Novel Electrochemical Systems

for

Asymmetric Oxidation

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ABBREVIATIONS

Ac	acetyl
AIBN	2,2'-azobis-(2-methylpropionitrile)
aq.	aqueous
Ar	aryl
arom.	aromatic
BDD	boron-doped diamond
BINAP	binaphthalene
BINOL	1,1'-bis(2-naphthol)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
c	concentration
cat.	catalyst (catalytic amount)
conc.	concentrated
conv.	conversion
δ	chemical shift
DCM	dichloromethane
DMM	dimethyl maleate
dppp	1,3-Bis(diphenylphosphino)propane
Δ	reflux
eq.	equivalent
hfc	(heptafluoropropylhydroxymethylene)camphorato
HPLC	high performance liquid chromatography
LAH	lithium aluminium hydride
m	molar
m-CPBA	*m*-chloroperbenzoic acid
m.p.	melting point

NBS	*N*-bromosuccinimide
Nu	nucleophile
Tf	trifluoromethanesulfonyl
Pd(OAc)$_2$	Palladium(II) acetate
PTC	phase-transfer catalyst
PTSA	toluene-*p*-sulfonic acid
quat.	quaternary
R	alkyl
rt	room temperature
salen	salicylideneaminato ligand
s.m.	starting material
TBAP	tetrabutylammonium perchlorate
TBHP	*tert*-butylhydroperoxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TPPP	tetraphenylphosphonium monoperoxysulphate

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1.0   <u>Introduction</u>

Epoxides are three-membered rings consisting of two carbon atoms and an oxygen atom; they are reactive due to strain within the three-membered ring.

The epoxidation of alkenes is a valuable synthetic transformation that can be used to introduce functionality into an organic molecule. Chiral epoxides are important versatile building blocks in organic synthesis, and are present in many biologically active compounds and natural products.[1]

Over the past twenty years some major advances have been made in the methodology for the asymmetric epoxidation of alkenes.[2] This has been mainly due to the market situation for chiral drugs, where the use of racemic compounds in the pharmaceutical industry is to be avoided according to national agencies such as the FDA (Food and Drug Administration) in the USA.[2, 3]

Epoxides are useful precursors because they can be opened with a range of nucleophiles, due to the strain of the three-membered ring system. Epoxides are also thought to be involved in the carcinogenic effects of aromatic hydrocarbons, which are produced by oxidation using cytochrome P450. This reaction facilitates nucleophilic attack by DNA, resulting in mutation.

A number of different methodologies have been developed for the epoxidation of olefins including metal and non-metal catalysed reactions. Olefin substrates are inexpensive and readily available, hence partly the reason they are regarded as such important synthetic organic intermediates.[4, 5]

1.1   Electrochemistry

A possible 'greener' route for oxidation reactions, be it sulfoxidation, Baeyer-Villiger oxidation or epoxidation is to consider generating the oxidant by electrochemical methods thus eliminating the need for a stoicheiometric oxidant.

Water is an ideal solvent for these reactions, as it is safe, cheap and does not harm the environment.   Thus, the ability to use water in electrosynthesis is an important electrosynthetic target.

A number of different oxidants have been successfully produced electrochemically, and been employed in both metal and non-metal catalysed reactions.   These include peroxycarbonate, peroxydisulfuric acid and peroxydiphosphate. [6, 7, 8, 9, 10, 11, 12, 13]

1.1.1   Metal catalysed oxidations

In 1986, Murray reported the first electrocatalytic epoxidation of an olefin using glassy carbon electrodes with manganese and Schiff-base complexes.   He achieved this by bubbling O_2 into the electrolyte in the presence of benzoic anhydride at –0.4 V, and successfully obtained the corresponding epoxide.[14]

In 1999, a further report on the enantioselective electrocatalytic epoxidation of olefins using chiral manganese Schiff-base complexes was reported.[15]   This was achieved by immobilising a chiral manganese Schiff-base complex onto a glassy carbon electrode surface using dioxygen as the oxidant, and a platinum wire loop as the counter electrode. Using this system, reasonable ees were achieved (65-77%).

Electrocatalytic epoxidation was carried out in dioxygen-saturated acetonitrile, with benzoic anhydride, 2-methylimidazole, TBAP and a manganese complex.   Oxygen was continuously bubbled through the solution during the electrochemical process.   Table 1 shows the electrocatalytic epoxidation of styrene.[15]

Table 1 Electrocatalytic epoxidation of styrene
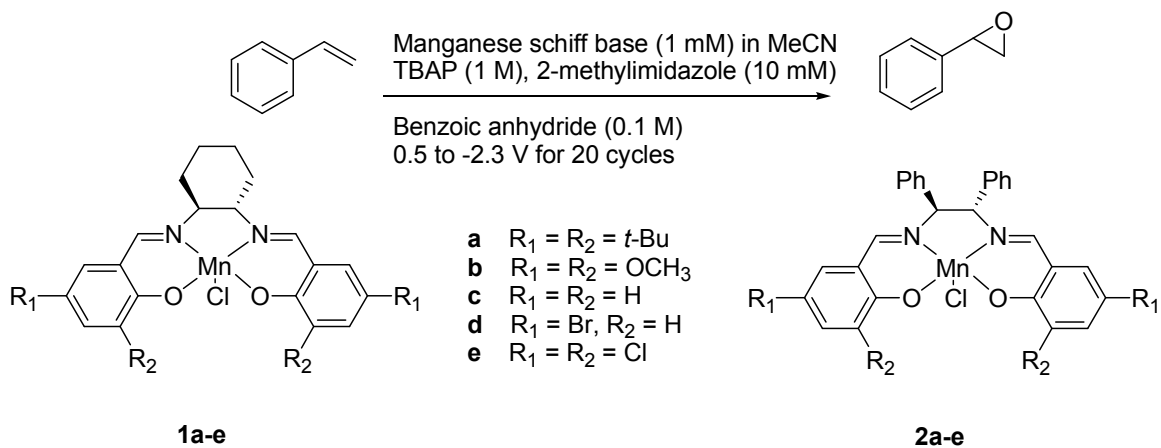
Entry	Catalyst	Current efficiency (%)	Epoxide yield (%)	ee (%)
1	**1a**	27.8	15	46
2	**1b**	31.5	18	48
3	**1c**	39.8	17	56
4	**1d**	56.9	26	67
5	**1e**	21.3	13	36
6	**2a**	19.8	16	26
7	**2b**	23.7	16	33
8	**2c**	29.6	20	32
9	**2d**	31.4	23	35
10	**2e**	15.9	16	30

