

**Applications of Asymmetric Iminium Salt
Epoxidation
in Natural Product Synthesis**

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Abstract

Asymmetric synthesis is a very important tool to the synthetic chemist. With many pharmaceutical targets often having at least one stereocenter within the compound, methods of asymmetrically synthesizing such targets is becoming increasingly important.

Pharmaceutical target molecules often have at least one, if not more, chiral centre, creating different enantiomers and diastereoisomers of the target compound. Different enantiomers and diastereoisomers of compounds may, potentially, have very different chemical and pharmaceutical properties. Consequently, asymmetric synthesis has achieved a lot of attention.

One particular asymmetric method is asymmetric epoxidation. Epoxides are three-membered rings that contain an oxygen and two carbon atoms. Epoxides are very reactive to nucleophilic attack due to strain in the three-membered ring system. This strain means epoxides are prone to ring opening when attacked by a nucleophile to restore the ideal tetrahedral bond angle. This reactivity is utilised in asymmetric epoxidation as it is an important method of obtaining an alcohol group stereospecifically.

One method of asymmetric epoxidation is by the use of organocatalysts such as iminium salts. Asymmetric iminium salt epoxidation catalysts have been found to have a high enantioselectivity to some substrates. However, their full potential has not yet been realised.

This research project focused on identifying further substrates and natural products for which the group's asymmetric epoxidation catalysts could be used. New method based applications were also investigated.

Dihydroquinoline, chromene, 3,4-dihydropyran and their enamine analogues were all investigated.

It was found that iminium salt catalysts did not work well with dihydroquinoline based substrates, probably due to an interaction between the oxaziridine on the catalyst and the nitrogen on substrate. Some protecting groups were investigated but no epoxidation could be achieved. Future research will investigate alternative methods of protecting the nitrogen.

Chromene based compounds were found to be easily epoxidised, achieving high enantioselectivities. Due to the high enantioselectivities achieved this substrate was then used to investigate the potential of iminium salt catalysts in kinetic resolution. A large number of chiral chromene compounds were synthesized and it was found that those with large substituents at the C2 position gave both high enantio- and diastereoselectivity, enabling the first iminium salt based kinetic resolution to be achieved.

The chiral chromene based natural products (-) lomatilin and trans-khellactone were synthesized using the group's iminium salt catalyst, with very high enantioselectivities being achieved.

Synthesis of epigallocatechin gallate (EGCG), using the newly developed kinetic resolution was also attempted, but synthesis of the chromene core proved difficult and research is continuing.

Unfortunately, neither the 3,4-dihydropyran or enamine analogue proved to be good epoxidation substrates.

Acknowledgements

I would like to thank my supervisor Professor Phil Page for giving me the chance to research this exciting area of synthetic chemistry and for his support and guidance.

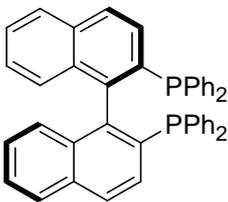
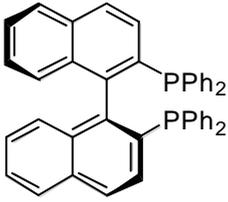
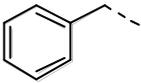
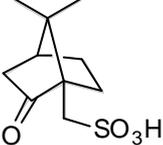
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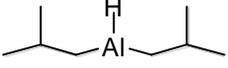
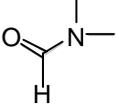
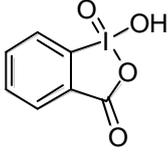
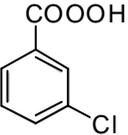
On a personal note, I would like to thank the members of the Page group lab, both past and present, for making the past few years so enjoyable.

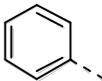
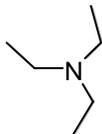
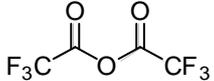
Contents

List Of Abbreviations.....	6
1.0 Introduction.....	9
1.1 Sharpless Epoxidation.....	10
1.2 Polypeptide Catalysis.....	14
1.3 Amine Catalysis.....	15
1.4 Chiral Amines Developed by Jørgensen and Cordova.....	21
1.5 Ketone Catalysis.....	24
1.5.1 Yang's Dioxirane Mediated Epoxidation.....	25
1.5.2 Denmark's Fluorinated Ketones.....	25
1.5.3 Armstrong's Fluorine-Containing Ketones.....	27
1.5.4 Cavello's Investigation into the Fluorine Effect.....	28
1.5.5 Shi's Fructose-Derived Ketones.....	30
1.5.6 Bile Acid Dioxiranes.....	31
1.6 Oxaziridines in Asymmetric Epoxidation.....	32
1.6.1 Use of Oxaziridinium Salts.....	33
1.6.2 Armstrong's Oxaziridinium Salts.....	34
1.6.3 Yang's Exocyclic Iminium Salt.....	37
1.6.4 Komatsu's Exocyclic Iminium Salts.....	38
1.6.5 Bohé's Improved Iminium Catalyst.....	39
1.6.6 Page's Unique Iminium Salt Catalysis.....	43
1.7 The Use of Epoxidation in Kinetic Resolution.....	54
1.7.1 Sharpless Kinetic Resolution.....	55
1.7.2 Jacobsen's Application of Kinetic Resolution Mediated by (salen)Mn Based Catalysts.....	56
1.7.3 Shi's Application of Kinetic Resolution Mediated by Dioxirane Based Catalysts.....	58
1.8 Conclusion.....	59
2.0 Results and Discussion.....	60
2.1 Conclusions.....	121
3.0 Experimental.....	124
3.1 General Experimental.....	124
References.....	190
Acknowledgement.....	198
Appendix.....	199

List Of Abbreviations

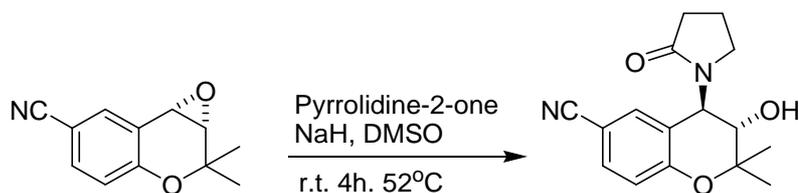
Abbreviation	Chemical Name	Chemical Structure
Ac	acetyl	
Aq	aqueous	NA
Ar	aryl (substituted aromatic ring)	NA
(R)- BINAP	(<i>R</i>)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl	
(S)- BINAP	(<i>S</i>)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl	
Bn	benzyl	
Bp	boiling point	NA
Bu (ⁿBu)	<i>n</i> -butyl	
CSA	camphorsulfonic acid	
DCM	dichloromethane	CH ₂ Cl ₂
De	diastereoisomeric excess	NA

DHP	3,4-dihydro-2 <i>H</i> -pyran	
DIBAL	diisobutylaluminium hydride	
DMF	<i>N,N</i> -dimethylformamide	
DMSO	dimethylsulfoxide	
Ee	enantiomeric excess	NA
Et	ethyl	
H	hours	NA
IBX	<i>o</i> -iodoxybenzoic acid	
IPA	isopropyl alcohol	
LAH	lithium aluminium hydride	LiAlH ₄
<i>M</i>	<i>meta</i>	NA
Min	minutes	NA
<i>m</i>-CPBA	<i>meta</i> -chloroperbenzoic acid	

Me	methyl	- -CH ₃
Mp	melting point	NA
O	<i>ortho</i>	NA
Oxone[®]	potassium peroxymonosulfate triple salt	2KHSO ₅ ·KHSO ₄ ·K ₂ SO ₄
P	<i>para</i>	NA
Ph	phenyl	
Py (pyr)	pyridine	
r.t.	room temperature	NA
TEA	triethylamine	
TFA	trifluoroacetic acid	F ₃ CCOOH
TFAA	trifluoroacetic anhydride	
TPPP	tetraphenylphosphonium monoperoxysulfate	NA

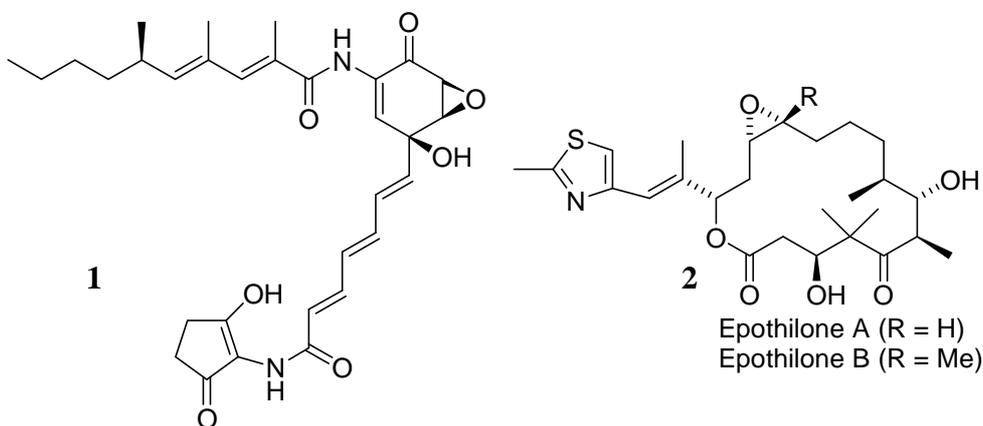
1.0 Introduction

The epoxide functional group is one of the most useful intermediates in organic synthesis.¹ Epoxides are three-membered rings that contain an oxygen and two carbon atoms.² Epoxides are very reactive to nucleophilic attack due to strain in the three-membered ring system. The ring strain in epoxides originates from the angle between the bonds in the three membered ring, which has to be 60° instead of the ideal tetrahedral angle of 109°. This strain means epoxides are prone to ring opening when attacked by a nucleophile to restore the ideal tetrahedral bond angle. This reactivity is utilised in organic synthesis as it is an important method of obtaining an alcohol group stereospecifically, such as in the synthesis of Levchromakalim (Scheme 1).



Scheme 1: Conversion of 6-cyano-2,2-dimethylbenzopyran to Levchromakalim.

It is also thought that epoxides are involved in the carcinogenic activity of aromatic hydrocarbons. Oxidation by cytochrome P450 can result in epoxidation of the hydrocarbons,³ which facilitates nucleophilic attack by DNA, resulting in the alkylation and mutation of the DNA. Interestingly, this effect has conversely been utilised to fight cancer, in a class of anti-tumour compounds such as the manumycin family of antibiotics,⁴ for example manumycin A (**1**), and the epothilones (**2**).⁵



Because of these and other important biological compounds, synthetic methods of asymmetric epoxidation have received a great deal of attention over the past forty years, with the first widely used epoxidation technique being that of Prilezhaev using organic peroxides.⁶ However, this technique was not asymmetric, and it was not until Sharpless in 1980 that the first highly successful chiral epoxidation technique was documented.⁷

This was an important step forward in organic synthesis as Emil Fischer had previously documented in 1894 that the configuration of the substrate had an effect on the activity of enzymes. Fischer wrote: “To use a metaphor, I would say that enzyme and substrate must fit together like lock and key in order to exert a chemical effect on each other. In any case, this notion becomes more likely and its value for stereochemical research increases when the phenomenon itself is transferred from the biological to the chemical realm”. In other words, chemical stereospecificity is of the utmost importance during chemical reactions in the body.⁸ Consequently, methods of synthesising biologically active compounds in a stereospecific manner are very important; mistakes can be costly as was seen with the drug Thalidomide.⁹ Although, in the case of Thalidomide, it is now known that blood pH causes the *in-vivo* racemisation of this drug, so the side effects could never have been avoided.

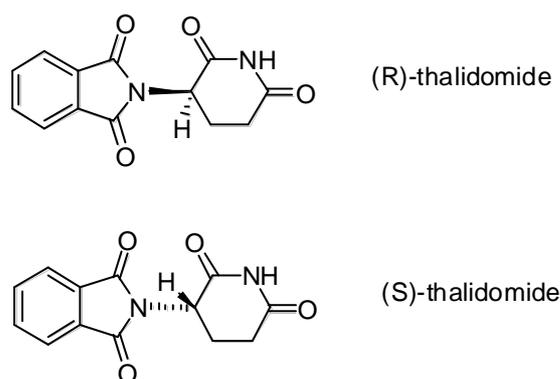


Figure 1: The two configurations of Thalidomide.

1.1 Sharpless Epoxidation

As noted previously, the need for enantiomerically pure or optically active chiral epoxides has increased with the development of biologically active natural products

that contain the epoxide functional group or where the group is used in the compounds synthesis.

Sharpless discovered the first practical method for the asymmetric epoxidation of allylic alcohols using (+)- or (-)-diethyl tartrate and a titanium tetraisopropoxide reagent ($\text{Ti}(\text{O}^i\text{Pr})_4$).⁷ He noted that it gave uniformly high asymmetric inductions throughout a range of substitution patterns, and that the enantiomer of the tartrate complex used delivered the oxygen from the same side of the olefin regardless of the substitution pattern (Figure 2), with generally greater than 90% enantiomeric excess (*ee*).

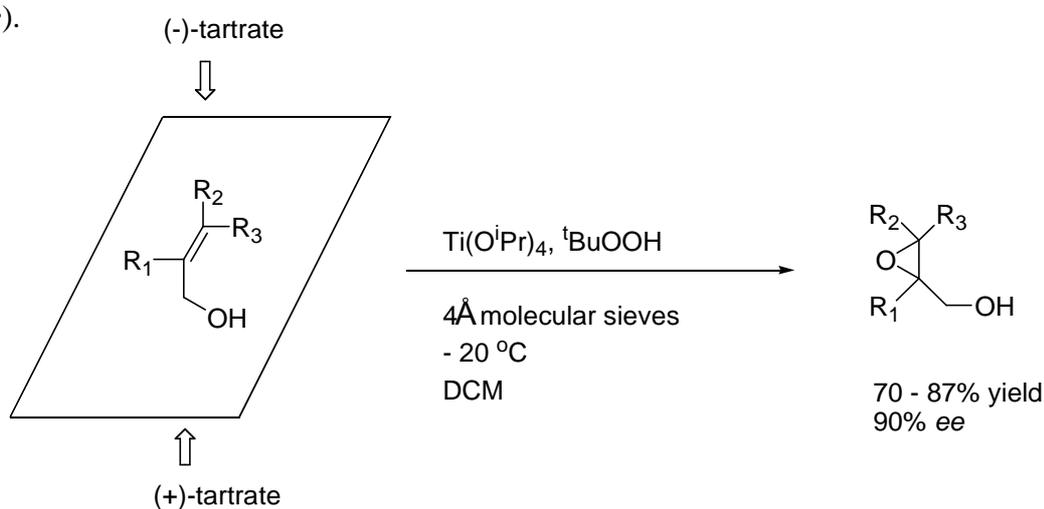


Figure 2: Sharpless epoxidation.

The effectiveness of this system was further exemplified using the synthesis of the three epoxides (**3**), (**4**) and (**5**), which are key intermediates in the synthesis of methymycin, erythromycin and leukotriene C-1 respectively.⁷

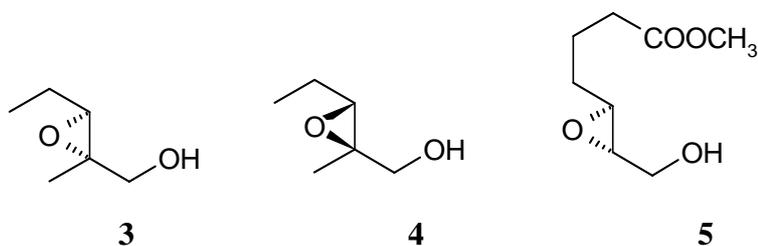
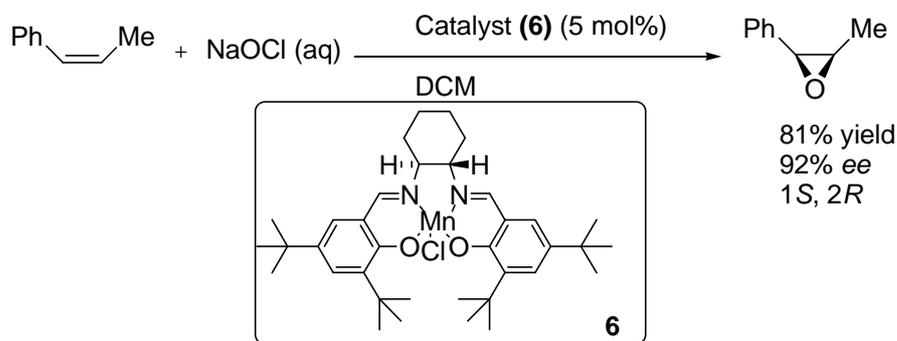
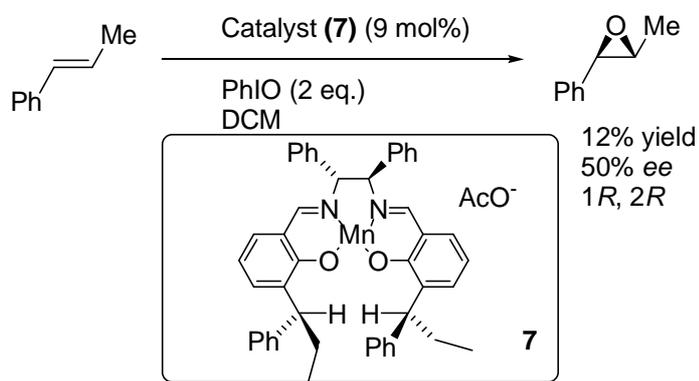


Figure 3: The three epoxide intermediates synthesized by Sharpless used in the synthesis of methymycin, erythromycin and leukotriene C-1 respectively.

The area of metal-based catalysis has since grown exponentially, with many new methods being developed. Two of the most well known are the manganese based catalytic methods of Jacobsen¹⁰ (Scheme 2) and Katsuki¹¹ (Scheme 3).



Scheme 2: Jacobsen's manganese based epoxidation.



Scheme 3: Katsuki's manganese based epoxidation.

Both Jacobsen and Katsuki utilise manganese N,N' -ethylenebis(salicylideneaminato)(salen) complexes in combination with a stoichiometric oxidant. At present, although a number of different catalyst structures have been prepared, Jacobsen's catalyst (6) tends to perform the best, with the highest ee values (up to 98%) being achieved using *cis* alkenes.¹⁰

The mechanism of action still remains a topic for debate. Kochi¹² proposed in 1986 that the active species was an OMn^{V} (salen) complex. This was later proved to be correct when Plattner¹³ showed, using ESI MS, that the addition of the Mn^{III} (salen) complex to a dispersion of PhIO in MeCN afforded an OMn^{V} (salen) species. However, discussions of the mechanism of oxygen transfer have led to two different routes being proposed depending on the substrate used, with the epoxidation of acyclic conjugated *cis* alkenes resulting in the formation of both *cis* and *trans* isomers.¹³ The formation of products with a *trans* stereochemistry points to a

stepwise oxygen transfer mechanism involving a radical intermediate which could ultimately lead to products (**13a** and **b**), whereas products with a *cis* stereochemistry point to a concerted mechanism which would result in only product (**13c**) being observed.¹³

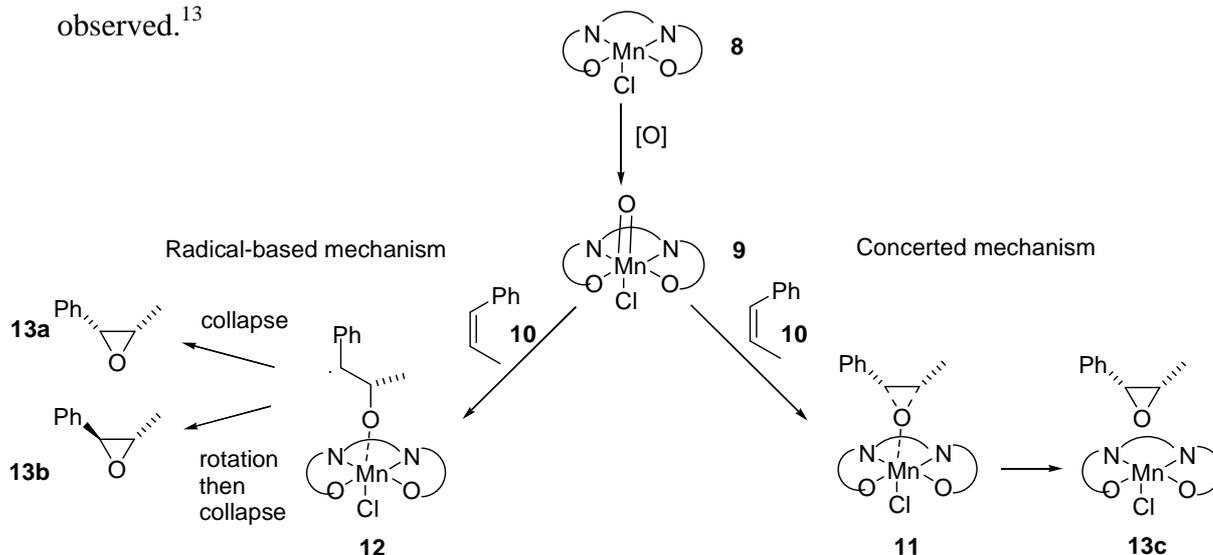
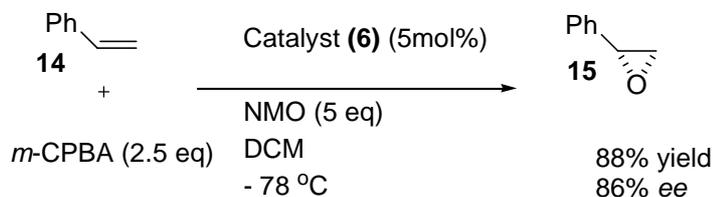


Figure 4: Two proposed mechanisms for oxygen transfer.

In these reactions the stoichiometric oxidant is typically iodosylbenzene (PhIO) or sodium hypochlorite. Recently, however, Jacobsen has developed a non-aqueous system using *m*-CPBA and NMO, which has allowed for the use of lower temperatures. This new system has also resulted in some high enantioselectivities being observed for terminal alkenes, which are typically poor substrates, with the epoxidation of styrene (**14**) yielding the epoxide (**15**) in an 88% yield and 86% *ee* at $-78\text{ }^{\circ}\text{C}$ (Scheme 4).¹⁴

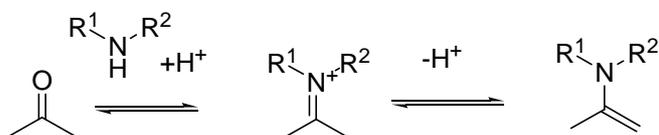


Scheme 4: Epoxidation of styrene (**14**) using Jacobsen's non-aqueous conditions.

However, although these metal-based epoxidation techniques work well, with high *ee* values being achieved, the reagents are often expensive. They also have to be used

under special anaerobic conditions and the metals used are, in some cases, toxic to the environment. This has led to an increased interest in the use of organocatalysts.

Organocatalysis is the acceleration of chemical reactions through the addition of a substoichiometric quantity of an organic compound.¹⁵ Organocatalysts often have the advantage of being inexpensive, more stable and being able to be used in an aerobic atmosphere with wet solvents. Most organocatalysts used currently are bifunctional with a Brønsted acid and a Lewis base centre.¹⁵ This enables them to both activate the donor and acceptor, resulting in an acceleration of the reaction rate. The large majority of organocatalytic reactions used currently are amine-based, proceeding through an enamine cycle or as charge accelerated reactions through the formation of imonium intermediates (Scheme 5).¹⁵



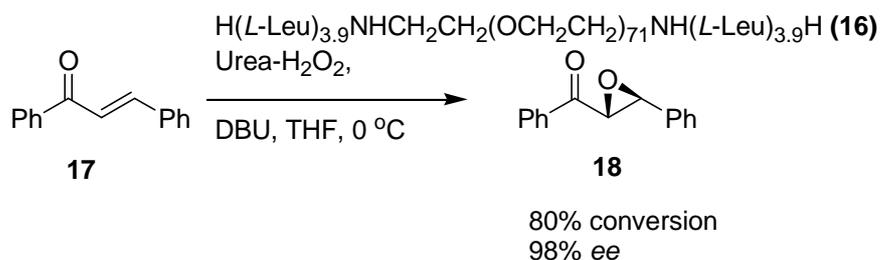
Scheme 5: Electrophilic or nucleophilic activation of a carbonyl group by a secondary amine.

Such methods of organocatalytic epoxidation are discussed here as well as other current organocatalyst-based methods of epoxidation, such as those using polypeptides, those using dioxirane-based structures, and those using oxaziridine-based precursors.

1.2 Polypeptide Catalysis

The use of polypeptide-catalysed epoxidation was pioneered by Julià¹⁶ in the epoxidation of α,β unsaturated ketones, using poly-(*L*)-alanine. More recently, Roberts *et al.* have developed the first organically soluble version of the Julià-Colonna catalyst (Scheme 6), using a polyethylene glycol (PEG)-bound poly-(*L*)-leucine as catalyst in THF. The percentage of conversion to the epoxide at 1 h was around 35%, however this increased to between 58-80% when the reaction was left for 24 h depending on the catalyst used, with the highest conversion of 80%, being achieved for catalyst (**16**) (Scheme 6).¹⁷ It is broadly believed that the mechanism of

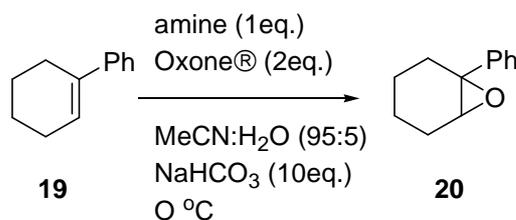
this type of Julià-Colonna system proceeds *via* fast reversible addition of hydroperoxide, followed by slow, intramolecular displacement of hydroxide.¹⁸ The presence of the poly-(*L*)-leucine is thought to provide the origin of the enantioselectivity seen in the reaction by providing binding points for the chalcone within its α -helical structure. The combination of the helical structure and hydrogen bonding wraps the poly-(*L*)-leucine around the chalcone shielding one of the faces of the alkene β -carbon atom, resulting in attack of the hydroperoxide occurring at the other face.



Scheme 6: Epoxidation of chalcone (**17**) to epoxychalcone (**18**) using PEG-bound poly-(*L*)-leucine (**16**) as catalyst.

1.3 Amine Catalysis

In 2000, Aggarwal reported that simple amines (as shown in Table 1) could be used as epoxidation catalysts when using Oxone[®]/NaHCO₃, with the standard procedure shown in Scheme 7.¹⁹



Scheme 7: Aggarwal's standard amine-catalysed epoxidation procedure.

Amine	Conversion (%)	Epoxide (%)	Diol (%)
Et ₂ NH	40	36	4
pyrrolidine	100	90	10
piperidine	90	87	3
pyrrolidinone	2	2	0
pyridine	1	1	0
pyrrolidine (10%) + pyridine (0.5eq)	100	95	4

Table 1: The amines used by Aggarwal in the standard amine catalysed epoxidation.

The study was originally investigating iminium salt catalysts, but the group found that simple amines could also epoxidise the test substrate, 1-phenylcyclohexene (**19**) to racemic 1-phenylcyclohexane oxide (**20**) (Table 1). Primary amines were found to be ineffective in the epoxidation of 1-phenylcyclohexene (**19**), but secondary and tertiary amines catalysed rapid conversion to the epoxide. Secondary amines gave the highest yields, for example, when using pyrrolidine, a 90% yield of 1-phenylcyclohexane oxide (**20**) was obtained (Table 1, second entry). Further investigations showed that substituted pyrrolidines, such as (*S*)-2-(diphenylmethyl)pyrrolidine (**21**), were more effective for a broader range of alkenes than pyrrolidine itself, showing a maximum *ee* value of 57% with 1-phenylcyclohexene (Table 2).

Alkene	Pyrrolidine			<i>(S)</i> -2-(diphenylmethyl)pyrrolidine (21)		
	Conversion (%)	Epoxide (%)	Diol (%)	Conversion (%)	Epoxide (%) (<i>ee</i> %)	Diol (%)
1-phenyl-cyclohexene	59	56	3	100	96 (57)	4
Styrene	30	27	2	100	93 (9)	6
<i>trans</i> -stilbene	2	2	0	6	6	0
<i>cis</i> -stilbene	6	6	0	9	9	0
1-methylcyclohexene	100	90	10	100	90 (15)	7
Indene	29	19	10	31	20 (25)	11

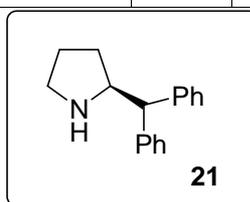
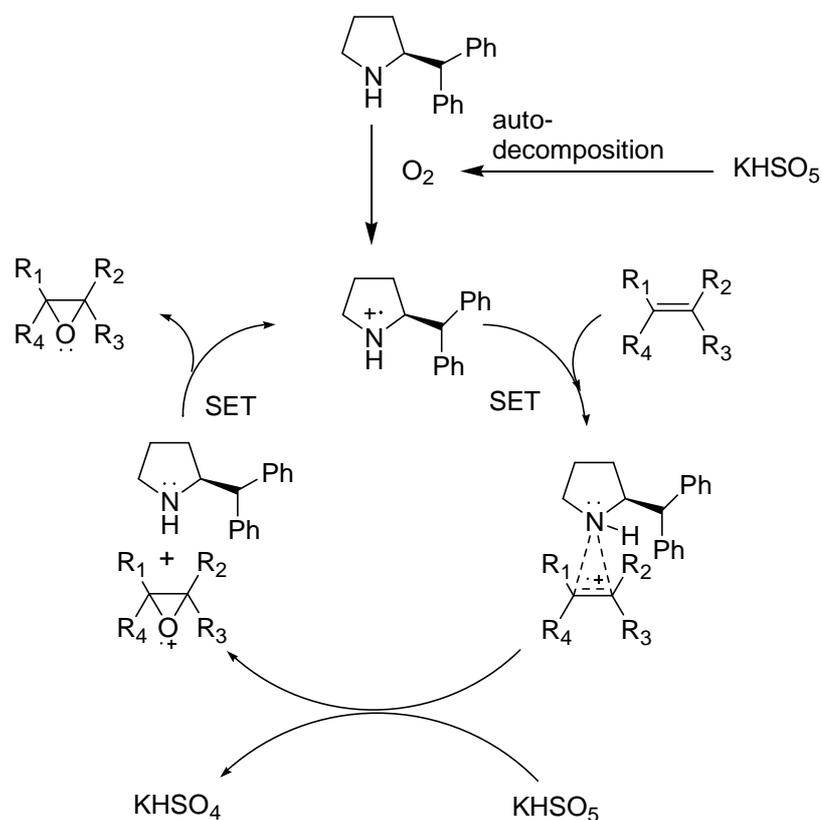


Table 2: Comparison of epoxidation substrates using pyrrolidine and *(S)*-2-(diphenylmethyl)pyrrolidine (**21**).

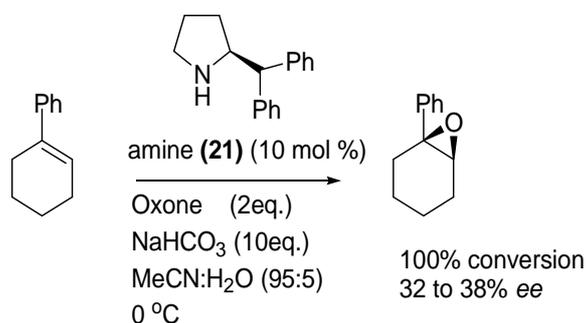
When investigating the mechanism, it was found that pyrrolidine was oxidized to the corresponding hydroxylamine (10%), nitron (60%) and *N*-hydroxylactam (2-3%), but none of these were found to act as oxygen transfer agents or catalysts in the reaction. Aggarwal reasoned, however, that as asymmetric induction is observed, the amine must be involved in the oxygen transfer process, possibly by a radical cation reaction (Scheme 8).¹⁹



Scheme 8: Proposed mechanism for amine catalysed epoxidation.

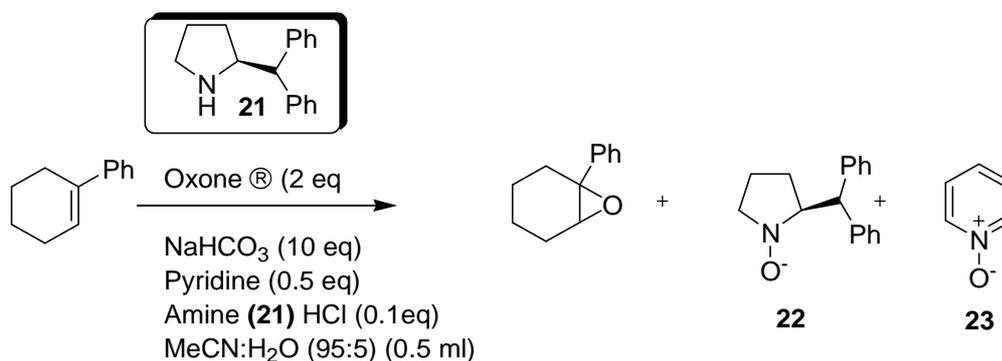
In an attempt to determine the mechanism of the epoxidation, Aggarwal carried out a series of competition experiments. In these experiments, structurally similar alkenes were subjected to either 1) electrophilic epoxidation, using *m*-CPBA or H₂O₂/MTO, or 2) a radical cation mediated epoxidation using a Ar₃N⁺SbCl₆⁻ method developed by Bauld and Mirafzal.²⁰ The selectivities were then compared to those observed by Aggarwal when using the amine catalysed epoxidation. In view of the close similarity in selectivity of the amine catalysed epoxidation to the selectivities observed when using Ar₃N⁺SbCl₆⁻, Aggarwal concluded that a radical cation mediated process was responsible for the amine catalysed epoxidation. However, Aggarwal later found both the competition experiments and Bauld and Mirafzal's original radical cation mediated epoxidation to be inconsistent and often irreproducible, which makes the radical cation mechanism as originally proposed less likely.²¹

Aggarwal also found the enantiomeric excesses achieved to be relatively variable, from 32 to 38% *ee*, when using the standard test reaction (Scheme 9).



Scheme 9: Aggarwal's standard test conditions using amine (**21**).

Aggarwal solved this problem by using the hydrochloride salt of the amine, and incorporating pyridine to reduce the amount of epoxide hydrolysis. This method also gave higher enantiomeric excess values and shorter reaction times (Scheme 10).



Scheme 10: The fate of the amine and pyridine after the epoxidation reaction.

Further investigation into the mechanism of the reaction showed that at the end of the reaction only the oxidation products were observed, with the starting amine (**21**) and pyridine completely oxidized to the nitron (**22**) and N-oxide (**23**) respectively (Scheme 10). This led Aggarwal to pose the question that 'if the amine and pyridine are both oxidized, how are they involved in the epoxidation process?'.²¹ Aggarwal attempted to answer this question by repeating the reaction and then quenching it after five minutes. The reaction mixture showed that despite substantial epoxidation occurring, the amine was un-oxidized at that time and only a small amount of the pyridine had been oxidized to the N-oxide (**23**).

This provided evidence that the alkene is oxidized at a faster rate than the amine, enabling the pyridine to act as a proton carrier during the epoxidation process, with

the amine being protected from oxidation by protonation. Only when all of the alkene has been consumed is the free base of the amine (which is present in equilibrium with the protonated salt form) slowly oxidized to give the nitron (22).

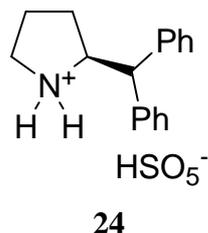


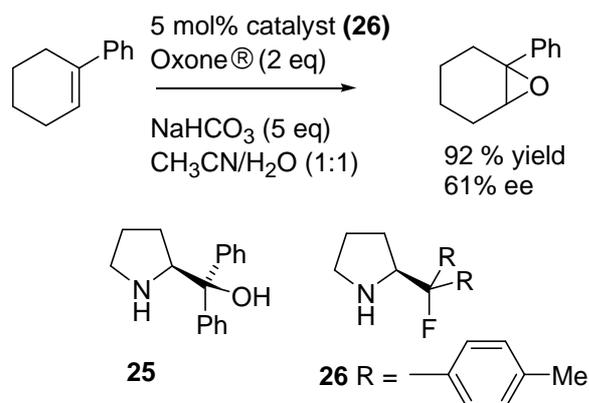
Figure 5: The suggested active ammonium salt.

Later, isolation of the active oxidizing species showed that it was ammonium salt (24) (Figure 5) that was the key oxidant in the reaction, providing evidence that the reaction mechanism occurs between a nucleophilic alkene and electrophilic oxidant, not the radical reaction previously suggested.²¹

During studies into chiral iminium salt catalysis, Yang also found that amines were able to promote epoxidation under slightly acidic conditions.²² Inspired by the previous work by Aggarwal, the group decided to investigate further into the effect the amines and their substituents have on epoxidation and, from this, ultimately confirm the mechanism of action. Their investigation found cyclic secondary amines to be better catalysts than either primary or secondary amines, and that 2-substituted pyrrolidines gave higher conversions and yields than pyrrolidine itself, with amine (25) bearing the bulky CPh₂OH group giving a 78% yield and a 33% *ee*.

Further investigations into these catalysts showed that substituents in the 4-position on the ring exert a strong effect on substrate conversion to the epoxide, with hydroxyl and methoxymethyl ether groups showing the greatest effect. When investigating the effects of different substituents positioned β to the amino group, it was found that a fluorine atom positioned at this point gave the highest catalytic efficiency, with 100% conversion and a 50% *ee*. This was improved further (56% *ee*) when the reactions were conducted at 0 °C to -20 °C, with the advantage that no epoxide hydrolysis occurred. The highest enantiomeric excess (61% *ee*) was found

with catalyst (**26**), a secondary amine bearing a fluorine atom at the β -position relative to the amino group (Scheme 11).

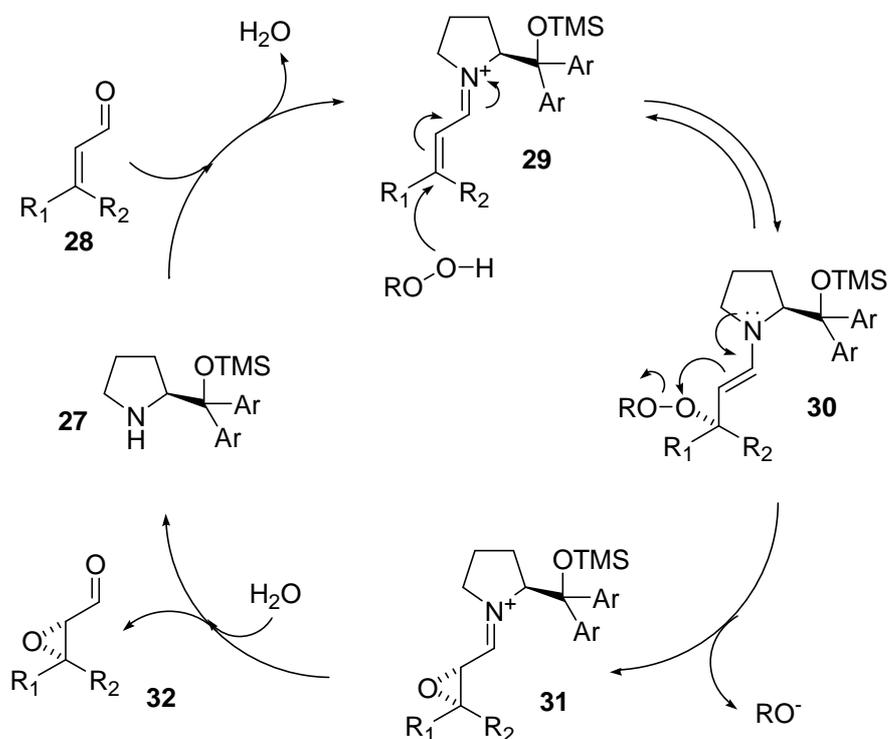


Scheme 11: Yang's cyclic amine catalysed epoxidation.

The results also showed that, as noted by Aggarwal, the oxidation products of the amines were not involved in the epoxidation process, and that under the acidic conditions of the experiment it was likely that the catalyst was indeed converted into its corresponding ammonium salt, confirming the proposal by Aggarwal that the role of the amine is to act as a phase transfer catalyst and Oxone[®] activator.

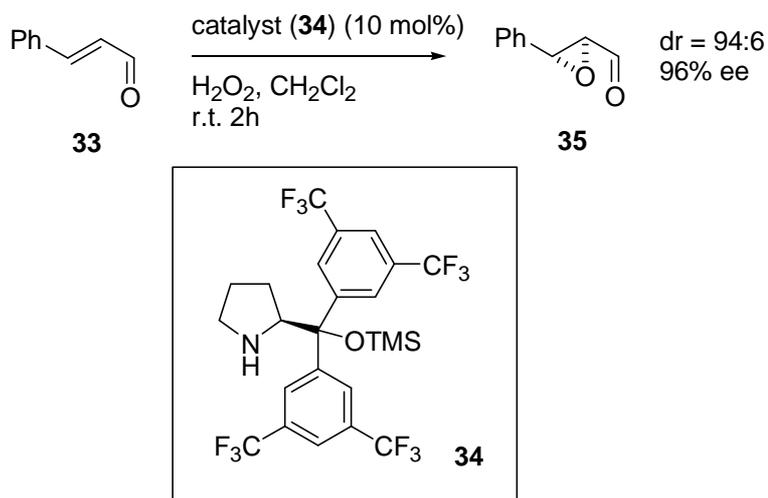
1.4 Chiral Amines Developed by Jørgensen and Cordova

Direct asymmetric epoxidation of α,β -unsaturated aldehydes using organocatalysts has been a challenge to achieve. Jørgensen and co-workers reported the first asymmetric organocatalytic epoxidation of α,β -unsaturated aldehydes using a range of peroxides, such as H₂O₂, as the oxidant.²³ Jørgensen envisioned utilising the properties in chiral amines (**27**) to create an in-situ formation an iminium ion (**29**) when reacted with an α,β -unsaturated aldehyde substrate (**28**). The peroxide oxidant reacts at the electrophilic β -carbon atom forming a carbon-oxygen bond, leading to enamine intermediate (**30**). The resulting nucleophilic enamine carbon atom then forms the epoxide by nucleophilic attack on the electrophilic peroxygen atom. Finally hydrolysis of the epoxy-iminium (**31**) results in the epoxy-aldehyde (**32**) and the regenerated chiral amine (**27**) (Scheme 12).



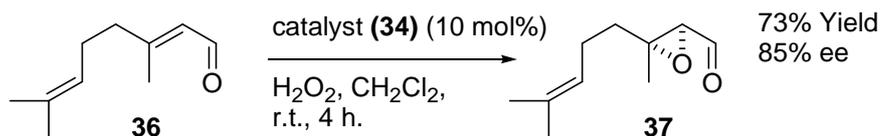
Scheme 12: Proposed mechanism of epoxidation of α,β -unsaturated aldehydes by Jørgensen.

The initial development of the reaction involved the screening of conditions for the epoxidation of cinnamaldehyde (**33**). Hydrogen peroxide (35% w/w in H_2O) was found to be the most efficient oxidant when combined with chiral amine (**34**) in a 10 mol% loading, with full conversion to the epoxide (**35**) being reached in 2 hours, with a high diastereomeric ratio of 94:6 and an *ee* of 96% (Scheme 13).



Scheme 13: Epoxidation of cinnamaldehyde using chiral amine (**34**).

This synthetic methodology has since been used to synthesize the sex pheromone from an acaric mite, where epoxidation of citral (**36**), under the conditions noted previously, gave the sex pheromone (**37**) in a 73% yield and 85% *ee* (Scheme 14).



Scheme 14: Epoxidation of citral using catalyst (**34**).

At this time Córdoba was starting his own investigations into this area.²⁴ The group also screened a variety of amines to act as catalysts, using cinnamaldehyde as the test substrate and hydrogen peroxide (50% wt%, aqueous solution, 1.2-7 eq.) as the oxidant. Similar results to Jørgensen were observed, with chiral pyrrolidine derivatives showing the best reaction profiles. The best enantioselectivity was observed with amines (**38**) and (**39**), with 66% and 97% *ee* respectively.

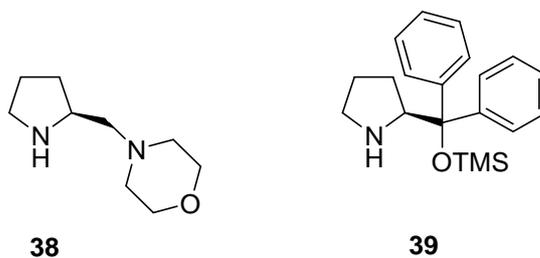
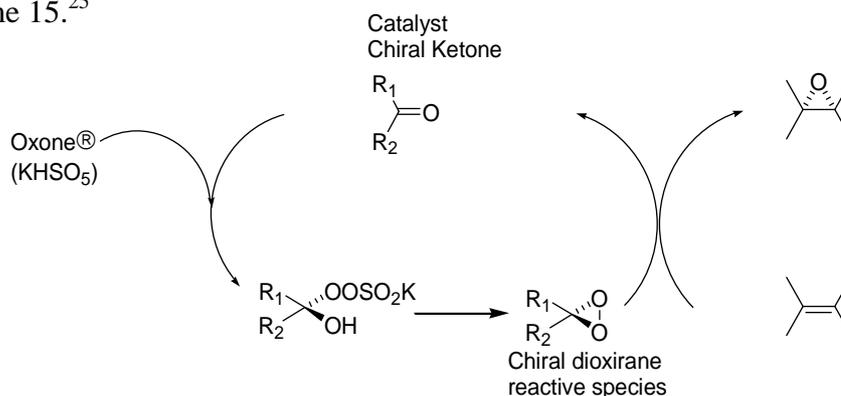


Figure 6: Córdoba's most enantioselective catalysts.

Once the catalysts with the best reaction profiles were determined, these catalysts ((**38**) and (**39**)) were then tested under various different conditions. Córdoba found that temperature had little effect on enantioselectivity when either catalyst was employed. However, catalyst (**39**) was found to show high diastereoselectivity and enantioselectivity for the epoxidation of cinnamaldehyde when a range of different oxidants was used. With the highest values being achieved at 4 °C in CHCl₃ using both H₂O₂ (95:5 *dr* and 98% *ee*) and sodium percarbonate (SPC) (84:16 *dr* and >95% *ee*), respectively. A further range of substrates was also tested with both catalysts (**38**) and (**39**), with the highest *ee* of 98% being observed when catalyst (**39**) was used in the epoxidation of fumaraldehyde monoethylester.

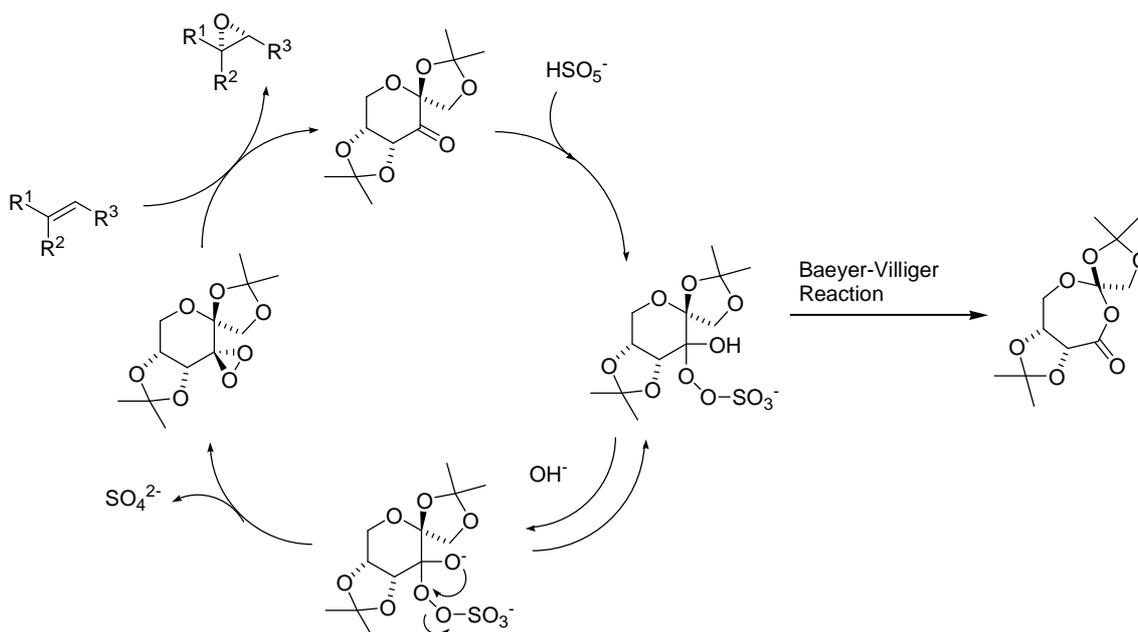
1.5 Ketone Catalysis

Dioxiranes are three membered rings containing two oxygen atoms and a carbon atom. Their reactivity stems from the fact that O-O bonds are weak, and dioxiranes are therefore prone to nucleophilic attack by even weak nucleophiles like olefins to give epoxide products. Dioxiranes are usually generated *in-situ* from ketones (chiral or achiral) and an oxidant such as Oxone[®] (potassium peroxomonosulfate) as shown in Scheme 15.²⁵



Scheme 15: General route for the generation of dioxiranes from chiral ketones.

The two main limiting factors of this method are (i) the competing Baeyer-Villiger reaction, which decreases the effectiveness of the dioxirane catalyst used (Scheme 16), and (ii) the high catalyst loadings required.²⁶



Scheme 16: Competition from Baeyer-Villiger oxidation during the generation of dioxiranes in Shi's fructose derived ketones.

1.5.1 Yang's Dioxirane Mediated Epoxidation

The first highly enantioselective system to utilise dioxiranes was developed by Yang²⁷ using a C₂ symmetric dioxirane generated from the corresponding C₂-symmetric ketone (**40**) and Oxone[®].

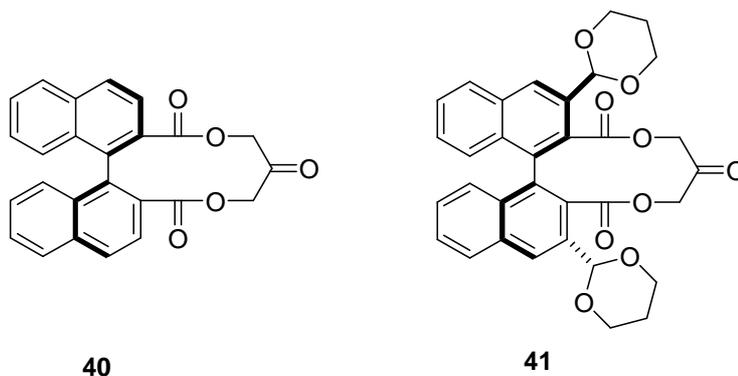


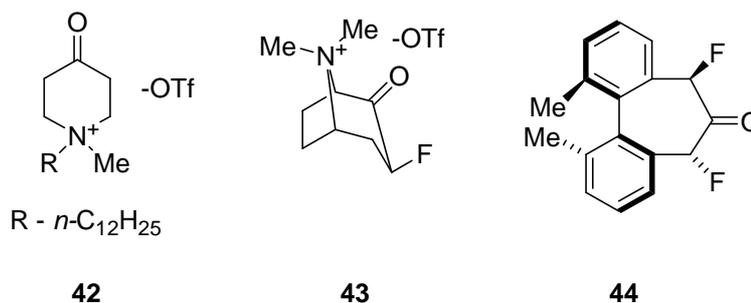
Figure 7: Yang's C₂-symmetric ketones.

The system was developed from the BINAP ligand, which was already known for its enantioselective properties in asymmetric hydrogenation²⁸ and many other processes. Using this system, Yang achieved moderate enantioselectivities, with the best substrate being *trans*-4,4'-diphenylstilbene, giving *ee* values of up to 87%. The selectivity of the catalyst was further improved when X-ray analysis showed that positions H3 and H3' were the closest in proximity to the dioxirane ring, indicating that this position could be exploited to provide more steric control during the oxygen transfer process. This led to the synthesis of catalyst (**41**), which gave a 95% *ee* for the highly hindered alkene, *trans*-4,4-di-*tert*-butylstilbene.

1.5.2 Denmark's Fluorinated Ketones

Denmark showed that dioxirane-mediated epoxidation accomplished with 1-dodecyl-1-methyl-4-oxopiperidinium triflate (**42**) gave high reactivity and yields, with the success of this ketone thought to be due to the ability of nearby electron-withdrawing groups to increase the reactivity of the carbonyl group towards nucleophiles.²⁹ Additionally, it had been reported that α -fluorine substituents tremendously increase the reactivity of the carbonyl in dioxirane-mediated epoxidations. On the basis of these observations, Denmark designed catalysts (**43**) and (**44**),³⁰ with catalyst (**43**)

bearing a fluorine atom and catalyst (**44**) also fluorinated but utilizing the ketone backbone originally designed by Yang.



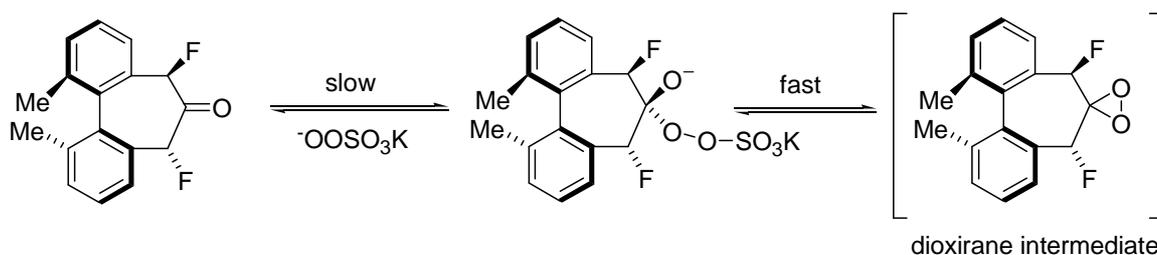
The α -fluorinated ketone (**43**) showed excellent catalytic activity with *ee* values ranging from 6 to 58%, with all the reactions complete within 12 h and a catalyst loading of 10 mol%. Cyclic difluoro ketone (**44**) also showed good asymmetric induction, although the *ee* values ranged from 12 to 94% (Table 3). Denmark reasoned this could be due to the two fluorine groups not providing sufficient activation for the carbonyl group or that the actual conformation of the ketone may somehow restrict the activity.

Catalyst (43)			Catalyst (44)		
Substrate	Yield of epoxide (%)	Enantiomeric Excess (%)	Substrate	Yield of epoxide (%)	Enantiomeric Excess (%)
	97	6		72	68
	85	35		80	88
	79	58		46	94
	78	14		67	12

Table 3: Catalytic activity achieved with Denmark's catalysts (**43**) and (**44**) on a range of olefins.

The reaction conditions were then investigated to see if optimal conditions could be found. Shi had reported earlier that changing the buffer solution to potassium

carbonate resulted in an increase in the reaction rate;³¹ Denmark reasoned that this is because at higher pH the concentration of the peroxydisulfate dianion is higher, and so the concentration of the conjugate base would also be higher which would facilitate the formation of the dioxirane (Scheme 17).²⁹ Increasing the pH, by changing the base used from NaHCO₃ to K₂CO₃ resulted in a 55% conversion of the alkene after 8 h, using 10 mol % of the catalyst.



Scheme 17: Generation of the Dioxirane.

1.5.3 Armstrong's Fluorine-Containing Ketones

It has been suggested that the presence of a fluorine-containing substituent can increase or decrease the reactivity of the dioxirane as a catalyst, depending on the orientation of the fluorine.³² Armstrong demonstrated that α -fluoro-*N*-carbethoxytropinone (**45**) was a stable catalyst that resisted decomposition through Baeyer-Villiger reaction.³³ The first substrate to be investigated was *trans*-stilbene, and good *ee* values, 76% from an 88% conversion, were obtained at room temperature with a 10% catalyst loading. Importantly, as dioxiranes are generally regarded as electrophilic oxidants, the successful epoxidations of *trans*-ethyl cinnamate, 64% from a 51% conversion, and *trans*-chalcone 54% *ee* from a 94% conversion, were encouraging.

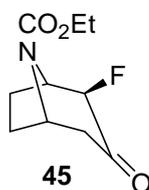


Figure 8: Armstrong's α -fluoro-*N*-carbethoxytropinone ketone (**45**).

Armstrong believed that this increased stability for the fluorine-containing compound (**45**) was due to the α -fluoro group exerting a stabilising and directing effect in the spiro transition state.³³

1.5.4 Cavello's Investigation into the Fluorine Effect

Cavello³² further investigated the effect of fluorine on dioxirane epoxidation by examining the rigid *trans*-decalone ketones, **46**, **47** and **48**, as chiral catalysts for the epoxidation of *trans*-olefins (such as stilbene, β -methylstyrene and *p*-methoxy cinnamate).

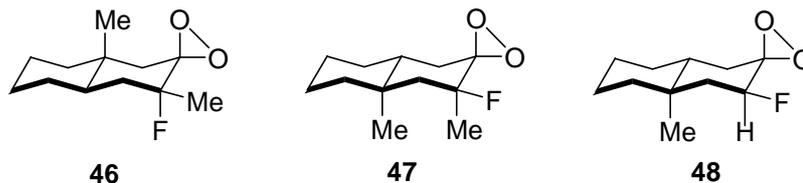


Figure 9: Cavello's *trans*-decalone ketones.

These particular catalysts were used as they are unable to undergo chair-chair ring inversion; hence they can be used to probe the importance of ring inversion and fluorine orientation. The formation of the resulting dioxiranes showed (i) that dioxiranes with an equatorial α -fluorine (such as **(47)** and **(48)**) on the dioxirane ring are less reactive and provide lower *ee* values than dioxiranes with an axial fluorine (such as **(46)**) and having otherwise the same chirality and (ii) that an axial methyl group gives significantly lower conversions and *ee* values than an axial α -fluorine.

When suggesting reasons for why this effect was observed Cavello considered several different things; 1) the effect of the fluorine on activation energy, 2) electrostatic interactions, and 3) the approach of the alkene.

In all cases it would be expected that the inductive effect of the fluorine atom would lower the activation energy. Cavello reasoned therefore, that the increased reactivity of catalyst **(46)**, which contained an axial fluorine atom, must be due to interactions occurring during the epoxidation reaction itself.

Cavello noted that when considering the approach of the alkene to the dioxirane for catalysts **(46 – 48)**, there are interactions in all possible approach routes when catalysts **(47)** and **(48)** are used (Figure 10). These interactions, however small, would result in a decrease in the reactivity of the catalysts. However, when catalyst **(46)** is used (Figure 11), interactions would only be expected in the A1 route (due to

Me/Ph repulsion) and the E2 route (due to F/Ph repulsion), resulting in a more reactive catalyst.

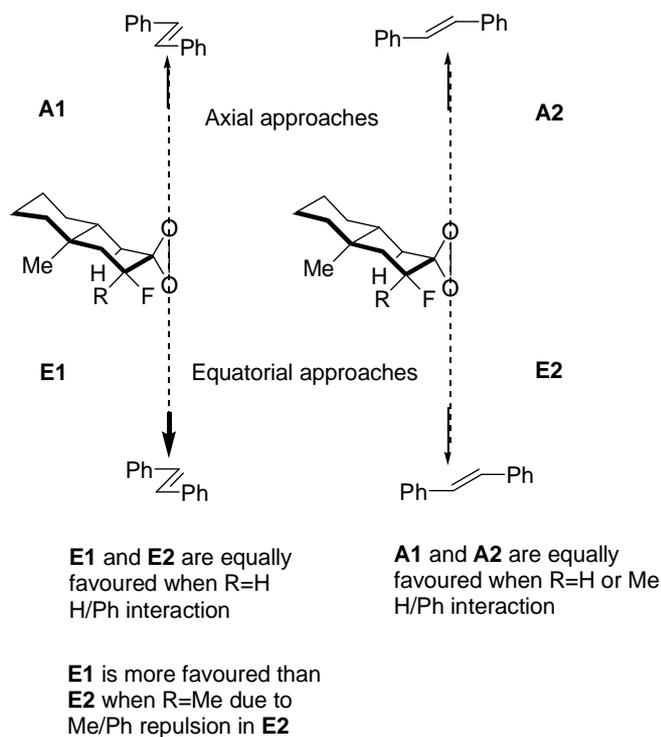


Figure 10: Cavello's explanation of the epoxidation reactivity seen in the epoxidation of *trans*-stilbene using catalysts (47) and (48).

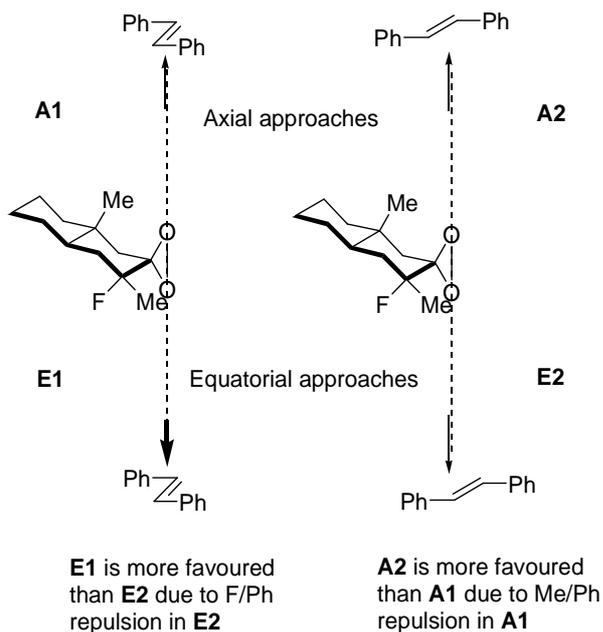


Figure 11: Cavello's explanation of the epoxidation reactivity seen in the epoxidation of *trans*-stilbene using catalyst (46).

Cavello also noted that if the alkene approaches the dioxirane equatorially, and the fluorine is in an axial position, the fluorine is anti to the dioxirane oxygen that is not transferred. Cavello reasoned (based on previous calculations by Armstrong)³⁴ that this arrangement would minimise electrostatic interactions between the oxygen with greater the developing negative charge and the fluorine atom. In catalysts where the fluorine is in an equatorial position this interaction is unavoidable, thereby decreasing reactivity of the catalyst.

When combined, each of these factors point to catalysts with an axial fluorine (such as catalyst (46)) being more reactive, and this was seen to be the case.

1.5.5 Shi's Fructose-Derived Ketones

More recently, the fructose-derived ketones developed initially by Shi have been found to show considerable reactivity, particularly in the catalytic epoxidation of *E* configured and tri-substituted olefins,²⁶ with a 95% *ee* for *trans*-stilbene being achieved when using catalyst (49), shown in figure 12.

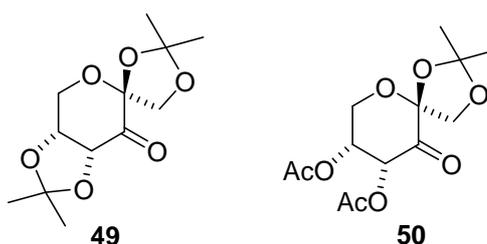


Figure 12: Shi's fructose derived ketones.

However, the main drawback of Shi's system is that if the epoxidation proceeds slowly, the catalyst is prone to decomposition *via* Baeyer-Villiger oxidation. Experimentation showed that this could be minimised by raising the pH from the typical pH of between 7.0 and 8.0 for an epoxidation reaction using Oxone[®] to a pH of 10.5. This increase resulted in an enhanced effect on catalyst activity, with the conversion of *trans*-methylstyrene using 20 mol% catalyst increasing from less than 10% at pH 7-8, to around 80% at pH 10.5. Importantly the enantioselectivity remained high at 90-92% *ee*.³⁵

The highly enantioselective epoxidation of α,β -unsaturated esters using fructose based catalysts still remained a challenging problem, due to the electrophilic catalyst reacting slowly with the electron deficient substrates. However, Shi found that catalyst (**50**), the acetate analogue of (**49**), provided a highly active and enantioselective catalyst for the epoxidation of α,β -unsaturated esters, with a 73% yield and 96% *ee* being achieved in the epoxidation of ethyl *trans*-cinnamate.

