Asymmetric Epoxidation of Enol Ethers and Esters Using Iminium Salt Catalysts Synthesis of α-Hydroxy-Carbonyls

By

Saud Muslih Almutairi

A thesis submitted is partial fulfilment of the requirements for the degree of

Doctor of Philosophy

School of Chemistry
University of East Anglia
United Kingdom

2017

DECLARATION

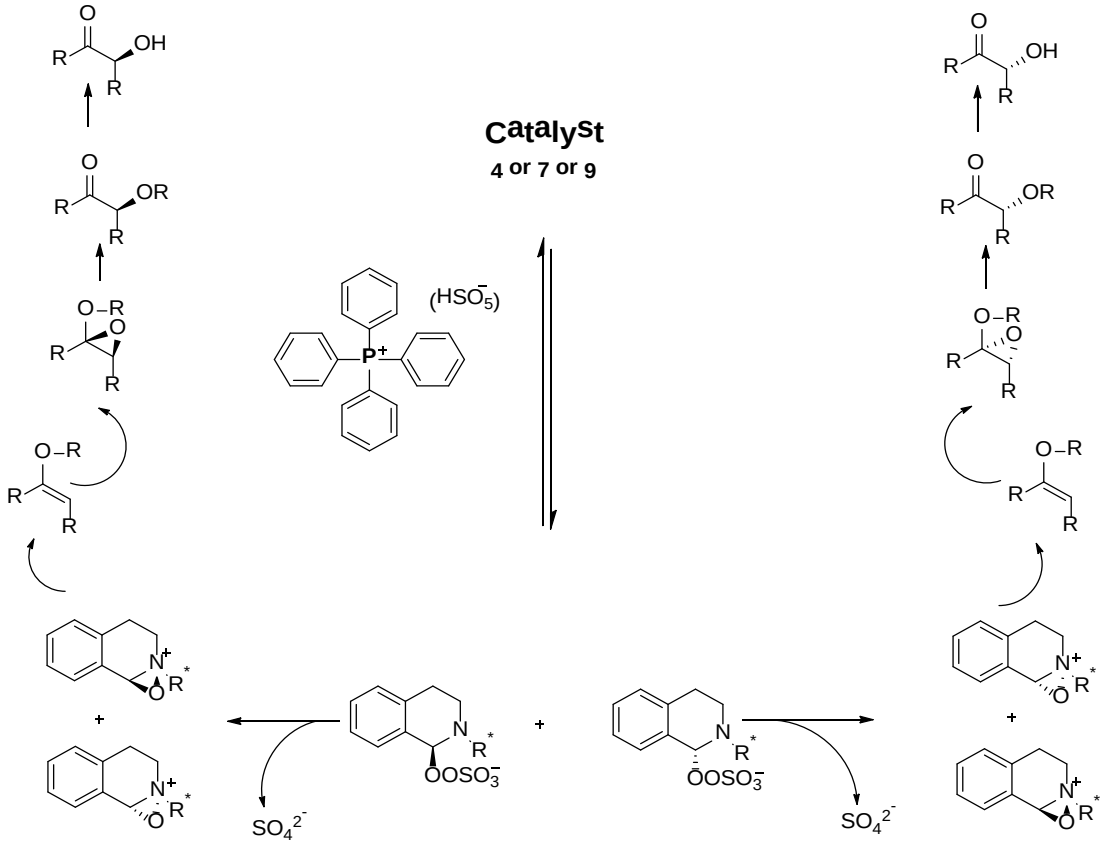
This thesis is submitted to the University of East Anglia for the Degree of Doctor of Philosophy and has not been previously submitted at this or any university for assessment. This work is original and has been carried out by the author alone.

Saud Muslih Almutairi

Abstract

Asymmetric Epoxidation of Enol Ethers and Esters Using Iminium Salt Catalysts Synthesis of α-Hydroxy-Carbonyls

Iminium salt organocatalysts can provide high selectivity and high efficiency in catalytic asymmetric epoxidation. Enantiomerically-enriched epoxides are useful intermediates that have found many applications in asymmetric synthesis, and development of efficient catalysts for asymmetric epoxidation has received considerable attention. In this manuscript, we describe the preparation, and use of highly selective iminium salt organocatalysts for asymmetric epoxidation. The new catalysts have been tested in the catalytic asymmetric oxidation of enols, and provide up to 98% *ee*. Also we tried to synthesize tatarinoid B **74** which used for the treatment of central nervous system diseases in traditional Chinese medicine.



Acknowledgements

During my studies, there are a few people I would like to acknowledge.

Firstly, I would like to thank Professor P.C. Bulman Page, for allowing me to work in his laboratory.

Secondly, I wish to thank Dr. Yohan Chan for guiding me in my work and giving me advice during my project.

I would like to thank all past and present page group members.

I like to thank the Head of Environment department at King Abdulaziz City for Science and Technology Dr. Badr Alharbi.

I would like to give thanks to my best friends Dr. Mouslim Messali and Dr. Ateyat allah for their support during my life.

Finally, I would like to thank my family for supporting me during my studies at UEA, these include my father, my mother Rhma, my love Mashael, my son Albaraa, my daughter Aya, my brother Naif, my sisters Nouf and Nora.

ABBREVIATIONS

Ac	acetyl
Ac_2O	acetic anhydride
$[\alpha]_D$	specific optical rotation at the sodium D line
aq.	aqueous
Ar	aryl
Arom.	Aromatic
AIBN	azobis(isobutyronitrile)
B:	base
n-BuLi	n-Butyl lithium (in hexanes, 2.5 M)
b.p.	boiling point
n-Bu	normal butyl
t-Bu	tertiary butyl
t-BuOH	tert-butanol
Bz	benzoyl
°C	degrees Celcius
$CDCl_3$	deuterated chloroform
conv.	conversion
CSA	10-camphorsulfonic acid
δ	chemical shift
DET	diethyl tartrate
DHQ	dihydroquinoline
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMP	dimethyoxypropane

E+	electrophile
ee	enantiomeric excess
eq.	equivalent(s)
Et	ethyl
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
g	gram(s)
h	hour(s)
H_2	hydrogen gas
HPLC	high performance liquid chromatography
Hz	hertz
IR	infra red
J	coupling constant
M	molar
m-CpBA	meta-chloroperbenzoic acid
Me	methyl
MeOH	methanol
MHz	megaHertz
min	minutes(s)
mmol	millimole(s)
mL	millilitre(s)
m.p.	melting point
NBS	*N*-bromosuccinamide
NMR	nuclear magnetic resonance
Nuc	nucleophile

sat.	saturated
Oxone	potassium monoperoxysulfate
Ph	phenyl
ppm	parts per million
pTSA	para-toluenesulfonic acid
i-Pr	iso-propyl
i-PrOH	isopropanol
n-Pr	normal propyl
R	alkyl
r.t.	room temperature
SM	starting material
TEA	triethylamine
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TPPP	tetraphenylphosphonium monoperoxysulfate
Ts	para-toluenesulfonyl

CONTENTS

CHAPTER ONE

1.0 Introduction: Chirality..... 1

1.1 Chirality in our life..... 3

1.2 Asymmetric synthesis..... 3

1.3 Chiral auxiliaries..... 4

1.4 Asymmetric catalysis..... 6

1.5 Epoxides..... 6

1.5.1 Epoxides in natural products..... 7

1.6 Epoxidation Reactions..... 8

1.6.1 Prilezhaev Reaction..... 8

16.2 Sharpless Asymmetric Epoxidation..... 9

16.3 Jacobsen-Katsuki Epoxidation.....10

1.7 Asymmetric Epoxidation of Silyl Enol Ethers and Enol Esters..... 14

1.7.1 Rubottom Reaction 14

1.7.2 Shi Asymmetric Epoxidation..... 15

1.8 Organocatalysis.....16

1.8.1 Davis Oxaziridine - Mediated Epoxidations..... 17

1.8.2 Lusinchi and Bohé's Initial Studies..... 18

1.8.3 Aggarwal's Chiral Binaphthalene Azepinium Salt Catalyst..... 21

1.8.4 Armstrong's Catalysts..... 22

1.8.5 Yang's Chiral Iminium Salt..... 23

1.8.6 Page's Studies..... 23

1.8.6.1 Page's catalysts conditions..... 27

1.8.6.2 Effect of the solvent..... 27

1.8.6.3 Effect of temperature..... 28

1.8.6.4 Effect of Counter-Ion..... 28

1.8.6.5 Effect of catalyst loading..... 29

1.8.6.6 Page's Catalysts from Chiral 1,2-Amino Alcohol Precursors Containing a Primary Hydroxyl Group..... 30

1.8.6.7 Page's Catalysts From Chiral 1,2-Amino Alcohol Precursors Containing A Secondary Hydroxyl Group..... 31
1.8.6.8 Page's Catalysts from Amino Ether Precursors..... 31
1.8.6.9 Page's Catalysts from Amino Acetal Precursors..... 32
1.8.6.10 Tetraphenylphosphonium Monoperoxysulfate..... 33
1.9 Conclusions..... 33
1.10 Introduction references.....35

CHAPTER TWO

2.0 RESULTS AND DISCUSSION..... 39
2.1 Synthesis of catalysts..... 45
2.1.1 Synthesis of Dihydroisoquinolinium Salt Catalyst 4..... 46
2.1.2 Synthesis of biphenyl iminium salt catalyst 7..... 49
2.1.3 Synthesis of binaphthalene iminium salt catalyst 9..... 51
2.2 Synthesis of Tetraphenylphosphonium Monoperoxysulphate 11 (TPPP)…….….. 54
2.3 Synthesis and epoxidation of the enol ethers and esters..... 54
2.3.1 Synthesis and epoxidation of enol ethers…….... 55
2.3.1.1 Synthesis of (3,4-(dihydronaphthalen-1-yl)oxy)triisopropylsilane 22..……..... 55
2.3.1.2 Synthesis of 2,2-dimethyl-2H-chromen-4-yl)oxy)triisopropylsilane 16..... 57
2.3.1.3 Synthesis of tert-butyl (3,4-dihydronaphthalen-1-yl)oxy) diphenylsilane 18…. 59
2.3.2 Synthesis and epoxidation of enol esters..... 60
2.3.2.1 Synthesis of 3,4-dihydronaphthalen-1-yl acetate 19……..... 60
2.3.2.2 Synthesis of 3,4-dihydronaphthalen-1-yl diethyl phosphate 14..... 63
2.3.2.3 Synthesis of 3,4-dihydronaphthalen-1-yl 2,2,2-trifluoroacetate 12 65
2.3.2.4 Synthesis of 3,4-dihydronaphthalen-1-yl benzoate 20..... 66
2.3.2.5 Enol Acetate synthesis …….…. 67

2.3.2.6 Synthesis of 1-(2,2,2-trifluoroacetyl)-1,2-dihydroquinolin-4-yl acetate 17.... 66

2.3.2.7 Synthesis of (-)Tatarinoid B 70……..…….. 71

2.4 Summary of the results.....77

2.5 Conclusions and Future Work..... 83

2.6 References..... 84

CHAPTER THREE

3.0 Experimental..... 88

3.1 General experimental details..... 88

3.1.1 Physical Characterisation and Spectroscopic Techniques..... 88

3.2 Individual experiments..... 90

3.2.1 General procedure for the synthesis of acetate enol esters..... 90

3.2.1.1 3,4-Dihydronaphth-1-yl acetate..... 91

3.2.1.2 6,7-Dihydro-5H-benzo[7]annulen-9-yl acetate..... 92

3.2.1.3 3,4-Dihydronaphthalen-2-yl acetate..... 93

3.2.1.4 1H-Inden-3-yl acetate 94

3.2.1.5 1-Phenylprop-1-enyl acetate.....95

3.2.1.6 3,4-Dihydronaphthalen-1-yl 2,2,2-trifluoroacetate.....96

3.2.2 3-Bromo-N-phenylpropanamide.....97

3.2.3 1- Phenylazetidin-2-one.....98

3.2.4 2,3-Dihydroquinolin-4(1H)-one.....99

3.2.5 1-(2,2,2-Trifluoroacetyl)-2,3-dihydroquinolin-4(1H)-one.....100

3.2.6 1-(2,2,2-Trifluoroacetyl)-1,2-dihydroquinolin-4-yl acetate.....101

3.2.7 2,2-Dimethylchroman-4-one.....102

3.2.8 (3,4-Dihydronaphthalen-1-yl)oxy)triisopropylsilane.....103

3.2.9 3,4-Dihydronaphthalen-1-yl diethylphosphinate.....104

3.2.10 3,4-Dihydronaphthalen-1-yl benzoate.....105

3.2.11 tert-Butyl-((3,4-dihydronaphthalen-1-yl)oxy)diphenylsilane.....106

3.2.12 1-(Diethoxyphosphoryl)ethyl acetate.....107

3.2.13 1,2,4-Trimethoxy-5-(2-methoxyvinyl)benzene.....108

3.2.14 2-(2,4,5-Trimethoxyphenyl)acetaldehyde.....109

3.2.15 1-(2,4,5-Trimethoxyphenyl)propan-2-ol.....110

3.2.16 General Procedure for enol oxidation.....111

3.2.16.1 Using mCpBA.....111

3.2.16.2 Using TPPP.....111

3.2.16.3 2-((Triisopropylsilyl)oxy)-3,4-dihydronaphthalen-1(2H)-one.....112

3.2.16.4 2,2-Dimethyl-3-((triisopropylsilyl)oxy)chroman-4-one.....112

3.2.16.5 1-Oxo-2,3-dihydro-1H-inden-2-yl acetate.....113

3.2.16.6 1-Oxo-1-phenylpropan-2-yl acetate.....114

3.2.16.7 5-Oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-yl acetate.....115

3.2.16.8 2-Hydroxy-3,4-dihydronaphthalen-1(2H)-one.....116

3.2.17 General Procedure for Protecting group removal.....117

3.2.17.1 2-Hydroxy-2,3-dihydro-1H-inden-1-one.....117

3.2.17.2 2-Hydroxy-1-phenylpropan-1-one.....118

3.2.17.3 6-Hydroxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one.....119

3.2.17.4 3-Hydroxy-2,2-dimethylchroman-4-one.....120

3.2.17.5 3-Hydroxy-1-(2,2,2-trifluoroacetyl)-2,3-dihydroquinolin-4(1H)-one.....121

3.3 Catalysts section.....122

3.3.1 Synthesis of dihydroisoquinolinium salt catalyst.....122

3.3.1.1 2-(2-Bromoethyl)benzaldehyde.....122

3.3.1.2 (4S,5S)-N-Formyl-Amino-4-(4-methylsulfide)-2,2-dimethyl-1,3-dioxane….123

3.3.1.3 (4S,5S)-N-Formyl-Amino-4-(4-methylsulfone)-2,2-dimethyl-1,3-dioxane....124

3.3.1.4 (4S,5S)- 5-Amino-6-(4-methylsulfone)-2,2-dimethyl-1,3-dioxane.....125

3.3.1.5 (+)-N-(4S,5S)-2,2-Dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-yl)-3,4-dihydroisoquinolinium tetraphenylborate.....126

3.3.2 Synthesis of biphenyl-derived iminium salt catalyst.....127

3.3.2.1 2,2'-bis(Bromomethyl)biphenyl.....127

3.3.2.2 (4S,5S)-5-Amino-6-phenyl-2,2-dimethyl-1,3-dioxane.....128

3.3.2.3 3 (−)-N-[(4S,5S)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl]-5H dibenzo[c,e]azepinium Tetraphenylborate.....129

3.3.3 Synthesis of binaphthalene-derived iminium salt catalyst……...131

3.3.3.1 (S)-[1,1']-Binaphthalene-2,2'-diol-bis-trifluoromethanesulfonate……...131

3.3.3.2 (+)-(S)-Dimethyl-[1,1']-binaphthalene.....132

3.3.3.3 (–)-(Sa)-Bis-bromomethyl-[1,1']-binaphthylenyl.....133

3.3.3.4 (+)-(Sa)-4-((4S,5S)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-3H-dinaphtho[2,1-c:1',2'-e]azepin-4-ium tetraphenylborate.....134

3.4 Tetraphenylphosphonium monoperoxysulfate (TPPP) synthesis procedure.....136

3.5 References.....137

CHAPTER FOUR

4.0 Appendix 141

4.1 HPLC trace of racemic epoxidation of 3-Hydroxy-2,2-dimethylchroman-4-one 141

4.2 Asymmetric epoxidation of 3-Hydroxy-2,2-dimethylchroman-4-one.....142

4.3 HPLC trace of racemic epoxidation of 2-Hydroxy-3,4-dihydronaphthalen-1(2H) one…….143

4.4 Asymmetric epoxidation of 2-Hydroxy-3,4-dihydronaphthalen-1(2H)-one…….....144

CHAPTER 1 Introduction

1.1 Introduction: Chirality

A chiral molecule is a molecule that is not superimposable on its mirror image; and, mirror images of a chiral molecule are enantiomers with respect to each other. For example, our hands are chiral (Figure 1.1).[1]

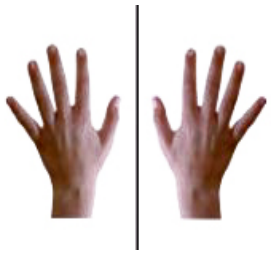


Figure 1.1: Our hands are chiral

Most chiral molecules encountered in synthetic organic chemistry are chiral due to the presence of a stereogenic centre, in most cases, a carbon atom attached to four different substituents, and the absence of a plane of symmetry. Examples of chiral molecules include amino acids, containing a carbon centre bound to a proton, a carboxylic acid moiety, an amino group and another substituent (often represented as a R group) which differs from amino acid to amino acid (except glycine, where the substituent is a proton). For example, alanine's R group is a methyl group (Figure 1.2).[1]

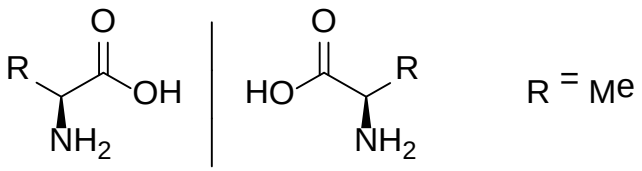


Figure 1.2: (*S)* - and *(R)*-alanine

1.1.2 Chirality in our life

In 1957, a drug called thalidomide was launched to help women who suffer from morning sickness during pregnancy.[2] The drug was distributed and used in many places. After a short time, thalidomide side-effects appeared. Miscarriages increased and many babies were born with malformed limbs.[2] When investigating the causes for the increase, researchers identified one thalidomide enantiomer as the source of the problem. Indeed, thalidomide was sold as a racemic mixture and (*S*)-thalidomide causes birth defects while (*R*)-thalidomide cures morning sickness (Figure 1.3).[3] The adverse consequences observed show us the importance of chirality. Stereoselective synthesis is the key to producing new drugs as single enantiomers.

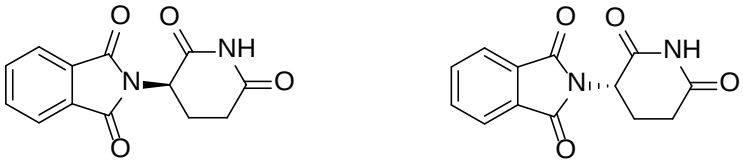
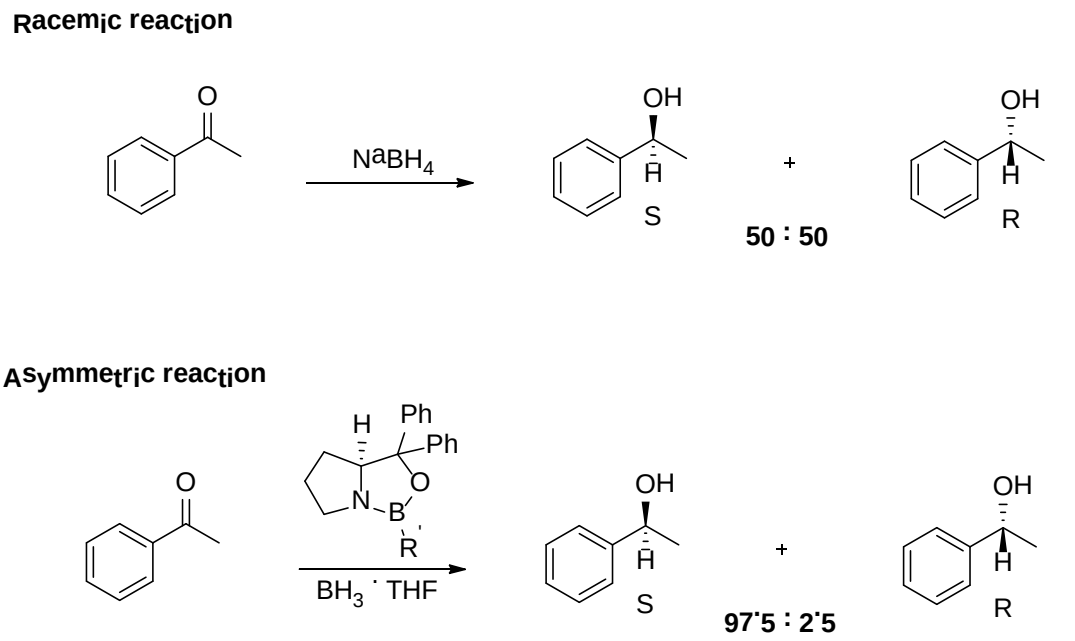


Figure 1.3: Thalidomide enantiomers.

1.2 Asymmetric synthesis

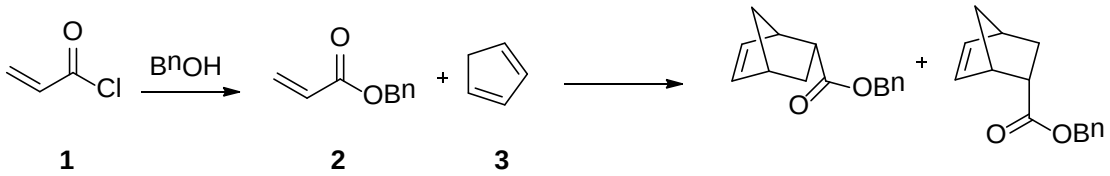
Asymmetric synthesis, also called chiral synthesis or enantioselective synthesis is a chemical reaction which produces unequal amount of one isomer of the product due to the influence of chirality present in the reagent(s) and/or catalysts.[4] (Scheme 1).[5]



Scheme 1: Non-selective and asymmetric reductions.

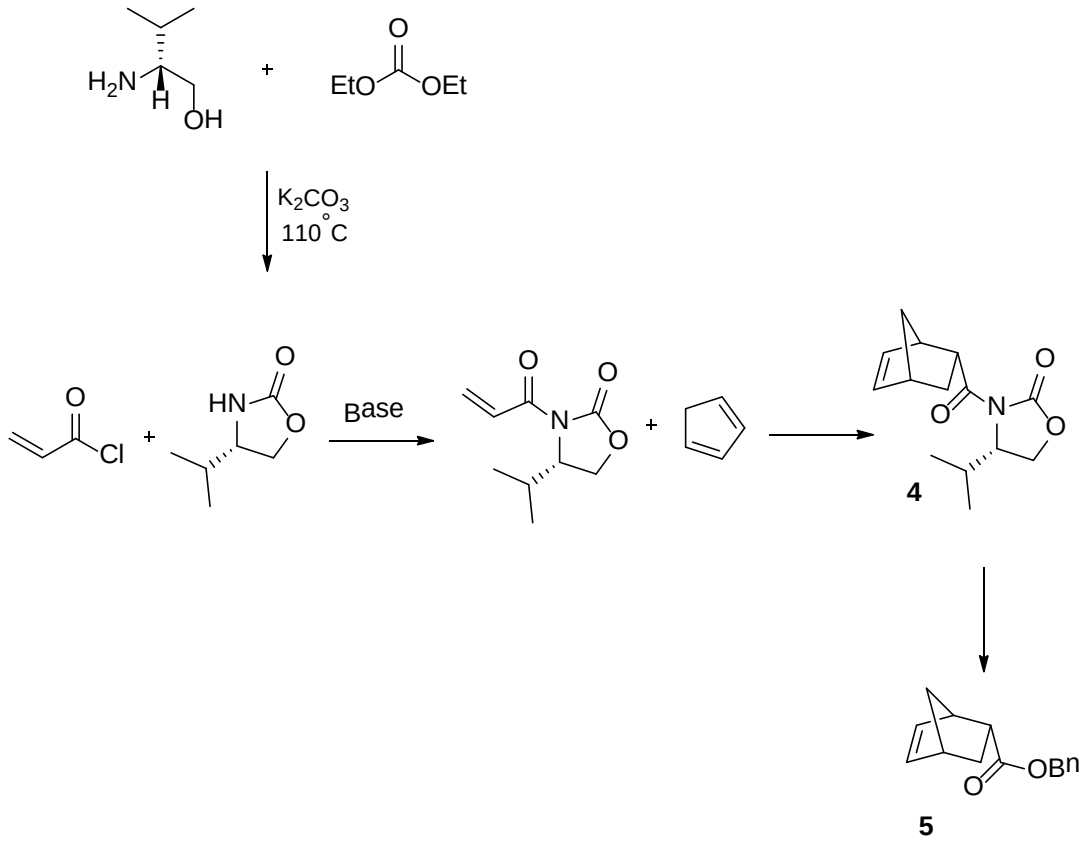
1.3 Chiral auxiliaries

A chiral auxiliary is an enantiomerically pure group that is temporarily attached onto a substrate in order to control the stereochemical outcome of a reaction.[6] For example, the reaction between cyclopentadiene **3** and benzyl acrylate **2**, both achiral reagents, leads to the formation of the product as a single diastereoisomer (the endo product) and as a racemic mixture (Scheme 2).[4]



Scheme 2: Non-selective Diels Alder reaction

However, when a chiral auxiliary formed from natural amino acid (*S*)-valine is attached to the dienophile, the product is obtained as a single diastereoisomer and a single enantiomer **4**. The chiral auxiliary is removed following hydrolysis to give product **5** in 93% ee (Scheme 3).[4]



Scheme 3: Chiral auxiliary-controlled Diels Alder reaction

1.4 Asymmetric catalysis

Asymmetric catalysis promotes the formation of one product stereoisomer over the possible other(s) through a catalytic mechanism.[7] The mechanisms of generating the new chiral

center(s) can be complicated and are not well understood in many systems.[8] Alkenes and carbonyl-containing compounds are widely used as prochiral starting materials. Epoxidation reactions are one of the most effective asymmetric transformations to convert a prochiral compound into a chiral product.[4] The asymmetric epoxidation of olefins is an effective way to synthesize enantiomerically pure epoxides.[5]

1.5 Epoxides

An epoxide or oxirane is a three-membered ring which has an oxygen atom attached to two carbon atoms (Figure 1.4). Currently, epoxides are one of the most important synthetic tools used to prepare many natural products.[9]

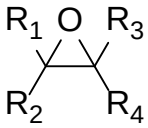
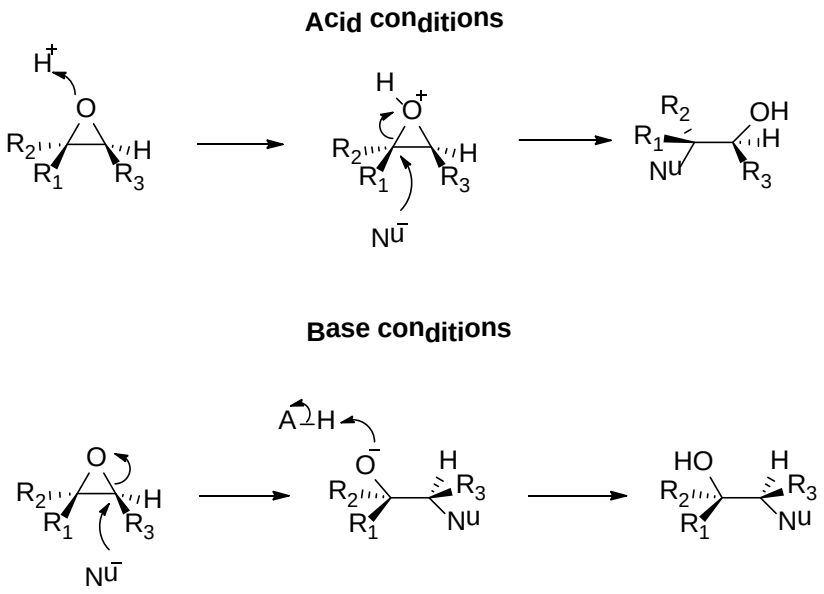


Figure 1.4: The epoxide moiety

The angle between the atoms in the ring is about 60° (versus a 109° angle for a tetrahedral carbon centre) which means the ring strain is high. Because of high strain and the electronegative oxygen which increases the δ+ character of the carbon atoms, epoxides can be attacked by nucleophiles.[10] Indeed, the carbon centres can be attacked under basic or acidic conditions when a nucleophile is added (Scheme 4).

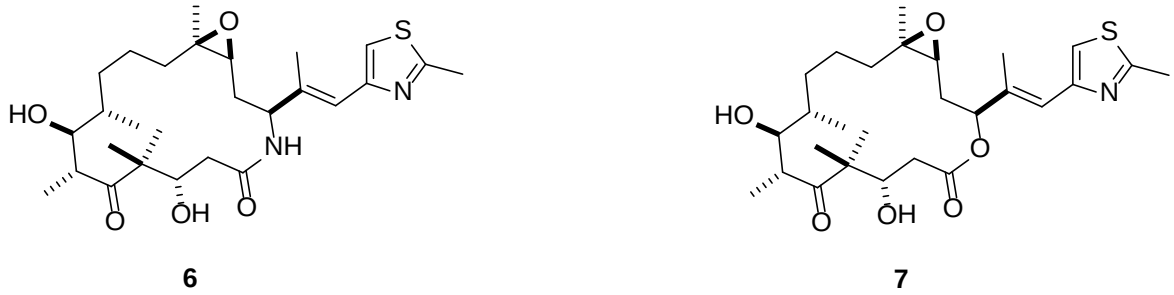


Scheme 4: Nucleophilic addition to an epoxide

Under acidic conditions, the nucleophilic attack occurs at the most substituted carbon centre, due to the higher stability of the developing partial cation. In contrast, under basic conditions, the least substituted carbon is attacked.

1.5.1 Epoxides in natural products

The epoxide functional group can be found in many natural products. Moreover, many drug molecules are derived from natural products. There is pressure on pharmaceutical companies to provide more potent pharmaceuticals to use in the treatment or curing of illnesses. For instance, Ixempra **6** is used as an anti-cancer drug. Ixempra is a semi-synthetic analog of the bacterial natural product epothilone B 7 (Figure 1.5**)**.[11]



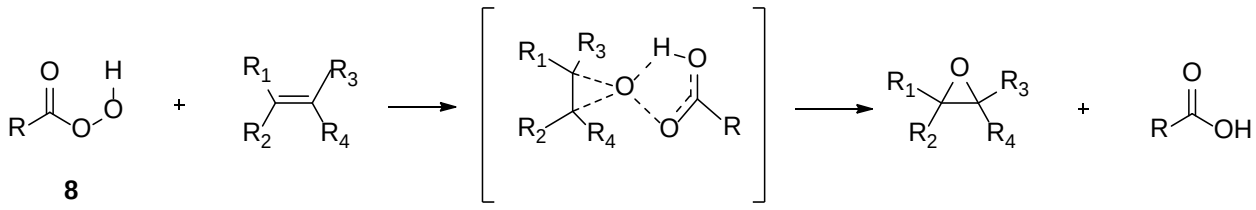
6 **7**

Figure 1.5: Advanced breast cancer drug Ixempra **6** and epothilone B **7.**

1.6 Epoxidation Reactions

1.6.1 Prilezhaev Reaction

In 1909, Prilezhaev reported the use of peroxycarboxylic acids **8** for the first non-selective epoxidation reaction.[12] The mechanism of this alkene epoxidation begins with alkene double bond nucleophilic attack on the peroxyacid electrophilic oxygen atom **(Scheme 5)**.[13] The reaction is sterospecific as both C-O bonds are formed concurrently. A theoretical study by Houk supported a spiro transition state.[14]

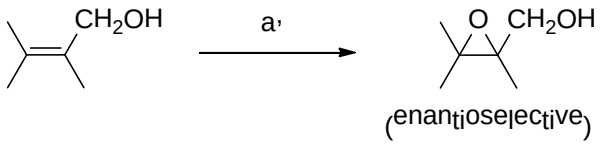


8

Scheme 5: Use of peroxycarboxylic acids.

1.6.2 Sharpless Asymmetric Epoxidation

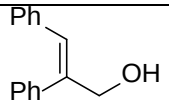
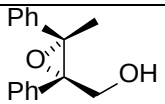
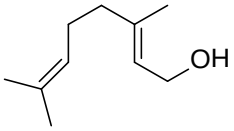
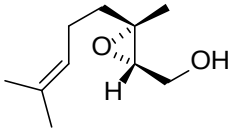
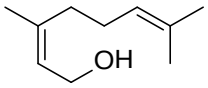
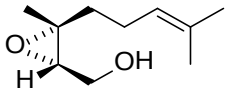
Sharpless was the first to enter the field of asymmetric epoxidation using metal catalysts. Sharpless used titanium tetraisopropoxide, $Ti(Oi\text{-}Pr)_4$. He believed that the presence of a chiral ligand with the titanium catalyst would lead to asymmetric induction. The best ligand is diethyl tartrate (Scheme 7).[18]



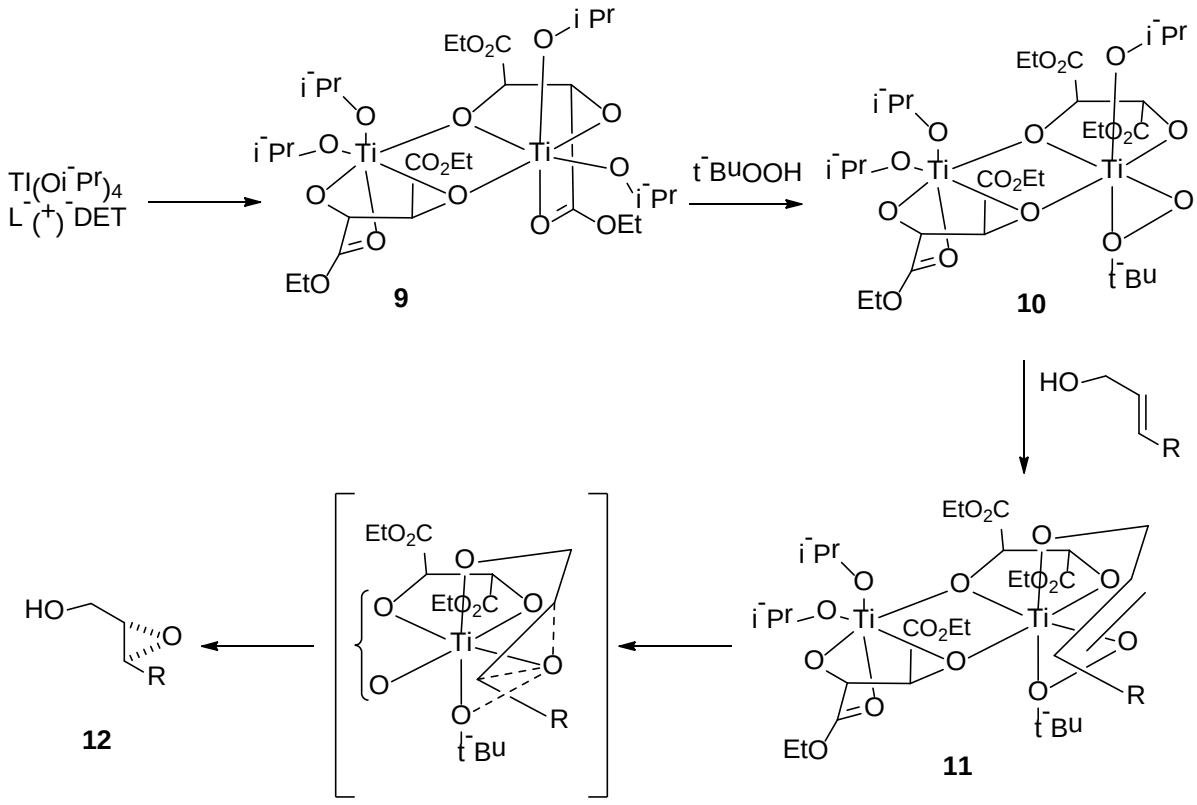
Scheme 7: a) $Ti(O^iPr)_4$, (+) or (–) DET, ^{t}BuOOH, DCM, –20 °C.

In 1981, when this reaction was first reported, it was the first highly enantioselective epoxidation reaction. For this work, he was awarded a Nobel Prize in 2001.[19] The Sharpless system reacts with substrates which have an allylic alcohol moiety. Excellent enantiomeric excesses of up to 95% ee for epoxide products and high yields were achieved using his methodology. Hydroperoxide reagents are used as the stoichiometric oxidant, usually t-butyl hydroperoxide. The oxidizing agent, the catalyst titanium tetraisopropoxide $Ti(Oi\text{-}Pr)_4$, with diethyltartrate ligand (DET) are a very important mixture to furnish high enantioselectivity.[20] Sharpless tested many different allylic alcohol substrates types and most gave enantioselectivities higher than 90% (Table 1).[21]

Table 1. Asymmetric epoxidation of various allylic alcohols.

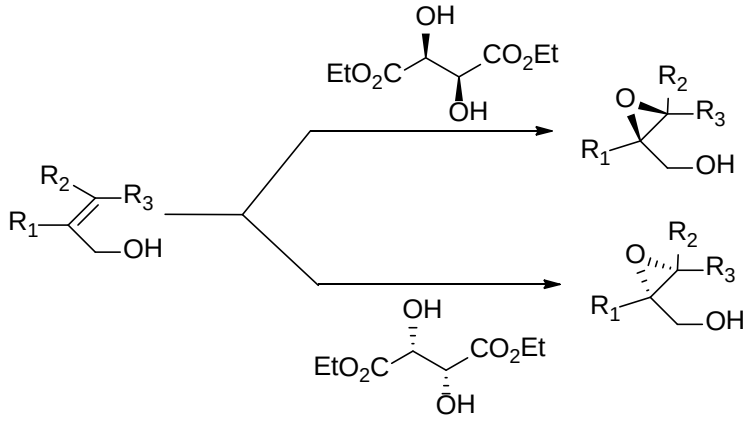
Substrate	Epoxide Product	ee (%)
		**95**
		**95**
		**94**

Much work has been carried out to elucidate the reaction mechanism: first, an active complex involving two titanium atoms and two tartrate ligands **9** is formed. The oxidizing agent (t-BuOOH) displaces an isopropoxide ligand and one of the tartrate carbonyl groups when it is added to complex **10**. Next, the allylic alcohol reacts with the complex and displaces the last isopropoxide ligand from the reactive titanium center of complex **11**. In this case, the reactive oxygen atom of the hydroperoxide is delivered to the lower face of the alkene because of the shape of complex to give epoxide **12** in high enantiomeric excess (Scheme 8).[22]



Scheme 8: Sharpless epoxidation mechanism

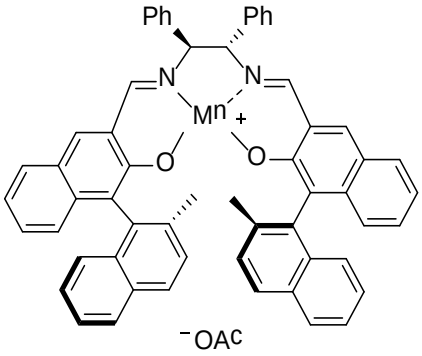
The oxygen atom is added onto the top or bottom face of the alkene depending on the configuration of the tartrate ligand: when the natural L-(+) tartrate is used, the oxygen is added onto the bottom face and the peroxide attacks the top face when unnatural D-(–)-tartrate is used **(Scheme 9)**.[23]



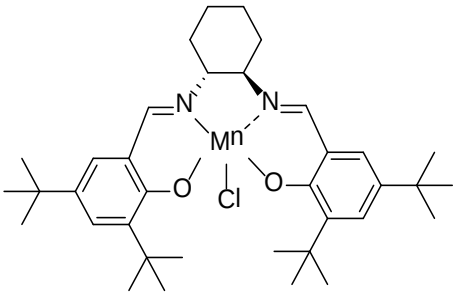
Scheme 9: Selectivity mnemonic for the Sharpless epoxidation

16.3 Jacobsen-Katsuki Epoxidation

In 1990, another example of a transition metal-mediated epoxidation was discovered. The Jacobsen-Katsuki epoxidation was the first epoxidation reaction involving metal to convert alkenes into the corresponding epoxides.[24] This reaction involves a manganese-salen based catalyst (Figure 1.6).[24] The metal catalyst does not require the presence of an allylic hydroxyl group in the substrate to obtain high enantioselectivities unlike Sharpless's epoxidation.