In epoxidizing styrene, the highest ee of 67% was observed when using catalyst **1d** (Table 1, entry 4). Using manganese complex **3** (Table 2), gave ees of up to 55% in the epoxidation of styrene (entry 3).[15]

Table 2 Electrochemical epoxidation of olefins

3 R_1 = CH=CH$_2$
4 R_1 = OCH$_2$C$_6$H$_4$CH=CH$_2$
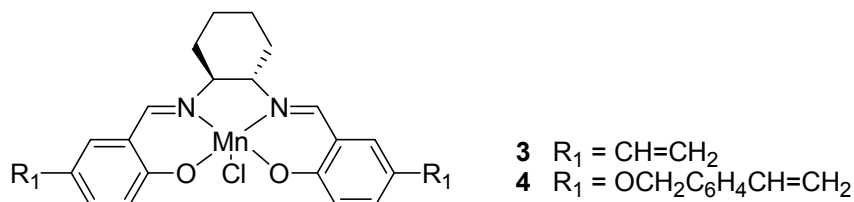
Entry	Catalyst	Substrate	Epoxide yield (%)	Current Efficiency (%)	ee (%)
1	**3**	cis-stilbene	27	15.3	46
2	**3**	trans-stilbene	31	17.9	48
3	**3**	styrene	40	17.3	56
4	**4**	cis-stilbene	28	15.3	46
5	**4**	trans-stilbene	32	17.9	48
6	**4**	styrene	40	17.3	56

Reaction conditions: catalyst, MeCN, TBAP (0.1 M), molecular oxygen, substrates (0.1 M), 0.5 to -2.3 V for 20 cycles

In 2000, Tanaka reported the electrochemical asymmetric epoxidation of olefins using an optically active Mn-salen complex, in a dichloromethane and sodium chloride two-phase electrochemical system using two Pt electrodes.[16]

Table 3 shows the asymmetric electro-epoxidation of *cis*-β-methylstyrene. At 0 °C (entry 1) the desired *cis*-epoxide **5a**, was obtained in 82% yield, with 87% ee, as well as the *trans*-epoxide (11%). These results are similar to those obtained by Jacobsen in 1991 for epoxidation using NaOCl as a co-oxidant.[16, 17]

Table 3 Asymmetric electro-epoxidation of cis-β-methylstyrene
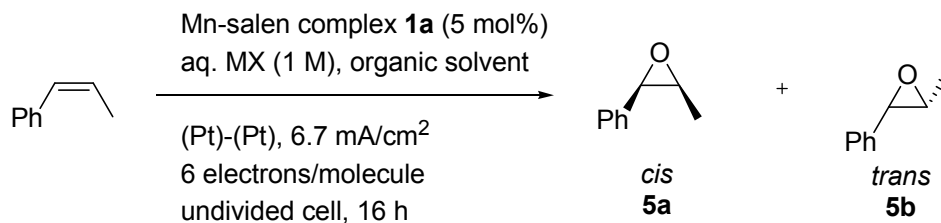
Entry	Organic Solvent	MX	Temperature (°C)	Yield (%) 5a	Yield (%) 5b	ee (%) 5a
1	DCM	NaCl	0	82	11	87
2	DCM	KCl	0	73	7	87
3	DCM	NaBr	0	37	3	89
4	DCM	NaI	0	<1	<1	-
5	tBuOH	NaCl	20	0	0	-
6	MeOH	NaCl	20	0	0	-
7	AcOEt	NaCl	20	28	35	70

For the reaction to proceed efficiently, the authors reported that a two-phase water/dichloromethane system is vital, as without it the desired *cis*-epoxide is not obtained (Table 3, entries 5 and 6). It is possible that this is due to decomposition of the Mn-salen complex by oxidation at the anode. This does not occur in the two-phase system, because the electro-oxidation process only occurs in the aqueous phase, thus oxidation of the complex can be avoided by adding it to the organic phase.[16]

A temperature study (Table 4) showed that as the temperature decreases so does the ee and the yield of *cis*-epoxide formed.

Table 4 Temperature study on asymmetric electro-epoxidation of

cis-β-methylstyrene

Entry	Temperature (°C)	Yield (%)		ee (%)	Substrate recovery (%)
		5a	**5b**	**5a**	
1	20	68	11	81	1
2	10	80	11	85	1
3	5	80	8	87	1
4	0	82	9	87	1
5	-5	42	6	79	52
6	-10	0	0	-	90
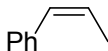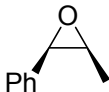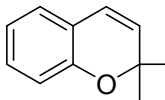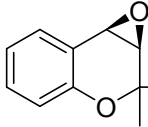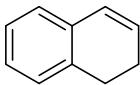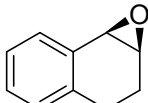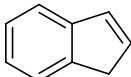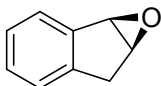
Further studies considered the effect of concentration of sodium chloride on the reaction (Table 5). This showed that ees of the *cis*-epoxide were almost unchanged (80%), over the range 0.1-6 M sodium chloride, whereas the yields did change. The best results were obtained in 1-2 M solutions (entries 3 and 4), with lower and higher concentrations decreasing the yield.[16]

Table 5 Electro-epoxidation with various sodium chloride concentrations

Entry	[NaCl] (M)	Yield (%)		ee (%)	Substrate recovery (%)
		5a	**5b**	**5a**	
1	6	26	5	86	60
2	4	38	8	86	49
3	5	65	12	84	1
4	1	68	11	81	1
5	0.1	45	9	79	23

The best reaction conditions were applied to a series of olefins (Table 6), and showed that ees of up to 87% could be achieved in up to 93% yield (entry 1). These ees obtained are almost comparable with those obtained from chemical epoxidations by Katsuki, using similar Mn-salen catalysts.[18]

Table 6 Epoxidation in a dichloromethane/sodium chloride two-phase system

Entry	Olefin	Epoxide	Epoxide			Substrate recovery (%)
			Yield (%)	ee (%)	configuration	
1	Ph—=—	(Ph epoxide)	93	87	1S,2R	<1
2	(chromene)	(chromene epoxide)	80	81	1S,2R	9
3	(α-methylstyrene) Ph	(epoxide) Ph	69	43	S	<1
4	(dihydronaphthalene)	(epoxide)	47	70	1S,2R	<1
5	(indene)	(indene oxide)	30	26	1S,2R	34

