NEW GREEN TECHNOLOGIES FOR ORGANOCATALYTIC ASYMMETRIC EPOXIDATION APPLICATIONS IN SYNTHESIS

Noor Armylisas Binti Abu Hassan

Submitted in partial fulfillment for the requirements for the award of Doctor of Philosophy

University of East Anglia

School of Chemistry

University of East Anglia

March 2014

©This copy of the thesis has been supplied on condition that anyone who consults it is understood to recognise that its copyright rests with the author and that no quotation from the thesis, nor any information derived there from, may be published without the author’s prior, without consent
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 or for any other degree. Except where stated, and reference and acknowledgement is given, this work is original and has been carried out by the author alone.

NOOR ARMYLISAS BINTI ABU HASSAN
ABSTRACT

New Green Technologies for Organocatalytic Asymmetric Epoxidation Applications in Synthesis

Noor Armylisas Binti Abu Hassan

This thesis describes the application of asymmetric epoxidation reactions on chromene substrates mediated by Page’s iminium salt catalysts. Organocatalytic asymmetric epoxidation is an efficient tool to access enantiomerically rich epoxides. This study is divided into three main parts which are discussed in each chapter. The first part of this research is the preparation of iminium salt catalysts followed by synthesis of several chromene substrates. The final part is the application of the asymmetric epoxidation of the readily prepared iminium salts on chromene substrates.

The first chapter reviews brief introduction and historical background of organocatalysis, chromene substrates and asymmetric epoxidation reactions. Towards the end of the chapter, several examples are described of past and current development of asymmetric epoxidation by organocatalysts. In the last part of Chapter 1, the discussion focuses on asymmetric epoxidation on chromene substrates. Chapter 2 discusses the preparation of Page’s iminium salts and improvement of previous methods followed by several approaches to synthesis of chromene substrates. The final part is discussing application of asymmetric epoxidation using synthesized iminium salts on the chromene substrates. Excellent enantioselectivities were observed in nonaqueous condition using TPPP as oxidant for 6-cyano-2,2′-dimethylchromene giving ee >99% while reactions under aqueous conditions afforded the corresponding diol giving ees as high as 71%.

In Chapter 3, experimental procedures and data for all the compounds synthesized are included. Appendices contain HPLC trace data, NMR and IR data of several compounds.
Acknowledgements

Firstly thank you Allah, Alhamdulillah for this blessing and the chance YOU gave me. I am very grateful and will always be for everything I’ve received throughout my life.

I would like to extend my sincere gratitude to my supervisor Professor Philip Bulman Page for giving me the wonderful opportunity to come to Norwich and conducting my PhD research under his instruction at University of East Anglia. The guidance, support, patience and repeated explanations were invaluable. Also, I would like to thank Dr. Yohan Chan for being there in the lab, giving advice and teaching me the chemistry, fixing the HPLC. Thanks Yo! To my second supervisor, Dr. Chris Richards and all the lecturers in Organic Chemistry Department, UEA, I am indebted for all the lessons and help I got for the past three and half years.

I would like also to thank past members; Dr. Wei-Wei Wang and Miklos de Kiss – the lovely couple who helping me going through my first year in the lab, zillion thanks to Dr. David Day – patiently answering my epoxidation and mechanism questions, willingly scanning through my thesis and helped me with my poor English, Brian Mahoney – the one who is always having fun in the lab, Dr. Chris Bartlett, Dr. Chris Pearce, Priscilla Mendonca, Ian Strutt, Tara Dixon, unforgettable and cheerful guy Franklin Frimpong – RIP. All the present members of Page’s group, especially go to Cristina Macarov for always trying to cheer me up, Mohammed – who always sharing the papers he found, Francesca Kinsey, James Harvey, Saud for all the fun and banter along the way.

To all Malaysian fellows in Norwich who had been with me throughout my PhD study years – Cik Umi, kak Yana and family, thanks for accepting me in your lovely home, all my sisters I met here in Norwich especially Dr. Sharifah, for showing me the fun living in England, kak Suriyani, kak Widad and abang Rizal, Dr. Anis Shobirin and family, and also all other families. I would like to also show my appreciation to Dr. Sam Chan, Leong Ka-Hui, Elmie Abu Bakar, Amirul, Diba Rinol, Sara Syahrain, and all the other Malaysians I’ve known all
these years. Special thanks to kak Laili and family for taking care of me, cooked for me and gave me advice in so many things in life.

To my wonderful family, I couldn’t have completed my PhD without you all. You are everything to me. Special thanks to my parents, Azizah binti Long and Abu Hassan bin Mahmad. Your encouragement and love has gotten me through all the difficult times and I am so grateful for the non-stop support and life-guidance from both of you. Thank you for always telling me I could achieve whatever I want to do in life. This whole thesis is dedicated to both of you. To all my beloved sisters – Azians, Noor Hassliza’s, Noor Azleen’s, Noorulakmar Fakhiah, my brothers – Noorkamarul Hairuls, Noor Azlizan’s, my little brother – Noor Hazerul Hisyam’s, sister-in-laws and brother-in-laws – thanks for all the support you showed from preparing all the needs for me to start studying overseas, sending me off to England, picking me up from the airport, the advice and love had all gave me strength to keep my study going. I love you all.

I strongly believe I wouldn’t be able to finish my PhD successfully without everyone I mentioned above and everyone around me that I missed out here.

The loss of two treasures in my life; my “Tok Wan” in 2012 and my 3-day-old little niece whom I couldn’t even meet on 21st February 2014; Fiqah Alaisya binti Ahmad Izwan. Words cannot even begin the sorrow but my prayers will always be with you.
### Abbreviation

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Ac₂O</td>
<td>acetic anhydride</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobis(isobutyronitrile)</td>
</tr>
<tr>
<td>ANDA</td>
<td>abbreviated new drug application</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>argon gas</td>
</tr>
<tr>
<td>BPh₄</td>
<td>tetraphenylborate ion</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>BzCl</td>
<td>benzoyl chloride</td>
</tr>
<tr>
<td>CSA</td>
<td>camphorsulfonic acid</td>
</tr>
<tr>
<td>DBU</td>
<td>1, 8-diazabicycloundec-7-ene</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>2, 3-dichloro-5, 6-dicyanobenzoquinone</td>
</tr>
<tr>
<td>DET</td>
<td>diethyl tartrate</td>
</tr>
<tr>
<td>DIPT</td>
<td>diisopropyl tartrate</td>
</tr>
<tr>
<td>DMAP</td>
<td>(N,N)-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMDO</td>
<td>dimethyldioxirane</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent</td>
</tr>
</tbody>
</table>
er enantiomeric ratio
Et$_2$O diethyl ether
EtOAc ethyl acetate
EtOH ethanol
g gram(s)
GC gas chromatography
h hour(s)
HPLC high performance liquid chromatography
Hz Hertz
IUPAC International Union of Pure and Applied Chemistry
IVIVC in-vitro and in vivo correlation
J coupling constant
KR kinetic resolution
M molar
$m$-CPBA meta-chloroperoxybenzoic acid
MeCN acetonitrile
MeOH methanol
MHz mega hertz
mL millilitre
mmol milimol
MsCl mesyl chloride
NaBPh$_4$ sodium tetraphenylborate
NaOMe sodium methoxide
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NDA</td>
<td>new drug application</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>o-</td>
<td>ortho-</td>
</tr>
<tr>
<td>p-</td>
<td>para-</td>
</tr>
<tr>
<td>p-TsOH</td>
<td>para-toluenesulfonic acid</td>
</tr>
<tr>
<td>PhB(OH)$_2$</td>
<td>phenylboronic acid</td>
</tr>
<tr>
<td>PMC</td>
<td>2,2,5,7,8-pentamethyl-6-hydroxychroman</td>
</tr>
<tr>
<td>RBF</td>
<td>round bottom flask</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>SUPAC</td>
<td>scale-up and post-approval changes</td>
</tr>
<tr>
<td>TBARS</td>
<td>thiobarbituric acid-reactive substance</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBHP</td>
<td>tert-butyl hydroperoxide</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>trifluoroacetic anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>Ti</td>
<td>titanium</td>
</tr>
<tr>
<td>Ti (O-i-Pr)$_4$</td>
<td>titanium tetra-isopropoxide</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMHQ</td>
<td>trimethylhydroquinone</td>
</tr>
<tr>
<td>TMS</td>
<td>tetramethylsilane</td>
</tr>
</tbody>
</table>
TPPP  
 tetraphenylphosphonium monoperoxysulfate

TRF  
 tocotrienol-rich-fraction
Table of Contents

CHAPTER 1 INTRODUCTION ................................................................. 1

1.1 Green Technologies and Green Chemistry................................. 1

1.2 Organocatalysis ........................................................................ 1

1.2.1 Asymmetric Organocatalysis ............................................. 4

1.2.1.1 Historical Background of Asymmetric Organocatalysis .......... 4

1.2.2 Advantages of Organocatalytic Research ............................. 9

1.2.3 Iminium Salts as Organocatalysts in Asymmetric Epoxidation ..... 11

1.2.3.1 Introduction to Iminium Catalysis ................................. 11

1.2.3.2 Historical Development of Iminium Catalysis .................. 11

1.2.3.3 Chiral Iminium Salt-Catalysed Epoxidation ..................... 14

1.3 Chromene Substrates ............................................................. 21

1.3.1 2H-Chromenes (2H-1-Benzopyrans) .................................... 21

1.3.2 Properties of 2H-Chromene Compounds and Their Derivatives .......... 22

1.3.2.1 Biological Activities .................................................... 22

1.3.2.2 Photochromism .......................................................... 26

1.3.3 Syntheses of 2H-Chromenes ............................................. 26
1.3.4  Asymmetric Epoxidation of Chromenes................................. 30

1.4  Asymmetric Epoxidation.......................................................... 34

1.4.1  Some Definitions in Asymmetric Synthesis............................. 34

1.4.1.1  Enantioselectivity, Chirality and Stereochemistry.................. 34

1.4.1.2  Stereochemistry............................................................... 35

1.4.1.3  Chirality........................................................................... 35

1.4.1.4  Enantiomeric Excess (ee).................................................. 36

1.4.2  Asymmetric Epoxidation......................................................... 36

1.4.3  Catalytic Asymmetric Epoxidation.......................................... 37

1.4.4  Metal-Catalysed Asymmetric Epoxidation............................... 38

1.4.4.1  Sharpless Epoxidation....................................................... 39

1.4.4.2  Jacobsen-Katsuki Epoxidation............................................ 40

1.4.5  Organocatalysed Asymmetric Epoxidation............................... 42

1.4.5.1  Dioxirane-Catalysed Epoxidations....................................... 42

1.4.5.2  Juliá Epoxidations............................................................. 45

1.4.5.3  Chiral-Oxaziridinium-Catalysed Asymmetric Epoxidation......... 45

1.5  Conclusion................................................................................. 53

1.6  References for Chapter 1............................................................. 54
CHAPTER 2 RESULTS AND DISCUSSION

2.1 Synthesis of Oxaziridinium Salts

2.1.1 Catalysts Selection and Preparation

2.1.2 Synthesis of Chiral Primary Amines

2.1.3 Synthesis of Catalysts based on Dihydroisoquinoline Motif

2.1.4 Synthesis of Catalysts based on Biphenyl-Azepinium Motif

2.1.5 Synthesis of Catalysts based on Binaphthyl-Azepinium Motif

2.2 Synthesis of Chromene Substrates

2.2.1 6-Hydroxy-2, 5, 7, 8-tetramethyl-2-(4-methylpent-3-ene) chroman

2.2.2 6-Hydroxy-2, 2, 5, 7, 8-pentamethylchroman

2.2.3 6-Cyano-2, 2-dimethylchromene

2.2.4 6-Hydroxy-2, 5, 7, 8-tetramethylchromene-2-carboxylate

2.2.5 Protection of the Phenolic Hydroxyl Functional Group

2.2.5.1 Acetate Protection of the Phenolic Hydroxyl Group

2.2.5.2 Trifluoroacetate Protection of the Phenolic Hydroxyl Functional Group

2.2.5.3 Benzoate Protection of the Phenolic Hydroxyl Functional Group
2.2.5.4 Methyl Ether Protection of the Phenolic Hydroxyl Functional Group........................................... 110

2.2.6 Synthesis of 3, 4-Dehydro Derivatives of Chromane................................................................. 112

2.3 Asymmetric Epoxidation of Chromene Substrates................................................................. 116

2.3.1 Determination of Enantiomeric Excess........................................................................... 116

2.3.1.1 Chiral HPLC.................................................................................................................. 116

2.3.1.2 1H-NMR with the Chiral Shift Reagent

Eu(hfc)₃............................................................................................................................................... 119

2.3.2 Preparation of Racemic Epoxides.................................................................................. 121

2.3.3 General Reaction Conditions of Asymmetric Epoxidation.................................................. 128

2.3.4 Catalysts Testing on Asymmetric Epoxidation...................................................................... 129

2.3.5 Asymmetric Epoxidation of Chromene by Iminium Salt Catalysts........................................ 131

2.4 Conclusion and Future Works......................................................................................... 137

2.5 References for Chapter 2............................................................................................. 139
CHAPTER 3 EXPERIMENTAL PROCEDURES ................................................................. 145

3.1 General Experimental ................................................................. 145

3.1.1 Physical Characterisation and Spectroscopic Techniques ......................... 145

3.1.2 Enantiomeric Excess Determination ...................................................... 146

3.1.3 Chromatographic Techniques .......................................................... 146

3.1.4 Reagent, Solvent and Apparatus Preparation ........................................ 147

3.2 Numbering Systems ................................................................. 147

3.3 Individual Experimental Procedures ................................................ 149

3.3.1 Synthesis of Iminium Salt Organocatalysts ......................................... 149

3.3.2 Synthesis of Chromene Substrates ....................................................... 174

3.3.3 Catalytic Asymmetric Epoxidation Reaction ........................................ 196

3.4 References for Chapter 3 .............................................................. 205

APPENDICES ............................................................................................ 207

xiv
CHAPTER 1
INTRODUCTION
1 INTRODUCTION

1.1 Green Technologies and Green Chemistry

The field of “green technology” encompasses a continuously evolving group of methods and materials, to monitor, model and conserve the natural environment and resources, and to control the negative impacts of human involvement. Examples of green technology subject areas include energy, green building, environmentally preferred purchasing, green chemistry and green nanotechnology.\(^1\)

As for this thesis, we are focusing on the green chemistry scope for the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances. We are investigating the development of a green and highly efficient asymmetric epoxidation system mediated by metal-free organocatalyst, and less hazardous oxidant such as Oxone\(^\circledR\) and TPPP.

1.2 Organocatalysis

In the modern world of chemistry, the field of organocatalysis has attracted a lot of attention. The term organocatalyst comes from concatenation of two general words in chemistry, “organic” and “catalyst”. It is a small organic molecule where an inorganic element or transition metal is not involved in the active principle.\(^2\) Organocatalysis provides a means of accelerating chemical reactions with a substoichiometric amount of organic molecules, which do not contain a metal element.\(^3\) Generally the term catalysis is synonymous with transition metal-mediated reactions or enzyme-aided biocatalysis. However, since the field of organocatalysis developed, it has become topical in the chemistry world, with at least 1,500 manuscripts describing the use of organocatalysts in more than 130 discrete reaction types published between 1998 and 2000.\(^4\) Over 4,000 publications have been reported in the area of organocatalysis up until 2011. In year 2010 alone, there were over 1,000 articles published compared to just over 800 in 2009.
Considering the word organocatalyst was coined only 10 years ago – even though organocatalyst reactions have been around longer – this is considered as an impressive achievement in organic chemistry.\(^5\)

Since then, organocatalysis has become an additional efficient tool that can achieve remarkably selective and efficient transformations – as intense research efforts in this emerging area are proving, complementing the current methods rather than competing. Organocatalysts offer several advantages. They are usually robust, inexpensive and readily available, non-toxic and they are often available as both enantiomers. No harsh reaction conditions, such as inert atmosphere, extremely low temperature, dry solvents, etc., in many instances, are required due to their inertness toward moisture and oxygen.\(^6\) Organocatalytic methods seem to be especially attractive for the preparation of compounds that do not tolerate any metal contamination, for instance, pharmaceutical products, because of the absence of transition metal. A selection of typical organocatalysts is shown in Figure 1.1.

**Figure 1.1 - Some typical organocatalysts**

![Figure 1.1 - Some typical organocatalysts](image-url)
Some organocatalytic reactions have evolved from the ligand chemistry of organometallic reactions. Large arrays of ligands were developed for metal-mediated enantioselective catalytic reactions and are still among the most effective organocatalysts. It is thus not surprising that there are metal catalysed reactions in which the metal-free ligand is known to be active by itself, even in the same enantioselective transformation. One example is the use of L-proline 1 for the Michael addition reaction. Yamaguchi reported the asymmetric Michael addition catalysed by L-proline rubidium.\textsuperscript{7–9} In 2001, List reported efficient proline-catalysed Michael additions of unmodified ketones to nitro olefins with moderate ee values.\textsuperscript{10}

Compared to organometallic processes, organocatalytic reactions can be more closely related to enzyme- or antibody-catalysed reactions. Indeed, these small organic molecules, which are sometimes also described as artificial enzymes\textsuperscript{11} or as enzyme mimetics, show some characteristic features of bioorganic reactions which often follow saturation or Michaelis-Menten kinetics reminiscent of a mechanism that involves the reversible formation of an enzyme-substrate complex.\textsuperscript{12}

\textbf{Table 1-1 - Examples of simple well-established metal-based catalysis process and biocatalysis reactions}

<table>
<thead>
<tr>
<th>Metal-based Catalysis</th>
<th>Biocatalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) \textbf{Iron in the Haber process}\textsuperscript{13}</td>
<td>(1) Enantioselective reduction of ketone by yeast</td>
</tr>
<tr>
<td>( \text{N}_2(\text{g}) + 3 \text{H}_2(\text{g}) \xleftrightarrow{\text{Fe}} 2 \text{NH}_3(\text{g}) )</td>
<td>Yeast Petroleum ether</td>
</tr>
<tr>
<td>(2) \textbf{Nickel in the hydrogenation of C=C bonds}</td>
<td>(2) Lyases – addition-elimination on C=C, C=N, C=O bonds</td>
</tr>
<tr>
<td>( \text{CH}_2=\text{CH}_2 + \text{H}_2 \xleftrightarrow{\text{Ni}} \text{CH}_3\text{CH}_3 )</td>
<td>( \text{NH}_3 ) aspartase</td>
</tr>
<tr>
<td>(3) \textbf{Vanadium(V) oxide in the Contact Process}\textsuperscript{14}</td>
<td>(3) Hydrolases – formation/breakdown of</td>
</tr>
</tbody>
</table>
1.2.1 Asymmetric Organocatalysis

Asymmetric organocatalysis, in which a chiral organic molecule catalyses an enantioselective transformation, is a rapidly growing field. A collection of chiral organocatalysts have been involved in asymmetric synthesis, such as the typical examples of proline, cinchona alkaloids, such as quinine and various sugar-, amino acid-, or peptide-derived compounds. Although the first examples were reported many decades ago, the area of asymmetric organocatalysis became a main focus of research only recently while the last decade has seen an exponential growth in the field.

1.2.1.1 Historical Background of Asymmetric Organocatalysis

Until a few years ago, it was generally accepted that transition-metal complexes and enzymes were the two main classes of very efficient asymmetric catalysts. Throughout the last century, small organic molecules were rarely used as catalysts despite the fact that some of the very first asymmetric catalysts were purely organic. In 1871, the first “pure” organocatalytic reaction was discovered accidentally, with the transformation of dicyan to oxamide in the presence of an aqueous solution of acetaldehyde by J. von Liebig (Scheme 1-1). This role of acetaldehyde was identified to be similar to “ferment” which was the term used for enzymes. This efficient reaction forms the basis of the Degussa oxamide synthesis that is applicable on an industrial scale.
1.2.1.1 Cinchona Alkaloids

![Figure 1.2 - Structure of (-)-quinine 2 and (+)-quinidine 11](image)

In the beginning of the 20\textsuperscript{th} century, the use of small organic molecules as catalysts in chemical transformations was reported by G. Bredig.\textsuperscript{17} This finding was the first example of an organocatalytic enantioselective reaction ever reported. He reported a modestly enantioselective cinchona-catalysed cyanohydrin synthesis. The cinchona alkaloids represent a class of natural products that possess several important features rendering them useful as asymmetric organocatalysts. They are readily available, inexpensive, and as in the case of diastereomeric pairs such as quinine 2 and quinidine 11 (Figure 1.2), allow access to either enantiomeric product. The enantioselectivities were less than 10\%, however this work was conceptually important (Scheme 1-2).

![Scheme 1-2- Bredig’s decarboxylation of camphorcarboxylic acid](image)

Later, after a century of transition from achiral to asymmetric organocatalytic reactions, in 1960, by using O-acetylquinine 13 as catalyst, (R)-phenyl methylproionate 14 was generated from methylphenyl ketene 12 with up to 74\% \textit{ee} (Scheme 1-3),\textsuperscript{18} reported by Pracejus. This process showed that organocatalysts could give significant enantioselectivities.
1.2.1.1.2 Proline

In 1970s, the development of the Hajos-Parrish-Eder-Sauer-Wiechert reaction, i.e. the proline 1-catalysed intramolecular asymmetric aldol cyclodehydration of the achiral triketone by Hajos et al. and Eder et al. has become a major contributor in this organocatalysis field. Eder, Sauer and Wiechert isolated the cyclized aldol condensation product in one step using 1 and an acid co-catalyst (Scheme 1-4a). This finding brought a milestone in the area of asymmetric organocatalysis as they published the first highly enantioselective catalytic aldol reactions using a small amount of simple amino acid 1 as the catalyst. Excellent yield and ee was reported for the asymmetric Robinson annulations of achiral triketones 17 where in the second step acid catalysed dehydration furnished the condensation products 19 reported by Hajos and Parrish in excellent yields and ees for both steps (Scheme 1-4b).
Hajos suggested the role of H bonding in the asymmetric cyclization reaction and that the use of aprotic solvent should interfere less with a H-bonded transition state. Subsequent investigation by Agami et al. led to the proposed mechanism involving formation of enamine intermediate 20 (Figure 1.3) which then has been confirmed by mechanistic study as reported by Barbas. L-Proline 1 contains both a nucleophilic secondary amino group and a carboxylic acid moiety functioning as a Brønsted acid. This facilitates a highly pre-organized transition state during the reaction pathway, which results in exceptionally high enantioselectivities.

The transformation of the side-chain carbonyl into an enamine by proline was possible due to secondary amine function of proline, and is followed by nucleophilic attack of the enamine at a ring carbonyl group that gives rise to the cyclization. Less-substituted tertiary enamine is known for its greater reactivity which led to the selective activation of the side-chain carbonyl group.

List, Lerner and Barbas have reported a direct intermolecular aldol reaction between unmodified acetone and a variety of aldehydes (Scheme 1-5). They proposed in the aldol reaction, enamine attack occurs on the re-face of the aldehyde (21, Figure 1.4). This high enantiofacial selectivity is controlled by minimising steric interactions of the aldehyde substituent. Thus attack of the enamine on the si-face of the aldehyde leads to the unfavourable transition state 22 (Figure 1.4). The hydrogen transfer between the carboxylate on proline and the oxygen of the aldehyde also plays an important role in the enantioselectivity by limiting which face of the enamine attacks the aldehyde.
The work of List, Lerner and Barbas was significant because it showed that the underlying mechanism of the Hajos-Parrish reaction could be extended and applied to transformations that have broader applicability (specifically, the intermolecular aldol reaction). Moreover this work showed that small organic molecules (such as proline) could catalyse the same chemical reactions as much as larger organic molecules (enzymes) by using similar mechanisms.

The quinidine alkaloids 11 and \( l \)-proline 1 were the best known organocatalysts for some time. The revival of this chemistry is continuously growing with an increasing number of research groups all over the world focusing on a wide range of new organocatalysis systems with a variety of chemical reactions. Examples of research groups involved in developing a new system for asymmetric organocatalysis include hydrogenation by Wills, aziridination using bifunctional organocatalysis by Dixon, alcoholysis by Schreiner and many more. This rapid growth is due to the advantages offered by this field.
1.2.2 Advantages of Organocatalytic Research

Organocatalysis has now become one of the main branches of enantioselective synthesis alongside the other, previously accepted branches, enzymatic catalysis and organometallic catalysis. The sudden and rapid growth of the field of organocatalysis is contributed by three factors as suggested by MacMillan: first, the conceptualization of the field; second, the advantages of organocatalytic research; and the third, the advent of generic modes of catalyst activation.4

The field of organocatalysis grew quickly, once it had been defined. Such rapid adoption is possible only when a field offers real advantages to those who exploit the resulting technologies. In this case, the fundamental advantages of organocatalysis were quickly recognised by the chemical synthesis community, namely the ease and low cost of carrying out such reactions in the laboratory and the potential for new lines of academic thought and investigation.

Before 1998, the state of the art in asymmetric catalysis involved metal-based chiral catalysts almost exclusively, and these catalysts allowed a wealth of oxidations, reductions, σ-bond insertions, π-bond activations and Lewis-acid catalysed reactions. Although the impact of metal-based catalysts on chemical synthesis cannot be understated, some (but certainly not all) organometallic systems can be expensive, toxic and/or sensitive to air and moisture.

The growth of organocatalysis brought prospects of a complementary mode of catalysis, with the potential for savings in cost, time and energy, an easier experimental procedure, and reductions in chemical waste. These benefits arise from three factors. First, organic molecules are generally insensitive to oxygen and moisture in the atmosphere. Because of their inertness towards water and oxygen, demanding reaction conditions, e.g. inert atmosphere, low temperature, absolute solvents, etc., are in many instances not needed, so there is no need for special vessel, storage containers and experimental technique, or for ultra-dry reagents and solvents. Second, a wide variety of organic reagents – such as
amino acids, carbohydrates, and hydroxy acids – are naturally available from biologically sources as single enantiomers. Simple organocatalysts are therefore usually cheap to prepare and readily accessible in a range of quantities, suitable for small-scale reactions. Third, small organic molecules are typically non-toxic and environmentally friendly, increasing the safety of catalysis in both biological research and chemical research across all research settings, including industry and academic institutions.

The combinations of these factors substantially lowered the entry costs for researchers who were interested in developing enantioselective catalysis. With no need for glove boxes, inert gases, ultra-dry solvents or even a high level of experimental expertise, it is not surprising that the field quickly become flooded with research groups from around the globe. Indeed, the increase in competition helped to accelerate the pace of innovation and discovery, albeit perhaps at the expense of ‘elbow room’ for those in this popular field.

Some critics suggest that low turnover numbers might limit the potential uses of organocatalysis for industrial applications, but this view is simplistic and dogmatic for any larger quantities than metal-based ones for the same price. Moreover, it is widely recognised in manufacturing that the removal of toxic catalyst-related impurities from the waste stream can often have a larger financial impact than the turnover number of the catalyst. Organocatalysts are typically less toxic than metal-based catalysts. Because of the absence of transition metals, organocatalytic methods seem to be especially attractive for preparation of compounds in which metal contamination is not tolerated, such as pharmaceutical and agrochemical products, in which the presence of hazardous metallic traces is inadmissible in the final product. Consequently, this methodology will be important in industry, due to its versatility and its favourable environmental impact.
1.2.3  Iminium Salts as Organocatalysts in Asymmetric Epoxidation

1.2.3.1  Introduction to Iminium Catalysis

Iminium salts are more electrophilic than the corresponding aldehydes or ketones. For this reason, the reversible formation of the iminium salt activates the carbonyl component towards nucleophilic attack. This type of activation is thus related to that induced by Lewis or Brønsted acids. It should be emphasized that the activation provided by iminium ion formation is very general, and many types of nucleophile – electrophile interactions can be envisaged.

The iminium-activated reaction will be catalytic only if the amine catalyst is released in a final hydrolysis or elimination step. As an example, nucleophilic addition of hydride ion to the C=N double bond is the basis of reductive amination processes. These reactions proceed via iminium intermediates and are properly called iminium-activated reactions. However, they are not iminium-catalysed, since the amine becomes trapped in the reduction step.

1.2.3.2  Historical Development of Iminium Catalysis

Iminium salt catalysts are Lewis base catalysts, which is one of the most powerful and general strategies of organocatalysis. The historical development of the introduction of the concept of iminium catalysis is quite unclear. Knoevenagel condensation is probably the earliest recorded example of an iminium-catalysed process mediated by primary or secondary amines. The idea that the Knoevenagel reaction might proceed using iminium catalysis emerged slowly. Knoevenagel himself suggested a possible role for the aldehyde-derived imines or aminals in this reaction. After more than 40 years, in 1931, Blanchard et al. suggested that positive ions are involved in the catalysis of the Knoevenagel reaction with secondary amines, and twenty years later, kinetic evidence for imine/iminium intermediates in Knoevenagel-type condensations was presented by Crowell and Peck. Today, the contribution of iminium catalysis to the Knoevenagel reaction is generally recognised.
The decarboxylation of $\beta$-ketocarboxylic acids was the first reaction where iminium ions were postulated as active intermediates. In 1907, Pollak reported different proteins and extracts as well as different amino acids and ammonium salts catalyzed the decarboxylation of acetoacetic acid and suggested that imines are likely intermediates in these reactions. In 1933, Pederson also suggested the iminium ion as intermediate in the decarboxylation reaction.

Table 1-2 – Summary of iminium catalysis development history

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1894-1898</td>
<td>Knoevenagel discovers a family of iminium-catalysed condensation reactions:</td>
</tr>
<tr>
<td>1907</td>
<td>$\beta$-decarboxylation reactions discovered by Pollak and he suggested imine as intermediate</td>
</tr>
<tr>
<td>1931</td>
<td>Blanchard suggested positive ion catalysis in Knoevenagel reaction</td>
</tr>
<tr>
<td>1934</td>
<td>Pederson proposes the intermediacy of iminium ions as intermediates in the decarboxylation reaction</td>
</tr>
<tr>
<td>1937</td>
<td>Langenback discovers the first iminium-catalysed conjugate addition</td>
</tr>
<tr>
<td>Year</td>
<td>Event</td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
</tr>
<tr>
<td>1953</td>
<td>Crowell and Peck showed kinetic evidence for a Schiff base intermediate in the Knoevenagel condensation.</td>
</tr>
<tr>
<td>1962</td>
<td>Jencks discovers aniline catalysis of semicarbazone formation.</td>
</tr>
<tr>
<td>1976</td>
<td>Lusinchi and Hanquet first reported an oxaziridinium salt as a reactive intermediate, which is able to transfer oxygen to alkene substrates with regeneration of the iminium salts.</td>
</tr>
<tr>
<td>1976</td>
<td>The role of iminium activation in cycloadditions recognised by Viehe and Baum.</td>
</tr>
<tr>
<td>1981</td>
<td>Woodward and co-workers use asymmetric proline catalysis to effect an iminium-catalysed deracemization and intramolecular aldol reaction in the total synthesis of erythromycin.</td>
</tr>
<tr>
<td>1991</td>
<td>The first catalytic asymmetric iminium-catalysed conjugate addition reactions discovered by Yamaguchi.</td>
</tr>
</tbody>
</table>
MacMillan reports the first asymmetric iminium-catalysed cycloaddition reaction.

**1.2.3.3 Chiral Iminium Salt-Catalysed Epoxidation**

Oxaziridines are organic molecules that feature a three-membered ring containing a carbon atom and two heteroatoms, nitrogen and oxygen, and are generally prepared from imines by oxidation with peroxo compounds such as m-CPBA and Oxone® (Scheme 1-6). Oxaziridines are nitrogen analogues of dioxiranes, and constitute an important class of organic oxidants under non-aqueous conditions. N-H oxaziridines, first reported in the early 1960s, induce amination of nitrogen, oxygen, sulphur and carbon nucleophiles, including aziridination of alkenes and amination of enolates. Indeed, Davis and co-workers developed very successful systems of asymmetric oxidation of sulphides to sulfoxides by oxaziridines, but the systems are less successful for alkenes.

Scheme 1-6 - Preparation of oxaziridine using m-CPBA

Oxaziridines were first discovered in 1956 by Emmons. Since the first discovery of this structure, it has received an enormous attention from researchers – principally for two reasons. Due to the presence of the highly strained three-membered ring and the relatively weak N-O bond, oxaziridines allow for electrophilic transfer, despite the nucleophilic property of nitrogen and oxygen, which also results in low basicity of the oxaziridine.
nitrogen compared to amines. When the substituent of nitrogen atom of the oxaziridine is small, it is the preferred site of nucleophilic attack, and when the nitrogen substituent has greater steric bulk, nucleophiles tend to attack on oxygen. Another remarkable property is that this system possesses the structural elements that seem to be required to observe stereochemical isomerism at nitrogen: ring strain and an atom with unshared electron pairs attached to nitrogen.

Chiral oxaziridine reagents were also developed later, which allow for stereospecific transfer of heteroatoms. Oxaziridines are unique in their exceptionally high inversion barrier for nitrogen to retain its stereochemical configuration. Chiral (camphorsulfonyl)oxaziridines 24, first synthesized in 1988 by Davis have become a cornerstone in asymmetric synthesis (Scheme 1-7) which were reported to oxidize non-functionalized sulfides giving up to 91% ee, and to epoxidize olefins (up to 65% ee). He first reported the epoxidation of olefins by oxaziridines back in 1981.

In 1995, Page reported high enantioselectivity for asymmetric sulfoxidation of dialkyl sulfides using [(3,3-dimethoxycamphoryl)sulfonyl]oxaziridine giving excellent ee up to 98% (Scheme 1-8).
Application of oxygen transfer using oxaziridine system in total synthesis has been proved to be a success following a report by Papeo in 2009. Papeo et al. reported high selectivity of oxygen transfer by oxaziridine in the total synthesis of (-)-chaetominine 28. Oxidation of the double bond on the pyrrole ring of the tetracyclic intermediate 25 was achieved using oxaziridine 26 (Scheme 1-9) giving only one cis-diastereoisomer 27. Oxaziridinium ions are the derivative of the oxaziridine with positively charged nitrogen. Oxaziridinium salts, a related electrophilic oxygen source were first reported in 1976 by Lusinchi and Hanquet as reactive intermediates for oxygen transfer to nucleophilic substrates, including sulphides and alkenes. The oxaziridinium species is able to transfer oxygen to alkene substrates with regeneration of the iminium salts under the reaction conditions, giving overall a catalytic process. Moreover, the propensity of iminium ions to react with the Oxone® triple salt to generate the oxaziridinium species renders the development of catalytic processes possible. Oxaziridinium salts have also been obtained.
by either methylation of the corresponding oxaziridine with FSO$_3$Me or oxidation of the corresponding iminium salt with peracid (Scheme 1-10). The steroidal pyrrolinic immonium salt plays a vital role in oxidation of peracid.

![Scheme 1-10 - Initial approach by Hanquet](image)

It was, however, not until some eleven years later that a second, racemic, oxaziridinium salt 29 (Figure 1.5) was derived from dihydroisoquinolinium reported by Hanquet and his co-workers. This second oxaziridinium salt was prepared by alkylation of an oxaziridine and by oxidation of the iminium salt. In 1988, Hanquet and co-workers reported that this oxaziridinium salt can efficiently epoxidize various olefins. They further reported that the epoxidation can be carried out with in situ generated oxaziridinium salt 29 using a catalytic amount of its corresponding iminium salt with Oxone®-NaHCO$_3$ in CH$_3$CN-H$_2$O or m-CPBA- NaHCO$_3$ in CH$_2$Cl$_2$ as oxidant.

![Figure 1.5 - Compound 29, second oxaziridinium salt by Hanquet in 1987; compound 30, first enantiomerically pure chiral oxaziridinium salt by Lusinchi in 1993](image)
A reaction pathway for iminium salt-catalysed epoxidation is shown in Scheme 1-11. The iminium salt catalyst is regenerated upon epoxidation of olefin.

Asymmetric epoxidation using chiral oxaziridinium salts has also been investigated. The first enantiomerically pure chiral oxaziridinium salt 30 (Figure 1.5) was reported by Lusinchi and co-workers in 1993. This enantiomerically pure chiral oxaziridinium salt was derived from (1S, 2R)-(+) -norephedrine 34 by methylation with Meerwein’s salt and oxidation with m-CPBA from dihydroisoquinoline. Alternatively the salt could also be produced by switching the reaction order (Scheme 1-12). Epoxidations were carried out with either stoichiometric amounts of recrystallized salt or a catalytic amount of \textit{in situ} generated salt using Oxone® as the oxidant giving 89% conversion and 61% ee. Lusinchi also showed that the transition states of such reaction have strong ionic character since the reaction rate increased in polar aprotic solvents such as nitrobenzene and nitromethane as compared to reaction in DCM.\textsuperscript{52}
Since then, iminium salt catalysis has become a significant interest to be developed for epoxidation for olefins. Epoxidation is a very important reaction in organic synthesis, and the catalytic oxaziridinium-mediated epoxidation of olefins is a promising method in this field. This can be seen by contributions made into this area by a number of research groups including ours.

In 1996, Aggarwal developed binaphthyl-derived oxaziridinium system for asymmetric epoxidation giving ee as high as 71% using 1-phenylcyclohexene as substrate. Armstrong et al. reported intramolecular epoxidation using unsaturated oxaziridines, presumably via oxaziridinium salts and previously reported iminium salts derived from pyrrolidine for alkene epoxidation.

Our group has also extensively investigated the oxaziridinium system for asymmetric epoxidation since 1998. We have successfully developed several iminium salt catalysts (Figure 1.6), which are further discussed in Chapter 1.3. A range of dihydroisoquinolinium salts was developed for initial study. We then included biphenyl-derived and binaphthyl-derived iminium salt to investigate the system further.
In 2000, Rozwadowska and co-workers reported the synthesis of the single enantiomer of iminium salt 41, derived from thiomicamine 42 (Figure 1.7).\(^6\)

Naturally, any improvement in the global efficiency of the catalytic system may contribute to the development of this new methodology as an attractive and convenient alternative to the known and widely used epoxidation methods.
1.3 Chromene Substrates

Natural products play important roles in both drug discovery and chemical biology. In fact, many approved therapeutics as well as drug candidates are derived from natural sources. The chromene ring system has a central position in various classes of naturally occurring products. Chromene, as it is named in IUPAC nomenclature also known as benzopyran, has a naphthopyran cyclic skeleton as can be seen in Figure 1.8 – a benzene ring fused to heterocyclic pyran ring. Generally there are two isomers of chromene, 1-benzopyran (chromene) and 2-benzopyran (isochromene) – depending on the orientation of the fusion of the two rings.

