NEW GREEN TECHNOLOGIES FOR ORGANOCATALYTIC ASYMMETRIC EPOXIDATION APPLICATIONS IN SYNTHESIS

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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.

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ABSTRACT

New Green Technologies for Organocatalytic Asymmetric Epoxidation Applications in Synthesis

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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 *ee*s 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.

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Abbreviation

Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
AIBN	azobis(isobutyronitrile)
ANDA	abbreviated new drug application
aq	aqueous
Ar	argon gas
BPh_4^-	tetraphenylborate ion
Bz	benzoyl
BzCl	benzoyl chloride
CSA	camphorsulfonic acid
DBU	1, 8-diazabicycloundec-7-ene
DCM	dichloromethane
DDQ	2, 3-dichloro-5, 6-dicyanobenzoquinone
DET	diethyl tartrate
DIPT	diisopropyl tartrate
DMAP	(*N*,*N*)-dimethylaminopyridine
DMDO	dimethyldioxirane
DNA	deoxyribonucleic acid
ee	enantiomeric excess
equiv	equivalent

er	enantiomeric ratio
Et_2O	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

NBS	*N*-bromosuccinimide
NDA	new drug application
NMR	nuclear magnetic resonance
o-	*ortho*-
p-	*para*-
p-TsOH	*para*-toluenesulfonic acid
$PhB(OH)_2$	phenylboronic acid
PMC	2,2,5,7,8-pentamethyl-6-hydroxychroman
RBF	round bottom flask
rt	room temperature
SUPAC	scale-up and post-approval changes
TBARS	thiobarbituric acid-reactive substance
TBS	*tert*-butyldimethylsilyl
TBHP	*tert*-butyl hydroperoxide
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
Ti	titanium
Ti (O-*i*-Pr)$_4$	titanium tetra-isopropoxide
TLC	thin layer chromatography
TMHQ	trimethylhydroquinone
TMS	tetramethylsilane

TPPP	tetraphenylphosphonium monoperoxysulfate
TRF	tocotrienol-rich-fraction

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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® 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.

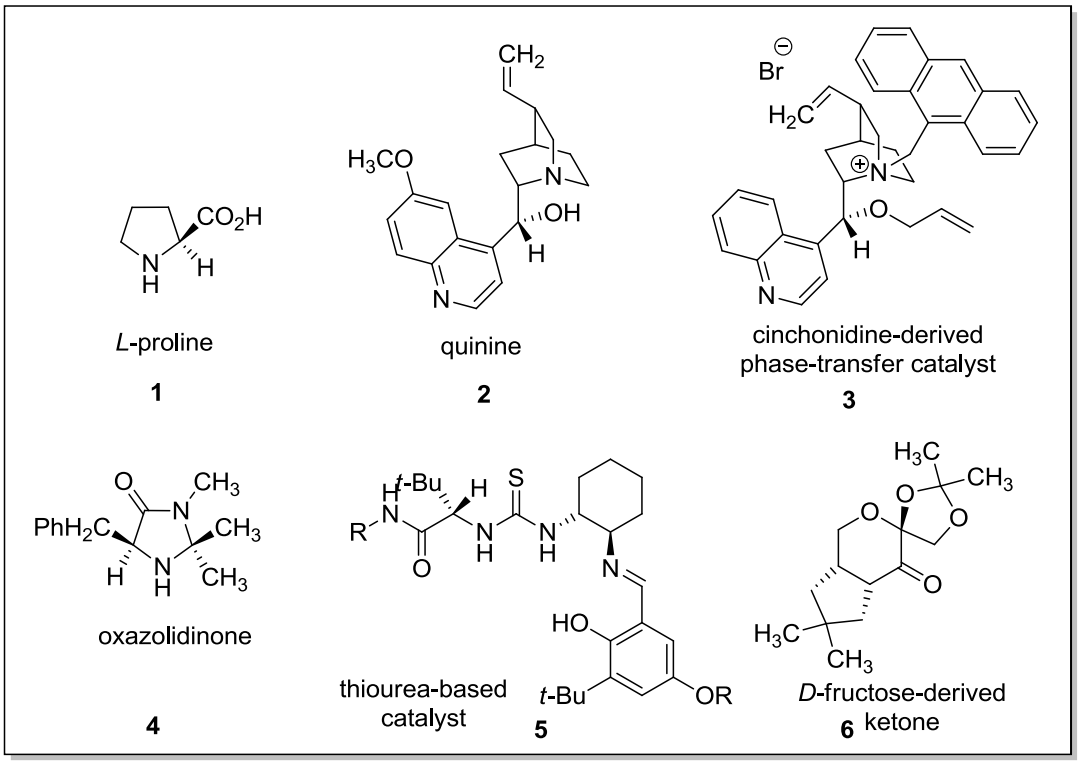
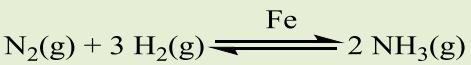
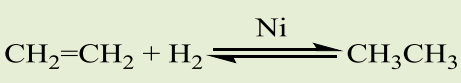
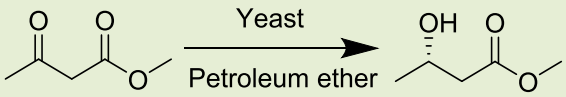
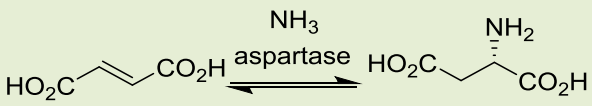


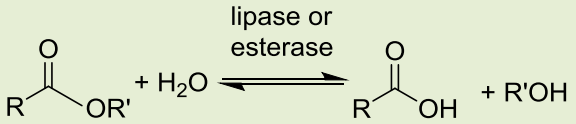
Figure 1.1 - Some typical organocatalysts

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.[7–9] In 2001, List reported efficient proline-catalysed Michael additions of unmodified ketones to nitro olefins with moderate *ee* values.[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[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.[12]

Table 1-1 - Examples of simple well-established metal-based catalysis process and biocatalysis reactions

Metal-based Catalysis	**Biocatalysis**
(1) **Iron in the Haber process**[13]  (2) **Nickel in the hydrogenation of C=C bonds**  (3) **Vanadium(V) oxide in the Contact Process**[14]	(1) Enantioselective reduction of ketone by yeast  (2) Lyases – addition-elimination on C=C, C=N, C=O bonds  (3) Hydrolases – formation/breakdown of

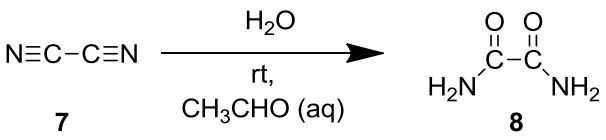
$2SO_2(g) + O_2(g) \rightleftharpoons[V_2O_5]{} 2SO_3(g)$	esters, amides, lactones, etc. 

1.2.1 Asymmetric Organocatalysis

Asymmetric organocatalysis, in which a chiral organic molecule catalyses an enantioselective transformation, is a rapidly growing field.[3] A collection of chiral organocatalysts have been involved in asymmetric synthesis, such as the typical examples of proline, cinchona alkaloids, such as quinine **2** and various sugar-, amino acid-, or peptide-derived compounds. Although the first examples were reported many decades ago,[15,16] 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.[6] In 1871, the first "pure" organocatalytic reaction was discovered accidentally, with the transformation of dicyan **7** to oxamide **8** 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.[3]



Scheme 1-1 - von Liebig's oxamide synthesis

1.2.1.1.1 Cinchona Alkaloids

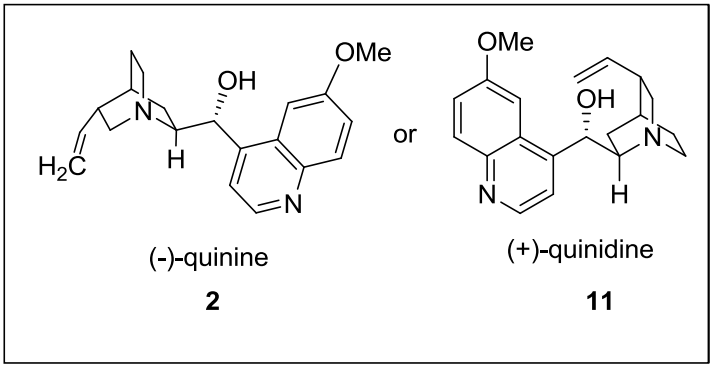
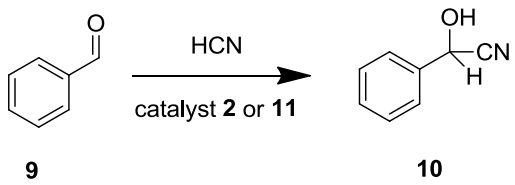


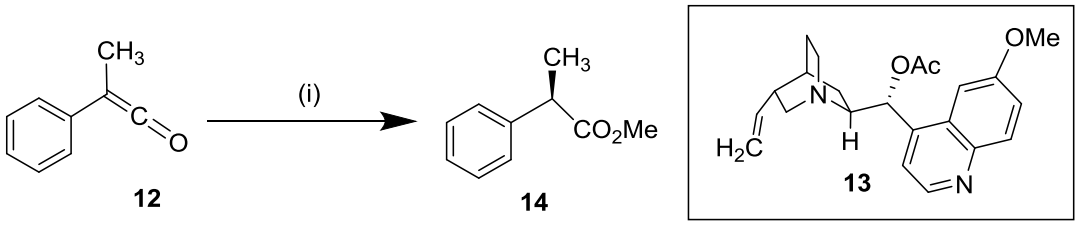
Figure 1.2 - Structure of (–)-quinine **2** and (+)-quinidine **11**

In the beginning of the 20th century, the use of small organic molecules as catalysts in chemical transformations was reported by G. Bredig.[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

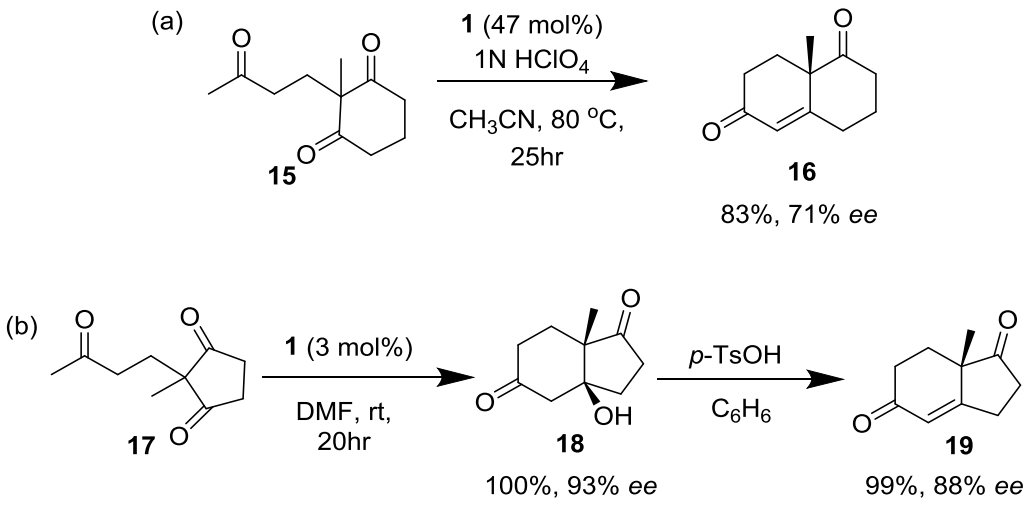
Later, after a century of transition from achiral to asymmetric organocatalytic reactions, in 1960, by using *O*-acetylquinine **13** as catalyst, (*R*)-phenyl methylpropionate **14** was generated from methylphenyl ketene **12** with up to 74% *ee* (Scheme 1-3),[18] reported by Pracejus. This process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



Scheme 1-3 - Reagents and conditions: (i) Catalyst 13 (1 mol%), MeOH (1.1 equiv), toluene, –111 °C, 93% yield, 74% *ee*

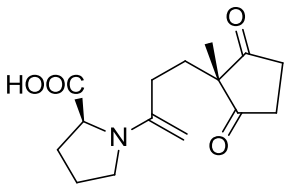
1.2.1.1.2 Proline

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).[15] 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 *ee*s for both steps (Scheme 1-4b).[19]



Scheme 1-4 - The Hajos-Parrish-Eder-Sauer-Wiechert reaction; (a) acid co-catalysed isolation of the cyclized aldol condensation product by Eder, Sauer and Wiechert in 1971[19] and (b) intramolecular aldol reaction of achiral triketones by Hajos and Parrish in 1974.[15]

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.[15] Subsequent investigation by Agami *et al.* led to the proposed mechanism involving formation of enamine intermediate **20** (Figure 1.3)[20] which then has been confirmed by mechanistic study as reported by Barbas.[21] *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.

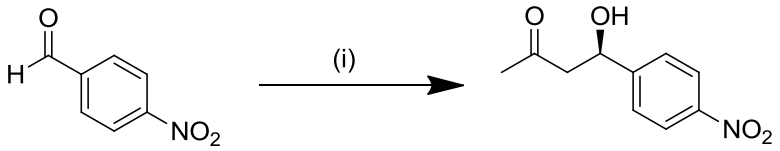


20

Figure 1.3 - Enamine intermediate 20

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.[22]

List, Lerner and Barbas have reported a direct intermolecular aldol reaction between unmodified acetone and a variety of aldehydes (Scheme 1-5).[23] 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.[24]



Scheme 1-5 - Reagents & conditions: (i) Acetone (20 vol%), proline 1 (30 mol%), DMSO, rt, 4 h, 68% yield, 76% *ee*[23]

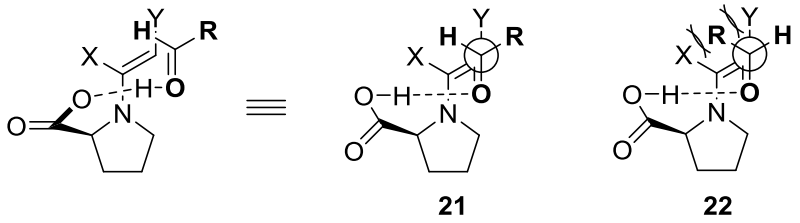


Figure 1.4 - Proposed transition state of enamine intermediate[24]

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,[25–27] aziridination using bifunctional organocatalysis by Dixon,[28] alcoholysis by Schreiner[29] 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.

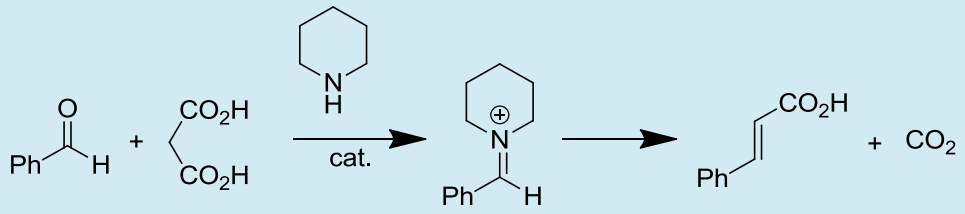
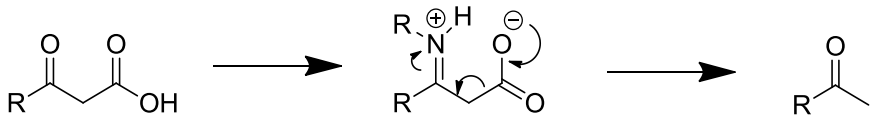
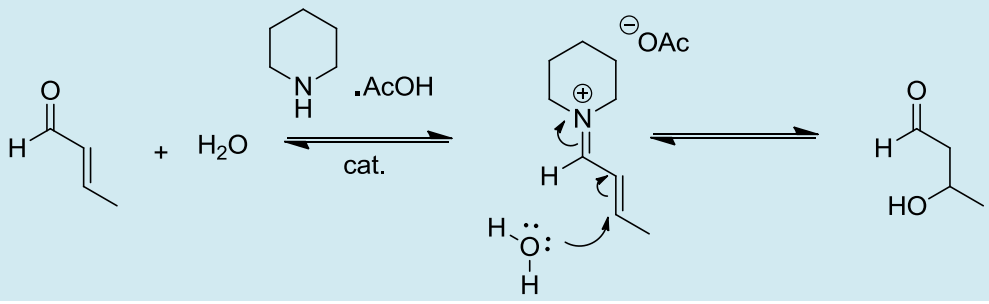
The iminium-activated reaction will be catalytic only if the amine catalyst is released in a final hydrolysis or elimination step. As an example, nucleophilic addition of hydride ion to the C=N double bond is the basis of reductive amination processes. These reactions proceed *via* iminium intermediates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

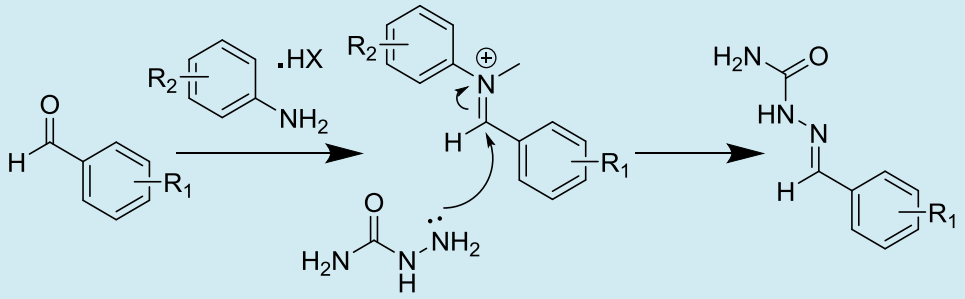
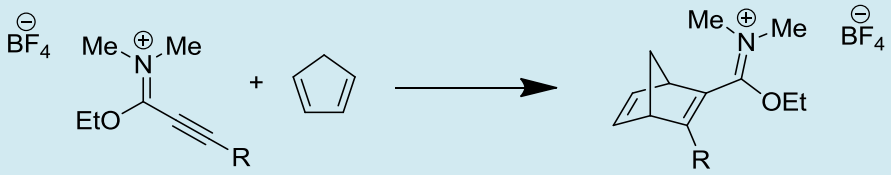
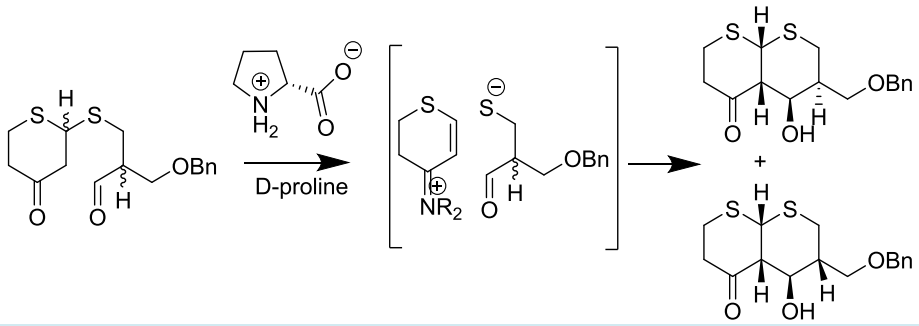
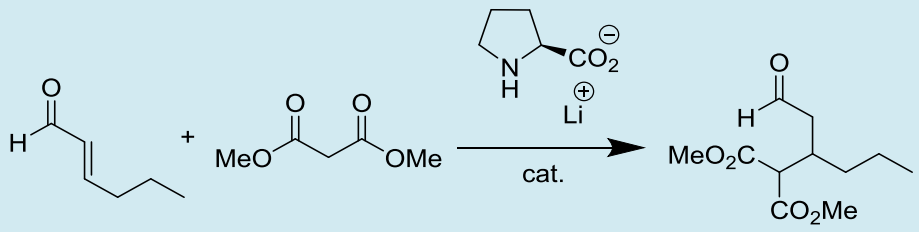
1.2.3.2 Historical Development of Iminium Catalysis

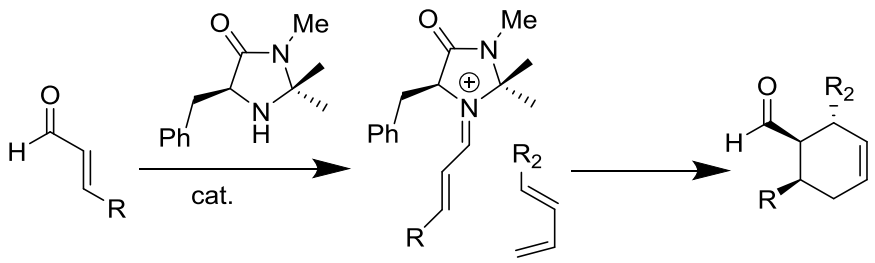
Iminium salt catalysts are Lewis base catalysts, which is one of the most powerful and general strategies of organocatalysis.[2] The historical development of the introduction of the concept of iminium catalysis is quite unclear. Knoevenagel condensation is probably the earliest recorded example of an 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.[30] 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,[31] and twenty years later, kinetic evidence for imine/iminium intermediates in Knoevenagel-type condensations was presented by Crowell and Peck.[32] Today, the contribution of iminium catalysis to the Knoevenagel reaction is generally recognised.

The decarboxylation of β-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.[33] In 1933, Pederson also suggested the iminium ion as intermediate in the decarboxylation reaction.[34]

Table 1-2 – Summary of iminium catalysis development history[35]

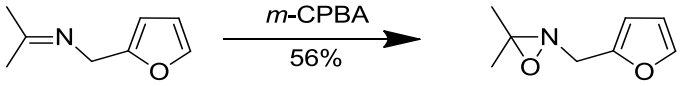
Year	
1894 – 1898	Knoevenagel discovers a family of iminium-catalysed condensation reactions: 
1907	β-decarboxylation reactions discovered by Pollak and he suggested imine as intermediate 
1931	Blanchard suggested positive ion catalysis in Knoevenagel reaction[31]
1934	Pederson proposes the intermediacy of iminium ions as intermediates in the decarboxylation reaction[34]
1937	Langenback discovers the first iminium-catalysed conjugate addition 

1953	Crowell and Peck showed kinetic evidence for a Schiff base intermediate in the Knoevenagel condensation[32]
1962	Jencks discovers aniline catalysis of semicarbazone formation 
1976	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.
1976	The role of iminium activation in cycloadditions recognised by Viehe and Baum 
1981	Woodward and co-workers use asymmetric proline catalysis to effect an iminium-catalysed deracemization and intramolecular aldol reaction in the total synthesis of erythromycin 
1991	The first catalytic asymmetric iminium-catalysed conjugate addition reactions discovered by Yamaguchi 

2000	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 peroxy 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.[36] 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.

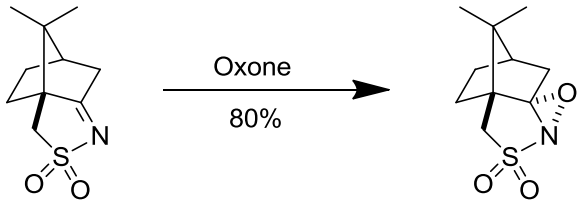


Scheme 1-6 - Preparation of oxaziridine using *m*-CPBA[37]

Oxaziridines were first discovered in 1956 by Emmons.[38] Since the first discovery of this structure, it has received an enormous attention from researchers[39] – 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.[40] 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.

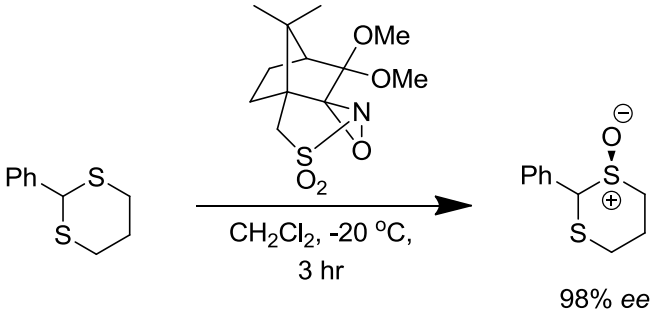
Chiral oxaziridine reagents were also developed later, which allow for stereospecific transfer of heteroatoms. Oxaziridines are unique in their exceptionally high inversion barrier for nitrogen to retain its stereochemical configuration. Chiral (camphorsulfonyl)oxaziridines **24**, first synthesized in 1988 by Davis have become a cornerstone in asymmetric synthesis (Scheme 1-7)[41] which were reported to oxidize non-functionalized sulfides giving up to 91% *ee*,[42] and to epoxidize olefins (up to 65% *ee*).[43] He first reported the epoxidation of olefins by oxaziridines back in 1981.[44]



23 **24**

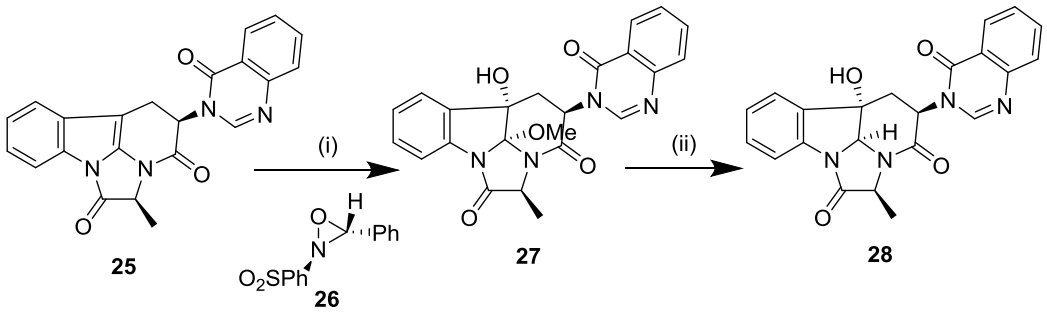
Scheme 1-7 - First chiral (camphorsulfonyl)oxaziridine by Davis[41]

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).[45]



Scheme 1-8 - Page oxaziridine system for oxidation of sulfide[45]

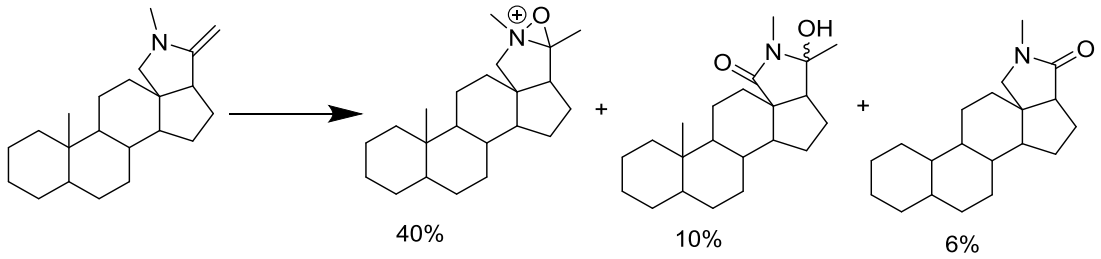
Application of oxygen transfer using oxaziridine system in total synthesis has been proved to be a success following a report by Papeo in 2009. Papeo *et al.* reported high selectivity of oxygen transfer by oxaziridine in the total synthesis of (–)-chaetominine **28**. Oxidation of the double bond on the pyrrole ring of the tetracyclic intermediate **25** was achieved using oxaziridine **26** (Scheme 1-9) giving only one *cis*-diastereoisomer **27**.[46]



Scheme 1-9 - Reagents and conditions: (i) **26** (1.1 equiv), CH_2Cl_2/MeOH 2:1, rt, 50%; (ii) Et_3SiH, CH_2Cl_2, TFA, rt, 65%

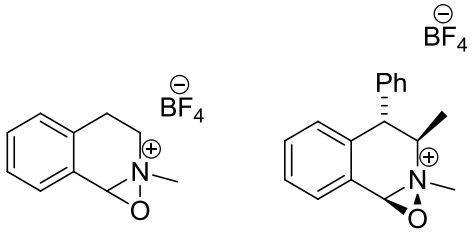
Oxaziridinium ions are the derivative of the oxaziridine with positively charged nitrogen. Oxaziridinium salts, a related electrophilic oxygen source were first reported in 1976 by Lusinchi and Hanquet as reactive intermediates for oxygen transfer to nucleophilic substrates, including sulphides and alkenes. 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.[47] Oxaziridinium salts have also been obtained

by either methylation of the corresponding oxaziridine with FSO_3Me or oxidation of the corresponding iminium salt with peracid (Scheme 1-10).[48,49] The steroidal pyrrolinic immonium salt plays a vital role in oxidation of peracid.



Scheme 1-10 - Initial approach by Hanquet

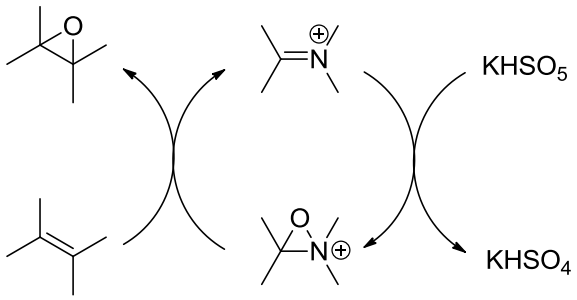
It was, however, not until some eleven years later that a second, racemic, oxaziridinium salt **29** (Figure 1.5) was derived from dihydroisoquinolinium reported by Hanquet and his co-workers. This second oxaziridinium salt was prepared by alkylation of an oxaziridine and by oxidation of the iminium salt.[50,51] In 1988, Hanquet and co-workers reported that this oxaziridinium salt can efficiently epoxidize various olefins.[47,51] 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_3CN-H_2O or *m*-CPBA- $NaHCO_3$ in CH_2Cl_2 as oxidant.



29 **30**

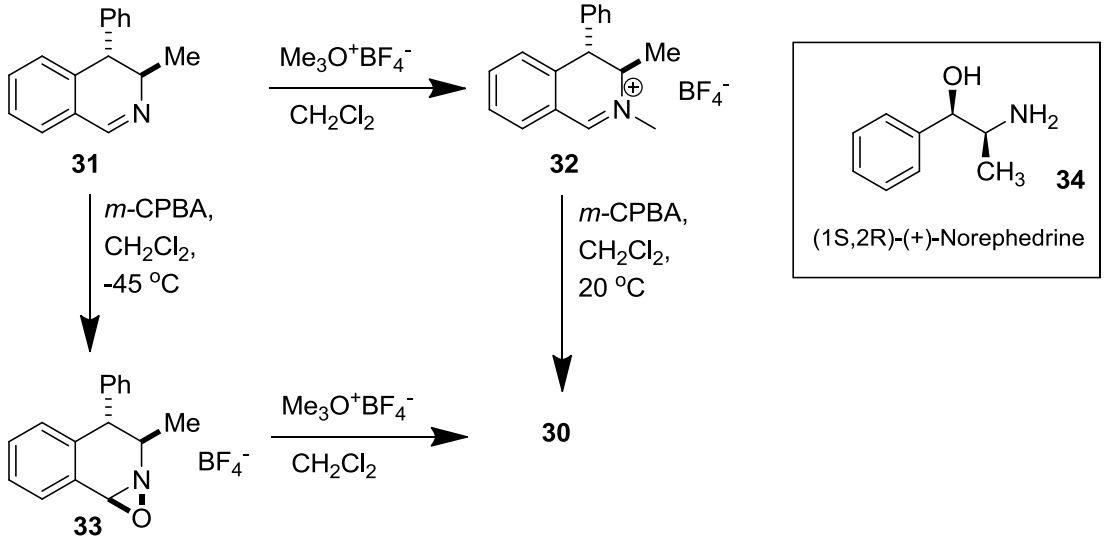
Figure 1.5 - Compound **29**, second oxaziridinium salt by Hanquet in 1987;[50] compound **30**, first enantiomerically pure chiral oxaziridinium salt by Lusinchi in 1993[52]

A reaction pathway for iminium salt-catalysed epoxidation is shown in Scheme 1-11. The iminium salt catalyst is regenerated upon epoxidation of olefin.



Scheme 1-11 - Catalytic cycle for iminium salt-catalysed epoxidation by using Oxone® as oxidant[53]

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 enantiomercially pure chiral oxaziridinium salt was derived from (1*S*, 2*R*)-(+)-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 *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.[52]



Scheme 1-12 - Synthesis of oxaziridinium salt 30 by Lusinchi's group[52]

Since then, iminium salt catalysis has become a significant interest to be developed for epoxidation for olefins.[54] 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.[53–55]

In 1996, Aggarwal developed binaphthyl-derived oxaziridinium system for asymmetric epoxidation giving *ee* as high as 71% using 1-phenylcyclohexene as substrate.[56] Armstrong *et al.* reported intramolecular epoxidation using unsaturated oxaziridines, presumably *via* oxaziridinium salts[57] and previously reported iminium salts derived from pyrrolidine for alkene epoxidation.[58]

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.[59,60] We then included biphenyl-derived[61] and binaphthyl-derived[62] iminium salt to investigate the system further.

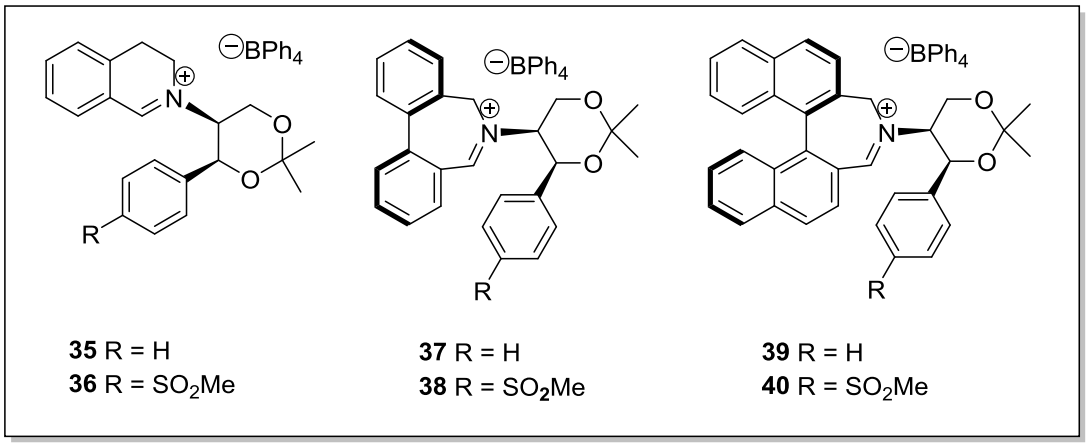


Figure 1.6 - Iminium salts developed in Page's group

In 2000, Rozwadowska and co-workers reported the synthesis of the single enantiomer of iminium salt **41**, derived from thiomicamine **42** (Figure 1.7).[63]

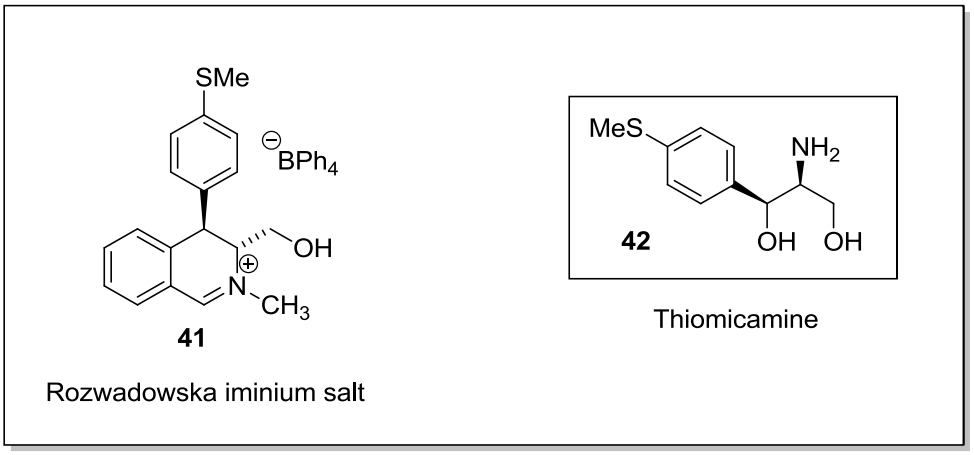


Figure 1.7 - Rozwadowska iminium salt derived from thiomicamine **42**

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.[64] 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.

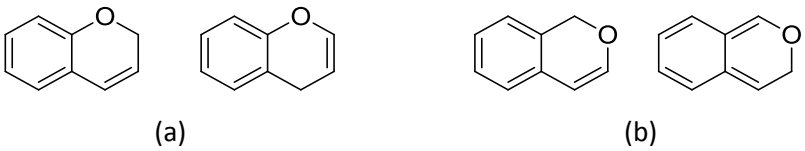
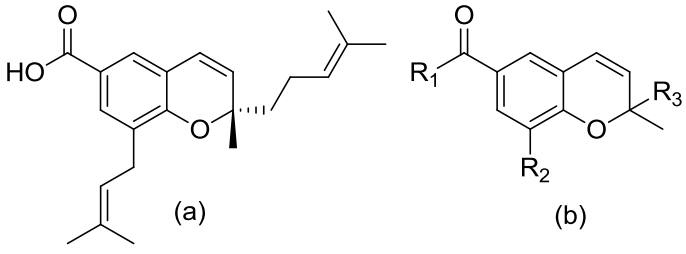


Figure 1.8 - (a) Structural isomers of chromene, left: 2*H*-chromene and right: 4*H*-chromene; (b) structural isomers of isochromene, left: 1*H*-isochromene and right: 3*H*-isochromene

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

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



	R_1	R_2	R_3
43	OH	H	CH_3
44	OCH_3	H	CH_3
45	OCH_3	OH	CH_3
46	OCH_3		CH_3

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

There are many 2*H*-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*,[65] 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.[66] These biologically active chromenes have also been shown to exhibit anti-fungal[67,68] and anti-tumour[69] properties. This core structure is also found in a number of flavonoids isolated from green tea extracts such as epigallocatechin-3-gallate **47** (EGCG) and catechin **48** (Figure 1.10).

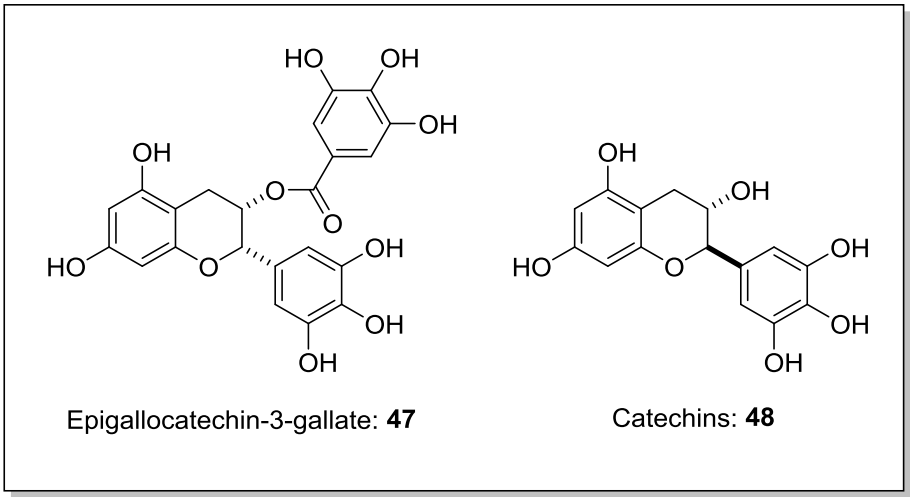


Figure 1.10 – Flavonoids extracted from green tea

1.3.2 Properties of 2*H*-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 **49**, and BRL 55834, **50** (Figure 1.11).[70] 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.[64] 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,[71] suggesting the importance of 2*H*-chromenes in natural product synthesis.

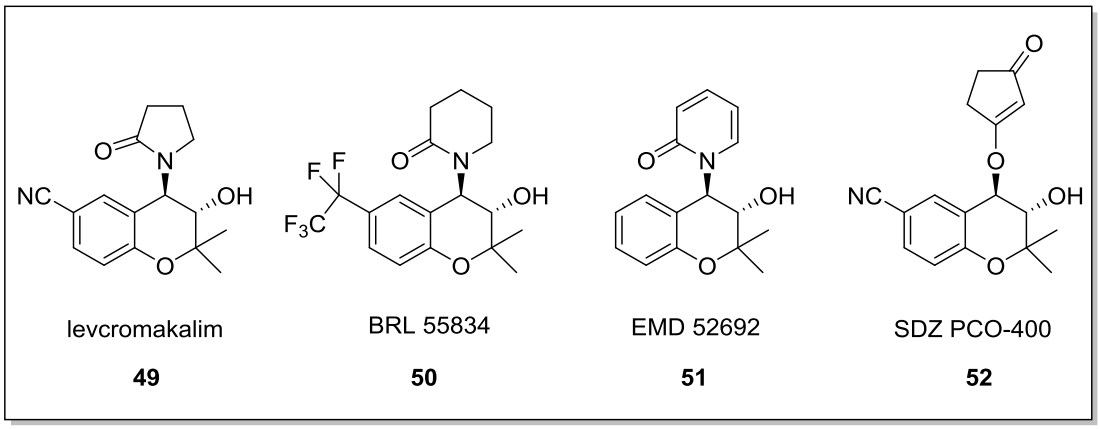


Figure 1.11 - Examples of potassium channel activator with chromane structure

Isoflav-3-enes bearing containing chromene units are featured in well-known oestrogens – morpholino- **53** and piperidinylisoflav-3-enes **54** (Figure 1.12).[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.[73] Another remarkable property is as an anti-juvenile hormone in insects shown by compounds like precocene I **55** and precocene II **56** (Figure 1.12) that have been isolated from plants.[74–76]

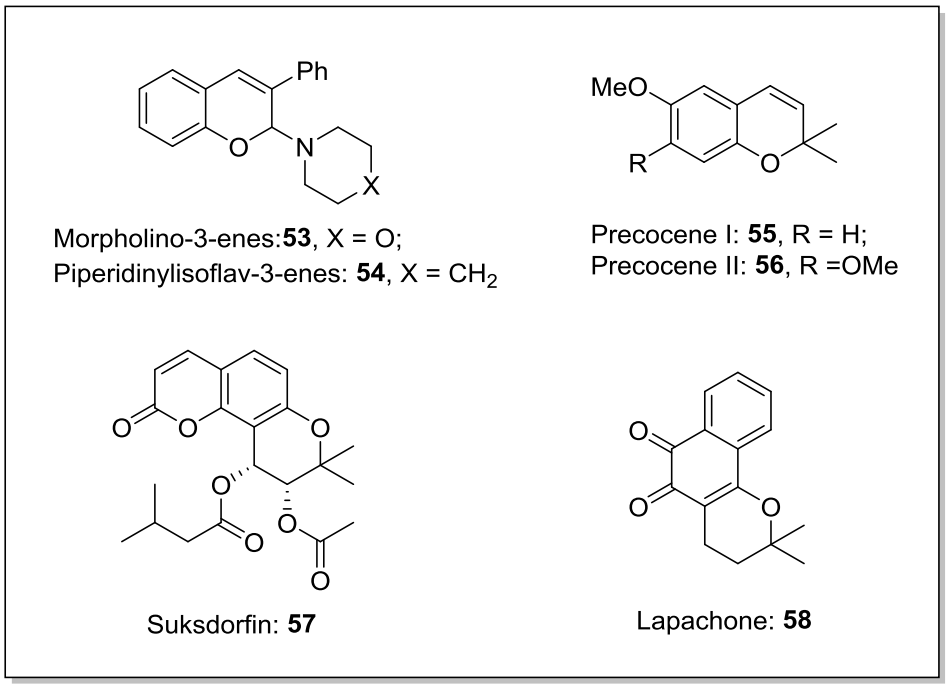
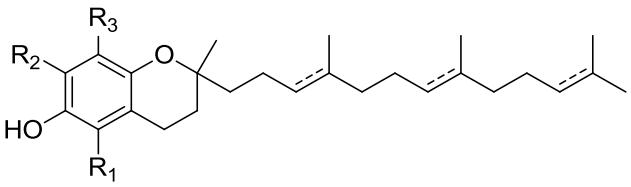


Figure 1.12 - Several chromene examples from natural product

The chromane ring can also be found in vitamin E constituents, tocopherols and tocotrienols. The basic chemical structure of tocopherol has a long phytyl chain attached at the 2-position of the chromane ring, while tocotrienols differ from tocopherols by the presence of three *E* double bonds in the phytyl tail. Moreover, the tocopherols and tocotrienols have α, β, γ, and δ forms, named on the basis of the number and position of the methyl groups on the chromane ring (Figure 1.13).



