. It was observed from the *Table 2.2.2* that the nature of alkyl group and electronic effect of the aryl substituent play an important role in enantioselection. The electron-donating groups in aromatic ring increase the enantioselectivity (entry g-i), whereas the electron-withdrawing groups reduce the enantioselectivity (entry j, k). On the other hand the increase in size of alkyl groups in an alkyl side chain of phenyl alkyl sulfide, increase the enantioselectivity (entry a-c), which is reverse in the case of naphthyl alkyl sulfides (entry m,n). Branching in a side chain increases the enantioselection (entry d). Olefinic and aromatic ring in a alkyl side chain reduce the enantioselectivity (entry e, f).

***Table 2.2.2**. Synthesis of chiral sulfoxide from sulfides*



Entry	Substrate **7**	Time/h	Product **8**	Yield (%)[a]	*ee* (%)[b] **8** / Abs.Conf.[c]
a		36		59	52 (*R*)
b		40		65	72 (*R*)
c		40		60	75 (*R*)
d		40		61	80 (*R*)
e		24		59	50 (*R*)
f		36		70	54 (*R*)
g		36		60	87 (*R*)
h		40		65	78 (*R*)

Continued……

Entry	Substrate **7**	Time/h	Product **8**	Yield (%)[a]	*ee* (%)[b]**8** / Abs.Conf.[c]
i		40		69	45 (*R*)
j		36		64	43 (*R*)
k		48		60	41 (*R*)
l		36		55	39 (*R*)
m		48		52	72 (*R*)
n		48		52	67 (*R*)

[a]Yield refers to isolated yield of sulfoxides, the remaining is isolated as sulfone . [b]Determined by HPLC using Chiralcel OD and OD-H columns. [c]Determined by comparison of its sign of specific rotation with the literature data.

Conclusion

In conclusion we have investigated a new chiral ligand, 1,3-diol for the oxidation of prochiral sulfide using titanium peroxo complex as oxidant. The new catalytic system provided chiral sulfoxides in moderate to good *ee* values. The use of this chiral ligand for other asymmetric synthesis is under investigation in our laboratory.

2.3. Experimental section

2.3.1. Instrumentation and Characterization

As described in chapter 2 section 2.4.1

2.3.2. General procedure for the synthesis of 2-alkyl/benzyl-1,3-diphenylpropane-1,3-dione, (3a-d)

To a stirred suspension of dibenzoyl methane (1.0 mmol), K_2CO_3 (1.1 mmol) and NaI (1.1 mmol) in dry acetone (5 ml) was added alkyl/benzyl bromide (1.2 mmol) dropwise under N_2 atmosphere. The mixture was stirred at reflux for 12 h. The reaction was monitored by TLC and after completion of the reaction it was cooled to room temperature and filtered through a celite pad. The filtrate was evaporated under vacuo and the residue was purified by silica gel column chromatography (hexane: ethyl acetate) to give the pure product.

2.3.3. General procedure for the synthesis of 2-alkyl/benzyl-1,3-diphenylpropane-1,3-diol, (±)-4aα/β-4dα/β

To a suspension of $LiAlH_4$ (4.0 mmol), in dry THF (3 ml), *t*-BuOH (12.0 mmol) was added at 0 ^oC. Evolution of hydrogen gas was monitored. When the evolution of gas ceased, diketone **3a** (1.0 mmol) in dry THF (2 ml) was added to the reaction mixture at the same temperature. After completion of the addition, it was slowly warmed to room temperature and stirred for 6h. The reaction was monitored by TLC. After completion of the reaction, dry methanol was added to the reaction mixture at 0 ^oC followed by the drop wise addition of 2N H_2SO_4. It was then filtered through a celite pad, washed with CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried (Na_2SO_4) and evaporated under vacuo. The crude residue was suspended in a mixture of hexane and diethyl ether. The slurry was filtered and the insoluble part was washed with hexane-diethyl ether (9:1), dried (Na_2SO_4) and recrystallized to give the product.

2.3.4. General procedure for the synthesis of diesters 6aα / 6bβ-6dα / 6dβ

A solution of (±) **4** (1.6 mmol) in dry pyridine (12.4 mmol), was added to a 1 M solution (4 ml) of acid chloride **5** at 0℃. The progress of the reaction was monitored by TLC. After completion the reaction mixture was diluted with CH_2Cl_2, washed successively with 1 N HCl, water and saturated $NaHCO_3$. The organic layer was dried (Na_2SO_4), and concentrated under vacuo to give crude product. The two diastereomers are finally separated by preparative TLC (hexane: ethyl acetate).

2.3.5. General procedure for the hydrolysis of 6aα-6dα and 6aβ-6dβ to 4aα-4dα and 4aβ-4dβ

The diesters **6aα-6dα** (0.46 mmol) and **6aβ-6aβ** (0.46 mmol) were refluxed with 1 N methanolic KOH solution (10 mL) for 2h. The solvent was removed under vacuo and diluted with water and then extracted with ethyl acetate (3x 10 mL). The organic layer was washed with brine, dried (Na_2SO_4) and evaporated under vacuo to give a residue which was recrystallized from hexane: chloroform.

Typical experimental procedure for the synthesis of chiral sulfoxides

To a solution 1,3-diol (16 mg, 0.05 mmol) containing MS 4Å (70 mg) was added $Ti(^iOPr)_4$ (7.4 µL, 0.025 mmol) in toluene (1 mL). The mixture was stirred for 2h at rt and then methyl-p-tollyl sulphide (68 µL, 0.5 mmol) was added. The mixture was cooled to -20 ^oC and t-butylhydroperoxide (0.2 mL, 1 mmol) was added. After stirring for 36 h at the same temperature, the reaction was quenched with 10% aqueous solution of sodium sulfite. The aqueous layer was extracted with ethyl acetate (3x15 mL) and organic layer was dried (Na_2SO_4). The solvent was evaporated under reduced pressure and separated by preparative TLC (3:2; hexane:ethyl acetate). The enantiomeric excess was measured by chiral HPLC analysis using chiracel OD-H column.

2.4. References

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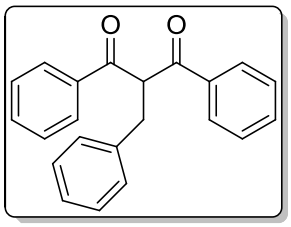
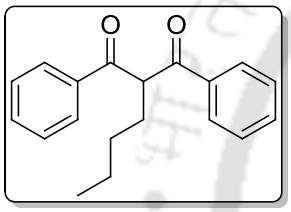
2.5. Characterization Data

2-Benzyl-1,3-diphenylpropane-1,3-dione (3a):



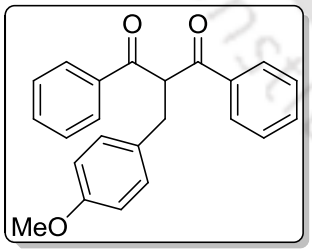
Colourless solid, M.P.: 105-106 ^{o}C: (1.28 g, 91%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.45 (d, *J* = 6.8 Hz, 2 H, -CH_2-), 5.52 (t, *J* = 6.8 Hz, 1 H, -CH_2-), 7.20-7.25 (m, 4 H. ArH), 7.38-7.42 (m, 5 H. ArH), 7.51-7.55 (m, 2 H, ArH), 7.87-7.90 (m, 4 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.3, 58.8, 126.7, 128.6, 128.9, 129.0, 133.6, 136.0, 139.0, 195.5; IR: 3062, 2917, 1694, 1665, 1333, 1271, 1233, 1199, 754, 692 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{22}H_{18}O_2$ $(M+H)^+$ 315.1380, found 315.1377.

2-Butyl-1,3-diphenylpropane-1,3-dione (3b)



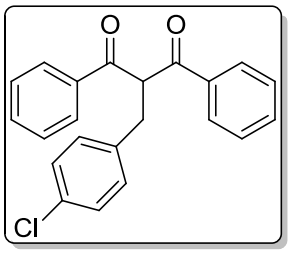
Colourless solid, M.P.: 60-61 ^{o}C: (1.02 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.2 Hz, 3 H, -CH_3), 1.34-1.42 (m, 4 H, -CH_2-), 2.08-2.15 (m, 2 H, -CH_2-), 5.19 (t, *J* = 6.8 Hz, 1 H, -CH-), 7.43-7.47 (m, 4 H, ArH), 7.54-7.59 (m, 4 H. ArH), 7.95-7.98 (m, 2 H. ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.9, 29.4, 30.7, 57.4, 128.7, 129.0, 133.6, 136.3, 196.4; IR: 2957, 2872, 1692, 1667, 1282, 1232, 1200, 1000, 758, 692 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{19}H_{20}O_2$ $(M+H)^+$ 281.1542, found 281.1551.

2-(4-Methoxybenzyl)-1,3-diphenylpropane-1,3-dione (3c)



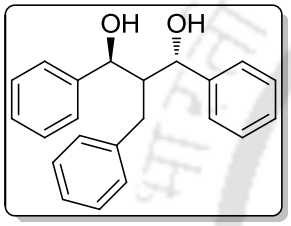
Colourless solid, M.P.: 96-98 ^{o}C: (1.01 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.39 (d, *J* = 6.8 Hz, 2 H, -CH_2-), 3.74 (s, 3 H, -OCH_3), 5.49 (t, *J* = 6.8 Hz, 1 H, -CH-), 6.77 (d, *J* = 8.8 Hz, 2 H, ArH), 7.17 (d, *J* = 8.8 Hz, 2 H, ArH), 7.38-7.43 (m, 4 H. ArH), 7.53 (t, *J* = 7.2 Hz, 2 H. ArH), 7.88-7.90 (m, 4 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.6, 55.4, 59.5, 114.2, 128.8, 129.0, 130.2, 131.3, 133.7, 136.2, 158.5, 195.7; IR: 2957, 2929, 1692, 1647, 1247, 1177, 1029, 741, 691 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{23}H_{20}NaO_3$ $(M+Na)^+$ requires 367.1310, found 367.1313; Anal calcd for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85. Found: C, 80.30; H, 5.79.

2-(4-Chlorobenzyl)-1,3-diphenylpropane-1,3-dione (3d)



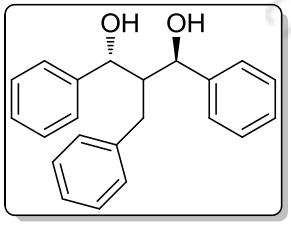
Colourless solid, M.P.:104-106 ^{o}C: (1.08 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.40 (d, *J* = 6.8 Hz, 2 H, -CH_2-), 5.49 (t, *J* = 6.8 Hz, 1 H, -CH-), 7.12-7.21 (m, 4 H, ArH), 7.38-7.42 (m, 4 H, ArH), 7.51-7.55 (m, 2 H. ArH), 7.87-7.90 (m, 4 H. ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.7, 59.0, 128.7, 128.9, 129.1, 130.6, 132.6, 133.8, 136.1, 137.7, 195.4; IR: 2924, 1672, 1263, 761, 682 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{22}H_{17}ClO_2$ $(M+H)^+$ requires 349.0995, found 349.0498; Anal calcd for $C_{22}H_{17}ClO_2$: C, 75.75; H, 4.91. Found: C, 75.86; H, 4.83.