Reaction conditions: **1a**, DCM, aqueous NaCl, two phase system

In 2005, Elliott continued the work started by Groves and Gilbert in 1986 on electrochemical olefin epoxidation using iron(IV) porphyrin/trisbipyridineruthenium(III) polymer catalysts. In nature, these reactions are performed by cytochrome P450 and horseradish peroxidase.[17]

In the epoxidation reaction using water, it is necessary that the iron porphyrin catalyst is oxidized to Fe(V), in order to provide the necessary two oxidizing equivalents. Initial studies have shown that these catalysts are capable of oxidizing cyclohexane when used as thin films on the electrode.[17]

1.1.2 Bio-catalysed oxidations

Other electrochemical oxidation reactions have been reported using electroenzyme-catalysed oxidations, using cytochrome P450 and myoglobin.[19, 20]

In 1986, Murray reported an electrocatalytic epoxidation using cytochrome P450. Molecular oxygen is activated and used in the reaction to epoxidize an olefin by electrolytic reduction (Scheme 1).[14]
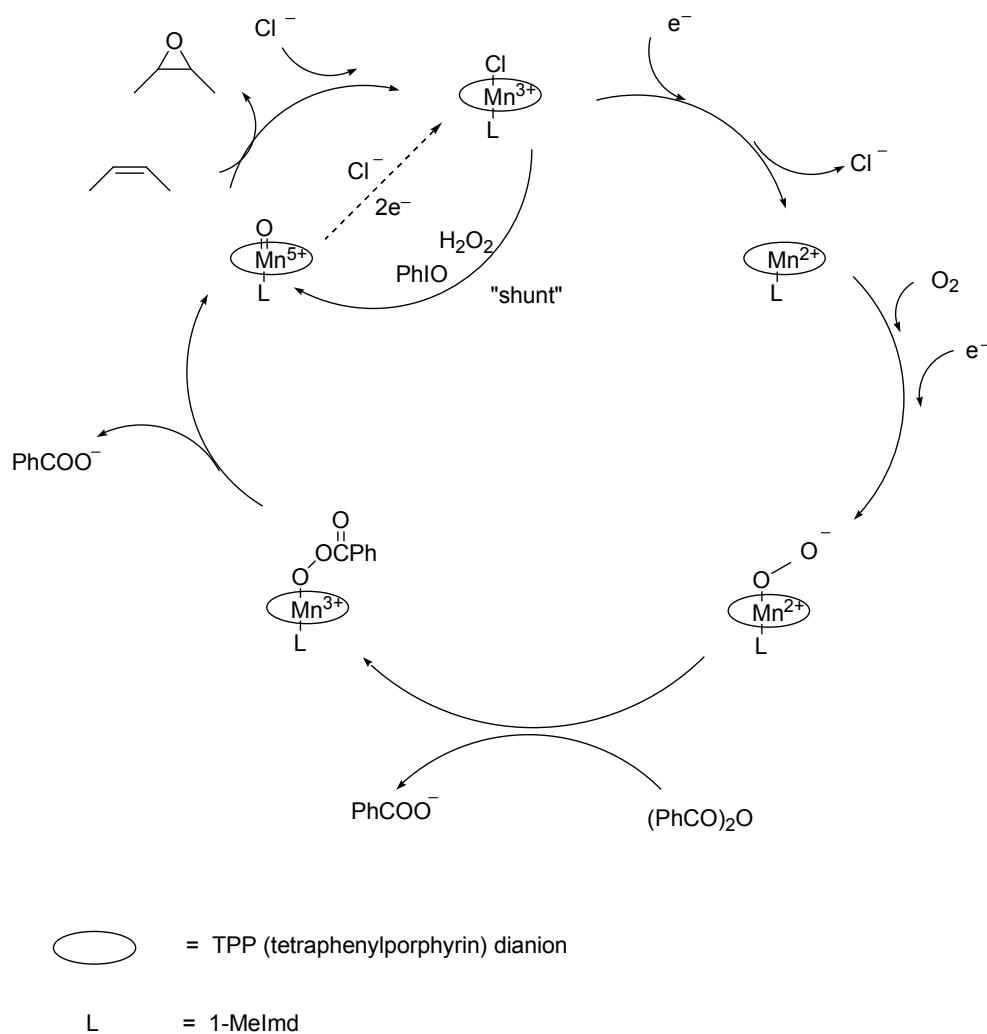
Scheme 1 Electrocatalytic epoxidation cycle

The catalytic cycle has three main steps: (1) Initial reduction to Mn(III) with loss of chloride, followed by strong dioxygen binding which promotes a second reduction step to a Mn(II) complex. (2) The latter, $(MnIIPor)O_2^-$, complex has been shown to react with benzoyl chloride, and to give metallo-acrylperoxy complexes.[14, 21]

(3) These complexes can undergo O–O bond hydrolysis at room temperature, to yield high-valent manganese-polphyrin complexes capable of transferring one oxygen atom to a suitable substrate. The reactivity of high-valent manganese with olefins has been studied.[14, 21]

Table 7 shows a number of different olefin epoxidation systems that have been studied. Electrolysis without the presence of anhydride (entry 1), results in no product where as when anhydrides are used (entry 2) the corresponding epoxide is obtained.

The results show that Metalloporphyrin-base epoxidations favour *cis* olefins, whereas more conventional oxidants such as *m*CPBA favour *trans*. In a competition electrolysis carried out (Table 7, entries 3-5), using a 1:1 mixture of *cis*/*trans* olefin, the selectivity seen in entry 3 to form the epoxide from the *cis*-olefin, matches entry 4 using Mn-(TTP)Cl / iodobenzene / 1-MeIm, not the system using *m*CPBA (entry 5). This therefore confirms that the reaction is porphyrin-based.[14]

Table 7 Olefin epoxidation systems

Entry	System	Substrate ratio[c]	Product Ratio[d]
1	Mn(TPP)Cl (0.5 mM), O_2, electrons[a]	C	-
2	Mn(TPP)Cl (0.5 mM), O_2, electrons, anhydride[a,b]	C	CO
3	Mn(TPP)Cl (0.5 mM), O_2, electrons, anhydride[a,b]	C:T (1:1)	CO:TO (15:1)
4	Mn(TPP)Cl (0.5 mM), PhIO (12.5 mM)	C:T (1:1)	CO:TO (15:1)
5	m-CPBA (12.5 mM)	C:T (1:1)	CO:TO (4:1)
6	Mn(TPP)Cl (0.5 mM), H_2O_2 (20 eq.)	C	CO
7	H_2O_2 (20 eq.), anhydride[b]	C	CO