	R_1	R_2	R_3
α	CH_3	CH_3	CH_3
β	CH_3	H	CH_3
δ	H	H	CH_3
γ	H	CH_3	CH_3

Figure 1.13 - Vitamin E constituents

Vitamin E exerts important functions in anti-oxidative defence in mammalian cells.[77] Extensive investigations have been carried out on α-tocopherol and its model compound 2,2,5,7,8-pentamethylchroman-6-ol due to the chemical oxidant activity shown by the former.[78] One of the vitamin E derivatives developed, α-tocopherol ether-linked acetic acid (α-TEA), exhibits potent anticancer activity in a wide variety of epithelial cancer cell types[79] in combination with the cyclooxygenase-2 inhibitor celecoxib and the chemotherapeutic drug 9-nitro-camptothecin.[80]

In order to produce new derivatives, chemical modifications of vitamin E can occur at the following distinct regions of the molecule (Figure 1.14):[79] (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[81–83] while amides derived from α- and δ-tocopheramines have been reported to have improved anticancer activity.[81,84,85]

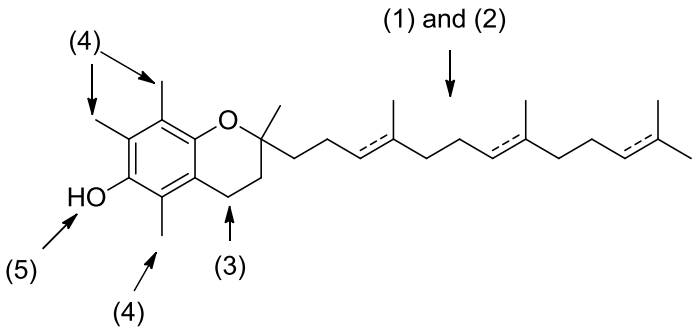
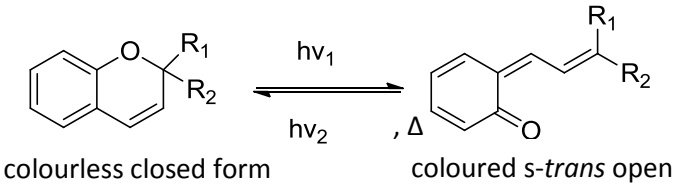


Figure 1.14 – Possible modification positions of vitamin E[79]

1.3.2.2 *Photochromism*[86,87]

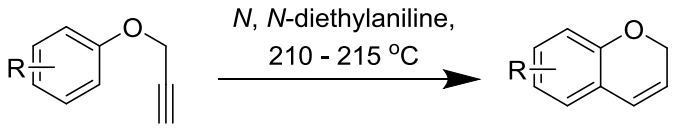


Scheme 1-13 - Photochromic activity[86]

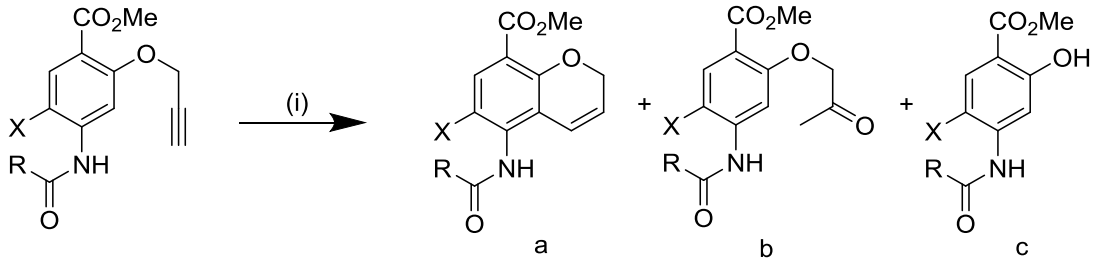
Photochromism is one of the properties of 2*H*-chromene that has drawn attention among scientists. The reversible action of rapid colour changing of a compound when irradiated with light containing ultraviolet rays such as sunlight or light of a fluorescent lamp, and resumption of the initial colour 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, *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*H*-Chromenes

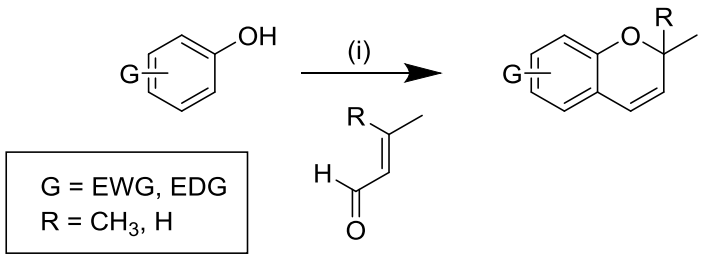
Due to these interesting properties of 2*H*-chromenes, many synthetic methods for their preparation have been introduced from various starting materials. These methods include rearrangement of propargyl phenol ethers by high temperature Claisen rearrangement (Scheme 1-14)[88–93] or recent reports of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



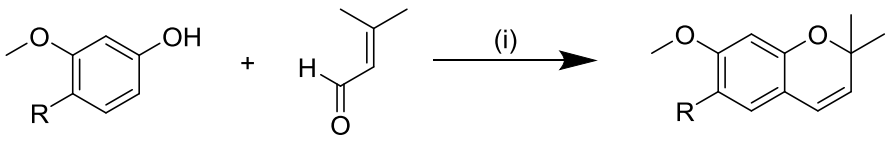
Scheme 1-14 - Thermal Claisen rearrangement of propargyl ether[93]



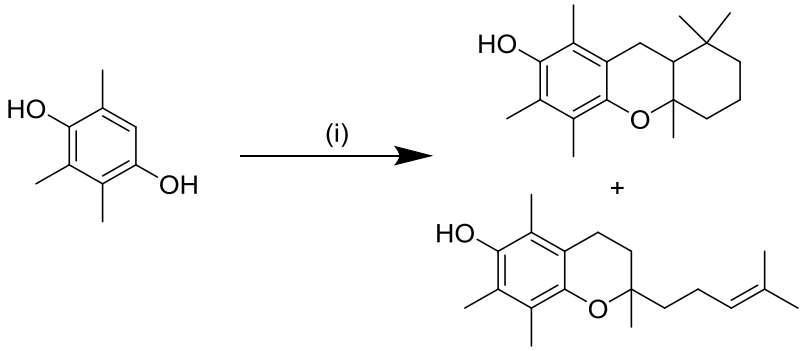
Scheme 1-15 - Reagents and conditions: (i) $(Ph_3P)AuNTf_2$ (0.1 m0l%), toluene, 85 °C, 2 h, HPLC ratio of a/b/c: 94.0/2.3/0.9[94]



Scheme 1-16 - Reagents and conditions: (i) $PhB(OH)_2$: HOAc (1:88), toluene, reflux[95]

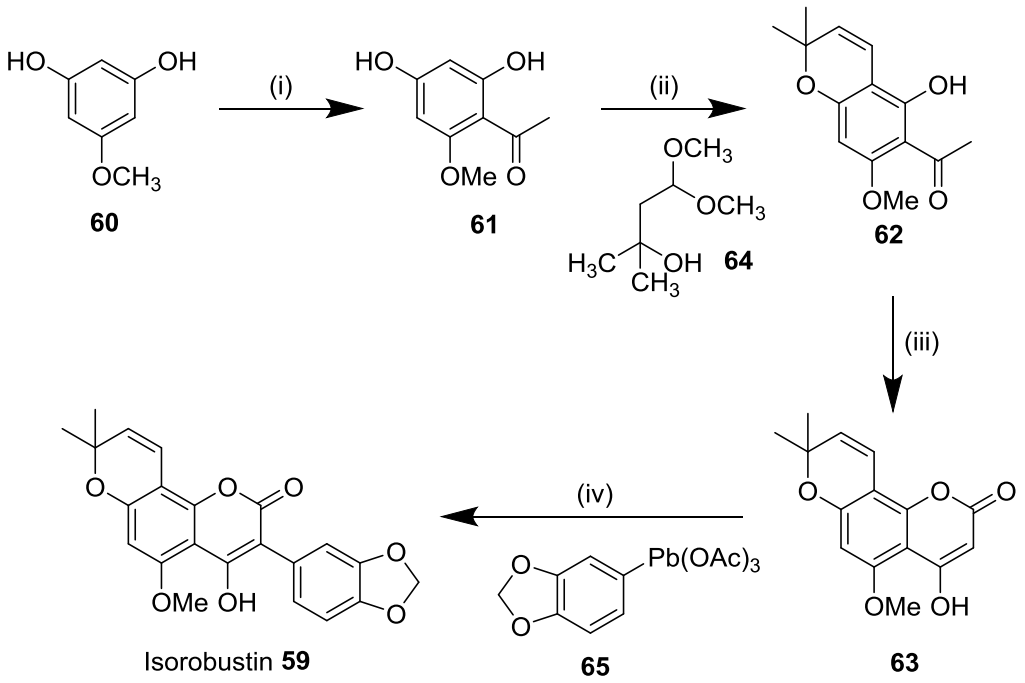


Scheme 1-17 - Reagents and conditions: (i) Pyridine, 140 °C, 2 h[96]



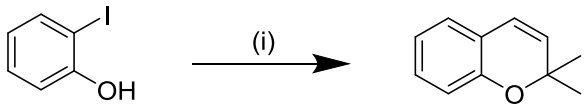
Scheme 1-18 - Reagents and conditions: (i) $BF_3(OEt)_2$ (50 mol%), geraniol (2 equiv), anhydrous benzene, reflux, 3 h[103]

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).[100]

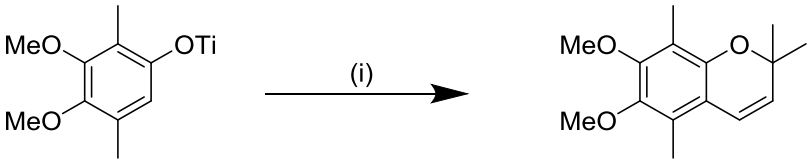


Scheme 1-19 - (i) CH_3CN, HCl, 73%; (ii) 64, pyridine, 170 °C, 10 h, 68%; (iii) NaH, $(EtO)_2CO$, reflux, 20 min, 81%; (iv) 65, anhydrous pyridine, anhydrous chloroform, 60 °C, 12 h, 84%[100]

Several metal-based methods have also been reported for the synthesis of chromene compounds such as palladium-catalysis (Scheme 1-20),[107] and metal-phenoxide (Scheme 1-21),[108] as a few examples.



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%[107]



Scheme 1-21 - 3-Methyl-2-butenal (1.5 equiv), reflux, 8 h, 81%[98]

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.

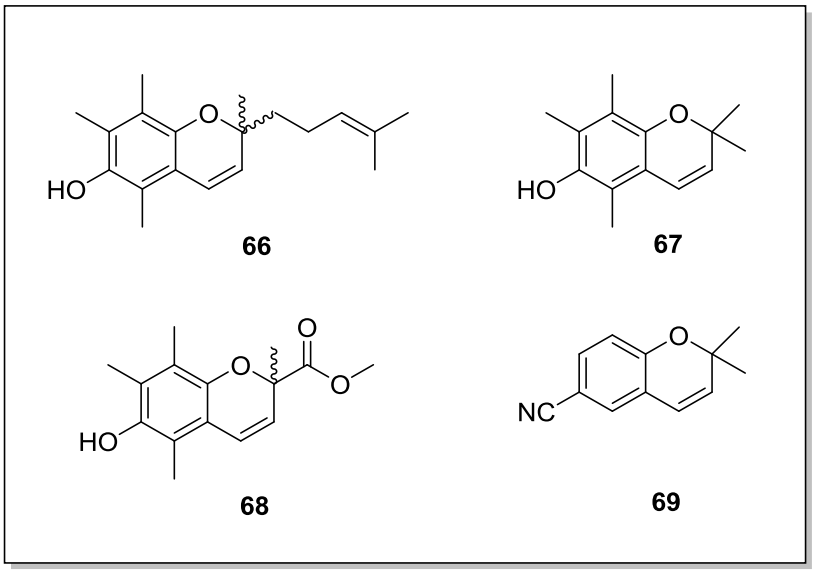
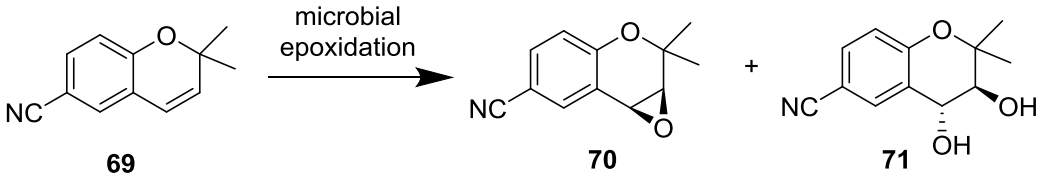


Figure 1.15 - Chromene substrates synthesized in this research

1.3.4 Asymmetric Epoxidation of Chromene

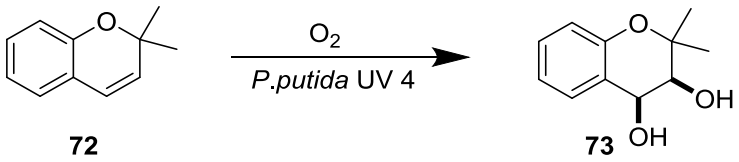
The functionalization of the double bond on the pyran ring of the chromene had been reported previously using both chemical and bio-transformations.[75,76,109] Such pyran olefins are readily modified by hydrogenation,[110] epoxidation,[76,111,112] and dihydroxylation,[76] giving rise to a large number of biologically active compounds, well-known examples of which include the ATP-dependent potassium channel activator levcromakalim (**49**, Figure 1.11), the anti-HIV agent suksdorfin **57**,[113] and the breast cancer cell inhibitor natural product β-lapachone (**58**, Figure 1.12).[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 *Mortierella ramanniana* SC 13840 to give a mixture of epoxide **70** and (+)-*trans*-diol **71** (Scheme 1-22).[109]



Scheme 1-22 - Microbial epoxidation of **69**

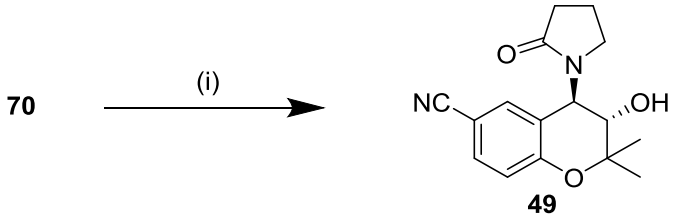
Another example is asymmetric dihydroxylation of chromene **72** by using the soil bacterium *Pseudomonas putida* to give enantiopure *cis*-diol **73** in as high as 98% *ee* (Scheme 1-23). This enzyme-catalysed method of asymmetric dihydroxylation may be regarded as complementary to the developed chemical 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.



Scheme 1-23 - Asymmetric dihydroxylation of **72**

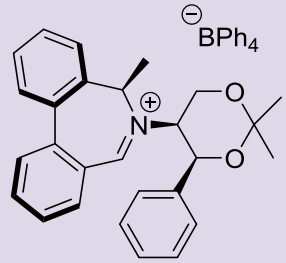
In our group we have also demonstrated the asymmetric epoxidation reaction on several chromenes plus recent investigations of kinetic resolution in 2-monosubstituted chromenes.[115] Page has reported several synthesis of natural products containing a chromene ring, including levcromakalim **49**,[116] (–)-(3'*S*)-lomatin **75**,[117] (+)-(3'*S*, 4'*R*)-*trans*-khellactone **76**, and (+)-scuteflorin A **80**.[118]

The synthesis of levcromakalim **49** was achieved *via* its epoxide **70** using our iminium salt catalysts to afford *ee* as high as 98% (Table 1-3).[112,116] The corresponding (*S*, *S*)-epoxide **70** was then treated with pyrrolidin-2-one using the conditions described by Evans to afford the (–)-(3*S*, 4*R*) enantiomer of **49** in 52% yield (Scheme 1-24).[92]



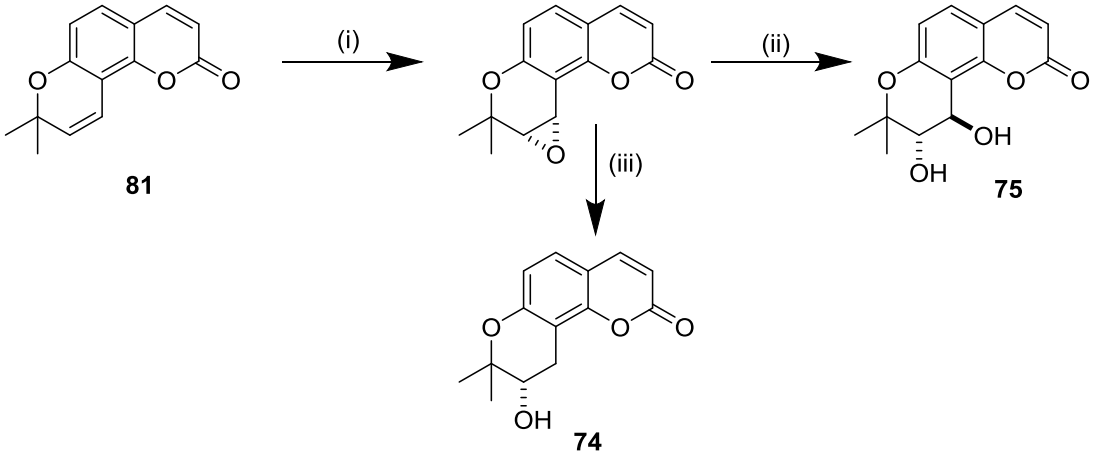
Scheme 1-24 - Reagents and condition: (i) pyrrolidin-2-one, NaH, DMSO, rt, 4 h, 52%

Table 1-3 - Asymmetric epoxidation of chromene **69**[a]

Iminium Salt Catalyst	Conversion/ %[b]	Reaction time/h	Yield/ %	*ee*/%[c]	Configuration[d]
36[116]	–	24[e]	59	97	(–)-1*S*, 2*S*
37[112]	90	20	–	97	(–)-1*S*, 2*S*
 **74**[112]	100	48	–	98	(–)-1*S*, 2*S*

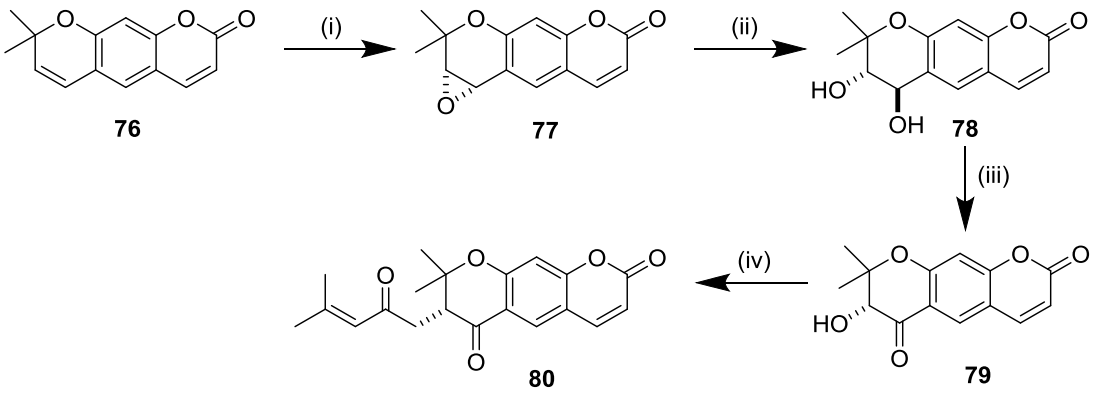
[a]Epoxidation conditions: iminium salt catalyst (10 mol%), TPPP (2 equiv), $CHCl_3$, 0 °C. [b]Conversions were evaluated from the ^1H NMR spectra by integration of the alkene and epoxide signals. [c]*ee* was determined using chiral HPLC using a Chiracel OD-H column. [d]Absolute configurations of the major enantiomers were determined by comparison of optical rotation with those reported in the literature. [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[102] and could also be achieved using microwave irradiation in neat 3-picoline, affording 94% yield.[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'*S*)-lomatin **74** was achieved by reductive cleavage with $NaBH_3CN$ at 0 °C in 92% yield and 97% *ee*. Acid-catalysed ring opening of the chiral epoxide yielded (+)-(3'*S*, 4'*R*)-*trans*-khellactone **75** in 95% yield (Scheme 1-25).[117]



Scheme 1-25 - Reagents and conditions: (i) TPPP (2 equiv), catalyst **36** (10 mol%), $CHCl_3$, 24 h, –30 °C, 65%; (ii) 1 M H_2SO_4 (5.5 equiv), acetone (1:2 ratio), rt, 1 h, 95%; (iii) $NaBH_3CN$ (1 equiv), BF_3OEt_2, THF, 0 °C, 0.5 h, 92%[117]

In 2012, Page reported the first enantioselective total synthesis of (+)-scuteflorin A **80** in very high *ee*, 97%, *via* (+)-*trans*-decursinol **78**.[118] The seven step synthesis of **80** started with the synthesis of xanthyletin **76** from 7-hydroxycoumarin using a method outlined by Ahluwalia,[90] 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).[118]



Scheme 1-26 - Reagents and conditions: (i) TPPP (2 equiv), catalyst **37** (10 mol%), $CHCl_3$, 30 h, –30 °C, 97%; (ii) acetone/1 M H_2SO_4 (2:1), rt, 10 min, 60%; (iii) DMP (1 equiv), $CHCl_3$, rt, 95%; (iv) 3, 3-dimethyl acrolyl chloride (5 equiv), $NaHCO_3$ (1.1 equiv), THF, rt[118]

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.[120] 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.[121] Stereochemistry involves diastereomers and enantiomers. Therefore 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.[122]

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:

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

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.[123] 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.[124,125] In addition, many biologically active compounds and natural products contain epoxide functionalities.[125,126] 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),[127] GABOB **82** (*γ*-amino-*β*-hydroxybutyric acid),[128]

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]

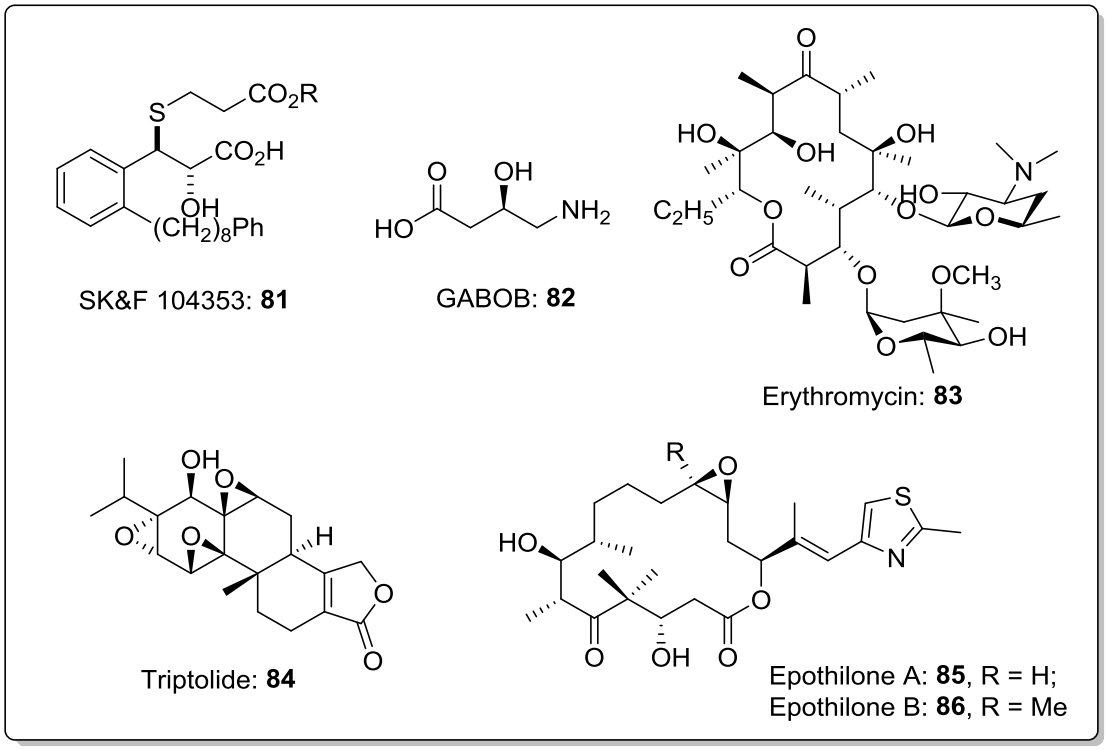


Figure 1.16 - Biologically active compounds with chiral epoxides as key intermediate

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.

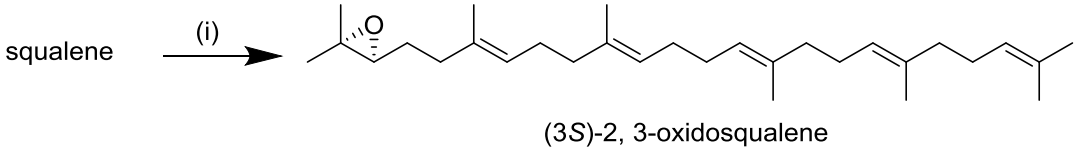
The highly effective system has been widely used in organic synthesis and has been the subject of several review articles.[123]

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*.[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

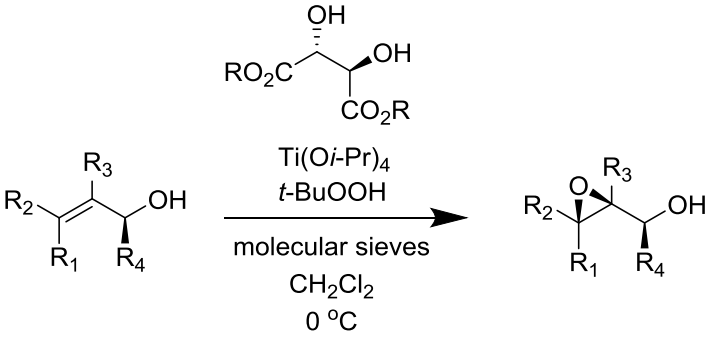
Metal-catalysed asymmetric epoxidation was first reported in 1979 by Otsuka. However, the *ee* was quite low (1 – 7%, in most cases) for unfunctionalized alkenes with *t*-BuOOH in the presence of Mo(IV) and optically active dialkyl tartrate esters, (+)-DIPT at 20 – 25 ^{o}C. This system was applied to the asymmetric synthesis of (3*S*)-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.[134]



Scheme 1-27 - Reagents and conditions: (i) $MoO_2(acac)_2$, *t*-BuOOH, (+)-DIPT, 31%, 14% *ee*[134]

1.4.4.1 Sharpless Epoxidation

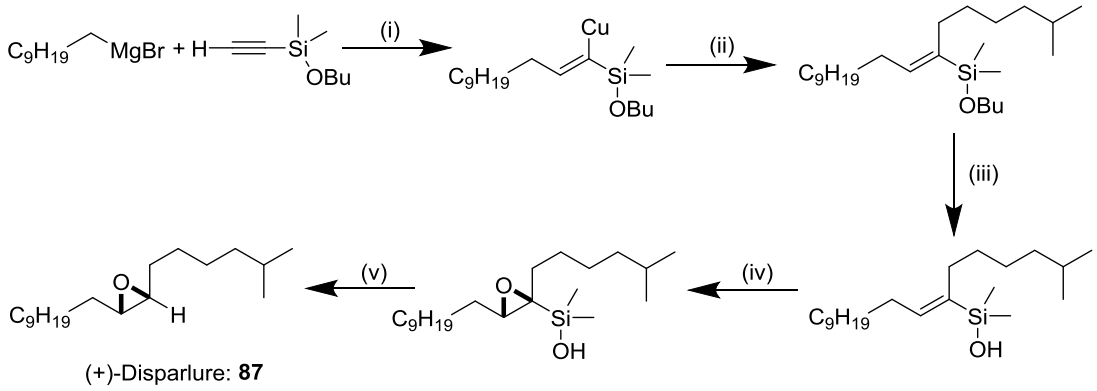
In 1980, a highly enantioselective epoxidation of allylic alcohols was reported by Katsuki and Sharpless. They successfully converted allylic alcohols into asymmetric epoxides in high chemical yields with more than 90% *ee*, under the catalysis of a transition metal catalyst titanium tetra(isopropoxide), $Ti(OPr^i)_4$ by using *t*-BuOOH as the oxidant with a chiral additive diethyl tartrate (DET) or diisopropyl tartrate (DIPT)(Scheme 1-28).[132,135,136]



Scheme 1-28 - Sharpless epoxidation[136]

The original Sharpless asymmetric epoxidation reaction requires large amount of $Ti(OPr^i)_4$, 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 3Å or 4Å molecular sieve dramatically reduced the requirement of Ti catalyst to a catalytic amount.[136] Since the discovery, the system has undergone rapid development.

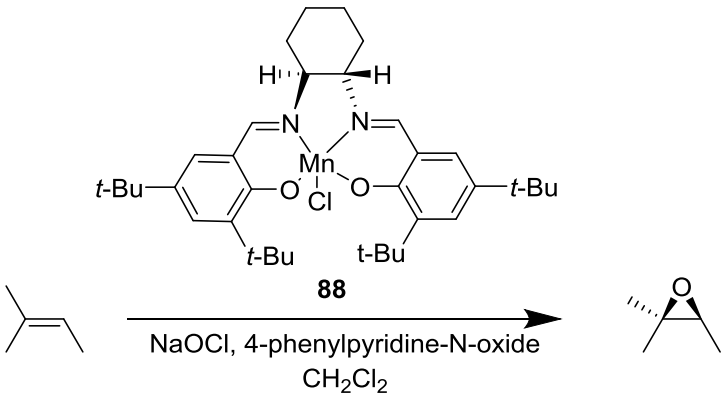
Epoxidation of a vinyl silanol under Sharpless condition with *t*-butyl hydroperoxide (*t*-BuOOH), Ti(O-*i*-Pr)$_4$ and (+)-diisopropyl tartrate (DIPT) in CH_2Cl_2 was applied to the enantioselective synthesis of (+)-disparlure **87** (Scheme 1-29), giving up to 52% *ee*.[130]



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_2Cl_2, –20 °C, 13 h, 67%; (v) F$^-$, 67%[130]

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

The influence of additives on the reaction rate, yield, and enantioselectivity of Jacobsen-Katsuki epoxidation was first proposed by Kochi[138] and was then further investigated.[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.[139,141,142]

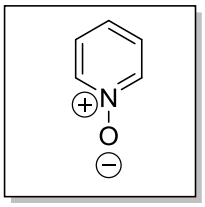
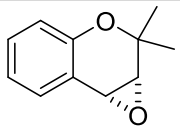
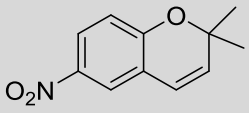
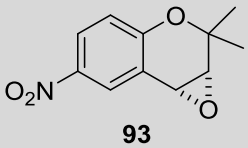
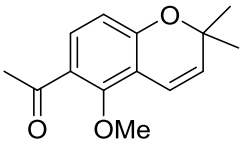
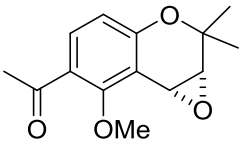
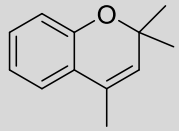
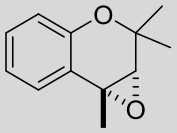
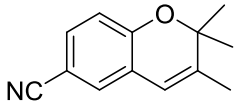
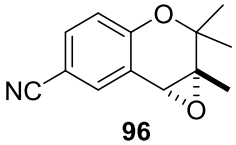


Figure 1.8 - Py-*N*-oxide

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**.[111]

Table 1-4 - Asymmetric epoxidation of chromene by Jacobsen[111]

Olefin	Major product	*ee*(%)	Isolated yield (%)	Absolute configuration
69	**70**	97	96	(+)-(3*R*, 4*R*)
72		98	87	(+)-(3*R*, 4*R*)
 **89**	 **93**	94	76	(+)-(3*R*, 4*R*)
 **90**	 **94**	98	75	(+)-(3*R*, 4*R*)

 **91**	 **95**	97	51	(+)-(3*R*, 4*R*)
 **92**	 **96**	>98	82	(+)-(3*R*, 4*R*)

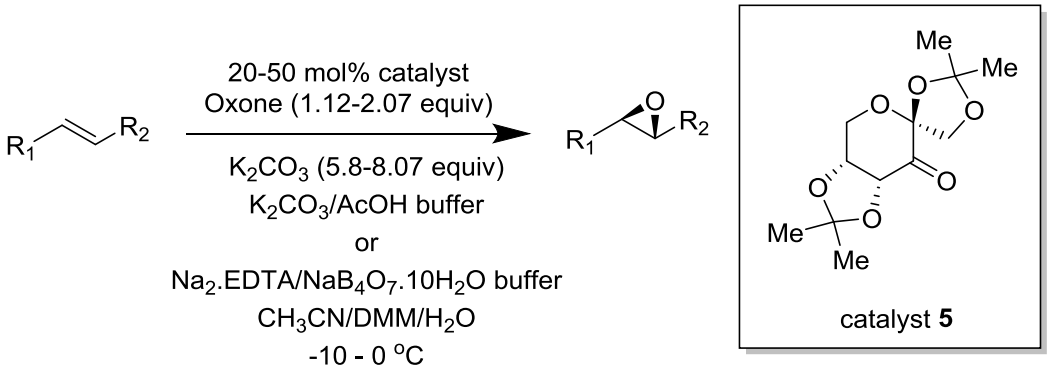
1.4.5 Organocatalysed Asymmetric Epoxidation

1.4.5.1 Dioxirane-Catalysed Epoxidations

Chiral dioxiranes are also promising reagents for asymmetric epoxidation reactions.[143] The first attempts to effect asymmetric epoxidation using chiral dioxiranes were reported by Curci *et al.* in 1984, giving *ee*s between 9 – 12.5%.[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.[145–147] Steric and electronic factors need to be considered to design efficient ketone catalysts as highlighted by Yang[146] to achieve good selectivity and reactivity.[143]

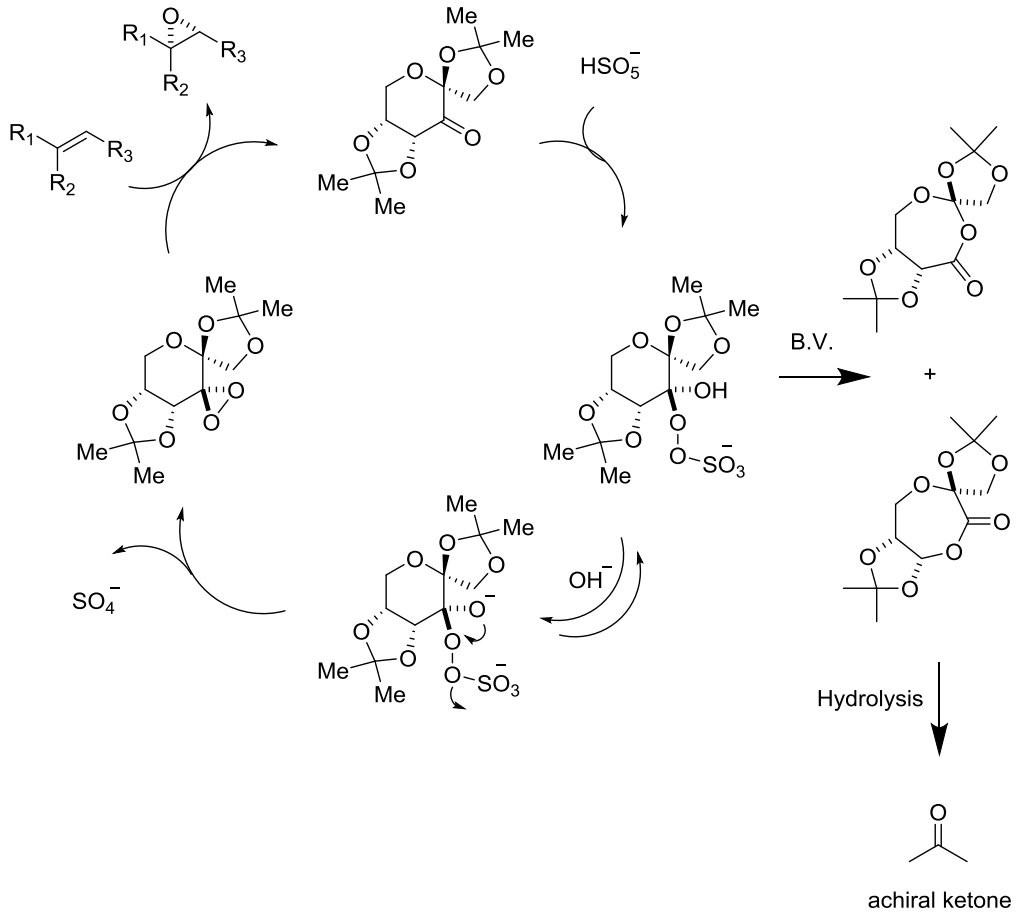
1.4.5.1.1 Shi Epoxidation

This catalyst was derived from D-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).[145]



Scheme 1-31 - Shi epoxidation

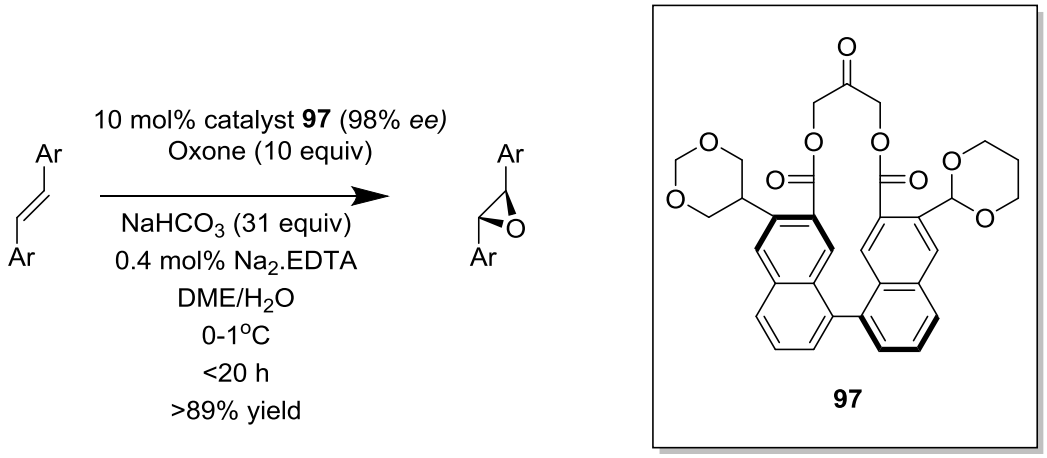
Due to rapid decomposition of the ketone at pH 7 – 8 involving Baeyer-Villiger reaction, the initial epoxidation procedure required excess catalyst (3 equiv). Shi subsequently showed that the catalytic efficiency of the ketone catalyst is highly pH dependent.[148] At pH 10, the conversion to epoxide 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.[143,148]



Scheme 1-32 - Shi epoxidation catalytic cycle[143]

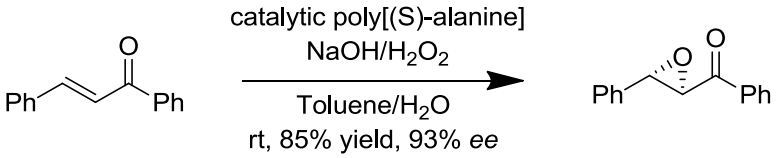
1.4.5.1.2 Yang Epoxidation

In 1996, Yang *et al.* successfully reported good enantioselectivity for epoxidation of *trans*-olefins and trisubstituted olefins by a C_2 symmetric chiral ketone **97** (10 mol%) using Oxone® as oxidant giving as high as 87% *ee*.[146,147,149] 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.[146]



1.4.5.2 Juliá-Colonna Epoxidation

In 1980, Juliá *et al.* reported the poly-L-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_2O_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® as the primary oxidant.

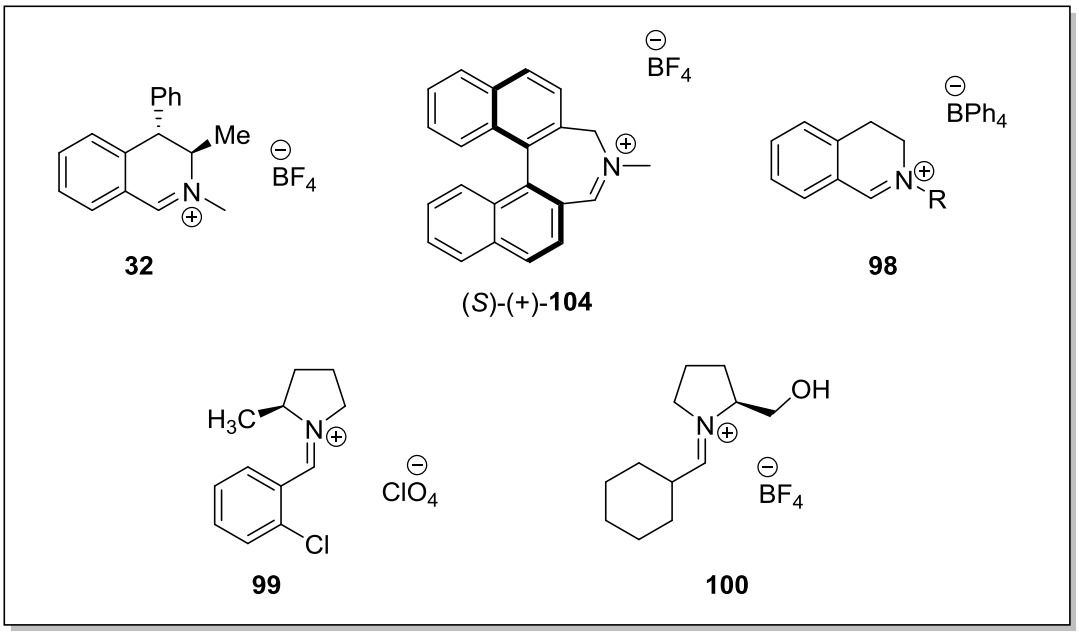
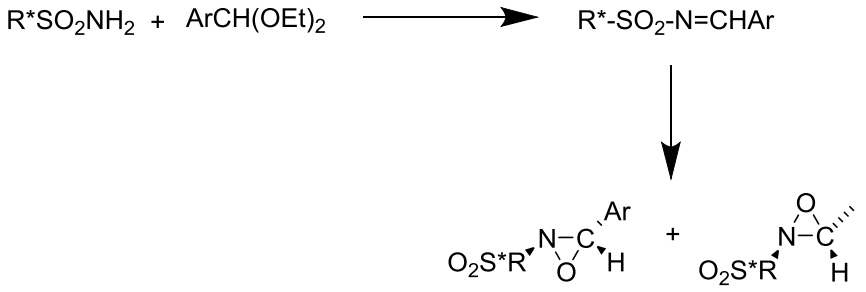


Figure 1.16 - Chiral iminium salts developed by several research groups[151]

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).[154]

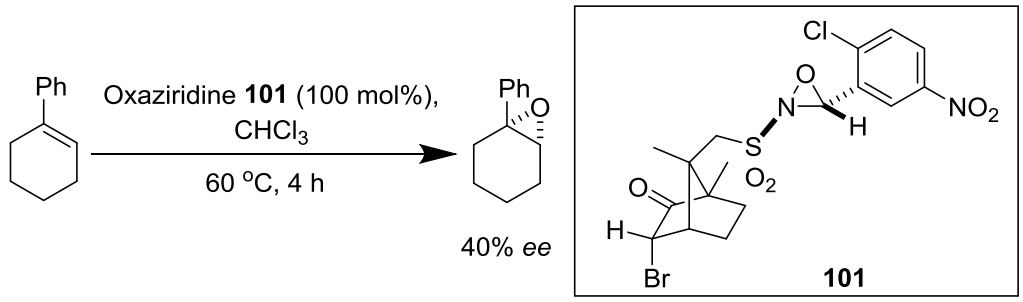
1.4.5.3.1 Davis Oxaziridines-mediated Epoxidation

Davis reported the first chiral oxaziridine **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).[155]



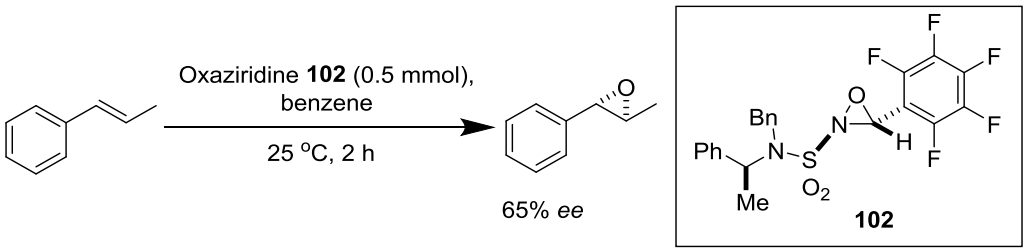
Scheme 1-33 - Synthesis of chiral oxaziridine by Davis[155]

However, the highest *ee* observed was only 40% for epoxidation of 1-phenylcyclohexene (Scheme 1-34).[156]



Scheme 1-34 - Davis's first chiral oxaziridine for asymmetric epoxidation[156]

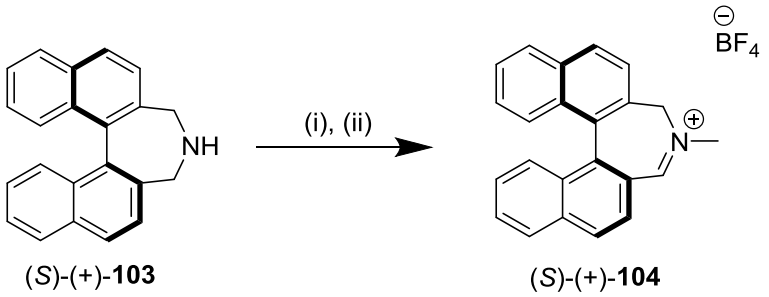
Further investigation by Davis using chiral sulfamyloxaziridines **102** then improved the enantioselectivity, giving up to 65% *ee* for asymmetric epoxidation of unfunctionalized alkenes (Scheme 1-35).[43]



Scheme 1-35 - Asymmetric epoxidation of unfunctionalised alkene using sulfamyloxaziridine[43]

1.4.5.3.2 Aggarwal's Epoxidation

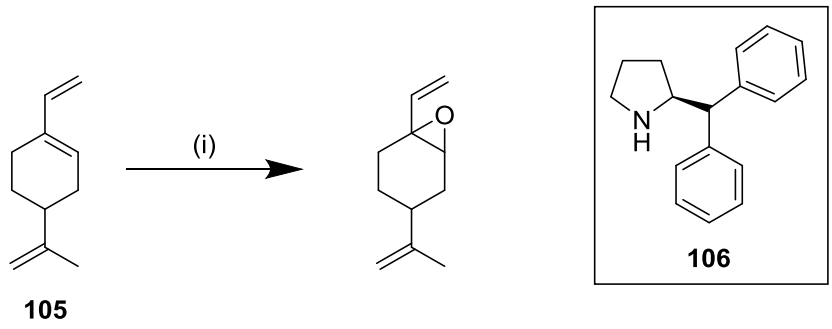
Aggarwal designed a chiral iminium salt combined with binaphthyl based system due to its emergence as one of the best general ligand motifs in asymmetric synthesis.[120,157] This system was reported to provide enantioselectivity as high as 71% for 1-phenylcyclohexene using catalyst (*S*)-(+)-**104**, derived from oxidation of (*S*)-(+)-binaphthylamine **103** followed by methylation using Meerwein's reagent (Scheme 1-36).[56]



(*S*)-(+)-**103** (*S*)-(+)-**104**

Scheme 1-36 - Reagents and conditions: (i) $KMnO_4$, THF, 80%; (ii) $Me_3O^+BF_4^-$, CH_2Cl_2, 96%[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).[158]



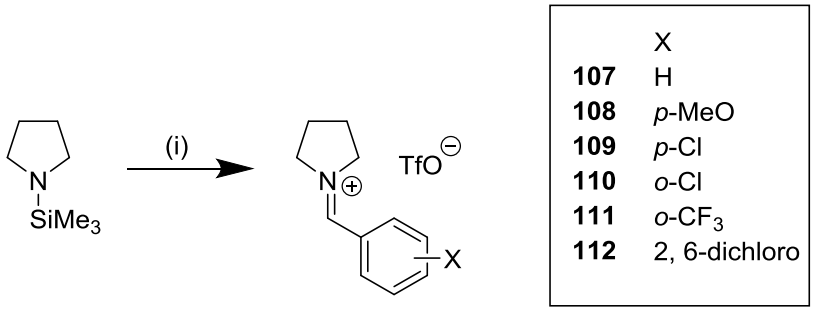
105 **106**

Scheme 1-37 - Chiral amine **106** (10 mol%), Oxone® (2 equiv), pyridine (0.5 equiv), $NaHCO_3$ (10 equiv), $MeCN/H_2O$ (95:5), rt, 2 h, 61%

1.4.5.3.3 Armstrong's Acyclic Iminium Salt-mediated Epoxidation

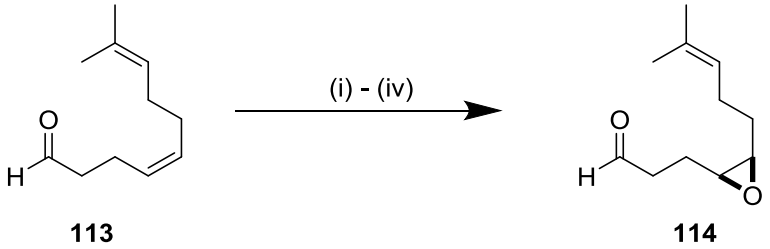
In 1997, Armstrong reported asymmetric epoxidation using several acyclic iminium salts (Scheme 1-38), synthesized by intermolecular condensation, suggesting such an approach would allow greater range in the preparation of chiral iminium salts. The catalyst was prepared by condensation of commercially available *N*-trimethylsilylpyrrolidine (1 equiv) and an aromatic aldehyde (1 equiv) with trimethylsilyl triflate (1 equiv) in ether.[159] Amongst all the catalysts, iminium salts with *ortho*-withdrawing group, i.e. catalysts **110** and **111**,

gave 100% conversion at low catalyst loading, 25 and 10 mol% respectively.[58] 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*).[153]



Scheme 1-38 - Reagents and conditions: (i) ArCHO (1 equiv), TMSOTf (1 equiv), ether[58]

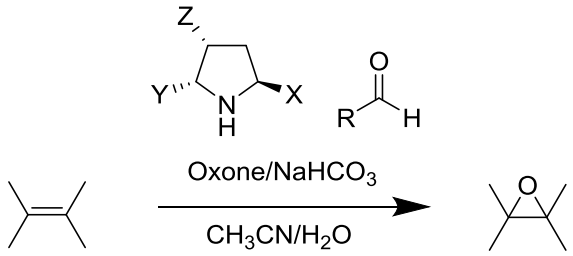
He also showed that intramolecular epoxidation can occur by treatment of unsaturated oxaziridines with MeOTf, presumably *via* oxaziridinium salts. This method has been applied for regioselective epoxidation of a nonconjugated diene (Scheme 1-39).[57]



113 **114**

Scheme 1-39 - Reagents and conditions: (i) $BnNH_2$, 4Å mol. sieves, CH_2Cl_2; (ii) Oxone®, $NaHCO_3$, CH_3CN/H_2O, 47%; (iii) MeOTf, CH_2Cl_2; (iv) Aq. $NaHCO_3$, 48%[57]

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 CH_2Cl_2 followed by brief exposure to aqueous $NaHCO_3$, giving epoxide **114** in 48% yield (Scheme 1-39). Komatsu (catalyst **100**, figure 1.16)[152] and Yang[151] also reported asymmetric epoxidations employing acyclic iminium salts generated *in situ* (Scheme 1-40), giving *ee* up to 39% and 65% respectively.