2-Benzyl-1,3-diphenylpropane-1,3-diol (+)-4aα



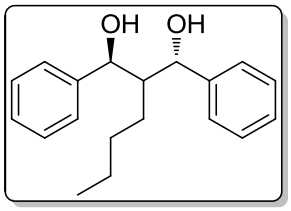
White solid, M. P.:129-131 ^{o}C; (125 mg, 86%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20-2.25 (m, 1 H, -OH), 2.59 (dd, *J* = 14.4 and 4.8 Hz, 1 H, -CH_2-), 2.93 (dd, *J* = 14.0 and 10.4 Hz, 1 H, -CH_2-), 3.19 (d, *J* = 4.8 Hz, 1 H, -OH), 3.37 (s, 1 H, -OH), 4.81-4.84 (m, 1 H, -CH-), 4.99 (brs, 1 H, -CH-); 7.08 (d, *J* = 7.6 Hz, 1 H, ArH), 7.15-7.19 (m, 1 H, ArH), 7.21-7.27 (m, 7 H, ArH), 7.28-7.38 (m, 6 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.2, 53.6, 72.6, 74.0, 125.6, 125.7, 126.0, 127.0, 127.2, 128.2, 128.4, 128.5, 129.2, 140.8, 142.7, 143.7; IR: 3257, 3030, 2896, 1603, 1452, 1343, 1056, 1042, 755, 700 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{22}H_{22}O_2$ $(M+H)^+$ 319.1698, found 319.1692; $[\alpha]_D^{25}$ +76 (C 0.2, CH_2Cl_2).

2-Benzyl-1,3-diphenylpropane-1,3-diol, (-)-4aβ



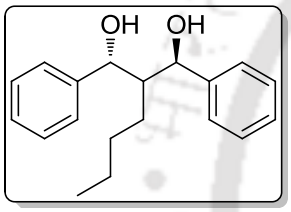
White solid, M. P.:129-131 ^{o}C; (129 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20-2.25 (m, 1 H, -OH), 2.59 (dd, *J* = 14.4 and 4.8 Hz, 1 H, -CH_2-), 2.93 (dd, *J* = 14.0 and 10.4 Hz, 1 H, -CH_2-), 3.19 (d, *J* = 4.8 Hz, 1 H, -OH), 3.37 (s, 1 H, -OH), 4.81-4.84 (m, 1 H, -CH-), 4.99 (brs, 1 H, -CH-); 7.08 (d, *J* = 7.6 Hz, 1 H, ArH), 7.15-7.19 (m, 1 H, ArH), 7.21-7.27 (m, 7 H, ArH), 7.28-7.38 (m, 6 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.2, 53.6, 72.6, 74.0, 125.6, 125.7, 126.0, 127.0, 127.2, 128.2, 128.4, 128.5, 129.2, 140.8, 142.7, 143.7; IR: 3257, 3030, 2896, 1603, 1452, 1343, 1056, 1042, 755, 700 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{22}H_{22}O_2$ $(M+H)^+$ 319.1698, found 319.1692; $[\alpha]_D^{25}$ -74 (C 0.2, CH_2Cl_2).

2-Butyl-1,3-diphenylpropane-1,3-diol, (+)-4bα



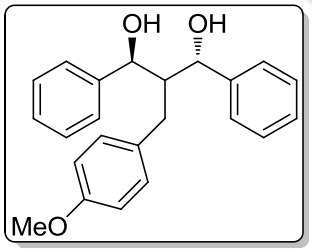
White solid, M. P.: 110-112 ^{o}C; (120 mg, 88%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (t, *J* = 7.2 Hz, 3 H, -CH_3), 1.04-1.36 (m, 5 H, -CH_2-), 1.46-1.56 (1 H, -CH_2-), 1.91-1.97 (m, 1 H, -CH-), 3.30 (brs, 2 H, 2x-OH), 4.94-4.97 (m, 2 H, 2x-CH-), 7.08 (d, *J* = 7.6 Hz, 1 H, ArH), 7.16-7.23 (m, 3 H, ArH), 7.25-7.32 (m, 3 H, ArH), 7.37-7.43 (m, 4 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ14.1, 22.7, 23.8, 29.9, 50.9, 73.3, 75.4, 125.9, 126.0, 126.9, 127.3, 128.1, 128.5, 142.8, 144.0; IR: 3337, 2928, 1621, 1451, 1024, 700 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{22}H_{22}O_2$ $(M+H)^+$ 319.1698, found 319.1692. Anal calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.32; H, 8.39; $[\alpha]_D^{25}$ +25 (C 0.2, CH_2Cl_2) .

2-Butyl-1,3-diphenylpropane-1,3-diol, (-)-4bβ



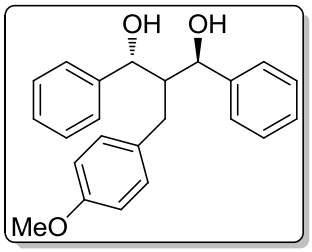
White solid, M. P.: 110-112 ^{o}C; (122 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (t, *J* = 7.2 Hz, 3 H, -CH_3), 1.04-1.36 (m, 5 H, -CH_2-), 1.46-1.56 (1 H, -CH_2-), 1.91-1.97 (m, 1 H, -CH-), 3.30 (brs, 2 H, 2x-OH), 4.94-4.97 (m, 2 H, 2x-CH-), 7.08 (d, *J* = 7.6 Hz, 1 H, ArH), 7.16-7.23 (m, 3 H, ArH), 7.25-7.32 (m, 3 H, ArH), 7.37-7.43 (m, 4 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ14.1, 22.7, 23.8, 29.9, 50.9, 73.3, 75.4, 125.9, 126.0, 126.9, 127.3, 128.1, 128.5, 142.8, 144.0; IR: 3337, 2928, 1621, 1451, 1024, 700 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{22}H_{22}O_2$ $(M+H)^+$ 319.1698, found 319.1692. Anal calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.32; H, 8.39; $[\alpha]_D^{25}$ -26 (C 0.2, CH_2Cl_2).

2-(4-Methoxybenzyl)-1,3-diphenylpropane-1,3-diol, (+)-4cα



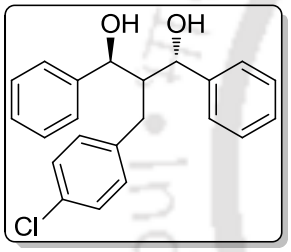
White solid, M. P.: 139-141 ^{o}C; (118mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12-2.17 (m, 1 H, -CH-), 2.51 (dd, *J* = 14.0 and 4.4 Hz, 1 H, -CH_2-), 2.85 (dd, *J* = 14.0 and 10.8 Hz, 1 H, -CH_2-), 3.41 (d, *J* = 5.2 Hz, 1 H, -OH), 3.51 (d, *J* = 2.4 Hz, 1 H, -OH), 3.76 (s, 3 H, -OCH_3), 4.78-4.80 (m, 1 H, -CH-), 4.94 (brs, 1 H, -CH-), 6.77 (d, *J* = 8.8 Hz, 2 H, ArH), 6.97 (d, *J* = 8.8 Hz, 2 H, ArH), 7.18-7.36 (m, 10 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.3, 29.9, 53.9, 55.3, 72.6, 74.1, 114.0, 125.6, 125.7, 127.0, 127.2, 128.2, 128.5, 130.1, 132.7, 142.9, 143.9, 157.9; IR: 3243, 2999, 2928, 1609, 1510, 1451, 1245, 1058, 1044, 757, 704 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{23}H_{24}NaO_3$ $(M+Na)^+$ 371.1623, found 371.1630; $[\alpha]_D^{25}$ +49 (C 0.2, CH_2Cl_2).

2-(4-Methoxybenzyl)-1,3-diphenylpropane-1,3-diol, (-)-4cβ



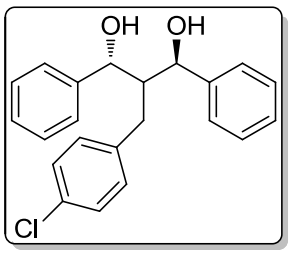
White solid, M. P.: 139-141 ^{o}C; (0.59 g, 84%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12-2.17 (m, 1 H, -CH-), 2.51 (dd, *J* = 14.0 and 4.4 Hz, 1 H, -CH_2-), 2.85 (dd, *J* = 14.0 and 10.8 Hz, 1 H, -CH_2-), 3.41 (d, *J* = 5.2 Hz, 1 H, -OH), 3.51 (d, *J* = 2.4 Hz, 1 H, -OH), 3.76 (s, 3 H, -OCH_3), 4.78-4.80 (m, 1 H, -CH-), 4.94 (brs, 1 H, -CH-), 6.77 (d, *J* = 8.8 Hz, 2 H, ArH), 6.97 (d, *J* = 8.8 Hz, 2 H, ArH), 7.18-7.36 (m, 10 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.3, 29.9, 53.9, 55.3, 72.6, 74.1, 114.0, 125.6, 125.7, 127.0, 127.2, 128.2, 128.5, 130.1, 132.7, 142.9, 143.9, 157.9; IR: 3243, 2999, 2928, 1609, 1510, 1451, 1245, 1058, 1044, 757, 704 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{23}H_{24}NaO_3$ $(M+Na)^+$ 371.1623, found 371.1630; $[\alpha]_D^{25}$ -46 (C 0.4, CH_2Cl_2).

2-(4-Chlorobenzyl)-1,3-diphenylpropane-1,3-diol, (+)-4dα



White solid, M. P.: 119-121 ^{o}C; (126 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06-2.14 (m, 1 H, -CH-), 2.51 (dd, *J* = 14.4 and 4.4 Hz, 1 H, -CH_2-), 2.86 (dd, *J* = 14.4 and 10.8 Hz, 1 H, -CH_2-), 3.67 (brs, 1 H, -OH), 3.73 (brs, 1 H, -OH), 4.68-4.71 (m, 1 H, -CH-), 4.91 (brs, 1 H, -CH-), 6.93 (d, *J* = 8.0 Hz, 2 H, ArH), 7.15 (t, *J* = 8.0 Hz, 4 H, ArH), 7.21-7.35 (m, 8 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7, 53.8, 72.6, 74.2, 125.6, 125.7, 127.2, 127.5, 128.4, 128.7 (2C), 130.6, 131.8, 139.3, 142.7, 143.6; IR: 3233, 2907, 2873, 1602, 1491, 1449, 1234, 1064, 1045, 726, 701 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{22}H_{21}ClO_2$ $(M+H)^+$ 353.1308, found 353.2003; Anal calcd for $C_{22}H_{21}ClO_2$: C, 74.89; H, 6.00. Found: C, 74.83; H, 6.12; $[\alpha]_D^{25}$ +45 (C 0.25, CH_2Cl_2).