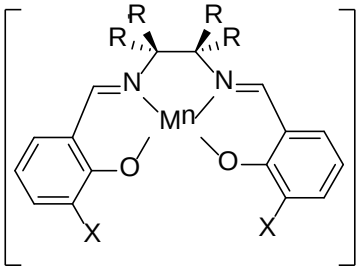
13



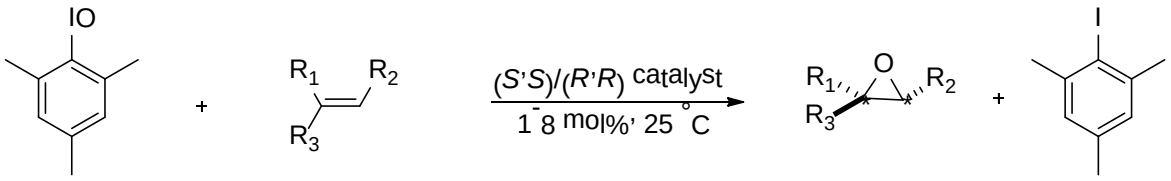
14

Figure 1.6. Examples of Katsuki's **13** and Jacobsen's **14** manganese-salen catalysts.

A range of oxidants can be used to oxidize the manganese (III) metal centre to manganese (V) such as Oxone, sodium hypochlorite and hydrogen peroxide.[24] A range of alkyl and aryl substituted olefins were oxidized by Jacobsen's manganese-salen catalysts in good to high enantioselectivities (Table **2**).[25]



15^{-}(*S*,*S*): R = Ph, R' = H, X = H
16^{-}(*R*,*R*): R = H, R' = Ph, X = ^{t}Bu



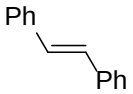
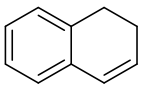
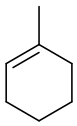
Alkene	Catalyst	Yield%	ee%	Configuration
	15	63	33	(-)*S*,*S*
	16	72	78	(+)1*R*,2*S*
	16	50	59	(-)1*R*,2*S*

Table 2. The first examples of using a manganese-salen catalyst.

Subsequently, Jacobsen tried different olefins with catalyst **14** and gave high enantioselectivities above 90% (Table 3).[25]

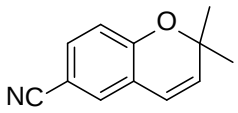
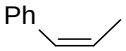
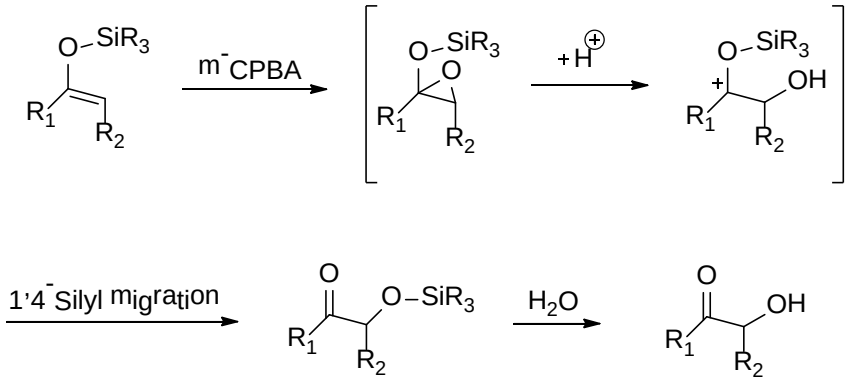
Olefin	ee%	Yield%
	**97**	**96**
	**92**	**84**

Table 3. Asymmetric epoxidation of olefins using catalyst **14.**

1.7 Asymmetric Epoxidation of Silyl Enol Ethers and Enol Esters

1.7.1 Rubottom Reaction

In 1974, Rubottom reported the transformation of a ketone into an α-hydroxycarbonyl by means of epoxidation of the corresponding trimethylsilyl enol ether with m-chloroperbenzoic acid (*m*-CpBA) under basic or acidic conditions.[17] The epoxidation of the silyl enol ether first leads to a silyloxy carbocation, a 1,4-silyl migration gives the *α*-silyloxy ketone, and finally the silyl group is removed to afford the α-hydroxycarbonyl (Scheme 6).[5]

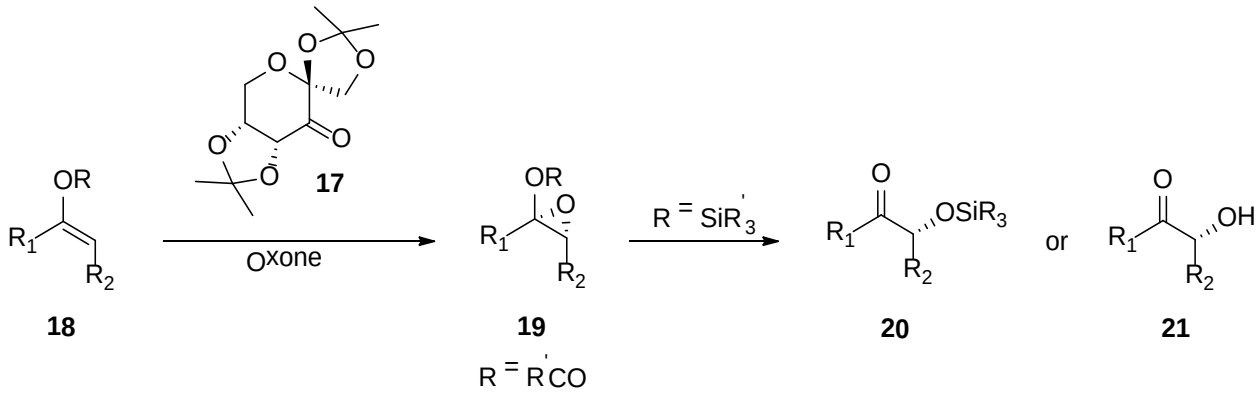


Scheme 6: Rubottom oxidation.

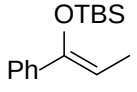
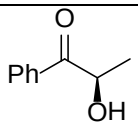
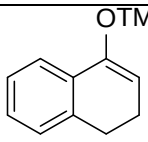
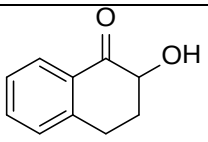
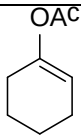
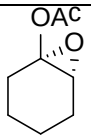
1.7.2 Shi Asymmetric Epoxidation

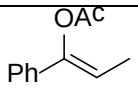
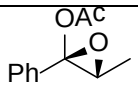
Shi prepared chiral hydroxyl ketones using asymmetric epoxidation of enol ethers and enol esters. Fructose derived ketone **17** was used as catalyst and Oxone as oxidant. Shi found that enol esters and enol ethers are effective substrates, giving hydroxy ketones **21** or oxy-substituted epoxides **19** in high enantioselectivities.

Table 4. Asymmetric Epoxidation of Silyl Enol Ethers and Esters by Ketone 17



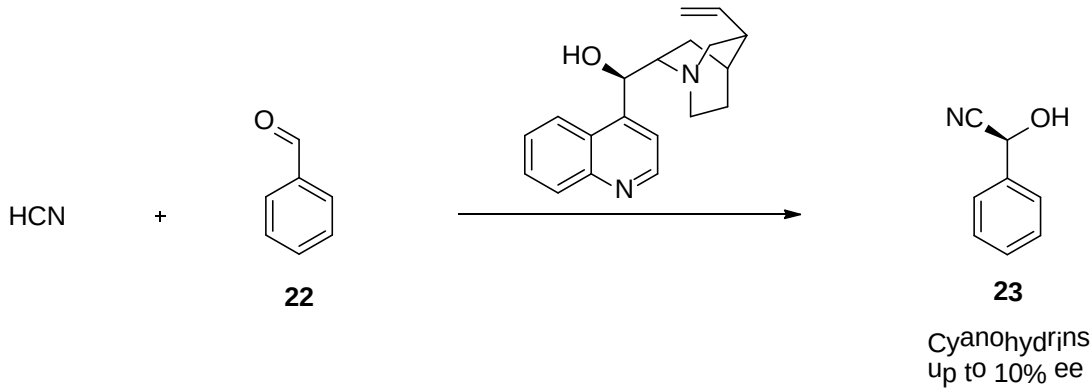
All reactions were carried out at 0 °C (bath temperature) with substrate (1 equiv.), ketone (0.3 equiv.), Oxone (1.38 equiv.) and K_2CO_3 (5.8 equiv.) in organic solvent (15 mL)

Substrate	Product	t (h)	Yield (%)	ee (%)
		2	80	90
		1	70	83
		2	59	74

		2	66	91

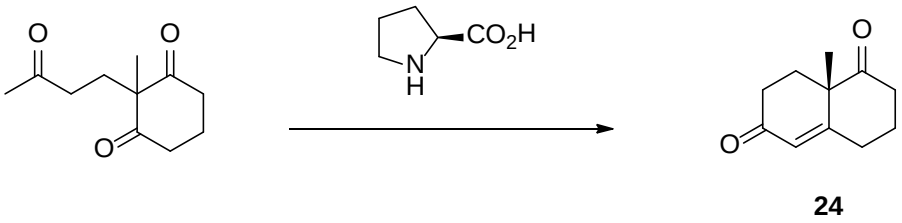
1.7 Organocatalysis

Organocatalysts are organic molecules, typically formed from hydrogen, carbon, nitrogen, phosphorus and sulfur atoms.[26] There are many advantages to the use of organocatalysts, including the fact that many organocatalysts are prepared from cheap, simple and low-weighting starting materials, do not contain metals, and are usually not toxic. The first reported asymmetric organocatalytic reaction was published by Fiske and Bredig. They observed that the addition of hydrogen cyanide to benzaldehyde **22** was catalyzed by quinine, and that the resulting cyanohydrin **23** was optically active **(**Scheme 10).[27]



Scheme 10: Fiske and Bredig asymmetric organocatalytic reaction

In 1974, Hajos and Parrish reported one of the earliest enantioselective reactions used in synthetic organic chemistry. L-proline was used as a catalyst to produce the Wieland-Miescher ketone (Scheme 11).[28]

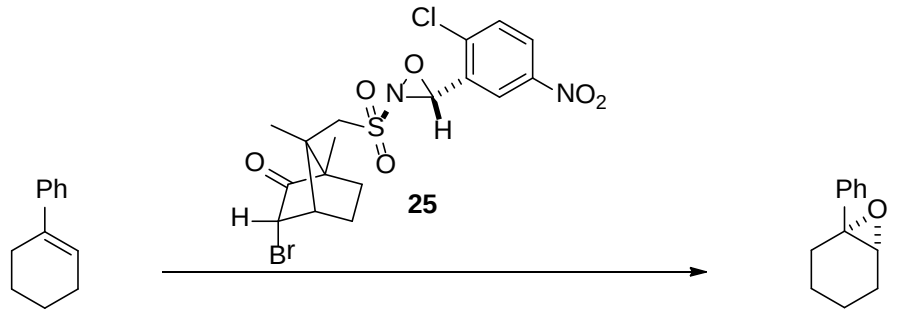


24

Scheme 11. The Wieland-Miescher ketone.

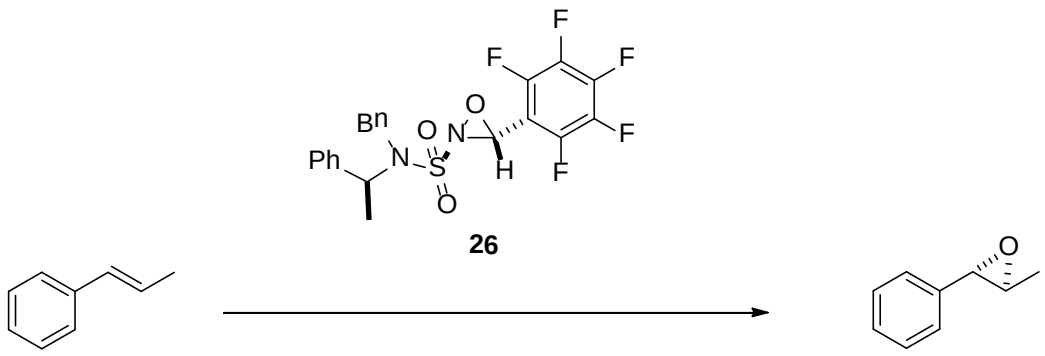
1.8.1 Oxaziridine - Mediated Epoxidations

The first chiral oxaziridine **25** was reported by Davis in 1982. Davis used Oxone or *m*-CpBA to oxidize a sulfonylimine or sulfamylimine formed from the reaction between the diethyl acetal of an aromatic aldehyde and bromocamphor sulfonamide**.** For the epoxidation of 1-phenylcyclohexene, the highest enantiomeric excess was 41% (Scheme 12).[29]



Scheme 12: Davis's oxaziridine **25.**

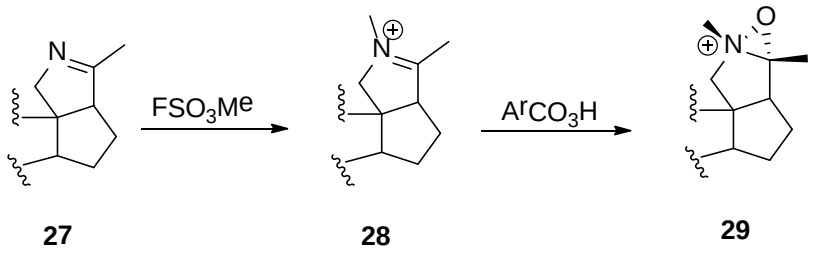
Davis tried to improve the enantioselectivity by a using new chiral oxaziridine **26**. The asymmetric epoxidation of methylstyrene produced the corresponding epoxide in 61% enantiomeric excess (Scheme 13).[30]



Scheme 13: Davis's oxaziridine **26.**

1.8.2 Lusinchi and Bohé's Initial Studies

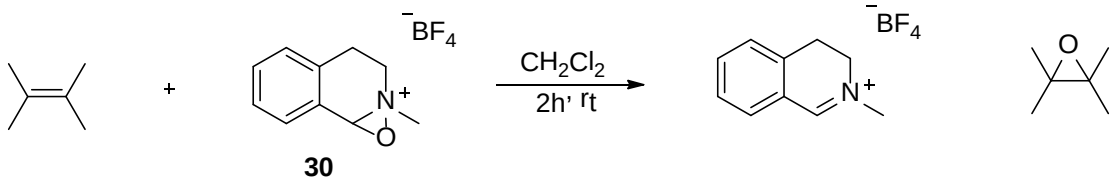
Oxaziridinium salts were reported by Lusinchi in 1976. Oxaziridinium salts have the ability to transfer the oxygen to nucleophilic substrates such as alkenes, amines, sulfides and imines. Lusinchi prepared the first oxaziridinium salts (Scheme 14) starting from imine **27**. Methylation of imine **27** affords the corresponding iminium salt **28** followed by oxidation to furnish oxaziridinium salt **29**.[31]



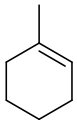
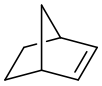
Scheme 14: Synthesis of the first oxaziridinium salt.

Later, they reported the synthesis of dihydroisoquinolinium-derived oxaziridinium salt **30** which was then applied to the epoxidation of alkenes (Table 5).[32]

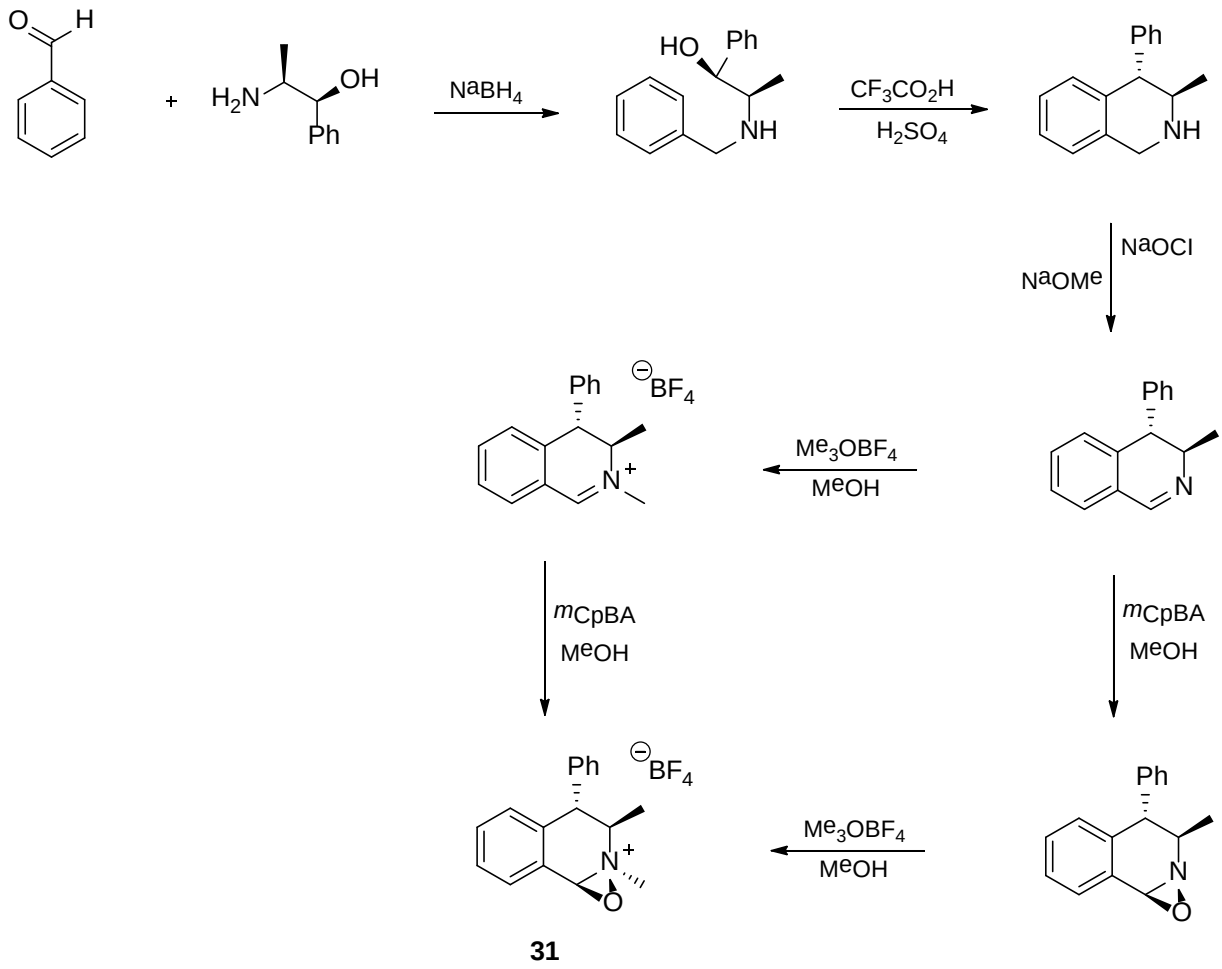
Table 5. Lusinchi's epoxidation using oxaziridinium salt **30**



30

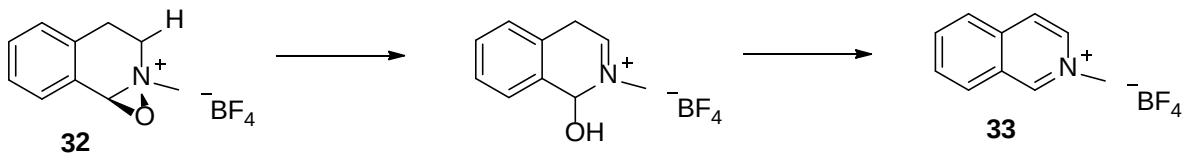
Substrate	Yield (%)
	84
	75

In 1993, the first chiral oxaziridinium salt **31** was prepared by Lusinchi and Bohé in five steps starting from (1*R*,2*R*)-(+)-norephedrine (Scheme 15).[33]



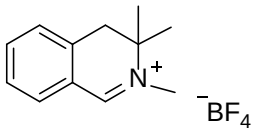
Scheme 15. Synthesis of chiral oxaziridinium salt **31**.

Bohé subsequently showed that analogues of dihydroisoquinolinium **32** containing protons on the carbon α to the nitrogen lose their activity through dehydration to form the corresponding isoquinolinium salt **33 (**Scheme 16) .[34]



Scheme 16. Base-catalysed oxaziridinium decomposition.

Bohé prepared achiral 3,3-disubstituted-dihydroisoquinolinium catalyst **34** to mediate the epoxidation of alkenes. He prevented irreversible isomerisation from happening by replacing all the protons on the carbon α to the nitrogen with methyl groups (Figure 1.7) .[35]

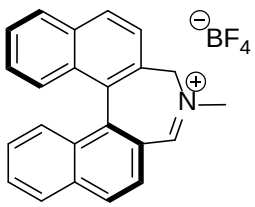


34

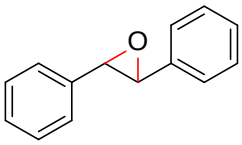
Figure 1.7 Bohé's improved 3,3-disubstituted-dihydroisoquinolinium catalyst **34.**

1.8.3 Aggarwal's Chiral Binaphthalene Azepinium Salt Catalyst

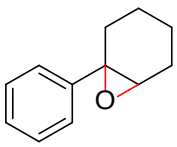
In 1996, the chiral binaphthyl-based iminium salt **35** was prepared by Aggarwal. Epoxidation of 1-phenylcyclohexene gave the corresponding product in 71% ee (Figure 1.8) using Oxone as the oxidant and $NaHCO_3$ in a mixture of acetonitrile/water.[35]



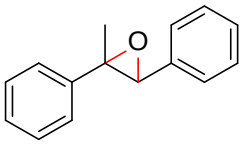
35



(R' R)
31% ee



(R' R)
71% ee

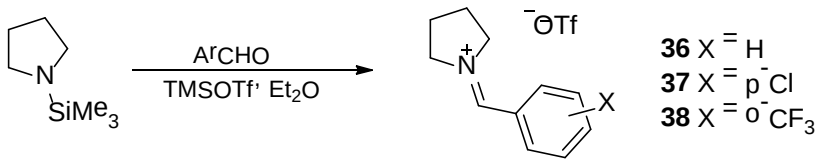


(R' R)
45% ee

Figure 1.8

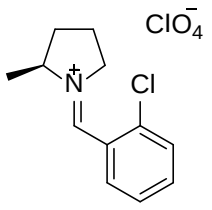
1.8.4 Armstrong's Catalysts

The first a range of exocyclic iminium triflate salts formed and used as epoxidation catalysts were made by Armstrong. These catalysts were prepared by condensation of *N*-trimethylsilyl pyrrolidine with aromatic aldehydes. Some catalysts gave high yields, for example, the catalyst ortho-trifluoromethyl group **38** reached up to 94% yield for the epoxidation of various alkenes (Scheme 17).[37, 38]



Scheme 17. Armstrong's Catalysts.

Later, he tested the effectiveness of chiral iminium salt **39** using oxone to oxidize 1-phenylcyclohexene, giving the corresponding epoxide in 22% ee (Figure 1.9).[38]

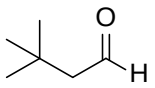


39

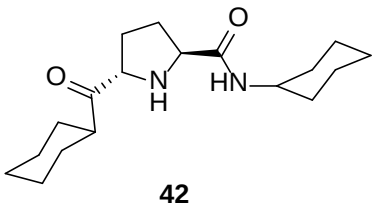
Figure 1.9

1.8.5 Yang's Chiral Iminium Salts

Yang reported chiral iminium salts which were made from the condensation of amines with aldehydes *in-situ* under acidic conditions. For example, the epoxidation of *trans*-stilbene gave 65% enantiomeric excess by using 3,3-dimethylbutanal (aldehyde) **41** and (2*S*,5*S*)-5-(cyclohexanecarbonyl)-*N*-cyclohexyl-pyrrolidine-2-carboxamide (amine) **42** in presence of Oxone and $NaHCO_3$ **(**Figure 1.10) .[39]



41



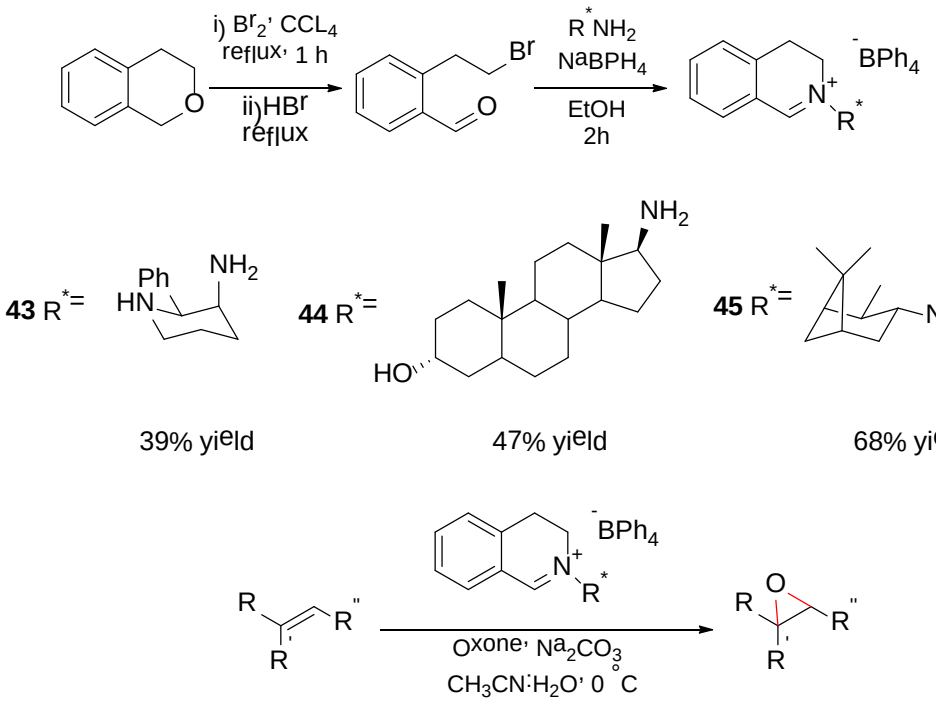
42

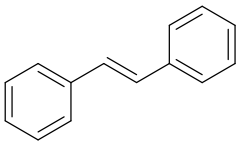
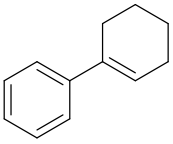
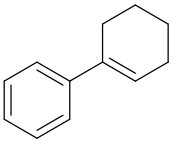
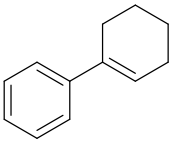
Figure 1.10

1.8.6 Page's Studies

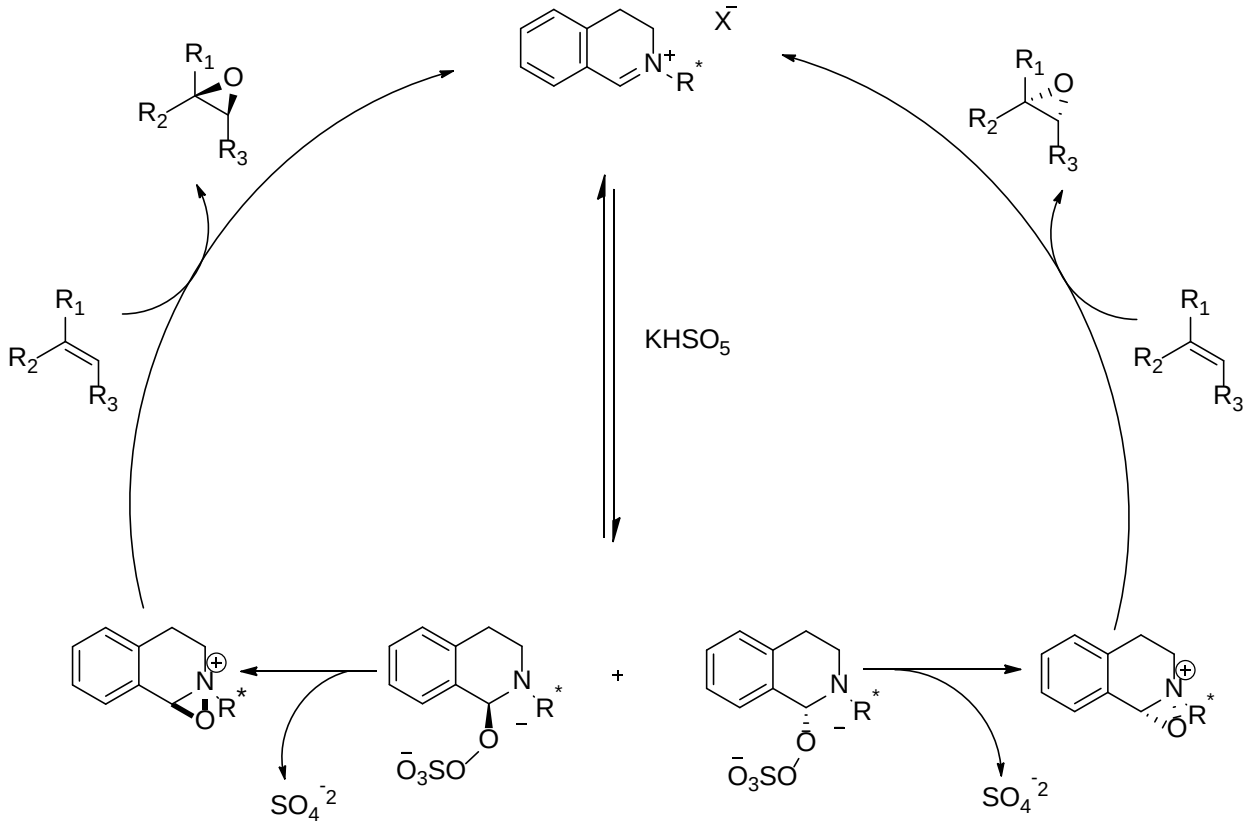
In 1998, Page designed new iminium salts for organocatalytic asymmetric epoxidation. Page tried to increase the enantioselectivity by bringing the chiral centre closer to the site of the reaction.[39] In his procedure he used dihydroisoquinolinium iminium salts **43 - 45** (5-10 mol%) and Oxone as the oxidant for asymmetric epoxidation of olefins, reaching 73% enantiomeric excess (Table 6). [40]

Table 6. Screening of dihydroisoquinolinium salts for the epoxidation of olefins.



Alkene	Catalyst	ee (%)	Yield (%)	major enantiomer
	**45**	73	78	(+)-(*R*,*R*)
	**45**	40	68	(+)-(*R*,*R*)
	**43**	25	39	(-)-(*S*,*S*)
	**43**	14	47	(-)-(*S*,*S*)

Catalyst **45** gave the highest enantiomeric excess for the epoxidation of 1-phenylcyclohexene and gave 73% ee for the epoxidation of *trans*-stilbene. There are many advantages to Page's iminium salt catalysts; they are easy and rapid to prepare because they do not require column chromatography for purification at any stage and some of the starting materials are commercially available or easy to make. Page's iminium salt catalysts can be used for the epoxidation of many different olefins. Page used tetraphenylborate as a counter ion to obtain crystalline iminium salts instead of the bromide counter ion, which often gave an oily product to make purification easier.[39] Page suggested a catalytic cycle to understand how the oxygen transfer from the oxaziridinium salt to the olefin occurs (Scheme 18).[41]



Scheme 18. Page's suggested catalytic cycle for oxaziridinium-mediated asymmetric epoxidation.

The first step of Page's proposed mechanism involves an attack from the nucleophilic persulfate anion onto the carbon of the iminium bond. Two diastereoisomers can be formed from the persulfate attack because the nucleophilic species can attack the *si* or *re* face of the iminium species.[41] Two diastereoisomeric oxaziridinium species can be formed by irreversible expulsion of sulfate. Page believed this step was the rate determining step under the reaction conditions.[41] Each diastereoisomeric oxaziridinium species can transfer the oxygen atom to one prochiral face of the substrate with a different degree of enantiomeric excess.[41]

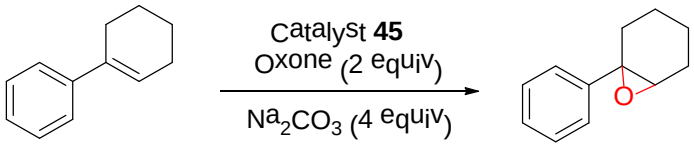
1.8.6.1 Page's catalysts conditions

Many different factors can influence the selectivity of the epoxidation reaction; for example, the effect of the temperature, the effect of the solvent system, the effect of the counter ion and catalyst loading were studied to improve the selectivity.[41]

1.8.6.2 Effect of the solvent

Page tested different solvents as mixtures with water in a 1:1 ratio using catalyst **45** and tetraphenylborate and perchlorate anions as the counter ions for the epoxidation of 1-phenylcyclohexene. Page started with formamide as the solvent: after 3 h, no reaction was observed using the perchlorate or the tetraphenylborate salts. The reaction gave 26% ee with 100% conversion using trifluoroethanol. When dichloromethane was used, 50% conversion was observed, maybe due to Oxone's low solubility providing lower reactivity. Acetonitrile gave the best result. For example when catalyst **45** was used with tetraphenylborate as the counter ion for epoxidation of 1-phenylcyclohexene in a mixture of acetonitrile and water (1:1) at low catalyst loading (0.5 mol%) gave 40% ee after 1 h.[41]

Table 7. Effect of co-solvents on epoxidation of 1-phenylcyclohexene.



Organic Solvent	Counter Ion	Conv. (%)	ee (%)	Configuration
CF_3CH_2OH	$^-ClO_4$	100	26	(-)-(*R*,*R*)
CF_3CH_2OH	$^-BPh_4$	100	26	(-)-(*R*,*R*)
CH_2Cl_2	$^-ClO_4$	50	33	(-)-(*R*,*R*)
CH_2Cl_2	$^-BPh_4$	0	-	
MeCN	$^-ClO_4$	100	20	(-)-(*R*,*R*)
MeCN	$^-BPh_4$	100	40	(-)-(*R*,*R*)
H_2NCHO	$^-ClO_4$	0	-	
H_2NCHO	$^-BPh_4$	0	-	

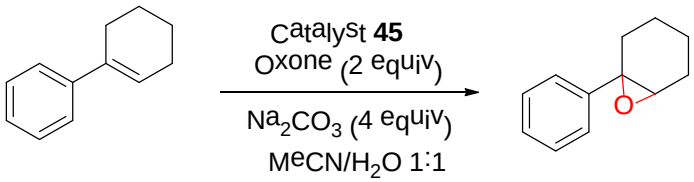
1.8.6.3 Effect of temperature

Page studied the effect of temperature on his methodology for the epoxidation of olefins. Limitations were quickly discovered: at −10 °C, a 1:1 mixture of acetonitrile/water solvent system freezes, and, at room temperature, decomposition of Oxone occurs.[41]

1.8.6.4 Effect of Counter-Ion

Page used catalyst **45** for the epoxidation of 1-phenylcyclohexene with different counter-ions: the tetrafluoroborate, hexafluorophosphate, perchlorate, periodate and the tetrafluoroborate anions were evaluated under the same reaction conditions: sodium carbonate as the base, Oxone as the stoichiometric oxidant and the best solvent system acetonitrile/water (1:1) at 0 °C. The highest enantioselectivities were produced by using the tetraphenylborate (40%) and the periodate salts (35%) (Table 8). The perchlorate salt gave 20% ee, which was the lowest enantioselectivity.[41]

Table 8. Effect of counter-ion on epoxidation of 1-phenylcyclohexene.



Counter-Ion	ee (%)	Conv. (%)	Configuration
$^{-}ClO_4$	20	100	(-)-(*R*,*R*)
$^{-}IO_4$	35	100	(-)-(*R*,*R*)
$^{-}PF_6$	28	100	(-)-(*R*,*R*)
$^{-}BF_4$	28	100	(-)-(*R*,*R*)
$^{-}BPh_4$	40	100	(-)-(*R*,*R*)

1.8.6.5 Effect of catalyst loading

To improve the enantioselectivity, Page tried to increase the catalyst loading from 0.1 to 0.5 and found the enantioselectivity increased with increased catalyst loading.[41]

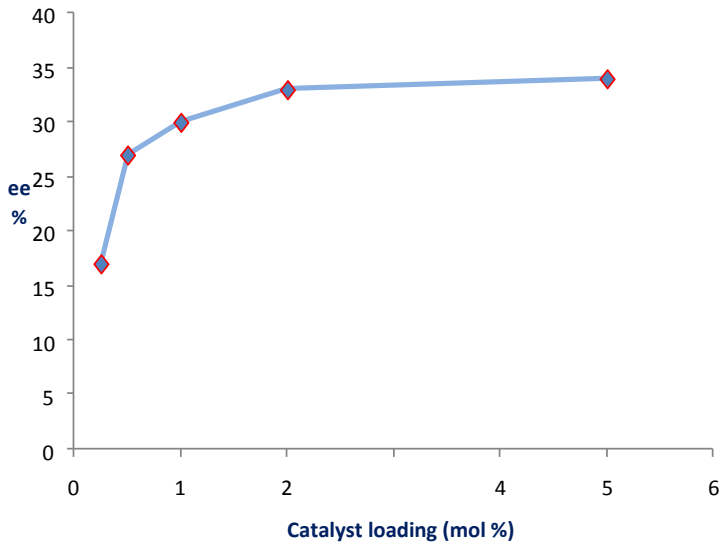


Figure 1.11. Effect of catalyst loading on the asymmetric epoxidation using iminium salt **45**.

1.8.6.6 Page's Catalysts From Chiral 1,2-Amino Alcohol Precursors Containing a Primary Hydroxyl Group.

Page prepared catalysts **46-49** (Figure 1.12) by condensation reactions between 2-(2-bromoethyl) benzaldehyde and 1,2-amino alcohols. When these catalysts were employed in the epoxidation of 1-phenylcyclohexene, a racemic mixture of 1-phenylcyclohexene oxide was obtained. For the reactions with catalysts **46-48**, 2 mol% of catalyst were used to complete the reaction, but with catalyst **49** the reaction gave full conversion in one hour using 0.5 mol% of the catalyst.[43]

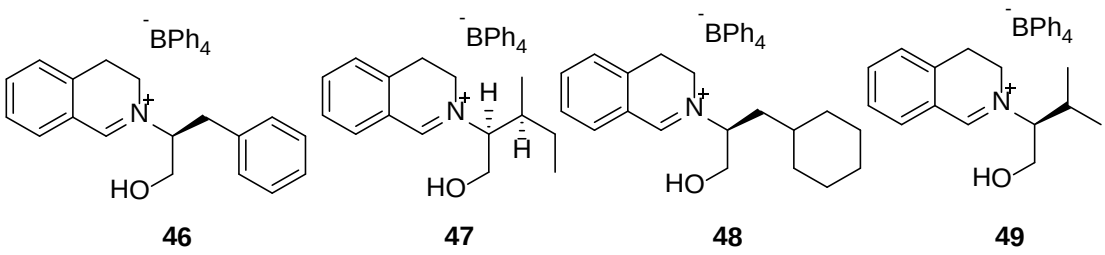


Figure 1.12. Page's Catalysts Containing a Primary Hydroxyl Group.