1.5.6 Bile Acid Dioxiranes

Bile acid dioxiranes from bile acid ketones (**51**) have been reported in the epoxidation of cinnamic acids. The structure of the bile acids is characterised by a rigid and robust skeleton, which limits conformational changes, and so maintains any steric factors in the ketone after its conversion into the dioxirane.³⁶

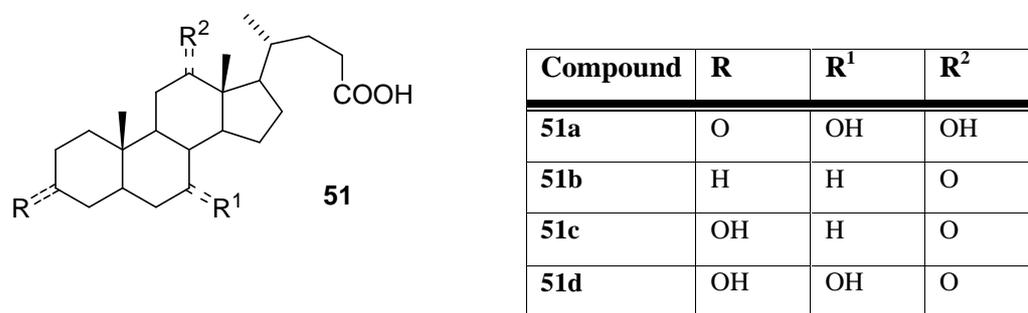
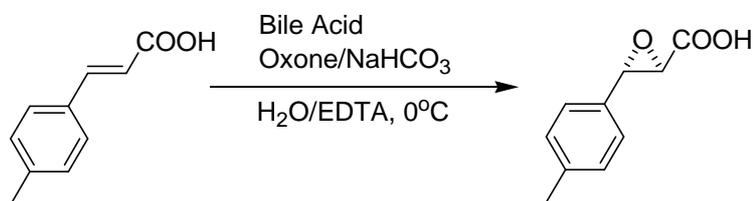


Figure 13: Bortolini's bile acid ketones.

The ketones can be obtained from commercial sources or can easily be prepared from bile acids. The epoxidation reaction is performed in an aqueous NaHCO₃ solution at 0 °C in the presence of an excess of Oxone[®] (Scheme 18).



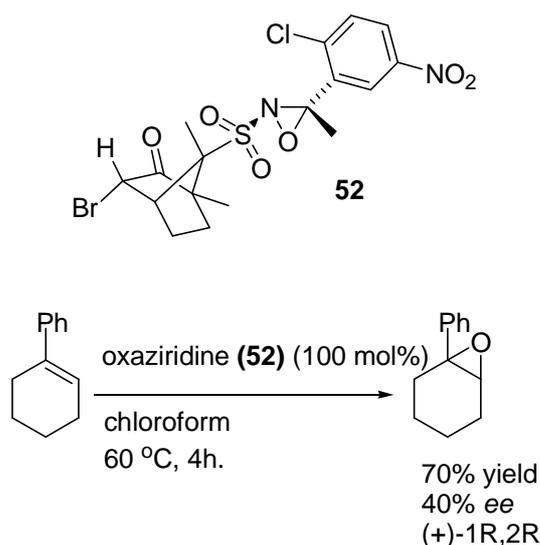
Scheme 18: Bortolini's bile acid epoxidation method.

Epoxidation *ee* values varied from 95% using catalyst **51a** to zero when catalysts **51b**, **c** and **d** were used. The conclusion was that the use of bile acid inducers which

have a carbonyl function at carbon three (R group), as well as specific and stereochemically appropriate carbon seven (R¹ group) and carbon twelve (R² group) substituents, has a large effect on the reactivity and stereoselectivity during asymmetric epoxidations with Oxone[®].

1.6 Oxaziridines in Asymmetric Epoxidation

Oxaziridines are the nitrogen analogues of dioxiranes, and can also act as oxygen transfer agents.³⁷ Lusinchi *et al.* first highlighted the use of oxaziridines as epoxidation agents in 1976.³⁸ However, Davis was the first to show examples of epoxidation using oxaziridines and 2-benzenesulfonyl-3-aryloxaziridines, in 1981. Davis showed that the similarity between oxygen transfer systems in heteroaromatic *N*-oxides and enzyme-catalysed oxidations made the photolysis of such heteroaromatic systems a useful model for potential synthetic epoxidation reactions.³⁹ The first chiral epoxidation used chiral 2-sulfonyloxaziridine diastereoisomers, however, the *ee* values were still low, with a highest figure of 40% *ee* being achieved by (-)-(S,S)-2-(δ - α -bromo- π -camphorsulfonyl)-3-(2-chloro-5-nitrophenyl)-oxaziridine (**52**) for 1-phenylcyclohexene oxide (Scheme 19).⁴⁰



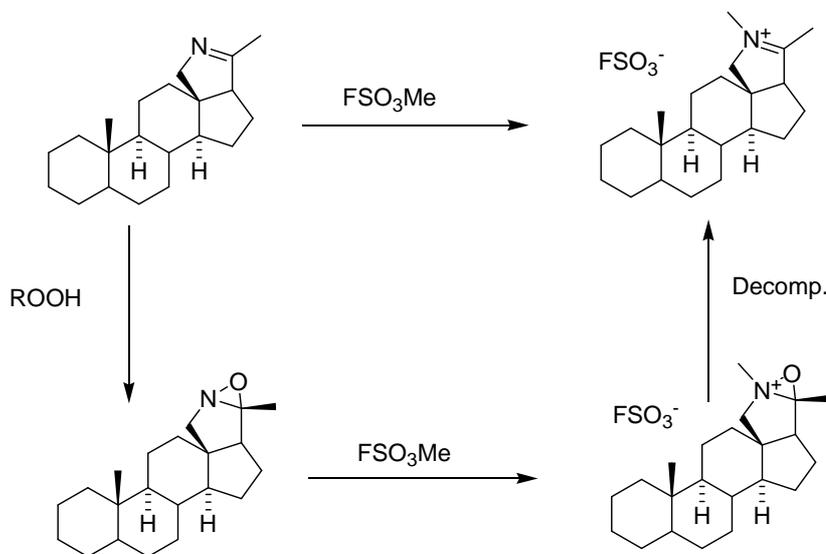
Scheme 19: Davis's first chiral oxaziridine asymmetric epoxidation.

Greater *ee* values were later achieved,³⁷ but the main drawback was the lack of reactivity of oxaziridines towards most alkenes, and this has led to the investigation of using oxaziridinium salts for asymmetric epoxidation.

1.6.1 Use of Oxaziridinium Salts

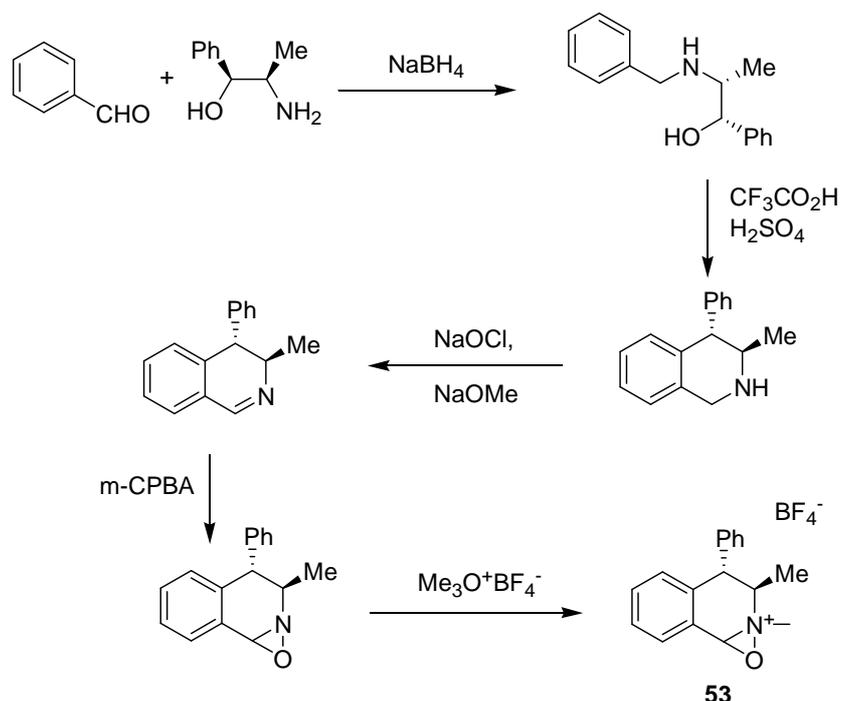
Oxaziridinium salts are the quaternised analogues of oxaziridines, and as such are more electrophilic and able to transfer oxygen more efficiently to nucleophilic substrates, with epoxidation rates decreasing as the olefin becomes increasingly nucleophilic.⁴⁰

Lusinchi was the first to show that oxaziridinium salts could be used as reactive intermediates in the epoxidation of olefins.³⁸ The presence of the two nucleophilic centres appeared to be the basis of the oxaziridine reactivity in epoxidation reactions. The salt was based on a conanine steroidal pyrrolinic imine skeleton, which was oxidized using peracid and then quaternised using methyl fluorosulfonate (FSO₃Me). This salt is rather unstable and rapidly decomposes to the iminium salt, and it is during this decomposition that the oxygen is thought to be transferred to the olefin. (Scheme 20).⁴¹



Scheme 20: Lusinchi's first example of an oxaziridinium salt catalyst.

Further work in this area resulted in the first enantiomerically pure oxaziridinium salt, prepared from (1*S*,2*R*)-(+)-norephedrine (Scheme 21), with *ee* values of 33% in the epoxidation of *trans*-stilbene using iminium salt (**53**) when carried out in the presence of trifluoroacetic acid, being observed in preliminary experiments.⁴² An exciting prospect was the possibility of a catalytic system being developed from the side product of the reaction, which was a regenerated iminium salt.

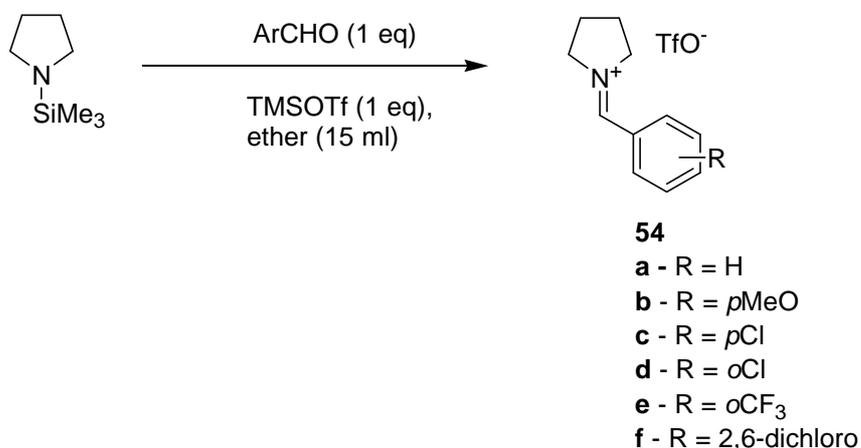


Scheme 21: Synthesis of Lusinchi's first enantiomerically pure oxaziridinium salt.

This was achieved using Oxone[®] in a similar system to that developed for dioxiranes, though less pH control is required as there is no competitive Baeyer-Villiger oxidation. From this initial research, many other catalytic oxaziridinium salt systems have been proposed; a few are considered here.

1.6.2 Armstrong's Oxaziridinium Salts

Armstrong was drawn to the aforementioned work of Lusinchi and Hanquet with oxaziridinium salts, in which one of the ring oxygens is replaced with a nitrogen atom. However, Armstrong felt that previous systems, in which the iminium part is bonded as part of a ring (endocyclic iminiums), were limited in the number of chiral salts that could be synthesized and evaluated as epoxidation catalysts. Hence, he examined iminium salts (**54a-f**) derived from intermolecular condensations from separate amines and carbonyl compounds (Scheme 22).⁴³



Scheme 22: Armstrong's first exocyclic iminium salt catalysts.

Epoxidation reactions were performed using the system described by Lusinchi and Hanquet (Oxone[®]/CH₃CN/H₂O). The iminium salts derived from pyrrolidine and aromatic aldehydes with electron-withdrawing substituents in the *para*- or (particularly) the *ortho*-position were by far the most reactive catalysts (**54d**) and (**54e**), with the latter giving an 89% yield in the epoxidation of *trans*-stilbene. The exact reason for the increased performance of the *ortho*-isomers is not known, but Armstrong believed it may be related to the reduced tendency for the aromatic ring to adopt planarity with respect to the iminium bond, thus resulting in a loss of conjugation. However, extension to the use of more hindered, chiral amines was unsuccessful possibly due to hydrolysis of the iminium salts and / or the low reactivity of the oxaziridiniums.⁴³

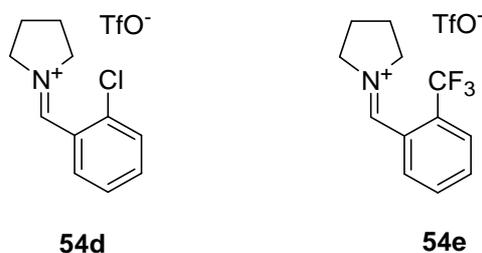
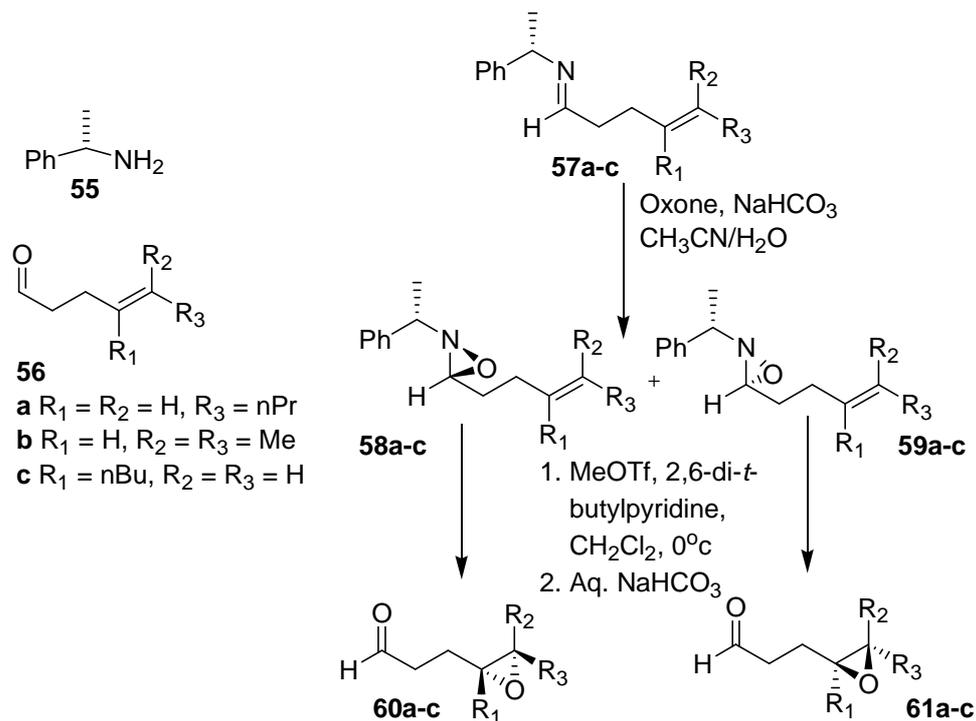


Figure 14: Armstrong's most successful exocyclic iminium salts.

Armstrong then went on to investigate intramolecular epoxidation as a way of maintaining regio- and stereochemistry. Armstrong was able to show that highly stereoselective intramolecular epoxidation of 98% *ee* was possible when using (*S*)- α -

methylbenzylamine (**55**) and an unsaturated aldehyde (**56a-c**). In this procedure, the imine is oxidized with Oxone[®] to produce two separable diastereoisomers (4:1 ratio) (Scheme 23). Each diastereoisomer was dissolved in DCM and treated with MeOTf in the presence of 2,6-di-*t*-butylpyridine, leading to highly enantiopure epoxy-aldehydes. However, despite the high selectivity observed with these types of substituents, it was noted that if the chain between the imine and alkene was more than three atoms a loss of selectivity occurred.⁴⁴



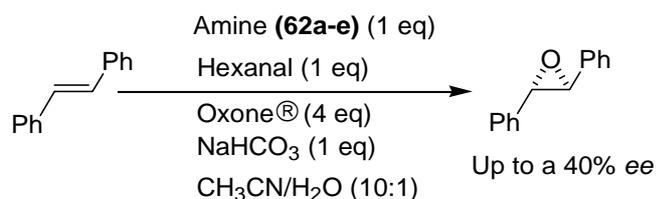
Scheme 23: Armstrong's intramolecular epoxidation.

Substrate	Ratio of 60:61	<i>de</i> %	<i>ee</i> %	Yield %	<i>de</i> %	<i>ee</i> %	Yield %
56a	4:1	90	93	35	90	92	47
56b	3:1	83	81	60	90	94	40
56c	3:1	90	98	55	n/a	84	70

Table 4: Results achieved by Armstrong's intramolecular epoxidation on substrates **56a-c**.

1.6.3 Yang's Exocyclic Iminium Salt

Yang has also developed an exocyclic iminium salt system, using salts that are generated *in situ* from amines and aldehydes under slightly acidic conditions, oxidized with Oxone[®] and then used to epoxidise olefins (Scheme 24).⁴⁵ This *in situ* method avoids the intrinsic problems associated with the usual preparation and isolation of the unstable iminium salts. The results from the initial test conditions are shown in Table 5.



Scheme 24: Wong and Yang's initial test conditions investigating exocyclic iminium salt epoxidation using an exocyclic iminium salt generated *in situ* from amines (**62a-e**) and hexanal.

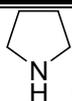
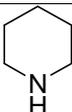
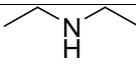
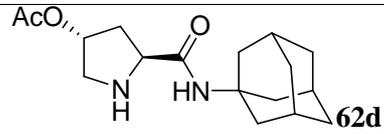
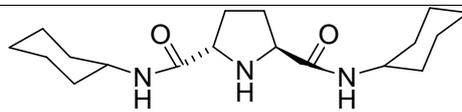
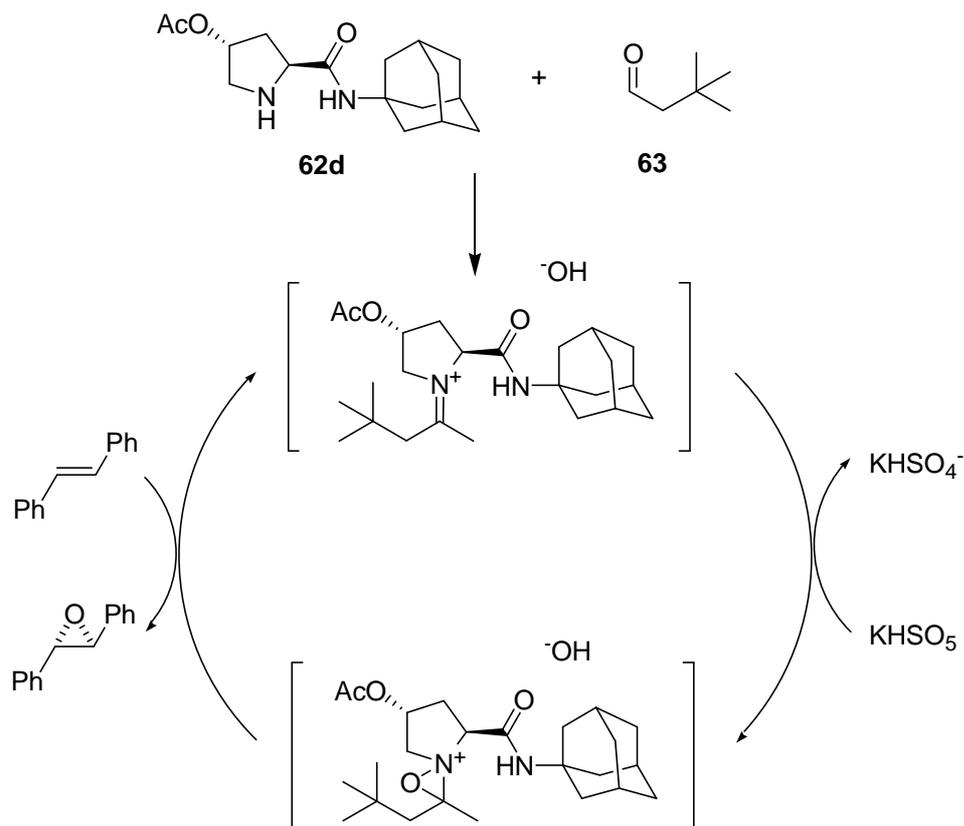
Amine	Conversion (%)	Yield (%)	Enantiomeric excess (%)
 62a	77	84	-
 62b	32	99	-
 62c	33	48	-
 62d	95	99	30
 62e	63	92	40

Table 5: Results of Wong and Yang's asymmetric epoxidation of *trans*-stilbene.

Encouraged by the results obtained using amines (**62d**) and (**62e**), Wong and Yang then tested a range of aldehydes and found the best *ee* values were obtained using amine (**62d**) and aldehyde (**63**) (Scheme 25) with values of around 50% *ee*. Unfortunately, the major limitation for this system is that the catalyst loading needs to be 50 mol% to obtain an efficient rate of reaction.

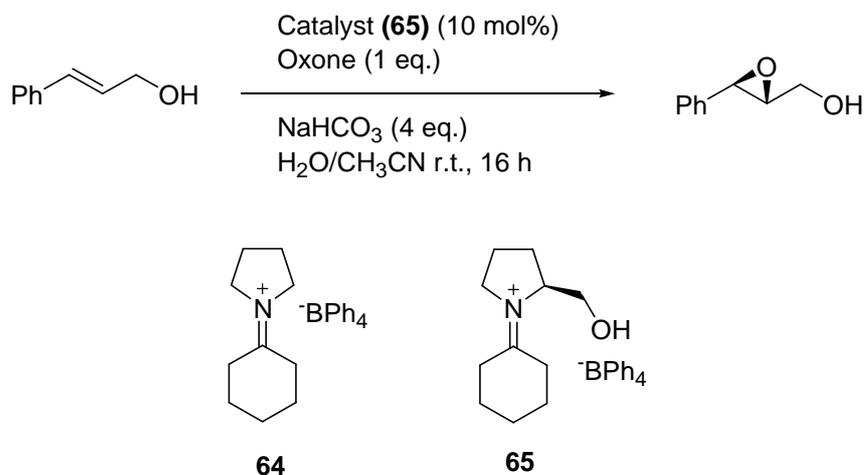


Scheme 25: Wong and Yang's catalytic epoxidation using amine **62d** and aldehyde **63**.

1.6.4 Komatsu's Exocyclic Iminium Salts.

Komatsu *et al.*⁴⁶ also decided to examine exocyclic iminium salts for asymmetric epoxidation. Initially, achiral salts were synthesized by the simple condensation of cyclic amines with cyclic ketones under Dean Stark condition. The catalyst which was found to display the best reactivity was catalyst (**64**) which was prepared from pyrrolidine and cyclohexanone. This basic structure was then used in the preparation of a chiral version (**65**) using L-prolinol and cyclohexanone. The resulting catalyst

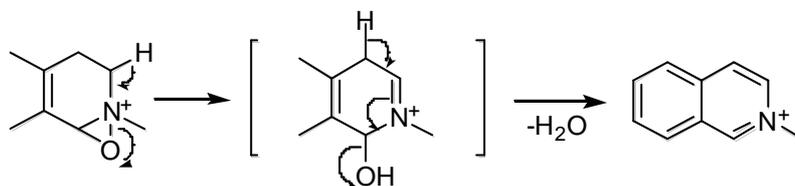
was then used in the epoxidation of cinnamyl alcohol giving a 70% yield and 39% *ee* (Scheme 26).



Scheme 26: Komatsu's exocyclic epoxidation conditions using catalyst **(65)**.

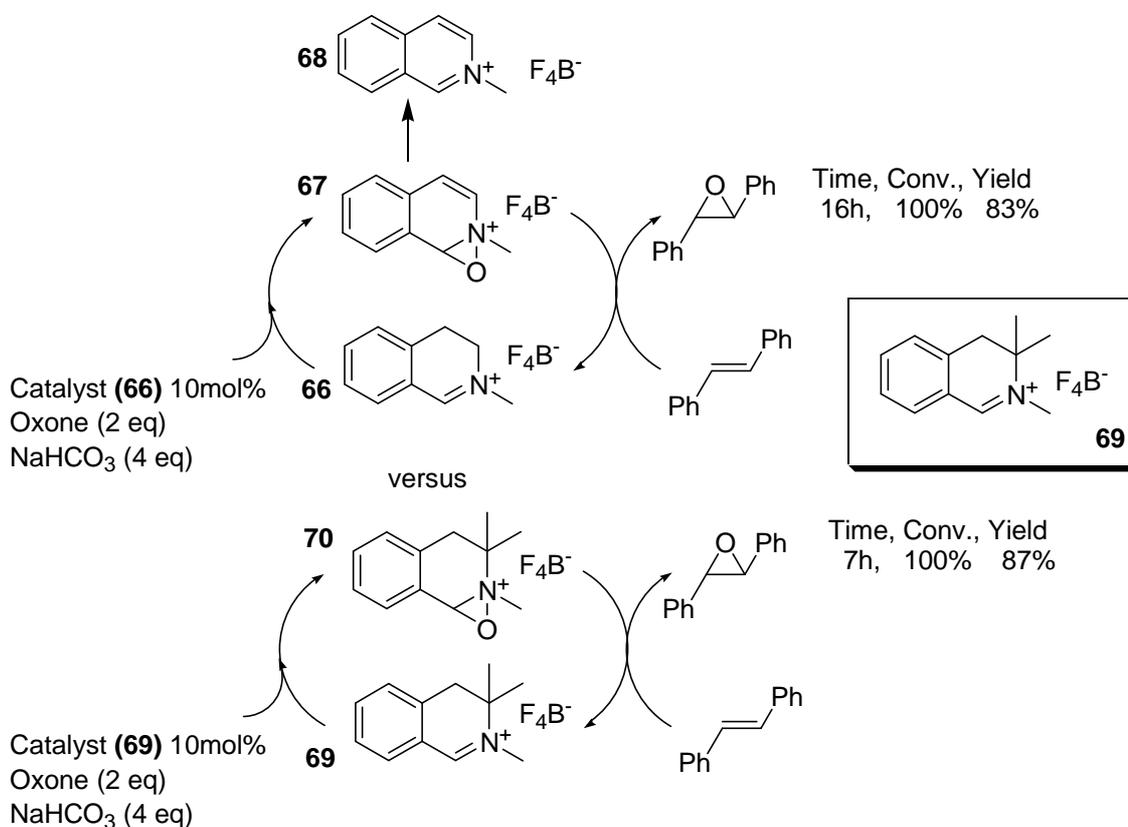
1.6.5 Bohé's Improved Iminium Catalyst

In 2001 Bohé reported the group's investigations into the factors which lower the catalytic efficiency of the epoxidation process when using oxaziridinium salts.⁴⁷ The group reported that there were two main factors which result in the reduction of catalytic efficiency: hydrolysis of the iminium salt in the reaction, and the loss of oxygen from the active oxaziridinium intermediate, in a reaction that does not result in the regeneration of the iminium salt. This loss of oxygen occurs by the irreversible base catalysed isomerisation of oxaziridinium salts containing protons in the α position to the nitrogen atom (Scheme 27).⁴⁷



Scheme 27: Loss of oxygen resulting in rearomatisation of the iminium salt.

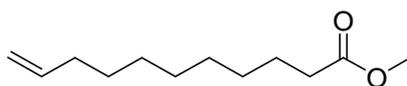
Bohé postulated that this loss of oxygen could be reduced if a 3,3-disubstituted-dihydroisoquinolinium salt was used as the oxaziridinium catalyst.⁴¹ The most successful iminium salt was found to be iminium salt (**69**), which was synthesized from the commercially available tertiary alcohol; the active oxaziridinium was then prepared from this salt by an oxidation pathway using Oxone[®] and NaHCO₃, but unlike previous iminium catalysts, this salt is unable to re-aromatise. This is shown in Scheme 28, where (**66**) and (**67**) show the previous method, with the possibility of re-aromatisation occurring to give (**68**). However, in the new method, shown by (**69**) and (**70**), this cannot occur due to the lack of an available proton, resulting in a faster and high yielding reaction.



Scheme 28: Bohé's new racemic catalytic epoxidation method in comparison to the old.

The epoxidation of *trans*-stilbene involving salt (**69**) was observed to be much faster than the reference salt (**66**), and because the actual intermediates of both species are likely to be very similar the only likely explanation is that the exclusion of the aromatisation pathway allows improved catalytic turnover.⁴⁷ Overall good yields were observed for *trans*-stilbene and di- and tri-substituted alkenes (72-92%);

however, for the less reactive terminal double bond of the undecylenic methyl ester (**71**) epoxidation resulted in only a 28% yield.⁴⁸

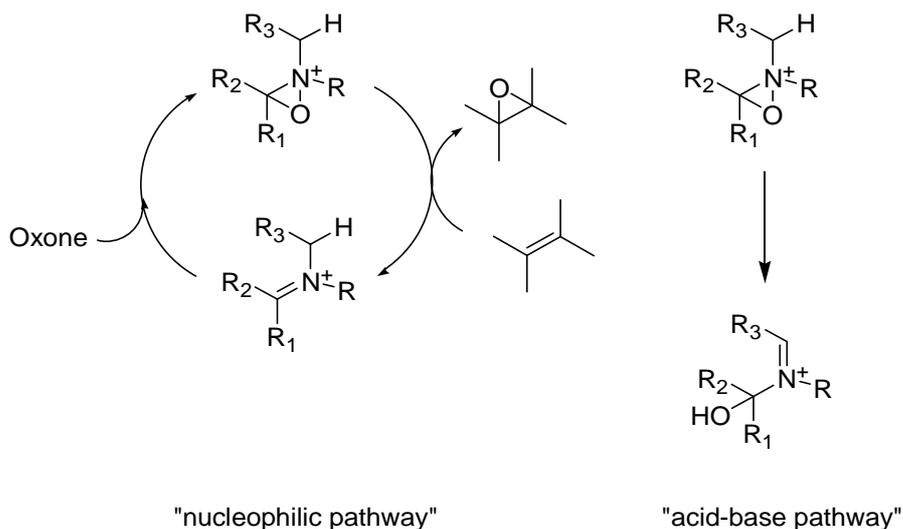


71

Figure 15: Undecylenic methyl ester (**71**).

However, Bohé noted that this base catalysed method of destruction is not observed in all iminium salt epoxidations. He felt that this may be due to the reactivity of the catalyst, which would favour the nucleophilic pathway over the base catalysed isomerisation and that further catalytic enhancement could be achieved by increasing the probability of the catalyst favouring the nucleophilic pathway.

Bohé decided to examine this by looking at ways to increase the electrophilicity of the catalyst, this consisted of reinforcing the ratio of electrophilicity to acidity, which would consequently favour the nucleophilic pathway over the acid-base degradation pathway (Scheme 29).⁴⁷



Scheme 29: The nucleophilic and acid-base pathways.

To test this strategy, which allows the based catalysed aromatisation to remain in action whilst reinforcing the nucleophilic pathway, Bohé placed an electron withdrawing group on the aromatic ring, though not in conjugation with the imine

bond. This resulted in the preparation of iminium salt (**72**) where a nitro group is present on the C-7 position. Having reported earlier that iminium salt (**69**) was a more efficient catalyst than (**66**) due to the absence of protons α to the nitrogen, it was postulated that the synergistic effect between these two systems could be utilised resulting in the synthesis of iminium salt (**73**). This resulted in a highly efficient catalyst for the oxaziridinium-mediated epoxidation of olefins by Oxone[®], with 100% conversion being obtained after 1.5 hours with only 5 mol% catalyst loading (Table 6) required compared to 10 mol% for catalysts (**66**) and (**69**). However, to date, no chiral versions have been reported.

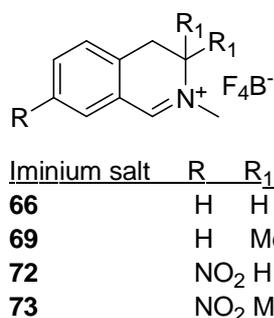


Figure 16: Bohé's improved iminium salt catalysts.

Olefin	Catalyst loading (mol%)	Time (h)	Conversion (%)
74	10	6	92
75	10	6	85
76	10	6	89
77	10	6	85
78	5	2	100
79	5	4	100
80	5	4	100
81	5	4	100
82	5	2	100
83	5	6	100
84	5	2	100

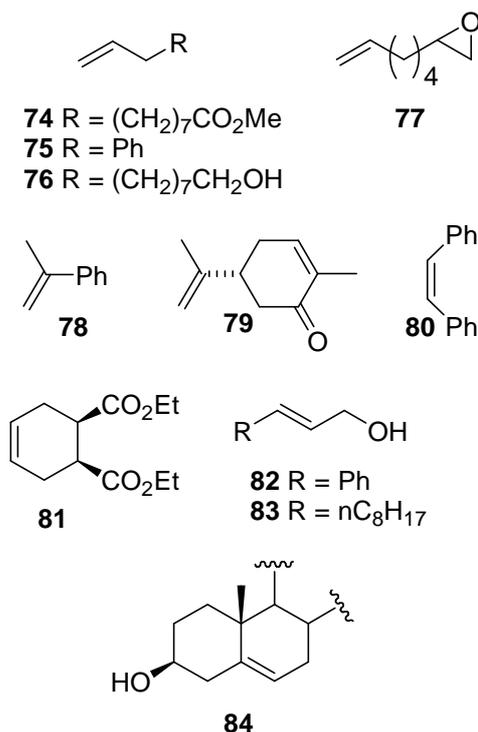
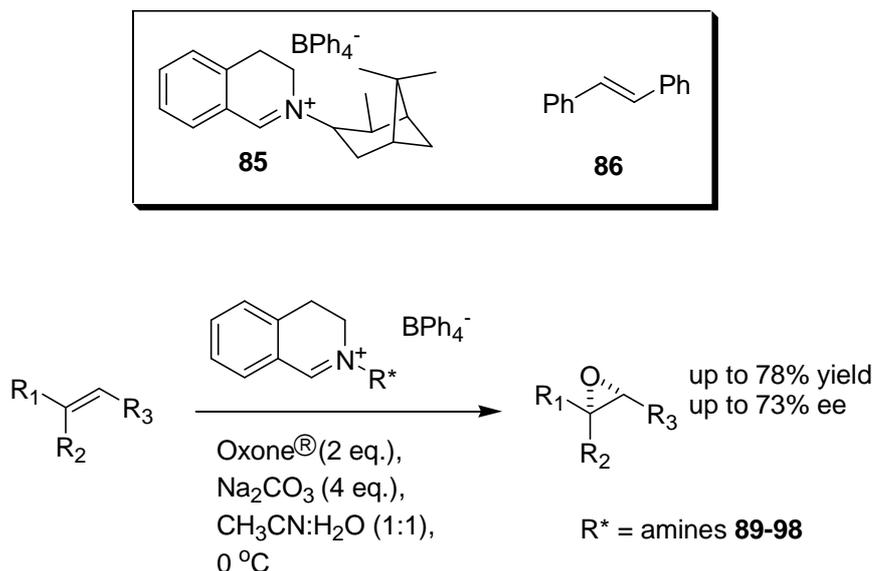


Table 6: Conversion rates achieved by Bohé's optimised catalyst (**73**).

1.6.6 Page's Unique Iminium Salt Catalysis

Page demonstrated in 1997 that if the iminium salt derived from a dihydroisoquinoline and primary amine had a chiral exocyclic nitrogen substituent, this could be used to achieve catalytic asymmetric epoxidation with Oxone[®], with *ee* values of up to 73% (with catalyst **(85)** and alkene **(86)**), in clean reactions carried out at 0 °C with catalyst loading as low as 0.3 mol% (Scheme 30).^{49, 50}

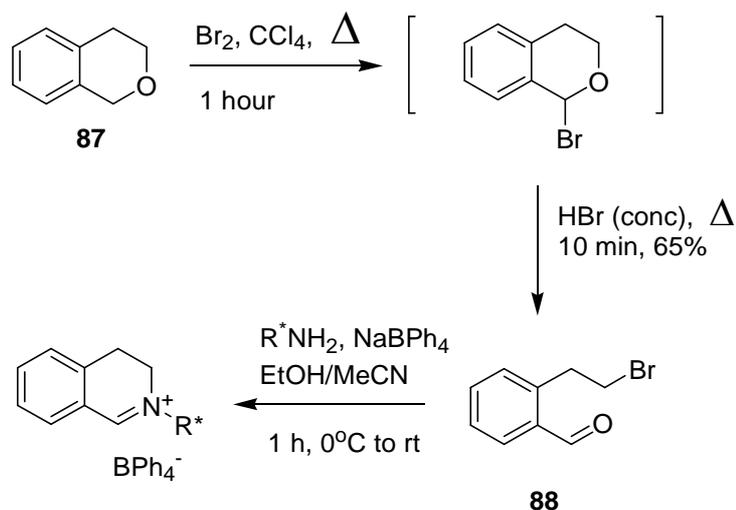


Scheme 30: General scheme of Page's asymmetric iminium salt epoxidation using iminium salts derived from primary amines (**89-98**).

It was reasoned that attachment of the controlling asymmetric centres to the iminium nitrogen atom makes the system more selective than the Lusinchi-Hanquet system because the positioning of the asymmetric centre was closer to the reacting centre.

Along these lines, a range of catalysts was easily prepared by condensation of a range of enantiomerically pure primary amines (**89-98**) with 2-(2-bromoethyl)benzaldehyde (**88**), which itself is prepared from treatment of isochroman (**87**) with bromine in carbon tetrachloride. The condensation between the amine and aldehyde furnishes the dihydroisoquinolinium bromide salt, however these are often oils and can be difficult to purify. This problem was alleviated by doing a simple counter ion exchange with NaBPh₄, yielding crystalline iminium salts

(30-80%) (Scheme 31). This method is advantageous as a wide range of catalysts can be derived quickly from a large variety of readily available chiral primary amines.



Scheme 31: General scheme of the preparation of the iminium salt catalysts.

As noted previously, it was found that this route provided a large variation of catalysts, as the chirality was only present in the amine component, although more hindered amines were found to give inferior conversions, typically 25-30%, possibly due to an increased tendency to act as bases rather than nucleophiles. Using the above method, the primary amines (**89-98**) were converted to their corresponding iminium salt catalysts. The catalysts were then used in the epoxidation of 1-phenylcyclohexene under the standard conditions (Scheme 30). Out of this selection of catalysts, the one derived from *N*-isopinocampheyl (**93**) showed the best reaction profile giving up to 40% *ee* and 68% yield. Even better results were obtained using *trans*-stilbene as substrate where a 73% *ee* and 78% yield were obtained when using 10mol% catalyst. Although steric hindrance near the reaction site appears to be important, as shown with the *N*-isopinocampheyl (**93**) salt, the more sterically demanding systems such as the steroidal (**98**) salt, showed a decrease in enantioselectivity, with a maximum 14% *ee* for 1-phenylcyclohexene, although the overall conversion rate was similar with a 47% yield.

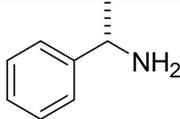
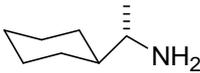
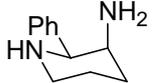
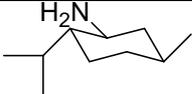
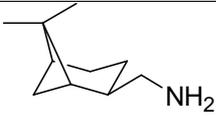
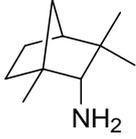
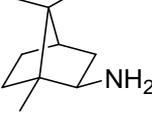
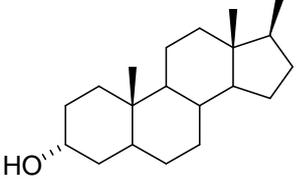
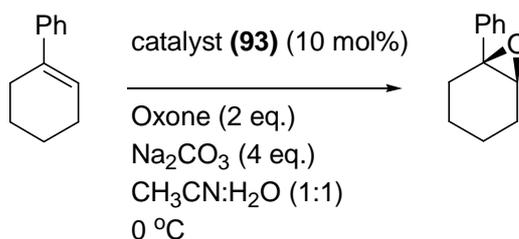
Amine in catalyst	Compound No.	Catalyst loading (mol%)	Yield (%)	Enantiomeric excess (%)
	89	5	54	0
	90	5	70	0
	91	1	39	25
	92	0.5	63	19
	93	5	68	40
	94	0.5	66	12
	95	0.5	45	32
	96	0.5	60	18
	97	0.5	58	8
	98	0.5	47	14

Table 7: Catalytic asymmetric epoxidation results using amines (**89-98**) in the epoxidation of 1-phenylcyclohexene under the standard conditions..

However, these systems are complicated by the possibility that two diastereoisomeric oxaziridinium salts may be formed depending on whether the nucleophilic attack of the oxidant occurs on the front or back face of the iminium species.⁵¹

Page then set about optimising the reaction conditions using the *N*-isopinocampheyl derived catalyst (**93**)⁵². It was felt that the counter ion, solvent system temperature and catalyst loading may all have a bearing on the reactivity and selectivity of the catalyst, so these were examined in turn.

To examine the change in counter ion, the corresponding perchlorate, hexafluorophosphate, tetrafluoroborate and periodate salts were prepared and used in the epoxidation of 1-phenylcyclohexene, executed under the standard conditions (Scheme 32). The tetraphenylborate and periodate salts gave similar *ee* values (40% and 35% respectively), but the fluoride containing salts and perchlorate salt gave significantly lower *ee* values (28% and 20% respectively), though all gave the same enantiomer of the epoxide product (*R,R*) and all were complete within 45 minutes.



Scheme 32: The Page group's standard epoxidation conditions using catalyst (**93**).

The solvent system used in the standard epoxidation conditions (Scheme 32), is a 1:1 ratio of acetonitrile and water, however an increase in the water to acetonitrile ratio was found to result in an increase in the reaction rate, with the effect being greater the smaller the quantity of catalyst used. The *N*-isopinocampheyl derived catalyst showed 30% conversion after 1 hour when a 1:1 ratio of solvents was used, this increased to an essentially quantitative yield, after the same time, when the ratio was increased to 2:1 (water:acetonitrile). However, it was noted that the change in solvent composition had no influence over the enantioselectivity of the reaction with *ee* values of 18 to 20% seen whether a 1:1 ratio or a 2:1 ratio of solvents was used. This

increase in reaction rate is most likely due to an increase in Oxone[®] solubility, resulting in an increase in nucleophilic attack by the persulfate species on the iminium species.

Page also looked at the effect of co-solvent polarity, which could provide insight into the reaction mechanism and the factors that control enantioselectivity. The co-solvents were selected to provide a range of dielectric constants (ϵ , given in brackets): dichloromethane (8.9), trifluoroethanol (26.7), acetonitrile (37.5), water (78.4) and formamide (111). The epoxidation was performed as shown in Scheme 32 using both the perchlorate and tetraphenylborate *N*-isopinocampheyl derived catalysts (10 mol%), with the co-solvents and water in a 1:1 ratio. Both salts showed quantitative conversion after 30 minutes when using trifluoroethanol and *ee* values of 26%, but interestingly the perchlorate salt was also reactive in dichloromethane giving a 33% *ee* in 3 hours, where the tetraphenylborate salt was completely unreactive. The perchlorate and tetraphenylborate catalysts were both unreactive in formamide, and Page felt this was probably due to the iminium species being too well stabilised/solvated. Acetonitrile remained the best co-solvent with an *ee* of 40% when using the tetraphenylborate *N*-isopinocampheyl derived catalyst.

The effect of temperature is fairly limited when using Oxone[®] as oxidant, due to the instability of Oxone[®] under alkaline conditions, which increases at higher temperatures and the necessity to have water for Oxone[®] solubility which restricts the reactions to a minimum of 0 °C. When the epoxidation of 1-phenylcyclohexene was performed at -10 °C, using catalyst (**93**) under standard conditions, low conversion was observed. This is most likely to be due to the limited solubility of Oxone[®] and sodium carbonate at this temperature, and was resolved by changing the ratio to 3:1 (water:acetonitrile), which gave complete epoxidation and 35% *ee*, though this was still lower than when the reaction was performed at 0 °C. Higher temperature reactions resulted in negligible conversion, presumably due to the auto-decomposition of Oxone[®] at higher temperatures.

The effect of catalyst loading was expected to be an important parameter in the reaction system in relation to conversion and, possibly, enantiomeric excess. Again using the *N*-isopinocampheyl derived catalyst (**93**), a graph of catalyst loading

versus *ee* % could be compiled. Using 1-phenylcyclohexene as substrate, the results showed that enantioselectivity does increase with catalyst loading, but only to a point, with the maximum *ee* value being obtained at 2 mol% catalyst loading.

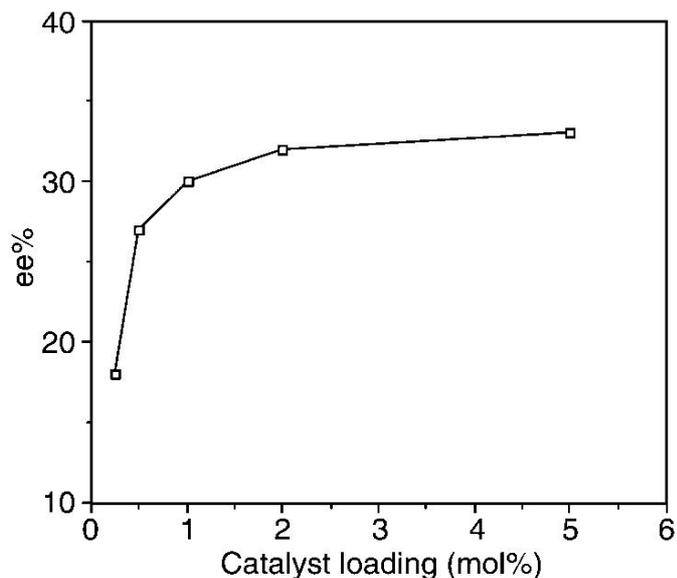


Figure 16: Graph showing the relationship between catalyst loading and enantiomeric excess using catalyst (**93**).

After the optimization trials, the Page group's attention refocused on the role of the catalyst structure within the epoxidation reactions in a continued effort to develop a catalyst capable of mediating the highly enantioselective epoxidation of alkenes. Various amine groups were considered (Figures 17 to 20) containing alcohol, ether and acetal functionalities, with the idea that the polar groups within these type of structure may act as a directional aid, by either controlling the persulfate attack on the iminium or the alignment of the alkene with the oxaziridinium.

The catalysts prepared from chiral 1,2-aminoalcohols that contained a primary hydroxyl group (**99-102**) were found to produce (almost) racemic 1-phenylcyclohexene oxide when used in the epoxidation procedure under Page's standard conditions (Scheme 32), and the reactions proceed much slower than catalysts that lack the hydroxyl group.

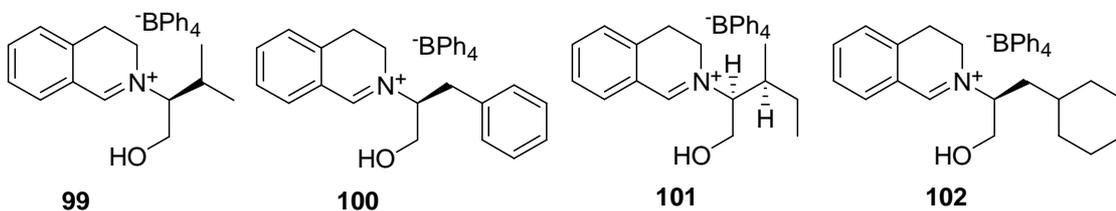
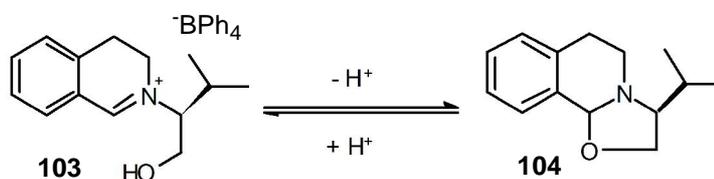


Figure 17: Page's catalysts derived from primary alcohols.

Page believed this to be because of an equilibrium between the ring open iminium salt (active) (**103**) and the ring closed oxazolidine (inactive) (**104**) forms of the catalyst under the slightly alkaline conditions used (Scheme 33).



Scheme 33: The proposed ring open and ring closed equilibrium.

The catalysts prepared from 1,2-aminoalcohols (**105-107**), which contained a secondary hydroxyl group, were formed equally as readily and showed improved *ee* values on testing, with catalyst (**105**), a (1*S*,2*R*)-norephedrine derivative, giving a 30% *ee* when catalysing the epoxidation of 1-phenylcyclohexene. This improved selectivity was at the cost of the catalyst loadings, which were higher, with at least 5 mol% required for complete oxidation of 1-phenylcyclohexene in 1 h compared with 2 mol% of catalyst which contained a primary hydroxyl group. Unfortunately, catalysts containing a tertiary hydroxyl group could not be prepared.

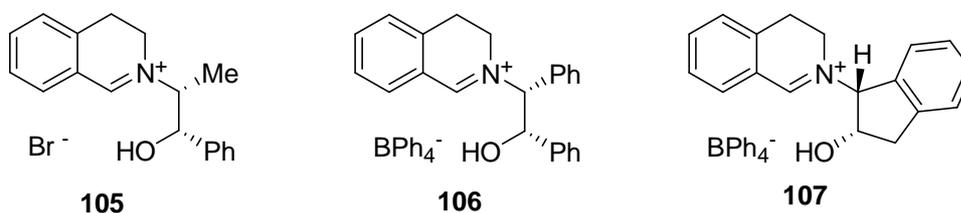


Figure 18: Page's catalysts derived from secondary alcohols.

It was also not possible to prepare catalysts from aminodiols, and the catalysts prepared from aminoether precursors proving to be difficult to isolate, with the (1*S*,2*S*)-2-amino-3-methoxy-1-phenylpropanol-derived salt only being isolated in low yield. In an attempt to increase the yield, simpler amino-ethers were used, resulting in the catalysts (**108-110**), but despite good conversions being achieved, these catalyst gave poor *ee* values.

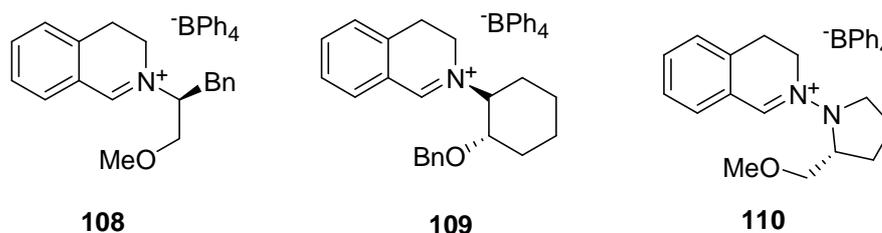


Figure 19: Page's catalysts derived from amino ethers.

It was found that the catalysts derived from aminoacetal precursors gave the best *ee* values, with catalyst (**111**) giving an enantioselectivity of up to 59% *ee* when using the standard epoxidation conditions (Scheme 32), compared to catalyst (**93**) which only gave a 40% *ee* at its highest under the same conditions. These results demonstrate that this catalyst, in general, induced much higher enantioselectivity in the asymmetric epoxidation than the previous catalysts.

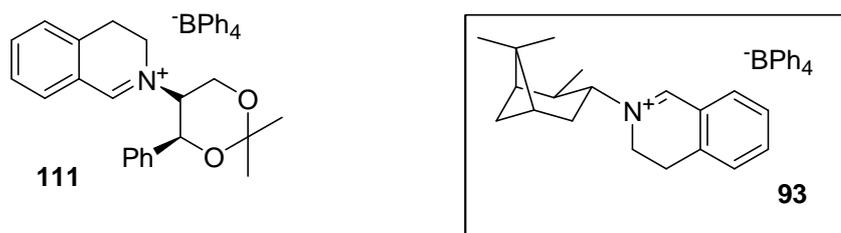


Figure 20: Page's catalyst (**111**) derived from amino acetal precursors and the previous best enantioselective catalyst (**93**).

The amino acetal derived catalyst (**111**) also provides some interesting features such as the *cis* relationship between the nitrogen heterocycle and the phenyl group, implying that the one group must be axial for the dioxane to retain the chair conformation. ¹H NMR spectroscopy supports the chair conformation of the 1,3-dioxane ring and on the basis of this and single-crystal X-ray analysis, Page postulated two possible reasons for the catalyst adopting this conformation. The first

was that conformer (**112**) may be more favoured due to a possible interaction between the oxygen lone pairs and the electron depleted carbon atom of the iminium salt (Figure 21). The second is the lack of 1,3-diaxial interactions when the catalyst adopts this conformation, which is the most likely explanation for the observed conformation.

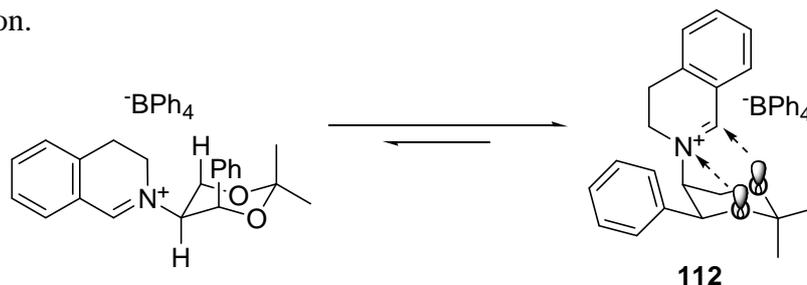
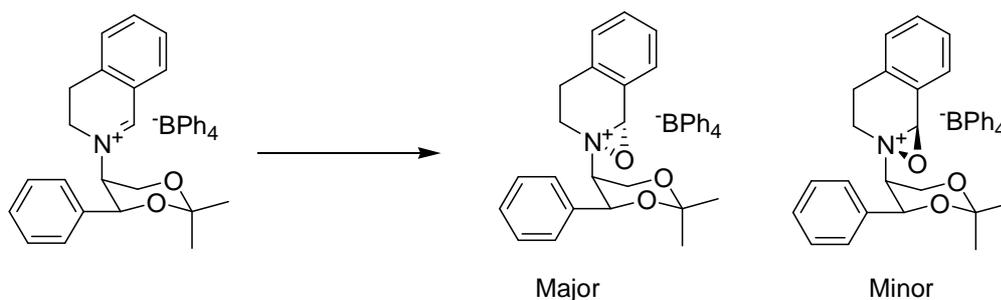


Figure 21: Possible influence of oxygen lone pairs on the chair-conformation of catalyst.

This conformational analysis also provided a possible explanation of the higher enantioselectivities observed when using catalyst (**111**) when compared to catalyst (**93**). In catalyst (**93**) both conformers are equally favoured, resulting in attack by the oxidant coming from both faces of the iminium salt decreasing its asymmetric epoxidation capabilities. However for salt (**111**), in its more stable conformer, the phenyl substituent is positioned such that it may hinder the attack of the oxidant from that side, making the other side more accessible. This leads to the possibility of major and minor diastereoisomeric intermediates existing (Scheme 34).



Scheme 34: The two possible diastereoisomeric oxaziridinium intermediates of catalyst (**111**).

Page has also reported more reactive catalysts where the dihydroisoquinolinium moiety has been replaced with a biphenyl (**113**)⁵³ and binaphthalene (**114**)⁵⁴ structures.

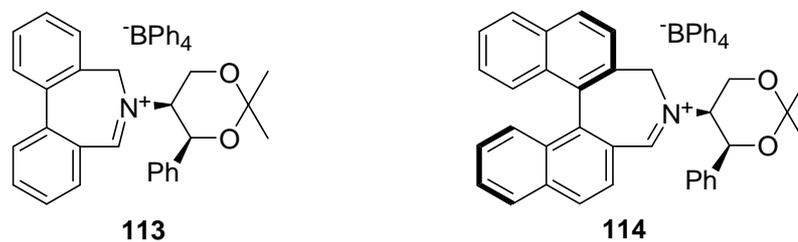


Figure 22: Page's biphenyl (**113**) and binaphthalene (**114**) based asymmetric epoxidation catalysts.

Epoxidation of most alkenes with catalyst (**113**) proceeded within 10 minutes, making it the most reactive catalyst at that time. The enantioselectivities ranged from 10-60% *ee*.

Binaphthalene-derived iminium salts have been reported previously by Aggarwal to achieve enantiomeric excesses of up to 71% *ee*.⁵⁵ Page has also developed a range of azepinium salt catalysts containing the binaphthalene backbone. The most successful of this series proved to be catalyst (**114**), which when employed in epoxidation reactions gave *ee* values of up to 95%. Interestingly, unlike previous catalysts, decreasing the catalyst loading did not result in a loss of enantioselectivity. As such, a loading of just 0.1 mol% was used to achieve complete epoxidation of 1-phenylcyclohexene in 88% *ee*, compared to 91% *ee* when using a loading of 5 mol%.

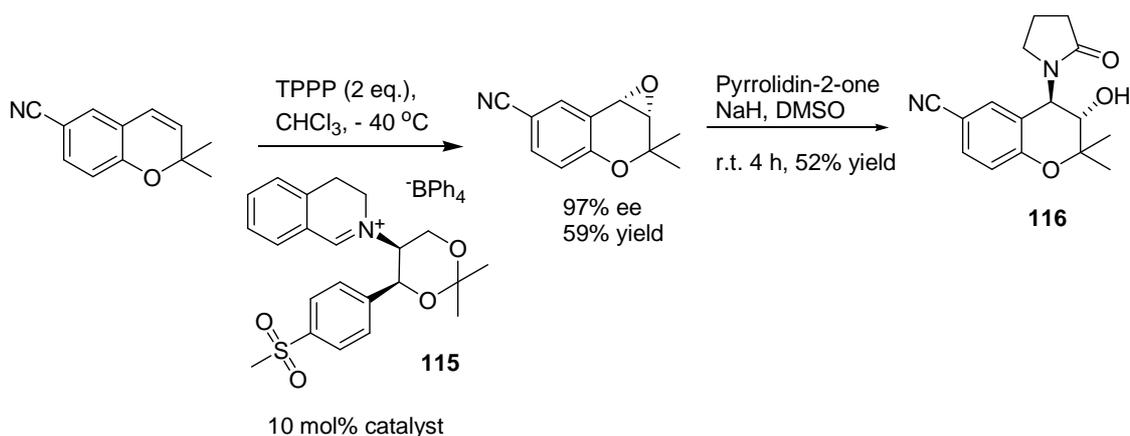
It was felt that the remaining limitation in the Page group's system was the range of temperatures at which the epoxidation can be performed (0 °C – room temperature) using the conditions reported by Page previously.^{49-54,56} This is because Oxone[®] decomposes relatively quickly in the basic medium used at room temperature, but the aqueous medium used freezes at about -10 °C.

Page felt the enantioselectivity could be enhanced if the reaction could be carried out at lower temperatures and so sought non-aqueous reaction conditions. After testing a range of oxidants, Page reported the first non-aqueous epoxidation system mediated by iminium salt catalysts using tetraphenylphosphonium monoperoxybisulfate (TPPP) as the oxidant, and acetonitrile as the solvent.⁵⁶ The oxidant TPPP has

previously been reported by Di Fura, where it was used to transfer oxygen to manganese porphyrins and is prepared by simple cation exchange between Oxone[®] and tetraphenylphosphonium chloride. In contrast to the Oxone[®] system, no base is required, in fact the addition of amine bases was found to be harmful for the epoxidation reaction. The optimum temperature was found to be $-40\text{ }^{\circ}\text{C}$ and under these conditions the biphenyl catalyst (**113**) performed the best, giving 100% conversion in 3 minutes with 67% *ee* for 1-phenylcyclohexene.

Recently Page has developed this non-aqueous system further by using chloroform as the solvent in the epoxidation of *cis*-alkenes. Using iminium salt (**115**), *ee* values of 67% for *trans*-stilbene, 70% for *cis*- β -methyl styrene and 82% for dihydronaphthalene were observed; these were superior to those obtained under either aqueous conditions or non-aqueous conditions with acetonitrile as the solvent.

Results were equally promising when benzopyran substrates were used, with the epoxidation of 6-cyano-2,2-dimethylbenzopyran achieving the highest *ee* to date with a 97% *ee* in 59% yield. This was particularly important due to its possible use in the synthesis of levcromakalim (**116**) an antihypertensive agent which acts through the opening of K^+ channels. This synthesis was subsequently achieved by the Page group as shown in (Scheme 35).⁵⁷



Scheme 35: Page's synthesis of levcromakalim.

1.7 The Use of Epoxidation in Kinetic Resolution

Although numerous methods are known for the synthesis of enantioenriched compounds, one of the major drawbacks is that they can consist of rather lengthy procedures.

In selecting a method for the synthesis of enantioenriched compounds there are many different alternatives to consider, with the main three approaches being 1) using a starting material from the available chiral pool, 2) enantioselective synthesis or 3) resolution of enantiomers by chemical or physical means.

Resolution itself can be classified in to three broad groups:

- 1) The use of a chiral resolving agent to form a diastereomeric pair, enabling the diastereoisomers to be separated either by chemical or physical means, due to their different properties.
- 2) The use of chiral chromatography.
- 3) Kinetic resolution.

Kinetic resolution is defined as ‘the achievement of partial or complete resolution by virtue of unequal rates of reaction of the enantiomers in a racemate with a chiral agent (reagent, catalyst, solvent, etc.)’.^{58, 61}

The major drawback of kinetic resolutions is that the maximum theoretical yield of enantiomerically pure recovered starting material is 50%. However, if the product is the desired compound, it is sometimes possible to racemise the starting material *in situ*, allowing the isolation of enantiomerically pure product in 100% yield starting from racemic starting material. This process is known as dynamic kinetic resolution.⁵⁹ In other cases it is possible to racemise the remaining enantiomer of the starting material after isolation.

However, regardless of the drawbacks, there are also advantages to using kinetic resolution. For example, despite the fact that in most cases the maximum yield will

be 50%, the racemates are often less than half as expensive as their enantiomerically pure counterparts.⁶⁰

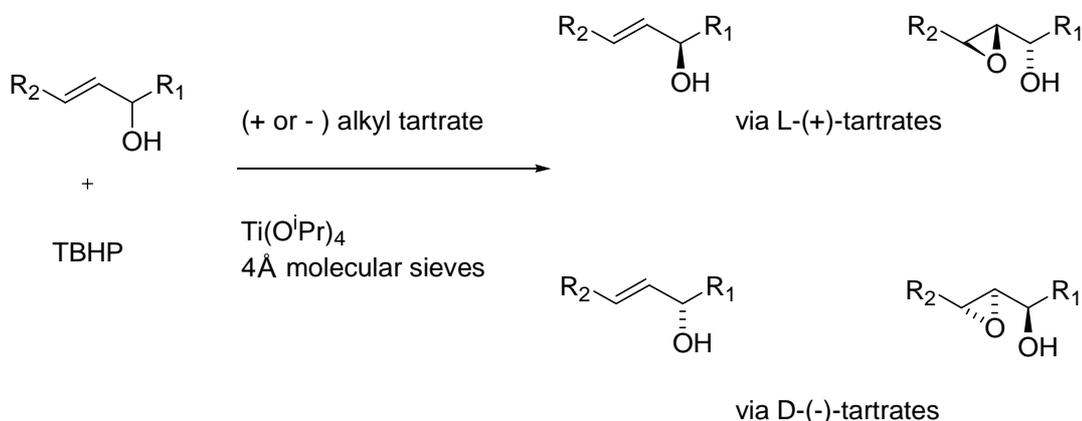
Another attractive feature of kinetic resolutions from a practical point of view is that even with a relatively low selectivity, the unreacted substrate can be obtained with high *ee* simply by carrying the reaction to high enough conversion.