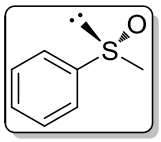
2-(4-Chlorobenzyl)-1,3-diphenylpropane-1,3-diol, (-)-4dβ



White solid, M. P.: 119-121 ^{o}C; (130 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06-2.14 (m, 1 H, -CH-), 2.51 (dd, *J* = 14.4 and 4.4 Hz, 1 H, -CH_2-), 2.86 (dd, *J* = 14.4 and 10.8 Hz, 1 H, -CH_2-), 3.67 (brs, 1 H, -OH), 3.73 (brs, 1 H, -OH), 4.68-4.71 (m, 1 H, -CH-), 4.91 (brs, 1 H, -CH-), 6.93 (d, *J* = 8.0 Hz, 2 H, ArH), 7.15 (t, *J* = 8.0 Hz, 4 H, ArH), 7.21-7.35 (m, 8 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7, 53.8, 72.6, 74.2, 125.6, 125.7, 127.2, 127.5, 128.4, 128.7 (2C), 130.6, 131.8, 139.3, 142.7, 143.6; IR: 3233, 2907, 2873, 1602, 1491, 1449, 1234, 1064, 1045, 726, 701 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{22}H_{21}ClO_2$ $(M+H)^+$

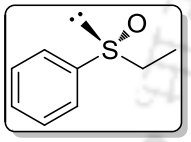
353.1308, found 353.2003; Anal calcd for $C_{22}H_{21}ClO_2$: C, 74.89; H, 6.00. Found: C, 74.83; H, 6.12. $[\alpha]_D^{25}$ -42 (C 0.3, CH_2Cl_2).

(*R*)-1-(Methylsulfinyl)benzene (8a):



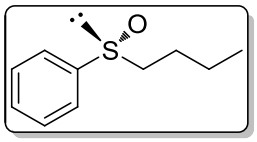
Colourless oil; (45 mg, 59%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.73 (s, 3 H, -CH_3), 7.52-7.54 (m, 3 H. ArH), 7.64-7.67 (m, 2 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.9,123.4, 129.4, 131.1, 145.6; IR: 2920, 2851, 1639, 1443, 1089, 1036, 757, 749 cm^{-1}; HRMS (APCI) *m/z* calcd for C_7H_8OS $(M+H)^+$ 141.0374, found 141.0369. Enantiomeric excess was determined by chiral HPLC on a Chiralcel OD-H (250 x 10 mm) column eluting with a hexane:isopropanol (9:1) mixture (0.5 ml /min, λ = 254 nm). $[\alpha]_D^{25}$ +80 (C 0.2, CH_2Cl_2).

(*R*)-1-(Ethylsulfinyl)benzene (8b):



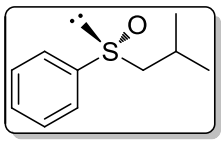
Colourless oil; (54 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, *J* = 7.2 Hz, 3 H, -CH_3), 2.77 (dq, *J* = 13.2 and 7.2 Hz, 1 H, -$SOCH_2$-), 2.91 (dq, *J* = 13.2 and 7.2 Hz, 1 H, -$SOCH_2$-), 7.49-7.55 (m, 3 H, ArH), 7.59-7.63 (m, 2 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 6.1, 50.4, 124.3, 129.3, 131.1, 143.4; IR: 2924, 2851, 1640, 1444, 1374, 1078, 1042, 1020, 747, 691 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_8H_{10}OS$ $(M+H)^+$ 155.0531, found 155.0535. Enantiomeric excess was determined by chiral HPLC on a Chiralcel OD-H (250 x 4.6 mm) column eluting with a hexane:isopropanol (9:1) mixture (0.5ml /min, λ = 252 nm); $[\alpha]_D^{25}$ +262 (C 0.2, CH_2Cl_2).

(*R*)-1-(Butylsulfinyl)benzene (8c):



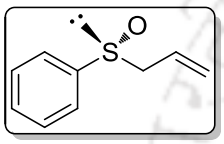
Colourless oil; (59 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (d, *J* = 7.6 Hz, 3 H, -CH_3), 1.36-1. 52 (m, 2 H, -CH_2-), 1.54-1.64 (m, 1 H, -CH_2-), 1.67-1.77 (m, 1 H, -CH_2-), 2.80 (dd, *J* = 6.8 and 2.0 Hz, 1 H, -$SOCH_2$-), 2.81 (dd, *J* = 6.8 and 2.0 Hz, 1 H, -$SOCH_2$-), 7.49-7.55 (m, 3 H, ArH), 7.61-7.64 (m, 2 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 22.0, 24.3, 57.1, 124.2, 129.3, 131.1, 144.0; IR: 2959, 2931, 1637, 1443, 1088, 1037, 750, 692 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{10}H_{14}NaOS$ $(M+Na)^+$ 205.0663, found 205.0665. Enantiomeric excess was determined by chiral HPLC on a Chiralcel OD-H (250 x 4.6 mm) column eluting with a hexane:isopropanol (9:1) mixture (0.8ml /min, λ = 254 nm). $[\alpha]_D^{25}$ +150 (C 0.1, CH_2Cl_2).

(*R*)-1-(Isopropylsulfinyl)benzene (8d):



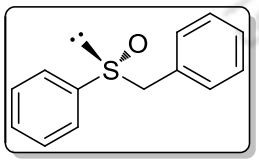
Colourless oil; (59 mg, 61%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (d, *J* = 6.8 Hz, 3 H, -CH_3), 1.23 (d, *J* = 7.2 Hz, 3 H, -CH_3), 2.84 (septet, *J* = 6.8 Hz, 1 H, -CH-), 7.48-7.54 (m, 3 H, ArH), 7.58-7.61 (m, 2 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 16.0, 54.7, 125.2, 129.0, 131.1, 141.9; IR: 2926, 2855, 1643, 1459, 1444, 1087, 1023, 751, 693 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_9H_{12}OS$ $(M+H)^+$ 169.0687, found 169.0680. Enantiomeric excess was determined by chiral HPLC on a Chiralcel OD (250 x 10 mm) column eluting with a hexane:isopropanol (9:1) mixture (1ml /min, λ = 254 nm). $[\alpha]_D^{25}$ +139 (C 0.3, CH_2Cl_2), lit.[2] $[\alpha]_D^{25}$ +145 (C 1, $CHCl_3$) for 83% ee (*R*).

(*R*)-1-(Allylsulfinyl)benzene (8e):



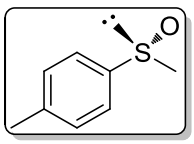
Colourless oil; (53 mg, 59%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.48-3.61 (m, 2 H, -CH_2-), 5.20 (dd, *J* = 16.8 and 1.2 Hz, 1 H, -CH-), 5.33 (d, *J* = 10.4 Hz, 1 H, -CH-), 5.59-5.70 (m, 1 H, -CH-), 7.50-7.53 (m, 3 H, ArH), 7.57-7.62 (m, 2 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 60.9, 123.9, 124.3, 124.4, 129.0, 129.1, 131.2; IR: 2923, 2853, 1636, 1443, 1088, 1041, 930, 750 cm^{-1}. HRMS (APCI) *m/z* calcd for $C_9H_{10}OS$ $(M+H)^+$ 167.0531, found 167.0535. Enantiomeric excess was determined by chiral HPLC on a Chiralcel OD-H (250 x 4.6 mm) column eluting with a hexane:isopropanol (9:1) mixture (1ml /min, λ = 254 nm). $[\alpha]_D^{25}$ +76 (C 0.4, CH_2Cl_2).

(*R*)-1-((Phenylsulfinyl)methyl)benzene (8f):



White solid, M.P. 120-121 ^{o}C; (80 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 4.00 (d, *J* = 12.8 Hz, 1 H, -$SOCH_2$-), 4.11 (d, *J* = 12.8 Hz, 1 H, -$SOCH_2$-), 6.98 (d, *J* = 7.6 Hz, 2 H. ArH), 7.23-7.30 (m, 3 H. ArH), 7.36-7.47 (m, 5 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 63.8, 124.6, 128.4, 128.6, 129.1, 129.3, 130.6, 131.4, 142.9; IR: 2920, 2852, 1442, 1084, 1035, 745, 694 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{13}H_{12}OS$ $(M+H)^+$ 217.0687, found 217.0687. Enantiomeric excess was determined by chiral HPLC on a Chiralcel OD-H (250 x 4.6 mm) column eluting with a hexane:isopropanol (9:1) mixture (1ml /min, λ = 254 nm). $[\alpha]_D^{25}$ +98 (C 0.3, CH_2Cl_2).

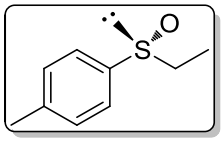
(*R*)-1-Methyl-4-(methylsulfinyl)benzene (8g):



Semisolid; (50 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3 H, -CH_3), 2.71 (s, 3 H, -$SOCH_3$), 7.34 (d, *J* = 7.6 Hz, 2 H, ArH), 7.54 (d, *J* = 8.0 Hz, 2 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 44.0, 123.6, 130.1, 141.6, 142.4;

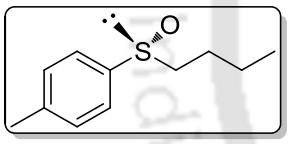
IR: 2922, 2862, 1644, 1410, 1083, 1041, 954, 811 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_8H_{10}OS$ $(M+H)^+$ 155.0531, found 155.0528. Enantiomeric excess was determined by chiral HPLC on a Chiralcel OD-H (250 x 4.6 mm) column eluting with a hexane:isopropanol (9:1) mixture (1ml /min, λ = 250 nm). $[\alpha]_D^{25}$ +127 (C 0.2, CH_2Cl_2), lit.[1] $[\alpha]_D^{25}$ +132 (C 2, $CHCl_3$) for 91% ee (R).

(*R*)-1-(Ethylsulfinyl)-4-methylbenzene (8h):



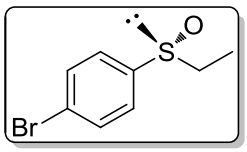
Colourless oil; (59 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (t, *J* = 7.2 Hz, 3 H, $-CH_3$), 2.42 (s, 3 H, $-CH_3$), 2.76 (dq, *J* = 13.2 and 7.2 Hz, 1 H, $-SOCH_2-$), 2.86 (dq, *J* = 13.2 and 7.2 Hz, 1 H, $-SOCH_2-$), 7.33 (d, *J* = 8.0 Hz, 2 H, ArH), 7.50 (d, *J* = 8.0 Hz, 2 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 5.9, 21.3, 50.1, 124.1, 129.7, 139.8, 141.3; IR: 2932, 2868, 1651, 1453, 1087, 1044, 1014, 813 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_9H_{12}NaOS$ $(M+Na)^+$ 191.0507, found 191.0501. Enantiomeric excess was determined by chiral HPLC on a Chiralcel OD-H (250 x 4.6 mm) column eluting with a hexane:isopropanol (9:1) mixture (0.5ml /min, λ = 254 nm). $[\alpha]_D^{25}$ +145 (C 0.32, CH_2Cl_2).