Figure 1.8 - (a) Structural isomers of chromene, left: 2H-chromene and right: 4H-chromene; (b) structural isomers of isochromene, left: 1H-isochromene and right: 3H-isochromene

1.3.1 2H-Chromenes (2H-1-Benzopyrans)

In this thesis, the research is focused on the synthesis of 2H-chromenes for the application of Page group’s iminium salt catalyst for asymmetric epoxidation specifically of the C3-C4 double bond.

Figure 1.9 - Structures of chromenes isolated from (a) Piper gaudichaudianum and (b, 43 - 46) P. Aduncum
CHAPTER 1 - INTRODUCTION

There are many 2H-chromenes isolated as natural products. For example, there are several natural chromenes isolated from *Piper gaudichaudianum* and *Piper aduncum* (Figure 1.9), along with a series of semisynthetic derivatives, have been shown to exhibit potential trypanocidal activities against the flagellate protozoan *Trypanosoma cruzi*, the etiological agent of Chagas disease, which is responsible for the deaths of approximately 400,000 per year and affects more than 18 million people in Latin America. These biologically active chromenes have also been shown to exhibit anti-fungal and anti-tumour properties. This core structure is also found in a number of flavonoids isolated from green tea extracts such as epigallocatechin-3-gallate (EGCG) and catechin (Figure 1.10).

![Epigallocatechin-3-gallate and Catechin Structures](image)

**Figure 1.10 – Flavonoids extracted from green tea**

1.3.2 Properties of 2H-Chromene Compounds and Their Derivatives

1.3.2.1 Biological Activities

One of well-known biological activities of chromenes is as an airways selective potassium channel activator for the treatment of asthma, which include levcromakalim, and BRL 55834, (Figure 1.11). All the structures shown are biologically active 2, 2-dimethylchromenes, in which the pyran olefin has been modified in order to improve the properties of a particular lead structure or to increase library diversity. Such pyran olefins
are readily modified by hydrogenation, epoxidation, dihydroxylation, and amino hydroxylation giving rise to a large number of biologically active structures. A search of Chemical Abstracts for 2, 2-dimethylchromene alone revealed approximately 4,000 structures,\textsuperscript{71} suggesting the importance of 2H-chromenes in natural product synthesis.

![Figure 1.11 - Examples of potassium channel activator with chromane structure](image)

Isoflav-3-enes bearing containing chromene units are featured in well-known oestrogens – morpholino-\textsuperscript{53} and piperidylisoflav-3-enes\textsuperscript{54} (Figure 1.12).\textsuperscript{72} The oestrogenic properties of these compounds are very important in the treatment of various oestrogen dependent diseases such as breast cancer, osteoporosis, Alzheimer’s disease, and coronary heart disease.\textsuperscript{73} Another remarkable property is as an anti-juvenile hormone in insects shown by compounds like precocene I\textsuperscript{55} and precocene II\textsuperscript{56} (Figure 1.12) that have been isolated from plants.\textsuperscript{74–76}
The chromane ring can also be found in vitamin E constituents, tocopherols and tocotrienols. The basic chemical structure of tocopherol has a long phytol chain attached at the 2-position of the chromane ring, while tocotrienols differ from tocopherols by the presence of three $\textit{E}$ double bonds in the phytol tail. Moreover, the tocopherols and tocotrienols have $\alpha$, $\beta$, $\gamma$, and $\delta$ forms, named on the basis of the number and position of the methyl groups on the chromane ring (Figure 1.13).
Vitamin E exerts important functions in anti-oxidative defence in mammalian cells. Extensive investigations have been carried out on \( \alpha \)-tocopherol and its model compound 2,2,5,7,8-pentamethylchroman-6-ol due to the chemical oxidant activity shown by the former. One of the vitamin E derivatives developed, \( \alpha \)-tocopherol ether-linked acetic acid (\( \alpha \)-TEA), exhibits potent anticancer activity in a wide variety of epithelial cancer cell types in combination with the cyclooxygenase-2 inhibitor celecoxib and the chemotherapeutic drug 9-nitro-camptothecin.

In order to produce new derivatives, chemical modifications of vitamin E can occur at the following distinct regions of the molecule (Figure 1.14): (1) side chain length and saturation, (2) the position and geometry (E or Z) of the double bonds, (3) the heteroatom member of the saturated ring, (4) numbers of methyl substitutions on the benzene ring, and (5) esterification and amidation of the hydroxyl on the benzene ring. The water solubility and potency of the molecule can be enhanced by esterification of the hydroxyl group on the benzene ring while amides derived from \( \alpha \)- and \( \delta \)-tocopheramines have been reported to have improved anticancer activity.

![Figure 1.14 – Possible modification positions of vitamin E](image-url)
1.3.2.2 Photochromism\textsuperscript{86,87}

Photochromism is one of the properties of 2\textit{H}-chromene that has drawn attention among scientists. The reversible action of rapid colour changing of a compound when irradiated with light containing ultraviolet rays such as sunlight or light of a fluorescent lamp, and resumption of the initial colour when placed in dark place is called photochromism (Scheme 1-13). It is the result of the ability of this compound to undergo a reversible cleavage of the alkylic C-O bond, leading to a quasi-planar ‘open form’ with a distinct absorption spectrum, \textit{i.e.} different colours. These colour change phenomena are classified and named after the stimulus that causes the change. Accordingly, photochromism is a change in colour, usually colourless to coloured, brought about normally by UV light, electrochromism is a reversible colour change upon oxidation or reduction brought by an electrical current or potential, thermochromism is a colour change brought about by heat, solvatochromism by solvents and ionochromism by ions, etc.

1.3.3 Syntheses of 2\textit{H}-Chromenes

Due to these interesting properties of 2\textit{H}-chromenes, many synthetic methods for their preparation have been introduced from various starting materials. These methods include rearrangement of propargyl phenol ethers by high temperature Claisen rearrangement (Scheme 1-14)\textsuperscript{88-93} or recent reports of metal-catalysed cycloisomerization (Scheme 1-15),\textsuperscript{94} phenylboronic acid-mediated reaction of a phenol with an unsaturated aldehyde (Scheme 1-16),\textsuperscript{95} base-catalysed condensation of phenols with \(\alpha, \beta\)-unsaturated aldehyde (Scheme 1-17)\textsuperscript{96-99} or their acetal equivalents,\textsuperscript{100-102} Lewis acid-catalysed condensation (Scheme 1-18).\textsuperscript{103-106}
Scheme 1-14 - Thermal Claisen rearrangement of propargyl ether

Scheme 1-15 - Reagents and conditions: (i) (Ph₃P)AuNTf₂ (0.1 mol%), toluene, 85 °C, 2 h, HPLC ratio of a/b/c: 94.0/2.3/0.9

Scheme 1-16 - Reagents and conditions: (i) PhB(OH)₂: HOAc (1:88), toluene, reflux

Scheme 1-17 - Reagents and conditions: (i) Pyridine, 140 °C, 2 h
Barton used a pyridine-catalysed condensation reaction to afford a good yield of 2, 2-dimethylchromene 62 from ortho-hydroxyacetophenone 61 and 1,1-dimethoxy-3-methylbutan-3-ol 64 in a total synthesis of isorobustin 59 in four steps using 5-methoxyresorcinol 60 as precursor (Scheme 1-19).\textsuperscript{100}
Several metal-based methods have also been reported for the synthesis of chromene compounds such as palladium-catalysis (Scheme 1-20),\textsuperscript{107} and metal-phenoxide (Scheme 1-21),\textsuperscript{108} as a few examples.

![Scheme 1-20](image1.png)

Scheme 1-20 - 2-methyl-3-buten-2-ol (1.5 eq), NaHCO$_3$ (2.5 equiv), Pd(OAc)$_2$ (0.02 equiv), DMF, 120 °C, 3 h, 95\%\textsuperscript{107}

![Scheme 1-21](image2.png)

Scheme 1-21 - 3-Methyl-2-butenal (1.5 equiv), reflux, 8 h, 81\%\textsuperscript{108}

Described in this thesis, the following synthetic approaches are used in this research to obtain chromene substrates 66 – 69 (Figure 1.15), and are discussed further in Chapter 2.2: thermal cyclization of aryl propargyl ethers, phenylboronic acid-mediated reaction of a phenol with an unsaturated aldehyde, pressure-induced condensation of phenol, methyl methacrylate and formaldehyde, and base-catalysed condensation of phenol with diethyl acetal.
1.3.4 Asymmetric Epoxidation of Chromene

The functionalization of the double bond on the pyran ring of the chromene had been reported previously using both chemical and bio-transformations.\textsuperscript{75,76,109} Such pyran olefins are readily modified by hydrogenation,\textsuperscript{110} epoxidation,\textsuperscript{76,111,112} and dihydroxylation,\textsuperscript{76} giving rise to a large number of biologically active compounds, well-known examples of which include the ATP-dependent potassium channel activator levocromakalim (49, Figure 1.11), the anti-HIV agent suksdorfin\textsuperscript{57,113} and the breast cancer cell inhibitor natural product $\beta$-lapachone (58, Figure 1.12).\textsuperscript{114}

Chiral epoxychromanes can be intermediates in the synthesis of natural or synthetic compounds with biological activities. The initial chromene structure of modified compounds 47 and 50, 6-cyano-2, 2-dimethylchromene 69, had also previously modified by Patel et al. using stereoselective microbial epoxidation using culture \textit{Mortierella ramanniana} SC 13840 to give a mixture of epoxide 70 and (+)-trans-diol 71 (Scheme 1-22).\textsuperscript{109}
Another example is asymmetric dihydroxylation of chromene 72 by using the soil bacterium *Pseudomonas putida* to give enantiopure cis-diol 73 in as high as 98% ee (Scheme 1-23). This enzyme-catalysed method of asymmetric dihydroxylation may be regarded as complementary to the developed chemical methods of asymmetric dihydroxylation. This group demonstrated earlier the chemical transformation of the chromene to cis- and trans-diol enantiomers, even though the chemical oxidation method appears to be less stereoselective as compared to the enzyme-catalysed transformation.

In our group we have also demonstrated the asymmetric epoxidation reaction on several chromenes plus recent investigations of kinetic resolution in 2-monosubstituted chromenes. Page has reported several synthesis of natural products containing a chromene ring, including levocromakalim 49, (–)-(3'S)-lomatrin 75, (+)-(3'S, 4'R)-trans-khellactone 76, and (+)-scuteflorin A 80.

The synthesis of levocromakalim 49 was achieved via its epoxide 70 using our iminium salt catalysts to afford ee as high as 98% (Table 1-3). The corresponding (S, S)-epoxide 70 was then treated with pyrrolidin-2-one using the conditions described by Evans to afford the (−)-(3S, 4R) enantiomer of 49 in 52% yield (Scheme 1-24).
Scheme 1-24 - Reagents and condition: (i) pyrrolidin-2-one, NaH, DMSO, rt, 4 h, 52%

Table 1-3 - Asymmetric epoxidation of chromene 69\textsuperscript{a}

<table>
<thead>
<tr>
<th>Iminium Salt Catalyst</th>
<th>Conversion/(%)\textsuperscript{b}</th>
<th>Reaction time/h</th>
<th>Yield/(%)</th>
<th>ee/(%)\textsuperscript{c}</th>
<th>Configuration\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>36\textsuperscript{116}</td>
<td>–</td>
<td>24\textsuperscript{e}</td>
<td>59</td>
<td>97</td>
<td>(–)-1\textsuperscript{S}, 2\textsuperscript{S}</td>
</tr>
<tr>
<td>37\textsuperscript{112}</td>
<td>90</td>
<td>20</td>
<td>–</td>
<td>97</td>
<td>(–)-1\textsuperscript{S}, 2\textsuperscript{S}</td>
</tr>
<tr>
<td>74\textsuperscript{112}</td>
<td>100</td>
<td>48</td>
<td>–</td>
<td>98</td>
<td>(–)-1\textsuperscript{S}, 2\textsuperscript{S}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Epoxidation conditions: iminium salt catalyst (10 mol%), TPPP (2 equiv), CHCl\textsubscript{3}, 0 °C.
\textsuperscript{b}Conversions were evaluated from the \textsuperscript{1}H NMR spectra by integration of the alkene and epoxide signals. \textsuperscript{c}ee was determined using chiral HPLC using a Chiracel OD-H column. \textsuperscript{d}Absolute configurations of the major enantiomers were determined by comparison of optical rotation with those reported in the literature. \textsuperscript{e}Temperature: –40 °C.

Compounds 74 and 75 were obtained by asymmetric epoxidation of seselin 81 followed by ring opening of the epoxide. The precursor seselin was synthesized according to the method of North\textsuperscript{102} and could also be achieved using microwave irradiation in neat 3-picoline, affording 94% yield.\textsuperscript{119} Asymmetric epoxidation was carried out under standard non-aqueous conditions used in our laboratory using iminium salt 36 to afford the epoxide in 65% yield with excellent ee, 97%. Conversion of the epoxide into (–)-(3'\textsuperscript{S})-lomatín 74 was achieved by reductive cleavage with NaBH\textsubscript{3}CN at 0 °C in 92% yield and 97% ee. Acid-catalysed ring opening of the chiral epoxide yielded (+)-(3'\textsuperscript{S}, 4'R)-\textit{trans}-khellactone 75 in 95% yield (Scheme 1-25).\textsuperscript{117}
In 2012, Page reported the first enantioselective total synthesis of (+)-scuteflorin A 80 in very high ee, 97%, via (+)-trans-decursinol 78. The seven step synthesis of 80 started with the synthesis of xanthyletin 76 from 7-hydroxycoumarin using a method outlined by Ahluwalia, giving 29% yield. Enantioselective epoxidation of xanthyletin gave chiral epoxide 77 in excellent ee, ≥99% using catalyst 37 under non-aqueous conditions (Scheme 1-26).
1.4 Asymmetric Epoxidation

Asymmetric epoxidation of olefins is an effective approach for the synthesis of enantiomerically enriched epoxides. A variety of efficient methods have been developed, including Sharpless epoxidation of allylic alcohols, metal-catalysed epoxidation of unfunctionalized olefins, and nucleophilic epoxidation of electron-deficient olefins.

1.4.1 Some Definitions in Asymmetric Synthesis

The spatial arrangements of the substituents of chiral molecules can have a significant impact on reactivity and interaction towards other molecules. Many chiral drugs must be made with high enantiomeric purity because the other enantiomer may be inactive or have side effects. Thus, there is need to develop methods to synthesize organic compounds as one pure enantiomer and the use of these techniques is referred to as asymmetric synthesis.

Research in the field of asymmetric synthesis has witnessed an explosive growth in the last 10 – 20 years as documented by several books and review articles. The aim of asymmetric synthesis is to produce chiral product (as a single enantiomer as the ultimate goal) starting from a prochiral or achiral substrate, by exploiting the presence of a chiral auxiliary or catalyst.

1.4.1.1 Enantioselectivity, Chirality and Stereochemistry

The enantioselective production of compounds is one of the major themes of organic chemistry. The agrochemical and pharmaceutical industries are fields in which chirality and stereochemical control are of special relevance. Drug chirality is now a major theme in the design, discovery and development, launching and marketing of new drugs and, therefore, stereochemistry is an essential dimension to be taken into account. The thalidomide case in the 1960s is a paradigmatic example of this behaviour. This drug was prescribed in Europe
in a racemic form to pregnant women to alleviate sickness, but, while one of the enantiomers had sedative and antiemetic activities, the opposite enantiomer had teratogenic effects. This tragedy led to a new awareness of the importance of stereoselective pharmacodynamics and pharmacokinetics, enabling the differentiation of the relative contributions of enantiomers to overall drug action. There are two main methods for the preparation of enantiopure compounds: chiral resolution and asymmetric synthesis. Asymmetric synthesis is the method that is discussed in this thesis. This method introduces a mixture of isomers with an excess of one desired enantiomer. Enantiomeric excess (ee) is a measure of extent to which a particular enantiomer dominates the mixture and is readily calculated.

1.4.1.2 Stereochemistry

Isomers are different compounds which have the same molecular formula and are divided into two groups: stereoisomers and constitutional isomers. Stereoisomers are isomeric molecules that have the same molecular formula and sequence of bonded atoms (constitution), but that differ only in the three-dimensional position of the atoms in space. Stereochemistry is chemistry that studies the properties of stereoisomers. This contrasts with constitutional isomers, which share the same molecular formula, but the bond connections are different. Stereoselectivity encompasses diastereoselectivity (product diastereomer discrimination) and enantioselectivity (product enantiomer discrimination).

1.4.1.3 Chirality

Chirality (from the Greek meaning hand) is a concept well known to organic chemists and, indeed to all chemists concerned in any way with structure. It has numerous applications ranging from those affecting physical properties of matter to those related to biological mechanisms. These implications extend far beyond the borders of pure chemistry. Chiral molecules may exist as a pair of stereoisomers (enantiomers). If plane polarized light is passed through a sample of each enantiomer, one will rotate the light to the left (a levorotatory or (-)-enantiomer or l-form), and the other will rotate the light to the right.
(dextrorotatory or (+)-enantiomer or d-form). Rotation of light will not be observed if the light is passed through an equimolar mixture also known as a racemic mixture. Racemic mixture is the definition of compound having same amount of left- and right-handed enantiomers of a chiral molecule. 

1.4.1.4 Enantiomeric Excess (ee)

The enantiomeric excess of a substance is an indicator of the purity of a chiral chemical compound. The impurity is the undesired enantiomer that occurs frequently as by-product in asymmetric syntheses. ee is determined by the following equation:

\[
\text{Enantiomeric excess (ee)} = \frac{[R]-[S]}{[R]+[S]} \times 100
\]

\(R\) and \(S\) stand for the individual optical isomer in the mixture where \(R\) is the major enantiomer and \(S\) is the minor enantiomer.

ee determinations are important in the pharmaceutical industry because undesired optical isomers of a drug can potentially alter pharmaceutical efficacy or result in toxicity, as mentioned above regarding the case of thalidomide.

1.4.2 Asymmetric epoxidation

The optically active epoxides are versatile intermediates in organic chemistry that can be converted into a wide variety of enantiomerically enriched molecules. The inherent polarity and strain of their three-membered ring makes them readily undergo stereospecific ring-opening reactions with a large number of reagents – electrophiles, nucleophiles, acids, bases, reducing agents, and some oxidizing agents – to form 1, 2-difunctional compounds. In addition, many biologically active compounds and natural products contain epoxide functionalities. The chiral epoxides can be used either as key intermediates in the preparation of more complex optically bioactive compounds such as leukotriene 81 (SK&F 104353), GABOB 82 (γ-amino-δ-hydroxybutyric acid),
erythromycin $^{83,129}$ or as end products which also have biological activities, such as triptolide $^{84}$, epothilones $^{85} & ^{86}$ (Figure 1.16), and the gipsy moth pheromone: $(+)$-disparlure $^{87}$ (Scheme 1-29).$^{130}$

![Figure 1.16 - Biologically active compounds with chiral epoxides as key intermediate](image)

1.4.3 Catalytic Asymmetric Epoxidation

The first attempts to prepare optically active epoxides were reported in 1965 by Henbest. He used a chiral peracid reagent, $(+)$-monoperoxycamphoric acid, and epoxidation reactions were carried out with various terminal olefins to give up to 10% $ee$.$^{131}$ Since then considerable attention has been paid to asymmetric epoxidation of olefins. Particularly, the use of chiral transition-metal complexes as epoxidation catalysts has received increased attention over the past three decades. The asymmetric epoxidation of allylic alcohols, discovered by Sharpless and Katsuki in 1980, which utilizes alkyl hydroperoxide together with titanium (IV)-dialkyltartrate catalyst, is a noteworthy example of catalytic methods.
The highly effective system has been widely used in organic synthesis and has been the subject of several review articles.\textsuperscript{123}

One of the recent challenges in asymmetric catalysis has been the achievement of high enantioselectivity in the epoxidation of unfunctionalized alkenes. While the Sharpless epoxidation works efficiently with substrates capable of precoordinating with the catalyst, it is not suitable for the asymmetric epoxidation of unfunctionalized alkenes. The greatest difficulty in the selective epoxidation of alkenes bearing only hydrocarbon substituents is control of olefin approach to the active oxidant, since selectivity is determined only through low-energy, non-bonded interactions between the catalyst and the substrates.

Over recent years, a number of research groups around the world have worked towards the development of methodologies to access chiral epoxides with high enantioselectivities. The greatest impact in the construction of chiral epoxides has been made with the introduction of catalytic systems. Undoubtedly the best-known catalytic process is that of Sharpless for the epoxidation of allylic alcohols, usually with greater than 90\% ee.\textsuperscript{132,133} Shown below are several examples of well-known catalytic asymmetric epoxidation systems grouped into two categories: metal-catalysed and organocatalysed asymmetric epoxidation.

1.4.4 Metal-Catalysed Asymmetric Epoxidation

Metal-catalysed asymmetric epoxidation was first reported in 1979 by Otsuka. However, the ee was quite low (1 – 7\%, in most cases) for unfunctionalized alkenes with t-BuOOH in the presence of Mo(IV) and optically active dialkyl tartrate esters, (+)-DIPT at 20 – 25 °C. This system was applied to the asymmetric synthesis of (3S)-2, 3-oxidosqualene (Scheme 1-27) giving mixture of epoxides – 31\% of 2, 3-epoxide, 47\% of a mixture of the 6, 7- and 10, 11-epoxide and 23\% of a mixture of the diepoxides.\textsuperscript{134}
1.4.4.1 Sharpless Epoxidation

In 1980, a highly enantioselective epoxidation of allylic alcohols was reported by Katsuki and Sharpless. They successfully converted allylic alcohols into asymmetric epoxides in high chemical yields with more than 90% ee, under the catalysis of a transition metal catalyst titanium tetra(isopropoxide), Ti(OPr)₄, by using t-BuOOH as the oxidant with a chiral additive diethyl tartrate (DET) or diisopropyl tartrate (DIPT) (Scheme 1-28).¹³²,¹³⁵,¹³⁶

The original Sharpless asymmetric epoxidation reaction requires large amount of Ti(OPr)₄, as high as 50 mol%. The main reason for this is the presence of water that destroys the catalyst, and a large amount of titanium-tartrate species and isopropyl alcohol ring-opens the epoxide. Further investigation by Sharpless showed that addition of 3 Å or 4 Å molecular sieve dramatically reduced the requirement of Ti catalyst to a catalytic amount.¹³⁶ Since the discovery, the system has undergone rapid development.
Epoxidation of a vinyl silanol under Sharpless condition with t-butyl hydroperoxide (t-BuOOH), Ti(O-i-Pr)$_4$ and (+)-diisopropyl tartrate (DIPT) in CH$_2$Cl$_2$ was applied to the enantioselective synthesis of (+)-disparlure 87 (Scheme 1-29), giving up to 52% ee.$^{130}$

![Scheme 1-29 - Reagents and conditions: (i) CuI, P(OMe)$_3$; (ii) 1-iodo-5-methylhexane, 56%; (iii) NiBr, THF, 81%; (iv) t-BuOOH, Ti(O-i-Pr)$_4$, (+)-diisopropyl tartrate (DIPT), CH$_2$Cl$_2$, –20 °C, 13 h, 67%; (v) F, 67%$^{130}$](image)

1.4.4.2 Jacobsen-Katsuki Epoxidation

Jacobsen epoxidation was the first metal-catalysed epoxidation to result in high ee values for alkenes without an allylic OH group.$^{111}$ This system uses a Mn-salen catalyst based on Kochi’s achiral salen catalyst,$^{137}$ and allows a broader scope of substrate than the Sharpless system.

![Scheme 1-30 - Jacobsen-Katsuki asymmetric epoxidation system](image)
The influence of additives on the reaction rate, yield, and enantioselectivity of Jacobsen-Katsuki epoxidation was first proposed by Kochi\textsuperscript{138} and was then further investigated.\textsuperscript{139,140} Amine N-oxides such as Py-N-oxide proved to be the best axial co-ligands, because they also stabilize the manganese(v)-oxo complex.\textsuperscript{139,141,142}

![Figure 1.8 - Py-N-oxide](image)

The application of the catalyst has also been investigated on dimethylchromene derivatives using catalyst 88, affording >90% ee (Table 1-4). As can be seen in Table 1-4, Jacobsen showed that the catalyst system is applicable to chromene substrates with various substituents at the 6-position as well as at the reaction site 3- and 4-positions of chromene. Epoxidations were carried out using commercial bleach, NaOCl as oxidant at 0 °C or room temperature with catalyst 88.\textsuperscript{111}

<table>
<thead>
<tr>
<th>Olefin</th>
<th>Major product</th>
<th>ee(%)</th>
<th>Isolated yield (%)</th>
<th>Absolute configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>69</td>
<td>70</td>
<td>97</td>
<td>96</td>
<td>(+)-(3R, 4R)</td>
</tr>
<tr>
<td>72</td>
<td></td>
<td>98</td>
<td>87</td>
<td>(+)-(3R, 4R)</td>
</tr>
<tr>
<td>89</td>
<td></td>
<td>94</td>
<td>76</td>
<td>(+)-(3R, 4R)</td>
</tr>
<tr>
<td>90</td>
<td></td>
<td>98</td>
<td>75</td>
<td>(+)-(3R, 4R)</td>
</tr>
<tr>
<td>93</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>94</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1.4.5 Organocatalysed Asymmetric Epoxidation

1.4.5.1 Dioxirane-Catalysed Epoxidations

Chiral dioxiranes are also promising reagents for asymmetric epoxidation reactions.\textsuperscript{143} The first attempts to effect asymmetric epoxidation using chiral dioxiranes were reported by Curci \textit{et al.} in 1984, giving $ee$s between 9 – 12.5\%.\textsuperscript{144} It was more than ten years later, that chiral ketones, the precursors of the corresponding dioxiranes, were developed that allow the epoxidation of a wide range of alkenes with good enantioselectivities.\textsuperscript{145–147} Steric and electronic factors need to be considered to design efficient ketone catalysts as highlighted by Yang\textsuperscript{146} to achieve good selectivity and reactivity.\textsuperscript{143}

1.4.5.1.1 Shi Epoxidation

This catalyst was derived from $\delta$-fructose and is one of the most notable ketone catalysts. In 1996, Shi provided the first general enantioselective dioxirane epoxidation of $trans$-olefins (Scheme 1-31).\textsuperscript{145}
Due to rapid decomposition of the ketone at pH 7 – 8 involving Baeyer-Villiger reaction, the initial epoxidation procedure required excess catalyst (3 equiv). Shi subsequently showed that the catalytic efficiency of the ketone catalyst is highly pH dependent. At pH 10, the conversion to epoxide increased dramatically as he suggested that the Baeyer-Villiger reaction might be suppressed at higher pH. One concern when the reaction was carried out at higher pH was the decomposition of the oxidant, Oxone®. However, by increasing the pH, the amount of ketone used can be reduced to a catalytic amount and the amount of Oxone® can be reduced to a near-stoichiometric amount (1.5 equiv), suggesting at this pH the ketone is sufficiently reactive to compete with Oxone® decomposition. The catalytic cycle of Shi’s asymmetric epoxidation system can be seen in Scheme 1-32.
1.4.5.1.2 Yang Epoxidation

In 1996, Yang et al. successfully reported good enantioselectivity for epoxidation of trans-olefins and trisubstituted olefins by a C₂ symmetric chiral ketone 97 (10 mol%) using Oxone® as oxidant giving as high as 87% ee. She showed that ketones with electron-withdrawing groups at α positions give higher activity, which then led to her design of the catalyst. On the other hand, the reactivity of ketone catalysts decreased in the presence of steric hindrance at the α-positions. The optimized chiral ketone was derived from 1, 1′-binaphthyl-2, 2′-dicarboxylic acid.

Scheme 1-32 - Shi epoxidation catalytic cycle
1.4.5.2 Juliá-Colonna Epoxidation

In 1980, Juliá et al. reported the poly-\(\ell\)-alanine catalysed asymmetric epoxidation of chalcone, giving \(ee\)s as high as 93\%.\(^{150}\) The Juliá reaction conditions were triphasic, consisting of the insoluble polyamino acid catalyst, an aqueous solution of NaOH and H\(_2\)O\(_2\), and a solution of chalcone in an organic solvent.

1.4.5.3 Chiral Oxaziridinium-Catalysed Asymmetric Epoxidation

Early reports on asymmetric epoxidation using oxaziridines by Davis\(^ {41}\) are discussed above in Chapter 1.1.3.3. Since the discovery of the efficiency of oxaziridinium salts as powerful electrophilic oxidants by Lusinchi,\(^ {52}\) the number of research groups investigating this system has grown rapidly, this includes Aggarwal,\(^ {56}\) Yang,\(^ {151}\) Komatsu,\(^ {152}\) Armstrong,\(^ {153}\) and our group\(^ {59}\) (Figure 1.16). Asymmetric epoxidation by chiral iminium salts is normally carried out using Oxone\(^ \text{®}\) as the primary oxidant.
Lusinchi subsequently demonstrated that iminium salts could be converted by Oxone® into the corresponding oxaziridinium species, which could then effect alkene epoxidation in a catalytic cycle (Scheme 1-11, page 18).\textsuperscript{154}

\section*{1.4.5.3.1 Davis Oxaziridines-mediated Epoxidation}

Davis reported the first chiral oxaziridine $\text{101}$ in 1983 derived from condensation of optically active bromocamphor sulfonamide ($R^*SO_2NH_2$) with the diethyl acetal of an aromatic aldehyde at 150 – 180 °C (Scheme 1-33).\textsuperscript{155}

\begin{equation}
R^*SO_2NH_2 + \text{ArCH(OEt)}_2 \rightarrow R^*-\text{SO}_2\text{N=CHAr}
\end{equation}

\textbf{Scheme 1-33 - Synthesis of chiral oxaziridine by Davis}$^{155}$
However, the highest ee observed was only 40% for epoxidation of 1-phenylcyclohexene (Scheme 1-34).\textsuperscript{156}

![Scheme 1-34 - Davis’s first chiral oxaziridine for asymmetric epoxidation\textsuperscript{156}](image)

Further investigation by Davis using chiral sulfamyloxaziridines 102 then improved the enantioselectivity, giving up to 65% ee for asymmetric epoxidation of unfunctionalized alkenes (Scheme 1-35).\textsuperscript{43}

![Scheme 1-35 - Asymmetric epoxidation of unfunctionalised alkene using sulfamyloxaziridine\textsuperscript{43}](image)

1.4.5.3.2 Aggarwal’s Epoxidation

Aggarwal designed a chiral iminium salt combined with binaphthyl based system due to its emergence as one of the best general ligand motifs in asymmetric synthesis.\textsuperscript{120,157} This system was reported to provide enantioselectivity as high as 71% for 1-phenylcyclohexene using catalyst (S)-(+) 104, derived from oxidation of (S)-(+)binaphthylamine 103 followed by methylation using Meerwein’s reagent (Scheme 1-36).\textsuperscript{56}
Aggarwal later reported that asymmetric epoxidation of alkenes by simple chiral secondary amines can also be achieved, for example by catalyst 106, on 1-phenylcyclohexene, giving up to 57% ee. He suggested that the reaction occurred via radical cations. The regioselectivity of the catalyst is shown by reaction with triene 105, which gave a single mono-epoxide, uncontaminated by other regioisomers (Scheme 1-37).\textsuperscript{158}

\begin{align*}
\text{Scheme 1-36 - Reagents and conditions: (i) KMnO}_4, \text{THF}, 80\%; (ii) Me}_3\text{O}^+\text{BF}_4^-, \text{CH}_2\text{Cl}_2, 96\% \textsuperscript{156}
\end{align*}

1.4.5.3.3 Armstrong’s Acyclic Iminium Salt-mediated Epoxidation

In 1997, Armstrong reported asymmetric epoxidation using several acyclic iminium salts (Scheme 1-38), synthesized by intermolecular condensation, suggesting such an approach would allow greater range in the preparation of chiral iminium salts. The catalyst was prepared by condensation of commercially available \(N\)-trimethylsilylpyrrolidine (1 equiv) and an aromatic aldehyde (1 equiv) with trimethylsilyl triflate (1 equiv) in ether.\textsuperscript{159} Amongst all the catalysts, iminium salts with \textit{ortho}-withdrawing group, i.e. catalysts 110 and 111,
gave 100% conversion at low catalyst loading, 25 and 10 mol% respectively. In this acyclic iminium salt-mediated system, catalyst 100 (Figure 1.16) was found to give the best result for asymmetric epoxidation of 1-phenylcyclohexene (100% conversion, 22% ee).

He also showed that intramolecular epoxidation can occur by treatment of unsaturated oxaziridines with MeOTf, presumably via oxaziridinium salts. This method has been applied for regioselective epoxidation of a nonconjugated diene (Scheme 1-39).

Aldehyde 113 was first converted into the imine, which was then selectively oxidized by Oxone® to give the corresponding oxaziridine. This was treated with MeOTf in CH₂Cl₂ followed by brief exposure to aqueous NaHCO₃, giving epoxide 114 in 48% yield (Scheme 1-39). Komatsu (catalyst 100, figure 1.16) and Yang also reported asymmetric epoxidations employing acyclic iminium salts generated in situ (Scheme 1-40), giving ee up to 39% and 65% respectively.
1.4.5.3.4 Page Epoxidation

Our group has also continuously contributed to the development of iminium salt-mediated asymmetric epoxidation. Page has previously designed chiral iminium salts that contain asymmetric centres in the exocyclic nitrogen substituent. Several series of catalysts that contain a number of chiral moieties have been reported, with the catalysts bearing \((4S, 5S)\)-5-amino-2, 2-dimethyl-4-phenyl-1, 3-dioxane (acetonamine) moiety reported to be among of the most reactive. Inspired by work of Hanquet and Lusinchi, Page designed the chiral iminium salts derived from dihydroisoquinoline and a primary amine, but chiral at the exocyclic nitrogen substituent. The advantages of the chiral iminium salts used are the preparation can be done on any scale and large structural variation is available as the chirality is resident in the amine component (Figure 1.1). 10 mol% of catalyst 98d gave the best ee of 73% for asymmetric epoxidation of trans-stilbene\(^{59}\) and gave 40% ee with catalyst loading as low as 0.5 mol%\(^{60}\).
Later, iminium salts with additional functionality at the nitrogen atom prepared from amino alcohols, aminoethers, and aminoacetals were studied. Page reasoned that the presence of polar units within the chiral exocyclic substituent might help to control the diastereofacial selectivity of attack of the iminium unit by persulfate and/or the diastereofacial selectivity of approach by the alkene substrate to the reactive oxidizing intermediate and hence improve epoxide ee.

The study revealed that catalyst 35 (Figure 1.6) derived from an amino acetal precursor, (1S, 2S)-2-amino-1-phenylpropane-1, 3-dioxane, 115 (Figure 1.18), induces much higher enantioselectivities in the asymmetric epoxidation than the previously synthesized catalysts. The comparison of the results with those obtained using catalyst 98d is presented in Table 1-5.160
Table 1-5 - Asymmetric epoxidation results comparison

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst/Alkene</th>
<th>98d</th>
<th>35</th>
<th>37</th>
<th>116</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yield/%; ee%; configuration</td>
<td>68; 8; (+)-(R)</td>
<td>64; 20; (+)-(R)</td>
<td>100; 24; (+)-(R)</td>
<td>90; 3; (+)-(R)</td>
</tr>
<tr>
<td>1</td>
<td>Ph&lt;sup&gt;Me&lt;/sup&gt;</td>
<td>72; 15; (+)-(1R, 2R)</td>
<td>52; 52; (−)-(1S, 2S)</td>
<td>95; 37; (−)-(1S, 2S)</td>
<td>93; 14; (+)-(1R, 2R)</td>
</tr>
<tr>
<td>2</td>
<td>Ph=Ph&lt;sup&gt;Me&lt;/sup&gt;</td>
<td>43; 5; (+)-(S)</td>
<td>54; 59; (+)-(S)</td>
<td>90; 59; (+)-(S)</td>
<td>100; 17; (+)-(S)</td>
</tr>
<tr>
<td>3</td>
<td>Ph=Ph&lt;sup&gt;Ph&lt;/sup&gt;</td>
<td>68; 40; (+)-(1R, 2R)</td>
<td>55; 41; (−)-(1S, 2S)</td>
<td>100; 60; (−)-(1S, 2S)</td>
<td>100; 29; (+)-(1R, 2R)</td>
</tr>
<tr>
<td>4</td>
<td>Ph&lt;sup&gt;Cyc&lt;/sup&gt;</td>
<td>34; 3; (+)-(1S, 2R)</td>
<td>52; 17; (+)-(1S, 2R)</td>
<td>100; 10; (+)-(1S, 2R)</td>
<td>95; 8; (+)-(1S, 2R)</td>
</tr>
<tr>
<td>5</td>
<td>Ph&lt;sup&gt;Bip&lt;/sup&gt;</td>
<td>73; 20; (−)-(1S, 2R)</td>
<td>64; 49; (−)-(1S, 2R)</td>
<td>90; 41; (−)-(1S, 2R)</td>
<td>95; 38; (−)-(1S, 2R)</td>
</tr>
</tbody>
</table>

Following this finding, in 2002, Page developed new iminium salt catalysts replacing the dihydroisoquinoline moiety of catalyst 98 with a biphenyl structure fused to a seven-membered azepinium salt, with the chirality retained in the exocyclic nitrogen substituent. Two new iminium salt catalysts, 37 (Figure 1.6) and 116 (Figure 1.18) were prepared from the (−)-isophenylcamphenyl (IPC) 98d and amino acetal precursor 115, respectively. These two chiral primary amines were later used to synthesize azepinium salt catalysts, fused to (R)- or (S)-binaphthylene units. The binaphthyl-derived catalyst 39 (Figure 1.6) appeared to be the most enantioselective iminium salt catalyst known in our group at that time, as 95% ee was recorded for asymmetric epoxidation of 1, 2-dihydro-1-phenynaphthalene.
Page has also developed non-aqueous conditions for iminium salt-catalysed epoxidation, which eliminates the use of both water and base. This new system uses tetraphenylphosphonium monoperoxysulfate, which is soluble in organic solvents, as oxidant. This study also revealed the use of chloroform (CHCl₃) to be the best solvent for this system.⁵⁴

1.5 Conclusion

This chapter has covered brief introduction and historical background of topics discussed in this research; organocatalysis, chromene substrates and asymmetric epoxidation. The discovery of oxaziridinium salt as an effective electrophilic oxygen transfer reagent leads to its development.