Scheme 1-40 - Acyclic iminium salts prepared *in situ* by Yang[151]

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 (4*S*, 5*S*)-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 1.17). 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]

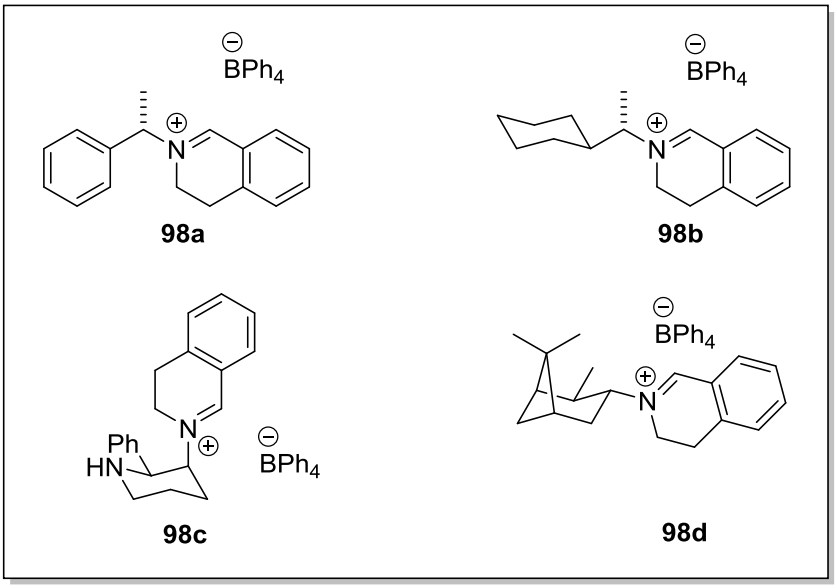


Figure 1.17 – Example of catalyst **98** derived from various chiral primary amine[59]

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*.

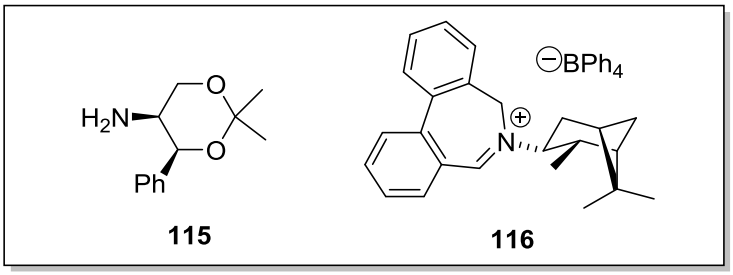
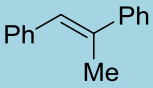
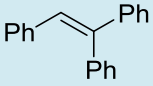
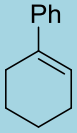
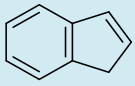
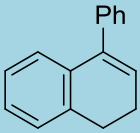


Figure 1.18 – Chiral primary amine **115** and new iminium catalyst **116** by Page

The study revealed that catalyst **35** (Figure 1.6) derived from an amino acetal precursor, (1*S*, 2*S*)-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[61,160]

Entry	Catalyst/ Alkene	98d	35	37	116
		Yield/%; *ee*/%; configuration			
1		68; 8; (+)-(*R*)	64; 20; (+)-(*R*)	100; 24; (+)-(*R*)	90; 3; (+)-(*R*)
2		72; 15; (+)-(1*R*, 2*R*)	52; 52; (–)-(1*S*, 2*S*)	95; 37; (–)-(1*S*, 2*S*)	93; 14; (+)-(1*R*, 2*R*)
3		43; 5; (+)-(*S*)	54; 59; (+)-(*S*)	90; 59; (+)-(*S*)	100; 17; (+)-(*S*)
4		68; 40; (+)-(1*R*, 2*R*)	55; 41; (–)-(1*S*, 2*S*)	100; 60; (–)-(1*S*, 2*S*)	100; 29; (+)-(1*R*, 2*R*)
5		34; 3; (+)-(1*S*, 2*R*)	52; 17; (+)-(1*S*, 2*R*)	100; 10; (+)-(1*S*, 2*R*)	95; 8; (+)-(1*S*, 2*R*)
6		73; 20; (–)-(1*S*, 2*R*)	64;49; (–)-(1*S*, 2*R*)	90; 41; (–)-(1*S*, 2*R*)	95; 38; (–)-(1*S*, 2*R*)

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.[61] These two chiral primary amines were later used to synthesize azepinium salt catalysts, fused to (*R*)- or (*S*)-binaphthalene units.[55] 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-phenylnaphthalene.

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 ($CHCl_3$) 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 levcromakalim **49**, suksdorfin **57** and *β*-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 levcromakalim **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

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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.[1–4] Addition of Oxone® 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 *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 *trans*-stilbene.[5]

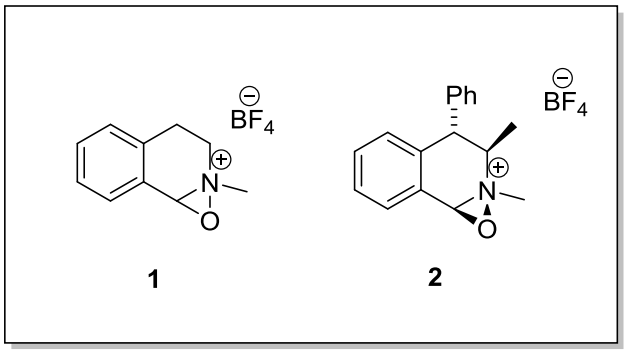


Figure 2.1 - Compound 1, second oxaziridinium salt by Hanquet in 1987; compound 2, first enantiomerically pure chiral oxaziridinium salt by Bohé, Lusinchi and Hanquet

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).[6]

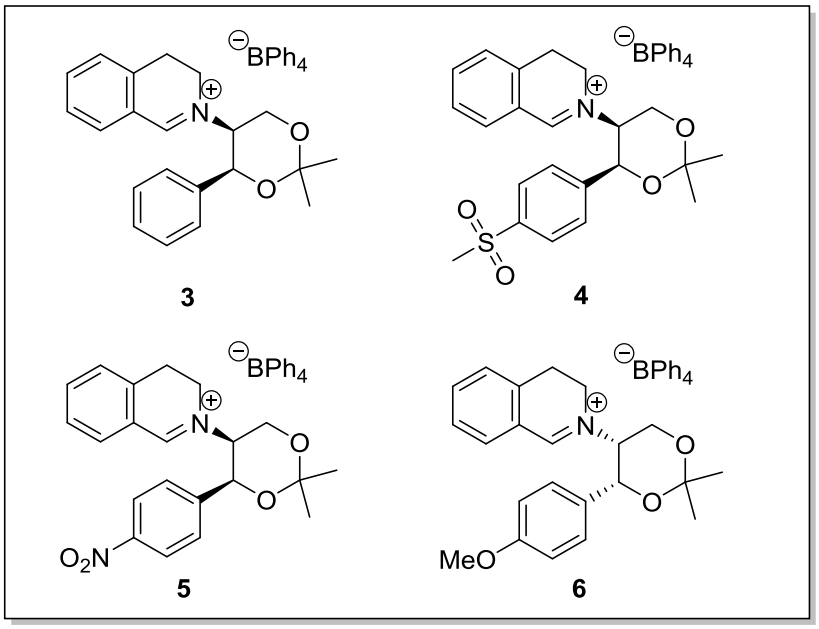


Figure 2.2 - Several dihydroisoquinolinium-based catalysts developed by Page

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]

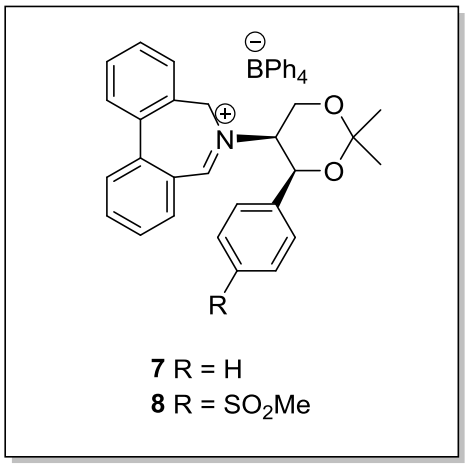


Figure 2.3 - The most reactive biphenyl-derived catalysts from the Page group

The biphenyl-derived catalysts induced better *ee*s 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 *ee*s 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]

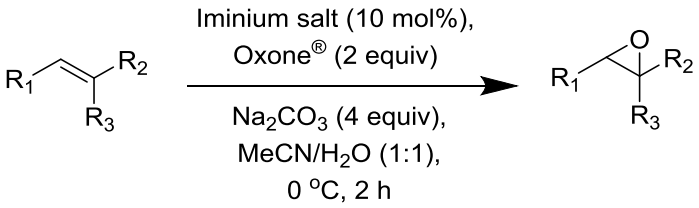
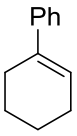
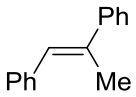
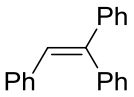
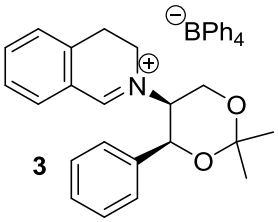
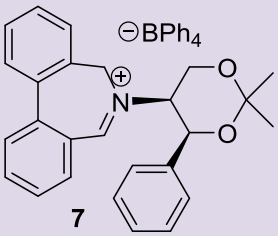
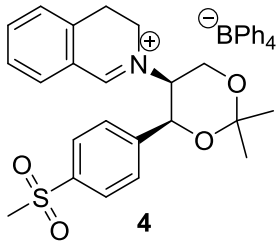
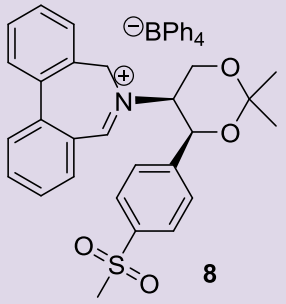
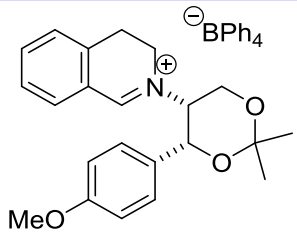
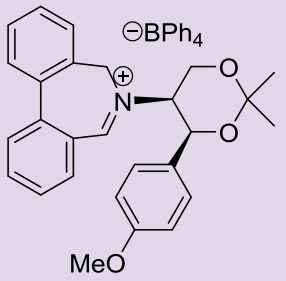


Table 2-1 - Comparison of catalytic asymmetric epoxidation of unfunctionalized alkenes using dihydroisoquinolinium salts and dibenzazepinium salts[a]

	Alkene			
Entry	Catalyst	In each case: *ee*[b](%)/Conv.(%)/Configuration[c]		
1	 **3**	41/55/ (–)-(1*S*, 2*S*)	52/52/ (–)-(1*S*, 2*R*)	59/54/ (+)-(*S*)
2	 **7**	60/100/ (–)-(1*S*, 2*S*)	37/95/ (–)-(1*S*, 2*S*)	59/90/ (+)-(*S*)

3	 **4**	39/100/ (–)-(1*S*, 2*S*)	32/100/ (–)-(1*S*, 2*R*)	50/100/ (+)-(*S*)
4	 **8**	47/56/ (–)-(1*S*, 2*S*)	21/100/ (–)-(1*S*, 2*S*)	10/55/ (+)-(*S*)
5		45/54/ (+)-(1*R*,2*R*)	60/55/ (+)-(1*R*,2*S*)	71/60/ (–)-(*R*)
6		63/50/ (+)-(1*R*,2*R*)	50/61/ (+)-(1*R*,2*R*)	26/63/ (–)-(*R*)

[a]Reagents and conditions: Iminium salt (10 mol%), Oxone® (2 equiv), Na_2CO_3 (4 equiv), MeCN/H_2O (1:1), 0 °C, 2 h; [b]Enantiomeric excesses were determined by ^{1}H NMR spectroscopy in the presence of (+)-Eu(hfc)$_3$ or 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

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.[9]

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

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 *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.

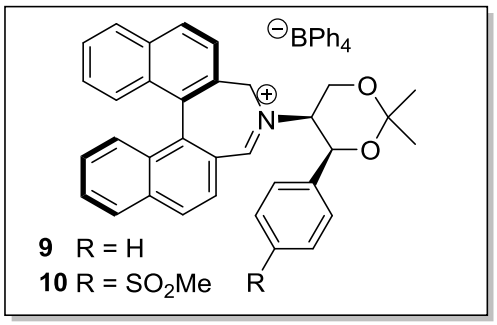


Figure 2.4 - Binaphthyl-derived iminium salts synthesized for this research

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 *ee*s 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.[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.[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 (*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.

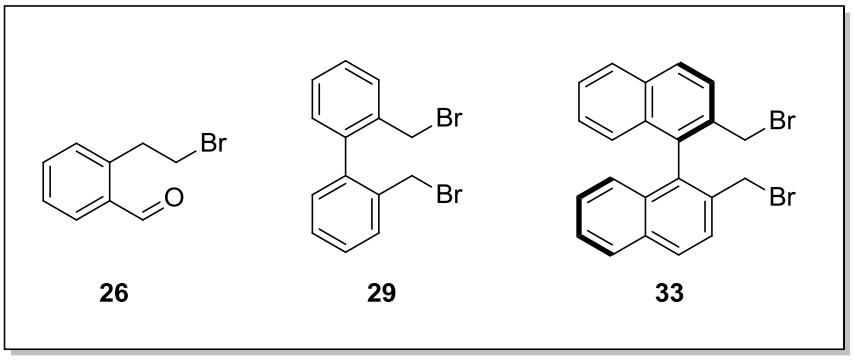


Figure 2.5 - Backbone moieties used to synthesize the iminium catalysts

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).

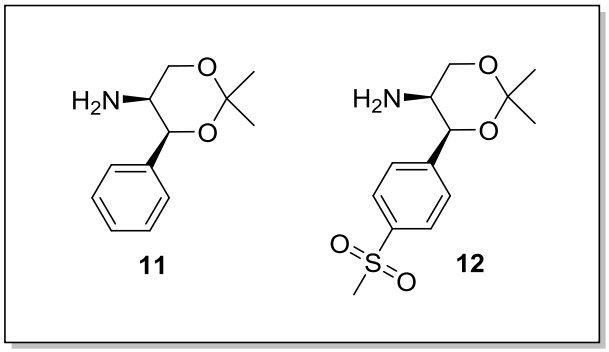
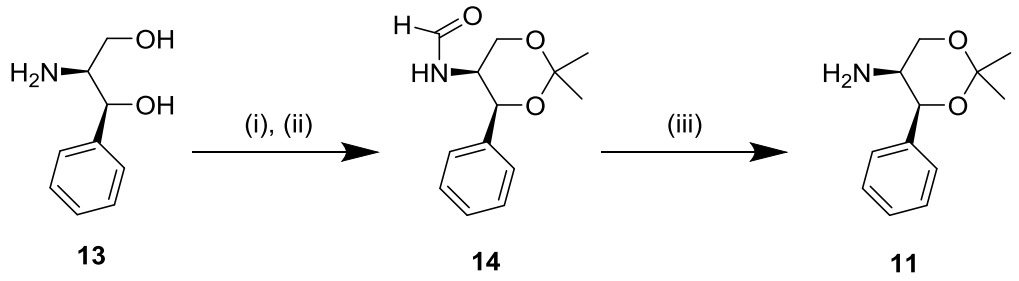


Figure 2.6 - Chiral amine motifs for iminium salt catalysts

These two amine precursors, having aminoacetal functionalities, were selected as they are more effective amine parents for the catalysts as reported in our group,[7] 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.[14]

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.[7]

(*S,S*)-Acetonamine **11** was synthesized from the commercially available diol (1*S,*2*S*)-(+)-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)**.**[16] 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.



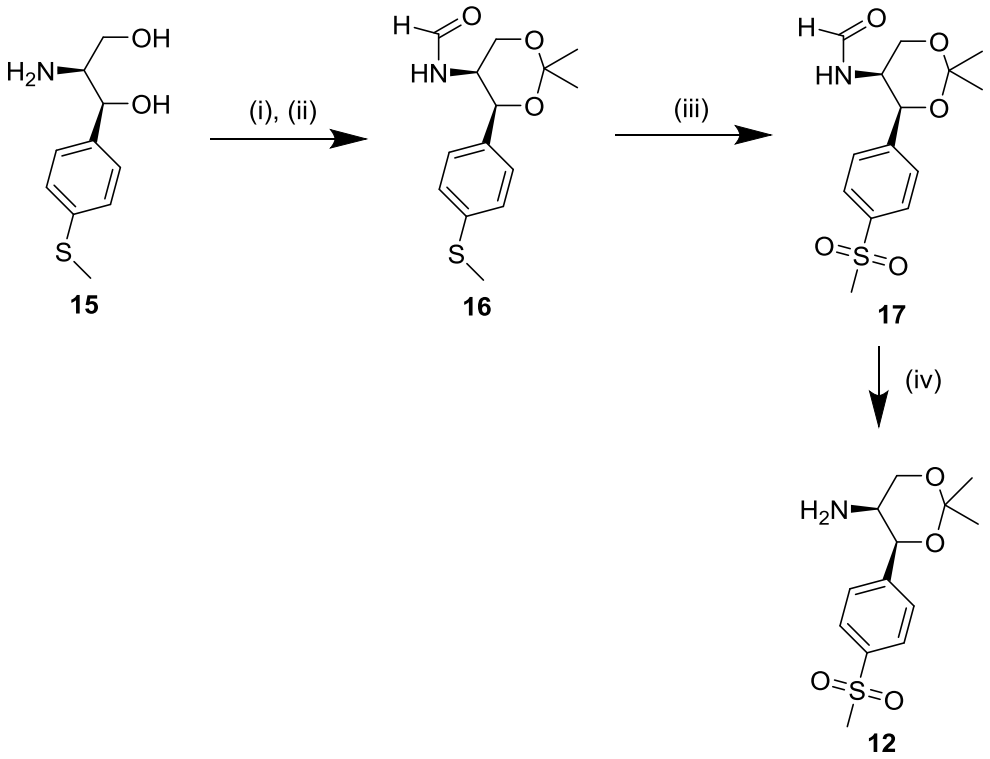
Scheme 2-1 - Reagents and conditions: (i) MeOH, methyl formate (1.1 equiv), NaOMe (0.1 equiv), rt, overnight; (ii) Acetone, (±)-CSA (0.1 equiv), 2, 2-dimethoxypropane (10.0 equiv), 95%; (iii) Hydrazine hydrate (98%), reflux, 3 h, 96%

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 (4*S*,5*S*)-5-(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[16] 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[14] 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.

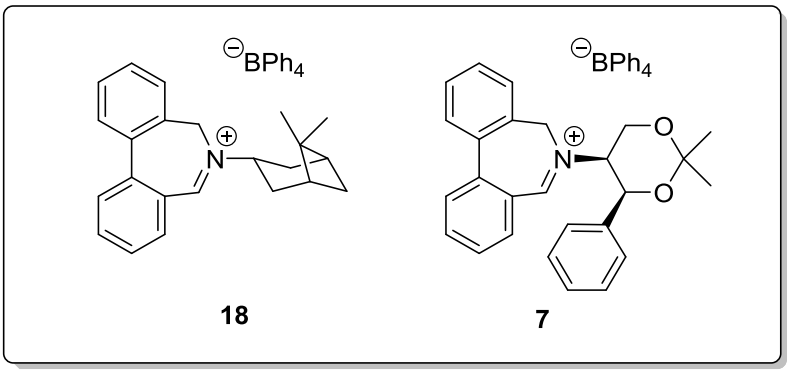


Scheme 2-2 – Reagents and conditions: (i) MeOH, methyl formate (1.1 equiv), NaOMe (0.1 equiv), rt; (ii) Acetone, (±)-CSA (0.1 equiv), 2, 2-dimethoxypropane (10.0 equiv), 87%; (iii) *m*-CPBA (3.1 equiv) in $CHCl_3$, DCM, 0 °C, 2 h, 98%; (iv) Hydrazine hydrate (98%), reflux, 3 h, 73%

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® 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

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 crystaline **12** in a good yield of 73%.

The presence of the dioxane core in (*S,S*)-(+)-acetonamine 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% *ee*s respectively using 1-phenylcyclohexene as substrate under typical aqueous reaction conditions using Oxone® as oxidant.



18 **7**

Figure 2.7 - Biphenylazepinium salts without and with dioxane core, catalysts 18 and 7 respectively

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]

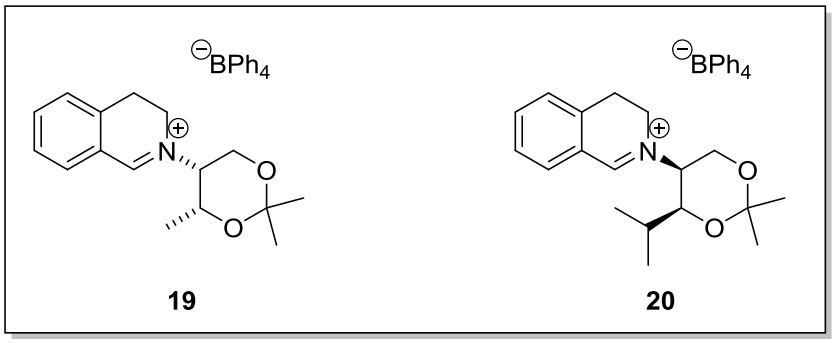


Figure 2.8 - Catalysts **19** and **20** bearing methyl group and isopropyl group at C4 respectively

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,[20] in accord with previous reports of substituted 2,2-dimethyl-1,3-dioxane rings (Figure 2.9).[21]

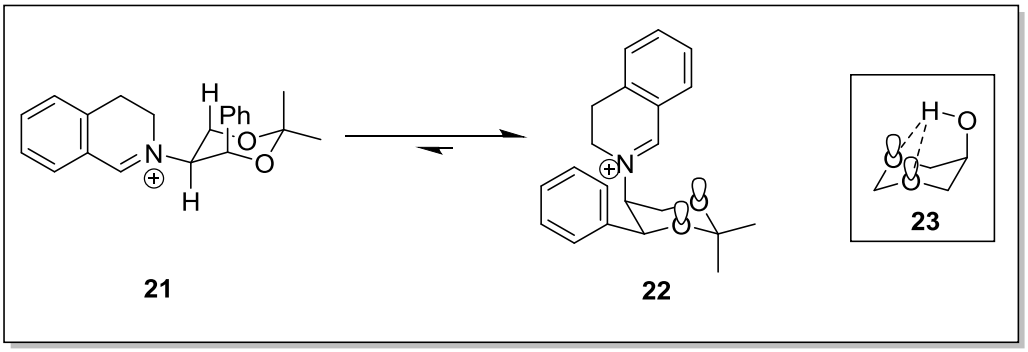


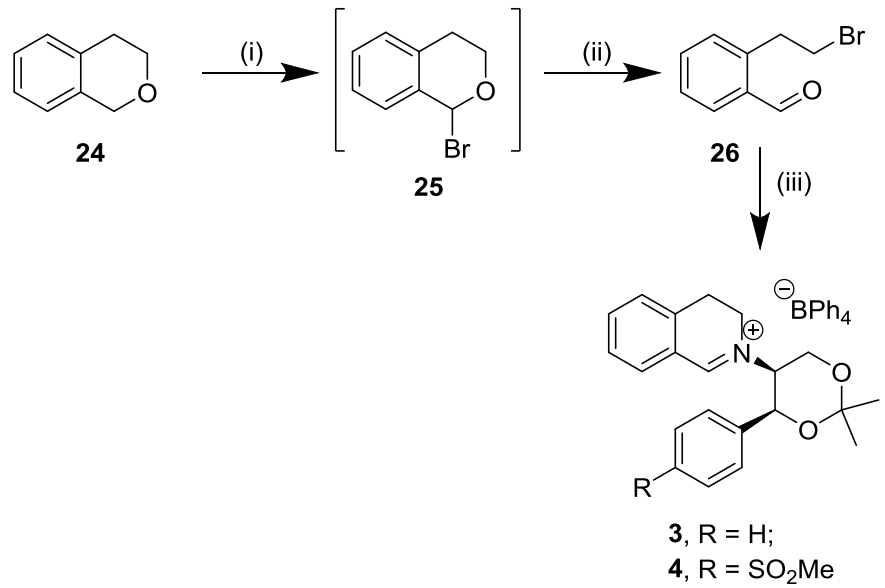
Figure 2.9 - Chair conformation of acetal-containing iminium salts[20]

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.[20]

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

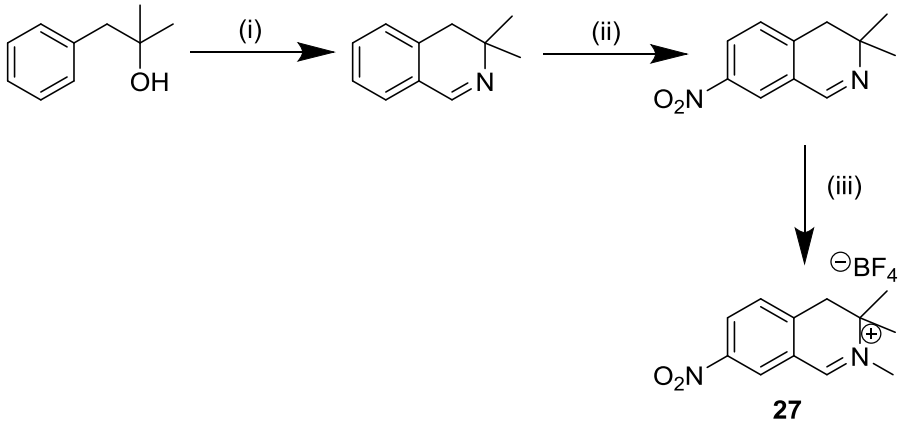
The precursor 2-(2-bromoethyl)benzaldehyde **26** was prepared according to the procedure of Rieche and Schmitz.[22] Bromination of isochromane **24** afforded the expected 1-bromoisochromane **25**, which may be isolated by distillation if required. Treatment of product **25** with concentrated aqueous 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) Br_2, CCl_4, 1.5 h; (ii) HBr (48%), reflux, 10 – 15 min, 85%; (iii) Primary amine 11 or 12, EtOH/MeCN, $NaBPh_4$

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.

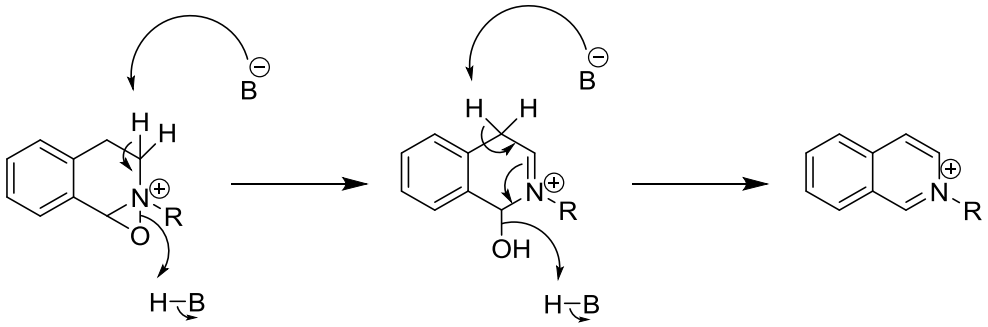
Bohé has showed that incorporating a *gem*-dimethyl group alpha to the iminium unit as in **27** (Scheme 2-4) can increase the catalyst's reactivity and extend the lifetime of the catalysts.



27

Scheme 2-4 - Active iminium salt reported by Bohé. Reagents and conditions: (i) (a) KCN, AcOH.H_2SO_4, rt; (b) Oxalyl chloride, CH_2Cl_2,; (c) $FeCl_3$; (d) MeOH, H_2SO_4, 73%; (ii) KNO_3.H_2SO_4, rt, 2 h, 60 °C, 4 h, 90%; (iii) $Me_3O^+F_4B^-$, CH_2Cl_2, rt, 90%

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]

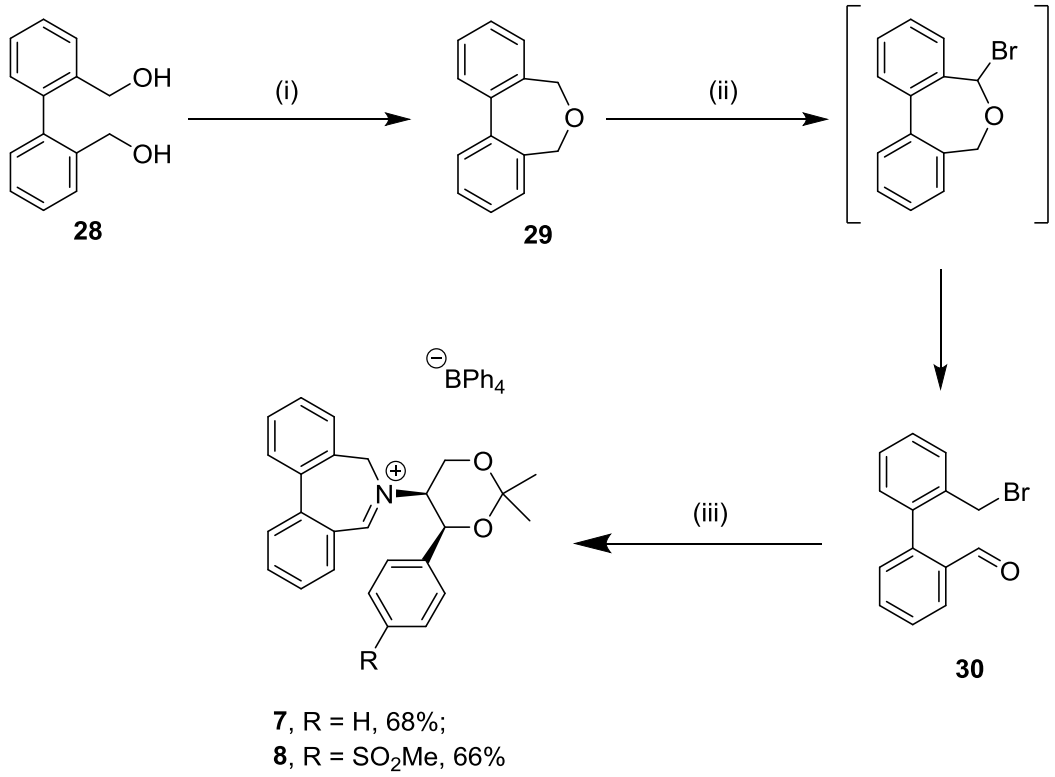


Scheme 2-5 - Bohé's proposed mechanism for iminium salt aromatization[23]

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[9] suggested by Bohé.

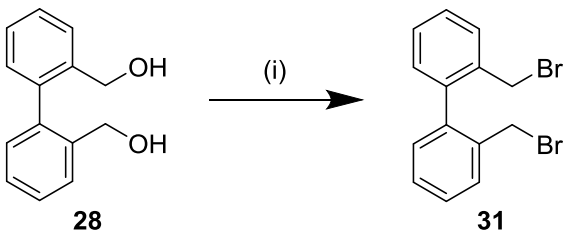
2.1.4 Synthesis of Catalysts based on the Biphenyl-Azepinium Motif

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 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).[7]



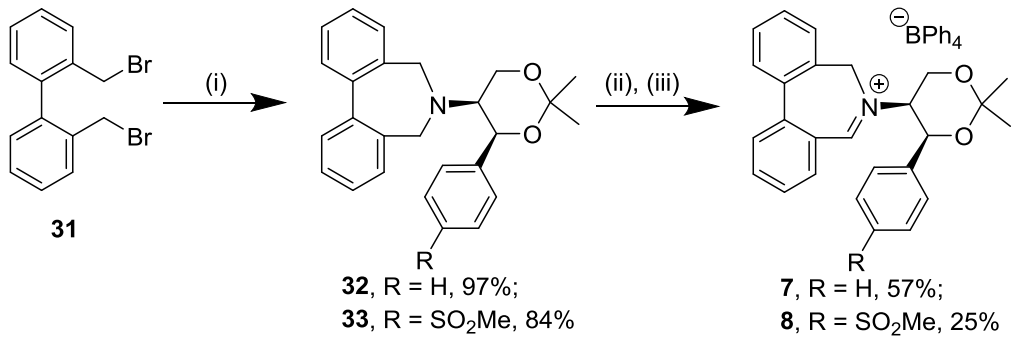
Scheme 2-6 – Reagents and conditions: (i) 24% HBr (15 mL/g of 28), 100 °C, 40 min, 96%; (ii) Br_2 (1.1 equiv), CCl_4 (20 mL/g of 29), 0 °C – reflux, 99%; (iii) Primary amine 11 or 12 (1 equiv), 0 °C – reflux, overnight, $NaBPh_4$ (1.1 equiv), 5 min

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).[7]



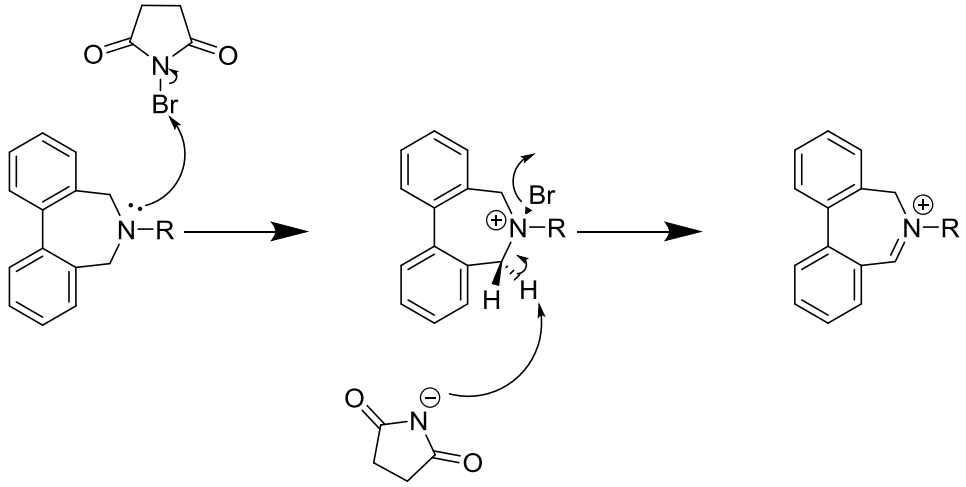
Scheme 2-7 – Reagents and conditions: (i) 48% HBr (10 mL/g of 28), reflux, 2 h, 92%

Cyclocondensation of the (*S,S*)-acetonamines **11** and **12** with 2,2'-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).



Scheme 2-8 – Reagents and conditions: (i) Cs_2CO_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).



Scheme 2-9 - Mechanism for formation of biphenyl-derived iminium salt catalyst

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.[24] The binaphthyl skeleton itself is known to have superior chirality recognition and induction abilities.[25]

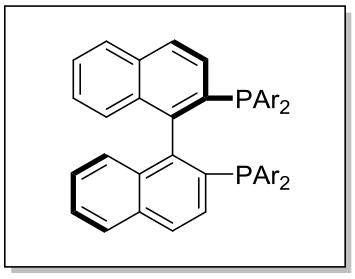


Figure 2.10 - 2, 2'-bis(diarylphosphino)-1, 1'-binaphthyl ligand[24]

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.[26] 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 *ee*s of up to 94%.[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).[28]

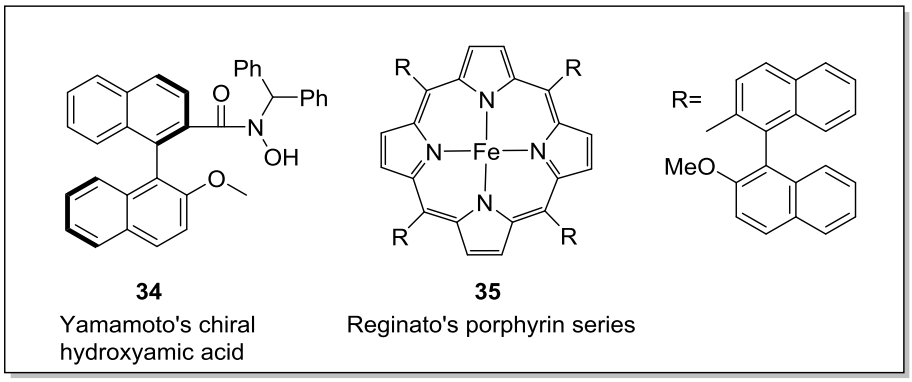


Figure 2.11 - Examples of metal-based catalyst with binaphthyl motif

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).[29–31]

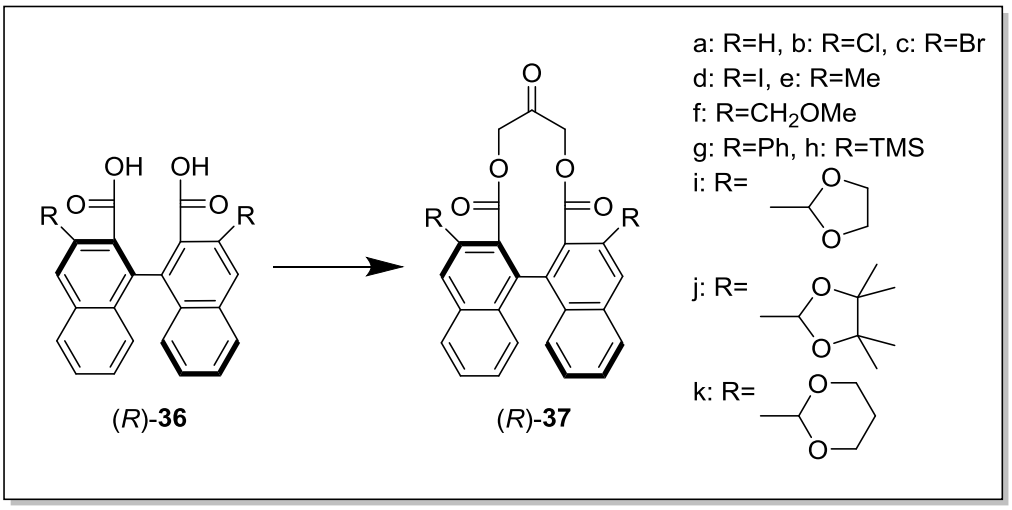
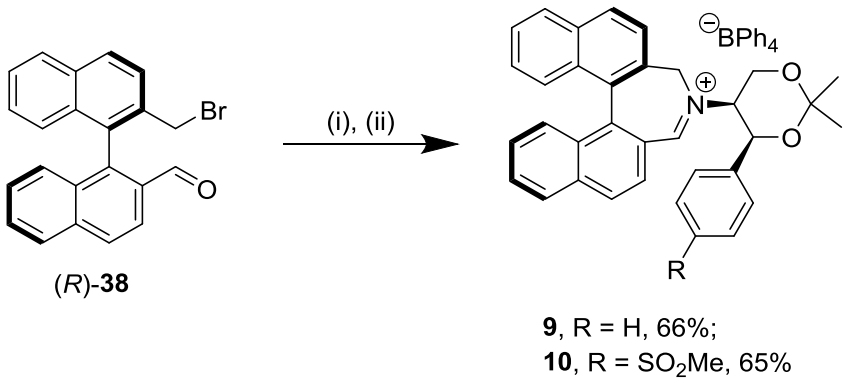


Figure 2.12 - Yang's ketone catalyst[29,30]

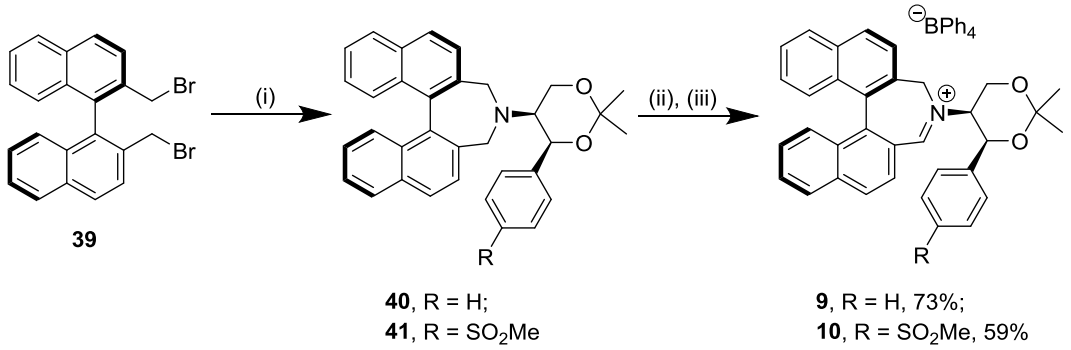
Similarly, Aggarwal *et al.* designed iminium salts based on the (*S*)-(+)-binaphthyl motif. These binaphthalene-fused azepinium salt catalysts, achiral at the nitrogen substituent, afforded *ee*s of 71% and 45% for the oxidation of 1-phenylcyclohexene and α-methylstilbene, respectively.[32]

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]



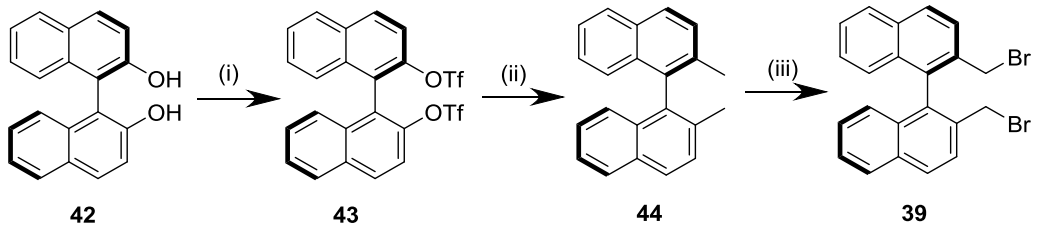
Scheme 2-10 - Reagents and conditions: (i) Primary amine 11 or 12 (1 equiv), EtOH, 40 °C, overnight; (ii) $NaBPH_4$ (1.1 equiv) in minimum amount of MeCN, 5 min

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**.



Scheme 2-11 - Reagents and conditions: (i) Primary amine 11 or 12 (1.1 equiv), K_2CO_3 (3 equiv), MeCN, reflux, overnight; (ii) NBS (1.2equiv), DCM, reflux, 3 h; (iii) $NaBPh_4$ in minimum amount of MeCN, EtOH, 5 min

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]



Scheme 2-12 – Reagents and conditions: (i) Tf_2O, 2, 6-lutidine, DMAP, DCM, –30 °C to rt, overnight, 98%; (ii) MeMgBr (4 equiv), $NiCl_2(dppp)_2$ (0.07 equiv), Et_2O, –78 °C to rt, 16 h, 95%; (iii) NBS (2 equiv), AIBN (10 mol%), cyclohexane, reflux, 3 h, 51%

Subsequent Kumada-type cross-coupling of **43** with methylmagnesium bromide and the nickel catalyst [$NiCl_2(dppp)_2$] in Et_2O 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).[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.[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_2CO_3 in acetonitrile followed by the oxidation of the binaphthyl azepine compounds **40** and **41** by NBS. Addition of sodium tetraphenylborate provided the iminium tetraphenylborate 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.

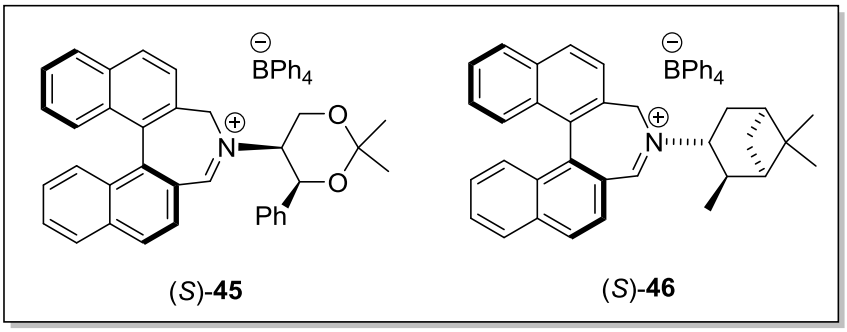


Figure 2.13 - (*S*)-Binaphthyl-derived catalysts by Page

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.

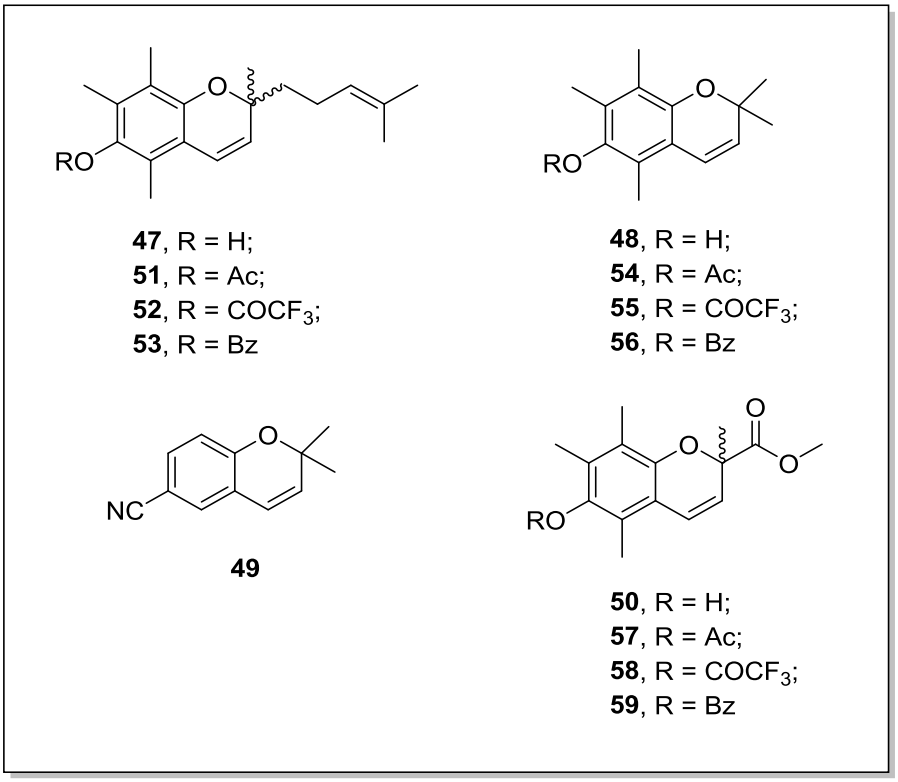


Figure 2.14 – The chromene substrates and their derivatives synthesized

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]

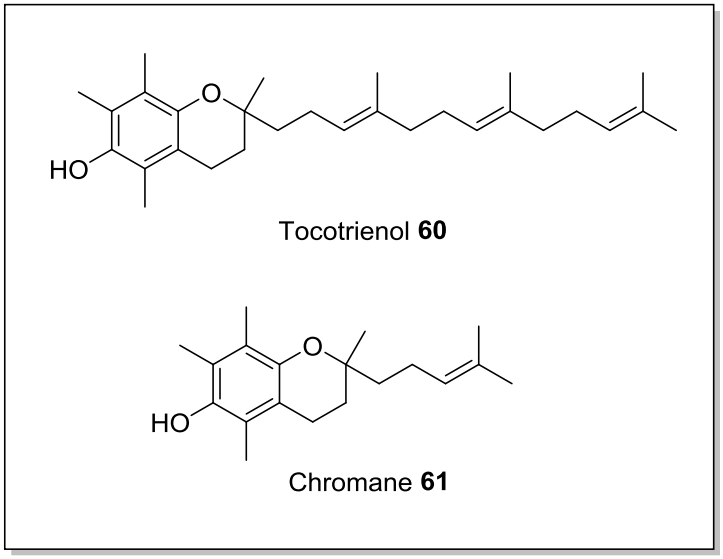
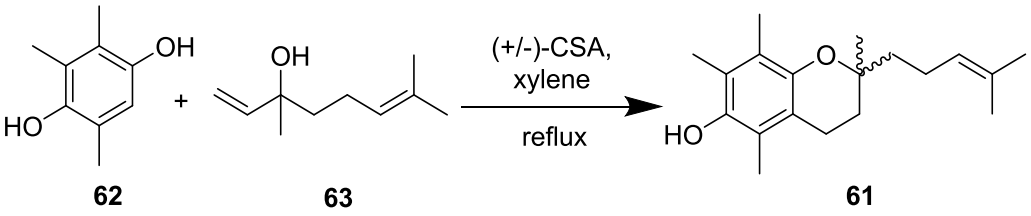


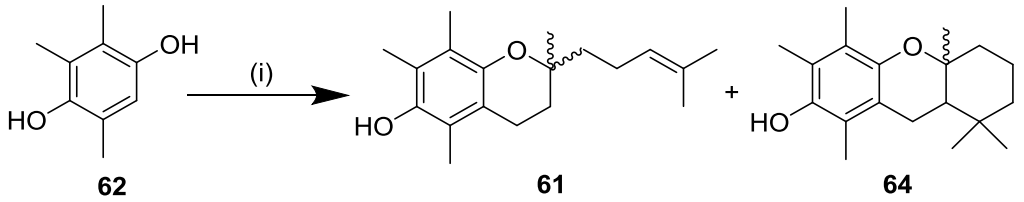
Figure 2.15 – The structures of the vitamin E constituent, *α*-tocotrienol, 60 and its analogue, chromane 61

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.