(*R*)-1-(Butylsulfinyl)-4-methylbenzene (8i):



Gum; (72 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.2 Hz, 3 H, $-CH_3$), 1.35-1.51 (m, 2 H, $-CH_2-$), 1.53-1.63 (m, 1 H, $-CH_2-$), 1.64-1.76 (m, 1 H, $-CH_2-$), 2.42 (s, 3 H, $-CH_3$), 2.72-2.84 (m, 2 H, $-SOCH_2-$), 7.32 (d, *J* = 8.0 Hz, 2 H, ArH), 7.51 (d, *J* = 8.0 Hz, 2 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 21.3, 21.8, 24.1, 57.0, 124.0, 129.8, 140.6, 141.2; IR: 2958, 2872, 1634, 1456, 1087, 1038, 913, 812 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{11}H_{16}OS$ $(M+H)^+$ 197.1000, found 197.0092. Enantiomeric excess was determined by chiral HPLC on a Chiralcel OD-H (250 x 4.6 mm) column eluting with a hexane:isopropanol (9:1) mixture (1ml /min, λ = 254 nm). $[\alpha]_D^{25}$ +94 (C 0.2, CH_2Cl_2), lit.[4] $[\alpha]_D^{25}$ +72 (C 1, acetone) for 34.2% ee (R).

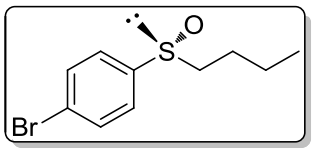
(*R*)-1-Bromo-4-(ethylsulfinyl)benzene (8j):



Colourless solid, M.P. 52-54 ^oC; (78 mg, 64%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, *J* = 7.2 Hz, 3 H, $-CH_3$), 2.76 (dq, *J* = 13.2 and 7.2 Hz, 1 H, $-SOCH_2-$), 2.91 (dq, *J* = 13.2 and 7.2 Hz, 1 H, $-SOCH_2-$), 7.48 (d, *J* = 8.4 Hz, 2 H, ArH), 7.66 (d, *J* = 8.4 Hz 2 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 5.9, 50.3, 125.5, 125.9, 132.5, 142.5; IR: 3071, 2912, 1634, 1572, 1471, 1387, 1152, 1083, 1045, 818, 724 cm^{-1}; HRMS (APCI) *m/z* calcd for C_8H_9BrOS $(M+H)^+$ 232.9636, found 232.9640 (^{79}Br). Enantiomeric excess was determined by chiral HPLC on a Chiralcel OD-H (250 x 4.6 mm)

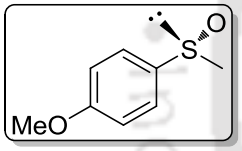
column eluting with a hexane:isopropanol (95:5) mixture (0.5ml /min, λ = 252 nm). $[\alpha]_D^{25}$ +69 (C 0.2, CH_2Cl_2), lit.[3] $[\alpha]_D^{25}$ +162 (C 1, $CHCl_3$) for >98% ee (R).

(*R*)-1-Bromo-4-(butylsulfinyl)benzene (8k):



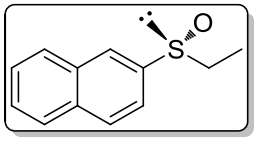
Colourless oil; (82 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, *J* = 7.2 Hz, 3 H, -CH_3), 1.34-1.50 (m, 2 H, -CH_2-), 1.52-1.64 (m, 1 H, -CH_2-), 1.68-1.79 (m, 1 H, -CH_2-), 2.78 (t, *J* = 7.2 Hz, 2 H, -$SOCH_2$-), 7.50 (d, *J* = 8.8 Hz, 2 H, ArH), 7.67 (d, *J* = 8.8 Hz 2 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 21.8, 23.9, 56.9, 125.2, 125.6, 132.3, 143.1; IR: 2956, 2927, 1637, 1572, 1470, 1385, 1064, 1040, 820, 724 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{10}H_{13}BrNaOS$ $(M+Na)^+$ 282.9768, found 282.9765 (^{79}Br). Enantiomeric excess was determined by chiral HPLC on a Chiralcel OD-H (250 x 4.6 mm) column eluting with a hexane:isopropanol (9:1) mixture (0.8ml /min, λ = 254 nm). $[\alpha]_D^{25}$ +68 (C 0.2, CH_2Cl_2).

(*R*)-1-Methoxy-4-(methylsulfinyl)benzene (8l):



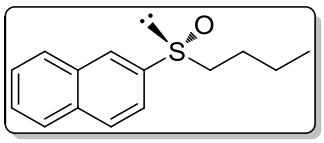
Colourless solid, M.P. 52-54 ^oC; (50 mg, 55%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72 (s, 3 H, -$SOCH_3$), 3.86 (s, 3 H, -OCH_3), 7.03 (d, *J* = 8.4 Hz, 2 H, ArH), 7.61 (d, *J* = 8.4 Hz 2 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.9, 55.5, 114.8, 125.4, 136.5, 161.9; IR: 2945, 1595, 1497, 1256, 1090, 1026, 831, 687 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_8H_{10}O_2S$ $(M+H)^+$ 171.0480, found 171.0484. Enantiomeric excess was determined by chiral HPLC on a Chiralcel OD-H (250 x 4.6 mm) column eluting with a hexane:isopropanol (9:1) mixture (1 ml /min, λ = 252 nm). $[\alpha]_D^{25}$ +66 (C 0.52, CH_2Cl_2).

(*R*)-2-(Ethylsulfinyl)naphthalene (8m):



Gum; (56 mg, 52%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, *J* = 7.2 Hz, 3 H, -CH_3), 2.80 (dq, *J* = 15.2 and 7.6 Hz, 1 H, -$SOCH_2$-), 2.95 (dq, *J* = 15.2 and 7.6 Hz, 1 H, -$SOCH_2$-), 7.49-7.55 (m, 3 H, ArH), 7.82-7.92 (m, 3 H, ArH), 8.12 (s, 1 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 6.0, 49.9, 120.0, 125.1, 127.4, 127.8, 128.1, 128.5, 129.5, 132.8, 134.5, 140.0; IR: 2931, 2868, 1640, 1454, 1268, 1069, 1042, 1020, 818, 748 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{12}H_{12}OS$ $(M+H)^+$ 205.0687, found 205.0676. Enantiomeric excess was determined by chiral HPLC on a Chiralcel OD-H (250 x 4.6 mm) column eluting with a hexane:isopropanol (9:1) mixture (1ml /min, λ = 254 nm). $[\alpha]_D^{25}$ +138 (C 0.2, CH_2Cl_2).

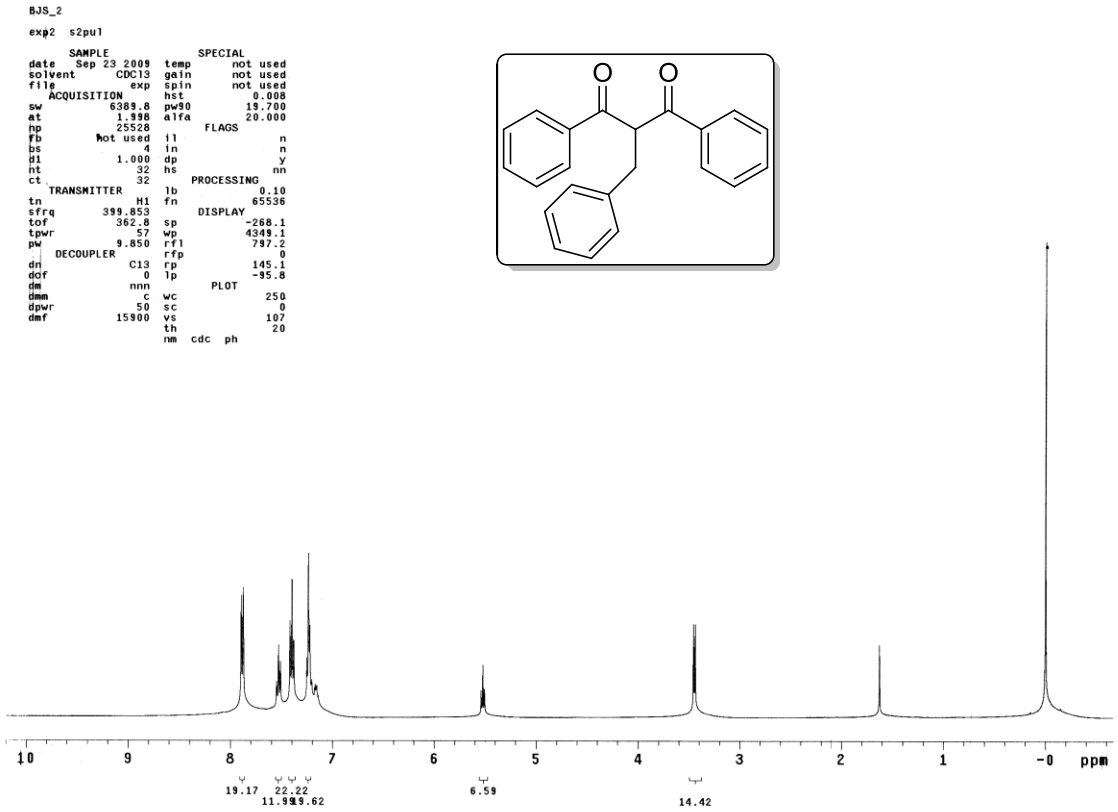
(*R*)-2-(Butylsulfinyl)naphthalene (8n):