1.8.6.7 Page's Catalysts From Chiral 1,2-Amino Alcohol Precursors Containing A Secondary Hydroxyl Group

The catalysts **50 – 52** (Figure 1.13) contain a secondary hydroxyl group furnished from chiral 1.2-amino alcohols. These catalysts gave better enantioselectivities (up to 33% ee) for the epoxidation of 1-phenyl-3,4-dihydronaphthalene using iminium salt **50** than the catalysts containing a primary hydroxyl group.[43]

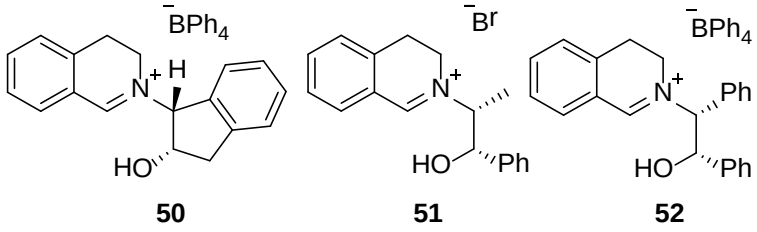
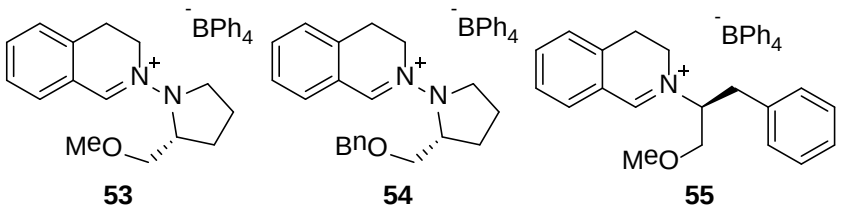


Figure 1.13. Page's Catalysts Containing a Secondary Hydroxyl Group.

1.8.6.8 Page's Catalysts From Amino Ether Precursors

Page reported catalysts **53** – **55** (Figure 1.14) prepared from amino ethers. Catalyst **55** afforded poor enantioselectivity for the epoxidation of 1-phenylcyclohexene, up to 7% ee higher than catalyst **56**. Catalysts **53** and **54** gave lower enantioselectivity than **55**.[43]

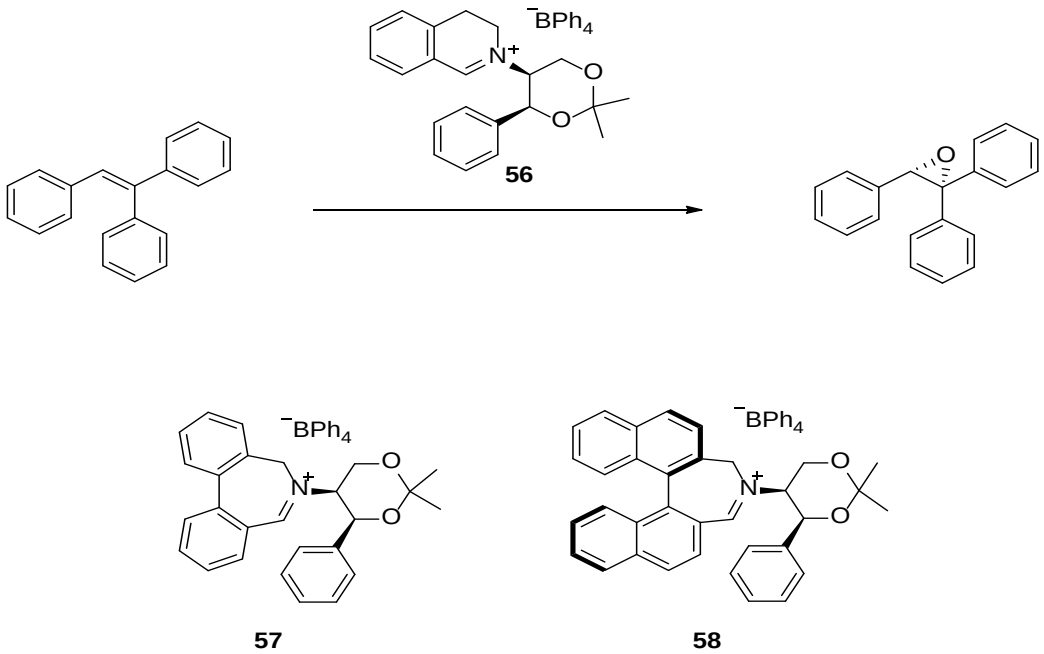


53 **54** **55**

Figure 1.14. Page's Catalysts Containing Amino Ether Group.

1.8.6.9 Page's Catalysts From Amino Acetal Precursors

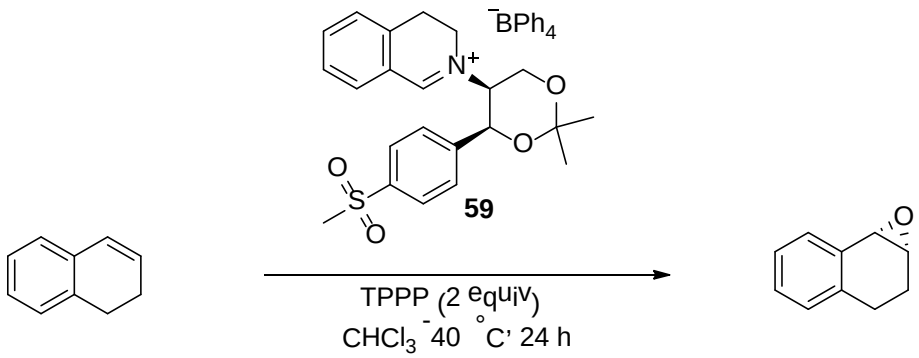
Page reported and tested catalyst **56**, an acetonide-derived dihydroisoquinolinium tetraphenylborate salt, for the epoxidation of triphenylethylene, and observed similar enantioselectivities to catalyst **45** (up to 59% ee, Figure 1.14**)**.[43] Encouraged by the success of catalyst **56**, Page prepared biphenyl iminium salt catalyst **57** and binaphthyl iminium salt catalyst **58**. Biphenyl iminium salt catalyst **57** afforded 60% ee for the epoxidation of 1-phenylcyclohexene with full conversion (Scheme 19**)**.[44,45]



Scheme 19. *Reagents and conditions*: iminium-salt **56-58** (5 mol%), Oxone (2 equiv.), Na_2CO_3 (4 equiv.), CH_3CN-H_2O (1:1), 0 °C.

1.8.6.10 Tetraphenylphosphonium Monoperoxysulfate

Page attempted to find alternative stoichiometric oxidants to Oxone, which requires the presence of water due to its poor solubility in common organic solvents. He looked for an oxidant that could be dissolved in organic solvent. That means the reaction could be conducted under non-aqueous conditions, and, crucially, the reaction temperature could be lowered below 0°C. The best stoichiometric oxidant to replace Oxone was tetraphenylphosphonium monoperoxysulfate (TPPP), which had been reported by Di Furia.[44] Indeed, tetraphenylphosphonium monoperoxysulfate is soluble in many organic solvents. For example, the epoxidation of dihydronaphthalene using Oxone as the oxidant and catalyst **59** afforded dihydronaphthalene oxide in 45% ee, but when tetraphenylphosphonium monoperoxysulfate with catalyst **59** in $CHCl_3$ at -40 °C, was used instead of Oxone, the product was obtained in 82% enantiomeric excesses (Scheme 20).[47]



Scheme 20. Page's catalyst **59** shows increased enantioselectivities when changing from aqueous to non-aqueous conditions.

1.9 Conclusion

This introduction has covered the importance of enantioselective synthesis and the field of asymmetric epoxidation in particular. Some asymmetric epoxidation reactions have been discussed including non-metal based and metal-based catalysis. This chapter also discussed the preparation and the use of oxaziridinium salts as oxygen transfer reagents. Finally, Page's study in asymmetric catalytic oxygen transfer reactions was highlighted.

1.10 References

1. Wothers, P.; Greeves, N.; Warren, S.; Clayden, J, *Organic Chemistry*. Oxford University Press, **2005**, 383.

2. McBride, W. B. *Lancet*, **1961**, 1358.

3. Therapontos, C.; Erskine, L.; Gardner, E. R.; Figg, W. D.; Vargesson, N. *PNAS*, **2004**, *106*, 8573.

4. Wothers, P.; Greeves, N.; Wqrren, S.; Clayden, *J. Organic Chemistry*. Fifth Edition New York: Oxford University Press, **2005**.

5. Procters, G.; Stereoselectivity In Organic Synthesis, New York: Oxford University Press, **1998**.

6. *Key Chiral Auxiliary Applications (Second Edition), Academic Press, Boston, **2014**. ISBN 978-0-12-417034-6*.

7. Caine, D. *Alkylsyions of Enols and Enolates in Comprehensive Organic Synthesis* Vol. 3**,** eds Trost B. M., Fleming I. 1–63 Pergamon, **1991**.

8. Whitesell, J. K. C_2-Symmetry and Asymmetric Induction. *Chem. Rev*. **1989**, *89*, 1581–1615.

9. Amano, S.; Ogawa, N.; Ohtsuka, M.; Chida, N. *Tetrahedron*, **1999**, *55*, 2205.

10. Paterson, I.; Gardner, N. M.; Guzman, E.; Wright, A. E. *Bioorg. Med. Chem.* **2009**, *17*, 2282.

11. Prileschajew, N. *Ber*. **1909**, 42, 4811.

12. Bartlett, P. D. *Rec. Chem. Prog*. **1950**, 11, 47.

13. Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem*. Soc. **1997**, 1017.

14. Henbest, H. B.; Wilson, A. L. *J. Chem. Soc.* **1985**, 1957.

15. Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta*, **1979**, 12, 63.

16. Rubottom, G. M.; Vazquez, M. A.; Pelegrin. D. R. *Tetrahedron Lett*. **1974**, 4319.

17. Frontier, A. J.; Raghavan, S.; Danishefsky, S. J., *J. Am. Chem. Soc.* **2000**, 6151.

18. Li, H.; Sharpless, K. B.; *Angew. Chem. Int. Ed*. **1996**, 35, 451.

19. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc*. **1980**, 102, 5974.

20. Sharpless K. B.; Hanson, R. M. *J. Org. Chem*. **1986**, *51*, 1922

21. Sharpless K. B.; *Angew. Chem. Int. Ed*. **2002**, 41, 2024.

22. Hoye, T. R.; Ye, Z.; *J. Am. Chem. Soc*. **1996**, *118*, 1801.

23. Alexakis, A. *Chimima*, **2007**, 61, 212.

24. Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1990**, 112, 2801.

25. Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc*. **1991**, 113, 7063.

26. Bredig, G.; Fiske, P. S.; *Biochem. Z*. **1912**, *46*, 7.

27. Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, 39, 1619.

28. Davis, F. A.; Stringer, O. D. *J. Org. Chem*. **1982**, 47, 1774.

29. Davis, F. A.; Chattopadhyay, S. *Tetrahedron Lett.* **1986**, 27, 5079.

30. Picot, A.; Milliet, P.; Lusinchi, X. *Tetrahedron Lett*. **1981**, *37*, 4201.

31. Picot, A.; Milliet, P.; Lusinchi, X. *Tetrahedron Lett*. **1976**, *19*, 1577.

32. Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron. Lett*. **1988**, *29*, 3941.

33. Bohé, L.; Hanquet, G.; Lusinchi, M.; Lusinchi, X. *Tetrahedron. Lett*. **1993**, *34*, 7271.

34. Bohé, L.; Kammoun, M. *Tetrahedron. Lett*. **2002**, *43*, 803.

35. Bohé, L.; Kammoun, M. *Tetrahedron. Lett*. **2004**, *45*, 747.

36. Aggarwal, V. K.; Wang, M. F. *Chem. Commun.* **1996**, 191.

37. Armstrong, A.; Ahmed, G.; Garnett, I.; Gioacolou, K. *Synlett*, **1997**, 1075.

38. Armstrong, A.; Ahmed, G.; Garnett, I.; Gioacolou, K.; Wailes, J. S. *Tetrahedron*, **1999**, 55, 2341.

39. Wong, M. K.; Ho, L. M.; Zheng, Y. S.; Ho, C. Y.; Yang, D. *Org. Lett*. **2001**, *16*, 2587.

40. Page, P. C. B.; Rassias, G. A.; Bethell, D.; Schilling, M. B. *J. Org. Chem.* **1998**, *63*, 2774.

41. Page, P. C. B.; Rassias, G. A.; Barros, D.; Bethell, D.; Schilling, M. B. *J. Chem. Soc. Perkin Trans. 1*, **2000**, 3325.

42. Page, P. C. B.; Rassias, G. A.; Barros, D.; Aradakani, A.; Buckley, B.; Bethell, D.; Smith, T. A. D.; Slawin, A. M. Z. *J. Org. Chem*. **2001**, *66*, 6926.

43. Page, P. C. B.; Rassias, G. A.; Barros, D.; Aradakani, A.; Bethell, D.; Merrifield, E. *Synlett*, **2002**, 4, 580.

44. Page, P. C. B.; Barros, D.; Aradakani, A.; Buckley, B.; Marples, B. A. *J. Org. Chem.* **2004**, 69, 3595.

45. Campestrini, S.; Furia, F. D.; Labat, G.; Novello, F. *J. Chem. Soc., Perkin Trans*. 2, **1994**, 2175.

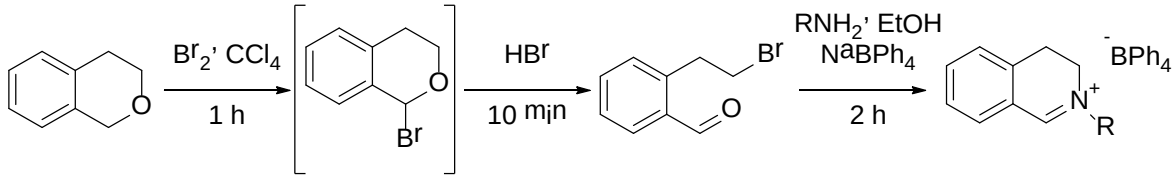
46. Page, P. C. B.; Buckley, B. R.; Heaney, H.; Blacker, A. J. *Org. Lett*. **2005**, 7, 375 – 377.

CHAPTER 2
Results
&
Discussions

2.0 Results and Discussions

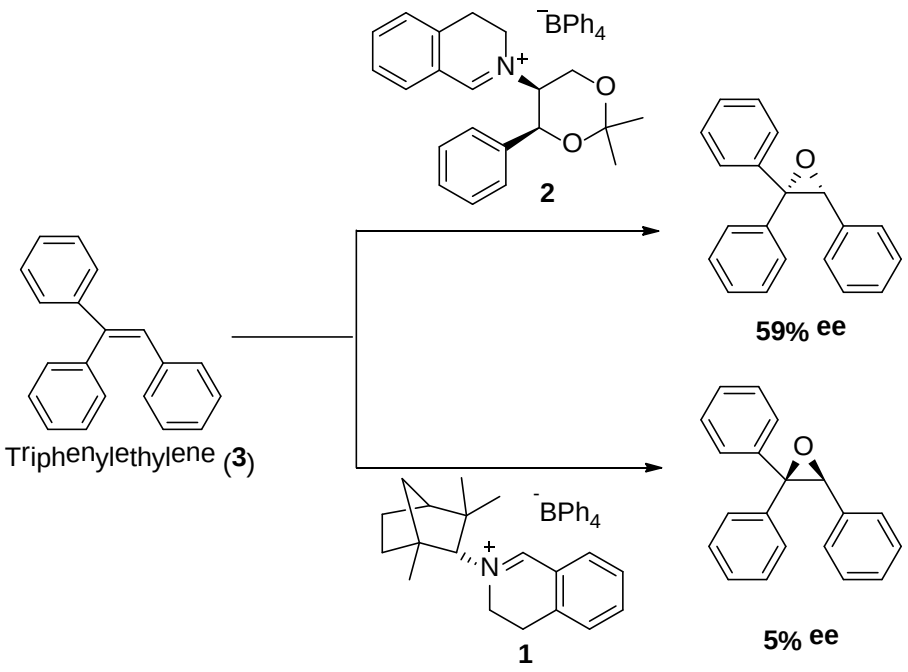
Page started his work in 1998 on designing catalysts for asymmetric epoxidation by producing a number of iminium-based catalysts from chiral primary amines and an achiral bromoaldehyde (Scheme 2.1).[1]

The idea behind the first design new cyclic chiral iminium salts based on a dihydroisoquinolinium moiety is to place the chiral centre in the exocyclic group close to the iminium nitrogen atom. Page thought this may lead to an increase in the enantiomeric excess by bringing the asymmetric centre closer to the site of oxygen transfer.[2,3] Examples of this include binaphthyl azepinium salts **9** and **10**, dihydroisoquinolinium salts **2**, **4**, **5** and **6**, and biphenyl azepinium salts **7** and **8.**[4]



Scheme 2.1 - Page's concise route towards dihydroisoquinolinium-based catalysts

Early work using fenchylamine-derived catalyst **1** gave 73% ee for the epoxidation of stilbene. Page also prepared acetal containing iminium catalyst **2**, which performed better than fenchylamine catalyst **1**, leading to higher enantioselectivity. For example, epoxidation of triphenylethylene **3** with catalysts **1** and **2** gave 5% and 59% ee, respectively (Scheme 2.2).[5, 6]



Scheme 2.2 - Iminium-based catalysts tested for epoxidation of triphenylethylene **3**.

In 2005, new catalysts were designed based on catalyst **2**, adding substituents to the 4 position on the phenyl ring: a sulfone group **4**, nitro group **5** and methoxy group **6.** Catalyst **4** provided higher enantiomeric excess than 4-methoxy-substituted salt **6** and 4-nitro substituted salt **5 (**Figure 2.1)**.**[7, 8]

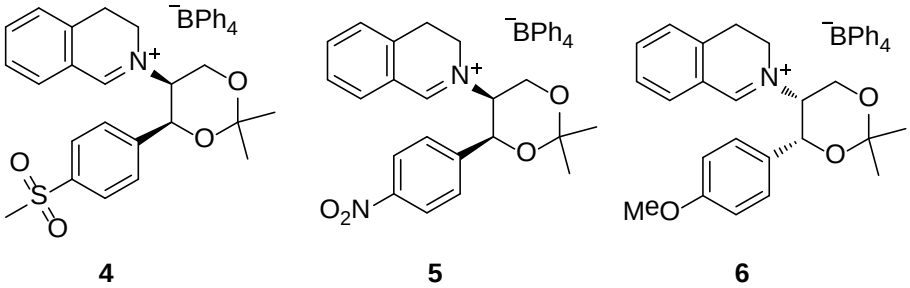
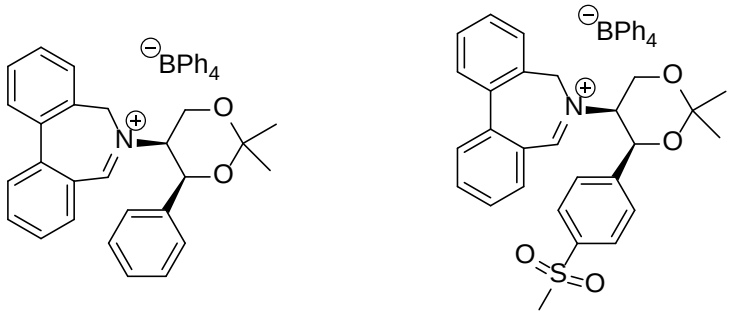


Figure 2.1 – Several dihydroisoquinolinium-based catalysts improved by Page.

The dihydroisoquinolinium moiety was replaced by a biphenyl backbone fused with a seven-membered azepinium salt to yield a new generation of iminium salts, such as **7** and **8** (Figure 2.2).[5]



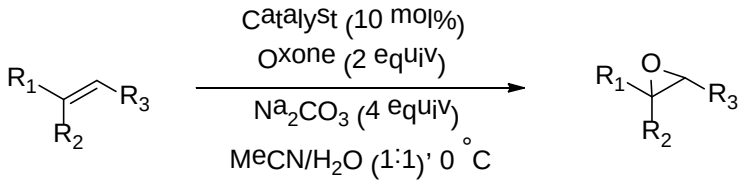
7 **8**

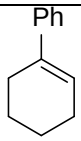
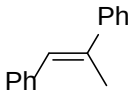
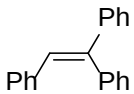
Figure 2.2 – The most reactive biphenyl-derived catalysts from Page.

In general, asymmetric epoxidation of 1-phenylcyclohexene with the biphenyl-derived catalysts induced higher ees than the six-membered ring dihydroisoquinolinium catalysts. Biphenyl catalyst **7** produced 1-phenylcyclohexene oxide in 60% ee compared to 41% ee for the six-membered ring catalyst **2.**

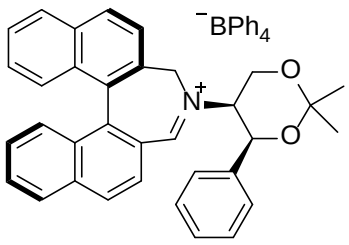
Moreover, the biphenyl-derived catalysts provide faster reactions: indeed, complete the consumption of the alkene substrate is observed after five to ten minutes whereas dihydroisoquinolinium catalysts need one hour under the same conditions (Table 2.1).[9]

Table 2.1 – Catalytic asymmetric epoxidation of alkenes using dihydroisoquinolinium and azepinium salts.

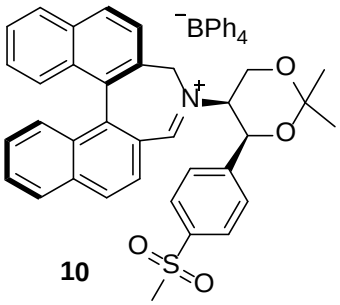


Alkene						
Catalyst	**ee (%)**	**Conv. (%)**	**ee (%)**	**Conv. (%)**	**ee (%)**	**Conv. (%)**
7	60	100	37	95	59	90
2	41	55	52	52	59	54
8	47	56	21	100	10	55
4	39	100	32	100	50	100

Subsequently Page reported binaphthyl-derived catalysts **9** and **10** which were used to oxidize 1-phenylcyclohexene in 91% ee under aqueous conditions (Figure 2.3).[10]



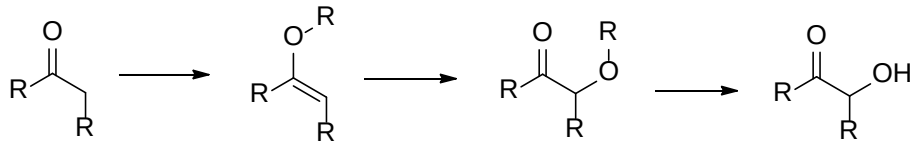
9



10

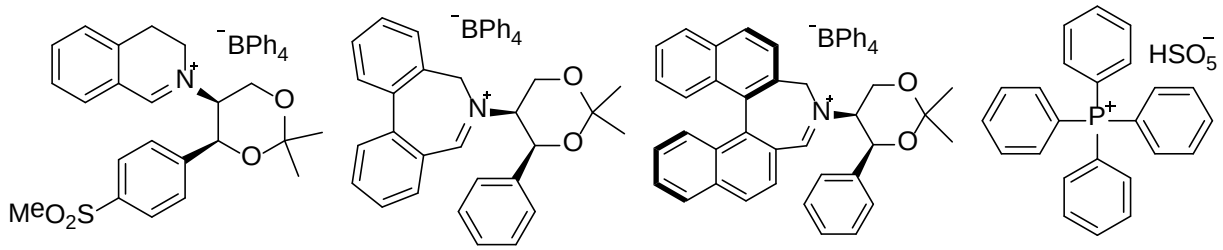
Figure 2.3 – Page's binaphthyl azepinium catalysts

The aim of this project is to prepare a number of enantiomerically enriched α-hydroxy carbonyls by epoxidation of enol ethers and esters (Scheme 2.3).



Scheme 2.3

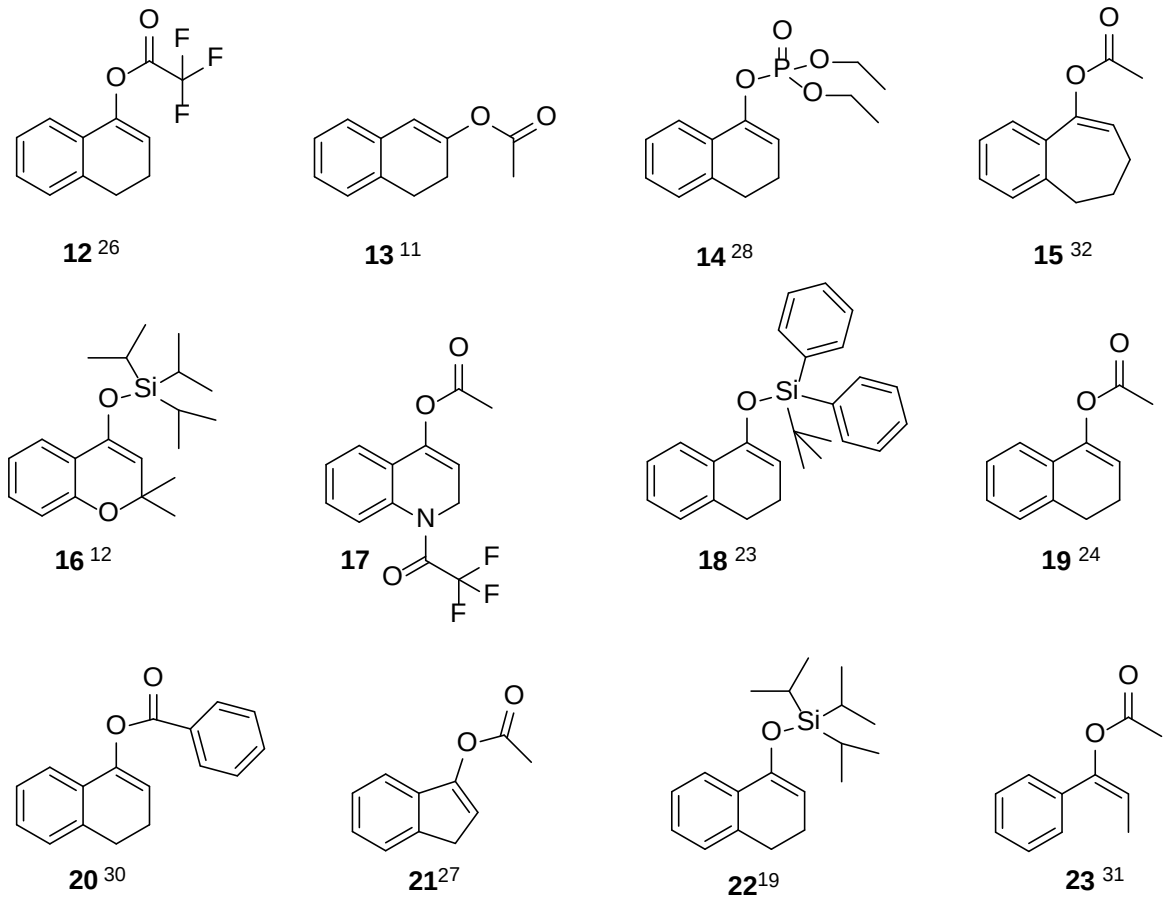
The epoxidation process involves iminium salt catalysts **7**, **4** and **9** and tetraphenylphosphonium monoperoxysulfate **11** as the oxidant under non-aqueous conditions (Figure 2.4).



4 **7** **9** **11**

Figure 2.4 – iminium salt catalysts and TPPP.

We have synthesised 12 enol ethers and esters from different substrates (Figure 2.5). We have chosen Silyl enol ethers **16** [12], **18** [23], acetate enol esters **13**[11], **15** [32], **19** [24], **21**[27], **23** [31], phosphate enol ether **14** [28], Trifluoroacetate enol ester **12** [26] and enol benzoate **20** [30]. All enol ethers and esters have good enantiomeric excess and yields in the literatures.



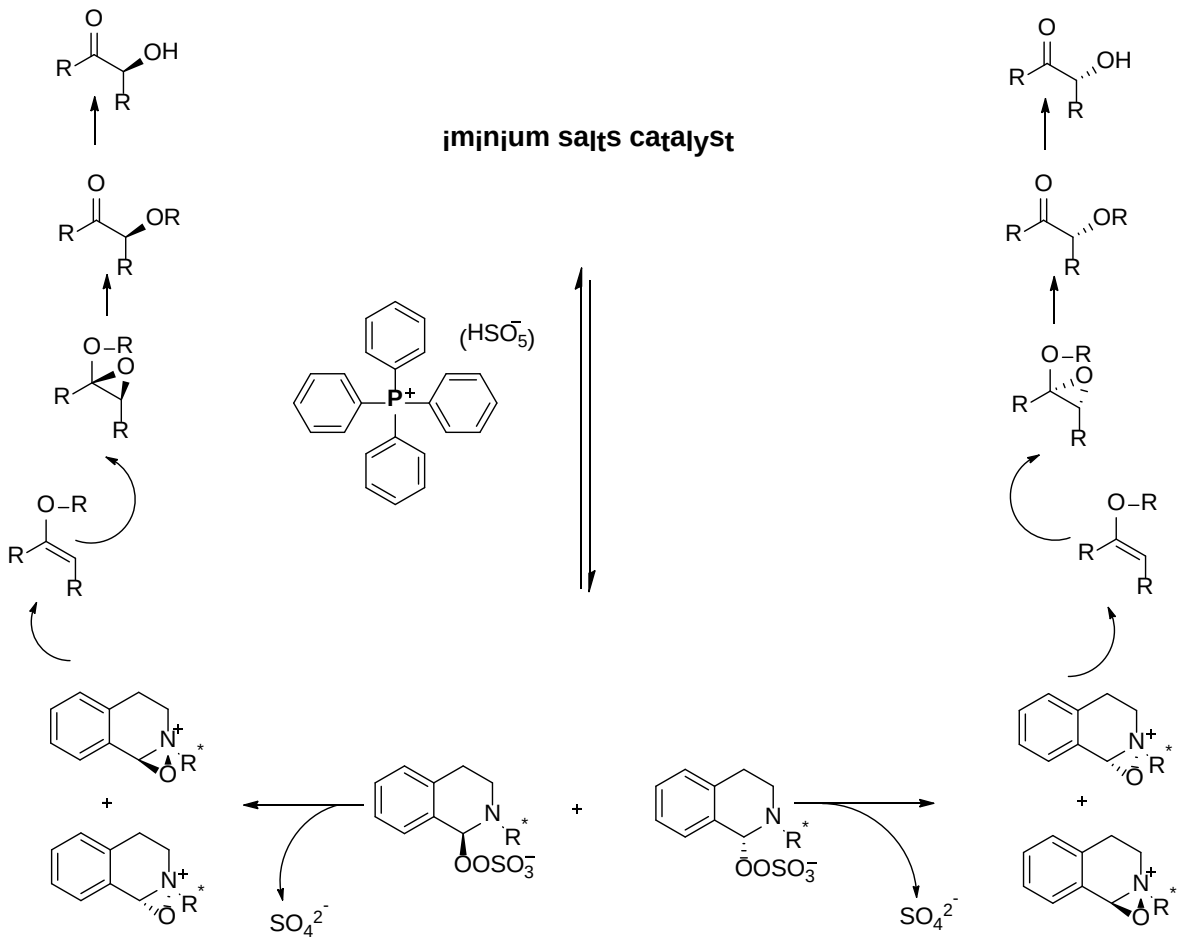
12 [26] **13** [11] **14** [28] **15** [32]

16 [12] **17** **18** [23] **19** [24]

20 [30] **21**[27] **22**[19] **23** [31]

Figure 2.5 – Enol ethers and esters

The enol ethers and esters were oxidized in two different ways: the non-selective route employs meta-chloroperoxybenzoic acid (*m*-CpBA) to prepare a racemic mixture, followed by the removal of the protecting group, if necessary. The enantioselective way involves the epoxidation of enols using iminium salt catalysts in the presence of tetraphenylphosphonium monoperoxysulfate to achieve α-hydroxy carbonyls (Scheme 2.4).

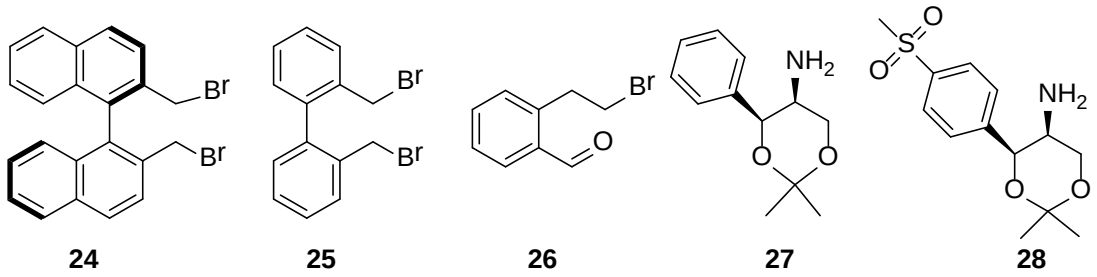


The catalytic cycle is shown above; the epoxidation of enol ethers and esters using iminium salts catalyst.

Scheme 2.4.

2.1 Synthesis of catalysts

Biphenyl, dihydroisoquinoline and binaphthyl moieties were used in the synthesis of iminium salt catalysts as backbones. (*R*)-Bis-bromomethyl-[1,1']-binaphthylenyl **24** and 2,2'-bis(bromomethyl) biphenyl **25** (Figure 2.4) were reacted with chiral primary amine **27** to produce the corresponding biphenyl catalyst **7** and binaphthyl catalyst **9**, and 2-(2-bromomethyl)benzaldehyde **26** was condensed with amine **28** to furnish dihydroisoquinoline catalyst **4**.

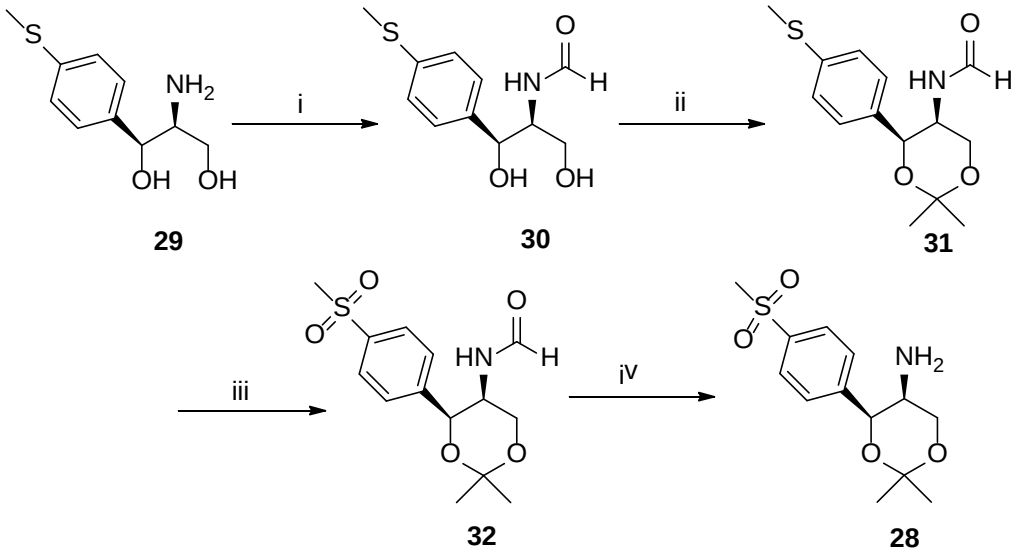


24 **25** **26** **27** **28**

Figure 2.4 – Backbone moieties and chiral primary amines.

2.1.1 Synthesis of Dihydroisoquinolinium Salt Catalyst 4

The synthesis of iminium catalyst **4** is divided into two parts: the first part is the formation of (4*S*, 5*S*)-5-amino-6-(4-methylsulfone)-2,2-dimethyl-1,3-dioxane **28** from thiomicamine **29**, and the second part is the formation of 2-(2-bromoethyl)benzaldehyde **26**. Methyl formate was used to protect the amine group in thiomicamine **29** to give diol **30**, followed by the addition of 2,2-dimethoxypropane with camphorsulfonic acid to protect diol **31**. Then, meta-chloroperoxybenzoic acid was added to oxidize the sulfide group followed by deprotection of the formyl group using hydrazine monohydrate to give (4*S*,5*S*)-5-amino-6-(4-methylsulfone)-2,2-dimethyl-1,3-dioxane **28** (Scheme 2.3).[10]

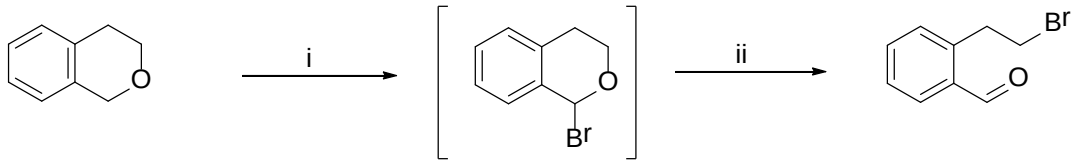


Reagents and conditions: (i) NaOMe (0.1 equiv), Methyl formate (1.1 equiv.), MeOH, rt; (ii) 2,2-Dimethoxypropane (5 equiv.), Camphorsulfonic acid (0.1 equiv.),Acetone, 83%; (iii) *m*-CpBA (3 equiv.) in DCM, 0 °C, 2 h, 78 %; (iv) hydrazine hydrate (98%), reflux, 3 h, 50%.

Scheme 2.3

^{1}H NMR data analysis confirmed the presence of each intermediate. The amine protection (step 1) using a formyl protecting group led to an observable signal at 8.4 ppm, indicating the presence of the amide. Diol protection (step 2) was observed when (2x) CH_3 group signals were seen at 1.59 ppm. Oxidation of the sulphur atom using m-CPBA (step 3) shifts the SMe signal from 2.5 ppm to SO_2Me at 3.1 ppm. Deprotection of the amide (step 4) was observed using ^{1}H NMR spectrum analysis where the signal at 8.4 ppm disappears.

The formation of 2-(2-bromoethyl) benzaldehyde **26** was achieved according to the procedure of Rieche and Schmitz.[13] Bromoaldehyde **26** was obtained from the bromination of isochroman **33** and isolated after distillation of the crude mixture (Scheme 2.4).[1]

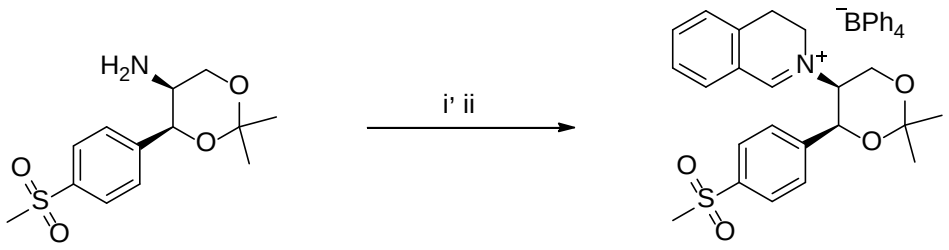


33 **34** **26**

Reagents and conditions: (i): Bromine, cyclohexane, reflux, 15 min; (ii): HBr, reflux, 10 min, 57%

Scheme 2.4.