A number of biological properties such as potassium channel activator, anti-oxidant, anti-HIV and the oestrogenic property exhibit by natural compound containing chromene as core structure show the importance of synthetic approach of this class of compounds. Further modification of double bond on pyran ring gave rise to a large number of biologically active compounds such as levocromakalim 49, suksdorfin 57 and 6-lapachone 58.

Application of our asymmetric epoxidation systems to the synthesis of natural products and biological active compounds containing chromene core structures had been investigated previously, giving excellent enantioselectivities, such as synthesis of levocromakalim 49, (−)-(3′S)-lomatin 74, (+)-(3′S, 4′R)-trans-khellactone 75 and (+)-scuteflorin A 80, giving >97% ee for each reaction.
1.6 References


(104) Kane, V. V.; Razdan, R. K. J. Am. Chem. Soc. 1968, 90, 6551–6553.


CHAPTER 2
RESULTS & DISCUSSION
2 RESULTS AND DISCUSSION

2.1 Synthesis of Oxaziridinium Salts

2.1.1 Catalysts Selection and Preparation

As mentioned earlier in Chapter 1.1, Lusinchi and co-workers reported the first oxaziridinium salt as effective electrophilic oxygen-transfer reagent for epoxidation of sulfides and alkenes.\textsuperscript{1-4} Addition of Oxone\textsuperscript{®} as the oxidant to an iminium ion species produces a highly reactive oxidative intermediate, an oxaziridinium species. The oxygen transfer from electrophilic oxaziridinium ion to nucleophilic sulfide or alkene substrate regenerates the iminium species, giving overall a catalytic cycle. Lusinchi also showed that the oxygen transfer reactions can be done either by a separately prepared oxaziridinium salt 1 or by one prepared \textit{in situ} (Figure 2.1). They then successfully developed related enantiomerically pure oxaziridinium salt 2 (Figure 2.1), giving up to 33\% ee for asymmetric epoxidation of \textit{trans}-stilbene.\textsuperscript{5}

![Figure 2.1 - Compound 1, second oxaziridinium salt by Hanquet in 1987; compound 2, first enantiomerically pure chiral oxaziridinium salt by Bohé, Lusinchi and Hanquet](image)

In Page’s group, the catalysts for asymmetric epoxidation were first designed with the dihydroisoquinolinium nucleus generated from variety of chiral amines as a basis for study (Figure 2.2).\textsuperscript{6}
Later in 2002, new catalysts were designed by replacing the dihydroisoquinolinium moiety with a biphenyl structure fused to a seven-membered ring azepinium salt (Figure 2.3) and these new catalysts were shown to be more reactive than the six-membered ring catalysts, although with a somewhat different pattern of selectivity.\(^7\)
The biphenyl-derived catalysts induced better ees for asymmetric epoxidation of 1-phenylcyclohexene than their six-membered ring dihydroisoquinolinium counterparts. However, reactions with trans-α-methylstilbene and triphenylethylene showed poorer or same ees were obtained for the biphenyl-derived catalysts 7 as compared to the corresponding dihydroisoquinolinium catalyst 3 (Table 2-1). These seven-membered ring catalysts, however, provide dramatically faster reactions, providing complete consumption of alkene substrates in ten minutes or even less, as opposed to around one hour for the six-membered ring systems under the same conditions.\(^8\)

![Chemical reaction diagram]

**Table 2-1 - Comparison of catalytic asymmetric epoxidation of unfunctionalized alkenes using dihydroisoquinolinium salts and dibenzazepinium salts**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>In each case: ee(^b)(%)/Conv.(%)/Configuration(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Catalyst 3" /></td>
<td>41/55/(-)-(1S, 2S)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Catalyst 7" /></td>
<td>60/100/(-)-(1S, 2S)</td>
</tr>
</tbody>
</table>
In 2004, Page reported several new binaphthyl-derived catalysts, of which catalyst 9 (Figure 2.4) was reported to give the highest ee, as high as 91% for iminium salt-catalysed asymmetric epoxidation of 1-phenylcyclohexene under aqueous conditions.  

It is common for the epoxidation catalysts to have the iminium bond as part of a ring, and is therefore effectively derived from intramolecular condensation of a carbonyl compound and an amine. An initial concern was that simple acyclic iminium salts might prove too

<table>
<thead>
<tr>
<th></th>
<th>![Chemical Structure 4]</th>
<th>39/100/ (–)-(1S, 2S)</th>
<th>32/100/ (–)-(1S, 2R)</th>
<th>50/100/ (+)-(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>![Chemical Structure 8]</td>
<td>47/56/ (–)-(1S, 2S)</td>
<td>21/100/ (–)-(1S, 2S)</td>
<td>10/55/ (+)-(S)</td>
</tr>
<tr>
<td>4</td>
<td>![Chemical Structure 5]</td>
<td>45/54/ (+)-(1R,2R)</td>
<td>60/55/ (+)-(1R,2S)</td>
<td>71/60/ (–)-(R)</td>
</tr>
<tr>
<td>5</td>
<td>![Chemical Structure 6]</td>
<td>63/50/ (+)-(1R,2R)</td>
<td>50/61/ (+)-(1R,2R)</td>
<td>26/63/ (–)-(R)</td>
</tr>
</tbody>
</table>

Reagents and conditions: Iminium salt (10 mol%), Oxone® (2 equiv), Na$_2$CO$_3$ (4 equiv), MeCN/H$_2$O (1:1), 0 °C, 2 h; Enantiomeric excesses were determined by $^1$H NMR spectroscopy in the presence of (+)-Eu(hfc)$_3$ or by chiral HPLC on Chiracel OD column; The absolute configuration of the major enantiomers were determined by comparison of optical rotations with those reported in the literature.
sensitive to hydrolysis to be useful as epoxidation catalysts. It has been previously proved by preliminary experiments in our group that acyclic iminium salts derived from carbonyl compounds do not promote the desired reaction to any reasonable extent\(^6\) which is in accord with the work of Armstrong et al. (Scheme 1-38, page 49) and Yang et al., reporting high catalyst loading is required (as high as 100 mol%) for better conversion to epoxides due to the hydrolysis of the catalysts. Moderate enantiomeric excesses were observed utilizing acyclic chiral iminium salts generated \textit{in situ} from chiral amines and aldehydes.\(^{10–12}\) Page therefore chose cyclic iminium salts for investigation and the dihydroisoquinolinium nucleus was selected as the basis for initial study.

The first attempt to design new cyclic chiral iminium salts in our group derived from dihydroisoquinoline was based on the idea to have the controlling asymmetric centres close to the iminium nitrogen atom, in an exocyclic group, on the basis that this might lead to higher \(e.e\) by bringing the asymmetric centre near to site of oxygen transfer.\(^6\) Our group was the first to report enantioselective iminium salt catalysts bearing an exocyclic chiral stereocontrolling groups as substituents on the nitrogen atom\(^{13}\) such as dihydroisoquinolinium salts 3 – 6 (Figure 2.2),\(^8\) biphenylazepinium salts 7 & 8 (Figure 2.3),\(^7\) and binaphthazepinium salts 9 & 10 (Figure 2.4).\(^{14}\)

Counter-anion exchange is used to overcome the difficulties encountered on attempts to purify the salts by conventional methods, which takes place readily simply by addition of appropriate inorganic salts to the cyclocondensation reaction mixture before work up. Fluoroborate, hexafluorophosphate, perchlorate, and periodate salts did not prove ideal,
but the tetraphenylborate salts, produced using sodium tetraphenylborate, are the most suitable: they are all solids, with the degree of crystallinities varying with the alkyl group of the parent amines.\textsuperscript{15} Tetraphenylborate salts gave the best ee (40\%) when all the salts were tested in the asymmetric catalytic epoxidation of 1-phenylcyclohex-1-ene under aqueous conditions.\textsuperscript{6}

For this research, all three backbone moieties that had been established in our lab – dihydroisoquinoline, biphenyl and binaphthyl moieties – are used in the synthesis of the iminium salts as backbone for the investigation. The catalysts were prepared through condensation of the backbone moiety precursors – 2-(2-bromoethyl)benzaldehyde 26, 2, 2'-bis(bromomethyl) biphenyl 29, and (\textit{R})-2,2'-bis(bromomethyl)[1,1']-binaphthalene 33 (Figure 2.5) – with enantiomerically pure chiral primary amines 11 & 12 (Figure 2.6), to obtain the corresponding dihydroisoquinoline-derived catalysts 3 and 4, biphenyl-derived catalysts 7 and 8, and binaphthyl-derived catalysts 9 and 10 respectively.

This approach has the great advantage that asymmetric catalysts may be derived rapidly from a wide variety of readily available chiral primary amines.

\begin{center}
\textbf{Figure 2.5 - Backbone moieties used to synthesize the iminium catalysts}
\end{center}
2.1.2 Synthesis of Chiral Primary Amines

The syntheses of iminium salts were started with the preparation of the chiral amine moieties 11 and 12. The primary amines 11 and 12 (Figure 2.6) are required for the preparation of all selected iminium salt catalysts 3, 4 (Figure 2.2), 7, 8 (Figure 2.3), 9 and 10 (Figure 2.4).

![Figure 2.6 - Chiral amine motifs for iminium salt catalysts](image)

These two amine precursors, having aminoacetal functionalities, were selected as they are more effective amine parents for the catalysts as reported in our group, some of which are extremely active and selective, giving ee of up to 97% with catalyst loading as low as 0.1 mol% in epoxidation reactions.

The catalysts derived from (S,S)-acetonamine 11 have been demonstrated to be one of the most reactive chiral amine motifs for iminium salt-mediated asymmetric epoxidation reactions and also display the highest levels of enantiocontrol.

(S,S)-Acetonamine 11 was synthesized from the commercially available diol (1S,2S)-(+) -2-amino-1-phenyl-1,3-propanediol 13 in a good yield, using a method similar to that developed by Nordin and Thomas (Scheme 2-1). This method can be conducted in one pot, the product is suitably pure for most purposes without distillation, and the reaction is easily scaled up.
The preparation of (S,S)-acetonamine 11 was started by formyl protection of the primary amine followed by ketalization of 1,3-diol 13 to obtain (4S,5S)-(formylamino)-2,2-dimethyl-4-phenyl-1,3-dioxane 14. The formyl protection of the amine was achieved by dissolving the amino diol 13 in methanol in the presence of methyl formate as the source of formyl group and sodium methoxide as the catalyst. The mixture was then stirred overnight at ambient temperature. Dimethoxypropane was then added under acidic conditions using catalytic amount of camphorsulfonic acid (CSA) for the ketalization reaction (Scheme 2-1). These two steps afforded 14 in excellent yield as a yellow foam.

According to Nordin, a catalytic amount of HBr was used as the acid catalyst in the ketalization step, giving 71% overall yield but the use of CSA was found to give a better yield of 14 as a yellow foam, up to 95%. This is the general procedure for both the protection of primary amine and ketalization of diol which can also be applied to (S,S)-thiomicamine 15, afforded 16 as yellow oil (Scheme 2-2) in 87% yield. The amine must first be protected as its formamide prior to ketalization due to the greater nucleophilicity of the primary amine as compared to diol.

The deprotection of the amines completed the preparation of the chiral amine motifs by heating under reflux the formate-protected acetonide in hydrazine hydrate (98%) for 3 hours, giving compound 11 as yellow oil in 96% yield (Scheme 2-1). Previously, hydrazine hydrate was diluted to 85% aqueous solution for this deprotection step but the commercially available 98% solution of hydrazine hydrate gave a better yield.
For the preparation of \((S,S)\)-acetonamine 12, there is one extra step prior to the deprotection of formyl group. The sulfide must first be oxidized to sulfone, which was accomplished in 98% yield at the formate-protected stage using 3.1 equivalent of \(m\)-CPBA in dichloromethane at 0 °C to obtain colourless crystalline solid methylsulfonyl moiety 17, crystallized from chloroform/diethyl ether (1:3) (Scheme 2-2). The methyl group of the sulfone 17 shifted slightly downfield compared to sulfide 16 from δ 2.46 ppm to δ 3.05 ppm in the \(^1\)H NMR spectrum. In the IR spectrum, two strong peaks at 1383 and 1149 cm\(^{-1}\) show the presence of S=O bonds in the compound.

The oxidation of sulfide to sulfone is important due to the susceptibility of the thiomethyl group to undergo oxidation to sulfone during the epoxidation reaction, and so consuming the oxidant; it is well known that Oxone\(^\circledast\) can oxidize sulfides to sulfoxides or sulfones.\(^{17-19}\) Catalysts bearing a sulfide group on the \(para\) position of the phenyl substituent gave similar ee values to the sulfone-based catalysts but gave poorer epoxide conversion.\(^{8}\) After the

\[
\begin{align*}
\text{H}_2\text{N} & \text{OH} \quad \text{H}_2\text{N} \text{OH} \quad \text{H}_2\text{N} \text{OH} \\
\text{S} \quad \text{S} \quad \text{S} \\
15 & \quad 16 & \quad 17 \\
\text{(i), (ii)} & \quad \text{(iii)} & \\
\quad & \quad & \\
\quad & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quarter
oxidation step of 16 to 17, the deprotection of the formyl group gave crude 12 as a
colourless oil, which was then recrystallized from diethyl ether/ethyl acetate (1:1),
affording yellowish crystalline 12 in a good yield of 73%.

The presence of the dioxane core in (S,S)-(+-)acetronamine has proven to provide catalysts
 generating excellent yields and induction of enantioselectivities in epoxidation reactions.
For example, biphenylazepinium salts 18 and 7 induced 29% and 60% ees respectively using
1-phenylcyclohexene as substrate under typical aqueous reaction conditions using Oxone®
as oxidant.

![Figure 2.7 - Biphenylazepinium salts without and with dioxane core, catalysts 18 and 7 respectively](image)

The aromatic substituents in the acetal moieties of the catalysts are important for
asymmetric induction during the epoxidation reactions. According to the previous studies
in our group, catalysts 19 and 20 containing alkyl group substituents in the acetal moieties,
gave less than 5% ee in the epoxidation of 1-phenyl-cyclohexene. These results suggest that
the aromatic nature of the C4 substituent of the catalysts is vital for catalyst
enantioselectivities, perhaps due to interactions of the aryl substituents with the biaryl
moieties and/or with the substrates.\(^8\)
The feature of the acetal-containing iminium salts which may contribute to the enantioselectivities is the syn relationship between the nitrogen heterocycle and the phenyl group. It has been shown in a previous study by Page that the 1,3-dioxane ring retains a chair conformation consistent with both $^1$H NMR and $^{13}$C NMR spectrum, in accord with previous reports of substituted 2,2-dimethyl-1,3-dioxane rings (Figure 2.9).

Page proposed that there may be a stabilizing interaction between the electron cloud associated with the oxygen lone pairs and the electron-depleted carbon atom of the iminium unit as can be seen in Figure 2.9. This stereoelectronic effect may contribute to high conformational rigidity leading to relative success of the dioxane-derived catalysts. Such a conformation has a strong preference in the related system 23 and has been documented both experimentally and theoretically.
After successfully synthesizing the chiral amine motifs 11 and 12, we next prepared the backbone moieties for the iminium catalysts – the dihydroisoquinoline motif 26 and the biaryl motifs, 2,2′-bis (bromomethyl) [1,1′] biphenyl 29 and (R)-2,2′-bis(bromomethyl) [1,1′]-binaphthalene 33 – were then synthesized followed by cyclization to obtain the corresponding azepinium iminium salts 3, 4 and 7 – 10.

### 2.1.3 Synthesis of Catalysts based on the Dihydroisoquinoline Motif

The precursor 2-(2-bromoethyl)benzaldehyde 26 was prepared according to the procedure of Rieche and Schmitz.22 Bromination of isochromane 24 afforded the expected 1-bromoisochromane 25, which may be isolated by distillation if required. Treatment of product 25 with concentrated aqueous HBr (48%) furnished the desired bromoaldehyde 26 in a good yield of 85% (Scheme 2-3). Compound 26 may also be purified by distillation, but the crude product can be used with equal success in most cases.

Scheme 2-3 – Reagents and conditions: (i) Br₂, CCl₄, 1.5 h; (ii) HBr (48%), reflux, 10 – 15 min, 85%; (iii) Primary amine 11 or 12, EtOH/MeCN, NaBPh₄
Cyclocondensation of chiral primary amines 11 and 12 proceeded smoothly and rapidly with 2-(2-bromoethyl) benzaldehyde, affording the corresponding dihydroisoquinolinium bromide salts. The crude hydrobromide salts are then reliably converted into easily handled crystalline material by counter-ion exchange with sodium tetraphenylborate (Scheme 2-3). The salts can be purified by crystallization from ethanol, giving iminium salts 3 and 4 as bright yellow solids in 58% and 80% yields respectively.

Bohé has showed that incorporating a gem-dimethyl group alpha to the iminium unit as in 27 (Scheme 2-4) can increase the catalyst’s reactivity and extend the lifetime of the catalysts.

The presence of a dimethyl group at that position can block possible deprotonation and subsequent loss of catalytic activity through aromatization of the isoquinolinium moiety (Scheme 2-5) as suggested by Bohé. Salt 27 is one of the most reactive iminium salts reported in Bohé’s group, epoxidizing trans-stilbene with 100% conversion in 1.5 hours when employing 5 mol% catalyst loading.23
Our approach to synthesize the dihydroisoquinoline iminium salts involving functionalization at the nitrogen atom provides catalysts that are generally very reactive in the catalytic epoxidation of functionalized alkenes, and in some cases the catalysts can be used at just 0.1 mol% loading, suggesting that these catalysts do not suffer the degradative aromatization suggested by Bohé.

2.1.4 Synthesis of Catalysts based on the Biphenyl-Azepinium Motif

There are two routes available to access the biphenyl-based iminium salts by reacting the chiral primary amines with one of these biphenyl precursors; 2-[2-(bromomethyl)phenyl]benzene carbaldehyde 30 or 2,2′-bis(bromomethyl) biphenyl 31 – both are synthesized from 2,2′-biphenyldimethanol 28. Treating compound 28 with 24% HBr afforded dibenzoxepine 29 in 96% yield, which can be used directly for the next step without purification. Reaction of 29 with bromine in carbon tetrachloride \(\text{CCl}_4\) afforded the bromoaldehyde 30 in 98% yield. Cyclocondensation with primary amine 11 and 12 produced the corresponding iminium salt catalysts 7 and 8, both as yellow solids in 68% and 66% yields respectively after recrystallization from ethanol (Scheme 2-6).
Another route for the preparation of the biphenyl-derived azepinium salts is carried out by treatment of 28 with HBr (48%), to afford 2,2’-bis(bromomethyl) biphenyl 31. Diol 28 undergoes a double nucleophilic substitution of hydroxyl groups by bromide ions. The mixture was heated under reflux for 2 hours and compound 31 was recrystallized as colourless crystals from a mixture of ethyl acetate/light petroleum in excellent yield (Scheme 2-7).
Cyclocondensation of the \((S,S)\)-acetonamines 11 and 12 with 2,2\textquotesingle-bis(bromomethyl) biphenyl 31 using CsCO\(_3\) as the base in acetonitrile proceeded smoothly, generating the corresponding compounds 32 and 33 in 97% and 84% yields, respectively. The oxidation of the biphenyl azepine compounds 32 and 33 was carried out by addition of NBS in dichloromethane and the solution was heated under reflux for 3 hours. This was followed by an anion exchange with sodium tetraphenylborate. After recrystallization from ethanol, iminium salts 7 and 8 were obtained in 57% and 25% yields respectively as yellow foams (Scheme 2-8). The proposed mechanism of the oxidation reaction can be seen below (Scheme 2-9).

\[ \text{Scheme 2-8} \]

Reagents and conditions: (i) CsCO\(_3\) (2 equiv), primary amine 11 or 12 (1 equiv), MeCN, reflux, overnight; (ii) NBS (1.2 equiv), DCM, reflux, 3 h; (iii) NaBPh\(_4\) (1.1 equiv) in minimum amount of MeCN, EtOH, rt, 5 min.

The oxidation is believed to proceed through bromination of the nitrogen atom on the seven-membered ring forming the positively charged intermediate. The iminium species is then formed by abstraction of a proton and simultaneous expulsion of bromide in an E2 mechanism (Scheme 2-9).

78
2.1.5 Synthesis of Catalysts based on the Binaphthyl-Azepinium Motif

Binaphthyl-based systems have emerged as some of the best ligands in asymmetric synthesis. In metal catalysis, for example, 2,2'-bis(diarylphosphino)-1,1'-binaphthyl (Figure 2.10) ligands exhibit extremely high chiral recognition ability in catalytic reactions. The binaphthyl skeleton itself is known to have superior chirality recognition and induction abilities.

1,1'-Binaphthyl compounds represent a special class of biaryl molecules. The important role played by \( C_2 \)-symmetric chiral auxiliaries has been shown to provide a high level of stereoselectivity in a wide range of asymmetric syntheses. For catalytic asymmetric
epoxidation reactions, the binaphthyl motifs have been widely used in designing both metal- and organo-catalysts. In 1999, Yamamoto et al. successfully prepared a new chiral hydroxamic acid 34, derived from 2,2′-binaphthol, serving as a monovalent ligand coordinated with a vanadium complex used for the asymmetric epoxidation of allylic alcohols giving ees of up to 94%.\(^\text{27}\) In 2000, a new series of porphyrins 35 that incorporate four identical chiral binaphthyl derivatives in the meso-positions was synthesized by Reginato et al. (Figure 2.11).\(^\text{28}\)

![Figure 2.11 - Examples of metal-based catalyst with binaphthyl motif](image)

Examples of binaphthyl-based organocatalysts include the \(C_2\)-symmetric cyclic chiral ketones \((R)\)-37, derived from 1,1′-binaphthyl-2,2′-dicarboxylic acid \((R)\)-36, which were prepared by Yang et al. (Figure 2.12).\(^\text{29-31}\)

![Figure 2.12 - Yang’s ketone catalyst](image)
Similarly, Aggarwal et al. designed iminium salts based on the (S)-(+-)binaphthyl motif. These binaphthalene-fused azepinium salt catalysts, achiral at the nitrogen substituent, afforded ees of 71% and 45% for the oxidation of 1-phenylcyclohexene and \( \alpha \)-methylstilbene, respectively.\(^{32}\)

There are two different routes reported by Page’s group to access the binaphthyl azepinium salts. The required catalysts were readily prepared over two steps from bromoaldehyde 38 by cyclocondensation with primary amines, affording catalysts 9 and 10 in good yields, 66% and 65%, respectively (Scheme 2-10).\(^{14}\)

![Scheme 2-10](image)

**Scheme 2-10 - Reagents and conditions:** (i) Primary amine 11 or 12 (1 equiv), EtOH, 40 °C, overnight; (ii) NaBPH\(_4\) (1.1 equiv) in minimum amount of MeCN, 5 min

The second route involves the formation of an azepine from (R)-2,2′-bis(bromomethyl)-[1,1′]-binaphthalene 39, by substitution of the two bromides with a primary amine; oxidation to the iminium species and anion exchange yields the desired catalysts (Scheme 2-11). Within this report, we have exclusively used the latter route, as isolation of compound 39 is far easier than that of bromoaldehyde 38.
Compound 39 is not commercially available, but can be obtained from several steps in high yield (Scheme 2-12). The synthesis can be started from a commercially available enantiomerically pure (R)-BINOL 42. The bistriflate (R)-43 was prepared in 98% yield by treatment of (R)-BINOL 42 with an excess of trifluoromethanesulfonic anhydride (triflic anhydride), and 2,6-lutidine in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in dichloromethane at −30 °C (Scheme 2-12). The triflate moiety is one of the perfluoroalkane sulfonic acid derivatives, which are important reagents in modern synthetic as well as mechanistic organic chemistry. Due to their excellent leaving group properties, the triflate group has considerably extended the range of sulfonic ester reactivity and thereby added a new dimension to its chemistry.33

Subsequent Kumada-type cross-coupling of 43 with methylmagnesium bromide and the nickel catalyst \([\text{NiCl}_2(\text{dppp})_2]\) in Et\(_2\)O or THF afforded the dimethylated compound (R)-44, again in excellent yield (95%). Grignard reagents occupy a prominent position among
organometallics used in aromatic cross-coupling reactions with a relatively fast rate of oxidative addition to Ni(0).\textsuperscript{34} The conversion of compound (R)-44 into the bis(bromomethyl)binaphthalene (R)-39 was achieved using a free radical bromination which involved the use of NBS and azobis(isobutyronitrile) (AIBN) as the initiator in cyclohexane. The product was afforded as a crystalline solid in 51\% yield. Previously, Zhang et al. reported the bromination of 44 using NBS and benzoyl peroxide in the carcinogenic carbon tetrachloride as the solvent in 69\% yield.\textsuperscript{35}

(R)-bis(Bromomethyl)binaphthalene (R)-39 can be directly converted into the corresponding amines (R)-40 and 41 by heating under reflux with primary amines 11 and 12 in the presence of K\textsubscript{2}CO\textsubscript{3} in acetonitrile followed by the oxidation of the binaphthyl azepine compounds 40 and 41 by NBS. Addition of sodium tetr phenylborate provided the iminium tetr phenylborate salts 9 and 10, which are generally highly crystalline, in 73\% and 59\% yields, respectively, after recrystallization from ethanol (Scheme 2-11). The synthesis follows the procedure described above for the preparation of biphenyl-derived catalysts 7 and 8 (Scheme 2-8).

For this project, the (R)-binaphthalene enantiomer was specifically chosen because the (S)-binaphthyl-derived catalysts prepared with the enantiomerically pure amine 11 are poor in terms of selectivity and reactivity.
2.2 Synthesis of Chromene Substrates

The aim of the second part of this research is to synthesize chromene analogues with different substituents on the aromatic ring for the application of asymmetric epoxidation reactions (Figure 2.14).

The use of various synthetic approaches is discussed in order to achieve the synthesis of the chromene substrates. Several different phenol-protecting groups – acetate, trifluoroacetate and benzoate – have been used to derivatise chromenols 47, 48 and 50 and to study their reactivity under asymmetric epoxidation conditions using iminium salt catalysts.

![Diagram of chromene substrates and their derivatives](image-url)
2.2.1 6-Hydroxy-2, 5, 7, 8-tetramethyl-2-(4-methylpent-3-ene)chromene 47

Chromane 61 is an analogue with a shorter isoprenoid chain than α-tocotrienol 60 (Figure 2.15), a class of chemical compounds related to vitamin E, which is an interesting compound for its biological properties such as anti-oxidant.36

Figure 2.15 – The structures of the vitamin E constituent, α-tocotrienol, 60 and its analogue, chromane 61

The initial plan to synthesize 6-hydroxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-ene)chromane 61 was based on an acid-catalysed condensation procedure reported by Gembus et al.37 followed by oxidation using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Trimethylhydroquinone (TMHQ) 62 was heated under reflux in xylene with linalool 63 in the presence of camphorsulfonic acid ((±)-CSA) as the acid catalyst to obtain compound 61 (Scheme 2-13). This reaction, however, was unsuccessful.

Scheme 2-13 – The initial plan for synthesis of 6-hydroxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-ene)chromane 61
In 2006, Odinokov described the same reaction but using n-octane as the solvent. When we used n-octane as the solvent, a mixture of inseparable cyclic isomers in 5:1 ratio (61:64) was obtained in 95% yield (Scheme 2-14). This ratio was determined using $^1$H NMR spectroscopic analysis by integration of the areas of the signals corresponding to the protons from the methyl group on C2 of compound 61 and the cyclic isomer 64.

![Scheme 2-14 - Reagents and conditions: (i) 63 (2 equiv), (±)-CSA (0.1 equiv), n-octane, reflux overnight, 95%, 5:1 ratio of compound 61 and 64](image)

Analysis of the $^1$H NMR of the mixture of 61 and 64 does not allow for easy identification of the structure of the major compound. The formation of cyclic isomers has also been reported by Ichikawa in 1968. Ichikawa synthesized the $\alpha$-tocopherol analogue 61 by condensation of 62 and geraniol 67 in benzene in the presence of boron trifluoride (Scheme 2-15). He then reported that the two cyclic isomers 61 and 64 could be separated as their acetates.

![Scheme 2-15 - Reagents and conditions: (i) 67 (2 equiv), BF$_3$ (10 mol%), benzene](image)
In our hands, acetate protection of the mixture of 61 and 64 yielded product 65 in 73% yield (Scheme 2-16). Compound 66 co-elutes with compound 65 and we were unable to separate compound 66 using column chromatography.

![Scheme 2-16 - Reagents and conditions: (i) Ac₂O (25 equiv), pyridine (2 mL/g of starting material), rt, 73% yield of 65](image)

Ichikawa reported the isolation of 66. The \(^1\)H NMR spectroscopic analysis of 66 showed signals at \(\delta\) 0.90 (singlet, 3 H, CH\(_3\)C–), 1.00 (singlet, 3 H, CH\(_3\)C–), 1.16 (singlet, 3 H, CH\(_3\)CO–), 2.35 – 2.60 (multiplet, 2 H, Ar–CH\(_2\)–), 1.30 – 1.80 (multiplet, 6 H, –CH\(_2\)–), 2.23 (singlet, 3 H, CH\(_3\)COO–), 2.05 (singlet, 3 H, CH\(_3\)–Ar) and 1.95 (singlet, 6 H, CH\(_3\)–Ar), with no signal of the olefinic proton. The similarities between the \(^1\)H NMR spectra of 66 and the minor compound from the mixture of 61 and 64 allowed us to confirm the structure of compound 64. Analysis of the \(^1\)H NMR spectrum of 65 indicates the presence of the core structure of chromanol 61, further confirming that 61 is the major compound in the inseparable mixture. We were then able to determine the ratio of \(61:64\) (5:1) in the inseparable mixture from the cyclization reaction.

Odinokov reported the use of heptane which gave a 2:1 ratio of 61:64 while the reaction in aromatic solvents such as benzene and toluene gave nearly equimolar mixtures, and the reaction in dioxane did not proceed at all.
Odinokov suggested that the ratio of the products is greatly influenced by the catalyst activity. Thus, several other mild acid catalysts were used to improve the isomer ratio but to no avail. The use of p-TsOH in our hands for this reaction was found to be less reactive, giving only 21% yield with the ratio of the isomers in accord with Odinokov’s report. The use of other acids, Amberlyst® 15 and silica gave no reaction at all. The collected results can be seen in Table 2-2.

<table>
<thead>
<tr>
<th>Acid</th>
<th>Solvent</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-CSA</td>
<td>Xylene</td>
<td>No reaction</td>
</tr>
<tr>
<td>(±)-CSA</td>
<td>n-octane</td>
<td>Mixture of isomers 61 and 64, 5:1, 95%</td>
</tr>
<tr>
<td>p-TsOH</td>
<td>n-octane</td>
<td>Mixture of isomers 61 and 64, 5:1, 21%</td>
</tr>
<tr>
<td>Amberlyst® 15</td>
<td>Toluene</td>
<td>No reaction</td>
</tr>
<tr>
<td>Amberlyst® 15</td>
<td>Dichloromethane</td>
<td>No reaction</td>
</tr>
<tr>
<td>Silica</td>
<td>Toluene</td>
<td>No reaction</td>
</tr>
<tr>
<td>Silica</td>
<td>Dichloromethane</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

In 2005, Odinokov reported the use of this approach to synthesize the vitamin K$_1$ dihydro derivative (naphthotocopherol) 68 and an analogue 69. Compound 68 and its cyclic isomer 69 were obtained as a mixture in a 3:7 ratio according to GLC (Scheme 2-17).
Using the approach discussed above, propargyl alcohol 70 (3,7-dimethyl-6-octen-3-ol-1-yne) would be the desired precursor to obtain the chromene substrate 47 directly (Scheme 2-18).

The precursor 70 was readily accessed by us through the addition of a Grignard reagent, ethynylmagnesium bromide 72, to commercially available 6-methylhept-5-en-2-one 71 (Table 2-3).

Table 2-3 – Reaction conditions for synthesis of 3,7-dimethyloct-6-en-3-ol-1-yne 70

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound 71</th>
<th>Compound 72</th>
<th>Solvent</th>
<th>Temp, °C</th>
<th>Product 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 equiv</td>
<td>1.5 equiv</td>
<td>THF</td>
<td>–78 °C – rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>1 equiv</td>
<td>4.5 equiv</td>
<td>THF</td>
<td>0 °C – rt</td>
<td>62%</td>
</tr>
<tr>
<td>3</td>
<td>1 equiv</td>
<td>10.0 equiv</td>
<td>THF</td>
<td>0 °C – rt</td>
<td>70%</td>
</tr>
<tr>
<td>4</td>
<td>1 equiv</td>
<td>1.2 equiv</td>
<td>THF/Et₂O</td>
<td>rt (1:1)</td>
<td>88%</td>
</tr>
</tbody>
</table>

No reaction progress was observed when the reagent 71 was added at –78 °C. When the addition of 71 took place at 0 °C, 70 was obtained in 62% yield. Increasing the number of equivalents of 72 also led to an increase in the yield. Nevertheless, the best outcome was obtained when 1.2 equiv. of 72 were used at room temperature: ketone 71 was dissolved in a mixture of anhydrous Et₂O/THF (1:1) and this solution was added dropwise to a solution of the Grignard reagent 72 at room temperature under argon. The residue was purified by column chromatography on neutral alumina, giving the product 70 in 88% yield.
The product decomposed when silica was used for the separation (Scheme 2-19). Under these conditions, increasing the number of equivalents of 70 did not improve the yield.

![Scheme 2-19 – Reagents and conditions: (i) 72 (1.2 equiv), anhydrous Et₂O/THF (1:1), rt, Ar, 3 h, 88%]

With propargyl alcohol 70 in our hands, we then attempted the synthesis of chromene 47 under acid catalysis, by reacting with phenol 62 in the presence of a catalytic amount of (±)-CSA and heating under reflux (Scheme 2-20).

![Scheme 2-20 - Reagents and conditions: (i) (±)-CSA, n-octane, reflux]

Unfortunately, the desired product was not isolated and the starting material was decomposed under these conditions. A base-catalysed reaction was also attempted using propargyl alcohol 70 and trimethylhydroquinone 62. According to a method by Godfrey (used to prepare compound 49), propargyl alcohol 70 was first converted into the corresponding trifluoroacetate analogue by addition of trifluoroacetic anhydride (TFAA) in an ice-brine bath in the presence of DBU. The solution was stirred at 0 °C for 30 min. The solution of phenol 62 in CH₂CN in the presence of DBU and a catalytic amount of CuCl₂.H₂O was then added into the trifluoroacetyl solution. However this attempt also failed (Scheme 2-21).
Due to unsuccessful attempts to synthesize compound 47 using both acid- and base-catalysed condensation procedures presented above, we turned our attention towards another method. We finally managed to obtain chromene 47 through reaction of trimethylhydroquinone 62 with citral 73 in the presence of phenylboronic acid by heating under reflux for 1.5 hours in toluene, affording 45% yield of chromene 47 (Scheme 2-22). This method was reported previously by Jung et al. to synthesize (+)-decursinol 81 and is further discussed in Chapter 2.2.2.
2.2.2 6-Hydroxy-2,2,5,7,8-pentamethylchromene 48

Zhou prepared chromane 75 (2,2,5,7,8-pentamethyl-6-hydroxychromane or PMC) using an acid-catalysed method (Scheme 2-23). Phenol 62 was coupled with 2-methyl-3-buten-2-ol 74 using trifluoroacetic acid (TFA) as catalyst under inert atmosphere followed by cyclization to give PMC in 80% yield. An earlier report of this trifluoroacetic acid-catalysed reaction at room temperature by Ismail et al. described the isolation of 75 in 63% yield. Ismail also reported that the presence of water (up to 10% v/v) in the reaction was found to increase the reaction rate.

Our first attempt to synthesize compound 48 was modelled on Zhou’s approach. This procedure failed to yield 48 from related dimethyl propargyl alcohol 76 (Scheme 2-24).

The failure of the acid-catalysed condensation of phenol 62 and propargyl alcohol 76 is probably due to Rupe/Meyer-Schuster rearrangement forming the corresponding α, β-unsaturated carbonyl compounds. Protonation of the propargylic alcohol followed by the
removal of water as leaving group formed the carbocation intermediate (Scheme 2-25). This intermediate rearranges in two pathways: Rupe rearrangement or Meyer-Schuster rearrangement.\textsuperscript{50,51} The difference between these two reaction pathways occurs early on: initial β-elimination of the propargyl alcohol provides an enyne \textit{en route} to the Rupe product (path a), whereas as 1, 3-hydroxyl shift and tautomerization in path b leads to the Meyer-Schuster product. This also explains our failure to synthesize compound 47 using propargyl alcohol 70 (Scheme 2-19).\textsuperscript{50}

\begin{center}
\textbf{Scheme 2-25 – Path a: Rupe rearrangement and; Path b: Meyer-Schuster rearrangement mechanism}\textsuperscript{50}
\end{center}

The synthesis of compound 48 was achieved by the ring formation of 62 with 3-methyl-2-butenal 77, using phenylboronic acid (2 equiv) with an excess of acetic acid in toluene afforded the desired chromene 48 in 61\% yield (Scheme 2-26). The mixture was heated under reflux in toluene overnight under \textit{N}_2 atmosphere. The use of a Dean-Stark apparatus did not improve the yield.
This method was outlined by Jung et al. to synthesize (+)-decursinol 81 from a commercially available starting material, umbelliferone 78. Umbelliferone 78 was first reduced using H\textsubscript{2}/Pd-C at room temperature for 10 hours to afford compound 79 in 94% yield, which was then subjected to ring formation reaction of the chromanone 79 with aldehyde 77 in the presence of phenylboronic acid and propionic acid to afford compound 80 in 62% yield (Scheme 2-27).\textsuperscript{47}

Phenylboronic acid is a useful reagent to produce quinonemethide intermediates, such as 85, catalysing a reaction between a phenol and an aldehyde.\textsuperscript{52} Nagata first reported this reaction in 1976; he later proposed that the mechanism proceeded through a [3,3]-sigmatropic rearrangement pathway, and he was able to isolate benzodioxaborines, such as 84 (Scheme 2-28). Phenylboronic acid adduct 82 reacted with the required aldehyde to
form benzodioxaborine 84, which rearranged to produce quinonemethide intermediate 85. The substituted 2-phenyl-4H-1,3,2-benzodioxaborin 84 is a stable compound that can be stored indefinitely at room temperature. Intramolecular hetero electrocyclization of the exo-quinonemethide 85 with the α-double bond gave the desired product 48 in a good yield (61%).