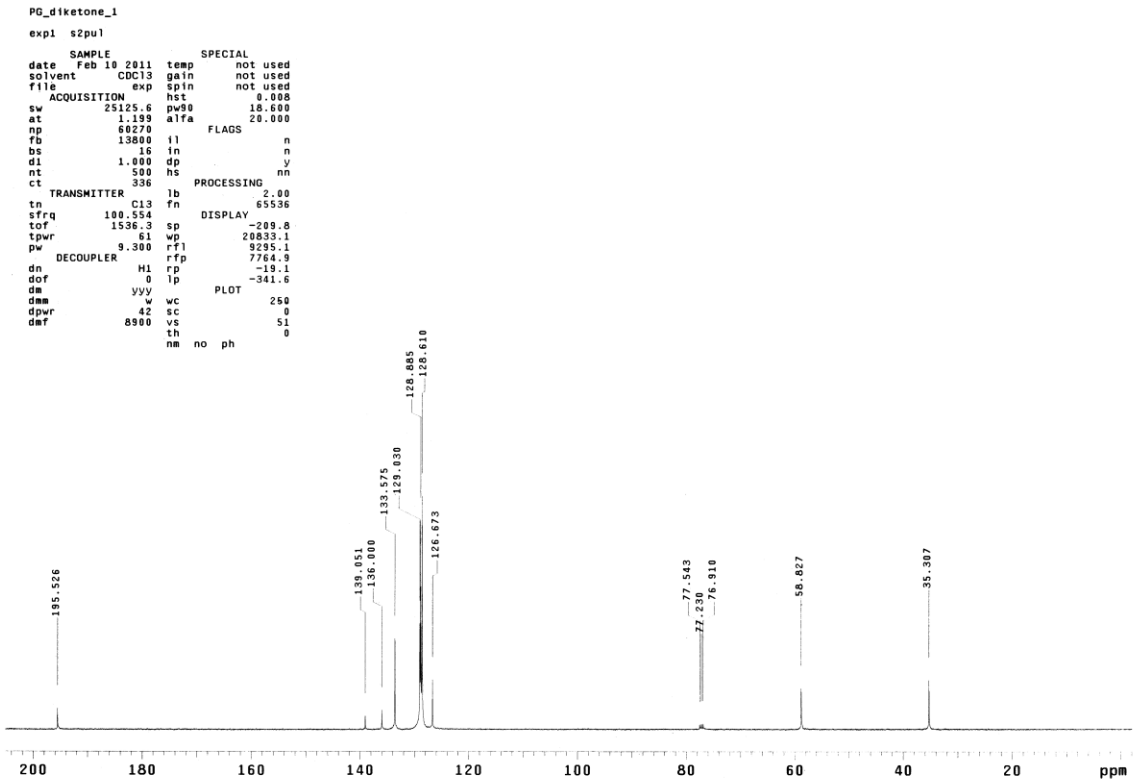


White solid, M.P. 66-67 ^{o}C; (64 mg, 52%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, J = 7.2 Hz, 3 H, -CH_3), 1.37-1.53 (m, 2 H, -CH_2-), 1.54-1.65 (m, 1 H, -CH_2-), 1.71-1.83 (m, 1 H, -CH_2-), 2.85-2.90 (m, 2 H, -$SOCH_2$-), 7.57-7.61 (m, 3 H, ArH), 7.90-7.99 (m, 3 H, ArH), 8.19 (s, 1 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ13.8, 22.0, 24.2, 56.8, 120.0, 124.8, 127.4, 127.8, 128.2, 128.6, 129.5, 133.0, 134.5, 141.2; IR: 2953, 2870, 1586, 1465, 1344, 1060, 1033, 820, 741 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{14}H_{16}NaOS$ $(M+Na)^+$ 255.0820, found 255.0816. Enantiomeric excess was determined by chiral HPLC on a Chiralcel OD-H (250 x 4.6 mm) column eluting with a hexane:isopropanol (9:1) mixture (0.8ml /min, λ = 254 nm). $[\alpha]_D^{25}$ +188 (C 0.12, CH_2Cl_2).