Finally, cyclocondensation of 2-(2-bromoethyl)benzaldehyde **26** with (4*S*,5*S*)-5-amino-6-(4-methylsulfone)-2,2-dimethyl-1,3-dioxane **28** gave the corresponding dihydroisoquinolinium bromide salt, and subsequent anion exchange with sodium tetraphenylborate yielded iminium salt catalyst **4** as yellow crystals in 54% yield.



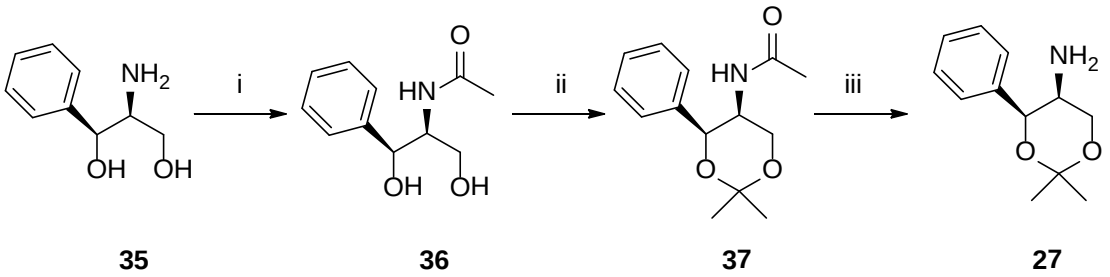
28 **4**

Reagents and conditions: (i) **26** (1.1 equiv.), EtOH, 0 °C; (ii) $NaBPh_4$ (1.1 equiv.), MeCN, rt, 54%.

Scheme 2.5.

2.1.2 Synthesis of biphenyl iminium salt catalyst 7

To synthesize biphenyl iminium salt catalyst **7**, aminodioxane **27** was prepared from chiral (*S*)-(−)-2-amino-3-phenyl-1-propanediol **35** in three steps (Scheme 2.6).[14] Amine **35** was dissolved in methanol in the presence of sodium methoxide and methyl formate to furnish diol **36**, followed by treatment with 2,2-dimethoxypropane in the presence of camphorsulfonic acid to obtain *N*-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-formamide **37** in 86% yield. The last step towards aminodioxane **27** is the removal of the formyl group using hydrazine monohydrate, giving aminodioxane **27** in 86% yield.

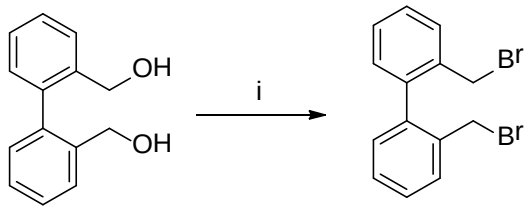


35 **36** **37** **27**

Reagents and conditions: (i) NaOMe (0.1 equiv), Methyl formate (1.1 equiv.), MeOH, rt, 12 h; (ii) 2,2-Dimethoxypropane (5 equiv.), Camphorsulfonic acid (0.1 equiv.), acetone; (iii) hydrazine hydrate (98%), reflux, 3 h, 86%.

Scheme 2.6

The biphenyl backbone of the catalyst was obtained by heating 2,2'-biphenyldimethanol **38** in hydrobromic acid for 2 h under reflux, which afforded 2,2'-*bis*(bromomethyl)biphenyl **25** as colourless crystals in a good yield (Scheme 2.7).[15]

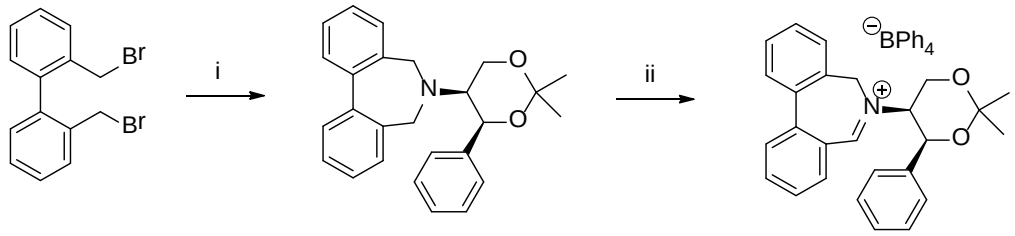


38 **25**

Reagents and conditions: (i) Hydrobromic acid (48%), reflux, 2 h, 93%.

Scheme 2.7.

2,2'-*bis*(Bromomethyl)biphenyl **25** and aminodioxane **27** were dissolved in acetonitrile under basic conditions (potassium carbonate) and heated under reflux for 24 h. *N*-Bromosuccinimide was added to the biphenyl compound **39** in dichloromethane to afford the bromide salt**.** Finally, the bromide counter ion was exchanged for a tetraphenylborate anion by adding sodium tetraphenylborate, yielding the biphenyl iminium salt catalyst **7** (Scheme 2.8). [2, 3]



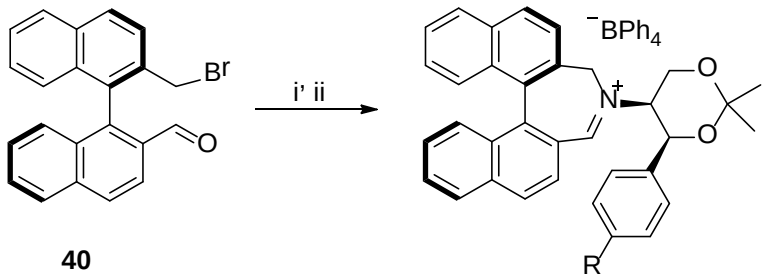
25 **39** **7**

Reagents and conditions: (i) aminodioxane **27** (1 equiv.), K_2CO_3 (2 equiv.), MeCN, reflux, 24 h (ii) NBS (1.1 equiv.), CH_2Cl_2, rt, 1 h; $NaBPh_4$ (1.2 equiv.) in the minimum amount of MeCN, rt, 5 min.

Scheme 2.8.

2.1.3 Synthesis of binaphthalene iminium salt catalyst 9

Binaphthalene catalyst **9** was the final catalyst prepared for our project. The synthesis of this catalyst does not need column chromatography and is as rapid as the biphenyl iminium and dihydroisoquinolinium salts **7** and **4**, respectively. Two possible routes were devised to access catalyst **9**. The first way started with bromoaldehyde binaphthalene **40** which reacted with primary amine **27** and **28** which provided catalysts **9** and **41** (Scheme 2.9).[8]



40

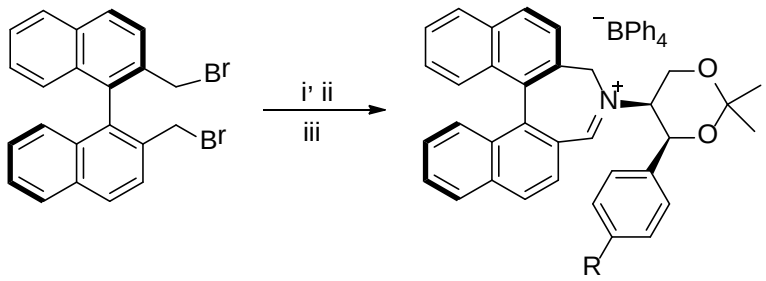
9, R = H, 65%
41, R = SO_2Me, 66%

Reagents and conditions: (i) primary amine **27, 28** (1 equiv.), EtOH, 24 h; (ii) $NaBPh_4$ (1.2 equiv.) in the minimum amount of MeCN, rt, 5 min.

Scheme 2.9.

The second method involves dibromomethyl binaphthalene **24** instead of bromoaldehyde binaphthalene **40**. The two bromides were substituted with primary amine **27** and **28**, followed by oxidation of the iminium species and cation exchange (Scheme 2.10).[8]

In this project, the second method was used to prepare binaphthalene iminium salt catalyst **9** as it was found experimentally easier than the first method.



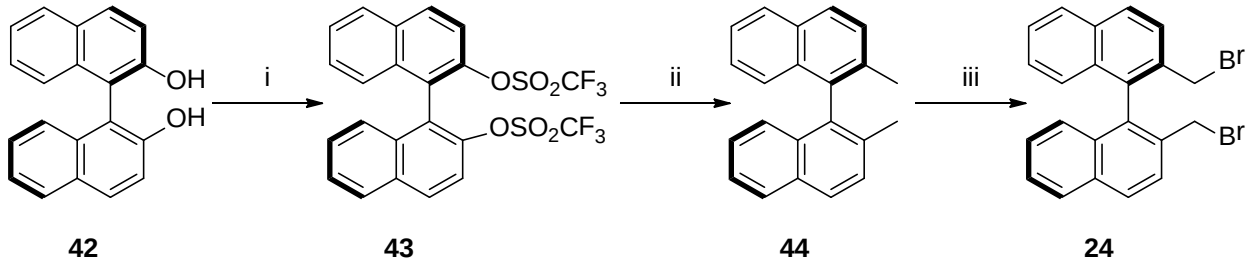
24

9, R = H, 65%
41, R = SO_2Me, 66%

Reagents and conditions: (i) primary amine **27, 28** (1 equiv.), K_2CO_3 (2 equiv.), MeCN, reflux, 24 h (ii) NBS (1.1 equiv.), CH_2Cl_2, rt, 1 h; (iii) $NaBPh_4$ (1.2 equiv.) in the minimum amount of MeCN, rt, 5 min.

Scheme 2.10.

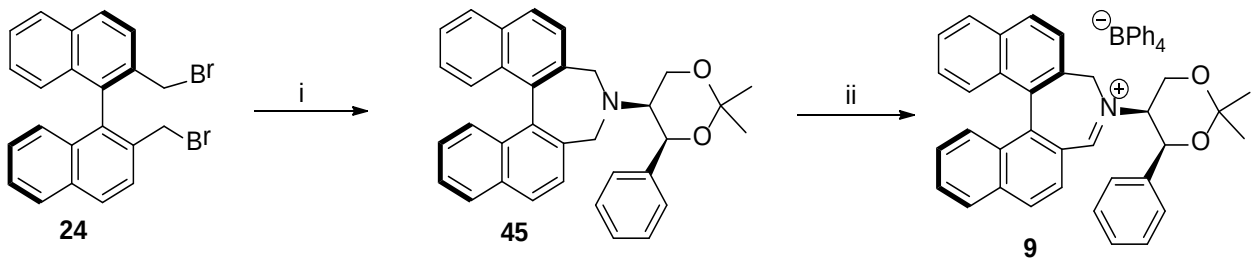
Dibromomethyl binaphthalene **24** was formed in 3 steps. We started from (*R*)-(+)-BINOL **42**. Triflation of (*R*)-(+)-BINOL **42** gave bistriflate **43** in good yield using 2,6-lutidine, triflic anhydride and 4-dimethylaminopyridine in dichloromethane. (*R*)-Dimethylated compound **44** was afforded by Kumada cross-coupling using a nickel catalyst and methylmagnesium bromide.[14, 15] Dibromomethyl binaphthalene **24** was obtained through bromination of compound **44** using azobisisobutyronitrile (AIBN) and *N*-bromosuccinimide (NBS), furnishing bis(bromomethyl) **24** in 56% yield (Scheme 2.11).[9]



Reagents and conditions: (i) Tf_2O (3 equiv.), DMAP (0.4 equiv.), 2,6-lutidine (3 equiv.), CH_2Cl_2, overnight, –30°C to rt, 92%; (ii) MeMgBr (4 equiv.), Ni(II)Cl dppe, Et_2O, 16 h, –30°C to rt, 80%; (iii) NBS (2.2 equiv.), AIBN (5 mol%), cyclohexane, reflux, 3 h, 56%.

Scheme 2.11.

Subsequently, the primary amine **27** was reacted with (*R*)-bis(bromomethyl)binaphthalene **24** in the presence of K_2CO_3 in MeCN to afford the corresponding amine **45**. NBS was added to oxidize the compound **45** to the iminium species, followed by counter anion exchange using sodium tetraphenylborate, to furnish iminium salt catalyst **9** as yellow powder in 49% yield (Scheme 2.12).

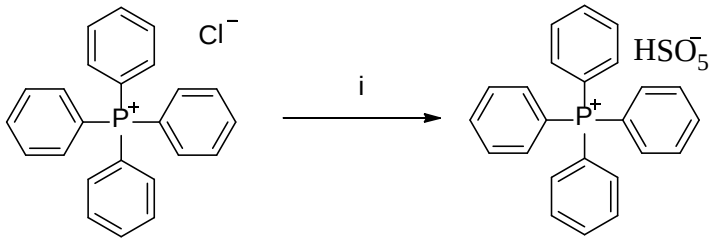


Reagents and conditions: (i) primary amine **27** (1 equiv.), K_2CO_3 (2 equiv.), MeCN, reflux, 24 h (ii) NBS (1.1 equiv.), CH_2Cl_2, rt, 1 h; $NaBPh_4$ (1.2 equiv.) in the minimum amount of MeCN, rt, 5 min, 49%.

Scheme 2.12.

2.2 Synthesis of Tetraphenylphosphonium Monoperoxysulphate 11 (TPPP)

Page showed that tetraphenylphosphonium monoperoxysulfate can be used for asymmetric epoxidation of olefins with iminium salt catalysts. Tetraphenylphosphonium monoperoxysulfate (TPPP) is an oxidant designed for non-aqueous conditions; the oxidant commonly employed, Oxone, is used under aqueous conditions.[10] In 1994, Di Furia reported the preparation of TPPP.[18] The procedure for the formation of TPPP is shown below (Scheme 2.13), affording the product in 69% yield after recrystallization in hexane. Tetraphenylphosphonium monoperoxysulfate was formed by anion exchange between Oxone and tetraphenylphosphonium chloride.



46 **11**

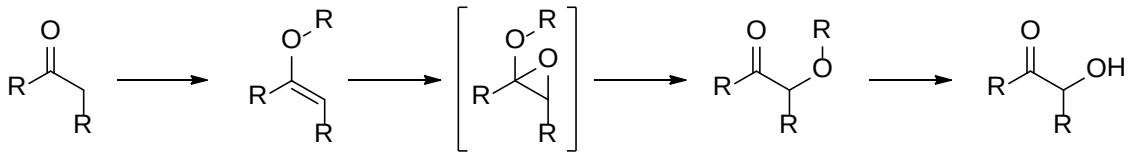
Reagents and conditions: (i): Oxone (1 equiv.), $CHCl_3$:H_2O, 10 °C, 0.5 h

Scheme 2.13.

2.3 Synthesis and epoxidation of enol ethers and esters

As indicated above, we intended to prepare α-hydroxy carbonyls from different ketone starting materials. The ketone substrates would be converted into the corresponding enol esters or ethers, and oxidation would lead to the corresponding epoxides using *m*-CpBA and

catalysts **7**, **9** and **4**. In situ ring opening of the epoxide moiety would yield the desired α-hydroxy carbonyls (Scheme 2.14).

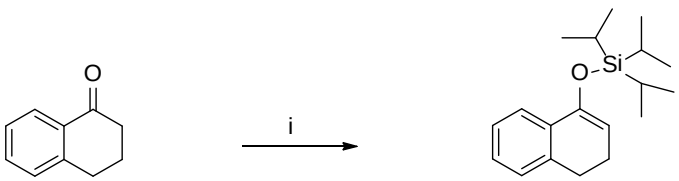


Scheme 2.14

2.3.1 Synthesis and epoxidation of enol ethers

2.3.1.1 Synthesis of (3,4-(dihydronaphthalen-1-yl)oxy)triisopropylsilane 22[17]

For the preparation of (3,4-(dihydronaphthalen-1-yl)oxy)triisopropylsilane **22**, 3,4-dihydro-2*H*-naphthalen-1-one (or α-tetralone) **47** was used as the starting material. Triisopropylsilyl triflate was added to a solution of α-tetralone **47** in dichloromethane in the presence of triethylamine, affording silyl enol ether **22** in 40% yield (Scheme 2.15)**.**[19]



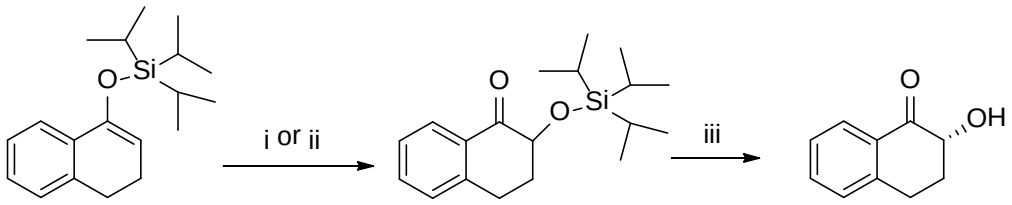
47 **22**

Reagents and conditions: (i): Triisopropylsilyl triflate, triethylamine, CH_2Cl_2, 40%.

Scheme 2.15.

The racemic α-hydroxy carbonyl **49** was prepared by adding *m*-CpBA and sodium bicarbonate to a solution of (3,4-dihydronaphthalen-1-yl)oxy)triisopropylsilane **22** in dichloromethane; 2-((triisopropylsilyl)oxy)-3,4-dihydronaphthalen-1(2H)-one **48** was obtained in 89% yield **(**Table 2.2). Compound **48** was dissolved in methanol and camphorsulphonic acid was added to remove the silyl group, forming racemic α-hydroxy carbonyl **49**.[18] Dihydroisoquinolinium salt catalyst **4** was used to prepare the non-racemic compound. Silyl enol ether **22**, catalyst **4** and TPPP were dissolved in chloroform for 24 h followed by the removal of the protecting group. The reaction afforded 2-hydroxy-3,4-dihydronaphthalen-1(2H)-one **49** in 35 % enantiomeric excess.[18]

Table 2.2 *Epoxidation of* ***(****3,4-dihydronaphthalen-1-yl)oxy)triisopropylsilane* ***22***



22 **48** **49**

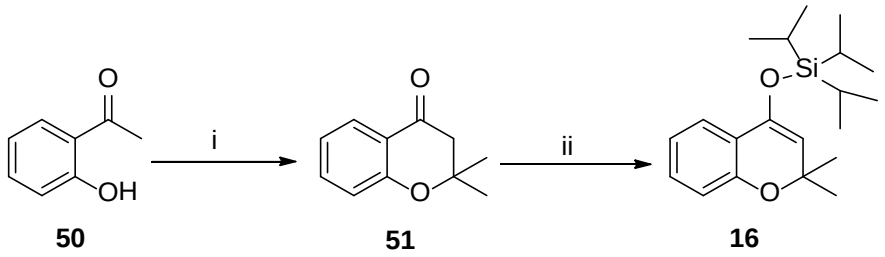
Reagents and conditions: (i): m-CPBA (1.5 equiv.), $NaHCO_3$, CH_2Cl_2, 0°C; (ii) Catalyst **4** (0.1 equiv.), TPPP (2 equiv.), chloroform, 0°C; (iii) camphorsulphonic acid (1.1 equiv), methanol.

Catalyst (10 mol%)	Oxidant (2 equiv.)	Time (h)	Solvent	Conversion[a] (%)	ee[b] (%)	Abs conf.[c] maj. enant.
-	*m*-CpBA	2	CH_2Cl_2	100	-	-
4	TPPP	24	$CHCl_3$	52	35	(+)-(*R*)

[a] Estimated by integration of the crude ^1H NMR spectrum. [b] Enantiomeric excesses were determined by chiral HPLC analysis. (Chiralcel OD-H column using a mixture of isopropanol and hexane as eluent). [c] The absolute configuration of 2-hydroxy-3,4-dihydronaphthalen-1(2H)-one **49** was determined by comparison of the sign of its specific rotation with that reported in the literature.[18]

2.3.1.2 Synthesis of 2,2-dimethyl-2H-chromen-4-yl)oxy)triisopropylsilane 16

To achieve the synthesis 2,2-dimethyl-2H-chromen-4-yl)oxy)triisopropylsilane **16**, hydroxyacetophenone **50** was used as the starting material. The cyclization of hydroxyacetophenone **50** with acetone and pyrrolidine under reflux for 12 h gave 2,2-dimethylchroman-4-one **51** in good yield.[21] 2,2-Dimethyl-2H-chromen-4-yl)oxy)triisopropylsilane **16** was prepared from **51** using the same reaction conditions as above (Scheme 2.16).



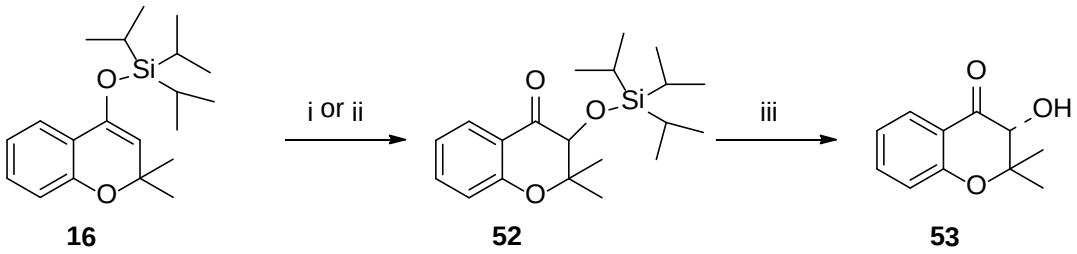
50 **51** **16**

Reagents and conditions: (i): Pyrrolidine, acetone, EtOH, 12 h (ii): Triisopropylsilyl triflate, triethylamine, CH_2Cl_2, 93%.

Scheme 2.16.

Enol ether **16** was submitted to the non-selective and the enantioselective reaction conditions described in (*Table 2.3).* α-Hydroxy carbonyl **53** was obtained in 36% ee after 24 h using the enantioselective method The absolute configuration of α-hydroxy carbonyl **53** was not previously determined in the literature.

Table 2.3 *Epoxidation of 2,2-dimethyl-2H-chromen-4-yl)oxy)triisopropylsilane* ***16***



16 **52** **53**

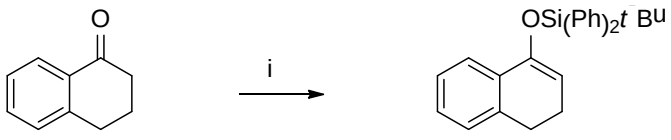
Reagents and conditions: (i): m-CPBA (1.5 equiv.), $NaHCO_3$, CH_2Cl_2, 0°C; (ii): Catalyst **4** (0.1 eq uiv.), TPPP (2 equiv.), chloroform, 0°C; (iii): camphorsulphonic acid (1.1 equiv), methanol.

Catalyst (10 mol%)	Oxidant (2 equiv.)	Time (h)	Conv.[a] (%)	ee[b] (%)	Rotation
-	*m*-CpBA	2	100	-	-
4	TPPP	24	100	36	(+)

[a] Estimated by integration of the crude ^{1}H NMR spectrum. [b] Enantiomeric excesses were determined by chiral HPLC analysis. (Chiralcel OD-H column using a mixture of isopropanol and hexane as eluent).

2.3.1.3 Synthesis of tert-butyl(3,4-dihydronaphthalen-1-yl)oxy)diphenylsilane 18

To synthesise tert-butyl(3,4-dihydronaphthalen-1-yl)oxy)diphenylsilane **18**, α-tetralone was added to a solution of potassium hexamethyldisilazide in tetrahydrofuran at –78 °C. t*ert*-Butylchlorodiphenylsilane was then added to the reaction at –78 °C. The silyl enol ether was formed in 45% yield.[23] The epoxidation of silyl enol ether **18** was achieved in high conversions of 91% and 95 % using catalysts **7** and **9**, respectively (Table 2.4).



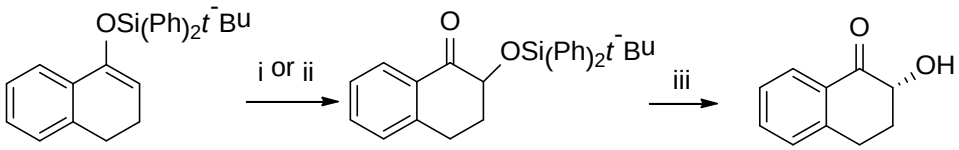
47 **18**

Reagents and conditions: (i): *tert*-Butylchlorodiphenylsilane, potassium hexamethyldisilazide, tetrahydrofuran, 40%.

Scheme 2.17.

The enantiomeric excesses obtained for the epoxidation of silyl enol ether **18** were higher than the ee obtained for the epoxidation of silyl enol ether **16**. One possible reason may involve the relative size of the silyl groups. Indeed, enol ether **18** has the bulkier TBDPS group attached.

Table 2.4 *Epoxidation of tert-butyl (3,4-dihydronaphthalen-1-yl)oxy)diphenylsilane **18***



18 **54** **49**

Reagents and conditions: (i): m-CPBA (1.5 equiv.), $NaHCO_3$, CH_2Cl_2, 0°C; (ii) Catalyst **4, 7** (0.1 equiv.), TPPP (2 equiv.), chloroform, 0°C; (iii) camphorsulphonic acid (1.1 equiv), methanol.

Catalyst (10 mol%)	Time (h)	Conv.[a] (%)	ee[b] (%)	Abs. conf.[c] maj. enant.
9	24	95	50	(+)-(*R*)

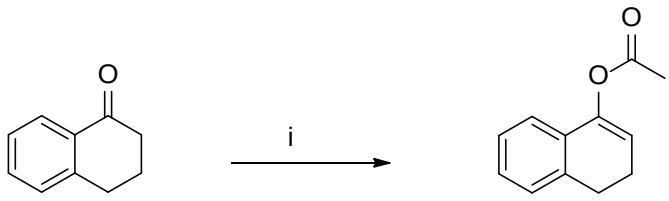
7	24	91	52	(+)-(*R*)

[a] Estimated by integration of the crude ^{1}H NMR spectrum. [b] Enantiomeric excesses were determined by chiral HPLC analysis. (Chiralcel OD-H column using a mixture of isopropanol and hexane as eluent). [c] The absolute configuration of 2-hydroxy-3,4-dihydronaphthalen-1(2H)-one **49** was determined by comparison of the sign of its specific rotation with that reported in the literature.[18]

2.3.2 Synthesis and epoxidation of enol esters

2.3.2.1 Synthesis of 3,4-dihydronaphthalen-1-yl acetate 19

The synthesis of acetate enol ester **19** was attempted using three different methods. First, we used DMAP, a useful nucleophilic catalyst, with acetyl chloride and triethylamine as the base. Unfortunately, only starting material was recovered. Next, acetic anhydride was used instead of acetyl chloride but the same result was obtained. Finally, another procedure to prepare acetate enol ester **19** using *para*-toluenesulfonic acid and isopropenyl acetate was tested. The reaction was reflux for 24 h to allow for acetone removal. The corresponding enol acetate was isolated using column chromatography in 76% yield. (Scheme 2.18).[24, 25]



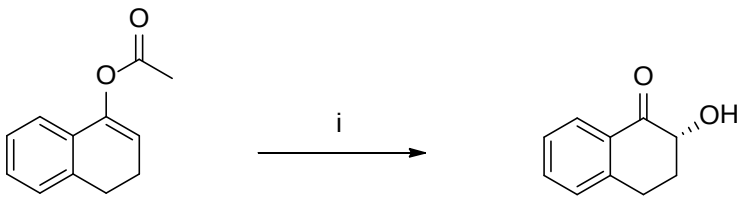
47 **19**

Reagents and conditions: (i): isopropenyl acetate, *p*-toluenesulfonic acid monohydrate, 12 h, 76%.

Scheme 2.18

The racemic 2-hydroxy-3,4-dihydronaphthalen-1(2H)-one **49** had already been prepared using silyl enol ether **22**. The epoxidation of acetate enol ester **19** was achieved using conditions similar to that used to obtain enol ethers **22** and **16** (Catalyst **4**, TPPP, $CHCl_3$, 24 h, 0 °C). However, acetate enol ester **19** was obtained in 66% ee, substantially higher than the corresponding oxidation of silyl enol ethers **22** and **16** (35% ee and 36% ee, respectively). Another advantage of the synthesis is that it affords α-hydroxy carbonyl **49** without requiring the protecting group removal step as the acetate group is cleaved during the epoxidation step. Subsequently, different solvents were tested, such as acetonitrile, dichloromethane and chloroform with catalyst **4** at −30 °C. Acetonitrile and dichloromethane led to lower enantiomeric excesses than chloroform when they were used as the reaction solvent (Table 2.5).

Table 2.5 *Epoxidation of 3,4-dihydronaphthalen-1-yl acetate **19***



19 **49**

Reagents and conditions: (i): Catalyst **4, 7** or **9** (0.1 equiv.), TPPP (2 equiv.).

Catalyst (10 mol%)	Temp. (°C)	Time (h)	Solvent	Conv.[a] (%)	ee[b] (%)	Abs conf.[c] maj. enant.
4	0	24	$CHCl_3$	62	66	(–)-(*R*)
9	0	48	$CHCl_3$	12	31	(+)-(*R*)

7	0	48	$CHCl_3$	99	88	(+)-(*R*)
4	−30	24	CH_2Cl_2	62	70	(−)-(*R*)
4	−30	24	MeCN	70	67	(−)-(*R*)
4	−30	24	$CHCl_3$	42	72	(−)-(*R*)
9	−30	48	$CHCl_3$	5	-	-
7	−30	48	$CHCl_3$	95	97	(+)-(*R*)
7	−45	48	$CHCl_3$	95	98	(+)-(*R*)

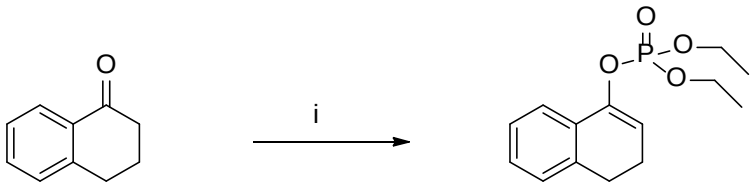
[a] Estimated by integration of the crude ^{1}H NMR spectrum. [b] Enantiomeric excesses were determined by chiral HPLC analysis. (Chiralcel OD-H column using a mixture of isopropanol and hexane as eluent). [c] The configuration of α-hydroxy carbonyl **49** were assessed by comparison of their specific rotation with literature data.[24, 25]

With the optimum solvent found, catalysts **4**, **7** and **9** were tested at 0 °C. Biphenyl catalyst **7** gave the highest enantiomeric excess and conversion (88% and 99%, respectively). Disappointingly, binaphthyl catalyst **9** afforded α-hydroxy carbonyl **49** in 31% ee. It was clear that biphenyl catalyst **7** and chloroform provided the best conditions. The temperature was lowered in an attempt to increase the enantioselectivity. At 0 °C, α-hydroxy carbonyl **49** was obtained in 88% ee. As expected, when the temperature was reduced to –30 °C and –45 °C, α-hydroxy carbonyl **49** was obtained in 97% and 98% ee, respectively (*Table 2.5)*.

2.3.2.2 Synthesis of 3,4-dihydronaphthalen-1-yl diethyl phosphate 14

We then turned our attention to enol phosphates. Enol phosphate **14** was prepared using LDA and diethyl phosphorochloridate. LDA was prepared by dissolving diisopropylamine in anhydrous THF at –78 °C followed by addition of *n*-BuLi. Subsequently, the LDA solution was added to α-tetralone **47** in THF at –78 °C. The mixture was stirred for 1 h under an argon

atmosphere. The solution of diethyl phosphorochloridate was added dropwise at the same temperature. Finally, enol phosphate **14** was obtained using column chromatography in 69% yield.[28]



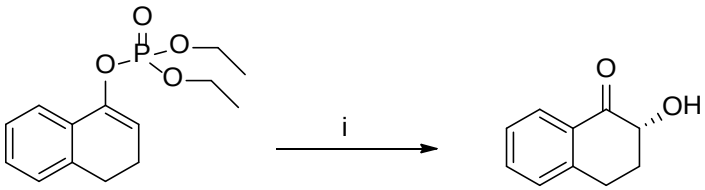
47 **14**

Reagents and conditions: (i): Diethyl phosphorochloridate, Lithium diisopropylamide, −78 °C, 69%.

Scheme 2.19

Chloroform was also chosen as the solvent for enantioselective oxidation of phosphate enol ether **14** at different temperatures (0 °C, −30 °C, −50 °C) with catalysts **4** and **7** (Table 2.6).

Table 2.6 *Epoxidation of 3,4-dihydronaphthalen-1-yl diethyl phosphate **14***



14 **49**

Reagents and conditions: (i): Catalyst **4** or **7** (0.1 equiv.), TPPP (2 equiv.), chloroform.

Catalyst (10 mol%)	Temp. (°C)	Time (h)	Conv.[a] (%)	ee[b] (%)	Abs conf.[c] maj. enant.
4	0	48	45	25	(–)-(*R*)
4	−30	48	22	35	(–)-(*R*)
4	−50	72	-	-	-

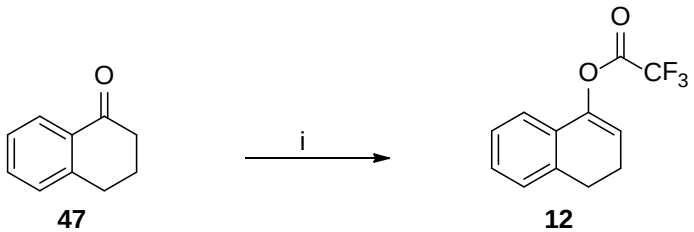
7	−30	72	45	90	(+)-(*R*)

[a] Estimated by integration of the crude ^{1}H NMR spectrum. [b] Enantiomeric excesses were determined by chiral HPLC analysis. (Chiralcel OD-H column using a mixture of isopropanol and hexane as eluent). [c] The absolute configuration were determined by comparison of the sign of its specific rotation with that reported in the literature.[27]

We observed that when the temperature was reduced, the enantiomeric excess increased: for example, using catalyst **4** at 0 °C, the product was obtained in 25% ee, while at −30 °C the enantiomeric excess was 35% ee. Biphenyl catalyst **7** gave excellent enantiomeric excess of 90% ee; however, the conversion is lower when compared with acetate enol ester **19.**

2.3.2.3 Synthesis of 3,4-dihydronaphthalen-1-yl 2,2,2-trifluoroacetate 12

Trifluoroacetate enol ester **12** was prepared using 1-tetralone and trifluoroacetic anhydride affording 3,4-dihydronaphthalen-1-yl 2,2,2-trifluoroacetate **12** in excellent yield (Scheme 2.20). We were delighted to find that the epoxidation of **12** proceeded in 90% ee when the reaction was performed in chloroform with catalyst **7** at 0°C, higher than catalysts **4** and **9** using the same reaction conditions (Table 2.7).



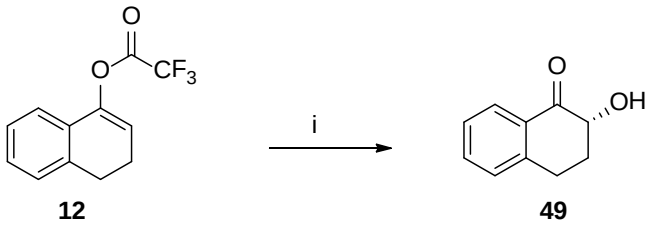
47 **12**

Reagents and conditions: (i): trifluoroacetic anhydride, *p*-toluenesulfonic acid monohydrate, 12 h

(ii): Catalyst **4**, **7** and **9** (0.1 equiv.), TPPP (2 equiv.), 91%.

Scheme 2.20.

Table 2.7 *Epoxidation of* 3,4-dihydronaphthalen-1-yl 2,2,2-trifluoroacetate **12**.



12 **49**

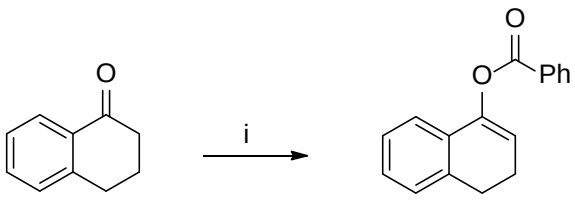
Reagents and conditions: (i): Catalyst **4, 7** and **9** (0.1 equiv.), TPPP (2 equiv.), chloroform, 0°C.

Catalyst (10 mol%)	Time (h)	Conv.[a] (%)	ee[b] (%)	Abs conf.[c] maj. enant.
4	24	23	54	(−)-(*R*)
7	24	65	90	(+)-(*R*)
9	24	63	43	(+)-(*R*)

[a] Estimated by integration of the crude ^{1}H NMR spectrum. [b] Enantiomeric excesses were determined by chiral HPLC analysis. (Chiralcel OD-H column using a mixture of isopropanol and hexane as eluent). [c] The absolute configuration were determined by comparison of the sign of its specific rotation with that reported in the literature.27

2.3.2.4 Synthesis of 3,4-dihydronaphthalen-1-yl benzoate 20

The enol benzoate **20** was obtained by addition of perchloric acid into a solution of benzoic anhydride and 1-tetralone in hexane. (Scheme 2.21). [30]



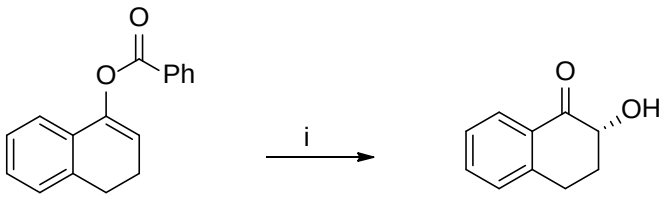
47 **20**

Reagents and conditions: (i): benzoic anhydride, perchloric acid, hexane, r.t., 2 h, 26%.

Scheme 2.21

The epoxidation of enol benzoate **20** was achieved in good enantioselectivities of 89%, 54% and 43% using catalysts **7**, **4** and **9**, respectively.

Table 2.8 *Epoxidation of* 3,4-dihydronaphthalen-1-yl benzoate **20**.



20 **49**

Reagents and conditions: (i): Catalyst **4, 7** and **9** (0.1 equiv.), TPPP (2 equiv.), chloroform, 0°C.

Catalyst (10 mol%)	Time (h)	Conv.[a] (%)	ee[b] (%)	Abs conf.[c] maj. enant.
4	24	23	54	(−)-(*R*)
7	24	35	89	(+)-(*R*)
9	24	33	43	(+)-(*R*)

[a] Estimated by integration of the crude ^{1}H NMR spectrum. [b] Enantiomeric excesses were determined by chiral HPLC analysis. (Chiralcel OD-H column using a mixture of isopropanol and hexane as eluent). [c] The absolute configuration were determined by comparison of the sign of its specific rotation with that reported in the literature.[27]

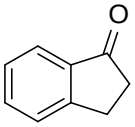
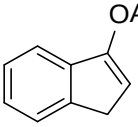
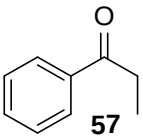
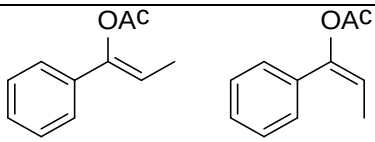
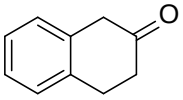
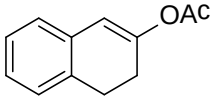
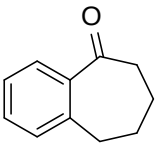
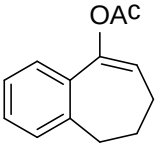
2.3.2.5 Enol Acetate synthesis

After we tested different enol esters we found that the epoxidation of enol acetate **19** gave high enantioselectivity using iminium salt catalysts. Moreover, enols acetate **19** provided

high conversion, up to 99%. In order to expand the methodology, enol acetates from different substrates, such as **1**-indanone **55**, propiophenone **57**, 2-tetralone **59** and 1-benzosuberone **61**, were prepared.