Reaction conditions: All carried out in stirred dichloromethane, containing 1-methylimidazole (20 mM)
[a] electrolysis potential = -0.4 V
[b] benzoic anhydride (0.44 M)
[c] substrates: C = cyclooctene, T = *trans*-2-octene (all used in 100 mM)
[d] products: CO = cyclooctene oxide, TO = *trans*-2-octene oxide

1.2 Epoxidation

1.2.1 Sharpless Epoxidation

Sharpless developed the first asymmetric epoxidation that was chemoselective for allylic alcohol substrates.[22]

Using t-butylhydroperoxide, titanium tetraisopropoxide and (+)- or (−)-diethyl tartrate, Sharpless discovered that these reagents gave uniformly high asymmetric inductions throughout a range of substitution patterns, and that, the system would deliver the epoxide oxygen atom from the same face of the olefin regardless of the substitution pattern (Scheme 2).[23]
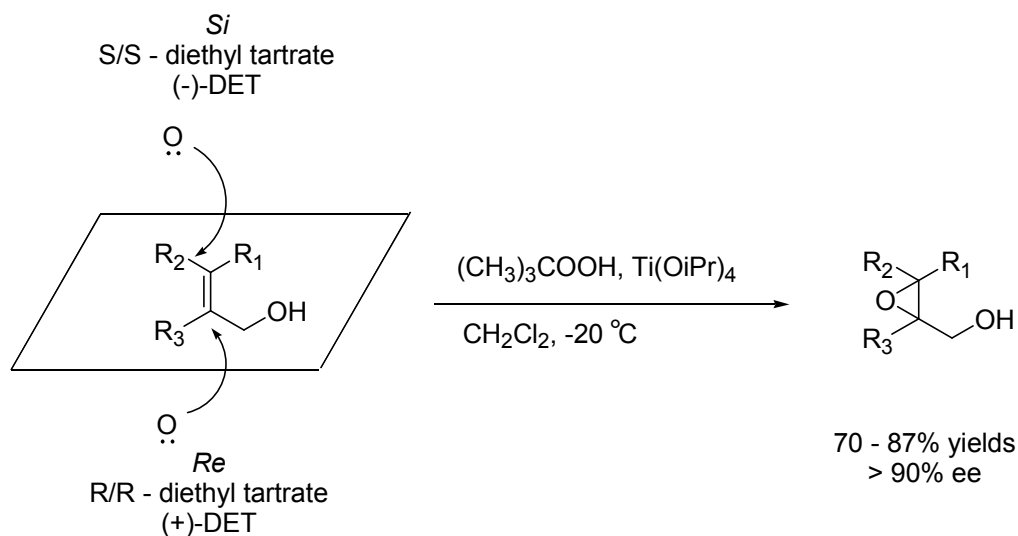
Scheme 2 Addition of Epoxide Oxygen

The epoxy alcohol products are key intermediates in the synthesis of compounds such as erythromycin.[24]

The discovery of the Sharpless–Katsuki asymmetric epoxidation in 1980 represented a major breakthrough in the enantioselective oxidation of olefins. However, its major drawback was its limitation to the oxidation of allylic alcohols.[24]

In 2001 Sharpless won the Nobel Prize for his work on chirally catalysed oxidation reactions, along with Noyori and Knowles for their work on catalysed hydrogenation reactions.[25]

Following on from work carried out by the Sharpless group using metal catalysis, Katsuki and Jacobsen further developed the field of asymmetric epoxidation with a range of new catalysts, some of which are now commercially available.[26] Although their work showed high enantioselectivities for certain alkenes, others gave poor results.[27] However, there is a disadvantage in using metal catalysts in that the reagents are often expensive and toxic, so despite good ees being obtained there has been interest in the use of organocatalysts.

Other major advances in asymmetric oxidation of olefins followed, with the Sharpless asymmetric dihydroxylation in 1988, the Jacobsen and Katsuki Salen-asymmetric epoxidation of unfunctionalized olefins in 1990 and then the Sharpless asymmetric aminohydroxylation in 1996.[26]

1.2.2 Jacobsen and Katsuki

The Jacobsen – Katsuki asymmetric epoxidation utilises chiral Mn-salen catalysts. This discovery, reported almost simultaneously by the Jacobsen and Katsuki groups, is similar to the achiral olefin epoxidation catalysed by the salen–metal (III) complexes, reported in a study by Kochi.[28]
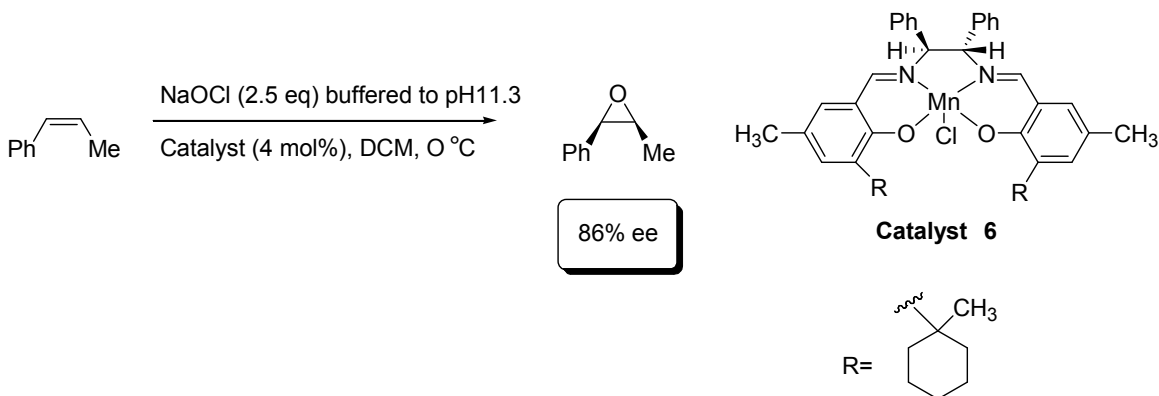
Scheme 3 Jacobsen Epoxidation

Both Jacobsen and Katsuki independently developed and optimised a range of catalysts, the main difference between the two being the presence of four different stereoisomers in the Katsuki complexes, and in the substitution at the stereogenic centres in the Jacobsen complexes. After a study of different reaction conditions the epoxidation of *cis* ß-methylstyrene with commercial bleach (buffered to pH11.3) gave the best ee of 86%, in DCM at 0 ºC (Scheme 3).[17]

Jacobsen's Catalysts   **Katsuki's Catalysts**

(S,S)   (S,S)