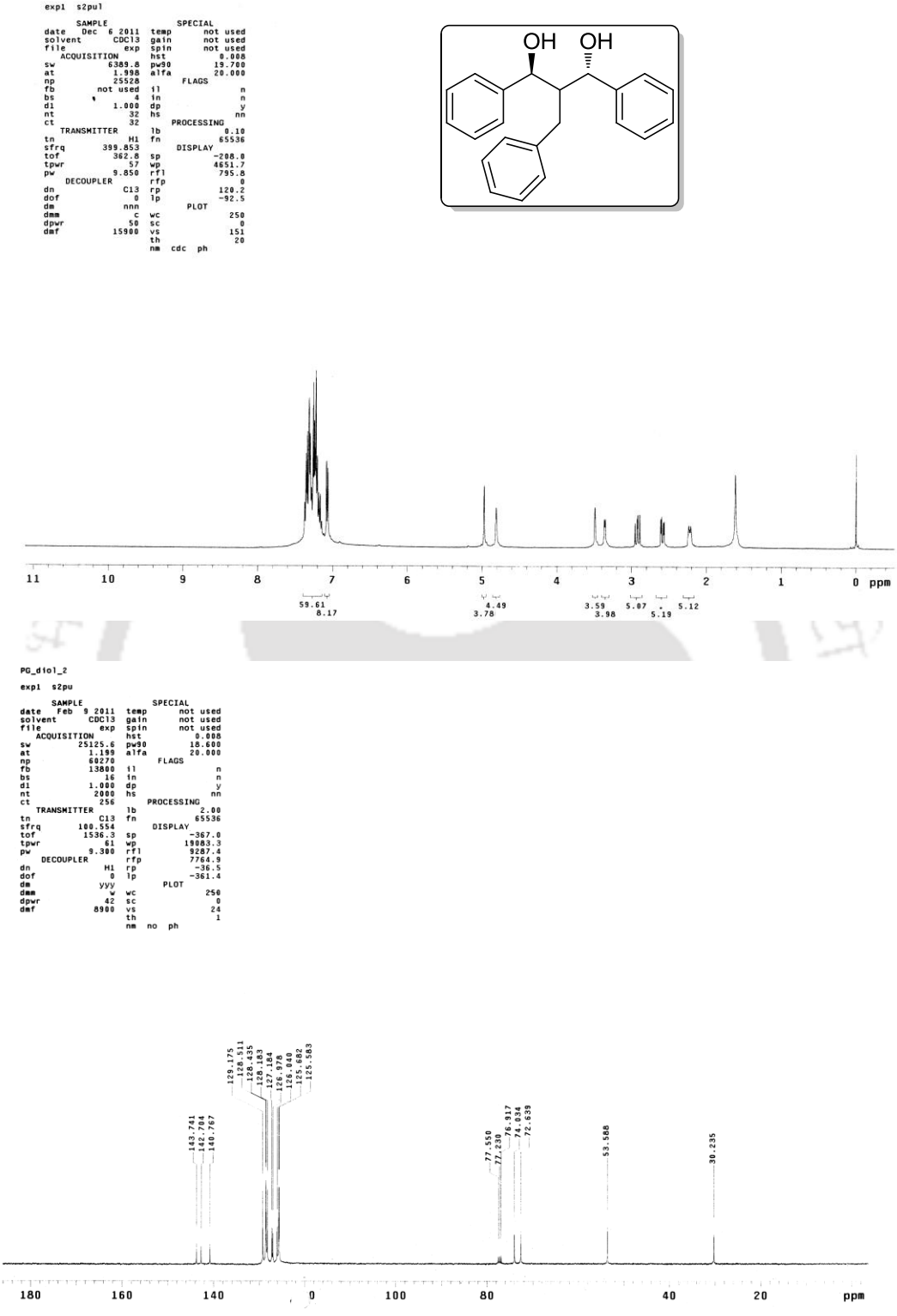
2.6. Selected Spectra

^{1}H and ^{13}C NMR spectra of 2-benzyl-1,3-diphenylpropane-1,3-dione, **3a**

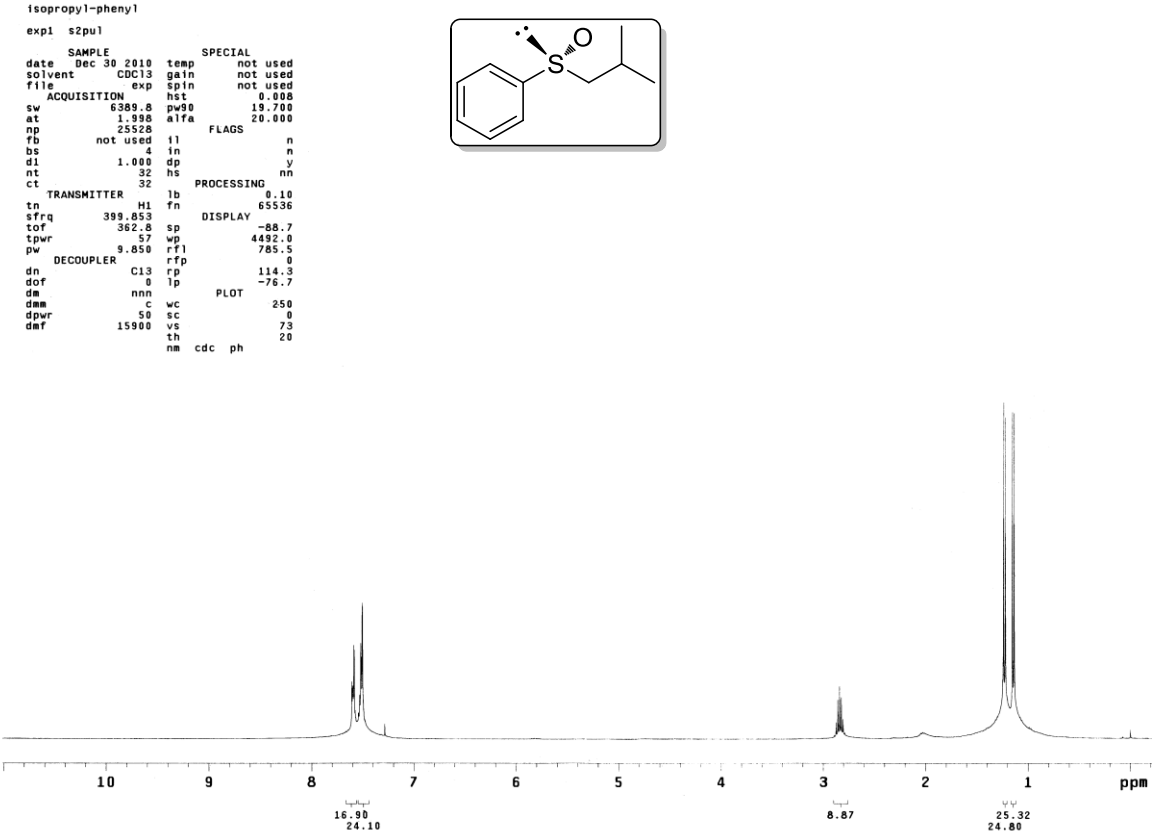


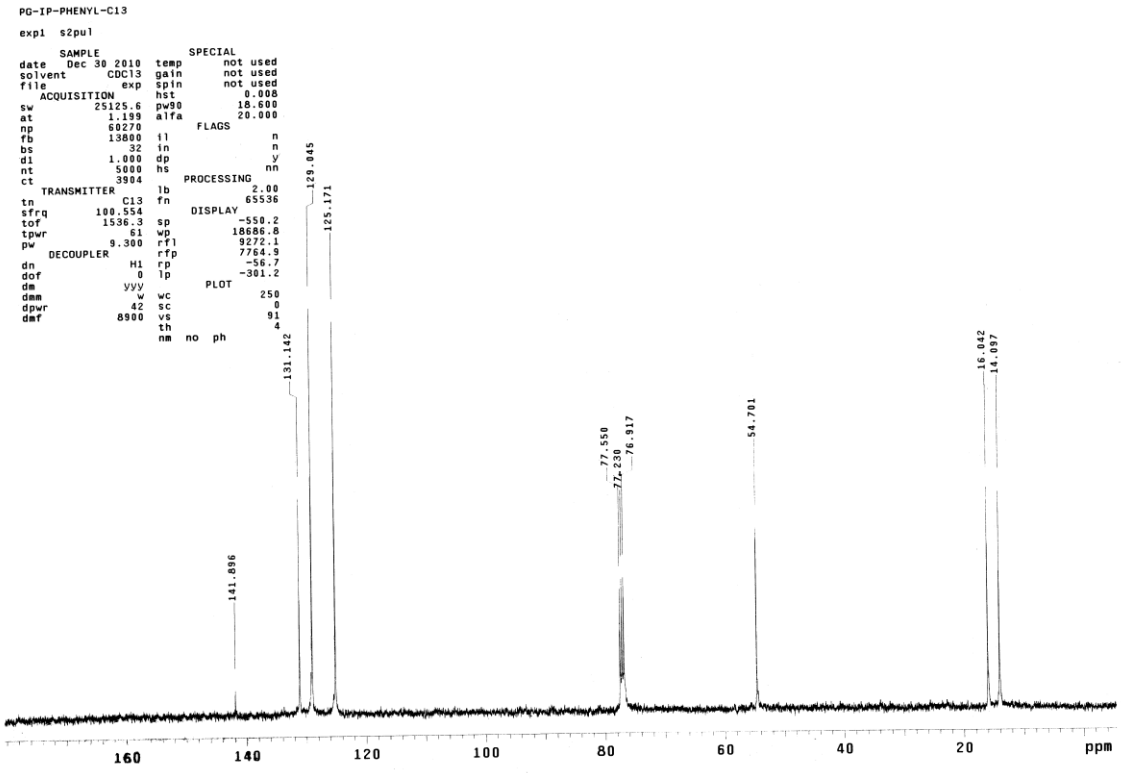


^{1}H and ^{13}C NMR spectra of 2-benzyl-1,3-diphenylpropane-1,3-diol, **4aα**

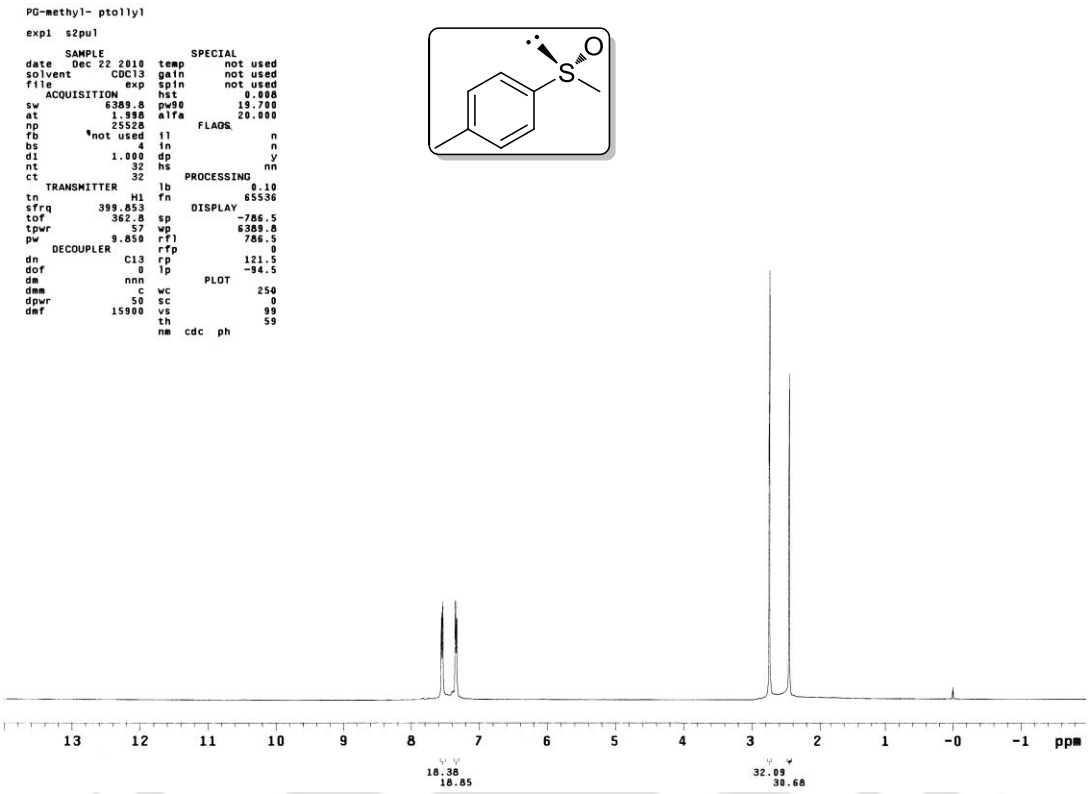


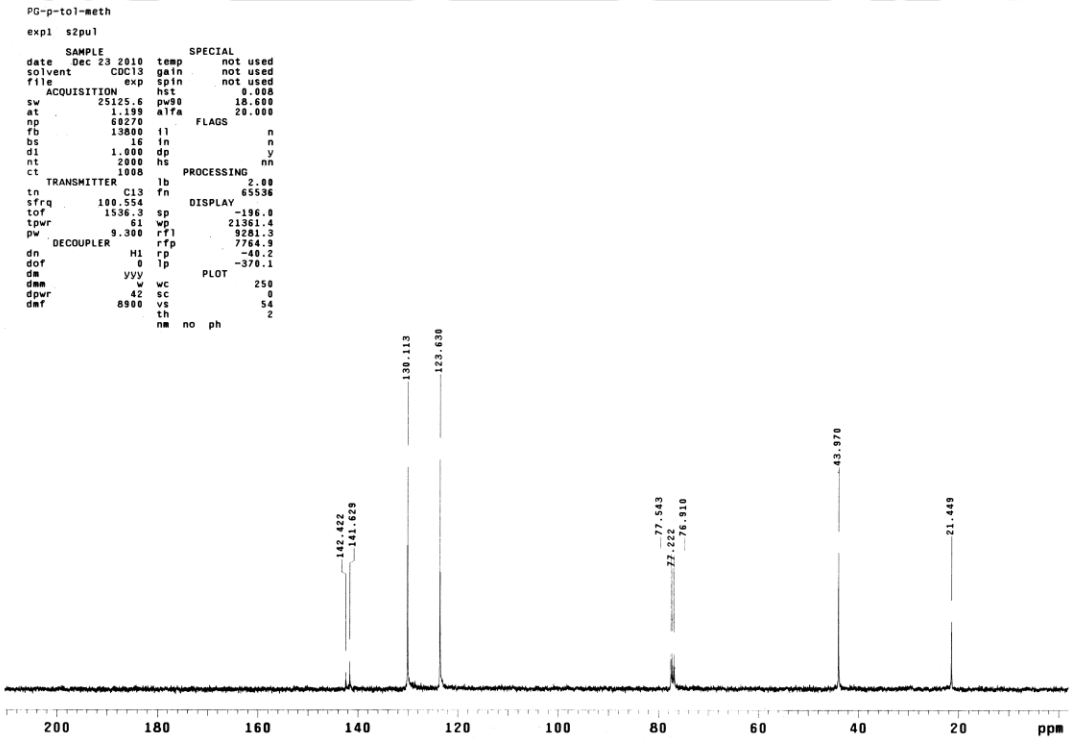
^{1}H and ^{13}C NMR spectra of (*R*)-1-(Isopropylsulfinyl)benzene, **8d**