Scheme 2.28 - Ring formation mechanism with phenylboronic acid via [3,3]-sigmatropic rearrangement pathway

The reaction is regioselective, attack occurring exclusively at the ortho position with regards to the phenolic hydroxyl. No reaction was observed without phenylboronic acid, or acetic acid. Besides Jung, this methodology has been successfully applied by Broadhurst and Hassan to the synthesis of anthracyclines (Figure 2.16).
We attempted to use this method to synthesize compound 47, taking into account our previous experience of inseparable mixture of isomers in synthesizing 47 via acid-catalysed reaction. This was carried out by heating under reflux a mixture of the corresponding phenol, trimethylhydroquinone 62 (1 equiv), citral 73 (3 equiv), and PhB(OH)$_2$ (1.6 equiv) in the presence of a catalytic amount of propionic acid (0.3 equiv) in toluene. The first attempt using PhB(OH)$_2$ and an excess of acetic acid, following the method to synthesize 48, failed. However, Chambers et al. reported the use of propionic acid (0.3 equiv) instead of acetic acid for the synthesis of compound 47 (Scheme 2-22). This one-pot reaction is very much preferable even though the yield is just 45% as no mixture of inseparable cyclic isomers is formed. The crude product was purified by column chromatography in 95/5: petroleum ether/ethyl acetate as eluent to obtain compound 47.

### 2.2.3 6-Cyano-2, 2-dimethyl-2H-1-benzopyran 49

Within the Page group, two methods have been used to access the chromene substrate 49. The first procedure to synthesize 2,2-dimethyl chromenes from electron-deficient phenols has been developed by North et al.,$^{55}$ which is complementary to that of Crombie$^{56}$ and Camps.$^{57}$ This methodology involves a base-catalysed condensation of 4-cyanophenol 86 with diethyl acetal 87 in $p$-xylene and affords 6-cyano-2,2-dimethylchromene 49 in 87% yield (Scheme 2-29). The second method proceeds through the thermal rearrangement of a suitable propargyl ether (Scheme 2-30).
The synthesis of chromene 49 using the first method begins with the preparation of the diethyl acetal 87 (Scheme 2-31). The synthesis of diethyl acetal 87 from ethanol, triethyl orthoformate 88, and 3-methyl-2-butenal 77 in the presence of p-toluenesulfonic acid was found unsuccessful due to polymerization of the aldehyde as reported by North et al. North then ultimately found that KHSO₄ afforded the best yield of 87, up to 86% yield.55

In 1986, Mori et al. reported the use of NH₄NO₃ as a solid acid catalyst to synthesize the α,β-unsaturated acetal 87 which was then used without further purification for asymmetric Simmons-Smith reactions.58 In our hands, the reaction was complete within 24 hours. Evaporation of the reaction solvent however had to be carried out carefully at low temperature (approx. room temperature) due to the boiling point of the acetal. According to NMR spectroscopic analysis, the brownish liquid obtained is a pure sample of acetal 87. The use of orthoesters, such as trimethyl- or triethyl orthoformate, with aldehydes or
ketones in the carbon-oxygen bond formation is a well-established reaction. The proposed mechanism of acetalization is shown below (Scheme 2-32).

Acetal 87 was freshly prepared due to the instability of this compound at room temperature. This compound also tends to decompose when kept in the refrigerator for a period of time. Acetal 87 was subsequently heated under reflux with 4-cyanophenol 86 in \( p \)-xylene in the presence of 3-picoline as the base.
The suggested mechanism of the base-catalysed condensation of an α,β-unsaturated acetal and a phenol is illustrated below (Scheme 2-33).\textsuperscript{55,61} First, the phenol is deprotonated. North suggested that the phenol also acts as an acid catalyst to activate the acetal.\textsuperscript{55} The ethanolysis of the acetal produced the oxonium ion, which then attacked by phenolate to give the corresponding dienone 89. Rearomatization of 89 leads to 90, and subsequent elimination of ethanol allows formation of enone 91. Finally, electrocyclic ring closure provides chromene 49.

\begin{center}
\includegraphics[width=\textwidth]{diagram.png}
\end{center}

Scheme 2-33 - Mechanism of the base-catalysed condensation of an acetal and a phenol to form a chromene

The rearrangement/cyclization of propargyl ether 93 is another potential method developed by Harfenist and Thom to access chromenes such as 49 (Scheme 2-34),\textsuperscript{62} and has been recognised as one of the general methods for the synthesis of chromenes.\textsuperscript{63} The dimethylated propargyl alcohol 76 was first converted to the corresponding dimethylated propargyl chloride 92 using calcium chloride, cuprous chloride and a catalytic amount of copper powder and cold concentrated hydrochloric acid, according to a method by Boisselle.\textsuperscript{64}
The α-alkylation of 4-cyanophenol 86 was achieved by heating the phenol and 3-chloro-3-methyl-1-butyne 92 with potassium carbonate and potassium iodide in acetone: the propargyl ether 93 was obtained in excellent yield, as high as 99%. Thermal rearrangement of the ether 93 in high boiling point solvent (>150 °C) allowed cyclization of the ether in an almost quantitative yield.65

![Scheme 2-34 - Reagents and conditions: (i) CaCl₂, CuCl₂, Cu, cold conc. HCl, 0 °C, 5 hrs; (ii) 4-cyanophenol, K₂CO₃ (1.0 eq), KI (0.1 eq), N₂, acetone, reflux; (iii) N,N-diethylaniline, N₂, reflux.](image)

Previously, the thermal Claisen rearrangement had been performed by heating a solution of 93 in o-chlorobenzene,62 a mixture of dry DMF, N, N-diethylaniline66, and poly(ethylene glycol).67 The thermal rearrangement of simple propargyl ethers to produce chromenes was first reported by Iwai and Ide68 in 1963 and remains a convenient method for the preparation of 2,2-dimethylchromenes.69–73 Ethylene glycol was used by us as the solvent as its high miscibility with water facilitates the work-up; indeed, a simple extraction with diethyl ether and a water wash are sufficient to separate the ethylene glycol from the desired product. The chromene 49 was then recrystallized from the residue using light petroleum.

Godfrey showed that the conversion of 76 to 93 could also be achieved by converting the propargyl alcohol into trifluoroacetate 94. The trifluoroacetate 94 is an effective leaving group for the alkylation in the presence of a copper catalyst (Scheme 2-35). Base-catalysed condensation of compound 94 was achieved in 86% yield using DBU as the base with the presence of a catalytic amount of copper chloride at 0 °C for five hours.74,75
The mechanism of the thermal cyclization of aryl propargyl ethers into chromenes was proposed by Zsindley and Schmid (Scheme 2-36) and involves an initial Claisen rearrangement of aryl propargyl ether 95 to give γ,δ-unsaturated allene carbonyl intermediate 96. Enolization of 96 gives intermediate 97 which then undergoes a [1,5]-sigmatropic hydrogen shift to yield 98 followed by an electrocyclic reaction to give the related chromene 99.

Scheme 2-35 - Reagents and conditions: (i) (CF₃CO)₂O, DBU, CH₃CN, 0 °C, %; (ii) 4-cyanophenol, DBU, CH₃CN, CuCl₂ (0.1 mol%), 0 °C, 5 hr, 86%; (iii) reflux

Scheme 2-36 - Proposed mechanism of thermal cyclization of aryl propargyl ethers
2.2.4 6-Hydroxy-2,5,7,8-tetramethylchromene-2-carboxylate 50

The chromene substrate 50 was synthesized by heating the trimethylhydroquinone 62 and methyl methacrylate 100 in a formalin solution (37 wt%) at 180 °C in a pressure tube to afford a white solid, which was recrystallized from methanol giving 101, in up to 71% yield, followed by protection of the phenol group and dehydrogenation at C3 and C4 (Scheme 2-37).
The Mitsubishi Corporation developed this method on an industrial scale. In most literature reports, compound 101 was readily synthesized from the commercially available Trolox® (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid), 104 after a simple methyl esterification (Scheme 2-38). Compounds 101 is a very useful intermediate for functionalization at both the ester functionality and the phenol group.

Scheme 2-38 – p-TsOH (0.3 equiv), MeOH (20 mL/g of 104), CH₂Cl₂ (4 mL/g of 104), rt, 95%.

For example, Atkinson et al. reported the preparation of photoaffinity analogues of α-tocopherol 108. Starting from (S)-Trolox® 104, the carboxylic acid was first transformed into its methyl ester 101, followed by protection of the phenolic hydroxyl as the corresponding tert-butyldimethylsilyl ether 105. Selective reduction of the ester group into aldehyde 106 was carried out using diisobutylaluminium hydride (DIBAL). Then, the incorporation of the photolabile group to the side chain was accomplished using ω-hydroxyalkyl phosphonium bromide 109. Treatment of 109 with a strong base produced the ylide, which was coupled to the aldehyde 106 in a Wittig reaction to form the alkenol 107. The saturated side chain was then obtained by catalytic reduction using Pd/C. Compound 108 was obtained after several further steps (Scheme 2-39).
Naumann et al. studied the functionalization at the phenolic hydroxyl position. Previously, this group reported that the presence of both a lipophilic and an acid moiety on the carbazole or the carprofen scaffold seemed to be essential for the modulatory effect on the \( \gamma \)-secretase enzyme, displaying activities as low as a micromolar range for the most active derivatives (Figure 2.18, compound \textbf{110} and \textbf{111}).\textsuperscript{79} The \( \gamma \)-secretase enzyme has been demonstrated to reduce the production of amyloid-\( \beta \)\textsubscript{42} peptides (A\( \beta \)\textsubscript{42}) and to increase the formation of shorter A\( \beta \)-peptides like A\( \beta \)\textsubscript{38}. The more hydrophobic A\( \beta \)\textsubscript{42} species has a higher tendency to aggregate compared to A\( \beta \)\textsubscript{38} which is more soluble. The aggregation-prone A\( \beta \)\textsubscript{42} peptides are the central drivers of the pathological process in Alzheimer’s disease.\textsuperscript{80–83}
Referring to these previous studies, Naumann et al. synthesized tocopherol derivatives by adding lipophilic chains to the chromane derivative $104$ to study the impact of the acidic moiety's location on the $\gamma$-secretase modulators' (GSM) activity and to compare the influence of several lipophilic chains of various lengths including octyl- ($112a$), undecyl- ($112b$), tetradecyl- ($112c$), the terpene-related farnesyl- ($112d$), and phytyl- ($112e$) (Scheme 2-40). The study revealed that all the synthesized chromane derivatives with an acidic moiety ($112b$ – $112e$) exhibited GSM activity, increased the generation of $A\beta_{38}$ and reduced the generation of $A\beta_{42}$, except for compound $112a$, which contains only eight carbon atoms on the lipophilic chain, which is too short to provide stable anchoring in the membrane.
As discussed above, the modification of the methyl ester or phenol in compound 101 gives rise to a number of biologically active compounds. However, to the best of our knowledge, there is no report on potential modifications at the C3-C4 position of 101, which would be interesting to explore.

### 2.2.5 Protection of the Phenolic Hydroxyl Functional Group

After we had successfully synthesized all the desired chromene substrates, chromenes 47, 48, and 50 were subjected to phenolic hydroxyl group protection. Protection is necessary prior to the asymmetric epoxidation reaction. Oxidation attempts on compounds 47, 48, and 50 were unsuccessful perhaps due to the electron-donating properties of the hydroxyl group, which may stabilize the carbocation issued from the ring opening of the epoxide; this is discussed further below (Chapter 2.3). Several hydroxyl protecting groups had been chosen with electron-withdrawing abilities on the basis that this would increase the stability of the resulting epoxide. We successfully prepared the protected chromene compounds using several protecting groups, including the acetate, trifluoroacetate and benzoate groups.
2.2.5.1 Acetate Protection of the Phenolic Hydroxyl Group

Acetate protection of the phenolic hydroxyl moiety proceeded smoothly, the chromene or chromane compound, pyridine and acetic anhydride, stirred at room temperature according to method by Ordinokov et al. affording yields as high as 86% yield (Table 2-4). Another method, reported by Patti et al., gives up to 74% yield of the desired acetate, when triethylamine and acetic anhydride were used in t-butylmethyl ether as the solvent.

Table 2-4 - Acetate protection of chromane/chromene

<table>
<thead>
<tr>
<th>Chromene/Chromane</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Chemical shift of acetyl, δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td><img src="47" alt="Image" /></td>
<td>86</td>
<td>2.33</td>
</tr>
<tr>
<td>48</td>
<td><img src="48" alt="Image" /></td>
<td>82</td>
<td>2.32</td>
</tr>
<tr>
<td>61</td>
<td><img src="61" alt="Image" /></td>
<td>73</td>
<td>2.32</td>
</tr>
<tr>
<td>99</td>
<td><img src="99" alt="Image" /></td>
<td>59</td>
<td>2.25</td>
</tr>
</tbody>
</table>
The presence of the acetate group can be confirmed using $^1$H NMR spectroscopic analysis. The signal corresponding to the protons from the acetate group is observed as a singlet between 2.2 and 2.4 ppm. Analysis of the IR spectrum confirms the presence of carbonyl group of the acetate which gives a strong peak in the range of 1750 – 1760 cm$^{-1}$.

For chromane 61, we only protected this compound using acetate group as the phenolic hydroxyl protection of this compound was carried out in order to separate the cyclic mixture (Chapter 2.2.1). We did not protect this compound using other protecting groups.

### 2.2.5.2 Trifluoroacetate Protection of the Phenolic Hydroxyl Group

Trifluoroacetylation of phenolic hydroxyl group was carried out using trifluoroacetic anhydride (TFAA) in anhydrous THF as the solvent and pyridine as the base at 0 °C. The trifluoroacetate-protected compounds were obtained in 65 – 99% yields (Table 2-5). Unexpectedly, we obtained almost quantitative yield of 52 after 24 hours reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Chromene/Chromane</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td><img src="52.png" alt="Image" /></td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td><img src="55.png" alt="Image" /></td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>99</td>
<td><img src="114.png" alt="Image" /></td>
<td>65</td>
</tr>
</tbody>
</table>

Table 2-5 - Trifluoroacetate protection of chromane/chromene
As no additional signal is expected when the $^1$H NMR spectrum of the compounds is analysed, the attachment of trifluoroacetate group can be confirmed by analysing their $^{13}$C NMR spectrum: indeed, the presence of two quartet signals in the 110 – 120 ppm ($^J_{C-F} = 284 – 287$ Hz, CF$_3$) and 150 – 160 ppm regions ($^J_{C-F} = 40.0 – 45.0$ Hz, C=O) proves it. Analysis of the IR spectrum confirms the presence of the trifluoroacetyl group which gives two strong and broad peaks between 1100 – 1200 cm$^{-1}$. It was also determined that the compound contained a carbonyl group from the peak between 1790 – 1800 cm$^{-1}$. The carbonyl stretching of the trifluoroacetate group is higher than the average ester carbonyl frequency (ca. 1740 cm$^{-1}$). The force constant of the C=O bond is higher relative to the hydrogenated ester due to the presence of the highly electronegative fluorine atoms.

### 2.2.5.3 Benzoate Protection of the Phenolic Hydroxyl Group

Benzoylation of the phenolic hydroxyl groups were successfully achieved by reacting the phenol with sodium hydride as the base and benzoyl chloride under anhydrous conditions. The addition of the phenol (dissolved in anhydrous THF) into a suspension of the base in THF under inert atmosphere gave the corresponding phenoxide ion. Hydrogen evolution immediately occurred and the colour of the solution changed as the phenol solution was slowly added. Benzoyl chloride was then added into the mixture and the benzoate protected product was obtained in good to excellent yield (Table 2-6).

<table>
<thead>
<tr>
<th>Chromene/Chromane</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Reaction time (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td><img src="image" alt="Product 53" /></td>
<td>75</td>
<td>Overnight</td>
</tr>
</tbody>
</table>

Table 2-6 - Benzoate protection chromene/chromane: NaH (1.1 equiv), benzoyl chloride (1.0 equiv), dry THF, $N_2$.
Initial attempts to use pyridine as the base were disappointing as the benzoylation reaction was found to be very slow: the desired benzoate was obtained in 20% yield when the reaction was left overnight. Addition of a catalytic amount of DMAP did not improve the yield.

2.2.5.4 Methyl Ether Protection of the Phenolic Hydroxyl Group

Apart from protecting the phenolic hydroxyl using an electron withdrawing group, we also attempted an electron donating group protection, methyl ether protection, in this research. Methyl ether is one of the simplest protecting groups. This type of protection is normally avoided except when the hydroxyl needs to survive strongly basic or acidic conditions as the deprotection is difficult in which harsh conditions are required. But the removal is not as difficult with phenols.

The introduction of the methyl group was carried out via Williamson Ether synthesis. The use of sodium hydride and methyl iodide under inert atmosphere, afforded the corresponding products in good yield (Table 2-7) after few hours of stirring at room temperature (Scheme 2-41). In contrast, when we used an approach by Pan, reaction of
chromene 48 with potassium carbonate as the base in acetone and stirred for 48 hours, disappointingly, we obtained only 11.6% yield of 117, as compared to 87% yield using sodium hydride as the base.

Scheme 2-41 - Reagents and conditions: (i) NaH (1.1 equiv), anhydrous THF, MeI (1 equiv), rt

Table 2-7 Methyl ether protection of the phenolic hydroxyl

<table>
<thead>
<tr>
<th>Chromene/Chromane</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Reaction time (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td><img src="image1.png" alt="Image" /></td>
<td>87</td>
<td>3</td>
</tr>
<tr>
<td>99</td>
<td><img src="image2.png" alt="Image" /></td>
<td>69</td>
<td>24</td>
</tr>
</tbody>
</table>
2.2.6 Synthesis of 3, 4-Dehydro Derivatives of Chromane

It has been reported that chromane compounds can be dehydrogenated to the corresponding chromenes by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (Scheme 2-42).\(^9\)

![Scheme 2-42 – Reagents and conditions: (i) DDQ, dry toluene, 105 °C – reflux, 24 h](image)

DDQ is a chemical reagent widely used in organic synthesis. It is a member of the large quinones family and is one of the most versatile reagents because it has high oxidant ability and relative stability compared to others. The dehydrogenation of hydroaromatic compounds by quinones was first reported in 1930 by Clar and John.\(^9\) However it failed to gain general acceptance until the more extensive investigations of Braude, Jackman, Linstead, and co-workers, 20 years later.\(^9\) The advantage of quinone hydrogenation as a method of selective abstraction of hydrogen from hydroaromatic compounds is the mild conditions used.

The suggested mechanism for dehydrogenation involves a 2-step reaction mechanism: an initial rate-determining transfer of a hydride ion followed by a rapid proton transfer leading to the hydroquinone formation (Scheme 2-43).\(^9,9\)
Rosenau has reported that mixtures of different dimers were obtained when non-protected chromanols were reacted with DDQ, whereas the reaction with appropriately O-protected chromanols proceeded smoothly. Thus, suitable protection of the phenolic hydroxyl is essential before the actual dehydrogenation step, and deprotection can be done afterwards.\textsuperscript{89} Previously, the acetate protecting group was chosen due to simplicity and near-quantitative yields of both attachment and removal of protecting group.\textsuperscript{89} Thus, we decided to do the oxidation reaction using the acetate-protected chromane.

Both working in an inert atmosphere and using carefully dried solvents were imperative to obtain good yields (about 70\% after purification). Anhydrous reaction conditions are essential when using DDQ as this oxidant decomposes in the presence of water with the evolution of HCN.\textsuperscript{92}
CHAPTER 2 - RESULTS AND DISCUSSIONS

Table 2-8 - Oxidation using DDQ

<table>
<thead>
<tr>
<th>Entry</th>
<th>Chromane</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>113</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>115</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>43</td>
</tr>
</tbody>
</table>

As can be seen in Table 2-8, the yield of the oxidation reactions we obtained in our lab, is moderate, below 50% yield. Rosenau reported oxidation of 2,2,5,7,8-pentamethylchromane 119, afforded the corresponding chromene 54 in 76% yield (Scheme 2-44). The lower yield obtained with our chromanes could be explained by the difference between the steric hindrance caused by the side chains at the C2 position (methyl group vs. long alkyl chain or carboxylate group). There is no significant difference in the reaction yield observed when the acetate group is replaced with a benzoate group (Table 2-8, entry 2 and 3).

![Scheme 2-44 - Reagents and conditions: (i) DDQ, toluene, reflux, 24 h, 76%](image)

TLC analysis of the reaction mixture showed the product and the starting material have the same Rf, but the starting material can be distinguished from the product by charring the TLC plate with 4% H2SO4 in MeOH. The starting material and the product turn yellow and brown, respectively.
An example of dehydrogenation of a chromene derivative was reported by Chauncey et al. in 1980; the chromane 120 was heated under reflux in anhydrous benzene for 48 hours to give the corresponding chromene 121 in 77% yield (Scheme 2-45).^{93}

![Scheme 2-45 – Reagents and conditions: (i) DDQ, dry benzene, reflux, 48 h, 77%]^{93}

A functionality that is capable of stabilizing the cation formed and initiate hydrogen transfer is needed, typically an aromatic moiety. Hydrocarbons lacking these functionalities are stable to the action of DDQ. In 1982, Ahluwalia reported that the presence of an electron-donating group on the aromatic ring can facilitate the oxidation reaction. Ahluwalia showed an example using chromanes 122a and 122b bearing a methoxy group on the aromatic ring, gave the corresponding chromenes 123a and 123b in 80 and 85% yields, respectively (Scheme 2-46).^{53}

![Scheme 2-46 - Reagents and conditions: (i) DDQ, anhydrous benzene, reflux, 20 h]^{53}

\[ 120 \xrightarrow{(i)} 121 \]

\[ 122a, R_1 = \text{OCH}_3, R_2 = \text{H}; \]
\[ 122b, R_1 = \text{H}, R_2 = \text{OCH}_3 \]
\[ 123a, R_1 = \text{OCH}_3, R_2 = \text{H}, 80\%; \]
\[ 123b, R_1 = \text{H}, R_2 = \text{OCH}_3, 85\% \]
2.3 Asymmetric Epoxidation of Chromene Substrates

Epoxidation reactions are important transformations of alkenes, as epoxides are versatile intermediates in organic syntheses. In the final part of this research, we aimed to apply asymmetric epoxidation reactions, using our iminium salt catalysts 3, 4, 7 – 10, to the chromene substrates and their derivatives. Chromenes and 3,4-epoxychromane derivatives have attracted much attention because of their biological activities and importance as synthetic intermediates for biologically active compounds.41,94–100

The chromene substrates and their derivatives we synthesized earlier are not natural compounds. However, asymmetric epoxidation of compound 49 followed by the treatment with pyrrolidin-2-one allows access to levromakalim, a hypertensive agent, as discussed in Chapter 1.2.4 (Scheme 1-24, page 32).101 As for compound 47, 48, and 50, these compounds are analogues of the vitamin E constituent, tocotrienol, a very interesting compound with antioxidant property. Thus, application of asymmetric epoxidation reactions to these compounds can be used to study the antioxidant property of the modified analogues.

2.3.1 Determination of Enantiomeric Excess

In asymmetric synthesis, determination of the enantiomeric excess (ee) is important to evaluate the dominance of major enantiomer. In this research, there are two methods used in evaluating the enantiomeric excesses of the chiral epoxides i.e. using chiral HPLC or using 1H NMR spectroscopy with addition of chiral shift reagent, Eu (hfc).1

2.3.1.1 By Chiral HPLC

Chiral HPLC is one of the most common methods to determine the ee of a chiral compound. A racemic sample is first synthesized and the purified racemic product is then subjected to analysis to determine a suitable HPLC system. The solvent flow rate and the
solvent mixture (in this research we used HPLC grade hexane and isopropanol) can be adjusted to optimize the HPLC system to provide well-separated peaks of the enantiomers. When a system has been determined for the racemic mixture of one compound, the system can then be applied to enantioenriched samples.

For example, an analytical method using HPLC was established with the racemic (±)-124 using a Chiralpak column at flow rate of 0.5 mL/min; the enantiomers appeared at 36.2 – 38.9 min and 40.6 – 44.2 min retention time. Racemic (±)-124 was afforded from the reaction of 49 with 2 equiv of m-CPBA in DCM at 0 °C (Scheme 2-47). The HPLC trace of the racemic (±)-124 can be seen in Figure 2.19 below, showing the presence of a mixture of enantiomers in 50:50 ratio in the sample by measuring the areas of the peaks:

Once the HPLC system for the racemic sample is predetermined, the analysis of enantiopure sample can be carried out. In the example below, reaction of 49 under non-aqueous conditions in the presence of the iminium salt catalyst 7 (10 mol%), afforded (−)-15,2S-124 in ≥99% ee (Scheme 2-48). The enantiomeric excess of the enantiomerically
enriched epoxide can be calculated from the areas of peaks obtained from chromatographic data (Table 2-9).

$\text{Scheme 2-48 - Asymmetric epoxidation of chromene 49}$

$\text{Table 2-9 - Peaks area and height}$

<table>
<thead>
<tr>
<th>Retention Time</th>
<th>Area</th>
<th>Area %</th>
<th>Height</th>
<th>Height %</th>
</tr>
</thead>
<tbody>
<tr>
<td>36.623</td>
<td>347322</td>
<td>0.33</td>
<td>11791</td>
<td>0.61</td>
</tr>
<tr>
<td>40.790</td>
<td>104456189</td>
<td>99.67</td>
<td>1922846</td>
<td>99.39</td>
</tr>
<tr>
<td>Totals</td>
<td>104803511</td>
<td>100.00</td>
<td>1934637</td>
<td>100.00</td>
</tr>
</tbody>
</table>

From the example of the HPLC trace of the enantiopure compound 124 (Figure 2.20), the enantiomeric excess is ≥99% using the formula below:

$$\% \text{ ee} = \frac{\text{area } A - \text{area } B}{\text{area } A + \text{area } B} \times 100\%$$
2.3.1.2 By $^1$H NMR Spectroscopy with the Chiral Shift Reagent Eu (hfc)$_3$

In some cases, the enantiomeric excess for epoxide samples cannot be determined using chiral HPLC as the peaks corresponding to both enantiomer are not resolved; therefore alternative methods of determining enantiomeric excess are required. In this research, the other method used to determine the ee is using chiral shift reagent. The mixture of epoxide enantiomers forms a pair of diastereomeric complexes in the presence of the chiral shift reagent. The two resulting complexes exhibit a different set of signals using $^1$H NMR spectroscopy and integration of a proton signal corresponding to each complex allows ee to be determined. Currently several chiral shift reagents are commercially available, including the europium shift reagent Eu(hfc)$_3$, Kagan’s amide shift reagent and Pirkle reagent. The best chiral shift reagent used for epoxide samples in our group is europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate], Eu(hfc)$_3$ \textbf{125} (Figure 2.21).

One example of chiral epoxides that cannot be resolved using chiral HPLC is 1-phenylcyclohexene oxide \textbf{127}; hence the chiral shift reagent was used to determine the ee of the chiral epoxide \textbf{127}. The method involved sequential addition of the chiral shift reagent Eu(hfc)$_3$ into the analysed compound in a deuteriated solvent until the signals corresponding to each complex appeared. Enantioenriched epoxide \textbf{127} was prepared under aqueous conditions to test this method (Scheme 2-49).
The signal corresponding to the protons at the 2-position of compound 127 is observed at 3.08 ppm in deuterated chloroform (Figure 2.22). After addition of chiral shift reagent, the peak corresponding to the same proton in each diastereoisomeric complex can be seen at 3.45 and 3.55 ppm, respectively (Figure 2.23).
The ee can be calculated using the same formula as used for chiral HPLC. In the example above, the percentage of ee is 53%.

2.3.2 Preparation of Racemic Epoxides

Generally, racemic epoxidation of alkenes in our laboratory is carried out by reaction of the alkene with \( m \)-CPBA in DCM or chloroform reacting at 0 °C for few hours. After the reaction is complete, the organic layer is extracted a few times by using a saturated solution of NaHCO\(_3\) or 10% Na\(_2\)CO\(_3\); otherwise some of the \( m \)-chlorobenzoic acid still remains in the organic layers. The crude epoxides can be further purified by column chromatography. The epoxide is not stable to acidic silica gel which leads to epoxide decomposition, thus addition of 2% TEA to the solvent is crucial. The solvents can then be easily removed using a water bath maintained at 40 – 50 °C. Higher temperatures should be avoided because the epoxide is very reactive and undergoes decomposition at higher temperature.
Racemic epoxides can also be prepared using DMDO as oxidant. This method is normally used for acidic-sensitive epoxides as this reagent is neutral. DMDO can be prepared using the procedure by Adam et al. in a large scale.\textsuperscript{103} It was prepared by us by the reaction of Oxone\textsuperscript{®} in mixture of acetone/water with the presence of NaHCO\textsubscript{3} (Scheme 2-50) in 3 L three-neck flask and DMDO was collected under a moderate vacuum (80 – 100 Torr) in receiving flask immersed in acetone/dry ice at $-78 \, ^\circ\text{C}$ with vigorous stirring. The acetone solution of dimethyldioxirane was dried with K\textsubscript{2}CO\textsubscript{3}, filtered off and stored in the freezer ($-20 \, ^\circ\text{C}$) over molecular sieve (4Å). Due to stability problems during transport and storage, it is still not possible to purchase this reagent from common suppliers of research and fine chemicals.

![Scheme 2-50 - Reagents and conditions: (i) H\textsubscript{2}O (254 mL), acetone (192 mL), NaHCO\textsubscript{3} (58 g), 5 \, ^\circ\text{C} to 10 \, ^\circ\text{C}]

The concentration of DMDO was determined by iodometric titration. The acetone solution of DMDO was added to an Erlenmeyer flask containing water (20 mL), glacial acetic acid (1 mL) and a freshly prepared solution of NaI, and was titrated using a 0.02 M aqueous solution of sodium thiosulfate (Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3}). The concentration was then calculated using the following equation:

$$\text{Concentration of DMDO} = \frac{\text{Molarity of titrant} \times \text{mL of titrant}}{\text{mL of DMDO solution} \times 2}$$

For a smaller scale, a simplified preparation of DMDO, the method reported by Taber can also be used.\textsuperscript{104} In this method, a mixture of distilled H\textsubscript{2}O (20 mL), acetone (30 mL) and NaHCO\textsubscript{3} (24 g, 0.285 mol) was stirred at 0 \, ^\circ\text{C} prior to addition of Oxone\textsuperscript{®}. The slurry was then attached to a rotary evaporator with the bath at room temperature, which was then increased up to 40 \, ^\circ\text{C} after 15 min. DMDO was collected in the rotary evaporator splash trap, which was chilled in acetone/dry ice bath as the vacuum of 115 mmHg applied, giving average volume of 25 mL of the pale yellow acetone solution of DMDO. The solution was then dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and transferred into a 50 mL round bottom flask (dried in the oven overnight) containing molecular sieve. The concentration of DMDO solution obtained is typically in the range of 60 – 65 mM.
The latter method of DMDO preparation is much more convenient as the concentration of DMDO is much higher than the former method, and no apparatus involving large glassware is required. Since the amount of DMDO obtained is on the average of 25 mL per batch, the reagent can be freshly prepared for the racemic epoxidation reaction.

The choice of reaction temperature is critical in epoxidation reactions. Hence, an investigation was carried out to study the best reaction temperature for racemic epoxidation reactions using chromene 54 as the substrate mediated by DMDO as the oxidant (Scheme 2-51). The data collected in Table 2-10, shows that 20 min is the fastest reaction time for complete conversion of chromene 54 to the corresponding epoxide (±)-128, observed for the reactions carried out at 0 °C and room temperature. At lower temperatures, longer reaction times were required for the reactions to reach to completion. Thus, 0 °C was chosen as the standard temperature for racemic epoxidation reactions using DMDO as the oxidant rather than room temperature to avoid possible decomposition of the epoxides at higher temperatures.

Scheme 2-51 - Reagents and conditions: (i) DMDO (1.5 equiv), DCM, 100% conversion

Table 2-10 - Racemic epoxidation at different temperature

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Reaction time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>–45</td>
<td>240</td>
</tr>
<tr>
<td>–20</td>
<td>80</td>
</tr>
<tr>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Room temperature</td>
<td>20</td>
</tr>
</tbody>
</table>
Using these several approaches of preparation of the racemic epoxides, we started our investigation of the racemic epoxidation reactions on the chromenes 47 – 50. The chromene 49 is quite stable under mild acidic conditions as the racemic epoxidation using m-CPBA as the oxidant afforded the corresponding epoxide 124. Unfortunately, the racemic epoxidation reactions of compounds 47 and 48 were unsuccessful due to the decomposition of the starting material under all the reaction conditions mentioned above.

In the case of acetyl-, trifluoroacetyl and benzoyl-protected 2,2,5,7,8-pentamethylchromenes, 54, 55 and 56 respectively, unfortunately preparation of racemic 3, 4-epoxychromane using m-CPBA was unsuccessful probably due to inherent instability of the epoxides in acidic solutions. Commercially available m-CPBA contains up to 15% m-chlorobenzoic acid105 which may react with acid-sensitive epoxides to give hydroxyester as the major product. This is supported by the IR spectrum of the products from racemic epoxidation of the acetyl-protected chromene 54 and the benzoyl-protected chromene 56, showing that the products contain a hydroxyl group by the presence of broad peak at 3475 cm\(^{-1}\) and 3450 cm\(^{-1}\) respectively resulting from the epoxide ring opening (Scheme 2-52).

![Scheme 2-52 – Possible ring-opening of the epoxide by m-chlorobenzoic acid](image-url)
The use of pre-purified \textit{m}-CPBA also disappointingly did not work for the racemic epoxidation of chromenes due to the presence of acidic \textit{m}-chlorobenzoic acid as the by-product of the reaction, even though the reactions were worked-up using Na$_2$CO$_3$ several times. The purification of \textit{m}-CPBA was carried out by dissolving the commercial \textit{m}-CPBA in ether followed by washing with a phosphate buffer solution (410 mL of 0.1 M NaOH, 250 mL of 0.2 M KH$_2$PO$_4$ made up to 1 L, pH 7.5) several times as reported by Aggarwal,\textsuperscript{106} affording 72\% yield of pure \textit{m}-CPBA. However this has to be done carefully at room temperature as the peroxyacid is potentially explosive.

Addition of 10\% aqueous Na$_2$CO$_3$ solution in racemic epoxidation of the chromene using pre-purified \textit{m}-CPBA was found to be successful for chromene \textit{54}. The base was added to neutralize the acidic by-product formed in the reaction. According to $^1$H NMR spectroscopic analysis, the signals corresponding to the H(3) and H(4) of the (±)-\textit{128} are observed as doublets at 3.47 and 4.13 ppm respectively. A conversion of 81\% of alkene to epoxide was obtained after 6 hours reaction.

\textbf{Table 2-11 - Racemic epoxidation of protected 2,2,5,7,8-pentamethylchromene}

<table>
<thead>
<tr>
<th>Chromene/Oxidant</th>
<th>\textit{m}-CPBA</th>
<th>10%Na$_2$CO$_3$+ \textit{m}-CPBA</th>
<th>DMDO</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{54}</td>
<td>No epoxide</td>
<td>No epoxide</td>
<td>\textit{128}</td>
</tr>
<tr>
<td>\textit{55}</td>
<td>No epoxide</td>
<td>No epoxide</td>
<td>\textit{129}</td>
</tr>
<tr>
<td>\textit{56}</td>
<td>No epoxide</td>
<td>No epoxide</td>
<td>\textit{130}</td>
</tr>
</tbody>
</table>
The racemic epoxidation reactions using DMDO as the oxidant were found to be more convenient for the protected chromene substrates. All the protected chromene substrates, acetyl-, trifluoroacetyl- and benzoyl-protected chromenes 54, 55 and 56, were easily converted into their corresponding epoxy chromanes 128, 129 and 130 respectively at 0 °C (Table 2-11).

The 6-trifluoroacetyl-3,4-epoxy-2,2,5,7,8-pentamethylchromane 129 is the most unstable epoxide compared to the related 6-acetyl- and 6-benzoyl-3,4-epoxy-2,2,5,7,8-pentamethylchromanes 128 and 130. If compound 129 was stored in the refrigerator for some time, it would ring-open to form the corresponding diols 131 (Scheme 2-53). The instability of the trifluoroacetate-protected compounds is also observed on 6-trifluoroacetyl-2,2,5,7,8-pentamethylchromene 55 and 6-trifluoroacetyl-2,5,7,8-tetramethylchroman-2-carboxylate 114. These compounds decomposed when left on the open bench for few weeks.

As DMDO was found to be the most suitable oxidant, we decided to carry out the racemic epoxidation reactions under these conditions for the other chromenes. Racemic epoxidation of chromene 57 afforded the related epoxide 132 in 35% yield (Scheme 2-54).
Interestingly, the racemic epoxidation of compound 51 using DMDO did not give the expected epoxide 133 (Scheme 2-55). Generally, cis-alkenes are more reactive towards the electrophilic DMDO\textsuperscript{107} due to the steric interactions compared to trans-alkenes (Figure 2.24). However, this was not observed in the epoxidation of chromene 51.

![Figure 2.24 - Interaction of alkenes and DMDO](image)

According to the $^1$H NMR spectroscopic analysis, the disappearance of the triplet peak of the olefinic proton of the side chain at C3-C4 was observed suggesting that the epoxidation reaction by DMDO is much preferable on the double bond of the side chain to afford two pairs of diastereomers of compound 134 (Scheme 2-55). It is probably because the double bond in the pyran ring is much more hindered as compared to the double bond in the side chain.