Table 2.9: synthesis of different enol acetates

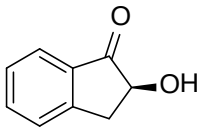
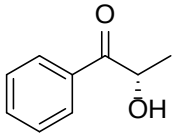
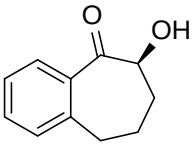
Reagents and conditions: (i): isopropenyl acetate, *p*-toluenesulfonic acid monohydrate, 12 h.

Substrates	Enols	Yield
 **55**	 **21**	80%
 **57**	 **23**	73%
 **59**	 **13**	71%
 **61**	 **15**	95%

Biphenyl catalyst **7** with TPPP and chloroform as the solvent were used for the epoxidation of acetate enol esters **21**, **23** and **15**. All the enol esters provided high conversion and high

enantioselectivity. Enol acetate **23** was isolated as an inseparable mixture of two isomers, *E* and *Z* in a 10:1 ratio. The mixture of (*E*)-1-phenylprop-1-en-1-yl acetate and (*Z*)-1-phenylprop-1-en-1-yl acetate **23**, catalyst **7** and TPPP were dissolved in chloroform for 72 h to afford (S)-2-hydroxy-1-phenylpropan-1-one **58** in 57 % enantiomeric excess. The presence of a mixture could explain the low enantioselectivity (57%) observed.

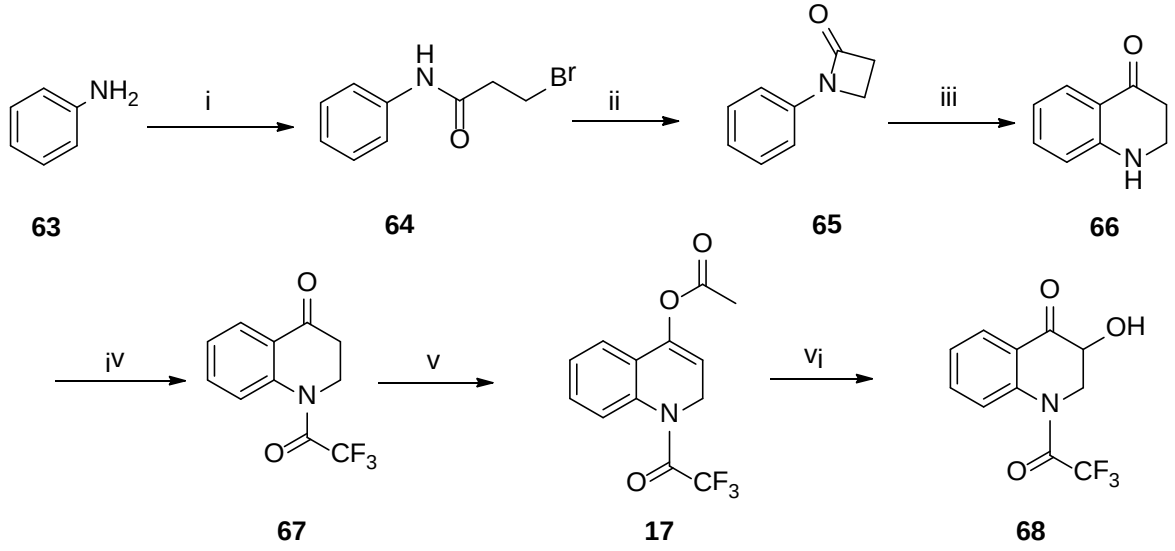
Table 2.10 *Epoxidation of* different acetate enol esters by catalyst **7**.

Enol	α-Hydroxy-carbonyl	Oxidant	Temp. (°C)	Time (h)	Solvent	Conv.[a] (%)	ee (%)	Abs conf. maj. enant.
21	 **56**	*m*-CpBA	0	4	CH_2Cl_2	100	-	-
		TPPP	−30	48	$CHCl_3$	70	80[b]	(–)-(*S*)[e]
23	 **58**	*m*-CpBA	0	3	CH_2Cl_2	100	-	-
		TPPP	−30	72	$CHCl_3$	95	57[c]	(–)-(*S*)[f]
15	 **62**	*m*-CpBA	0	3	CH_2Cl_2	85	-	-
		TPPP	0	24	$CHCl_3$	99	87[b]	(+)-(S)[g]
		TPPP	−30	48	$CHCl_3$	95	92[b]	(+)-(S)[g]

[a] Estimated by integration of the crude ^{1}H NMR spectrum. [b] Enantiomeric excesses were determined by chiral HPLC analysis. (Chiralcel OD-H column using a mixture of isopropanol and hexane as eluent). [c] Enantiomeric excesses were determined by chiral HPLC analysis. (XD 6 Eurocel 01 column using a mixture of isopropanol and hexane as eluent).[e] The configuration of the (S)-2-hydroxy-2,3-dihydro-1H-inden-1-one **56** were assessed by comparison of their specific rotation with literature data.[24, 25] [f] The assignment of the absolute configuration to (S)-2-hydroxy-1-phenylpropan-1-one **58** was confirmed by Tsuchihashi and co-workers.[29] [g] The absolute configuration of (S)-6-hydroxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one **62** was determined via ^{1}H-NMR analysis of Mosher's esters of the products according to the protocol of Hoye and coworkers.[30,31]

2.3.2.6 Synthesis of 1-(2,2,2-trifluoroacetyl)-1,2-dihydroquinolin-4-yl acetate 17

We utilized our methodology for the preparation of 3-hydroxy-1-(2,2,2-trifluoroacetyl)-2,3-dihydroquinolin-4(1H)-one **68** through epoxidation of acetate enol ester **17**. To obtain 1-(2,2,2-trifluoroacetyl)-1,2-dihydroquinolin-4-yl acetate **17**, aniline **65** was targeted. Bromopropanoyl chloride was added to aniline with potassium carbonate in dichloromethane, which yielded 3-bromo-*N*-phenylpropanamide **64**.[34] Compound **64** was dissolved in dimethylformamide and a strong base was added to afford β-lactam **65**.[35] 2,3-Dihydroquinolin-4(1H)-one **66** was prepared by a Fries-type rearrangement.[36] Subsequently, trifluoroacetic anhydride was added dropwise at 0 °C in the presence of triethylamine to protect the amine, which yielded 1-(2,2,2-trifluoroacetyl)-2,3-dihydroquinolin-4(1H)-one **67** in 78% yield (Scheme 2.22).[36] Finally, acetate enol ester **17** was prepared using *para*-toluenesulfonic acid and isopropenyl acetate.

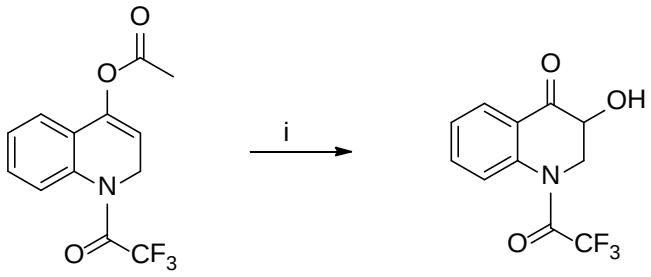


Reagents and conditions: (i): 3-Bromopropanoyl chloride, K_2CO_3, CH_2Cl_2, 0 °C, 3h, 63%. (ii): Sodium *tert*-butoxide, dimethylformamide, 55%. (iii): Trifluoromethanesulfonic acid, 1,2-dichloroethane, 86%. (iv): Trifluoroacetic anhydride, triethylamine, dichloromethane, 4h, 78%. (v): isopropenyl acetate, *p*-toluenesulfonic acid monohydrate, 12 h, 41% (vi): Catalyst **4** (0.1 equiv.), TPPP (2 equiv.), chloroform.

Scheme 2.22.

The racemic 3-hydroxy-1-(2,2,2-trifluoroacetyl)-2,3-dihydroquinolin-4(1H)-one **68** was prepared using meta-chloroperoxybenzoic acid, and, using our best conditions, compound **68** was obtained in 70% ee (Table 2.11).

Table 2.11 *Epoxidation of* 1-(2,2,2-trifluoroacetyl)-1,2-dihydroquinolin-4-yl acetate **17**



17 **68**

Reagents and conditions: (i): Catalyst **7** (0.1 equiv.), TPPP (2 equiv.), chloroform.

Catalyst (10 mol%)	Oxidant (2 equiv.)	Temp. (°C)	Time (h)	Solvent	Conv.[a] (%)	ee[b] (%)	Rotation.
-	*m*-CpBA	0	2	CH_2Cl_2	80	-	-
7	TPPP	−30	72	$CHCl_3$	65	70	(–)

[a] Estimated by integration of the crude ^{1}H NMR spectrum. [b] Enantiomeric excesses were determined by chiral HPLC analysis. Measured by chiral HPLC (XD 6 Eurocel 01 column using a mixture of isopropanol and hexane as eluent).

2.3.2.7 Synthesis of (-)Tatarinoid B 74

(−)-Tatarinoids A, B and C are three natural products of 19 compounds that have been isolated from the rhizome of the plant *Acorus tatarinowii*. (−)-Tatarinoids are used for the

treatment of central nervous system diseases in traditional Chinese medicine. For instance, in China, it is believed to improve memory and learning.[37, 38]

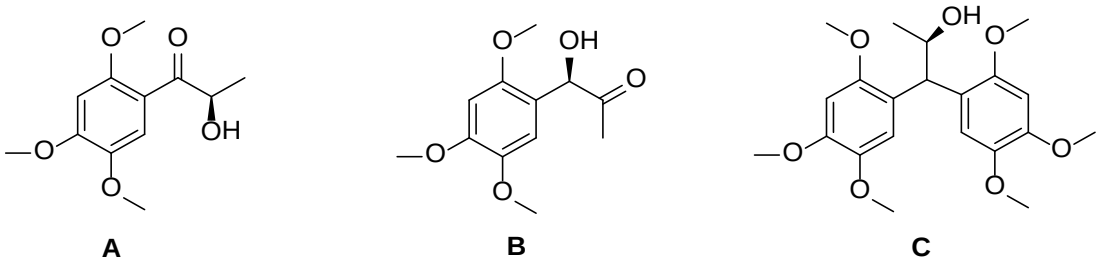
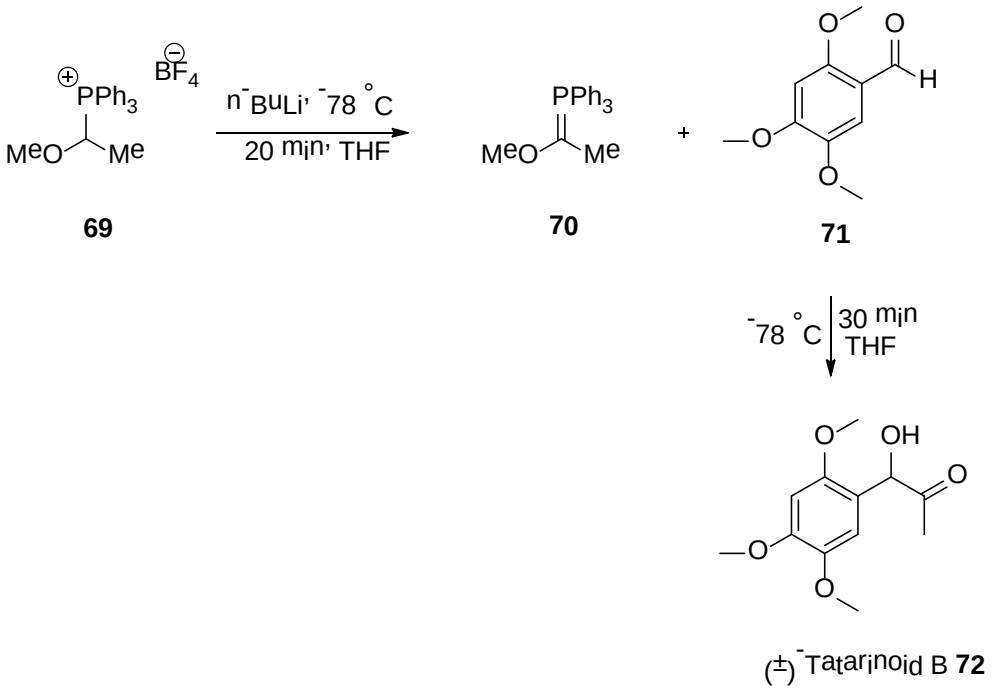


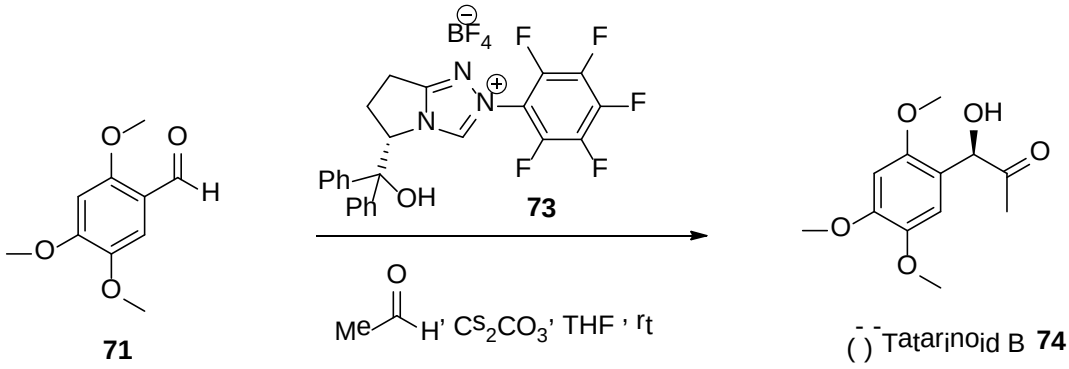
Figure 2.7 - *Tatarinoids.*

The racemic Tatarinoid B was obtained by treatment of 2,4,5-trimethoxybenzaldehyde **71** with Wittig ylide **70** which formed from the reaction between (1-methoxyethyl)triphenylphosphonium salt **69** and n-BuLi (Scheme 2.23).[39, 40]



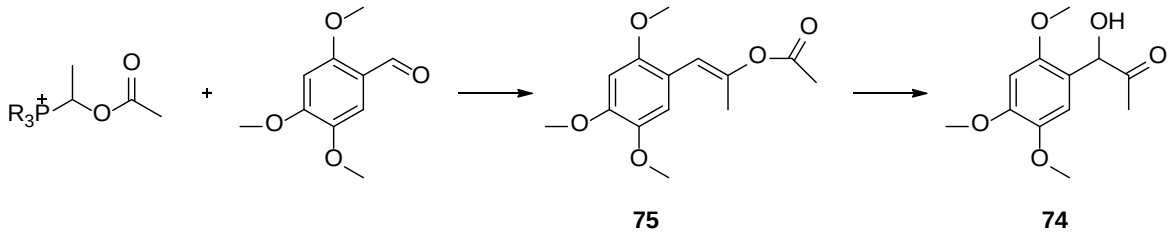
Scheme 2.23: Synthesis of (±)-Tatarinoid B **72.**

The reaction between 2,4,5-trimethoxybenzaldehyde **71** and acetaldehyde using a chiral triazolium salt **73** as a catalyst formed (-)-Tatarinoid B **74** in one step (Scheme 2.24).[41, 42]



Scheme 2.24: Synthesis of (-)-Tatarinoid B **74.**

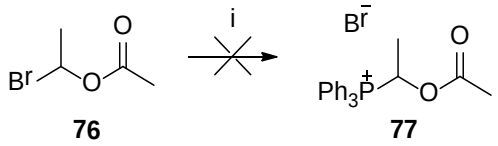
We planned to synthesize tatarinoid A and B. In the synthesis of tatarinoid B **74**, our initial strategy was to obtain enol acetate **75** using a Wittig or Horner-Wadsworth-Emmons reaction from 2,4,5-trimethoxybenzaldehyde.



Scheme 2.25: Strategy towards tatarinoid B

The first route involved using the Wittig reaction to allow us to make enol acetate **75**. We have used triphenylphosphine with 1-bromoethyl acetate **76** to generate the corresponding

phosphonium salt to react with benzaldehyde, but unfortunately the reaction was unsuccessful and we were unable to isolate the Wittig salt (Scheme 2.26).[43]

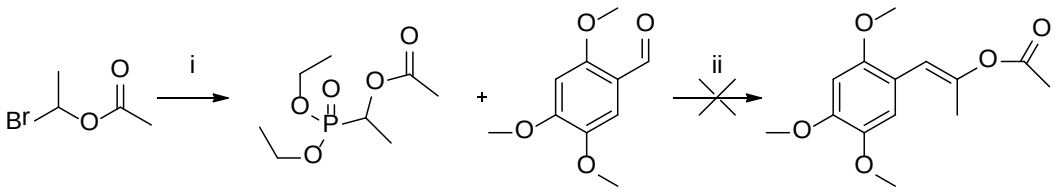


76 **77**

Reagents and conditions: (i): triphenylphosphine, toluene.

Scheme 2.26

In the second route, the Arbuzov reaction was used to prepare phosphonate **78** to replace phosphonium salt **77**. 1-(Diethoxyphosphoryl)ethyl acetate **78** was prepared by treating 1-bromoethyl acetate with triethylphosphite.[33] A Horner-Wadsworth-Emmons reaction was attempted between benzaldehyde **71** and 1-(diethoxyphosphoryl)ethyl acetate **78** to furnish the enol acetate **75**, but no reaction occurred and the starting material was recovered (Scheme 2.27).[44, 45]

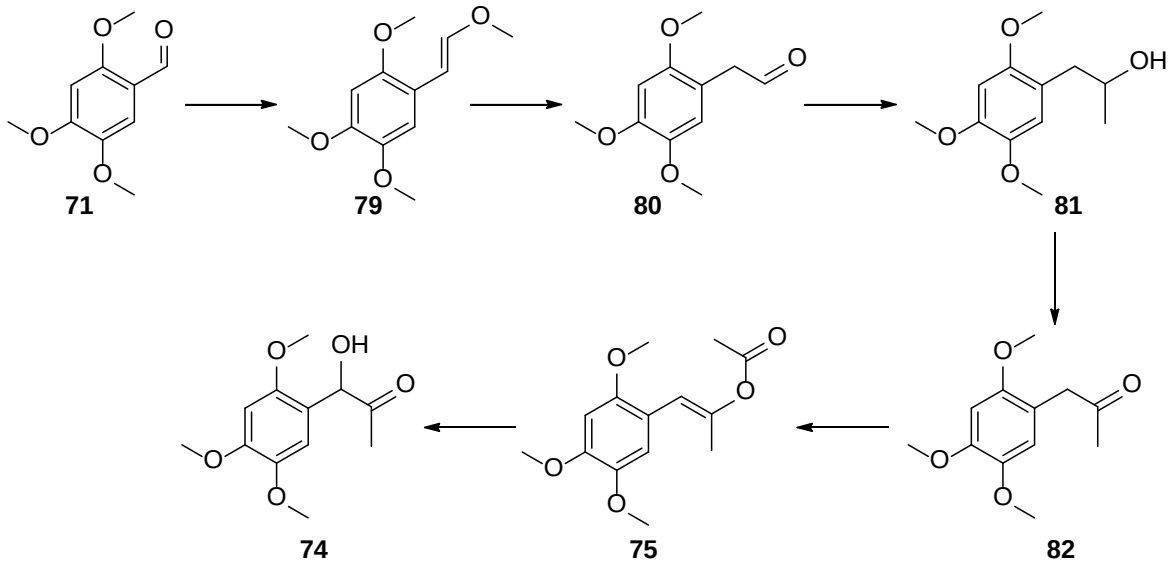


76 **78** **71** **75**

Reagents and conditions: (i): triethylphosphite, 45% (ii): Potassium tert-butoxide, tetrahydrofuran.

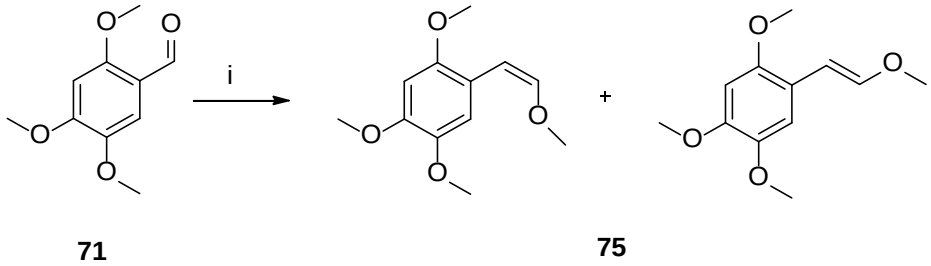
Scheme 2.27

Due to the failure of the Wittig and HWE routes to enol acetate **75**, a longer synthesis was devised to access tatarinoid B **74** (Scheme 2.28).



Scheme 2.28

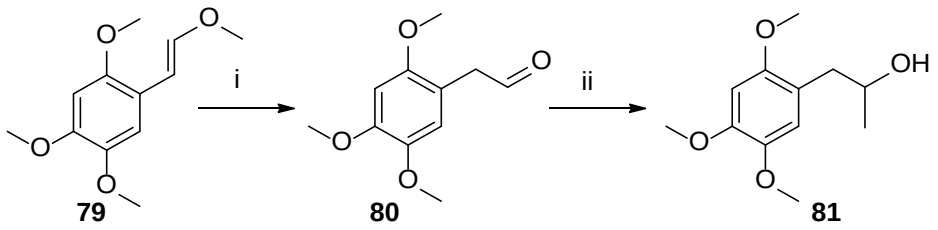
1,2,4-Trimethoxy-5-(2-methoxyvinyl)benzene **79** was obtained during the reaction between methoxymethyl triphenylphosphonium chloride and 2,4,5-trimethoxybenzaldehyde **71** in presence of n-butyllithium using anhydrous tetrahydrofuran as the solvent.[46]



Reagents and conditions: (i): methoxymethyl triphenylphosphonium chloride, n-butyllithium, anhydrous tetrahydrofuran, 65%.

Scheme 2.29

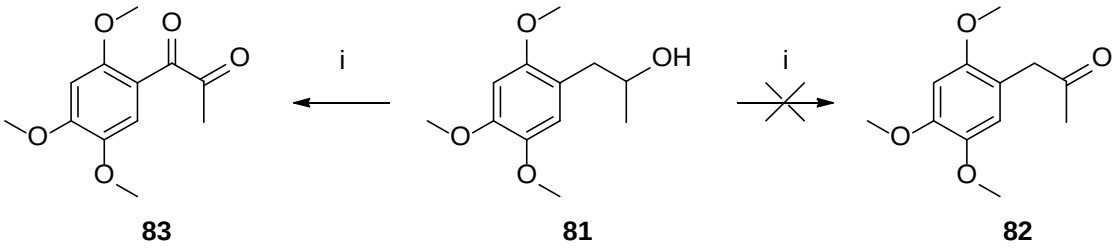
Following this, an aqueous HCl solution was added to compound **79**, which furnished the aldehyde **80** in good yield (75%).[47] The aldehyde **80** was converted to the secondary alcohol **81** by the addition of methyllithium (Scheme 2.30).[48]



Reagents and conditions: (i): aqueous HCl, tetrahydrofuran, reflux, 5 h, 75%. (ii): MeLi, anhydrous tetrahydrofuran, 0 °C, 30 min.

Scheme 2.30

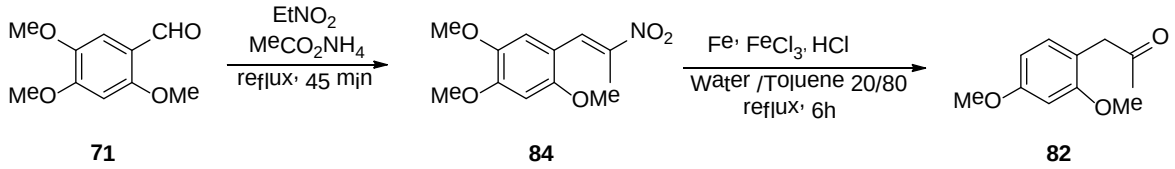
We attempted to oxidize the alcohol moiety using pyridinium chlorochromate but the reaction did not produce our target **82**.



Reagents and conditions: (i): Pyridinium chlorochromate, dichloromethane.

Scheme 2.31

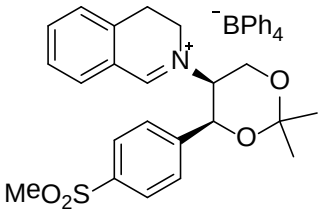
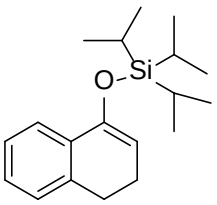
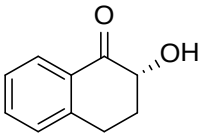
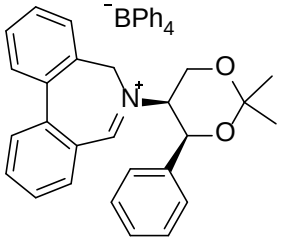
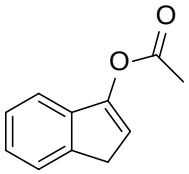
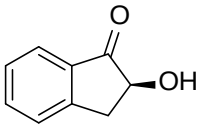
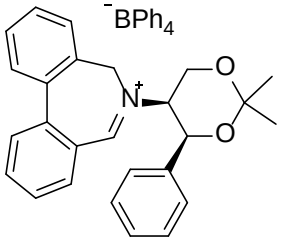
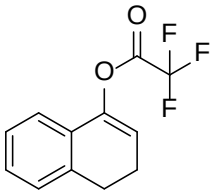
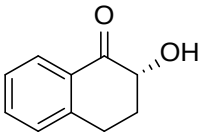
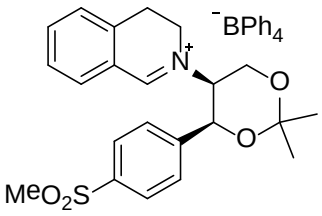
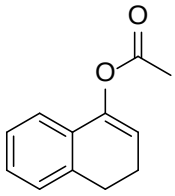
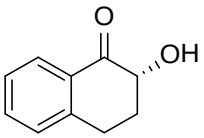
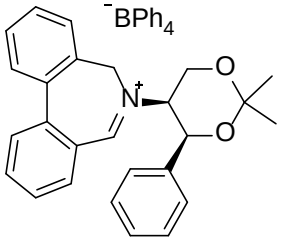
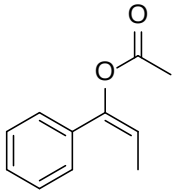
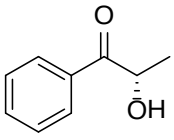
Instead, we obtained 1-(2,4,5-trimethoxyphenyl)propane-1,2-dione **83**, which means pyridinium chlorochromate oxidized both the secondary alcohol and the benzylic methylene. 1-(2,4,5-Trimethoxyphenyl)propane-1,2-dione **83** was identified by NMR spectra analysis. Analysis of the ^{1}H NMR spectrum did not exhibit signals corresponding to the methylene protons and two signals corresponding to carbonyl carbon (195 and 200 ppm, corresponding to two ketone moieties) were observed when the ^{13}C NMR spectrum was analysed. To solve this problem, we will try in future to oxidize the secondary alcohol moiety in compound **81** using the Swern oxidation. If the reaction does not work we are going to synthesize 2,4,5-Trimethoxyphenylacetone **82** in two steps from commercially available 2,4,5-trimethoxybenzaldehyde **71** (Scheme 2.32).[49]

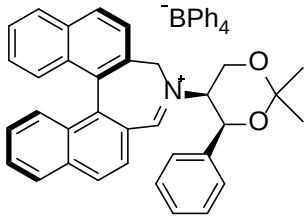
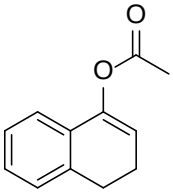
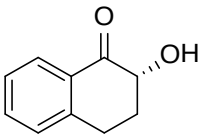
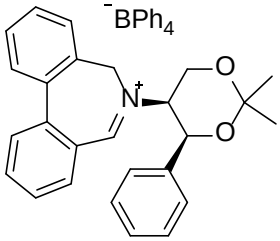
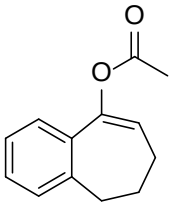
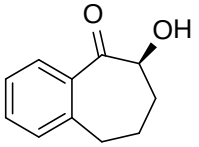
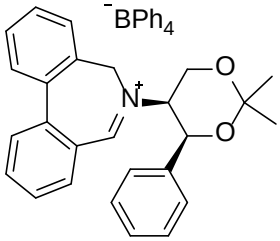
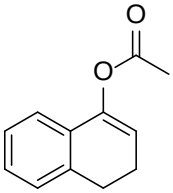
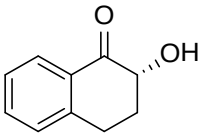
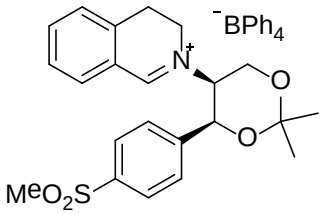
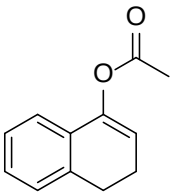
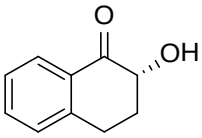
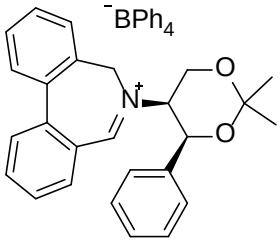
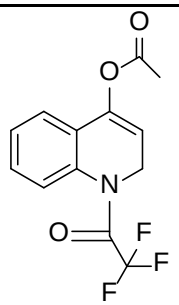
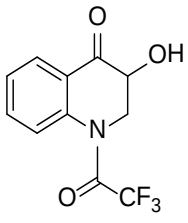
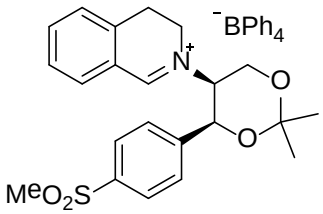
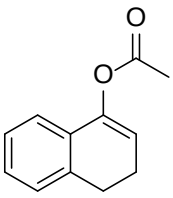
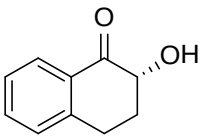


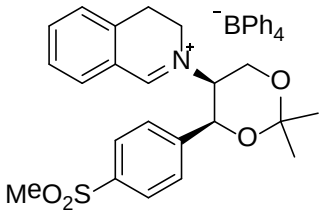
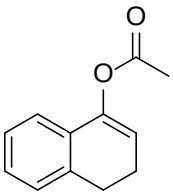
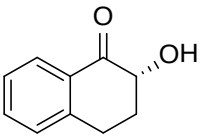
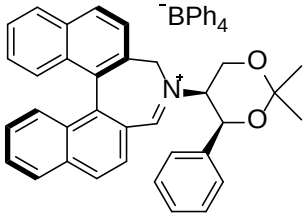
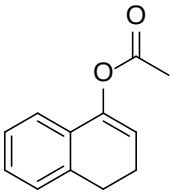
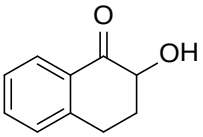
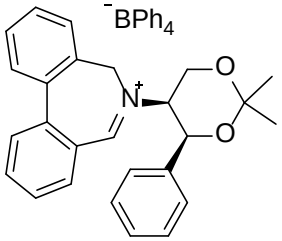
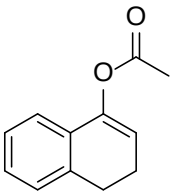
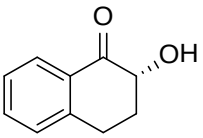
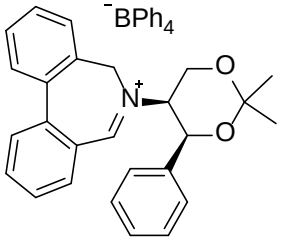
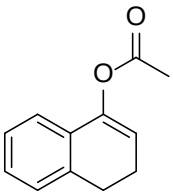
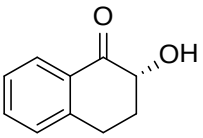
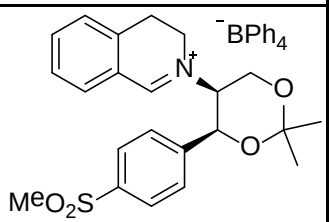
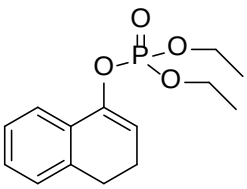
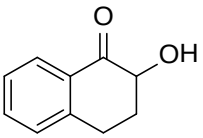
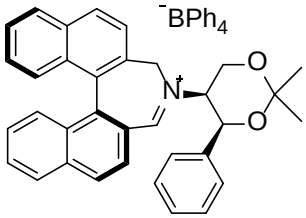
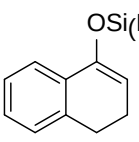
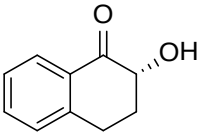
71 **84** **82**

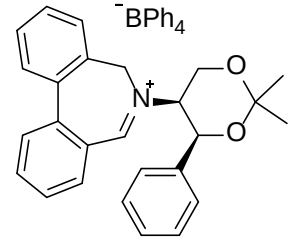
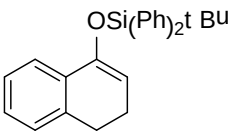
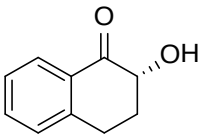
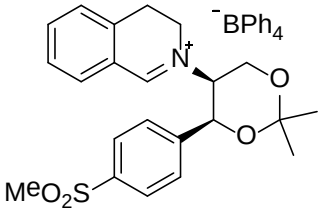
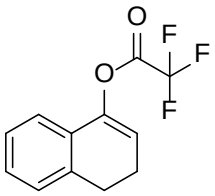
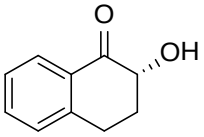
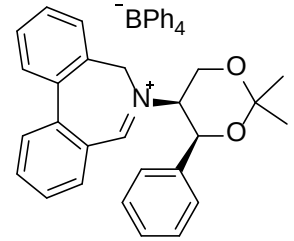
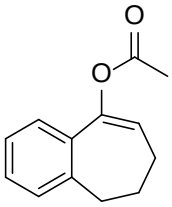
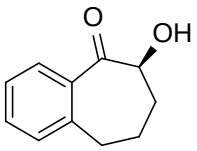
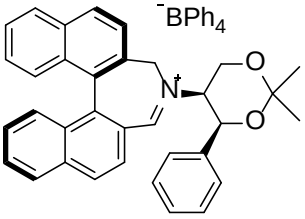
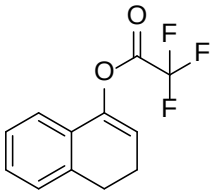
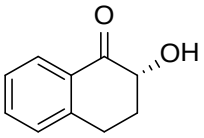
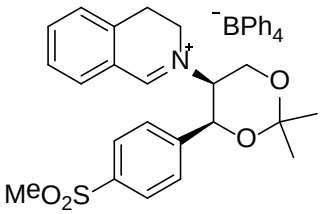
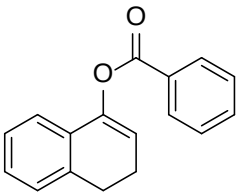
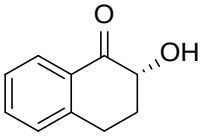
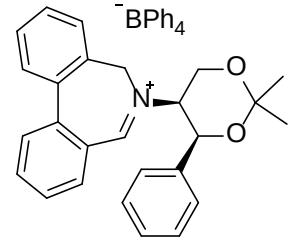
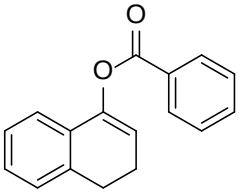
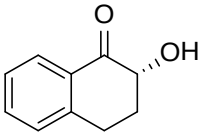
Scheme 2.32: Synthesis of 2,4,5-Trimethoxyphenylacetone **82.**

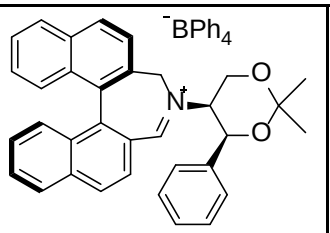
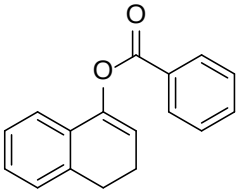
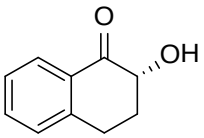
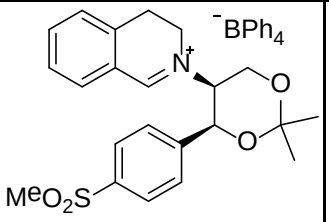
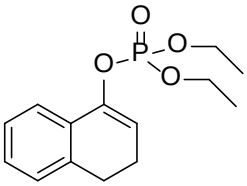
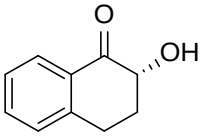
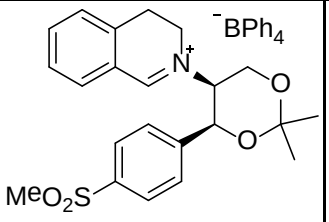
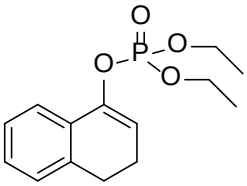
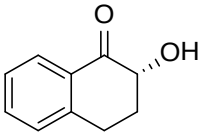
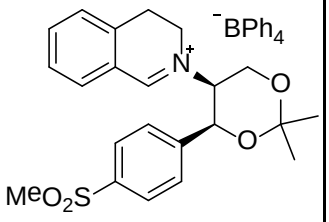
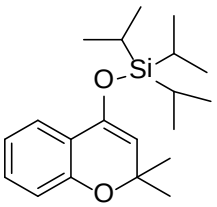
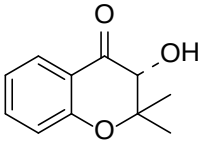
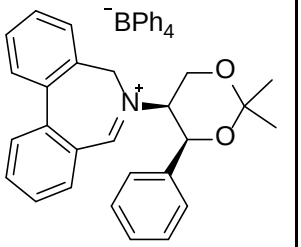
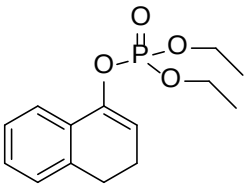
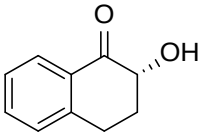
2.4 Summary of the results

Catalyst (10 mol%)	Enol	Temp (°C)	Time (h)	Solvent	Product	Conversion (%)	ee (%)	Abs conf. maj. enant.
		0	24	$CHCl_3$		52	35	(+)-(*R*)[20]
		-30	48	$CHCl_3$		70	80	(–)-(*S*)[27]
		0	24	$CHCl_3$		65	90	(+)-(*R*) [26]
		0	24	$CHCl_3$		62	66	(–)-(*R*)[26]
		-30	72	$CHCl_3$		95	57	(–)-(*S*)[31]

		0	48	$CHCl_3$		12	31	(+)-(*R*)[26]
		0	24	$CHCl_3$		99	87	(+)-(S)[32]
		0	48	$CHCl_3$		99	88	(+)-(*R*)[26]
		-30	24	CH_2Cl_2		62	70	(–)-(*R*)[26]
		-30	72	$CHCl_3$		65	70	(–)
		-30	24	MeCN		70	67	(–)-(*R*)[26]

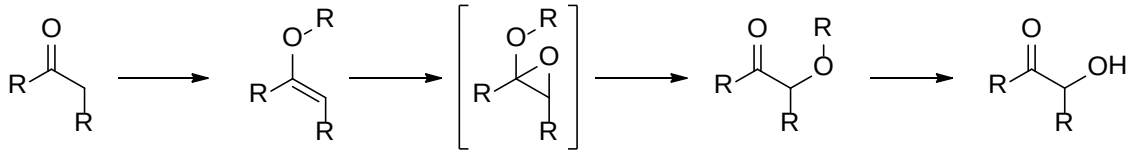
		-30	24	$CHCl_3$		42	72	(–)-(*R*)[26]
		-30	48	$CHCl_3$		5	-	-
		-30	48	$CHCl_3$		95	97	(+)-(*R*)[26]
		-45	48	$CHCl_3$		95	98	(+)-(*R*)[26]
		-50	72	$CHCl_3$		-	-	-
		0	24	$CHCl_3$		95	50	(+)-(*R*)[20]

		0	24	$CHCl_3$		91	52	(+)-(*R*)[20]
		0	24	$CHCl_3$		23	54	(–)-(*R*)[26]
		-30	48	$CHCl_3$		95	92	(+)-(S)[32]
		0	24	$CHCl_3$		63	43	(+)-(*R*)[26]
		0	24	$CHCl_3$		23	54	(–)-(*R*)[27]
		0	24	$CHCl_3$		35	89	(+)-(*R*)[27]

		0	24	$CHCl_3$		33	43	(+)-(*R*)[27]
		0	48	$CHCl_3$		45	25	(−)-(*R*)[29]
		-30	48	$CHCl_3$		22	35	(−)-(*R*)[29]
		0	24	$CHCl_3$		100	36	(+)
		-35	72	$CHCl_3$		45	90	(+)-(*R*)[27]

2.5 Conclusion and future work

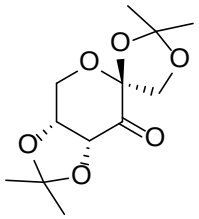
At the first of this work, we challenged ourselves to prepare a number of enantiomerically enriched α-hydroxy carbonyls by epoxidation of enol ethers and esters (Scheme 2.30).