7	R, R = -(CH$_2$)$_4$-	R^l = *t*-Bu	
8	R, R = Ph	R^l = Me	
9	R, R = -(CH$_2$)$_4$-	R^l = OSi(*i*Pr)$_3$	
10	R, R = Ph	R^l = OSi(*i*Pr)$_3$	

11	R = 3,5-Me$_2$C$_6$H$_3$	X= OAc
12	R = Ph	X = PF$_6^-$
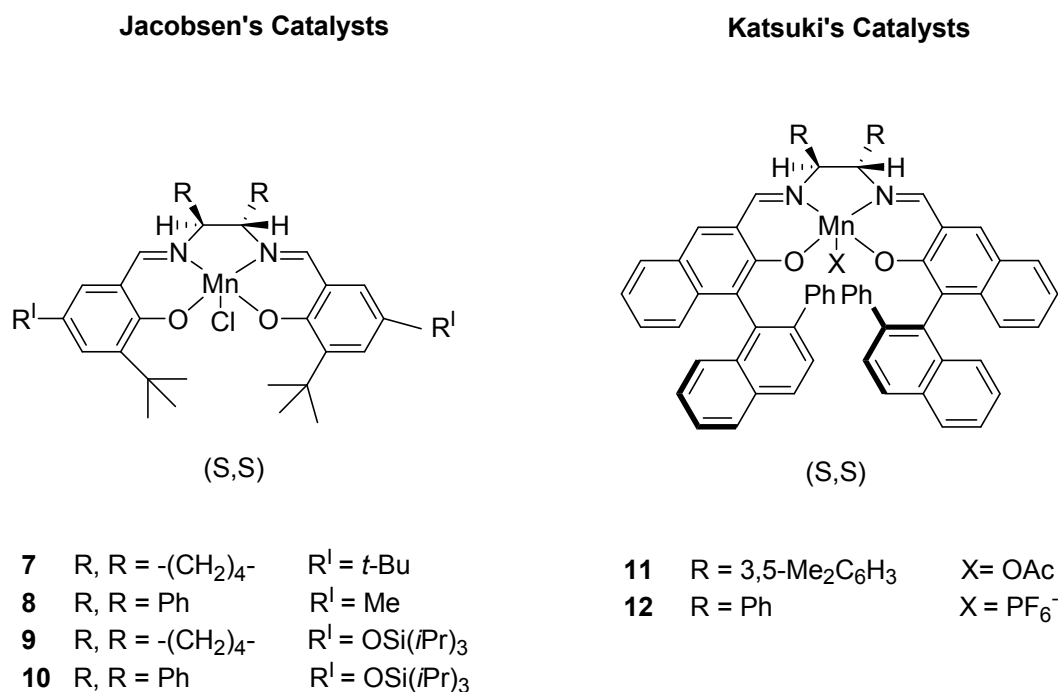
Figure 1 Jacobsen's and Katsuki's Catalysts

Results for Jacobsen's and Katsuki's work can vary depending on the catalyst and temperature used, although generally the Katsuki catalysts performed better than the Jacobsen catalysts. In work carried out by Katsuki using catalyst **12** (0.025 eq.) in the presence of AcO⁻ counterion, PhIO (2 eq.) and pyridine *N*-oxide in acetonitrile solution it was possible to obtain 92% ee for epoxidation of 1,2-dihydronaphthalene.[29]

With both the Jacobsen and Katsuki catalysts, one negative point is the instability of the most commonly used catalysts, but further studies are looking into prolonging the oxidative conditions of the catalysts by incorporating the salen ligand into a matrix or support as a means of recycling the chiral catalyst. [29]

Catalyst **7** (Figure 1) was shown to be the optimum with regards to availability, cost and its broad application to the enantioselective oxidation of many unfunctionalized olefins. It is now available commercially as a chiral ligand. [29]

1.2.3   Amine Catalysis

In 2000, Aggarwal reported the use of simple amines as epoxidation catalysts, where the oxidant is Oxone®/NaHCO$_3$.[30]

Aggarwal was looking at iminium salts as catalysts, but found that simple amines could also be used to carry out epoxidations. Secondary amines gave the highest conversion to epoxide (90%).[30]

The asymmetric epoxidation process was somewhat problematic and the group could not gain reproducible results. This was resolved by using the hydrochloride salt of the amine in the presence of sodium hydrogen carbonate and pyridine. This slight alteration gave higher ees with shorter reaction times.[30]
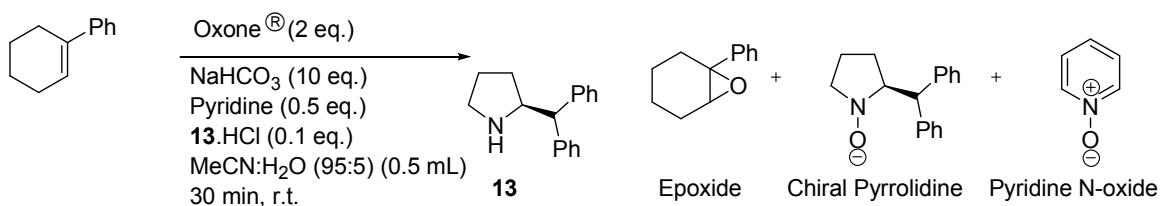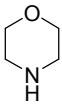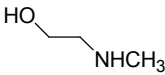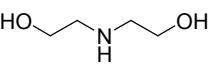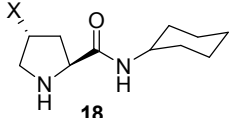
Scheme 4   Aggarwal's reaction conditions

A study carried out by Aggarwal's group showed that when the reaction is quenched after five minutes, a high percentage of epoxide is already present even though only a small

amount of pyridine *N*-oxide was observed and the amine had not been oxidized. This led him to believe that the alkene is oxidized as a faster rate than the pyridine, hence enabling the pyridine to act as proton storage during epoxidation, and thus limit hydrolysis of the epoxide.