Jacobsen,⁶⁰ proposed that kinetic resolution can be considered a viable resolution method providing certain conditions are met:

- 1) The racemate is cheap and/or readily available and no satisfactory enantioselective, chiral pool, or classical resolution route to the product exists.
- 2) The catalyst is highly selective for one enantiomer and is effective at low loadings.
- 3) The catalyst is inexpensive and/or it can be recycled efficiently.
- 4) The reaction is economical and safe: inexpensive stoichiometric reagents, no undue dangers associated with the reagents, high volumetric throughput, and a minimum of waste generated.
- 5) The resolved starting material and converted product are easily separated.
- 6) In the ideal case, both the product and resolved substrate are valuable and recoverable in highly enantioenriched form.

1.7.1 Sharpless Kinetic Resolution.

The first example of a successful kinetic resolution using a chemical catalyst, although in stoichiometric amounts, was published in 1981 by Sharpless *et al.*,⁶² where the group's previously reported procedure⁷ for the catalytic asymmetric epoxidation of allylic alcohols, was adapted to the kinetic resolution of chiral allylic alcohols (Scheme 36).



Scheme 36: Sharpless kinetic resolution.

Using this kinetic resolution technique, Sharpless was able to obtain enantiopure allylic alcohols in up to 96% *ee* depending on the substrate used. Sharpless found that the enantioselectivities could further be improved by modification of the alkyl groups present in the tartrate ester, with the best values being achieved using (+)-diisopropyl tartrate (DIPT). Sharpless reasoned that this was due to the larger alkyl group further retarding the rate of reaction of the slower reacting enantiomer.

The impact of the Sharpless kinetic resolution was very important, as although enzyme based resolutions were well known, there had been very little work done with respect to synthetic catalysts. This has led to other synthetic catalysts being investigated for use in kinetic resolution reactions, two of which are discussed in more detail below.

1.7.2 Jacobsen's Application of Kinetic Resolution Mediated by (salen)Mn Based Catalysts.

Jacobsen realised that the (salen) Mn-catalyst's ability to epoxidise prochiral 2,2-dimethylchromans, with high enantioselectivity, could be exploited for use in the kinetic resolution of chromenes bearing a quaternary stereocentre next to the oxidizable olefinic moiety.⁶¹

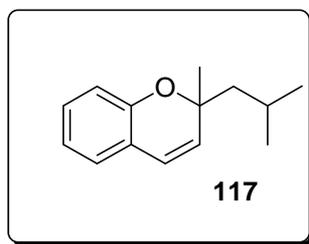
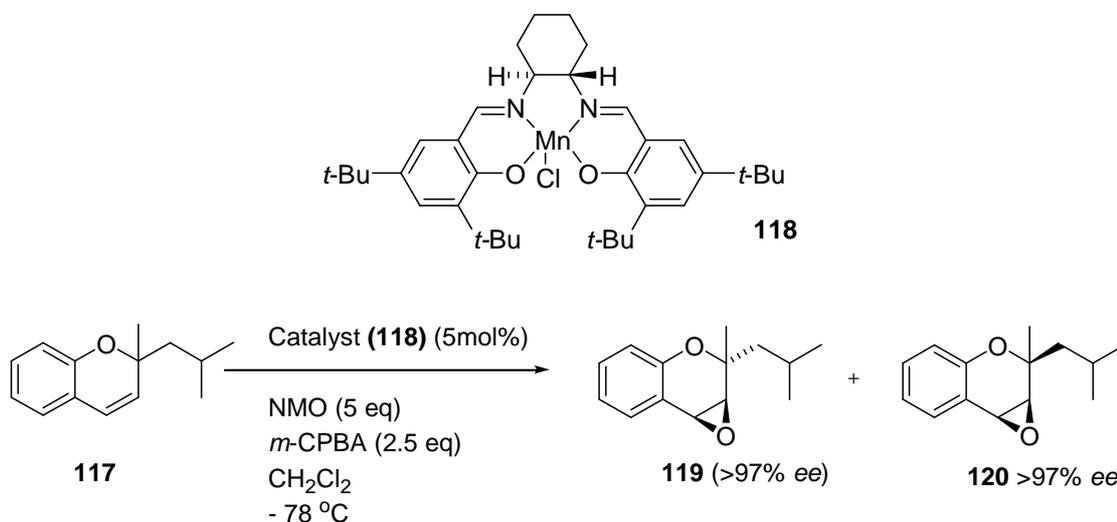


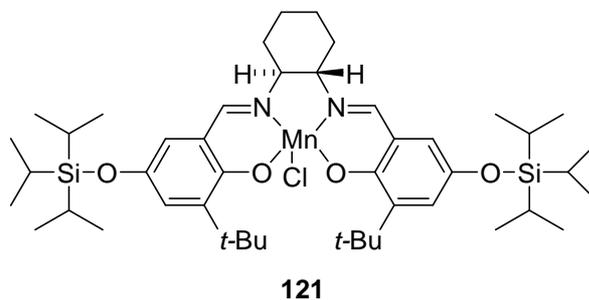
Figure 23: Jacobsen's model substrate.

Compound (**117**) was first evaluated as a model substrate using catalyst (**118**), and at full conversion showed high enantioselectivity for both diastereomers. Importantly for a kinetic resolution when the reaction was stopped at partial conversion a preference for the *trans*-diastereomer (**119**) was shown (Scheme 37).



Scheme 37: Evaluation of compound **117** at full conversion.

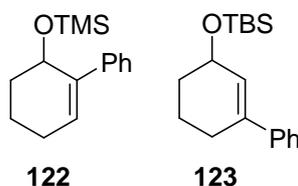
Jacobsen had found previously that enantioselectivity in the chromene substrates is sensitive to the presence of electron-donating groups on the catalyst. Using this knowledge Jacobsen was able to improve selectivity still further by the use of the electron rich and sterically hindered catalyst (**121**).



On the substrates themselves it was noted that selectivity increased with increasing steric demand from the alkyl substituent. This kinetic resolution methodology was then utilized in the synthesis of (+)-Teretifolione B.⁶³

1.7.3 Shi's Application of Kinetic Resolution Mediated by Dioxirane Based Catalysts.

At present the only known organocatalytic kinetic resolution has been reported by Shi using his dioxirane based catalysts.⁶⁴ In the examples explored by Shi, the substrates were based on cyclic olefins with the chiral center at the allylic position. Initially 1,6-disubstituted cyclohexenes were examined, using (\pm)-1-phenyl-6-(trimethylsilyloxy)cyclohexene (**122**) as the test substrate. Shi postulated that the proposed spiro transition state would favour the formation of the *trans*-epoxide and it was found that this was indeed the case, with the reaction giving a 95% *ee* of the *trans*-epoxide at 49% conversion in a >20:1 ratio of *trans/cis*. Analysis of the recovered starting material showed the enriched *S* isomer at a 96% *ee*, reinforcing the transition state proposal.



Shi then investigated 1,3-disubstituted cyclohexenes with the TBS ether of 3-phenyl-2-cyclohexenol (**123**) as the test substrate. Although it was found that the selectivity of *trans* to *cis* was less at 4:1, the unreacted starting material had an *ee* of 99% at 70% conversion, showing that the kinetic resolution of such compound is at least feasible.

1.8 Conclusion

This introduction has briefly reviewed the fast developing area of asymmetric epoxidation that is mediated by organocatalysts. As can be seen, many methods have been implemented and some have ultimately been more successful than others. The Page group is now interested in looking at further applications of their highly successful enantioselective epoxidation techniques, such as in kinetic resolution and in the synthesis of other natural products, such as enediyne antibiotics and epogallocatechin-3-gallate (EGCG). This is the aim of this research project and will be discussed below.

2.0 Results and Discussion

The main aim of this project was to further the use of the group's asymmetric catalysts in the synthesis of some natural products. Previously within the group the asymmetric epoxidation methodology had been applied to the synthesis of Levromakalim,⁵⁷ an antihypertensive drug based on a chromene-type structure (**124**). Many other natural products contain this core structure, and the similar dihydroquinoline structure (**125**). The chromene-type structure had previously yielded very good enantioselectivities, and, as no research had previously been attempted on compounds containing nitrogen we decided that the project would initially concentrate on dihydroquinoline-based structures, especially as this core structure is found in a range of natural products, such as dynemicin A, which is part of the enediyne family of antibiotics (**126**).⁶⁵

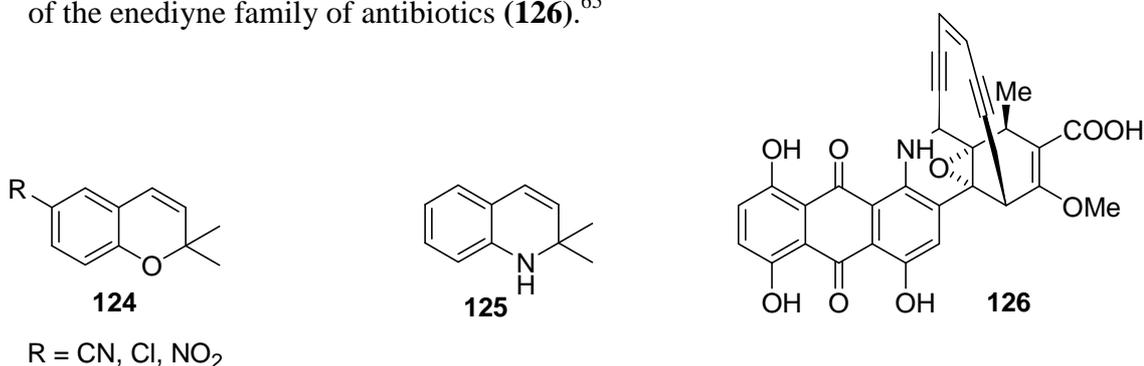
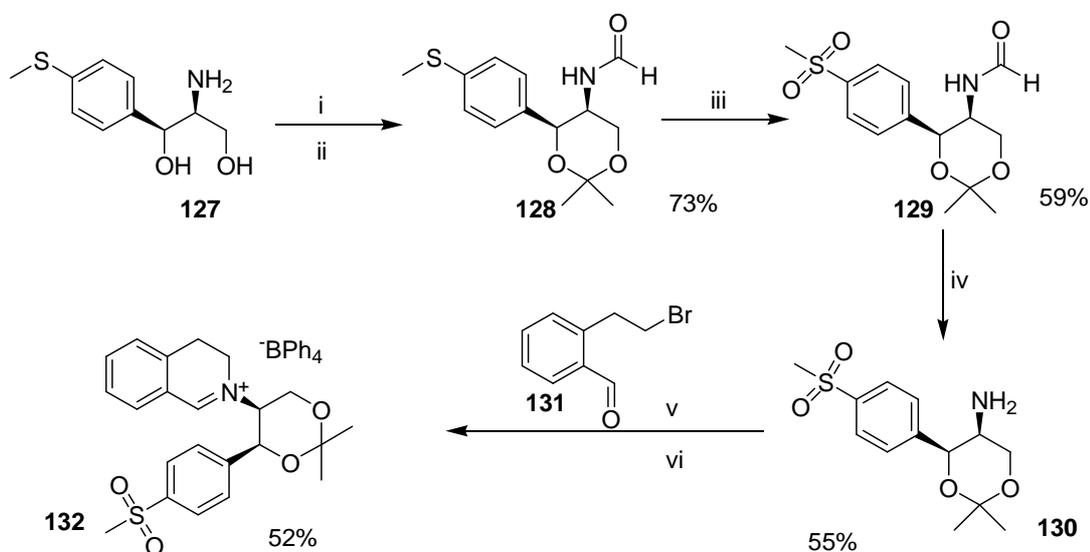


Figure 24: Previous (**124**) and potential future (**125-126**) asymmetric epoxidation targets.

The catalyst (**132**) had provided the best enantioselectivity to date with the chromene-based structures, so it was decided that this catalyst would be used to investigate the epoxidation of the dihydroquinoline-based structures. The catalyst was prepared using the procedure described by Norden and Thomas.⁶⁶ (1*S*,2*S*)-(+)-Thiomicamine (**127**) was protected with methyl formate, then the diol closed to form the six membered ring (**128**) using dimethoxypropane and *p*-TSA, both in good yields. The sulfide was then oxidized to the sulfone (**129**) using *m*-CPBA, followed by removal of the protecting group with aqueous hydrazine. The resulting amine (**130**) was then stirred with 2-(2-bromoethyl) benzaldehyde (**131**) in ethanol overnight to yield, on reaction with sodium tetraphenylborate, the required catalyst (**132**) (Scheme 38).

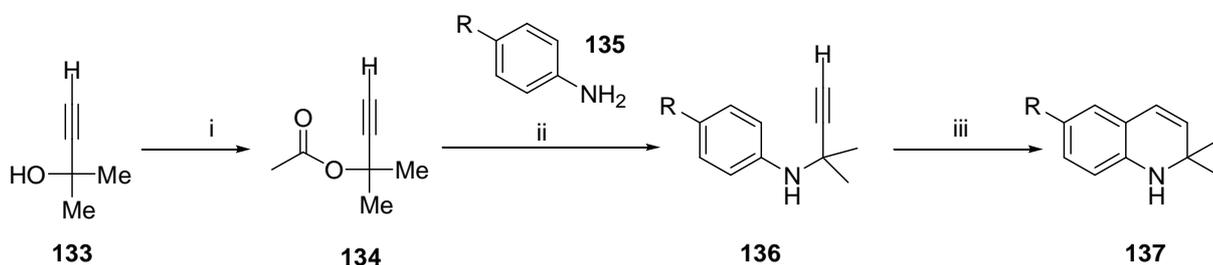


Reagents and Conditions : i: MeOCHO, MeOH, r.t.; ii: 2,2-DMP, acetone, CSA, r.t.; iii: *m*-CPBA (2.2eq.), DCM/CHCl₃, 0 °C, iv: H₂NNH₂·H₂O, Δ; v: EtOH, 0 °C-r.t.; vi: NaBPh₄, MeCN

Scheme 38: Synthetic route for the formation of the catalyst.

An examination of the literature provided a relatively simple route to the basic dihydroquinoline structure (**137**) by Hamann *et. al.*,⁶⁷ and in such a way that various analogues could easily be synthesized by alteration of the aniline (**135**) used (Scheme 39).

The dihydroquinoline compounds were prepared in three steps according to Scheme 39, with 2-methyl-3-butyn-2-ol (**133**) being converted to 2-methylbut-3-yn-2-yl acetate (**134**) using acetic anhydride, and then being heated under reflux with the appropriate aniline (**135**) and 10 mol% CuCl in dry THF for 3 hours, at which point the intermediate product (**136**) was isolated and used in the next step of the reaction without further purification. The intermediate structure was confirmed by crude IR and ¹H NMR spectroscopy, which clearly indicated the formation of the secondary amine from the primary amine, the loss of the acetate group and the presence of the alkyne group. The intermediate (**136**) was then reacted under similar conditions, with 11 mol% CuCl, for 14 hours resulting in the required cyclised product (**137**), which could be easily purified using column chromatography.

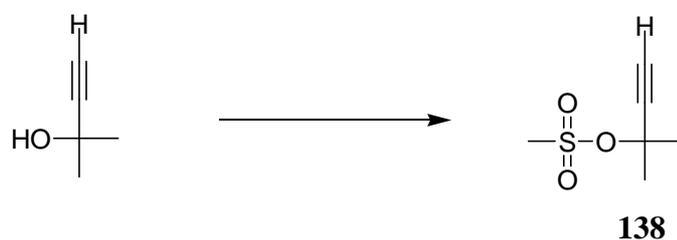


Reagents and Conditions: i: Alkyne (1.3 eq), Ac₂O (1.5 eq), Et₃N (1.4 eq), DMAP (5 mol%), r.t.; ii: CuCl (10 mol%), aniline (1 eq), THF, Δ; iii: CuCl (11 mol%), THF, Δ.

Scheme 39: Synthetic route for the formation of the dihydroquinoline substrate (**137**).

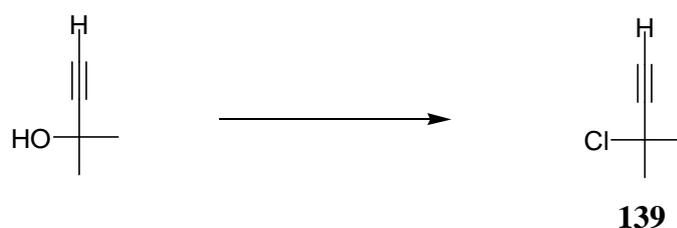
The reaction depicted above in Scheme 39 was also attempted without the intermediate (**136**) being isolated, with the addition of the 11 mol% CuCl being performed after 3 hours without stopping the reaction. The reaction was then continued in the same manner as when the intermediate was isolated and left overnight. However, although the reaction was found to proceed to the fully cyclised product, far lower conversions were achieved than when the intermediate was isolated.

Initially, problems were encountered using this reaction system with low conversions being recorded, and we thought that this maybe due to the acetate leaving group not being sufficiently active. We felt that a sulfonyl group on the alcohol might provide a more active leaving group, and as such reaction of the alcohol with mesyl chloride was attempted (Scheme 40), but unfortunately the desired product (**138**) could not be isolated. The literature also reported a similar reaction being carried out using 3-chloro-3-methyl-but-1-yne (**139**),⁶⁸ so we felt that perhaps this might provide a more successful pathway to the required product. However, the isolation of this compound proved difficult at that time (Scheme 41), and this approach was abandoned.



Reagents and Conditions: Et₃N (1.2 eq), Mesyl chloride (1.1 eq), DCM, r.t.

Scheme 40: Attempted preparation of the sulfonyl protected of 2-methyl-3-butyn-2-ol.



Reagents and Conditions: CaCl₂ (1 eq), hydroquinone (10 mol%), HCl (5 eq), r.t.

Scheme 41: Attempted route for the deoxychlorination of 2-methyl-3-butyn-2-ol.

Reaction Type	Temperature	Time Taken (Hours)	Overall yield of compound 137 (%)
Aniline + 2-methylbut-3-yn-2-yl acetate	Room temperature	96	46
Aniline + 2-methylbut-3-yn-2-yl acetate	60°C	48	51
Aniline + 2-methylbut-3-yn-2-yl acetate	Reflux (80°C)	17	83
Aniline + 2-methylbut-3-yn-2-yl acetate	Reflux (80°C) – THF left 2 hours	17	54

Table 8: Optimised conditions for the formation of product **137**.

The original paper by Hamann *et.al.*,⁶⁷ stated that dry conditions were to be used and we considered it possible that the failure of the reaction could be due to the THF being used in the reaction not being sufficiently dry enough. To examine this, a test

reaction was performed in THF which had been directly distilled from the sodium benzophenone ketyl radical before being used, and the reaction was found to proceed well. Following on from this a series of reactions was carried out to determine the optimum reaction conditions, and these were found to be when dry THF was taken directly from the still and the reaction heated under reflux at 80 °C (Table 8). We found that if the reaction temperature was too high the reaction mixture appeared to decompose to give unidentifiable products, and if the reaction temperature was too low then the reaction proceeded very slowly, with a large amount of starting material remaining even after 96 hours. We also noted that if the THF was left to stand for even a couple of hours the reaction proceeded less efficiently, resulting in a much lower overall yield.

With the reaction conditions now optimized, a selection of the dihydroquinoline substrates were prepared using five different anilines (Table 9), with some examples found to proceed in good overall yields. However, it was found that when the synthesis of the *para*-nitroaniline (**147**) and *para*-cyanoaniline (**149**) compounds was attempted, it was not possible to obtain the fully cyclised product, probably due to the electron-withdrawing nature of the groups reducing the overall nucleophilicity of the aniline. As previous research within the group had found that epoxidation reactions tended to proceed better with electron rich alkenes,^{49,50,56} it was decided to continue this investigation with the dihydroquinoline compounds containing electron-donating groups without further attempts to synthesize the dihydroquinoline compounds containing the electron-withdrawing groups.

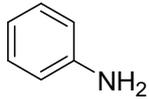
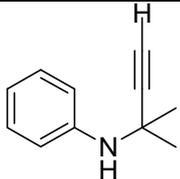
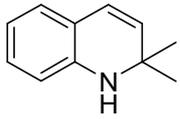
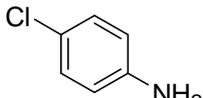
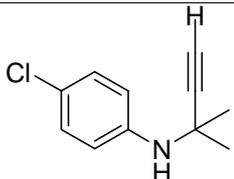
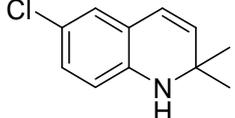
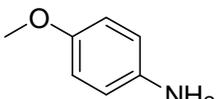
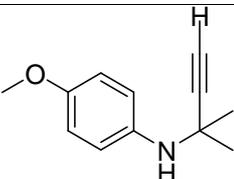
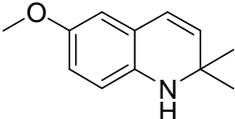
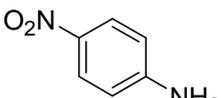
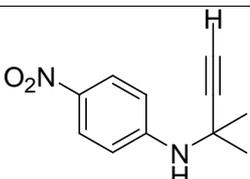
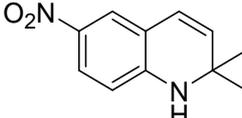
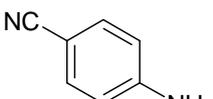
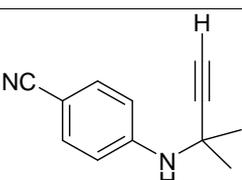
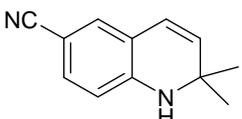
Aniline	Intermediate Yield	Product and Yield
	 85%	 76%
	 87%	 75%
	 79%	 72%
	 -	 -
	 -	 -

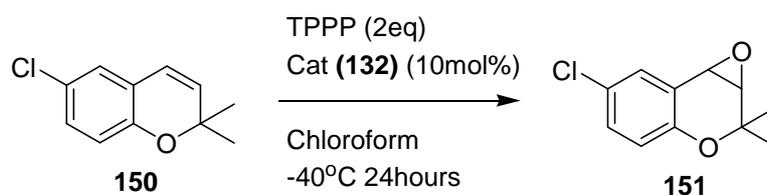
Table 9: Dihydroquinoline intermediates and products formed.

With a selection of dihydroquinoline substrates and the required catalyst synthesized, it was then necessary to prepare the required oxidant, and as such tetraphenylphosphonium monoperoxysulfate (TPPP) was prepared according to the literature procedure (Scheme 42).^{53,69} The TPPP oxidant was then isolated and stored in the freezer to be used as required.

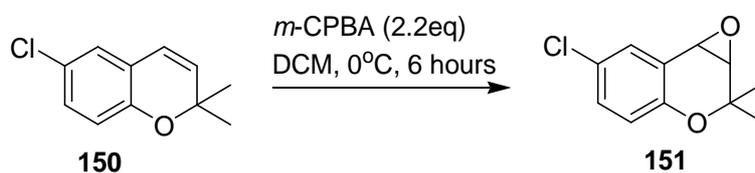


Scheme 42: Preparation of tetraphenylphosphonium monoperoxsulfate.

Before commencing reaction on the dihydroquinoline substrates we decided to test that both the oxidant and catalyst were working. A test reaction was performed using 6-chloro-2,2-dimethyl-2H-chromene (**150**). As this substrate had been previously epoxidised within the group, it would enable an easy comparison to be made. The reaction was performed as shown in Scheme 43 and the required epoxide (**151**) was formed in 81% yield. A racemic epoxide was then prepared to enable the enantiomeric excess (*ee*) to be determined by chiral HPLC. For this 6-chloro-2,2-dimethyl-2H-chromene was reacted with 2.2eq of *m*-CPBA in DCM (Scheme 44). The *ee* value was then determined by chiral HPLC using a 99:1 mixture of hexane and isopropyl alcohol. The racemic epoxide was run first to provide standard peaks for the two enantiomers, followed by the chiral racemic epoxide, and the peaks compared. Using the standard enantiomeric excess equation (major - minor / major + minor) x 100%, the *ee* value was determined, which was found to be in this case 85% *ee*. This compared well to the 93% *ee* achieved previously in the group,^{49,50,56} showing that the catalyst and oxidant were both of suitable quality for further epoxidations on the new substrates to be attempted.



Scheme 43: Chiral epoxidation of 6-chloro-2,2-dimethyl-2H-chromene



Scheme 44: Racemic epoxidation of 6-chloro-2,2-dimethyl-2H-chromene

The same reaction procedure as previously described in Scheme 43, was then performed on the corresponding nitrogen based dihydroquinoline (**143**). Unfortunately, epoxidation of this compound did not occur; surprisingly however, analysis of the reaction mixture showed no formation of the possible *N*-oxide product. Instead, all of the original starting material had disappeared and only an unidentifiable mixture remained.

We thought that this maybe due to an interaction between the catalyst and the nitrogen lone pair, and therefore, we felt that the reaction might proceed better if the nitrogen was protected in some way. Acetate protection was attempted first, as it was postulated that the carbonyl group might withdraw electron density away from the nitrogen, making the catalyst more reactive to the olefin. The acetate protection of the aniline based dihydroquinoline compound (**141**) and the chlorodihydroquinoline compound (**143**) was achieved efficiently by dissolving the compounds in DMC, with acetyl chloride and DMAP and stirring the reaction mixture overnight at room temperature. Both reactions were found to proceed well, with yields of the acetate protected compounds (**152**) and (**153**) of 74% and 72% respectively.

Disappointingly, however, when epoxidation of the acetate protected chlorodihydroquinoline compound (**153**) was attempted using the TPPP conditions above, only starting material was retrieved from the reaction (Table 10, entry 6), and this continued to be the case when the epoxidation was attempted with the other acetyl-protected dihydroquinoline compound (**152**) (Table 10, entry 4).

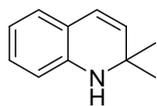
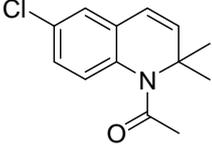
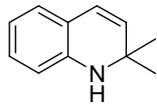
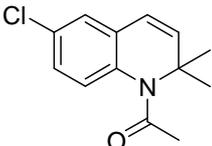
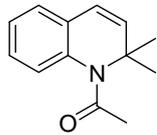
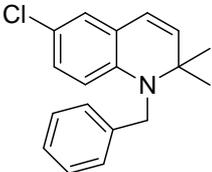
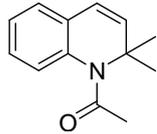
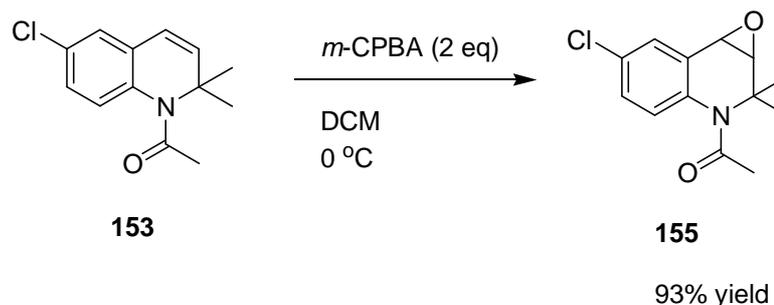
Entry	Substrate	Oxidant	Yield	Entry	Substrate	Oxidant	Yield
1		<i>m</i> -CPBA	Intractable mixture	5	 153	<i>m</i> -CPBA	93%
2		TPPP	Intractable mixture	6	 153	TPPP	SM
3	 152	<i>m</i> -CPBA	95%	7	 154	TPPP	SM
4	 152	TPPP	SM				

Table 10: Attempted epoxidations of various protected dihydroquinolines.

Previous research within the group^{49,50,52,56} had shown that electron-rich alkenes underwent epoxidation better than electron-poor ones, and in the case of the acetate protected dihydroquinolines it was possible that the acetate group may have been pulling too much electron density out of the alkene bond making it less reactive to the oxaziridinium. It could also be that the low temperatures used in the TPPP reaction may result in a further decrease in epoxidation reactivity.

To test the first of these hypotheses the reaction was attempted using the acetate protected chloro-dihydroquinoline compound (**153**) and *m*-CPBA (Scheme 45), and this was found to proceed well (Table 10, entry 5), resulting in the desired epoxide

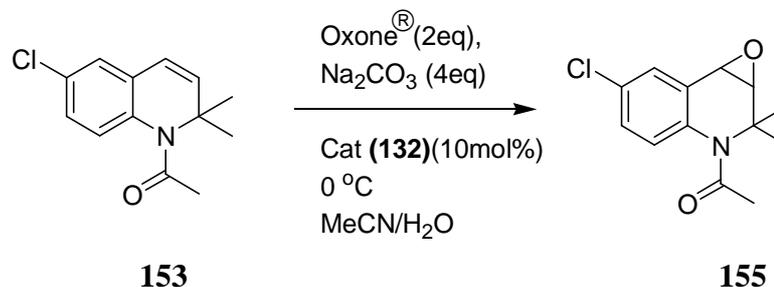
(**155**) in a near quantitative yield. This indicated that it may indeed be the case that the acetate group is decreasing the reactivity of the olefin to the oxaziridinium, which would make epoxidation all the more difficult when coupled with the low reaction temperatures used in the TPPP reaction.



Scheme 45: Reaction of the acetate protected chloro-dihydroquinoline compound (**153**) with *m*-CPBA.

To assess the implication of the reaction temperature on reactivity it was decided to attempt the reaction using both the group's original Oxone[®] conditions, where the reaction is carried out at 0 °C (Scheme 46) and the TPPP conditions, also at 0 °C instead of -40 °C.

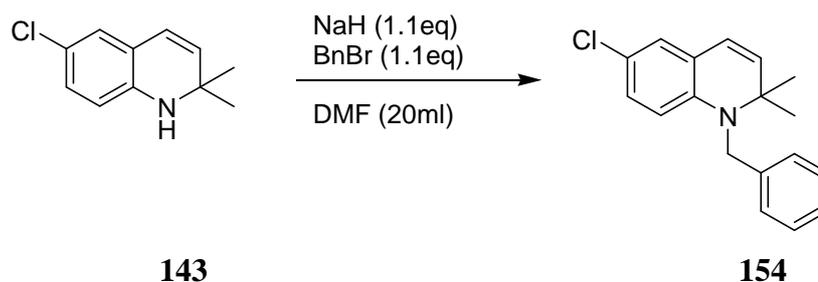
Both TLC and ¹H NMR analysis showed slight epoxide formation (*ca.* 5%) in the Oxone[®] system after 24 hours. The reaction was then stopped at this point, as the likelihood of any further epoxidation occurring was unlikely due to decomposition of the Oxone[®] oxidant. Disappointingly, there was still no epoxide spot present in the TLC from the corresponding TPPP reaction.



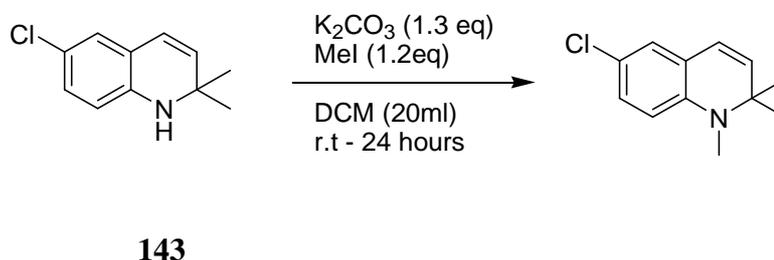
Scheme 46: The standard epoxidation conditions using Oxone[®].

These results indicated that although epoxidation did appear to be possible, it was likely that a less electron-withdrawing protecting group would be required for the

reaction to proceed in a high yield. We decided that the use of a more electron rich protecting group, such as a benzyl or methyl protecting group, may provide a more reactive substrate and potentially provide better results. Both benzyl protection (Scheme 47) and *N*-methylation (Scheme 48) were attempted.



Scheme 47: Reaction conditions used for the benzyl protection of compound (**143**).



Scheme 48: Reaction conditions of the attempted methylation of compound (**143**).

The benzyl protection of the chlorodihydroquinoline compound (**143**) proceeded well yielding the benzyl protected compound (**154**) in an 80-85% yield. Unfortunately, despite repeated attempts, methylation of the chlorodihydroquinoline compound (**143**) proved impossible. The methylation was initially attempted using MeI, however this only yielded starting material. Methylation was also attempted using a range of bases, such as *n*-BuLi and NaH, and different methylating reagents such as dimethyl sulfate, but even with repeated attempts the reactions all still only yielded starting material.

Further disappointment followed, as despite a less electron-withdrawing protecting group being present, the epoxidation in the TPPP system at $-40\text{ }^{\circ}\text{C}$, $0\text{ }^{\circ}\text{C}$ or room temperature still did not occur with the benzyl protected compound (**154**), with the reactions still yielding only starting material. The epoxidation reactions were repeated with the Oxone[®] system and even this system also showed no epoxidation product. At this point we felt that the nitrogen may be unavoidably interacting with

the catalyst and inhibiting its activity completely. This proposal is supported by the fact the epoxidation can occur with *m*-CPBA, where no catalyst is used, even with a very electron-withdrawing group in place on the nitrogen.

As mentioned above, other research within the group had focused on prochiral 2,2-dimethylchromenes (**124**), and had shown that these particular substrates could be epoxidised with very high enantioselectivities.⁵⁷ Following on from this initial research, we felt that it would be interesting to examine whether chiral 2-substituted chromenes would display the same high enantioselectivities. If this was found to be the case then the epoxidation could possibly be used in a kinetic resolution-based synthesis of a natural product, such as had been reported by Jacobsen,⁶³ where he had looked at the use of enantioselective epoxidation as a form of kinetic resolution, and applied this to the synthesis of (+) teretifolione B (Figure 25).

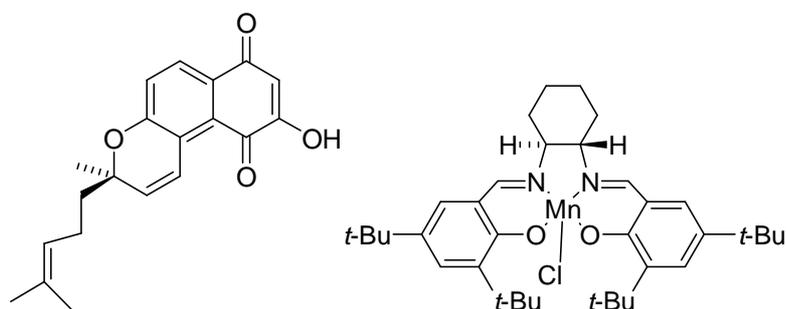


Figure 25: (+) Teretifolione B and the (salen)Mn catalyst used by Jacobsen.

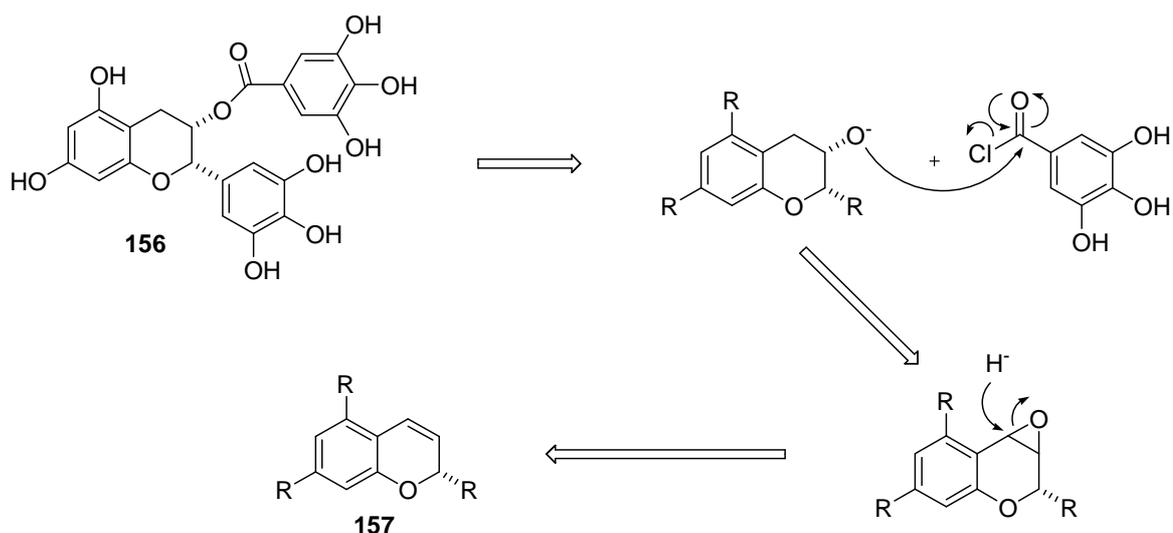
Even more importantly, if it was found that the group's epoxidation system could be used as a kinetic resolution technique, then this would be the first example of kinetic resolution performed using an oxaziridinium salt-based catalyst.

To test the possibilities of kinetic resolution we began looking for a possible natural product target of which the synthesis of a basic analogue of the target could be used to obtain an idea on the epoxidation rate and enantioselectivity of that type of substrate. Due to the previous work within the group we felt that the best target would be one based on a similar structure to the prochiral 2,2-dimethylchromenes tested previously, and examination of the literature led to a paper by Schram⁷⁰ describing the synthesis of epigallocatechin gallate (EGCG). Due to EGCG's

chromene-based structure we felt it could be considered as a potential natural product target.

Epigallocatechin gallate (EGCG) (**156**) is a natural product found in green tea and it is thought to be the responsible agent for the antioxidant properties of green tea.⁷¹ Antioxidants have received a considerable amount of attention in the media recently because of their alleged ability to counteract cancers, thought to be made possible by the antioxidant mopping/scavenging up some of the radicals that cause cells to become cancerous in the first place. The presence of such radicals may be caused by such environmental factors as smoke, pollution, radiation and some herbicides.⁷¹

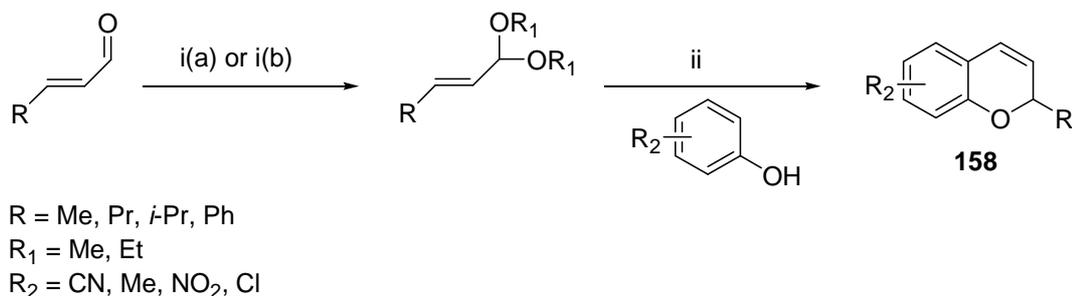
Epigallocatechin gallate (EGCG) has a chromene-based core structure and we envisaged that a selective epoxidation of the chiral 2-substituted chromene (**157**), and kinetic resolution, as shown below in the proposed retrosynthetic route (Scheme 49), could provide a simple route to its synthesis. We decided that it would be easiest to synthesize an EGCG analogue, with the alcohols protected to lessen the probability of side reactions occurring.



Scheme 49: Possible retrosynthetic route to EGCG.

A review of the literature found several routes to basic chiral 2-substituted chromene structures (**158**). North's procedure,⁷² in which a phenol is cyclised with an α,β -unsaturated acetal (Scheme 50), was thought to be a simple route which could easily be modified by varying both the phenol and acetal used to produce various chromene

analogues, which would be useful when examining the potential application to kinetic resolution.



Reagents and Conditions: i(a): (R₁O)₃CH (1.2 eq), NH₄NO₃, ethanol (50ml), or i(b): R₁OH (10 eq.), Et₃N (0.5 eq), TiCl₄ (0.25 eq.); ii: phenol (2 eq), 3-picoline (0.25 eq), *p*-xylene (40ml), reflux.

Scheme 50: Formation of the chromene by acetalization and cyclization.

The α,β -unsaturated acetals were initially prepared using a method by Clerici *et al.* which involved reacting the corresponding aldehyde under nitrogen, with a dry alcohol (ethanol or methanol), in the presence of a catalytic amount of TiCl₄ to form the corresponding alcohol-derived acetal (Scheme 50, ib).⁷³ However, this reaction proved both very capricious, with yields varying from quantitative to as low as 30%, and very time consuming, as it required dry glasswear, an inert atmosphere and a very slow addition of TiCl₄ due to the volatility of the reaction. This led to a more reliable reaction being sought. A paper by Mori *et al.*⁷⁴ provided an ideal alternative, where a mixture of the aldehyde, triethyl orthoformate and a catalytic amount of ammonium nitrate in ethanol stirred at room temperature yielded the required α,β -unsaturated acetal in a quantitative (and reproducible) yield (Scheme 50, ia), with no special considerations being required. Using this improved technique it was possible to synthesize four different α,β -unsaturated acetals, which would provide a good variety of substitution at the 2 position (Table 11). The acetalisation reaction was also attempted with methanol as the alcohol. However, despite also giving a quantitative yield of the acetal, the acetal (**163**) itself was found to be less stable.

Starting Aldehyde	Acetal	Conversion (%)	Yield of Acetal (%)
		100	92
		100	95
		100	91
		100	96
		100	91

Table 11: Acetalisation of aldehydes.

With a selection of acetals synthesized it was then possible, using the procedure developed by North,⁷² to react the acetals with some chosen phenols to form the corresponding cyclised chromene compounds (Scheme 50).

The cyclisation reaction was attempted first using 4-cyanophenol and 3,5-dimethoxyphenol, and the acetal derived from cinnamaldehyde (**162**), with both proceeding in good yields (>80%). These particular phenols and acetal were chosen first for three main reasons, 1) the acetal used would result in a similar group at the 2-position as in the natural product, 2) 3,5-dimethoxyphenol could be used in the natural product analogue and 3) *para*-cyanophenol was used in the synthesis of Levcromakalim, which gave the group's highest ever *ee*.⁵⁷ Advantageously, upon

purification by column chromatography, 2-phenyl-2H-chromene-6-carbonitrile (**164**) spontaneously crystallized straight from the column fractions, enabling a crystal structure to be obtained of this new chromene species.

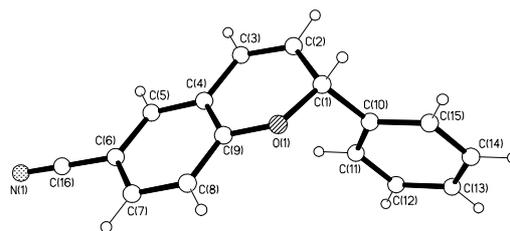
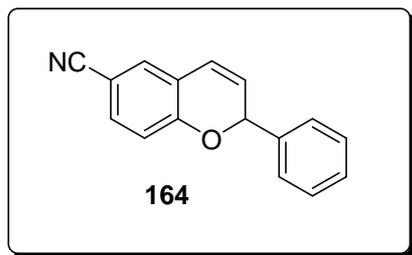
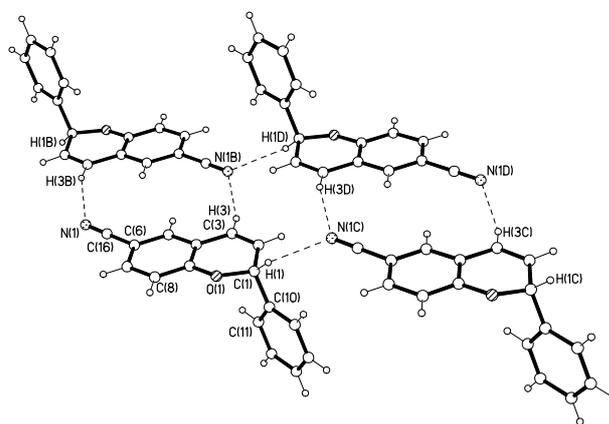


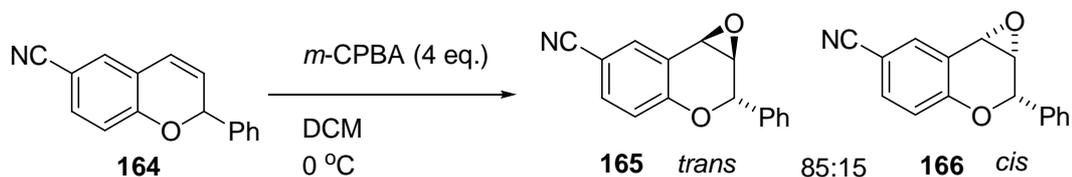
Figure 26: Diagram and crystal structures of 2-phenyl-2H-chromene-6-carbonitrile.

It was also found that by increasing the number of equivalents of the phenol used compared to North's original procedure, higher and purer yields of the chromenes could be produced. This is because whereas the acetal and the cyclised product have a similar polarity on silica, the phenol is much more polar. With an excess of phenol present the reaction is driven forward until all the acetal is reacted. Then during purification the polar phenol elutes at a much slower rate than the cyclised product, resulting in both high yields and pure compounds.



Once these two chromene compounds had been synthesized, it was then possible to attempt epoxidation of the compounds.

We felt that the 2-phenyl-2H-chromene-6-carbonitrile compound (**164**) would be best to start with, as it was both the purest and the easiest compound to synthesize and purify. A racemic *m*-CPBA epoxidation was attempted first, using 4 equivalents of *m*-CPBA, as shown in Scheme 51.



Scheme 51: Epoxidation of 2-phenyl-2H-chromene-6-carbonitrile (**164**) using *m*-CPBA.

The reaction proceeded well, yielding the corresponding racemic epoxide in a quantitative yield. Interestingly the reaction also proved to be diastereoselective, with major (**165**) and minor (**166**) epoxides being produced in a 85:15 ratio. We felt that the major epoxide was likely to be the *trans*-isomer as this would be more favoured due to the approach of the *m*-CPBA towards the opposite side to the phenyl substituent as this would be least hindered, thus favouring the *trans*-epoxide formation. Luckily, a crystal of the major product (as determined by ¹H NMR) was obtained, and subsequent crystal structure analysis of the major product showed that the *trans*-product was indeed the major product formed in the reaction.

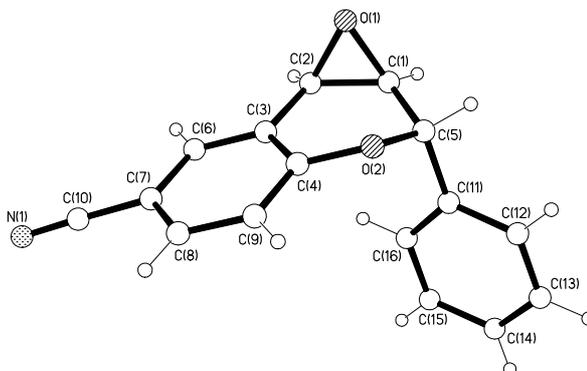


Figure 27: Crystal structure of the major *trans*-epoxide (**165**).

The diastereoisomeric mixture containing the epoxides (**165**) and (**166**) was purified by column chromatography and an HPLC trace obtained using a chiral column. The trace below (Figure 28) shows the minor diastereoisomeric product at 16.120 and 19.907 minutes and the major at 17.533 and 23.263 minutes.

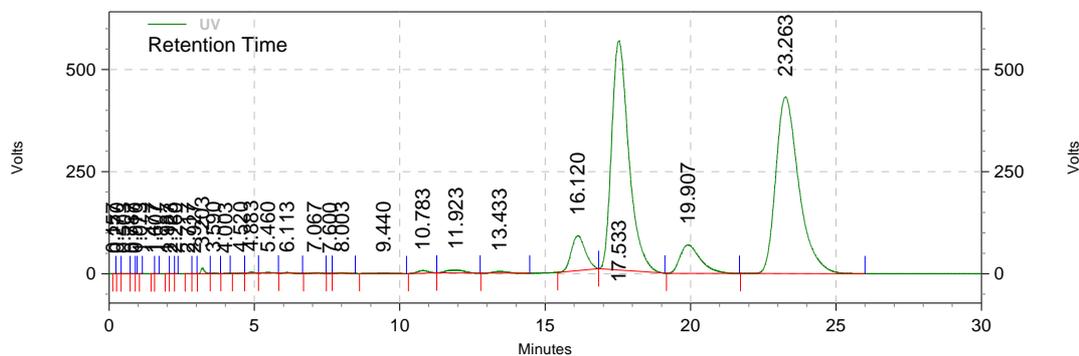
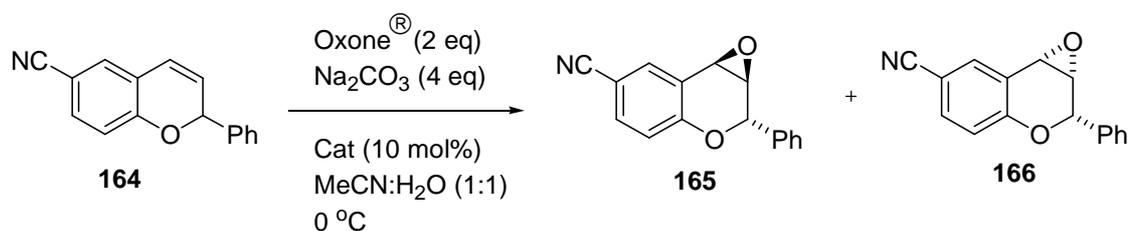


Figure 28: HPLC trace of the diastereoisomeric mixture containing the epoxides **(165)** and **(166)**.

UV Results					
Retention Time	Area	Area %	Height	Height %	Major or Minor Diastereoisomer
16.120	11386400	5.26	341325	10.89	Minor (166)
17.533	92241012	42.63	2244114	47.03	Major (165)
19.907	13493320	8.06	278414	5.83	Minor (166)
23.263	95325378	44.05	1729502	36.25	Major (165)
Totals	212446110	100.00	13958291	100.00	

For a kinetic resolution using a chiral epoxidation, we decided that the Oxone[®] conditions would be attempted first (Scheme 52), as we felt that although these conditions are generally less enantioselective, the higher reactivity would mean it would be easier to gauge the potential of a kinetic resolution on these type of substrates, which could then perhaps be further enhanced with the use of lower temperatures with the TPPP conditions.



Scheme 52: Kinetic resolution of 2-phenyl-2H-chromene-6-carbonitrile (**164**) using Oxone[®] conditions.

This first asymmetric epoxidation reaction also proceeded well, with the experiment being stopped when a $^1\text{H NMR}$ spectrum of the crude reaction mixture showed that the reaction contained roughly half the epoxide product and half the original alkene starting material. As shown by the racemic epoxidation, the *trans*-diastereoisomer (**165**) was already known to be formed in preference to the *cis*-diastereoisomer (**166**), however, for a kinetic resolution to have good potential it is necessary that the preferential diastereoisomer be formed at a much faster rate than the other, so that at an approximate 50% conversion it would be the only diastereoisomer formed. It is also important that one enantiomer of the preferred diastereoisomer should also be formed with high enantioselectivity.

Purification of the epoxide product from the Oxone[®] epoxidation and subsequent HPLC analysis showed both a good diastereoselectivity at 50% conversion and some selectivity between the enantiomers, when compared to the racemic HPLC trace. As can be seen from Figure 29, the Oxone[®] trace shows the same epoxide peaks, but with an enhanced selectivity for the peak at 19 minutes compared to that at 16 minutes for the minor product, and for the peak at 17 compared to that at 23 minutes for the major product. Analysis of the peak areas gave *ee* values of 98.6% for the minor epoxide and 60% for the major epoxide.

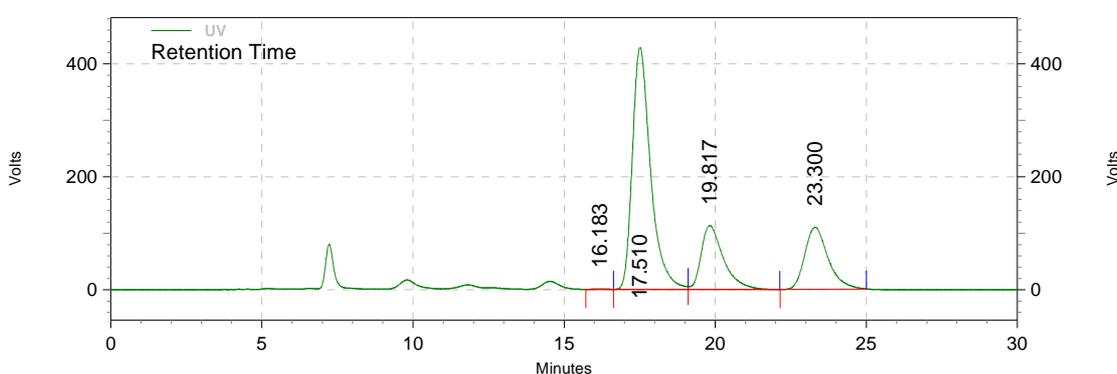
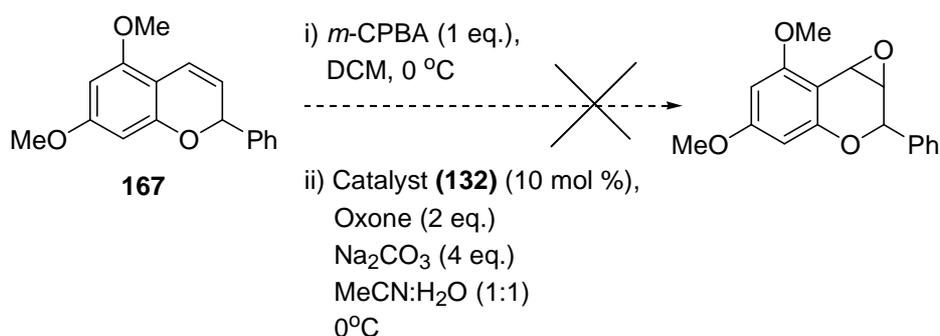


Figure 29: HPLC trace of the diastereomeric mixture containing the epoxides (**165**) and (**166**) from the Oxone[®] epoxidation reaction.

UV Results					
Retention Time	Area	Area %	Height	Height %	Major or Minor Diastereoisomer
16.183	94189	0.08	3258	0.12	Minor (166)
17.510	71979014	60.65	1712652	65.68	Major (165)
19.817	23069777	19.44	452298	17.34	Minor (166)
23.300	23527579	19.83	439498	16.85	Major (165)
Totals	118670559	100.00	2607706	100.00	

The results obtained from this Oxone[®] epoxidation were encouraging and showed that a kinetic resolution using an oxaziridinium based catalyst is at least feasible. Using the TPPP epoxidation system, which enables the reactions to be carried out at lower temperatures, should enhance the reaction even further as it is these conditions which have given the best enantioselectivities to date.

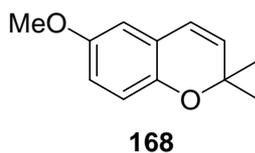
Unfortunately, both the attempted *m*-CPBA (Scheme 53, conditions i) and Oxone[®] epoxidation (Scheme 53, conditions ii) of the dimethoxy-chromene compound (**167**) only yielded an unidentifiable mixture.



Scheme 53: Attempted epoxidation of the dimethoxy-chromene (**167**).

Previously within the group, an attempted epoxidation of the *para*-methoxy chromene compound (**168**) had also failed to result in the epoxidised product. It was postulated that due to the presence of the electron-rich methoxy group, the olefin was

very reactive and therefore prone to over oxidation, an effect which would be even more pronounced in a compound where two methoxy groups were present.



However, despite the initial disappointment of the reaction not resulting in the epoxidised product, we felt that an important lesson had been learned, and that for the synthesis of the natural product it would be necessary to use alternative protecting groups.

Encouraged by the initial results from the epoxidation of the cyanochromene (**164**) for the potential kinetic resolution, a range of chromene based substrates were synthesized to enable a full picture of the applicability of an oxaziridinium based kinetic resolution to be obtained (Tables 12a and 12b). The variety of chromene substrates were chosen to enable both steric and electronic effects to be examined.

Compound	Acetal	Phenol	Product	Yield
169				86%
170				86%
171				91%
172				80%
173				89%

Table 12a: The range of chromene substrates synthesized.

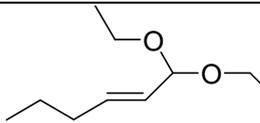
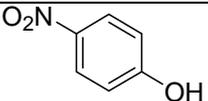
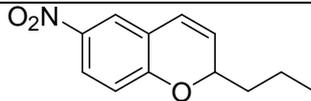
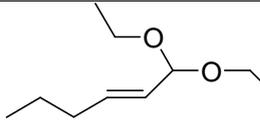
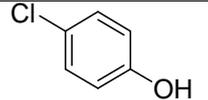
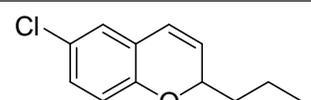
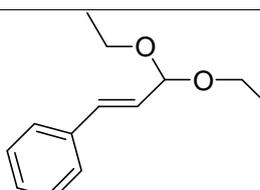
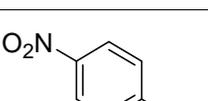
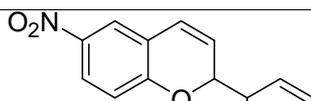
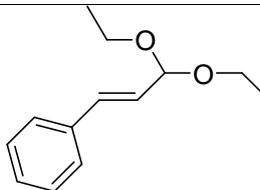
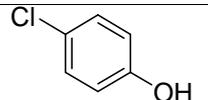
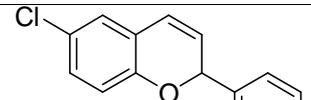
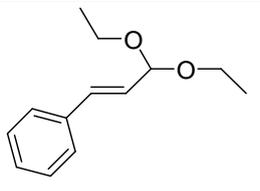
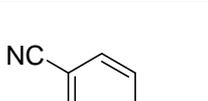
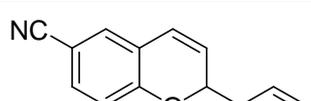
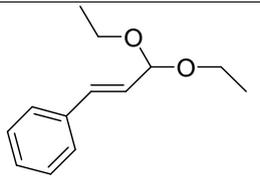
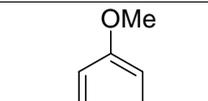
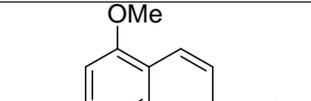
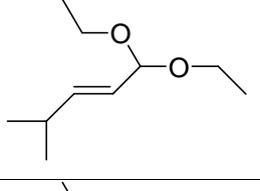
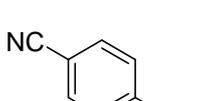
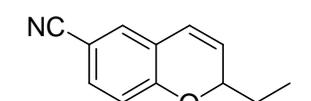
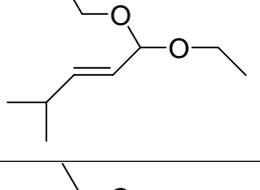
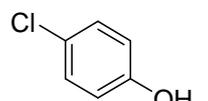
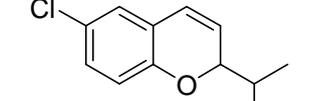
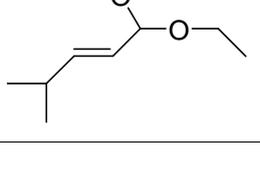
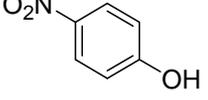
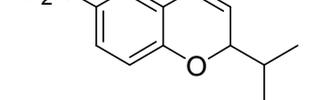
Compound	Acetal	Phenol	Product	Yield
174				89%
175				86%
176				70%
177				68%
164				71%
167				58%
178				84%
179				62%
180				80%

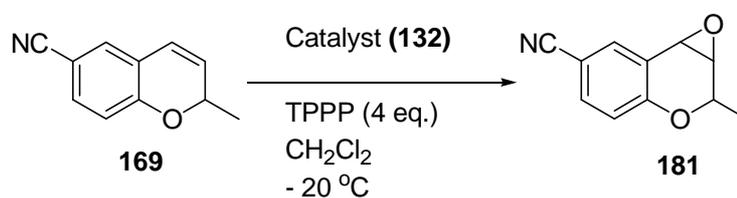
Table 12b: The range of chromene substrates synthesized.

In the case of investigating steric effects, methyl, propyl and *iso*-propyl were chosen as alternative 2-substituents, as we felt that they would provide a progressive increase in the amount of steric hinderance represented by the group. It would also be interesting to examine the effect a straight chain group has when compared to its branched equivalent as in the case of the straight chain propyl and branched *iso*-propyl groups. Also, in the case of the compounds with a methyl substituent, previous racemic epoxidation of the cyanomethyl chromene (**169**) by Buckle⁷⁵ had shown that this was produced as a 1:1 ratio of diastereoisomers, which is very different from the 85:15 ratio obtained from the phenyl-substituted compound, and we therefore felt that it would be interesting to see what level of enantioselectivity (if any) could be obtained from the methyl substituted compounds.

When looking at what effects changes in electronic properties would have, we felt that *para*-nitro, cyano, methyl and chloro groups would provide an interesting range of effects, in comparing electron-withdrawing substituents to electron-donating ones. Previous research within the group had shown that similar compounds containing a chloro substituent on the aromatic ring were more reactive substrate compared to both cyano and nitro, all of which could prove important when attempting epoxidation using the TPPP system.

After synthesis and subsequent purification by column chromatography, each compound was epoxidised using *m*-CPBA in order to obtain a racemic HPLC trace and ¹H NMR standard of the product epoxide to compare to future chiral epoxidations. It was interesting to note that all racemic compounds containing the methyl substituent were obtained as the expected 1:1 mixture of *trans*:*cis* diastereoisomers, whereas the propyl substituent gave roughly a 60:40 ratio, and the phenyl and *isopropyl* substituents a 85:15 ratio.

To gauge the reactivity and selectivity of the TPPP epoxidation on the chromene substrates, a test chiral epoxidation using the TPPP conditions was attempted on the methyl substituted cyanochromene (**169**) (Scheme 54).



Scheme 54: Test TPPP epoxidation using chromene (**169**).

It was felt that this compound was best as an initial test substrate for the TPPP reaction as the compound was less sterically hindered than the previous test substrate (**164**) and due to TPPP being a less reactive oxidant, the epoxidation reaction was more likely to proceed when using a compound with minimal steric hindrance than in the case of the epoxidation of a compound which was more sterically hindered.

Unfortunately, it was found that no reaction occurred when the TPPP epoxidation of the methyl substituted cyanochromene (**169**) was performed at $-40\text{ }^{\circ}\text{C}$, so the reaction was re-tried at $-20\text{ }^{\circ}\text{C}$. Pleasingly, the reaction proceeded well at this temperature with the reaction running to 65% conversion (as determined by ¹H NMR spectroscopy) after 2 days, though it was interesting to note that even if the reaction was left for more than 3 days, it never reached completion, probably due to decomposition of the oxidant.

Purification of the TPPP epoxidation product (**181**) of the methyl substituted cyanochromene (**169**) enabled analysis by chiral HPLC, thereby allowing a comparison to be made with the trace of the racemic epoxide product run previously. The trace of the racemic epoxidation product (Figure 30) showed four equal peaks at 26, 32, 42, and 44 minutes. It is important to note that this particular HPLC had to be run in 90:10 hexane:isopropyl alcohol due to the peaks co-eluting when run at 80:20, which is the value that was used for the epoxidation products obtained from the epoxidation of the phenyl cyanochromene (**164**).