Scheme 2.30

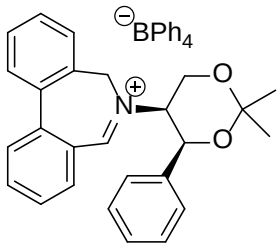
We believed we achieved that goal by using 6-((4S,5S)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-5H-dibenzo[c,e]azepin-6-ium catalyst **7**, with acetate enol esters **15, 17, 19, 21** and **23**. From our research, it is clear that acetate enol esters provided high enantioselectivity (up to

98% ee) and achieved high conversions up to 99%. Our results are good comparing with some results in the literature. For example Shi reported good enantioselective epoxidation method for enol esters using fructose derived ketone **17** as catalyst and Oxone as oxidant. Shi produced hydroxy ketones up to 91% ee and 66% conversions.[49]



17

In our method, the enantioselectivity of the reaction was influenced by a variety of reaction conditions, especially temperature, solvent, the structure of the iminium salt catalyst and the structure of the substrates. The best solvent was chloroform. It was found that lowering the reaction temperature increases the enantiomeric purity of the products. Catalyst (**7**) is one of the most active iminium salt catalysts that we have tested. It is also one of the most enantioselective iminium salt epoxidation catalysts ever reported.



catalyst 7

In future, because of our encouraging results, it could be possible to generate different natural products with our methodology for the epoxidation of enols.

2.6 References

1. Page, P. C. B.; Rassias, G. A.; Bethell, D.; Schilling, M. B. *J. Org. Chem.* **1998**, 63, 2774.

2. Page, P. C. B.; Rassias, G. A.; Barros, D.; Bethell, D.; Schilling, M. B. *J. Chem. Soc. Perkin Trans. 1*, **2000**, 3325.

3. Page, P. C. B.; Buckley, B. R.; Farah, M.; Blacker, A. J. *J. Org. Chem.* **2009**, 3413.

4. Page, P. C. B.; Farah, M. M.; Buckley, B. R.; Blacker, A. J. *J. Org. Chem.* **2007**, 72, 4424.

5. Page, P. C. B.; Rassias, G. A.; Barros, D.; Ardakani, A.; Bethell, D.; Merrifield, E. *Synlett*, **2002**, 4, 580.

6. Page, P. C. B.; Barros, D.; Ardakani, A.; Buckley, B.; Marples, B. A. *J. Org. Chem*. **2004**, 69, 3595.

7. Page, P. C. B.; Buckley, B. R.; Barros, D.; Blacker, A. J,; Heaney, H,; Marples, B. A. *Tetrahedron*, **2006**, 62, 6607.

8. Page, P. C. B.; Buckley, B. R.; Rassias, G. A.; Blacker, A. J, Eur. *J. Org. Chem*. **2006**, 803.

9. Page, P. C. B.; Buckley, B. R.; Blacker, A. *J. Org. Lett*. **2004**, 6, 1543.

10. Page, P. C. B.; Buckley, B. R.; Heaney, H.; Blacker, A. *J. Org. Lett*. **2005**, 7, 375.

11. Arribas, I.; Rubio, M.; Kleman, P.; Pizzano, A. *J. Org. Chem*. **2013**, 78, 3997.

12. Yuesi, F.; Donald C.; Richard, C.; Feng Shi, *J. Org. Chem.* **2012**, 77, 6262−6270.

13. Rieche, A.; Schmitz, E. *Chem. Ber*. **1956**, 89, 1254.

14. Nordin, I. C.; Thomas, J. A. *Tetrahedron Lett*. **1988**, 29, 5177.

15. Lygo, B. L.; Davison, C.; Evans, T.; Gilks, J. A. R.; Leonard, J.; Roy, C. E. *Tetrahedron*, **2011**, 67, 10164

16. Sengupta, S.; Leite, M.; Rasian, D. S.; Quesnelle, C.; Nieckus, V. *J. Org. Chem*. **1992**, 57, 4066;

17. Mecca, T.; Superchi, S.; Giorgio, E.; Rosini, C. *Tetrahedron: Asymmetry* **2001**, 12, 1225.

18. Campestrini, S.; Di Furia, F.; Labat, G.; Novello, F. *J. Chem. Soc., Perkin Trans. 2*, **1994**, 2175.

19. Jin, Y.; Chen, W.; Corey, E. *J. Org. Lett.* **2005**.

20. Kilian, M.; Claas, H¨ovelmann, H.; Amparo, V.; Rub´en, V.; Jan, S. *J. Molecular Catalysis* **2006**.

21. Mingyan, Z.; Myung, H.; Sanghee, L.; Su, J.; Seong, H,; Seung, B, *J. Med. Chem.* **2010**, 53, 8760.

22. Herbert, L.; Holland, J.; T, S. *J. Chem.* 1399-1405 **1995**.

23. Sang, L.; Nicholas, H.; Myers, G. *J. Am. Chem. Soc*. **2009**, 131, 5763-5765.

24. Bedoukian, P.; Synthesis of bromoketones. *J. Am. Chem. Soc*. **1945**; 67-1430–1431.

25. House, HO.; Gall, M.; Olinstead, H.; The chemistry of carbanions XIX. The alkylation of enolates from unsaturated ketones. *J. Org. Chem*. **1971**. 36. 2361.

26. Davis, F. A.; Sheppard, A. C.; Chen, B. C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, 112, 6679–6690.

27. Davis, A.; Clark, C.; Kumar, A.; Chen, C. *J. Org. Chem.* **1994**, 1184.

28. Hayashi, T.; Fujiwa, T.; Okamoto, Y.; Katsuro, Y; Kumada, M. *Synthesis* **1981**.

29. Jeffrey, M.; Yeh, C.; Jerina, M.; Patel, R.; Davey, E.; Gibson, T.; *Biochemistry*, **1975**, 14, 575.

30. Yuanming, Z.; Lianhe, S.; Yong T.; Yian Shi, *J. Org. Chem*. **2001**, 66, 1818-1826.

31. Honda, Y.; Ori, A.; Tsuchihashi, G. Bull. *Chem. Soc. Jpn.* **1987**, 60, 1027.

32. Akira, Y.; Yuqin, L.; Kazuhiro, Y. E. *J. Org. Chem*. **2016**, 5355–5359.

33. Hoye, R.; Jeffrey S.; Shao, F. M. *Nat. Protoc*. **2007**, 2(10), 2451–2458.

34. Schmidt, R. G.; Bayburt, E. K.; Latshaw, S. P.; Koenig, J. R.; Daanen, J. F.; McDonald, H. A.; Bianchi, B. R.; Zhong, C.; Joshi, S.; Honore, P.; Marsh, K. C.; Lee, C.-H.; Faltynek, C. R.; Gomtsyan, A. Bioorg. *Med. Chem. Lett*. **2011**, 21, 1338.

35. Yuesi, F.; Donald, C.; Rogness, R. C.; Larock, S. *J. Org. Chem.* **2012**, 77, 6262−6270.

36. Uldam, H.; Henriette, K.; Thygesen, M. B. From *PCT Int. Appl*, **2009**.

37. Tong, X. G.; Wu, G. S.; Huang, C. G.; Lu, Q.; Wang, Y. H.; Long, C. L.; Luo, H. R.; Zhu, H. J.; Cheng, Y. X. *J. Nat. Prod.* **2010**, 73, 1160–1163.

38. Liao, W. E.; Chen, L.; Yi, Y. H.; Sun, W. W.; Gao, M. M.; Su, T.; Yang, S. Q. *Epilepsia* **2005**, 46, 24.

39. Wittig, G.; Schoch, W.; *Justus. L. Ann. Chem.* **1971** 749.

40. Okada, H.; Mori, T.; Saikawa, Y.; Nakata, M. *Tetrahedron Lett.* **2009**, 50, 1276–1278.

41. Lin, Y.-L.; Wu, C.-S.; Lin, S.-W.; Huang, J.-L.; Sun, Y.-S.; Yand, D.-Y. *Bioorg. Med. Chem.* **2002**, 10, 685–690.

42. (a) Kerr, M.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem*. **2005**, 70, 5725–5728; (b)Vora, H. U.; Lathrop, S. P.; Reynolds, N. T.; Kerr, M.; Readdealaniz, J.; Rovis, T. *Org. Synth*. **2010**, 87, 350–357.

43. (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jorgensen, K. A. Angew. *Chem., Int. Ed*. **2005**, 44, 794–797; (b) Ostendorf, M.; Dijkink, J.; Rutjes, F. P. J. T.; Hiemstra, H. Eur. *J. Org. Chem*. **2000**, 115–124; (c) Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett*. **2008**, 10, 277–280.

44. Arbuzov, J.; Russ, P. *Chem. Soc*. **1906**, 687.

45. Schauer, D. J.; Helquist, P, *Synthesis*, **2006**, 3654-3660.

46. Deepak, B.; Ghorpade, S.; Liu, R. *J. Eur. Chem.* **2013**, 12965.

47. Blakemore, P. R.; Marsden, S. P.; Vater, H. D. *J. Org. Lett*. **2006**, 8,773-776.

48. Yuanming, Z.; Yong, T.; Hongwu, Y.; Shi, Y. *Tetrahedron Lett*. **1998**, 39, 7819.

49. Anne, N.; Melanie, M.; Claire, M.; Annis, M.; Una, M.; George, A.; Martine, L. *Chem. Res. Toxicol.* **2011**, 24, 968–978.

CHAPTER 3
EXPERIMENTAL PROCEDURES

3.0 Experimental

3.1 General experimental details

3.1.1 Physical Characterisation and Spectroscopic Techniques

Infrared spectra were acquired using a Perkin Elmer System 2000 FT-IR spectrophotometer. Solid samples were run as nujol mulls or as thin films of their solution in dichloromethane on sodium chloride plates. Liquid samples were run neat.

^{1}H and ^{13}C NMR spectra were measured respectively at 400.13 and 100.62 MHz using Varian Unity Plus (400 MHz) spectrometer, at 300.05 and 75.45 MHz using a Varian Gemini 200 (300 MHz) instrument, at 400.13 and 100.03 MHz using a 400 MHz Bruker Avance III 2 channel nanobay NMR spectrometer, or at 500.21 and 125.05 MHz using a Bruker Avance III 500 MHz NMR spectrometer. Multiplicities in the NMR spectra are described as: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets t = triplet, td = triplet of doublets, q = quartet, sept. = septet, m = multiplet, br = broad; coupling constants are reported in Hz. The solvent used for NMR spectroscopy was deuteriated chloroform unless stated otherwise, using the solvent peak as the reference. Chemical shifts are given in parts per million (ppm) and *J* values are given in Hertz (Hz).

High resolution mass spectra were obtained from the EPSRC Mass Spectrometry Service at the University of Swansea. Melting points were recorded using a Büchi B- 545 melting point instrument and are reported uncorrected. Optical rotation values were measured with a Bellingham and Stanley ADP-440 instrument, operating at λ=589 nm, corresponding to

the sodium D line at the temperatures indicated. The solvents used for these measurements were of spectrophotometric grade. The solutions for these measurements were prepared in volumetric flasks for maximum accuracy of the volume of solvent used.

Enantiomeric excesses were determined by chiral high performance liquid chromatography. HPLC samples were prepared by using silica gel preparative TLC plates. Data was recorded using a Hitachi Elite LaChrom instrument fitted with a L2400 UV detector (256 nm unless stated otherwise), L2300 column oven, L2200 autosampler, L2130 pump. Chiral HPLC traces were run using two different chiral stationary phase columns: XD 6 Eurocel 01, 5μm,(derivatized cellulose poysaccharide) and Chiracel OD-H 5μm (Cellulose tris 3,5-dimethylphenylcarbamate coated on 5μm silica-gel).[1,2] All HPLC samples were run using a mixture of hexane and isopropanol as the eluent.

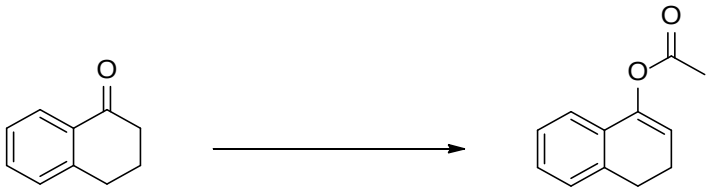
All the starting materials and reagents were bought from Alfa Aesar and Sigma Aldrich. Et_2O and THF were dried over sodium and benzophenone and distilled; toluene was dried over sodium wire and distilled.

3.2 Individual experiments

3.2.1 General procedure for the synthesis of acetate enol esters:[3]

The ketone, isopropenyl acetate (100 mL) and *p*-toluenesulfonic acid monohydrate (0.1 equiv) were placed in round bottomed flask fitted with a Dean-Stark apparatus. The mixture was heated overnight to remove acetone continuously. The mixture was poured into a two-layer solution of aqueous saturated $NaHCO_3$ (50 mL) and diethyl ether (100 mL). The organic phase was separated and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined ethereal solutions were washed with aqueous saturated $NaHCO_3$ and aqueous saturated NaCl, dried over anhydrous $MgSO_4$, filtered and the solvents were removed under reduced pressure. The corresponding enol acetate was isolated by column chromatography on silica gel (eluent: hexanes/ethyl acetate 5:1) to give the desired compound.

3.2.1.1 3,4-Dihydronaphth-1-yl acetate:[4]

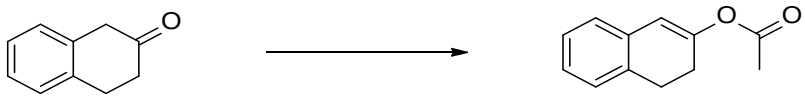


Prepared according to the general procedure for the synthesis of acetate enol esters using 1-tetralone (2.5 g, 17 mmol), isopropenyl acetate (100 mL) and *p*-toluenesulfonic acid monohydrate (0.3 g, 0.1 equiv., 1.7 mmol) to give the desired product as a colorless oil (2.4 g, 75%). ν_{max} (film)/cm^{-1} 3100, 2900, 1740, 1650, 1570, 1200; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.10 (m, 4H), 5.73 (t, J = 4.7 Hz, 1H), 2.89 (t, J = 8.1 Hz, 2H), 2.53 – 2.43 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 145.6, 136.3, 130.1, 128.6, 127.8, 126.2, 120.4, 115.1, 26.9, 23.4, 20.3.

3.2.1.2 6,7-Dihydro-5H-benzo[7]annulen-9-yl acetate:[5]

Prepared according to the general procedure for the synthesis of acetate enol esters using 1-benzosuberone (2.5 g, 15 mmol), isopropenyl acetate (100 mL) and *p*-toluenesulfonic acid monohydrate (0.26 g, 0.1 equiv., 1.5 mmol) to give the desired product as a colorless oil (3.0 g, 95%). ν_{max} (film) /cm^{-1}: 2930, 2858, 1755; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 6.3 Hz, 1H), 7.32 – 7.25 (m, 3H), 5.91 (t, *J* = 6.2 Hz, 1H), 2.92 (t, *J* = 1.7 Hz, 2H), 2.24 (s, 3H), 2.23 – 2.19 (m, 2H), 2.16 – 2.10 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 146.0, 141.9, 134.6, 129.2, 128.2, 126.1, 125.5, 119.7, 33.8, 31.3, 25.4, 20.9.

3.2.1.3 3,4-Dihydronaphthalen-2-yl acetate:[6]

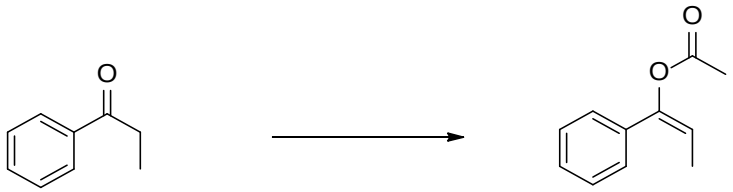


Prepared according to the general procedure for the synthesis of acetate enol esters using 2-tetralone (2.5 g, 17 mmol), isopropenyl acetate (100 mL) and *p*-toluenesulfonic acid monohydrate (0.3 g, 0.1 equiv., 1.7 mmol) to give the desired product as a colourless oil (2.3 g, 71%). ν_{max} (film) /cm^{-1}: 3018, 2800, 1759; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 – 7.12 (m, 3H), 7.04 (d, *J* = 6.6 Hz, 1H), 6.25 (s,1H), 3.03 (t, *J* = 8.3 Hz, 2H), 2.55 (t, *J* = 8.3 Hz, 2H), 2.23 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 150.9, 133.2, 127.2, 126.8, 126.6, 126.5, 126.3, 114.7, 28.5, 26.3, 21.1.

3.2.1.4 1H-Inden-3-yl acetate:[7]

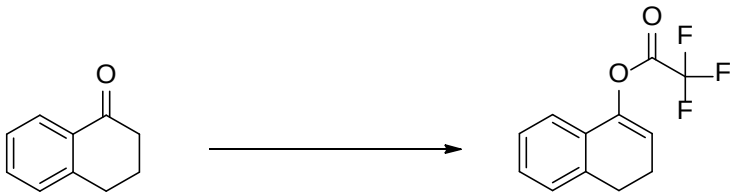
Prepared according to the general procedure for the synthesis of acetate enol esters using 1-indanone (2.5 g, 19 mmol), isopropenyl acetate (100 mL) and *p*-toluenesulfonic acid monohydrate (0.3 g, 0.1 equiv., 1.9 mmol) to give the desired product as a yellow oil (2.66 g, 80%). ν_{max} (film)/cm^{-1}: 2991, 1700, 1450, 1200; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 6.5 Hz, 1H), 7.44 – 7.30 (m, 3H), 6.42 (t, *J* = 2.3 Hz, 1H), 3.47 (d, *J* = 2.4 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 149.1, 141.8, 139.1, 126.3, 125.7, 124.1, 118.1, 115.5, 35.0, 21.1.

3.2.1.5 1-Phenylprop-1-enyl acetate: [8]



Prepared according to the general procedure for the synthesis of acetate enol esters using propiophenone (2.5 g, 18 mmol), isopropenyl acetate (100 mL) and *p*-toluenesulfonic acid monohydrate (0.3 g, 0.1 equiv., 1.8 mmol) to give the desired product as a yellow oil (2.4 g, 73%). ν_{max} (film) /cm^{-1}: 3000, 1696, 1500; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.31 (m, 5H), 7.31 – 7.29 (m, 0.5H), 5.93 (q, *J* = 7.0 Hz, 1H), 5.57 (q, *J* = 7.4 Hz, 0.1H), 2.34 (s,3H), 2.18 (s, 0.3H), 1.85 (d, *J* = 7.4 Hz, 0.3H), 1.75 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 146.9, 146.2, 128.4, 128.0, 124.2, 112.6, 20.6, 11.5.

3.2.1.6 3,4-Dihydronaphthalen-1-yl 2,2,2-trifluoroacetate:[9]

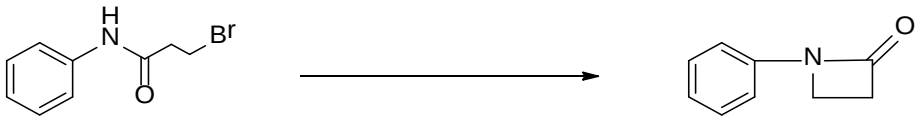


Prepared according to the general procedure for the synthesis of acetate enol esters using 1-tetralone (1:0 g, 6.8 mmol), trifluoroacetic anhydride (50 mL) and *p*-toluenesulfonic acid monohydrate (0.1 g, 0.1 equiv, 0.6 mmol) to give the desired product as a yellow oil (1.5 g, 91%). ν_{max} (film) /cm^{-1}; 2944, 2838, 1700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.20 (m, 3H), 7.13 (d, *J* = 6.7 Hz, 1H), 5.96 (t, *J* = 4.7 Hz, 1H), 2.93 (t, *J* = 8.2 Hz, 2H), 2.57 – 2.50 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.8, 136.3, 128.7, 128.6, 127.8, 126.7, 120.3, 115.1 (q, CF_3, *J* = 298 Hz), 30.9, 27.1, 21.9;

3.2.2 3-Bromo-*N*-phenylpropanamide:[10, 11]

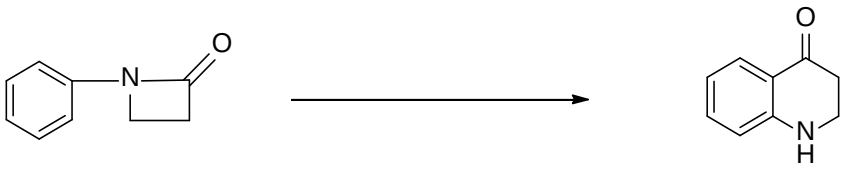
Aniline (1.8 mL, 20 mmol) and K_2CO_3 (3.3 g, 24 mmol) were suspended in CH_2Cl_2 (20 mL) at 0 °C. 3-Bromopropanoyl chloride (2.5 mL, 24 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 minutes and allowed to reach room temperature for another 3 h. The reaction was quenched with water and extracted with EtOAc three times. The combined organic layers were evaporated under reduced pressure, and the residue was recrystallized from a mixture of petroleum ether/EtOAc in a 1:1 ratio to afford 3-bromo-N-phenylpropanamide as colourless crystals (2.8g, 63%). mp 120 °C; ν_{max} (film)/cm^{-1}: 3200, 3000, 1657; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.9 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 3.75 (t, *J* = 6.6 Hz, 2H), 2.98 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 137.4, 129.0, 124.7, 120.3, 40.5, 27.1.

3.2.3 1- Phenylazetidin-2-one:[10, 11]



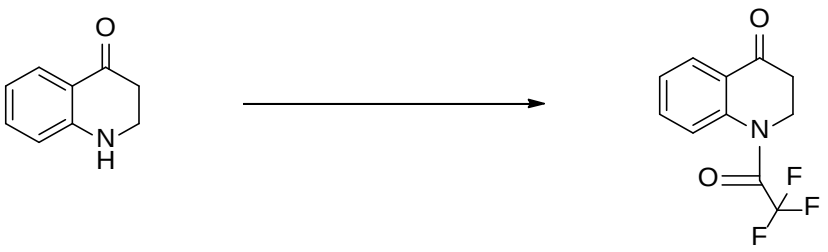
3-Bromo-N-phenylpropanamide (2.8 g, 12.2 mmol) was dissolved in dimethylformamide and the reaction was cooled to 0 °C. Sodium tert-butoxide (1.28 g, 13.0 mmol) was added in one portion, and the mixture was allowed to reach room temperature gradually. The reaction was quenched with water after 3 h and extracted with EtOAc. The combined organic layers were evaporated under reduced pressure, and the residue was recrystallized from a hot mixture of petroleum ether/EtOAc in a 1:1 ratio to afford 1- phenylazetidin-2-one as a colourless solid (1 g, 55%). mp 80 °C [Lit.[11] mp 78-80 °C]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.07 (m, 5H), 3.63 (t, *J* = 4.5 Hz, 2H), 3.11 (t, *J* = 4.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.5, 138.5, 129.1, 123.8, 116.1, 38.0, 36.0.

3.2.4 2,3-Dihydroquinolin-4(1H)-one:[12]



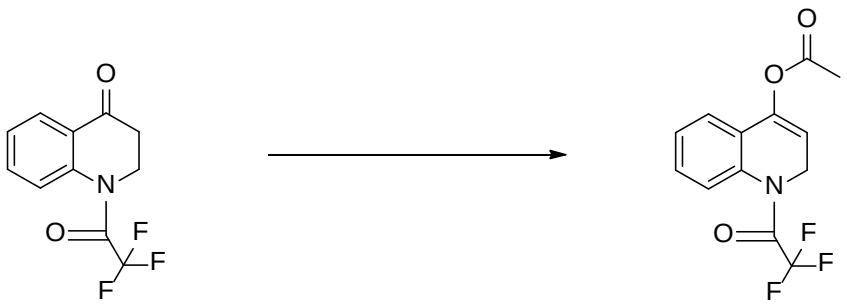
1-phenylazetidin-2-one (0.82 g, 5.5 mmol) was dissolved in 1,2-dichloroethane (30 mL) and the solution was cooled to 0 °C. Trifluoromethanesulfonic acid (0.83 g, 5.5 mmol) was added dropwise to the stirred solution at 0 °C. The mixture was allowed to reach room temperature and stirred for 15 minutes. Water (30 mL) was added and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the desired product as colourless oil (0.7 g, 86%). ν_{max} (film)/cm^{-1}: 3300, 2900, 1655; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.36 – 7.30 (m, 1H), 6.80 – 6.75 (m, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 3.62 (t, *J* = 4.6 Hz, 2H), 2.74 (t, *J* = 4.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.2, 152.4, 135.2, 127.4, 118.9, 117.5, 116.1, 42.0, 38.0.

3.2.5 1-(2,2,2-Trifluoroacetyl)-2,3-dihydroquinolin-4(1H)-one:[13]



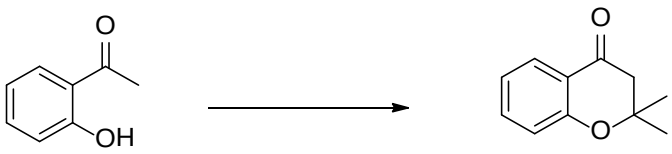
2,3-Dihydroquinolin-4(1H)-one (1.0 g, 6.8 mmol) was dissolved in dichloromethane (30 mL). Triethylamine (2.1 g, 20.7 mmol) was added and the mixture was stirred for 10 min and cooled to 0 °C. Trifluoroacetic anhydride (3.0 g, 14.2 mmol) was added dropwise and the mixture was allowed to reach room temperature. The reaction mixture was stirred for 4 h at room temperature and water (50 mL) was added. The organic phase was removed and the aqueous phase was extracted with dichloromethane (100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 1-(2,2,2-trifluoroacetyl)-2,3-dihydroquinolin-4(1H)-one as colourless liquid (1.3 g, 78%). ν_{max} (film)/cm^{-1}: 3076, 1690, 1600, 1480, 1202; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 9.0 Hz, 1H), 7.68 (s, 1H), 7.52 – 7.45 (m, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 4.11 (t, *J* = 6.0 Hz, 2H), 2.78 – 2.75 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.4, 127.8, 127.1, 126.4, 115.1 (q, CF_3, *J* = 288 Hz), 46.5, 45.6, 45.5, 39.2, 14.4, 10.5.

3.2.6 1-(2,2,2-Trifluoroacetyl)-1,2-dihydroquinolin-4-yl acetate:



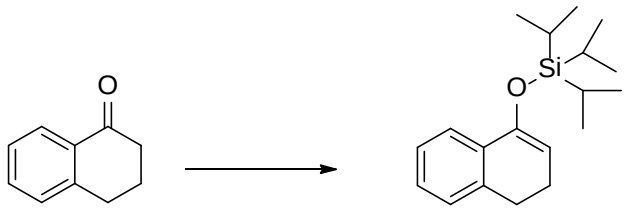
Following the general procedure for the synthesis of acetate enol esters using 1-(2,2,2-trifluoroacetyl)-2,3-dihydroquinolin-4(1H)-one (2.5 g, 10 mmol), isopropenyl acetate (100 mL) and *p*-toluenesulfonic acid monohydrate (0.2 g, 0.1 equiv., 1.1 mmol) to give the desired product as yellow oil (1.2 g, 41%). ν_{max} (film) /cm^{-1}; 3000, 1755, 1702, 1600, 1484, 1269, 1209; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.73 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.63 – 7.56 (m, 1H), 7.39 – 7.32 (m, 1H), 5.44 (dd, *J* = 9.6, 4.4 Hz, 1H), 4.35 (dd, *J* = 13.7, 4.4 Hz, 1H), 4.14 (dd, *J* = 13.8, 9.6 Hz, 1H), 2.13 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.2, 169.3, 141.4, 135.1, 128.5, 127.4, 125.1, 124.1, 117.3, 115.1 (q, CF_3, *J* = 288 Hz), 70.7, 48.9, 20.4. *m/z*: $[M+H]^+$: 286.0685; [$C_{13}H_{10}F_3NO_3$+H] requires 286.0686.

3.2.7 2,2-Dimethylchroman-4-one:[14]



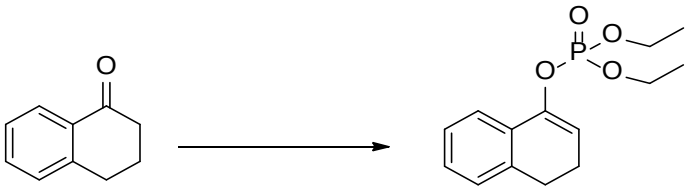
Hydroxyacetophenone (4 g, 29.4 mmol) was dissolved in EtOH (50 mL). Pyrrolidine (4.1 g, 57.7 mmol) and acetone (17 mL) were added sequentially and the reaction mixture was heated under reflux for 12 h. After the completion of the reaction was observed by TLC, the reaction mixture was concentrated *in vacuo*. The residue was re-dissolved in dichloromethane and washed several times with 1M HCl solution. After washing with brine, the combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel using n-pentane/ethylactate (6:1) to afford the desired product as colorless crystal (4.5 g, 86%). ν_{max} (film)/cm^{-1}: 3000, 1768, 1208; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.52 – 7.47 (m, 1H), 7.00 (td, *J* = 7.6, 1.0 Hz, 1H), 6.95 (dd, *J* = 8.4, 0.6 Hz, 1H), 2.75 (s, 2H), 1.49 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.5, 159.9, 136.1, 126.5, 120.6, 120.2, 118.3, 79.1, 48.9, 26.6.

3.2.8 (3,4-Dihydronaphthalen-1-yl)oxy)triisopropylsilane:[15]



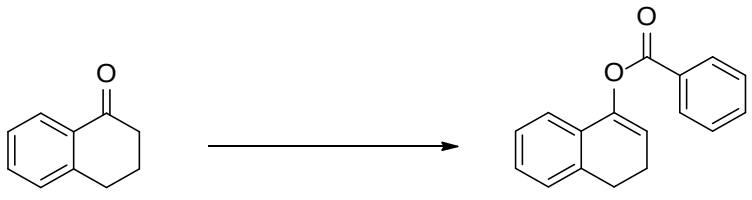
The ketone (1.45 g, 5 mmol) and triethylamine (2.09 ml, 9.0 mmol) were dissolved in dichloromethane (15 ml). Triisopropylsilyl triflate (4 ml, 6.0 mmol) was added and the reaction mixture stirred overnight. The ether solution was concentrated under reduced pressure and the residue purified using basic alumina column chromatography using hexane as the eluent to give the desired compound as yellow oil (1.20 g, 40%). ν_{max} (film) /cm^{-1}: 2943, 2860, 1640, 1256,; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 6.3 Hz, 1H), 7.25 – 7.11 (m, 3H), 5.19 (t, *J* = 4.7 Hz, 1H), 2.82 – 2.73 (t, *J* = 8.2 Hz, 2H), 2.37 – 2.27 (m, 2H), 1.36 – 1.26 (m, 3H), 1.16 (d, *J* = 7.2 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4, 137.1, 133.7, 127.1, 126.8, 126.1, 121.9, 103.8, 28.2, 22.2, 18.1, 12.8.

3.2.9 3,4-Dihydronaphthalen-1-yl diethylphosphinate:[16]



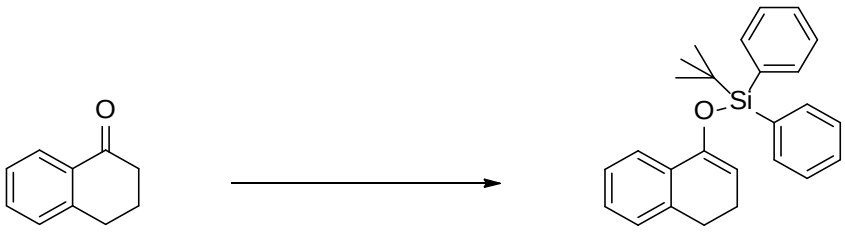
Diisopropylamine (2.94 ml, 21 mmol) was dissolved in anhydrous THF (50 ml) and the solution was cooled to –78 °C. *n*-BuLi (8.4 ml, 21 mmol, 2.5 M in hexane) was slowly added. α-Tetralone (2.68 g, 20 mmol) was dissolved in anhydrous THF (10 ml) at –78 °C and the LDA solution was added. The mixture was stirred under an argon atmosphere for 1 h at –78 °C. Diethylphosphorochloridate (5.1 g, 30 mmol) was dissolved in anhydrous THF (5 ml) and the solution was added dropwise to the reaction mixture. The mixture was allowed to reach room temperature and stirred for 1 h at ambient temperature. The solvents were removed under reduce pressure, the residue was dissolved in diethyl ether (100 mL), and washed with saturated NH_4Cl (50 mL), and water (50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvents removed under reduced pressure. The residue was purified using silica gel column chromatography using petroleum ether-EtOAc (5:1 v/v) as the eluent to give the desired enol phosphate as a yellow oil (2.93 g, 69%). ν_{max} (film) /cm^{-1}: 3000, 1240, 1600; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 6.2 Hz, 1H), 7.25 – 7.13 (m, 3H), 5.91 (t, *J* = 4.7 Hz, 1H), 4.28 – 4.19 (m, 4H), 2.83 (t, *J* = 8.1 Hz, 2H), 2.47 – 2.40 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.4, 137.0, 131.2, 128.3, 127.6, 126.8, 121.9, 111.5, 67.0, 65.9, 26.2, 22.1, 16.8.

3.2.10 3,4-Dihydronaphthalen-1-yl benzoate:[17]



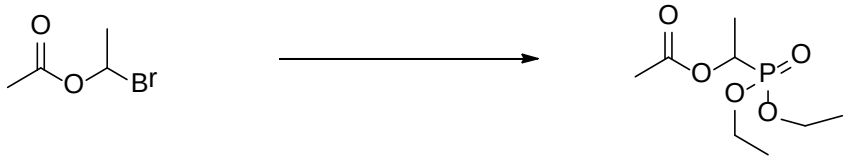
1-Tetralone (2.5 g, 17 mmol) and benzoic anhydride (3.8 g, 16 mmol) were dissolved in hexane (100 mL) and perchloric acid (0.2 mL) was added. The reaction mixture was stirred at room temperature for 2 h. The mixture was filtered to remove the solids formed. The filtrate was washed with NaOH (1N, 100 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified using silica gel column chromatography using n-pentane/ethylactate (6:2) to afford 1-benzoyloxy-1-cyclohexene as a colourless liquid (1.09 g, 26%). ν_{max} (film) /cm^{-1}: 3000, 2841, 1736, 1500; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.71 – 7.65 (m, 1H), 7.56 (t, *J* = 7.7 Hz, 2H), 7.24 – 7.15 (m, 4H), 5.88 (t, *J* = 4.7 Hz, 1H), 2.97 (t, *J* = 8.1 Hz, 2H), 2.59 – 2.52 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 145.8, 136.4, 133.5, 130.5, 130.1, 129.5, 128.6, 128.0, 127.6, 126.4, 120.8, 115.7, 27.5, 22.1.

3.2.11 *Tert*-Butyl-((3, 4-dihydronaphthalen-1-yl)oxy)diphenylsilane:[18]



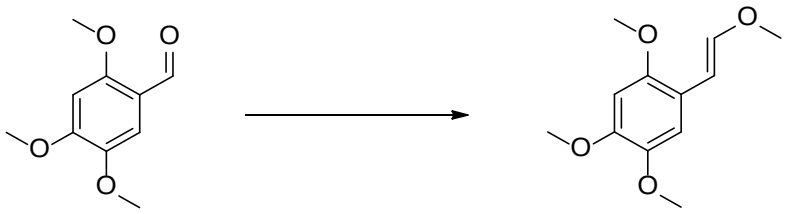
Potassium hexamethyldisilazide (0.7 g, 3.5 mmol) was dissolved in tetrahydrofuran (12 mL) and the solution as cooled to –78 °C. A-Tetralone (0.3 g, 2.0 mmol) was added dropwise by syringe. The resulting pale-brown solution was stirred for 20 min at –78 °C. *tert*-butylchlorodiphenylsilane (0.75 mL, 2.7 mmol) was added dropwise by syringe, and the reaction mixture was stirred for 5 min at –78 °C. The reaction mixture was allowed to reach room temperature and was stirred for 1 h. The solvents were removed under reduced pressure. The pale-yellow oily residue was dissolved in pentane (20 mL), the solution was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified using silica gel column chromatography (hexanes) to provide *tert*-butyl(3,4-dihydronaphthalen-1-yloxy)diphenylsilane as a colourless solid (0.35 g, 45%). mp = 64-69 °C [Lit.[18] mp 69 °C]; ν_{max} (film) /cm^{-1}: 2937, 2700, 1638, 1250, 1113; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.69 (m, 4H), 7.35 – 7.02 (m, 10H), 4.69 (t, *J* = 4.7 Hz, 1H), 2.58 (t, *J* = 7.9 Hz, 2H), 2.09 – 1.89 (m, 2H), 1.04 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.6, 135.1, 133.3, 131.3, 130.7, 127.6, 125.5, 125.2, 124.9, 124.2, 119.7, 103.6, 25.9, 24.5, 19.9, 17.4.