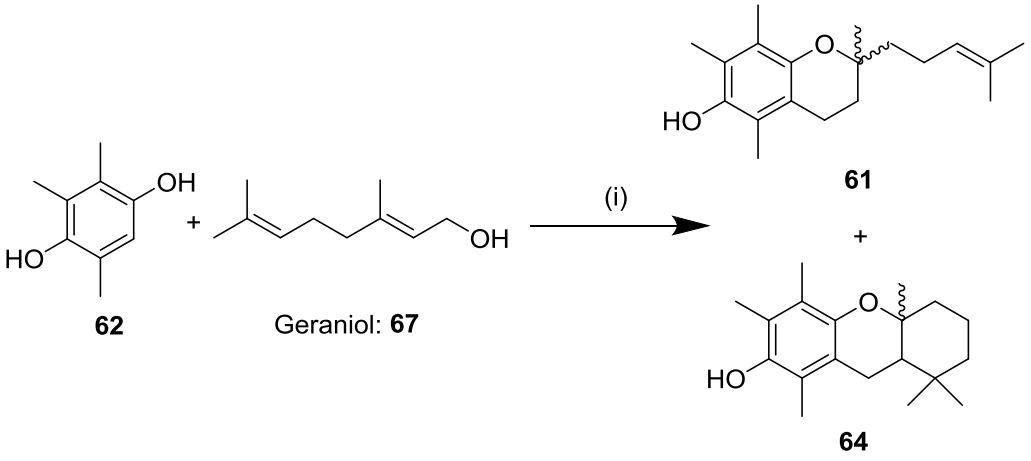
Scheme 2-13 – The initial plan for synthesis of 6-hydroxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-ene)chromane 61

In 2006, Odinokov described the same reaction but using *n*-octane as the solvent.[38] 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**.



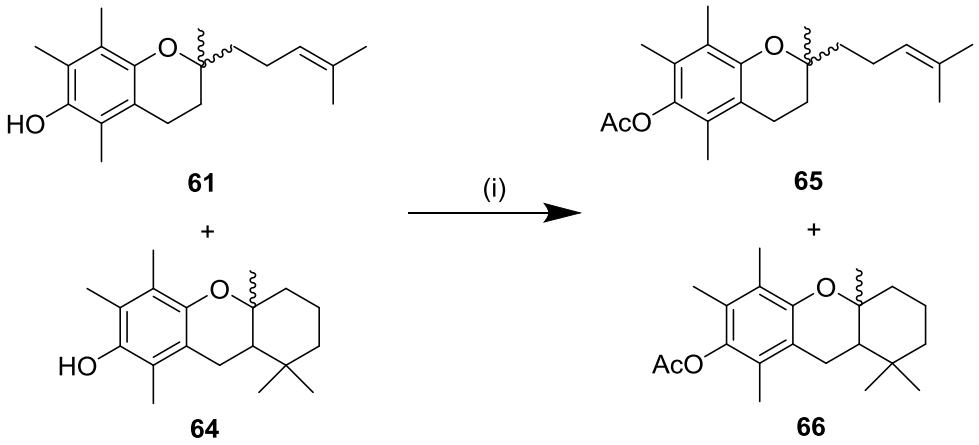
Scheme 2-14 - Reagents and conditions: (i) 63 (2 equiv), (±)-CSA (0.1 equiv), *n*-octane, reflux overnight, 95%, 5:1 ratio of compound 61 and 64

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 α-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[39]

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) Ac_2O (25 equiv), pyridine (2 mL/g of starting material), rt, 73% yield of 65

Ichikawa reported the isolation of **66**. The ^{1}H NMR spectroscopic analysis of **66** showed signals at δ 0.90 (singlet, 3 H, CH_3C–), 1.00 (singlet, 3 H, CH_3C–), 1.16 (singlet, 3 H, CH_3CO–), 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_3COO–), 2.05 (singlet, 3 H, CH_3–Ar) and 1.95 (singlet, 6 H, CH_3–Ar), with no signal of the olefinic proton.[39] 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.

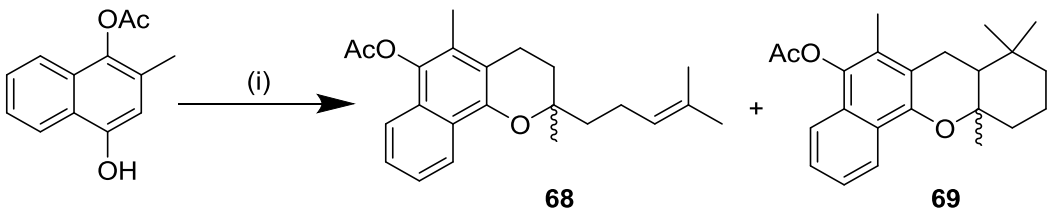
Odinokov reported the use of heptane which gave a 2:1 ratio of **61**:**64** while the reaction in aromatic solvents such as benzene and toluene gave nearly equimolar mixtures, and the reaction in dioxane did not proceed at all.[40]

Odinokov suggested that the ratio of the products is greatly influenced by the catalyst activity.[41] 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.[38] 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 2-2 - Acid-catalysed condensation of **62** and **63**

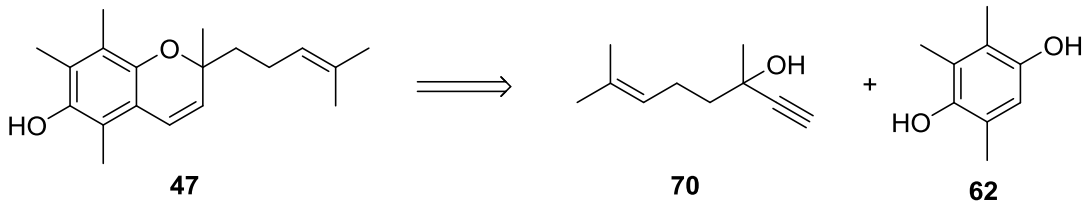
Acid	Solvent	Product
(±)-CSA	Xylene	No reaction
(±)-CSA	*n*-octane	Mixture of isomers **61** and **64**, 5:1, 95%
p-TsOH	*n*-octane	Mixture of isomers **61** and **64**, 5:1, 21%
Amberlyst® 15	Toluene	No reaction
Amberlyst® 15	Dichloromethane	No reaction
Silica	Toluene	No reaction
Silica	Dichloromethane	No reaction

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).[42]



Scheme 2-17 - Reagents and conditions: (i) **63** (1.0 equiv), (±)-CSA (0.1 equiv), *n*-octane, reflux, 3 h, 3:7 ratio of **68** and **69** by GLC[42]

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).



47 **70** **62**

Scheme 2-18 - Synthesis of **47** using propargyl alcohol **70**

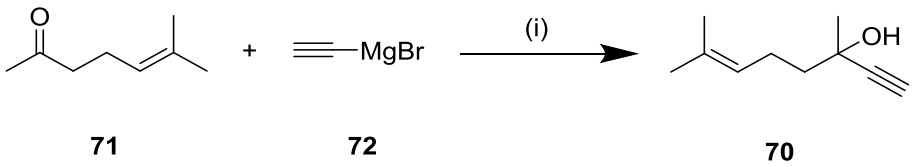
The precursor **70** was readily accessed by us through the addition of a Grignard reagent, ethynylmagnesium bromide **72**, to commercially available 6-methylhept-5-en-2-one **71** (Table 2-3).

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

Entry	Compound **71**	Compound **72**	Solvent	Temp, °C	Product **70**
1	1 equiv	1.5 equiv	THF	–78 °C – rt	No reaction
2	1 equiv	4.5 equiv	THF	0 °C – rt	62%
3	1 equiv	10.0 equiv	THF	0 °C – rt	70%
4	1 equiv	1.2 equiv	THF/Et_2O (1:1)	rt	88%

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 Et_2O/THF (1:1)[43] 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.

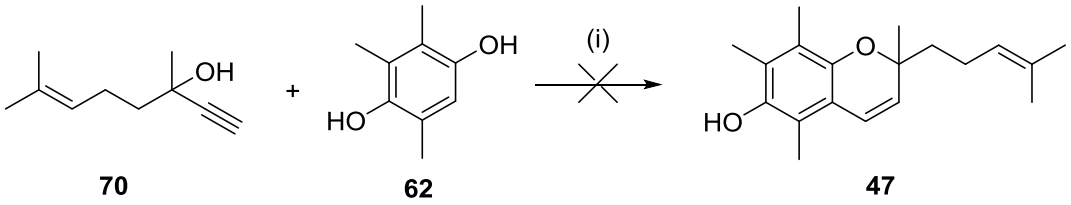
The product decomposed when silica was used for the separation (Scheme 2-19). Under these conditions, increasing the number of equivalents of **70** did not improve the yield.



71 **72** **70**

Scheme 2-19 – Reagents and comditions: (i) 72 (1.2 equiv), anhydrous Et_2O/THF (1:1), rt, Ar, 3 h, 88%

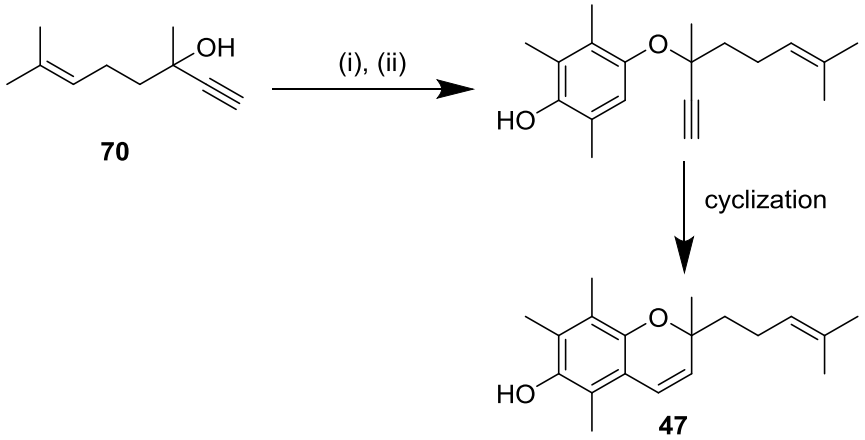
With propargyl alcohol **70** in our hands, we then attempted the synthesis of chromene **47** under acid catalysis, by reacting with phenol **62** in the presence of a catalytic amount of (±)-CSA and heating under reflux (Scheme 2-20).



70 **62** **47**

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

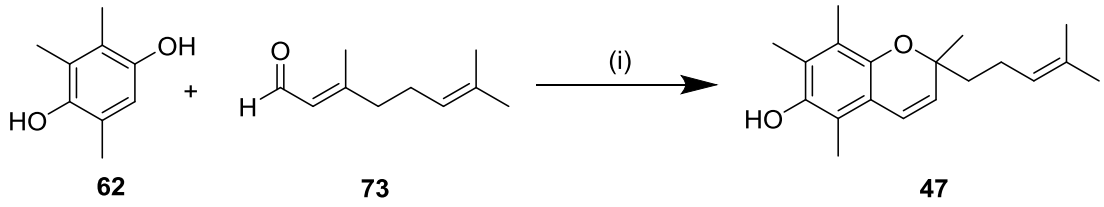
Unfortunately, the desired product was not isolated and the starting material was decomposed under these conditions. A base-catalysed reaction was also attempted using propargyl alcohol **70** and trimethylhydroquinone **62**. According to a method by Godfrey (used to prepare compound **49**),[44] propargyl 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 ^{o}C for 30 min. The solution of phenol **62** in CH_3CN in the presence of DBU and a catalytic amount of $CuCl_2.H_2O$ was then added into the trifluoroacetyl solution. However this attempt also failed (Scheme 2-21).



70 47

Scheme 2-21 - Reagents and conditions: (i) DBU (1.3 equiv), TFAA (1 equiv), 0 °C; (ii) 62, DBU (1.12 equiv), $CuCl_2.H_2O$ (10 mol%), CH_3CN, 0 °C

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).[45,46] This method was reported previously by Jung *et al.* to synthesize (+)-decursinol **81**[47] and is further discussed in Chapter 2.2.2.

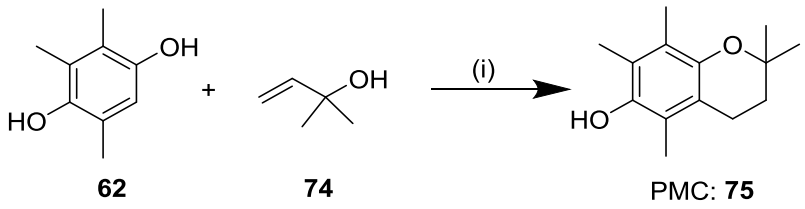


62 73 47

Scheme 2-22 – Reagents and conditions: (i) 73 (3 equiv), $PhB(OH)_2$ (1.6 equiv), propionic acid (0.3 equiv), toluene, reflux, 1.5 h, 45%

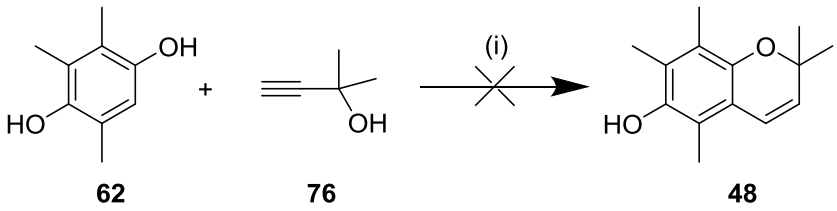
2.2.2 6-Hydroxy-2,2,5,7,8-pentamethylchromene **48**

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.[48] 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.[49]



Scheme 2-23 - Reagents and conditions: (i) 2-methyl-3-buten-2-ol **74**, TFA, N_2, 80%[48]

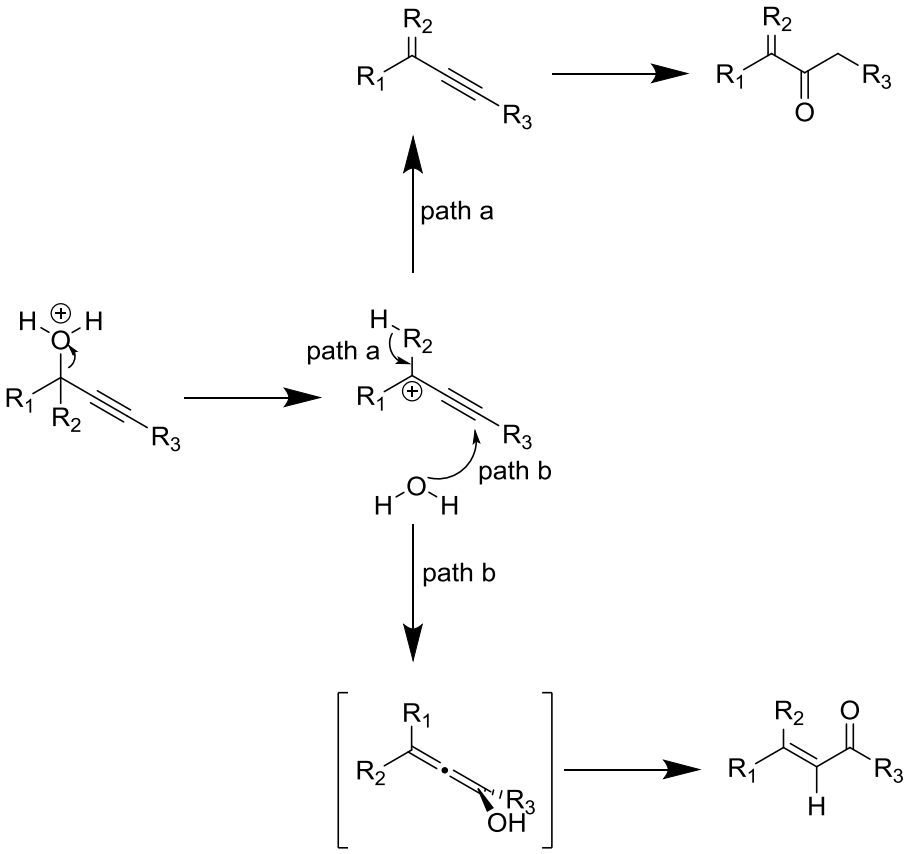
Our first attempt to synthesize compound **48** was modelled on Zhou's approach. This procedure failed to yield **48** from related dimethyl propargyl alcohol **76** (Scheme 2-24).



Scheme 2-24 - Reagents and conditions: (i) 2-methyl-3-butyn-2-ol **76**, TFA, N_2

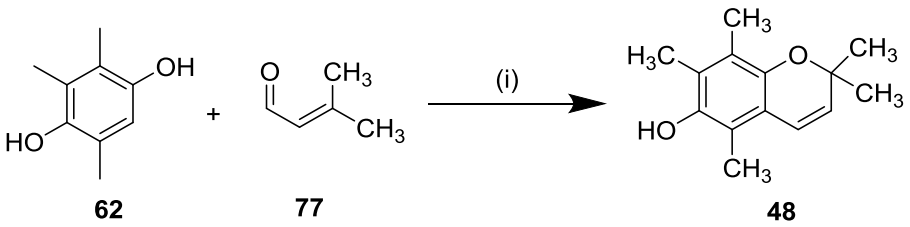
The failure of the acid-catalysed condensation of phenol **62** and propargyl alcohol **76** is probably due to Rupe/Meyer-Schuster rearrangement forming the corresponding *α*, *β*-unsaturated carbonyl compounds. Protonation of the propargylic alcohol followed by the

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.[50,51] The difference between these two reaction pathways occurs early on: initial *β*-elimination of the propargyl alcohol provides an enyne *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).[50]



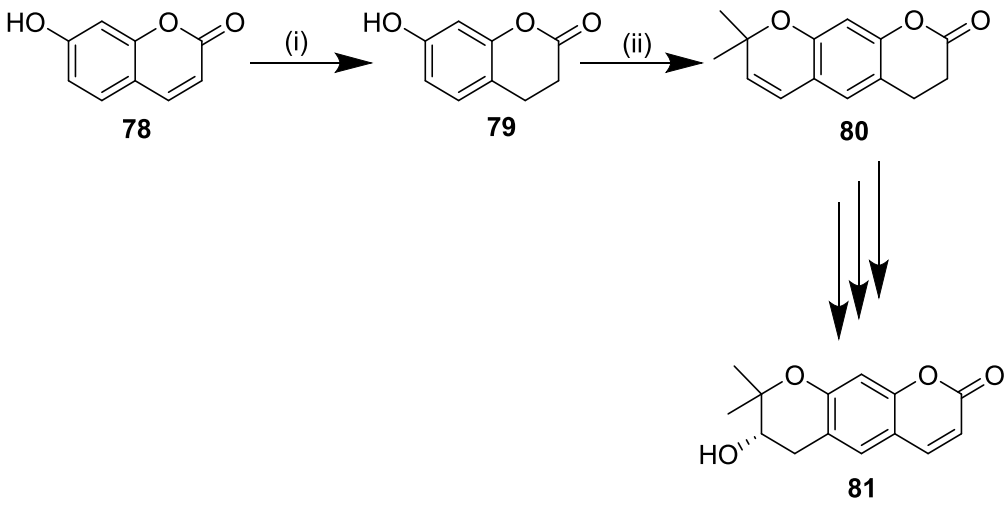
Scheme 2-25 – Path a: Rupe rearrangement and; Path b: Meyer-Schuster rearrangement mechanism[50]

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 N_2 atmosphere. The use of a Dean-Stark apparatus did not improve the yield.



Scheme 2-26 – Reagents and conditions: (i) 77 (1.5 equiv), $PhB(OH)_2$ (2 equiv), acetic acid (excess), toluene, reflux, N_2, 61%

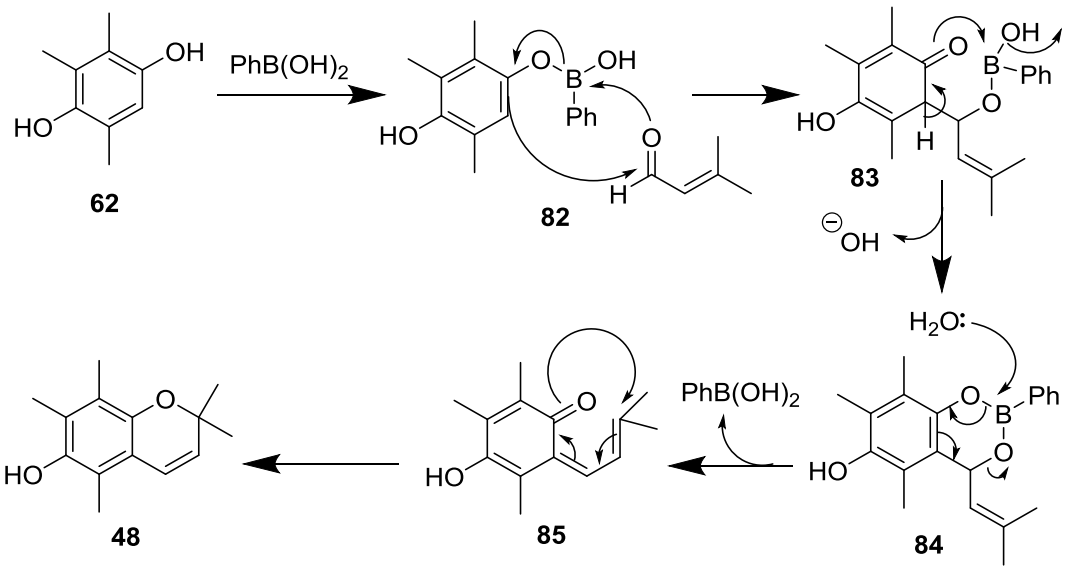
This method was outlined by Jung *et al.* to synthesize (+)-decursinol **81** from a commercially available starting material, umbelliferone **78**. Umbelliferone **78** was first reduced using H_2/Pd-C at room temperature for 10 hours to afford compound **79** in 94% yield, which was then subjected 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).[47]



Scheme 2-27 – Reagents and conditions: (i) Pd-C/H_2, AcOH, rt, 10 h, 94%; (ii) $PhB(OH)_2$ (1.5 equiv), 77 (1.5 equiv), propionic acid (1.5 equiv), toluene, reflux, 36 h, 62%[47]

Phenylboronic acid is a useful reagent to produce quinonemethide intermediates, such as **85**, catalysing a reaction between a phenol and an aldehyde.[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-4*H*-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[53]

The reaction is regioselective, attack occurring exclusively at the *ortho* position with regards to the phenolic hydroxyl.[54] 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).[45]

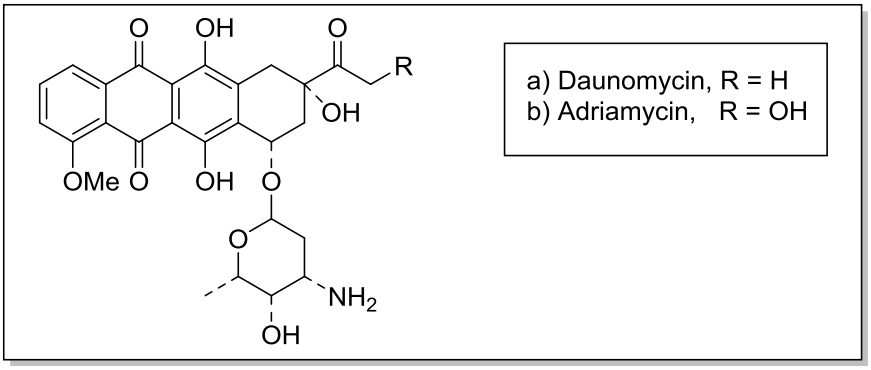
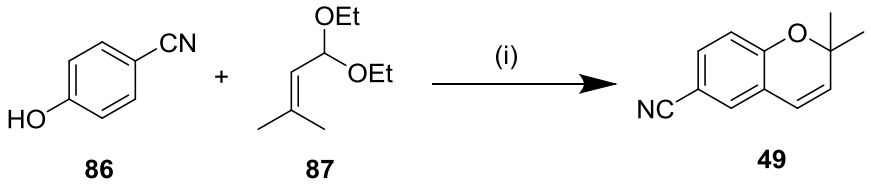


Figure 2.16 - Two types of anthracyclines synthesized by Broadhurst *et al.*[45]

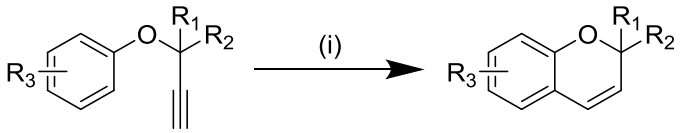
We attempted to use this method to synthesize compound **47**, taking into account our previous experience of inseparable mixture of isomers in synthesizing **47** *via* acid-catalysed reaction. This was carried out by heating under reflux a mixture of the corresponding phenol, trimethylhydroquinone **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-2*H*-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).

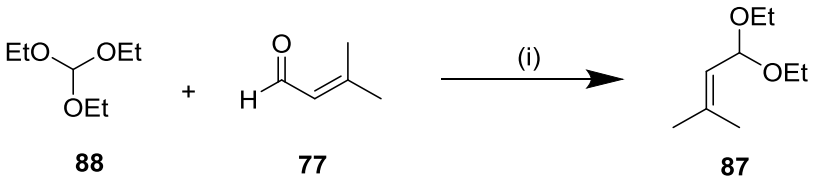


Scheme 2-29 - Reagents and conditions: (i) **86** (2 equiv), *p*-xylene, 3-picoline (0.25 equiv), reflux, 24 h, 87%



Scheme 2-30 - Thermal rearrangement of a propargyl ether

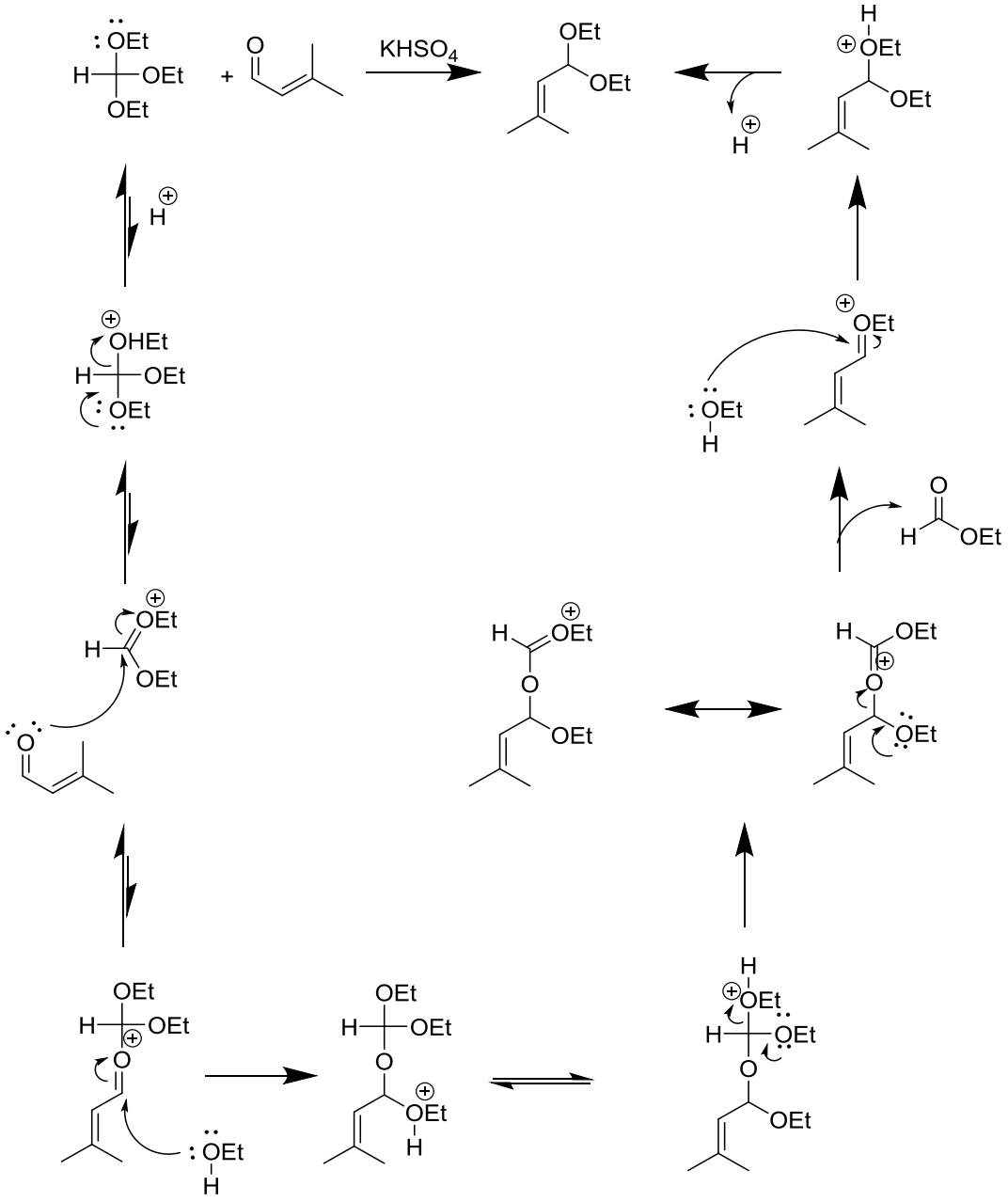
The synthesis of chromene **49** using the first method begins with the preparation of the diethyl acetal **87** (Scheme 2-31). The synthesis of diethyl acetal **87** from ethanol, triethyl orthoformate **88**, and 3-methyl-2-butenal **77** in the presence of *p*-toluenesulfonic acid was found unsuccessful due to polymerization of the aldehyde as reported by North *et al*. North then ultimately found that $KHSO_4$ afforded the best yield of **87**, up to 86% yield.[55]



Scheme 2-31 - Preparation of diethyl acetal **87**. Reagents and conditions: (i) NH_4NO_3 (25 mol%), EtOH, rt, 24 h

In 1986, Mori *et al.* reported the use of NH_4NO_3 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

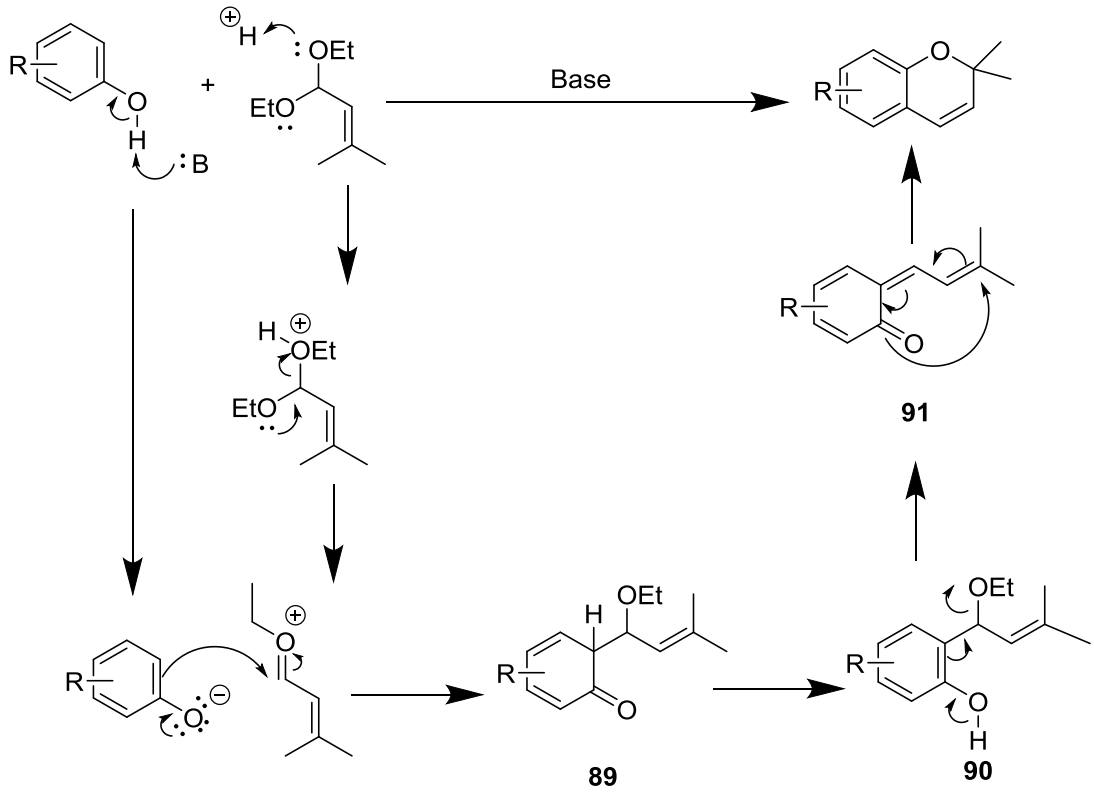
ketones in the carbon-oxygen bond formation is a well-established reaction.[59] The proposed mechanism of acetalization is shown below (Scheme 2-32).



Scheme 2-32 - Acetalization mechanism[60]

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.

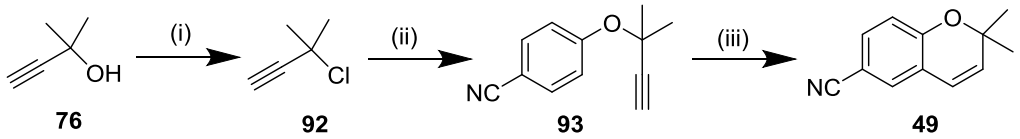
The suggested mechanism of the base-catalysed condensation of an *α,β*-unsaturated acetal and a phenol is illustrated below (Scheme 2-33).[55,61] First, the phenol is deprotonated. North suggested that the phenol also acts as an acid catalyst to activate the acetal.[55] The ethanolysis of the acetal 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.**



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),[62] and has been recognised as one of the general methods for the synthesis of chromenes.[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.[64]

The *o*-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]

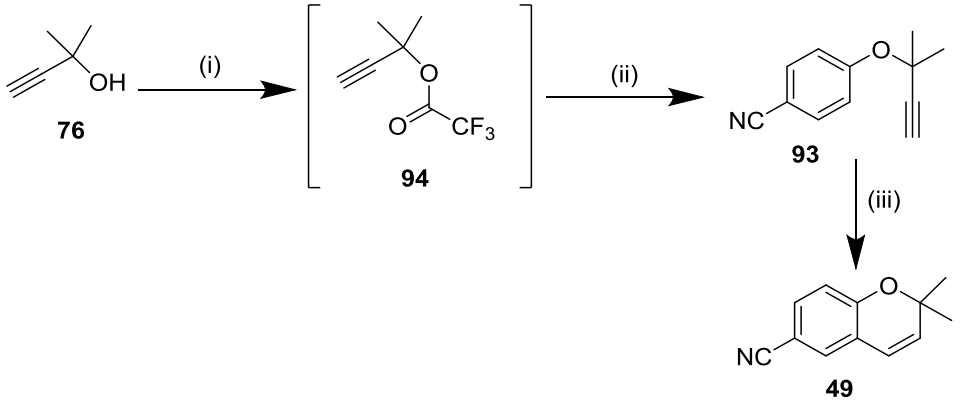


76 **92** **93** **49**

Scheme 2-34 - Reagents and conditions: (i) $CaCl_2$, $CuCl_2$, Cu, cold conc. HCl, 0 °C, 5 hrs; (ii) 4-cyanophenol, K_2CO_3 (1.0 eq), KI (0.1 eq), N_2, acetone, reflux; (iii) *N,N*-diethylaniline, N_2, reflux.

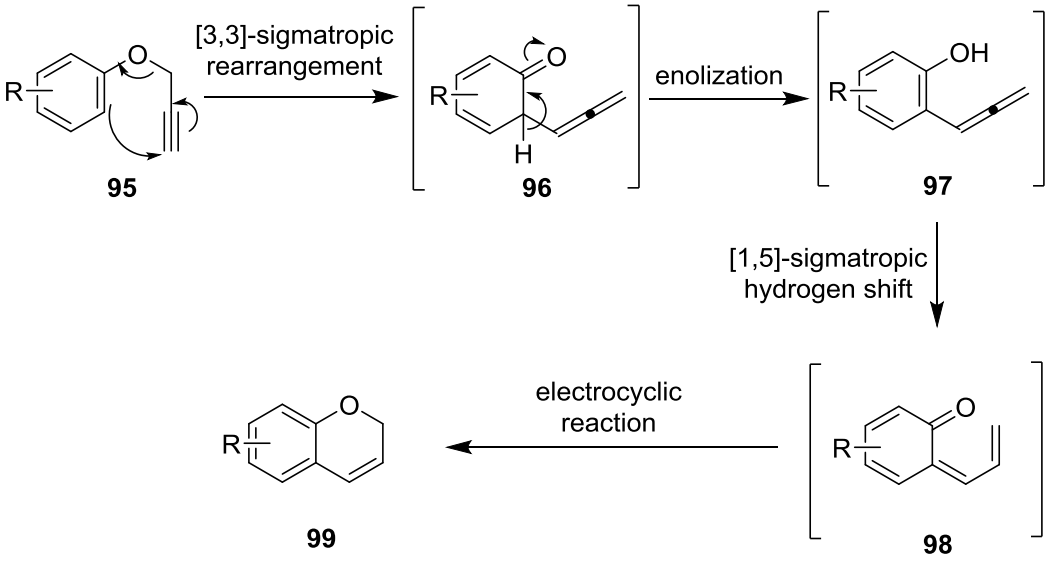
Previously, the thermal Claisen rearrangement had been performed by heating a solution of **93** in *o*-chlorobenzene,[62] a mixture of dry DMF, *N, N*-diethylaniline[66], and poly(ethylene glycol).[67] The thermal rearrangement of simple propargyl ethers to produce chromenes was first reported by Iwai and Ide[68] 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]



Scheme 2-35 - Reagents and conditions: (i) $(CF_3CO)_2O$, DBU, CH_3CN, 0 °C, %; (ii) 4-cyanophenol, DBU, CH_3CN, Cu_2Cl_2 (0.1 mol%), 0 °C, 5 hr, 86%; (iii) reflux[74,75]

The mechanism of the thermal cyclization of aryl propargyl ethers into chromenes was proposed by Zsindley and Schmid (Scheme 2-36)[70] 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**.[72]



Scheme 2-36 - Proposed mechanism of thermal cyclization of aryl propargyl ethers[70]

2.2.4 6-Hydroxy-2,5,7,8-tetramethylchromene-2-carboxylate **50**

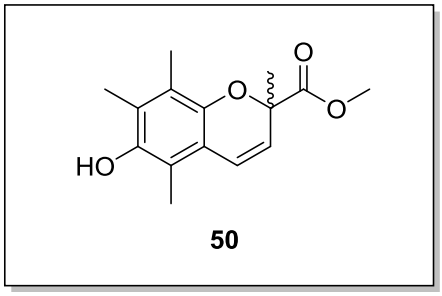
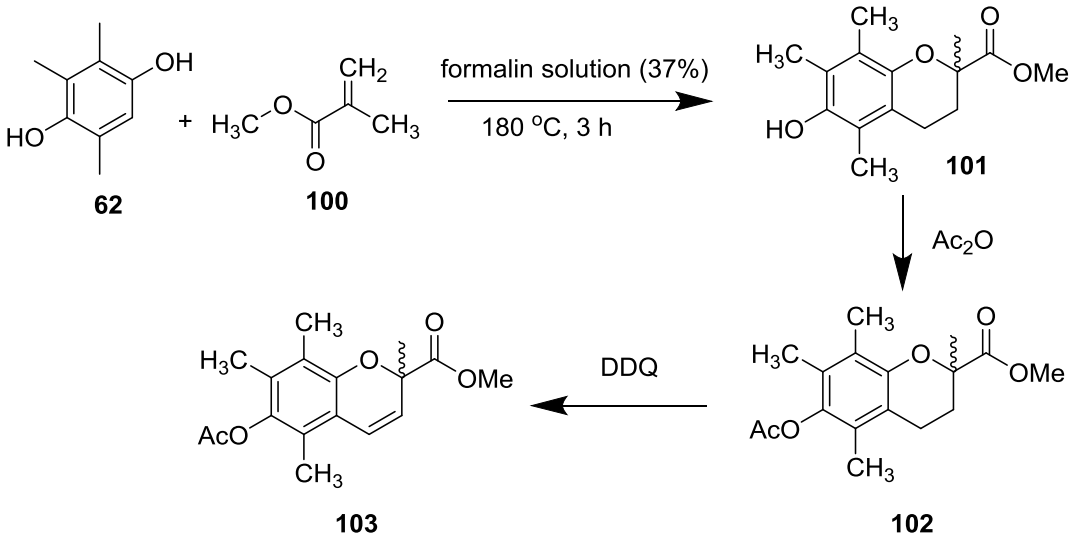


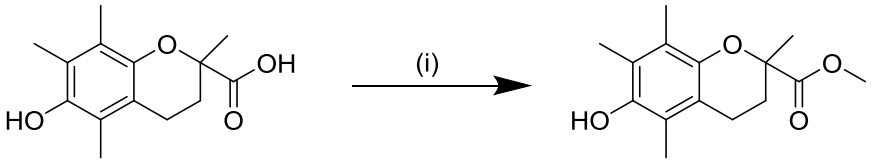
Figure 2.17 - Structure of the chromene substrate **50**

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).



Scheme 2-37 - Synthesis plan of chromene substrate **103**

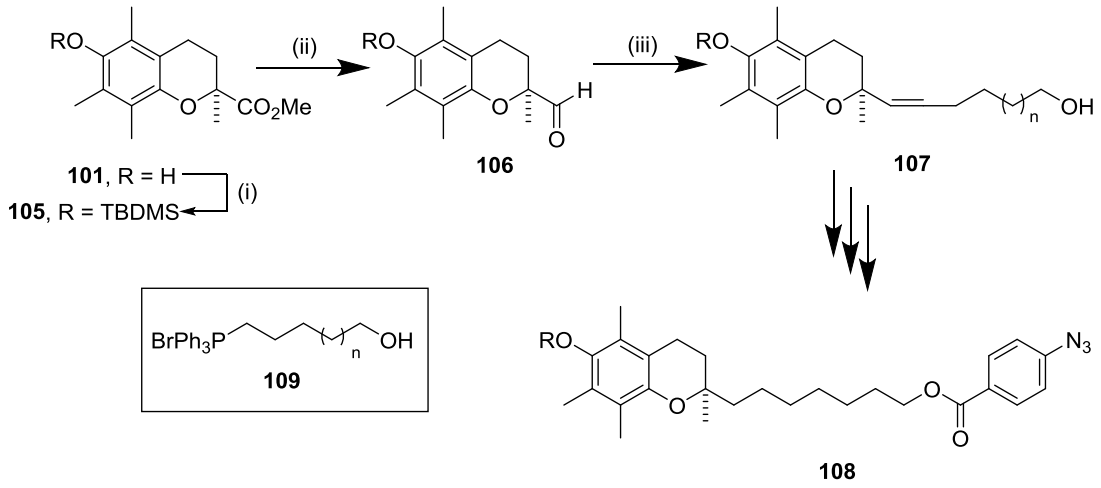
The Mitsubishi Corporation developed this method on an industrial scale. In most literature reports, compound **101** was readily synthesized from the commercially available Trolox® (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid), **104** after a simple methyl esterification (Scheme 2-38).[76–78] Compound **101** is a very useful intermediate for functionalization at both the ester functionality and the phenol group.