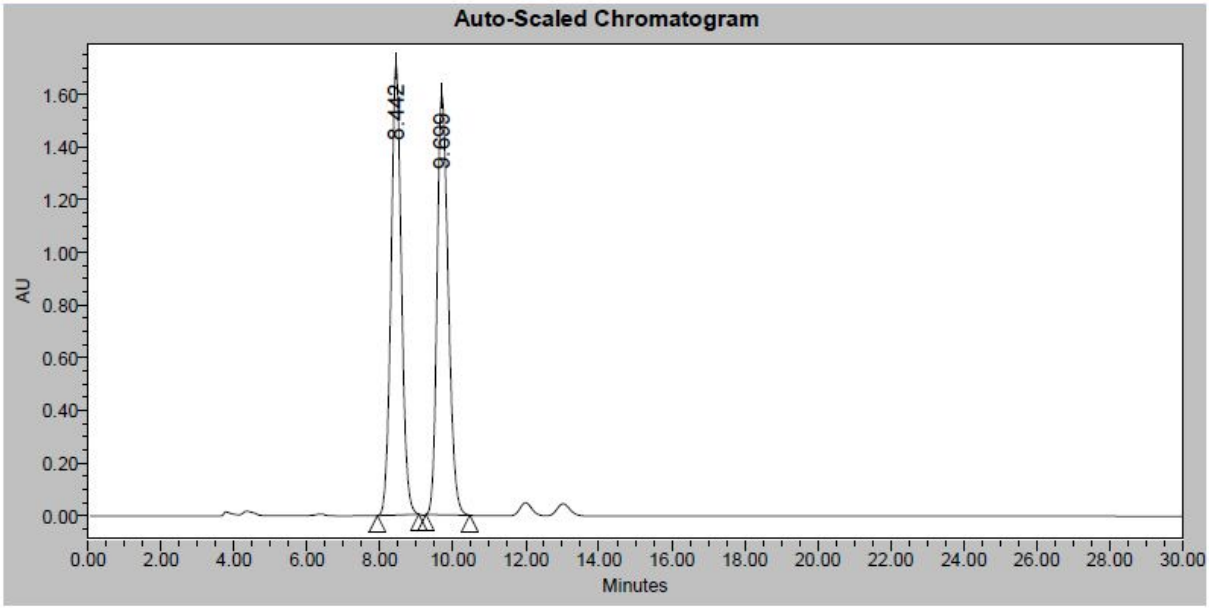


^{1}H and ^{13}C NMR spectra of (*R*)-1-Methyl-4-(methylsulfinyl)benzene, **8g**



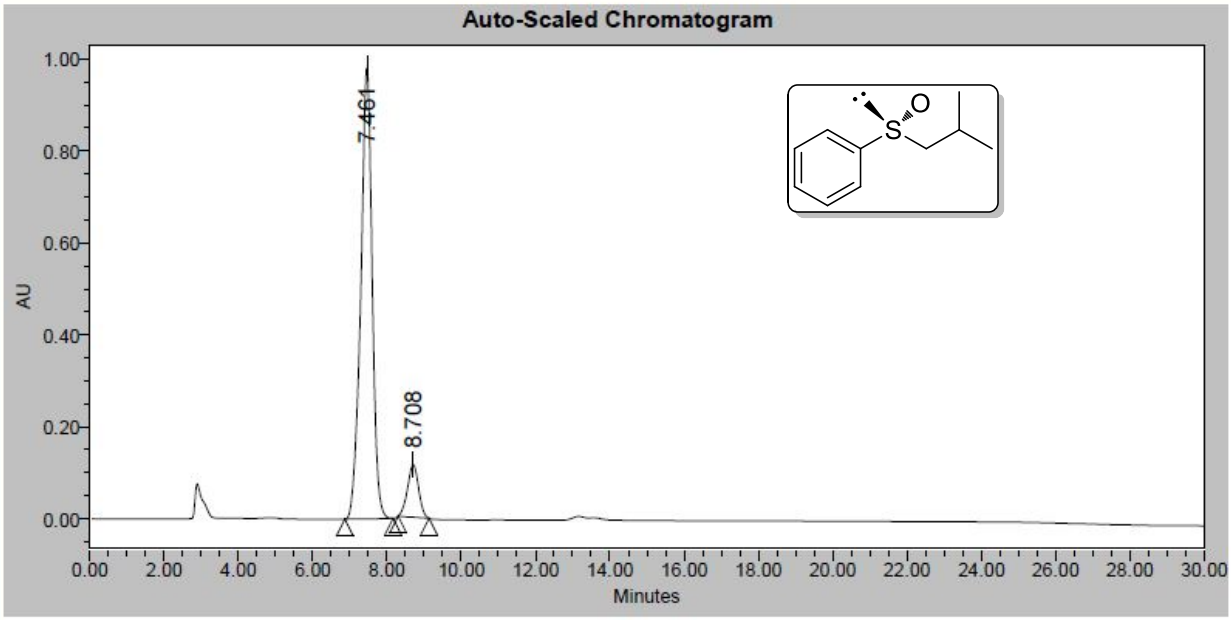


HPLC analysis of 1-(Isopropylsulfinyl)benzene, **8d**



Peak Results

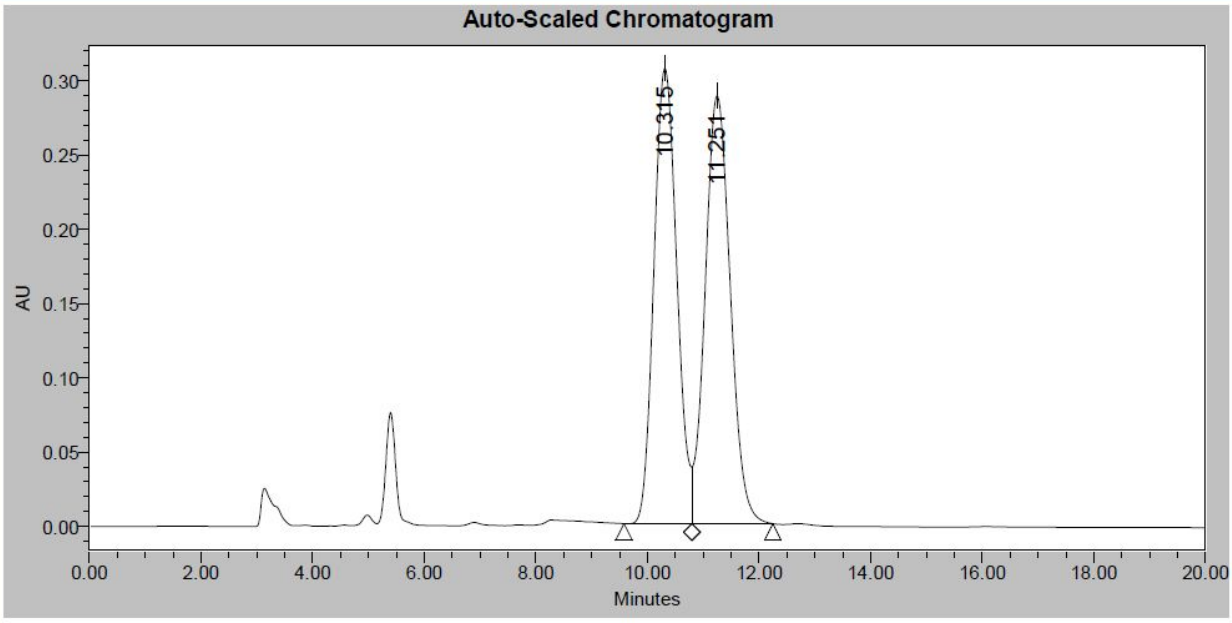
	Name	RT	Area	Height	% Area
1		8.442	33853286	1707992	49.89
2		9.699	34007932	1593303	50.11



Peak Results

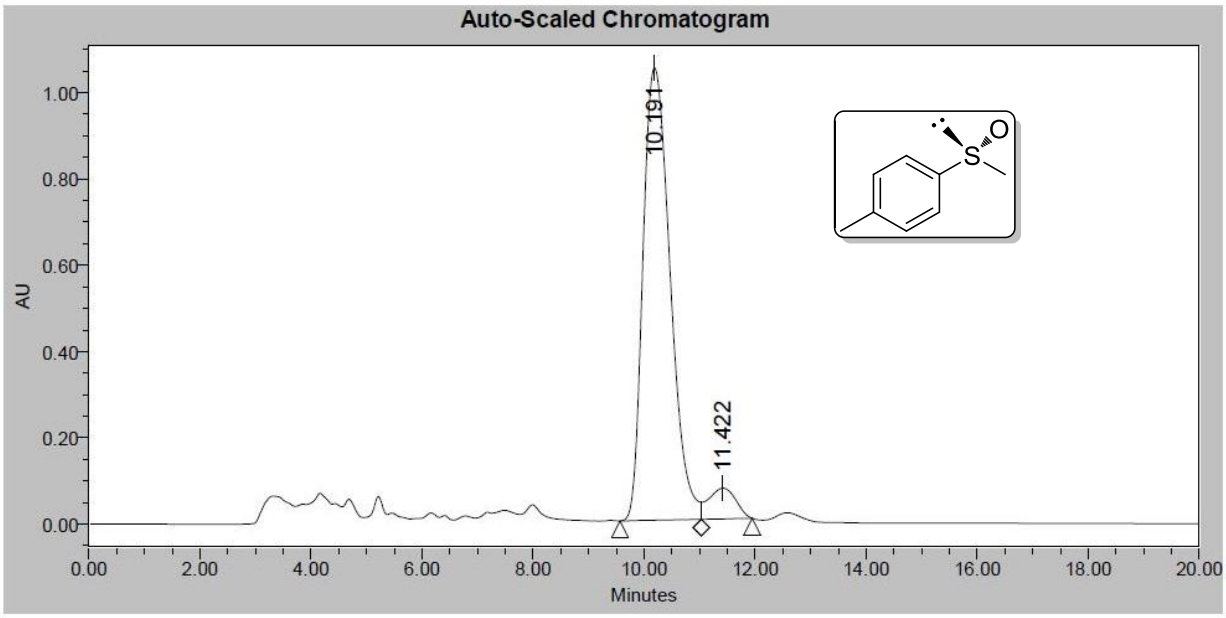
	Name	RT	Area	Height	% Area
1		7.461	20944966	982841	89.84
2		8.708	2367864	113806	10.16

HPLC analysis of 1-Methyl-4-(methylsulfinyl)benzene, **8g**



Peak Results

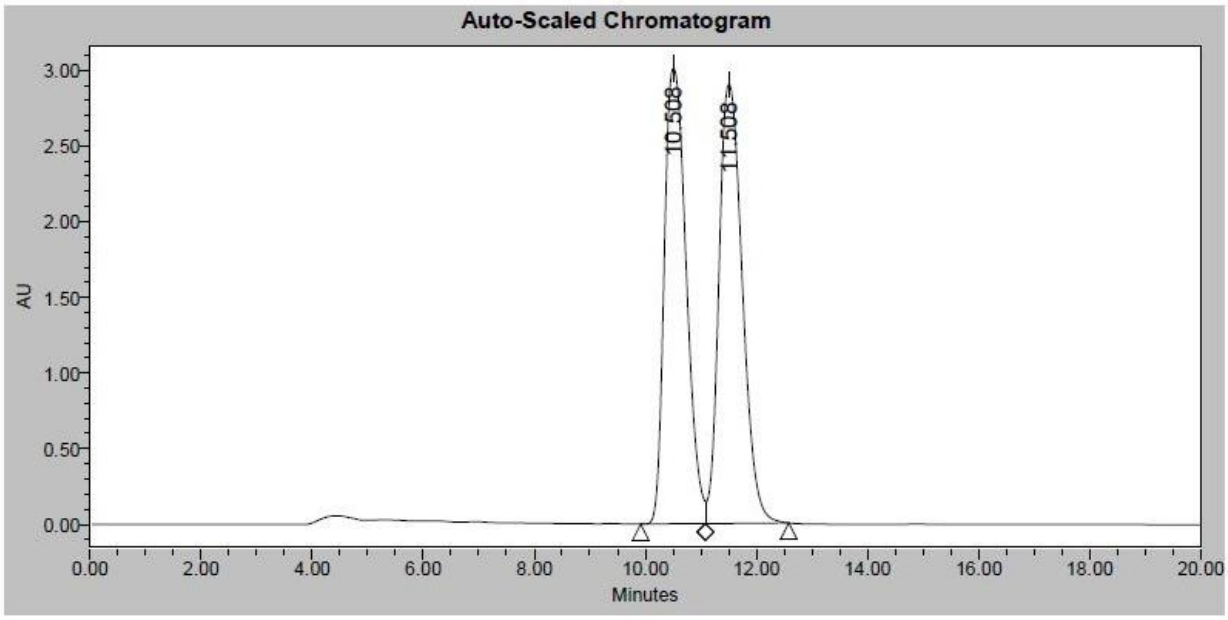
	Name	RT	Area	Height	% Area
1		10.315	8706606	306592	49.08
2		11.251	9032992	288076	50.92