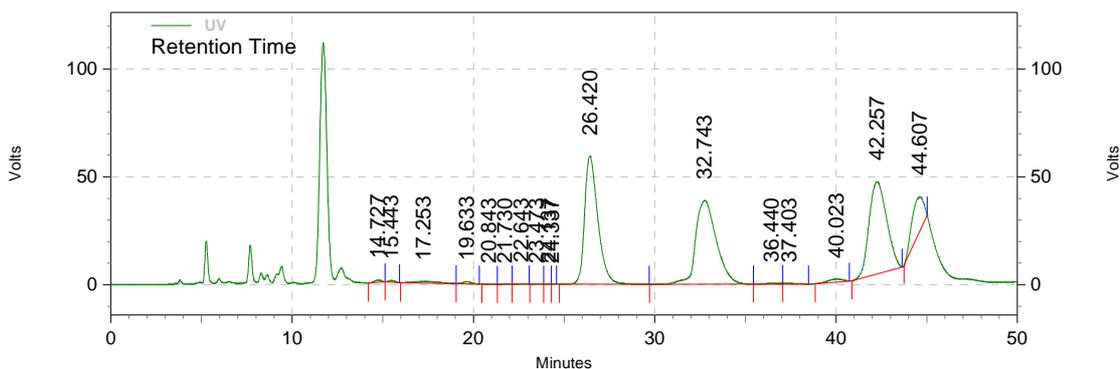


Figure 30: Trace of the product (**181**) of the racemic epoxidation of compound (**169**).

The trace of the asymmetric epoxidation reaction product (Figure 31) appeared to show some selectivity, but as can be seen from the HPLC trace of the racemate (Figure 30), due to the racemic epoxidation reaction resulting in a 1:1 mixture of diastereoisomers (i.e. there were no major and minor products formed), it was not possible to determine which peaks related to which diastereoisomer from the trace of the racemate alone.

This was unlike the previous epoxidation example of the phenyl substituted cyanochromene (**164**) where there were obvious major and minor diastereoisomeric products in the racemic reaction, enabling quick identification of which peaks corresponded to which diastereoisomer. Therefore, to establish which peaks related to which diastereoisomer for the methyl substituted cyanochromene (**169**), a preparative HPLC was run on the racemic epoxide. This showed two peaks at 65 and 70 minutes when run in 90:10 hexane:isopropyl alcohol. These fractions were collected and run using the chiral HPLC, showing that the peaks at 26 and 33 minutes were from one diastereoisomer and the peaks at 42 and 45 minutes from the other. From this, *ee* values of 66% and 47% respectively were calculated, with a diastereoisomeric ratio of 3:1.

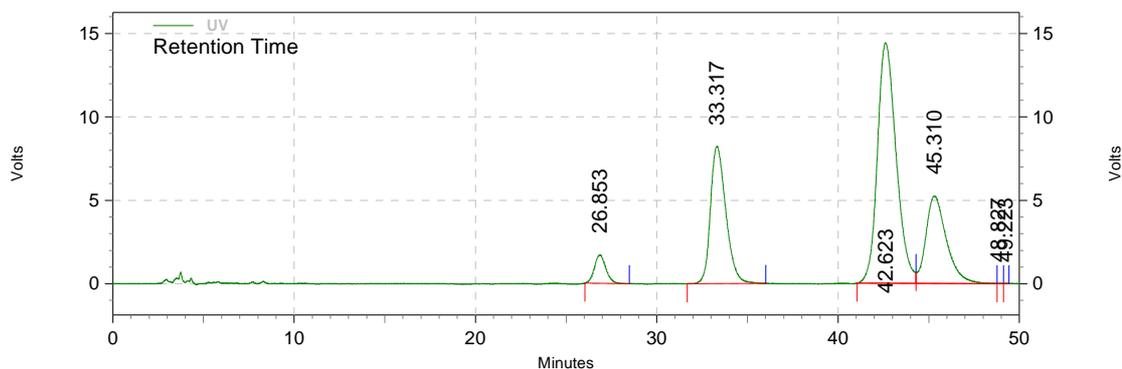
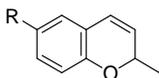
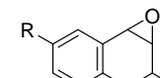
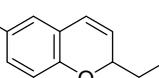
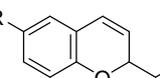
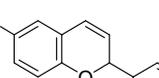
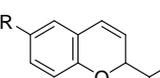
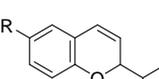
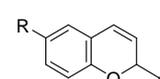


Figure 31: Trace of the epoxidation product (**181**) from the asymmetric epoxidation reaction.

UV Results					
Retention Time	Area	Area %	Height	Height %	Major or Minor Diastereoisomer
26.853	298317	3.72	6810	5.75	Minor
33.317	1949413	24.28	32908	27.79	Minor
42.623	4139333	51.55	57686	48.71	Major
45.310	1641132	20.44	20941	17.68	Major
Totals	8029241	100.00	118435	100.00	

These results were really promising, as the enantioselectivity was good and even the diastereoselectivity was reasonable considering that the reaction had run to 65% completion, whereas an optimum kinetic resolution would typically require the reaction to be stopped at or below 50%.

Asymmetric epoxidations using the TPPP system at $-20\text{ }^{\circ}\text{C}$ were then performed on all the substrates, as shown in Table 13, this time attempting to stop the reaction at or before 50% conversion.

Compound	Product	Conversion (%) ^b	Major Enantiomer <i>ee</i> (%) ^c	Recovered Starting Material <i>ee</i> (%) ^c	Diastereoisomer Ratio (cis:trans) ^d												
 R = <table border="0"> <tr><td>CN</td><td>(169)</td></tr> <tr><td>NO₂</td><td>(170)</td></tr> <tr><td>Cl</td><td>(171)</td></tr> </table>	CN	(169)	NO ₂	(170)	Cl	(171)	 R = <table border="0"> <tr><td>CN</td><td>(181)</td></tr> <tr><td>NO₂</td><td>(182)</td></tr> <tr><td>Cl</td><td>(183)</td></tr> </table>	CN	(181)	NO ₂	(182)	Cl	(183)	48 45 52	76 63 75	69 na ^e 57	15:1 20:1 10:1
CN	(169)																
NO ₂	(170)																
Cl	(171)																
CN	(181)																
NO ₂	(182)																
Cl	(183)																
 R = <table border="0"> <tr><td>NO₂</td><td>(174)</td></tr> <tr><td>Cl</td><td>(175)</td></tr> </table>	NO ₂	(174)	Cl	(175)	 R = <table border="0"> <tr><td>NO₂</td><td>(184)</td></tr> <tr><td>Cl</td><td>(185)</td></tr> </table>	NO ₂	(184)	Cl	(185)	42 53	81 80	79 na ^e	25:1 14:1				
NO ₂	(174)																
Cl	(175)																
NO ₂	(184)																
Cl	(185)																
 R = <table border="0"> <tr><td>CN</td><td>(164)</td></tr> <tr><td>NO₂</td><td>(176)</td></tr> <tr><td>Cl</td><td>(177)</td></tr> </table>	CN	(164)	NO ₂	(176)	Cl	(177)	 R = <table border="0"> <tr><td>CN</td><td>(186)</td></tr> <tr><td>NO₂</td><td>(187)</td></tr> <tr><td>Cl</td><td>(188)</td></tr> </table>	CN	(186)	NO ₂	(187)	Cl	(188)	42 20 48	72 na ^f 78	na ^e na ^e na ^e	24:1 na 20:1
CN	(164)																
NO ₂	(176)																
Cl	(177)																
CN	(186)																
NO ₂	(187)																
Cl	(188)																
 R = <table border="0"> <tr><td>CN</td><td>(178)</td></tr> <tr><td>Cl</td><td>(179)</td></tr> <tr><td>NO₂</td><td>(180)</td></tr> </table>	CN	(178)	Cl	(179)	NO ₂	(180)	 R = <table border="0"> <tr><td>CN</td><td>(189)</td></tr> <tr><td>Cl</td><td>(190)</td></tr> <tr><td>NO₂</td><td>(191)</td></tr> </table>	CN	(189)	Cl	(190)	NO ₂	(191)	26 45 20	na ^f 82 na ^f	na ^e na ^e na ^e	na ^f 26:1 na ^f
CN	(178)																
Cl	(179)																
NO ₂	(180)																
CN	(189)																
Cl	(190)																
NO ₂	(191)																

^a All reactions were carried out with substrate (1 equiv.), catalyst (10 mol%) and tetraphenylphosphonium monoperoxy sulfate (TPPP) (4 equiv.) in CHCl₃ at -20 °C. The temperature was then slowly raised to -10 °C overnight.

^b Conversion was determined by NMR analysis of the crude reaction mixture.

^c Enantioselectivity was determined using a Chiralcel ODH column, with the chiral traces being compared to those obtained for the racemic compound and starting material.

^d The diastereomeric ratios were determined from the chiral HPLC trace.

^e It was not possible to separate the diastereomers to obtain an *ee* value.

^f These compounds proved too unreactive to be used in the kinetic resolution.

Table 13: Kinetic resolution of olefins using asymmetric epoxidation mediated by catalyst (132).^a

In all cases, it was found that the compounds containing the chlorosubstituent on the aromatic ring were the most reactive and although this slightly affected the diastereoselectivity, with ratios of around 10:1 to 15:1, the enantioselectivities remained relatively high with *ee* values at around 75 to 85%. The highest

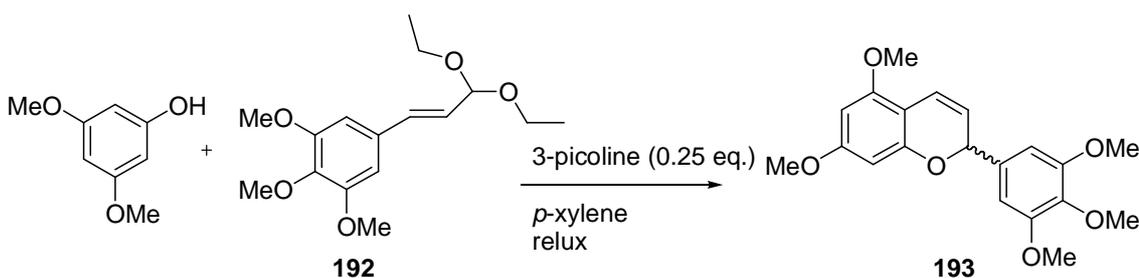
diastereoselectivities were observed using those compounds containing electron-withdrawing groups, with the nitro containing chromene yielding diastereoisomeric ratios of around 20:1 to 25:1.

Increasing the size of the group at the C2 position does seem to effect a small increase in both diastereo- and enantioselectivity, probably due to this group restricting access to one face of the chromene, and therefore enhancing *trans*-diastereoselectivity. Although this effect is also observed in the racemic epoxidations, with the propyl, phenyl and isopropyl groups showing preference for the *trans*-epoxidation product in 1.5:1, 4:1 and 9:1 ratios respectively, the effect is enhanced even further when using the TPPP epoxidation system. In fact this steric effect is so pronounced that in the case of the isopropyl compounds, only the chloro substituted example (**179**) was sufficiently reactive to provide a high enough conversion to assess the kinetic resolution for that substrate; all the remaining compounds in that group showed little or no conversion to the epoxide after 4 days, and even raising the reaction temperature to 0 °C had no effect on conversion.

As kinetic resolution reactions are terminated at approximately 50% conversion, the reaction also results in the resolution of the remaining starting material. In order to establish the degree to which the kinetic resolution using the epoxidation reaction on the chromene substrates had resulted in the resolution of the starting material, we obtained HPLC traces of both the racemic starting material and the starting material remaining after the asymmetric epoxidation reactions were performed. As can be seen from the results in Table 13, in some cases it was not possible to separate the starting material enantiomers by HPLC, despite varying the ratio of eluents and the elution rate. Separation by gas chromatography was also attempted on the more volatile substrates; unfortunately it was still not possible to separate the enantiomers resulting in the determination of an *ee* being impossible. However, in the cases where it was possible to separate the enantiomers, it can be seen that the reaction indeed led to resolved starting material, with *ees* of up to 71%.

With a kinetic resolution now feasible using the TPPP epoxidation system, we felt that the methodology should be applied to the synthesis of epigallocatechin gallate (EGCG) as previously proposed. EGCG (**156**) is a poly-hydroxylated compound, so

in order to decrease its polarity and minimize the possibility of side reactions with the free hydroxyl groups, a protected version would need to be synthesized, with the protecting groups being removed at the end of the synthesis. To synthesize a protected chromene which could be used as the EGCG precursor it was decided to test potential routes using easily available and cheap starting materials. Although, as noted previously, alternative protecting groups would need to be used, the simplest initial route appeared to be to cyclise commercially available 3,5-dimethoxyphenol with the acetal (**192**), as shown in Scheme 48, using the procedure developed by North,⁷² which had proved so efficient previously. This would result in the methoxy-protected chromene (**193**) product as shown (Scheme 55).

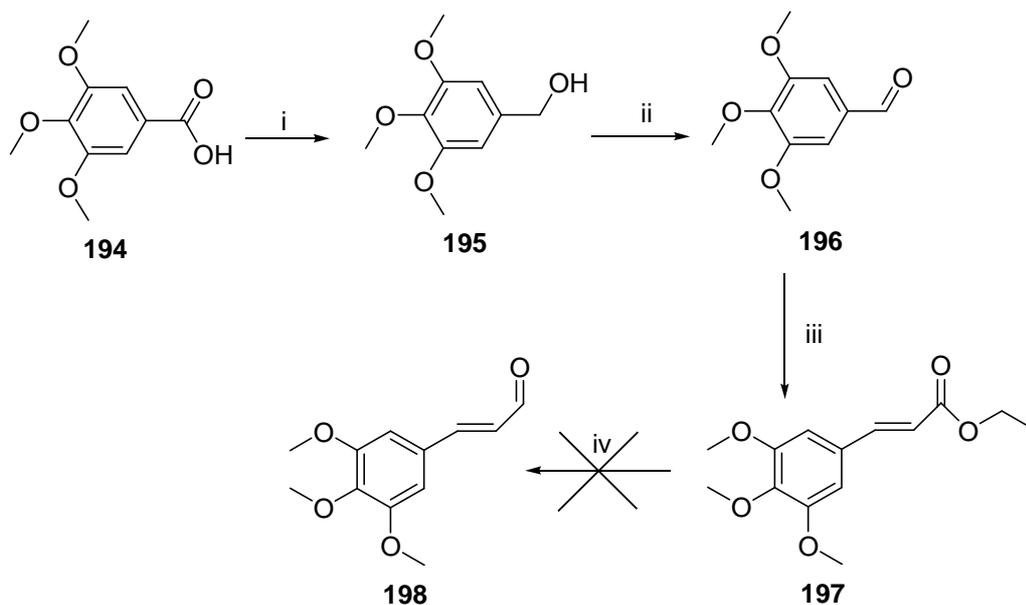


Scheme 55: Possible route to a close EGCG analogue.

As the acetal (**192**) was not commercially available and neither was the corresponding aldehyde, the first step of the potential synthetic route was to prepare this compound, either directly or indirectly through the aldehyde.

A review of the literature showed that the only known routes to the acetal were through the aldehyde. The synthesis of the aldehyde was attempted by following part of the literature procedure shown in scheme 56,⁷⁶ where 3,4,5-trimethoxybenzaldehyde (**196**) is converted to the α,β -unsaturated ester (**197**) and then reduced to the aldehyde (**198**). To obtain 3,4,5-trimethoxybenzaldehyde (**196**), 3,4,5-trimethoxybenzoic acid (**194**) was converted to the alcohol (**195**) using a LiAlH_4 reduction, a subsequent PDC oxidation then provided the aldehyde (**196**) in excellent yield. Later, to save time, these steps were replaced by buying 3,4,5-trimethoxybenzaldehyde. The aldehyde was then converted to the 3-(3,4,5-trimethoxyphenyl)acrylic acid ethyl ester (**197**) using a Horner-Wadsworth-Emmons reaction also in a good yield. Unfortunately this route proved to be ultimately

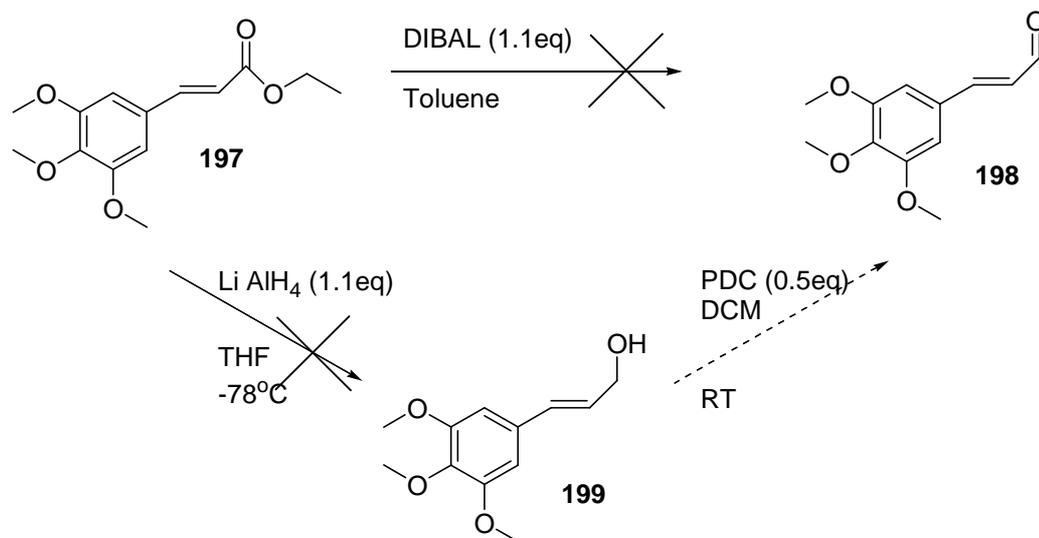
unsuccessful, as despite repeated attempts the reduction of the ester (**197**) to the aldehyde (**198**) using DIBAL proved futile. The reaction did not even yield the alcohol, which would have resulted if over-reduction of the ester had occurred. Analysis of the H^1 NMR spectrum showed only an unidentifiable mixture.



Reagents and Conditions: i: $LiAlH_4$ (1.1 eq), THF, $-78^\circ C$, (95%); ii: PDC (0.75 eq), DCM, 4A molecular sieves, (86%); iii: $OP(OEt)_2CH_2COOEt$ (1.2 eq), NaH (1.2 eq), THF, $-78^\circ C$, (80%), iv: DIBAL (1.1 eq), toluene, $-78^\circ C$.

Scheme 56: Formation of 3-(3,4,5-trimethoxyphenyl)acrylic acid ethyl ester.

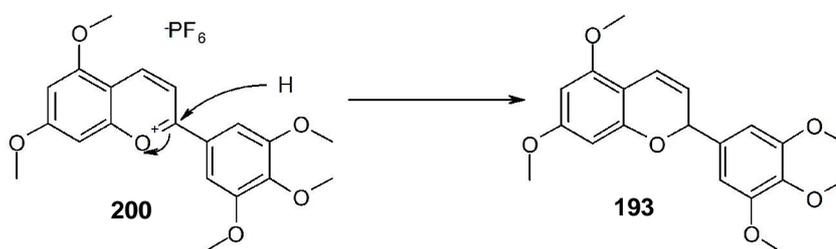
Knowing how capricious DIBAL reductions can be, a $LiAlH_4$ reduction was also attempted (Scheme 57), with the thought that if the ester (**197**) could be reduced down to the alcohol (**199**), it would be possible to oxidize it back to the aldehyde (**198**) using the PDC method employed in the previous oxidation of the alcohol (**195**) to the aldehyde (**196**). However, analysis of the reduction product showed only an unidentifiable complex mixture, and none of the expected alcohol product.



Scheme 57: Attempted routes to 3-(3,4,5-trimethoxyphenyl)propenal (**198**).

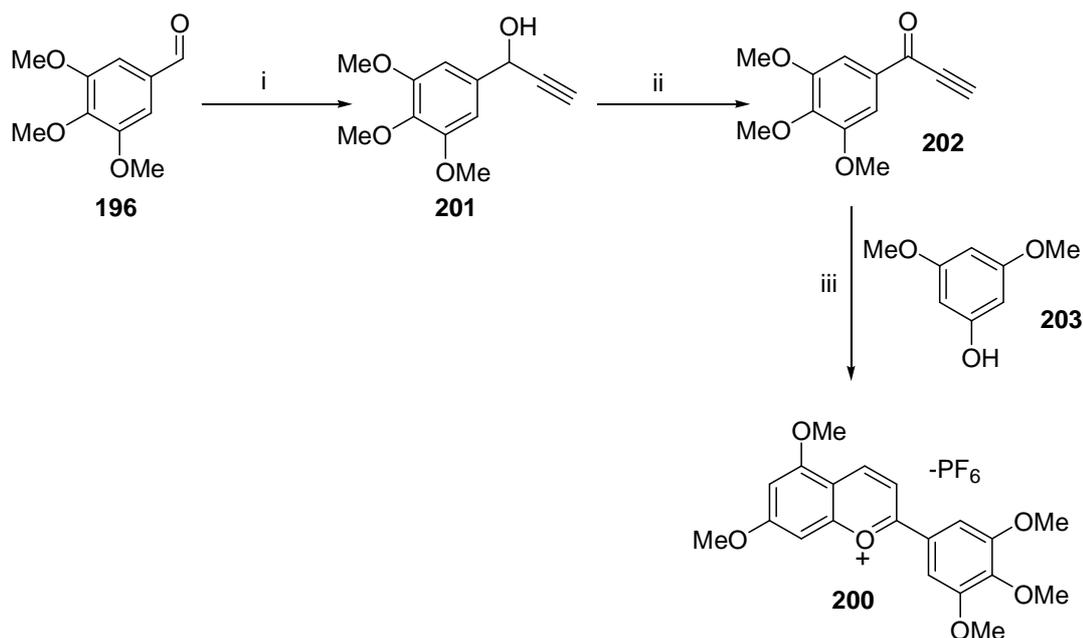
Another method found in the literature showed a route to the aldehyde straight from the ester, this time using LiAlH₄ and diethylamine.⁷⁷ The paper proposed that during the reaction, the amine coordinates to the aluminium, forming an alane-amine complex with AlH₃, leaving only one hydride equivalent available for the reduction. However, attempts using this route also led to an intractable mixture with no identifiable products being isolated.

At this point we decided that other routes to the chromene precursor which did not require the acetal, should also be explored. A further examination of the literature for other potential routes to a suitable chromene precursor led to the discovery of a paper by Chassaing *et al.*⁷⁸ This paper showed the formation of a flavylum salt skeleton from an aryl ethynyl ketone and phenol and we thought that once the salt (**200**) had been synthesized, it could then be reduced to yield the required chromene for the natural product EGCG (**193**) (Scheme 58).



Scheme 58: Possible reduction of flavylum salt (**200**) to yield the EGCG precursor (**193**).

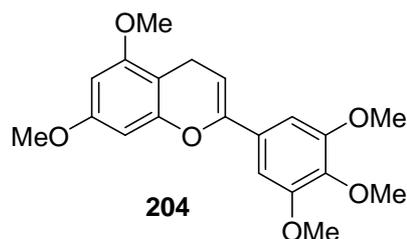
To form methoxy flavylum salt (**200**), it was first necessary to synthesize the required aryl ethynyl ketone (**202**). This was achieved by reacting 3,4,5-trimethoxybenzaldehyde (**196**) with ethynyl magnesium bromide to furnish the alcohol (**201**) in good yield. The alcohol was then oxidized to the ketone (**202**) using IBX, also in good yield. The aryl ethynyl ketone and the required phenol, in this case 3,5-dimethoxyphenol (**203**), were then placed in a flask and an excess of hexafluorophosphoric acid, in the minimum of acetic acid, was added, causing the reaction to turn a dark red colour. The reaction mixture was stirred for a further two days, after which diethyl ether was added causing a dark red precipitate to form. The solid was filtered off and washed, yielding the clean product (**200**) in good yield with no need for further purification (Scheme 59).



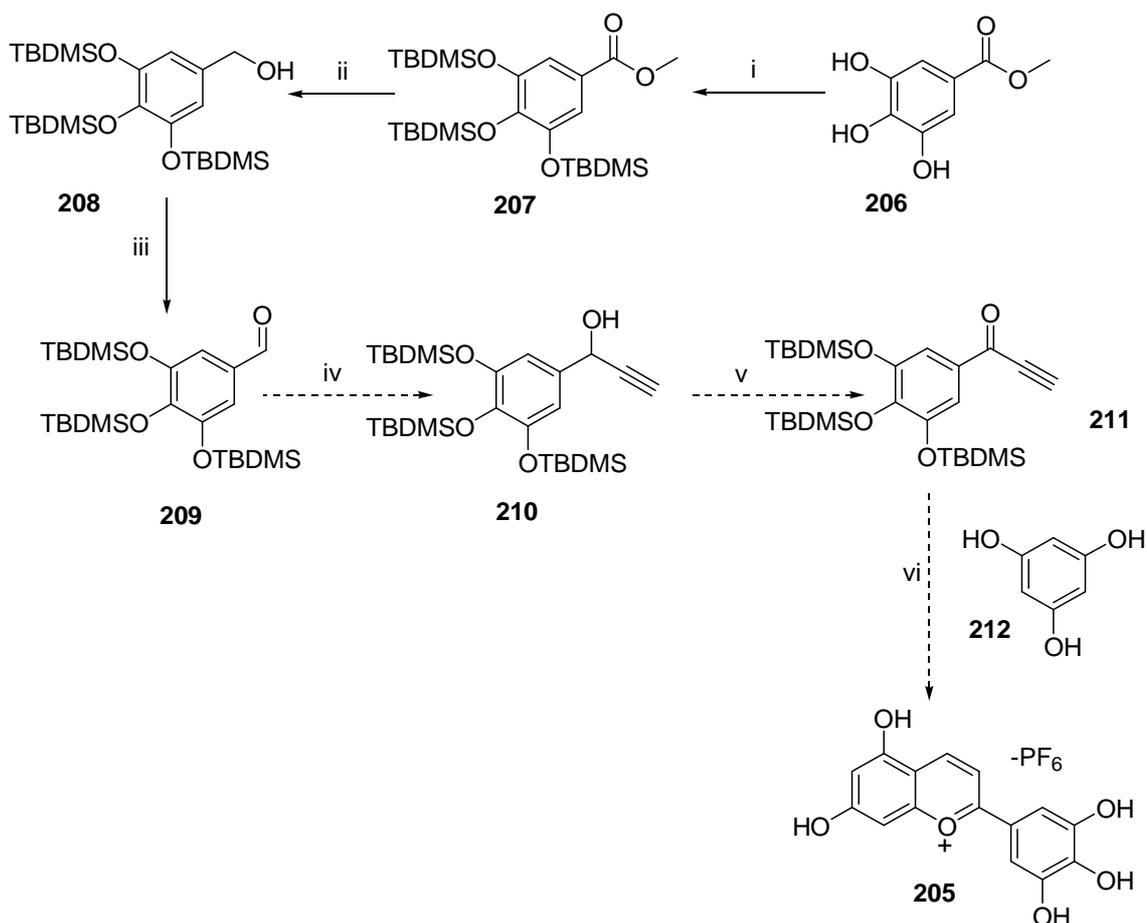
Reagents and Conditions: i: MgBrCCH (1.1eq), THF, N₂, 0 °C, (87%); ii: IBX (1.2 eq), acetone, reflux (78%); iii: HPF₆ (2 eq), AcOH (0.1 eq), 2 days (89%).

Scheme 59: Synthesis of flavylum salt (**200**).

The methoxy-protected flavylum salt (**200**) was then reduced using LiAlH_4 , though it was not known at which carbon the hydride attack would occur. We hoped that the attack would occur at the C2 carbon to yield the flav-3-ene, but we feared that the bulky phenyl group also present at the C2 position would cause the hydride attack to occur at the C4 position to yield the flav-2-ene (**204**), and this indeed proved to be the case.



Despite this it was felt that an epoxidation should still be attempted and accordingly a TPPP-mediated epoxidation was performed. Disappointingly, no epoxidation was detected by TLC, and workup of the reaction showed no epoxide present in the ^1H NMR spectrum only an unidentifiable mixture. Two possible reasons were postulated; 1) it was felt that the presence of a large number of methoxy groups may have made the olefin very reactive and so prone to over-oxidation even in the less reactive TPPP conditions, as seen in previous epoxidation attempts on compounds containing methoxy groups; or 2) it was also possible that the location of the oxygen next to the olefin may have made the epoxide inherently unstable, resulting in formation of the alcohol or diol, even though no alcohol or diol were observed in the ^1H NMR spectrum. As this had been a known possible complication, a route to the corresponding TBDMS protected ketone (**211**) had also been started. Chassaing had reported in his paper that when reacted with resorcinol (**212**) using the same conditions used in the synthesis of the methoxy-protected compound (**200**), the acid labile silicone protecting groups “fell off” during the reaction, resulting in the formation of the polyphenolic compound (**205**), which could then be protected using whatever protecting groups were required, and so eliminating the potential over-oxidation resulting from the methoxy protecting groups (Scheme 60).



Reagents and Conditions: i: TBDMS-Cl (4 eq), imidazole (4 eq), DMF, r.t. 20 h, (92%); ii: LiAlH₄ (1 eq), THF, reflux, (60%); iii: PCC (1 eq), DCM, 2 h, r.t. (85%); iv: MgBrCCH (1.1eq), THF, N₂, 0 °C, (87%); v: IBX (1.2 eq), acetone, reflux (78%); vi: HPF₆ (2 eq), AcOH (0.1 eq), 2 days (89%).

Scheme 60: Possible synthesis of polyphenolic flavylium salt (**205**).

To form the polyphenolic compound (**205**), methyl gallate (**206**) was protected using *tert*-butyldimethylsilyl chloride to yield the tri-protected compound (**207**). This compound was then reduced to the alcohol (**208**) using LiAlH₄, before being oxidized to the aldehyde (**209**) using PCC. However, in light of the flav-2-ene being produced during the reduction step, it was decided that the synthesis should be halted at this point to pursue methods which would lead more directly to the required compound.

Whilst attempting the flavylium salt synthesis route, we located another route to another potential EGCG chromene precursor (**213**).⁷⁹

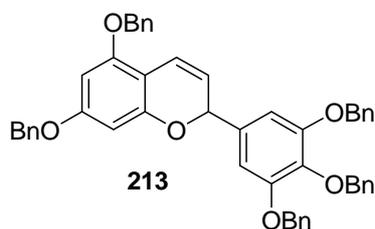
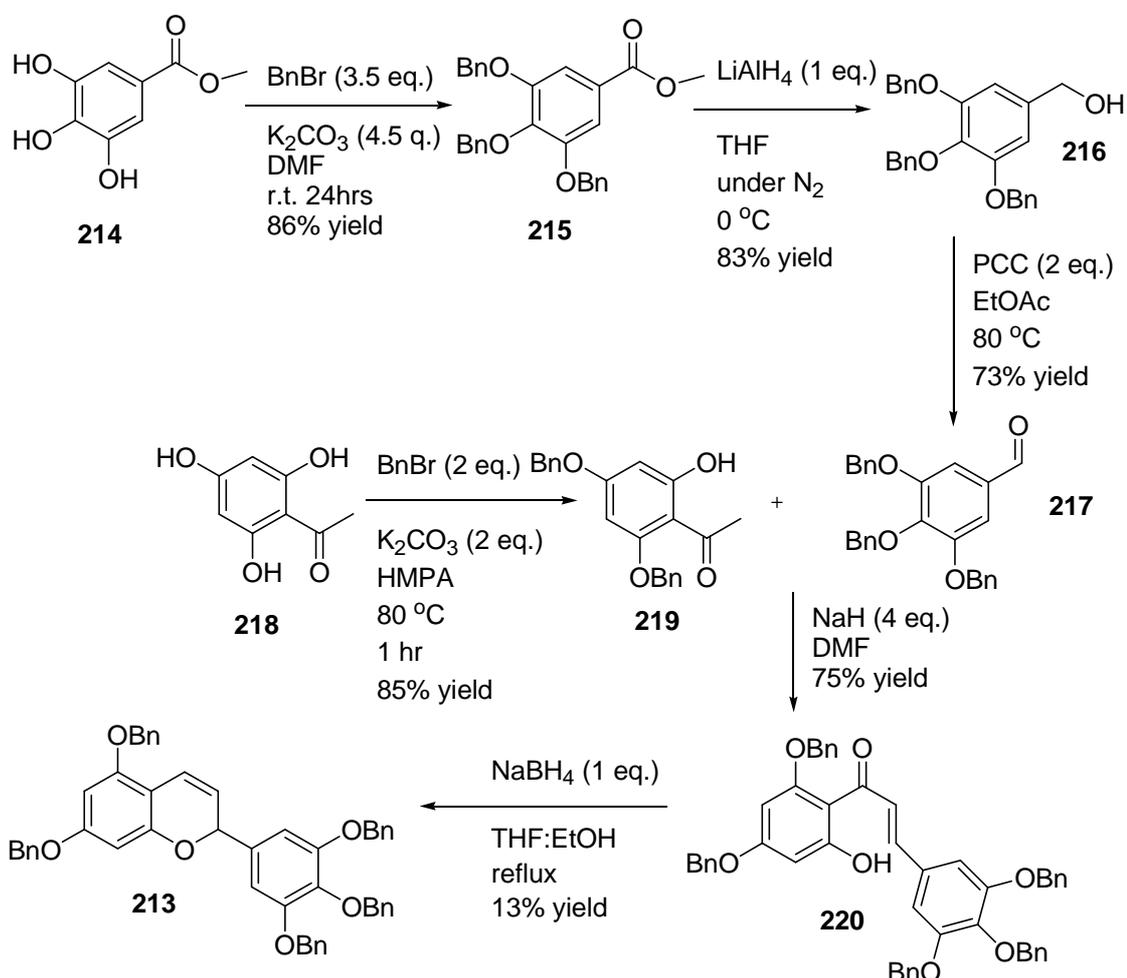


Figure 32: Potential benzyl protected EGCG chromene precursor (**213**).

In this synthetic route, a chalcone intermediate structure (**220**) is formed from reaction between a substituted hydroxyacetophenone (**219**) and a substituted benzaldehyde (**217**); the chalcone (**220**) is then condensed to form the required chromene (**213**) (Scheme 61).⁷⁹ We decided that for our synthesis of the EGCG chromene intermediate the compounds would be benzyl protected, as this protecting group would be easier to remove and is less electron donating than in the previously used methoxy protecting group.



Scheme 61: Synthesis of the EGCG precursor (**213**).

To obtain the required benzyl protected aldehyde (**217**), methyl 3,4,5-trihydroxybenzoate (**214**) was tri-benzyl protected (**215**) and reduced to the alcohol (**216**) using LiAlH_4 , both in good yields. The alcohol was then oxidized to the aldehyde (**217**) using PCC, also in good yield. The protected acetophenone (**219**) was obtained by di-benzyl protecting 2',4',6'-Trihydroxyacetophenone (**218**) using a method by Kumazawa⁸⁰ in a good yield. The protected acetophenone (**219**) and aldehyde (**217**) were then reacted together in an aldol condensation to form the chalcone (**220**). This was followed by reduction and dehydration of the chalcone with NaBH_4 . Unfortunately this final step to the product (**213**) proceeded in a very low yield (~ 20%), with the rest of the starting material remaining un-reacted. Subsequent purification by column chromatography reduced this yield even further (<10%). Despite this, enough material was collected to enable a test epoxidation to be performed, however no epoxide product could be isolated with only starting material being obtained after workup of the reaction. Interestingly, TLC of the epoxidation reaction had appeared to indicate the formation of an epoxide, with the appearance of a spot below the starting material. As epoxides are inherently unstable, during workup of the epoxidation reaction it is possible that some of the epoxide present will react further or decompose. Due to the small amount of starting material used in this epoxidation reaction it was felt that the failure to isolate any epoxide product was most likely due to the small amount of epoxide that had formed in the reaction decomposing during workup. It was decided to leave the work on EGCG at this time and concentrate on other potential natural product targets.

As noted above, the procedure by North⁷² is an efficient pathway for the formation of chromenes, allowing for many different substitution patterns and groups. A brief examination into the versatility of this reaction led to some multiple cyclisations being attempted; we felt that as well as providing potentially interesting epoxidation substrates, an insight into the scope of the cyclisation reaction would also be obtained. For example, the reaction between resorcinol and 1,1-diethoxy-3-methyl-but-2-ene, resulted in a 65% yield of the 2,2,8,8-tetramethyl-2H,8H-pyrano[3,2-g]chromene (**221**). However, steric effects appear to limit the scope of the reaction, as an attempted synthesis of 2,8-diphenyl-2H,8H-pyrano[3,2-g]chromene (**222**) from (3,3-diethoxy-propenyl)-benzene yielded only starting material.

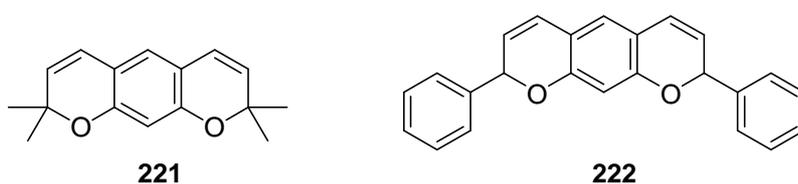


Figure 33: Interesting double cyclisations

Examination of the literature for further possible natural products which could be synthesized using the group's asymmetric epoxidation yielded two interesting papers. The first, a paper by Lee *et al.*⁸¹ showed the synthesis of (+)-decursinol from xanthelitin using a Jacobsen epoxidation. Knowing the high levels of enantioselectivity observed with our catalysts on this type of substrate, it was felt that it would be interesting to compare our organocatalytic asymmetric epoxidation with that of Jacobsen's Mn(salen) based epoxidation.

A search of the literature showed that coumarins are widely distributed in nature, both in angular (such as seselin (**223**)) and linear (such as xanthelitin (**224**)) form, and have been shown to exhibit a broad range of pharmacological profiles.⁸² Such wide-ranging biological effects include anti-bacterial,⁸³ anti-inflammatory,⁸⁴ anti-cancer⁸⁵ and anti-HIV.⁸⁶ With cancer and HIV posing serious threats to public health, the need for new and better treatments is ever more important. Coumarins have also been found to be extremely variable in structure due to the many substitution patterns that can be incorporated onto the basic skeleton, which in turn can influence biological activity.⁸²

Examples of some naturally occurring pyranocoumarins include seselin (**223**), predominantly isolated from *Plumbago zeylanica*, *Naucleopsis caloneura*, *Carum roxburghianum*, and *Citrus grandis*;⁸⁷ xanthyetin (**224**) isolated from many sources including *Zanthoxylum americanum*;⁸⁸ selinidin (**225**) isolated from *Angelica keiskei*,⁸⁴ both enantiomers of lomatin (**226**) isolated from *Lomatium nutalli* and various Umbelliferae,⁸⁹ (+)-decursinol (**227**) isolated from *Angelica gigas*,⁹⁰ and (+) *trans*-khellactone (**228**) isolated from the aerial parts of *Ligusticum elatum*⁹¹ with

each having shown interesting anti-inflammatory, cytotoxic and/or antitumour-promoting activity.

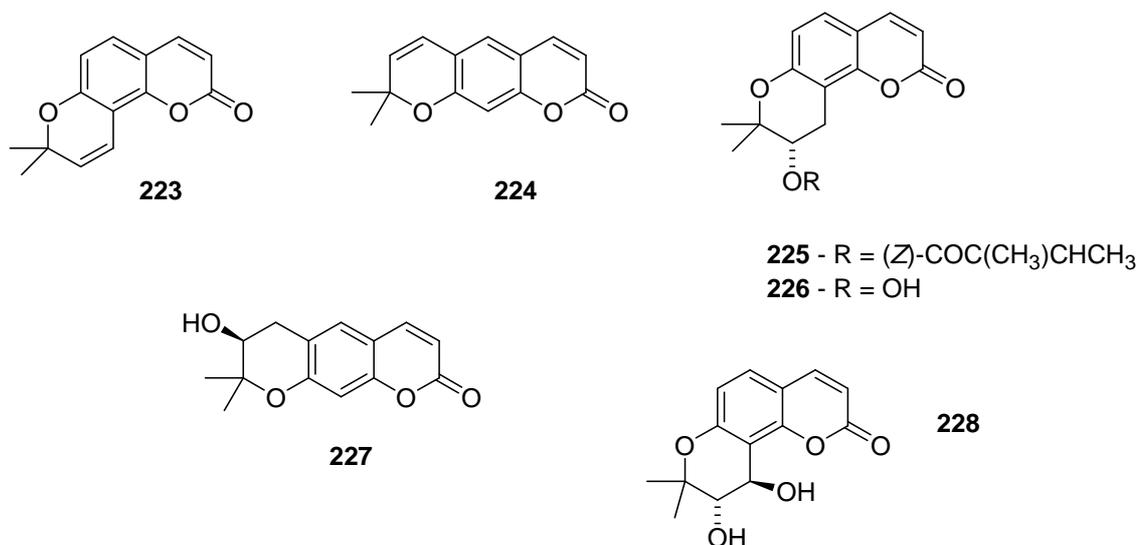
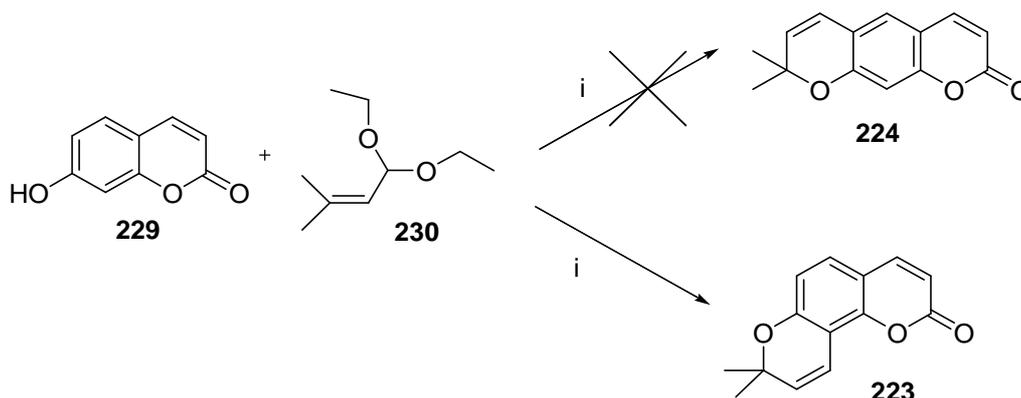


Figure 34: Some naturally occurring pyrano-coumarins.

As well as being interesting synthetic targets in their own right, we felt that an enantioselective synthesis of decursinol and its analogues from the xanthyletin core, would provide useful information about the ring-opening reaction which would be required for the eventual synthesis of EGCG.

As North's procedure had been shown to be very adaptable, the synthesis of xanthyletin (**224**) was attempted from 7-hydroxycoumarin (**229**) and 1,1-diethoxy-3-methyl-2-butene (**230**), using the conditions described previously (Scheme 62).



Reagents and conditions: (i) 3-picoline (0.25 eq), *p*-xylene (40ml), reflux.

Scheme 62: Attempted synthesis of xanthyletin by North's procedure.

However, workup of the reaction yielded not xanthyetin (**224**) but its angular structural isomer seselin (**223**), in a very good yield. Although unexpected, this proved not to be a great problem as this particular core structure is also found in many natural products such as lomatin (**226**) and khellactone (**228**).

An examination of the literature showed that lomatin (**226**) has only previously been prepared by achiral synthesis, using osthénol (**231**),⁹² 2,4-dihydroxybenzaldehyde,⁹³ visnadin (provismine) (**232**),⁹⁴ and seselin (**223**)⁸⁷ as starting materials, although the enantiomers of lomatin have been resolved.⁸⁷ Racemic *trans*-khellactone has been prepared from seselin (**223**) using *m*-CPBA followed by saponification.⁸⁶ (+)-*trans*-khellactone (**228**) has been isolated alongside the *cis* isomer in a 1:1 ratio from the alkaline hydrolysis of a number of dihydropyranocoumarins, such as peujaponisin (**233**), (-)-visnadin (**232**), and (+)-anomalin (**234**).

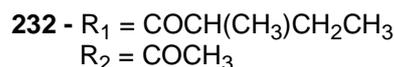
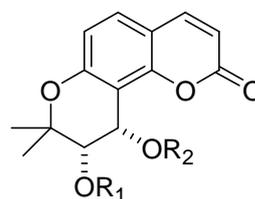
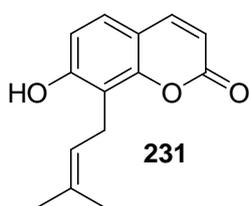
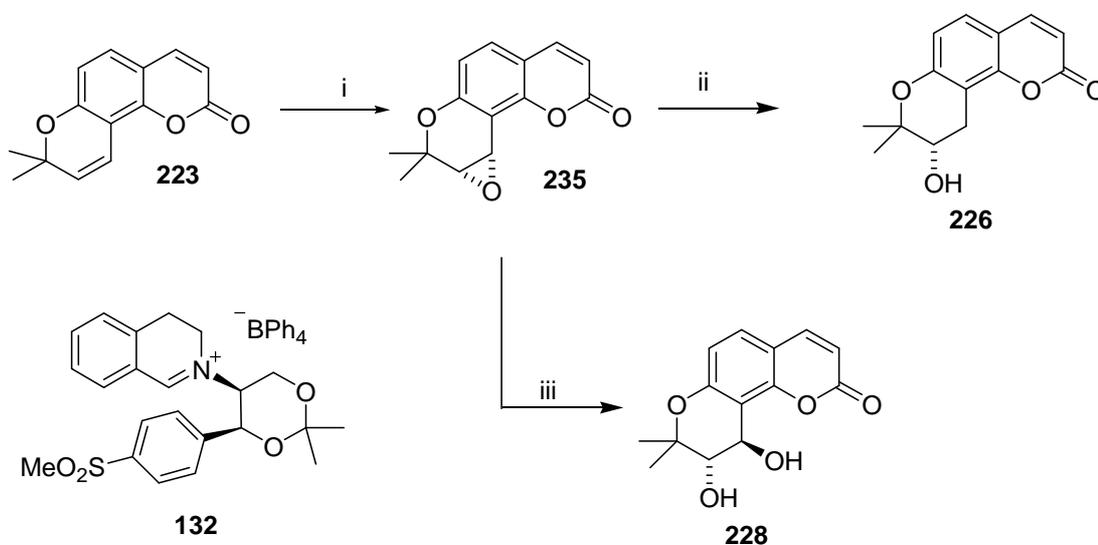


Figure 35: Known synthetic precursors of lomatin (**226**) and *trans*-khellactone (**228**).

To synthesize lomatin (**226**) the isolated seselin (**223**) was subjected to both an *m*-CPBA and asymmetric TPPP epoxidation (Scheme 63) using the conditions described previously. Pleasingly, workup of both reactions yielded the desired epoxide (**235**) in good yields.

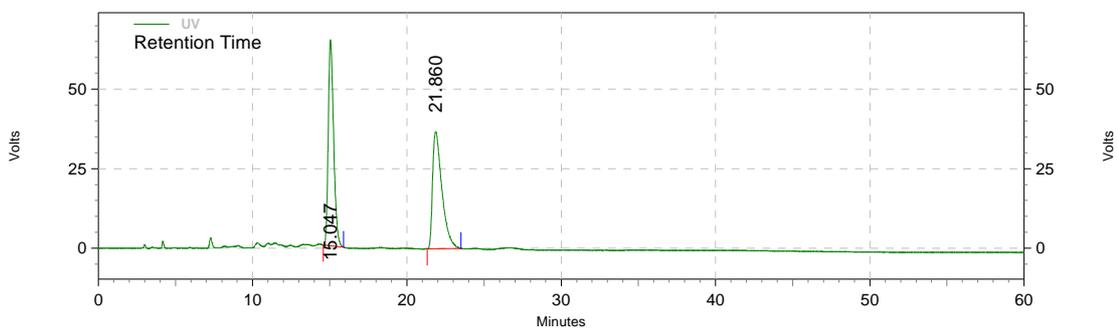


Reagent and conditions: (i) TPPP (2 eq.), cat (**132**) (10 mol%), CHCl_3 , $-30\text{ }^\circ\text{C}$, 24 h, 65%; (ii) NaBH_3CN (1 eq.), $\text{BF}_3\cdot\text{OEt}_2$, THF, $0\text{ }^\circ\text{C}$, 0.5 h, 92%; (iii) 1M aq. H_2SO_4 (5.5 eq.), acetone (1:2 ratio), r.t., 1 h.

Scheme 63: Enantioselective synthesis of (-) lomatin (**226**) and (+) khellactone (**228**).

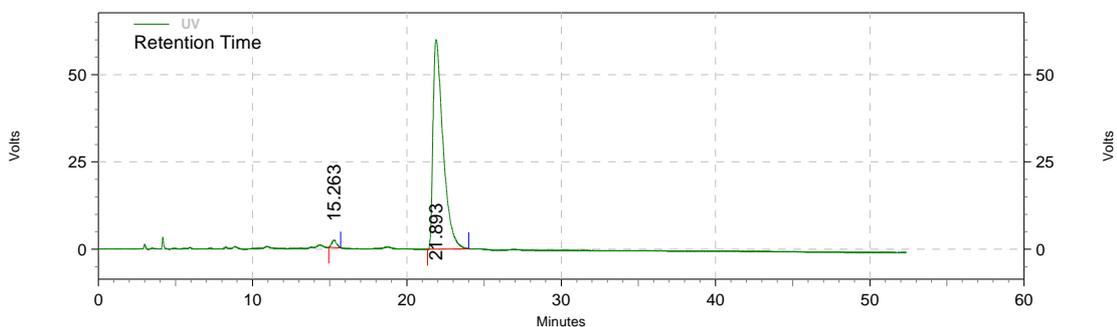
Purification of both epoxide samples enabled a HPLC trace of both to be recorded using a chiral column. The trace of the racemate (Figure 36) derived from the *m*-CPBA reaction showed the two enantiomer peaks at 15.0 and 21.8 minutes, in a 1:1 ratio. The trace from the asymmetric epoxidation (Figure 37) reaction showed the same peaks at the same times, but with an obvious selectivity for one epoxide enantiomer. Subsequent calculation of the *ee* showed that seselin had undergone epoxidation in a 97% *ee*, which was equal to the highest *ee* achieved in our group so far. Conversion of the epoxide to lomatin (**226**) was achieved by simple reductive cleavage with NaBH_3CN at $0\text{ }^\circ\text{C}$ in 92% yield. ^1H NMR and ^{13}C NMR spectroscopy confirmed the formation of lomatin, and optical rotation matched the known data for (-)-lomatin,⁸⁷ enabling the stereochemistry of the epoxide to be determined as the (+)-(3'*S*,4'*S*)-seselin epoxide.

Acid catalysed ring opening of the epoxide (**235**) yielded (+)-(3'*S*,4'*R*)-*trans*-khellactone (**228**) in a 95% yield using an acetone/1M H_2SO_4 mixture.⁹⁵



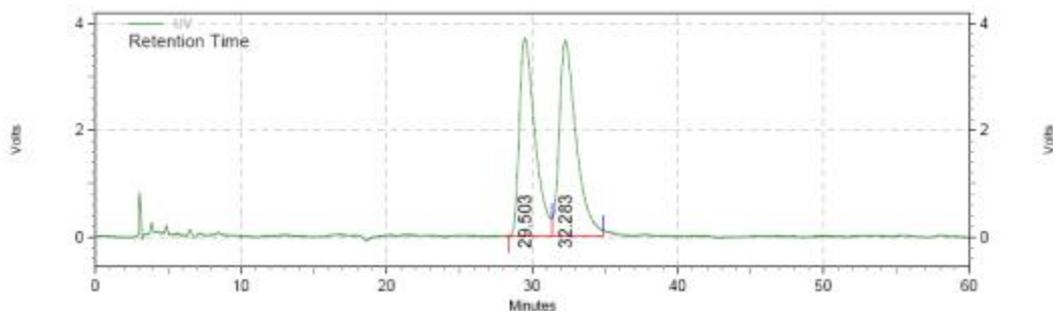
UV Results				
Retention Time	Area	Area %	Height	Height %
15.047	6291253	50.38	259924	63.79
21.860	6196574	49.62	147549	36.21
Totals	12487827	100.00	407473	100.00

Figure 36: Chiral HPLC trace of the racemic epoxidation of Seselin.



UV Results				
Retention Time	Area	Area %	Height	Height %
15.263	186713	1.69	8440	3.39
21.893	10837392	98.31	240338	96.61
Totals	11024105	100.00	248778	100.00

Figure 37: Chiral HPLC trace of the enantioselective epoxidation of Seselin.



UV Results				
Retention Time	Area	Area %	Height	Height %
29.503	1105171	48.10	14866	50.28
32.283	1192560	51.90	14701	49.72
Totals	2297731	100.00	29567	100.00

Figure 38: HPLC trace of racemic *trans*-khellactone.

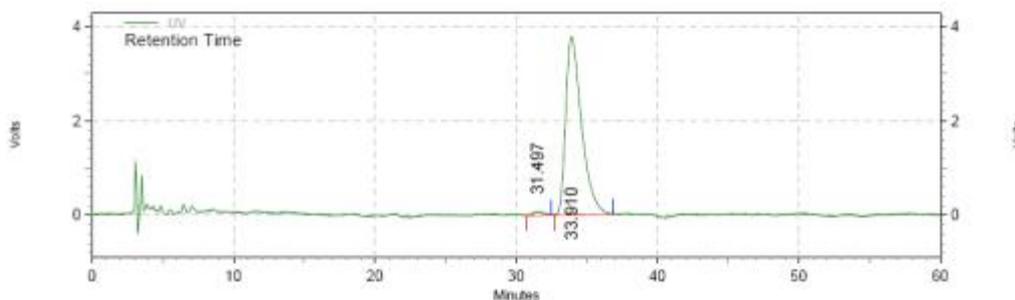
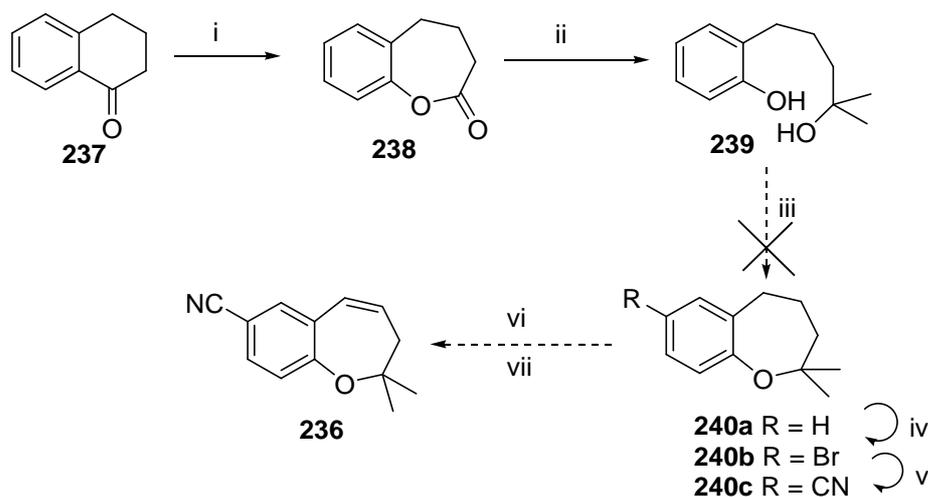


Figure 39: HPLC trace of (+)-(3'*S*,4'*R*)-*trans*-khellactone.

UV Results				
Retention Time	Area	Area %	Height	Height %
31.497	17965	1.50	327	2.12
33.910	1176008	98.50	15097	97.88
Totals	1193973	100.00	15424	100.00

The second paper of interest was a paper by Buckle,⁷⁵ which provided another possible epoxidation substrate. Buckle was looking at analogues of the known antihypertensive, Levchromakalim, and during the investigations the group had synthesized a seven-membered analogue of Levchromakalim (**236**). As Levchromakalim had previously been enantioselectively synthesized within the group

using an asymmetric epoxidation, and it had been this epoxidation which had resulted in the highest *ee* using an oxaziridinium based catalyst at that time, it seemed both interesting and logical to apply the same epoxidation technique to the seven membered ring analogue. A synthesis of the seven membered ring compound was proposed using the same route as Buckle, in 7 steps from alpha-tetralone, as shown in Scheme 64.



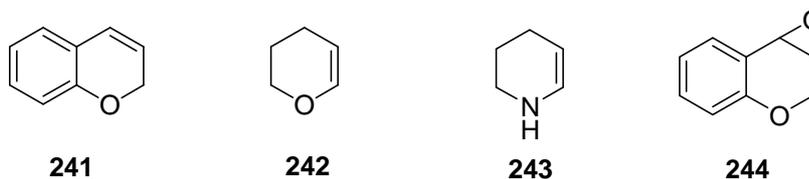
Reagents and Condition: i: *m*-CPBA (2 eq), CHCl₃, r.t, 5 days, ii: MeMgI, Et₂O; iii: PTSA, toluene, reflux, iv: Br₂, MeCO₂H, MeCO₂Na, v: CuCN, DMF, reflux, vi: NBS, CCl₄, vii: DBN, THF, r.t.

Scheme 64: Route to a seven membered chromene analogue.

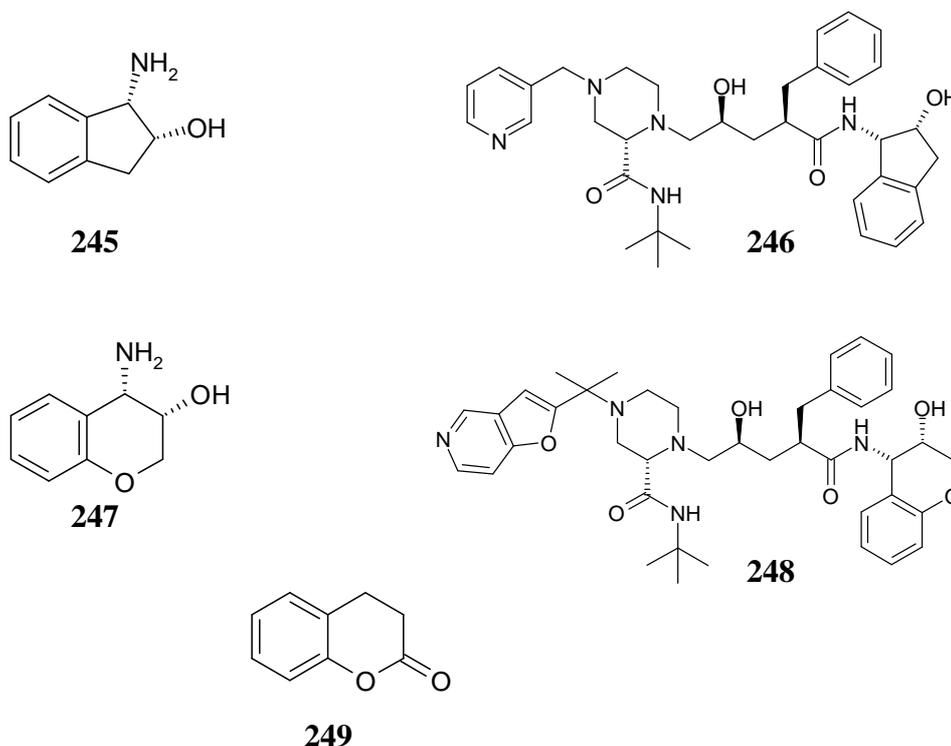
This route began with the Baeyer-Villiger oxidation of alpha-tetralone (**237**) with *m*-CPBA, which yielded the required lactone (**238**) in an 83% yield. The lactone was then reacted with MeMgI to yield the hydroxyl phenol (**239**) in a 96% yield. However, attempted dehydration with PTSA did not yield the expected cyclised product (**240a**) only an unidentifiable mess. Consequently, due to time constraints we decided to leave the synthesis of this compound to concentrate on other potential epoxidation substrates, with the hope of returning to this compound at a later date.

For a continued examination into further possible applications of the asymmetric iminium salt epoxidation, we felt that it would be interesting to examine the scope of compounds that could be used in the epoxidation reaction, particularly those which could then provide simple routes to normally less accessible substrates, such as

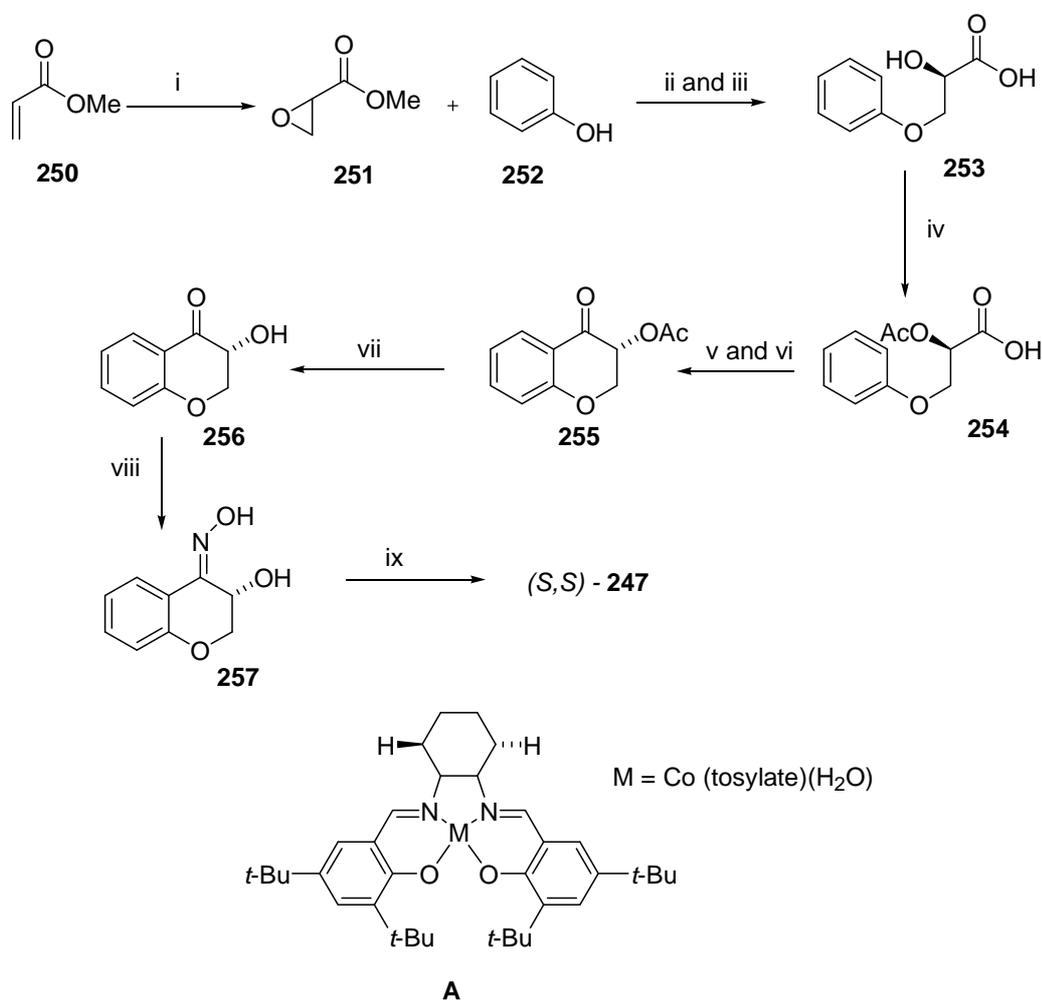
further chromene-based compounds, hydroxy-pyran based compounds or enamine-based compounds. In this vain it was decided to examine three other substrates. The chromene (**241**), the 3,4-Dihydro-2H-pyran (**242**) and the enamine analogue (**243**).