Continuing on with work from the Aggarwal group, Yang began to study the effect that substituents on the amine may have in epoxidation reactions. They found that cyclic secondary amines give results that are far superior to primary and secondary amines, and on further study found that substituents at the 4-position on the ring exert a strong effect on substrate conversion, with methyoxymethyl ether (OMOM) and hydroxyl groups showing the greatest effect (Table 8).[31]

Table 8 Amine Catalysed Epoxidation

Amine (1 eq.)
Oxone® (4 eq.)
NaHCO$_3$ (10 eq.)
CH$_3$CN/H$_2$O (10:1)
r.t., 5 h

Entry	Amine		Conversion (%)	Yield (5)	ee (5)
1	morpholine	**14**	56	98	-
2	HO—NHCH$_3$	**15**	74	92	-
3	HO—N(H)—OH	**16**	89	96	-
4	**17a** X = H		19	50	-
5	**17b** X = CH$_2$OH		84	99	1
6	**17c** X = CPh$_2$OH		59	78	33
7	**17h** X = COOMe		22	68	4
8	**18a** X = OAc		<5	100	20
9	**18b** X = OH		96	92	7
10	**18c** X = OMOM		86	86	13
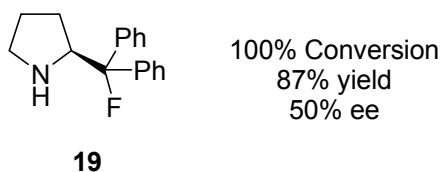
100% Conversion
87% yield
50% ee

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Figure 2 Yang's catalyst

In a second study Yang went on to look at the effect of the position of the substituent in relation to the amino group. It was found that fluorine atoms (Figure 2) give the highest catalytic efficiency with 100% conversion, 87% yield and ees of up to 50%.   These results were then improved by repeating the reactions at lower temperatures of 0 °C to -20 °C.[31]

In concluding her work, Yang found that under slightly acidic reaction conditions, the fluorinated amine could be protonated *in-situ*, which removes the need to preform the ammonium salts that are essential for epoxidation. These findings agree with those of Aggarwal, in that the amine's role in the reaction is to act as a phase transfer catalyst as well as an Oxone[®] activator.[31]

Yang showed this by carrying out an epoxidation of 1-phenylcyclohexene using the conditions in Scheme 5. If this same reaction is carried out with the phase transfer catalyst 18-Crown-6, which is known to increase the solubility of Oxone[®] in the organic solvent and thus favor epoxidation, an increase in conversion from 22% to 53% is seen. If the amine is absent from this reaction, then there is nothing to provide Oxone[®] activation, and the use of 18-Crown-6 alone results in only 7% conversion.

These results show that, although Oxone[®] transfer to the organic layer has an important effect on the rate of catalysis, the efficient activation of Oxone[®] provided by the amine is equally important to alkene conversion. Once a sufficient amount of Oxone[®] is transferred to the organic layer by 18-Crown-6, the amine can activate Oxone[®] toward alkene epoxidation. [31]

Yang's Epoxidation

Amine (0.5 eq.)

Oxone® (2 eq.)
NaHCO₃ (5 eq.)
MeCN/H₂O
(10:1) (1.1 mL)
r.t. 2 h

87% yield
50% ee

Aggarwal's Epoxidation

Ammonium Salt (0.5 eq.)

Oxone® (2 eq.)
NaHCO₃ (10 eq.)
MeCN/H₂O
(95:5) (0.5 mL)
pyridine (0.5 eq.)
r.t. 40 min

91% yield
46% ee
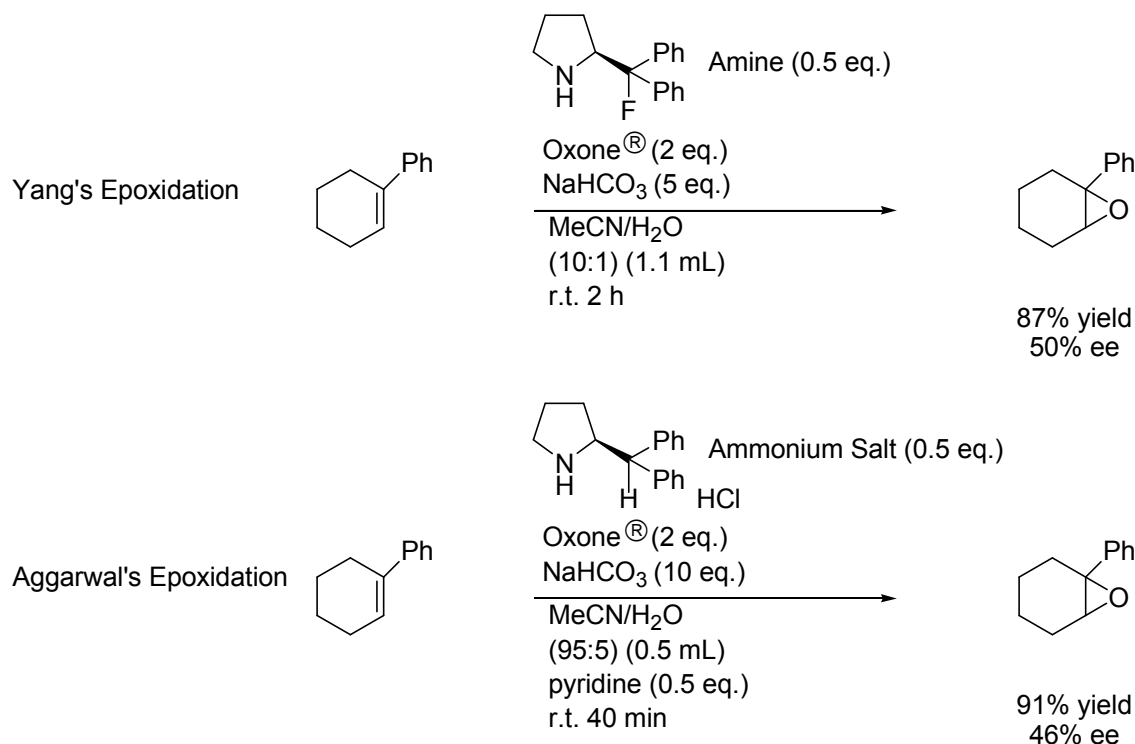
Scheme 5 Aggarwal's and Yang's Epoxidation Conditions

1.2.4   Asymmetric Epoxidation By Chiral Dioxirane Derivatives – Shi Group

Dioxiranes are three-membered heterocyclic rings containing two oxygen atoms. Their reactivity is due to weak O-O bonds that are prone to nucleophilic attack by even weak nucleophiles such as olefins.