104 **101**

Scheme 2-38 – *p*-TsOH (0.3 equiv), MeOH (20 mL/g of 104), CH_2Cl_2 (4 mL/g of 104), rt, 95%[77]

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).[76]



Scheme 2-39 - Reagents and conditions: (i) TBDMSCl, imidazole, DMF, 85 °C, 97%; (ii) DIBAL, CH_2Cl_2, –60 °C, 86%; (iii) 109, LiHMDS, THF, –60 °C, 81 – 89%[76]

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 *γ*-secretase enzyme, displaying activities as low as a micromolar range for the most active derivatives (Figure 2.18, compound **110** and **111**).[79] The *γ*-secretase enzyme has been demonstrated to reduce the production of amyloid-β_{42} peptides ($A\beta_{42}$) and to increase the formation of shorter A*β*-peptides like $A\beta_{38}$. The more hydrophobic $A\beta_{42}$ species has a higher tendency to aggregate compared to $A\beta_{38}$ which is more soluble. The aggregation-prone $A\beta_{42}$ peptides are the central drivers of the pathological process in Alzheimer's disease.[80–83]

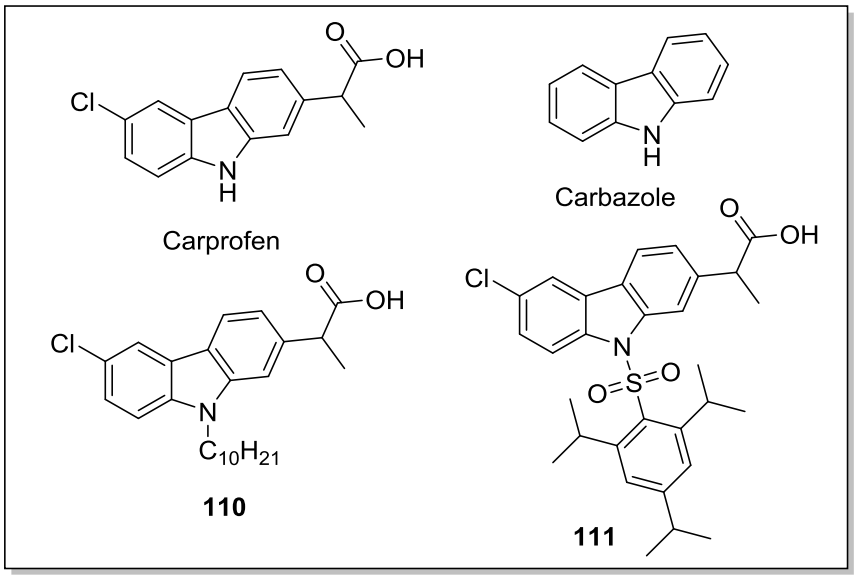
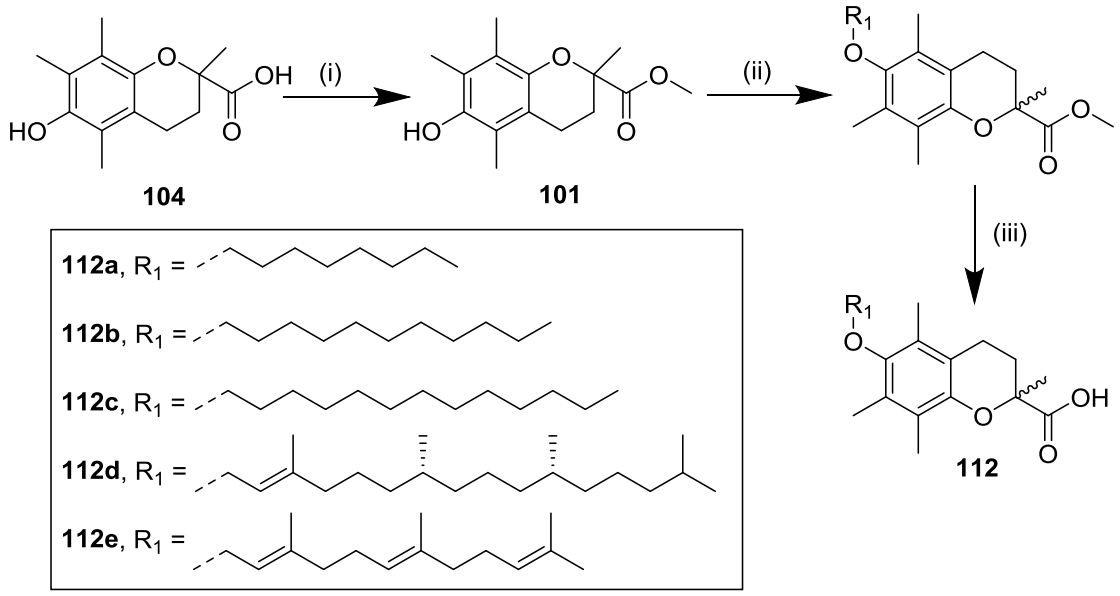


Figure 2.18 - Structures of carprofen, carbazole, and two selected *γ*-secretase modulators[79]

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 *γ*-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).[79] 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.[79]



Scheme 2-40 - Reagents and conditions: (i) K_2CO_3, MeI, DMF, rt; (ii) Cs_2CO_3, R_1-X, DMF, 100 °C; (iii) KOH, dioxane/water (5:1), 75 °C

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.

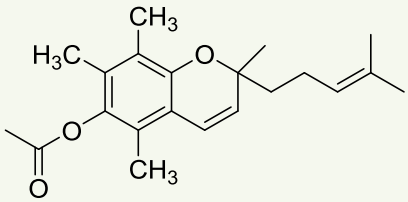
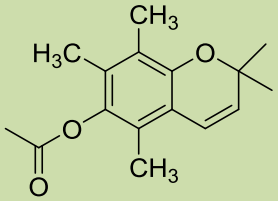
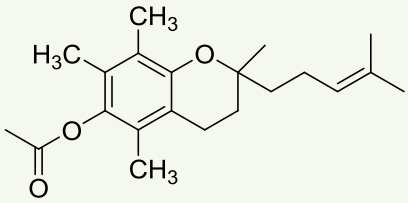
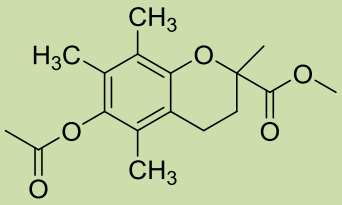
2.2.5 Protection of the Phenolic Hydroxyl Functional Group

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*.[40] affording yields as high as 86% yield (Table 2-4). Another method, reported by Patti *et al.,*[84] 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

Chromene/ Chromane	Product	Yield (%)	Chemical shift of acetyl, δ (ppm)
47	 **51**	86	2.33
48	 **54**	82	2.32
61	 **65**	73	2.32
99	 **113**	59	2.25

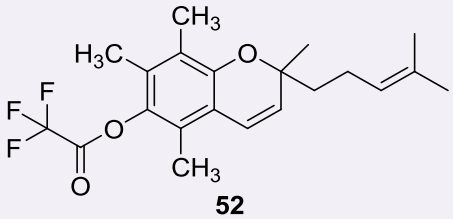
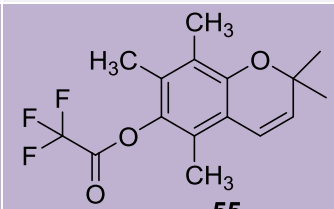
The presence of the acetate group can be confirmed using ^{1}H NMR spectroscopic analysis. The signal corresponding to the protons from the acetate group is observed as a singlet between 2.2 and 2.4 ppm. Analysis of the IR spectrum confirms the presence of carbonyl group of the acetate which gives a 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 2-5 - Trifluoroacetate protection of chromane/chromene

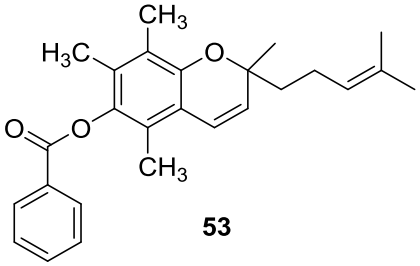
Entry	Chromene/ Chromane	Product	Yield (%)
1	**47**	 **52**	99
2	**48**	 **55**	84
3	**99**	 **114**	65

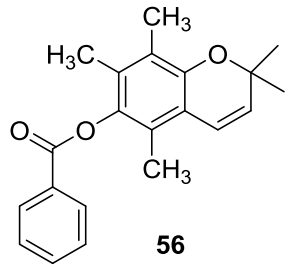
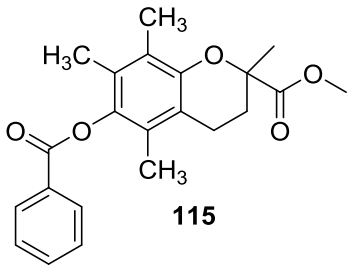
As no additional signal is expected when the ^{1}H NMR spectrum of the compounds is analysed, the attachment of trifluoroacetate group can be confirmed by analysing their ^{13}C NMR spectrum: indeed, the presence of two quartet signals in the 110 – 120 ppm ($^{1}J_{C-F}$ = 284 – 287 Hz, CF_3) and 150 – 160 ppm regions ($^{2}J_{C-F}$ = 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}.[85] 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.[86]

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 2-6 - Benzoate protection chromane/chromene: NaH (1.1 equiv), benzoyl chloride (1.0 equiv), dry THF, N_2

Chromene/ Chromane	Product	Yield (%)	Reaction time (hours)
47	 **53**	75	Overnight

48	 **56**	84	0.5
99	 **115**	50	Overnight

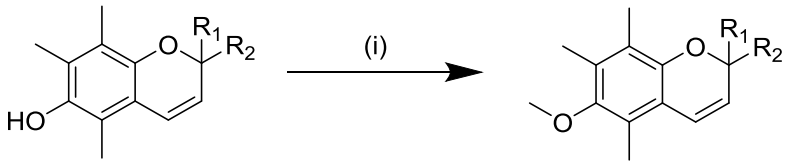
Initial attempts to use pyridine as the base were disappointing as the benzoylation reaction was found to be very slow: the desired benzoate was obtained in 20% yield when the reaction was left overnight. Addition of a catalytic amount of DMAP did not improve the yield.

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.[87] But the removal is not as difficult with phenols.

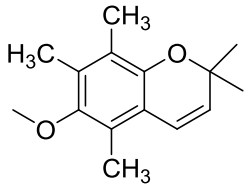
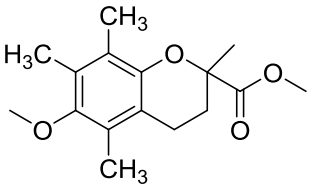
The introduction of the methyl group was carried out *via* Williamson Ether synthesis. The use of sodium hydride and methyl iodide under inert atmosphere, afforded the corresponding products in good yield (Table 2-7) after few hours of stirring at room temperature (Scheme 2-41). In contrast, when we used an approach by Pan,[88] 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.



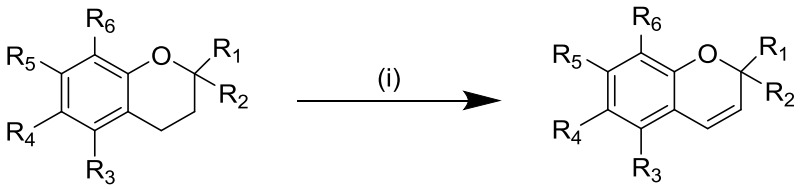
Scheme 2-41 - Reagents and conditions: (i) NaH (1.1 equiv), anhydrous THF, MeI (1 equiv), rt

Table 2-7 Methyl ether protection of the phenolic hydroxyl

Chromene/ Chromane	Product	Yield (%)	Reaction time (hours)
48	 **117**	87	3
99	 **118**	69	24

2.2.6 Synthesis of 3, 4-Dehydro Derivatives of Chromane

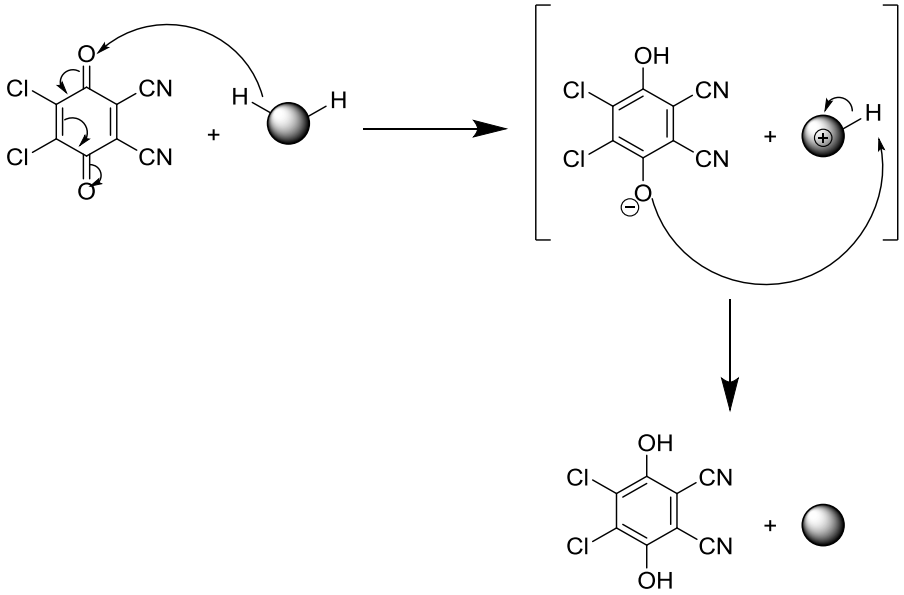
It has been reported that chromane compounds can be dehydrogenated to the corresponding chromenes by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (Scheme 2-42).[89]



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

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.[90] However it failed to gain general acceptance until the more extensive investigations of Braude, Jackman, Linstead, and co-workers, 20 years later.[91] 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).[90,92]

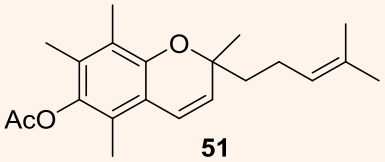
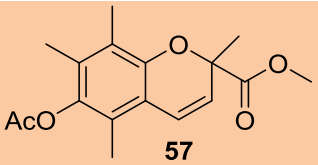
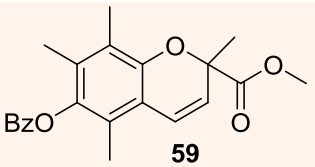


Scheme 2-43 - Suggested reaction mechanism for dehydrogenation of hydrocarbons using DDQ[90,92]

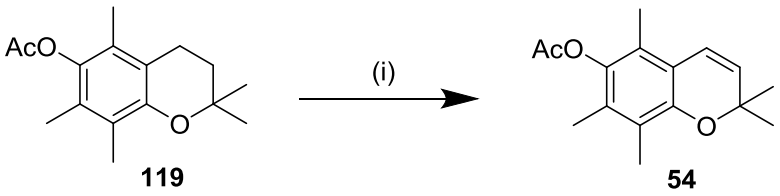
Rosenau has reported that mixtures of different dimers were obtained when non-protected chromanols were reacted with DDQ, whereas the reaction with appropriately *O*-protected chromanols proceeded smoothly. Thus, suitable protection of the phenolic hydroxyl is essential before the actual dehydrogenation step, and deprotection can be done afterwards.[89] Previously, the acetate protecting group was chosen due to simplicity and near-quantitative yields of both attachment and removal of protecting group.[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.[92]

Table 2-8 - Oxidation using DDQ

Entry	Chromane	Product	Yield (%)
1	**65**	 **51**	24
2	**113**	 **57**	48
3	**115**	 **59**	43

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).[89] 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).

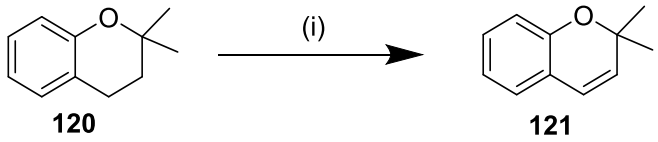


119 **54**

Scheme 2-44 - Reagents and conditions: (i) DDQ, toluene, reflux, 24 h, 76%[89]

TLC analysis of the reaction mixture showed the product and the starting material have the same R_f, but the starting material can be distinguished from the product by charring the TLC plate with 4% H_2SO_4 in MeOH. The starting material and the product turn yellow and brown, respectively.[76]

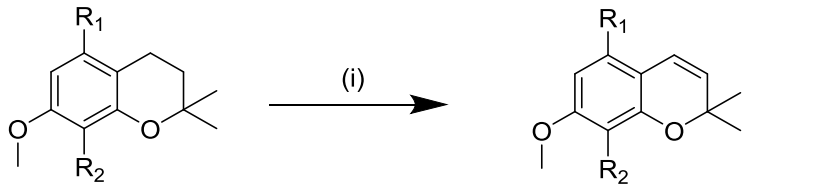
An example of dehydrogenation of a chromene derivative was reported by Chauncey *et al.* in 1980; the chromane **120** was heated under reflux in anhydrous benzene for 48 hours to give the corresponding chromene **121** in 77% yield (Scheme 2-45).[93]



120 **121**

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]



122a, $R_1 = OCH_3$, $R_2 = H$;
122b, $R_1 = H$, $R_2 = OCH_3$

123a, $R_1 = OCH_3$, $R_2 = H$, 80%;
123b, $R_1 = H$, $R_2 = OCH_3$, 85%

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

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 levcromakalim, 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

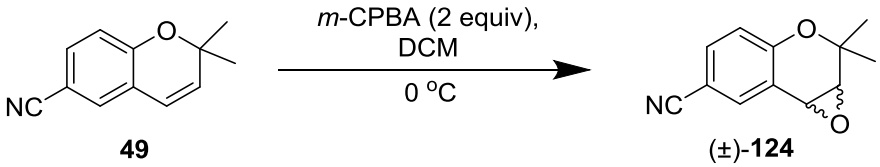
In asymmetric synthesis, determination of the enantiomeric excess (*ee*) is important to evaluate the dominance of major enantiomer. In this research, there are two methods used in evaluating the enantiomeric excesses of the chiral epoxides *i.e.* using chiral HPLC or using ^{1}H NMR spectroscopy with addition of chiral shift reagent, Eu (hfc)$_3$.

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:



Scheme 2-47 - Preparation of the racemic epoxide **124**

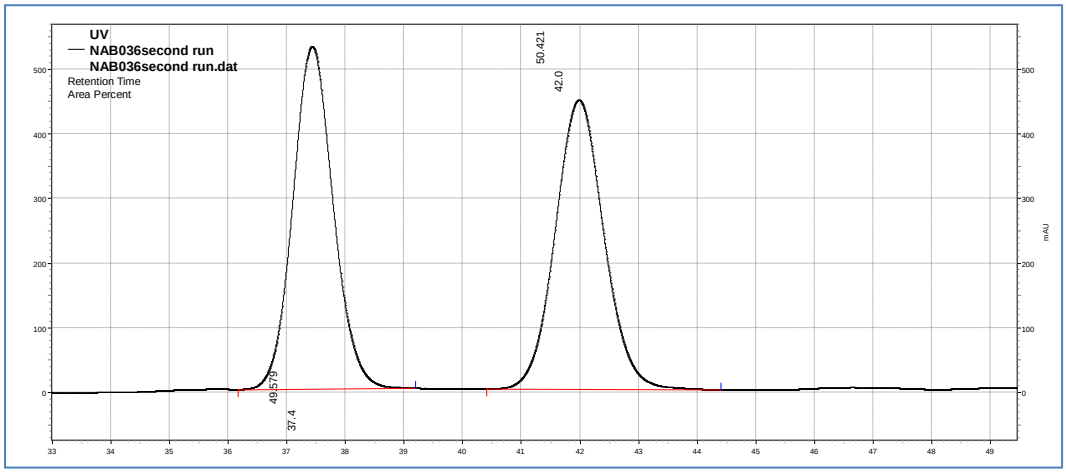
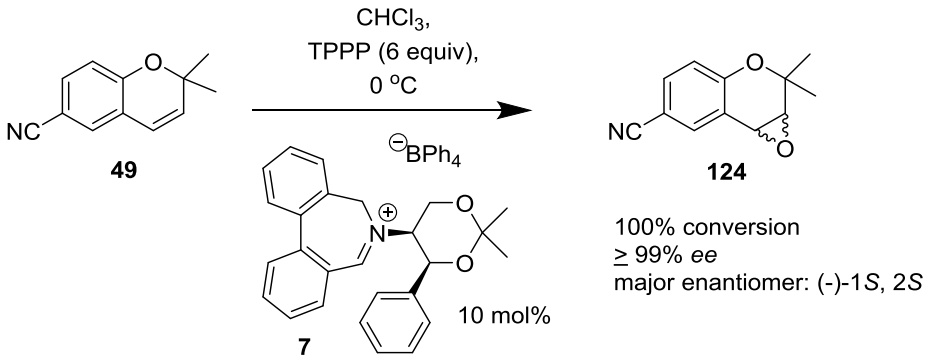


Figure 2.19 - HPLC trace of the racemic epoxide **124**

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 (–)-1*S*,2*S*-**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).



Scheme 2-48 - Asymmetric epoxidation of chromene **49**

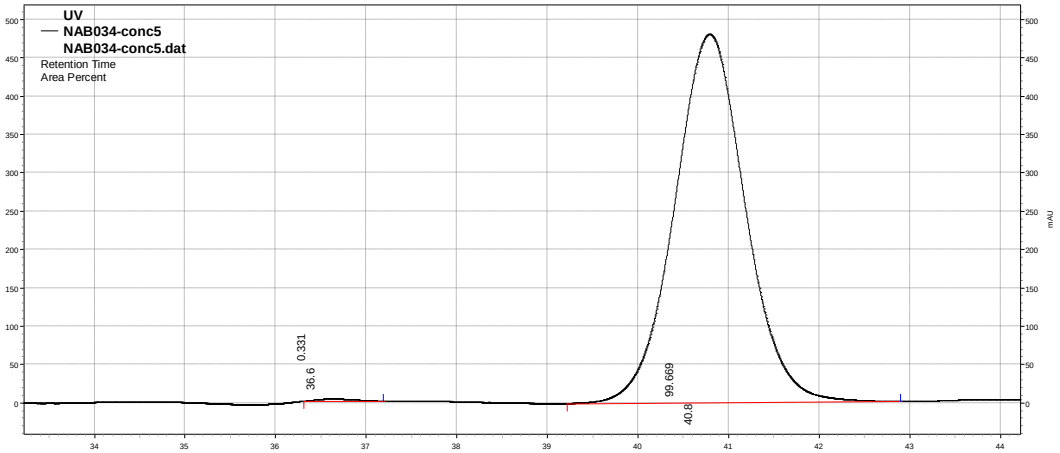


Figure 2.20 - Enantioenrich sample of **124**

Table 2-9 - Peaks area and height

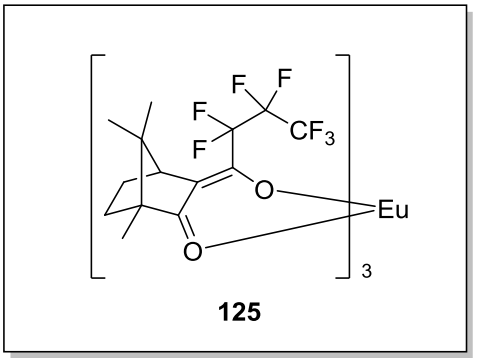
UV Results Retention Time	Area	Area %	Height	Height %
36.623	347322	0.33	11791	0.61
40.790	104456189	99.67	1922846	99.39
Totals	104803511	100.00	1934637	100.00

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

$$\%\ ee = \left[\frac{area\ A - area\ B}{area\ A + area\ B}\right] X\ 100\%$$

2.3.1.2 By ^{1}H NMR Spectroscopy with the Chiral Shift Reagent Eu (hfc)$_3$

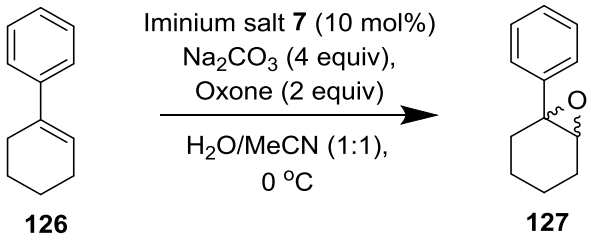
In some cases, the enantiomeric excess for epoxide samples cannot be determined using chiral HPLC as the peaks corresponding to both enantiomer are not resolved; therefore alternative methods of determining enantiomeric excess are required. In this research, the other method used to determine the *ee* 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)$_3$ **125** (Figure 2.21).



125

Figure 2.21 - Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate][102]

One example of chiral epoxides that cannot be resolved using chiral HPLC is 1-phenylcyclohexene oxide **127**; hence the chiral shift reagent was used to determine the *ee* of the chiral epoxide **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 **127** was prepared under aqueous conditions to test this method (Scheme 2-49).



Scheme 2-49 - Asymmetric epoxidation reaction on alkene 126 under aqueous conditions

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)

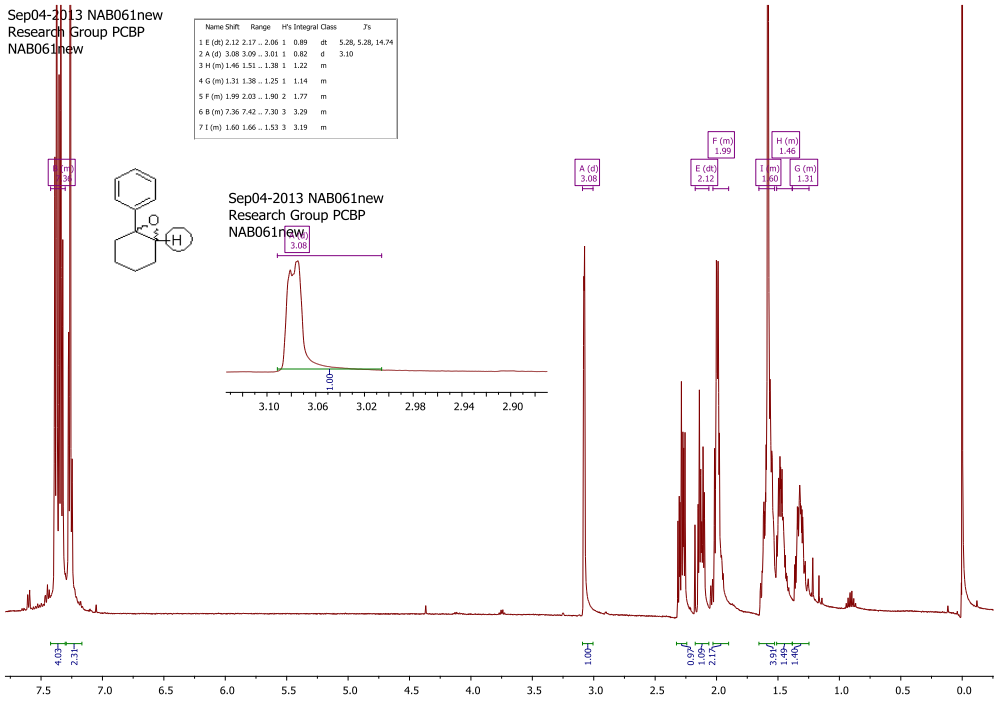


Figure 2.22 - ^{1}H NMR of enantioenrich sample of 1-phenylcyclohexene oxide 127

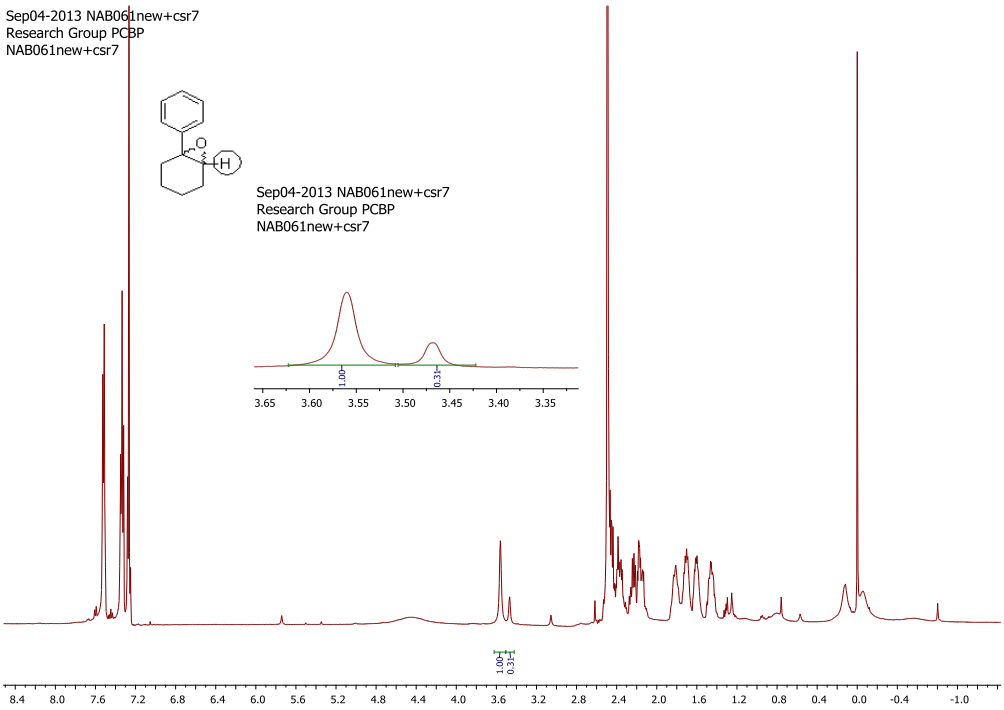


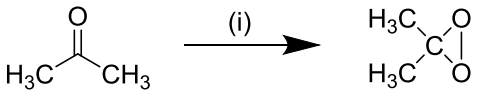
Figure 2.23 - ^{1}H NMR of enantioenriched sample of 1-phenylcyclohexene oxide 127 + Eu(hfc)$_3$ 125

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 ^{o}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_2CO_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 ^{o}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.[103] It was prepared by us by the reaction of Oxone® in mixture of acetone/water with the presence of $NaHCO_3$ (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 °C with vigorous stirring. The acetone solution of dimethyldioxirane was dried with K_2CO_3, filtered off and stored in the freezer (–20 °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_2O (254 mL), acetone (192 mL), $NaHCO_3$ (58 g), 5 °C to 10 °C

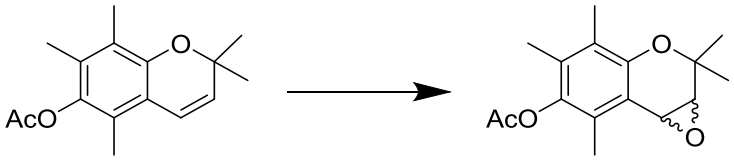
The concentration of DMDO was determined by iodometric titration. The acetone solution of DMDO was added to an Erlenmeyer flask containing water (20 mL), glacial acetic acid (1 mL) and a freshly prepared solution of NaI, and was titrated using a 0.02 M aqueous solution of sodium thiosulfate ($Na_2S_2O_3$). The concentration was then calculated using the following equation:

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

For a smaller scale, a simplified preparation of DMDO, the method reported by Taber can also be used.[104] In this method, a mixture of distilled H_2O (20 mL), acetone (30 mL) and $NaHCO_3$ (24 g, 0.285 mol) was stirred at 0 °C prior to addition of Oxone®. The slurry was then attached to a rotary evaporator with the bath at room temperature, which was then increased up to 40 °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_2SO_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.



54 (±)-**128**

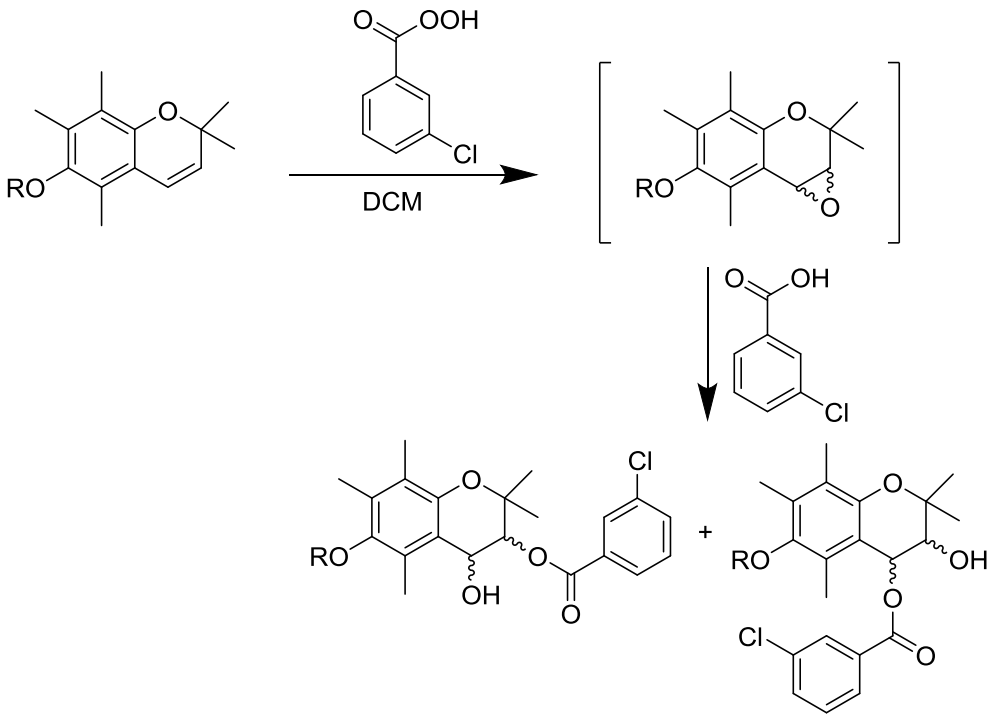
Scheme 2-51 - Reagents and conditions: (i) DMDO (1.5 equiv), DCM, 100% conversion

Table 2-10 - Racemic epoxidation at different temperature

Temperature (°C)	Reaction time (min)
–45	240
–20	80
0	20
Room temperature	20

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 acid[105] 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).

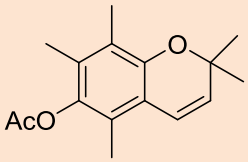
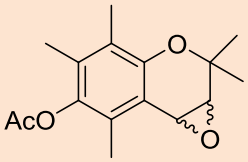
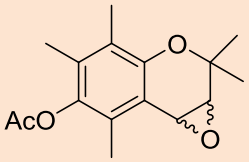
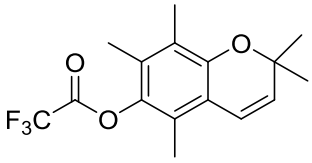
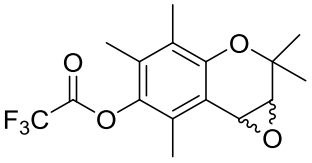
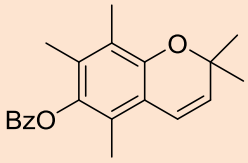
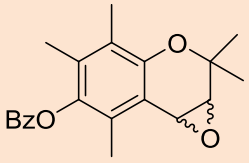


Scheme 2-52 – Possible ring-opening of the epoxide by *m*-chlorobenzoic acid

The use of pre-purified *m*-CPBA also disappointingly did not work for the racemic epoxidation of chromenes due to the presence of acidic *m*-chlorobenzoic acid as the by-product of the reaction, even though the reactions were worked-up using Na_2CO_3 several times. The purification of *m*-CPBA was carried out by dissolving the commercial *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_2PO_4 made up to 1 L, pH 7.5) several times as reported by Aggarwal,[106] affording 72% yield of pure *m*-CPBA. However this has to be done carefully at room temperature as the peroxyacid is potentially explosive.

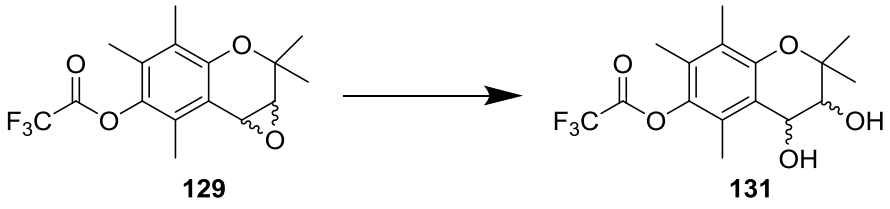
Addition of 10% aqueous Na_2CO_3 solution in racemic epoxidation of the chromene using pre-purified *m*-CPBA was found to be successful for chromene **54**. The base was added to neutralize the acidic by-product formed in the reaction. According to ^{1}H NMR spectroscopic analysis, the signals corresponding to the H(3) and H(4) of the (±)-**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.

Table 2-11 - Racemic epoxidation of protected 2,2,5,7,8-pentamethylchromene

Chromene/ Oxidant	***m*-CPBA**	**10%Na_2CO_3+ *m*-CPBA**	**DMDO**
 **54**	No epoxide	 **128**	 **128**
 **55**	No epoxide	No epoxide	 **129**
 **56**	No epoxide	No epoxide	 **130**

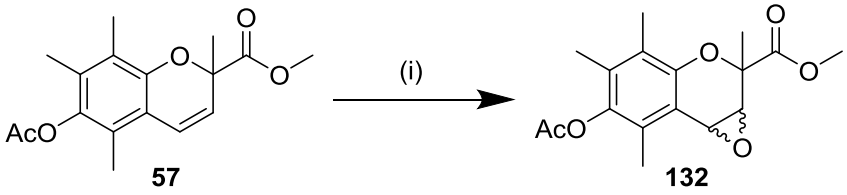
The racemic epoxidation reactions using DMDO as the oxidant were found to be more convenient for the protected chromene substrates. All the protected chromene substrates, acetyl-, trifluoroacetyl- and benzoyl-protected chromenes **54**, **55** and **56**, were easily converted into their corresponding 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.



Scheme 2-53 - Ring-opening of epoxide **129**

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).



Scheme 2-54 - Reagents and conditions: (i) DMDO (1.5 equiv), $CHCl_3$, 100% conversion

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[107] due to the steric interactions compared to *trans*-alkenes (Figure 2.24). However, this was not observed in the epoxidation of chromene **51**.

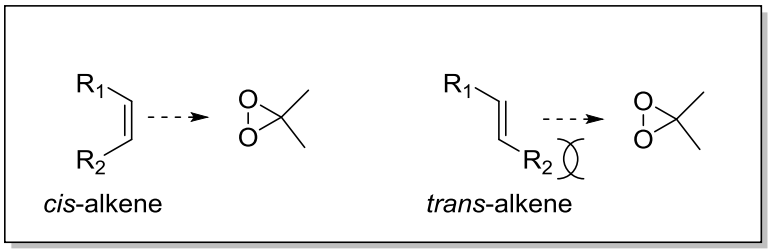
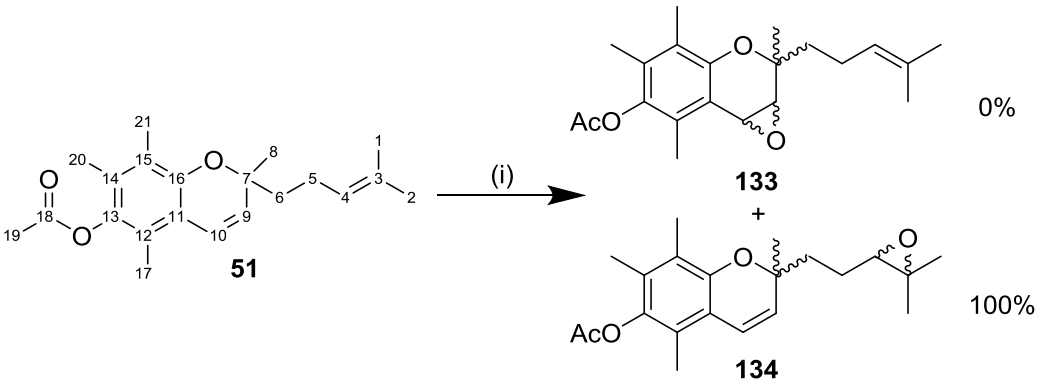


Figure 2.24 - Interaction of alkenes and DMDO

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

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.[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 $KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$) as a stoichiometric oxidant, Na_2CO_3 or $NaHCO_3$ 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 ^{o}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.[109] 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 ^{o}C.[110] Epoxidation reactions in aqueous conditions have to be carried out carefully. Any addition of oxidant has to be accompanied by addition of Na_2CO_3 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 monoperoxysulfate (TPPP), which is soluble in organic solvent, as oxidant.[109,111] TPPP is prepared as a colourless solid by treating Oxone® with tetraphenylphosphonium chloride:[109]

$$Ph_4P^+ Cl^- + \text{Oxone®}\ (2\ KHSO_5 \bullet KHSO_4 \bullet K_2SO_4) \rightarrow Ph_4P^+ (HSO_5)^-$$

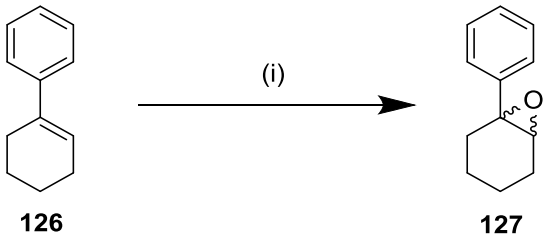
The use of TPPP eliminates the need of water as solvent and base. The presence of base under aqueous conditions is essential to neutralize the acidity of triple salt Oxone® and the absence of base in the reaction can improve the reaction as addition of base suppresses the epoxidation process. In organic solvent, typically chloroform,[109] the reaction can be carried out at much lower temperature, down to –40 ^{o}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.

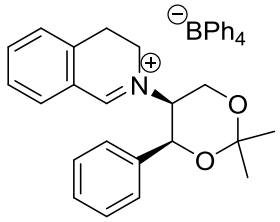
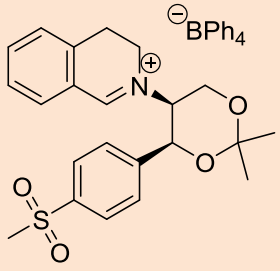
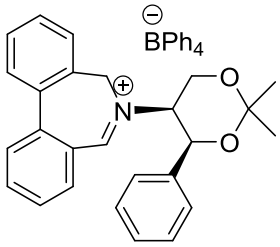
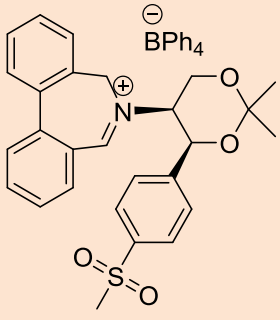
2.3.4 Catalysts Testing on Asymmetric Epoxidation

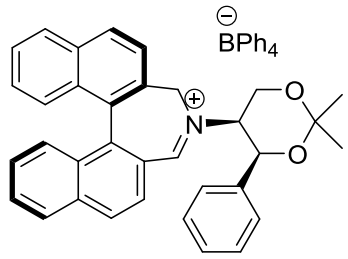
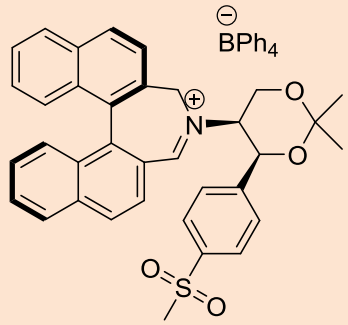
Before investigating the asymmetric epoxidation reactions, all the iminium salt catalysts **3**, **4**, **7** – **10** synthesized were tested on the commercially available unfunctionalized alkene, 1-phenylcyclohexene **126** under aqueous conditions, and the *ee* values and yields were compared to the 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.



Scheme 2-56 - Reagents and conditions: (i) Na_2CO_3 (4 equiv), Oxone® (2 equiv), iminium salt (5 mol%), MeCN/H_2O (1:1), 0 °C, 24 h

Table 2-12 - [a]Enantiomeric excesses were determined by ^{1}H NMR spectroscopy in the presence of (+)-Eu(hfc)$_3$; [b]The absolute configuration of the major enantiomers were determined by comparison of optical rotations with those reported in the literature

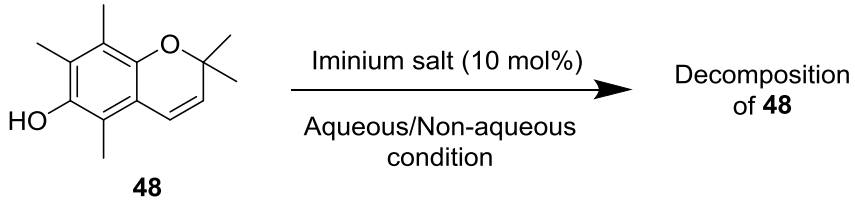
Iminium salt catalyst	Conversion, (%)	*Ee*, (%)[a]	Configuration[b]
In each case: Actual results/Literature value			
 **3**	100/55[20]	35/41	(–)-(1*S*, 2*S*)/(–)-(1*S*, 2*S*)
 **4**	100/100[8]	26/39	(–)-(1*S*, 2*S*)/(–)-(1*S*, 2*S*)
 **7**	100/100[7]	56/60	(–)-(1*S*, 2*S*)/(–)-(1*S*, 2*S*)
 **8**	100/47[8]	40/56	(–)-(1*S*, 2*S*)/(–)-(1*S*, 2*S*)

 **9**	100/69[9]	71/91	(–)-(1*S*, 2*S*)/(–)-(1*S*, 2*S*)
 **10**	100/70[14]	67/76	(–)-(1*S*, 2*S*)/(–)-(1*S*, 2*S*)

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.

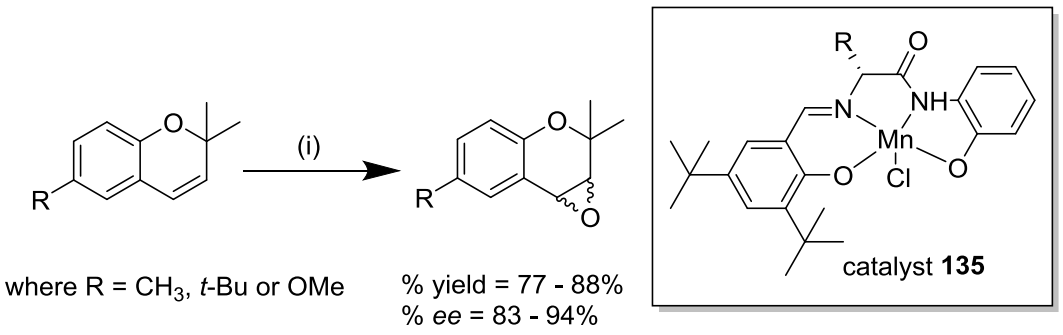
2.3.5 Asymmetric Epoxidation of Chromene by Iminium Salt Catalysts

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.



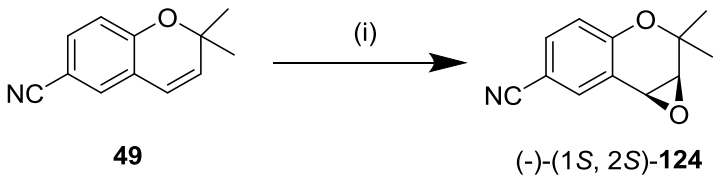
Scheme 2-57 – Decomposition of the chromenol during asymmetric epoxidation of non-protected chromene

Surprisingly, in contrast with this result, epoxidation of 6-substituted 2,2-dimethylchromenes bearing an electron donating group have been reported previously.[88,112] In one of the latest reports, in 2012, Cheng demonstrated the asymmetric catalytic activity of Mn(III) complexes **131** towards the oxidation of the mono-substituted 2,2-dimethylchromene, affording excellent *ee*s between 80 – 95% (Scheme 2-58).[112]



Scheme 2-58 - Reagents and conditions: (i) Mn(III) catalyst 135 (5 mol%), NaOCl (2 equiv), PyNO (15 mol%), ionic liquid (*L*-1-ethyl-(1'hydroxy-2'-propanyl)imidazolium bromide)[112]

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 **49**, bearing an electron-withdrawing group at the 6-position of the chromene substrate (Scheme 2-59).



49 (-)-(1*S*, 2*S*)-**124**

Scheme 2-59 - Reagents and conditions: (i) TPPP (4 equiv), $CHCl_3$, 0 °C, 2 days

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 dihydroisoquinoline-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*.

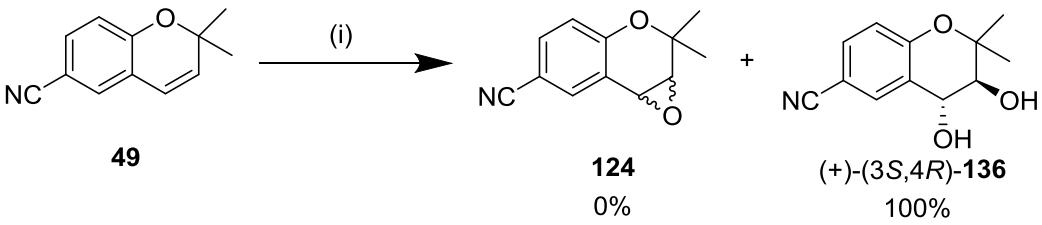
Table 2-13 - Asymmetric epoxidation of **49** under non-aqueous conditions[a]

Iminium salt catalyst	Yield (%)	*ee* (%)[b]	Configuration[c]
3	–	–	–
4	59	97.0	(–)-1*S*, 2*S*
7	20	99.3	(–)-1*S*, 2*S*
8	20	96.6	(–)-1*S*, 2*S*
9	–	–	–
10	–	–	–

[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.[13]

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 (+)-(3*S*,4*R*)-**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 *ee*s 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.*[113]



Scheme 2-60 - Reagents and conditions: (i) Na_2CO_3 (4 equiv), Oxone® (6 equiv), iminium salt catalyst (10 mol%), MeCN/H_2O (1:1), 0 °C, 24 h

Table 2-14 – Formation of diol 136 under aqueous conditions[a]

Iminium salt catalyst	Conversion (%)	*ee* (%)[b]	Configuration[c]
3	65	60	(+)-(3*S*, 4*R*)
4	44	57	(+)-(3*S*, 4*R*)
7	100	68	(+)-(3*S*, 4*R*)
8	100	71	(+)-(3*S*, 4*R*)
9	25	-	-
10	52	20	(+)-(3*S*, 4*R*)

[a]Reagents and conditions: Iminium salt catalyst (10 mol%), Oxone® (6 equiv), Na_2CO_3 (4 equiv), MeCN/H_2O (1:1), 0 °C, 24 h; [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.