The chromene (**241**) was chosen as a target because of the potential application of its epoxide (**244**). It has recently been found that replacement of the *cis*-aminoindanol (**245**), as found in Crixivan (**246**), with the related *cis*-aminochromanol (**247**), affords compounds, such as (**248**) which have been found to have greater potency against both the wide-type (NL4-3) virus and PI-resistant HIV strains,⁹⁶ and although it is possible to synthesize the *cis*-aminoindanol (**245**) *via* a Jacobsen epoxidation and subsequent Ritter-type reaction,⁹⁷ the use of the same synthetic route using the corresponding chromene (**241**) results in formation of the coumarin (**249**).



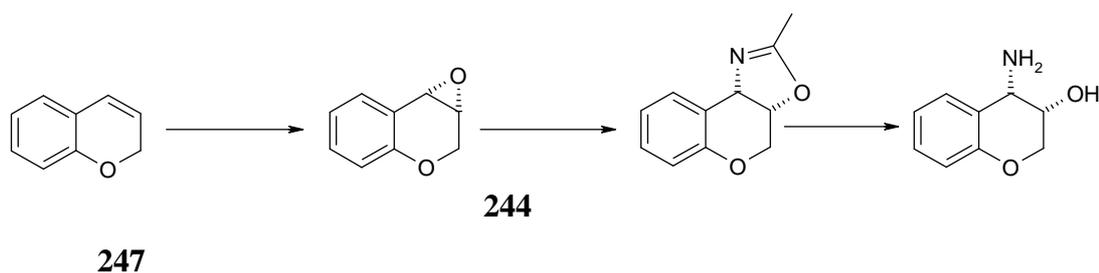
Previously, the enantioselective synthesis of the *cis*-aminochromanol (**247**) has required many steps, such as that used by Hansen in 2001 (Scheme 65).⁹⁸



Reagents and conditions: (i) NaOCl (aq); (ii) catalyst (A) (6.7 mol%); (iii) KOH, H₂O; (iv) AcCl, MTBE; (v) Oxalyl chloride, DMF, DCM; (vi) AlCl₃, DCM -15 °C; (vii) LiOOH, -15 °C; (viii) (NH₃OH)SO₄, NaOAc, THF/H₂O; (ix) H₂, Pd/C, HBr, MeOH, 5 °C.

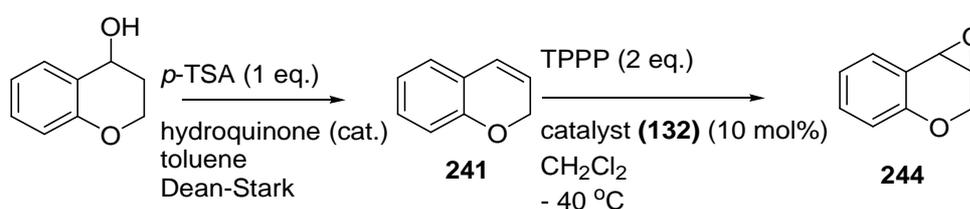
Scheme 65: Hansen's synthesis of aminochromanol (**247**).

We felt that this could be significantly reduced if an epoxidation of the starting material could be achieved as suggested in Scheme 66.



Scheme 66: Potential synthesis of *cis*-aminochromanol (**247**) using asymmetric epoxidation.

Chromene (**241**) was synthesized by dehydration of 4-chromanol using *p*-TSA in toluene yielding the chromene in an 86% yield. Epoxidation of the chromene (**241**) was then attempted using the TPPP conditions at $-40\text{ }^{\circ}\text{C}$, whilst being monitored by TLC (Scheme 67). After 24 hours another spot appeared on the TLC below the original alkene starting material, indicating the formation of the epoxide. Once the starting material spot had completely disappeared the reaction was diluted with cold diethyl ether to precipitate excess TPPP in the reaction. The solution was then filtered through celite[®] to remove the precipitated TPPP and the catalyst, and the filtrate was then reduced by rotary evaporation to yield the epoxide (**244**) as a clear oil which was immediately submitted for ^1H NMR, as it was believed to be likely that the epoxide would be highly unstable.



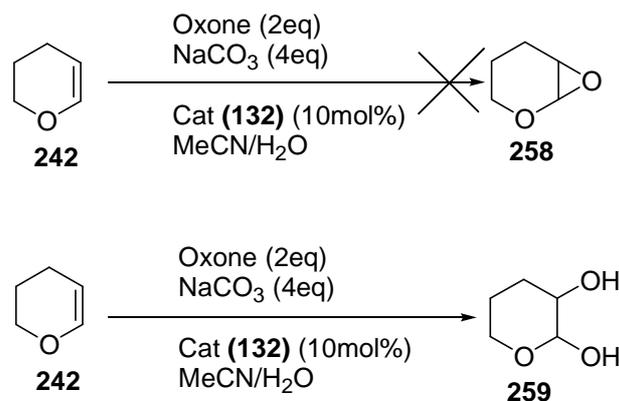
Scheme 67: Synthesis and subsequent epoxidation of chromene substrate.

Pleasingly, ^1H NMR confirmed the formation of the epoxide (**244**) by the disappearance of the alkene protons from 5.87 and 6.53 ppm and the appearance of epoxide protons at 3.43 and 3.78 ppm. Work on completing the synthesis of the *cis*-aminochromanol (**247**) is currently being continued within the group.

As mentioned previously, we felt that 3,4-dihydro-2H-pyran (**242**) would provide another interesting initial test substrate, as any epoxide formation would provide a selective route to functionalised tetrahydropyran derivatives, which would be very advantageous as many natural products have been found which contain tetrahydropyran moieties.

The epoxidation reaction was first attempted using the Page group's Oxone[®]-driven conditions (Scheme 68), as these were known to provide more rapid reactions, and we felt that using these conditions would enable a quick initial result to be obtained

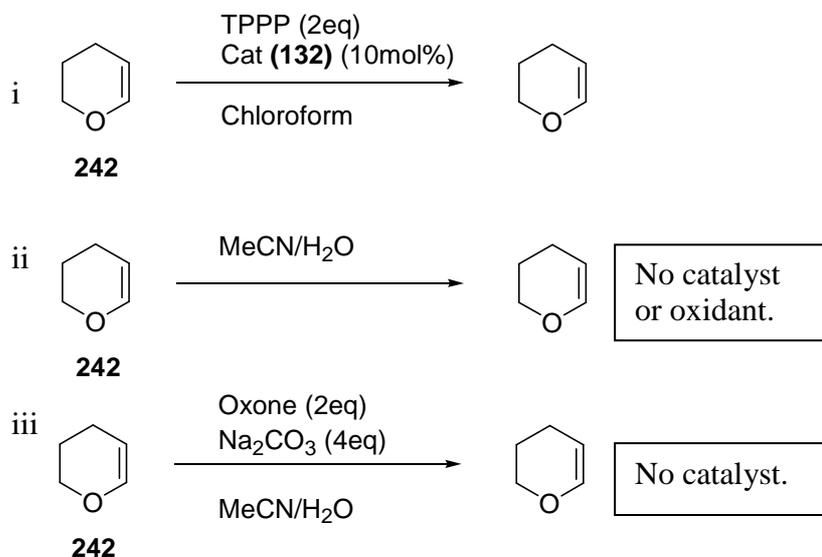
to determine the potential of the reaction. TLC analysis of the reaction mixture showed, what appeared to be, full conversion to a new compound after only 3 hours.



Scheme 68: Attempted epoxidation of 3, 4-dihydro-2H-pyran.

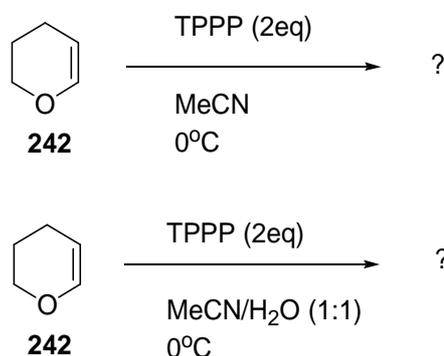
However, workup of the epoxidation reaction and subsequent analysis by FT-IR, ¹H and ¹³C NMR spectroscopy showed the formation of the diol (259) not the epoxide (258). The formation of the diol versus the epoxide is likely to be due to one of two reasons, 1) water had added across the double bond in a hydration reaction, or 2) the epoxide had indeed formed but was unstable, and ring opened during workup of the reaction mixture.

To examine whether water had indeed added to the double bond, it was felt that the reaction should be carried out under our non-aqueous TPPP conditions using chloroform (Scheme 69, part i). Interestingly, this reaction showed no formation of any product by TLC when performed at -40 °C, though this could also be due to the TPPP not being reactive enough with this substrate at this low temperature. To investigate whether epoxidation followed by subsequent ring opening was responsible for the formation of the diol (259), two blank reactions were also carried out (Scheme 69 parts ii and iii). One contained only water and solvent, and would show if the presence of water was playing a part in the formation of the diol. The other was missing the catalyst, and would show if the oxidant alone could be responsible for the formation of the diol. Interestingly, neither of these reactions showed any reaction, indicating that it was likely that epoxidation, followed by ring opening was most likely to be responsible for the formation of the diol.



Scheme 69: TPPP epoxidation of 3,4-dihydro-2H-pyran (**242**), and two blank reactions examining the importance of the catalyst.

To further investigate this, two further epoxidation reactions were performed on the pyran substrate (**242**), one under anhydrous conditions with anhydrous acetonitrile in place of chloroform in the TPPP-driven reaction at 0 °C instead of -40 °C and one under aqueous conditions using a mixture of water:acetonitrile (1:1) as a solvent (Scheme 70). Both reactions were monitored carefully and after 12 hours, TLC analysis showed the formation of a product in both of the reactions, though the spot in the reaction containing the water:acetonitrile as a solvent was lower than that in the anhydrous reaction, indicating that in this reaction either the diol had formed directly or the epoxide was being ring opened due to the presence of water in the reaction. However, subsequent workup of both of the reaction mixtures and subsequent analysis by ^1H NMR spectroscopy showed only an unidentifiable mess in each case.

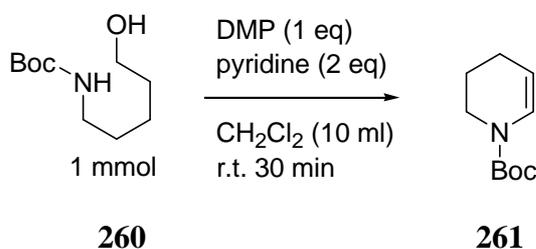


Scheme 70: Comparison of anhydrous and non-anhydrous TPPP epoxidations performed at 0 °C.

It was concluded from these investigations that it was most likely that the epoxide had indeed formed in the reaction, but was too unstable to be isolated without either reaction with water to yield the diol or decomposition to an unidentifiable product.

As a complementary investigation to the 3,4-dihydro-2H-pyran epoxidations, we also decided to investigate analogous enamine substrates (**243**). No exact enamine analogues of 3,4-dihydro-2H-pyran were available commercially, but the literature provided various routes to the required compounds.

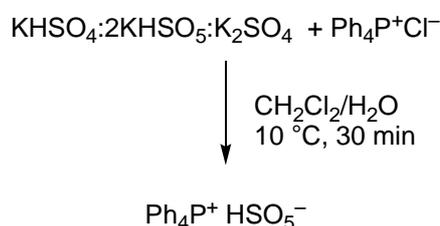
The route of Hu *et al.*⁹⁹ derived a Boc protected enamine compound (**261**) from a simple cyclisation of Boc protected-hydroxycarbamate (**260**), with an *in situ* oxidation using Dess-Martin periodinane (DMP) (Scheme 71).



Scheme 71: Hu's synthesis of a Boc protected enamine

We felt that due to the instability of DMP, the reaction would be best attempted with the DMP precursor IBX. It was at this point that an interesting side investigation

appeared. A recent paper by Vinod¹⁰⁰ had shown that IBX could be generated catalytically *in situ* using 2-iodobenzoic acid and Oxone[®] and used in the generation of carboxylic acids and ketones. As our group had recently shown that the oxidant tetraphenylphosphonium mono-peroxysulfate (TPPP), which is derived from Oxone[®] by simple counterion exchange with tetraphenyl phosphonium chloride (Scheme 72), can act as an Oxone[®] equivalent in non-aqueous organic solvents,^{52,53,57} we felt that it would be interesting to test TPPP as an oxidant for catalytic IBX production in the oxidation of alcohols. The use of TPPP could have possible further implications as, unlike Oxone[®], it does not require water for solubility in organic solvents. Therefore, we hoped that being able to perform the reactions in the absence of water would result in only the formation of the aldehyde from primary alcohols, whereas Vinod's conditions using Oxone[®] has resulted in production of the acid.



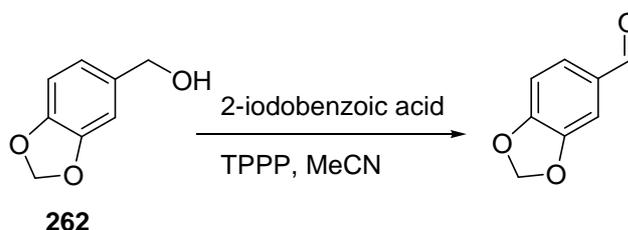
Scheme 72: The formation of TPPP from Oxone[®].

It was first necessary to identify the optimum molar ratios of 2-iodobenzoic acid and TPPP required to effect complete conversion in the oxidation of alcohols. Santagostino had originally reported the use of 1.3 molar equivalents of Oxone[®] in the formation of IBX from 2-iodobenzoic acid.¹⁰¹ For a direct comparison to Vinod's original paper, acetonitrile was chosen as the reaction solvent, although in this case the reaction would be conducted in the absence of water in an attempt to synthesize the corresponding aldehydes instead of the carboxylic acids as shown in the original paper.

Oxone[®] (2KHSO₅·KHSO₄·K₂SO₄) contains twice the molar active potassium persulfate as does TPPP (Ph₄P⁺ HSO₅⁻), and with this in mind the initial reaction was carried out with 2.6 equivalents of TPPP and 0.5 equivalents of 2-iodobenzoic acid, using piperonyl alcohol (**262**) as the test substrate (Scheme 73). Pleasingly,

formation of the corresponding carboxylic acid was not observed, and the reaction proceeded to 75% conversion to the aldehyde. In the presence of 3 equivalents of TPPP, the oxidation proceeded to 100% conversion to the corresponding aldehyde, again with no trace of the carboxylic acid.

We then decided to reduce the quantity of 2-iodobenzoic acid from 0.5 equivalents to 0.3 and 0.1 to find the minimum loading that would allow the reaction to proceed (Table 14).



Scheme 73: Test oxidation on piperonyl alcohol (**262**).

2-Iodobenzoic Acid (equiv)	TPPP (equiv)	Time/h	Yield/% (Conversion) R = H	Yield/% R = OH
0.5	2.6	24	75 (75)	0
0.5	3	6	92 (100)	0
0.3	3	6.5	91 (100)	0
0.1	3	8	95 (100)	0

Table 14: Oxidation of piperonyl alcohol (**262**) with varying amounts of 2-iodobenzoic acid

The investigation next centred around the optimization of reaction solvents. Acetone and THF were discounted immediately due to previous reports of *in-situ* dioxirane and γ -butyrolactone formation respectively from oxidation of the solvent.¹⁰⁰ Previous work within the group has found that TPPP has good solubility in acetonitrile, dichloromethane and chloroform;^{52,53,57} and as such these three solvents were investigated first in the oxidation of piperonyl alcohol (**262**), additionally 1,2-dichloroethane, ethyl acetate and 4-methylpentan-2-one were also investigated, using

2-iodobenzoic acid (0.1 equiv) and TPPP (3 equiv). The results are shown in Table 15.

Solvent	Time/h	Yield/%
Chloroform	12	89
Acetonitrile	6	81
Dichloromethane	8	78
1,2-Dichloroethane	4.5	89
Ethyl acetate	16	72
4-Methylpentan-2-one	15	81

Table 15: Effect of solvent variation of the oxidation of piperonyl alcohol (**262**).

The reaction was found to proceed effectively in acetonitrile and 1,2-dichloroethane (1,2-DCE), with 1,2-dichloroethane permitting particularly ready isolation of clean product as all reaction by-products were insoluble in the cooled reaction medium. Simple addition of diethyl ether to precipitate the excess TPPP, followed by filtration through a pad of celite, was sufficient to allow isolation of the products.

The reactions performed in ethyl acetate and 4-methylpentan-2-one proceeded to completion only after greatly extended reaction times, perhaps as a result of the poor solubility of TPPP in these solvents. As a direct comparison with the previous study using Oxone[®] by Vinod,¹⁰⁰ the reaction was also tested in aqueous acetonitrile (50:50), and interestingly, was found to proceed well with no formation of the carboxylic acid observed, in contrast to the Oxone[®]-driven process.

Having established optimum conditions for the reaction, a variety of alcohols (**262-268**), both primary and secondary, were oxidized by *in-situ* generation of catalytic IBX in the presence of three equivalents of TPPP as stoichiometric oxidant, in the more successful solvents (Table 16). The protocol appears widely applicable, and both primary and secondary alcohols are cleanly oxidized to their corresponding carbonyl compounds (**269-275**). Work-up and purification was carried out as described above.

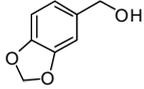
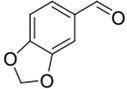
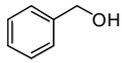
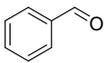
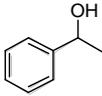
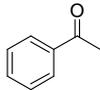
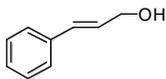
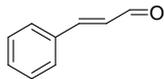
Substrate	Product	Solvent	Time/h	Yield/%
 262	 269	MeCN	6	81
		1,2-DCE	4.5	89
		2-methyl-pentan-4-one	12	71
 263	 270	MeCN	5.5	85
		1,2-DCE	4	89
		2-methyl-pentan-4-one	16	74
 264	 271	MeCN	3.5	91
		1,2-DCE	3	93
		2-methyl-pentan-4-one	12	82
 265	 272	MeCN	7.5	77
		1,2-DCE	6	76
		2-methyl-pentan-4-one	10	71
 266	 273	MeCN	8	85
		1,2-DCE	7	87
		2-methyl-pentan-4-one	-	-
 267	 274	MeCN	11.5	74 ^a
		1,2-DCE	12	79 ^a
		2-methyl-pentan-4-one	-	-
 268	 275	MeCN	5	91
		1,2-DCE	4.5	92
		2-methyl-pentan-4-one	11	87

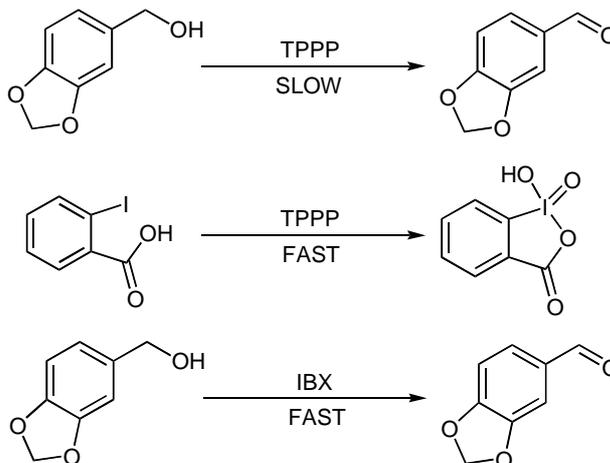
Table 16: Oxidation of a range of alcohols.

A reaction was also performed in the absence of 2-iodobenzoic acid to test any background oxidation from the oxidant alone. Interestingly, treatment of piperonyl

alcohol (**262**) with three equivalents of TPPP in a 1,2-dichloroethane solution did show slight formation of the aldehyde (*ca.* 5%) after stirring for three hours (TLC monitoring). For comparison, in the added presence of 2-iodobenzoic acid (0.1 equiv), almost complete conversion was observed after three hours in dichloroethane solution.

Hajipour has reported that benzyltriphenylphosphonium peroxymonosulfate is an oxidant capable of oxidizing alcohols to their corresponding carbonyl compounds, but in that case a Lewis acid is required for the reaction to proceed.¹⁰² We found that completion of the reaction in the absence of 2-iodobenzoic acid was only achieved when more than six equivalents of TPPP were used, and, even then, the reaction was substantially slower, at 10 hours, for piperonyl alcohol as substrate.

We therefore conjectured that during the reaction, 2-iodobenzoic acid is oxidized much more rapidly by TPPP, presumably to IBX, than the alcohol is, and that it is the IBX so generated which oxidizes the alcohols in the catalytic system (Scheme 74).



Scheme 74: Suggested reasoning for the change in reactivity when 2-iodobenzoic acid is not present.

Oxidation with TPPP (6 equiv) in the absence of 2-iodobenzoic acid was repeated under the same conditions with all of our test substrates, and each showed that, although carbonyl formation did indeed occur, the reaction time was roughly double that observed when 2-iodobenzoic acid (0.1 equiv) was present (Table 17).

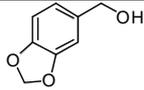
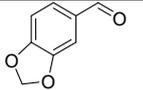
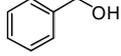
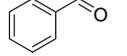
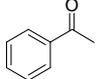
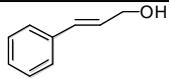
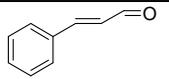
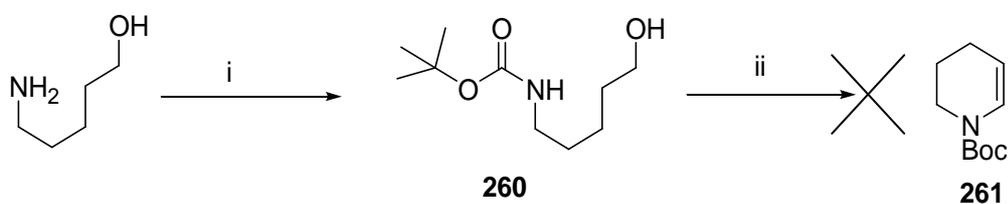
Substrate	Product	MeCN		DCE	
		Time /h	Yield %	Time /h	Yield %
 262	 269	10	84	7.5	82
 263	 270	9	75	9.5	79
 264	 271	8	81	6.5	87
 265	 272	10	76	10.5	71
 266	 273	8.5	65	8	68
 268	 275	9.5	83	8	79

Table 17: Results of the oxidation of alcohols by TPPP.

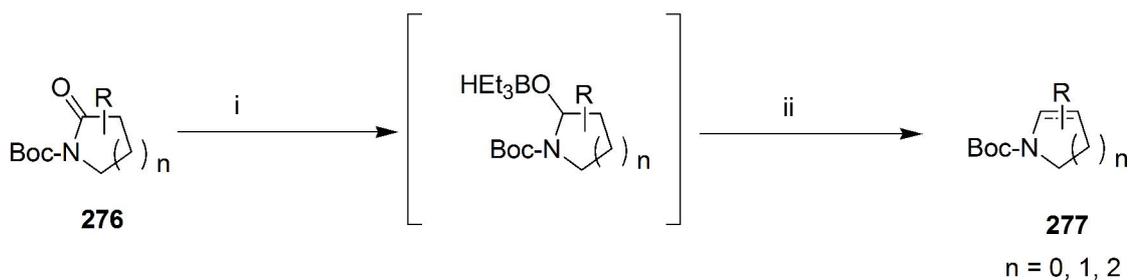
Unfortunately, when this new TPPP-mediated catalytic oxidation was attempted on the required Boc protected-hydroxycarbamate (**260**) (Scheme 75), in this case a BOC protected 5-amino-pentan-1-ol, the cyclic enecarbamate product was not isolated, with only starting material being recovered. We felt that this may be due to IBX not being a reactive enough oxidant and that ultimately the reaction may only proceed using Dess-Martin Periodinane (DMP).



Reagents and Conditions: i: Boc Anhydride (2 eq), H₂O:dioxane (1:1), NaOH (1N, 10 ml); ii: 2-iodobenzoic acid (0.2 eq), TPPP (3 eq), MeCN, r.t.

Scheme 75: Attempted cyclic enecarbamate formation using the procedure by Hu *et al.*⁹⁹

Despite this disappointment another paper by Yu¹⁰³ and co-workers was found, which reported a possible route to cyclic enecarbamates (**277**), this time from lactam carbamates (**276**). The one pot procedure uses ‘Super-Hydride’ (lithium triethylborohydride), followed by diisopropylethylamine (DIPEA), DMAP and trifluoroacetic anhydride (Scheme 76).



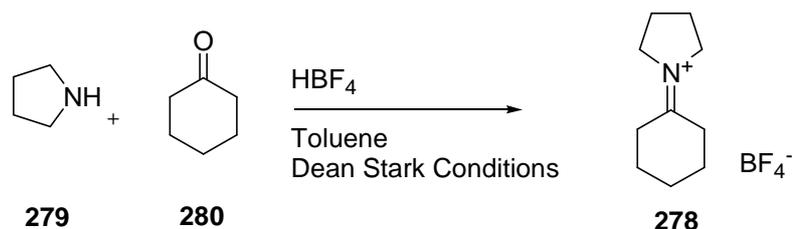
Reagents and Conditions: i: LiEt₃BH (1.1 eq), PhMe, -70 °C; ii: TFAA/DIPEA, cat. DMAP, -70 °C to r.t.

Scheme 76: Yu’s route to cyclic enecarbamates.

However, despite repeated attempts no cyclic enecarbamate was ever isolated in our hands. Therefore, due to time constraints it was decided to leave this work at this time with the hope that it could be returned to in the future.

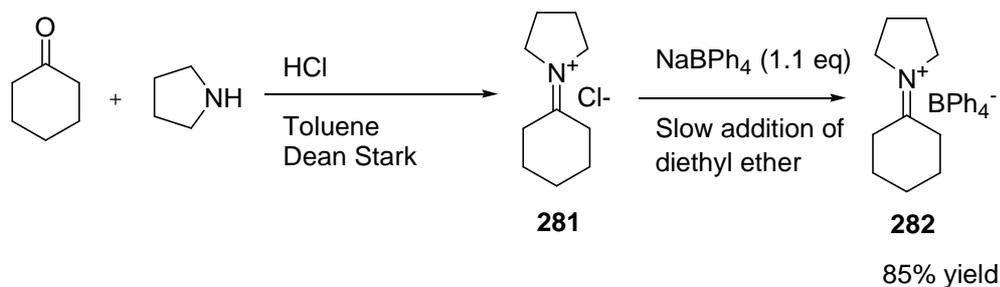
As well as looking into the applications of the iminium salt epoxidation, the research project also briefly examined the area of exocyclic catalysts, as opposed to the cyclic ones already in use within the group, such as those described by Armstrong⁴³ and Komatsu.⁴⁶ In the past the group has felt that these are unpredictable and temperamental, due to the possibility that hydrolysis of the catalyst could occur when used under aqueous conditions. Due to our recent development of non-aqueous TPPP conditions, it was felt that it would be prudent to re-examine this type of catalyst. Both Aggarwal¹⁹ and Yang²² have shown that simple amines can promote epoxidation under the Oxone[®] conditions, with pyrrolidine derivatives giving the best conversions, acting as phase transfer catalysts and Oxone[®] activators. We therefore felt that exocyclic catalysts based on pyrrolidine could potentially provide efficient epoxidation catalysts.

Both Armstrong and Komatsu had prepared catalysts from a cyclic amine and a carbonyl compound, by simple condensation and we felt this would be the best place to start. The simplest catalyst (**278**) was prepared by Komatsu from pyrrolidine (**279**) and cyclohexanone (**280**), under Dean Stark conditions, using tetrafluoroboric acid (Scheme 77).



Scheme 77: Komatsu's method for the preparation of exocyclic catalysts.

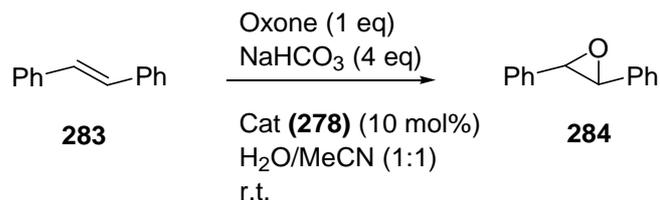
However, when we attempted to repeat this in a test reaction, it was not possible to isolate a stable crystalline product from the reaction. We therefore decided that it may be simpler to form the HCl salt of the compound (**281**) and then perform a counter-ion exchange with NaBPh₄. This was carried as shown in Scheme 78, and, upon addition of diethyl ether, the product (**282**) precipitated from the reaction as a white solid in an 85% yield.



Scheme 78: Procedure used for the formation of the exocyclic iminium salt catalyst.

As it was possible that the enamine might have been formed instead of the required imine, the analytical data was closely examined. Examination of the FT-IR showed no enamine peak and ¹H and ¹³C NMR spectrum showed that the structure was completely symmetrical with the presence of the expected three CH₂ groups on the cyclohexanone ring. It was therefore concluded that no enamine was present.

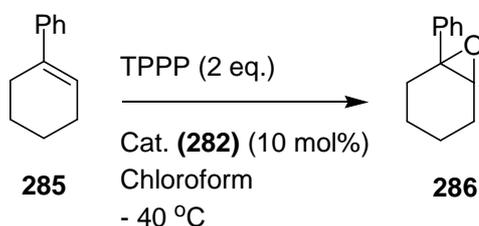
Once the catalyst had been synthesized we then wished to carry out some epoxidation reactions. Komatsu had shown his catalyst (**278**) could epoxidise *trans*-stilbene (**283**) to the corresponding epoxide (**284**) in an 88% yield, under the conditions shown below (Scheme 79).⁴⁶



Scheme 79: Komatsu's epoxidation conditions using catalyst (**278**).

As a comparison this reaction was repeated with the newly synthesized catalyst (**282**), giving a comparable 80% yield in 17 hours. The catalyst was then tested under the Oxone[®] conditions used within the Page group,^{52,53,57} except that the reaction was performed at room temperature so as to be comparable to the Komatsu reaction. Pleasingly this resulted in the reaction proceeding in a 62% yield in a shorter 8 hour time period. Using the same conditions, the temperature was then decreased to the usual 0 °C and it was found that the reaction proceeded at a slightly slower rate, giving only a 55% yield in the same 8 hour time period.

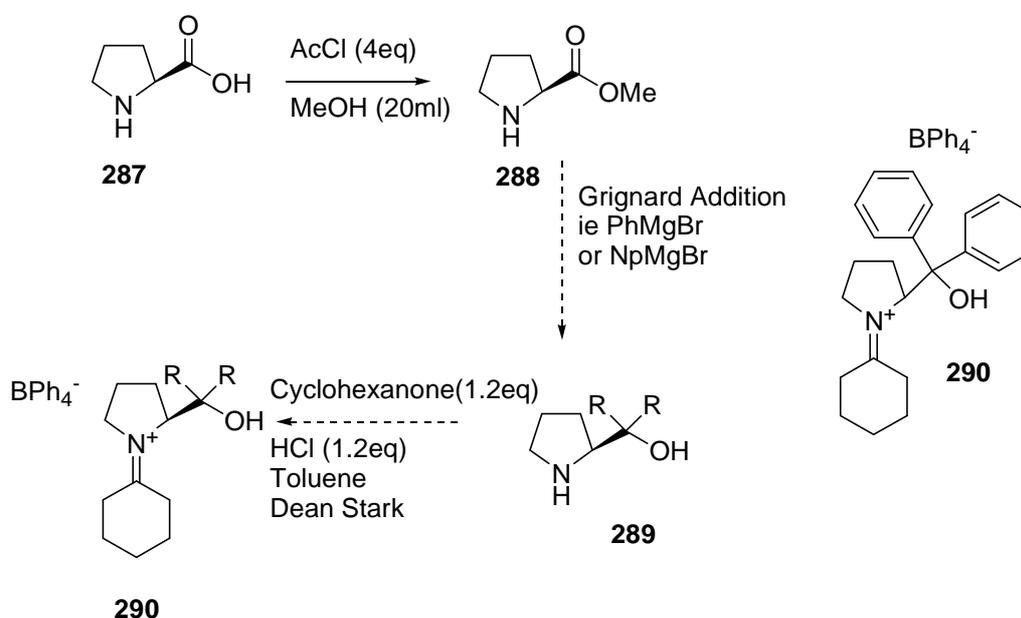
With this confirmation of catalyst activity, an epoxidation under the TPPP conditions was attempted, however when *trans*-stilbene (**283**) was used under these conditions, none of the epoxidised compound (**284**) could be detected even after 48 hours. This may mean that the reactivity of TPPP at -40 °C is insufficient with *trans*-stilbene, so the reaction was repeated this time using the slightly more reactive 1-phenylcyclohexene (**285**) as the substrate (Scheme 80). Pleasingly, the reaction proceeded well giving a 55% yield of the epoxide (**286**) after 8 hours at -40 °C.



Scheme 80: TPPP epoxidation using exocyclic catalyst (**282**).

Although the conditions of the racemic epoxidation still required some optimization it was decided to start work on a possible chiral derivative. The most obvious structure to use would be similar to the pyrrolidine based catalyst used in the racemic epoxidations, as such a catalyst based on *L*-(-)-proline (**287**) was chosen.

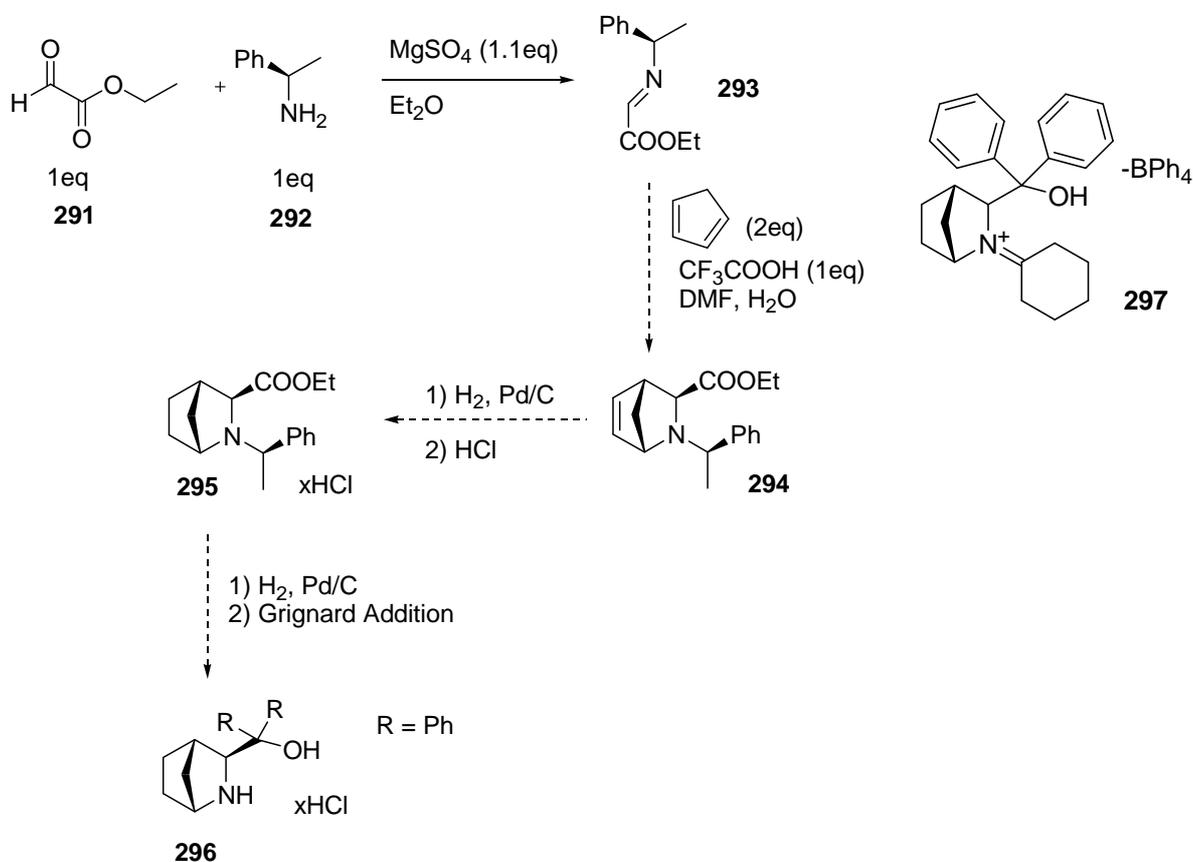
We decided to attempt the synthesis of chiral catalyst 1-cyclohexylidene-2-(hydroxydiphenylmethyl)pyrrolidinium tetraphenylborate (**290**) by taking *L*-(-)-proline (**287**) and converting it to its methyl ester (**288**) as shown in Scheme 81. A double Grignard addition could then be performed (**289**) with various R groups enabling the steric bulk of the catalyst to be varied, which in turn was hoped to enable the enantioselectivity to be enhanced. After the Grignard addition, the free amine could then be condensed in a similar way as previously with an aldehyde or ketone, to give the required catalyst (**290**) (Scheme 81).



Scheme 81: Formation of 1-Cyclohexylidene-2-(hydroxy-diphenyl-methyl)-pyrrolidinium tetraphenylborate (**290**).

Unfortunately, despite the conversion of *L*-proline to the methyl ester proceeding well, subsequent Grignard additions all proved unsuccessful, resulting only in the re-isolation of the starting material. This was probably due to moisture contamination in the commercially available Grignard which was used. Future work will use an *in-situ* generation of the Grignard to minimize any moisture contamination.

It was also decided to look at a possible catalyst based on an azo-bicyclic structure which was being examined in the group as a potential catalyst ligand. For the synthesis of the azo-bicyclic based catalyst (**297**) it was decided to start by forming the imine (**293**) from ethyl glyoxylate (**291**) and (R)-1-phenylethylamine (**292**), it was then envisaged that a Diels Alder reaction could then be performed using cyclopentadiene, to give the azo bicyclic structure (**294**) shown in Scheme 82. A review of the literature has shown that this compound could then be hydrogenated and converted to the HCl salt (**295**),¹⁰⁴ at which point it would then be possible to perform a double Grignard addition and remove the protecting group to yield the amine (**296**). This could then be condensed with a ketone or aldehyde to give the catalyst (**297**) (Scheme 82).



Scheme 82: Formation of 2-Cyclohexylidene-3-(hydroxy-diphenyl-methyl)-2-azonia-bicyclo[2.2.1]heptane tetraphenylborate (**297**).

The initial imine (**293**) formation between ethyl glyoxylate (**291**) and (R)-1-phenylethylamine (**292**) proceeded well in a good yield, but the subsequent Diels-Alder reaction with cyclopentadiene proved difficult, with the resulting product

being difficult to purify. Future work will look to optimize the Diels-Alder reaction to enable enough product to be obtained to continue the synthesis of the amine for the catalyst (**297**).

2.1 Conclusions

This research has investigated potential future applications of the Page group's asymmetric epoxidation, studying both asymmetric natural product synthesis and new methodology to which the group's catalysts and conditions could be applied.

Initially, compounds containing nitrogen were investigated using dihydroquinoline based structures. This type of compound was chosen as the basic structure is similar to the chromene based compounds which have shown high enantioselectivities when epoxidised previously within the group. However, although a range of compounds was synthesized, it was not possible to form an epoxide when using the group's catalyst, only when using *m*-CPBA. It was felt that this could be because the nitrogen present in the dihydroquinoline compound may interact with the catalyst used in the reaction, reducing its reactivity. As such, this work is to be continued within the group looking at both different protecting groups on the nitrogen and different catalysts.

In view of the high enantioselectivities achieved with the group's catalyst in the epoxidation of chromene based compounds, the next area which was investigated was the possible use of the group's asymmetric epoxidation in a kinetic resolution. To begin with, a range of basic pro-chiral chromenes were investigated to gain an overall insight into the potential of a kinetic resolution when using these types of compounds. These initial investigations proceeded well, confirming that a kinetic resolution could indeed be achieved. Epigallocatechin gallate (EGCG), with its chromene based structure, was then chosen as the natural product target to which a kinetic resolution could be applied. Several routes were investigated to a core structure to which the epoxidation based kinetic resolution could be applied. Work is currently being continued on both optimising the synthesis of this core structure and the conditions for the kinetic resolution.

The focus of the research project then turned to further natural product targets which could be synthesized enantioselectively using the group's asymmetric epoxidation conditions. As it had recently been synthesized by another group using a Jacobsen epoxidation, (+)-decursinol was chosen as the natural product target, as this would

enable a comparison of the two epoxidation methods to be made. However, when attempting the synthesis of the precursor compound xanthyetin using the procedure by North, the structural isomer seselin was found to be the product. As such, the natural product target was changed from (+)-decursinol to (-)-lomatin and (+)-khellactone. Epoxidation of seselin was found to proceed well and in a high enantioselectivity of 97% *ee*. The epoxide was then reacted further to yield both the natural product targets ((-)-lomatin and (+)-khellactone) in good yields.

Other compounds which were examined during this research project were those the epoxidation of which could provide key synthetic intermediates in the synthesis of larger biological molecules. Although epoxidation of 2*H*-chromene was achieved, as yet the total synthesis of the *cis*-aminochromanol has not been achieved and work on this area is currently being continued within the group. The epoxidation of dihydropyran was found to yield the diol rather than the epoxide, probably due to the instability of the epoxide generated. However, it is hoped that this will be reinvestigated in the future, looking at the conditions and catalysts used. It was not possible to investigate the epoxidation of cyclic enamine based compounds, as at the time no suitable substrate could be synthesized. Also, given the results obtained when attempting the epoxidation of the dihydroquinoline based compounds, it was felt that these types of compound may also prove to be difficult epoxidation substrates due to the presence of the nitrogen.

However, an interesting aside appeared when looking at a possible synthetic pathway to the cyclic enamine based structures. A simple route to the cyclic enamine based compounds was found using an *in-situ* oxidation and cyclisation of a Boc protected-hydroxycarbamate using DMP. It was felt that given the instability of DMP, the reaction would be attempted using IBX instead. A paper found previously within the group reported the *in-situ* generation of IBX using Oxone[®] and 2-iodobenzoic acid, in the oxidation of alcohols to carboxylic acids. It was felt that by using the oxidant TPPP, which could be used under non-aqueous conditions, the reactions could be altered to yield the aldehyde instead of the carboxylic acid, when the oxidation of primary alcohols was attempted. By using piperonal alcohol as the test substrate this was indeed found to be the case. A range of alcohols were then subjected to these new reaction conditions showing that the use of TPPP in place of Oxone[®] resulted in

the efficient and simple generation of aldehydes from primary alcohols and could also be used in the generation of ketones from secondary alcohols.

The final area of focus for this research project was the re-examination of exocyclic catalysts. These had previously been examined within the group using the Oxone[®] conditions. However, such catalysts had not been used with the new non-aqueous TPPP conditions. A basic exocyclic catalyst, prepared from pyrrolidine and cyclohexanone, was synthesized as the initial test catalyst and this was found to epoxidise 1-phenylcyclohexene under the TPPP conditions in a 55% yield in 8 hours. As the use of the TPPP conditions is primarily to enable the reaction to be carried out at low temperatures to increase enantioselectivity, the next step would be the synthesis and subsequent testing of chiral exocyclic catalysts under these conditions. The initial synthesis of such catalysts was started and is currently being continued within the group.

3.0 Experimental

3.1 General Experimental

All infrared spectra were obtained using a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer; thin layer spectra were acquired using sodium chloride plates.

All ^1H and ^{13}C NMR spectra recorded at Loughborough University were measured at 400 and 100 MHz respectively, using a Bruker DXP 400 MHz spectrometer. The solvent used for NMR spectroscopy was CDCl_3 (unless stated otherwise) using TMS (tetramethylsilane) as the internal reference. Chemical shifts are given in parts per million (ppm) and J values are given in Hertz (Hz).

All ^1H and ^{13}C NMR spectra recorded at the University of East Anglia were measured at 300 and 75 MHz with a Varian Gemini 2000, at 400 MHz and 100 MHz with a Varian Unity+ in deuteriochloroform solution unless otherwise stated, using TMS (tetramethylsilane) as the internal reference.

Microwave-assisted reactions were conducted using a CEM Discover apparatus set at a maximum power of 300 W.

Mass spectra were recorded using a Jeol-SX102 instrument utilizing electron impact (E.I.), fast atom bombardment (F.A.B) and by the EPSRC national mass spectrometry service at the University of Wales, Swansea, utilizing electrospray (E.S.) ionization. Mass spectra recorded at the University of East Anglia were recorded using a Shimadzu LCMS system.

Melting points at Loughborough University were recorded using an Electrothermal-IA 9100 melting point instrument and are uncorrected.

Melting points at the University of East Anglia were recorded using a Büchi B-545 melting point instrument and are uncorrected.

Optical rotation values recorded at Loughborough University were measured with an Optical Activity-polAAar 2001 instrument, operating at $\lambda = 589$ nm, corresponding to the sodium line, (D), at the temperatures indicated.

Optical rotations recorded at the University of East Anglia were measured using a B&S ADP-440 spectrometer, operating at $\lambda = 589$ nm, corresponding to the sodium line, (D), at the temperatures indicated.

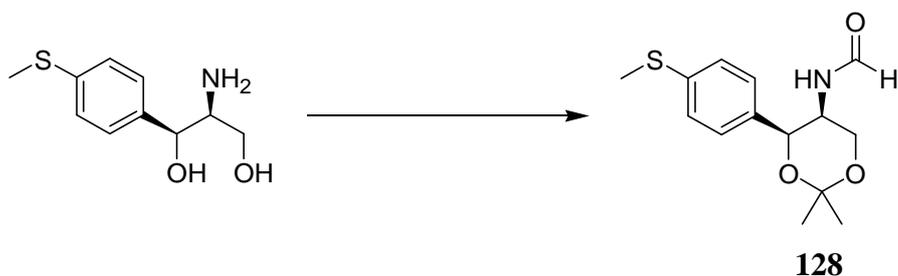
The solvents in used in both universities were of spectrophotometric grade, and the solutions for these measurements were prepared in volumetric flasks for maximum accuracy.

Microanalyses at Loughborough University were performed on a Perkin Elmer Elemental Analyser 2400 CHN.

All chromatographic manipulations used silica gel as the adsorbent. Reactions were monitored using thin layer chromatography (TLC). TLC plates were visualized by UV irradiation at a wavelength of 254 nm, or stained by exposure to an ethanolic solution of phosphomolybdic acid (acidified with concentrated sulfuric acid), followed by charring where appropriate. Purification by column chromatography used silica absorbent.

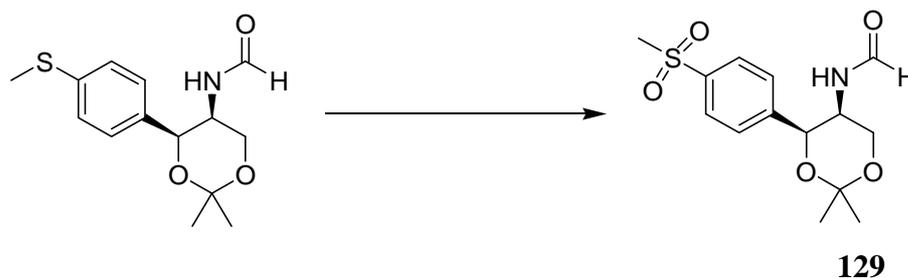
The reactions requiring anhydrous conditions were carried out using glassware dried overnight at 150 °C, unless otherwise stated. Reaction solvents were obtained commercially dry, except light petroleum (b.p. 40-60 °C), which was distilled from calcium chloride prior to use; ethyl acetate, which was distilled from calcium sulfate or chloride; dichloromethane, which was distilled from calcium hydride; and tetrahydrofuran (THF), which was distilled under a nitrogen atmosphere, from the sodium/benzophenone ketyl radical.

(+)-(4*S*,5*S*)-*N*-Formyl-2,2-dimethyl-4-(4-(methylthio)phenyl)-5-amino-1,3-dioxane⁵⁷



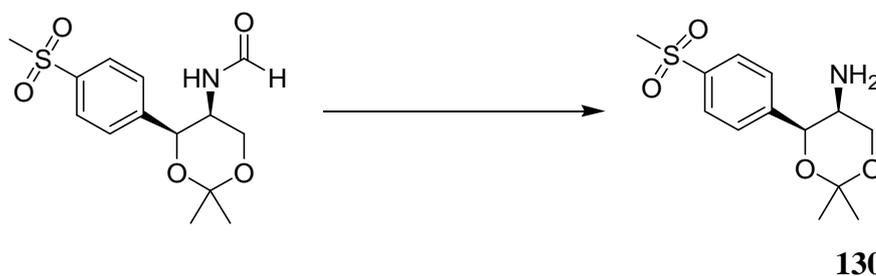
(1*S*,2*S*)-(+)-2-Amino-1-(4-(methylthio)phenyl)-1,3-propanediol (10.0 g, 46.8 mmol) was dissolved in methanol (100 ml). Methyl formate (3.2 ml, 0.98 g/cm³, 51.5 mmol) was then added, followed by commercially available aqueous sodium methoxide (10 mol%, 1 ml). The reaction mixture was stirred for 3.5 hours at room temperature and the solvent removed under reduced pressure. The resulting yellow oil was dissolved in acetone (500 ml) and 2,2-dimethoxypropane (60 ml, 0.84 g/cm³, 46.8 mmol) and *para*-toluenesulfonic acid (0.9 g, 10 mol%) was added. The reaction mixture was stirred for a further 4 hours at room temperature and monitored by TLC. The solvents were removed under reduced pressure and the residue re-dissolved in ethyl acetate, washed with saturated aqueous sodium hydrogen carbonate, dried (MgSO₄), and the solvents removed under reduced pressure to give the product as a colourless oil, which was used without further purification (9.6 g, 73%), [α]_D + 1.4° (*c* 1.26, CHCl₃), ν_{max} (film) / cm⁻¹ 3316, 3010, 2263, 1664, 1497, 1378, 1197, 1064, 956; δ_{H} (400 MHz; CDCl₃) 1.55 (3H, s, CH₃), 1.59 (3H, s, CH₃), 2.44 (3H, s, SCH₃, C16), 3.87 (1H, dd, *J* 7.0, 1.0 Hz, upfield portion of ABX system C6, N-CHCHH-O), 4.25 (1H, dd, *J* 7.0, 1.0 Hz, downfield portion of ABX system C6, N-CHCHH-O), 4.25-4.29 (1H, m, NCH, C5), 5.17 (1H, d, *J* 1.0 Hz, CH, C4), 6.28 (1H, d, *J* 5.6 Hz, NH), 7.21 (4H, s, 4 x CH arom.), 7.99 (1H, s, NCHO, C18); δ_{C} (100 MHz; CDCl₃) 15.8 (SCH₃, C16), 18.5 (CH₃), 29.7 (CH₃), 45.3 (NCH₃), 64.6 (CH₂), 71.4 (Ar-CH, C4), 99.7 (C quat., C2), 125.9 (2 x CH arom., C10,11), 126.4 (2 x CH arom., C12,13), 135.1 (C quat., arom., C14), 138.7 C quat., arom., C9), 161.0 (NCHO).

(-)-(4*S*,5*S*)-*N*-Formyl-2,2-dimethyl-4-(4-(methylsulfonyl)phenyl)-5-amino-1,3-dioxane⁵⁷



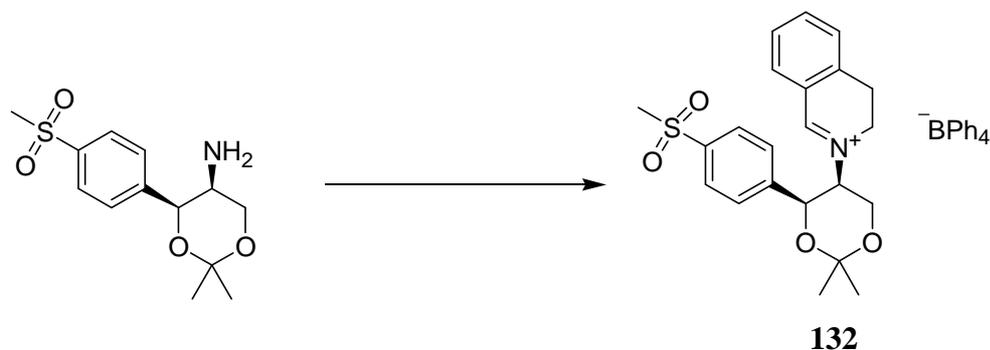
(+)-(4*S*,5*S*)-*N*-[2,2-Dimethyl-4-(4-methylsulfonyl-phenyl)-[1,3]dioxan-5-yl]-formamide (9.6 g, 34 mmol) was dissolved in dichloromethane (200 ml), and the solution cooled to 0 °C. A solution of *m*-CPBA (2.2 eq, 35.5 g, 0.103 mol) in chloroform (40 ml) was added dropwise over 15 min. The reaction mixture was stirred for 2 hours, transferred to a separating funnel, and washed with sat. sodium hydrogen carbonate (2 x 40 ml) and brine (2 x 40 ml), and dried (MgSO₄). The solvent was then removed under reduced pressure to give colourless crystals (6.4 g, 59%) m.p. 146-149 °C (lit – 146-147 °C);⁵⁷ [α]_D - 11.4° (*c* 1.23, CHCl₃), ν_{max} (film) / cm⁻¹ 3055, 2991, 1654, 1514, 1386, 1301, 1234, 1200, 1149, 1086, 950; δ_H (400 MHz; CDCl₃) 1.55 (3H, s, CH₃), 1.60 (3H, s, CH₃), 3.05 (3H, s, SO₂CH₃, C16), 3.88 (3H, dd, *J* 12.0, 2.0 Hz, upfield portion of ABX system, C6, N-CHCHH-O), 4.34 (1H, dd, *J* 12.0, 1.8 Hz, downfield portion of ABX system, C6, N-CHCHH-O), 4.43 (1H, dd, *J* 10.0, 1.8 Hz, NCH, C5), 5.28 (1H, s, CH, C4), 6.37 (1H, d, *J* 10.0 Hz, NH), 7.52 (2H, d, *J* 8.2 Hz, 2 x CH arom., C10,11), 7.85 (2H, d, *J* 8.2 Hz, 2 x CH arom., C12,13), 7.94 (1H, s, NCHO); δ_C (100 MHz; CDCl₃) 18.7 (CH₃), 29.8 (CH₃), 45.0 (SO₂CH₃, C16), 45.8 (NCH, C5), 65.1 (CH₂, C6), 72.5 (Ar-CH, C4), 100.6 (C quat., arom., C2), 127.4 (2 x CH arom., C10,13), 127.9 (2 x CH arom., C11,12), 140.2 (C quat., arom., C14), 144.9 (C quat., arom., C9), 161.1 (NCHO, C18).

(+)-(4*S*,5*S*)-5-amino-2,2-dimethyl-4-(4-(methylsulfonyl)phenyl)-1,3-dioxane⁵⁷



(-)-(4*S*,5*S*)-*N*-[4-(4-Methanesulfonyl-phenyl)-2,2-dimethyl-[1,3]dioxan-5-yl]-formamide (6.4 g, 20 mmol) was dissolved in aqueous hydrazine hydrate (85%) (140 ml) and the solution heated under reflux for 2.5 hours. The reaction mixture was allowed to cool to room temperature and extracted with ethyl acetate (3 x 40 ml). The organic layers were washed with water (2 x 50 ml), dried (MgSO₄) and the solvents removed under reduced pressure to give colourless crystals (3.2 g, 55%); m.p. 124-126 °C (lit – 120-122 °C);⁵⁷ [α]_D + 45° (*c* 1.10, CHCl₃), ν_{max} (film) / cm⁻¹ 3372, 3001, 1602, 1370, 1197, 1065, 950; δ_{H} (400 MHz; CDCl₃) 1.56 (6H, s, 2 x CH₃, C7,8), 2.85 (1H, dd, *J* 3.6, 2.0 Hz, NH₂CH, C5), 3.06 (3H, s, SO₂CH₃, C16), 3.88 (1H, dd, *J* 12.0, 2.0 Hz, upfield portion of ABX system, C6, N-CHCHH-O), 4.24 (1H, dd, *J* 12.0, 2.0 Hz, downfield portion of ABX system, C6, N-CHCHH-O), 5.18 (1H, d, *J* 3.6 Hz, CH, C4), 7.55 (2H, d, *J* 8.0 Hz, 2 x CH, arom., C10,11), 7.95 (2H, d, *J* 8.0 Hz, 2 x CH, arom., C12,13); δ_{C} (100 MHz; CDCl₃) 19.0 (CH₃), 30.1 (CH₃), 44.5 (SO₂CH₃), 50.1 (NCH, C5), 66.8 (CH₂, C6), 73.6 (CH, C4), 100.1 (C quat., C2), 127.4 (2 x CH arom., C10,11), 127.9 (2 x CH arom., C12,13), 140.2 (C quat., arom., C14), 146.5 (C quat., arom., C9).

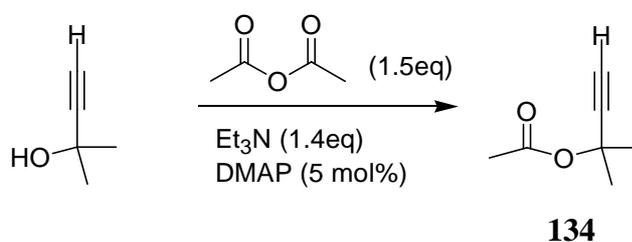
(+)-N-[(4S,5S)-2,2-Dimethyl-4-[4-(methylsulfonyl)phenyl]-1,3-dioxan-5-yl]-3,4-dihydroisoquinolinium tetraphenylborate.⁵⁷



(+)-(4S,5S)- 5-amino-2,2-dimethyl-4-(4-(methylsulfonyl)phenyl)-1,3-dioxane (5.2 g, 18 mmol) in ethanol (30 ml) was added dropwise to ice cooled 2-(2-bromoethyl)benzaldehyde (3.3 g, 1.3 eq). After the addition was complete the reaction flask was lightly stoppered to contain the hydrogen bromide generated temporarily in the reaction, and the reaction stirred overnight whilst attaining room temperature. A solution of sodium tetraphenylborate (1.2 eq) in acetonitrile (2 ml) was added in one portion to the reaction and stirred for a further 5 minutes, resulting in the formation of a yellow precipitate. The organic solvents were then removed under reduced pressure. The yellow solid was then washed with ethanol (20 ml) and water (20 ml) and the yellow crystals collected by suction filtration (4.2 g, 52%); m.p. 198-201 °C (lit – 199-201 °C);⁵⁷ $[\alpha]_D + 124.7^\circ$ (*c* 1.24 acetone); ν_{max} (film) / cm^{-1} 1636, 1602, 1507, 1478, 1370, 1266, 1202, 1197, 1065, 950; δ_{H} (400 MHz; acetone- d_6) 1.56 (3H, s, CH_3 , C7, eq.), 1.60 (3H, s, CH_3 , C8, ax.), 2.55-2.60 (1H, m, Ar- CHH , *isoq-4*), 2.76-2.82 (1H, m, Ar- CHH , *isoq-4*), 2.89 (3H, s, S CH_3), 3.65-3.70 (1H, m, Ar- CHH , *isoq-3*), 4.12-4.25 (1H, m, Ar- CHH , *isoq-3*), 4.44 (1H, d, *J* 13.6 Hz, upfield portion of ABX system, C6, N- CHCHH-O), 4.53 (1H, dd, *J* 2.6, 2.5 Hz, NCH, C5), 4.66 (1H, dd, *J* 13.6, 2.6 Hz, downfield portion of ABX system, C6, N- CHCHH-O) 5.97 (1H, d, *J* 2.5, Ar- CH , C4), 6.77 (4H, t, *J* 7.4 Hz, 4 x CH arom., *para* in BPh_4 group), 6.80 (8H, t, *J* 7.2 Hz, 8 x CH arom., *ortho* in BPh_4 group), 7.18-7.21 (8H, m, 8 x CH arom., *meta* in BPh_4 group), 7.40 (1H, t, *J* 7.6 Hz, CH arom., *isoq-8*), 7.73-7.83 (3H, m, 3 x CH arom., *isoq-6,7,9*), 7.82 (2H, d, *J* 8.2 Hz, 2 x CH arom., C10,11), 7.95 (2H, d, *J* 8.2 Hz, 2 x CH arom., C12,13), 9.21 (1H, s, HC=N , *isoq-1*); δ_{C} (100 MHz; acetone- d_6) 18.8 (CH_3 , C7), 25.4 (Ar- CH_2 , *isoq-4*),

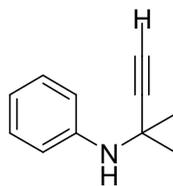
29.4 (CH₃, C8), 44.3 (SO₂CH₃), 52.3 (CH₂N, *isoq-3*), 62.9 (CH₂, C6), 66.1 (NCH), 71.5 (Ar-CH, C4), 101.3 C quat., C2), 122.5 (8 x CH arom., *ortho* in BPh₄), 125.9 (C quat., arom., *isoq-10*), 127.5 (2 x CH arom., C12,13), 128.6 (2 x CH arom., C10,11), 130.1 (4 x CH arom., *para* in BPh₄), 130.5 (CH arom., *isoq-7*), 135.4 (CH arom., *isoq-9*), 137.0 (8 x CH arom., *meta* in BPh₄), 137.9 (C quat., arom., C14), 139.9 (C quat., arom., *isoq-5*), 143.2 (C quat., arom., C9), 165.0 (4 x C, quat., arom in BPh₄), 169.1 (HC=N).

2-Methylbut-3-yn-2-yl-acetate⁶⁷



2-Methylbut-3-yn-2-ol (10 g, 0.10 mol) was placed in a 200 ml round bottomed flask, to this triethylamine (15 ml, 0.11 mol), acetic anhydride (11.6 ml, 0.12 mol) and DMAP (0.6 g, 4.91 mmol) were added with stirring. The reaction was then left stirring overnight at room temperature. The reaction was stopped when TLC showed no remaining starting material. The reaction was then dissolved in DCM and extracted with brine. All the organic layers were combined, dried (MgSO₄) and the solvent removed under reduced pressure to yield the product as a dark yellow oil (9.6 g, 73% yield); ν_{max} (film) / cm⁻¹ 3090, 2954, 1610, 1578, 1476, 1355, 1339, 1268, 1234, 1202, 1164, 1103, 1087, 1034, 956; δ_{H} (400 MHz; CDCl₃) 1.66 (6H, s, 2 x CH₃), 2.02 (3H, s, COCH₃), 2.58 (1H, s, CH, C4); δ_{C} (100 MHz; CDCl₃) 20.1 (2 x CH₃), 25.8 (C quat., C2), 65.4 (COCH₃), 72.2 (C quat., C3), 89.1 (CH, C4), 170.5 (C=O).

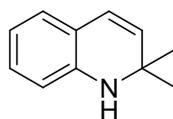
2-Methylbut-3-yn-2-yl-aniline⁶⁷



140

2-Methylbut-3-yn-2-yl-acetate (5.00 g, 39.5 mmol) and aniline (3.67 ml, 39.5 mmol) were placed in a dry flask containing CuCl (0.39 g, 10 mol%, 3.9 mmol) and magnetic flea under nitrogen. To this freshly distilled THF (100 ml), was added and a reflux condenser placed on the flask. The reaction was then heated under reflux under a nitrogen atmosphere for 3 hours. When the reaction was cool, ethyl acetate was added to the reaction and the organic layer extracted with brine. The organic layers were then combined, dried and the solvent removed under reduced pressure to yield the intermediate as an orange oil (5.6 g, 73%), which was used immediately without further purification; ν_{max} (film) / cm^{-1} 3324, 3010, 2245, 2140, 1620, 1499, 1283, 1154, 1068; δ_{H} (400 MHz; CDCl_3) 1.58 (6H, s, 2 x CH_3), 2.37 (1H, s, CH, C4), 4.50 (1H, s, broad NH), 6.77 (1H, t, J 8.0 Hz, CH arom., *para* on aniline), 6.93 (2H, d, J 9.6 Hz, 2 x CH, arom., *ortho* on aniline), 7.16 (2H, dd, J 9.6, 8.0 Hz, 2 x CH arom., *meta* on aniline); δ_{C} (100 MHz; CDCl_3) 30.4 (2 x CH_3), 48.2 (C quat., C2), 71.6 (CH, C4), 87.9 (C quat., C3), 117.2 (2 x CH arom., *ortho* on aniline), 120.0 (CH arom., *para* on aniline), 128.8 (2 x CH arom., *meta* on aniline), 145.4 (C quat., $\text{CNHC}(\text{CH}_3)_2$).