![Scheme 2-55 - Reagents and conditions: (i) DMDO (1.5 equiv), CHCl$_3$, 100% conversion](image)

This chemoselectivity observed for the epoxidation of the less electron-rich alkene over the more electron-rich alkene by DMDO is an attractive finding. In the oleochemistry industry, epoxidation of the unsaturated fatty acid is an important reaction. The oxygenated fatty acids are employed industrially as lubricants and as secondary plasticizers.\textsuperscript{108}
2.3.3 General Reaction Conditions of Asymmetric Epoxidation

There are two standard iminium salt epoxidation conditions being used in our laboratory – aqueous and non-aqueous conditions. Aqueous conditions employ the triple salt Oxone® (2 KHSO₅•KHSO₄•K₂SO₄) as a stoichiometric oxidant, Na₂CO₃ or NaHCO₃ as the base, and acetonitrile: water as the solvent mixture. The presence of water is crucial for the epoxidation reaction to proceed, as the Oxone® is not soluble in organic solvent. The major limitation to these systems is the restricted range of temperatures at which the epoxidation can be performed (0 °C to room temperature). The upper limit is determined by the stability of Oxone®, which decomposes relatively quickly in the basic medium at room temperature. The aqueous medium used determines the lower limit: the typical ratios of acetonitrile to water solvent used as solvent lie between 1:1 and 10:1, and the medium freezes at around –10 °C. Epoxidation reactions in aqueous conditions have to be carried out carefully. Any addition of oxidant has to be accompanied by addition of Na₂CO₃ as the presence of water can cause the epoxide to ring open.

In the non-aqueous system for the asymmetric epoxidation reactions developed in our group, we use tetraphenylphosphonium monoperoxydisulfate (TPPP), which is soluble in organic solvent, as oxidant. TPPP is prepared as a colourless solid by treating Oxone® with tetraphenylphosphonium chloride:

\[
\text{Ph}_4\text{P}^+ \text{Cl}^- + \text{Oxone}® \rightarrow \text{Ph}_4\text{P}^+ (\text{HSO}_5^-)\
\]

The use of TPPP eliminates the need of water as solvent and base. The presence of base under aqueous conditions is essential to neutralize the acidity of triple salt Oxone® and the absence of base in the reaction can improve the reaction as addition of base suppresses the epoxidation process. In organic solvent, typically chloroform, the reaction can be carried out at much lower temperature, down to –40 °C or lower.

The reaction time was limited to 48 hours with addition of 2 equiv. of oxidant every 8 hours if there was still starting material observed by TLC. The time limit was set; as the epoxide decompose after a long period of time, as observed by TLC.
The most favourable conditions involved the cooling of all reagents — the oxidant, catalyst and substrate — separately in the reaction medium to the desired temperature. The oxidant was first dissolved in the reaction solvent and cooled down to the desired temperature. This was followed by dropwise addition of catalyst, in order to minimize the increase in reaction temperature. This mixture was stirred for some time prior to dropwise addition of the substrate to allow stabilization of the mixture.

2.3.4 Catalysts Testing on Asymmetric Epoxidation

Before investigating the asymmetric epoxidation reactions, all the iminium salt catalysts 3, 4, 7 – 10 synthesized were tested on the commercially available unfunctionalized alkene, 1-phenylcyclohexene 126 under aqueous conditions, and the ee values and yields were compared to the literature values (Scheme 2-56 and Table 2-12). 1-Phenylcyclohexene 126 was chosen as the test substrate for the investigation as both percentage of conversion and ee (using chiral shift reagent) can be easily determined using $^1$H NMR spectroscopic analysis. Asymmetric epoxidation of this substrate has also been reported previously in our group using some of the catalysts, thus our results can be compared with our previous literature reports.

\[ \text{126} \xrightarrow{(i)} \text{127} \]

Scheme 2-56 - Reagents and conditions: (i) Na$_2$CO$_3$ (4 equiv), Oxone® (2 equiv), iminium salt (5 mol%), MeCN/H$_2$O (1:1), 0 °C, 24 h
Table 2-12 -  

Enantiomeric excesses were determined by $^1$H NMR spectroscopy in the presence of (+)-Eu(hfc)$_3$.

The absolute configuration of the major enantiomers were determined by comparison of optical rotations with those reported in the literature.

<table>
<thead>
<tr>
<th>Iminium salt catalyst</th>
<th>Conversion, (%)</th>
<th>$Ee$, (%)$^a$</th>
<th>Configuration$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>In each case: Actual results/Literature value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Structure 3" /></td>
<td>100/55$^a$</td>
<td>35/41</td>
<td>(−)-(1S, 2S)/</td>
</tr>
<tr>
<td><img src="image" alt="Structure 4" /></td>
<td>100/100$^b$</td>
<td>26/39</td>
<td>(−)-(1S, 2S)/(−)-(1S, 2S)</td>
</tr>
<tr>
<td><img src="image" alt="Structure 7" /></td>
<td>100/100$^c$</td>
<td>56/60</td>
<td>(−)-(1S, 2S)/(−)-(1S, 2S)</td>
</tr>
<tr>
<td><img src="image" alt="Structure 8" /></td>
<td>100/47$^d$</td>
<td>40/56</td>
<td>(−)-(1S, 2S)/(−)-(1S, 2S)</td>
</tr>
</tbody>
</table>
The data collected in Table 2-12 show that the ee values are comparable to those previously reported although slightly lower for all the catalysts. The configuration of the product 1-phenylcyclohexene oxide 127 is identical in all cases. Full conversion of the alkene to the corresponding epoxide was attained by stirring the reaction overnight. As our results were in line with the previous reports, we proceeded with the investigation of the asymmetric epoxidation of chromenes.

2.3.5 Asymmetric Epoxidation of Chromene by Iminium Salt Catalysts

Our initial attempt at a catalytic asymmetric epoxidation reaction on the 6-hydroxy-2,2,5,7,8-pentamethyl-3-chromene 48 using the synthesized iminium salts was unsuccessful. Under both aqueous and non-aqueous conditions, the starting material was decomposed (Scheme 2-57), as shown by the presence of a large number of products using TLC analysis.
Surprisingly, in contrast with this result, epoxidation of 6-substituted 2,2-dimethylchromenes bearing an electron donating group have been reported previously. In one of the latest reports, in 2012, Cheng demonstrated the asymmetric catalytic activity of Mn(III) complexes towards the oxidation of the mono-substituted 2,2-dimethylchromene, affording excellent ees between 80 – 95% (Scheme 2-58). The presence of the four electron-donating groups on the aromatic ring of the chromenes may have led to the decomposition of the starting material and/or possibly the corresponding product under oxidative conditions during the asymmetric epoxidation reactions. However there is no further evidence to prove this. Based on this, asymmetric epoxidation reactions were attempted with our iminium salt catalysts – both under aqueous and non-aqueous conditions – using 4-cyano-2,2-dimethylchromene bearing an electron-withdrawing group at the 6-position of the chromene substrate (Scheme 2-59).
Under non-aqueous conditions, excellent enantioselectivity was observed for catalysts 4, 7 and 8 for the asymmetric epoxidation reactions of chromene 49, affording the corresponding epoxy-chromane 124 (Scheme 2-59). When the dihydroisouquinoline-derived catalyst 3 was used, however, decomposition of the starting material was observed. When the binaphthyl-derived catalysts 9 and 10 were used under non-aqueous conditions, no conversion to the epoxide was detected using $^1$H NMR spectroscopic analysis of the unpurified reaction mixtures. The highest ee was observed using iminium salt 7 as the catalyst, affording the epoxide in >99% ee.

**Table 2-13 - Asymmetric epoxidation of 49 under non-aqueous conditions**

<table>
<thead>
<tr>
<th>Iminium salt catalyst</th>
<th>Yield (%)</th>
<th>ee (%)$^b$</th>
<th>Configuration$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>97.0</td>
<td>(–)-1S, 2S</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>99.3</td>
<td>(–)-1S, 2S</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>96.6</td>
<td>(–)-1S, 2S</td>
</tr>
<tr>
<td>9</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

$^a$Reagents and conditions: Iminium salt (10 mol%), TPPP (6 equiv), CHCl$_3$, 0 °C, 1 day; $^b$Enantiomeric excesses were determined by chiral HPLC on Chiracel OD column; $^c$The absolute configuration of the major enantiomers were determined by comparison of optical rotations with those reported in the literature;

The binaphthyl-derived catalysts 9 and 10 are much less reactive compared to the others. As can be seen in Table 2-13, under non-aqueous conditions, reaction with chromene 49 shows no conversion occurred even after 48 hours of reaction. This reduced reactivity for these catalysts has been reported previously in our group.\(^1\)
We were expecting that the reactions using binaphthyl-derived catalysts 9 and 10 under aqueous conditions would be more successful, as these catalysts were reported to be more reactive under aqueous conditions. The corresponding epoxide products were obtained from asymmetric epoxidation reactions mediated by 9 and 10, but unfortunately the epoxy-chromane 124 was unstable under aqueous conditions, fully converting to the corresponding diol 136, the product of the ring opening of the epoxide 124 (Scheme 2-60). Fortunately, we were able to determine the enantiomeric purity of the diol using chiral HPLC analysis. Following this result, we attempted the reaction using other catalysts, and evaluated the ee of the diol products using chiral HPLC analysis (Table 2-14). Reactions of chromene 49 under aqueous conditions afforded (+)-(3S,4R)-136. The data collected in Table 2-14 show that both biphenyl-derived catalysts 7 and 8 are the most reactive and selective, giving the best ees of 68% and 71%, respectively. The absolute configuration of the diol was determined by comparing the optical rotations to those in the literature as reported by Patel et al.\textsuperscript{113}

\[
\begin{array}{cccc}
\text{Reagents and conditions: (i) } & \text{Conversion} & \text{ee} & \text{Configuration} \\
\text{Na}_2\text{CO}_3 (4 \text{ equiv}), \text{ Oxone}^{\text{\textregistered}} (6 \text{ equiv}), \text{ iminium salt catalyst (10} \text{ mol%), } & \% & (\%) & \\
\text{MeCN/H}_2\text{O (1:1), } 0^\circ \text{C, 24 h} & & & \\
\end{array}
\]

Table 2-14 – Formation of diol 136 under aqueous conditions\textsuperscript{a}

<table>
<thead>
<tr>
<th>Iminium salt catalyst</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>Configuration</th>
<th>Configuration</th>
<th>Configuration</th>
<th>Configuration</th>
<th>Configuration</th>
<th>Configuration</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>65</td>
<td>60</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>57</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
<td>68</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>71</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
</tr>
<tr>
<td>9</td>
<td>25</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>52</td>
<td>20</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
<td>(+)-(3S, 4R)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reagents and conditions: Iminium salt catalyst (10 mol%), Oxone\textsuperscript{\textregistered} (6 equiv), Na\textsubscript{2}CO\textsubscript{3} (4 equiv), MeCN/H\textsubscript{2}O (1:1), 0 \textdegree \text{C, 24 h}; \textsuperscript{b}Enantiomeric excesses were determined by chiral HPLC on Chiracel OD column; \textsuperscript{c}The absolute configuration of the major enantiomers were determined by comparison of optical rotations with those reported in the literature.
We next attempted to apply the non-aqueous reaction conditions to the 2,2,5,7,8-pentamethylchromenol compounds 54, 55 and 56. Protection of the hydroxyl moiety at the 6-position using acetate, trifluoroacetate and benzoate groups was targeted to improve the stability of the chromene by reducing the electron-donating effect of the free hydroxyl (Figure 2.25).

![Figure 2.25 - The protected derivatives of 2,2,5,7,8-pentamethylchromenol 48](image)

Investigation of the asymmetric epoxidation on acetyl protected chromene 54, using the most selective iminium catalyst in our hands, catalyst 7, showed that the acetyl-protected chromene is quite stable under the reaction conditions compared to the corresponding non-protected chromene 47 (Scheme 2-61). Under non-aqueous conditions, compound 128 was obtained in 48% conversion and 20% yield.

![Scheme 2-61 - Asymmetric epoxidation reactions of acetyl-protected chromene 54. Reagents and conditions:](image)

(i) TPPP (4 equiv), CHCl₃, 0 °C, 2 days

135
Unfortunately, we were unable to resolve the epoxy-chromane 128 enantiomers using chiral HPLC. Attempts to determine the ee using chiral shift reagent also failed. Thus, no ee values of the asymmetric epoxidation reaction on chromene 54 could be recorded. The same problem was also identified for 6-trifluoroacetate- and 6-benzoate-3,4-epoxy-2,2,5,7,8-pentamethylchromanes, 55 and 56, respectively. Compound 55 was obtained in 93% conversion and 62% yield while compound 56 was obtained in 63% conversion and 33% yield.

Asymmetric epoxidation reactions on chromene 57 were also unsuccessful. No reaction was observed when the chromene was subjected to epoxidation reactions under our standard non-aqueous conditions after 48 hours (Scheme 2-62). These results were expected as the alkene moiety is relatively electron-poor due to the presence of an electron-withdrawing group, a carboxylate, at the α-position.

![Scheme 2-62 - Reagents and conditions: (i) TPPP (4 equiv), CHCl₃, 0 °C, 2 days](image)

This low reactivity of the electron-poor alkenes in the asymmetric epoxidation mediated by these iminium salts has been observed previously in our group for reactions on both seselin 137 and xanthyletin 138. ¹¹⁴,¹¹⁵

![Figure 2.26 - Structures of seselin 137 and xanthyletin 138](image)
2.4 Conclusion and Future Works

Iminium salt catalysts 3, 4, 7 – 10 were successfully synthesized using a condensation reaction of the chiral primary amines 11 and 12 with the corresponding backbone moieties – 2-(2-bromoethyl)benzaldehyde 26, 2,2’-bis(bromomethyl) biphenyl 29, and (R)-2,2’-bis(bromomethyl)[1, 1’]-binaphthalene 33. Several improvements to the previously reported procedures afforded better yield of the products, such as the use of (±)-CSA instead of HBr in the ketalization of diols 13 and 15. The deprotection of formate of 14 and 17 was carried out in 98% hydrazine hydrate solution compared to 85% solution in previous method, giving 11 and 12 in better yields, 96% and 73% respectively.

In the second part of the research, the desired chromenes were successfully synthesized using various approaches (Figure 2.27).

![Figure 2.27 - Various synthetic approaches for the synthesis of chromenes 47–50](image)
Various approaches were used including: A: oxidation of chromanes using DDQ; B: acid-catalysed condensation mediated by PhB(OH)$_2$; C: Claisen thermal rearrangement of propargyl ether; D: Williamson synthesis of ether; E: base-catalysed condensation of phenol and dialkyl acetal; F: pressure-induced condensation of phenol, formaldehyde and methyl methacrylate; G: acid-catalysed condensation of phenol and allylic alcohol to produce chromane.

In the asymmetric epoxidation reactions of the chromene substrates mediated by iminium salts, we eventually found that the 6-cyano-3,4-epoxy-2,2-dimethylchromane 124 is unstable under aqueous conditions, forming the corresponding diols, 6-cyano-3,4-diol-2,2-dimethylchromanes 136, giving as high as 71% ee of (+)-(3S, 4R)-136 as the major enantiomer using catalyst 8. Under non-aqueous conditions, we obtained as high as 99.3% ee of (S,S)-epoxide 124 using the biphenyl-catalyst 7. From these results we obtained, we concluded that the biphenyl-derived catalysts 7 and 8 are the most selective iminium salt for the asymmetric epoxidation reactions under our standard conditions.

Future work should aim to achieve the separation of the epoxy chromanes bearing three methyl groups on the aromatic rings, followed by kinetic resolution studies. The effect of the protecting group at the 6-position on the asymmetric epoxidation of the chromene could also be further studied. Further investigation of the formation of diols from the chromene substrates under aqueous conditions by our iminium salts would also be interesting.
2.5 References


CHAPTER 3
EXPERIMENTAL PROCEDURES
3 EXPERIMENTAL PROCEDURES

3.1 General Experimental

3.1.1 Physical Characterisation and Spectroscopic Techniques

$^1$H- and $^{13}$C-NMR spectra were recorded in Fourier Transform mode either on a Varian Unity Plus 400 machine operating at a nominal frequency of 400.13 and 100.62 MHz, on a Varian Gemini 300 spectrometer, at 300.05 and 75.45 MHz, on a 400 MHz Bruker Avance III 2 channel nanobay NMR spectrometer, at 400.13 and 100.03 MHz, or on a Bruker Avance III 500 MHz NMR spectrometer, at 500.21 and 125.05 MHz, using the specified deuterated solvent. All spectra were processed using MestR-C Nova software. The chemical shifts for both $^1$H- and $^{13}$C-NMR were recorded in ppm and were referenced to the residual solvent peak or TMS peak. Multiplicities in the NMR 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, J values are reported in Hertz (Hz).

Low resolution mass spectra were recorded using Shimadzu LCMS 2010EV operated under electrospray ionisation in positive (ES+) or negative (ES-) modes. Mass spectra were recorded by the ESPRC national mass spectrometry service at the University of Wales, Swansea, utilising electron-impact (EI), fast atom bombardment (FAB), electrospray (ES) and MALDI-TOF.

Melting points were recorded using open capillary tubes on a Büchi B-545 melting point instrument and are uncorrected; melting points are quoted as a range, and were observed manually whilst those quoted as a specific value were recorded by the instrument and correspond to the temperature at which the sample reached 40% translucency in accordance with the British Pharmacopeia.
Infrared spectra were recorded as neat samples using a Perkin-Elmer Spectrum BX FT-IR. All IR data were manipulated using Spectrum v5.0.1 software. Optical rotation measurements were obtained using a Bellingham and Stanley ADP-440 polarimeter operating at the sodium (D) line emission of $\lambda = 589$ nm at the temperature specified. 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.

3.1.2 Enantiomeric Excess Determination

Enantiomeric excesses were determined either by Chiral HPLC, Chiral GC-FID or $^1$H NMR. Chiral HPLC traces were run on a Chiracel OD column eluting with HPLC grade Hexane/IPA. Data were recorded using a Hitachi Elite LaChrom instrument fitted with a L2400 UV detector (256 nm unless otherwise stated), L2300 column oven, L2200 autosampler, L2130 pump, a chiracel OD-H 5$\mu$m particle size column. The $^1$H-NMR spectra were run on a Bruker Avance III 500 MHz NMR spectrometer in the presence of europium (III) tris[3-(hepta-fluoropropylhydroxymethylene)-(+)-camphorate], [(+)-Eu(hfc)$_3$] as the chiral shift reagent and TMS as the internal standard.

3.1.3 Chromatographic Techniques

The reactions were monitored by thin-layer chromatography (TLC). Thin layer chromatography was carried out on Merck aluminium-backed plates coated with 0.2 mm Kieselgel 60 GF$_{254}$ (40 mm x 80 mm, 0.20 mm thickness) and mixtures of ethyl acetate/light petroleum, dichloromethane/light petroleum as eluent. After elution, the TLC plates were visualized under UV light followed by staining with phosphomolybdic acid (10% solution in EtOH), potassium permanganate (KMnO$_4$), or vanillin stains and developed by heating. Flash chromatography was carried out using glass columns packed with Merck Kieselgel 45-60 silica-gel with mixtures of ethyl acetate/light petroleum, dichloromethane/light petroleum as eluent.
3.1.4 Reagent, Solvent and Apparatus Preparation

Commercially available reagents were used as supplied, without any further purification, unless stated otherwise and stored according to the manufacturer’s recommendations. Optical purity of chiral starting material was also not checked prior usage. Light petroleum refers to the fraction of petroleum ether which boils between 40 °C and 60 °C and was obtained from manufacturer, labelled as petroleum ether 40/60.

Diethyl ether (Et₂O) and tetrahydrofuran (THF) were dried over the sodium/benzoquinone ketyl radical system and distilled; toluene was dried over sodium wire and distilled; dichloromethane and petroleum ether 40/60 was distilled over calcium hydride prior to use. The reactions requiring anhydrous conditions were carried out using glassware dried overnight at 150 °C and the apparatus was dried using a flame gun and a stream of Ar for procedures where the exclusion of water was necessary. Brine refers to a saturated aqueous solution of sodium chloride.

3.2 Numbering Systems

The assignments of the proton and carbon-13 resonances have been made according to numbering systems (Figure 3.1). Some of these systems used are standard chemical nomenclature while others were introduced arbitrarily by the present author. In the latter case, the introduced system was based on the structural resemblance of the compounds with others that possessed a formal system.

Aromatic systems are numbered according to the standard protocol. Aromatic carbon atoms bearing a substituent are always quaternary (C quat. arom.). All aromatic carbon atoms which are attached to a hydrogen atom are termed C arom. (¹³C spectra) or CH arom. (¹H spectra). The dihydroisoquinolinium nucleus is numbered according to a standard system but the carbon atoms of this moiety are termed isoq. except for those in the dimethylene part which are designated Ar-CH₂ and CH₂N in the assignment. The biphenyl
system is also numbered and carbon atoms of this moiety are termed biphenyl. The binaphthalene nucleus is numbered, with the carbon atoms termed binap (Figure 3.1).

Figure 3.1 - Nomenclature of catalysts backbone moities

*N*-protected amino acid derivatives are numbered with the carboxylic acid carbon first as in the example given in Figure 3.2. The protecting group will be referred to by its abbreviation. The 1,3-dioxane nucleus is numbered according to the standard protocol as are the 5-membered oxazolidines, with substituents off the ring being numbered in order.

Figure 3.2 - Numbering system
3.3 Individual Experimental Procedures

3.3.1 Synthesis of Iminium Salt Organocatalysts

3.3.1.1 General Procedure for Formyl Protection of the Amino Group

The amino diol (1.0 equiv) was dissolved in methanol (10 mL per gram of amino diol), and methyl formate (1.1 equiv) was added with sodium methoxide (0.1 equiv). The reaction mixture was stirred overnight at room temperature and the solvent removed under reduced pressure. The crude oil was dissolved in a solution of CSA (0.1 equiv) in acetone (50 mL per gram of amino diol) and 2,2-dimethoxypropane (10.0 equiv). The reaction was stirred up to 4 hours and monitored by TLC. Solvents were removed under reduced pressure and the residue re-dissolved in ethyl acetate, which was washed with saturated sodium hydrogen carbonate (2 X 20 mL per gram of amino diol) and brine (2 X 20 mL per gram of amino diol). The organic layer was dried (MgSO₄) and the solvents were removed under reduced pressure.
3.3.1.2 \((4S,5S)-5\)-(Formylamino)-2,2-dimethyl-4-phenyl-1,3-dioxane\)

Prepared according to the general procedure from \((1S,2S)-(+-)2\)-amino-1-phenylpropane-1, 3-diol 13 (0.5 g, 2.99 mmol). The product 14 was isolated as yellowish oil (0.66 g, 95%). \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 3295, 2992, 1668, 1500, 1382, 1200, 1088, 844, 700; \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 1.56 (s, 3 H, CH\(_2\)OC(CH\(_3\))\(_2\)), 1.60 (s, 3 H, OC(CH\(_3\))\(_2\)), 3.91 (dd, \(J = 12, 2\) Hz, 1H, CH\(_2\)OC(CH\(_3\))\(_2\)), 4.28 (dd, \(J = 12, 2\) Hz, 1H, CH\(_2\)OC(CH\(_3\))\(_2\)), 3.31 (dd, \(J = 8, 2\) Hz, 1H, (CHO)NHCH), 5.23 (d, \(J = 2\) Hz, 1H, (CHO)NHCH), 7.26 – 7.35 (m, 5H, C arom.), 7.99 (s, 1H, (CHO)NHCH); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 18.5 (CH\(_2\)OC(CH\(_3\))\(_2\)), 29.7 (CH\(_2\)OC(CH\(_3\))\(_2\)), 45.5 ((CHO)NHCH), 64.6 ((CHO)NHCH), 71.7 ((CHO)NHCHCHAr), 99.7 (C quat., CH\(_2\)OC(CH\(_3\))\(_2\)), 125.2 (2C, 2 X C, C arom.), 127.7 (C arom.), 128.3 (2C, 2 X C, C arom.), 138.0 (C quat. arom.), 160.5 ((CHO)NHCH).
3.3.1.3 (4S,5S)-5-(Formylamino)-2,2-dimethyl-4-[4-(methylthio)phenyl]-1,3-dioxane\textsuperscript{2-4}

![Chemical Structures]

Prepared according to the general procedure from (15,2S)-(+)2-amino-1-[4-(methylthio)phenyl]-1,3-propanediol 15 (10.0 g, 46.88 mmol). The crude compound was isolated as yellowish oil and was purified by column chromatography eluting with 2:1 (EtOAc/light petroleum) as yellow oil (11.426 g, 87%); [\(\alpha\)]\textsubscript{D} = +0.9° (c = 1.00, CHCl\textsubscript{3}), [Lit.\textsuperscript{4} [\(\alpha\)]\textsubscript{D} = +1.3° (c = 1.27, CHCl\textsubscript{3})]. \(\nu_{\text{max}}\) (neat)/cm\textsuperscript{-1} 3429, 3054, 2991, 1686, 1602, 1497, 1383, 1265, 1199, 1085, 948. \(^1\)H-NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 1.55 (s, 3H, CCH\textsubscript{3}), 1.58 (s, 3H, CCH\textsubscript{3}), 2.46 (s, 3H, S-CH\textsubscript{3}), 3.89 (d, \(J = 12\) Hz, 1H, OCHCHNH), 4.27 (d, \(J = 12\) Hz, 1H, OCH\textsubscript{2}CHNH), 4.28 (d, \(J = 8\) Hz, 1H, OCH\textsubscript{2}CHNH), 5.18 (s, 1H, CHNCOH), 6.16 (d, \(J = 8\) Hz, 1H, Ar-CH), 7.17 – 7.30 (m, 4H, 4 X CH arom.), 7.98 (s, 1, NHCOH); \(^{13}\)C-NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 14.2 (SCH\textsubscript{3}), 18.5 (C quat., C(CH\textsubscript{3})\textsubscript{2}), 29.7 (C(CH\textsubscript{3})\textsubscript{2}), 45.3 (OCH\textsubscript{2}CHNH), 64.6 (OCH\textsubscript{2}CHNH), 71.4 (Ar-CH), 99.7 (OC(CH\textsubscript{3})O), 125.8 (2 X C arom.), 126.4 (2 X C arom.), 134.9 (C quat. arom., C-SCH\textsubscript{3}), 137.8 (C quat. arom., OCH-C), 160.5 (NHCOH).
3.3.1.4 \( (4S,5S) \)-5-(Formylamino)-2,2-dimethyl-4-[4-(methylsulfonyl)phenyl]-1,3-dioxane\(^{4,5} \)

(4S,5S)-5-(Formylamino)-2,2-dimethyl-4-[4-(methylthio)phenyl]-1,3-dioxane (11.43 g, 38.7 mmol) 16 was dissolved in dichloromethane (100 mL), and the solution cooled to 0 °C. A solution of \( m \)-CPBA (20.7 g, 120 mmol) in chloroform (20 mL) was added dropwise over 10 min. The reaction was stirred for 2 h, washed with saturated sodium hydrogen carbonate (2 \( \times \) 40 mL), and dried (MgSO\(_4\)). The solvents were removed under reduced pressure to give colourless oil. Crystallization from chloroform/diethyl ether (1:3) gave the product as colourless crystalline solid (12.18 g, 98%); mp 126 – 127 °C [Lit.\(^4\) mp 146 – 147 °C]; [\( \alpha \)]\(_D\) = –14.5° (c = 1.11, CHCl\(_3\)), [Lit.\(^4\) [\( \alpha \)]\(_D\) = –11.6° (c = 1.21, CHCl\(_3\))] \( \nu \)\(_{max}\) (neat)/\( cm^{-1}\) 3357, 2995, 1671, 1515, 1383, 1300, 1239, 1149, 1086, 949. \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.59 (s, 3H, CCH\(_3\)), 1.61 (s, 3H, CCH\(_3\)), 3.05 (s, 3H, SO\(_2\)CH\(_3\)), 3.88 (d, \( J = 12 \) Hz, 1H, OCHHCH), 4.33 (d, \( J = 12 \) Hz, 1H, OCHHCH), 4.43 (d, \( J = 10 \) Hz, 1H, CH\(_2\)CHNH), 5.27 (s, 1H, CHNHCOH), 6.31 (d, \( J = 10 \) Hz, 1H, Ar-CH), 7.56 (d, \( J = 8 \) Hz, 2H, 2 X CH arom), 7.92 (d, \( J = 8 \) Hz, 2H, 2 X CH arom), 7.96 (s, 1H, NHCOH); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \( \delta \) 18.5, 19.5, 44.5, 45.0, 46.6, 71.6, 100.1, 126.5, 127.3, 139.7, 144.4, 160.3.
3.3.1.5 General Procedure for the Deprotection of Formamides with Hydrazine Hydrates

The formate protected of acetonide was dissolved in aqueous hydrazine hydrate (98%) (20 mL per gram of acetonide) and the solution was heated under reflux up to 3 hours. The solution was allowed to reach ambient temperature and extracted with ethyl acetate (3 X 30 mL per gram of acetonide). The organic layers were washed with water (2 X 30 mL per gram of acetonide), brine (2 X 30 mL per gram of acetonide) and dried with MgSO₄ and the solvent removed under reduced pressure.

3.3.1.6 (4S, 5S)-5-Amino-2,2-dimethyl-4-phenyl-1,3-dioxane¹,4

Prepared according to the general procedure from (4S,5S)-5-(formylamino)- 2,2-dimethyl-4-phenyl-1,3-dioxane 14 (0.667 g, 2.84 mmol). The title compound 11 was isolated as pale yellow oil without further purification (0.562 g, 96%); [α]₀ = +61.5° (c = 2.15, ethanol), [Lit.⁴ [α]₀ = +45.5° (c = 2.33, ethanol)]. νₘₐₓ (neat)/cm⁻¹ 3367, 2991, 1663, 1498, 1380, 1271, 1239, 1160, 1198, 1130, 1088, 1052, 945, 845, 739, 700. ¹H-NMR (400 MHz, CDCl₃): δ 1.55 (s, 3H, CH₃), 1.56 (s, 3H, CCH₃), 2.79 (d, J = 4 Hz, 1H, OCH₂CHNH₂), 3.93 (dd, J = 12, 4 Hz, 1H, OCHHCHNH), 4.31 (dd, J = 12, 4 Hz, 1H, OCHHCHNH), 5.12 (s, 1H, NH₂CHCH(Ph)O), 7.28 – 7.37 (m, 5H, 5 X Ar-H); ¹³C-NMR (100 MHz, CDCl₃): δ 18.60 (CH₃), 29.75 (CH₃), 49.58 (NCH),
65.88 (CH₂), 73.76 (Ar-CH), 99.22 (C quat.), 125.69 (2C, 2 X C arom.), 129.59 (2C, 2 X C arom.), 139.43 (C quat. arom.).

3.3.1.7 (4S,5S)-5-Amino-4-[4-(methylsulfonyl)phenyl]-1,3-dioxane\textsuperscript{1,5}

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\text{N} & \quad \text{H} \\
\text{O} & \quad \text{S} \\
\text{O} & \quad \text{S} \\
\end{align*}
\]

\begin{align*}
\text{17} & \quad \text{12}
\end{align*}

Prepared according to the general procedure from (4S,5S)-5-(formylamino)-4-[4-(methylsulfonyl)phenyl]-2,2-dimethyl-1,3-dioxane 17 (0.60 g, 1.92 mmol). The title compound was isolated as a colourless oil, and crystallized from diethyl ether/ethyl acetate (1:1) to obtain yellowish crystalline 12 (0.40 g, 73%); 121 – 123 °C [Lit.\textsuperscript{5} mp 120 – 122 °C]; [\alpha]_D = +65.3° (c = 1.05, CHCl₃), [Lit.\textsuperscript{5} [\alpha]_D = +50.0° (c = 1.00, CHCl₃)]. \nu\text{max} (neat)/cm\textsuperscript{-1} 3055, 2990, 1382, 1316, 1265, 1152, 1077, 957, 739. \textsuperscript{1}H-NMR (400 MHz, CDCl₃): \delta 1.53 (s, 6H, OCCH₃), 2.83 (s, 1H, OCH₂CHNH₂), 3.03 (s, 3H, SO₂CH₃), 3.86 (d, J = 12 Hz, 1H, OCHHCHNH), 4.30 (d, J = 12 Hz, 1H, OCHHCHNH), 5.15 (s, 1H, Ph-CH), 7.52 (d, J = 8 Hz, 2H, 2 X Ar-CH), 7.92 (d, J = 8 Hz, 2H, 2 X Ar-CH); \textsuperscript{13}C-NMR (100 MHz, CDCl₃): \delta 18.6, 29.7, 44.6, 49.4, 66.3, 73.4, 99.5, 126.8 (2C, 2 X C arom.), 127.5 (2C, 2 X C arom.), 139.5, 146.1.
3.3.1.8 General Procedure for the Synthesis of 2-(2-bromoethyl)benzaldehyde

Bromine (1.0 equiv) was added slowly over a period of 10 minutes to an ice-cooled solution of isochroman (1.0 equiv) in carbon tetrachloride (CCl₄) with stirring. After the exothermic reaction subsided, the cooling bath was removed and dark brown solution heated under reflux until the reaction mixture became pale yellow, and liberation of HBr ceased (ca. 1.5 hours). The solution was then allowed to reach ambient temperature and the solvent removed under reduced pressure. To the yellow oil obtained (1-bromoisochromane), aqueous hydrobromic acid (48%, 1.5 mL per gram of isochromane) was added and the reaction mixture heated under reflux. After 10 – 15 minutes the solution was allowed to cool and extracted with Et₂O (4 X 1 mL per gram of isochromane). The organic extracts were washed with water (2 X 1 mL per gram of isochromane) and dilute aqueous Na₂CO₃, and dried over magnesium sulphate. The solvent removed under reduced pressure furnished crude 2-(2-bromoethyl)benzaldehyde 26 as a brownish liquid. 

ν_max (film)/cm⁻¹: 3021, 2969, 2743, 1703, 1599, 1291. ¹H-NMR (500 MHz, CDCl₃): δ 3.36 – 3.64 (m, 4H, Ph(CH₂)₂Br), 7.34 (d, J = 8 Hz, 1H, CH arom., ortho to bromoethyl group), 7.49 (t, J = 8 Hz, 1H, CH arom., para to bromoethyl group), 7.56 (t, J = 8 Hz, 1H, CH arom., para to formyl group), 7.83 (d, J = 8 Hz, 1H, CH arom., ortho to formyl group) 10.15 (s, 1H, CHO); ¹³C-NMR (125 MHz, CDCl₃): δ 32.8 (PhCH₂), 36.3 (CH₂Br), 127.7 (C arom.), 132.1 (C arom.), 133.7 (C arom.), 133.9 (C quat. arom.), 134.5 (C arom.), 140.5 (C quat. arom.), 192.9 (1 C, CHO). Analytically pure samples may be obtained by distillation under reduced pressure at ca. 150 °C and 0.5 bar; chromatography is not recommended. Both the crude and the distilled compound can be used in the synthesis of dihydroisoquinolinium salts.
3.3.1.9 General Procedure for the Synthesis of Dihydroisoquinolinium Salts from 2-(2-bromoethyl)benzaldehyde and Primary Amines

A solution of the primary amine in ethanol (10 mL per gram of amine) was added dropwise to 2-(2-bromoethyl)benzaldehyde 26 (1.2 equiv.; 1.8 equiv. If crude material was used), externally cooled using an ice bath. The reaction mixture was stirred for a few hours or overnight (depending on the amine used) while attaining ambient temperature. A solution of sodium tetraphenylborate (1.1 equiv.) in the minimum amount of acetonitrile was added in one portion, and after 5 minutes the organic solvents were evaporated under reduced pressure. Ethanol was added to the residue and the resulted solid collected by filtration and washed with additional ethanol and diethyl ether.