Peak Results

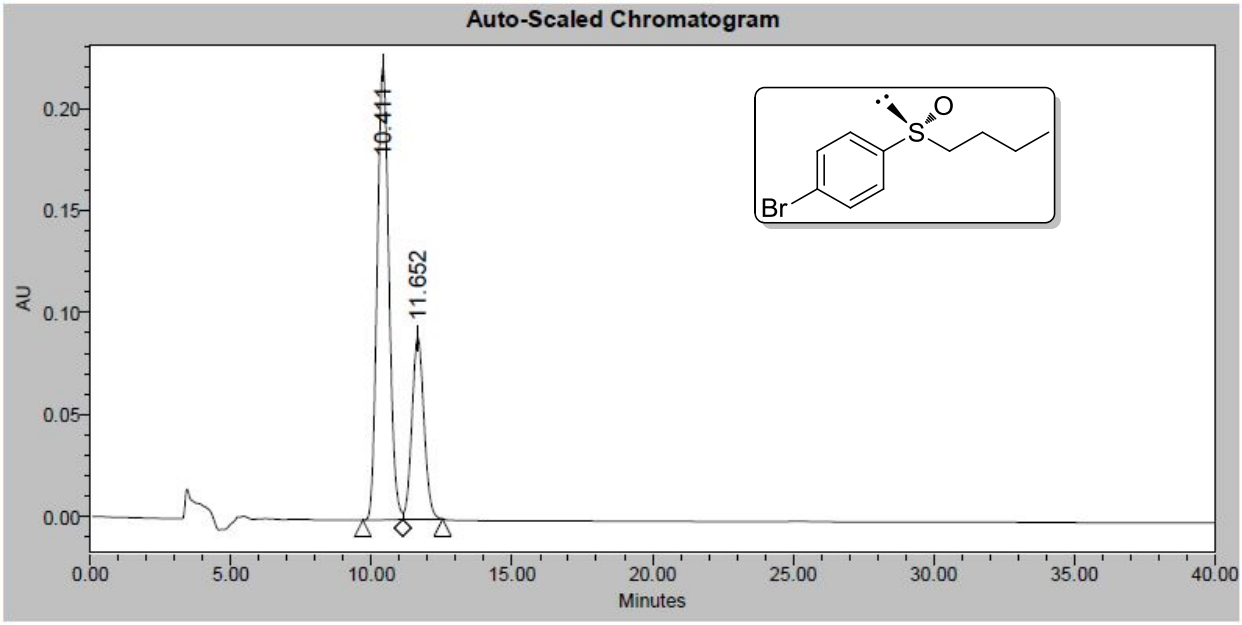
	Name	RT	Area	Height	% Area
1		10.191	35587587	1048968	93.57
2		11.422	2447307	71253	6.43

HPLC analysis of 1-Bromo-4-(butylsulfinyl)benzene, **8k**



Peak Results

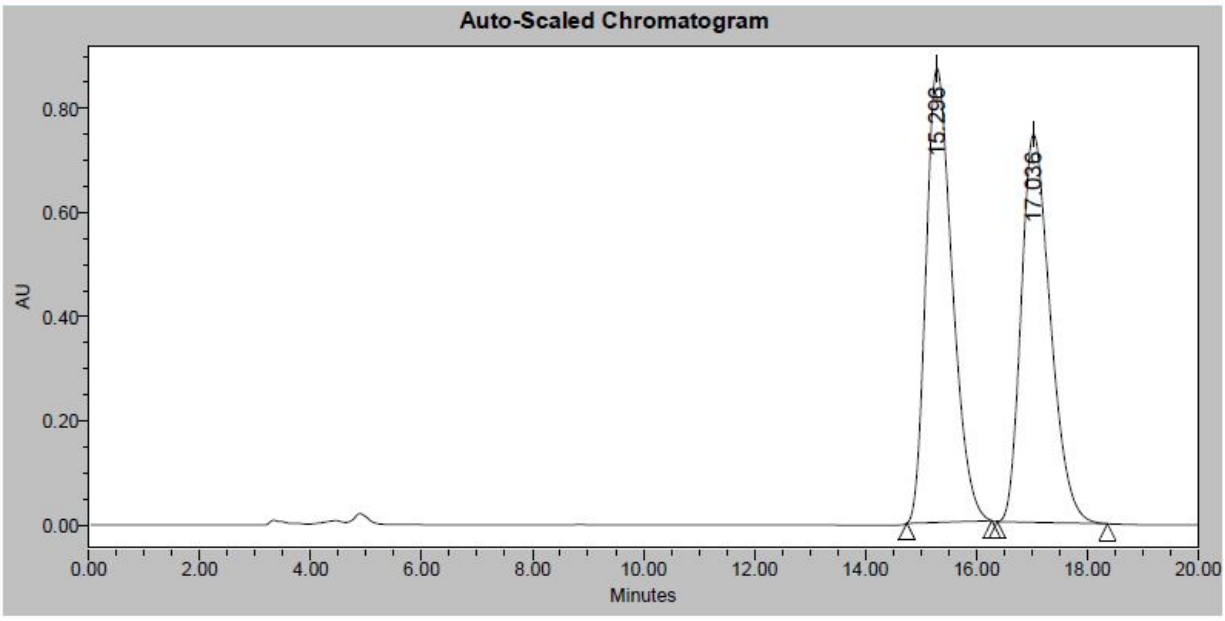
	Name	RT	Area	Height	% Area
1		10.508	82207243	3010542	49.21
2		11.508	84850944	2901171	50.79



Peak Results

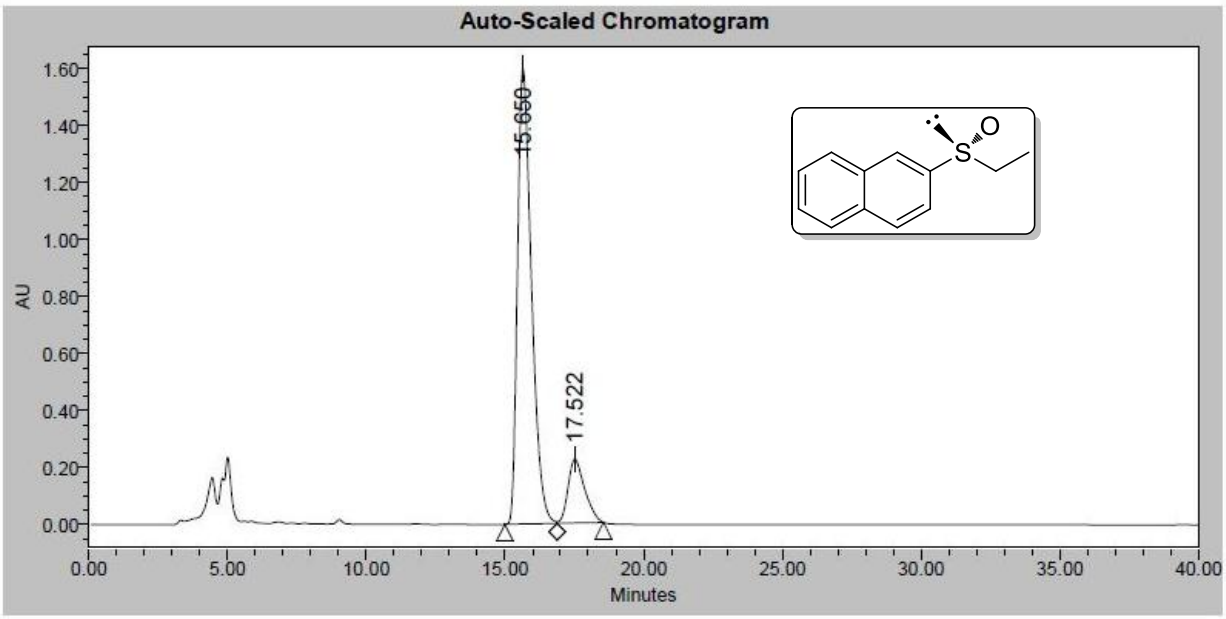
	Name	RT	Area	Height	% Area
1		10.411	6422811	221595	70.64
2		11.652	2669119	88984	29.36

HPLC analysis of 2-(Ethylsulfinyl)naphthalene, **8m**



Peak Results

	Name	RT	Area	Height	% Area
1		15.296	28695044	871469	51.39
2		17.036	27144414	745097	48.61



Peak Results

	Name	RT	Area	Height	% Area
1		15.650	55807639	1596096	85.71
2		17.522	9307078	223430	14.29

2.7. Crystal Parameters

The crystal parameters of compound 4a*α*

	4a*α* - CCDC 816383
Formula	C_{22} H_{22} O_2
Formula weight	318.40
T/K	296(2)
Crystal system	Monoclinic
Space group	P2(1)
a/Å	12.5169 (7)
b/Å	9.7928(5)
c/Å	14.9192(8)
α/°	90.00
β/°	90.823 (4)
γ/°	90.00
V/Å^3	1828.54 (17)
Z	4
Abs. Coeff./mm^{-1}	0.073
Abs. Correction	None
GOF on F^2	0.916
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0672
	wR2 = 0.1777
R indices [all data]	*R1* = 0.1157
	wR2 = 0.1938

List of Publications

1. "Axial-selectivity in Prins Cyclization Reaction: Synthesis of 4-Iodotetrahydropyrans" Saikia, A. K.; Bondalapati, S.; Indukuri, K.: **Gogoi, P.** *Chem. Lett.* **2011**, 1176-1178.
2. "Application of a Novel 1,3-Diol with a Benzyl Backbone as Chiral Ligand for Asymmetric Oxidation of Sulfides to Sulfoxides" **Gogoi, P.**; Kotipalli, T.; Indukuri, K.; Bondalapati, S.; Saha, P.; Saikia, A. K. *Tetrahedron Lett.* **2012**, *53*, 2726-2729.
3. "Diastereoselective Synthesis of Substituted Tetrahydrofurans *via* Prins Cyclization of Enol Ethers" **Gogoi, P.**; Das, V. K.; Saikia, A. K. *J. Org. Chem.* **2014**, *79*, 8592-8598.
4. "Diastereoselective Synthesis of Substituted Thiotetrahydropyrans *via* Thionium-Ene Cyclization Reaction" Bondalapati, S.; **Gogoi, P.**; Indukuri, K.; Saikia, A. K. *J. Org. Chem.* **2012**, *77*, 2608-2612.
5. "Synthesis of Oxabicyclo[3.3.1]nonenes and Substituted Tetrahydropyrans *via* (3,5)-Oxonium-ene reaction" Saha, P.; **Gogoi, P.**; Saikia, A. K. *Org. Biomol. Chem.* **2011**, *9*, 4626-4634.
6. "Stereoselective, One-pot, Three-Component Synthesis of 4-Aryltetrahydropyrans from Epoxides *via* Prins-cyclization Reaction" Indukuri, K.; Bondalapati, S.; Kotipalli, T.; **Gogoi, P.**; Saikia, A. K. *Synlett* **2011**, 233-238.
7. "Scandium(III) triflate Catalyzed Synthesis of Primary Homoallylic Alcohols *via* Carbonyl-ene Reaction" Sultana, S.; Bondalapati, S.; Indukuri, K.; **Gogoi, P.**; Saha, P.; Saikia, A. K. *Tetrahedron Lett.* **2013**, *54*, 1576-1579.
8. Diastereoselective Synthesis of Substituted Tetrahydrothiophenes and -thiopyrans via Thia-Prins Cyclization ReactionBorah, M.; **Gogoi. P**.; Indukuri, K. *J. Org. Chem.* **2015**, *80*, 2641-2648.