2,2-Dimethyl-1,2-dihydroquinoline⁶⁷

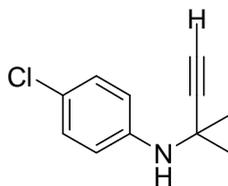


141

2-Methylbut-3-yn-2-yl-aniline (5.63 g, 35.4 mmol) was placed into a dry round bottomed flask under nitrogen which already contained CuCl (0.43 g, 11 mol%, 4.3 mmol). To this freshly distilled THF (100 ml) was added and the reaction heated

under reflux for 14 hours. The reaction was then allowed to cool and ethyl acetate (20 ml) added. The reaction was then extracted with brine and the organics combined, dried (MgSO₄) and the solvent removed under reduced pressure to yield the crude product as a light orange oil (4.5 g, 73%). The compound was then purified using column chromatography (20:1 petroleum ether:ethyl acetate), yielding the final product as an orange oil (4.0 g, 71%); ν_{max} (film) / cm^{-1} 3012, 1701, 1623, 1547, 1425, 1145, 1075; δ_{H} (400 MHz; CDCl₃) 1.25 (6H, s, 2 x CH₃), 4.50 (1H, br s, NH), 5.44 (1H, d, *J* 9.6 Hz, CH, C3), 6.24 (1H, d, *J* 9.6 Hz, CH, C4), 6.39 (1H, d, *J* 8.0 Hz, CH arom., C5), 6.55 (1H, dd, *J* 8.0, 6.0 Hz, CH arom., C7), 6.86 (1H, d, *J* 8.0 Hz, CH arom., C8), 6.92 (1H, dd, *J* 8.0, 6.0 Hz, CH arom., C6); δ_{C} (100 MHz; CDCl₃) 31.1 (2 x CH₃), 52.1 (C quat., C2), 112.8 (CH arom., C5), 117.3 (CH arom., C7), 120.0 (C quat., C9), 123.7 (CH, alkene, C4), 126.6 (CH arom., C8), 128.5 (CH arom., C6), 130.9 (CH, alkene C3), 143.0 (C quat., C10).

2-Methylbut-3-yn-2-yl-*para*-chloroaniline¹⁰⁵

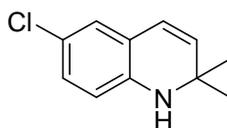


142

2-Methylbut-3-yn-2-yl-acetate (5.00 g, 39.5 mmol) and *para*-chloroaniline (4.96 g, 39.5 mmol) were placed in a dry flask containing CuCl (0.39 g, 10 mol%, 3.9 mmol) and magnetic flea under nitrogen. To this freshly distilled THF (100 ml) was added and a reflux condenser placed on the flask. The reaction was then heated under reflux under a nitrogen atmosphere for 3 hours. When the reaction was cool, ethyl acetate was added to the reaction and the organic layer extracted with brine. The organic layers were then combined, dried and the solvent removed under reduced pressure to yield the intermediate as a yellow oil (6.2 g, 81%), which was used immediately without further purification; ν_{max} (film) / cm^{-1} 3334, 3014, 2255, 2146, 1626, 1489, 1273, 1154, 1068; δ_{H} (400 MHz; CDCl₃) 1.56 (6H, s, 2 x CH₃), 2.38 (1H, s, CH, C4), 5.02 (1H, s, broad NH), 6.84 (2H, d, *J* 8.5 Hz, 2 x CH arom., *ortho* on aniline), 7.10 (2H, d, *J* 8.5 Hz, 2 x CH arom., *meta* on aniline); δ_{C} (100 MHz; CDCl₃) 30.4 (2 x

CH₃), 48.2 (C quat., C2), 71.6 (C quat., C3), 87.9 (CH, C4), 117.2 (CH arom., *ortho* on aniline), 128.8 (CH arom., *meta* on aniline), 141.2 (C quat., *para* on aniline) 145.4 (C quat., CNHC(CH₃)₂).

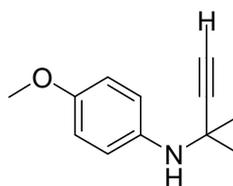
6-Chloro-2,2-dimethyl-1,2-dihydroquinoline¹⁰⁵



143

2-Methylbut-3-yn-2-yl-*para*-chloroaniline (6.22 g, 32.1 mmol) was placed into a dry round bottomed flask under nitrogen which already contained CuCl (0.43 g, 11 mol%, 4.3 mmol). To this freshly distilled THF (100 ml) was added and the reaction heated under reflux for 14 hours. The reaction was then allowed to cool and ethyl acetate (20 ml) added. The reaction was then extracted with brine and the organics combined, dried (MgSO₄) and the solvent removed under reduced pressure to yield the crude product as a light yellow oil (5.2 g, 83%). The crude product was purified using column chromatography (20:1 petroleum ether:ethyl acetate), yielding the final product as a yellow oil (4.1g, 66%); ν_{\max} (film) / cm⁻¹ 3018, 1711, 1627, 1541, 1426, 1155, 1075; δ_{H} (400 MHz; CDCl₃) 1.2 (6H, s, 2 x CH₃), 3.61 (1H, s, broad NH), 5.41 (1H, d, *J* 9.7 Hz, CH, C3), 6.10 (1H, d, *J* 9.7 Hz, CH, C4), 6.24 (1H, d, *J* 8.4 Hz, CH arom., C8), 6.75 (1H, d, *J* 2.4 Hz, CH arom., C5), 6.80 (1H, dd, *J* 8.4, 2.4 Hz, CH arom., C7); δ_{C} (100 MHz; CDCl₃) 30.9 (2 x CH₃), 52.2 (C quat., C2), 113.8 (CH arom., C8), 123.4 (CH, alkene, C4), 125.9 (CH arom., C5), 127.9 (CH arom., C7), 129.4 (C quat., C9), 132.2 (CH, alkene, C3), 144.2 (C quat., C10), 144.9 (C quat., C6).

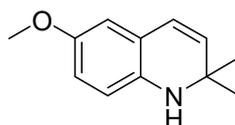
2-Methylbut-3-yn-2-yl-*para*-methoxyaniline¹⁰⁶



144

2-Methylbut-3-yn-2-yl-acetate (5.00 g, 39.7 mmol) and *para*-aniside (4.89 g, 39.7 mmol) were placed in a dry flask containing CuCl (0.39 g, 10 mol%, 3.9 mmol) and magnetic flea under nitrogen. To this THF (100 ml) straight from the still, was added and a reflux condenser placed on the flask. The reaction was then heated under reflux under a nitrogen atmosphere for 3 hours. When the reaction was cool, ethyl acetate was added to the reaction and the organic layer extracted with brine. The organic layers were then combined, dried and the solvent removed under reduced pressure to yield the intermediate as a dark yellow oil (4.9 g, 65%), which was used immediately without further purification; ν_{max} (film) / cm^{-1} 3314, 3008, 2235, 2120, 1615, 1495, 1286, 1154, 1068; δ_{H} (400 MHz; CDCl_3) 1.56 (6H, s, 2 x CH_3), 2.38 (1H, s, CH, C4), 5.0 (1H, s, broad NH), 6.84 (2H, d, J 8.8 Hz, 2 x CH arom., *ortho* on aniline), 7.10 (2H, d, J 8.8 Hz, 2 x CH arom., *meta* on aniline); δ_{C} (100MHz; CDCl_3) 30.4 (2 x CH_3), 48.2 (C quat., C2), 71.6 (OCH_3), 84.9 (CH, C4), 86.1 (C quat., C3), 117.2 (2 x CH arom., *ortho* on aniline), 128.8 (2 x CH arom., *meta* on aniline), 135.2 (C quat., *para* on aniline), 145.4 (C quat., $\text{CNHC}(\text{CH}_3)_2$).

6-Methoxy-2,2-dimethyl-1,2-dihydroquinoline¹⁰⁶



145

2-Methylbut-3-yn-2-yl-*para*-methoxyaniline (4.90 g, 25.9 mmol) was placed into a dry round bottomed flask under nitrogen which already contained CuCl (0.43 g, 11 mol%, 4.3 mmol). THF (100 ml) was added straight from the still and the reaction heated under reflux for 14 hours. The reaction was then allowed to cool and ethyl acetate (20 ml) added. The reaction was then extracted with brine and the organics combined, dried (MgSO_4) and the solvent removed under reduced pressure to yield the crude product as a dark yellow oil (5.2 g, 83%). The crude product was purified using column chromatography (20:1 petroleum ether:ethyl acetate), yielding the final product as a yellow oil (4.4 g, 75%); ν_{max} (film) / cm^{-1} 3018, 1698, 1633, 1540, 1421, 1149, 1075; δ_{H} (400 MHz; CDCl_3) 1.26 (6H, s, (2 x CH_3), 3.42 (1H, s, broad

NH), 3.74 (3H, s, OCH₃), 5.51 (1H, d, *J* 9.6 Hz, CH, C3), 6.22 (1H, d, *J* 9.6 Hz, CH, C4), 6.37 (1H, d, *J* 8.4 Hz, CH arom., C8), 6.51 (1H, d, *J* 2.4 Hz, CH arom., C5), 6.56 (1H, dd, *J* 8.4, 2.4 Hz, CH arom., C7); δ_C (100 MHz; CDCl₃) 30.2 (2 x CH₃), 52.0 (C quat., C2), 55.6 (OCH₃), 112.0 (CH arom., C5), 114.5 (CH arom., C8), 114.7 (CH arom., C7), 121.5 (C quat., C6), 123.6 (CH, alkene, C4), 132.3 (CH, alkene, C3), 137.3 (C quat., C9), 152.7 (C quat., C10)

Epoxidation Techniques

General procedure for the generation of racemic epoxides with *m*-CPBA.

The alkene substrate (1 eq) was dissolved in chloroform and cooled to 0 °C. When cold, *m*-CPBA (1.5 eq) was added slowly. The reaction was then allowed to warm to room temperature, whilst being monitored *via* TLC. When complete consumption of the substrate was observed the reaction was extracted with NaOH (3 x 20 ml), the organics combined, dried and the solvent removed under reduced pressure to yield the epoxide product.

General procedure for the epoxidation of alkenes mediated by iminium salts using Oxone[®].^{49,50}

Sodium carbonate (4 eq) was dissolved in water and cooled in an ice bath. To this Oxone[®] (2 eq) was added, followed by the catalyst (10 mol%) dissolved in acetonitrile (2 ml) was added with stirring. The reaction was then left stirring, whilst being monitored by TLC. When all starting material was consumed, diethyl ether was added and the reaction extracted with brine. The organics were then combined, dried (MgSO₄) and evaporated to yield the epoxide.

Tetraphenylphosphonium monoperoxysulfate (TPPP).⁵⁷

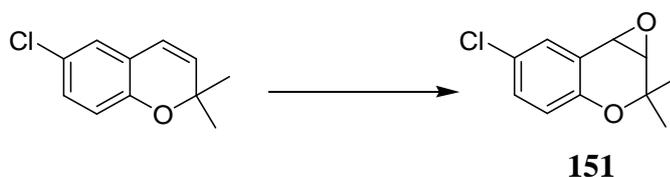
Oxone[®] triple salt (2KHSO₅:KHSO₄:K₂SO₄) (15.0 g, 48.8 mmol w.r.t. KHSO₅) was dissolved in deionized water (300 ml) and the solution stirred at 10-15 °C (water bath). A solution of tetraphenylphosphonium chloride (15.0 g, 40.0 mmol) in distilled dichloromethane (300 ml) was added over 5 min, and the reaction stirred for

an additional 30 min. The organic layer was then separated and the solvent removed under reduced pressure at room temperature. The colourless crude residue was then washed with distilled water (2 x 75 ml), dissolved in dichloromethane (180 ml) and dried (MgSO₄). Hexane was added until cloudiness developed and the flask was then placed in the freezer (-20°C) overnight, producing a white precipitate of the salt about 82% pure in peroxide (14.2 g, 60%); δ_{H} (400 MHz; CDCl₃) 7.64 (8H, m), 7.79 (8H, m), 7.90 (4H, m), 9.10 (1H, s).

General procedure for catalytic epoxidation of simple alkenes mediated by iminium salts using tetraphenylphosphonium monoperoxysulfate (TPPP).⁵⁷

Tetraphenylphosphonium monoperoxysulfate (2 eq with respect to the substrate) was dissolved in chloroform (2 ml per 0.1 g oxidant), and cooled to the required reaction temperature. Iminium salt (10 mol%) was dissolved in chloroform (0.5 ml per 0.1 g oxidant) and added dropwise to the solution of oxidant over 15-20 min; the reaction temperature was monitored throughout the addition, and any increase in temperature minimized. A solution of the alkene substrate in chloroform (0.5 ml per 0.1 g oxidant) was added in the same manner. The reaction was then stirred at the reaction temperature until the substrate was completely consumed. Diethyl ether was then added to induce precipitation of the remaining oxidant. The mixture was filtered through celite[®] and the solvent removed under reduced pressure to yield the epoxide.

6-Chloro-2,2-dimethylbenzopyran oxide⁵⁷



Prepared by the general procedure for the generation of racemic epoxides and the general procedure for the catalytic epoxidation of simple alkenes mediated by iminium salts using tetraphenylphosphonium monoperoxysulfate (TPPP). 6-Chloro-2,2-dimethylbenzopyran (0.194 g, 1.00 mmol) afforded 6-chloro-2,2-dimethylbenzopyran oxide as a colourless oil (0.134 g, 62%); ν_{max} (film) / cm⁻¹

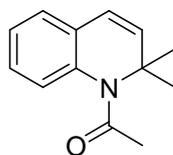
3090, 2954, 1610, 1578, 1476, 1355, 1339, 1268, 1234, 1202, 1164, 1103, 1087, 1034, 956; δ_{H} (400 MHz; CDCl_3) 1.22 (3H, s, CH_3), 1.50 (3H, s, CH_3), 3.48 (1H, d, J 4.4 Hz, CH, C3), 3.84 (1H, d, J 4.4 Hz, CH, C4), 6.74 (1H, d, J 8.6 Hz, CH arom., C8), 7.17 (1H, dd, J 8.6, 2.6 Hz, CH arom., C7), 7.29 (1H, d, J 2.6 Hz, CH arom., C5); δ_{C} (100 MHz; CDCl_3) 22.5 (CH_3), 25.7 (CH_3), 50.4 (CH, epoxide, C4) 60.4 (CH, epoxide, C3), 72.6 (quat., C, C2), 119.2 (CH arom., C5), 120.6 (quat., C, C9), 125.7 (quat., C, C6), 129.3 (CH arom., C7), 130.4 (CH arom., C8), 151.2 (quat., C, C10).

General procedure for the acetate protection of 2,2-dimethyl-1,2-dihydroquinoline compounds³



The appropriate dihydroquinoline compound (5 mmol) was dissolved in DCM (20 ml) and acetyl chloride (5 mmol) and DMAP (5 mol%) added. The reaction was then stirred at room temperature overnight. Ethyl acetate was then added and the mixture extracted with brine. The organics were then dried (MgSO_4) and reduced under vacuum, to yield the product as an off white oil.

1-Acetyl-2,2-dimethyl-1,2-dihydroquinoline¹⁰⁵

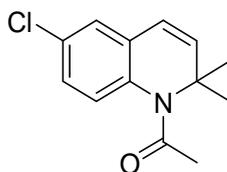


152

Prepared *via* the general procedure for the acetyl protection of 2,2-dimethyl-1,2-dihydroquinoline compounds. Product isolated as a yellow solid (0.74 g, 74%); ν_{max} (film) / cm^{-1} 3012, 1701, 1655, 1623, 1547, 1425, 1360, 1345, 1145, 1075; δ_{H} (400 MHz; CDCl_3) 1.22 (6H, s, 2 x CH_3), 2.09 (3H, s, COCH_3), 5.40 (1H, d, J 10.0 Hz,

CH, C3), 6.18 (1H, d, *J* 10.0 Hz, CH, C4), 6.34 (1H, d, *J* 7.6 Hz, CH arom., C8), 6.48 (1H, dd, *J* 8.2, 7.6 Hz, CH arom., C6), 6.79 (1H, d, *J* 7.6 Hz, CH arom., C5), 6.87 (1H, dd, *J* 8.2, 7.6 Hz, CH arom., C7); δ_C (100 MHz; CDCl₃) 30.9 (2 x CH₃), 40.0 (COCH₃), 52.1 (C quat., C2), 112.8 (CH arom., C8), 117.1 (CH arom., C6), 120.0 (C quat., C9), 123.6 (CH, C4), 125.5 (CH, C3), 126.5 (CH arom., C5), 128.4 (CH arom., C7), 166.4 (C quat., C10).

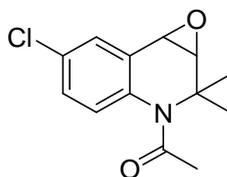
1-Acetyl-6-chloro-2,2-dimethyl-1,2-dihydroquinoline¹⁰⁵



153

Prepared *via* the general procedure for the acetyl protection of 2,2-dimethyl-1, 2-dihydroquinoline compounds. Product isolated as a brown gum (0.84 g, 72%); ν_{max} (film) / cm⁻¹ 3017, 1701, 1665, 1627, 1557, 1428, 1360, 1345, 1165, 1075; δ_H (400 MHz; CDCl₃) 1.40 (6H, s, 2 x CH₃), 1.94 (3H, s, COCH₃), 5.66 (1H, d, *J* 9.6 Hz, CH, C3), 6.19 (1H, d, *J* 9.6 Hz, CH, C4), 6.66 (1H, d, *J* 8.4 Hz, CH arom., C8), 6.93 (1H, d, *J* 2.4 Hz, CH arom., C5), 7.00 (1H, dd, *J* 8.4, 2.4 Hz, CH arom., C7); δ_C (100 MHz; CDCl₃) 31.9 (2 x CH₃), 42.1 (COCH₃), 50.1 (C quat., C2), 111.7 (CH arom., C8), 120.6 (C quat., C9), 124.8 (CH, C4), 127.5 (CH, C3), 129.4 (CH arom., C5), 132.1 (CH arom., C7), 134.2 (C quat., C6), 175.1 (C quat., C10).

1-Acetyl-6-chloro-2,2-dimethyl-3,4-epoxy-1,2,3,4-tetrahydroquinoline using Oxone[®] system

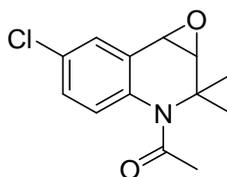


155

The reaction was performed *via* the general procedure for catalytic epoxidation of simple alkenes mediated by iminium salts using Oxone[®] and 1-acetyl-6-chloro-2,2-

dimethyl-1,2-dihydroquinoline. After 6 hours, crude ^1H NMR analysis revealed only slight epoxidation had occurred and after work up only starting material was recovered.

1-Acetyl-6-chloro-2,2-dimethyl-3,4-epoxy-1,2,3,4-tetrahydroquinoline using *m*-CPBA¹⁰⁵



155

Prepared using the general procedure for the generation of racemic epoxides using *m*-CPBA. 1-Acetyl-6-chloro-2,2-dimethyl-1,2-dihydroquinoline (0.20 g, 0.85 mmol) afforded 1-acetyl-6-chloro-2,2-dimethyl-3,4-epoxy-1,2,3,4-tetrahydroquinoline as a colourless oil (0.14 g, 72%); ν_{max} (film) / cm^{-1} 2985, 1745, 1610, 1584, 1486, 1385, 1255, 1075; δ_{H} (400 MHz; CDCl_3) 1.10 (3H, s, CH_3), 1.83 (3H, s, CH_3), 2.02 (3H, s, COCH_3), 3.34 (1H, d, J 4.2 Hz, CH, C3), 3.73 (1H, d, J 4.2 Hz, CH, C4), 6.71 (1H, d, J 8.4 Hz, CH arom., C8), 7.17 (1H, dd, J 8.4, 2.4 Hz, CH arom., C7), 7.30 (1H, d, J 2.4 Hz, CH arom., C5); δ_{C} (100 MHz; CDCl_3) 22.4 (CH_3), 25.6 (CH_3), 26.4 (COCH_3), 51.4 (CH, C4), 56.2 (C quat., C2), 66.8 (CH, C3), 126.7 (C quat., C9), 128.8 (CH arom., C8), 129.1 (CH arom., C5), 131.5 (CH arom., C7), 135.1 (C quat., C6), 161.4 (C quat., C10).

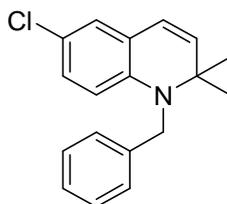
General procedure for the benzyl protection of 2,2-dimethyl-1,2-dihydroquinoline compounds



The required dihydroquinoline compound (5 mmol) was dissolved in DMF (20 ml). In a separate flask NaH (1.5 eq) was washed with petrol and then DMF (10 ml), the

flask was then cooled to -78°C . The dissolved dihydroquinoline compound was then added to the NaH slowly at a rate of 1 ml/min, followed by the slow addition of BnBr (1.1eq) also at a rate of 1 ml/min. The reaction was then left stirring overnight whilst warming to room temperature.

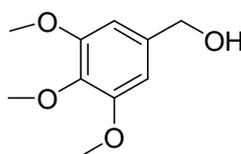
1-Benzyl-6-chloro-2,2-dimethyl-1,2-dihydroquinoline



154

Prepared *via* the general method for the benzyl protection of 2,2-dimethyl-1,2-dihydroquinoline compounds. Product isolated as a yellow oil (1.0 g, 72%). ν_{max} (film) / cm^{-1} 3012, 2912, 1698, 1601, 1586, 1456, 1262, 1054; δ_{H} (400 MHz; CDCl_3) 1.31 (6H, s, 2 x CH_3), 4.40 (2H, s, NCH_2Ph), 5.43 (1H, d, J 9.8 Hz, CH, C3), 6.03 (1H, d, J 8.8 Hz, CH arom., C8), 6.14 (1H, d, J 9.8 Hz, CH, C4), 6.71 (1H, dd, J 8.8, 2.4 Hz, CH arom., C7), 6.75 (1H, d, J 2.4 Hz, CH arom., C5), 7.047-7.147 (5H, m, $\text{CH}_2(\text{C}_6\text{H}_5)$); δ_{C} (100 MHz; CDCl_3) 28.6 (2 x CH_3), 33.6 (NCH_2Ph), 57.6 (C quat., C2), 112.9 (CH, C4), 121.0 (C quat., C9), 122.7 (CH arom., C8), 126.7 (CH arom., C5), 127.8 (CH arom., C7), 128.6 (2 x CH arom., *ortho* on Ph), 128.9 (2 x CH arom., *meta* on Ph), 132.8 (CH arom., *para* on Ph), 137.8 (C quat., C10), 138.9 (C quat., NCH_2C), 142.4 (C quat., C6). m/z : 283.11274; $\text{C}_{18}\text{H}_{18}\text{ClN}$ requires 283.11278.

(3,4,5-Trimethoxyphenyl)-methanol^{6,107}

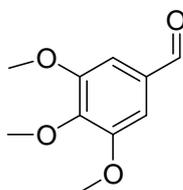


195

3,4,5-Trimethoxybenzoic acid (9.0 g, 45 mmol) was placed in a flask with a stirrer, the flask was then dried and fitted with a nitrogen bubbler. To the flask dry THF (80

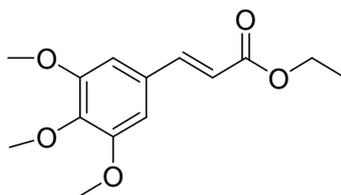
ml) was added, followed by the dropwise addition of LiAlH₄ (40 ml, 40 mmol, 1.0 M in THF). The reaction was then stirred overnight, at which point hexane (80 ml) and NH₄Cl (6 ml) was added. The reaction was stirred for a further hour, then filtered, dried (MgSO₄) and evaporated to yield the product as a clear oil (6.8 g, 81%). ν_{max} (film) / cm⁻¹ 3256, 3109, 2945, 1601, 1547, 1165, 1012; δ_{H} (400 MHz; CDCl₃) 1.88 (1H, s, OH), 3.83 (3H, s, *para* OCH₃), 3.85 (6H, s, 2 x *meta* OCH₃), 4.61 (2H, d, *J* 5.2 Hz, CH₂OH), 6.58 (2H, s, 2 x CH arom., C2,6); δ_{C} (100 MHz; CDCl₃) 56.0 (2 x *meta* OCH₃), 60.8 (*para* OCH₃), 65.4 (CH₂OH), 103.6 (2 x CH arom., C2,6), 136.8 (C quat., OHCH₂C), 137.1 (C quat., C4), 153.3 (2 x C quat., C3,5).

3,4,5-Trimethoxybenzaldehyde^{6,108}



196

(3,4,5-Trimethoxyphenyl)-methanol (3.0 g, 15 mmol) was placed in a dry flask under nitrogen, to this DCM (30 ml) was added. In a separate dry flask also under nitrogen was added PDC (2.7 g, 7.1 mmol) and 4Å molecular sieves. The DCM mixture was then added to the PDC and the reaction stirred at room temperature overnight. Diethyl ether (20ml) was then added to quench the reaction, and this was then run through silica to remove the chromium waste. The organics were then evaporated to yield the product as a white solid (1.9 g, 82%), m.p. 75-77 °C (lit – 73-76 °C)^{6,108}; ν_{max} (film) / cm⁻¹ 3078, 2975, 2756, 1738, 1689, 1526, 1496, 1263, 1056; δ_{H} (400 MHz; CDCl₃) 3.89 (6H, s, 2 x OCH₃, *meta*), 3.92 (3H, s, OCH₃, *para*) 7.20 (2H, s, 2 x CH arom., C2, 5), 9.90 (1H, s, CHO); δ_{C} (100 MHz; CDCl₃) 62.1 (2 x OCH₃, *meta*), 68.5 (1 x OCH₃, *para*), 105.4 (C quat., C4), 132.5 (C 2 x quat., C3, 5), 145.1 (2 x CH arom., C2, 6), 153.5 (C quat., CCHO), 178.9 (CHO).

Ethyl-(*E*)-3,4,5-trimethoxycinnamate^{6,109,110}**197**

3,4,5-Trimethoxy-benzaldehyde (1.0 g, 4.7 mmol) was dissolved under nitrogen in THF (10 ml). In a separate flask NaH (0.73 g, 18 mmol, 60% dispersion in mineral oil) was washed, and THF (10 ml) added, the flask was then cooled to -78°C . Triethylphosphonoacetate (1.4 ml, 1.2 eq) was added to this to form the ylid, at which point the aldehyde solution was added dropwise. The reaction was then slowly warmed up to room temperature and stirred. After 2 hours solid NaHCO_3 (2 g) was added and the organic layer separated. The aqueous layer was further washed with ethyl acetate and the organics combined, dried (MgSO_4) and evaporated to yield the product as an off white solid. This was further washed with hexane to remove any trace of the mineral oil and excess phosphonate reagent, yielding a clean product as a white solid (0.98 g, 77%); m.p. $69-70^{\circ}\text{C}$ (lit $68-69^{\circ}\text{C}$)¹¹⁰; ν_{max} (film) / cm^{-1} 3050, 2045, 1748, 1725, 1655, 1573, 1496, 1287, 1186, 1065; δ_{H} (400 MHz; CDCl_3) 1.35 (3H, t, J 9.6 Hz, CH_2CH_3), 3.81 (3H, s, OCH_3 , *para*), 3.86 (6H, s, 2 x OCH_3 , *meta*), 4.12 (2H, q, J 9.6 Hz, CH_2CH_3), 6.26 (1H, d, J 16.0 Hz, $\text{ArHC}=\text{CHCOOEt}$), 6.68 (2H, s, CH arom., C2,6), 7.51 (1H, d, J 16.0 Hz, $\text{ArHC}=\text{CHCOOEt}$); δ_{C} (100 MHz; CDCl_3) 14.3 (CH_2CH_3), 56.2 (2 x OCH_3 , *meta*), 56.9 (OCH_3 , *para*), 60.9 (CH_2CH_3), 105.1 (2 x CH arom., C2,6), 111.2 (C quat., C4) 117.5 ($\text{CH}=\text{CH}$), 129.9 (C quat., C1), 144.5 ($\text{CH}=\text{CH}$), 153.4 (C quat., C3,5), 166.9 (C quat., COCH_2CH_3).

General procedure for the acetalisation of aldehydes - route 1⁷³

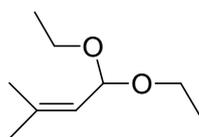
The required aldehyde (1 eq) was dissolved in the required alcohol (10 eq), the solution was then stirred at 0°C under N_2 and TiCl_4 (1.0 M, 5 mol%) added to the solution with a syringe, in one portion. After 15 min, triethylamine (0.5eq) was added and the reaction stirred for a further 2 hours at room temperature. Water (2 ml for each 10 ml of alcohol) was then added and the solution extracted into DCM (3 x 30 ml). The organics were then combined, dried (MgSO_4) and evaporated to yield the

required product. The acetals were used directly after preparation without further purification due to the instability of the acetal on silica.

General procedure for the acetalisation of aldehydes - route 2⁷⁴

The aldehyde (1 eq) was dissolved in required alcohol (10 eq), to which was added triethyl orthoformate (1.2eq) and ammonium nitrate (0.1eq). The resultant solution was left stirring overnight at room temperature. The reaction was then checked by TLC and stopped upon complete consumption of the starting aldehyde. The liquid was removed under vacuum and the resulting oil re-dissolved in DCM and washed with NaHCO₃ (3 x 50ml). The organic layers were then combined, dried (MgSO₄) and evaporated to yield the product. The acetals were used directly after preparation without further purification due to the instability of the acetal on silica.

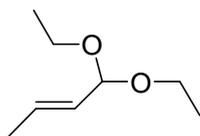
1,1-Diethoxy-3-methyl-but-2-ene⁷²



230

Prepared *via* the general procedure for the acetalisation of aldehydes routes 1 and 2, using ethanol (80 ml) as the alcohol. 3-Methyl-2-butenal (10 ml, 0.10 mol) yielded 1,1-diethoxy-3-methyl-but-2-ene (15 g, 98%) as a yellow oil. ν_{max} (film) / cm^{-1} 2976, 2932, 2915, 2880, 1680, 1447, 1377, 1358, 1348, 1206, 1146, 1115, 1086, 1053, 1017, 991 cm^{-1} , δ_{H} (400 MHz; CDCl₃); 0.85-0.89 (6H, m, 2 x CH₂CH₃), 1.38, (3H, s, CH=CCH₃, C4), 1.41 (3H, s, CH=CCH₃, C5), 3.16-3.23 (4H, m, 2 x CH₂CH₃), 4.78 (1H, d, *J* 8.0 Hz, CH, C2), 4.93 (1H, d, *J* 8.0 Hz, CH, C1); δ_{C} (100 MHz; CDCl₃) 14.8 (2 x CH₂CH₃), 17.0 (CH₃, C4), 23.9 (CH₃, C5), 58.8 (2 x CH₂CH₃), 101.0 (CH, C2), 122.9 (CH, C1), 137.3 (C quat., C3).

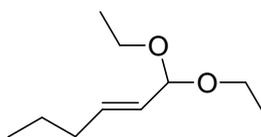
***trans*-1,1-Diethoxy-but-2-ene**¹¹¹



159

Prepared *via* the general procedure for the acetalisation of aldehydes routes 1 and 2, using ethanol (80 ml) as the alcohol. Crotonaldehyde (10 ml, 0.12 mol) yielded 1,1-diethoxybut-2-ene (17 g, 98%) as yellow oil. ν_{max} (film) / cm^{-1} 2846, 2810, 1677 (w), 1661 (w), 1446, 1371, 1338, 1125 (s), 1052 (s), 996, 971. δ_{H} (400 MHz; CDCl_3); 1.30 (6H, t, J 7.2 Hz, 2 x CH_2CH_3), 1.64 (3H, dd, J 6.4, 1.6 Hz, CH_3 , C4), 3.37-3.45 (2H, m, CH_2), 3.52-3.61 (2H, m, CH_2), 4.74 (1H, d, J 5.6 Hz, CH, C1), 5.43 (1H, ddq, J 15.6, 5.6, 1.6 Hz, $\text{CH}=\text{CHCH}_3$, C2), 5.74 (1H, ddq, J 15.6, 6.4, 1.6 Hz, $\text{CH}=\text{CHCH}_3$, C3); δ_{C} (100 MHz; CDCl_3) 15.1 (2 x CH_3 on acetal), 17.3 (CH_3 , C4), 61.0 (2 x CH_2 , on acetal), 101.7 (CH, C1), 128.4 (CH, C2), 128.9 (CH, C3).

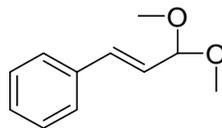
***trans*-2-Hexenal Diethyl Acetal**¹¹²



160

Prepared *via* the general procedure for the acetalisation of aldehydes route 2, using ethanol (80 ml) as the alcohol. The product was yielded as an orange oil (16 g, 88%); ν_{max} (film) / cm^{-1} 3105, 2799, 1587, 1491, 1301, 1255, 1087, δ_{H} (400 MHz; CDCl_3); 0.89-0.94 (3H, m, CH_3 , C6), 1.25-1.29 (6H, m, 2 x CH_3 , C7, 10), 1.42-1.45 (2H, m, CH_2 , C5), 2.01-2.04 (2H, m, CH_2 , C4), 3.51-3.56 (2H, m, CH_2 , C8), 3.58-3.64 (2H, m, CH_2 , C9), 4.82 (1H, d, J 6.2 Hz, C1), 5.52-5.56 (1H, m, CH, C3), 5.84-5.87 (1H, m, CH, C2); δ_{C} (100 MHz; CDCl_3) 15.1 (C6), 18.5 (C7, 10), 23.4 (C5), 36.8 (C4), 61.1 (C8, 9), 104.5 (C1), 128.4 (C3), 134.9 (C2).

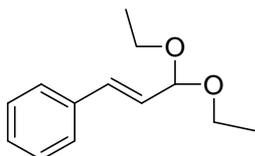
***trans*-Cinnamaldehyde dimethylacetal⁷⁴**



163

Prepared *via* the general procedure for the acetalisation of aldehydes route 1, using methanol (80 ml) as the alcohol. *trans*-cinnamaldehyde (10 ml, 0.071 mol) yielded *trans*-cinnamaldehyde dimethylacetal (12 g, 88%) as a clear oil. ν_{max} (film) / cm^{-1} 3095, 2847, 1567, 1495, 1275, 1150, 1087, δ_{H} (400 MHz; CDCl_3); 3.95 (6H, s, 2 x CH_3), 4.87 (1H, d, J 6.0 Hz, C1), 6.04 (1H, dd, J 15.8, 6.0 Hz, C2), 6.60 (1H, d, J 15.8 Hz, C3), 7.1-7.48 (5H, m, Ph), δ_{C} (100 MHz; CDCl_3) 52.7 (2 x CH_3), 102.8 ($\text{CH}(\text{OMe})_2$, C1), 125.6 ($\text{CHCH}=\text{CH}$, C2), 126.7 ($\text{CHCH}=\text{CHPh}$, C3), 128.8 (CH, *para* on Ph), 136.0 (2 x CH, *ortho* on Ph), 136.2 (2 x CH, *meta* on Ph), 152.8 ($\text{CH}=\text{CHC}$, C4).

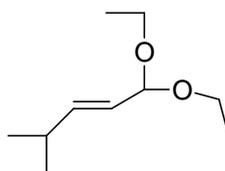
***trans*-Cinnamaldehyde diethylacetal⁷⁴**



162

Prepared *via* the general procedure for the acetalisation of aldehydes routes 1 and 2, using ethanol (80 ml) as the alcohol. *trans*-Cinnamaldehyde (10 ml, 0.071 mol) yielded *trans*-cinnamaldehyde diethylacetal (14 g, 96%) as a clear oil. ν_{max} (film) / cm^{-1} 3092, 2887, 1560, 1505, 1275, 1150, 1087, δ_{H} (400 MHz; CDCl_3); 1.12 (6H, t, J 7.4 Hz, 2 x CH_3), 3.43 (2H, q, J 7.2 Hz, CH_2), 3.58 (2H, q, J 7.2 Hz, CH_2), 4.96 (1H, d, J 5.2 Hz, C1), 6.09 (1H, dd, J 16.0, 5.2 Hz, C2), 6.59 (1H, d, J 16.0 Hz, C3), 7.17-7.48 (5H, m, Ph), δ_{C} (100 MHz; CDCl_3) 15.3 (2 x CH_3), 61.1 (2 x CH_2), 101.5 ($\text{CH}(\text{OEt})_2$, C1), 126.7 ($\text{CHCH}=\text{CH}$, C2), 128.5 ($\text{CHCH}=\text{CHPh}$, C3), 129.3 (CH, *para* on Ph), 135.5 (2 x CH, *ortho* on Ph), 136.2 (2 x CH, *meta* on Ph), 152.8 ($\text{CH}=\text{CHC}$, C4).

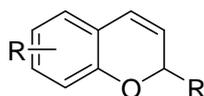
4-Methyl-2-pentenal-diethyl acetal¹¹³



161

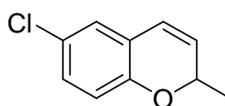
Prepared *via* the general procedure for the acetalisation of aldehydes routes 1 and 2, using ethanol (80 ml) as the alcohol. *trans*-2-Methyl-2-pentenal (10 ml, 0.083 mol) yielded 4-methyl-2-pentenal-diethyl acetal (13 g, 91%) as a yellow oil. ν_{max} (film) / cm^{-1} 3092, 2887, 1560, 1505, 1275, 1150, 1087, δ_{H} (400 MHz; CDCl_3); 1.41 (6H, d, J 5.2 Hz, 2 x CH_3 , C5, 6), 1.65 (6H, t, J 6.8 Hz, 2 x CH_3), 2.81 (1H, m, CH , C4), 3.91 (2H, m, CH_2), 4.05 (2H, m, CH_2), 5.25 (1H, d, J 6.2 Hz, CH , C1), 5.90 (1H, dd, J 15.8, 5.5 Hz, $\text{CH}=\text{CH}$, C3), 6.20 (1H, dd, J 15.8, 6.2 Hz, $\text{CH}=\text{CH}$, C2); δ_{C} (100 MHz; CDCl_3) 15.3 (2 x CH_3 , C5, 6), 21.1 (2 x CH_3), 30.1 (CH , C4), 61.1 (2 x CH_2), 110.5 ($\text{CH}(\text{OEt})_2$, C1), 120.7 ($\text{CH}=\text{CH}$, C3), 142.5 ($\text{CH}=\text{CH}$, C2).

General procedure for the formation of chromenes⁷⁴



The required acetalised aldehyde (1 eq) was dissolved in *p*-xylene (20 ml), the required phenol (2 eq) and 3-picoline (0.25 eq) were then added and the reaction heated under reflux overnight. The reaction was then left to cool and columned directly using either (i) a graded eluent from 100% petrol to 20:1 (petrol:ethyl acetate) or (ii) a petrol:toluene (1:1) mix. All of the products were obtained as either crystals or an oil.

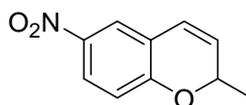
6-Chloro-2-methyl -2H-1-benzopyran¹¹⁴



171

Prepared *via* the general procedure for the formation of chromenes using *para* chlorophenol (8.9 g, 69 mmol) as the required phenol, *trans*-1,1-diethoxy-3-methylbut-2-ene (5.0 ml, 34 mmol) as the required acetal and 3-picoline (0.8 ml, 0.25 eq). The product was columned directly using light petroleum:toluene (1:1). Product was obtained as a slight yellow liquid (4.7 g, 91% yield). ν_{max} (film) / cm^{-1} 3092, 2887, 1560, 1505, 1275, 1150, 1087; δ_{H} (400 MHz; CDCl_3); 1.40 (3H, d, J 6.6 Hz, CH_3), 4.95 (1H, dd, J 6.6, 3.2 Hz, CHMe , C2), 5.65 (1H, dd, J 9.6, 3.2 Hz, C3), 6.26 (1H, d, J 9.6 Hz, C4), 6.67 (1H, d, J 8.5 Hz, C8), 6.90 (1H, d, J 2.4 Hz, C5), 7.01 (1H, dd, J 8.5, 2.4 Hz, C7); δ_{C} (100 MHz; CDCl_3) 22.4 (CH_3), 75.6 (C2), 119.4 (C8), 125.2 (quat., C, C9), 127.0 (C4), 128.3 (C3), 129.1 (C7), 129.2 (C5), 134.71 (quat., C, C6), 152.02 (quat., C, C10); m/z 180.0338; $\text{C}_{10}\text{H}_9\text{ClO}$ requires 180.0336.

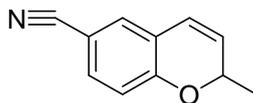
6-Nitro-2-methyl -2*H*-1-benzopyran¹¹⁴



170

Prepared *via* the general procedure for the formation of chromenes, using *para* nitrophenol (9.6 g, 69 mmol) as the required phenol, *trans*-1,1-diethoxy-3-methylbut-2-ene (5.0 ml, 34 mmol) as the required acetal and 3-picoline (0.8 ml, 0.25 eq).). The product was columned directly using light petroleum:toluene (1:1) yielding the product as yellow crystals (4.7 g, 86% yield); m.p. 65 °C (lit. 66-66.5 °C);¹¹⁴ ν_{max} (film) / cm^{-1} 3065, 2972, 2936, 2224, 1485, 1464, 1368, 1279, 1269, 1215, 1167, 961; δ_{H} (400 MHz; CDCl_3); 1.49 (3H, d, J 6.8 Hz, CH_3), 5.16 (1H, dd, J 6.8, 3.2 Hz, OCHMe , C2), 5.79 (1H, dd, J 10.0, 3.2 Hz, C3), 6.40 (1H, d, J 10.0 Hz, C4), 6.79 (1H, d, J 8.8 Hz, C8), 7.97 (1H, d, J 2.4 Hz, C5), 8.0 (1H, dd, J 8.8, 2.4 Hz, C7); δ_{C} (100 MHz; CDCl_3) 21.2 (CH_3), 71.6 (C2), 117.3 (C8), 123.1 (quat., C, C9), 126.0 (C4), 127.2 (C3), 128.3 (C5), 129.2 (C7), 145.7 (quat., C, C10), 162.1 (quat., C, C6). m/z : 191.05851; $\text{C}_{10}\text{H}_9\text{O}_3\text{N}$ requires 191.05824.

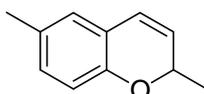
6-Cyano-2-methyl-2H-1-benzopyran⁷⁵



169

Prepared *via* the general procedure for the formation of chromenes, using *para*-cyanophenol (8.3 g, 69 mmol) as the required phenol, *trans*-1,1-diethoxy-3-methyl-but-2-ene (5.0 ml, 35 mmol) as the required acetal and 3-picoline (0.80 ml, 0.25 eq). The product was columned directly using petrol:toluene (1:1) yielding the product as colourless crystals (4.7 g, 86% yield); m.p. 57 °C (lit. 55.5-56 °C);⁷⁵ ν_{max} (film) / cm^{-1} 3020, 2972, 2936, 2324, 1485, 1468, 1379, 1269, 1215, 1167; δ_{H} (400 MHz; CDCl_3); 1.37 (3H, d, J 6.8 Hz, CH_3), 5.01 (1H, dd, J 6.8, 3.2 Hz, CH, C2), 5.66 (1H, dd, J 10.5, 3.2 Hz, C3), 6.24 (1H, d, J 10.5 Hz, C4), 6.70 (1H, d, J 8.4 Hz, C8), 7.12 (1H, d, J 2.0 Hz, C5), 7.27 (1H, dd, J 8.4, 2.0 Hz, C7); δ_{C} (100 MHz; CDCl_3) 21.7 (CH_3), 72.5 (C2), 116.9 (C4), 120.4 (quat., C, C9), 122.1 (C3), 128.4 (C5), 129.2 (quat., C, C6), 131.4 (C7), 133.3 (C8), 157.1 (quat., C, C10) 158.2 (quat., C, CN); m/z 171.0678; $\text{C}_{11}\text{H}_9\text{ON}$ requires 171.0679.

2,6-Dimethyl-2H-1-benzopyran¹¹⁵

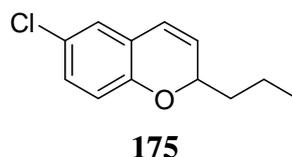


172

Prepared *via* the general procedure for the formation of chromenes using *para*-cresol (1.87g, 17.3 mmol) as the required phenol, *trans*-1,1-diethoxy-3-methyl-but-2-ene (2 ml, 11.5 mmol) as the required acetal and 3-picoline (0.30 ml, 0.25 eq.) The product was columned directly using toluene, yielding the product as a clear oil (1.49 g, 80% yield); ν_{max} (film) / cm^{-1} 3020, 2972, 2936, 2324, 1485, 1468, 1379, 1269, 1215, 1167; δ_{H} (400 MHz; CDCl_3); 1.42 (3H, d, J 1.5 Hz, CH_3 , C11), 2.22 (3H, s, arom., CH_3 , C12), 4.91 (1H, dd, J 3.0, 1.5 Hz, $\text{OC}(\text{CH}_3)\text{H}$, C2), 5.62 (1H, dd, J 9.7, 3.0 Hz, $\text{CH}=\text{CH}$, C3), 6.32 (1H, d, J 9.7 Hz, $\text{CH}=\text{CH}$, C4), 6.66 (1H, d, J 8.1 Hz, arom., CH, C9), 6.75 (1H, s, arom., CH, C6), 6.88 (1H, d, J 8.1 Hz, arom., CH, C8); δ_{C} (100 MHz; CDCl_3); 20.3 ($\underline{\text{C}}\text{H}_3$, C11), 21.0 (arom., $\underline{\text{C}}\text{H}_3$, C12), 71.2 (C2), 115.7

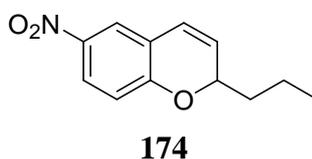
(C5), 121.6 (quat., C9), 123.9 (C4), 126.9 (C3), 128.4 (quat., C, C6), 129.5 (C7), 129.8 (C8), 151.3 (quat., C10); m/z 160.2; $C_{11}H_{12}O$ requires 160.2124. Mass spectra were obtained as low-resolution mass spectra after attempts to obtain high resolution spectra from Swansea failed due to decomposition during travel.

6-Chloro-2-propyl-2H-1-benzopyran



Prepared *via* the general procedure for the formation of chromenes using *para* chlorophenol (7.4 g, 58 mmol) as the required phenol, *trans*-2-hexenal diethyl acetal (5.0 ml, 29 mmol) as the required acetal and 3-picoline (0.80 ml, 0.25 eq). The reaction was columned directly using toluene, yielding the product as a yellow oil (5.2 g, 86%); ν_{\max} (film) / cm^{-1} 3065, 2950, 2736, 2224, 1585, 1464, 1368, 1315, 991; δ_{H} (400 MHz; CDCl_3) 0.95 (3H, t, J 7.4 Hz, CH_3), 1.38-1.52 (4H, m, 2 x CH_2), 4.75-4.77 (1H, m, CH, C2), 5.63 (1H, dd, J 9.8, 3.5 Hz, C3), 6.23 (1H, d, J 9.8 Hz, C4), 6.65 (1H, d, J 8.5 Hz, C8), 6.84 (1H, d, J 2.5 Hz, C5), 6.95 (1H, dd, J 8.5, 2.5 Hz, C7); δ_{C} (100 MHz; CDCl_3) 14.2 (CH_3), 37.4 (2 x CH_2), 76.8 (C2), 117.2 (C5), 123.0 (C4), 126.0 (C3), 127.1 (quat., C9), 127.3 (C8), 128.6 (C7), 134.7 (quat., C6), 152.1 (quat., C10); m/z 208.06; $C_{12}H_{13}\text{ClO}$ requires 208.0655. Mass spectra were obtained as low-resolution mass spectra after attempts to obtain high resolution spectra from Swansea failed due to decomposition during travel.

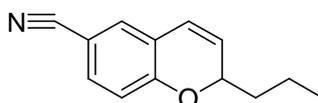
6-Nitro-2-propyl-2H-1-benzopyran



Prepared *via* the general procedure for the formation of chromenes using *para* nitrophenol (8.0 g, 58 mmol) as the required phenol, *trans*-2-hexenal diethyl acetal

(5.0 ml, 29 mmol) as the required acetal and 3-picoline (0.80 ml, 0.25 eq). The reaction was columned directly using toluene, yielding the product as a yellow oil (5.7 g, 89%) ν_{max} (film) / cm^{-1} 3015, 2875, 2936, 2128, 1520, 1479, 1220, 1190, 1068, 961; δ_{H} (400 MHz; CDCl_3) 0.83 (3H, t, J 6.6 Hz, CH_3), 1.32-1.43 (2H, m, CH_2 , $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.51-1.66 (2H, m, CH_2 , $\text{CH}_2\text{CH}_2\text{CH}_3$), 4.87-4.90 (1H, m, CH, C2), 5.66 (1H, dd, J 10.2, 3.2 Hz, C3), 6.26 (1H, d, J 10.2 Hz, C4), 6.67 (1H, d, J 9.5 Hz, C8), 7.65 (1H, d, J 2.8 Hz, C5), 7.82 (1H, dd, J 9.5, 2.8 Hz, C7); δ_{C} (100 MHz; CDCl_3) 13.4 (CH_3), 17.7 (2 x CH_2), 77.0 (C2), 115.8 (C5), 121.9 (quat., C9), 123.0 (C4), 124.9 (C3), 127.5 (C8), 130.0 (C7), 141.2 (quat., C6), 166.2 (quat., C10); m/z 219.08985; $\text{C}_{12}\text{H}_{13}\text{NO}_3$ requires 219.08959.

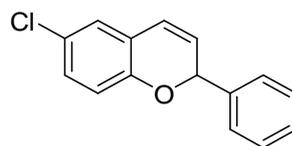
6-Cyano-2-propyl-2H-1-benzopyran



173

Prepared *via* the general procedure for the formation of chromenes using *para* cyanophenol (6.9 g, 58 mmol) as the required phenol, *trans*-2-hexenal diethyl acetal (5.0 ml, 29 mmol) as the required acetal and 3-picoline (0.80 ml, 0.25 eq). The reaction was columned directly using toluene, yielding the product as a yellow oil (5.1 g, 89%). ν_{max} (film) / cm^{-1} 3024, 2854, 2251, 1444, 1268, 1169, 1167, 981; δ_{H} (400 MHz; CDCl_3) 0.95 (3H, t, J 6.2 Hz, CH_3), 1.47-1.62 (4H, m, 2 x CH_2), 4.89-4.91 (1H, m, CH, C2), 5.75 (1H, dd, J 10.6, 3.2 Hz, C3), 6.31 (1H, d, J 10.6 Hz, C4), 6.76 (1H, d, J 8.1 Hz, C8), 7.18 (1H, d, J 2.0 Hz, C5), 7.33 (1H, dd, J 8.1, 2.0 Hz, C7); δ_{C} (100 MHz; CDCl_3) 14.4 (CH_3), 37.8 (2 x CH_2), 75.9 (C2), 103.8 (quat., C9), 116.7 (C5), 119.4 (quat., C6), 122.0 (C4), 122.3 (quat., C10), 127.5 (C3), 130.0 (C8), 133.2 (C7), 158.7 (quat., CN); m/z 199.1; $\text{C}_{13}\text{H}_{13}\text{NO}$ requires 199.0997. Mass spectra were obtained as low-resolution mass spectra after attempts to obtain high resolution spectra from Swansea failed due to decomposition during travel.

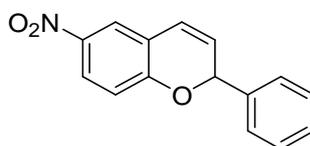
6-Chloro-2-phenyl-2H-1-benzopyran¹¹⁶



177

Prepared *via* the general procedure for the formation of chromenes using *para* chlorophenol (7.4 g, 58 mmol) as the required phenol, *trans*-cinnamaldehyde diethylacetal (5.0 ml, 29 mmol) as the required acetal and 3-picoline (0.70 ml, 0.25 eq). Product yielded as a clear yellow oil (4.8 g, 68%); ν_{max} (film) / cm^{-1} 2992, 2956, 1585, 1464, 1451, 1299, 1244, 1254, 1162; δ_{H} (400 MHz; CDCl_3) 5.93 (1H, dd, J 10.3, 3.6 Hz, C3), 6.00 (1H, dd, J 3.6, 1.6 Hz, CH, C2), 6.55 (1H, dd, J 10.3, 1.6 Hz, C4), 6.82 (1H, d, J 8.8 Hz, C8), 7.08 (1H, d, J 2.4 Hz, C5), 7.15 (1H, dd, J 8.8, 2.4 Hz, C7), 7.44-7.50 (3H, m, arom., *meta* and *para* on phenyl substituent), 7.52-7.56 (2H, m, arom., *ortho* on phenyl substituent); δ_{C} (100 MHz; CDCl_3) 77.4 (C2), 117.4 (C5), 122.7 (quat., C9), 123.2 (C4), 126.1 (C3), 126.2 (C8), 127.5 (2 x arom., *ortho* on phenyl substituent), 128.5 (2 x arom., *meta* on phenyl substituent), 128.7 (arom., *para* on phenyl substituent), 129.2 (C7), 134.7 (quat., C6), 140.3 (quat., C on phenyl substituent), 154.2 (quat., C10); m/z 242.7; $\text{C}_{15}\text{H}_{11}\text{ClO}$ requires 242.0498. Mass spectra were obtained as low-resolution mass spectra after attempts to obtain high resolution spectra from Swansea failed due to decomposition during travel.

6-Nitro-2-phenyl-2H-1-benzopyran¹¹⁶

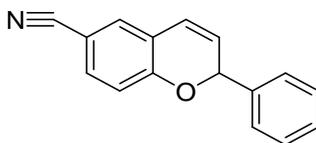


176

Prepared *via* the general procedure for the formation of chromenes using *para* nitrophenol (8.0 g, 58 mmol) as the required phenol, *trans*-cinnamaldehyde diethylacetal (5.0 ml, 29 mmol) as the required acetal and 3-picoline (0.70 ml, 0.25 eq). Product yielded as yellow oil (5.1 g, 70%); ν_{max} (film) / cm^{-1} 3024, 2104, 1585,

1564, 1486, 1298, 1278, 1155, 1067; δ_{H} (400 MHz; CDCl_3) 5.94 (1H, dd, J 10.4, 3.2 Hz, C3), 6.06 (1H, dd, J 3.2, 1.6 Hz, CH, C2), 6.59 (1H, dd, J 10.4, 1.6 Hz, C4), 6.81 (1H, d, J 8.8 Hz, C8), 7.35-7.42 (5H, m, phenyl substituent), 7.94 (1H, d, J 2.8 Hz, C5), 8.01 (1H, dd, J 8.8, 2.8 Hz, C7); δ_{C} (100 MHz; CDCl_3) 78.4 (C2), 116.3 (C5), 120.8 (quat., C9), 122.2 (C8), 122.3 (C4), 125.6 (C3), 126.3 (C7), 127.7 (3 x C arom., *meta* and *para* on phenyl substituent), 128.9 (2 x C arom., *ortho* on phenyl substituent), 139.4 (quat., C6), 158.4 (quat., C10), m/z : 253.07389; $\text{C}_{15}\text{H}_{11}\text{O}_3\text{N}$ requires 253.07389.

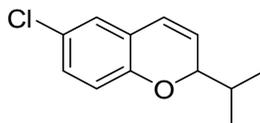
6-Cyano-2-phenyl-2H-1-benzopyran



164

Prepared *via* the general procedure for the formation of chromenes using *para*-cyanophenol (6.8 g, 58 mmol) as the phenol, *trans*-cinnamaldehyde diethylacetal (5.0 ml, 29 mmol) as the required acetal and 3-picoline (0.70 ml, 0.25 eq). Product yielded as clear crystals crystallized after column chromatography in light petroleum:ethyl acetate (10:1 to 1:1) and an off white oil (4.8 g, 71%) m.p. 118-120 °C; ν_{max} (film) / cm^{-1} 3092, 2887, 1560, 1505, 1275, 1150, 1087, Found C, 82.14; H, 4.96; N, 5.87. $\text{C}_{16}\text{H}_{11}\text{NO}$ requires C, 82.38; H, 4.75; N, 6.00; δ_{H} (400 MHz; CDCl_3); 5.82 (1H, dd, J 9.6, 3.2 Hz, C3), 5.94 (1H, dd, J 3.2, 1.6 Hz, C2), 6.43 (1H, dd, J 9.6, 1.6 Hz, C4), 6.72 (1H, d, J 8.4 Hz, C8), 7.22 (1H, d, J 2.0 Hz, C5), 7.32-7.38 (5H, m, phenyl substituent), 7.40 (1H, dd, J 8.4, 2.0 Hz, C7), δ_{C} (100 MHz; CDCl_3) 77.4 (C2), 104.3 (C5), 116.9 (C quat., C9), 119.1 (C8), 121.6 (C4), 122.2 (C3), 126.3 (CH arom., *para* on phenyl substituent), 127.0 (2 x CH arom., *ortho* on phenyl substituent), 130.3 (2 x CH arom., *meta* on phenyl substituent), 131.3 (C7), 133.7 (C quat., on phenyl substituent), 138.4 (C quat., C6), 154.6 (C quat., C10), 156.7 (CN); m/z 233.08406; $\text{C}_{16}\text{H}_{11}\text{NO}$ requires 233.26461. Crystal structure obtained, see page 199.

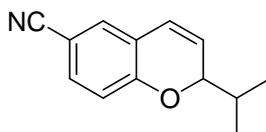
6-Chloro-2-isopropyl-2H-1-benzopyran



179

Prepared *via* the general procedure for the formation of chromenes using *para*-chlorophenol (7.4 g, 2 eq, 58 mmol) as the phenol, *trans*-4-methyl-2-pentenal-diethyl acetal (5.0 ml, 29 mmol) as the required acetal and 3-picoline (0.70 ml, 0.25 eq). Product yielded as clear white oil (3.5 g, 62%); ν_{max} (film) / cm^{-1} 3156, 2957, 1584, 1498, 1286, 1304, 1087; δ_{H} (400 MHz; CDCl_3); 1.00 (3H, d, J 9.1 Hz, CH_3), 1.02 (3H, d, J 9.1 Hz, CH_3), 1.94-2.05 (1H, m, $\text{CH}(\text{CH}_3)_2$), 4.61-4.65 (1H, m, C2), 5.74 (1H, dd, J 13.4, 4.4 Hz, C3), 6.35 (1H, d, J 13.4 Hz, C4), 6.69 (1H, d, J 8.4 Hz, C8), 6.90 (1H, d, J 3.4 Hz, C5), 7.02 (1H, dd, J 8.4, 3.4 Hz, C7); δ_{C} (100 MHz; CDCl_3) 17.7 (CH_3), 17.9 (CH_3), 33.7 ($\text{CH}(\text{CH}_3)_2$), 80.3 (C2), 117.0 (C5), 123.4 (C4), 123.7 (quat., C, C9), 125.4 (C3), 127.1 (C7), 134.8 (C8), 152.7 (quat., C, C6), 167.2 (quat., C, C10); m/z 208.6; $\text{C}_{12}\text{H}_{13}\text{ClO}$ requires 208.6825. Mass spectra were obtained as low-resolution mass spectra after attempts to obtain high resolution spectra from Swansea failed due to decomposition during travel.

6-Cyano-2-isopropyl-2H-1-benzopyran

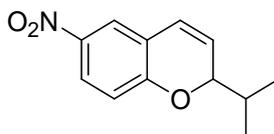


178

Prepared *via* the general procedure for the formation of chromenes using *para*-cyanophenol (6.9 g, 2 eq, 58 mmol) as the phenol, *trans*-4-methyl-2-pentenal-diethyl acetal (5.0 ml, 29 mmol) as the required acetal and 3-picoline (0.70 ml, 0.25 eq). Product yielded a yellow oil (4.8 g, 84%), ν_{max} (film) / cm^{-1} 3053, 2785, 1596, 1545, 1376, 1245, 1137; δ_{H} (400 MHz; CDCl_3); 0.96 (3H, d, J 8.6 Hz, CH_3), 0.99 (3H, d, J 8.6 Hz, CH_3), 1.91-2.01 (1H, m, $\text{CH}(\text{CH}_3)_2$), 4.86-4.93 (1H, m, C2), 5.65 (1H, dd, J 12.5, 4.2 Hz, C3), 6.36 (1H, d, J 12.5 Hz, C4), 6.72 (1H, d, J 8.3 Hz, C8),

7.18 (1H, d, J 2.4 Hz, C5), 7.38 (1H, dd, J 8.3, 2.4 Hz, C7); δ_C (100 MHz; CDCl_3) 18.9 (CH_3), 19.1 (CH_3), 34.2 ($\text{CH}(\text{CH}_3)_2$), 82.1 (C2), 104.3 (quat., C, C9), 116.9 (C5), 119.1 (quat., C, C6), 123.6 (quat., C, CN), 123.9 (C4), 126.5 (C3), 131.4 (C7), 134.9 (C8), 158.7 (quat., C, C10); m/z 199.2; $\text{C}_{13}\text{H}_{13}\text{NO}$ requires 199.2586. Mass spectra were obtained as low-resolution mass spectra after attempts to obtain high resolution spectra from Swansea failed due to decomposition during travel.

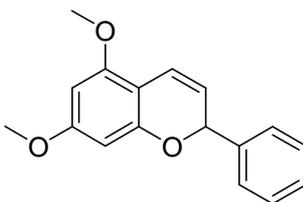
6-Nitro-2-isopropyl-2H-1-benzopyran



180

Prepared *via* the general procedure for the formation of chromenes using *para*-nitrophenol (8.0 g, 2 eq, 58 mmol) as the phenol, *trans*-4-methyl-2-pentenal-diethyl acetal (5.0 ml, 29 mmol) as the required acetal and 3-picoline (0.70 ml, 0.25 eq). Product yielded as yellow crystals (5.1 g, 80%) m.p. 124-126 °C; ν_{max} (film) / cm^{-1} 3021, 2667, 1560, 1535, 1365, 1230, 1084; δ_{H} (400 MHz; CDCl_3); 0.99 (3H, d, J 8.5 Hz, CH_3), 1.03 (3H, d, J 8.5 Hz, CH_3), 1.95-2.06 (1H, m, $\text{CH}(\text{CH}_3)_2$), 4.83-4.87 (1H, m, C2), 5.78 (1H, dd, J 13.6, 4.3 Hz, C3), 6.45 (1H, d, J 13.6 Hz, C4), 6.79 (1H, d, J 8.8 Hz, C8), 7.83 (1H, d, J 3.6 Hz, C5), 7.99 (1H, dd, J 8.8, 3.6 Hz, C7); δ_C (100 MHz; CDCl_3) 17.2 (CH_3), 17.8 (CH_3), 34.2 ($\text{CH}(\text{CH}_3)_2$), 81.5 (C2), 115.9 (C4), 121.4 (C5), 122.2 (C3), 125.6 (C7), 129.1 (quat., C, C9), 129.7 (C8), 141.5 (quat., C, C6), 159.8 (quat., C, C10); m/z 220.0968; $\text{C}_{12}\text{H}_{13}\text{NO}_3$ [$+\text{H}^+$] requires 220.0968.