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

Prepared according to the general procedure from (4S,5S)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane 11 (0.12 g, 0.56 mmol) and 2-(2-bromoethyl)benzaldehyde 26, and purified by recrystallization from acetone/Et₂O to give the product 3 as yellow solid, (0.21 g, 58%); mp 162 – 165 °C [Lit. [5] mp 169 – 170 °C]; [α]D = +48.2° (c = 2.64, CH₃CN), [Lit. [5] [α]D = +38.6° (c = 2.70, CH₃CN)]. νmax (neat)/cm⁻¹ 3270, 3054, 2998, 1637, 1603, 1572, 1479, 1450, 1425, 1383, 1342, 1315, 1285, 1265, 1238, 1225, 1202, 1163, 1114, 1083, 1069, 1031, 949, 842, 753, 704, 666, 623, 612. ^1H-NMR (500 MHz, CD₃CN): δ 1.69 (s, 3H, OCC₃, C7 or C8), 1.71 (s, 3H, OCCH₃, C7 or C8), 2.51 – 2.64 (m, 1H, Ar-CH₂, isoq-4), 2.83 – 2.92 (m, 1H, Ar-CH₂, isoq-4), 3.40 – 3.50 (m, 1H, CH₃N, isoq-3), 4.00 – 4.09 (m, 1H, CH₂N, isoq-3), 4.21 (t, J = 3 Hz, 1H,
C5, 4.42 (dd, J = 14, 1 Hz, 1H, C6), 4.68 (dd, J = 14, 1 Hz, 1H, C6), 5.79 (d, J = 3 Hz, 1H, C4), 6.88 (t, J = 8 Hz, 4H, CH arom., para in BPh₄), 7.03 (t, J = 8 Hz, 8H, meta in BPh₄), 7.33 – 7.35 (m, 8H, CH arom., ortho in BPh₄), 7.35 – 7.46 (m, 6H, 6 X CH arom.), 7.53 (t, J = 7 Hz, 1H, CH arom.), 7.78 (m, 2H, 2 X CH arom.), 7.87 (d, J = 7 Hz, 1H, CH arom.), 9.03 (s, 1H, N=CH); ¹³C-NMR (125 MHz, acetone-d₆): 17.9 (CH₃, C7 or C8), 24.5 (Ar-CH₂, isoq-4), 28.7 (CH₃, C7 or C8), 51.6 (CH₂N, isoq-3), 61.9 (CH₂, C6), 65.8 (NCH, C5), 70.9 (ArCH, C4), 100.5 (C quat., C2), 121.4 (4C, 4 X C arom., para in BPh₄), 124.6 (C quat. arom.), 125.1 (2C, 2 X C arom., meta in BPh₄), 125.1 (2C, 2 X C arom., meta in BPh₄), 125.2 (2C, 2 X C arom., meta in BPh₄), 125.5 (2C, 2 X C arom.), 128.3 (C arom.), 128.5 (C arom.), 128.5 (C arom.), 128.0 (4C, 4 X C arom., ortho in BPh₄), 134.4 (C arom.), 136.2 (6C, 4 X C arom., ortho in BPh₄, 2 X C arom.), 136.7 (C quat. arom.), 137.0 (C quat. arom.), 138.6 (C arom.), 163.5 (C quat. arom.), 163.88 (C quat. arom.), 164.27 (C quat. arom.), 164.66 (C quat. arom.), 167.75 (HC=N).
3.3.1.11 (+)-N-[(4S,5S)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl]-3,4-dihydroisoquinolinium tetrphenylborate

Prepared according to the general procedure from (4S,5S)-5-amino-6-(4-methylsulfone)phenyl-2,2-dimethyl-1,3-dioxane 12 (0.40 g, 1.39 mmol) and 2-(2-bromoethyl)benzaldehyde 26 (0.36 g, 1.67 mmol), and purified by crystallization from EtOH to give the product 4 as a yellow solid (0.80 g, 80%); mp 199 – 202 °C [Lit. mp 199 – 201 °C]; [α]D = +195° (c = 1.06, acetone), [Lit. [α]D = +126.7° (c = 1.20, acetone)]. νmax (film)/cm-1: 3419, 3278, 3055, 2999, 1719, 1636, 1603, 1572, 1479, 1426, 1384, 1315, 1266, 1202, 1150, 1122, 1077, 1032, 956. 1H-NMR (500 MHz, acetonitrile-D3): δ 1.69 (s, 3H, OCCH3, C7 or C8), 1.72 (s, 3H, OCCH3, C7 or C8), 2.62 (ddd, J = 18, 10, 7 Hz, 1H, Ar-CH2, isoq-4), 2.85 – 2.90 (m, 1H, Ar-CH2, isoq-4), 3.03 (s, 3H, C16), 3.46 – 3.54 (m, 1H, CH2N, isoq-3), 3.99 – 4.08 (m, 1H, CH2N, isoq-3), 4.25 (t, J = 3 Hz, 1H, C5), 4.42 (dd, J = 14, 1 Hz, 1H, C6), 4.68 (dd, J = 14, 1 Hz, 1H, C6), 5.87 (d, J = 3 Hz, 1H, C4), 6.88 (t, J = 8 Hz, 4H, para in BPh4), 7.03 (t, J = 8 Hz, 8H, meta in BPh4), 7.31 – 7.35 (m, 8H, ortho in BPh4), 7.37 (d, J = 8 Hz, 1H, CH arom.), 7.54 – 7.55 (m, 1H, CH arom.), 7.70 (d, J = 8 Hz, 2H, CH arom.), 7.96 (d, J = 8 Hz, 2H, CH arom.), 9.04 (s, 1H, C16); 13C-NMR (125 MHz, acetonitrile-D3): δ 18.5 (CH3, C7 or C8), 25.0 (Ar-CH2, isoq-4), 29.1 (CH3, C7 or C8), 44.1 (SCH3, C16), 52.1 (CH2N, isoq-3), 62.3 (CH2, C6), 65.5 (NCH2, C5), 71.0 (Ar-CH2, C4), 101.4 (C quat., C2), 122.4 (4C, 4 X C arom., para in BPh4), 124.8 (C quat. arom.), 126.2 (2C, 2 X C arom., meta in BPh4), 126.2 (2C, 2 X C arom., meta in BPh4), 126.2 (2C, 2 X C arom., meta in BPh4), 126.2 (2C, 2 X C arom., meta in BPh4), 127.0 (C arom.), 128.6 (C arom.), 129.0 (2C, 2 X C arom.), 129.0 (C arom.), 129.3 (C arom.), 135.1 (C arom.), 136.2 (4C, 4 X C arom., ortho in BPh4), 137.6 (C arom.), 139.5 (C arom.), 139.9 (C quat. arom.), 141.7 (Cquat. arom.), 142.8 (Cquat. arom.), 163.8 (Cquat. arom.), 164.2 (Cquat. arom.), 164.4 (Cquat. arom.), 165.0 (Cquat. arom.), 168.5 (HC=N).
3.3.1.12 5,7-Dihydrodibenzo\[c,e\]oxepine\(^7\)

A suspension of 2,2’-biphenyl dimethanol 28 (2.11 g, 9.75 mmol) in hydrobromic acid (30 mL, 24%) was heated to 100 °C for 40 min. The cloudy solution was allowed to cool to room temperature and the aqueous phase extracted with Et\(_2\)O (3 X 30 mL). The organic layers were washed with saturated aqueous NaHCO\(_3\) and brine (30 mL) and dried over MgSO\(_4\). The solvent was removed under reduced pressure to obtain a colourless solid of the title compound 29 (1.84 g, 96%); mp 66.6 – 68.8 °C [Lit.\(^7\) mp 56 – 58 °C]. \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 2987, 2305, 1421, 1377, 1265, 1198, 1156, 1075, 1044, 994, 944, 896, 739, 705, 621. \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 4.37 (s, 4H, 2 X OCH\(_2\)), 7.40 – 7.45 (m, 4H, 4 X CH arom.), 7.49 – 7.52 (m, 2H, CH arom.), 7.56 (m, 2H, CH arom.); \(^13\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 67.6 (2 C, 2 X OCH\(_2\)), 127.5 (2C, 2 X C arom.), 128.3 (2 C, 2 X C arom.), 129.0 (2C, 2 X C arom.), 129.7 (2C, 2 X C arom.), 135.2 (2C, 2 X Cquat. arom.), 141.2 (2C, 2 X Cquat. arom.).
3.3.1.13 2-[2-(Bromomethyl)phenyl]benzene carbaldehyde

To an ice-cooled solution of 5,7-dihydrodibenzo[c,e]oxepine 29 (1.8 g, 9.2 mmol, 1 equiv), in carbon tetrachloride (40 mL), in a round bottom flask equipped with a reflux condenser was added molecular bromine (1.16 g, 10.1 mmol, 1.1 equiv) in carbon tetrachloride (CCl₄) (6 mL), dropwise over 5 min (the reaction turned deep red). The cooling bath was removed and the reaction mixture heated under reflux until pale yellow and liberation of HBr ceased (ca 1 h.). The solvent was removed under reduced pressure, diluted with Et₂O (100 mL), washed with saturated Na₂CO₃ (2 X 50 mL) and brine (50 mL) and dried over MgSO₄. The solvents were removed under reduced pressure to yield brownish oil of 30 in excellent yield (2.50 g, 99%). νₘₐₓ (neat)/cm⁻¹ 3188, 1667, 1589, 1391, 1248, 1198, 774, 722, 630. ¹H-NMR (500 MHz, CDCl₃): δ 4.25 (d, J = 10 Hz, 1H, Ar-CH₂Br), 4.35 (d, J = 10 Hz, 1H, Ar-CHHBr), 7.22 (dd, J = 8, 1 Hz, 1H, CH arom.), 7.41 (m, 3H, 3 X CH arom.), 7.58 (m, 1H, CH arom.), 7.67 (td, J = 8, 1 Hz, 1H, CH arom.), 8.07 (dd, J = 8 Hz, 1 Hz, 1H, CH arom.), 9.74 (d, J = 1 Hz, 1H, H-aldehyde); ¹³C-NMR (125 MHz, CDCl₃): 31.4 (Ar-CH₂Br), 127.7 (C arom.), 128.4 (C arom.), 128.5 (C arom.), 129.05 (C arom.), 130.7 (C arom.), 130.7 (C arom.), 131.1 (C arom.), 133.6 (C arom.), 134.1 (C quat. arom.), 136.0 (C quat. arom.), 137.9 (C arom.), 143.3 (C quat. arom.), 191.7 (CH aldehyde).
3.3.1.14 General Procedure for the Synthesis of Iminium Salt Catalyst from 2-[2-(Bromoethyl)phenyl]benzene carbaldehyde and primary amines

A solution of the primary amine in ethanol (10 mL per gram of amine, 1 equiv), was added dropwise to a pre-cooled solution of 2-[2-(bromomethyl)phenyl]benzene carbaldehyde \(30\) (1.1 equiv) in ethanol (10 mL per gram) at 0 °C. The reaction mixture was stirred overnight while attaining ambient temperature. Sodium tetraphenylborate (1.1 equiv), dissolved in the minimum amount of acetonitrile, was added in one portion and the reaction mixture stirred for 5 min. The solvents were removed under reduced pressure and ethanol was added to the residue, followed by water. The resulting solid was collected by filtration and washed with ethanol followed by Et\(_2\)O.
3.3.1.15 Synthesis of 2,2'-Bis (bromomethyl)[1,1']biphenyl from [1,1']Biphenyl-2,2'-diol

2,2'-Biphenyldimethanol 28 (1.14 g, 5.30 mmol) was dissolved in 48% HBr (10 mL per gram of 2,2'-biphenyldimethanol) and reflux for 2 hours. Dichloromethane (50 mL) was added to the solution, followed by water (50 mL). The solution was separated in a separating funnel. The product was in the bottom layer and washed several times with DCM. The organic phase was separated and dried (MgSO₄). The solvent was removed under reduced pressure to yield the title compound 31 as a colourless solid, which was recrystallized from 1:1 (EtOAc/light petroleum) (1.66 g, 92%); mp 89 – 92 °C [Lit.⁸ mp 91 – 93 °C]. ν max (neat)/cm⁻¹ 3059, 2995, 1476, 1444, 1265, 1221, 1007, 829, 808, 738, 704, 607, 537. ¹H-NMR (400 MHz, CDCl₃): δ 4.20 (d, J = 8 Hz, 2H, 2 x Ph-CHH), 4.35 (d, J = 12 Hz, 2H, 2 x Ph-CHH), 7.28 (d, J = 2 Hz, 2H, 2 X CH arom., biphenyl-2,2'), 7.29 – 7.55 (m, 4H, 4 X CH arom., biphenyl-3,3', 4,4'), 7.57 (d, J = 2 Hz, 2H, 2 X CH arom., biphenyl-5,5'); ¹³C-NMR (100 MHz, CDCl₃): δ 31.9 (2C, 2 X CH₂Br), 128.3 (2C, 2 X C arom.), 128.7 (2C, 2 X C arom.), 130.2 (2C, 2 X C arom.), 130.7 (2C, 2 X C arom.), 135.9 (2C, 2 X C quat. arom.), 139.4 (2C, 2 X C quat. arom.).
3.3.1.16 General procedure for the preparation of the biphenyl azepines

Primary amine (1 equiv) dissolved in acetonitrile was added to a nitrogen purged stirred solution of 2,2'-Bis(bromomethyl)[1,1']biphenyl 31 (1 equiv) and Cs$_2$CO$_3$ (2 equiv) in MeCN at room temperature under an atmosphere of N$_2$. The solution mixture was heated under reflux overnight. The mixture was then cooled down to room temperature and the solvent was evaporated under reduced pressure and the residue re-dissolved in DCM. The resulting suspension was filtered into a separating funnel to remove excess Cs$_2$CO$_3$. The organic layer was washed several times with water and brine, and then dried (MgSO$_4$). The solvent was removed under reduced pressure.

3.3.1.17 (+)-6-[(4S,5S)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl]-6,7-dihydro-5H-diezo[c,e]azepine

Prepared according to the general procedure for the preparation of biphenyl azepines from (4S,5S)-5-amino-4-phenyl-2,2-dimethyl-1,3-dioxane 11 (0.56 g, 2.71 mmol) and 2,2'-bis(bromomethyl)[1,1']-biphenyl 31 (0.92 g, 2.71 mmol) to give the title compound 32 as yellow foam (1.02 g, 97%). $\nu_{\max }$ (neat)/cm$^{-1}$: 3054, 2987, 2684, 2305, 1721, 1688, 1449, 1441, 1421, 1381, 1265, 1198, 1174, 1152, 1079, 896, 706. $^1$H-NMR (500 MHz, acetone-d$_6$): $\delta$ 1.61 (s, 6H, 2 X OCH$_3$), 2.99 (d, $J = 3$ Hz, 1H, NCHCH$_2$O), 3.52 (d, $J = 12$ Hz, 1H, NCHCHHO), 3.70
(d, \( J = 12 \text{ Hz}, 1\text{H}, \text{NCHCH}_2\text{NO})\), 4.28 (d, \( J = 3 \text{ Hz}, 2\text{H}, \text{downfield portion of A system}, 2 \times \text{ArCH}_2\text{N})\), 4.40 (s, 2H, \text{upfield portion of A system}, 2 \times \text{ArCH}_2\text{N}), 5.23 (d, \( J = 3 \text{ Hz}, 1\text{H}, \text{NCHCHAr-O})\), 7.24 – 7.47 (m, 13H, 13 \times \text{CH arom.}); \(^{13}\text{C-NMR} \text{ (125 MHz, acetone-d}_6\)): \( \delta \) 19.2 (\text{CH}_3), 29.5 (\text{CH}_3), 54.0 (\text{NCHCH}_2\text{O}), 60.9 (\text{NCHCH}_2\text{O}), 62.2 (\text{ArCH}_2\text{N}), 67.6 (\text{ArCH}_2\text{N}), 74.7 (\text{NCHCHAr-O}), 99.1 (\text{quat.}, \text{OC(CH}_3\text{)O}), 126.3 (\text{C arom.}), 126.8 (\text{C arom.}), 127.3 (\text{C arom.}), 127.5 (\text{C arom.}), 127.72 (\text{C arom.}), 127.82 (\text{C arom.}), 128.29 (\text{C arom.}), 128.96 (\text{C arom.}), 129.38 (\text{C arom.}), 129.73 (\text{C arom.}), 135.16 (\text{C quat. arom.}), 136.63 (\text{quat. arom.}), 140.19 (\text{quat. arom.}), 140.96 (\text{quat. arom.}), 141.22 (\text{quat. arom.}).

3.3.1.18 \((+)-6\text{-[}(4S,5S)-2,2\text{-dimethyl-4-(4-methylsulfonyl)phenyl]-1,3-dioxan-5-yl]}\text{-6,7-dihydro-5H-diezo[c,e]azepine}^3\)

Prepared according to the general procedure for the preparation of biphenyl azepines from \((4S,5S)-5\text{-amino-6-(4-methylsulfonyl)phenyl-2,2-dimethyl-1,3-dioxane} \text{ 12} \text{ (2.75 g, 9.62 mmol)}\) and \text{2,2’-bis(bromomethyl)[1,1’]-biphenyl} \text{ 31} \text{ (3.272 g, 9.62 mmol)}\) to give the title compound \text{33} \text{ as yellow foam (3.75 g, 84%).}  \( \nu_{max} \text{(neat)}/\text{cm}^{-1} \) 3054, 2987, 1677, 1602, 1480, 1440, 1315, 1265, 1200, 1151, 1076, 1012, 957, 896, 852. \(^1\text{H-NMR} \text{ (400 MHz, acetone-d}_4\)): \( \delta \) 1.58 (s, 3H, \text{OCCH}_3), 1.60 (s, 3H, \text{OCCH}_3), 3.04 (s, 1H, \text{NCH}), 3.05 (s, 3H, -\text{SO}_2\text{CH}_3), 3.45 (d, \( J = 16 \text{ Hz}, 2\text{H, upfield portion of A system}, 2 \times \text{ArCH}_2\text{N})\), 3.68 (d, \( J = 16 \text{ Hz}, 2\text{H, downfield portion of A system}, 2 \times \text{ArCH}_2\text{N})\), 4.24 (m, 2H, \text{NCHCH}_2\text{O}), 5.30 (s, 1H, \text{NCHCH(Ph-\text{SO}_2\text{CH}_3)O}), 7.18 (dd, \( J = 8 \text{ Hz}, 1\text{Hz}, 2\text{H, 2} \times \text{CH arom.})\), 7.28 – 7.42 (m, 6H, 6 \times \text{CH arom.}), 7.65 (d, \( J = 8 \text{ Hz}, 2\text{H, 2} \times \text{CH arom.})\), 7.92 (d, \( J = 8 \text{ Hz}, 2\text{H, 2} \times \text{CH arom.})\); \(^{13}\text{C-NMR} \text{ (100 MHz, acetone-d}_6\)): \( \delta \) 19.1 (\text{CH}_3), 29.3 (\text{CH}_3), 44.6 (-\text{SO}_2\text{CH}_3), 530.9 (2 \text{C, 2} \times \text{ArCH}_2\text{N}), 60.4 (\text{NCHCH}_2\text{O}), 61.6 (\text{NCHCH}_2\text{O}), 74.2 (\text{NCHCH(PhSO}_2\text{CH}_3\text{)}), 99.3 (\text{quat.}, \text{OC(CH}_3\text{)O}), 126.7 (2\text{C, 2}}
3.3.1.19 General Procedure for the Synthesis of Biphenyl Iminium Salts

\[
\begin{align*}
\text{N-Bromosuccinimide (1.2 equiv)} & \text{ added to the resulting crude amine product in} \\
\text{dichloromethane, and the mixture was heated under reflux for 3 h, after which time the} \\
\text{reaction mixture was allowed to cool to room temperature. The solvent was removed} \\
\text{under reduced pressure and the residue re-dissolved in ethanol. A solution of sodium} \\
\text{tetraphenylborate (1.1 eq) in a minimum amount of acetonitrile was added in one portion.} \\
\text{The resulting mixture was stirred for 5 min, after which the solvent was removed under} \\
\text{reduced pressure. The yellow residue was dissolved in dichloromethane (40 mL per gram} \\
\text{of dibromide) and washed with water (2 X 30 mL per gram of dibromide) and brine 2 X 30} \\
\text{mL per gram of dibromide), the organic phase was dried (MgSO}_4\text{), and the solvents were} \\
\text{removed under reduced pressure. The yellow solid was recrystallized from ethanol, washed} \\
\text{with ethanol followed by hexanes, and dried at 90 °C.}
\end{align*}
\]
3.3.1.20 \((-\))\{\text{4S,5S}\}2,2\text{-dimethyl-4-phenyl-1,3-dioxan-5-yl}\}5\text{H-dibenzo[c,e]azepinium tetraphenyloborate}\)

Prepared according to the general procedure for the synthesis of biphenyl iminium salts from \(\text{(+\text{-\text{6-[(4S,5S)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-6,7-dihydro-5H-dibenzo[c,e]azepine}}\)

\(\text{32 (1.02 g, 2.64 mmol) to give the title compound 7 as yellow powder (1.06 g, 57\%); m.p. 183.4 – 184.0 °C [Lit.\textsuperscript{5} mp 187 – 188 °C]; [\alpha]\textsubscript{D}\textsuperscript{0} = –44.4° (c = 1.25, CH\textsubscript{3}CN), [Lit.\textsuperscript{5} [\alpha]\textsubscript{D}\textsuperscript{0} = –44.0° (c = 1.01, CH\textsubscript{3}CN)]. \nu\textsubscript{max} (neat)/\text{cm}\textsuperscript{-1} 3054, 2987, 1634, 1479, 1386, 1265, 1203, 1115, 896, 739, 705. \textsuperscript{1}H-NMR (400 MHz, acetone-d\textsubscript{6}): \delta 1.81 (s, 3H, OC(CH\textsubscript{3})\textsubscript{2}), 1.83 (s, 3H, OC(CH\textsubscript{3})\textsubscript{2}), 4.37 (br, 1H, NCHCHO), 4.49 (dd, J = 20, 4, 4 Hz, 1H, NCHCH\textsubscript{2}O), 4.82 – 4.92 (m, 2H, NCHCH\textsubscript{2}OH/1 X ArCH\textsubscript{2}N), 5.86 (br, 1H, ArCH\textsubscript{2}N), 6.03 (s, 1H, NCHCH\textsubscript{2}Ar-O), 6.79 (t, J = 4 Hz, 4H, \textit{para} in \textsuperscript{−}BP\textsubscript{4}), 6.93 (t, J = 8 Hz, 8H, 8 X CH arom., \textit{meta} in \textsuperscript{−}BP\textsubscript{4}), 7.33 – 7.67 (m, 13H, 5 X CH arom./8 X CH arom. \textit{ortho} in \textsuperscript{−}BP\textsubscript{4}), 7.70 – 7.77 (m, 6H, 6 X CH arom.), 7.99 – 8.05 (m, 2H, 2 X CH arom.), 9.05 (br, 1 H, N=CH); \textsuperscript{13}C-NMR (100 MHz, acetone-d\textsubscript{6}): Only the counter-ion \textsuperscript{13}C signals were observed.
3.3.1.21 \((-\cdot)\)-2-[(4S,5S)-2,2-Dimethyl-4-(methylsufonyl)phenyl-1,3-dioxan-5-yl]-5H-dibenzo[c,e]azepinium tetraphenylborate\(^5\)

![Chemical Structures](image)

Prepared according to the general procedure from \((+\cdot)\)-6-[(4S, 5S)-2,2-Dimethyl-4-(methylsulfonyl)phenyl]-1,3-dioxan-5-yl]6,7-dihydro-5H-die[3, e]azepine 33 (3.44 g, 12.05 mmol). The title compound 8 was isolated as a yellow crystalline solid (2.34 g, 25\%); mp 145 – 150 °C [Lit.\(^5\) mp 162 – 165 °C]; \([\alpha]_D^0 = -52.7° (c = 1.07, \text{acetone}), \text{[Lit.}^{5} [\alpha]_D^0 = -50.3° (c = 1.09, \text{acetone})]; \nu_{\text{max}} \text{(neat)/cm}^{-1} = 3052, 2997, 1635, 1600, 1580, 1554, 1480, 1426, 1404, 1382, 1303, 1265, 1239, 1199, 1147, 1091, 1054, 1030, 973, 948, 871, 841, 827, 782, 739, 711. \(^1\)H-NMR (400 MHz, acetone-d\(_6\)): \(\delta\) 1.81 (s, 3H, OC(CH\(_3\))\(_2\)), 1.84 (s, 3H, OC(CH\(_3\))\(_2\)), 3.02 (s, 3H, -SO\(_2\)C\(_6\)H\(_4\)). 4.40 – 4.43 (br, 1H, Ar-CH\(_2\)N, up-field portion of AB system). 4.51 (d, \(J = 12\) Hz, 1H, NCHCHHO, up-field portion of ABX system). 4.89 (d, \(J = 12\) Hz, 1H, NCHCHHO, down-field portion of ABX system). 5.62 (br, 1H, Ar-CH\(_2\)N, down-field portion of AB system). 6.13 (s, 1H, NCHCH\(_2\)O). 6.79 (t, \(J = 4\) Hz, 4H, 4 X CH arom., \textit{para} in BPh\(_4\)). 6.93 (t, \(J = 4\) Hz, 8H, 4 X CH arom., \textit{meta} in BPh\(_4\)). 7.43 – 7.46 (m, 8H, 4 X CH arom., \textit{ortho} in BPh\(_4\)). 7.67 – 7.70 (m, 5H, 5 X CH arom.), 7.80 – 7.82 (m, 5H, 5 X CH arom.), 7.96 – 8.03 (m, 5H, 5 X CH arom.), 9.23 (s, 1H, N=CH); \(^1\)C-NMR (100 MHz, acetone-d\(_6\)): Only the counter-ion \(^1\)C signals were observed.
3.3.1.22 (R)-1, 1’-Binaphthalene-2, 2’-dion bis-trifluoromethanesulfonate\(^{10}\)

(R)-[1,1’]Binaphthalene-2, 2’-dion 42 (3.00 g, 10.50 mmol, 2.5 equiv) was dissolved in dichloromethane (60 mL) and the solution cooled to -30 °C and stirred at this temperature for 5 min. before addition of 4-dimethylaminopyridine (0.51 g, 4.20 mmol, 1.0 equiv), 2, 6lutidine (3.70 mL, 31.40 mmol, 7.5 equiv) and triflic anhydride (5.30 mL, 31.40 mmol, 7.5 equiv). The resulting dark brown reaction mixture was allowed to reach ambient temperature and stirred overnight. Silica gel was added to the solvent and left stirred for ½ h and the solvent was then removed under reduced pressure. The product mixture, adsorbed onto silica gel, was then transferred to a sintered glass funnel, and the material washed with hexane until the product had eluted. The solvent was removed under reduced pressure to give a colourless solid, which was crystallized from hexane to afford the product 43 as colourless crystals (5.62 g, 98%); mp 83 – 84 °C [Lit.\(^4\) mp 76 – 78 °C]; [\(\alpha\)]\(_D\) = -150.9° (c = 1.01, CHCl\(_3\)), [Lit.\(^4\) [\(\alpha\)]\(_D\) = -147.7° (c = 1.01, CHCl\(_3\))]. \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 3062, 1509, 1424, 1247, 1140, 1066, 963, 867. \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.17 – 7.19 (m, 2H, 2 x CH arom., binap-3, -3’), 7.39 – 7.43 (m, 2H, 2 x CH arom., binap-7, -7’), 7.57 – 7.63 (m, 4H, 4 x CH arom., binap-8, -8’,-9,-9’), 8.01 (d, J = 10 Hz, 2H, 2 X CH arom., binap-4, -4’), 8.14 (d, J = 10 Hz, 2H, 2 X CH arom., binap-6, -6’); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 116.5 (2C, 2 X Cquat.), q, J = 79.5 Hz, 2 X CF\(_3\)), 119.3 (2C, 2 X C arom., binap-8, -8’), 123.4 (2C, 2 X Cquat. arom., binap-1, -1’), 126.8 (2C, 2 X C arom., binap-3, -3’), 128.0 (2C, 2 X C arom., binap-9, -9’), 128.3 (2C, 2 X C arom., binap-4, -4’), 132.0(2C, 2 X C arom., binap-6, -6’), 132.3 (2C, 2 X Cquat. arom., binap-5, -5’), 133.1 (2C, 2 X Cquat. arom., binap-10, -10’), 145.4 (2C, 2 X Cquat. arom., binap-2, -2’).
3.3.1.23 (R)-2,2’-Dimethyl-1,1’-binaphthalene

(R)-1,1’-Binaphthalene-2,2’-diol bis(trifluoromethanesulfonate) 43 (3.4 g, 6.24 mmol, 1 equiv) and [1,3-bis(diphenylphosphanyl)propane]nickel(II) chloride (0.24 g, 0.44 mmol, 0.07 equiv) were dissolved in anhydrous diethyl ether (100 mL). The reaction was cooled to −78 °C, and methylmagnesium bromide (3 M in Et₂O, 8.34 mL, 25 mmol) added dropwise over 30 min. The reaction was allowed to reach room temperature and stirred for 16 h. The resulting dark green reaction mixture was diluted with diethyl ether (100 mL) and filtered through a pad of Celite. The filtrate was washed with 2 M hydrochloric acid (20 mL), water (100 mL) and brine (100 mL). Removal of solvent under reduced pressure gave a reddish crude oil, which was purified by column chromatography, eluting with ethyl acetate/hexane (1:4), to give a colourless powder. Crystallization from methanol afforded the product 44 as a colourless crystalline solid (1.67 g, 95%); mp 68 – 72 °C [Lit.⁴ mp 74 – 78 °C]; [α]D₀ = −40.9° (c = 1.19, CHCl₃), [Lit.⁴ [α]D₀ = −40.0° (c = 1.12, CHCl₃)]; νmax (neat)/cm⁻¹ 3054, 2246, 1594, 1506, 1420, 1265, 1217, 1142, 958, 943, 836, 814, 739, 705. ¹H-NMR (400 MHz, CDCl₃): δ 2.13 (s, 6H, 2 X Ar-C₃H₃₇), 7.05 (d, J = 8 Hz, 2H, 2 x CH arom., binap-3,3’), 7.13 (d, J = 8 Hz, 2H, 2 x CH arom., binap-7,7’), 7.18 – 7.54 (m, 2H, 2 x CH arom., binap-9,9’), 7.29 – 7.47 (m, 2H, 2 x CH arom., binap-8,8’), 7.54 – 7.62 (m, 2H, 2 x CH arom., binap-9,9’), 7.92 – 7.98 (m, 4H, 4 X CH arom.), 8.03 (d, J = 8 Hz, 2H, 2 x CH arom., binap-4,4’), 8.09 (d, J = 8 Hz, 2H, 2 x CH arom., binap-6,6’); ¹³C-NMR (100 MHz, CDCl₃): δ 116.5 (2C, 2 X C quat., q, J = 79.5 Hz, 2 X CF₃), 119.3 (2C, 2 X C arom., binap-8,8’), 123.4 (2C, 2 X C quat. arom., binap-1,1’), 126.8 (2C, 2 X C arom., binap-3,3’), 128.0 (2C, 2 X C arom., binap-9,9’), 128.3 (2C, 2 X C arom., binap-4,4’), 132.0 (2C, 2 X C arom., binap-6,6’), 132.3 (2C, 2 X C quat. arom., binap-5,5’), 133.1 (2C, 2 X C quat. arom., binap-10,10’), 145.4 (2C, 2 X C quat. arom., binap-2,2’).
3.3.1.24 (R)-2,2’-Bis(bromomethyl)[1,1’]binaphthalene

(R)-2,2'-Dimethyl-1,1'-binaphthalene 44 (1.67 g, 5.9 mmol) was dissolved in cyclohexane (14 mL), and N-bromosuccinimide (2.10 g, 11.8 mmol) and azobis(isobutyronitrile) (0.10 g, 0.59 mmol) were added with stirring. The mixture was heated under reflux for 3 h, after which time complete disappearance of the starting material was observed by TLC. After cooling to room temperature, ethyl acetate (5 mL) and water (30 mL) were added to dissolve excess NBS and to allow trituration. The resulting suspension was stirred for 1 h, after which time precipitation had ceased. The mixture was filtered to afford the product 39 as a colourless solid (1.32 g, 51%); mp 180 – 183 °C [Lit. mp 180 – 183 °C]; [α]_D = +169.9° (c = 1.00, benzene), [α]_D = +186.4 (c = 1.00, benzene). ν_{max} (neat)/cm^{-1} 3049, 2925, 2929, 1507, 1361, 1328, 1212, 1025, 969, 821, 754, 726, 686, 626. 

^1^H-NMR (400 MHz, CDCl₃): δ 4.25 (s, 4H, 2 × CH₂Br), 7.07 (d, J = 8 Hz, 2H, CH arom.), 7.27 – 7.29 (m, 2H, CH arom.), 7.47 – 7.49 (m, 2H, CH arom.), 7.75 (d, J = 8 Hz, 2H, CH arom.), 7.92 (d, J = 8 Hz, 2H, CH arom.), 8.02 (d, J = 8 Hz, 2H, CH arom.) ; ^13^C-NMR (100 MHz, CDCl₃): δ 32.6 (2C, 2C, 2 × CH₂Br), 126.8 (2C, 2 X C arom., binap-5,-5'), 126.8 (2C, 2 X C arom., binap-6,-6'), 126.8 (2C, 2 X C arom., binap-7,-7'), 127.8 (2C, 2 X C arom., binap-3 or 4,-3’ or 4’), 128.0 (2C, 2 X C arom., binap-8,-8’), 129.4 (2C, 2 X C arom., -3 or 4,-3’ or 4’), 132.5 (2C, 2 X C quat. arom., binap-5,5’), 133.3 (2C, 2 X C quat. arom., binap-10,-10’), 134.1 (2C, 2 X C quat. arom., binap-2,-2’), 134.2 (2C, 2 X C quat. arom., binap-1,-1’).
**3.3.1.25 General Procedure for the Synthesis of Iminium Salt Catalyst from (R)-2,2'-Bis(bromomethyl)[1,1']binaphthalene and primary amines**

The primary amine (1.1 equiv) was added to a nitrogen-purged stirred solution of (R)-2,2'-bis(bromomethyl)[1,1']binaphthalene 39 and potassium carbonate (3 equiv) in acetonitrile (10 mL per gram of dibromide) at room temperature. The reaction mixture was heated under reflux overnight or until disappearance of starting material was observed by TLC. The mixture was diluted with dichloromethane (40 mL per gram of dibromide) and washed with water (2 X 30 mL per gram of dibromide) and brine (2 X 30 mL per gram of dibromide). The organic phase was separated and dried (MgSO₄). N-Bromosuccinimide (1.2 equiv) was added to the resulting crude amine product in dichloromethane, and the mixture was heated under reflux for 3 h, after which time the reaction mixture was allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue re-dissolved in ethanol. A solution of sodium tetraphenylborate (1.1 equiv) in a minimum amount of acetonitrile was added in one portion. The resulting mixture was stirred for 5 min, after which the solvent was removed under reduced pressure. The yellow residue was dissolved in dichloromethane (40 mL per gram of dibromide) and washed with water (2 X 30 mL per gram of dibromide) and brine (2 X 30 mL per gram of dibromide), the organic phase was dried (MgSO₄), and the solvents were removed under reduced pressure. The yellow solid was recrystallized from ethanol, washed with ethanol, followed by hexanes, and dried at 90 °C.
Prepared according to the general procedure from (+)-(4S,5S)-2,2-dimethyl-4-phenyl-1,3-dioxane-5-amine 11 (0.084 g, 0.41 mmol). The title compound 9 was isolated as bright yellow powder (0.24 g, 73%); mp 128.7 – 130.3 °C [Lit. mp 111 – 113 °C]; [α]D = -118.9° (c = 1.09, acetone), [α]D = -98.5° (c = 1.04, acetone). νmax (neat)/cm⁻¹: 3054, 2987, 1612, 1422, 1385, 1265, 1203, 1163, 1110, 896, 816, 738, 705. ¹H-NMR (400 MHz, CDCl₃): δ 1.81 (s, 3H, C(CH₃)), 1.87 (s, 3H, C(CH₃)), 4.42 (d, J = 16 Hz, 1H, ArCHHN, upfield portion of AB system), 4.53 (d, J = 12, 1H, NCH-CH-H, upfield portion of ABX system), 4.74 (s, 1H, NCH₂O), 4.82 (d, J = 12 Hz, 1H, NCH-CH-H, downfield portion of ABX system), 5.96 – 5.97 (m, 2H, 1 X ArCHHN, downfield portion of AB system/1 X NCH-CHAr-O), 6.77 (t, J = 8 Hz, 4H, 4 X CH arom., para in `BPh₄), 6.92(t, J = 8 Hz, 8H, 8 X CH arom., meta in `BPh₄, 6.97 – 7.07 (m, 4H, 4 X CH arom.), 7.27 – 7.29 (m, 2H, 2 X CH arom.), 7.34 – 7.37 (m, 11H, 8 X CH arom., ortho in `BPh₄/3 X CH arom.), 7.46 – 7.47 (m, 2H, 2 X CH arom.), 7.59 (t, J = 8 Hz, 1H, CH arom.), 7.77 – 7.81 (m, 1H, CH arom.), 7.88 (d, J = 12 Hz, 1H, CH arom.), 8.11 (d, J = 8 Hz, 1H, CH arom.), 8.17 – 8.25 (m, 3H, CH arom.), 9.11 (s, 1H, N=CH); ¹³C-NMR (100 MHz, CDCl₃): δ 18.9 (CH₃, C16 or C17), 29.7 (CH₃, C16 or C17), 57.0 (Ar-CH₂N), 61.9 (CH₂, C14), 168.1 (NCH, C13), 72.6 (Ar-CH, C18), 101.7 (C quat., C2), 120.5 (C quat. arom., binap.), 122.3 (4C, 4 X C arom., para in `BPh₄), 124.3 (C arom., C22), 126.0 (8C, 8 X C arom., ortho in `BPh₄), 126.2 (C quat. arom., binap.), 126.9 (C quat. arom., binap.), 127.8 (C arom., binap.), 128.0 (C arom., binap.), 128.2 (2C, 2 X C arom., C20, C24), 128.7 (2C, 2 X C arom., C21, C23), 128.9 (2C, 2 X C arom., binap), 129.5 (2C, 2 X C arom., binap), 129.6 (C arom., binap), 129.7 (C arom., binap), 130.2 (C arom., binap), 130.3 (C arom., binap), 131.3 (C arom., binap), 132.2 (C arom., binap), 132.6 (C quat. arom., binap.), 132.9 (C arom., binap), 134.9 (Cquat. arom., binap.), 136.3 (Cquat. arom., binap.), 136.6 (Cquat. arom., binap.), 137.2 (8 X C arom., meta in `BPh₄), 142.4 (Cquat. arom., C19), 164.7 (4 X Cquat., 170.9 (HC= N).
3.3.1.27 (R)-[(4S,5S)-2,2-dimethyl-4-(methylsulfanyl)phenyl-1,3-dioxan-5-yl]-3H-4-azepinium-cyclohepta[2,1-a;3,4-a']dinaphthalene tetr phenylborate

Prepared according to the general procedure from (4S,5S)-5-Amino-4-[4-(methylsulfanyl)phenyl]-1,3-dioxane 12 (0.29 g, 1.016 mmol) to obtain 10 as a yellow powder (0.52 g, 59%). mp 161 – 163 °C [Lit.4 mp 159 – 163 °C]; [α]D = -238.9° (c = 0.85, acetone), [Lit.4 [α]D = -283.7° (c = 0.86, acetone)]. 1H-NMR (400 MHz, acetone-d6): δ 1.87, 1.93, 3.00, 4.45 (d, J = 15 Hz, 1H), 4.57 (d, J = 15 Hz, 1H), 4.94 (dd, J = 15 Hz, 5 Hz, 1H), 5.12 (s, 1H, NCH, H13), 6.21 (d, J = 15 Hz, 1H, Ar-CHHN, H11), 6.25 (d, J = 5 Hz, 1H, Ar-CH, H18), 6.79 (t, J = 15 Hz, 4H, 4 X CH arom., para in BPh4), 6.94 (t, J = 15 Hz, 8H, 8 X CH arom., ortho in BPh4), 7.29 (ddd, J = 11, 6, 3 Hz, 1H, CH arom., binap.), 7.36 (m, 8H, 8 X CH arom., meta in BPh4), 7.49 (m, 3H, 3 X CH arom., binap.), 7.59 (dd, J = 8, 7, 1 Hz, 1H, CH arom., binap.), 7.82 – 7.84 (m, 5H, 5 X CH arom.), 8.00 (d, J = 8 Hz, 1H, CH arom., binap.), 8.13 (d, J = 8 Hz, 1H, CH arom.), 8.21 (d, J = 8 Hz, 1H, CH arom.), 8.24 (d, J = 9 Hz, 1H, CH arom.), 9.39 (s, 1H, HCC=N); 13C-NMR (100MHz, acetone-d6): δ 18.2 (CH3, C16 or C17), 29.1 (CH3, C16 or C17), 43.4, (CH3, SO2CH3, C25), 56.4 (CH2, ArCH2N, C11), 61.1 (CH3, NCH2CH2O, C14), 66.9 (CH, NCH, C13), 71.5 (CH, ArCH, C18), 101.1 (C quat., C15), 121.5 (4C, 4 X C arom., para in BPh4), 125.0 (C arom., binap), 125.1 (C arom., binap), 125.2 (C arom., binap), 125.3 (8C, 8 X C arom., ortho in BPh4), 126.0 (C quat., arom.), 126.5 (2C, 2 X C arom.), 126.8 (C arom., binap), 127.1 (C arom., binap), 127.3 (C arom., binap), 127.9 (2C, 2 X C arom., binap), 128.8 (C arom., binap), 128.9 (C arom., binap), 129.4 (C arom., binap), 129.6 (C arom., binap), 130.6 (C arom., binap), 131.2 (C quat., arom.), 131.4, 131.7 (C arom., binap), 131.7, 133.9, 135.5, 135.8, 136.2 (8C, 8 X C arom., meta in BPh4), 141.4, 142.2, 164.0 (4C, 4 X C quat., arom., q, J = 49 Hz, 4 C-B ipso in BPh4), 170.6 (HC=N).
3.3.2 Synthesis of Chromene Substrate