In 1996, Shi reported novel reaction conditions when he used a D-fructose derived ketone (Figure 3) for the epoxidation of unfunctionalized *trans* olefins. He showed that it is possible to synthesise the catalyst in both enantiomeric forms, with both catalysts giving ees of greater than 80% in both stoichiometric and catalytic amounts, with Oxone® as the oxidant. Durng the study of these reactions Shi also showed that it is important to control the pH of the reaction solution otherwise decomposition of the catayst can occur through the Baeyer-Villiger reaction. (Table 9).[32, 33]
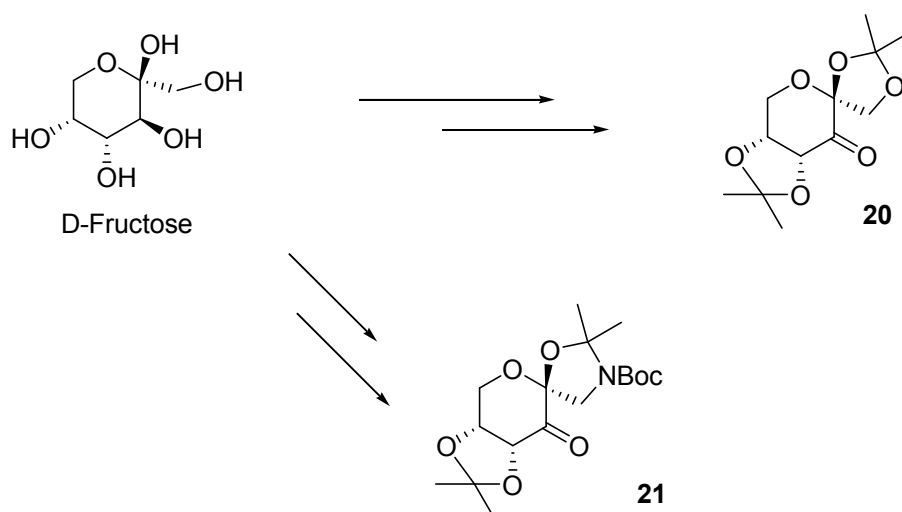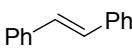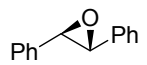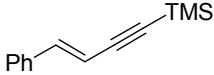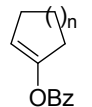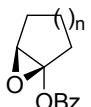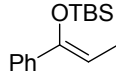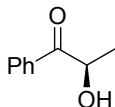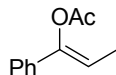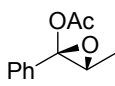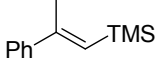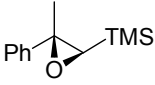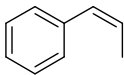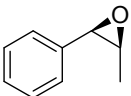
Figure 3 D-Fructose Derivatives

Table 9 Asymmetric Epoxidation on Various Olefins

Entry	Olefin	Product	Catalyst	Yield (%)	ee (%)
1			**20**	75	97
2			**20**	59	96
3			**20** n = 3	87	91
4			**20**	80	90
5			**20**	66	91
6			**20**	74	94
7			**21**	87	91

Shi also studied the epoxidation of conjugated dienes, enynes, enols, ethers, esters and 2,2-disubstituted vinylsilanes (Table 9). This study showed ees greater than 90%, in the functionalised epoxide products.[32, 33]

Using the catalyst derived from D-fructose (Figure 3), Shi reported high enantioselectivities for *trans*-disubstituted and trisubstituted olefins (Scheme 6).[33, 34]
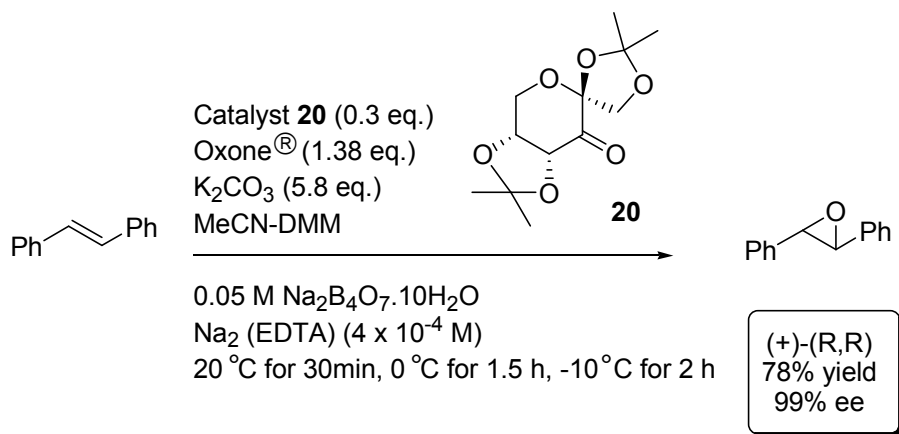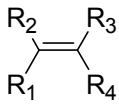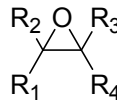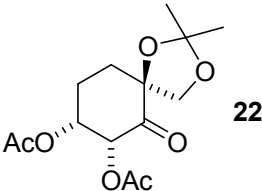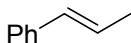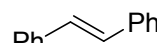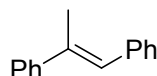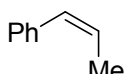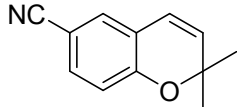
Scheme 6 Corey's Epoxidation of *trans*-Disubstituted Olefin

Other successful studies have been carried out and reported by the Denmark, Yang, and Armstrong groups, with different chiral ketones to give *trans*-olefin epoxidation, where Yang's highest ee was 61% for the epoxidation of 1-phenylcyclohexene. But these results are yet to match those achieved by the Shi group of 88% ee for the epoxidation of 4-chlorostyrene with Oxone[®].[2]

In 2009, Shi published his most recent work on ketone-catalysed asymmetric epoxidation of olefins. This catalyst (Table 10) has been shown to afford high ees for a variety of *trans* and trisubstituted olefins as well as some *cis* olefins.[35]

Table 10 Asymmetric Epoxidation of Olefins

Entry	Substrate	Time (h)	Yield (%)[a]	ee (%)[b]	Config.[c]
1	Ph	8	81	86	(+)-(R,R)
2	Ph, Ph	16	63	93	(+)-(R,R)
3	Ph, Ph	8	46	88	(+)-(R,R)
4	Ph, Me	8	81	49	(+)-(1S,2R)
5	NC...O	8	73	90	(−)-(S,S)

[a] isolated yields
[b] determined by chiral GC (Chiraldex B-DM), or chiral HPLC (Chiralcel OD)
[c] determined by comparing the measured optical rotations with the reported ones