3.2.12 1-(Diethoxyphosphoryl)ethyl acetate:[19]



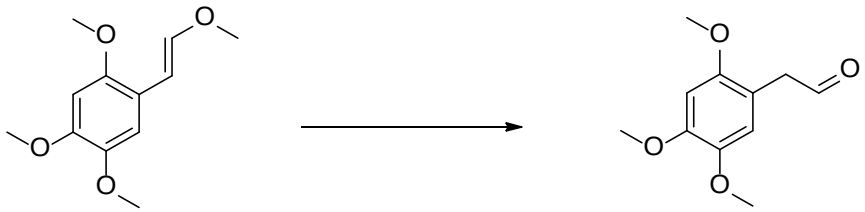
1-Bromoethyl acetate (0.66 mL, 5.9 mmol) was treated with triethylphosphite (1.30 mL) at room temperature and the resulting dark red mixture was heated to 100 °C. After 2 h, the mixture was allowed to reach room temperature and was directly loaded onto a short pad of silica gel (10 cm). The filtrate was concentrated by rotary evaporation yielding 1-(diethoxyphosphoryl)ethyl acetate as a yellow oil (0.6 g, 45%). ν_{max} (film) /cm^{-1}: 2986, 1751, 1228. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.23 (m, 1H), 4.10 (m, 4H), 2.05 (s, 3H), 1.40 (d, *J* = 7.8 Hz, 3H), 1.27 (t, *J* = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7, 62.9, 29.6, 20.9, 16.4, 15.1. ^{31}P NMR (202 MHz, $CDCl_3$) δ 21.50.

3.2.13 1,2,4-Trimethoxy-5-(2-methoxyvinyl)benzene:[19]



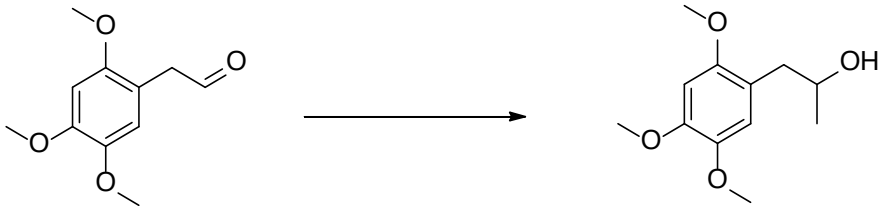
Methoxymethyl triphenylphosphonium chloride (4.39 g 12.8 mmol) was dissolved in anhydrous tetrahydrofuran (34 mL) and n-butyllithium (5.14 mL, 2.5 M in hexane, 19.2 mmol) was added at 0 °C. After 30 min, 2,4,5-trimethoxybenzaldehyde (2.00 g, 10.2 mmol) was dissolved in anhydrous tetrahydrofuran (10 mL) and the resulting solution was added to the reaction mixture. The mixture was stirred for a further 30 min. Water (30 mL) was added and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel using n-pentane/diethyl ether (5:1) to afford 1,2,4-trimethoxy-5-(2-methoxyvinyl)benzene (1.5 g, 65%). ν_{max} (film) /cm^{-1}: 2996, 1642, 1507, 1214. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.07 (d, *J* = 13.0 Hz, 1H), 6.82 (s, 1H), 6.55 (s, 1H), 6.53 (s, 1H), 6.13 (d, *J* = 7.2 Hz, 1H), 6.00 (d, *J* = 13.0 Hz, 1H), 5.60 (d, *J* = 7.2 Hz, 1H), 3.91 (s, 6H), 3.89 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 150.2, 148.4, 147.8, 147.7, 146.4, 143.3, 142.8, 117.1, 116.9, 113.5, 110.0, 100.2, 98.7, 98.3, 97.6, 60.5, 56.8, 56.6, 56.5, 56.4, 56.3, 56.2, 56.0. *m/z*: $[M+H]^+$: 225.1122; [$C_{12}H_6O_4$+H] requires 225.1121.

3.2.14 2-(2,4,5-Trimethoxyphenyl)acetaldehyde:[20]



1,2,4-Trimethoxy-5-(2-methoxyvinyl)benzene (0.25 g, 1.1 mmol) was dissolved in tetrahydrofuran (20 mL) and an aqueous HCl solution (3M, 1.8 mL) was added. The mixture was heated under reflux for 5 h, and quenched with saturated aqueous Na_2CO_3. The aqueous layer was extracted with EtOAc, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by a silica gel column chromatography using EtOAc/hexanes (2:3) to obtain 2-(2,4,5-trimethoxyphenyl)acetaldehyde as a colourless oil (0.18 g, 77%). ν_{max} (film) /cm^{-1}: 2936, 1721, 1516, 1206. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (t, *J* = 2.2 Hz, 1H), 6.61 (s, 1H), 6.49 (s, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 3.52 (d, *J* = 2.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.3, 151.9, 149.4, 149.2, 143.1, 115.0, 112.0, 97.5, 56.6, 56.2, 44.9. *m/z*: $[M+H]^+$: 211.0965; $[C_{11}H_{14}O_4+H]$ requires 211.0965.

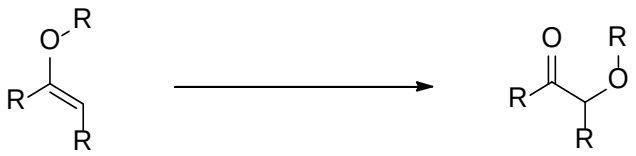
3.2.15 1-(2,4,5-Trimethoxyphenyl)propan-2-ol:[21]



2-(2,4,5-Trimethoxyphenyl)acetaldehyde (0.23 g, 1.0 mmol) was dissolved in anhydrous tetrahydrofuran (5 mL) at 0 °C and MeLi (1.5 mL, 1.60 M in Et_2O, 2.4 mmol) was added over 1 hour. The resulting mixture was stirred at 0 °C for 30 min and for a further 3h at rt. After this time, the mixture was poured into a saturated solution of NH_4Cl (25 mL) and the layers separated. The aqueous phase was extracted with Et_2O and the combined organic phases were washed successively with H_2O (25 mL) and brine (25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified using silica gel column chromatography using EtOAc/hexanes (4:6) to yield of 1-(2,4,5-trimethoxyphenyl)propan-2-ol as a colourless oil (0.08 g, 35%). ν_{max} (film) /cm^{-1}: 3401, 2932, 1513, 1204. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (s, 1H), 6.57 (s, 1H), 4.09 – 4.03 (m, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 2.82 (dd, *J* = 13.6, 4.1 Hz, 1H), 2.68 (dd, *J* = 13.6, 8.0 Hz, 1H), 1.26 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.7, 148.3, 143.0, 118.3, 115.3, 97.8, 68.3, 56.6, 56.3, 56.2, 39.9, 22.9. *m/z*: $[M+H]^+$: 227.1276; [$C_{12}H_{18}O_4$+H] requires 227.1278.

3.2.2 Oxidation section:

3.2.18 General Procedure for enol oxidation:



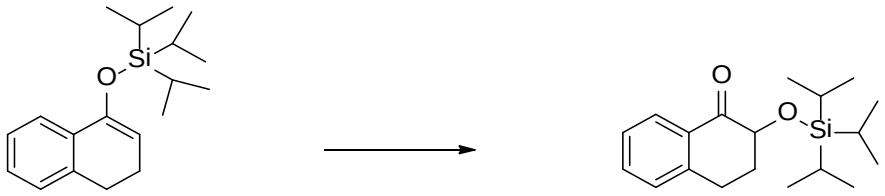
3.2.16.1 Using mCpBA:

$NaHCO_3$ (2 equiv.) was suspended in dichloromethane (2 mL per 100 mg of enol) and the mixture was cooled to 0 °C. Meta-chloroperoxybenzoic acid (1.5 equiv.) was then added. The mixture was stirred for 10 min. The enol ether (0.2 g) was added. The reaction was then followed by TLC till complete consumption of the starting material. Diethyl ether was then added (10 mL) and the reaction mixture was washed with water (10 mL), aqueous Na_2CO_3 (3 x 10 mL) and brine (10 mL). The organic phase was then dried on anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified using column chromatography on silica gel (eluent: hexanes/ethyl acetate 95:5) to give the desired compound.

3.2.16.2 Using TPPP:

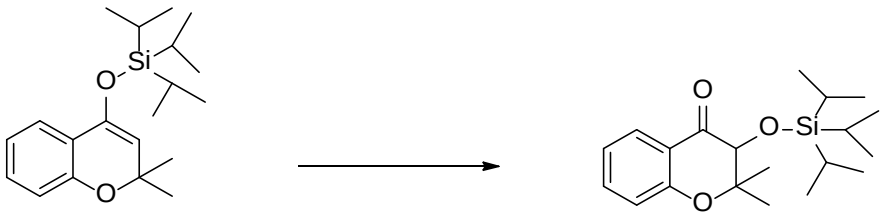
The catalyst (0.1 equiv.) and the enol ether were dissolved in chloroform/acetonitrile/dichloromethane (2 mL per 100 mg of enol) and the mixture was cooled. TPPP (2 equiv.) was then added to the mixture. The reaction was followed by TLC till complete consumption of the starting material. Diethyl ether was then added (10 mL) and the reaction mixture was filtered on a pad of celite. The mixture was then concentrated under reduced pressure and the residue was purified using column chromatography on silica gel (eluent: hexanes/ethyl acetate 95:5) to give the desired compound.

3.2.16.3 2-((Triisopropylsilyl)oxy)-3,4-dihydronaphthalen-1(2H)-one:[22]



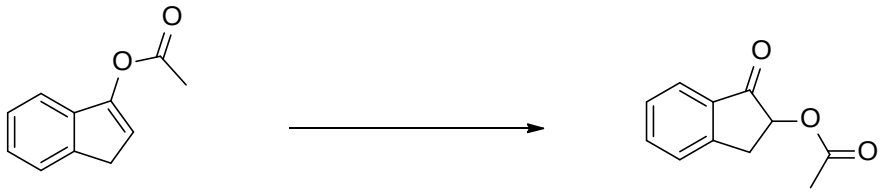
Prepared according to the general procedure for enol oxidation using ((3,4-dihydronaphthalen-1-yl)oxy)triisopropylsilane (0.20 g, 0.73 mmol), meta-chloroperoxybenzoic acid (0.17 g, 0.9 mmol) and sodium bicarbonate (0.10 g, 1.11 mmol) to give 2-((triisopropylsilyl)oxy)-3,4-dihydronaphthalen-1(2H)-one (0.19 g, 89%). ν_{max} (film) /cm^{-1}: 2941, 2865, 1700, 1903, 1295. ^{1}H NMR: δH (500 MHz; $CDCl_3$): 1.1 (d, *J* = 6.7 Hz, 18H); 1.25 (3H, m), 3 (2H, m); 3.15 (t, *J* = 7.1 Hz, 2H); 4.5 (dd, *J* = 7.1 Hz, 1H) 7.2 (3H, m); 8 (d, *J* = 7.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.2, 143.5, 133.3, 132.0, 128.6, 127.7, 126.5, 74.7, 32.9, 27.1, 17.9, 12.2.

3.2.16.4 2,2-Dimethyl-3-((triisopropylsilyl)oxy)chroman-4-one:[22]



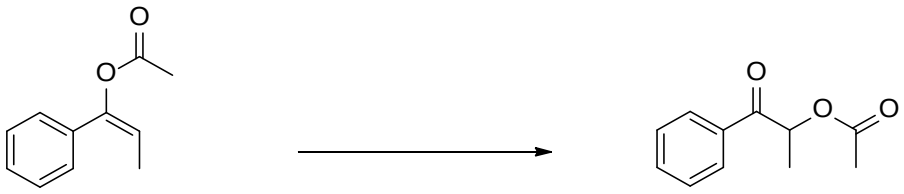
Prepared according to the general procedure for enol oxidation using (2,2-dimethyl-2H-chromen-4-yl)oxy)triisopropylsilane (0.20 g, 0.6 mmol), meta-chloroperoxybenzoic acid (0.15 g, 0.9 mmol) and sodium bicarbonate (0.10 g, 1.1 mmol) to give 2,2-dimethyl-3-((triisopropylsilyl)oxy)chroman-4-one (0.13 g, 62 %). ^{1}H NMR: δH (400 MHz; $CDCl_3$): 1.1 (d, *J* = 6.8 Hz, 18H); 1.25 (3H, m), 1.44 (6H, s); 4.49 (1H, s); 6.5-7.5 (4H, m).

3.2.16.5 1-Oxo-2,3-dihydro-1H-inden-2-yl acetate:[23]



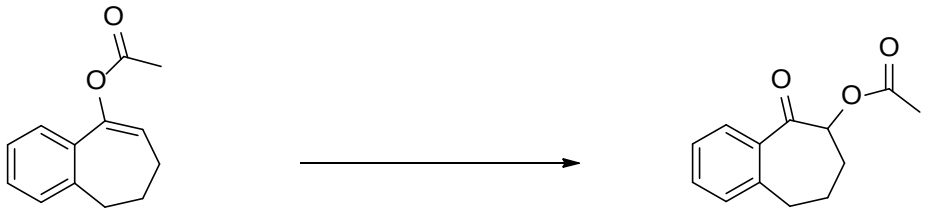
Prepared according to the general procedure for enol oxidation using 1H-inden-3-yl acetate (0.50 g, 2.8 mmol), meta-chloroperoxybenzoic acid (1.40 g, 8.13 mmol) and sodium bicarbonate (0.40 g, 4.7 mmol) to give the desired product (0.25 g, 46%). ν_{max} (film) /cm^{-1}: 2932, 1745, 1726. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.7 Hz, 1H), 7.67 (td, *J* = 7.6, 1.1 Hz, 1H), 7.50 – 7.41 (m, 2H), 5.45 (dd, *J* = 8.0, 4.9 Hz, 1H), 3.68 (dd, *J* = 16.9, 8.0 Hz, 1H), 3.07 (dd, *J* = 16.9, 4.8 Hz, 1H), 2.21 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.6, 170.4, 150.4, 135.9, 134.5, 128.1, 126.6, 124.5, 74.0, 33.4, 20.8.

3.2.16.6 1-Oxo-1-phenylpropan-2-yl acetate:[24]



Prepared according to the general procedure for enol oxidation using 1-phenylprop-1-en-1-yl acetate (0.2 g, 1.1 mmol), meta-chloroperoxybenzoic acid (0.3 g, 1.7 mmol) and sodium bicarbonate (0.2 g, 2.3 mmol) to give the desired product (0.1 g, 40%). ν_{max} (film) /cm^{-1}: 3004, 1764, 1206. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.22 (m, 5H), 3.12 (q, *J* = 5.3 Hz, 1H), 2.07 (s, 3H), 1.40 (d, *J* = 5.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 136.1, 128.8, 128.5, 125.5, 84.9, 61.3, 21.0, 13.8.

3.2.16.7 5-Oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-yl acetate:[25]



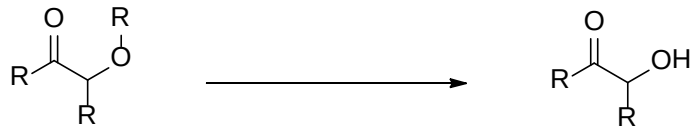
Prepared according to the general procedure for enol oxidation using 6,7-dihydro-5H-benzo[7]annulen-9-yl acetate (1 g, 5 mmol), meta-chloroperoxybenzoic acid (1.2 g, 7.4 mmol) and sodium bicarbonate (0.8 g, 9.5 mmol) to give the desired product (0.6 g, 56%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.68 (m, 1H), 7.19 (dd, *J* = 5.7, 3.4 Hz, 2H), 7.02 (dd, *J* = 5.4, 3.6 Hz, 1H), 3.52 (t, *J* = 4.7 Hz, 1H), 3.20 – 3.09 (m, 1H), 2.68 – 2.59 (m, 1H), 2.20 – 2.12 (m, 1H), 1.97 (s, 3H), 1.93 – 1.83 (m, 1H), 1.61 – 1.42 (m, 2H).

3.2.16.8 2-Hydroxy-3,4-dihydronaphthalen-1(2H)-one:

R= 1- acetate enol ester·
2- benzoic enol ester·
3- phosphinate enol ester·
4- trifluoroacetate enol ester·
5- tert-Butyl diphenylsilane enol ether·

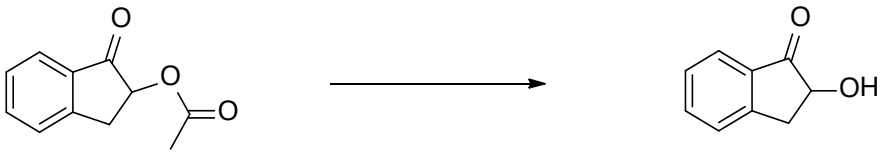
Prepared according to the general procedure for TPPP enol epoxidation, catalyst (0.1 equiv) and the enol ether (1 equiv). ν_{max} (film) /cm^{-1}: 3475, 3066, 1686, 1603. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.55 (td, *J* = 7.5, 1.4 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 4.41 (dd, *J* = 13.5, 5.4 Hz, 1H), 3.24 – 3.00 (m, 2H), 2.62 – 2.50 (m, 1H), 2.15 – 1.98 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200, 145, 135, 130, 129, 128, 127, 74, 32, 27.

General Procedure for protecting group removal:



The compound was dissolved in methanol (5 mL per 100 mg of starting material) and camphorsulphonic acid (1.1 equiv) was added. The reaction was followed by TLC till complete consumption of the starting material. The mixture was then concentrated under reduced pressure and the residue was purified using column chromatography on silica gel (eluent: hexanes/ethyl acetate 3:1) to give the corresponding α-hydroxy-carbonyl.

3.2.17.1 2-Hydroxy-2,3-dihydro-1H-inden-1-one:[26]



Prepared according to the general procedure for protecting group removal using 1-oxo-2,3-dihydro-1H-inden-2-yl acetate (0.15 g, 0.8 mmol) and camphorsulphonic acid (0.20 g, 0.9 mmol) to give 2-hydroxy-2,3-dihydro-1H-inden-1-one (0.1 g, 86%). ν_{max} (film) /cm^{-1}: 3414, 2923, 1718, 1609. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.7 Hz, 1H), 7.67 (td, *J* = 7.5, 1.2 Hz, 1H), 7.53 – 7.41 (m, 2H), 4.58 (dd, *J* = 7.9, 5.1 Hz, 1H), 3.62 (dd, *J* = 16.5, 7.9 Hz, 1H), 3.05 (dd, *J* = 16.5, 5.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.45, 150.9, 135.9, 134.0, 128.0, 126.8, 124.4, 74.3, 35.1.

3.2.17.2 2-Hydroxy-1-phenylpropan-1-one:[27]

Prepared according to the general procedure for protecting group removal using 1-oxo-1-phenylpropan-2-yl acetate (0.10 g, 0.5 mmol) and camphorsulphonic acid (0.10 g, 0.5 mmol) to give 2-hydroxy-1-phenylpropan-1-one (0.07 g, 89%). ν_{max} (film) /cm^{-1}: 3459, 2979, 1682. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.58 – 7.53 (m, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 5.15 – 5.04 (m, 1H), 1.38 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.4, 134.0, 133.3, 128.8, 128.6, 69.3, 22.3.

3.2.17.3 6-Hydroxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one:[28]

Prepared according to the general procedure for protecting group removal using 5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-yl acetate (0.10 g, 0.5 mmol) and camphorsulphonic acid (0.10 g, 0.5 mmol) to give the desired product (0.06 g, 75 %). ν_{max} (film) /cm^{-1}: 3420, 3055,2998,1635. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.34 (td, *J* = 7.5, 1.5 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 5.36 (dd, *J* = 10.7, 5.9 Hz, 1H), 3.02 – 2.86 (m, 2H), 2.21 – 2.11 (m, 2H), 2.00 – 1.89 (m, 1H), 1.82 – 1.70 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.6, 170.2, 141.6, 132.0, 130.0, 129.1, 126.8, 34.1, 29.2, 23.5, 20.7.

3.2.17.4 3-Hydroxy-2,2-dimethylchroman-4-one:[30]

Prepared according to the general procedure for protecting group removal using 2,2-dimethyl-4-oxochroman-3-yl acetate (0.10 g, 0.4 mmol) and camphorsulphonic acid (0.10 g, 0.4 mmol) to give 3-hydroxy-2,2-dimethylchroman-4-one (0.04 g, 49%). ν_{max} (film) /cm^{-1}: 3468, 2932, 1766, 1257. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.19 (m, 3H), 7.16 – 7.13 (m, 1H), 4.28 (s, 1H), 1.51 (s, 3H), 1.47 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 144.0, 126.8, 125.8, 125.7, 124.7, 119.9, 87.7, 73.3, 23.8, 21.6.

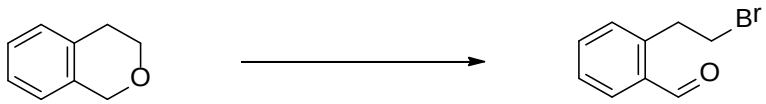
3.2.17.5 3-Hydroxy-1-(2,2,2-trifluoroacetyl)-2,3-dihydroquinolin-4(1H)-one:

Prepared according to the general procedure for protecting group removal using 4-oxo-1-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroquinolin-3-yl acetate (0.15 g, 0.5 mmol) and camphorsulphonic acid (0.1 g, 0.5 mmol) to give 3-hydroxy-1-(2,2,2-trifluoroacetyl)-2,3-dihydroquinolin-4(1H)-one (0.1 g, 78 %). ν_{max} (film) /cm^{-1}: 3394, 3000, 1696, 1257. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.62 – 7.56 (m, 1H), 7.33 (td, *J* = 7.9, 1.0 Hz, 1H), 4.45 (dd, *J* = 12.4, 5.3 Hz, 1H), 3.73 – 3.63 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.8, 142.3, 136.2, 135.2, 128.2, 127.2, 124.2, 123.6, 119.0, 115.1 (q, CF_3, *J* = 288 Hz) 71.5. *m/z*: $[M+H]^+$: 260.0535; $[C_{11}H_8F_3NO_3+H]$ requires 260.0529.

3.3 Catalysts section

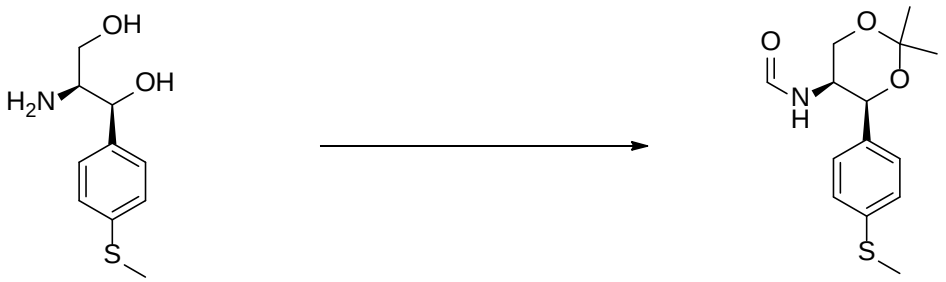
3.3.1 Synthesis of dihydroisoquinolinium salt catalyst

3.3.1.1 2-(2-Bromoethyl) benzaldehyde:[31]



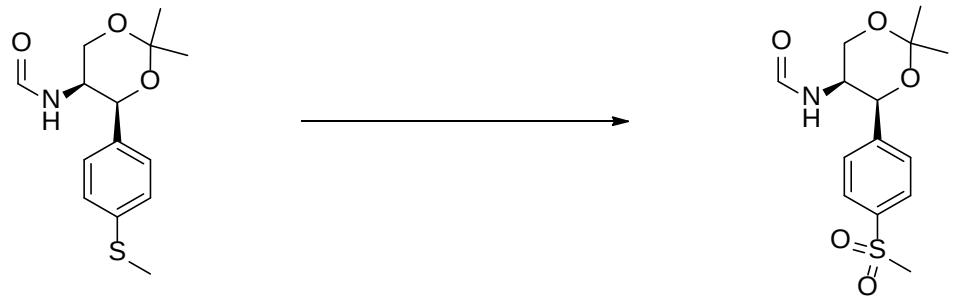
Bromine (4.2 mL, 81.97 mmol) was added to an ice-cooled solution of isochroman (10 g, 74.52 mmol) in cyclohexane (70 mL) slowly down a reflux condenser over 5 minutes with stirring. After the vigorous reaction had calmed, the solution was heated under reflux until the reaction turned pale yellow and the liberation of hydrogen bromide gas had ceased. The solution was cooled to room temperature, and solvents were removed *in vacuo.* The remaining oil was dissolved in hydrobromic acid (25 mL, 48% aq.) and heated under reflux for 10 minutes. The solution was then cooled and extracted with diethyl ether (3 x 100 mL). The organic extracts were washed with water (2 x 30 mL), dilute sodium hydrogen carbonate (2 x 30 mL), and dried over $MgSO_4$. Removal of the solvents under reduced pressure afforded crude 2-(2-bromoethyl) benzaldehyde as an orange-brown oil. Purification by vacuum distillation (2 mbar, 50-54 °C) afforded 2-(2-bromoethyl)benzaldehyde as a colourless liquid (8.9 g, 57%). ν_{max} (film) /cm^{-1}: 2969, 2743, 1697, 1599, 1291. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.09 (s, 1H), 7.76 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.49 (td, *J* = 7.5, 1.6 Hz, 1H), 7.42 (td, *J* = 7.5, 1.3 Hz, 1H), 7.27 (dd, *J* = 7.2, 0.7 Hz, 1H), 3.59 – 3.46 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.9, 140.5, 134.5, 133.7, 132.1, 127.7, 36.3, 32.7.

3.3.1.2 (4*S*,5*S*)-*N*-Formyl-amino-4-(4-methylsulfide)-2,2-dimethyl-1,3-dioxane:[32]



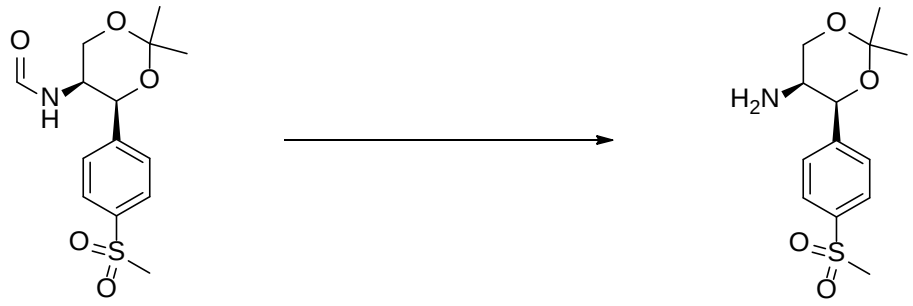
(*S*)-Thiomicamine (5.00 g, 23.4 mmol) was dissolved in MeOH (50 mL), and methyl formate (1.7 mL, 28.3 mmol) and sodium methoxide (0.1 mL, 2.3 mmol) were added. The mixture was stirred for 3.5 h and the solvent removed under reduced pressure to yield *N*-(1*S*, 2*S*)-1,3-dihydroxy-1-(4-(methylthio)phenyl)propan-2-yl)formamide as a yellow oil. The resulting formamide was dissolved in acetone (200 mL), and 2,2-dimethoxypropane (30 mL, 50.9 mmol) and camphorsulfonic acid (0.5 g, 2.9 mmol) were added. The reaction was stirred for 4 h and progress was monitored by TLC. The solvents were removed under reduced pressure, and the residue was re-dissolved in ethyl acetate. The solution was washed with saturated sodium hydrogen carbonate solution, dried ($MgSO_4$), and the solvents were removed under reduced pressure to afford (4*S*, 5*S*)-*N*-formyl-Amino-4-(4-methylsulfide)-2,2-dimethyl-1,3-dioxane as a colourless oil (5.5 g, 83%). $[\alpha]_D$ = + 1.2 ° (*c* 1.22, $CHCl_3$) [Lit.[31] $[\alpha]_D$ = + 0.9 ° (*c* 1.00, $CHCl_3$)]; ν_{max} (film) /cm^{-1}: 3296, 2990, 1667, 1496, 1381. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.28 – 7.22 (m, 4H), 6.16 (d, *J* = 9.1 Hz, 1H), 5.22 (d, *J* = 1.9 Hz, 1H), 4.37 – 4.33 (m, 1H), 4.30 (dd, *J* = 12.1, 1.7 Hz, 1H), 3.93 (dd, *J* = 12.1, 1.8 Hz, 1H), 2.50 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.9, 160.4, 126.5, 125.7, 99.7, 71.4, 64.6, 45.3, 30.9, 29.7, 18.5, 15.8.

3.3.1.3 (4*S*,5*S*)-*N*-Formyl-amino-4-(4-methylsulfone)-2,2-dimethyl-1,3-dioxane:[32]



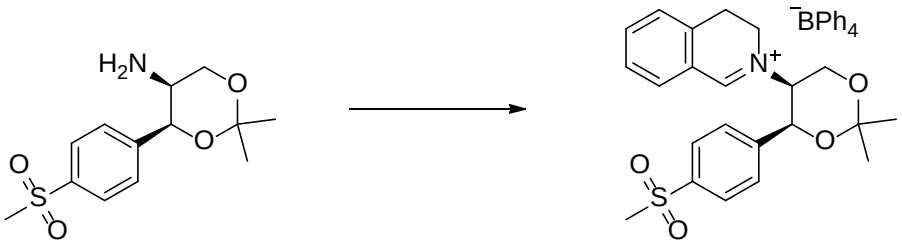
(4*S*,5*S*)-*N*-Formyl-amino-4-(4-methylsulfone)-2,2-dimethyl-1,3-dioxane (5.5 g, 19.5 mmol) was dissolved in dichloromethane (80 mL) and the solution cooled to 0 °C. m-CpBA (7.4 g, 43.0 mmol) was dissolved in dichloromethane (100 mL) and dried over $MgSO_4$ before being filtered into the cooled solution of the sulfide. The reaction was allowed to warm to ambient temperature slowly over 14 h, at which time the reaction was quenched with $NaHCO_3$ (sat. aq., 100 mL). The organic layer was separated and washed with 1M NaOH (200 mL) and then dried over $MgSO_4$ and carbon black. Solvents were then removed *in vacuo* to yield the product as a white foam of good purity (4.8 g, 78 %). $[\alpha]_D$ = - 11.1 ° (*c* 1.20, $CHCl_3$) [Lit.[31] $[\alpha]_D$ = - 14.5 ° (*c* 1.11, $CHCl_3$)]; ν_{max} (film) /cm^{-1}: 3000, 2874, 1676, 1513, 1382, 1300, 1202. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 6.22 (d, *J* = 9.5 Hz, 1H), 5.31 (s, 1H), 4.47 (dd, *J* = 12.1, 1.8 Hz, 1H), 4.35 (dd, *J* = 12.1, 1.7 Hz, 1H), 3.92 (dd, *J* = 12.1, 1.8 Hz, 1H), 3.07 (s, 3H), 1.64 (s, 3H), 1.62 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2, 144.3, 139.8, 127.4, 126.4, 100.0, 71.5, 64.6, 45.0, 44.5, 29.6, 18.5.

3.3.1.4 (4*S*,5*S*)- 5-Amino-6-(4-methylsulfone)-2,2-dimethyl-1,3-dioxane:[32]



(4*S*,5*S*)-*N*-Formyl-amino-4-(4-methylsulfone)-2,2-dimethyl-1,3-dioxane (4.8 g, 15.3 mmol) was dissolved in aqueous hydrazine hydrate (100 mL, 85%) and the solution heated under reflux for 3 h. The solution was allowed to reach ambient temperature and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with water (2 x 200 mL) and brine (2 x 200 mL), dried (Na_2SO_4), and the solvents were removed under reduced pressure to afford (4*S*,5*S*)-5-amino-6-(4-methylsulfone)-2,2-dimethyl-1,3-dioxane as a yellow oil (2.2 g, 50%). $[\alpha]_D$= + 48.2 ° (*c* 1.00, $CHCl_3$) [Lit.[31] $[\alpha]_D$ = + 65.3 ° (*c* 1.05, $CHCl_3$)]; ν_{max} (film) /cm^{-1}: 3429, 2997, 1642, 1383. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 5.25 – 5.13 (d, *J* = 9.1 Hz, 1H), 4.36 (dd, *J* = 11.9, 2.2 Hz, 1H), 3.97 (dd. *J* = 11.6, 2.3 Hz, 1H), 3.09 (s, 3H), 2.96 – 2.84 (m, 1H), 1.60 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.0, 139.6, 127.5, 126.8, 123.7, 99.6, 49.4, 44.5, 29.6, 18.6.

3.3.1.5 (+)-*N*-(4*S*,5*S*)-2,2-dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-yl)-3,4-dihydroisoquinolinium tetraphenylborate:[32]

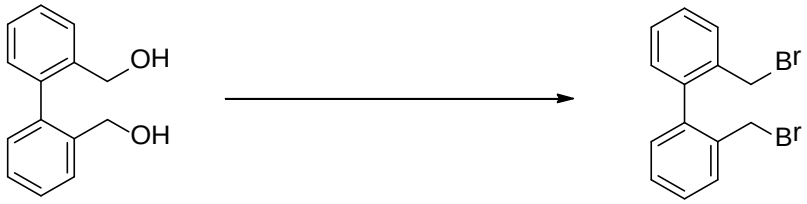


A solution of (4*S*,5*S*)-2,2-Dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-amine (5.2 g, 18.2 mmol) in ethanol (30 ml) was added dropwise to an ice-cooled 2-(2 bromoethyl) benzaldehyde (3.32 g, 15.4 mmol) solution in ethanol. After the addition was complete the reaction flask was lightly stoppered to contain the hydrogen bromide generated temporarily in the reaction, and the reaction stirred overnight whilst attaining room temperature. A solution of sodium tetraphenylborate (7.4 g, 21.8 mmol) in acetonitrile (4 ml) was added in one portion to the reaction and stirred for a further 5 minutes, resulting in the formation of a yellow precipitate. The yellow solid was then washed with ethanol (20 ml) and water (20 ml) and the yellow crystals collected by suction filtration (4 g, 54 %); mp 200-210 °C [Lit.[31] mp 199-200 °C]; $[\alpha]_D$ = + 126.5 (*c* 1.20, Acetone) [Lit.[31] $[\alpha]_D$ = + 195 ° (*c* 1.06, Acetone)]; ν_{max} (film) /cm^{-1}: 1635, 1602, 1571, 1477, 1382, 1313, 1265. ^{1}H NMR (400 MHz, acetone) δ 9.38 (s, 1H), 7.95 (d, *J* = 8.6 Hz, 2H), 7.88 (d, *J* = 8.6 Hz, 2H), 7.85 – 7.76 (m, 3H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.34 – 7.27 (m, 8H), 6.90 (t, *J* = 7.4 Hz, 8H), 6.75 (t, *J* = 7.1 Hz, 4H), 6.12 (d, *J* = 2.6 Hz, 1H), 4.84 (dd, *J* = 13.7, 3.1 Hz, 1H), 4.76 – 4.69 (m, 1H), 4.59 (d, *J* = 13.6 Hz, 1H), 4.35 – 4.23 (m, 1H), 3.84 – 3.71 (m, 1H), 3.02 (s, 3H), 3.00 – 2.95 (m, 1H), 2.79 – 2.69 (m, 1H), 1.73 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (100 MHz, acetoned6), δ 168.1,

164.4, 142.7, 141.0, 138.7, 137.2, 136.0, 134.6, 128.7, 128.6, 127.8, 126.9, 125.8, 125.7, 124.6, 121.9, 100.6, 70.4, 56.5, 50.4, 43.9, 29.5, 24.6, 19.04.

3.3.2 Synthesis of biphenyl-derived iminium salt catalyst

3.3.2.1 2,2'-bis(Bromomethyl)biphenyl:[34]



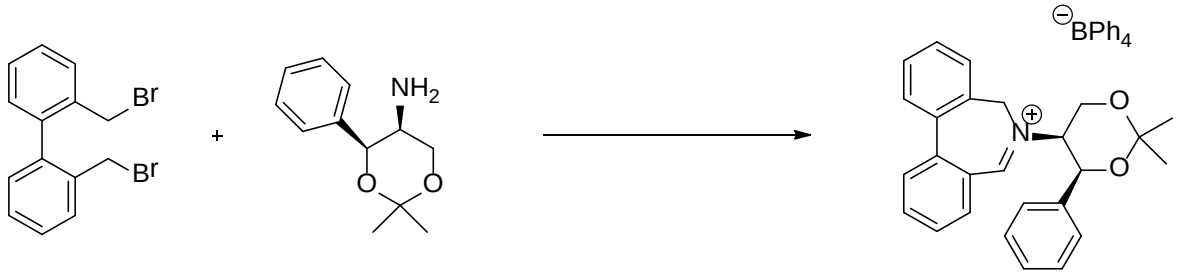
2,2'-Biphenyldimethanol (1 g, 4.6 mmol) was dissolved in neat hydrobromic acid (20 mL) at room temperature, and then submitted to reflux for 2.5 h. Reaction progress was monitored by TLC, and upon reaction completion, the solution was cooled, toluene (100 mL) added, and the organic layer was extracted. The organic extract was washed with saturated sodium hydrogen carbonate (100 mL), brine (100 mL), dried ($MgSO_4$), and excess organic solvents removed under reduced pressure, affording 2,2'-bis(bromomethyl)biphenyl as a colourless solid (0.82 g, 52%; mp 93 °C [Lit.[31] mp 92-94 °C]); ν_{max} (film) /cm^{-1}: 2990, 1736, 1652, 1598. ^{1}H NMR (500 MHz, CDCl3) δ 7.59 (dd, J = 7.6, 1.3 Hz, 2H), 7.45 (m, 4H), 7.31 (dd, J = 7.5, 1.5 Hz, 2H), 4.39 (d, J = 10.1 Hz, 2H), 4.23 (d, J = 10.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.4, 135.8, 130.7, 130.1, 128.6, 128.3, 31.9.

3.3.2.2 (4*S*,5*S*)-5-Amino-6-phenyl-2,2-dimethyl-1,3-dioxane:[35]

(1*S*,2*S*)–(+)–2-Amino-1-phenyl-1,3-propanediol (2.27 g, 9.6 mmol) was dissolved in MeOH (50 mL), and methyl formate (1 mL, 16.1 mmol) and sodium methoxide (0.1 mL) were added. The mixture was stirred for 3.5 h and the solvent removed under reduced pressure. The diol (2.0 g, 10.2 mmol) was then dissolved in acetone (150 mL), and 2,2-dimethoxypropane (6.4 mL, 50.9 mmol) and camphorsulfonic acid (0.23 g, 1.0 mmol) were added. The reaction was stirred for 4 h and progress was monitored by TLC. The solvents were removed under reduced pressure, and the residue was re-dissolved in ethyl acetate. The solution was washed with saturated sodium hydrogen carbonate solution, dried ($MgSO_4$), and the solvents were removed under reduced pressure to afford (4*S*,5*S*)-*N*-Formyl-5-Amino-4-phenyl-2,2-dimethyl-1,3-dioxane: as a colourless oil (2.3 g, 95 %). (4*S*,5*S*)-*N*-Formyl-5-amino-4-phenyl-2,2-dimethyl-1,3-dioxane (2.0 g, 8.5 mmol) was dissolved in aqueous hydrazine hydrate (100 mL, 85%) and the solution heated under reflux for 3 h. The solution was allowed to reach ambient temperature and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with water (2 x 200 mL) and brine (2 x 200 mL), dried (Na_2SO_4), and the solvents were removed under reduced pressure to afford (4*S*,5*S*)-5-Amino-6-phenyl-2,2-dimethyl-1,3-dioxane as a yellow oil (1.5 g, 86 %). ν_{max} (film) /cm^{-1}: 2991, 2940, 2868, 1673, 1586, 1378, 1270, 1239. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.23 (m, 5H), 5.05 (s, 1H), 4.24 (dd, *J* = 11.8, 2.2 Hz, 1H), 3.87 (dd, *J* = 11.8, 1.7

Hz, 1H), 2.75 (d, *J* = 1.8 Hz, 1H), 1.49 (s, 3H), 1.48 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.5, 128.2, 127.1, 125.5, 98.8, 73.5, 65.8, 49.4, 29.6, 18.5.