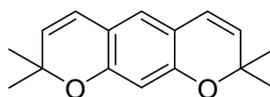
5,7-Dimethyl-2-phenyl-2H-1-benzopyran¹¹⁷



131

Prepared *via* the general procedure for the formation of chromenes, using 3,5-dimethoxyphenol (8.8 g, 58 mmol) as the required phenol, *trans*-cinnamaldehyde diethylacetal (5.0 ml, 29 mmol) as the required acetal and 3-picoline (0.70 ml, 0.25 eq).. Product yielded as a yellow oil (1.9 g, 58%) ν_{max} (film) / cm^{-1} 3092, 2887, 1560, 1505, 1275, 1150, 1087; δ_{H} (400 MHz; CDCl_3); 3.78 (3H, s, OCH_3 off C5), 3.84 (3H, s, OCH_3 off C7), 5.76 (1H, dd, J 9.9, 3.5 Hz, C3), 5.96 (1H, d, J 3.5, 1.8 Hz, C2), 6.18 (1H, d, J 2.2 Hz, C6), 6.24 (1H, d, J 2.2 Hz, C8), 7.00 (1H, dd, J 9.9, 1.8 Hz, C4), 7.42-7.49 (5H, m, Ph); δ_{C} (100 MHz; CDCl_3) 55.3 (OCH_3 off C5), 55.9 (CH_3 off C7), 77.8 (C2), 92.9 (C6), 94.7 (C8), 104.5 (C9), 119.0 (C4), 119.9 (C3), 126.0 (2 x CH, *ortho* on phenyl substituent), 127.6 (CH, *para* on phenyl substituent), 128.7 (2 x CH, *meta* on phenyl substituent), 141.1 (C quat., on phenyl substituent), 155.3 (C5), 159.2 (C10), 161.5 (C7).

2,2,8,8-Tetramethyl-2H,8H-pyrano[3,2-g]chromene¹¹⁸

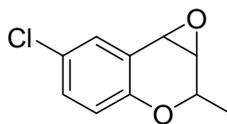


221

Prepared *via* the general procedure for the formation of chromenes using resorcinol (1.99 g, 18.1 mmol, 1 eq) as the required phenol, 3-methyl-2-butenal (5.7 ml, 36 mmol, 2 eq) as the required acetal and 3-picoline (0.90 ml, 0.50 eq) yielding the product as a clear oil. ν_{max} (film) / cm^{-1} 3125, 2951, 2654, 2012, 1645, 1485, 1327, 1240, 1058; δ_{H} (400 MHz; CDCl_3) 1.37 (12H, s, (2 x CH_3) x 2), 5.39 (2H, d, J 9.8 Hz, CH x 2, alkene, C3,7), 6.18 (2H, d, J 9.8 Hz, CH x 2, alkene, C4,6), 6.30 (1H, s, CH arom., C5), 6.53 (1H, s, CH arom., C10); δ_{C} (100 MHz; CDCl_3) 26.1 (4 x C of CH_3), 103.6 (CH arom., C5), 115.6 (2 x quat., C2,8), 122.7 (CH x 2 alkene, C4,6), 126.3, CH arom., C10), 127.0 (CH x 2 alkene, C3,7), 136.7 (2 x quat., C12,13), 159.4 (2 x quat., C11,14).

**The Epoxides - Prepared Via The General Epoxidation Routes Described
Earlier (See pages 135-136).**

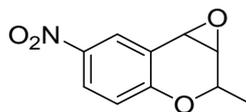
6-Chloro-2-methyl-benzopyran oxide



183

Prepared by the epoxidation routes described above. The product epoxide was obtained as a clear oil with a *cis:trans* ratio of 50:50 when using *m*-CPBA and 1:10 when using the chiral TPPP conditions with catalyst (**132**). ν_{\max} (film) / cm^{-1} 2922, 2853, 2226, 1462; δ_{H} (400 MHz; CDCl_3) 1.18 (3H, d, *J* 6.8 Hz, Me on *trans* epoxide), 1.46 (3H, d, *J* 6.4 Hz, Me on *cis* epoxide), 3.48 (1H, dd, *J* 14.4, 7.4 Hz, C3, epox CH on *trans* epoxide), 3.54 (1H, d, *J* 11.8, 7.4 Hz, C3, epox CH on *cis* epoxide), 3.71 (1H, d, *J* 7.4 Hz, C4, epox CH on *trans* epoxide), 3.75 (1H, d, *J* 7.4 Hz, C4, epox CH on *cis* epoxide), 4.13 (1H, dd, *J* 11.8, 6.4 Hz, C2, CH on *cis* epoxide), 4.63 (1H, dd, *J* 14.4, 6.8 Hz, C2, CH on *trans* epoxide), 6.66 (2H, d, *J* 8.4 Hz, C8 on *cis* and *trans* epoxide), 7.08 (2H, d, *J* 2.8 Hz, C5 on *cis* and *trans* epoxide), 7.21 (2H, dd, *J* 8.4, 2.8 Hz, C7 on *cis* and *trans* epoxide); δ_{C} (100 MHz; CDCl_3) 16.1 (CH_3 , on *trans* epoxide), 18.6 (CH_3 , on *cis* epoxide), 48.6 (epox CH on *trans* epoxide, C3), 50.0 (epox CH on *cis* epoxide, C3), 59.2 (epox CH on *trans* epoxide, C4), 59.6 (epox CH on *cis* epoxide, C4), 68.7 (CH, on *trans* epoxide, C2), 69.0 (CH, on *cis* epoxide, C2), 119.1 (2 x CH arom., on *cis* and *trans* epoxide, C5), 125.7 (2 x quat., on *cis* and *trans* epoxide, C9), 128.6 (2 x CH arom, on *cis* and *trans* epoxide, C6), 129.3 (2 x CH arom., on *cis* and *trans* epoxide, C8), 150.1 (2 x quat., on *cis* and *trans* epoxide, C10), 152.6 (2 x quat., on *cis* and *trans* epoxide, C6); *m/z* 196.01; $\text{C}_{10}\text{H}_9\text{ClO}_2$ requires 196.0291. Mass spectra were obtained as low-resolution mass spectra after attempts to obtain high resolution spectra from Swansea failed due to decomposition during travel.

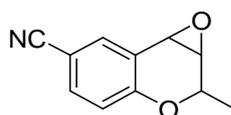
6-Nitro-2-methyl-benzopyran oxide



182

Prepared by the epoxidation routes described above. The product epoxide was obtained as a clear oil with a *cis:trans* ratio of 50:50 when using *m*-CPBA and 1:20 when using the chiral TPPP conditions with catalyst (**132**). ν_{max} (film) / cm^{-1} 2915, 2758, 2375, 1480, 1425, 1211 δ_{H} (400 MHz; CDCl_3) 1.28 (3H, d, J 6.8 Hz, Me on *trans* epoxide), 1.50 (3H, d, J 6.4 Hz, Me on *cis* epoxide), 3.59 (1H, dd, J 13.8, 7.2 Hz, C3, epox CH on *trans* epoxide), 3.65 (1H, dd, J 12.2, 7.4 Hz, C3, epox CH on *cis* epoxide), 3.88 (1H, d, J 7.2 Hz, C4, epox CH on *trans* epoxide), 3.92 (1H, d, J 7.4 Hz, C4, epox CH on *cis* epoxide), 4.35 (1H, dd, J 12.2, 6.4 Hz, C2, CH on *cis* epoxide), 4.79 (1H, dd, J 13.8, 6.8 Hz, C2, CH on *trans* epoxide), 6.81 (1H, dd, J 8.8 Hz, C8 on *cis* and *trans* epoxide), 8.03 (1H, d, J 1.2 Hz, C5 on *cis* and *trans* epoxide), 8.20 (1H, dd, J 8.8, 1.2 Hz, C7 on *cis* and *trans* epoxide); δ_{C} (100 MHz; CDCl_3) 17.1 (CH_3 , on *trans* epoxide), 18.9 (CH_3 , on *cis* epoxide), 49.9 (epox CH on *trans* epoxide, C3), 52.2 (epox CH on *cis* epoxide, C3), 60.2 (epox CH on *trans* epoxide, C4), 60.4 (epox CH on *cis* epoxide, C4), 69.7 (CH, on *trans* epoxide, C2), 70.0 (CH, on *cis* epoxide, C2), 120.1 (2 x CH arom., *cis* and *trans* epoxide, C6), 126.4 (2 x quat., *cis* and *trans* epoxide, C9), 128.9 (2 x CH arom., *cis* and *trans* epoxide, C8), 130.7 (2 x CH arom., *cis* and *trans* epoxide, C7), 152.8 (2 x quat., *cis* and *trans* epoxide, C10), 154.1 (2 x quat., *cis* and *trans* epoxide, C6); m/z 208.06072, $\text{C}_{10}\text{H}_9\text{NO}_4$ requires 207.05316 (+H = 208.06098).

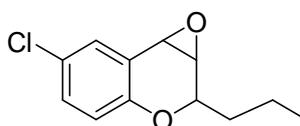
6-Cyano-2-methyl-benzopyran oxide⁷⁵



181

Prepared by the epoxidation routes described above. The product epoxide was obtained as clear crystals with a *cis:trans* ratio of 50:50 when using *m*-CPBA and 1:15 when using the chiral TPPP conditions with catalyst (**132**). m.p. 52 °C (lit 55-56 °C)¹³; ν_{max} (film) / cm^{-1} 2230, 1620, 1585; δ_{H} (400 MHz; CDCl_3) 1.35 (3H, d, *J* 7.0 Hz, Me on *trans* epoxide), 1.60 (3H, d, *J* 6.5 Hz, Me on *cis* epoxide), 3.65 (1H, d, *J* 14.2, 6.4 Hz, epox CH on *trans* epoxide, C3), 3.71 (1H, d, *J* 11.8, 6.4 Hz, epox CH on *cis* epoxide, C3), 3.89 (1H, d, *J* 6.4 Hz, epox CH on *trans* epoxide, C4), 3.94 (1H, d, *J* 6.4 Hz, epox CH on *cis* epoxide, C4), 4.39 (1H, dd, *J* 11.8, 6.5 Hz, CH on *cis* epoxide, C2), 4.84 (1H, dd, *J* 14.2, 7.0 Hz, CH on *trans* epoxide, C2), 6.89 (1H, d, *J* 8.5 Hz, on *trans* and *cis* epoxide *cis* and *trans*, C8), 7.53 (1H, dd, *J* 8.5, 2.0 Hz, on *trans* and *cis* epoxide, C7), 7.65 (1H, d, *J* 2.0 Hz, on *trans* epoxide, C5), 7.68 (1H, d, *J* 2.0 Hz, on *cis* epoxide, C5); δ_{C} (100 MHz; CDCl_3) 16.1 (CH_3 , on *trans* epoxide), 17.5 (CH_3 , on *cis* epoxide), 48.4 (epox CH on *trans* epoxide, C3), 51.4 (epox CH on *cis* epoxide, C3), 58.2 (epox CH on *trans* epoxide, C4), 59.4 (epox CH on *cis* epoxide, C4), 67.5 (CH, on *trans* epoxide, C2), 69.1 (CH, on *cis* epoxide, C2), 119.4 (2 x CH arom., on *trans* and *cis* epoxide, C5), 124.5 (2 x quat., on *trans* and *cis* epoxide, C9), 125.8 (2 x CH arom., on *trans* and *cis* epoxide, C8), 129.7 (2 x CH arom., on *trans* and *cis* epoxide, C7), 134.6 (quat., C, CN, on *trans* and *cis* epoxide), 152.8 (2 x quat., on *trans* and *cis* epoxide, C6), 153.1 (2 x quat., on *trans* and *cis* epoxide, C10).

6-Chloro-2-propyl-benzopyran oxide

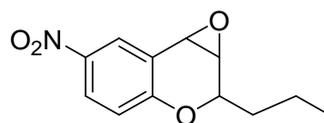


185

Prepared by the epoxidation routes described above. The product epoxide was obtained as a clear oil with a *cis:trans* ratio of 40:60 when using *m*-CPBA and 1:14 when using the chiral TPPP conditions with catalyst (**132**). ν_{max} (film) / cm^{-1} 2853, 2226, 1508, 1462, 1358; δ_{H} (400 MHz; CDCl_3) 0.85 (3H, t, *J* 7.2 Hz, CH_3 on *trans* epoxide), 0.92 (3H, t, *J* 6.8 Hz, CH_3 on *cis* epoxide), 1.38-1.42 (4H, m, 2 x CH_2 on *trans* epoxide), 1.42-1.53 (4H, m, 2 x CH_2 on *cis* epoxide), 3.50 (1H, dd, *J* 14.4, 4.2

Hz, epox *CH* on *trans* epoxide, C3), 3.58 (1H, d, *J* 11.4, 4.4 Hz, epox *CH* on *cis* epoxide, C3), 3.71 (1H, d, *J* 4.2 Hz, epox *CH* on *trans* epoxide, C4), 3.73 (1H, d, *J* 4.4 Hz, epox *CH* on *cis* epoxide, C4), 3.96-3.99 (1H, m, *CH*, on *cis* epoxide, C2), 4.44-4.47 (1H, m, *CH*, on *trans* epoxide, C2), 6.65-6.68 (1H, m, *CH* arom., on *trans* and *cis* epoxide, C5), 7.06-7.09 (1H, m, *CH* arom., on *trans* and *cis* epoxide, C8), 7.19-7.22 (1H, m, *CH* arom., on *trans* and *cis* epoxide, C7); δ_C (100 MHz; $CDCl_3$) 13.8 (CH_3 , on *trans* epoxide), 14.1 (CH_3 , on *cis* epoxide), 18.3 (CH_2 , on *trans* and *cis* epoxide), 32.5 (CH_2 , on *trans* and *cis* epoxide), 48.8 (epox., *CH* on *trans* epoxide, C3), 49.7 (epox., *CH* on *cis* epoxide, C3), 58.8 (epox., *CH* on *trans* epoxide, C4), 58.9 (epox., *CH* on *cis* epoxide, C4), 70.5 (on *cis* epoxide, C2), 72.1 (on *trans* epoxide, C2), 119.4 (arom *CH*, on *trans* and *cis* epoxide, C5), 128.1 (arom *CH*, on *trans* and *cis* epoxide, C8), 130.3 (arom *CH*, on *trans* and *cis* epoxide, C7), 134.6 (quat., on *trans* and *cis* epoxide, C9), 153.1 (quat., on *trans* and *cis* epoxide, C6), 164.4 (quat., on *trans* and *cis* epoxide, C10); *m/z* 224; $C_{12}H_{13}ClO_2$ requires 224.0604. Mass spectra were obtained as low-resolution mass spectra after attempts to obtain high resolution spectra from Swansea failed due to decomposition during travel.

6-Nitro-2-propyl-benzopyran oxide

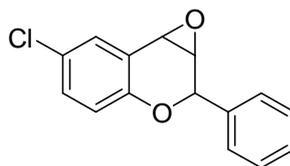


184

Prepared by the epoxidation routes described above. The product epoxide was obtained as a clear oil with a *cis:trans* ratio of 40:60 when using *m*-CPBA and 1:25 when using the chiral TPPP conditions with catalyst (**132**). ν_{max} (film) / cm^{-1} 2922, 2226, 1542, 1462, 1154; δ_H (400 MHz; $CDCl_3$) 0.88 (3H, t, *J* 9.5 Hz, CH_3 on *trans* epoxide), 0.96 (3H, t, *J* 9.0 Hz, CH_3 on *cis* epoxide), 1.45-1.55 (4H, m, 2 x CH_2 , on *trans* epoxide), 1.65-1.72 (4H, m, 2 x CH_2 , on *cis* epoxide), 3.61 (1H, d, *J* 14.2, 4.4 Hz, epox *CH* on *trans* epoxide, C3), 3.70 (1H, d, *J* 11.6, 4.4 Hz, epox *CH* on *cis* epoxide, C3), 3.88 (1H, d, *J* 4.4 Hz, epox *CH* on *trans* epoxide, C4), 3.91 (1H, d, *J* 4.4 Hz, epox *CH* on *cis* epoxide, C4), 4.19-4.22 (1H, m, *CH*, on *cis* epoxide, C2), 4.27-4.48 (1H, m, *CH*, on *trans* epoxide, C2), 6.83 (1H, d, *J* 9.2 Hz, arom *CH*, on

trans and *cis* epoxide, C8), 8.04-8.08 (1H, m, arom CH, on *trans* and *cis* epoxide, C5), 8.20-8.23 (1H, m, arom CH, on *trans* and *cis* epoxide, C7); δ_C (100 MHz; CDCl₃) 11.8 (on *trans* epoxide), 12.0 (on *cis* epoxide), 16.3 (CH₃, on *trans* epoxide), 17.0 (CH₃, on *cis* epoxide), 27.3 (2 x CH₂, on *trans* epoxide), 31.1 (2 x CH₂, on *cis* epoxide), 46.5 (epox., CH on *trans* epoxide, C3), 47.3 (epox., CH on *cis* epoxide, C3), 56.3 (epox., CH on *trans* and *cis* epoxide, C4), 71.2 (on *cis* epoxide, C2), 71.5 (on *trans* epoxide, C2), 116.6 (arom CH, on *trans* and *cis* epoxide, C5), 124.0 (arom CH, on *trans* and *cis* epoxide, C8), 125.3 (arom CH, on *trans* and *cis* epoxide, C7), 139.2 (quat., on *trans* and *cis* epoxide, C9), 155.8 (quat., on *trans* and *cis* epoxide, C10), 157.6 (quat., on *trans* and *cis* epoxide, C6); *m/z* 235; C₁₄H₁₉NO₄ requires 235.0845. Mass spectra were obtained as low-resolution mass spectra after attempts to obtain high resolution spectra from Swansea failed due to decomposition during travel.

6-Chloro-2-phenyl-benzopyran oxide

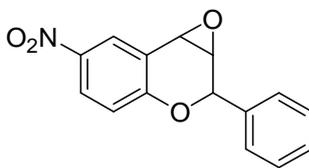


188

Prepared by the epoxidation routes described above. The product epoxide was obtained as a clear oil with a *cis:trans* ratio of 20:80 when using *m*-CPBA and 1:20 when using the chiral TPPP conditions with catalyst (**132**). ν_{\max} (film) / cm⁻¹ 2922, 2754, 2126, 1462; δ_H (400 MHz; CDCl₃) 3.82 (1H, dd, *J* 4.4, 1.2 Hz, epox CH on *trans* epoxide, C3), 3.84 (1H, d, *J* 4.4 Hz, epox CH on *cis* epoxide, C3), 3.90 (1H, d, *J* 4.4 Hz, epox CH on *cis* epoxide, C4), 3.91 (1H, d, *J* 4.4 Hz, epox CH on *trans* epoxide, C4), 4.99 (1H, s, CH, on *cis* epoxide, C2), 5.54 (1H, d, *J* 1.2 Hz, CH, on *trans* epoxide, C2), 6.69 (1H, d, *J* 8.8 Hz, arom CH, on *trans* and *cis* epoxide, C8), 7.13 (1H, dd, *J* 8.8, 2.4 Hz, arom CH, on *trans* and *cis* epoxide, C7), 7.24-7.27 (5H, m, phenyl substituent, on *trans* and *cis* epoxide), 7.30 (1H, d, *J* 2.8 Hz, arom CH, on *trans* and *cis* epoxide, C5); δ_C (100 MHz; CDCl₃) 48.7 (epox., CH on *trans* epoxide, C3), 50.0 (epox., CH on *cis* epoxide, C3), 58.0 (epox., CH on *trans* epoxide, C4),

59.9 (epox., CH on *cis* epoxide, C4), 75.4 (on *trans* and *cis* epoxide, C2), 125.3 (quat., on *trans* and *cis* epoxide, C9), 126.0 (arom CH, on *trans* and *cis* epoxide, C8), 126.6 (arom CH, on *trans* and *cis* epoxide, C5), 127.1 (arom CH, on *trans* and *cis* epoxide, C7), 127.5 (2 x arom., *ortho* on phenyl substituent), 128.5 (2 x arom., *meta* on phenyl substituent), 128.7 (arom., *para* on phenyl substituent), 136.0 (quat., on *trans* and *cis* epoxide, on phenyl substituent), 141.6 (quat., on *trans* and *cis* epoxide, C6), 157.8 (quat., on *trans* and *cis* epoxide, C10); m/z 258; C₁₅H₁₁ClO₂ requires 258.0448. Mass spectra were obtained as low-resolution mass spectra after attempts to obtain high resolution spectra from Swansea failed due to decomposition during travel.

6-Nitro-2-phenyl-benzopyran oxide

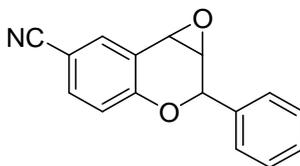


187

Prepared by the epoxidation routes described above. The product epoxide was obtained as a clear oil with a *cis:trans* ratio of 20:80 when using *m*-CPBA. The reaction did not proceed when using the TPPP conditions with catalyst (**132**). ν_{max} (film) / cm^{-1} 2820, 2226, 1442, 1385; δ_{H} (400 MHz; CDCl₃) 3.84 (1H, d, J 4.8 Hz, epox CH on *trans* epoxide, C3), 3.90 (1H, d, J 4.4 Hz, epox CH on *cis* epoxide, C3), 4.02-4.05 (1H, d, epox CH, J 4.8 Hz on *trans* and J 4.4 Hz on *cis* epoxide, C4), 5.14 (1H, s, CH, on *cis* epoxide, C2), 5.64 (1H, s, CH, on *trans* epoxide, C2), 6.81 (1H, d, J 8.8 Hz, arom CH, on *trans* epoxide, C8), 6.91 (1H, d, J 8.8 Hz, arom CH, on *cis* epoxide, C8), 8.06-8.08 (2H, m, arom CH, on *trans* and *cis* epoxide, *ortho* on phenyl substituent), 8.26-8.28 (3H, m, arom CH, on *trans* and *cis* epoxide, *meta* and *para* on phenyl substituent), 8.05 (1H, dd, J 8.8, 2.4 Hz, on *trans* and *cis* epoxide, C7), 8.25 (1H, d, J 2.4 Hz, C5 on *trans* epoxide), 8.28 (1H, d, J 2.4 Hz, C5 on *cis* epoxide); δ_{C} (100 MHz; CDCl₃) 48.7 (epox., CH on *trans* epoxide, C3), 50.0 (epox., CH on *cis* epoxide, C3), 58.0 (epox., CH on *trans* epoxide, C4), 59.9 (epox., CH on *cis* epoxide, C4), 75.4 (on *trans* and *cis* epoxide, C2), 125.3 (quat., on *trans* and *cis*

epoxide, C9), 126.0 (arom CH, on *trans* and *cis* epoxide, C8), 126.6 (arom CH, on *trans* and *cis* epoxide, C7), 127.1 (arom CH, on *trans* and *cis* epoxide, C5), 128.5 (2 x arom., *ortho* on phenyl substituent), 129.5 (2 x arom., *meta* on phenyl substituent), 129.7 (arom., *para* on phenyl substituent), 136.0 (quat., on *trans* and *cis* epoxide, on phenyl substituent), 141.6 (quat., on *trans* and *cis* epoxide, C10), 157.8 (quat., on *trans* and *cis* epoxide, C6); m/z 269; C₁₅H₁₁NO₄ requires 269.0688. Mass spectra were obtained as low-resolution mass spectra after attempts to obtain high resolution spectra from Swansea failed due to decomposition during travel.

6-Cyano-2-phenyl-benzopyran oxide

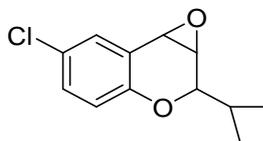


186

Prepared by the epoxidation routes described above. The product epoxide was obtained as a clear oil with a *cis:trans* ratio of 20:80 when using *m*-CPBA and 1:24 when using the chiral TPPP conditions with catalyst (**132**). ν_{max} (film) / cm^{-1} 2822, 2653, 2226, 1554, 1462; δ_{H} (400 MHz; CDCl₃) 3.83 (1H, dd, J 4.4, 1.2 Hz, epox CH on *trans* epoxide, C3), 3.90 (1H, d, J 4.4 Hz, epox CH on *cis* epoxide, C3), 3.96-3.97 (1H, d, epox CH, J 4.4 Hz on both *trans* and *cis* epoxide, C4), 5.14 (1H, s, CH, on *cis* epoxide, C2), 5.64 (1H, d, J 1.2 Hz, CH, on *trans* epoxide, C2), 6.81 (1H, d, J 8.5 Hz, arom CH, on *trans* epoxide, C8), 6.91 (1H, d, J 8.5 Hz, arom CH, on *cis* epoxide, C8), 8.06-8.08 (2H, m, arom CH, on *trans* and *cis* epoxide, *ortho* on phenyl substituent), 8.26-8.28 (3H, m, arom CH, on *trans* and *cis* epoxide, *meta* and *para* on phenyl substituent), 7.55 (1H, dd, J 8.5, 2.0 Hz, C7 on *trans* and *cis* epoxide), 7.70 (1H, d, J 2.0 Hz, C5 on *trans* epoxide), 7.74 (1H, d, J 2.0 Hz, C5 on *cis* epoxide); δ_{C} (100 MHz; CDCl₃) 47.4 (epox., CH on *trans* epoxide, C3), 50.0 (epox., CH on *cis* epoxide, C3), 58.0 (epox., CH on *trans* epoxide, C4), 60.9 (epox., CH on *cis* epoxide, C4), 75.8 (CH on *trans* and *cis* epoxide, C2), 126.3 (quat.,quat., on *trans* and *cis* epoxide, C9), 126.5 (2 x arom., *ortho* on phenyl substituent), 127.0 (arom CH, on *trans* and *cis* epoxide, C8), 127.6 (arom CH, on *trans* and *cis* epoxide, C7),

128.1 (arom CH, on *trans* and *cis* epoxide, C5), 129.5 (2 x arom., *meta* on phenyl substituent), 129.7 (arom., *para* on phenyl substituent), 134.0 (quat., on *trans* and *cis* epoxide, on phenyl substituent), 140.6 (quat., on *trans* and *cis* epoxide, C6), 148.2 (quat., CN), 155.8 (quat., on *trans* and *cis* epoxide, C10); m/z 249; C₁₆H₁₁NO₂ requires 249.0790. Mass spectra were obtained as low-resolution mass spectra after attempts to obtain high resolution spectra from Swansea failed due to decomposition during travel. Crystal structure obtained by slow evaporation from ethanol, see page 203.

6-Chloro-2-isopropyl-benzopyran oxide

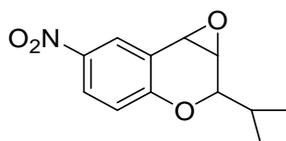


190

Prepared by the epoxidation routes described above. The product epoxide was obtained as a clear oil with a *cis:trans* ratio of 20:80 when using *m*-CPBA and 1:26 when using the chiral TPPP conditions with catalyst (**132**). ν_{max} (film) / cm^{-1} 2822, 2653, 2226, 1554, 1462; δ_{H} (400 MHz; CDCl₃) 1.92 (3H, d, J 8.0 Hz, on *trans* epoxide, CH₃), 1.94 (3H, d, J 8.0 Hz, on *cis* epoxide, CH₃), 1.12 (6H, d, J 8.0 Hz, on *trans* and *cis* epoxide, 2 x CH₃), 1.25-1.29 (1H, m, CH on *cis* epoxide, CH(CH₃)₂), 2.90-2.98 (1H, m, CH on *trans* epoxide, CH(CH₃)₂), 3.61 (1H, dd, J 8.2, 2.4 Hz, epox CH on *trans* epoxide, C3), 3.69 (1H, dd, J 7.8, 2.4 Hz, epox CH on *cis* epoxide, C3), 3.77 (1H, d, J 7.8 Hz, epox CH on *cis* epoxide, C4), 3.81 (1H, d, J 8.2 Hz, epox CH on *trans* epoxide, C4), 3.84 (1H, d, J 2.4 Hz, CH on *cis* epoxide, C2), 4.21 (1H, d, J 2.4 Hz, CH on *trans* epoxide, C2), 6.77 (1H, d, J 8.2 Hz, on *trans* and *cis* epoxide, C8), 7.15 (1H, dd, J 8.2, 2.4 Hz, on *trans* and *cis* epoxide, C7), 7.22 (1H, d, J 2.4 Hz, on *trans* and *cis* epoxide, C5); δ_{C} (100 MHz; CDCl₃) 17.3 (CH₃, on *trans* and *cis* epoxide), 18.0 (CH₃, on *trans* and *cis* epoxide), 31.8 (CH(CH₃)₂, on *trans* and *cis* epoxide), 46.2 (C3, on *trans* and *cis* epoxide), 55.4 (C4, on *trans* and *cis* epoxide), 77.8 (C2, on *trans* and *cis* epoxide), 117.1 (C5, on *trans* and *cis* epoxide), 125.4 (quat., C9, on *trans* and *cis* epoxide), 126.1 (C7, on *trans* and *cis* epoxide), 127.9 (C8, on *trans* and *cis* epoxide), 137.1 (quat., C, C6, on *trans* and *cis* epoxide),

152.7 (quat., C, C10, on *trans* and *cis* epoxide); m/z 224.6, $C_{12}H_{13}ClO_2$ requires 224.06. Mass spectra were obtained as low-resolution mass spectra after attempts to obtain high resolution spectra from Swansea failed due to decomposition during travel.

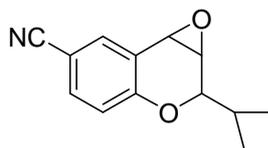
6-Nitro-2-isopropyl-benzopyran oxide



191

Prepared by the *m*-CPBA epoxidation route described above. Racemic epoxide was obtained as a clear oil in a *cis:trans* ratio of 20:80. ν_{\max} (film) / cm^{-1} 3102, 2822, 2653, 2226, 1554, 1462; δ_{H} (400 MHz; CDCl_3) 1.94 (3H, d, J 7.9 Hz, on *trans* epoxide, CH_3), 1.95 (3H, d, J 8.0 Hz, on *cis* epoxide, CH_3), 1.01 (3H, d, J 7.9 Hz, on *trans* epoxide, CH_3), 1.02 (3H, d, J 8.0 Hz, on *cis* epoxide, CH_3), 2.90-2.98 (1H, m, CH on *trans* epoxide, $\text{CH}(\text{CH}_3)_2$), 2.05-2.11 (1H, m, CH on *cis* epoxide, $\text{CH}(\text{CH}_3)_2$), 3.66 (1H, dd, J 9.2, 2.8 Hz, epox CH on *trans* epoxide, C3), 3.79 (1H, dd, J 8.8, 2.8 Hz, epox CH on *cis* epoxide, C3), 3.87 (1H, d, J 8.8 Hz, epox CH on *cis* epoxide, C4), 3.91 (1H, d, J 9.2 Hz, epox CH on *trans* epoxide, C4), 3.94 (1H, d, J 2.8 Hz, CH on *cis* epoxide, C2), 4.38 (1H, d, J 2.8 Hz, CH on *trans* epoxide, C2), 6.89 (1H, d, J 8.4 Hz, on *trans* and *cis* epoxide, C8), 8.08 (1H, dd, J 8.4, 2.2 Hz, on *trans* and *cis* epoxide, C7), 8.22 (1H, d, J 2.2 Hz, on *trans* and *cis* epoxide, C5); δ_{C} (100 MHz; CDCl_3) 19.1 (CH_3 , on *trans* and *cis* epoxide), 19.6 (CH_3 , on *trans* and *cis* epoxide), 32.4 ($\text{CH}(\text{CH}_3)_2$, on *trans* and *cis* epoxide), 49.5 (C3, on *trans* and *cis* epoxide), 58.4 (C4, on *trans* and *cis* epoxide), 79.3 (C2, on *trans* and *cis* epoxide), 119.4 (C5, on *trans* and *cis* epoxide), 126.1 (quat., C9, on *trans* and *cis* epoxide), 126.5 (C7, on *trans* and *cis* epoxide), 128.7 (C8, on *trans* and *cis* epoxide), 157.1 (quat., C, C6, on *trans* and *cis* epoxide), 162.7 (quat., C, C10, on *trans* and *cis* epoxide); m/z 236.0917, $C_{12}H_{13}NO_4$ requires 236.0917.

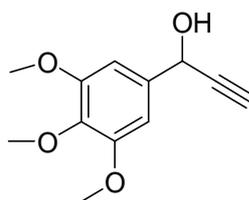
6-Cyano-2-isopropyl-benzopyran oxide



189

Prepared by the *m*-CPBA epoxidation route described above. Racemic epoxide was obtained as a clear oil in a *cis:trans* ratio of 20:80. ν_{max} (film) / cm^{-1} 2822, 2653, 2226, 1554, 1462; δ_{H} (400 MHz; CDCl_3) 1.94 (3H, d, *J* 7.9 Hz, on *trans* epoxide, CH_3), 1.95 (3H, d, *J* 8.0 Hz, on *cis* epoxide, CH_3), 1.01 (3H, d, *J* 7.9 Hz, on *trans* epoxide, CH_3), 1.02 (3H, d, *J* 8.0 Hz, on *cis* epoxide, CH_3), 2.90-2.98 (1H, m, CH on *trans* epoxide, $\text{CH}(\text{CH}_3)_2$), 2.05-2.11 (1H, m, CH on *cis* epoxide, $\text{CH}(\text{CH}_3)_2$), 3.66 (1H, dd, *J* 9.2, 2.5 Hz, epox CH on *trans* epoxide, C3), 3.79 (1H, dd, *J* 8.8, 2.5 Hz, epox CH on *cis* epoxide, C3), 3.87 (1H, d, *J* 8.8 Hz, epox CH on *cis* epoxide, C4), 3.91 (1H, d, *J* 9.2 Hz, epox CH on *trans* epoxide, C4), 3.94 (1H, d, *J* 2.5 Hz, CH on *cis* epoxide, C2), 4.38 (1H, d, *J* 2.5 Hz, CH on *trans* epoxide, C2), 6.89 (1H, d, *J* 8.4 Hz, on *trans* and *cis* epoxide, C8), 8.08 (1H, dd, *J* 8.4, 2.2 Hz, on *trans* and *cis* epoxide, C7), 8.22 (1H, d, *J* 2.2 Hz, on *trans* and *cis* epoxide, C5); δ_{C} (100 MHz; CDCl_3) 18.1 (CH_3 , on *trans* and *cis* epoxide), 18.9 (CH_3 , on *trans* and *cis* epoxide), 33.4 ($\text{CH}(\text{CH}_3)_2$, on *trans* and *cis* epoxide), 47.5 (C3, on *trans* and *cis* epoxide), 56.5 (C4, on *trans* and *cis* epoxide), 75.3 (C2, on *trans* and *cis* epoxide), 115.1 (C5, on *trans* and *cis* epoxide), 128.1 (quat., C9, on *trans* and *cis* epoxide), 128.9 (C7, on *trans* and *cis* epoxide), 129.7 (C8, on *trans* and *cis* epoxide), 137.1 (quat., C, C6, on *trans* and *cis* epoxide), 144.2 (quat., CN), 152.7 (quat., C, C10, on *trans* and *cis* epoxide); m/z 215; $\text{C}_{13}\text{H}_{13}\text{NO}_2$ requires 215.0946. Mass spectra were obtained as low-resolution mass spectra after attempts to obtain high resolution spectra from Swansea failed due to decomposition during travel.

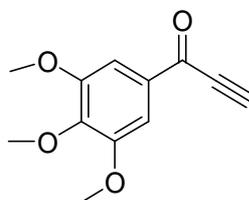
1-(3,4,5-Trimethoxy-phenyl)-prop-2-yn-1-ol⁷⁸



201

3,4,5-Trimethoxybenzaldehyde (2.0 g, 0.012 mol) was placed under N₂ in a round-bottomed flask containing THF (100ml). The solution was then cooled to 0 °C and ethynyl magnesium bromide (27 ml, 0.013 mol, 1.3 eq) added. The reaction was then stirred at room temperature for 2 hours at which point sat. aqueous ammonium chloride (20 ml) was added. The solvent was evaporated and the aqueous layer washed with EtOAc (3 x 20 ml). The combined organics were washed with brine, dried (MgSO₄) and evaporated to yield the title compound as a yellow oil (2.1 g, 89%); ν_{max} (film) / cm⁻¹ 3425, 2956, 1585, 1464, 1451, 1299, 1244, 1254, 1162; δ_{H} (400 MHz; CDCl₃) 2.46 (1H, s, broad, OH), 2.65 (1H, s, alkyne CH), 3.80 (3H, s, 1 x OCH₃ *para* on ring), 3.84 (6H, s, 2 x OCH₃, *meta* on ring), 5.37 (1H, s, CHOH), 6.75 (2H, s, CH arom., C2, 6); δ_{C} (100 MHz; CDCl₃) 56.3 (2 x OCH₃, *meta* on ring), 60.2 (OCH₃, *para* on ring), 66.1 (OHCH), 75.7 (CHCCH, alkyne), 83.6 (C quat., CHCCH, alkyne), 105.3 (2 x CH arom., C2, 6), 136.1 (C quat., C4), 138.8 (C quat., C1), 153.6 (2 x C quat., C3, 5).

1-(3,4,5-Trimethoxy-phenyl)-propynone⁷⁸

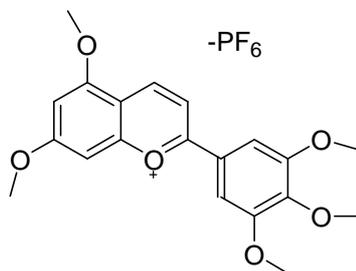


202

1-(3,4,5-Trimethoxy-phenyl)-prop-2-yn-1-ol (1.36 g, 6.11 mmol) was placed in a round bottomed flask in EtOAc (100ml) equipped with a reflux condenser. To this IBX (3.43 g, 12.0 mmol, 2 eq) was added. The reaction was then heated to 80 °C and

stirred overnight. The solution was then cooled, filtered through celite and evaporated to yield the title compound as a clear oil (1.05 g, 78%); ν_{max} (film) / cm^{-1} 2822, 2653, 2226, 1654, 1462; δ_{H} (400 MHz; CDCl_3) 3.78 (1H, s, alkyne CH), 3.82 (6H, s, 2 x OCH_3 , *meta* on ring), 3.87 (3H, s, 1 x OCH_3 *para* on ring), 7.37 (2H, s, arom., CH, C2, 6); δ_{C} (100 MHz; CDCl_3) 56.0 (2 x OCH_3 , *meta* on ring), 56.2 (OCH_3 , *para* on ring), 80.0 (CHCCH, alkyne), 80.3 (C quat., CHCCH, alkyne), 110.1 (2 x CH arom., C2, 6), 126.1 (C quat., C4), 129.7 (C quat., C1), 149.1 (C quat., C3), 154.7 (C quat., C5), 176.0 (C=O).

5,7-Dimethoxy-2-(3,4,5-trimethoxy-phenyl)-chromenylium-hexafluorophosphate⁷⁸

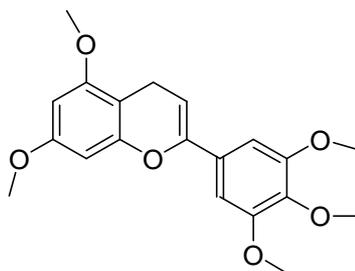


200

1-(3,4,5-Trimethoxy-phenyl)-propynone (1.0 g, 4.5 mmol) and 3,5-dimethoxyphenol (0.69 g, 4.5 mmol, 1 eq) were placed in a round bottomed flask in the minimum of acetic acid (5 ml). An excess of aq. hexafluorophosphoric acid (50% in H_2O) was then added and the reaction turned bright red. The reaction was then stirred for 48 hours after which it was plunged into diethyl ether (50 ml) causing the salt to precipitate out. The solid was filtered off and washed with more diethyl ether (3 x 10 ml) and dried, yielding the title compound as bright red crystals (1.9 g, 83%). M.p. 215 °C (lit 216-218 °C);⁷⁸ ν_{max} (film) / cm^{-1} 2822, 2653, 2226, 1554, 1462; δ_{H} (400 MHz; CD_3CN) 3.98 (3H, s, CH_3), 4.00 (6H, s, 2 x OCH_3 , *meta* on phenyl substituent), 4.09 (3H, s, OCH_3 , *para* on phenyl substituent), 4.11 (3H, s, OCH_3 , off C5), 4.85 (3H, s, OCH_3 , off C7), 6.85 (1H, d, J 8.2 Hz, C3), 7.41 (1H, d, J 8.2 Hz, C4), 7.59 (2H, s, CH arom., *ortho* on phenyl substituent), 8.21 (1H, d, J 4.2 Hz, C8), 9.18 (1H, d, J 4.2 Hz, C6); δ_{C} (100 MHz; CD_3CN) 55.9 (OCH_3 , *para* on phenyl substituent), 57.0 (OCH_3 , off C5), 57.2 (OCH_3 , off C7), 57.6 (2 x OCH_3 , *meta* on

phenyl substituent), 93.4 (C6), 99.8 (C8), 111.3 (C3), 113.4 (quat., C, C9), 120.8 (quat., C, on phenyl substituent), 131.9 (2 x CH arom., *ortho* on phenyl substituent), 148.7 (C4), 158.8 (quat., C, C2), 159.0 (quat., C, C5), 165.2 (2 x quat., C, *meta* on phenyl substituent), 167.0 (quat., C, C7), 171.4 (quat., C, *para* on phenyl substituent), 171.7 (quat., C, C10).

5,7-Dimethoxy-2-(3,4,5-trimethoxy-phenyl)-4H-chromene¹¹⁹

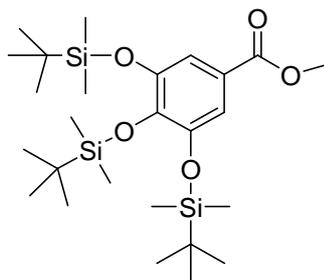


204

5,7-Dimethoxy-2-(3,4,5-trimethoxy-phenyl)-4H-chromene (0.502 g, 1 mmol) was placed in a round bottomed flask in the oven at 100 °C for 24 hours. Dry THF was then added under N₂ and the flask cooled to - 70 °C. Lithium aluminium hydride (2M, 0.5 ml, 1 mmol, 1 eq) was then added slowly and the temperature raised until the solvent began to boil. The reaction was then refluxed for a further 2 hours at which point the reaction was cooled and the solvent removed. The residue was then treated with wet ether (20 ml) and aq. potassium sodium tartrate tetrahydrate (20 ml). The aqueous layer was washed with ether (3 x 10 ml) and the combined organics washed with further potassium sodium tartrate tetrahydrate (3 x 10 ml). The organic layers were then dried (MgSO₄) and evaporated to yield the title compound as slight pink powder (0.25 g, 69% yield), m.p. 145-147 °C (lit 147-148 °C)¹¹⁹; ν_{max} (film) / cm⁻¹ 2822, 2653, 2226, 1554, 1462; δ_{H} (400 MHz; CD₃CN) 3.31 (2H, d, *J* 8.4 Hz, CH₂, C4), 3.77 (3H, s, OCH₃, off C5), 3.80 (3H, s, OCH₃, off C7), 3.82 (3H, s, OCH₃, *para* on phenyl substituent), 3.79 (6H, s, 2 x OCH₃, *meta* on phenyl substituent), 5.42 (1H, t, *J* 8.4 Hz, CH, C3), 6.12 (1H, d, *J* 7.8 Hz, CH arom., C8), 6.19 (1H, d, *J* 7.8 Hz, CH arom., C6), 6.84 (2H, s, CH arom., *ortho* on phenyl substituent); δ_{C} (100 MHz; CD₃CN) 18.3 (CH₂, C4), 56.1 (OCH₃, off C5), 56.4 (3 x OCH₃, on phenyl substituent), 56.7 (OCH₃, off C5), 62.4 (OCH₃, off C7), 95.3 (CH,

C3), 95.8 (CH, arom., C6), 96.4 (CH arom., C8), 103.2 (quat., C, C9), 105.2 (2 x CH arom., *ortho* on phenyl substituent), 128.1 (quat., C, C1 on phenyl substituent), 131.5 (quat., C, *para* on phenyl substituent) 145 (2 x quat., C, *meta* on phenyl substituent), 150.1 (quat., C, C2), 158.2 (quat., C, C10), 160.2 (quat., C, C7), 165.3 (quat., C, C5).

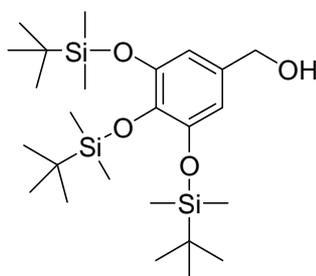
3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-benzoic acid methyl ester^{120,121}



207

Methyl gallate (9.2 g, 0.051 mol), *tert*-butyldimethylsilyl chloride (30.1 g, 0.202 mol) and imidazole (24 g, 0.36 mol) were stirred in dimethyl formamide (100 ml) for 20 h. The reaction mixture was then cast into NaHCO₃ (200 ml, 5% solution) and extracted with hexane (3 x 50 ml). The organics were then dried (Na₂SO₄) and evaporated to yield a green oil. This was then diluted with methanol (ca. 100 ml) and then placed in the fridge. The compound was yielded as white crystals (21.3 g, 92% yield), m.p. 68-70 °C (lit. 68-68.5 °C);²⁰ ν_{max} (film) / cm⁻¹ 2955, 2925, 1718, 1490, 1423, 1224, 1101, 840, 826; δ_{H} (400 MHz; CDCl₃) 0.11 (6H, s, *para* Si-(CH₃)₂), 0.21 (12H, s, *meta* 2 x Si-(CH₃)₂), 0.92 (18H, s, *meta* 2 x Si-*t*-Bu), 0.96 (9H, s, *para* Si-*t*-Bu), 3.83 (3H, s, OCH₃), 7.18 (2H, s, arom CH, C2, 6); δ_{C} (100 MHz; CDCl₃) 0.09 (2 x *meta* Si-(CH₃)₂), 18.1 (quat., C, *para* Si-*t*-Bu), 19.4 (2 x quat., C, *meta* Si-*t*-Bu), 22.0 (*para* Si-(CH₃)₂), 29.5 (*para* Si-*t*-Bu), 30.2 (2 x *meta* Si-*t*-Bu), 56.4 (OCH₃), 119.1 (2 x CH arom., C2, 6), 125.4 (quat., C, C1), 147.6 (2 x quat., C, *meta* on ring, C3, 5), 153.9 (quat., C, *para* on ring, C4), 171.1 (quat., C, C=O).

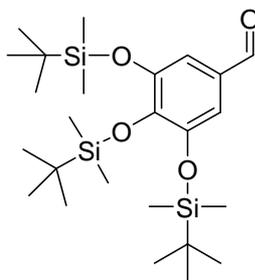
[3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-phenyl]-methanol^{120,122}



208

3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-benzoic acid methyl ester (2.0 g, 3.8 mmol) was dissolved in dry THF (100 ml) and added to a solution of LiAlH₄ (1.9 ml, 2M solution in THF, 3.8 mmol) in THF (100 ml) at such a rate as to maintain a gentle reflux. The reaction was then refluxed for a further 3 h, at which point it was cooled to room temperature and diluted with diethyl ether (200 ml). The mixture was then stirred rapidly whilst adding NaOH (1N, 10 ml) and filtered through celite. The filtrate was then washed with brine (3 x 50 ml), dried (Na₂SO₄) and evaporated to yield the crude product as a pale green oil which was used without further purification (1.1.g, 60% yield); ν_{max} (film) / cm⁻¹ 3410, 2930, 1580, 1100, 840, 830; δ_{H} (400 MHz; CDCl₃) 0.09 (6H, s, *para* Si-(CH₃)₂), 0.18 (12H, s, *meta* 2 x Si-(CH₃)₂), 0.91 (18H, s, *meta* Si-*t*-Bu), 0.97 (9H, s, *para* Si-*t*-Bu), 1.42 (1H, t, *J* 5.9 Hz, OH), 4.46 (2H, d, *J* 5.9 Hz, CH₂), 6.47 (2H, s, arom., CH, C2, 6); δ_{C} (100 MHz; CDCl₃) 0.20 (2 x *meta* Si-(CH₃)₂), 16.1 (quat., C, *para* Si-*t*-Bu), 18.9 (2 x quat., C, *meta* Si-*t*-Bu), 23.4 (*para* Si-(CH₃)₂), 29.5 (*para* Si-*t*-Bu), 30.2 (2 x *meta* Si-*t*-Bu), 66.4 (CH₂), 111.9 (2 x CH arom., C2, 6), 121.4 (quat., C, C1), 145.1 (2 x quat., C, *meta* on ring, C3, 5), 151.2 (quat., C, *para* on ring, C4).

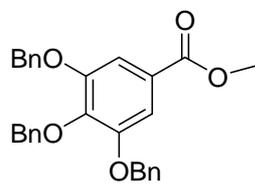
3,4,5-Tris-(*tert*-butyl-dimethyl-silanyloxy)-benzaldehyde¹²⁰



209

Pyridinium chlorochromate (3.5 g, 0.016 mol) was placed in dry round bottomed flask under N₂ containing dry DCM (20 ml). A solution of [3,4,5-tris-(*tert*-butyl-dimethyl-silanyloxy)-phenyl]-methanol (6.9 g, 0.016 mol) in dry DCM (20 ml) was added in one portion under efficient stirring. The reaction was then stirred at room temperature for 2 hours, whilst monitoring by TLC (3:7 acetone:hexane). When no starting material remained Et₂O was added and the reaction filtered through celite and evaporated to yield the product as a white powder. Mp 67-69 °C (lit 68-70 °C)¹²⁰; ν_{\max} (film) / cm⁻¹ 3060, 2950, 2930, 2780, 2700, 1695, 1255, 1100; δ_{H} (400 MHz; CDCl₃) 0.13 (6H, s, *para* Si-(CH₃)₂), 0.23 (12H, s, *meta* 2 x Si-(CH₃)₂), 0.93 (18H, s, *meta* Si-*t*-Bu), 0.97 (9H, s, *para* Si-*t*-Bu), 7.00 (2H, s, arom., CH, C2, 6), 9.70 (1H, s, CHO); δ_{C} (100 MHz; CDCl₃) 0.07 (2 x Si-(CH₃)₂), 14.8 (quat., C, *para* Si-*t*-Bu), 17.2 (2 x quat., C, *meta* Si-*t*-Bu), 21.5 (*para* Si-(CH₃)₂), 25.1 (*para* Si-*t*-Bu), 28.9 (2 x *meta* Si-*t*-Bu), 122.1 (2 x CH arom., C2, 6), 128.1 (quat., C, C1), 149.0 (2 x quat., C, *meta* on ring, C3, 5), 158.2 (quat., C, *para* on ring, C4), 189.1 (CHO)

3,4,5-Tris-benzyloxy-benzoic acid methyl ester^{123,124}

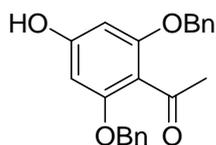


215

Methyl 3,4,5-trihydroxybenzoate (5.00 g, 27.1 mmol) was placed in a round bottomed flask under N₂ followed by DMF (50 ml) and K₂CO₃ (15.0 g, 109 mmol, 4

eq.). Benzyl bromide (13.9 g, 9.72 ml, 3 eq.) was then added dropwise and the reaction stirred overnight. The reaction was then poured into water (100 ml) and the solid filtered off and dried, yielding the title compound as a white solid (10.6 g, 86%), m.p. 104-105 °C (lit. 102-102.5 °C);²² ν_{max} (film) / cm^{-1} 1615; m.p. 98-99 °C (lit. 99-100 °C);¹²⁴ δ_{H} (400 MHz; CDCl_3) 3.88 (3H, s, OCH_3), 5.11 (2H, s, CH_2Ph , off C4), 5.13 (4H, s, 2 x CH_2Ph , off C3 and 5), 7.18 (2H, s, 2 x CH arom., C2, 6), 7.20-7.42 (15H, m, 3 x C_6H_5); δ_{C} (100 MHz; CDCl_3) 52.2 (OCH_3), 71.2 (CH_2Ph , off C4), 75.4 (2 x CH_2Ph , off C3 and 5), 109.1 (2 x CH arom., C2, 6), 125.2 (quat., C, C1), 127.9 (2 x CH arom., *para* on *meta* OBn groups), 128.0 (CH arom., *para* on *para* OBn), 128.1 (4 x CH arom., *meta* on *meta* OBn groups), 128.4 (2 x CH arom., *meta* on *para* OBn), 128.5 (4 x CH arom., *ortho* on *meta* OBn groups), 129.1 (2 x CH arom., *ortho* on *para* OBn), 136.6 (quat., C, on *para* OBn), 137.4 (2 x quat., C, on *meta* OBn), 142.4 (quat., C, C4), 152.5 (quat., C, C3, 5), 166.6 (quat., C=O).

2,6-dibenzyloxy-4-hydroxyacetophenone¹²³

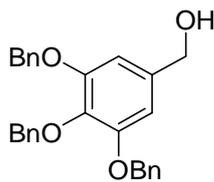


219

2,4,6-Trihydroxyacetophenone (3.2 g, 17 mmol) and anhydrous K_2CO_3 (4.9 g, 35 mmol) were placed in a round bottomed flask under N_2 . HMPA (20 ml) was then added, followed by BnBr (6.4 g, 37 mmol). The reaction was then stirred at 80 °C for 1 hour. The reaction was then cooled and filtered to remove any solid and washed with diethyl ether (3 x 10 ml). The organics were combined and further washed with water (3 x 10 ml) and brine (3 x 10 ml), dried (MgSO_4) and evaporated to yield the crude product as a yellow oil (5.2 g, 85%). ν_{max} (film) / cm^{-1} 3310, 1615, 1563, 1210; δ_{H} (400 MHz; CDCl_3) 1.42 (1H, s, OH), 2.26 (3H, s, CH_3), 4.98 (4H, s, 2 x CH_2Ph , off C2 and 6), 5.97 (1H, d, J 2.4 Hz, CH arom., C3), 6.01 (1H, d, J 2.4 Hz, CH arom., C5), 7.10-7.22 (10H, m, 2 x C_6H_5); δ_{C} (100 MHz; CDCl_3) 33.2 (CH_3), 70.1 (2 x CH_2Ph), 71.0 (CH_2Ph), 94.6 (2 x CH arom., C3, 5), 106.2 (quat., C, COH), 127.5 (2 x CH , *para* on OBn), 127.9 (4 x CH arom., *meta* on OBn), 128.2 (4 x CH

arom., *ortho* on OBn), 135.8 (2 x quat., C, on OBn), 165.0 (quat., C, COH, C4), 167.5 (2 x quat., C, CCH₂Ph, C2, 6), 203.1 (quat., C, C=O).

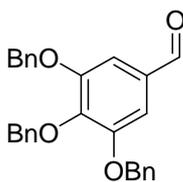
3,4,5-Tribenzyloxy-phenylmethanol¹²³



216

A solution of LiAlH₄ in THF was placed in a flask equipped with a reflux condenser under N₂ at 0 °C. To this a solution of 3,4,5-tris-benzyloxy-benzoic acid methyl ester (10 g, 0.022 mol) in THF (20 ml) was added dropwise at such rate as to maintain a gentle reflux. The reaction was then further refluxed for 3 hours, cooled and diluted with diethyl ether (40 ml). NaOH (10 ml) was then added whilst stirring rapidly and the reaction filtered through celite. The filtrate was washed with brine (3 x 10 ml), dried (MgSO₄) and evaporated to yield the product as a clear oil (7.8 g, 83%). ν_{max} (film) / cm⁻¹ 3351, 3258, 2954, 1547, 1456, 1210; δ_{H} (400 MHz; CDCl₃) 1.75 (1H, s, br OH), 4.55 (2H, s, CH₂), 5.02 (2H, s, CH₂Ph, off C4), 5.08 (4H, s, 2 x CH₂Ph, off C3 and 5), 6.68 (2H, s, 2 x CH arom., C2, 6), 7.23-4.41 (15H, m, OBn); δ_{C} (100 MHz; CDCl₃) 65.5 (CH₂Ph, off C4), 71.4 (2 x CH₂Ph, off C3 and 5), 75.5 (CH₂OH), 106.6 (quat., C, C1), 127.9 (2 x CH arom., *para* on *meta* OBn groups), 128.0 (CH arom., *para* on *para* OBn), 128.1 (4 x CH arom., *meta* on *meta* OBn groups), 128.4 (2 x CH arom., *meta* on *para* OBn), 128.5 (4 x CH arom., *ortho* on *meta* OBn groups), 129.1 (2 x CH arom., *ortho* on *para* OBn), 137.0 (2 x quat., C, on *meta* OBn groups), 137.4 (quat., C, on *para* OBn), 142.4 (2 x quat., C, C3, 5), 152.5 (quat., C, C4).

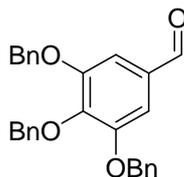
3,4,5-Tribenzyloxy-benzaldehyde¹²³



217

Pyridinium chlorochromate (3.5 g, 0.016 mol) was placed in dry round bottomed flask under N₂ containing dry DCM (20 ml). A solution of (3,4,5-tris-benzyloxy-phenyl)-methanol (6.9 g, 0.016 mol) in dry DCM (20 ml) was added in one portion under efficient stirring. The reaction was then stirred at room temperature for 2 hours, whilst being monitored by TLC (3:7 acetone:hexane). When no starting material remained Et₂O was added and the reaction filtered through celite and evaporated to yield the product as a white powder (4.9 g, 73%), m.p. 105-106 °C (lit. 103-104 °C)¹²³; ν_{max} (film) / cm⁻¹ 2678, 2367, 1876, 1567, 1290; δ_{H} (300 MHz; CDCl₃); 5.16 (6H, s, 3 x CH₂), 7.26 (2H, s, 2 x CH arom., C2, 6), 7.25-7.27 (3H, m, 3 x CH arom., *para* on OBn groups), 7.34-7.45 (12H, m, remaining CH arom on OBn groups), 9.80 (1H, s, CHO); δ_{C} (100 MHz; CDCl₃) 72.1 (2 x CH₂), 109.5 (quat., C, C1), 127.9 (3 x CH arom., *para* on OBn), 128.4 (6 x CH arom., *ortho* on OBn), 129.8 (6 x CH arom., *meta* on OBn), 136.4 (quat., C, C3, 5), 155.4 (quat., C, C4), 172.1 (CHO).

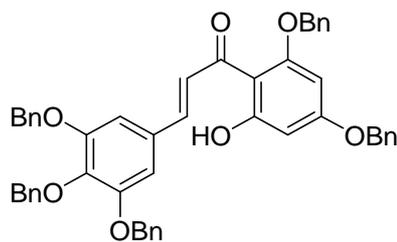
3,4,5-Tribenzyloxy-benzaldehyde^{123,125}



217

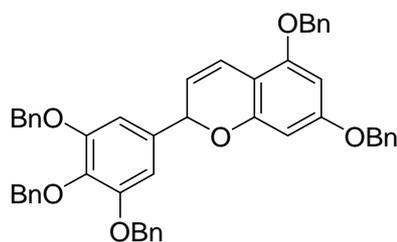
(3,4,5-Tris-benzyloxy-phenyl)-methanol (1.79 g, 4.20 mmol) was placed in a flask containing EtOAc (20 ml) and IBX (2.35 g, 8.40 mmol, 2 eq, 45% IBX) and was equipped with a reflux condenser. The reaction was then heated at 80 °C overnight, at which point the reaction was cooled, filtered to remove the insoluble by-products and evaporated to yield the product as a white solid. All data as previously obtained.

2'-Hydroxy-4',6',3,4,5-pentabenzoyloxy-chalcone^{123,126}

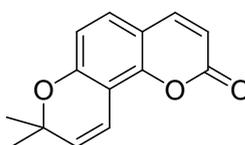


220

To a solution of 1-(2,6-*bis*-benzyloxy-4-hydroxy-phenyl)-ethanone (4.00 g, 11.5 mmol) in DMF (20 ml) was added NaH (0.55 g, 23 mmol, 2 eq.). A solution of 3,4,5-*tris*-benzyloxy-benzaldehyde (5.1 g, 12.0 mmol, 1.05 eq.) in DMF (20 ml) was then added dropwise, and the reaction stirred for a further 2 hours at room temperature. Water (20 ml) was then added to quench any unreacted NaH, followed by removal of DMF by vacuum evaporation. The resulting residue was dissolved in DCM (20 ml), washed with water (3 x 10 ml) and brine (3 x 10 ml), the organics were then combined, dried (MgSO₄) and evaporated to yield the product as a yellow solid (6.8 g, 75%); m.p. 147-149 °C (lit. 148-149 °C).¹²⁶ ν_{max} (film) / cm^{-1} δ_{H} (300 MHz; CDCl₃) 4.87 (4H, s, 2 x CH₂Ph), 5.12 (6H, s, 3 x CH₂Ph), 6.18 (1H, d, *J* 2.5 Hz, CH arom., C3'), 6.25 (1H, d, *J* 2.5 Hz, CH arom C5'), 6.70 (2H, s, 2 x CH arom., C2, 6), 7.19-7.45 (m, 25H, arom CH on OBn), 7.66 (1H, d, *J* 12.5 Hz, CH), 7.78 (1H, d, *J* 12.5 Hz, CH), OH not observed; δ_{C} (100 MHz; CDCl₃) 70.3 (CH₂), 71.2 (2 x CH₂), 75.2 (CH₂), 75.8 (CH₂), 93.0 (CH arom.), 95.2 (CH arom.), 102.5 (C quat.), 108.4 (2 x CH arom.), 127.1 (5 x CH arom., *para* on OBn), 127.2 (10 x CH arom., *ortho* on OBn), 128.8 (10 x CH arom., *meta* on OBn), 130.8 (CH alkene), 135.8 (C quat.), 135.9 (C quat.), 136.2 (C quat.), 136.8 (5 x C quat., on OBn), 142.4 (CH alkene), 152.9 (C quat.), 161.5 (C quat.), 165.2 (C quat.), 168.1 (C quat.), 192.6 (C=O).

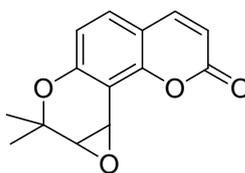
5,7,3',4',5'-Pentabenzoyloxyflav-3-ene^{123,126}**213**

1-(2,4-Bis-benzyloxy-6-hydroxy-phenyl)-3-(3,4,5-tris-benzyloxy-phenyl)-propenone (2.0 g, 2.6 mmol) was dissolved in THF:EtOH (2:1, 30 ml total volume) in a round bottomed flask equipped with a reflux condenser. NaBH₄ (0.1 g, 2.6 mmol, 1 eq.) was then added in one portion and the reaction refluxed overnight at 65-70 °C. The reaction was then cooled, evaporated and the resulting residue redissolved in DCM, dried (MgSO₄) and evaporated to yield the title compound as an off white solid 0.25 g, 13%); m.p. 106-109 °C (lit. 105-107 °C);¹²⁶ ν_{max} (film) / cm⁻¹ 2789, 2500, 2109, 1699, 1687, 1567, 1205, 1060; δ_{H} (300 MHz; CDCl₃) 5.00 (2H, s, CH₂Ph), 5.06 (2H, s, CH₂Ph), 5.09 (2H, s, CH₂Ph), 5.11 (2H, s, CH₂Ph), 5.15 (2H, s, CH₂Ph), 5.58 (1H, dd, *J* 6.9, 1.2 Hz, C2), 5.76 (1H, dd, *J* 9.8, 6.9 Hz, C3), 6.19 (1H, d, *J* 2.1, C6), 6.23 (1H, d, *J* 2.1, C8), 6.83 (2H, s, 2 x CH arom., *ortho* on phenyl substituent), 6.91-6.93 (1H, dd, *J* 9.8, 1.2 Hz, C4), 7.29-7.47 (25H, m, 5 x OBn); δ_{C} (100 MHz; CDCl₃) 78.4 (CH₂), 79.2 (2 x CH₂), 80.3 (CH₂), 82.8 (CH₂), 86.4 (CH), 98.1 (CH arom.), 101.2 (CH arom.), 102.5 (C quat.), 112.4 (2 x CH arom.), 124.8 (CH alkene), 126.4 (CH alkene), 128.0 (5 x CH arom., *para* on OBn), 128.5 (10 x CH arom., *ortho* on OBn), 129.8 (10 x CH arom., *meta* on OBn), 135.8 (C quat.), 135.9 (C quat.), 136.2 (C quat.), 136.8 (5 x C quat., on OBn), 152.9 (C quat.), 161.5 (C quat.), 165.2 (C quat.), 168.1 (C quat.).