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).

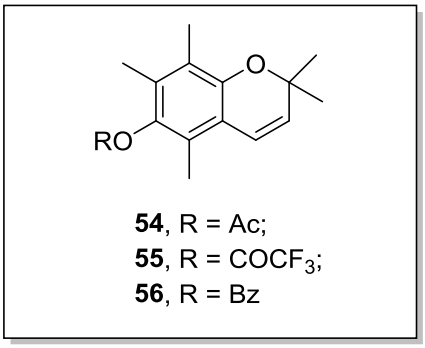
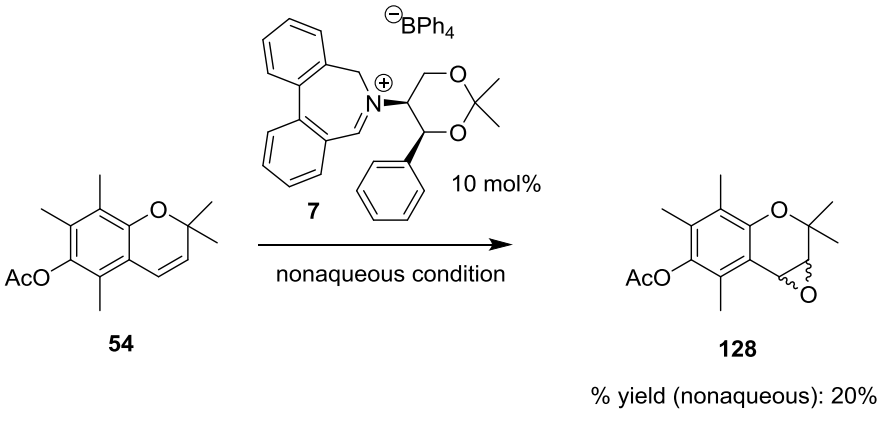


Figure 2.25 - The protected derivatives of 2,2,5,7,8-pentamethylchromenol 48

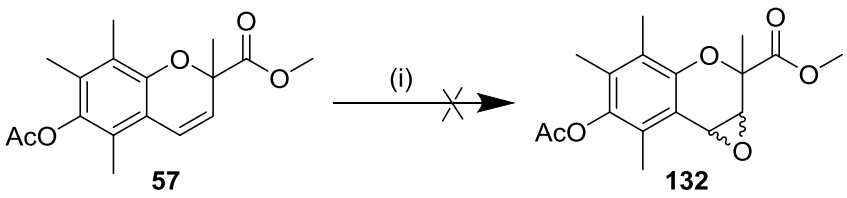
Investigation of the asymmetric epoxidation on acetyl protected chromene **54**, using the most selective iminium catalyst in our hands, catalyst **7**, showed that the acetyl-protected chromene is quite stable under the reaction conditions compared to the corresponding non-protected chromene **47** (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: (i) TPPP (4 equiv), $CHCl_3$, 0 °C, 2 days

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), $CHCl_3$, 0 °C, 2 days

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]

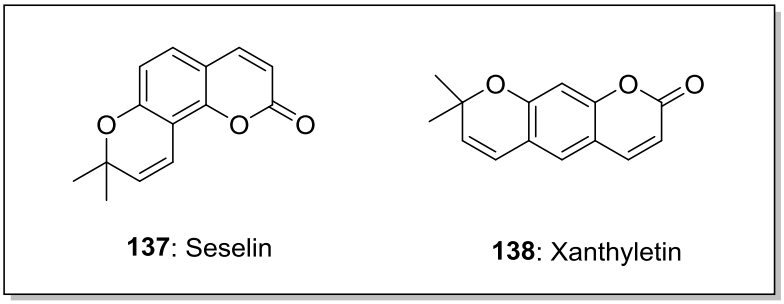


Figure 2.26 - Structures of seselin 137 and xanthyletin 138

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).

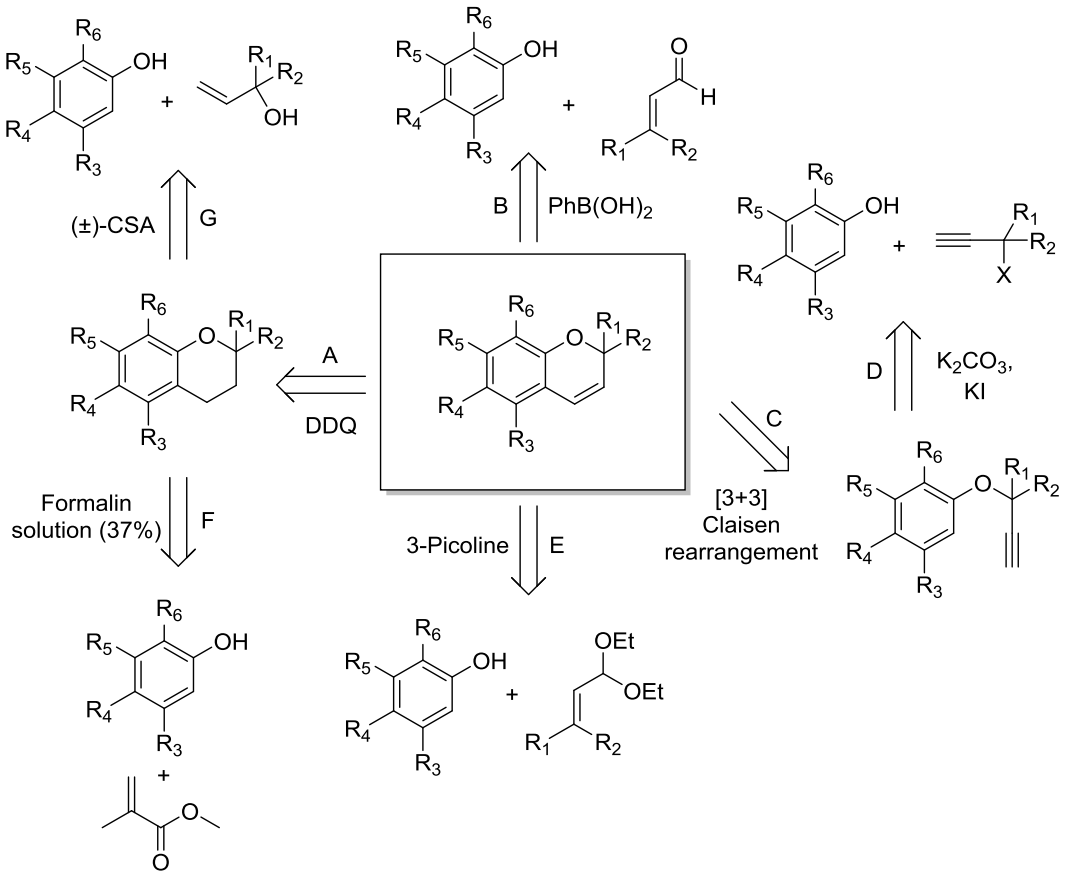


Figure 2.27 - Various synthetic approaches for the synthesis of chromenes **47** – **50**

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 (+)-(3*S*, 4*R*)-**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

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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 λ = 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 5μm 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-fluoroprophylhydroxymethylene)-(+)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 ^{o}C and 60 ^{o}C and was obtained from manufacturer, labelled as petroleum ether 40/60.

Diethyl ether (Et_2O) 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 ^{o}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. (^{13}C spectra) or C*H* arom. (^{1}H 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-CH_2 and CH_2N 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).

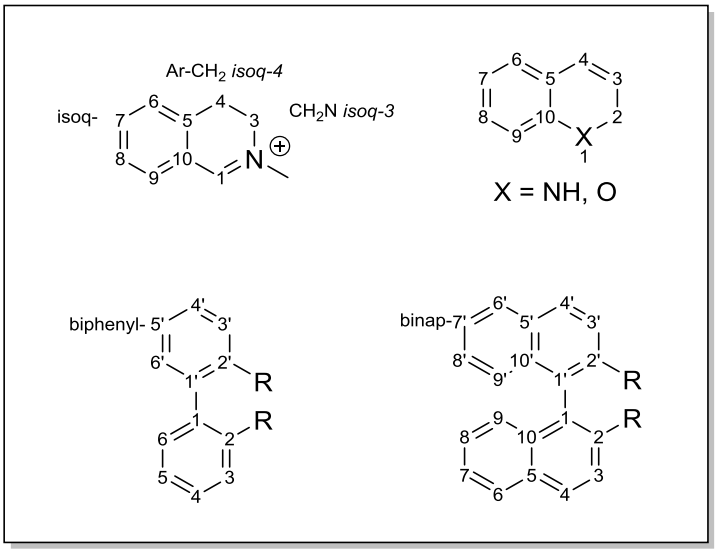


Figure 3.1 - Nomenclature of catalysts backbone moities

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.

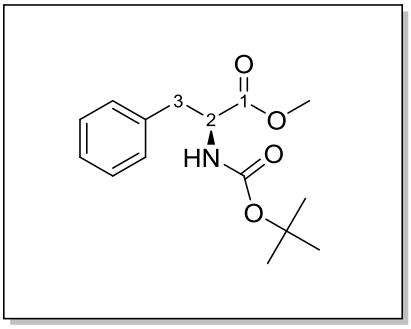
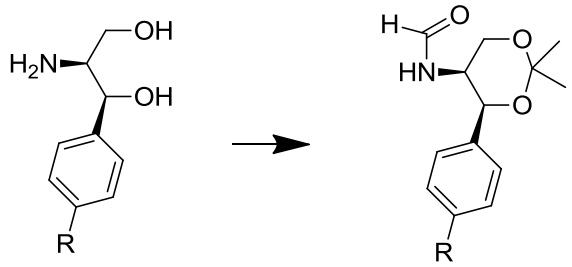


Figure 3.2 - Numbering system

3.3 Individual Experimental Procedures

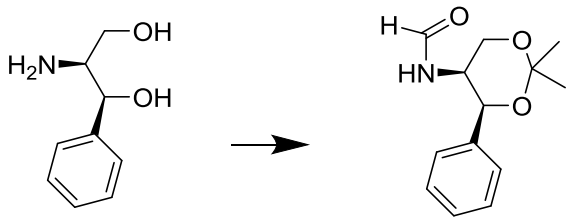
3.3.1 Synthesis of Iminium Salt Organocatalysts

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 ($MgSO_4$) and the solvents were removed under reduced pressure.

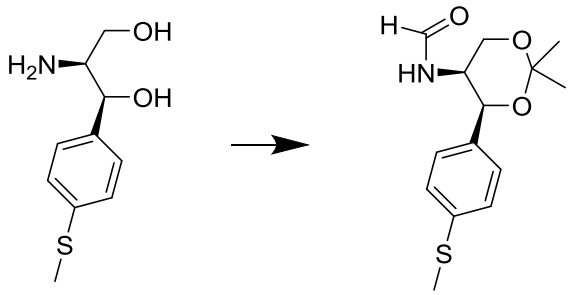
3.3.1.2 (4S,5S)-5-(Formylamino)-2,2-dimethyl-4-phenyl-1,3-dioxane[1]



13 **14**

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%). ν_{max} (neat)/cm^{-1} 3295, 2992, 1668, 1500, 1382, 1200, 1088, 844, 700; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.56 (s, 3H, $CH_2OC(CH_3)_2$), 1.60 (s, 3 H, $OC(CH_3)_2$), 3.91 (dd, J = 12, 2 Hz, 1H, $CH_2OC(CH_3)_2$), 4.28 (dd, J = 12, 2 Hz, 1H, $CH_2OC(CH_3)_2$), 4.33 (dd, J = 8, 2 Hz, 1H, (CHO)NHCH), 5.23 (d, J = 2 Hz, 1H, (CHO)NHCHCH-Ar), 6.14 (d, J = 8 Hz, 1H, (CHO)NHCH), 7.26 – 7.35 (m, 5H, Ar-CH), 7.99 (s, 1H, (CHO)NHCH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 18.5 ($CH_2OC(CH_3)_2$), 29.7 ($CH_2OC(CH_3)_2$), 45.5 ((CHO)NHCH), 64.6 ((CHO)$NHCH_2$), 71.7 ((CHO)NHCHCH-Ar), 99.7 (C quat., $CH_2OC(CH_3)_2$), 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).

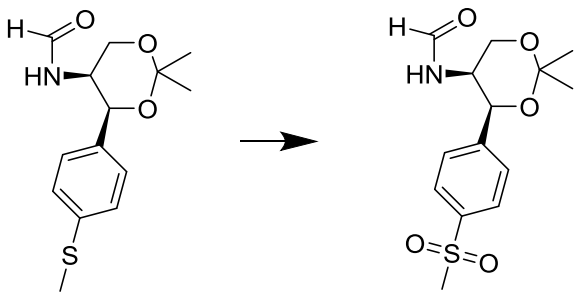
3.3.1.3 (4S,5S)-5-(Formylamino)-2,2-dimethyl-4-[4-(methylthio)phenyl]-1,3-dioxane[2–4]



15 **16**

Prepared according to the general procedure from (1S,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%); $[\alpha]_D$ = +0.9° (*c* = 1.00, $CHCl_3$), [Lit.[4] $[\alpha]_D$ = +1.3° (*c* = 1.27, $CHCl_3$)]. ν_{max} (neat)/cm^{-1} 3429, 3054, 2991, 1686, 1602, 1497, 1383, 1265, 1199, 1085, 948. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.55 (s, 3H, CC*H*$_3$), 1.58 (s, 3H, CC*H*$_3$), 2.46 (s, 3H, S-C*H*$_3$), 3.89 (d, *J* = 12 Hz, 1H, OC*H*HCHNH), 4.27 (d, *J* = 12 Hz, 1H, OCH$_2$C*H*NH), 4.28 (d, *J* = 8 Hz, 1H, OCH*H*CHNH), 5.18 (s, 1H, CHN*H*COH), 6.16 (d, *J* = 8 Hz, 1H, Ar-C*H*), 7.17 – 7.30 (m, 4H, 4 X C*H* arom.), 7.98 (s, 1, NHCO*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.2 (S*C*H$_3$), 18.5 (*C* quat., C(*C*H$_3$)$_2$), 29.7 (C(*C*H$_3$)$_2$), 45.3 (OCH$_2$*C*HNH), 64.6 (O*C*H$_2$CHNH), 71.4 (Ar-*C*H), 99.7 (O*C*(CH$_3$)O), 125.8 (2 X *C* arom.), 126.4 (2 X *C* arom.), 134.9 (*C* quat. arom., *C*-SCH$_3$), 137.8 (*C* quat. arom., OCH-*C*), 160.5 (NH*C*OH).

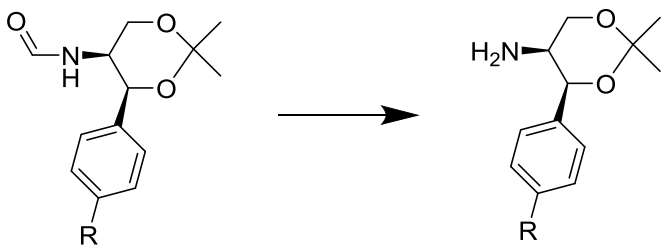
3.3.1.4 (4S,5S)-5-(Formylamino)-2,2-dimethyl-4-[4-(methylsulfonyl)phenyl]-1,3-dioxane[4,5]



16 **17**

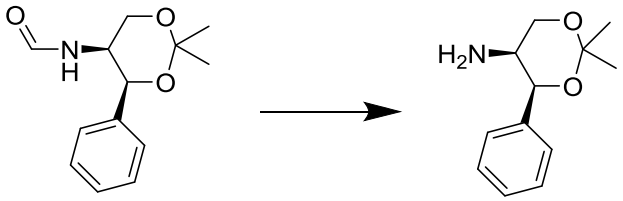
(4S,5S)-5-(Formylamino)-2,2-dimethyl-4-[4-(methylthio)phenyl]-1,3-dioxane (11.43 g, 38.7 mmol) **16** was dissolved in dichloromethane (100 mL), and the solution cooled to 0 °C. A solution of *m*-CPBA (20.7 g, 120 mmol) in chloroform (20 mL) was added dropwise over 10 min. The reaction was stirred for 2 h, washed with saturated sodium hydrogen carbonate (2 X 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, $CHCl_3$)]. ν_{max} (neat)/cm^{-1} 3357, 2995, 1671, 1515, 1383, 1300, 1239, 1202, 1149, 1086, 949. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.59 (s, 3H, CC*H*$_3$), 1.61 (s, 3H, CC*H*$_3$), 3.05 (s, 3H, SO_2CH_3), 3.88 (d, *J* = 12 Hz, 1H, OC*H*HCH), 4.33 (d, *J* = 12 Hz, 1H, OCH*H*CH), 4.43 (d, *J* = 10 Hz, 1H, CH_2CHNH), 5.27 (s, 1H, CHN*H*COH), 6.31 (d, *J* = 10 Hz, 1H, Ar-C*H*), 7.56 (d, *J* = 8 Hz, 2H, 2 X C*H* arom), 7.92 (d, *J* = 8 Hz, 2H, 2 X C*H* arom), 7.96 (s, 1H, NHCO*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 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 $MgSO_4$ and the solvent removed under reduced pressure.

3.3.1.6 (4S, 5S)-5-Amino-2,2-dimethyl-4-phenyl-1,3-dioxane[1,4]

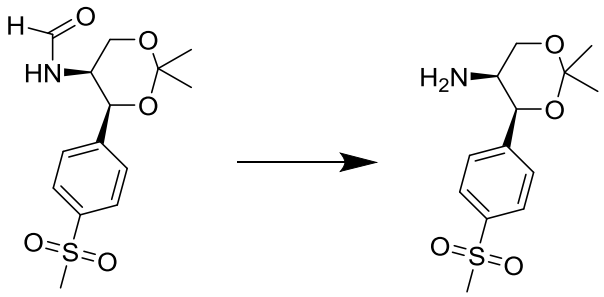


14 **11**

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%); $[\alpha]_D$ = +61.5° (*c* = 2.15, ethanol), [Lit.[4] $[\alpha]_D$ = +45.5° (*c* = 2.33, ethanol)]. ν_{max} (neat)/cm^{-1} 3367, 2991, 1663, 1498, 1380, 1271, 1239, 1160, 1198, 1130, 1088, 1052, 945, 845, 739, 700. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.55 (s, 3H, CC*H*$_3$), 1.56 (s, 3H, CC*H*$_3$), 2.79 (d, *J* = 4 Hz, 1H, OCH$_2$C*H*NH$_2$), 3.93 (dd, *J* = 12, 4 Hz, 1H, OC*H*HCHNH), 4.31 (dd, *J* = 12, 4 Hz, 1H, OCH*H*CHNH), 5.12 (s, 1H, NH$_2$CHC*H*(Ph)O), 7.28 – 7.37 (m, 5H, 5 X Ar-*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.60 (*C*H$_3$), 29.75 (*C*H$_3$), 49.58 (N*C*H),

65.88 (CH_2), 73.76 (Ar-*C*H), 99.22 (*C* quat.), 125.69 (2C, 2 X *C* arom.), 129.59 (2C, 2 X *C* arom.), 139.43 (*C* quat. arom.).

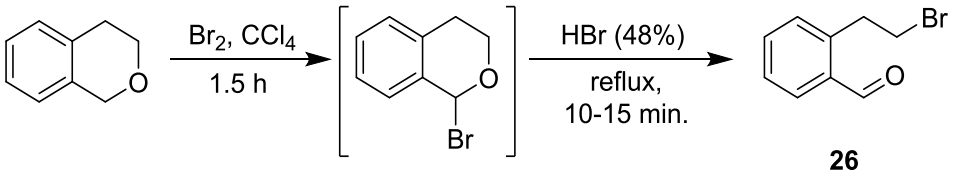
3.3.1.7 (4S,5S)-5-Amino-4-[4-(methylsulfonyl)phenyl]-1,3-dioxane[4,5]



17 **12**

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.[5] mp 120 – 122 °C]; $[\alpha]_D$ = +65.3° (*c* = 1.05, $CHCl_3$), [Lit.[5] $[\alpha]_D$ = +50.0° (*c* = 1.00, $CHCl_3$)]. ν_{max} (neat)/cm^{-1} 3055, 2990, 1382, 1316, 1265, 1152, 1077, 957, 739. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.53 (s, 6H, OCCH_3), 2.83 (s, 1H, OCH_2CHNH_2), 3.03 (s, 3H, SO_2CH_3), 3.86 (d, *J* = 12 Hz, 1H, OCH*H*CHNH), 4.30 (d, *J* = 12 Hz, 1H, OCH*H*CHNH), 5.15 (s, 1H, Ph-C*H*), 7.52 (d, *J* = 8 Hz, 2H, 2 X Ar-C*H*), 7.92 (d, *J* = 8 Hz, 2H, 2 X Ar-C*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 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.

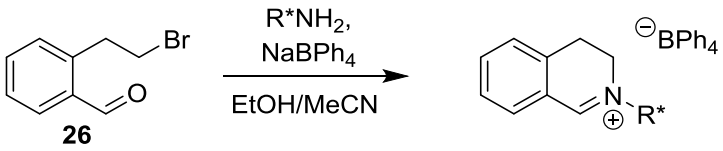
3.3.1.8 General Procedure for the Synthesis of 2-(2-bromoethyl)benzaldehyde[6]



26

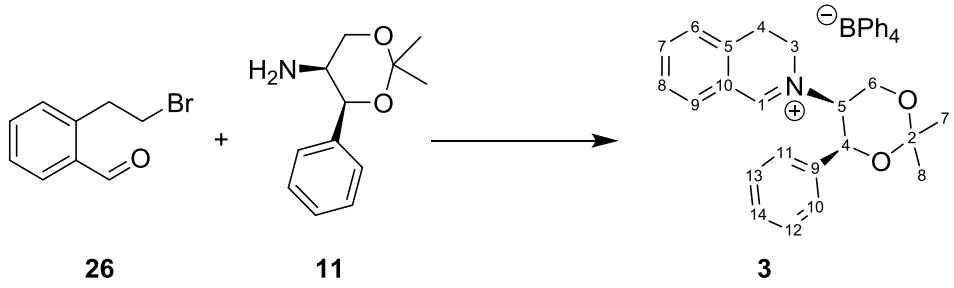
Bromine (1.0 equiv) was added slowly over a period of 10 minutes to an ice-cooled solution of isochromane (1.0 equiv) in carbon tetrachloride (CCl_4) with stirring. After the exothermic reaction subsided, the cooling bath was removed and dark brown solution heated under reflux until the reaction mixture 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 Et_2O (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 Na_2CO_3, 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. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.36 – 3.64 (m, 4H, Ph(C*H*$_2$)$_2$Br, 7.34 (d, *J* = 8 Hz, 1H, C*H* arom., *ortho* to bromoethyl group), 7.49 (t, *J* = 8 Hz, 1H, C*H* arom., *para* to bromoethyl group), 7.56 (t, *J* = 8 Hz, 1H, C*H* arom., *para* to formyl group), 7.83 (d, *J* = 8 Hz, 1H, C*H* arom., *ortho* to formyl group) 10.15 (s, 1H, C*H*O); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 32.8 (Ph*C*H$_2$), 36.3 (*C*H$_2$Br), 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, *C*HO). Analytically pure samples may be obtained by distillation under reduced pressure at *ca*. 150 ^{o}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.

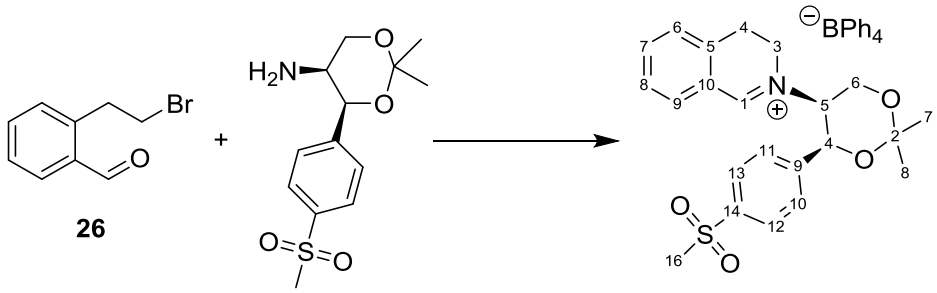
3.3.1.10 (+)-N-[(4S,5S)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl]-3,4-dihydroisoquinolinium tetraphenylborate[3,5]



Prepared according to the general procedure from (4*S*,5*S*)-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/Et_2O to give the product **3** as yellow solid, (0.21 g, 58%); mp 162 – 165 °C [Lit.[5] mp 169 – 170 °C]; $[\alpha_D]$ = +48.2° (*c* = 2.64, CH_3CN), [Lit.[5] $[\alpha]_D$ = +38.6° (*c* = 2.70, CH_3CN)]. ν_{max} (neat)/cm^{-1} 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. ^{1}H-NMR (500 MHz, CD_3CN): δ 1.69 (s, 3H, OCCH_3, C7 or C8), 1.71 (s, 3H, OCCH_3, C7 or C8), 2.51 – 2.64 (m, 1H, Ar-CH_2, *isoq*-4), 2.83 – 2.92 (m, 1H, Ar-CH_2, *isoq*-4), 3.40 – 3.50 (m, 1H, CH_2N, *isoq*-3), 4.00 – 4.09 (m, 1H, CH_2N, *isoq*-3), 4.21 (t, *J* = 3 Hz, 1H,

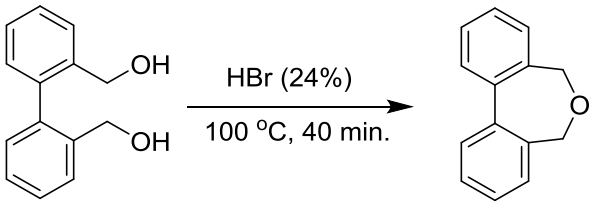
C5), 4.42 (dd, *J* = 14, 1 Hz, 1H, C6), 4.68 (dd, *J* = 14, 1 Hz, 1H, C6), 5.79 (d, *J* = 3 Hz, 1H, C4), 6.88 (t, *J* = 8 Hz, 4H, C*H* arom., *para* in $^{-}BPh_4$), 7.03 (t, *J* = 8 Hz, 8H, *meta* in $^{-}BPh_4$), 7.33 – 7.35 (m, 8H, C*H* arom., *ortho* in $^{-}BPh_4$), 7.35 – 7.46 (m, 6H, 6 X C*H* arom.), 7.53 (t, *J* = 7 Hz, 1H, C*H* arom.), 7.78 (m, 2H, 2 X C*H* arom.), 7.87 (d, *J* = 7 Hz, 1H, C*H* arom.), 9.03 (s, 1H, N=C*H*); ^{13}C-NMR (125 MHz, acetone-d_6): 17.9 (*C*H_3, C7 or C8), 24.5 (Ar-*C*H_2, *isoq*-4), 28.7 (*C*H_3, C7 or C8), 51.6 (*C*H_2N, *isoq*-3), 61.9 (CH_2, C6), 65.8 (N*C*H, C5), 70.9 (Ar*C*H, C4), 100.5 (C quat., C2), 121.4 (4C, 4 X *C* arom., *para* in $^{-}BPh_4$), 124.6 (C quat. arom.), 125.1 (2C, 2 X *C* arom., *meta* in $^{-}BPh_4$), 125.1 (2C, 2 X *C* arom., *meta* in $^{-}BPh_4$), 125.2 (2C, 2 X *C* arom., *meta* in $^{-}BPh_4$), 125.2 (2C, 2 X *C* arom., *meta* in $^{-}BPh_4$), 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 $^{-}BPh_4$), 134.4 (*C* arom.), 136.2 (6C, 4 X *C* arom., *ortho* in $^{-}BPh_4$, 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 (H*C*=N).

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



Prepared according to the general procedure from (4*S*,5*S*)-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.[2] mp 199 – 201 °C]; $[\alpha]_D$ = +195° (*c* = 1.06, acetone), [Lit.[2] $[\alpha]_D$ = +126.7° (*c* = 1.20, acetone)]. ν_{max} (film)/cm^{-1} 3419, 3278, 3055, 2999, 1719, 1636, 1603, 1572, 1479, 1426, 1384, 1315, 1266, 1202, 1150, 1122, 1077, 1032, 956. ^{1}H-NMR (500 MHz, acetonitrile-D_3): δ 1.69 (s, 3H, OCCH_3, C7 or C8), 1.72 (s, 3H, OCCH_3, C7 or C8), 2.62 (ddd, *J* = 18, 10, 7 Hz, 1H, Ar-CH_2, *isoq*-4), 2.85 – 2.90 (m, 1H, Ar-CH_2, *isoq*-4), 3.03 (s, 3H, C16), 3.46 – 3.54 (m, 1H, CH_2N, *isoq*-3), 3.99 – 4.08 (m, 1H, CH_2N, *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 $^-$BPh$_4$), 7.03 (t, *J* = 8 Hz, 8H, *meta* in $^-$BPh$_4$), 7.31 – 7.35 (m, 8H, *ortho* in $^-$BPh$_4$), 7.37 (d, *J* = 8 Hz, 1H, C*H* arom.), 7.54 – 7.55 (m, 1H, C*H* arom.), 7.70 (d, *J* = 8 Hz, 2H, C*H* arom.), 7.96 (d, *J* = 8 Hz, 2H, C*H* arom.), 9.04 (s, 1H, C16); ^{13}C-NMR (125 MHz, acetonitrile-D_3): δ 18.5 (*C*H$_3$, C7 or C8), 25.0 (Ar-*C*H$_2$, *isoq*-4), 29.1 (*C*H$_3$, C7 or C8), 44.1 (S*C*H$_3$, C16), 52.1 (*C*H$_2$N, *isoq*-3), 62.3 (*C*H$_2$, C6), 65.5 (N*C*H$_2$, C5), 71.0 (Ar-*C*H$_2$, C4), 101.4 (*C* quat., C2), 122.4 (4C, 4 X *C* arom., *para* in $^-$BPh$_4$), 124.8 (*C* quat. arom.), 126.2 (2C, 2 X *C* arom., *meta* in $^-$BPh$_4$), 126.2 (2C, 2 X *C* arom., *meta* in $^-$BPh$_4$), 126.2 (2C, 2 X *C* arom., *meta* in $^-$BPh$_4$), 126.2 (2C, 2 X *C* arom., *meta* in $^-$BPh$_4$), 127.2 (*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 $^-$BPh$_4$), 137.6 (*C* arom.), 139.5 (*C* arom.), 139.9 (*C* quat. arom.), 141.7 (*C* quat. arom.), 142.8 (*C* quat. arom.), 163.8 (*C* quat. arom.), 164.2 (*C* quat. arom.), 164.4 (*C* quat. arom.), 165.0 (*C* quat. arom.), 168.5 (H*C*=N).

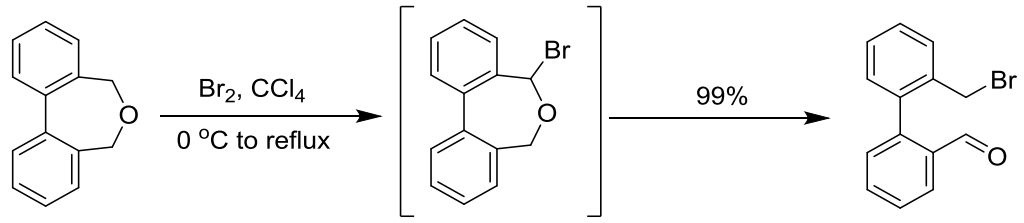
3.3.1.12 5,7-Dihydrodibenzo[c,e]oxepine[7]



28 **29**

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_2O (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]. ν_{max} (neat)/cm^{-1} 2987, 2305, 1421, 1377, 1265, 1198, 1156, 1075, 1044, 994, 944, 896, 739, 705, 621. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.37 (s, 4H, 2 X O*C*H_2), 7.40 – 7.45 (m, 4H, 4 X C*H* arom.), 7.49 – 7.52 (m, 2H, C*H* arom.), 7.56 (m, 2H, C*H* arom.); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 67.6 (2 C, 2 X O*C*H_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 *C* quat. arom.), 141.2 (2C, 2 X *C* quat. arom.).

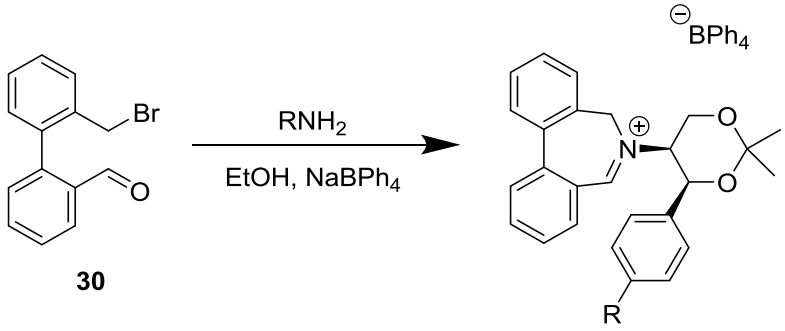
3.3.1.13 2-[2-(Bromomethyl)phenyl]benzene carbaldehyde[7]



29 **30**

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 (CCl_4) (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 Et_2O (100 mL), washed with saturated Na_2CO_3 (2 X 50 mL) and brine (50 mL) and dried over $MgSO_4$. The solvents were removed under reduced pressure to yield brownish oil of **30** in excellent yield (2.50 g, 99%). ν_{max} (neat)/cm^{-1} 3188, 1667, 1589, 1391, 1248, 1198, 774, 722, 630. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.25 (d, *J* = 10 Hz, 1H, Ar-C*H*HBr), 4.35 (d, *J* = 10 Hz, 1H, Ar-C*H*HBr), 7.22 (dd, *J* = 8, 1 Hz, 1H, C*H* arom.), 7.41 (m, 3H, 3 X C*H* arom.), 7.58 (m, 1H, C*H* arom.), 7.67 (td, *J* = 8, 1 Hz, 1H, C*H* arom.), 8.07 (dd, *J* = 8 Hz, 1 Hz, 1H, C*H* arom.), 9.74 (d, *J* = 1 Hz, 1H, *H*-aldehyde); ^{13}C-NMR (125 MHz, $CDCl_3$): 31.4 (Ar-*C*H_2Br), 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 (*C*H aldehyde).

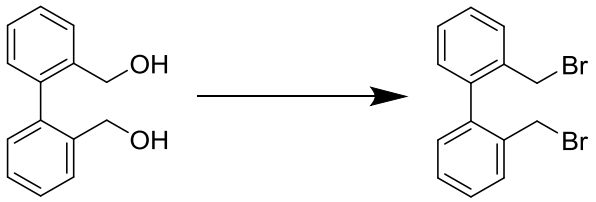
3.3.1.14 General Procedure for the Synthesis of Iminium Salt Catalyst from 2-[2-(Bromoethyl)phenyl]benzene carbaldehyde and primary amines[7]



30

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 ^{o}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_2O.

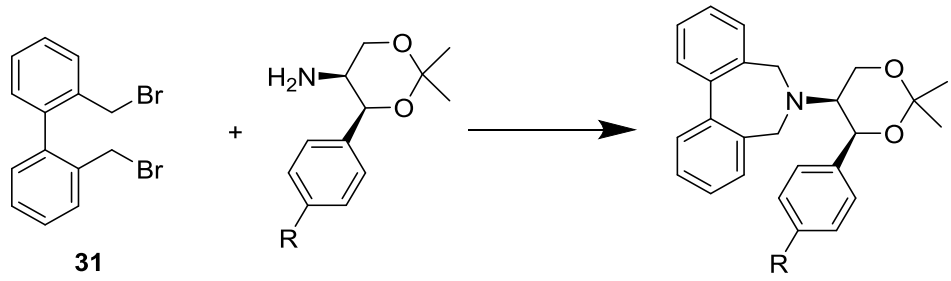
3.3.1.15 Synthesis of 2,2'-Bis (bromomethyl)[1,1']biphenyl from [1,1']Biphenyl-2,2'-diol[8]



28 **31**

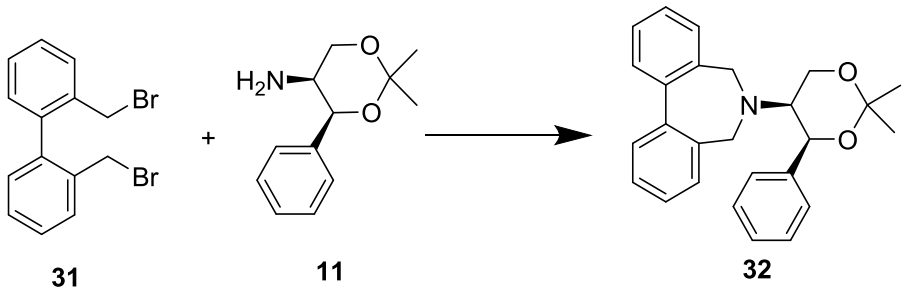
2,2'-Biphenyldimethanol **28** (1.14 g, 5.30 mmol) was dissolved in 48% HBr (10 mL per gram of 2,2'-biphenyldimethanol) and reflux for 2 hours. Dichloromethane (50 mL) was added to the solution, followed by water (50 mL). The solution was separated in a separating funnel. The product was in the bottom layer and washed several times with DCM. The organic phase was separated and dried ($MgSO_4$). 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 ^{o}C [Lit.[8] mp 91 – 93 ^{o}C]. ν_{max} (neat)/cm^{-1} 3059, 2995, 1476, 1444, 1265, 1221, 1007, 829, 808, 738, 704, 607, 537. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.20 (d, *J* = 8 Hz, 2H, 2 x Ph-C*H*H), 4.35 (d, *J* = 12 Hz, 2H, 2 x Ph-CH*H*), 7.28 (d, *J* = 2 Hz, 2H, 2 X C*H* arom., *biphenyl-2,2'*), 7.29 – 7.55 (m, 4H, 4 X C*H* arom., *biphenyl-3,3', 4,4'*), 7.57 (d, *J* = 2 Hz, 2H, 2 X C*H* arom., *biphenyl-5,5'*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 31.9 (2C, 2 X *C*H_2Br), 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_2CO_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_2CO_3. The organic layer was washed several times with water and brine, and then dried ($MgSO_4$). The solvent was removed under reduced pressure.

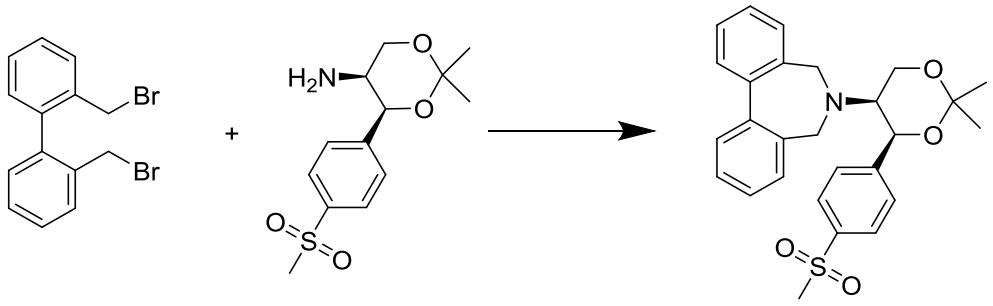
3.3.1.17 (+)-6-[(4S,5S)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl]-6,7-dihydro-5H-diezo[c,e]azepine[9]



Prepared according to the general procedure for the preparation of biphenyl azepines from (4*S*,5*S*)-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%). ν_{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): δ 1.61 (s, 6H, 2 X OCCH_3), 2.99 (d, *J* = 3 Hz, 1H, NC*H*CH_2O), 3.52 (d, *J* = 12 Hz, 1H, NCHCH*H*O), 3.70

(d, *J* = 12 Hz, 1H, NCHC*H*HO), 4.28 (d, *J* = 3 Hz, 2H, downfield portion of A system, 2 X ArCH_2N), 4.40 (s, 2H, upfield portion of A system, 2 X ArCH_2N), 5.23 (d, *J* = 3 Hz, 1H, NCHC*H*Ar-O), 7.24 – 7.47 (m, 13H, 13 X C*H* arom.); ^{13}C-NMR (125 MHz, acetone-d_6): *δ* 19.2 (C(*C*H_3)$_2$), 29.5 (C(*C*H_3)$_2$), 54.0 (NCH*C*H_2O), 60.9 (N*C*HCH$_2$O), 62.2 (Ar*C*H_2N), 67.6 (Ar*C*H_2N), 74.7 (NCH*C*HAr-O), 99.1 (C quat., O*C*(CH$_3$)O), 126.3 (*C* arom.), 126.8 (*C* arom.), 127.3 (*C* arom.), 127.5 (*C* arom.), 127.5 (*C* arom.), 127.72 (*C* arom.), 127.82 (*C* arom.), 128.29 (*C* arom.), 128.96 (*C* arom.), 129.38 (*C* arom.), 129.73 (*C* arom.), 135.16 (*C* quat. arom.), 136.63 (quat. arom.), 140.19 (*C* quat. arom.), 140.96 (*C* quat. arom.), 141.22 (*C* quat. arom.).

3.3.1.18 (+)-6-[(4S,5S)-2,2-Dimethyl-4-(4-(methylsulfonyl)phenyl)-1,3-dioxan-5-yl]-6,7-dihydro-5H-diezo[c,e]azepine[9]

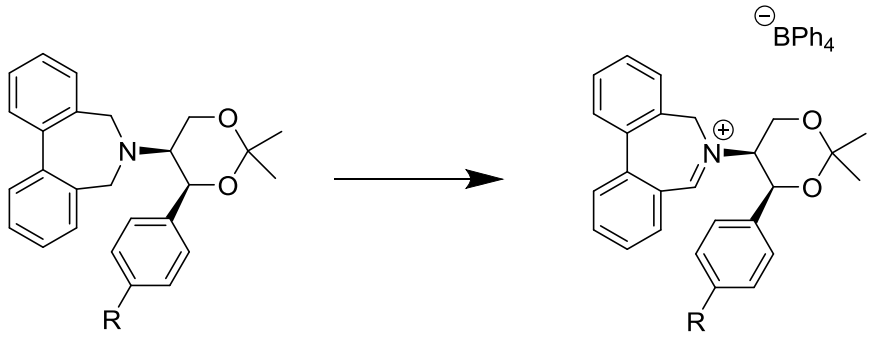


31 **12** **33**

Prepared according to the general procedure for the preparation of biphenyl azepines from (4*S*,5*S*)-5-amino-6-(4-methylsulfone)phenyl-2,2-dimethyl-1,3-dioxane **12** (2.75 g, 9.62 mmol) and 2,2'-bis(bromomethyl)[1,1']-biphenyl **31** (3.272 g, 9.62 mmol) to give the title compound **33** as yellow foam (3.75 g, 84%). ν_{max} (neat)/cm^{-1} 3054, 2987, 1677, 1602, 1480, 1440, 1315, 1265, 1200, 1151, 1076, 1012, 957, 896, 852. ^{1}H-NMR (400 MHz, acetone-d_6): *δ* 1.58 (s, 3H, OCC*H*$_3$), 1.60 (s, 3H, OCC*H*$_3$), 3.04 (s, 1H, NC*H*), 3.05 (s, 3H, -SO$_2$C*H*$_3$), 3.45 (d, *J* = 16 Hz, 2H, upfield portion of A system, 2 X ArCH_2N), 3.68 (d, *J* = 16 Hz, 2H, downfield portion of A system, 2 X ArCH_2N), 4.24 (m, 2H, NCHCH_2O), 5.30 (s, 1H, NCHC*H*(Ph-SO$_2$CH$_3$)O), 7.18 (dd, *J* = 8, 1 Hz, 2H, 2 X C*H* arom.), 7.28 – 7.42 (m, 6H, 6 X C*H* arom.), 7.65 (d, *J* = 8 Hz, 2H, 2 X C*H* arom.), 7.92 (d, *J* = 8 Hz, 2H, 2 X C*H* arom.); ^{13}C-NMR (100 MHz, acetone-d_6): *δ* 19.1 (C(*C*H$_3$)$_2$), 29.3 (C(*C*H$_3$)$_2$), 44.6 (-SO$_2$*C*H$_3$), 530.9 (2 C, 2 X Ar*C*H$_2$N), 60.4 (N*C*HCH$_2$O), 61.6 (NCH*C*H$_2$O), 74.2 (NCH*C*H(PhSO$_2$CH$_3$)), 99.3 (quat., O*C*(CH$_3$)O), 126.7 (2C, 2

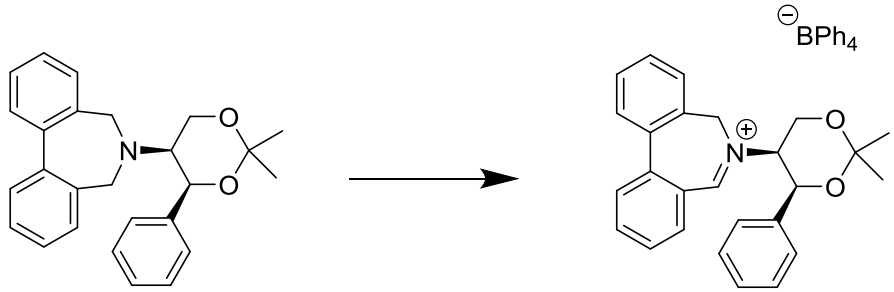
X *C* arom.), 127.1 (2C, 2 X *C* arom.), 127.5 (2C, 2 X *C* arom.), 127.7 (2C, 2 X *C* arom.), 127.9 (2C, 2 X *C* arom.), 136.2 (2C, 2 X *C* quat. arom.), 138.6 (2 C, 2 X *C* quat. arom.), 140.9 (2 C, 2 X *C* quat. arom.), 147.0 (2 C, 2 X *C* quat. arom.).

3.3.1.19 General Procedure for the Synthesis of Biphenyl Iminium Salts



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 eq) 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 ($MgSO_4$), 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 ^{o}C.