3.3.2.3 (−)-*N*-[(4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl]-5*H* dibenzo[*c*,*e*]azepinium Tetraphenylborate:[36]

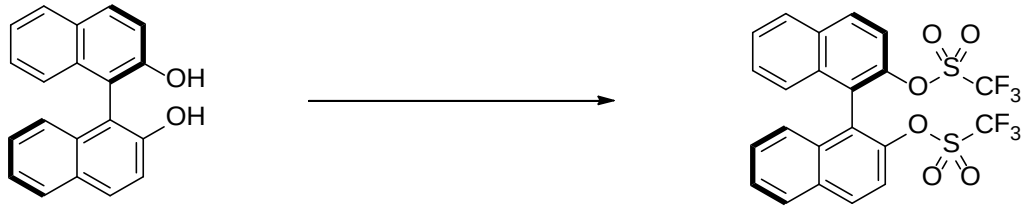


2,2'-bis(Bromomethyl)biphenyl (3.0 g, 8.8 mmol) and amine (1.8 g, 8.8 mmol) were dissolved in acetonitrile (30 mL). K_2CO_3 (2.4 g, 17.4 mmol) was added at room temperature. The reaction was submitted to reflux for 24 h, cooled, diluted with CH_2Cl_2 (100 mL), extracted with water (2x 50 mL), brine (2x 50 mL), and dried over $MgSO_4$. Excess solvents were removed under reduced pressure, affording 6-(4S,5S)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-6,7-dihydro-5H-dibenzo[c,e]azepine (3.2 g, 94 %). 6-(4S,5S)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-6,7-dihydro-5H-dibenzo[c,e]azepine (3.2 g, 8.3 mmol) was then dissolved in CH_2Cl_2 (15 mL), to which N-Bromosuccinimide (1.7 g, 9.9 mmol) was added, and left to stir for 5 minutes. Excess dichloromethane was removed under reduced pressure, and the remaining solid was re-dissolved in ethanol (30 mL). Sodium tetraphenylborate (3.0 g, 8.7 mmol) was dissolved in a minimum amount of acetonitrile (4 mL), and added to the stirring solution at room temperature. After 5 minutes, the reaction was stopped and excess organic solvents removed under reduced pressure, affording (−)-*N*-[(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-5*H*-dibenzo[*c*,*e*]azepinium tetraphenylborate as a pale orange

powder (2.2 g, 37 %, mp 170 °C [Lit.[31] mp 187 °C]); $[\alpha]_D$ = - 42.0 (*c* 1.01, CH_3CN) [Lit.[31] $[\alpha]_D$ = - 44° (*c* 1.01, CH_3CN)]; ν_{max} (film) /cm^{-1}: 3054, 3000, 2997, 1631, 1577,1479. ^1H NMR (400 MHz, DMSO-d6, 115 °C): δ = 1.80 (3H, s), 1.85 (3H, s), 4.41 (1H, d, *J* = 22 Hz), 4.51 (1H, d, *J* = 22 Hz), 4.70–4.73 (1H, m), 4.80 (1H, d, *J* = 22 Hz), 5.15 (1H, d, *J* = 22 Hz). 5.96 (1H, d, *J* = 4 Hz), 6.75 (4H, t, *J* = 12 Hz), 6.90 (8H, t, *J* = 12 Hz), 6.90 -7.11 (5H, m), 7.28-7.37 (8H, m), 7.42-7.62 (3H, m), 7.74-7.90 (3H, m), 8.06-8.26 (2H, m), 9.09 (1H, s). ^{13}C NMR (100 MHz, DMSO-d6, 120 °C): δ = 18.2, 28.7 , 54.0, 60.8, 66.1, 70.5, 99.9, 120.7, 124.46 , 124.47, 124.5, 124.5, 125.3, 127.3, 127.8, 127.9, 128.4, 129.2, 129.5, 129.6, 132.8, 133.7, 135.0, 136.0, 140.5, 163.3, 170.3.

3.3.3 Synthesis of binaphthalene-derived iminium salt catalyst

3.3.3.1 (*R*)-[1, 1]-Binaphthalene-2, 2'-diol-*bis*-trifluoromethanesulfonate:[37]



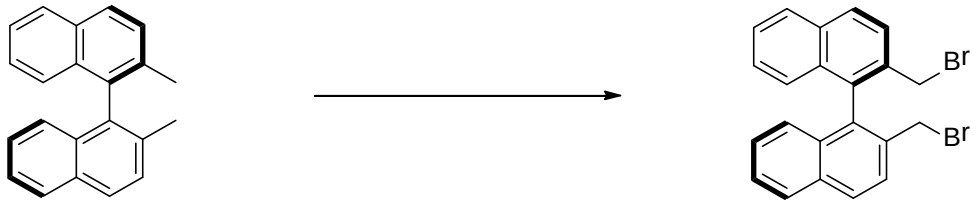
(*R*)-Binaphthalenyl-2,2-diol (15.0 g, 52.0 mmol) was dissolved in CH_2Cl_2 (100 mL) and cooled to – 30 °C. After the solution had cooled 4-dimethylaminopyridine (2.5 g, 5.2 mmol), 2,6-lutidine (18.3 mL, 3 equiv., 157 mmol) and triflic anhydride (44 mL, 3 equiv., 157 mmol) were added to the solution. The resulting brown solution was allowed to warm to ambient temperature with stirring overnight. Silica gel was added to the dark brown mixture and left to stir for 20 mins after which time solvents were removed *in vacuo*. The loaded silica gel was transferred to a sintered glass funnel containing a layer of silica gel under filter paper and eluted with hexane until the product had eluted. The solvent was removed under reduced pressure to yield (*R*)-[1,1']-binaphthalene-2,2'-diol-*bis*-trifluoromethanesulfonate as a white crystalline solid, (26.21 g, 92 %): $[\alpha]_D$ = +149.1 (c. 1.01, $CHCl_3$) [Lit.[36] $[\alpha]_D$ = - 150.9 (*c* 1.01, $CHCl_3$)]; ν_{max} (film) /cm^{-1}: 3065, 1509, 1422, 1215, 1139. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 9.1 Hz, 2H), 8.05 (d, *J* = 8.3 Hz, 2H), 7.69 – 7.58 (m, 2H), 7.48 – 7.41 (m, 4H), 7.29 (d, *J* = 7.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.3, 133.1, 132.3, 131.9, 128.3, 127.9, 127.3, 126.7, 123.2, 119.3, 116.8 (q, CF_3, *J* = 240 Hz).

3.3.3.2 (*R*)-Dimethyl-[1,1']-binaphthalene:[39]

(*R*)-[1,1']-Binaphthalene-2,2'-diol-*bis*-trifluoromethanesulfonate (26.2 g, 48 mmol) and 1,3-*bis*(diphenylphosphino)propane nickel (II) chloride (1.8 g, 3.3 mmol) were dissolved in diethyl ether (200 mL) and cooled to – 30 °C. A solution of methylmagnesium bromide (3 M in Et_2O, 64 mL, 192.0 mmol) was added dropwise. After 15 minutes the reaction was removed from the Dewar and left to reach ambient temperature with stirring overnight. The reaction mixture was diluted with diethyl ether (200 mL) and celite was added to the resultant dark brown mixture and stirred for 30 minutes. The suspension was filtered through a sintered glass funnel containing celite. The filtrate was washed with 2 M hydrochloric acid (40 mL), water (100 mL) and brine (100 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure yielded (*R*)-Dimethyl-[1,1']-binaphthalene as a white powder, (10.9 g, 80 %): $[\alpha]_D$ = - 40 (c = 1.1 , $CHCl_3$) [Lit.[36] $[\alpha]_D$ = - 40.9 (*c* 1.19, $CHCl_3$)]; ν_{max} (film) /cm^{-1}: 3051, 2917, 1594, 1506. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (t, *J* = 8.1 Hz, 4H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.47 – 7.39 (m, 2H), 7.28 – 7.21 (m, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 2.07 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.1, 134.3, 132.7, 132.2, 128.7, 127.9, 127.4, 126.0, 125.6, 124.9, 20.0.

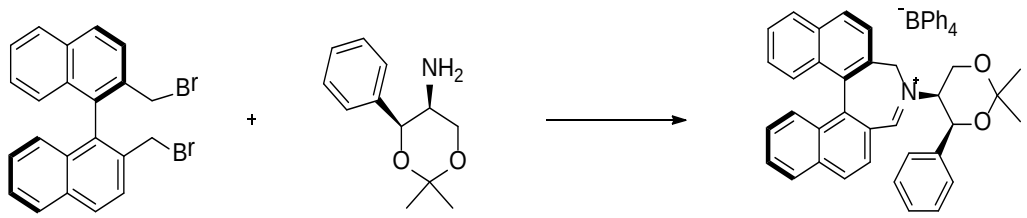
3.3.3.3 (*R*)-*Bis*-bromomethyl-[1,1']-binaphthylenyl:[40]

+



(*R*)-Dimethyl-[1,1']-binaphthalene (10.83 g, 38.4 mmol) was dissolved in cyclohexane (85 mL) with stirring. N-bromosuccinimide (15.0 g, 84.7 mmol) and azobisisobutyronitrile (0.61 g, 4.3 mmol) were added followed by heating to reflux until disappearance of starting material was observed by TLC. After cooling to ambient temperature, water (170 mL) and ethyl acetate (28 mL) were added to dissolve by-products and excess NBS. The resulting suspension was stirred for 1 h to allow the precipitation of product to complete. The mixture was filtered through a Büchner funnel equipped with filter paper and washed through with cold cyclohexane, to yield (*R*)-*Bis*-bromomethyl-[1,1']-binaphthylenyl as a white powder, (9.6 g, 56 %): $[\alpha]_D$ = + 160 (c = 1.0 , $CHCl_3$) [Lit.[36] $[\alpha]_D$ = + 162.2 (*c* 1.07, $CHCl_3$)]; ν_{max} (film) /cm^{-1}: 3052, 1719, 1508, 1434, 1212.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.6 H,+ 2H), 7.96 (d, *J* = 8.2 Hz, 2H), 7.80 – 7.77 (m, 2H), 7.55 – 7.50 (m, 2H), 7.34 – 7.30 (m, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 4.29 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.2, 134.1, 133.2, 132.5, 129.3, 128.0, 127.7, 126.8, 126.8, 126.8, 32.6.

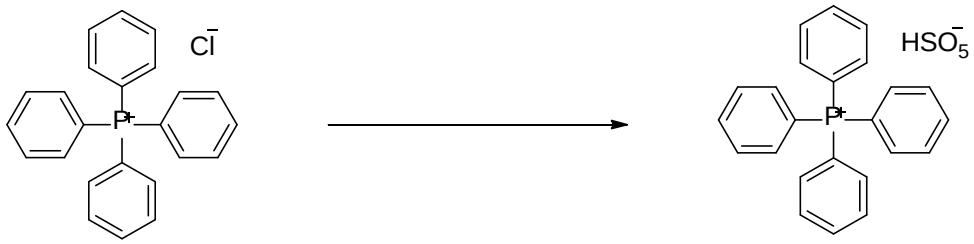
3.3.3.4 (*R*)-4-((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate:[41]



(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-amine (0.5 g, 2.4 mmol) was added to solution of (*R*)-*Bis*-bromomethyl-[1,1']-binaphthylenyl (1.0 g, 2.4 mmol) and potassium carbonate (1.0 g, 7.2 mmol) in acetonitrile (20 mL) at room temperature. The reaction mixture was heated under reflux overnight. Solvents were removed under reduced pressure and the residue was re-dissolved in dichloromethane (60 mL) and filtered into a separating funnel to remove excess K_2CO_3.The mixture was washed with water (60 mL) and brine (30 mL). The organic phase was separated, dried over $MgSO_4$ and solvents removed under reduced pressure to give (*R*)-4-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (1.1 g, 57%). (*R*)-4-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (1 g, 2.0 mmol) was then dissolve in CH_2Cl_2 in a flask equipped with a stirrer bar, was added *N*-Bromosuccinimide (0.4 g, 2.2 mmol). The resulting yellow solution was stirred for 1 h after which time the solvent removed under reduced pressure. Addition of EtOH the crude mixture was then performed. Sodium tetraphenylborate (0.8 g, 2.2 mmol) in the minimum amount of acetonitrile was added to this solution. Solvents were again removed under reduced pressure to yield an intense yellow foam. EtOH (20 mL) was added and heated until the solid had broken up to yield a fine bright yellow precipitate. The solution was allowed to cool to ambient temperature and the precipitate filtered off. The precipitate was washed with cold

EtOH followed by hexane. Affording (*R*)-4-((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate as a yellow powder (0.8 g, 49%); m.p. 238 °C [Lit.[36] mp 153 °C]); $[\alpha]_D$ = - 530 (c = 0.99, acetone) [Lit.[36] $[\alpha]_D$ = - 357.7 (*c* 0.99, acetone)]; ν_{max} (film) /cm^{-1}: 3055, 2998, 1626, 1609, 1588, 1548, 1462, 1383, 1265. ^{1}H NMR (400 MHz; acetone-D6) δ 9.26 (s, 1H), 8.24 (d, *J* = 8.6 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.6 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.74 (ddd, *J* = 8.1, 5.5, 2.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.39 – 7.36 (m, 2H), 7.28 – 7.23 (m, 8H), 7.23 – 7.19 (m, 1H), 7.12 (d, *J* = 7.1 Hz, 2H), 7.05 – 7.00 (m, 4H), 6.98 (t, *J* = 7.5 Hz, 8H), 6.83 (t, *J* = 7.2 Hz, 4H), 5.77 (d, *J* = 2.8 Hz, 1H), 4.76 (d, *J* = 13.4 Hz, 1H), 4.62 (dd, *J* = 14.0, 3.1 Hz, 1H), 4.58 (m, 1H), 4.11 (d, *J* = 14.0 Hz, 1H), 3.92 (d, *J* = 13.5 Hz, 1H), 1.73 (s, 3H), 1.67 (s, 3H).

3.4 Tetraphenylphosphonium monoperoxysulfate (TPPP) synthesis procedure:[42]



Oxone (15 g, 48.8 mmol) was dissolved in deionised water (300 mL) at 10 °C, and tetraphenylphosphonium chloride (15 g, 40.0 mmol) dissolved in CH_2Cl_2 (300 mL) was added. The solution was left to stir for ½ hour. Extraction of the organic layer was followed by removal of remaining CH_2Cl_2 under reduced pressure. The white solid was washed with distilled water (2 x 75 mL) and then dissolved in CH_2Cl_2 (200 mL), and dried ($MgSO_4$). To the CH_2Cl_2 solution, hexane (50 mL) was added, and left at –20 °C for 24 hours. The cloudy solution was filtered, and any remaining solvents removed under reduced pressure to yield white crystalline TPPP (12.506 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δH = 9.24-9.12 (1H, S), 7.89 (4H, m), 7.75 (8H, m), 7.59 (8H, m).

3.5 References

1. https://www.chromspec.com/pdf/e/kn06.pdf.
2. http://www.mz-at.de/resources/brochures/Chiralcel_ODH.pdf.
3. Maekawa, H.; Hoh, K.; Goda, S.; Nishiguchi, I. *Chirality* **2003**, 15, 95–100.
4. Noji, M.; Ohno, T.; Fuji, K.; Futaba, N.; Tajima, H.; Ishii, K. *J. Org. Chem*. **2003**, 68, 9340.
5. Jiang, H.; Cheng, Y.; Zhang, Y.; Yu, S. *J. Org. Chem.* **2013**, 24, 5485.
6. Arribas, I.; Rubio, M.; Kleman, P.; Pizzano, A. *J. Org. Chem*. **2013**, 78, 3997.
7. Tang, Y.; Fan, Y.; Zhang, Y.; Li, X.; Xu, X. *Synlett*, **2016**, 27, 1860.
8. Tang, Y.; Fan, Y.; Zhang, Y.; Li, X.; Xu, X. *Tetrahedron. Lett*. **2015**, 56, 5616.
9. Yanagisawa, A.; Lin, Y.; Takeishi, A.; Yoshida, K. *J. Org. Chem*. **2016**, 32, 5355.
10. Schmidt, R. G.; Bayburt, E. K.; Latshaw, S. P.; Koenig, J. R.; Daanen, J. F.; McDonald, H. A.; Bianchi, B. R.; Zhong, C.; Joshi, S.; Honore, P.; Marsh, K. C.; Lee, C.-H.; Faltynek, C. R.; Gomtsyan, A. Bioorg. *Med. Chem. Lett*. **2011**, 21, 1338.
11. Yuesi, F.; Donald C.; Richard, C.; Feng Shi, *J. Org. Chem*. **2012**, 77, 6262−6270.
12. Schmidt, R. G.; Bayburt, E. K.; Latshaw, S. P.; Koenig, J. R.; Daanen, J. F.; McDonald, H. A.; Bianchi, B. R.; Zhong, C.; Joshi, S.; Honore, P.; Marsh, K. C.; Lee, C.-H.; Faltynek, C. R.; Gomtsyan, A. Bioorg. *Med. Chem. Lett.* **2011**, 21, 1338.
13. Yuesi, F.; Donald, C.; Richard, C.; Feng, S. *J. Org. Chem*. **2012**, 77, 6262−6270.
14. Kevin, W.; Anderson, J. *J. Org. Lett.* **2002**, 4, 460 – 461.
15. Uldam, H.; Henriette, K.; Thygesen, M. B. From *PCT Int. Appl*, **2009**.
16. Mingyan, Z.; Myung, H.; Sanghee, L.; Su, J.; Seong, H.; Seung, B. *J. Med. chem*. **2010**, 53, 8760.
17. Jin-Quan, Y.; Hai-Chen, W. *Org. Lett*. 7, **2005**, 1415.

18. Hayashi, T.; Fujiwa, T.; Okamoto, Y.; Katsuro, Y.; Kumada, M. *Synthesis*, **1981**, 1001.

19. Clive, D. L. J.; Khodabocus, A.; Vernon, P. G.; Angoh, A. G.; Bordeleau, L; Middleton, D. S.; Lowe, C.; Kellner, D. *J. Chem. Soc., Perkin Trans.* 1, **1991**, 1433-1444.

20. Ogata, T.; Sugiyama, Y.; Nakano, S. K.; Torii, E.; Nishiuchi, A.; Kimachi, T. *Tetrahedron*. **2013**, 69, 10470-10476.

21. Caroline, E.; Patrick, J.; Martin, N. *Org. Biomol. Chem*. **2009**, 7, 5059–5062

22. Douteau, A. (**2011**). (Silyl Enol Ether Epoxidation) (Undergraduate Project Report, University of East Anglia, Norwich)

23. Langvik, O.; Maek, P.; Aho, A.; Saloranta, T.; Tiina, M.; Dmitry, L. *Catalysis Lett*. **2013**, 143.

24. Huang, X.; Liang, X.; Yuan, J.; Ni, Z.; Zhou, Y.; Pan, Y. *Org. Chem. Frontiers*, **2013**, 143.

25. Kajiro, H.; Mitamura, S.; Mori, A.; Hiyama, T. *Tetrahedron*, **1999**, 40, 1689.

26. Hayashi, T.; Fujiwa, T.; Okamoto, Y.; Katsuro, Y; Kumada, M. *Synthesis* **1981**.

27. Akira, Y.; Yuqin, L.; Kazuhiro, Y. E. *J. Org. Chem*. **2016**, 5355–5359.

28. Hoye, R.; Jeffrey S.; Shao, F. M. *Nat. Protoc*. **2007**, 2(10), 2451–2458.

29. Sang, L.; Nicholas, H.; Myers, G. *J. Am. Chem. Soc*. **2009**, 131, 5763-5765.

30. Deepak, B.; Ghorpade, S.; Liu, R. *J. Eur. Chem.* 2013, 12965.

31. Blakemore, P. R.; Marsden, S. P.; Vater, H. D. *Org. Lett*. **2006**, 8,773-776.

32. David, D. (**2013**). Recent Advances In Iminium Salt Catalysed Asymmetric Epoxidation (Doctoral thesis, University of East Anglia, Norwich)

33. (a) Page, P. C. B.; Rassias, G. A.; Bethell, D.; Schilling, M. B. *J. Org. Chem*. **1998**, 63, 2774. (b) Page, P. C. B.; Rassias, G. A.; Barros, D.; Aradakani, A.; Bethell, D.;

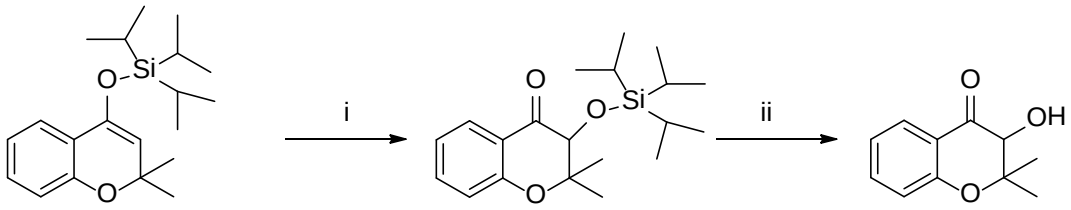
Merrifield, E. *Synlett*, **2002**, 4, 580. (c) Page, P. C. B.; Buckley, B. R.; Rassias, G. A.; Blacker, A. J. Eur. *J. Org. Chem*. **2006**, 803.

34. Page, P. C. B.; Buckley, B. R.; Heaney, H.; Blacker, A. *J. Org. Lett*. **2005**, 7, 375.
35. Lygo, B. L.; Davison, C.; Evans, T.; Gilks, J. A. R.; Leonard, J.; Roy, C. E. *Tetrahedron*, **2011**, 67, 10164.
36. Nordin, I. C.; J, A. T. *Tet. Lett.* **1984**, 25, 5723.
37. Christopher, B. (**2011**). (The Development and Application of Organocatalytic Asymmetric Epoxidation) (Doctoral thesis, University of East Anglia, Norwich)
38. Page, P. C. B.; Rassias, G. A.; Barros, D.; A. Ardakani, D. Aradakani, A.; Bethell, D.; Merrifield, E. *Synlett*, **2002**, 4, 580.
39. Farah, M. (**2007**), Doctoral thesis, Loughborough University.
40. Mecca, T.; Superchi, S.; Giorgio, E.; Rosini, C. *Tet. Asymm.* **2001**, 12, 1225.
41. Harris, J. M.; McDonald, R.; Vederas, J. C. *J. Chem. Soc*. **1996**, 2669.

APPENDICES

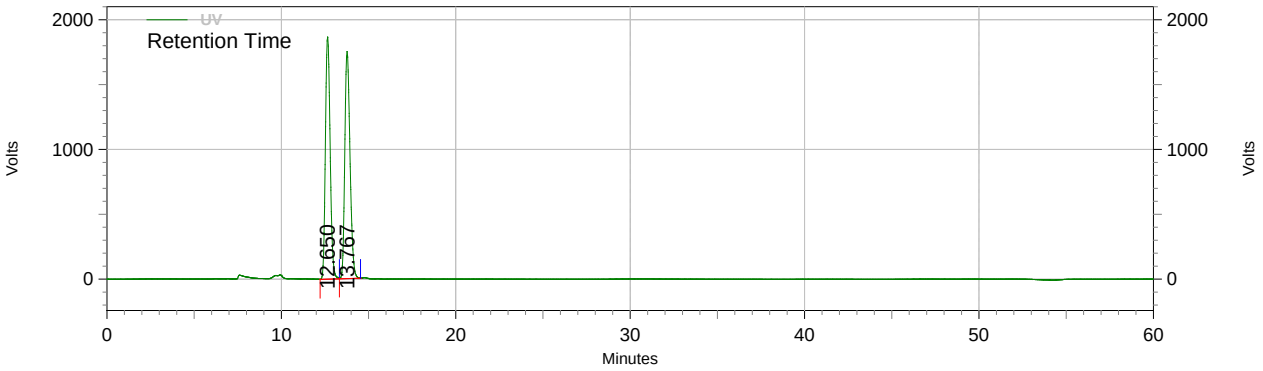
4.0 APPENDICES

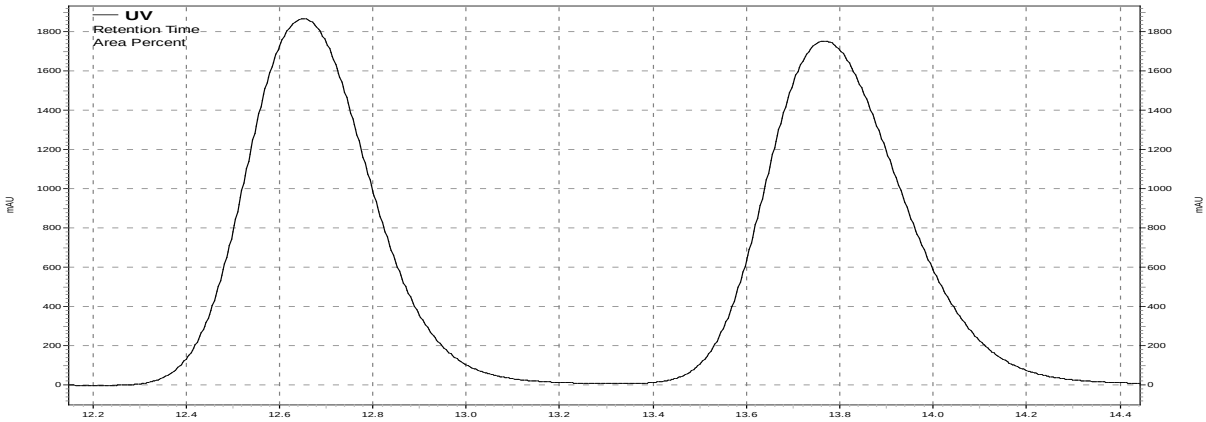
4.1 HPLC trace of racemic epoxidation of 3-Hydroxy-2,2-dimethylchroman-4-one



Reagents and conditions: (i): m-CPBA (1.5 equiv.), $NaHCO_3$, CH_2Cl_2; (ii): camphorsulphonic acid (1.1 equiv), methanol

Data File: C:\EZChrom Elite\Enterprise\Projects\Saud\sm16.dat
Method: C:\EZChrom Elite\Enterprise\Projects\yohan\Method\1 hour 99.5 0.5 0.5ml.met

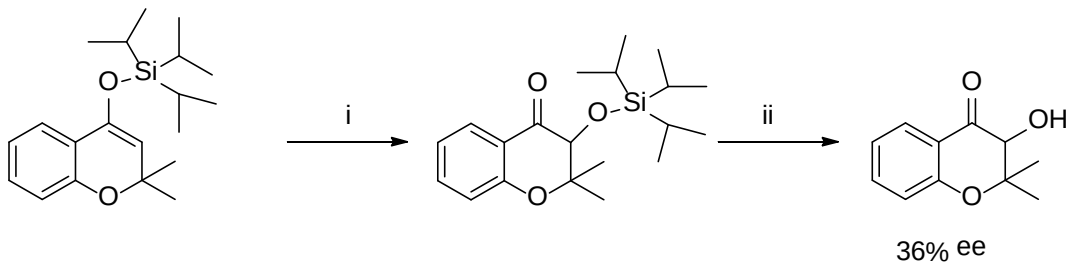




UV Results

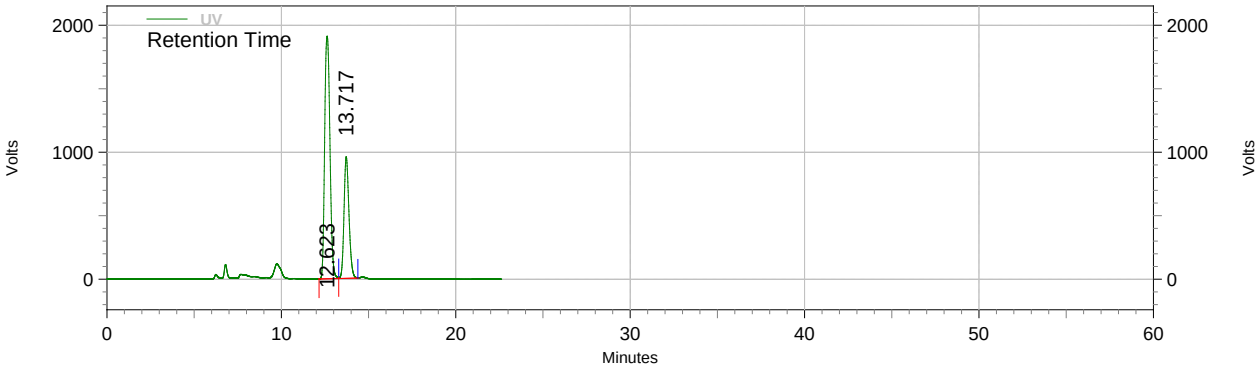
Retention Time	Area	Area %	Height	Height %
12.650	141498399	49.29	7469548	51.62
13.767	145566884	50.71	7001718	48.38
Totals	287065283	100.00	14471266	100.00

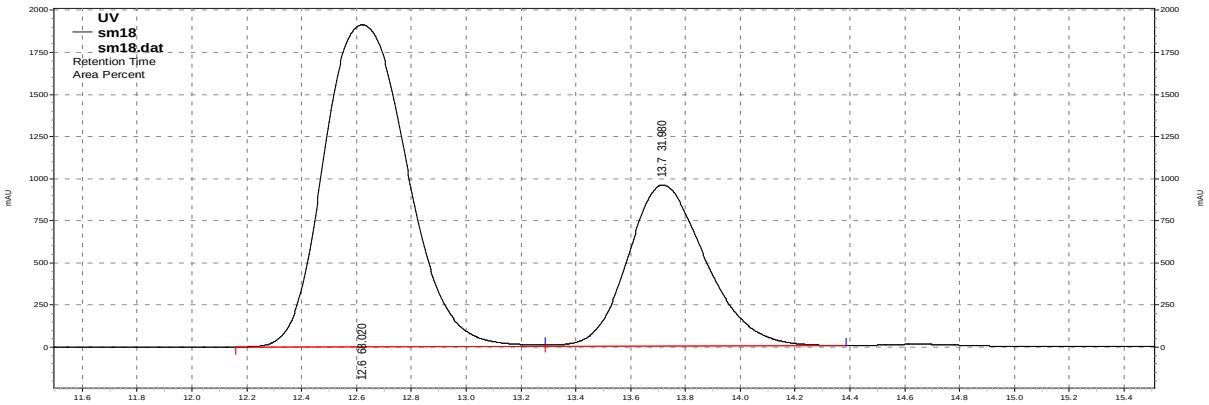
4.2 Asymmetric epoxidation of 3-Hydroxy-2,2-dimethylchroman-4-one



Reagents and conditions: (i): Catalyst **4** (0.1 equiv.), TPPP (2 equiv.), chloroform; (iii): camphorsulphonic acid (1.1 equiv), methanol.

Data File: C:\EZChrom Elite\Enterprise\Projects\Saud\sm18.dat
Method: C:\EZChrom Elite\Enterprise\Projects\yohan\Method\1 hour 99.5 0.5 0.5ml.met

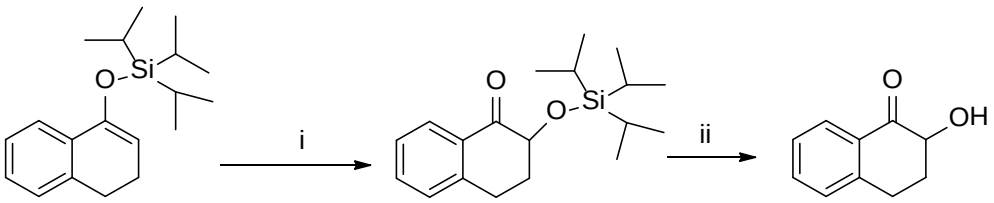




UV Results

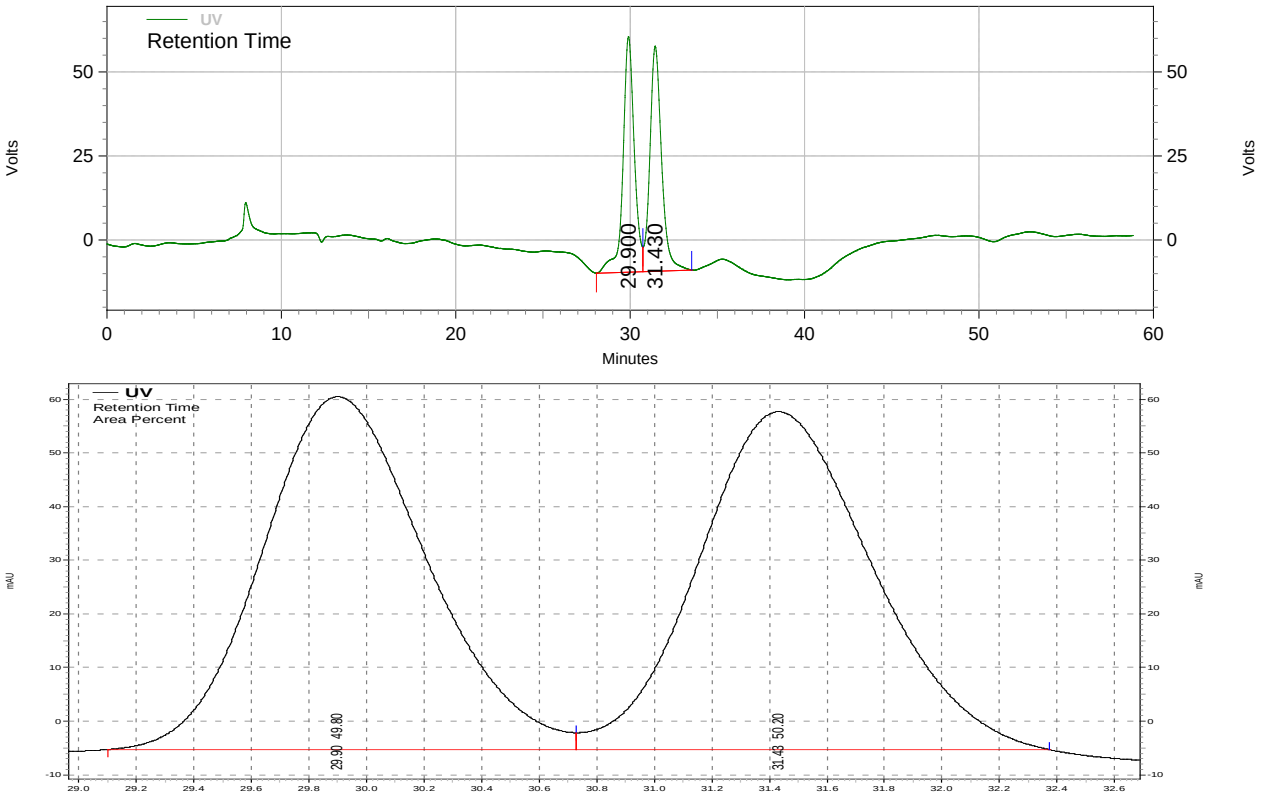
Retention Time	Area	Area %	Height	Height %
12.623	160818738	68.02	7639827	66.63
13.717	75610720	31.98	3826612	33.37
Totals	236429458	100.00	11466439	100.00

4.3 HPLC trace of racemic epoxidation of 2-Hydroxy-3,4-dihydronaphthalen-1(2H)-one



Reagents and conditions: (i): m-CPBA (1.5 equiv.), $NaHCO_3$, CH_2Cl_2; (ii) camphorsulphonic acid (1.1 equiv), methanol.

Data File: C:\EZChrom Elite\Enterprise\Projects\Saud\sm6.dat
Method: C:\EZChrom Elite\Enterprise\Projects\yohan\Method\1 hour 99.5 0.5 0.5ml.met
Acquired: 09/03/2012 12:18:22

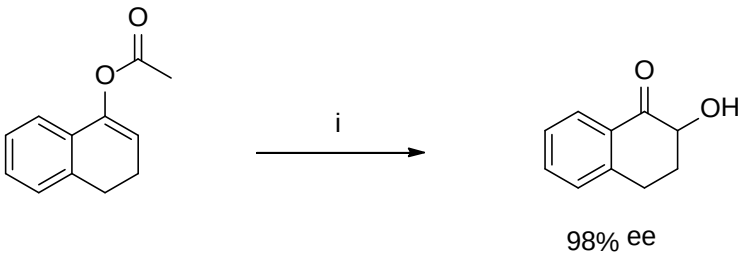


UV Results

Retention Time	Area	Area %	Height	Height %
29.900	12724692	50.50	280207	51.12
31.430	12474938	49.50	267907	48.88

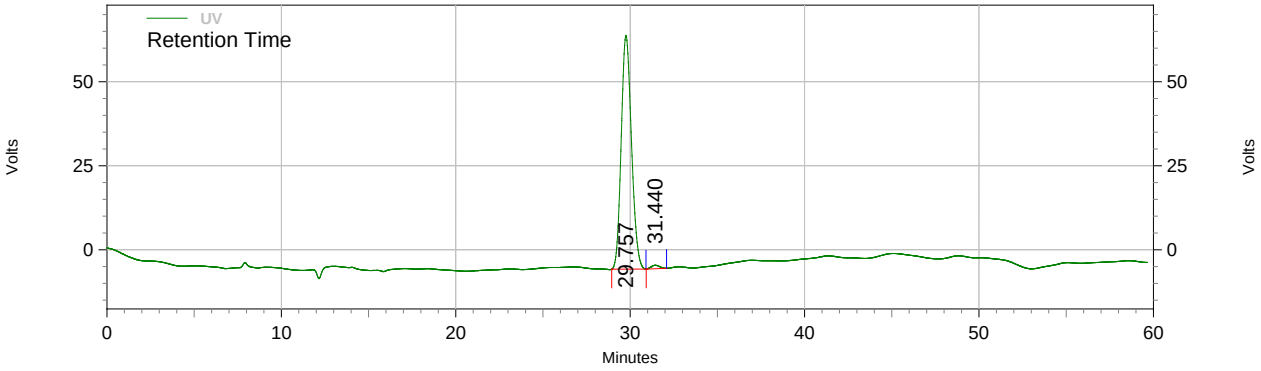
Totals	25199630	100.00	548114	100.00

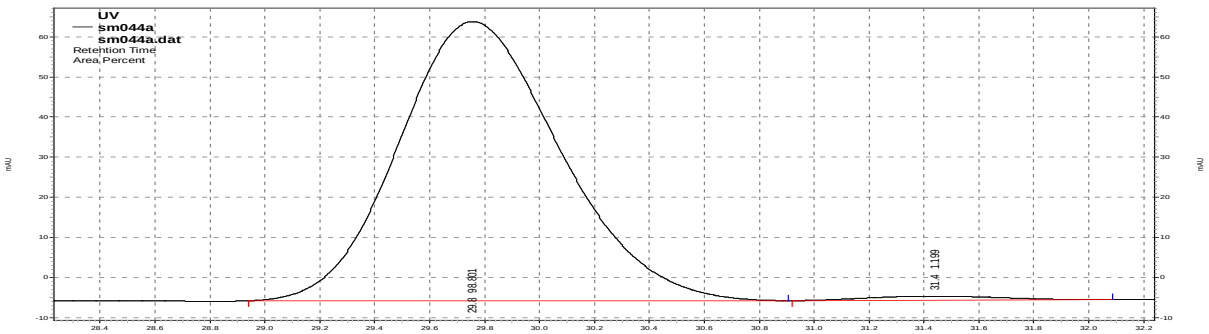
4.4 Asymmetric epoxidation of 2-Hydroxy-3,4-dihydronaphthalen-1(2H)-one



Reagents and conditions: (i): Catalyst **7** (0.1 equiv.), TPPP (2 equiv.).

Data File: C:\EZChrom Elite\Enterprise\Projects\Saud\sm044a.dat
Method: C:\EZChrom Elite\Enterprise\Projects\yohan\Method\1 hour 99.5 0.5 0.5ml.met





UV Results

Retention Time	Area	Area %	Height	Height %
29.757	11362872	98.80	278145	98.54
31.440	137941	1.20	4131	1.46
Totals	11500813	100.00	282276	100.00