3.3.2.1 3,7-Dimethyloct-6-en-1-yl-3-ol\textsuperscript{13}

A solution of 6-methyl-5-heptene-2-one 71 (1 mL, 6.8 mmol) in a mixture of anhydrous THF/Et\textsubscript{2}O (1:1) (4 mL) was added dropwise in 30 minutes, at room temperature, to a solution of ethynylmagnesium bromide (16 mL, 8.16 mmol, 0.5M in THF) in anhydrous diethyl ether (16 mL), under Ar. The reaction was stirred at room temperature for 3 hours. After the reaction had come to completion, the reaction was quenched with water and the mixture was extracted with Et\textsubscript{2}O. The combined organic layers were washed with brine and dried over MgSO\textsubscript{4}. The solvent was evaporated under vacuo. The solution was purified with neutral alumina using ethyl acetate/light petroleum (1:9) as the eluent. Product 70 was isolated as yellow oil (0.95 g, 88%). \( \nu_{\text{max}} \) (film)/\text{cm}\textsuperscript{-1} \( 3405 \) (OH), 3307 (acetylenic C – H stretch), 2927, 1725 (C=C), 1449, 1375, 1262 (C – OH), 627 (acetylenic C – H bend); \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 1.49 (s, 3H, CH\textsubscript{3}COH), 1.65 (s, 3H, CHCH\textsubscript{3}), 1.69 (s, 3H, CHCH\textsubscript{3}), 2.09 – 2.20 (m, 2H, CH\textsubscript{2}CH\textsubscript{2}CH or CH\textsubscript{2}CH\textsubscript{2}CH), 2.21 – 2.32 (m, 2H, CH\textsubscript{2}CH\textsubscript{2}CH or CH\textsubscript{2}CH\textsubscript{2}CH), 2.45 (s, 1H, CH alkyne), 5.16 (m, 1H, CH alkene); \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}): \( \delta \) 18.1 (C8 or C9), 24.0 (C8 or C9), 28.1 (C5), 30.2 (C10), 43.5 (C4), 68.7 (C quat., C3), 71.9 (acetylenic C), 87.9 (C quat., C2), 124.0 (C6), 133.1 (C quat., C7).
### 3.3.2.2 6-Hydroxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-ene)chroman\textsuperscript{14} – Method I

Linalool \textsuperscript{63} (7.09 mL, 39.42 mmol, 2 equiv) was added dropwise to a boiling suspension of trimethylhydroquinone \textsuperscript{62} (3.0 g, 19.71 mmol, 1 equiv) and (±)-CSA (0.1 equiv) in \textit{n}-octane at 98 °C. The reaction mixture was kept at reflux and stirred overnight. After the reaction has come to completion, it was cooled down to room temperature, and poured into 50 mL saturated \textit{NaHCO\textsubscript{3}} solution. The product was extracted with EtOAc, and then washed with brine and the organic layer was dried (MgSO\textsubscript{4}). The solvent was removed under \textit{vacuo} which was then purified by column chromatography, eluting with ethyl acetate/light petroleum (1:9), to give a mixture of the title compound \textsuperscript{61} and its cyclic isomer \textsuperscript{64} (5.39 g, 95%). \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 1.24 (s, 3H, OC\textsubscript{3}H\textsubscript{3}), 1.50 – 1.68 (m, 2H, \(C^1'H_2\) or \(C^2'H_2\)), 1.60 (3 H, s, \(C^3'H=\text{C}^4\text{(CH}_3\text{)}_2\)), 1.67 (s, 3 H, \(C^5'H=\text{C}^6\text{(CH}_3\text{)}_2\)), 1.70 – 1.84 (m, 2H, \(C^1'H_2\) or \(C^2'H_2\)), 2.11 (s, 6H, 2 X \text{Ar-CH}_3\)), 2.16 (s, 3H, \text{Ar-CH}_3\), 2.60 (t, \(J = 8\) Hz, 2H, \text{Ar-CH}_2\text{CH}_2\) or \text{Ar-CH}_2\text{CH}_2\), 4.18 (s, 1H, \text{Ar-OH}), 5.12 (t, \(J = 6\) Hz, 1H, \(C^5'H=\text{C}^6\text{(CH}_3\text{)}_2\)).
3.3.2.3 6-Hydroxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-ene)chroman\textsuperscript{15} – Method II

A mixture of trimethylhydroquinone \textit{62} (1 equiv), phenylboronic acid (1.6 equiv), citral \textit{73} (3 equiv) and propionic acid (0.3 equiv) in toluene was heated under reflux for 1.5 hours, with azeotropic removal of water using a Dean-Stark trap. The reaction mixture was concentrated and the resulting oil was chromatographed (95/5: light petroleum/ethyl acetate) to give the title compound \textit{47} as brownish oil, 45%. \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 3434, 2969, 2924, 1644, 1454, 1417, 1376, 1303, 1263, 1214, 1156, 1117, 1083, 1060, 923. \(^{1}\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.38 (s, 3H, OCC\(\text{H}_3\)), 1.61 (s, 3H, CH\(_2\)CH=C(C\(\text{H}_3\))\(_2\), C1 or C2), 1.69 (s, 3H, CH\(_2\)CH=C(C\(\text{H}_3\))\(_2\), C1 or C2), 1.62 – 1.75 (m, 2H, CH=C(CH\(_3\))\(_2\), C5), 2.16 (s, 3H, Ar-CH\(_3\)), 2.19 (s, 3H, Ar-CH\(_3\)), 2.19 (s, 3H, Ar-CH\(_3\)), 2.21 (s, 3H, Ar-CH\(_3\)), 2.10 – 2.20 (m, 2H, CH\(_2\)CH\(_2\)CH=C(CH\(_3\))\(_2\), C6), 4.21 (s, 1H, Ar-OH), 5.14 (t, \(J = 5\) Hz, 1H, CH\(_2\)CH=C(CH\(_3\))\(_2\), C4), 5.64 (d, \(J = 10\) Hz, 1H, CH=CH-Ar, C9), 6.57 (d, \(J = 10\) Hz, 1H, CH=CH-Ar, C10); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 10.9 (Ar-CH\(_3\)), 11.6 (Ar-CH\(_3\)), 12.4 (Ar-CH\(_3\)), 17.6 (C1/C2, OC(CH\(_3\))\(_2\)), 22.8 (C5/C6, C(CH\(_3\))\(_2\)CH=CH), 25.3 (C1/C2, OC(CH\(_3\))\(_2\)), 25.7 (C8, OC(CH\(_3\))\(_2\)), 40.4 (C5/C6, C(CH\(_3\))\(_2\)CH=CH), 76.6 (C7, OC(CH\(_3\))\(_2\)), 116.1 (C quat. arom.), 117.7 (C quat. arom.), 120.2 (C9/C10), 122.3 (C quat. arom.), 123.0 (C quat. arom.), 124.4 (C4), 129.8 (C9/C10), 131.5 (C quat., C3), 144.7 (C quat. arom.), 145.3 (C quat. arom.).
3.3.2.4 Methyl 6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromene-2-carboxylate\textsuperscript{16}

In a pressure tube equipped with a stirrer, trimethylhydroquinone 62 (1.55 g, 10.2 mmol), an aqueous formalin solution (37 wt\%, 1.66 g), and methyl methacrylate 100 (4.95 g, 52.65 mmol) were placed. The mixture was allowed to reach 180 °C and stirred for 3 hours, while the reactor was tightly closed. After completion of reaction, the reaction mixture was cooled down to room temperature, and methanol was added to the mixture, whereby crystals were precipitated. The crystals of the desired compound 101 were collected through filtration, and dried in the oven at 60 °C overnight (1.91 g, 71\%); mp 157 – 160 °C [Lit. mp 134.5 – 136 °C]. ν\textsubscript{max} (film)/cm\textsuperscript{-1} 3530, 2989, 2928, 1739, 1454, 1428, 1375, 1335, 1277, 1264, 1243, 1226, 1192, 1173, 1140, 1113, 1061, 1030, 967, 945. \textsuperscript{1}H-NMR (500 MHz, CDCl\textsubscript{3}): δ 1.59 (s, 3H, C11), 1.86 (m, 1H, C3), 2.05 (s, 3H, Ar-CH\textsubscript{3}, C15, C16 or C17), 2.14 (s, 3H, Ar-CH\textsubscript{3}, C15, C16 or C17), 2.18 (s, 3H, Ar-CH\textsubscript{3}, C15, C16 or C17), 2.42 (m, 1H, C3), 2.50 (m, 1H, C4), 2.64 (m, 1H, C4), 3.67 (s, 3H, C14); \textsuperscript{13}C-NMR (126 MHz, CDCl\textsubscript{3}): δ 11.3 (C15, C16 or C17), 11.8 (C15, C16 or C17), 12.2 (C15, C16 or C17), 21.0 (C4), 25.4 (C11), 30.6 (C3), 52.3 (C14), 77.1 (C2), 116.9 (C5), 118.5 (C6), 121.3 (C8), 122.6 (C9), 145.3 (C7), 145.5 (C10), 174.5 (C12); m/z 265.437, C\textsubscript{16}H\textsubscript{20}O\textsubscript{4}H [M + H]\textsuperscript{+} requires 265.1434.
3.3.2.5 1,1-Diethoxy-3-methyl-2-butene\textsuperscript{17}

Triethyl orthoformate 88 (1 equiv) and 3-methyl-2-butenal 77 (1 equiv) were added into a round bottom flask containing EtOH at room temperature. The mixture was stirred 5 min. prior to addition of NH\textsubscript{4}NO\textsubscript{3} (25 mol\%). The reaction mixture was left stirred for 24 hours. Saturated aqueous solution of NaHCO\textsubscript{3} was added to the reaction followed by brine. The mixture was the extracted by using Et\textsubscript{2}O several times to give the title compound 87 as a brownish liquid. No further purification was required. \(\nu_{\text{max}}\) (film)/cm\textsuperscript{-1} 2975, 2930, 2914, 2879, 1682, 1447, 1377, 1358, 1348, 1206, 1142, 1115, 1083, 1053, 1017, 991. \({}^1\text{H-NMR}\) (500 MHz, CDCl\textsubscript{3}): \(\delta\) 1.23 (m, 6H, C7 & C9), 1.72 (d, \(J = 1\) Hz, 3H, C1 or C3), 1.75 (d, \(J = 1\) Hz, 3H, C1 or C3), 3.42 – 3.58 (m, 2H C6 or C8), 3.60 – 3.63 (m, 2H C6 or C8), 5.14 (d, \(J = 7\) Hz, 1H, C5), 5.30 (d, \(J = 7\) Hz, 1H, C4); \({}^{13}\text{C-NMR}\) (125 MHz, CDCl\textsubscript{3}): \(\delta\) 15.5 (2C, C7 & C9), 18.4 (C6 or C8), 25.6 (C6 or C8), 60.4 (2C, C1 & C3), 98.6 (C5), 125.1 (C4), 137.6 (C2).
3.3.2.6 6-Cyano-2,2'-dimethylchromene – Method A

A reaction flask equipped with a distilling head was sequentially charged with the acetal compound 87 (1.74 g, 11.0 mmol), p-xylene (20 mL/g of phenol), 4-hydroxybenzonitrile 86 (2.65 g, 22.0 mmol) and 3-picoline (0.27 mL, 2.75 mmol). The reaction mixture was heated under reflux for 24 h, after which the reaction mixture was cooled to ambient temperature. The clear, golden reaction mixture was diluted with EtOAc and washed with 1 N HCl. The acidic, aqueous washes were back extracted with EtOAc. The combined organic phases were washed with 1 N NaOH, brine and dried (MgSO₄). The solvent was then evaporated under vacuo to give the title compound 49 as a bright yellow crystal. The yellow crystal was then recrystallized from light petroleum to give a yellowish powder (1.78 g, 87%); mp 47 – 48 °C [Lit. mp 47 °C]. ν_max (film)/cm⁻¹ 3054, 2985, 2226, 1605, 1487, 1421, 1369, 1265, 1212, 1148, 1128, 1107, 961, 896, 828, 739, 705. ¹H-NMR (400 MHz, CDCl₃): δ 1.45 (s, 6H, OC(CH₃)₂), 5.70 (d, J = 12 Hz, 1H, C(CH₃)₂CHCH), 6.28 (d, J = 12 Hz, 1H, C(CH₃)₂CHCH), 6.78 (d, J = 8 Hz, 1H, CH arom.), 7.24 (d, J = 4 Hz, 1H, CH arom.), 7.37 (dd, J = 8 Hz, 4 Hz, 1H, CH arom.); ¹³C-NMR (100 MHz, CDCl₃): δ 28.4 (2C, 2 X C(CH₃)₂), 77.9 (C(CH₃)₂, C quat.), 103.8 (C quat. arom.), 117.2 (C arom.), 119.3 (C quat., arom.), 120.6 (C(CH₃)₂CH=CH), 121.7 (C quat. arom.), 130.1 (C arom.), 132.2 (C(CH₃)₂CH=CH), 133.3 (C arom.), 156.8 (C≡N).
3.3.2.7 3-Chloro-3-methyl-1-butyne\textsuperscript{18}

\[
\begin{align*}
\text{OH} & \quad \rightarrow \\
\text{Cl} & \quad 76 & \quad 92
\end{align*}
\]

A 1-L, three-necked flask provided with a magnetic stirrer, thermometer, and dropping funnel was charged with 56 g (0.5 mol) of CaCl\(_2\), 40 g of CuCl\(_2\), 400 mg of Cu bronze powder, and 430 mL (5 mol) of cold concentrated HCl. The mixture was flushed with argon gas several times and cooled in ice bath with stirring. 2-Methyl-3-butyn-2-ol 76 (1 mol) was added over 30 min. Stirring was continued for 1 h at 0 – 5 °C. The upper organic layer was separated and washed immediately with three 100 mL portions of cold concentrated HCl, with two 100 mL portions of water, then dried over K\(_2\)CO\(_3\). The chloride was used without further purification. \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 2983, 2927, 1739, 1666, 1616, 1447, 1370, 1111, 938, 836, 604; \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 1.87 (s, 6H, HC≡CC(C\(_3\)H\(_3\))\(_2\)-Cl), 2.62 (s, 1H, HC≡CC(C\(_3\)H\(_3\))\(_2\)-Cl); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 34.6 (2C, 2 X HC≡CC(C\(_3\)H\(_3\))\(_2\)-Cl), 56.9 (C quat., HC≡CC(C\(_3\)H\(_3\))\(_2\)-Cl), 71.9 (acetylenic C, HC≡CC(C\(_3\)H\(_3\))\(_2\)-Cl), 86.5 (quat. C, HC≡CC(C\(_3\)H\(_3\))\(_2\)-Cl).

3.3.2.8 3-(3-Cyanophenoxy)-3-methylbut-1-ylene\textsuperscript{19}

\[
\begin{align*}
\text{Cl} & \quad + \\
\text{NC} & \quad \text{OH} & \quad \rightarrow \\
\text{NC} & \quad 92 & \quad 86 & \quad 93
\end{align*}
\]

4-Cyanophenol 86 (0.5 g, 4.2 mmol), anhydrous K\(_2\)CO\(_3\) (0.58 g, 4.2 mmol, 1.0 equiv), KI (0.07 g, 0.42 mmol, 0.1 equiv), were stirred in acetone (25mL per gram of phenol) under N\(_2\). Addition of 3-chloro-3-methyl-1-butylene 92 (1.3 g, 8.8 mmol, 2.1 equiv) was followed by refluxing for 18 h to obtain the title compound 93 as light yellow oil (0.77 g, 99%) without further purification. \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 3292, 3103, 3078, 3048, 2991, 2939, 2226, 2112, 1602, 1572, 1504, 1464, 1452, 1420, 1384, 1366, 1254, 1227, 1172, 1137, 956, 911, 839, 736, 696, 671, 651. \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 1.70 (s, 6H, OC(CH\(_3\))\(_2\)), 2.65 (s, 1H, alkyne), 7.28 (d, \(J = 9\) Hz, 2H, CH arom.), 7.57 (d, \(J = 9\) Hz, 2H, CH arom.); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 29.5 (2C, 2 X CH\(_3\)), 72.7 (OC(CH\(_3\)), C quat.), 75.3 (-C≡CH), 84.7 (1 C, -C≡CH), 105.1 (C quat.)
arom.), 119.1 (Ar-C≡N), 120.0 (2C, 2 X C arom.), 133.4 (2C, 2 X C arom.), 159.4 (C quat. arom.).

3.3.2.9 6-Cyano-2, 2-dimethylchromene\textsuperscript{19}

\[
\begin{array}{c}
\text{NC} \quad \text{O} \\
\text{93} \\
\end{array} \quad \rightarrow \\
\begin{array}{c}
\text{NC} \quad \text{O} \\
\text{49} \\
\end{array}
\]

A solution of the phenyl propargyl ether 93 in ethylene glycol (5 mL/g of the propargyl ether) was heated to 210 – 215 °C under a nitrogen atmosphere. After 24 hours of stirring at the reaction temperature, H\textsubscript{2}O was added to the crude and extracted with Et\textsubscript{2}O. The title compound 49 was crystallized using light petroleum.

3.3.2.10 6-Hydroxy-2, 2, 5, 7, 8-pentamethyl-3-chromene\textsuperscript{20}

\[
\begin{array}{c}
\text{HO} \\
\text{62} \\
\end{array} + \\
\begin{array}{c}
\text{HO} \quad \text{O} \\
\text{77} \\
\end{array} \quad \rightarrow \\
\begin{array}{c}
\text{HO} \\
\text{48} \\
\end{array}
\]

Trimethylhydroquinone 62 (0.535 g, 3.29 mmol) and phenylboronic acid (0.80 g, 6.57 mmol) were each dissolved in 10 mL of toluene and were placed in flame dried flask equipped with a Dean-Stark apparatus. AcOH (in excess) was then added into the mixture at room temperature and stirred for 5 min. before addition of 3-methyl-2-butenal 77 (0.48 mL, 4.70 mmol) was added in one portion and the clear colourless solution was wrapped in aluminium foil and heated to reflux under an atmosphere of N\textsubscript{2} until starting material was judged to have disappeared by TLC. The solvents were removed and the resulting residue was re-dissolved with Et\textsubscript{2}O (50 mL) and water. The ethereal layer was separated and washed with saturated NaHCO\textsubscript{3} (2 X 30 mL) and brine (50 mL). The organic layer was dried over MgSO\textsubscript{4} and solvents were removed under reduced pressure to yield orange oil. The crude was purified by column chromatography eluting with light petroleum/EtOAc (9:1) to
isolate the product 48 as an orange oil (0.44 g, 61%). $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3435, 2971, 2916, 1634, 1270, 1136, 1086, 1063. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 1.38 (s, 6H, OC(CH$_3$)$_2$), 2.12 (s, 3H, ArCH$_3$), 2.16 (s, 3H, ArCH$_3$), 2.18 (s, 3H, ArCH$_3$), 4.20 (s, 1H, phenol), 5.64 (d, $J = 10$ Hz, 1H, C(CH$_3$)$_2$CHCH), 6.51 (d, $J = 10$ Hz, 1H, C(CH$_3$)$_2$CHCH); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 10.9 (ArCH$_3$), 11.6 (ArCH$_3$), 12.4 (ArCH$_3$), 27.3 (2C, 2 X CH$_3$), 74.4 (OC(CH$_3$), C quat.), 116.1 (C quat. arom.), 117.9 (C quat. arom.), 112.0 (OC(CH$_3$)$_2$CH=CH-), 122.5 (C quat. arom.), 122.6 (C quat. arom.), 130.6 (OC(CH$_3$)$_2$CH=CH-), 144.6 (C quat. arom.), 145.4 (C quat. arom.).

3.3.2.11 General Procedure of Acetate Protection of the Phenolic Hydroxyl

A solution of chroman compound (1.0 equiv) in Ac$_2$O (25 equiv) and pyridine (2 mL per 100 mg of chroman compound) was kept and left stirred at room temperature until the reaction had come to completion according to TLC. The mixture was then poured into 20 mL of ice water and extracted with EtOAc. The extract was washed with 3 M HCl, a saturated solution of NaHCO$_3$, and H$_2$O which then finally dried with MgSO$_4$. The solvent was removed under reduced pressure.

3.3.2.12 6-Acetoxy-2,5,7,8-tetramethylchroman-2-(4-methyl-3-pentene)$^{21}$

Prepared according to the general procedure of acetyl protection of phenolic hydroxyl group of chromanols from 6-hydroxy-2,5,7,8-tetramethylchroman-2-(4-methyl-3-pentene) 61 (1.61 g, 5.59 mmol). The crude material was purified by column chromatography, typically eluting with ethyl acetate/light petroleum (1:99), to give the product 65 as a
yellow oil (1.34 g, 73%). \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2977, 2929, 2863, 1758, 1676, 1577, 1455, 1416, 1368, 1332, 1208, 1166, 1109, 1079, 1011, 918, 897, 850. \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.25 (s, 3H, C8), 1.59 (m, 2H), 1.60 (s, 3H, C1 or C2), 1.68 (s, 3H, C1 or C2), 1.80 (qd, \( J = 14, 7 \) Hz, 2H), 1.98 (s, 3H, C17, C20 or C21), 2.02 (s, 3H, C17, C20 or C21), 2.09 (s, 3H, C17, C20 or C21), 2.12 (m, 2H), 2.33 (s, 3H, C19), 2.60 (t, \( J = 7 \) Hz, 2H), 5.12 (t, \( J = 7 \) Hz, 1H, C4); \(^{13}\)C-NMR (126 MHz, CDCl\(_3\)): \( \delta \) 11.9 (C17, C20 or C21), 12.2 (C17, C20 or C21), 13.0 (C17, C20 or C21), 17.6 (C1 or C2), 20.6 (C10 or C18), 20.6 (C10 or C18), 22.3 (C3, C5), 25.7 (C1, C1 or C2), 31.0 (C9), 38.1 (C6), 74.8 (C7), 117.4 (C \text{quat. arom.}, C11), 123.1 (C \text{quat. arom.}), 124.5 (C4), 125.0 (C \text{quat. arom.}), 126.7 (C \text{quat. arom.}), 131.5 (C \text{quat. arom.}), 140.6 (C \text{quat. arom.}, C13), 149.4 (C \text{quat. arom.}, C16), 169.8 (C \text{quat. arom.}, C17); \[ m/z \ 348.2534, C_{21}H_{30}O_3NH_4 [M + NH_4]^+ \text{ requires } 348.2533. \]

3.3.2.13 Methyl 6-acetoxy-2,5,7,8-tetramethylchroman-2-carboxylate

Prepared according to the general procedure of acetyl protection of phenolic hydroxyl group of chromanols from methyl 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylate 101 (0.811 g, 3.07 mmol). The yellow crude was purified by column chromatography, typically eluting with ethyl acetate/light petroleum (1:9), to give the product 113 as a white solid (0.67 g, 59%); m.p. 94 – 96 °C. \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.60 (s, 3H, OCOC\(_3\)H), 1.81 – 1.94 (m, 1H, CHHCH\(_2\)Ar), 1.94 (s, 3H, ArCH\(_3\)), 2.03 (s, 3H, ArCH\(_3\)), 2.16 (s, 3H, ArCH\(_3\)), 2.32 (s, 3H, Ph-OCOCH\(_3\)), 2.38 – 2.44 (m, 1H, CHHCH\(_2\)Ar), 2.48 – 2.66 (m, 2H, CH\(_2\)CH\(_2\)Ar), 3.68 (s, 3H, COOCH\(_3\)); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \( \delta \) 11.9 (Ar-CH\(_3\)), 12.1 (Ar-CH\(_3\)), 13.0 (Ar-CH\(_3\)), 20.5 (Ar-OCOCH\(_3\)), 20.8 (C3 or C4), 25.5 (C11), 30.2 (C3 or C4), 30.4 (C2), 52.4 (C13), 77.3 (C \text{quat. arom.}, C10), 117.1 (C \text{quat. arom.}), 123.1 (C \text{quat. arom.}), 124.9 (C \text{quat. arom.}), 127.1 (C \text{quat. arom.}), 141.3 (C \text{quat. arom.}), 169.6 (C12), 174.2 (C15); \[ m/z \ 324.1803, C_{17}H_{22}O_5NH_4 [M + NH_4]^+ \text{ requires } 324.1805. \]
3.3.2.14 6-Acetoxy-2,2,5,7,8-pentamethylchromene

Prepared according to the general procedure of acetyl protection of phenolic hydroxyl group of chromanols from 6-hydroxy-2,2,5,7,8-pentamethyl-3-chromene 48 (0.55 g). The brown oil crude was purified by column chromatography eluting 1:9 (ethyl acetate/light petroleum) to obtain the title compound 54 as a white powder (0.53 g, 82%); m.p. 63–65 °C. ν<sub>max</sub> (film)/cm<sup>-1</sup> 3054, 2981, 2928, 1752, 1645, 1605, 1462, 1421, 1370, 1265, 1209, 1135, 1080, 1062, 739, 705. ¹H-NMR (400 MHz, CDCl<sub>3</sub>): δ 1.40 (s, 6H, OC(CH<sub>3</sub>)<sub>2</sub>), 2.02 (s, 3H, Ar-CH<sub>3</sub>), 2.05 (s, 3H, Ar-CH<sub>3</sub>), 2.10 (s, 3H, Ar-CH<sub>3</sub>), 2.32 (s, 3H, Ar-OCOC<sub>3</sub>H), 5.63 (d, J = 12 Hz, 1H, CH=CH-Ar), 6.47 (d, J = 12 Hz, 1H, CH=CH-Ar); ¹³C-NMR (100 MHz, CDCl<sub>3</sub>): δ 11.6 (Ar-CH<sub>3</sub>), 11.6 (Ar-CH<sub>3</sub>), 13.2 (Ar-CH<sub>3</sub>), 20.5 (Ar-OCOCH<sub>3</sub>), 27.7 (2C, 2 X CH<sub>3</sub>), 75.0 (C2), 117.9 (C quat. arom.), 119.6 (CH=CH-Ar), 122.4 (C quat. arom.), 122.8 (C quat. arom.), 129.0 (C quat. arom.), 130.3 (CH=CH-Ar), 141.4 (C quat. arom.), 148.4 (C quat. arom.), 169.5 (C14); m/z 261.1486, C<sub>16</sub>H<sub>20</sub>O<sub>3</sub>H [M + H]<sup>+</sup> requires 261.1485.

3.3.2.15 6-Acetoxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-ene)chromene

Prepared according to the general procedure of acetyl protection of phenolic hydroxyl group of chromanols from 6-hydroxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-ene)chromene 47 (3.0 g, 1 eq) to give title compound 51 as an orange oil (2.97 g, 86%). ν<sub>max</sub> (film)/cm<sup>-1</sup> 3051, 2968, 2924, 1758, 1647, 1618, 1605, 1451, 1368, 1316, 1261, 1204, 1113, 1078, 1062, 1008, 930, 913, 896, 849, 773, 742, 675, 659, 613. ¹H-NMR (400 MHz, CDCl<sub>3</sub>): δ 1.28
(s, 3H, OC(CH₃)), 1.51 (s, 3H, CH₂CH=C(CH₃)₂), 1.59 (s, 3H, -CH₂CH=CH(CH₃)₂, H1 or H2), 1.55 – 1.61 (m, 2H, -CH₂CH₂CH=CH(CH₃)₂, H6), 1.93 (s, 3H, Ar-CH₃), 1.97 (s, 3H, Ar-CH₃), 2.03 (s, 3H, Ar-CH₃), 1.98 – 2.10 (m, 2H, -CH₂CH₂CH=CH(CH₃)₂, H5), 2.25 (s, 3H, Ar-O-CO(CH₃), H19), 5.03 (t, J = 7 Hz, 1H, -CH₂CH=CH(CH₃)₂, H4), 5.51 (d, J = 10 Hz, 1H, H9 or H10), 6.42 (d, J = 10 Hz, 1H, H9 or H10); ¹³C-NMR (100 MHz, CDCl₃): δ 11.6, 11.6, 13.2, 17.6, 20.5, 22.8, 25.7, 40.9, 117.6, 120.0, 122.4, 122.6, 124.3 (2C, 2 X C quat. arom.), 129.0, 129.4, 131.6, 133.1, 141.3, 148.5, 169.5; m/z 346.2379, C₂₁H₂₈O₃N₄ [M + NH₄]⁺ requires 346.2377.

3.3.2.16 General Procedure of Trifluoroacetate Protection of the Phenolic Hydroxyl

Chromenol was dissolved in pyridine (2 equiv) and dry THF (30 mL per gram of chromenol) as the solvent under Ar. The mixture was cooled down in brine-ice bath (-3 °C – 0 °C). After 5 minutes of stirring, trifluoroacetic anhydride (TFAA, 1.2 equiv) was added dropwise over 10 min. at reaction temperature. The reaction progress was checked by TLC plate. After the reaction had come to completion, the reaction was quenched with Et₂O/DCM (2:1), and washed with 1% aqueous HCl. The organic layers were washed with saturated NaHCO₃ and brine. The solvent is then dried (MgSO₄) and reduced under pressure.

3.3.2.17 6-Trifluorocetoxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-ene)chromene

Prepared according to the general procedure of trifluoroacetate protection of phenols from 6-hydroxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-ene)chromene ⁴⁷ (0.10 g, 0.18 mmol) to
obtain the title compound 52 as brownish oil (0.07 g, 97%). $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2970, 2928, 2858, 1798, 1677, 1608, 1455, 1413, 1377, 1355, 1224, 1169, 1138, 875, 831. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.37 (s, 3H, CH$_3$, C1 or C2), 1.58 (s, 3H, CH$_3$, C1 or C2), 1.65 – 1.75 (m, 2H, CH$_2$), 1.66 (s, 3H, CH$_3$, C1 or C2), 2.03 (s, 3H, Ar-CH$_3$, C17, C20 or C21), 2.04 (s, 3H, Ar-CH$_3$, C17, C20 or C21), 2.12 (s, 3H, Ar-CH$_3$, C17, C20 or C21), 1.99 – 2.25 (m, 2H, CH$_2$), 5.10 (ddd, $J$ = 7, 6, 1 Hz, 1H, C9), 6.50 (d, $J$ = 10 Hz, C9); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 11.2 (Ar-CH$_3$, C17 or C18), 11.6 (Ar-CH$_3$, C17 or C20), 12.8 (Ar-CH$_3$, C21), 17.6, 22.7, 25.7, 25.9, 40.9, 77.7, 114.9 (q, $^1$J$_{C-F}$ = 284 Hz, CF$_3$), 116.1, 118.0, 119.5, 121.8, 123.3, 124.1, 128.3, 130.1, 140.0, 149.4, 155.7 (q, $^2$J$_{C-F}$ = 46 Hz, C=O); m/z 382.1799, C$_{21}$H$_{25}$F$_3$O$_3$H [M + H]$^+$ requires 382.1796.

3.3.2.18 6-Trifluorocetoxy-2,2,5,7,8-pentamethylchromene

Prepared according to the general procedure of trifluoroacetate protection of phenols from 6-hydroxy-2,2,5,7,8-pentamethylchromene 48 (1.66 g, 7.6 mmol) and purified by column chromatography using 1:99 (EtOAc/light petroleum) eluent to obtain the title compound 55 as a light yellow solid (2.02 g, 84%); m.p. 62 $^\circ$C. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3054, 2986, 2685, 2521, 2410, 2305, 1795, 1606, 1551, 1421, 1358, 1265, 1224, 1175, 1143, 1131, 1105, 896, 876, 743, 705. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.41 (s, 6H, OC(CH$_3$)$_2$), 2.03 (s, 3H, Ar-CH$_3$), 2.06 (s, 3H, Ar-CH$_3$), 2.12 (s, 3H, Ar-CH$_3$), 5.67 (d, $J$ = 10 Hz, 1H, CH=CHAr), 6.47 (d, $J$ = 10 Hz, 1H, CH=CHAr); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 11.2 (Ar-CH$_3$), 11.6 (Ar-CH$_3$), 12.8 (Ar-CH$_3$), 27.7 (2C, 2 X OC(CH$_3$)$_2$), 75.3 (C quat., OC(CH$_3$)$_2$), 113.8 (q, $^1$J$_{C-F}$ = 285Hz, CF$_3$), 118.3 (C quat. arom.), 119.1 (CH=CHAr), 121.8 (C quat. arom.), 123.6 (C quat. arom.), 128.2 (C quat. arom.), 130.9 (CH=CHAr), 140.2 (C quat. arom.), 149.3 (C quat. arom.), 155.5 (q, $^2$J$_{C-F}$ = 46 Hz, C=O); m/z 315.1201, C$_{16}$H$_{17}$F$_3$O$_3$H [M + H]$^+$ requires 315.1203.
### 3.3.2.19 Methyl 6-trifluoroacetoxy-2,5,7,8-tetramethylchroman-2-carboxylate

Prepared according to the general procedure of trifluoroacetate protection of phenols from methyl 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylate 101 (1.99 g, 7.52 mmol), TFAA (1.27 mL, 9.02 mmol) and pyridine (1.22 mL, 15.04 mmol). The reaction completed in 30 min and the solid obtained was recrystallized from MeOH to give the title compound 114 as a white powder (1.99 g, 73%); m.p. 124.0 – 125.5 °C. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3000, 2957, 2938, 1797, 1755, 1741, 1456, 1416, 1357, 1292, 1244, 1223, 1170, 1134, 1112, 875, 770. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.63 (s, 3H, C11), 1.87 (m, 1H, C3), 1.96 (s, 3H, C14, C17 or C18), 2.04 (s, 3H, C14, C17 or C18), 2.18 (s, 3H, C14, C17 or C18), 2.48 (m, 2H, C3 and C4), 2.65 (m, 1H, C4), 3.69 (s, 3H, C13); $^{13}$C-NMR (126 MHz, CDCl$_3$): $\delta$ 11.8, 11.9, 12.6, 20.8, 25.4, 30.1, 52.5, 77.5, 113.8, 114.9 (q, $^{1}J_{C-F} = 286$ Hz, CF$_3$), 116.0, 117.6, 123.8, 124.4, 126.4, 140.0, 150.2, 156.0 (q, $^{2}J_{C-F} = 42$ Hz, C=O), 173.9; m/z 361.1249, C$_{17}$H$_{19}$F$_{3}$O$_{5}$H [M + H]$^+$ requires 361.1247.

### 3.3.2.20 General Procedure of Benzoate Protection of the Phenolic Hydroxyl

A solution of the phenol in anhydrous THF was added dropwise over 30 min to a suspension of NaH (1.1 equiv) in the same solvent, under stirring and under N$_2$. An exothermic reaction with hydrogen evolution immediately occurred and the colour changed observed. After 10 min, a solution of benzoyl chloride (1.0 equiv) was added dropwise over 10 min. After the reaction has come to completion, mixture of Et$_2$O/H$_2$O (1:1) was slowly added into the reaction. The aqueous layer was separated and extracted again with Et$_2$O. The combined organic layers were washed with 5% aqueous NaOH and
then with H$_2$O and brine. The solvent was dried (Na$_2$SO$_4$), and evaporated under reduced pressure.

3.3.2.21 6-Benzoyloxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-ene)chromene

Prepared according to the general procedure for benzoate protection of phenols from 6-hydroxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-ene)chromene 47 (0.10 g, 0.18 mmol), NaH (0.005 g, 0.19 mmol) and benzoyl chloride (0.02 mL, 0.18 mmol). The reaction was complete after overnight. The crude was purified by column chromatography eluting with ethyl acetate/light petroleum (10:90) to afford the title compound 53 as yellow oil (0.05 g, 75%).