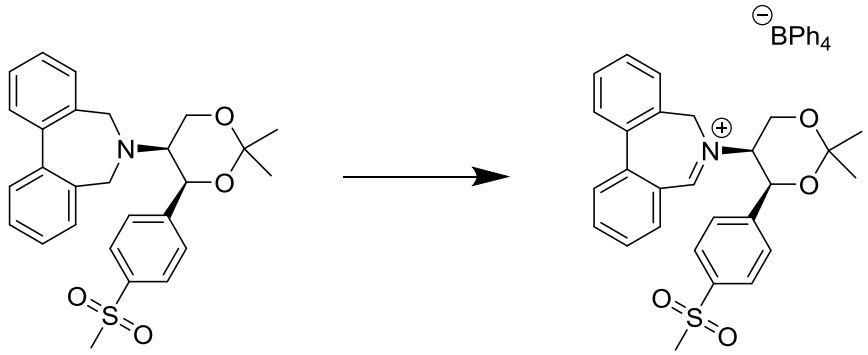
3.3.1.20 *(–)-2-[(4S,5S)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl]-5H-dibenzo[c,e]azepinium tetraphenylborate*[5]



32 **7**

Prepared according to the general procedure for the synthesis of biphenyl iminium salts from (+)-6-[(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-6,7-dihydro-5*H*-dibenzo[c,e] azepine **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.[5] mp 187 – 188 °C]; $[\alpha]_D$ = –44.4° (*c* = 1.25, CH_3CN), [Lit.[5] $[\alpha]_D$ = –44.0° (*c* = 1.01, CH_3CN)]. ν_{max} (neat)/cm^{-1} 3054, 2987, 1634, 1479, 1386, 1265, 1203, 1115, 896, 739, 705. ^{1}H-NMR (400 MHz, acetone-d_6): δ 1.81 (s, 3H, OC(C*H*$_3$)$_2$), 1.83 (s, 3H, OC(C*H*$_3$)$_2$), 4.37 (br, 1H, NCHC*H*HO), 4.49 (dd, *J* = 20, 4, 4 Hz, 1H, NC*H*CH$_2$O), 4.82 – 4.92 (m, 2H, NCHCH*H*O/1 X ArC*H*HN), 5.86 (br, 1H, ArC*H*HN), 6.03 (s, 1H, NCHC*H*Ar-O), 6.79 (t, *J* = 4 Hz, 4H, *para* in $^-$BPh$_4$), 6.93 (t, *J* = 8 Hz, 8H, 8 X C*H* arom., *meta* in $^-$BPh$_4$), 7.33 – 7.67 (m, 13H, 5 X C*H* arom./8 X C*H* arom. *ortho* in $^-$BPh$_4$), 7.70 – 7.77 (m, 6H, 6 X C*H* arom.), 7.99 – 8.05 (m, 2H, 2 X C*H* arom.), 9.05 (br, 1 H, N=C*H*); ^{13}C-NMR (100 MHz, acetone-d_6): Only the counter-ion ^{13}C signals were observed.

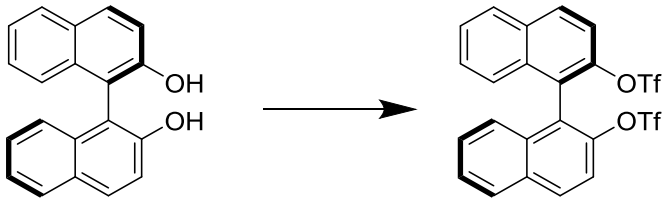
3.3.1.21 *(–)-2-[(4S,5S)-2,2-Dimethyl-4-(methylsufonyl)phenyl-1,3-dioxan-5-yl]-5H-dibenzo[c,e]azepinium tetraphenylborate*[5]



33 **8**

Prepared according to the general procedure from (+)-6-[(4S, 5S)-2,2-Dimethyl-4-(4-(methylsulfonyl)phenyl)-1,3-dioxan-5-yl]6,7-dihydro-5H-diezo[c,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]; $[\alpha]_D$ = –52.7° (*c* = 1.07, acetone), [Lit.[5] $[\alpha]_D$ = –50.3° (*c* = 1.09, acetone)]; ν_{max} (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): δ 1.81 (s, 3H, OC(CH_3)$_2$), 1.84 (s, 3H, OC(CH_3)$_2$), 3.02 (s, 3H, -SO_2CH_3), 4.40 – 4.43 (br, 1H, Ar-CH*H*N, up-field portion of AB system), 4.51 (d, *J* = 12 Hz, 1H, NCHCH*H*O, up-field portion of ABX system), 4.89 (d, *J* = 12 Hz, 1H, NCHCH*H*O, down-field portion of ABX system), 5.62 (br, 1H, Ar-CH*H*N, down-field portion of AB system), 6.13 (s, 1H, NC*H*CH_2O), 6.79 (t, *J* = 4 Hz, 4H, 4 X C*H* arom., *para* in $^-$BPh$_4$), 6.93 (t, *J* = 4 Hz, 8H, 4 X C*H* arom., *meta* in $^-$BPh$_4$), 7.43 – 7.46 (m, 8H, 4 X C*H* arom., *ortho* in $^-$BPh$_4$), 7.67 – 7.70 (m, 5H, 5 X C*H* arom), 7.80 – 7.82 (m, 5H, 5 X C*H* arom), 7.96 – 8.03 (m, 5H, 5 X C*H* arom), 9.23 (s, 1H, N=C*H*); ^{13}C-NMR (100 MHz, acetone-d_6): Only the counter-ion ^{13}C signals were observed.

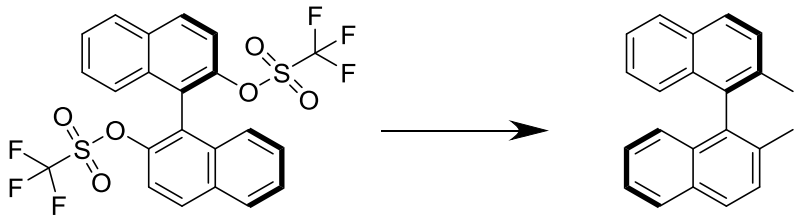
3.3.1.22 *(R)-1, 1'-Binaphthalene-2, 2'-diol bis-(trifluoromethanesulfonate)*[10]



42 **43**

(R)-[1,1']Binaphthalene-2,2'-diol **42** (3.00 g, 10.50 mmol, 2.5 equiv) was dissolved in dichloromethane (60 mL) and the solution cooled to -30 ^{o}C and stirred at this temperature for 5 min. before addition of 4-dimethylaminopyridine (0.51 g, 4.20 mmol, 1.0 equiv), 2, 6-lutidine (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 ^{o}C [Lit.[4] mp 76 – 78 ^{o}C]; $[\alpha]_D$ = –150.9^{o} (*c* = 1.01, $CHCl_3$), [Lit.[4] $[\alpha]_D$ = –147.7^{o} (*c* = 1.01, $CHCl_3$)]. ν_{max} (neat)/cm^{-1} 3062, 1509, 1424, 1247, 1140, 1066, 963, 867. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.17 – 7.19 (m, 2H, 2 x C*H* arom., *binap-3,-3'*), 7.39 – 7.43 (m, 2H, 2 x C*H* arom., *binap*-7,7'), 7.57 – 7.63 (m, 4H, 4 x C*H* arom., *binap*-8,-8',-9,-9'), 8.01 (d, *J* = 10 Hz, 2H, 2 X C*H* arom., *binap*-4,-4'), 8.14 (d, *J* = 10 Hz, 2H, 2 X C*H* arom., *binap*-6,-6'); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 116.5 (2C, 2 X *C* quat., q, *J* = 79.5 Hz, 2 X CF_3), 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').

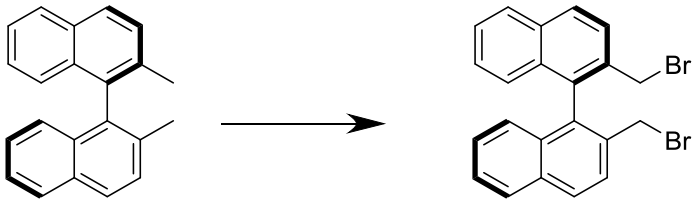
3.3.1.23 *(R)-2,2'-Dimethyl-1,1'-binaphthalene*[4]



43 **44**

(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 ^{o}C, and methylmagnesium bromide (3 M in Et_2O, 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 ^{o}C [Lit.[4] mp 74 – 78 ^{o}C]; $[\alpha]_D$ = –40.9^{o} (*c* = 1.19, $CHCl_3$), [Lit.[4] $[\alpha]_D$ = –40.0^{o} (*c* = 1.12, $CHCl_3$)]; ν_{max} (neat)/cm^{-1} 3054, 2246, 1594, 1506, 1420, 1265, 1217, 1142, 958, 943, 836, 814, 739, 705. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 6H, 2 X Ar-CH_3) 7.05 (d, *J* = 8 Hz, 2H, 2 x C*H* arom., *binap-3,-3'*), 7.29 (d, *J* = 8 Hz, 2H, 2 x C*H* arom., *binap*-7,7'), 7.38 – 7.47 (m, 2H, 2 x C*H* arom., *binap*-8,-8'), 7.54 – 7.62 (m, 2H, 2 x C*H* arom., *binap*-9,-9'), 7.92 – 7.98 (m, 4H, 4 X C*H* arom.), 8.03 (d, *J* = 8 Hz, 2H, 2 X C*H* arom., *binap*-4,-4'), 8.09 (d, *J* = 8 Hz, 2H, 2 X C*H* arom., *binap*-6,-6'); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 116.5 (2C, 2 X C quat., q, *J* = 79.5 Hz, 2 X *C*F_3), 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').

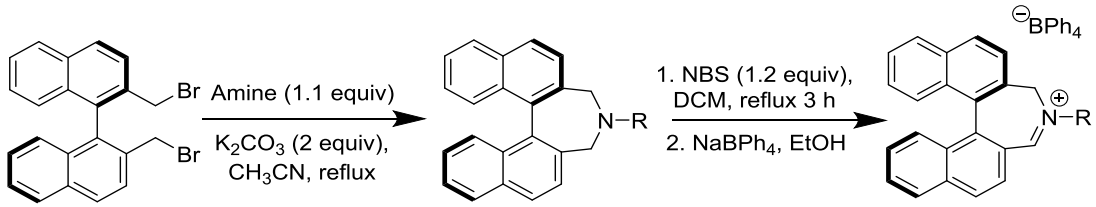
3.3.1.24 *(R)-2,2'-Bis(bromomethyl)[1,1']binaphthalene*[4]



44 **39**

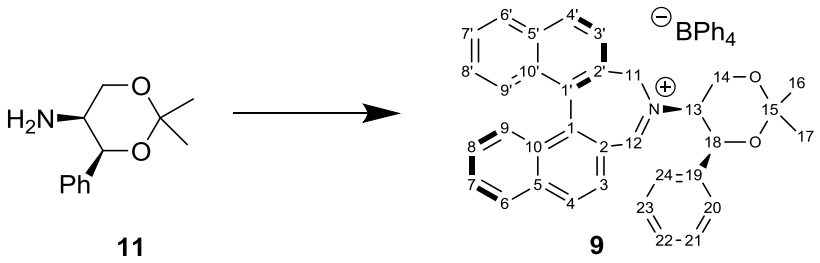
(R)-2,2'-Dimethyl-1,1'-binaphthalene **44** (1.67 g, 5.9 mmol) was dissolved in cyclohexane (14 mL), and *N*-bromosuccinimide (2.10 g, 11.8 mmol) and azobis(isobutyronitrile) (0.10 g, 0.59 mmol) were added with stirring. The mixture was heated under reflux for 3 h, after which time complete disappearance 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 ^{o}C [Lit.[4] mp 180 – 183 ^{o}C]; $[\alpha]_D$ = +169.9^{o} (*c* = 1.00, benzene), [Lit.[11] $[\alpha]_D$ = +186.4 (*c* = 1.00, benzene)]. ν_{max} (neat)/cm^{-1} 3049, 2925, 1777, 1725, 1507, 1433, 1361, 1328, 1212, 1025, 969, 821, 754, 726, 686, 626. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.25 (s, 4H, 2 X C*H*$_2$Br), 7.07 (d, *J* = 8 Hz, 2H, C*H* arom.), 7.27 – 7.29 (m, 2H, C*H* arom.), 7.47 – 7.49 (m, 2H, C*H* arom.), 7.75 (d, *J* = 8 Hz, 2H, C*H* arom.), 7.92 (d, *J* = 8 Hz, 2H, C*H* arom.), 8.02 (d, *J* = 8 Hz, 2H, C*H* arom.); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 32.6 (2C, 2*C*, 2 X *C*H$_2$Br), 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[12]



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 ($MgSO_4$). *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 5min, 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 ($MgSO_4$), 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 ^{o}C.

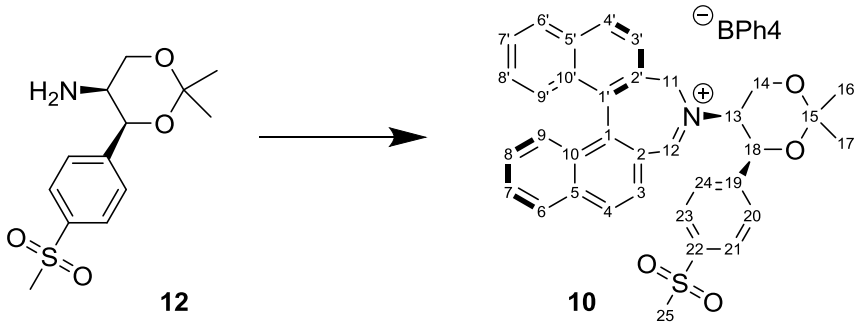
3.3.1.26 *(R)-[(4S,5S)-2, 2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-3H-4-azepinium-cyclohepta[2,1-a;3,4-a']dinaphthalene tetraphenylborate*[10]



11 **9**

Prepared according to the general procedure from (+)-(4*S*,5*S*)-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.[4] mp 111 – 113 °C]; $[\alpha]_D$ = –118.9° (*c* = 1.09, acetone), [Lit.[4] $[\alpha]_D$ = –98.5° (*c* = 1.04, acetone)]. ν_{max} (neat)/cm^{-1} 3054, 2987, 1612, 1422, 1385, 1265, 1203, 1163, 1110, 896, 816, 738, 705. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.81 (s, 3H, C(C*H*$_3$)), 1.87 (s, 3H, C(C*H*$_3$)), 4.42 (d, *J* = 16 Hz, 1H, ArC*H*HN, upfield portion of AB system), 4.53 (d, *J* = 12, 1H, NCH-C*H*H-O, upfield portion of ABX system), 4.74 (s, 1H, NC*H*CH$_2$O), 4.82 (d, *J* = 12 Hz, 1H, NCH-C*H*H-O, downfield portion of ABX system), 5.96 – 5.97 (m, 2H, 1 X ArC*H*HN, downfield portion of AB system/1 X NCH-C*H*Ar-O), 6.77 (t, *J* = 8 Hz, 4H, 4 X C*H* arom., *para* in $^-$BPh$_4$), 6.92(t, *J* = 8 Hz, 8H, 8 X C*H* arom., *meta* in $^-$BPh$_4$), 6.97 – 7.07 (m, 4H, 4 X C*H* arom.), 7.27 – 7.29 (m, 2H, 2 X C*H* arom.), 7.34 – 7.37 (m, 11H, 8 X C*H* arom., *ortho* in $^-$BPh$_4$/3 X C*H* arom.), 7.46 – 7.47 (m, 2H, 2 X C*H* arom.), 7.59 (t, *J* = 8 Hz, 1H, C*H* arom.), 7.77 – 7.81 (m, 1H, C*H* arom.), 7.88 (d, *J* = 12 Hz, 1H, C*H* arom.), 8.11 (d, *J* = 8 Hz, 1H, C*H* arom.), 8.17 – 8.25 (m, 3H, C*H* arom.), 9.11 (s, 1H, N=C*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.9 (*C*H$_3$, C16 or C17), 29.7 (*C*H$_3$, C16 or C17), 57.0 (Ar-*C*H$_2$N), 61.9 (*C*H$_2$, C14), 68.1 (N*C*H, C13), 72.6 (Ar-*C*H, C18), 101.7 (*C* quat., C2), 120.5 (*C* quat. arom., binap.), 122.3 (4C, 4 X *C* arom., *para* in BPh$_4$), 124.3 (*C* arom., C22), 126.0 (8C, 8 X *C* arom., *ortho* in BPh$_4$), 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 (*C* quat. arom., *binap.*), 136.3 (*C* quat. arom., *binap.*), 136.6 (*C* quat. arom., *binap.*), 137.2 (8 X *C* arom., *meta* in BPh$_4$), 142.4 (*C* quat. arom., C19), 164.7 (4 X *C* quat.), 170.9 (H*C*=N).

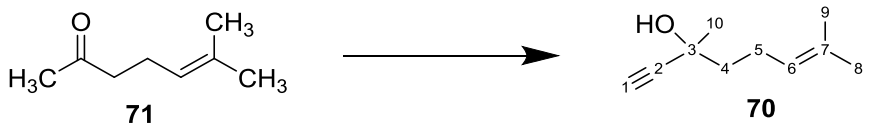
3.3.1.27 *(R)-[(4S,5S)-2,2-dimethyl-4-(methylsulfonyl)phenyl-1,3-dioxan-5-yl]-3H-4-azepinium-cyclohepta[2,1-a;3,4-a']dinaphthalene tetraphenylborate*[4]



Prepared according to the general procedure from (4S,5S)-5-Amino-4-[4-(methylsulfonyl)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]; $[\alpha]_D$ = –238.9° (*c* = 0.85, acetone), [Lit.[4] $[\alpha]_D$ = –283.7° (*c* = 0.86, acetone)]. ^{1}H-NMR (400 MHz, acetone-d_6): *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, NC*H*, H13), 6.21 (d, *J* = 15 Hz, 1H, Ar-CH*H*N, H11), 6.25 (d, *J* = 5 Hz, 1H, Ar-C*H*, H18), 6.79 (t, *J* = 15 Hz, 4H, 4 X C*H* arom., *para* in BPh_4), 6.94 (t, *J* = 15 Hz, 8H, 8 X C*H* arom., *ortho* in BPh_4), 7.29 (ddd, *J* = 11, 6, 3 Hz, 1H, C*H* arom., *binap.*), 7.36 (m, 8H, 8 X C*H* arom., *meta* in BPh_4), 7.49 (m, 3H, 3 X C*H* arom., *binap.*), 7.59 (dd, *J* = 8, 7, 1 Hz, 1H, C*H* arom., *binap.*), 7.82 – 7.84 (m, 5H, 5 X C*H* arom.), 8.00 (d, *J* = 8 Hz, 1H, C*H* arom., *binap.*), 8.13 (d, *J* = 8 Hz, 1H, C*H* arom.), 8.21 (d, *J* = 8 Hz, 1H, C*H* arom.), 8.24 (d, *J* = 9 Hz, 1H, C*H* arom.), 9.39 (s, 1H, *H*C=N); ^{13}C-NMR (100MHz, acetone-d_6): *δ* 18.2 (*C*H_3, C16 or C17), 29.1 (*C*H_3, C16 or C17), 43.4, (*C*H_3, SO_2*C*H_3, C25), 56.4 (*C*H_2, Ar*C*H_2N, C11), 61.1 (*C*H_3, NCH*C*H_2O, C14), 66.9 (*C*H, N*C*H, C13), 71.5 (*C*H, Ar*C*H, C18), 101.1 (*C* quat., C15), 121.5 (4C, 4 X *C* arom., *para* in BPh_4), 125.0 (*C* arom., *binap*), 125.1 (*C* arom., *binap*), 125.2 (*C* arom., *binap*), 125.3 (8C, 8 X *C* arom., *ortho* in BPh_4), 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 BPh_4), 141.4, 142.2, 164.0 (4C, 4 X *C* quat., arom., q, *J* = 49 Hz, 4 *C*-B *ipso* in BPh_4), 170.6 (H*C*=N).

3.3.2 Synthesis of Chromene Substrate

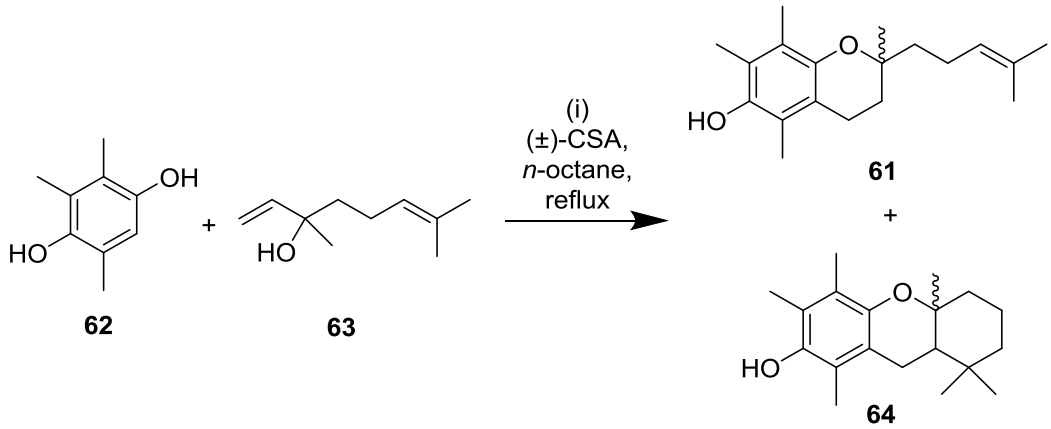
3.3.2.1 3,7-Dimethyloct-6-en-1-yl-3-ol[13]



71 **70**

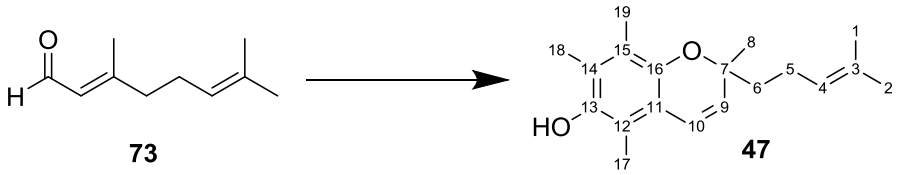
A solution of 6-methyl-5-heptene-2-one **71** (1 mL, 6.8 mmol) in a mixture of anhydrous THF/Et_2O (1:1) (4 mL) was added dropwise in 30 minutes, at room temperature, to a solution of ethynylmagnesium bromide (16 mL, 8.16 mmol, 0.5M in THF) in anhydrous diethyl ether (16 mL), under Ar. The reaction was 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_2O. The combined organic layers were washed with brine and dried over $MgSO_4$. 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%). ν_{max} (film)/cm^{-1} 3405 (OH), 3307 (acetylenic C – H stretch), 2927, 1725 (C=C), 1449, 1375, 1262 (C – OH), 627 (acetylenic C – H bend); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.49 (s, 3H, C*H*$_3$COH), 1.65 (s, 3H, CHC*H*$_3$), 1.69 (s, 3H, CHC*H*$_3$), 2.09 – 2.20 (m, 2H, C*H*$_2$CH$_2$CH or CH$_2$C*H*$_2$CH), 2.21 – 2.32 (m, 2H, C*H*$_2$CH$_2$CH or CH$_2$C*H*$_2$CH), 2.45 (s, 1H, C*H* alkyne), 5.16 (m, 1H, C*H* alkene); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 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[14] – Method I



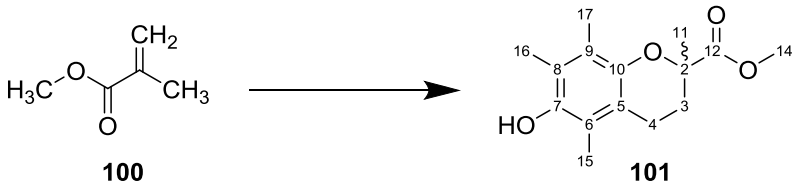
Linalool **63** (7.09 mL, 39.42 mmol, 2 equiv) was added dropwise to a boiling suspension of trimethylhydroquinone **62** (3.0 g, 19.71 mmol, 1 equiv) and (±)-CSA (0.1 equiv) in *n*-octane at 98 °C. The reaction mixture was kept at reflux and stirred overnight. After the reaction has come to completion, it was cooled down to room temperature, and poured into 50 mL saturated $NaHCO_3$ solution. The product was extracted with EtOAc, and then washed with brine and the organic layer was dried ($MgSO_4$). The solvent was removed under *vacuo* which was then purified by column chromatography, eluting with ethyl acetate/light petroleum (1:9), to give a mixture of the title compound **61** and its cyclic isomer **64** (5.39 g, 95%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.24 (s, 3H, OCCH_3), 1.50 – 1.68 (m, 2H, C$^{1'}H_2$ or C$^{2'}H_2$), 1.60 (3 H, s, C$^{3'}$H=C^4(CH_3)$_2$), 1.67 (s, 3 H, C$^{3'}$H=C^4(CH_3)$_2$), 1.70 – 1.84 (m, 2H, C$^{1'}H_2$ or C$^{2'}H_2$), 2.11 (s, 6H, 2 X Ar-CH_3), 2.16 (s, 3H, Ar-CH_3), 2.60 (t, J = 8 Hz, 2H, Ar-CH_2CH$_2$ or Ar-CH$_2$CH_2), 4.18 (s, 1H, Ar-O*H*), 5.12 (t, J = 6 Hz, 1H, C$^{3'}H$=C^4(CH$_3$)$_2$).

3.3.2.3 6-Hydroxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-ene)chroman[15] – Method II



A mixture of trimethylhydroquinone **62** (1 equiv), phenylboronic acid (1.6 equiv), citral **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 **47** as brownish oil, 45%. ν_{max} (film)/cm^{-1} 3434, 2969, 2924, 1644, 1454, 1417, 1376, 1303, 1263, 1214, 1156, 1117, 1083, 1060, 923. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 3H, OCCH_3, C8), 1.61 (s, 3H, CH_2CH=C(CH_3)$_2$, C1 or C2), 1.69 (s, 3H, CH_2CH=C(CH_3)$_2$, C1 or C2), 1.62 – 1.75 (m, 2H, CH_2CH_2CH=C$(CH_3)_2$, C5), 2.16 (s, 3H, Ar-CH_3, C17, C18 or C19), 2.19 (s, 3H, Ar-CH_3, C17, C18 or C19), 2.21 (s, 3H, Ar-CH_3, C17, C18 or C19), 2.10 – 2.20 (m, 2H, CH_2CH_2CH=C$(CH_3)_2$, C6), 4.21 (s, 1H, Ar-OH), 5.14 (t, J = 5 Hz, 1H, CH_2CH=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, $CDCl_3$): δ 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$_3$)$_2C$H=CH), 25.3 (C1/C2, OC(CH$_3$)$_2$), 25.7 (C8, OC(CH$_3$)), 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.).

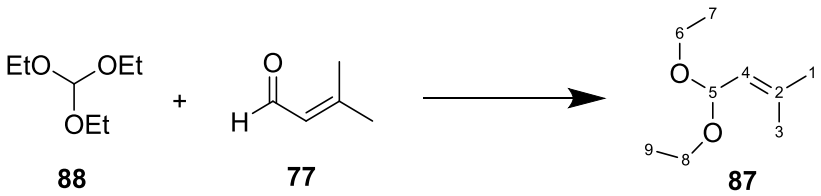
3.3.2.4 Methyl 6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromene-2-carboxylate[16]



100 **101**

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 ^{o}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 ^{o}C overnight (1.91 g, 71%); mp 157 – 160 ^{o}C [Lit. mp 134.5 – 136 ^{o}C]. ν_{max} (film)/cm^{-1} 3530, 2989, 2928, 1739, 1454, 1428, 1375, 1335, 1277, 1264, 1243, 1226, 1192, 1173, 1140, 1113, 1061, 1030, 967, 945. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.59 (s, 3H, C11), 1.86 (m, 1H, C3), 2.05 (s, 3H, Ar-CH_3, C15, C16 or C17), 2.14 (s, 3H, Ar-CH_3, C15, C16 or C17), 2.18 (s, 3H, Ar-CH_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); ^{13}C-NMR (126 MHz, $CDCl_3$): 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, $C_{15}H_{20}O_4H$ $[M + H]^+$ requires 265.1434.

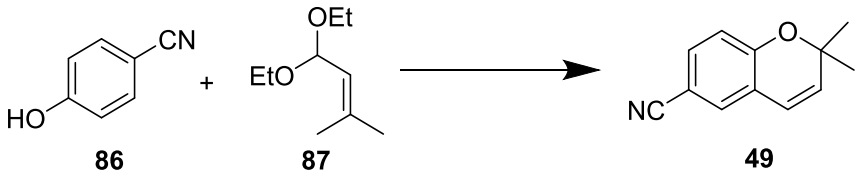
3.3.2.5 1,1-Diethoxy-3-methyl-2-butene[17]



88 **77** **87**

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_4NO_3 (25 mol%). The reaction mixture was left stirred for 24 hours. Saturated aqueous solution of $NaHCO_3$ was added to the reaction followed by brine. The mixture was the extracted by using Et_2O several times to give the title compound **87** as a brownish liquid. No further purification was required. ν_{max} (film)/cm^{-1} 2975, 2930, 2914, 2879, 1682, 1447, 1377, 1358, 1348, 1206, 1142, 1115, 1083, 1053, 1017, 991. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 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}C-NMR (125 MHz, $CDCl_3$): δ 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).

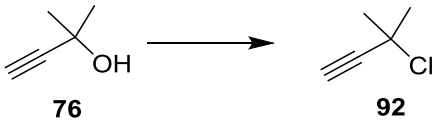
3.3.2.6 6-Cyano-2,2- dimethylchromene – Method A[17]



86 **87** **49**

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 ($MgSO_4$). 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 ^{o}C [Lit.[17] mp 47 ^{o}C]. ν_{max} (film)/cm^{-1} 3054, 2985, 2226, 1605, 1487, 1421, 1369, 1265, 1212, 1148, 1128, 1107, 961, 896, 828, 739, 705. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 6H, OC(C*H*$_3$)$_2$), 5.70 (d, *J* = 12 Hz, 1H, C(CH$_3$)$_2$C*H*CH), 6.28 (d, *J* = 12 Hz, 1H, C(CH$_3$)$_2$CHC*H*), 6.78 (d, *J* = 8 Hz, 1H, C*H* arom.), 7.24 (d, *J* = 4 Hz, 1H, C*H* arom.), 7.37 (dd, *J* = 8 Hz, 4 Hz, 1H, C*H* arom.); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.4 (2C, 2 X C(*C*H$_3$)$_2$), 77.9 (*C*(CH$_3$)$_2$, C quat.), 103.8 (*C* quat. arom.), 117.2 (*C* arom.), 119.3 (*C* quat., arom.), 120.6 (C(CH$_3$)$_2$*C*H=CH), 121.7 (*C* quat. arom.), 130.1 (*C* arom.), 132.2 (C(CH$_3$)$_2$CH=*C*H), 133.3 (*C* arom.), 156.8 (*C*≡N).

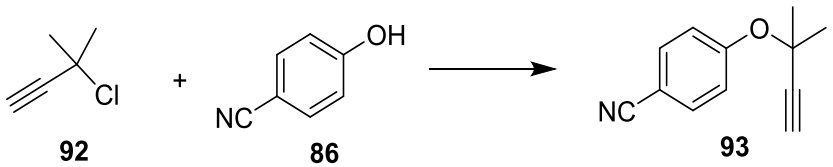
3.3.2.7 3-Chloro-3-methyl-1-butyne[18]



76 **92**

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_2CO_3. The chloride was used without further purification. ν_{max} (film)/cm^{-1} 2983, 2927, 1739, 1666, 1616, 1447, 1370, 1111, 938, 836, 604; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.87 (s, 6H, HC≡CC(C*H*$_3$)$_2$-Cl), 2.62 (s, 1H, *H*C≡CC(CH$_3$)$_2$-Cl); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 34.6 (2C, 2 X HC≡CC(*C*H$_3$)$_2$-Cl), 56.9 (*C* quat., HC≡C*C*(CH$_3$)$_2$-Cl), 71.9 (acetylenic C, H*C*≡CC(CH$_3$)$_2$-Cl), 86.5 (quat. C, HC≡*C*C(CH$_3$)$_2$-Cl).

3.3.2.8 3-(3-Cyanophenoxy)-3-methylbut-1-yne[19]

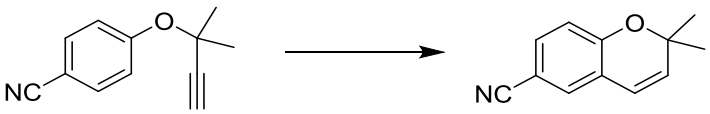


92 **86** **93**

4-Cyanophenol **86** (0.5 g, 4.2 mmol), anhydrous K_2CO_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-butyne **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. ν_{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, $CDCl_3$): δ 1.70 (s, 6H, OC(C*H*$_3$)$_2$), 2.65 (s, 1H, alkyne), 7.28 (d, *J* = 9 Hz, 2H, C*H* arom.), 7.57 (d, *J* = 9 Hz, 2H, C*H* arom.); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 29.5 (2C, 2 X *C*H$_3$), 72.7 (O*C*(CH$_3$), *C* quat.), 75.3 (-C≡*C*H), 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.).

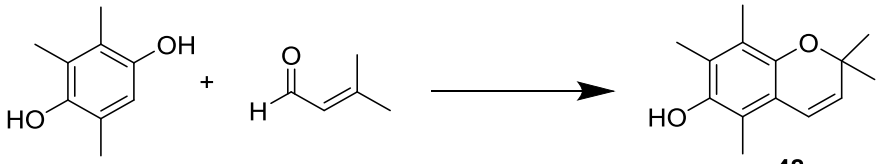
3.3.2.9 6-Cyano-2, 2- dimethylchromene[19]



93 **49**

A solution of the phenyl propargyl ether **93** in ethylene glycol (5 mL/g of the propargyl ether) was heated to 210 – 215 ^{o}C under a nitrogen atmosphere. After 24 hours of stirring at the reaction temperature, H_2O was added to the crude and extracted with Et_2O. The title compound **49** was crystallized using light petroleum.

3.3.2.10 6-Hydroxy-2, 2, 5, 7, 8-pentamethyl-3-chromene[20]

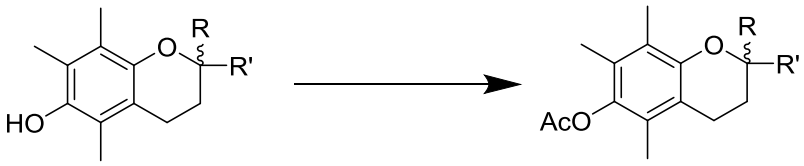


62 **77** **48**

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_2 until starting material was judged to have disappeared by TLC. The solvents were removed and the resulting residue was re-dissolved with Et_2O (50 mL) and water. The ethereal layer was separated and washed with saturated $NaHCO_3$ (2 X 30 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$ 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

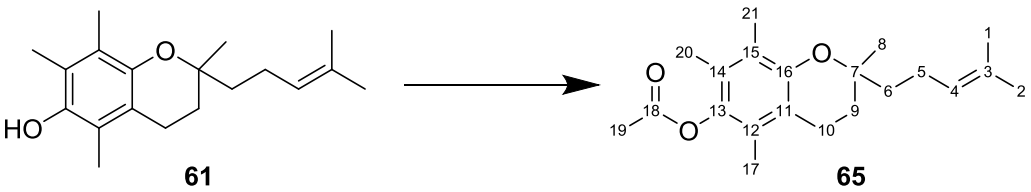
isolate the product **48** as an orange oil (0.44 g, 61%). ν_{max} (film)/cm^{-1} 3435, 2971, 2916, 1634, 1270, 1214, 1136, 1086, 1063. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 6H, OC(CH_3)$_2$), 2.12 (s, 3H, ArCH_3), 2.16 (s, 3H, ArCH_3), 2.18 (s, 3H, ArCH_3), 4.20 (s, 1H, phenol), 5.64 (d, J = 10 Hz, 1H, C(CH_3)$_2$C*H*CH), 6.51 (d, J = 10 Hz, 1H, C(CH_3)$_2$CHC*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 10.9 (Ar*C*H_3), 11.6 (Ar*C*H_3), 12.4 (Ar*C*H_3), 27.3 (2C, 2 X *C*H_3), 74.4 (O*C*(CH_3), *C* quat.), 116.1 (*C* quat. arom.), 117.9 (*C* quat. arom.), 112.0 (OC(CH_3)$_2$CH=*C*H-), 122.5 (*C* quat. arom.), 122.6 (*C* quat. arom.), 130.6 (OC(CH_3)$_2$CH=*C*H-), 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_2O (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_2O which then finally dried with $MgSO_4$. The solvent was removed under reduced pressure.

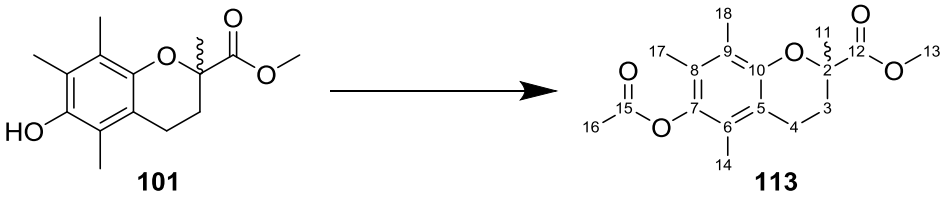
3.3.2.12 6-Acetoxy-2,5,7,8-tetramethylchroman-2-(4-methyl-3-pentene)[21]



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

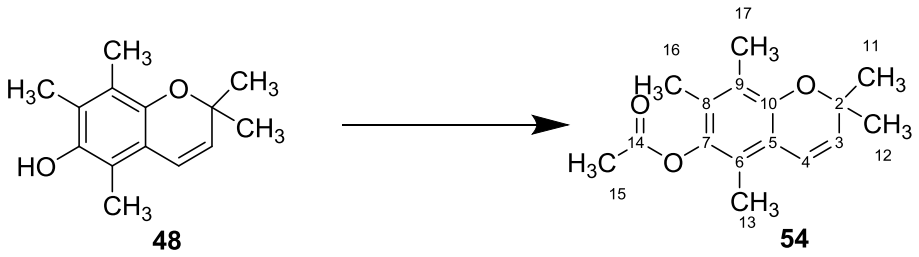
yellow oil (1.34 g, 73%). ν_{max} (film)/cm^{-1} 2977, 2929, 2863, 1758, 1676, 1577, 1455, 1416, 1368, 1332, 1208, 1166, 1109, 1079, 1011, 918, 897, 850. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 3H, C8), 1.59 (m, 2H), 1.60 (s, 3H, C1 or C2), 1.68 (s, 3H, C1 or C2), 1.80 (qd, J = 14, 7 Hz, 2H), 1.98 (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, $CDCl_3$): δ 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 (1 C, C5), 25.7 (C1, C1 or C2), 31.0 (C9), 38.1 (C6), 74.8 (C7), 117.4 (*C* quat. arom., C11), 123.1 (*C* quat. arom.), 124.5 (C4), 125.0 (*C* quat. arom.), 126.7 (*C* quat. arom.), 131.5 (*C* quat. arom.), 140.6 (*C* quat. arom., C13), 149.4 (*C* quat. arom., C16), 169.8 (*C* quat. arom., C17); *m/z* 348.2534, $C_{21}H_{30}O_3NH_4$ [M + NH_4]$^+$ requires 348.2533.

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



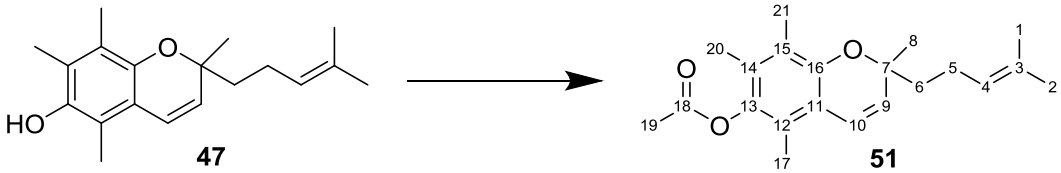
Prepared according to the general procedure of acetyl protection of phenolic hydroxyl group of chromanols from methyl 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylate **101** (0.811 g, 3.07 mmol). The yellow crude was purified by column chromatography, typically eluting with ethyl acetate/light petroleum (1:9), to give the product **113** as a white solid (0.67 g, 59%); m.p. 94 – 96 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.60 (s, 3H, OCCH_3), 1.81 – 1.94 (m, 1H, CHHCH_2Ar), 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_2Ar), 2.48 – 2.66 (m, 2H, CH_2CH_2Ar), 3.68 (s, 3H, COOCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 11.9 (Ar-CH$_3$), 12.1 (Ar-CH$_3$), 13.0 (Ar-CH$_3$), 20.5 (Ar-OCOCH$_3$), 20.8 (*C*3 or *C*4), 25.5 (*C*11), 30.2 (*C*3 or *C*4), 30.4 (*C*2), 52.4 (*C*13), 77.3 (*C* quat. arom., *C*10), 117.1 (*C* quat. arom.), 123.1 (*C* quat. arom.), 124.9 (*C* quat. arom.), 127.1 (*C* quat. arom.), 141.3 (*C* quat. arom.), 169.6 (*C*12), 174.2 (*C*15); *m/z* 324.1803, $C_{17}H_{22}O_5$ NH_4 [M + NH_4]$^+$ requires 324.1805.

3.3.2.14 6-Acetoxy-2,2,5,7,8-pentamethylchromene[20]



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 ^{o}C. ν_{max} (film)/cm^{-1} 3054, 2981, 2928, 1752, 1645, 1605, 1462, 1421, 1370, 1265, 1209, 1135, 1080, 1062, 739, 705. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 6H, OC(CH_3)$_2$), 2.02 (s, 3H, Ar-CH_3), 2.05 (s, 3H, Ar-CH_3), 2.10 (s, 3H, Ar-CH_3), 2.32 (s, 3H, Ar-OCOCH_3), 5.63 (d, *J* = 12 Hz, 1H, C*H*=CH-Ar), 6.47 (d, *J* = 12 Hz, 1H, CH=C*H*-Ar); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 11.6 (Ar-*C*H_3), 11.6 (Ar-*C*H_3), 13.2 (Ar-*C*H_3), 20.5 (Ar-OCO*C*H_3), 27.7 (2C, 2 X *C*H_3), 75.0 (*C*2), 117.9 (*C* quat. arom.), 119.6 (*C*H=CH-Ar), 122.4 (*C* quat. arom.), 122.8 (*C* quat. arom.), 129.0 (*C* quat. arom.), 130.3 (CH=*C*H-Ar), 141.4 (*C* quat. arom.), 148.4 (*C* quat. arom.), 169.5 (*C*14); *m/z* 261.1486, $C_{16}H_{20}O_3H$ $[M + H]^+$ requires 261.1485.

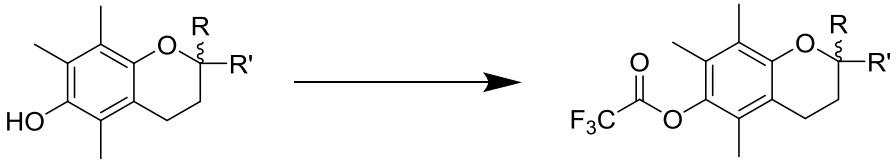
3.3.2.15 6-Acetoxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-ene)chromene[15]



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_{max} (film)/cm^{-1} 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. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.28

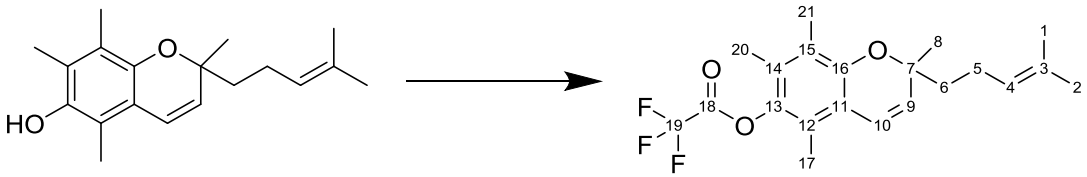
(s, 3H, OC(C*H*3)), 1.51 (s, 3H, $CH_2CH=C(CH_3)_2$), 1.59 (s, 3H, $-CH_2CH=C(CH_3)_2$, H1 or H2), 1.55 – 1.61 (m, 2H, $-CH_2CH_2CH=C(CH_3)_2$, H6), 1.93 (s, 3H, Ar-CH_3), 1.97 (s, 3H, Ar-CH_3), 2.03 (s, 3H, Ar-CH_3), 1.98 – 2.10 (m, 2H, $-CH_2CH_2CH=C(CH_3)_2$, H5), 2.25 (s, 3H, Ar-O-CO(CH_3), H19), 5.03 (t, *J* = 7 Hz, 1H, $-CH_2CH=C(CH_3)_2$, H4), 5.51 (d, *J* = 10 Hz, 1H, H9 or H10), 6.42 (d, *J* = 10 Hz, 1H, H9 or H10); ^{13}C-NMR (100 MHz, $CDCl_3$): *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, $C_{21}H_{28}O_3NH_4$ $[M + NH_4]^+$ 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 Et_2O/DCM (2:1), and washed with 1% aqueous HCl. The organic layers were washed with saturated $NaHCO_3$ and brine. The solvent is then dried ($MgSO_4$) and reduced under pressure.

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

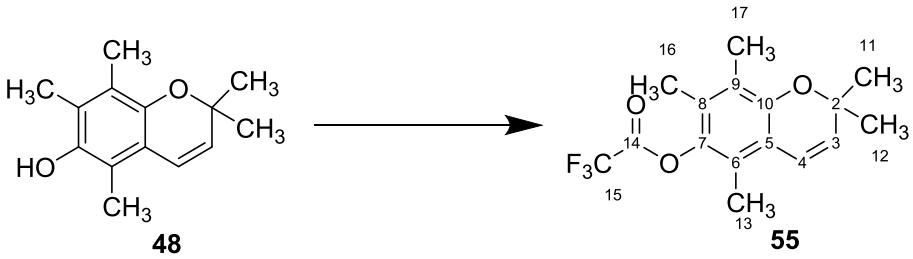


47 **52**

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

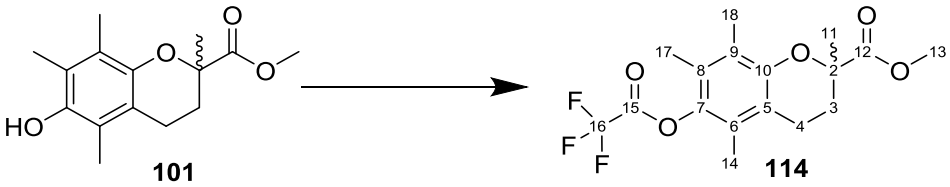
obtain the title compound **52** as brownish oil (0.07 g, 97%). ν_{max} (film)/cm^{-1} 2970, 2928, 2858, 1798, 1677, 1608, 1455, 1413, 1377, 1355, 1224, 1169, 1138, 875, 831. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.37 (s, 3H, CH_3, C1 or C2), 1.58 (s, 3H, CH_3, C1 or C2), 1.65 – 1.75 (m, 2H, CH_2), 1.66 (s, 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, C4), 5.64 (d, *J* = 10 Hz, C9), 6.50 (d, *J* = 10 Hz, C9); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 11.2 (Ar-*C*H_3, C17 or C18), 11.6 (Ar-*C*H_3, C17 or C20), 12.8 (Ar-*C*H_3, C21), 17.6, 22.7, 25.7, 25.9, 40.9, 77.7, 114.9 (q, $^{1}J_{C-F}$ = 284 Hz, *C*F_3), 116.1, 118.0, 119.5, 121.8, 123.3, 124.1, 128.3, 130.1, 140.0, 149.4, 155.7 (q, $^{2}J_{C-F}$ = 42 Hz, C=O); *m/z* 382.1799, $C_{21}H_{25}F_3O_3H$ $[M + H]^+$ requires 382.1796.

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



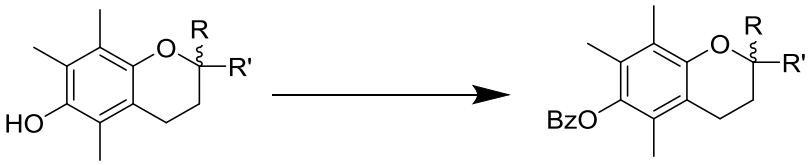
Prepared according to the general procedure of trifluoroacetate protection of phenols from 6-hydroxy-2,2,5,7,8-pentamethylchromene **48** (1.66 g, 7.6 mmol) and purified by column chromatography using 1:99 (EtOAc/light petroleum) eluent to obtain the title compound **55** as a light yellow solid (2.02 g, 84%); m.p. 62 ^{o}C. ν_{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, $CDCl_3$): δ 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, C*H*=CHAr), 6.47 (d, *J* = 10 Hz, 1H, CH=C*H*Ar); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 11.2 (Ar-*C*H_3), 11.6 (Ar-*C*H_3), 12.8 (Ar-*C*H_3), 27.7 (2C, 2 X OC(*C*H_3)$_2$), 75.3 (C quat., O*C*(CH$_3$)$_2$), 113.8 (q, $^{1}J_{C-F}$ = 285Hz, *C*F_3), 118.3 (*C* quat. arom.), 119.1 (CH=*C*HAr), 121.8 (*C* quat. arom.), 123.6 (*C* quat. arom.), 128.2 (*C* quat. arom.), 130.9 (*C*H=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, $C_{16}H_{17}F_3O_3H$ $[M + H]^+$ 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 recrystalized from MeOH to give the title compound **114** as a white powder (1.99 g, 73%); m.p. 124.0 – 125.5 °C. ν_{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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $C_{17}H_{19}F_3O_5H$ $[M + H]^+$ requires 361.1247.