Seselin^{127,128}**223**

7-Hydroxycoumarin (1.00 g, 6.17 mmol) was dissolved in *p*-xylene (20 ml). 1,1-Diethoxy-3-methyl-2-butene (1.47 ml, 7.40 mmol) and 3-picoline (0.15 mL, 1.50 mmol) were added, and the reaction mixture was heated under reflux for 24 h. Dichloromethane (20 ml) was added to the reaction mixture, the solution was filtered through a pad of silica gel and Celite, and the pad was rinsed with ethyl acetate (3 × 20 ml). The combined organic solvents were removed under reduced pressure, and the residue was purified by column chromatography on silica gel using ethyl acetate/toluene (1:1) as eluent to give seselin as a yellow solid (1.03 g, 73%): mp 119-120 °C (lit. 117-120 °C);¹²⁸ ν_{max} (film) /cm⁻¹ 2976, 2361, 1734, 1597, 1485, 1152; δ_{H} (400 MHz; CDCl₃) 1.45 (6H, s, 2 × CH₃), 5.71 (1H, d, *J* 10.1 Hz), 6.20 (1H, d, *J* 9.5 Hz), 6.70 (1H, d, *J* 8.5 Hz), 6.86 (1H, d, *J* 10.1 Hz), 7.20 (1H, d, *J* 8.5 Hz), 7.59 (1H, d, *J* 9.5 Hz); δ_{C} (100 MHz; CDCl₃) 28.3 (2 × CH₃), 53.4, 109.4, 112.7, 113.7, 115.1, 120.2, 127.9, 130.9, 144.1, 150.2, 156.4, 161.2.

(+)-(3'S,4'S)-Seselin Epoxide^{87,127,128}

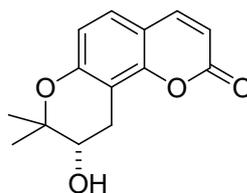


235

Seselin (0.50 g, 2.2 mmol) was dissolved in chloroform (30 ml) and the solution cooled to -30 °C. The sulfone catalyst (**132**) (0.16 g, 0.22 mmol) and TPPP (2.0 g, 4.38 mmol) were added, and the mixture was stirred at -30 °C for 24 h. Diethyl ether (50 ml) was added to the mixture and the resulting cloudy solution filtered through Celite. The solvents were removed under reduced pressure, and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate/triethylamine (3:1:0.1) as eluent to give (+)-(3'S,4'S)-seselin epoxide as a colourless solid (0.35 g, 65%) of 97% ee (HPLC conditions: hexane/2-propanol (90:10), oven temp 20 °C, column Eurocel 01 250 × 4.6 mm, 5 μm particle size, flow rate 1 ml/min): mp 143-144 °C (lit. mp 144-146 °C);^{87,128} $[\alpha]_{\text{D}} +7.2^{\circ}$ (*c* 0.1 CHCl₃); ν_{max} (film) /cm⁻¹ 2950, 2256, 1729, 1698, 1587, 1423, 1120; δ_{H} (400 MHz; CDCl₃) 1.24 (3H, s, CH₃), 1.53 (3H, s, CH₃), 3.49 (1H, d, *J* 6.0 Hz), 4.53 (1H, d, *J* 6.0 Hz), 6.19 (1H, d, *J* 12.7 Hz), 6.65 (1H, d, *J* 11.7 Hz), 7.24 (1H, d, *J* 11.7 Hz), 7.55 (1H, d,

J 12.7 Hz); δ_C (100 MHz; $CDCl_3$) 23.1 (CH_3), 25.8 (CH_3), 44.2 (epox., C9), 62.1 (quat., $C(CH_3)_2$), 75.0 (epox., C8), 108.4 (CH, C6), 113.1 (CH, α C of α,β system), 113.8 quat., C11), 115.8 (quat., C12), 129.4 (CH, C5), 144.2 (CH, β C of α,β system), 155.1 (quat., C13), 156.2 (quat., C10), 161.2 (ketone).

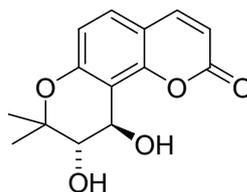
(-)-(3'S)-Lomatin^{89,127}



226

(+)-(3'S,4'S)-Seselin epoxide (20 mg, 0.080 mmol) was dissolved in tetrahydrofuran (3 ml) and the solution cooled to 0 °C. Boron trifluoride etherate (7 μ L, 0.12 mmol) was added. Sodium cyanoborohydride (0.0050 g, 0.12 mmol) was added in one portion and the mixture stirred for 30 min. Water (1 ml) and dichloromethane (3 ml) were added to the reaction mixture, and the organic phase was separated. The aqueous layer was extracted with dichloromethane (2 \times 3 ml), and the organic layers were combined and dried over magnesium sulfate. The solvents were removed under reduced pressure, and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (7:3) as eluent to give to give (-)-(3'S)-lomatin as a yellow solid (19 mg, 94%) of 97% ee (HPLC conditions: hexane/2-propanol (99:1), oven temp 20 °C, column Eurocel 01 250 \times 4.6 mm, 5 μ m particle size, flow rate 0.5 mL/ min): mp 164-165 °C (lit. mp 163-165 °C);⁸⁹ $[\alpha]_D$ -52 (c 0.4, EtOH), lit. $[\alpha]_D$ -51° (c 0.5, EtOH);⁸⁹ ν_{max} (film) / cm^{-1} 3452, 2935, 1723, 1604, 1405, 1117; δ_H (400 MHz; $CDCl_3$) 1.32 (3H, s, CH_3), 1.38 (3H, s, CH_3), 2.94 (1H, dd, J 17.6, 5.0 Hz), 3.11 (1H, dd, J 17.6, 5.0 Hz), 3.88 (1H, dd, J 5.0, 5.0 Hz), 6.19 (1H, d, J 9.4 Hz), 6.75 (1H, d, J 8.6 Hz), 7.22 (1H, d, J 8.6 Hz), 7.59 (1H, d, J 9.4 Hz); δ_C (100 MHz; $CDCl_3$) 22.3 (CH_3), 24.8 (CH_3), 25.9 (CH_2 , C9), 68.5 (alcohol, C8), 78.3 (quat., $C(CH_3)_2$), 107.6 (quat., C11), 112.3 (quat., C12), 112.5 (CH, C6), 114.5 (CH, α C of α,β system), 126.8 (CH, C5), 144.2 (CH, β C of α,β system), 153.7 (quat., C13), 156.5 (quat., C10), 161.6 (quat., ketone).

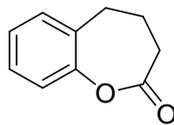
(+)-(3'S,4'R)-*trans*-khellactone^{127,130}



228

Seselin epoxide (20 mg, 0.080 mmol) was dissolved in acetone (1 ml) at room temperature. Aqueous sulfuric acid (1M, 0.5 ml) was added to the solution, and the mixture was stirred for 1 h. The reaction mixture was neutralized to pH 7 using sodium hydrogen carbonate. Dichloromethane (3 ml) was added to the reaction mixture and the organic phase separated. The aqueous layer was extracted with dichloromethane (2 × 3 mL), and the organic layers were combined and dried over magnesium sulfate. The solvents were removed under reduced pressure, and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (2:1) as eluent to give (+)-(3'S,4'R)-*trans*-khellactone as a colourless solid (20 mg, 95%) of 97% ee (HPLC conditions: hexane/2-propanol (99.5:0.5), oven temp 20 °C, column Eurocel 01 250 × 4.6 mm, 5 μm particle size, flow rate 1 mL/min): mp 182-184 °C (lit. mp 181-185 °C);¹³⁰ $[\alpha]_D +19^\circ$ (*c* 1.7, CHCl₃), (lit. $[\alpha]_D +19.6^\circ$ (*c* 0.6, CHCl₃));¹³⁰ ν_{\max} (film) /cm⁻¹ 3418, 1715, 1605, 1491, 1245; δ_H (300 MHz; CDCl₃) 1.30 (3H, s, CH₃), 1.51 (3H, s, CH₃), 3.08-3.35 (1H, s, OH), 3.85 (1H, d, *J* 6.9 Hz, CHOH), 4.09-4.46 (1H, br s, OH), 5.00 (1H, d, *J* 6.9 Hz, CHOH), 6.25 (1H, d, *J* 9.6 Hz, CH), 6.78 (1H, d, *J* 8.4 Hz, arom., CH), 7.32 (1H, d, *J* 8.4 Hz, arom., CH), 7.66 (1H, d, *J* 9.6 Hz, CH); δ_C (75 MHz; CDCl₃) 19.9 (CH₃), 25.4 (CH₃), 66.5 (quat., C(CH₃)₂), 74.8 (alcohol., CH), 79.3 (alcohol., CH), 111.6 (quat., C11), 112.2 (CH, C6), 112.5 (quat., C12), 114.8 (CH, α C of α,β system), 128.6 (CH, C5), 144.4 (CH, β C of α,β system), 154.4 (quat., C13), 156.3 (quat., C10), 161.2 (quat., C, ketone).

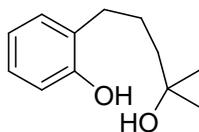
4,5-Dihydro-3H-benzo[b]oxepin-2-one⁷⁵



238

To a solution of *m*-CPBA (7.6 g, 34 mmol, 2 eq), in chloroform (50 ml) at 0 °C, was added α -tetralone (2.5 g, 17 mmol, 1 eq) as a solution in chloroform. After the addition was complete the reaction mixture was allowed to warm to room temperature. Stirring was continued for 5 days until complete consumption of the starting material was observed by TLC. Saturated aqueous sodium carbonate (100 ml) was carefully added and the mixture extracted further with saturated aqueous sodium bicarbonate and water, dried over MgSO₄ and concentrated in vacuo, to yield the product as an off white solid (2.3 g, 83%). No further purification was required. m.p. 35 °C (lit - 34-36 °C)⁷⁵; ν_{max} (film) / cm⁻¹ 2987, 2508, 1653, 1535, 1478, 1211, 1087; δ_{H} (400 MHz; CDCl₃) 2.13-2.22 (2H, m, CH₂, C5), 2.42-2.49 (2H, m, CH₂, C3), 2.77-2.84 (2H, m, CH₂, C3), 7.07-7.30 (4H, m, arom., CH); δ_{C} (100 MHz; CDCl₃) 22.6 (CH₂), 28.2 (CH₂), 31.0 (CH₂), 119.2 (arom., CH), 125.9 (arom., CH), 128.3 (arom., CH), 129.7 (arom., CH) 130.3 (quat.), 151.7 (quat.), 171.6 (quat.).

5-(2-hydroxyphenyl)-2-methyl-2-hydroxypentane⁷⁵

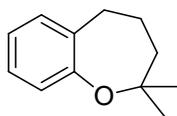


239

To a stirred solution of methylmagnesium iodide (3M soln. in ether, 22 ml, 67 mmol) in diethyl ether (50 ml) at 0 °C was added a solution of 4,5-dihydro-3H-benzo[b]oxepin-2-one (5.0 g, 31 mmol) in diethyl ether over a 90 min period. The mixture was then stirred for 1 hr at room temperature and then poured into aq. ammonium chloride (50 ml) and extracted with dichloromethane (3 x 20 ml). The combined organics were dried (MgSO₄) and evaporated to give the title compound (5.8 g, 96%) as an off white solid, m.p. 77 °C (lit 78-79 °C)⁷⁵, which was used

without further purification. ν_{max} (film) / cm^{-1} 3400, 3100, 1654, 1589, 1245, 1085; δ_{H} (400 MHz; CDCl_3) 1.22 (6H, s, 2 x CH_3), 1.50-1.56 (2H, m, CH_2 , C4), 1.66-1.72 (2H, m, CH_2 , C3), 2.64 (2H, t, J 7.2 Hz, CH_2 , C2), 6.78-6.85 (2H, m, 2 x arom CH), 7.04-7.09 (2H, m, 2 x arom., CH), OH protons not observed; δ_{C} (100 MHz; CDCl_3) 25.7 (CH_2), 29.4 (2 x CH_3), 31.7 (CH_2), 42.0 (CH_2), 72.1 (quat.), 115.6 (arom CH), 120.4 (arom CH), 129.5 (quat.), 126.9 (arom CH), 130.3 (arom CH), 154.1 (quat.).

2,2-Dimethyl-2,3,4,5-tetrahydro-benzo[b]oxepine⁷⁵



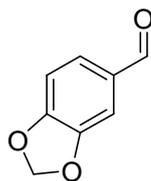
240a

A mixture of 2-(3-hydroxy-3-methyl-butyl)-phenol (4.0 g, 21 mmol) and PTSA (catalytic 0.2 g) in toluene (100 ml) was heated under reflux with a Dean and Stark head for 18 hrs. The solvent was then evaporated under reduced pressure yielding a green solid. ^1H NMR data did not confirm the expected product.

General procedure for the new system of catalytic oxidation of alcohols with 2-iodobenzoic acid and TPPP developed by the Page group.¹³¹

2-Iodobenzoic acid (0.1 eq) and TPPP (3 eq) were dissolved in dichloroethane (DCE) (20 ml). To this the required alcohol (1 eq) was added. The reaction was then warmed to 80 °C and the reaction monitored by TLC. Upon consumption of the starting material the reaction was cooled and diethyl ether added to precipitate out any excess TPPP. The reaction was then filtered through a pad of celite to yield the carbonyl compound.

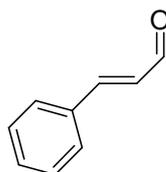
Benzo[1,3]dioxole-5-carbaldehyde¹³²



269

Prepared as the general procedure for the oxidation of alcohols with 2-iodobenzoic acid and TPPP using piperonyl alcohol (0.079 g, 0.50 mmol). Product yielded as a white solid (0.071 g, 94%). m.p. 37 °C (lit. 35-37 °C)¹³²; ν_{max} (film) / cm^{-1} 1778, 1567, 1234; δ_{H} (400 MHz; CDCl_3) 6.07 (2H, s, CH_2), 6.92 (1H, d, J 7.6 Hz, C3), 7.31 (1H, d, J 1.6 Hz, C6), 7.40 (1H, dd, J 7.6, 1.6 Hz, C2), 9.80 (1H, s, aldehyde); δ_{C} (100 MHz; CDCl_3) 102.1 (CH_2), 106.8 (CH arom., C6), 108.3 (CH arom., C3), 128.7 (CH arom., C2), 131.8 (quat., C, C1), 148.6 (quat., C, C4), 153.1 (quat., C, C5), 190.3 (CH, aldehyde).

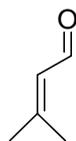
Trans-cinnamaldehyde¹³³



272

Prepared as the general procedure for the oxidation of alcohols with 2-iodobenzoic acid and TPPP using cinnamyl alcohol (0.067 g, 0.50 mmol). Product yielded as a yellow liquid (0.055 g, 83%); ν_{max} (film) / cm^{-1} 1749, 1601, 1578, 1471, 1156; δ_{H} (400 MHz; CDCl_3) 6.68 (1H, q, J 12.5), 7.45 (4H, m, 3 x arom., CH, 1 x alkene CH), 7.54 (2H, m, arom CH), 9.68 (1H, d, J 10.5); δ_{C} (100 MHz; CDCl_3) 128.2 (2 x *ortho* arom CH), 129.3 (2 x *meta* arom CH), 130.7 (*para* arom CH), 131.5 (alkene CH), 133.9 (quat., C, on phenyl), 153.0 (alkene CH), 193.7 (CH, aldehyde).

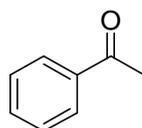
3-Methyl-but-2-enal¹³⁴



275

Prepared as the general procedure for the oxidation of alcohols with 2-iodobenzoic acid and TPPP using prenyl alcohol (0.043 g, 0.50 mmol). Product yielded as a clear liquid (0.039 g, 92%); ν_{max} (film) / cm^{-1} 1787, 1599, 1501, 1467; δ_{H} 1.99 (3H, s, CH_3), 2.18 (3H, s, CH_3), 5.88 (1H, d, J 8.0 Hz, CH, C2), 9.95 (1H, d, J 8.0 Hz, CHO, C1); δ_{C} (100 MHz; CDCl_3) 18.8 (CH_3), 27.1 (CH_3), 128.3 (CH, C2), 160.9 (C quat., C3), 191.2 (CH, aldehyde).

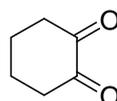
Acetophenone¹³⁵



271

Prepared as the general procedure for the oxidation of alcohols with 2-iodobenzoic acid and TPPP using alpha-methylbenzyl alcohol (0.061 g, 0.50 mmol). Product yielded as a clear liquid (0.055 g, 91%); ν_{max} (film) / cm^{-1} 1724, 1589, 1525, 1367; δ_{H} (400 MHz; CDCl_3) 2.52 (3H, s, CH_3), 7.38 (2H, t, J 15.0 Hz, CH arom., C3,5), 7.46 (1H, t, J 7.5 Hz, CH arom., C4), 7.88 (2H, d, J 9.5 Hz, CH arom., C2,6); δ_{C} (100 MHz; CDCl_3) 25.5 (CH_3), 126.7 (2 x CH arom., C3,5), 127.9 (2 x CH arom., C2,6), 139.9 (CH arom., C4), 136.4 (C quat., C1), 197.1 (quat., C, ketone).

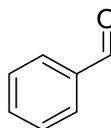
Cyclohexane-1,2-dione¹³⁶



274

Prepared as the general procedure for the oxidation of alcohols with 2-iodobenzoic acid and TPPP using cyclohexane-1,2-diol (0.058 g, 0.50 mmol). Product yielded as a clear liquid (0.049 g, 87%); ν_{max} (film) / cm^{-1} 3378, 1689, 1576, 1435, 1167; δ_{H} (400 MHz; CDCl_3) 1.99-2.03 (2H, m, CH_2), 2.39-2.40 (2H, m, CH_2), 2.52-2.55 (2H, m, CH_2), 6.06 (1H, s, broad enol OH), 6.14-6.17 (1H, m, enol CH); δ_{C} (100 MHz; CDCl_3) 23.3 (CH_2 , C3), 23.8 (CH_2 , C4), 36.4 (CH_2 , C6), 118.5 (CH_2 , C3), 147.0 (C quat., C2), 195.6 (C quat., C1).

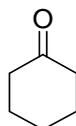
Benzaldehyde¹³⁷



270

Prepared as the general procedure for the oxidation of alcohols with 2-iodobenzoic acid and TPPP using benzyl alcohol (0.054 g, 0.50 mmol). Product yielded as a yellow liquid (0.041 g, 78%); ν_{max} (film) / cm^{-1} 1767, 1602, 1588, 1421, 1215; δ_{H} (400 MHz; CDCl_3) 7.46-7.48 (2H, m, 2 x CH arom., *meta*, C3,5), 7.54-7.56 (1H, m, CH arom., *para*, C4), 7.81-7.84 (2H, m, 2 x CH arom., *ortho*, C2,6), 9.96 (1H, s, aldehyde, CH); δ_{C} (100 MHz; CDCl_3) 128.4 (2 x CH *meta*, C3,5), 129.8 (2 x CH *ortho*, C2,6), 134.4 (CH *para*, C4), 136.3 (C quat., C1), 192.6 (aldehyde, C).

Cyclohexanone¹³⁸

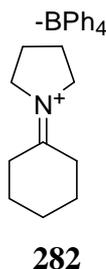


273

Prepared as the general procedure for the oxidation of alcohols with 2-iodobenzoic acid and TPPP using cyclohexanol (0.050 g, 0.50 mmol). Product yielded as a clear oil (0.042 g, 86%); ν_{max} (film) / cm^{-1} 1765, 1505, 1201, 1166, 1042; δ_{H} (400 MHz; CDCl_3) 1.70-1.76 (2H, m, CH_2 *para*, C4), 1.83-1.90 (4H, m, 2 x CH_2 , *meta*, C3,5), 2.32-2.35 (4H, m, 2 x CH_2 , *ortho*, C2,6); δ_{C} (100 MHz; CDCl_3) 21.7 (CH_2 , *para*,

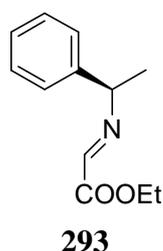
C4), 27.0 (2 x CH₂, *meta*, C3,5), 41.7 (2 x CH₂, *ortho*, C2,6), 211.8 (C quat., ketone, C1).

1-Cyclohexylidene-pyrrolidinium tetraphenyl borate⁴⁶



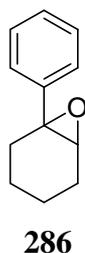
Pyrrolidine (2.00 ml, 23.9 mmol) and cyclohexanone (2.48 ml, 23.9 mmol) were dissolved in toluene (20 ml) and hydrochloric acid (6.00 ml, 23.9 mmol, 4M in dioxane) was added to this. The flask was then connected to Dean Stark apparatus and refluxed overnight. Analysis by TLC showed no trace of the starting materials, so sodium tetraphenylborate (8.00 g, 23.9 mmol) was added to achieve ion exchange. The reaction was stirred for a further 30 minutes, then diethyl ether was added and the product precipitated out of the reaction. This could then be filtered off and washed with more diethyl ether. The product was then re-crystallised from DCM with diethyl ether. The product was obtained as a white crystalline solid (9.2 g, 70%). M.p, 190-192°C (lit. 191-192 °C)⁴⁶; ν_{max} (film) / cm⁻¹ 3050, 2996, 1653, 1578, 1477, 1426, 1264, 1030; δ_{H} (400 MHz; CD₃CN); 1.641-1.697 (2H, m, CH₂), 1.802-1.905 (4H, m, 2 x CH₂), 2.05 (4H, m, 2 x CH₂), 2.612-2.645 (4H, m, 2 x CH₂), 3.764-3.782 (4H, m, 2 x CH₂), 6.88 (4H, m, BPh₄), 7.015-7.054 (8H, m, BPh₄), 7.295-7.321 (8H, m, BPh₄); δ_{C} (100 MHz; CD₃CN) 22.54 (CH₂, *para* on cycl.), 23.61 (2 x CH₂, pyr.), 24.29 (2 x CH₂, *meta* on cycl.), 33.45 (2 x CH₂, *ortho* on cycl.), 53.51 (2 x CH₂, pyr.), 121.45 (4 x CH, *para* on Ph), 125.25 (8 x CH, *ortho* on Ph), 135.40 (8 x CH, *meta* on Ph); m/z anion 319.1, cation 152.2.

Ethyl-2-[(R)-1-phenylethyl]iminoethanoate¹³⁹



A cooled (0 °C) solution of ethyl glyoxylate (2.0 ml, 19.6 mmol) in Et₂O (40 ml) was treated by the slow addition of (R)-1-phenylethylamine (2.50 ml, 19.6 mmol), followed by the addition of MgSO₄ (4.0 g, 1.8 eq). The reaction mixture was stirred overnight at ambient temperature; the solids were then filtered off and washed with Et₂O. The filtrate was concentrated to yield the expected product as a yellow oil (3.9 g, 95%); ν_{max} (film) / cm⁻¹ 3050, 2996, 1653, 1578, 1477, 1426, 1264, 1030; δ_{H} (400 MHz; CDCl₃) 1.31 (3H, t, *J* 7.0 Hz, CH₂CH₃), 1.59 (3H, d, *J* 6.7 Hz, CH₃CH), 4.31 (2H, q, *J* 7.0 Hz, CH₂CH₃), 4.58 (1H, q, *J* 6.7 Hz, CHCH₃), 7.20-7.38 (5H, m, CH arom., on phenyl substituent), 7.72 (1H, s, CH=N); δ_{C} (100 MHz; CDCl₃) 14.2 (CH₂CH₃), 23.8 (PhCCH₃), 61.8 (PhCCH₃), 69.7 (CH₂CH₃), 128.7 (CH, *para* on Ph), 127.6 (2 x CH, *ortho* on Ph), 128.9 (2 x CH, *meta* on Ph), 142.8 (quat., C, on phenyl substituent), 152.4 (COOEt), 163.3 (C=N).

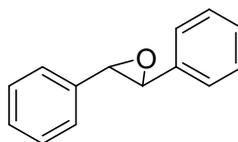
1-Phenyl-6-oxa-bicyclo[4.1.0]heptane^{49-54,56,57}



Prepared *via* the general procedure for the epoxidation of alkenes mediated by TPPP, using the achiral, exocyclic catalyst (**282**). Product isolated as a colourless oil, (0.095 g, 55%); ν_{max} (film) / cm⁻¹ 3034, 2929, 2827, 1604, 1498, 1438, 1343, 1065; δ_{H} (400 MHz; CDCl₃) 1.568-1.597 (4H, m, 2 x CH₂), 1.856-1.912 (2H, m, CH₂), 1.998-2.087 (2H, m, CH₂), 2.992-3.000 (1H, m, epox CH), 7.176-7.274 (5H, m, arom); δ_{C} (100

MHz; CDCl₃) 20.4 (CH₂ *meta* to Ph), 23.4 (CH₂ *para* to Ph), 26.1 (CH₂ *meta* to Ph and next to epox), 34.1 (CH₂ *ortho* to Ph), 64.8 (epox. CH, *ortho* to Ph), 75.4 (epox. C, PhC), 125.7 (CH, *para* on Ph), 126.4 (2 x CH, *ortho* on Ph), 128.4 (2 x CH, *meta* on Ph), 144.5 (quat., C, on phenyl substituent).

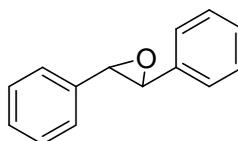
(E)-2,3-Diphenyloxirane^{49-54,56,57}



284

Prepared *via* the general procedure for the epoxidation of alkenes mediated by iminium salts using Oxone[®], using achiral exocyclic catalyst (**282**) with the reaction being performed at both 0 °C and 25 °C; Product isolated as a colourless solid (at 0 °C - 0.115 g, 59%; at 25 °C - 0.121 g, 62%); mp 64-66 °C, (lit. mp 61-63 °C);^{1,5} ν_{max} (film) / cm⁻¹ 1605, 1511, 1490, 1289, 1195, 1140, 1085, 1036; δ_{H} (400 MHz; CDCl₃) 3.851 (2H, s, PhCH-O), 7.278-7.369 (10H, m, arom., 2 x Ph gp.); δ_{C} (100 MHz; CDCl₃) 63.2 (2 x epox. CH), 125.4 (4 x CH arom., *ortho* to epox.), 127.9 (2 x CH arom., *para* to epox.), 129.4 (4 x CH arom., *meta* to epox.), 138.1 (2 x quat., C on phenyl substituents).

(E)-2,3-Diphenyloxirane^{49-54,56,57}

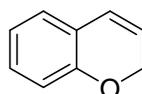


284

Prepared *via* the method used by Komatsu; NaHCO₃ (4 eq) was placed in a round bottomed flask with water (12 ml per 1.5 g carbonate). Oxone[®] (1 eq) was then added, and the reaction stirred until the effervescence had stopped. The catalyst (**282**) (10 mol%) was dissolved in MeCN (6 ml per 1.5 g carbonate) and added to the flask. The alkene (1 eq) was then added and the reaction stirred at room temperature, whilst being monitored *via* TLC. Product isolated as a colourless solid (0.133 g, 68%); mp

65-67°C, (lit. mp 61-63°C);^{1,5} ν_{max} (film) / cm^{-1} 1600, 1501, 1489, 1286, 1190, 1148, 1090, 1036; δ_{H} (400 MHz; CDCl_3) 3.851 (2H, s, PhCH-O), 7.278-7.369 (10H, m, arom., 2 x Ph gp.); δ_{C} (100 MHz; CDCl_3) 63.2 (2 x epox. CH), 125.4 (4 x CH arom., *ortho* to epox.), 127.9 (2 x CH arom., *para* to epox.), 129.4 (4 x CH arom., *meta* to epox.), 138.1 (2 x quat., C on phenyl substituents).

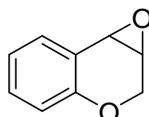
2H-benzopyran¹⁴⁰



241

4-chrominol (1.31 g, 8.73 mmol) was added to a round bottomed flask containing toluene (40 ml), *p*TSA (1.66 g, 1 eq) and hydroquinone (0.0080 g, cat.). The flask was equipped with a reflux condenser and the reaction refluxed until TLC confirmed no starting material remained. The reaction was then passed through a short pad of silica and the filtrate concentrated under vacuum, yielding the product as a clear oil (1.08 g, 93%). ν_{max} (film) / cm^{-1} 2854, 2054, 1685, 1456, 1397, 1186, 1036; δ_{H} (400 MHz; CDCl_3) 4.54-4.58 (2H, m, CH_2 , C2), 5.85-5.89 (1H, m, CH, C3), 6.52-6.55 (1H, m, CH, C4), 6.75 (1H, dd, *J* 8.4, 2.1 Hz, C8), 6.84 (1H, dd, *J* 8.8, 2.2 Hz, C6), 6.97 (1H, dd, *J* 8.4, 2.1 Hz, C7), 7.02 (1H, dd, *J* 8.8, 2.2 Hz, C5); δ_{C} (100 MHz; CDCl_3) 65.1 (C2), 115.2 (C4), 118.4 (C3), 121.2 (quat., C, C9), 124.3 (C5), 125.1 (C7), 125.2 (C6), 126.5 (C8), 131.2 (quat., C, C10).

2H-benzopyran oxide



244

Prepared by the TPPP epoxidation route described previously, yielding the title compound as a clear oil (0.11 g, 74%). ν_{max} (film) / cm^{-1} 3051, 3025, 1685, 1454; δ_{H} (400 MHz; CDCl_3) 3.42-3.45 (1H, m, CH, C3), 3.78-3.81 (1H, m, CH, C4), 4.10-

4.15 (2H, m, CH_2 , C2), 6.78 (1H, dd, J 8.6, 2.4 Hz, C8), 6.88 (1H, dd, J 8.7, 2.5 Hz, C6), 7.05 (1H, dd, J 8.6, 2.4 Hz, C7), 7.10 (1H, dd, J 8.7, 2.5 Hz, C5); δ_C (100 MHz; $CDCl_3$) 68.2 (C2), 75.3 (C3), 79.5 (C4), 119.2 (quat., C, C9), 125.1 (C5), 125.2 (C7), 125.7 (C6), 128.5 (C8), 132.0 (quat., C, C10).

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Appendix

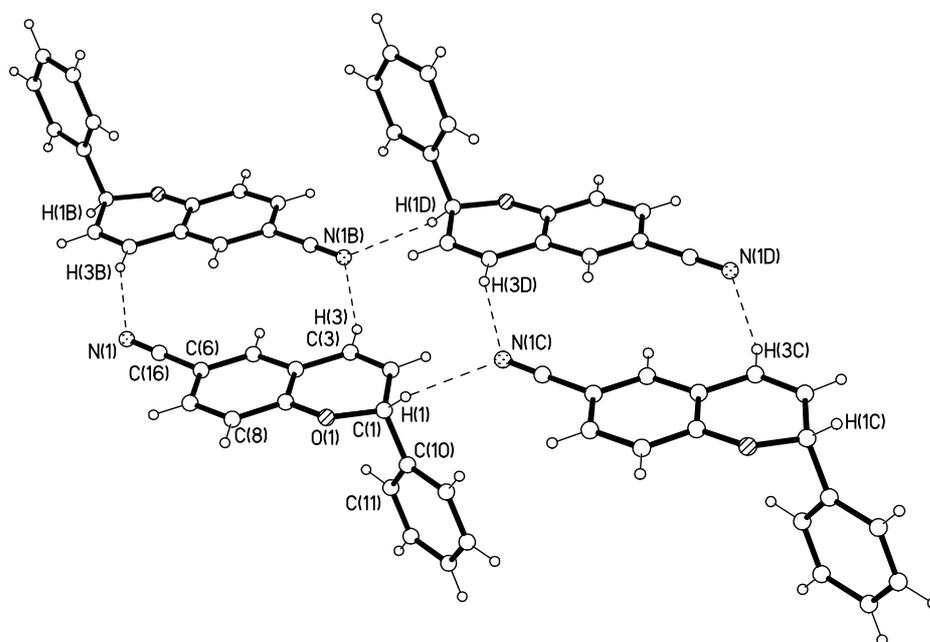
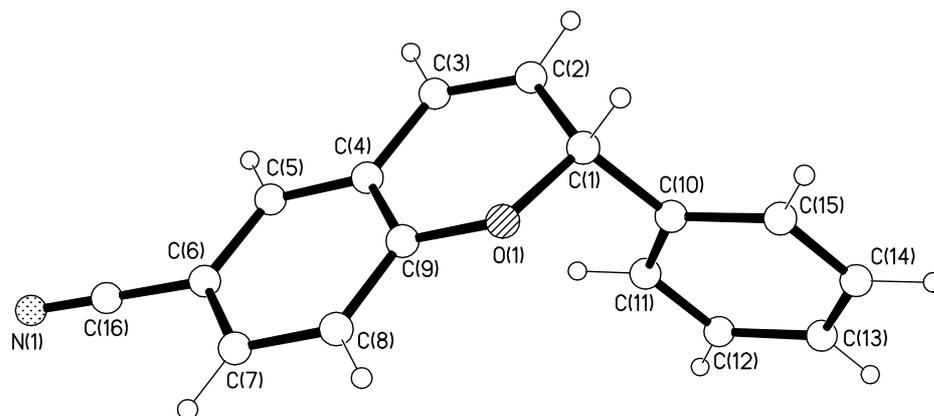


Table 1. Crystal data and structure refinement for pcbp62.

Identification code	pcbp62	
Chemical formula	C ₁₆ H ₁₁ NO	
Formula weight	233.26	
Temperature	120(2) K	
Radiation, wavelength	MoK α , 0.71073 Å	
Crystal system, space group	monoclinic, P2 ₁ /c	
Unit cell parameters	a = 5.70970(10) Å	$\alpha = 90^\circ$
	b = 8.8774(3) Å	$\beta = 94.203(2)^\circ$
	c = 23.3732(9) Å	$\gamma = 90^\circ$
Cell volume	1181.54(6) Å ³	
Z	4	
Calculated density	1.311 g/cm ³	
Absorption coefficient μ	0.082 mm ⁻¹	
F(000)	488	
Crystal colour and size	colourless, 0.46 × 0.04 × 0.03 mm ³	
Reflections for cell refinement	2688 (θ range 2.91 to 27.48°)	
Data collection method	Bruker-Nonius 95mm CCD camera on κ -goniostat	
	ϕ & ω scans	
θ range for data collection	3.48 to 27.54°	
Index ranges	h -7 to 7, k -11 to 11, l -30 to 30	
Completeness to $\theta = 27.54^\circ$	98.6 %	
Intensity decay	0%	
Reflections collected	13408	
Independent reflections	2692 ($R_{\text{int}} = 0.0379$)	
Reflections with $F^2 > 2\sigma$	2295	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.858 and 0.998	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0452, 0.5563	
Data / restraints / parameters	2692 / 0 / 164	
Final R indices [$F^2 > 2\sigma$]	R1 = 0.0462, wR2 = 0.1129	
R indices (all data)	R1 = 0.0555, wR2 = 0.1188	
Goodness-of-fit on F^2	1.079	
Extinction coefficient	0.017(5)	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.272 and -0.224 e Å ⁻³	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (Å²)

for pcbp62. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(1)	0.36053(16)	0.77756(10)	0.11147(4)	0.0249(3)
C(1)	0.3094(2)	0.61650(15)	0.10537(6)	0.0226(3)
C(2)	0.0914(3)	0.58442(16)	0.06769(6)	0.0246(3)
C(3)	-0.0665(2)	0.68902(15)	0.05235(6)	0.0230(3)
C(4)	-0.0263(2)	0.84484(15)	0.06985(5)	0.0202(3)
C(5)	-0.1869(2)	0.95932(15)	0.05695(5)	0.0214(3)
C(6)	-0.1362(2)	1.10777(15)	0.07338(6)	0.0218(3)
C(7)	0.0772(2)	1.14215(15)	0.10364(6)	0.0235(3)
C(8)	0.2396(2)	1.02932(15)	0.11656(6)	0.0228(3)
C(9)	0.1890(2)	0.88177(15)	0.09965(5)	0.0204(3)
C(10)	0.2965(2)	0.54828(15)	0.16452(6)	0.0238(3)
C(11)	0.1059(3)	0.5789(2)	0.19626(7)	0.0357(4)
C(12)	0.0947(3)	0.5186(2)	0.25071(7)	0.0488(5)
C(13)	0.2705(4)	0.4251(2)	0.27324(7)	0.0506(5)
C(14)	0.4581(4)	0.3923(2)	0.24197(8)	0.0482(5)
C(15)	0.4723(3)	0.45409(18)	0.18756(7)	0.0341(4)
C(16)	-0.3035(2)	1.22461(15)	0.05812(6)	0.0244(3)
N(1)	-0.4378(2)	1.31736(15)	0.04560(6)	0.0322(3)

Table 3. Bond lengths [\AA] and angles [$^\circ$] for pcbp62.

O(1)–C(9)	1.3609(16)	O(1)–C(1)	1.4640(16)
C(1)–C(2)	1.499(2)	C(1)–C(10)	1.5161(18)
C(2)–C(3)	1.325(2)	C(3)–C(4)	1.4559(18)
C(4)–C(5)	1.3872(18)	C(4)–C(9)	1.4062(18)
C(5)–C(6)	1.3970(19)	C(6)–C(7)	1.3972(19)
C(6)–C(16)	1.4370(19)	C(7)–C(8)	1.3832(19)
C(8)–C(9)	1.3925(18)	C(10)–C(15)	1.385(2)
C(10)–C(11)	1.388(2)	C(11)–C(12)	1.386(2)
C(12)–C(13)	1.377(3)	C(13)–C(14)	1.371(3)
C(14)–C(15)	1.393(2)	C(16)–N(1)	1.1486(18)
C(9)–O(1)–C(1)	120.58(10)	O(1)–C(1)–C(2)	113.19(11)
O(1)–C(1)–C(10)	108.91(11)	C(2)–C(1)–C(10)	111.47(11)
C(3)–C(2)–C(1)	123.04(13)	C(2)–C(3)–C(4)	119.96(13)
C(5)–C(4)–C(9)	118.47(12)	C(5)–C(4)–C(3)	123.15(12)
C(9)–C(4)–C(3)	118.35(12)	C(4)–C(5)–C(6)	120.74(12)
C(5)–C(6)–C(7)	120.03(12)	C(5)–C(6)–C(16)	119.49(12)
C(7)–C(6)–C(16)	120.47(12)	C(8)–C(7)–C(6)	119.89(12)
C(7)–C(8)–C(9)	119.82(12)	O(1)–C(9)–C(8)	116.77(12)
O(1)–C(9)–C(4)	122.14(12)	C(8)–C(9)–C(4)	121.04(12)
C(15)–C(10)–C(11)	118.99(14)	C(15)–C(10)–C(1)	120.89(13)
C(11)–C(10)–C(1)	120.11(13)	C(12)–C(11)–C(10)	120.38(17)
C(13)–C(12)–C(11)	120.15(17)	C(14)–C(13)–C(12)	120.01(16)
C(13)–C(14)–C(15)	120.19(17)	C(10)–C(15)–C(14)	120.26(16)
N(1)–C(16)–C(6)	179.51(17)		

Table 4. Hydrogen coordinates and isotropic displacement parameters (\AA^2) for pcbp62.

	x	y	z	U
H(1)	0.4443	0.5684	0.0874	0.027
H(2)	0.0651	0.4845	0.0542	0.029
H(3)	-0.2059	0.6623	0.0299	0.028
H(5)	-0.3330	0.9365	0.0367	0.026
H(7)	0.1107	1.2428	0.1153	0.028
H(8)	0.3853	1.0524	0.1369	0.027
H(11)	-0.0176	0.6415	0.1806	0.043
H(12)	-0.0346	0.5418	0.2725	0.059
H(13)	0.2619	0.3834	0.3105	0.061
H(14)	0.5787	0.3272	0.2575	0.058
H(15)	0.6030	0.4315	0.1662	0.041

Table 5. Torsion angles [°] for pcbp62.

C(9)–O(1)–C(1)–C(2)	19.69(16)	C(9)–O(1)–C(1)–C(10)	-104.89(13)
O(1)–C(1)–C(2)–C(3)	-14.53(18)	C(10)–C(1)–C(2)–C(3)	108.65(15)
C(1)–C(2)–C(3)–C(4)	3.1(2)	C(2)–C(3)–C(4)–C(5)	-177.88(13)
C(2)–C(3)–C(4)–C(9)	4.22(19)	C(9)–C(4)–C(5)–C(6)	-0.22(19)
C(3)–C(4)–C(5)–C(6)	-178.12(12)	C(4)–C(5)–C(6)–C(7)	-0.61(19)
C(4)–C(5)–C(6)–C(16)	178.38(12)	C(5)–C(6)–C(7)–C(8)	0.9(2)
C(16)–C(6)–C(7)–C(8)	-178.06(12)	C(6)–C(7)–C(8)–C(9)	-0.4(2)
C(1)–O(1)–C(9)–C(8)	168.38(11)	C(1)–O(1)–C(9)–C(4)	-14.04(18)
C(7)–C(8)–C(9)–O(1)	177.13(11)	C(7)–C(8)–C(9)–C(4)	-0.5(2)
C(5)–C(4)–C(9)–O(1)	-176.71(11)	C(3)–C(4)–C(9)–O(1)	1.30(18)
C(5)–C(4)–C(9)–C(8)	0.77(19)	C(3)–C(4)–C(9)–C(8)	178.77(12)
O(1)–C(1)–C(10)–C(15)	-108.08(14)	C(2)–C(1)–C(10)–C(15)	126.33(14)
O(1)–C(1)–C(10)–C(11)	72.41(16)	C(2)–C(1)–C(10)–C(11)	-53.18(17)
C(15)–C(10)–C(11)–C(12)	1.4(2)	C(1)–C(10)–C(11)–C(12)	-179.06(15)
C(10)–C(11)–C(12)–C(13)	-1.4(3)	C(11)–C(12)–C(13)–C(14)	0.4(3)
C(12)–C(13)–C(14)–C(15)	0.5(3)	C(11)–C(10)–C(15)–C(14)	-0.5(2)
C(1)–C(10)–C(15)–C(14)	179.96(14)	C(13)–C(14)–C(15)–C(10)	-0.4(3)

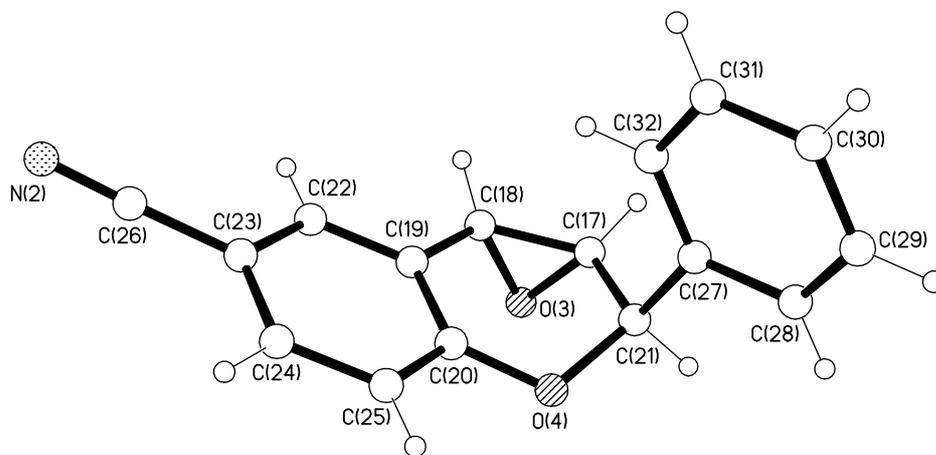
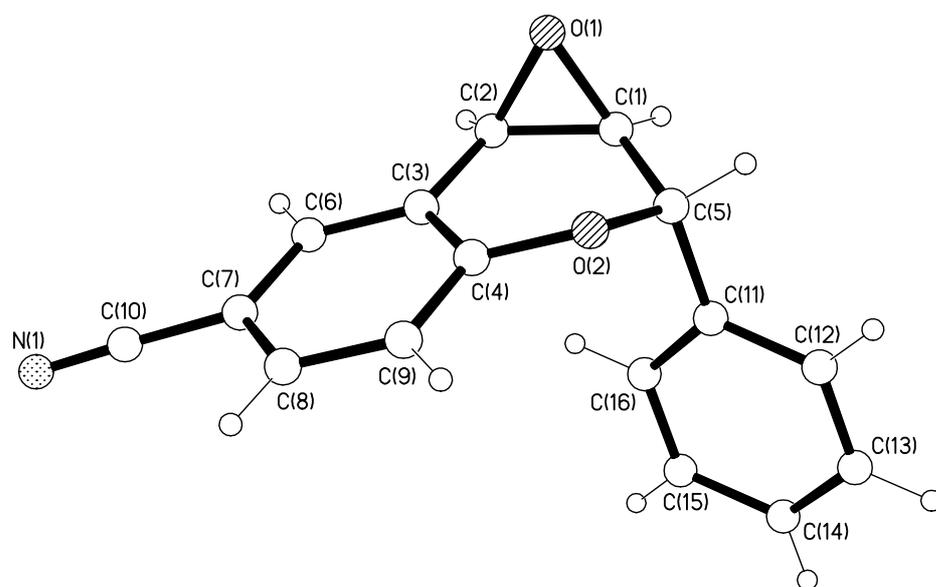


Table 1. Crystal data and structure refinement for pcbp75.

Identification code	pcbp75	
Chemical formula	$C_{16}H_{11}NO_2$	
Formula weight	249.26	
Temperature	150(2) K	
Radiation, wavelength	MoK α , 0.71073 Å	
Crystal system, space group	orthorhombic, Pca2 ₁	
Unit cell parameters	a = 25.5445(17) Å	$\alpha = 90^\circ$
	b = 5.8327(4) Å	$\beta = 90^\circ$
	c = 16.5222(11) Å	$\gamma = 90^\circ$
Cell volume	2461.7(3) Å ³	
Z	8	
Calculated density	1.345 g/cm ³	
Absorption coefficient μ	0.090 mm ⁻¹	
F(000)	1040	
Crystal colour and size	colourless, 0.46 × 0.43 × 0.09 mm ³	
Reflections for cell refinement	3765 (θ range 2.94 to 21.88°)	
Data collection method	Bruker APEX 2 CCD diffractometer ω rotation with narrow frames	
θ range for data collection	1.59 to 27.20°	
Index ranges	h -32 to 32, k -7 to 7, l -21 to 21	
Completeness to $\theta = 27.20^\circ$	100.0 %	
Intensity decay	0%	
Reflections collected	22235	
Independent reflections	2841 ($R_{int} = 0.0525$)	
Reflections with $F^2 > 2\sigma$	2442	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.960 and 0.992	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0322, 0.3228	
Data / restraints / parameters	2841 / 1 / 344	
Final R indices [$F^2 > 2\sigma$]	R1 = 0.0327, wR2 = 0.0676	
R indices (all data)	R1 = 0.0428, wR2 = 0.0721	
Goodness-of-fit on F^2	1.031	
Extinction coefficient	0.0016(4)	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.147 and -0.128 e Å ⁻³	
Absolute structure was not determined from the data. Friedels were merged.		

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (Å²)

for pcbp75. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(1)	0.49309(6)	-0.0721(3)	0.27694(9)	0.0343(4)
C(1)	0.43773(8)	-0.0974(4)	0.26338(13)	0.0303(5)
C(2)	0.47468(8)	-0.2332(4)	0.21565(13)	0.0271(5)
C(3)	0.48317(8)	-0.1594(4)	0.13094(12)	0.0240(4)
C(4)	0.46518(8)	0.0555(4)	0.10721(12)	0.0237(4)
O(2)	0.44182(6)	0.2033(2)	0.16031(9)	0.0302(3)
C(5)	0.41044(9)	0.1008(4)	0.22438(13)	0.0291(5)
C(6)	0.50774(8)	-0.2992(4)	0.07479(13)	0.0250(5)
C(7)	0.51433(8)	-0.2218(4)	-0.00435(13)	0.0268(5)
C(8)	0.49705(9)	-0.0046(4)	-0.02740(13)	0.0281(5)
C(9)	0.47219(8)	0.1332(4)	0.02820(13)	0.0271(5)
C(10)	0.53815(9)	-0.3684(4)	-0.06426(14)	0.0308(5)
N(1)	0.55626(9)	-0.4824(4)	-0.11320(12)	0.0414(5)
C(11)	0.35713(9)	0.0368(4)	0.19242(13)	0.0310(5)
C(12)	0.31596(10)	0.1894(5)	0.20189(16)	0.0430(6)
C(13)	0.26676(11)	0.1401(6)	0.1721(2)	0.0593(8)
C(14)	0.25782(11)	-0.0613(5)	0.1311(2)	0.0541(7)
C(15)	0.29820(11)	-0.2146(5)	0.11971(19)	0.0517(7)
C(16)	0.34756(9)	-0.1655(5)	0.15087(16)	0.0413(6)
O(3)	0.60284(7)	0.4493(3)	0.46576(10)	0.0419(4)
C(17)	0.59421(10)	0.4759(4)	0.38067(15)	0.0361(5)
C(18)	0.63367(9)	0.6164(4)	0.42122(15)	0.0351(5)
C(19)	0.68902(9)	0.5566(4)	0.40752(13)	0.0316(5)
C(20)	0.70079(9)	0.3441(4)	0.37290(14)	0.0309(5)
O(4)	0.66230(6)	0.1870(3)	0.35621(10)	0.0360(4)
C(21)	0.61175(9)	0.2769(4)	0.32973(15)	0.0354(6)
C(22)	0.72918(9)	0.7061(4)	0.42550(14)	0.0319(5)
C(23)	0.78079(9)	0.6454(4)	0.40880(14)	0.0325(5)
C(24)	0.79204(9)	0.4320(4)	0.37492(15)	0.0343(5)
C(25)	0.75213(10)	0.2827(4)	0.35626(14)	0.0333(5)
C(26)	0.82236(10)	0.8084(4)	0.42339(16)	0.0362(5)
N(2)	0.85530(8)	0.9394(4)	0.43215(15)	0.0452(5)
C(27)	0.61424(8)	0.3291(4)	0.24028(14)	0.0317(5)
C(28)	0.59957(9)	0.1601(4)	0.18558(15)	0.0350(6)
C(29)	0.60579(9)	0.1931(4)	0.10328(15)	0.0373(6)
C(30)	0.62668(9)	0.3952(4)	0.07479(16)	0.0366(6)
C(31)	0.64064(9)	0.5669(4)	0.12815(16)	0.0388(6)
C(32)	0.63449(9)	0.5348(4)	0.21103(16)	0.0349(5)

Table 3. Bond lengths [Å] and angles [°] for pcbp75.

O(1)–C(1)	1.439(3)	O(1)–C(2)	1.459(3)
C(1)–C(2)	1.463(3)	C(1)–C(5)	1.496(3)
C(2)–C(3)	1.480(3)	C(3)–C(6)	1.385(3)
C(3)–C(4)	1.392(3)	C(4)–O(2)	1.367(2)
C(4)–C(9)	1.393(3)	O(2)–C(5)	1.456(3)
C(5)–C(11)	1.507(3)	C(6)–C(7)	1.393(3)
C(7)–C(8)	1.395(3)	C(7)–C(10)	1.443(3)
C(8)–C(9)	1.376(3)	C(10)–N(1)	1.145(3)
C(11)–C(12)	1.387(3)	C(11)–C(16)	1.387(3)
C(12)–C(13)	1.380(4)	C(13)–C(14)	1.375(4)
C(14)–C(15)	1.378(4)	C(15)–C(16)	1.392(4)
O(3)–C(17)	1.432(3)	O(3)–C(18)	1.453(3)
C(17)–C(18)	1.462(3)	C(17)–C(21)	1.502(3)
C(18)–C(19)	1.474(3)	C(19)–C(22)	1.379(3)
C(19)–C(20)	1.398(3)	C(20)–O(4)	1.372(3)
C(20)–C(25)	1.387(3)	O(4)–C(21)	1.461(3)
C(21)–C(27)	1.510(3)	C(22)–C(23)	1.393(3)
C(23)–C(24)	1.395(3)	C(23)–C(26)	1.445(3)
C(24)–C(25)	1.376(3)	C(26)–N(2)	1.146(3)
C(27)–C(28)	1.389(3)	C(27)–C(32)	1.393(3)
C(28)–C(29)	1.383(4)	C(29)–C(30)	1.377(4)
C(30)–C(31)	1.381(4)	C(31)–C(32)	1.391(4)
C(1)–O(1)–C(2)	60.63(13)	O(1)–C(1)–C(2)	60.35(13)
O(1)–C(1)–C(5)	116.49(18)	C(2)–C(1)–C(5)	119.14(18)
O(1)–C(2)–C(1)	59.02(13)	O(1)–C(2)–C(3)	114.95(17)
C(1)–C(2)–C(3)	116.53(19)	C(6)–C(3)–C(4)	119.40(19)
C(6)–C(3)–C(2)	121.9(2)	C(4)–C(3)–C(2)	118.69(19)
O(2)–C(4)–C(3)	122.09(18)	O(2)–C(4)–C(9)	116.89(19)
C(3)–C(4)–C(9)	121.0(2)	C(4)–O(2)–C(5)	116.61(16)
O(2)–C(5)–C(1)	111.96(17)	O(2)–C(5)–C(11)	110.14(17)
C(1)–C(5)–C(11)	112.37(18)	C(3)–C(6)–C(7)	119.5(2)
C(6)–C(7)–C(8)	120.8(2)	C(6)–C(7)–C(10)	120.2(2)
C(8)–C(7)–C(10)	119.0(2)	C(9)–C(8)–C(7)	119.6(2)
C(8)–C(9)–C(4)	119.6(2)	N(1)–C(10)–C(7)	178.3(3)
C(12)–C(11)–C(5)	117.9(2)	C(12)–C(11)–C(5)	119.1(2)
C(16)–C(11)–C(5)	122.9(2)	C(13)–C(12)–C(11)	121.1(3)
C(14)–C(13)–C(12)	120.3(3)	C(13)–C(14)–C(15)	119.8(3)
C(14)–C(15)–C(16)	119.6(3)	C(11)–C(16)–C(15)	121.2(3)
C(17)–O(3)–C(18)	60.89(15)	O(3)–C(17)–C(18)	60.29(16)
O(3)–C(17)–C(21)	114.9(2)	C(18)–C(17)–C(21)	119.0(2)
O(3)–C(18)–C(17)	58.82(14)	O(3)–C(18)–C(19)	116.0(2)
C(17)–C(18)–C(19)	117.3(2)	C(22)–C(19)–C(20)	119.3(2)
C(22)–C(19)–C(18)	122.1(2)	C(20)–C(19)–C(18)	118.6(2)
O(4)–C(20)–C(25)	117.7(2)	O(4)–C(20)–C(19)	121.3(2)
C(25)–C(20)–C(19)	120.9(2)	C(20)–O(4)–C(21)	117.00(17)
O(4)–C(21)–C(17)	111.91(19)	O(4)–C(21)–C(27)	109.16(19)
C(17)–C(21)–C(27)	113.9(2)	C(19)–C(22)–C(23)	120.1(2)
C(22)–C(23)–C(24)	120.1(2)	C(22)–C(23)–C(26)	119.7(2)
C(24)–C(23)–C(26)	120.2(2)	C(25)–C(24)–C(23)	120.1(2)
C(24)–C(25)–C(20)	119.5(2)	N(2)–C(26)–C(23)	177.6(3)
C(28)–C(27)–C(32)	119.0(2)	C(28)–C(27)–C(21)	118.9(2)
C(32)–C(27)–C(21)	121.9(2)	C(29)–C(28)–C(27)	120.7(2)

C(30)–C(29)–C(28)	120.0(2)	C(29)–C(30)–C(31)	120.2(2)
C(30)–C(31)–C(32)	120.1(2)	C(31)–C(32)–C(27)	120.0(2)

Table 4. Hydrogen coordinates and isotropic displacement parameters (\AA^2) for pcbp75.

	x	y	z	U
H(1)	0.4177	-0.1816	0.3060	0.036
H(2)	0.4775	-0.4006	0.2279	0.033
H(5)	0.4052	0.2204	0.2670	0.035
H(6)	0.5200	-0.4467	0.0901	0.030
H(8)	0.5024	0.0479	-0.0812	0.034
H(9)	0.4599	0.2806	0.0128	0.033
H(12)	0.3217	0.3303	0.2293	0.052
H(13)	0.2389	0.2458	0.1800	0.071
H(14)	0.2239	-0.0947	0.1107	0.065
H(15)	0.2924	-0.3529	0.0907	0.062
H(16)	0.3752	-0.2726	0.1436	0.050
H(17)	0.5612	0.5546	0.3639	0.043
H(18)	0.6252	0.7820	0.4299	0.042
H(21)	0.5854	0.1517	0.3371	0.043
H(22)	0.7216	0.8506	0.4493	0.038
H(24)	0.8273	0.3896	0.3647	0.041
H(25)	0.7597	0.1386	0.3321	0.040
H(28)	0.5851	0.0204	0.2049	0.042
H(29)	0.5956	0.0764	0.0664	0.045
H(30)	0.6315	0.4166	0.0183	0.044
H(31)	0.6545	0.7072	0.1082	0.047
H(32)	0.6441	0.6530	0.2477	0.042

Table 5. Torsion angles [$^\circ$] for pcbp75.

C(2)–O(1)–C(1)–C(5)	-110.0(2)	C(1)–O(1)–C(2)–C(3)	107.2(2)
C(5)–C(1)–C(2)–O(1)	105.7(2)	O(1)–C(1)–C(2)–C(3)	-104.5(2)
C(5)–C(1)–C(2)–C(3)	1.2(3)	O(1)–C(2)–C(3)–C(6)	128.1(2)
C(1)–C(2)–C(3)–C(6)	-165.65(19)	O(1)–C(2)–C(3)–C(4)	-52.8(3)
C(1)–C(2)–C(3)–C(4)	13.4(3)	C(6)–C(3)–C(4)–O(2)	-178.34(18)
C(2)–C(3)–C(4)–O(2)	2.5(3)	C(6)–C(3)–C(4)–C(9)	-0.9(3)
C(2)–C(3)–C(4)–C(9)	179.98(18)	C(3)–C(4)–O(2)–C(5)	-33.6(3)
C(9)–C(4)–O(2)–C(5)	148.89(18)	C(4)–O(2)–C(5)–C(1)	45.5(2)
C(4)–O(2)–C(5)–C(11)	-80.3(2)	O(1)–C(1)–C(5)–O(2)	39.9(2)
C(2)–C(1)–C(5)–O(2)	-29.3(3)	O(1)–C(1)–C(5)–C(11)	164.51(18)
C(2)–C(1)–C(5)–C(11)	95.3(2)	C(4)–C(3)–C(6)–C(7)	0.4(3)
C(2)–C(3)–C(6)–C(7)	179.47(19)	C(3)–C(6)–C(7)–C(8)	0.7(3)
C(3)–C(6)–C(7)–C(10)	-177.77(19)	C(6)–C(7)–C(8)–C(9)	-1.4(3)
C(10)–C(7)–C(8)–C(9)	177.2(2)	C(7)–C(8)–C(9)–C(4)	0.9(3)
O(2)–C(4)–C(9)–C(8)	177.84(19)	C(3)–C(4)–C(9)–C(8)	0.3(3)
O(2)–C(5)–C(11)–C(12)	-94.8(2)	C(1)–C(5)–C(11)–C(12)	139.7(2)
O(2)–C(5)–C(11)–C(16)	82.7(3)	C(1)–C(5)–C(11)–C(16)	-42.9(3)
C(16)–C(11)–C(12)–C(13)	1.1(4)	C(5)–C(11)–C(12)–C(13)	178.6(2)
C(11)–C(12)–C(13)–C(14)	-1.0(5)	C(12)–C(13)–C(14)–C(15)	0.0(5)
C(13)–C(14)–C(15)–C(16)	0.9(5)	C(12)–C(11)–C(16)–C(15)	-0.1(4)
C(5)–C(11)–C(16)–C(15)	-177.6(2)	C(14)–C(15)–C(16)–C(11)	-0.9(4)

C(18)–O(3)–C(17)–C(21)	110.5(2)	C(17)–O(3)–C(18)–C(19)	–107.5(2)
C(21)–C(17)–C(18)–O(3)	–103.7(2)	O(3)–C(17)–C(18)–C(19)	105.4(2)
C(21)–C(17)–C(18)–C(19)	1.6(3)	O(3)–C(18)–C(19)–C(22)	–129.6(2)
C(17)–C(18)–C(19)–C(22)	163.8(2)	O(3)–C(18)–C(19)–C(20)	52.4(3)
C(17)–C(18)–C(19)–C(20)	–14.3(3)	C(22)–C(19)–C(20)–O(4)	178.0(2)
C(18)–C(19)–C(20)–O(4)	–3.9(3)	C(22)–C(19)–C(20)–C(25)	–0.2(3)
C(18)–C(19)–C(20)–C(25)	177.8(2)	C(25)–C(20)–O(4)–C(21)	–146.5(2)
C(19)–C(20)–O(4)–C(21)	35.2(3)	C(20)–O(4)–C(21)–C(17)	–45.0(3)
C(20)–O(4)–C(21)–C(27)	82.0(2)	O(3)–C(17)–C(21)–O(4)	–41.9(3)
C(18)–C(17)–C(21)–O(4)	26.5(3)	O(3)–C(17)–C(21)–C(27)	–166.3(2)
C(18)–C(17)–C(21)–C(27)	–97.9(3)	C(20)–C(19)–C(22)–C(23)	0.3(3)
C(18)–C(19)–C(22)–C(23)	–177.7(2)	C(19)–C(22)–C(23)–C(24)	–0.9(3)
C(19)–C(22)–C(23)–C(26)	176.4(2)	C(22)–C(23)–C(24)–C(25)	1.4(3)
C(26)–C(23)–C(24)–C(25)	–175.8(2)	C(23)–C(24)–C(25)–C(20)	–1.3(4)
O(4)–C(20)–C(25)–C(24)	–177.6(2)	C(19)–C(20)–C(25)–C(24)	0.7(3)
O(4)–C(21)–C(27)–C(28)	91.4(2)	C(17)–C(21)–C(27)–C(28)	–142.7(2)
O(4)–C(21)–C(27)–C(32)	–83.7(3)	C(17)–C(21)–C(27)–C(32)	42.2(3)
C(32)–C(27)–C(28)–C(29)	1.2(3)	C(21)–C(27)–C(28)–C(29)	–174.0(2)
C(27)–C(28)–C(29)–C(30)	0.0(4)	C(28)–C(29)–C(30)–C(31)	–1.1(4)
C(29)–C(30)–C(31)–C(32)	1.1(4)	C(30)–C(31)–C(32)–C(27)	0.0(4)
C(28)–C(27)–C(32)–C(31)	–1.2(3)	C(21)–C(27)–C(32)–C(31)	173.9(2)