$\nu_{max}\ (\text{film})/\text{cm}^{-1}$ 3061, 2968, 2857, 1774, 1737, 1644, 1603, 1585, 1451, 1413, 1377, 1267, 1245, 1205, 1177, 1025, 1002, 922, 870. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.16 (CH$_3$, C8), 1.51 (CH$_3$, C1 or C2), 1.61 (CH$_3$, C1 or C2), 1.98 (Ar-CH$_3$, C17, C25 or C26), 2.00 (Ar-CH$_3$, C17, C25 or C26), 2.06 (Ar-CH$_3$, C17, C25 or C26), 5.00 – 5.10 (m, 1H, C4), 5.53 (d, $J = 10$ Hz, 1H, C10), 6.45 (d, $J = 10$ Hz, 1H, C9), 7.43 – 7.51 (m, 2H, CH arom.), 7.58 – 7.63 (m, 1H, CH arom.), 8.17 (dd, 2H, CH arom.); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 11.7, 11.7, 13.3, 17.6, 22.8, 25.7, 29.8, 40.8, 117.8, 120.1, 122.7, 124.3, 128.6, 129.0, 129.3, 129.5, 130.2, 131.5, 131.6, 133.5, 135.4, 141.4 (C quat. arom.), 148.6 (C quat. arom.), 165.0 (C=O, C18). No quaternary C of C2 is observed. $m/z$ 408.2535, C$_{26}$H$_{30}$O$_3$NH$_4$ [M + NH$_4$]$^+$ requires 408.2533.
Prepared according to the general procedure for benzoate protection of phenols from 6-hydroxy-2,2,5,7,8-pentamethylchromene 48 (1.35 g, 6.20 mmol), NaH (0.16 g, 6.82 mmol) and benzoyl chloride (0.72 mL, 6.2 mmol). The reaction completed in 30 min. The crude material was purified by column chromatography eluting with ethyl acetate/light petroleum (5:95). The residue was recrystallized from MeOH to provide the title compound 56 as a yellow solid (1.68 g, 84%): m.p. 108 – 110 °C; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3067, 2975, 2926, 1735, 1643, 1603, 1451, 1416, 1377, 1277, 1250, 1216, 1176, 1138, 1092, 1066, 1024, 905, 773, 712. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.42 (s, 6H, C11 & C12), 2.06 (s, 3H, C13, C15 or C16), 2.09 (s, 3H, C13, C15 or C16), 2.14 (s, 3H, C13, C15 or C16), 5.65 (d, $J = 10$ Hz, 1H, C3), 6.50 (d, $J = 10$ Hz, 1H, C4), 7.53 (m, 2H, CH arom.), 7.65 (m, 1H, CH arom.), 8.25 (m, 2H, CH arom.); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 11.7 (C13, C14 or C15), 11.7 (C13, C14 or C15), 27.7 (C13, C14 or C15), 75.0 (quat. C, C2), 118.0 (C quat. arom., C17), 119.7 (C3), 122.7 (C quat. arom., C9), 123.0 (C quat. arom., C5), 128.6 (2C, 2 X C arom., C18 & C22), 129.3 (C quat. arom., C6 or C8), 129.5 (C quat. arom., C6 or C8), 130.2 (2C, 2 X C arom., C19 & C21), 130.4 (C4), 133.5 (C arom., C20), 141.6 (C quat. arom., C7), 148.5 (C quat. arom., C10), 165.0 (C=O, C16); $m/z$ 323.1644, C$_{21}$H$_{22}$O$_3$H [M + H]$^+$ requires 323.1642. No quaternary C of C2 is observed.
3.3.2.23 Methyl 6-benzoyloxy-2,5,7,8-tetramethyl-3-chroman-2-carboxylate

Prepared according to the general procedure for benzoate protection of phenols from methyl 6-hydroxy-2,5,7,8-tetramethyl-3-chroman-2-carboxylate 101 (1.503 g, 5.69 mmol), NaH (0.15 g, 6.25 mmol) and benzoyl chloride (0.66 mL, 5.69 mmol). The reaction was left stirred overnight. The crude was then purified by column chromatography eluting with ethyl acetate/light petroleum (10:90). White solid obtained was recrystallized from ethanol to give the title compound 115 as a white power (1.05 g, 50%): m.p. 130 – 132 °C; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3071, 2996, 2953, 2934, 1733, 1644, 1601, 1584, 1451, 1414, 1374, 1334, 1239, 1195, 1176, 1134, 1094, 1071, 1024, 978, 943, 802, 712; $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.63 (s, 3H, C11), 1.89 (m, 1H, C3), 1.98 (s, 3H, C14, C15, C16), 2.46 (m, 2H, C3 & C4), 2.67 (m, 1H, C4), 3.69 (s, 3H, C13), 7.53 (m, 2H, CH arom.), 7.65 (m, 1H, CH arom.), 8.25 (m, 1H, CH arom.); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 11.9 (C14, C15 or C16), 12.2 (C14, C15 or C16), 13.1 (C14, C15 or C16), 20.9 (C4), 25.5 (C11), 30.3 (C3), 52.4 (C13), 117.2 (C2), 123.17 (C quat. arom., C5), 125.2 (C quat. arom., C8), 127.4 (C quat. arom., C7), 128.6 (2C, 2 X C arom., C20 & C22), 129.6 (C quat. arom., C9), 130.2, 133.5 (C arom., C21), 165.1 (C=O, C12), 174.3 (Ar-C=O, C17); m/z 386.1963, C$_{22}$H$_{24}$O$_5$NH$_4$ [M + NH$_4$]$^+$ requires 386.1962. No quaternary C of C2 is observed.

3.3.2.24 General Procedure of Methyl Ether Protection of the Phenolic Hydroxyl

NaH (1.1 equiv) was dissolved in anhydrous THF (10 mL/g of phenol) and transferred into a flame-dried flask, flushed with N$_2$. The phenol was dissolved in anhydrous THF was then added into the solution dropwise over 20 min. The reaction was stirred for 20 min prior to
addition of Mel (1 equiv). The solution was stirred at room temperature until complete disappearance of the starting material was observed on TLC plate. After the reaction had come to completion, it was treated with Et₂O/H₂O (20 mL/g of phenol, 1:1). The organic layer was washed with water and brine. The solvent was then reduced under pressure.

3.3.2.25 6-Methoxy-2,2,5,7,8-pentamethylchromene

Prepared according to the general procedure of methyl protection of the phenolic hydroxyl using NaH (0.018 g, 0.76 mmol), 6-hydroxy-2,2,5,7,8-pentamethylchromene 48 (0.151 g, 0.69 mmol) and Mel (0.043 mL, 0.69 mmol). The brownish crude oil was purified by column chromatography eluting with ethyl acetate/light petroleum (5:95) to give the title compound 117 as a yellowish oil (0.14 g, 87.2%). ν<sub>max</sub> (film)/cm<sup>-1</sup> 3047, 2975, 2932, 1641, 1597, 1461, 1406, 1387, 1359, 1270, 1217, 1174, 1137, 1089, 1064, 1046, 1004, 943, 903, 831. ¹H-NMR (500 MHz, CDCl₃): δ 1.39 (s, 6H, C11 & C12), 2.09 (s, 3H, C13, C15 or C16), 2.18 (s, 3H, C13, C15 or C16), 2.21 (s, 3H, C13, C15 or C16), 3.62 (s, 3H, C14), 5.61 (d, J = 10 Hz, 1H, C3 or C4), 6.49 (d, J = 10 Hz, 1H, C3 or C4); ¹³C-NMR (125 MHz, CDCl₃): δ 11.6 (Ar-CH₃, C13, C15 or C16), 11.2 (Ar-CH₃, C13, C15 or C16), 12.8 (Ar-CH₃, C13, C15 or C16), 27.6 (2C, 2 X CH₃, C11 and C12), 60.4 (Ar-O-CH₃, C14), 74.7 (OC(CH₃)₂, C2), 118.0 (C quat. arom.), 120.0 (-CH=CH-Ar, C3), 122.8 (C quat. arom.), 123.2 (C quat. arom.), 130.1 (-CH=CH-Ar, C4), 146.8 (C quat. arom.), 150.3 (C quat. arom.). 1 sp² C not located.

22
3.3.2.26 Methyl 6-methoxy-2,5,7,8-tetramethylchromene-2-carboxylate

Prepared according to the general procedure of methyl ether protection of the phenolic hydroxyl using NaH (0.03 g, 1.26 mmol), methyl 6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydrochromen-2-carboxylate 101 (0.303 g, 1.15 mmol) and MeI (0.07 mL, 1.15 mmol). The brownish crude oil was purified by column chromatography eluting with ethyl acetate/light petroleum (20:80) to give the title compound 118 as a yellowish oil (0.22 g, 69%). $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2985, 2935, 1754, 1736, 1457, 1404, 1375, 1293, 1255, 1199, 1173, 1142, 1090, 1066, 1011, 915. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.60 (s, 3H, C11), 1.75 – 1.86 (m, 1H, C3), 2.10 (s, 3H, C14, C15 or C16), 2.16 (s, 3H, C14, C15 or C16), 2.19 (s, 3H, C14, C15 or C16), 2.37 – 2.42 (m, 1H, C3), 2.44 – 2.48 (m, 1H, C4), 2.56 – 2.65 (m, 1H, C4), 3.61 (s, 3H, C13), 3.68 (s, 3H, C17). $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 11.8 (Ar-CH$_3$, C14 or C15), 12.6 (Ar-CH$_3$, C16), 20.9 (CH$_3$, C11), 25.5 (CH$_3$, C3), 30.5 (CH$_3$, C3), 52.4 (-OCH$_3$, C14), 60.4 (-OCH$_3$, C16), 77.2 (C quat., C2), 117.2 (C quat. arom.), 122.9 (C quat. arom.), 125.7 (C quat. arom.), 128.1 (C quat. arom.), 147.7 (C quat. arom.), 150.1 (C quat. arom.), 174.4 (CO$_2$Me).

3.3.2.27 General Procedure for Dehydrogenation of the Phenol-Protected Chroman with DDQ

The solution of the respective chromane in anhydrous toluene (6 mL) was heated at 105 °C for 30 min. A solution of 2,3-dichloro-4,5-dicyanoquinone (DDQ) in anhydrous toluene was added dropwise over 30 min, and this mixture refluxed overnight. The solution was cooled down to room temperature and filtered, and the solvent was evaporated under reduced pressure. The residue was dissolved in diethyl ether, washed with 5% NaHCO$_3$.
solution and water, and brine. The solvent was dried over Na$_2$SO$_4$, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography in silica gel. TLC showed the product nearly at the same position as the starting material, but on spraying with 4% H$_2$SO$_4$ in methanol and heating the starting material turned yellow and the product brown, and became thus distinguishable.

3.3.2.28 6-Acetoxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-ene)chromene$^{15}$

Prepared according to the general procedure of dehydrogenation of the acetyl-protected chroman from 6-acetoxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-ene) chromane 65 (0.17 g, 0.5 mmol) to give the title compound 51 as an orange oil (0.04 g, 24%).

3.3.2.29 Methyl 6-acetoxy-2,5,7,8-tetramethylchromene-2-carboxylate

Prepared according to the general procedure of dehydrogenation of the acetyl-protected chroman from methyl 6-acetoxy-2,5,7,8-tetramethyl-3,4-dihydrochromene-2-carboxylate 113 (0.4 g, 1.31 mmol). The reddish crude was purified by column chromatography, typically eluting with ethyl acetate/light petroleum (10:90), and recrystallized from MeOH and dried at 60 °C to give the title compound 57 as a white solid (0.19 g, 48%); m.p. 114.5 – 116.0 °C; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3011, 2992, 2956, 2941, 1751, 1644, 1612, 1453, 1369, 1261, 1202, 1117, 1085, 1064, 750. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.69 (s, 3H, CCH$_3$), 2.04 (s, 3H, ArCH$_3$), 2.04 (s, 3H, ArCH$_3$), 2.19 (s, 3H, OCOCH$_3$), 2.33 (s, 3H, ArCH$_3$), 3.70 (s, 3H, COOCH$_3$),
5.78 (d, $J = 10$ Hz, 1H, CCH=CH), 6.68 (d, $J = 10$ Hz, 1H, CH=CHAr); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 11.5 (Ar-CH$_3$), 11.7 (Ar-CH$_3$), 13.3 (Ar-CH$_3$), 20.5 (C16), 25.6 (C11), 52.5 (C13), 77.2 (C quat., C2, or C quat. arom., C10), 77.5 (C2 or C10), 117.0 (C quat. arom.), 121.9 (Ar-CH=CH), 122.9 (C quat. arom.), 123.1 (C quat. arom.), 124.5 (Ar-CH=CH), 130.0 (C quat. arom.), 142.1 (C quat. arom.), 142.4 (C12), 173.1 (C15); $m/z$ 322.1650, C$_{17}$H$_{20}$O$_5$NH$_4$ [M + NH$_4^+$] requires 322.1649.

3.3.2.30 Methyl 6-benzoyloxy-2,5,8-tetramethylchromene-2-carboxylate

Prepared according to the general procedure of dehydrogenation of the chroman from methyl 6-benzoate-2,5,7,8-tetramethyl-3,4-dihydrochromen-2-carboxylate 115 (0.51 g, 1.38 mmol). The reddish crude was purified by column chromatography to give the title compound 59 as a colourless oil (0.22 g, 42.7%). $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.71 (s, 3H, C11), 2.08 (s, 3H, C14, C15 or C16), 2.08 (s, 3H, C14, C15 or C16), 2.23 (s, 3H, C14, C15 or C16), 3.72 (s, 3H, C13), 5.79 (d, $J = 10$ Hz, 1H, C3), 6.64 (d, $J = 10$ Hz, 1H, C4), 7.52 (td, $J = 8$, 4 Hz, 2H, CH arom.), 7.65 (m, 1H, CH arom.), 8.23 (dd, $J = 10$, 8 Hz, 2H, CH arom.); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 11.7 (2C, 2 X Ar-CH$_3$), 13.4 (Ar-CH$_3$), 52.5 (CO$_2$-CH$_3$, C13), 77.6 (C quat., C2), 117.2 (C arom.), 121.8 (C quat. arom.), 122.1 (C quat. arom.), 123.2 (C arom.), 124.5 (C quat. arom.), 128.7 (Ar-CH=CH, C4), 128.9 (C quat. arom.), 129.4 (C arom.), 130.2 (Ar-CH=CH, C3), 133.6 (2C, 2 X C arom.), 142.2 (C quat. arom.), 148.3 (C quat. arom.), 148.6 (C quat. arom.), 164.9 (CO$_2$-Ar, C19), 173.1 (CO$_2$-CH$_3$, C12); $m/z$ 367.1542, C$_{17}$H$_{22}$O$_5$NH$_4$ [M + H]$^+$ requires 367.1540.
3.3.3  Catalytic Asymmetric Epoxidation Reaction

3.3.3.1  General Procedure for the Preparation of Racemic Epoxides Using m-CPBA

The alkene was dissolved in CH₂Cl₂ (10 mL/g) and the solution cooled using an ice bath. A solution of m-CPBA (2 equiv) in CH₂Cl₂ (10 mL/g, pre-dried over MgSO₄) was added. The reaction was allowed to reach ambient temperature and stirred until complete consumption of the substrate was observed by TLC. Saturated aqueous NaHCO₃ (10 mL/g) was added and the layers were separated. The organic layer was washed with saturated aqueous NaOH (1.0 M, 10 ml/g) and dried (MgSO₄). The solvents were removed under reduced pressure and the residue purified by column chromatography, typically eluting with ethyl acetate/light petroleum (1:99), to give the pure epoxide.

3.3.3.2  Purification of m-CPBA

10.0 g of commercial m-CPBA was dissolved in 100mL Et₂O and washed with 3 X 50mL buffer solution (410 mL of 0.1 M NaOH, 250 mL of 0.2M KH₂PO₄ made up to 1 L, pH 7.5). The ether layer was dried over MgSO₄ and carefully evaporated under reduced pressure to give ca. 7.0 g pure m-CPBA.

3.3.3.3  General Procedure for the Preparation of Racemic Epoxides Using m-CPBA and 10% aqueous Na₂CO₃

m-CPBA (4 equiv) was dissolved in a mixture of DCM (40 mL/g of alkene) and 10% aqueous solution of Na₂CO₃ (40 mL/g of alkene) at 0 °C. The alkene was then added into the solution in one portion. The reaction progress is observed by TLC. After the reaction has come to completion, the mixture is washed using 10% aqueous solution of Na₂CO₃ and brine. The organic layer was dried (Na₂SO₄) and reduced under pressure.
3.3.3.4 Preparation of Dimethyldioxirane (DMDO) on a Large Scale

A 2-L, three-necked, round-bottom flask containing a mixture of water, acetone, and NaHCO₃, was equipped with a large magnetic stirring bar and connected via a U-tube to a vacuum distilling adapter and a receiver, which was cooled at −78 °C. The mixture of water, acetone and NaHCO₃ was cooled to 5 – 10 °C. While cooling and stirring vigorously, Oxone® was added in 5 portions in 30 min intervals. The reaction was left stirred for 15 min then a moderate vacuum was applied. The DMDO/acetone solution was distilled and collected in the cooled (−78 °C) receiver. The DMDO solution was dried over anhydrous K₂CO₃ and filtered into a pre-cooled 1 L round bottom flask. The solution was flushed with Ar, stoppered with glass stopper and stored in the freezer (−20 °C) over molecular sieves (4 Å). (DMDO is slowly decomposed by K₂CO₃ therefore storage on K₂CO₃ should be avoided).

3.3.3.5 Preparation of Dimethyldioxirane (DMDO) on a Small Scale

Distilled H₂O (20 mL), acetone (30 mL), and NaHCO₃ (24 g, 0.285 mol) were combined in a 1-L round bottom flask and chilled in an ice/water bath with magnetic stirring for 20 min. After 20 min, stirring is halted and Oxone® (25 g, 0.164 mol) was added in a single portion. The flask was loosely covered and the slurry was stirred vigorously for 15 min while still submerged in the ice bath. After 15 min, the stir bar was removed from the reaction flask and rinsed with a small portion of distilled water.

The flask containing the reaction slurry was then attached to a rotary evaporator with the bath at room temperature. The rotary evaporator splash trap (250 mL) was chilled in a dry ice/acetone bath and a vacuum of 155 mmHg was applied via a benchtop diaphragm pump and an accompanying in-line vacuum regulator. During this process, the flask was rotated vigorously (210 rpm) to prevent bumping of the slurry into the bump trap. After 15 min, the bath temperature was raised to 40 °C over the course of 10 min. When the bath reached 40
°C, the distillation was halted immediately by releasing the vacuum and raising the flask from the heated water bath.

The pale yellow solution of DMDO was decanted from the rotary evaporator splash trap directly into a graduated cylinder to measure the total volume of the solution (an average of 25 mL) and the solution was dried over Na₂SO₄. The Na₂SO₄ was removed by filtration and rinsed with 10 mL acetone.

3.3.3.6 Determination of the Concentration of DMDO

The concentration of DMDO was determined by iodometric titration as follows: 25 mL of 0.02 M aqueous solution of sodium thiosulfate (496 mg Na₂S₂O₃·5H₂O in 100 mL H₂O) was placed in 25 mL graduated burette. A 100 mL Erlenmeyer flask was charged with water (20 mL), glacial acetic acid (1 mL), a freshly prepared solution of sodium iodide (10 mL)(10 g NaI in 50 mL H₂O) and then the solution DMDO (2 mL) was added. The solution was titrated rapidly with 0.02 M sodium thiosulfate until the disappearance of the yellow iodine colour. The concentration was calculated according to the following equation:

\[
\text{Concentration of DMDO} = \frac{\text{Molarity of titrant} \times \text{mL of titrant}}{\text{mL of DMDO solution} \times 2}
\]

3.3.3.7 General Procedure for the Preparation of Racemic Epoxides Using DMDO

To a solution of an alkene in CHCl₃ (2 mL per 0.1 g alkene) which was cooled to 0 °C, the DMDO solution in acetone (0.03 M, 1.5 equiv) was gradually added. After 5 min of stirring, the reaction progress was checked by TLC. After the reaction had come to completion, the solvent was dried under reduced pressure at room temperature. The crude material was purified by column chromatography.
3.3.3.8 General Procedure for the Catalytic Asymmetric Epoxidation of Alkenes Mediated by Iminium Salts using Oxone under Aqueous Conditions

Oxone® (2 equiv with respect to alkene) was added with stirring to an iced-cooled solution of sodium carbonate (4 equiv) in water (12 mL per 1.50 g of Na₂CO₃), and the resulting foaming solution was stirred for 5-10 minutes, until most of the effervescence subsided. A solution of the iminium salt (10 mol% with respect to alkene) in CH₃CN (6 mL per 1.50 g of Na₂CO₃), was added, followed by a solution of the alkene substrate in CH₃CN (6 mL per 1.50 g of Na₂CO₃). The suspension was stirred with ice-bath cooling until the substrate was completely consumed according to TLC. The reaction mixture was then diluted with ice-cooled diethyl ether (20 mL per 100 mg substrate) and the same volume of water was added immediately. The aqueous phase was washed four times with diethyl ether and the combined organic solutions was then washed with brine and dried (MgSO₄). Filtration and removal of solvents gave a yellow or light brown residue, which was purified by column chromatography, typically using ethyl acetate/light petroleum (1:99) to provide pure epoxide.

3.3.3.9 Tetraphenylphosphonium monoperoxysulfate (TPPP)

Tetraphenylphosphonium chloride (15.0 g, 40 mmol) was dissolved in DCM (200 mL) and cooled in ice-water bath in a round bottomed flask equipped with a stirrer bar. Oxone® (15.0 g, 48 mmol) which was dissolved in deionised water (300 mL) at 0°C, was added to the solution of tetraphenylphosphonium chloride over a period of 5 min. The resulting biphasic mixture was stirred vigorously for 1 h in the ice-water bath, after which time the organic layer was separated off and solvents were removed under reduced pressure at room temperature. The crude white solid was transferred to a sintered glass funnel and washed with deionised water (3 X 80 mL). The solid was re-dissolved in DCM (150 mL) and dried over MgSO₄, hexane was added to this solution until a solid precipitate just started to form, and the flask was then placed in the freezer overnight, producing a white crystalline solid with 94% purity in peroxide. ¹H-NMR (400 MHz, CDCl₃): δ 7.63 – 7.67 (m, 8H, 8 CH X
arom.), 7.76 – 7.80 (m, 8H, 8 X CH arom.), 7.88 – 7.92 (m, 4H, 4 X CH arom.), 9.34 (s, 1H, OH). The oxygen content was measured by comparing the integrals of the aromatic signals with the hydroxyl proton.

3.3.3.10 General Procedure for Catalytic Asymmetric Epoxidation of Simple Alkenes Mediated by Iminium Salts using Tetraphenylphosphonium Monoperoxysulfate (TPPP)

Tetraphenylphosphonium monoperoxysulfate (2 equiv with respect to alkene) was dissolved in the desired solvent (2 mL per 0.1 g oxidant) and the solution cooled to the required temperature. To this was added the iminium salt as a solution (0.5 mL per 0.1 g oxidant). This iminium salt solution was cooled to the same temperature as the solution containing the oxidant and added dropwise to it over 15-20 min; the temperature of the reaction vessel was monitored to minimise increase in the temperature during the addition. A solution of the alkene in the reaction solvent (0.5 mL per 0.1 g oxidant) was added dropwise. The mixture was stirred at the reaction temperature until the alkene was completely consumed according to TLC. Et₂O (pre-cooled to the reaction temperature) (20 mL per 0.1 g oxidant) was added to induce precipitation of the remaining oxidant and the mixture filtered through Celite. The solvents were removed, Et₂O (40 mL) was added to the residue and the solution was passed through a short pad of silica gel to remove catalyst residues. The solvents were removed to give the epoxide. If the reaction did not reach to completion then the epoxide could be separated from the alkene by column chromatography, eluting with ethyl acetate/light petroleum 1:99.

3.3.3.11 1-Phenylcyclohexene Oxide²⁶
The title compound 127 was isolated as a colourless oil after purification by column chromatography eluting with EtOAc/light petroleum (1:99). $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3063, 3028, 2937, 2858, 1603, 1495, 1446, 1360, 1298, 1249, 1177, 1079, 1031, 993, 975, 913, 853, 823, 775, 749, 698; $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.32 (m, 1H), 1.47 (m, 1H), 1.59 (m, 2H), 1.98 (m, 2H), 2.12 (m, 1H), 2.28 (m, 1H), 3.08 (d, $J = 3$ Hz, 1H), 7.26 (m, 1H, CH arom.), 7.35 (m, 4H, CH arom.); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 19.8, 20.1, 24.7, 28.2, 60.1, 61.8, 125.3, 127.1, 128.2, 142.8.

3.3.3.12 6-Acetoxy-3,4-epoxy-2,2,5,7,8-pentamethylchromene

The title compound 128 was isolated as a yellow oil after purification by column chromatography eluting with EtOAc/light petroleum (5:95) + 2% TEA. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2978, 2932, 1761, 1616, 1582, 1459, 1367, 1330, 1269, 1204, 1166, 1103, 1081, 1048, 1010, 947, 918, 900, 880, 844, 785, 735, 697, 681, 611; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 1.26 (s, 3H, OC(CH$_3$)$_2$), 1.61 (s, 3H, OC(CH$_3$)$_2$), 2.08 (s, 3H, Ar-CH$_3$), 2.10 (s, 3H, Ar-CH$_3$), 2.24 (s, 3H, Ar-CH$_3$), 2.37 (s, 3H, Ar-OCOCH$_3$), 3.47 (d, $J = 5$ Hz, epoxide), 4.13 (d, $J = 5$ Hz, epoxide); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 11.5 (Ar-CH$_3$, C14 or C17), 11.7 (Ar-CH$_3$, C14 or C17), 13.3 (Ar-CH$_3$, C18), 20.5 (CH$_3$, C11 or C12), 22.9 (CH$_3$-CO$_2$-Ar, C15), 25.7 (CH$_3$, C11 or C12), 48.2 (C-epoxide), 62.2 (C-epoxide), 72.2 (C quat., C2), 115.7 (C quat. arom.), 124.5 (C quat. arom.), 126.7 (C quat. arom.), 130.5 (C quat. arom.), 141.8 (C quat. arom.), 148.0 (C quat. arom.), 169.4 (C=O, C14); m/z 277.1435, C$_{16}$H$_{20}$O$_4$H [M + H]$^+$ requires 277.1434.
3.3.3.13 6-Trifluorocetoxy-3,4-epoxy-2,2,5,7,8-pentamethylchromene

The title compound 129 was isolated as foam after purification by column chromatography eluting with EtOAc/light petroleum (10:90) + 2% TEA. $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2989, 2937, 1798, 1464, 1420, 1358, 1276, 1228, 1173, 1139, 1104, 1042, 918, 877. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.24 (s, 3H, OC(CH$_3$)$_2$), 1.60 (s, 3H, OC(CH$_3$)$_2$), 2.04 (s, 3H, Ar-CH$_3$), 2.09 (s, 3H, Ar-CH$_3$), 2.22 (s, 3H, Ar-CH$_3$), 3.48 (d, $J$ = 5 Hz, 1H, epoxide), 4.10 (d, $J$ = 5 Hz, 1H, epoxide); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 11.1 (Ar-CH$_3$, C13 or C16), 11.6 (Ar-CH$_3$, C13 or C16), 12.9 (Ar-CH$_3$, C17), 22.8 (CH$_3$, C11 or C12), 25.6 (CH$_3$, C11 or C12), 47.8 (C-epoxide, C4), 62.2 (C-epoxide, C3), 72.6 (C quat., C2), 114.9 (q, $^{13}$C$_F$ = 284 Hz, CF$_3$, C15), 116.3 (C quat. arom.), 125.3 (C quat. arom.), 126.1 (C quat. arom.), 129.8 (C quat. arom.), 140.4 (C quat. arom.), 149.1 (C quat. arom.); $m/z$ 331.1152, C$_{16}$H$_{17}$F$_3$O$_4$H [M + H]$^+$ requires 331.1152.

3.3.3.14 6-Cyano-3,4-epoxy-2,2-dimethylchromene

The title compound 124 was isolated as a white solid after purification by column chromatography eluting with EtOAc/light petroleum (5:95) + 2% TEA. $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3055, 2987, 2305, 2228, 1616, 1580, 1494, 1466, 1421, 1385, 1369, 1344, 1265, 1236, 1207, 1162, 1133, 1100, 1040, 958, 935, 920, 896, 868, 828, 816, 737, 705. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.30 (s, 3H, OC(CH$_3$)$_2$), 1.60 (s, 3H, OC(CH$_3$)$_2$), 3.54 (d, $J$ = 4 Hz, 1H, C(CH$_3$)-CH(O)CH-Ar), 3.91 (d, $J$ = 4 Hz, 1H, C(CH$_3$)$_2$CH(O)CH-Ar), 6.87 (d, $J$ = 9 Hz, 1H, CH arom.), 7.53 (dd, $J$ = 9 Hz, 2 Hz, 1H, CH arom.), 7.65 (d, $J$ = 2 Hz, 1H, CH arom.); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 23.0 (CH$_3$, C11 or C12), 25.5 (CH$_3$, C11 or C12), 49.9 (C-epoxide, C3), 62.3 (C-
epoxide, C4), 74.7 (C quat., C2), 104.3 (C quat. arom.), 118.8 (C quat. arom.), 119.1 (C arom.), 121.1 (C quat. arom.), 133.8 (C arom.), 134.4 (C arom.), 156.5 (-C≡N).

### 3.3.3.15 Methyl 6-acetoxy-3,4-epoxy-2,5,7,8-tetramethylchromene-2-carboxylate

![57](image_url) → ![132](image_url)

Prepared according to the general procedure for the preparation of racemic epoxide using DMDO from methyl 6-acetoxy-2,5,7,8-tetramethylchromene-2-carboxylate 57 (0.051 g, 0.17 mmol). The title compound 132 was isolated as a yellow oil after purification by column chromatography eluting with EtOAc/light petroleum (20:80) + 2% TEA (0.02 g, 35%). ν<sub>max</sub> (film)/cm<sup>-1</sup> 2960, 2918, 2851, 1756, 1620, 1583, 1453, 1370, 1292, 1245, 1201, 1136, 1113, 1087, 1050, 1009, 895. ¹H-NMR (500 MHz, CDCl₃): δ 1.80 (s, 3H, C₁₁), 2.04 (s, 3H, C₁4, C₁7 or C₁₈), 2.17 (s, 3H, C₁₄, C₁₇ or C₁₈), 2.19 (s, 3H, C₁₄, C₁₁ or C₁₈), 2.33 (s, 3H, C₁₆), 3.70 (s, 3H, C₁₃), 3.97 (br, 1H, C₃), 4.14 (d, J = 4 Hz, 1H, C₄); ¹³C-NMR (125 MHz, CDCl₃): δ 11.4, 11.5, 13.3, 20.5, 23.0, 52.7, 52.9, 60.0, 115.3, 124.7, 126.8, 130.9, 142.4, 147.1, 169.2, 171.3, 171.9; m/z 321.1334, C₁₇H₂₀O₆H [M + H]<sup>+</sup> requires 321.1333.

### 3.3.3.16 6-Benzoyloxy-3,4-epoxy-2,2,5,7,8-pentamethylchromene

![56](image_url) → ![130](image_url)

The title compound 130 was isolated as a yellowish oil after purification by column chromatography eluting with EtOAc/light petroleum (5:95) + 2% TEA. ν<sub>max</sub> (film)/cm<sup>-1</sup> 2974, 2931, 1733, 1601, 1581, 1452, 1416, 1382, 1315, 1265, 1247, 1231, 1177, 1149, 1094, 1058, 1025, 913. ¹H-NMR (500 MHz, CDCl₃): δ 1.26 (s, 3H, C₁₁ or C₁₂), 1.60 (s, 3H, C₁₁ or
C12), 2.06 (s, 3H, Ar-CH3, C13, C15 or C16), 2.10 (s, 3H, Ar-CH3, C13, C15 or C16), 2.25 (s, 3H, Ar-CH3, C13, C15 or C16), 3.48 (d, J = 5 Hz, 1H, C13 or C16), 4.14 (d, J = 5 Hz, 1H, C3 or C4), 7.53 (t, J = 7 Hz, 2H, 2 X CH arom.), 7.66 (t, J = 7 Hz, 1H, CH arom.), 8.25 (d, J = 7 Hz, 2H, 2 X CH arom.); 13C-NMR (125 MHz, CDCl3): δ 11.6 (Ar-CH3, C13 or C15), 11.7 (Ar-CH3, C13 or C15), 13.4 (Ar-CH3, C14), 22.9 (CH3, C11 or C12), 25.7 (CH3, C11 or C12), 48.3 (C-epoxide, C4), 62.2 (C-epoxide, C3), 72.3 (C quat., C2), 115.8 (C quat. arom.), 124.6 (C arom.), 127.0 (C arom.), 128.7 (2C, 2 X C arom.), 129.3 (C quat. arom.), 130.2 (2C, 2 X C arom.), 130.7 (C quat. arom.), 133.7 (C quat. arom.), 134.1 (C quat. arom.), 165.0 (C=O, C17); m/z 339.1593, C21H22O4H [M + H]+ requires 339.1591.

**3.3.3.17 6-Trifluoroacetoxy-3,4-diol-2,2,5,7,8-pentamethylchromene**

![Chemical structure](image)

Isolated as a brownish oil after purification by column chromatography eluting with EtOAc/light petroleum (5:95) + 2% TEA. νmax (film)/cm⁻¹ 3388, 2981, 2926, 2851, 1797, 1462, 1360, 1230, 1174, 1139, 1109, 876. ¹H-NMR (500 MHz, CDCl3): δ 1.33 (s, 3H, C11 or C12), 1.49 (s, 3H, C11 or C12), 2.09 (s, 3H, C13, C16 or C17), 2.16 (s, 3H, C13, C16 or C17), 2.24 (s, 3H, C13, C16 or C17), 3.76 (d, J = 6 Hz, 1H, C3 or C4), 4.69 (d, J = 6 Hz, 1H, C3 or C4); m/z 339.1633, C16H19F3O5H [M + H]+ requires 339.1631.

**3.3.3.18 6-Cyano-3,4-dihydroxy-2,2-dimethyl-6-cyanochromene**

![Chemical structure](image)

The chiral diol was obtained by asymmetric epoxidation reaction of the chromene 49 under aqueous conditions. Isolated as a brownish solid after purification by column
chromatography eluting with EtOAc/light petroleum (50:50) + 2% TEA. Drying the product at 60 °C under reduced pressure, afforded the title compound 136 as a yellow solid. m.p. 147 – 149 °C; \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 3397, 2984, 2919, 2851, 1611, 1580, 1489, 1372, 1311, 1273, 1195, 1147, 1126, 1072, 1037, 1000, 952, 921, 836. \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \( \delta \) 1.25 (s, 3H, C11 or C12), 1.52 (s, 3H, C11 or C12), 3.62 (d, \( J = 9 \) Hz, 1H, C3), 4.59 (d, \( J = 9 \) Hz, 1H, C4), 6.85 (d, \( J = 9 \) Hz, 1H, C9), 7.46 (ddd, \( J = 9 \), 2, 1 Hz, 1H, C8), 7.81 (dd, \( J = 2 \), 1 Hz, 1H, C6); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \( \delta \) 19.3 (CH\(_3\), C11 or C12), 26.6 (CH\(_3\), C11 or C12), 68.6 (CH\(_2\)-OH, C3), 75.8 (CH\(_2\)-OH, C4), 79.8 (Cquat., C2), 104.0 (Cquat. arom.), 118.0 (C arom.), 119.2 (Cquat. arom.), 124.4 (Cquat. arom.), 132.4 (C arom.), 133.3 (C arom.), 156.0 (Ar-C≡N).

### 3.3.3.19 General Procedure for the Formation of Racemic Diols\(^{28}\)

The racemic epoxide was dissolved in acetone (50 mL/g of epoxide) and stirred at room temperature for 5 min. Aqueous sulfuric acid (1 M, 5.5 equiv) was added to the solution, and the mixture was stirred for 1 hour at room temperature. After the reaction had reached completion, the reaction mixture was neutralized to pH 7 using sodium hydrogen carbonate. Dichloromethane (150 mL/g of epoxide) was added to the reaction mixture and the organic phase was separated. The aqueous layer was extracted with dichloromethane (2 X 150 mL/g of epoxide), and the organic layers were combined and dried (Na\(_2\)SO\(_4\)). The solvents were removed under reduced pressure, and the crude was purified by column chromatography.
3.4 References


APPENDICES
$^1$H NMR of 6-Cyano-3,4-epoxy-2,2-dimethylchromene 49
HPLC trace of racemic epoxidation of 6-cyano-2,2-dimethylchromene

Data File: C:\EZChrom Elite\Enterprise\Projects\AMy\NAB036second run.dat
Method: C:\EZChrom Elite\Enterprise\Projects\yohan\Method\99.1 0.5ml 90min.met
Acquired: 04/04/2013 14:21:05
Printed: 05/04/2013 10:49:24

UV Results

<table>
<thead>
<tr>
<th>Retention Time</th>
<th>Area</th>
<th>Area %</th>
<th>Height</th>
<th>Height %</th>
</tr>
</thead>
<tbody>
<tr>
<td>37.430</td>
<td>101873260</td>
<td>49.58</td>
<td>2120052</td>
<td>54.22</td>
</tr>
<tr>
<td>41.977</td>
<td>103601872</td>
<td>50.42</td>
<td>1790157</td>
<td>45.78</td>
</tr>
</tbody>
</table>

Totals | 205475132 | 100.00 | 3910209  | 100.00 |
Asymmetric epoxidation of 6-cyano-2,2-dimethylchromene under non-aqueous conditions

Data File: C:\EZChrom Elite\Enterprise\Projects\AMY\NAB034-conc5.dat
Method: C:\EZChrom Elite\Enterprise\Projects\yohan\Method\99.1 0.5ml 90min.met
Acquired: 04/04/2013 19:00:38
Printed: 05/04/2013 10:58:53

UV Results

<table>
<thead>
<tr>
<th>Retention Time</th>
<th>Area</th>
<th>Area %</th>
<th>Height</th>
<th>Height %</th>
</tr>
</thead>
<tbody>
<tr>
<td>36.623</td>
<td>347322</td>
<td>0.33</td>
<td>11791</td>
<td>0.61</td>
</tr>
<tr>
<td>40.790</td>
<td>104456189</td>
<td>99.67</td>
<td>1922846</td>
<td>99.39</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>104803511</strong></td>
<td><strong>100.00</strong></td>
<td><strong>1934637</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>
TPPP (4 equiv),
CHCl₃,
0 °C
catalyst 8,
2 days

Area % Report

Data File:  C:\EZChrom Elite\Enterprise\Projects\AMy\NAB082B-22~26run.dat
Method:  C:\EZChrom Elite\Enterprise\Projects\AMy\99.1 1.0mL 90min.met
Acquired:  01/11/2013 16:58:59
Printed:  01/11/2013 20:17:45

UV Results

<table>
<thead>
<tr>
<th>Retention Time</th>
<th>Area</th>
<th>Area %</th>
<th>Height</th>
<th>Height %</th>
</tr>
</thead>
<tbody>
<tr>
<td>22.677</td>
<td>8392677</td>
<td>1.70</td>
<td>137278</td>
<td>2.27</td>
</tr>
<tr>
<td>25.583</td>
<td>483867773</td>
<td>98.30</td>
<td>5897355</td>
<td>97.73</td>
</tr>
<tr>
<td>Totals</td>
<td>492260450</td>
<td>100.00</td>
<td>6034633</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Formation of 6-Cyano-3,4-dihydroxy-2,2-dimethylchromene

Data File: C:\EZChrom Elite\Enterprise\Projects\AMY\NAB099Crun2.dat
Method: C:\EZChrom Elite\Enterprise\Projects\AMY\99.1 1.0mL 140min DIOL.met
Acquired: 01/03/2014 04:28:59
Printed: 01/03/2014 08:07:41

<table>
<thead>
<tr>
<th>UV Results</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area %</th>
<th>Height</th>
<th>Height %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>123.603</td>
<td>462058207</td>
<td>85.65</td>
<td>1167354</td>
<td>87.78</td>
</tr>
<tr>
<td></td>
<td>146.573</td>
<td>77404027</td>
<td>14.35</td>
<td>162440</td>
<td>12.22</td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td>539462234</td>
<td>100.00</td>
<td>1329794</td>
<td>100.00</td>
</tr>
</tbody>
</table>
$^1$H NMR Comparison for Oxidation reaction using DDQ