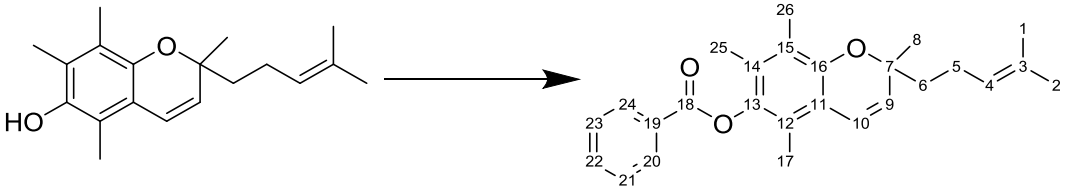
3.3.2.20 General Procedure of Benzoate Protection of the Phenolic Hydroxyl



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_2O/H_2O (1:1) was slowly added into the reaction. The aqueous layer was separated and extracted again with Et_2O. The combined organic layers were washed with 5% aqueous NaOH and

then with H_2O and brine. The solvent was dried (Na_2SO_4), and evaporated under reduced pressure.

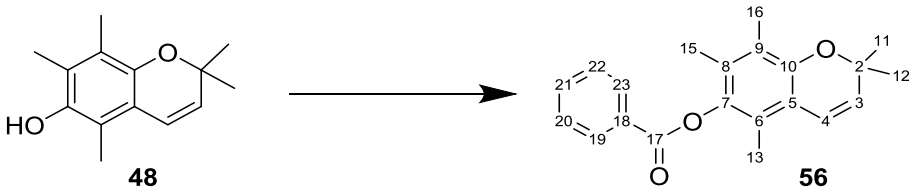
3.3.2.21 6-Benzoyloxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-ene)chromene



47 **53**

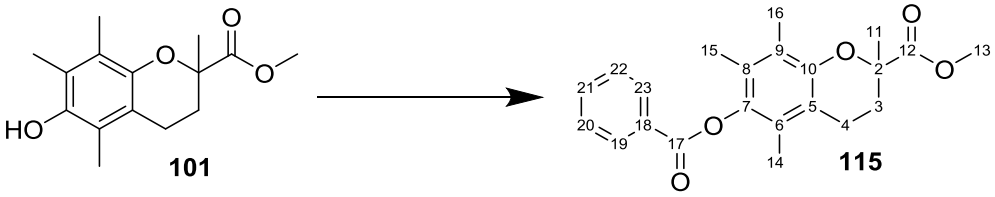
Prepared according to the general procedure for benzoate protection of phenols from 6-hydroxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-ene)chromene **47** (0.10 g, 0.18 mmol), NaH (0.005 g, 0.19 mmol) and benzoyl chloride (0.02 mL, 0.18 mmol). The reaction was complete after overnight. The crude was purified by column chromatography eluting with ethyl acetate/light petroleum (10:90) to afford the title compound **53** as yellow oil (0.05 g, 75%). ν_{max} (film)/cm^{-1} 3061, 2968, 2925, 2857, 1774, 1737, 1644, 1603, 1585, 1451, 1413, 1377, 1267, 1245, 1205, 1177, 1025, 1002, 922, 870. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 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, C*H* arom.), 7.58 – 7.63 (m, 1H, C*H* arom.), 8.17 (dd, 2H, C*H* arom.); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 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, 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, $C_{26}H_{30}O_3NH_4$ $[M + NH_4]^+$ requires 408.2533.

3.3.2.22 6-Benzoyloxy-2,2,5,7,8-pentamethylchromene



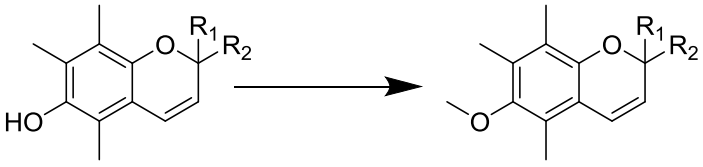
Prepared according to the general procedure for benzoate protection of phenols from 6-hydroxy-2,2,5,7,8-pentamethylchromene **48** (1.35 g, 6.20 mmol), NaH (0.16 g, 6.82 mmol) and benzoyl chloride (0.72 mL, 6.2 mmol). The reaction completed in 30 min. The crude material was purified by column chromatography 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 ^{o}C; ν_{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, $CDCl_3$): δ 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, C*H* arom.), 7.65 (m, 1H, C*H* arom.), 8.25 (m, 2H, C*H* arom.); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 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, $C_{21}H_{22}O_3H$ $[M + H]^+$ 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 ^{o}C; ν_{max} (film)/cm^{-1} 3071, 2996, 2953, 2934, 1733, 1644, 1601, 1584, 1451, 1414, 1374, 1334, 1239, 1195, 1176, 1134, 1105, 1094, 1071, 1024, 978, 943, 802, 712; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 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, C*H* arom.), 7.65 (m, 1H, C*H* arom.), 8.25 (m, 1H, C*H* arom.); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 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, $C_{22}H_{24}O_5NH_4$ $[M + NH_4]^+$ requires 386.1962. No quaternary C of C2 is observed.

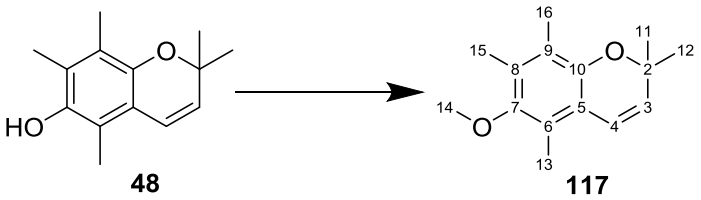
3.3.2.24 General Procedure of Methyl Ether Protection of the Phenolic Hydroxyl



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

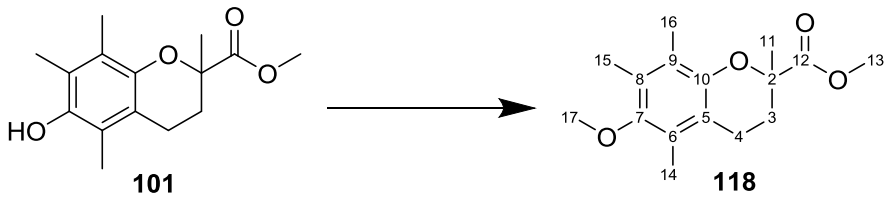
addition of MeI (1 equiv). The solution was stirred at room temperature until complete disappearance of the starting material was observed on TLC plate. After the reaction had come to completion, it was treated with Et_2O/H_2O (20 mL/g of phenol, 1:1). The organic layer was washed with water and brine. The solvent was then reduced under pressure.

3.3.2.25 6-Methoxy-2,2,5,7,8-pentamethylchromene[22]



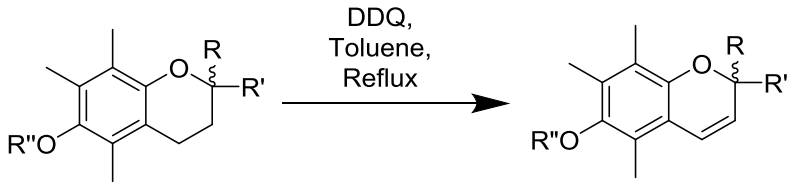
Prepared according to the general procedure of methyl protection of the phenolic hydroxyl using NaH (0.018 g, 0.76 mmol), 6-hydroxy-2,2,5,7,8-pentamethylchromene **48** (0.151 g, 0.69 mmol) and MeI (0.043 mL, 0.69 mmol). The brownish crude oil was purified by column chromatography eluting with ethyl acetate/light petroleum (5:95) to give the title compound **117** as a yellowish oil (0.14 g, 87.2%). ν_{max} (film)/cm^{-1} 3047, 2975, 2932, 1641, 1597, 1461, 1406,1387, 1359, 1270, 1217, 1174, 1137, 1089, 1064, 1046, 1004, 943, 903, 831. ^{1}H-NMR (500 MHz, $CDCl_3$): 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); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 11.6 (Ar-*C*H_3, C13, C15 or C16), 11.2 (Ar-*C*H_3, C13, C15 or C16), 12.8 (Ar-*C*H_3, C13, C15 or C16), 27.6 (2C, 2 X *C*H_3, C11 and C12), 60.4 (Ar-O-*C*H_3, C14), 74.7 (O*C*$(CH_3)_2$, C2), 118.0 (*C* quat. arom.), 120.0 (-*C*H=CH-Ar, C3), 122.8 (*C* quat. arom.), 123.2 (*C* quat. arom.), 130.1 (-CH=*C*H-Ar, C4), 146.8 (*C* quat. arom.), 150.3 (*C* quat. arom.). 1 sp^2 C not located.[22]

3.3.2.26 Methyl 6-methoxy-2,5,7,8-tetramethylchromene-2-carboxylate[23]



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%). ν_{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, $CDCl_3$): δ 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, $CDCl_3$): δ 11.8 (Ar-*C*H$_3$, C14 or C15), 12.6 (Ar-*C*H$_3$, C16), 20.9 (*C*H$_3$, C11), 25.5 (*C*H$_2$, C3), 30.5 (*C*H$_2$, C3), 52.4 (-O*C*H$_3$, C14), 60.4 (-O*C*H$_3$, 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 (*C*O$_2$Me).

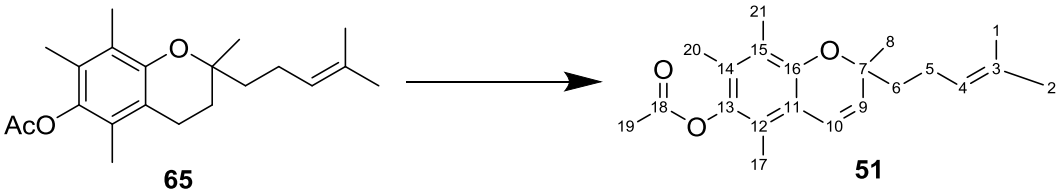
3.3.2.27 General Procedure for Dehydrogenation of the Phenol-Protected Chroman with DDQ



The solution of the respective chromane in anhydrous toluene (6 mL) was heated at 105 ^{o}C for 30 min. A solution of 2,3-dichloro-4,5-dicyanohydroquinone (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% $NaHCO_3$

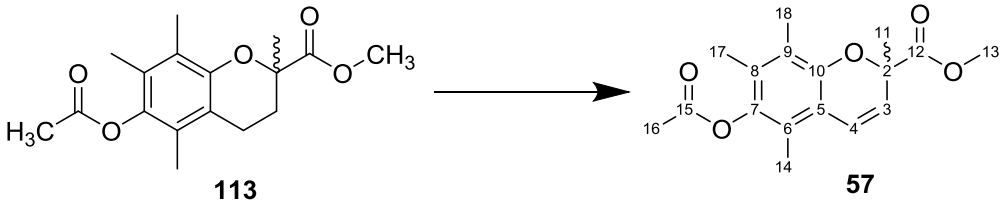
solution and water, and brine. The solvent was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography in silica gel. TLC showed the product nearly at the same position as the starting material, but on spraying with 4% H_2SO_4 in methanol 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%).

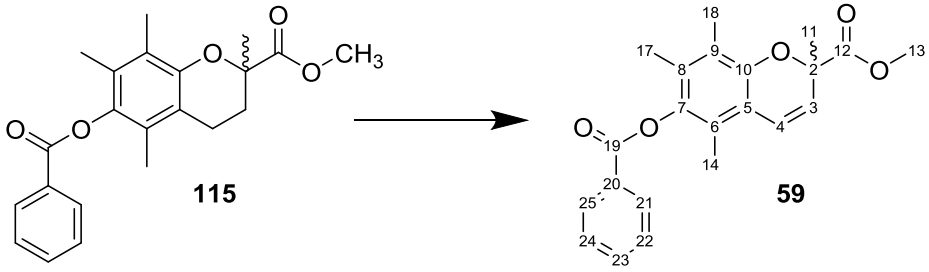
3.3.2.29 Methyl 6-acetoxy-2,5,7,8-tetramethylchromene-2-carboxylate



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; ν_{max} (film)/cm^{-1} 3011, 2992, 2956, 2941, 1751, 1644, 1612, 1453, 1369, 1261, 1202, 1117, 1085, 1064, 750. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 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, CC*H*=CH), 6.68 (d, *J* = 10 Hz, 1H, CH=C*H*Ar); ^{13}C-NMR (125 MHz, $CDCl_3$): *δ* 11.5 (Ar-*C*H_3), 11.7 (Ar-*C*H_3), 13.3 (Ar-*C*H_3), 20.5 (*C*16), 25.6 (*C*11), 52.5 (*C*13), 77.2 (*C* quat., *C*2, or *C* quat. arom., *C*10), 77.5 (*C*2 or *C*10), 117.0 (*C* quat. arom.), 121.9 (Ar-CH=*C*H), 122.9 (*C* quat. arom.), 123.1 (*C* quat. arom.), 124.5 (Ar-*C*H=CH), 130.0 (*C* quat. arom.), 142.1 (*C* quat. arom.), 169.4 (*C*12), 173.1 (*C*15); *m/z* 322.1650, $C_{17}H_{20}O_5NH_4$ [M + NH_4]$^+$ requires 322.1649.

3.3.2.30 Methyl 6-benzoyloxy-2,5,7,8-tetramethylchromene-2-carboxylate



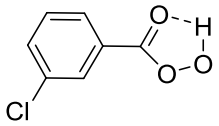
Prepared according to the general procedure of dehydrogenation of the chroman from methyl 6-benzoate-2,5,7,8-tetramethyl-3,4-dihydrochromen-2-carboxylate **115** (0.51 g, 1.38 mmol). The reddish crude was purified by column chromatography to give the title compound **59** as a colourless oil (0.22 g, 42.7%). ^{1}H-NMR (500 MHz, $CDCl_3$): *δ* 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, C*H* arom.), 7.65 (m, 1H, C*H* arom.), 8.23 (dd, *J* = 10, 8 Hz, 2H, C*H* arom.); ^{13}C-NMR (125 MHz, $CDCl_3$): *δ* 11.7 (2C, 2 X Ar-*C*H_3), 13.4 (Ar-*C*H_3), 52.5 (CO_2-*C*H_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-*C*H=CH, C4), 128.9 (*C* quat. arom.), 129.4 (*C* arom.), 130.2 (Ar-CH=*C*H, 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 (*C*O_2-Ar, C19), 173.1 (*C*O_2-CH_3, C12); *m/z* 367.1542, $C_{22}H_{22}O_5H$ [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 CH_2Cl_2 (10 mL/g) and the solution cooled using an ice bath. A solution of *m*-CPBA (2 equiv) in CH_2Cl_2 (10 mL/g, pre-dried over $MgSO_4$) was added. The reaction was allowed to reach ambient temperature and stirred until complete consumption of the substrate was observed by TLC. Saturated aqueous $NaHCO_3$ (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 ($MgSO_4$). 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

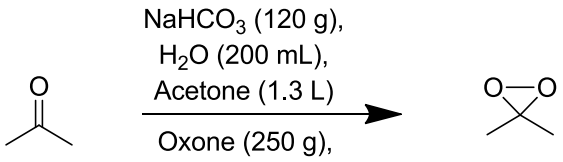


10.0 g of commercial *m*-CPBA was dissolved in 100mL Et_2O and washed with 3 X 50mL buffer solution (410 mL of 0.1 M NaOH, 250 mL of 0.2M KH_2PO_4 made up to 1 L, pH 7.5). The ether layer was dried over $MgSO_4$ and carefully evaporated under reduced pressure to give ca. 7.0 g pure *m*-CPBA.

3.3.3.3 General Procedure for the Preparation of Racemic Epoxides Using m-CPBA and 10% aqueous Na_2CO_3

m-CPBA (4 equiv) was dissolved in a mixture of DCM (40 mL/g of alkene) and 10% aqueous solution of Na_2CO_3 (40 mL/g of alkene) at 0 ^{o}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 Na_2CO_3 and brine. The organic layer was dried (Na_2SO_4) and reduced under pressure.

3.3.3.4 Preparation of Dimethyldioxirane (DMDO) on a Large Scale[24]



A 2-L, three-necked, round-bottom flask containing a mixture of water, acetone, and $NaHCO_3$, 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 $NaHCO_3$ 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 K_2CO_3 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 K_2CO_3 therefore storage on K_2CO_3 should be avoided).

3.3.3.5 Preparation of Dimethyldioxirane (DMDO) on a Small Scale[25]

Distilled H_2O (20 mL), acetone (30 mL), and $NaHCO_3$ (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

^{o}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 Na_2SO_4. The Na_2SO_4 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 $Na_2S_2O_3.5H_2O$ in 100 mL H_2O) 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 H_2O) 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:

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

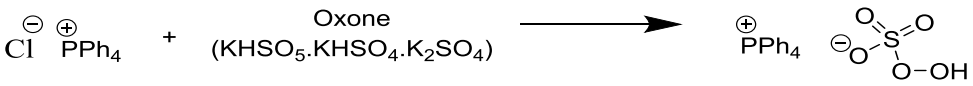
3.3.3.7 General Procedure for the Preparation of Racemic Epoxides Using DMDO

To a solution of an alkene in $CHCl_3$ (2 mL per 0.1 g alkene) which was cooled to 0 ^{o}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[5]

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 Na_2CO_3), 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 CH_3CN (6 mL per 1.50 g of Na_2CO_3), was added, followed by a solution of the alkene substrate in CH_3CN (6 mL per 1.50 g of Na_2CO_3). 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 ($MgSO_4$). 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)



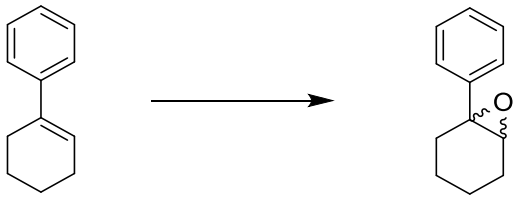
Tetraphenylphosphonium chloride (15.0 g, 40 mmol) was dissolved in DCM (200 mL) and cooled in ice-water bath in a round bottomed flask equipped with a stirrer bar. Oxone® (15.0 g, 48 mmol) which was dissolved in deionised water (300 mL) at 0°C, was added to the solution of tetraphenylphosphonium chloride 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 $MgSO_4$, 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. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.63 – 7.67 (m, 8H, 8 C*H* X

arom.), 7.76 – 7.80 (m, 8H, 8 X C*H* arom.), 7.88 – 7.92 (m, 4H, 4 X C*H* arom.), 9.34 (s, 1H, O*H*). 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. Et_2O (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, Et_2O (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.

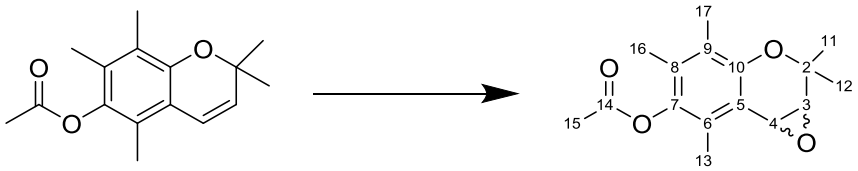
3.3.3.11 1-Phenylcyclohexene Oxide[26]



126 **127**

The title compound **127** was isolated as a colourless oil after purification by column chromatography eluting with EtOAc/light petroleum (1:99). ν_{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, $CDCl_3$): δ 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, C*H* arom.), 7.35 (m, 4H, C*H* arom.); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 19.8, 20.1, 24.7, 28.2, 60.1, 61.8, 125.3, 127.1, 128.2, 142.8.

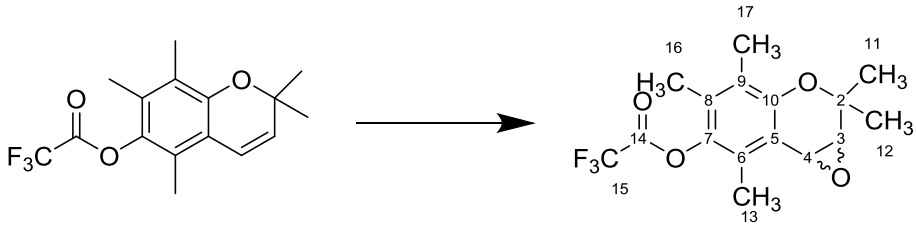
3.3.3.12 6-Acetoxy-3,4-epoxy-2,2,5,7,8-pentamethylchromene



54 **128**

The title compound **128** was isolated as a yellow oil after purification by column chromatography eluting with EtOAc/light petroleum (5:95) + 2% TEA. ν_{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, $CDCl_3$): δ 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, 3 H, Ar-CH_3), 2.37 (s, 3 H, Ar-OCOCH_3), 3.47 (d, *J* = 5 Hz, epoxide), 4.13 (d, *J* = 5 Hz, epoxide); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 11.5 (Ar-*C*H_3, C14 or C17), 11.7 (Ar-*C*H_3, C14 or C17), 13.3 (Ar-*C*H_3, C18), 20.5 (*C*H_3, C11 or C12), 22.9 (*C*H_3-CO_2-Ar, C15), 25.7 (*C*H_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, $C_{16}H_{20}O_4H$ $[M + H]^+$ requires 277.1434.

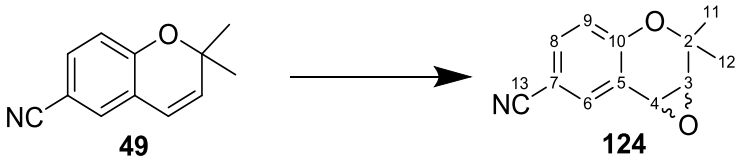
3.3.3.13 6-Trifluorocetoxy-3,4-epoxy-2,2,5,7,8-pentamethylchromene



55 **129**

The title compound **129** was isolated as foam after purification by column chromatography eluting with EtOAc/light petroleum (10:90) + 2% TEA. ν_{max} (film)/cm^{-1} 2989, 2937, 1798, 1464, 1420, 1358, 1276, 1228, 1173, 1139, 1104, 1042, 918, 877. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $^{1}J_{C-F}$ = 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, $C_{16}H_{17}F_3O_4H$ [M + H]$^+$ requires 331.1152.

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

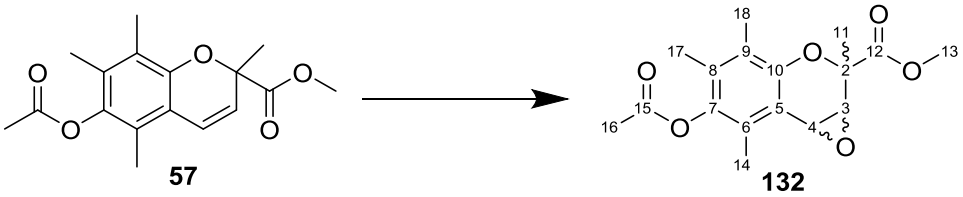


49 **124**

The title compound **124** was isolated as a white solid after purification by column chromatography eluting with EtOAc/light petroleum (5:95) + 2% TEA. ν_{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, $CDCl_3$): δ 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)-$_2$$CH$(O)CH-Ar), 3.91 (d, J = 4 Hz, 1H, C(CH_3)$_2$$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, $CDCl_3$): δ 23.0 (CH$_3$, C11 or C12), 25.5 (CH$_3$, C11 or C12), 49.9 (*C*-epoxide, C3), 62.3 (*C*-

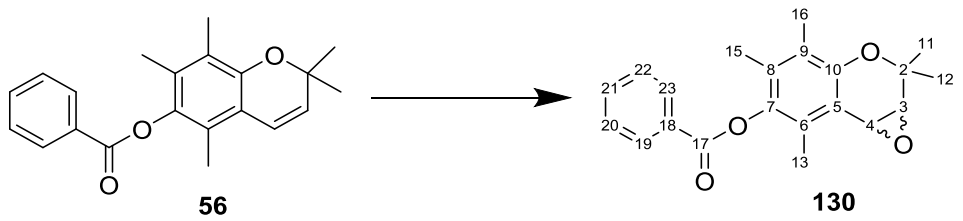
epoxide, C4), 74.7 (*C* quat., C2), 104.3 (*C* quat. arom.), 118.8 (*C* quat. arom.), 119.1 (*C* arom.), 121.1 (*C* quat. arom.), 133.8 (*C* arom.), 134.4 (*C* arom.), 156.5 (-*C*≡N).

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



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_{max} (film)/cm^{-1} 2960, 2918, 2851, 1756, 1620, 1583, 1453, 1370, 1292, 1245, 1201, 1136, 1113, 1087, 1050, 1009, 895. ^{1}H-NMR (500 MHz, $CDCl_3$): 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, C17 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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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, $C_{17}H_{20}O_6H$ [M + H]$^+$ requires 321.1333.

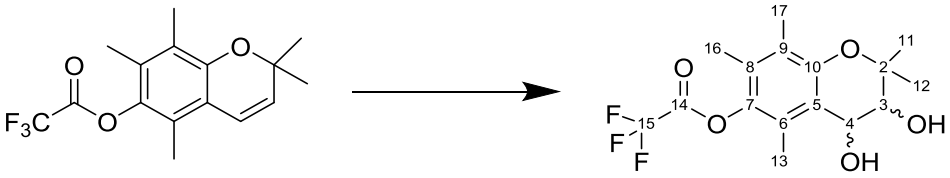
3.3.3.16 6-Benzoyloxy-3,4-epoxy-2,2,5,7,8-pentamethylchromene



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_{max} (film)/cm^{-1} 2974, 2931, 1733, 1601, 1581, 1452, 1416, 1382, 1315, 1265, 1247, 1231, 1177, 1149, 1094, 1058, 1025, 913. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.26 (s, 3H, C11 or C12), 1.60 (s, 3H, C11 or

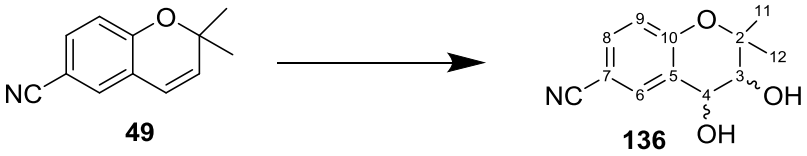
C12), 2.06 (s, 3H, Ar-C*H*$_3$, C13, C15 or C16), 2.10 (s, 3H, Ar-C*H*$_3$, C13, C15 or C16), 2.25 (s, 3H, Ar-C*H*$_3$, C13, C15 or C16), 3.48 (d, *J* = 5 Hz, 1H, C3 or C4), 4.14 (d, *J* = 5 Hz, 1H, C3 or C4), 7.53 (t, *J* = 7 Hz, 2H, 2 X C*H* arom.), 7.66 (t, *J* = 7 Hz, 1H, C*H* arom.), 8.25 (d, *J* = 7 Hz, 2H, 2 X C*H* arom.); ^{13}C-NMR (125 MHz, $CDCl_3$): *δ* 11.6 (Ar-*C*H$_3$, C13 or C15), 11.7 (Ar-*C*H$_3$, C13 or C15), 13.4 (Ar-*C*H$_3$, C14), 22.9 (*C*H$_3$, C11 or C12), 25.7 (*C*H$_3$, 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.), 148.1 (*C* quat. arom.), 165.0 (*C*=O, C17); *m/z* 339.1593, $C_{21}H_{22}O_4H$ $[M + H]^+$ requires 339.1591.

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



Isolated as a brownish oil after purification by column chromatography eluting with EtOAc/light petroleum (5:95) + 2% TEA. ν_{max} (film)/cm^{-1} 3388, 2981, 2926, 2851, 1797, 1462, 1360, 1230, 1174, 1139, 1109, 876. ^{1}H-NMR (500 MHz, $CDCl_3$): *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, $C_{16}H_{19}F_3O_5H$ $[M + H]^+$ requires 339.1631.

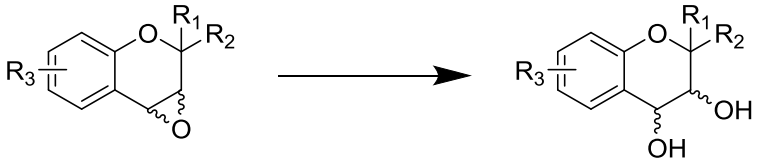
3.3.3.18 6-Cyano-3,4-dihydroxy-2,2-dimethyl-6-cyanochromene[27]



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; ν_{max} (film)/cm^{-1} 3397, 2984, 2919, 2851, 2229, 1611, 1580, 1489, 1372, 1311, 1273, 1195, 1147, 1126, 1072, 1037, 1000, 952, 921, 836. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 19.3 (*C*H_3, C11 or C12), 26.6 (*C*H_3, C11 or C12), 68.6 (*C*H_2-OH, C3), 75.8 (*C*H_2-OH, C4), 79.8 (C quat., C2), 104.0 (C quat. arom.), 118.0 (C arom.), 119.2 (C quat. arom.), 124.4 (C quat. 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_2SO_4). The solvents were removed under reduced pressure, and the crude was purified by column chromatography.

3.4 References

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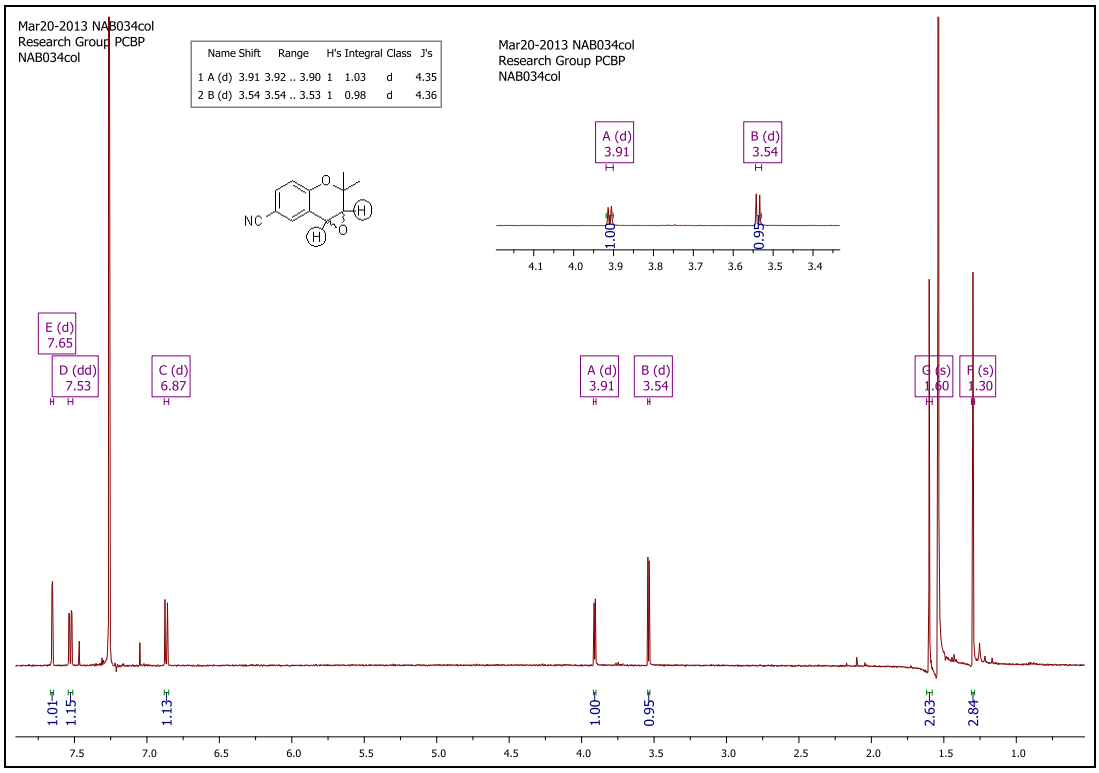
APPENDICES

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

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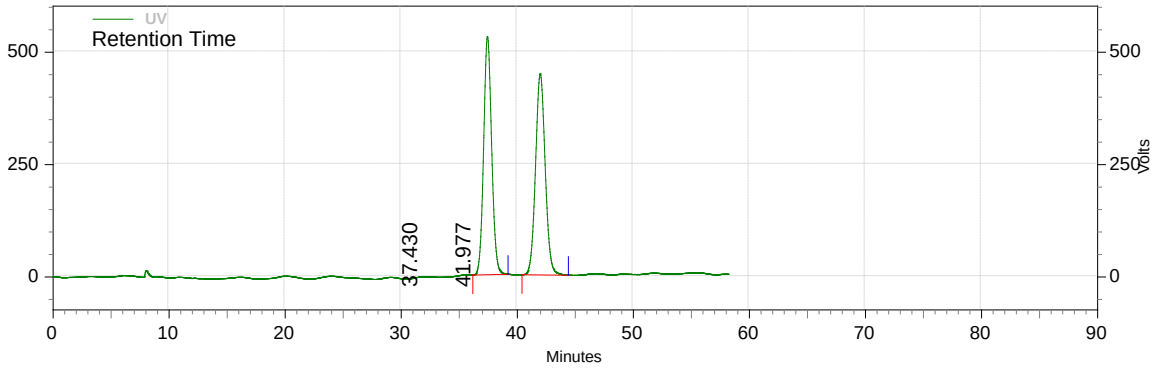

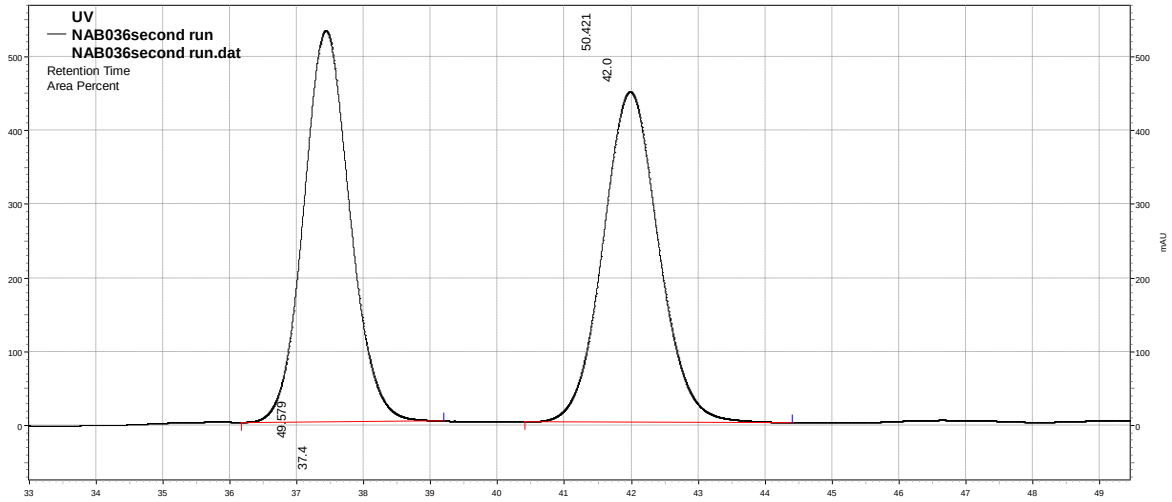

UV Results

Retention Time	Area	Area %	Height	Height %
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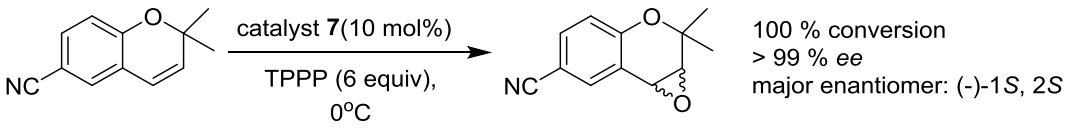
41.977	103601872	50.42	1790157	45.78
Totals	205475132	100.00	3910209	100.00

Asymmetric epoxidation of 6-cyano-2,2-dimethylchromene under non-aqueous conditions



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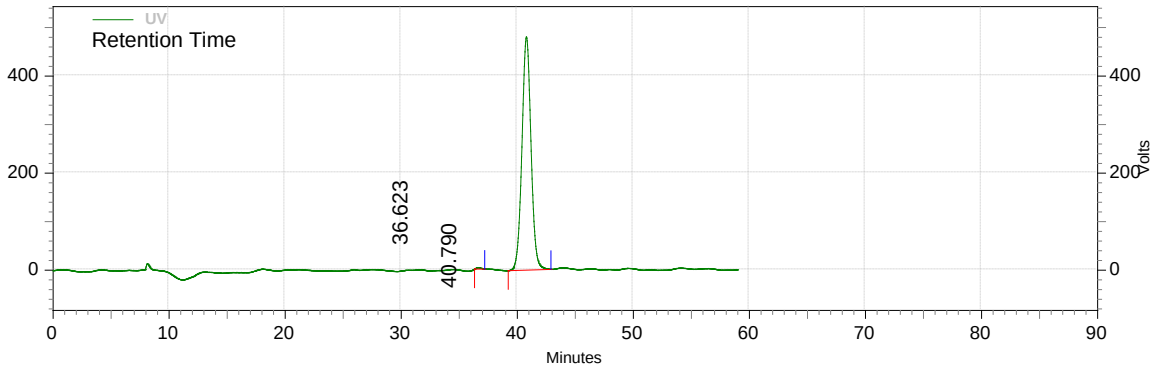
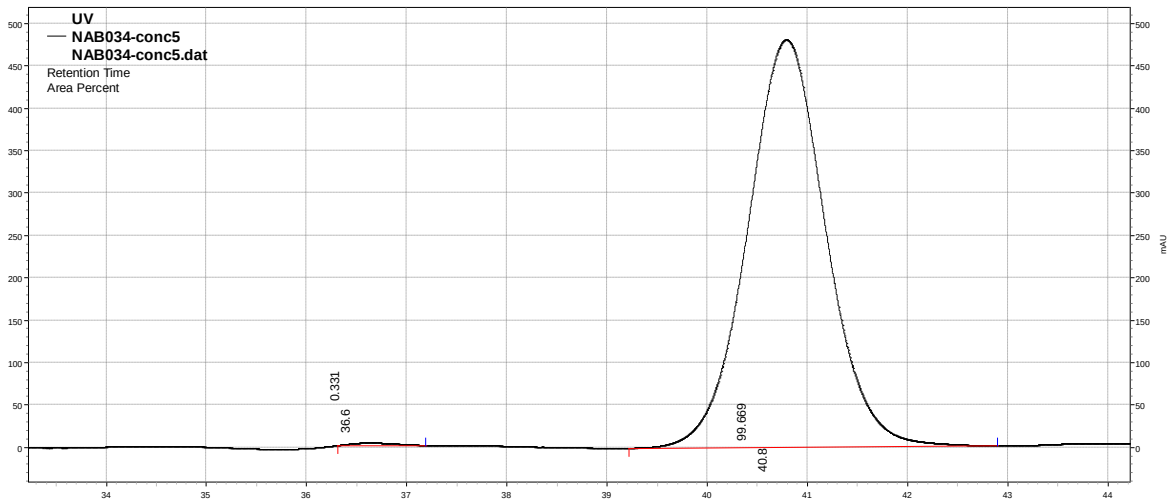
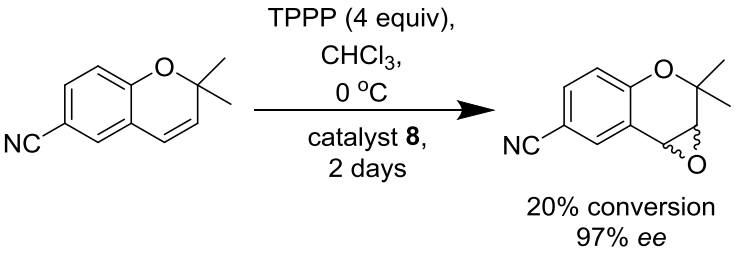




UV Results

Retention Time	Area	Area %	Height	Height %
36.623	347322	0.33	11791	0.61
40.790	104456189	99.67	1922846	99.39
Totals	104803511	100.00	1934637	100.00



Area % Report

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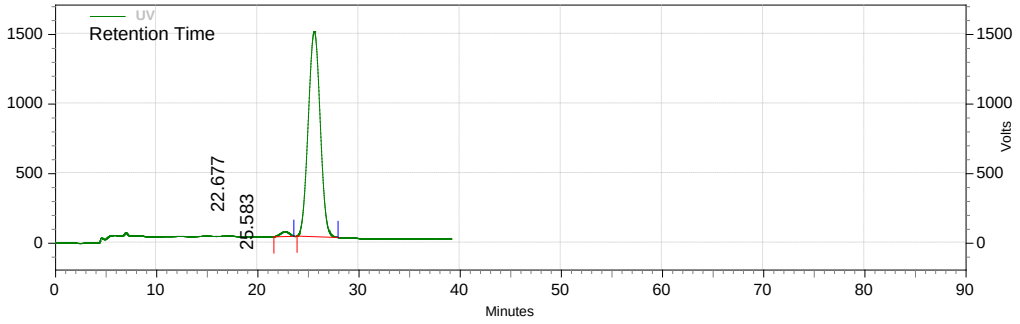
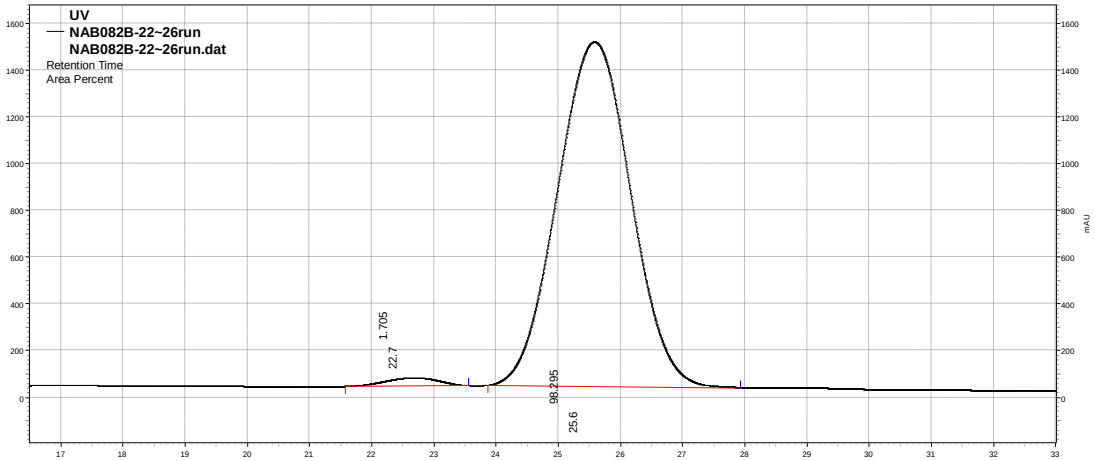


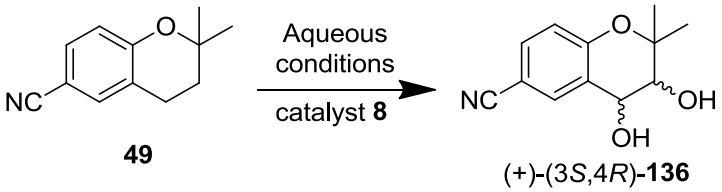


UV Results

Retention Time	Area	Area %	Height	Height %
22.677	8392677	1.70	137278	2.27
25.583	483867773	98.30	5897355	97.73

Totals	492260450	100.00	6034633	100.00

Formation of 6-Cyano-3,4-dihydroy-2,2-dimethylchromene



49 (+)-(3*S*,4*R*)-**136**

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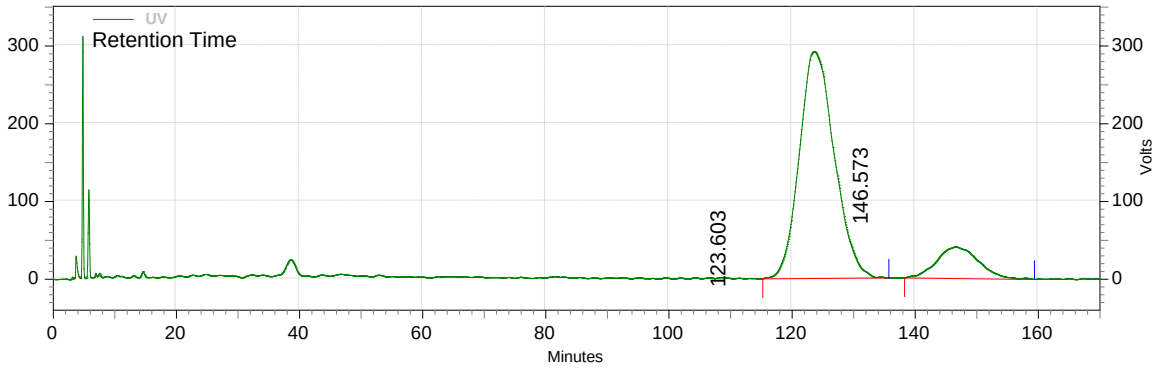

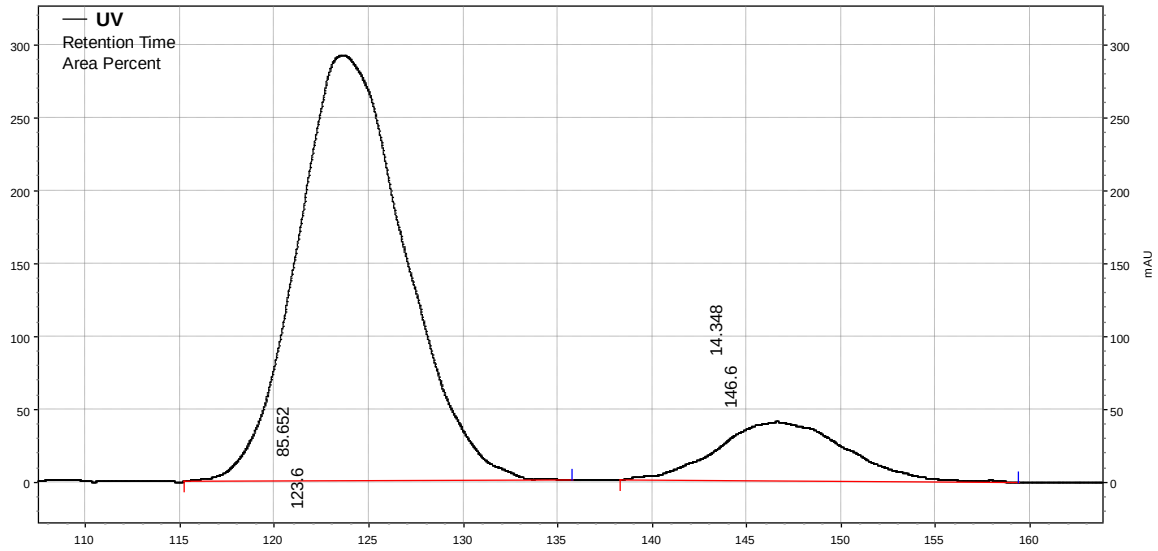

UV Results

Retention Time	Area	Area %	Height	Height %
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146.573	77404027	14.35	162440	12.22

Totals	539462234	100.00	1329794	100.00

^{1}H NMR Comparison for Oxidation reaction using DDQ