1.2.5 Oxaziridines in Asymmetric Epoxidation

Oxaziridines are nitrogen analogues of dioxiranes, and also have the ability to act as oxygen transfer agents. In 1981, Davis reported the first example of epoxidations using oxaziridines and 2-benzenesulfonyl-3-aryloxaziridines. His work showed the similarities

between oxygen transfer systems in heteroaromatic *N*-oxides and in enzyme-catalysed oxidations.[36, 37]

The first epoxidation carried out by Davis (Scheme 7) was using chiral 2-sulfonyloxaziridine diastereoisomers, and he showed yields of up to 95% epoxide from *trans*-stilbene in twelve hours.[36, 37]
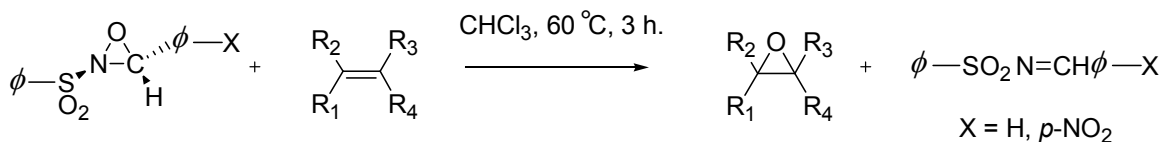
Scheme 7 Davis's first asymmetric epoxidation using a chiral oxaziridine

Later work achieved high ees, but a disadvantage in this instance is the oxaziridines' lack of reactivity towards all alkenes, which led to further studies looking at the use of oxaziridinium salts for asymmetric epoxidation.

1.2.6   Oxaziridinium Salts

Oxaziridinium salts are more electrophilic than oxaziridines, so can transfer oxygen more efficiently to nucleophiles; this results in a decrease in reaction times for epoxidation reactions. Lusinchi first discovered their potential and went on to successfully oxidize thioethers, amines and imines, and further found that oxaziridinium salts epoxidize the carbon-carbon double bonds of simple olefins.[4]

1.2.6.1 Lusinchi Epoxidation

In the early 1990's, Lusinchi and Bohé reported the first enantiomerically pure oxaziridinium salt, which they prepared from (1*S*,2*R*)-(+)-norephedrine (Scheme 8). Epoxidation of *trans*-stilbene using the oxaziridinium salt and trifluoroacetic acid, gave ees of 30%. [38, 39, 40]
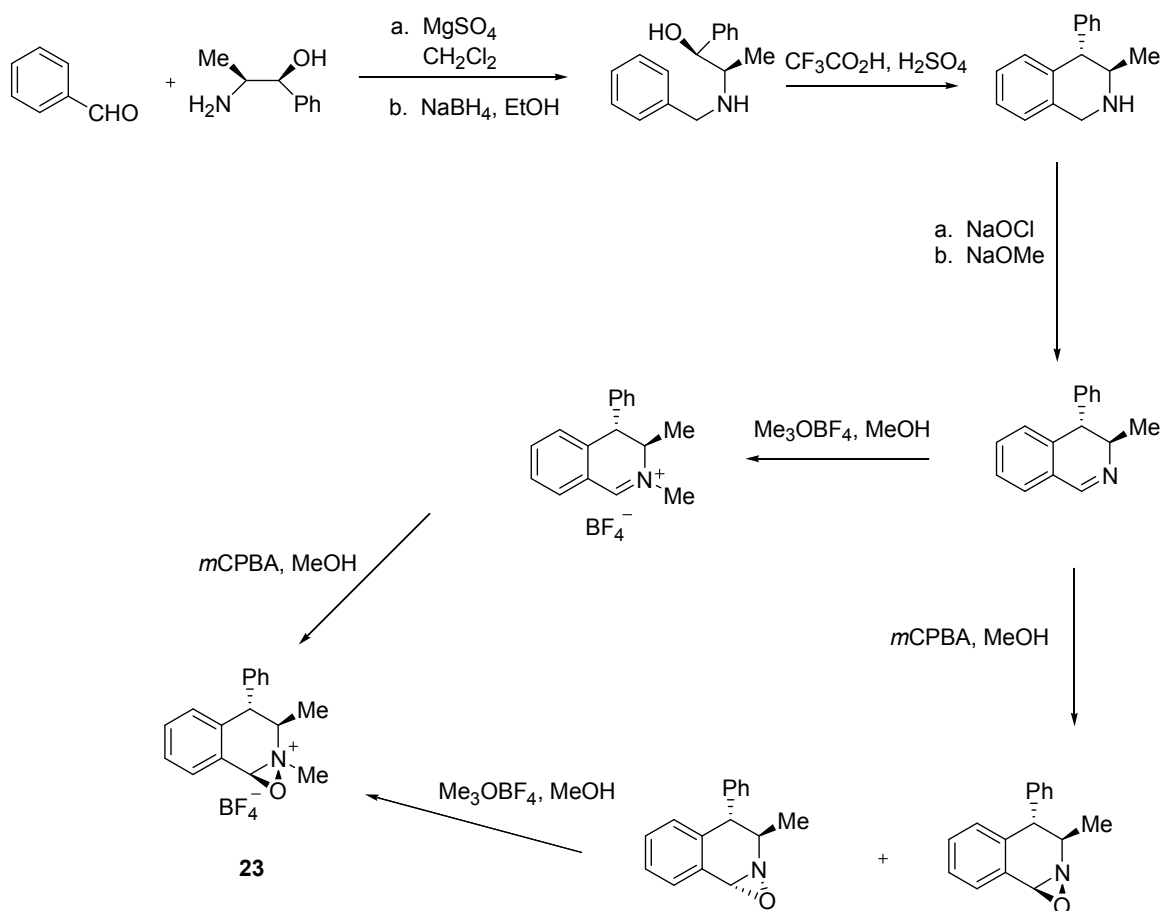
Scheme 8 Lusinchi's first enantiomerically pure oxaziridinium salt

More recently Lusinchi developed a catalytic cycle, which uses a regenerated iminium salt. This method is similar to that of dioxiranes, except pH is not so important as there is no competition from Baeyer-Villiger oxidation.[41]

1.2.6.2 Armstrong's Oxaziridinium Salts

Armstrong reported a oxaziridinium salt-mediated epoxidation, after realising that the downside of dioxiranes as catalysts is a result of the di-valency of oxygen, which results in an 'achiral' reagent being present but remote from the chiral substituents on the ring carbon. He expected that the replacement of one of the ring oxygens with a nitrogen atom would allow greater flexibility in the design of chiral catalysts, so went back to

previous work carried out by Lusinchi and Hanquet on oxaziridinium salts using Oxone[®], acetonitrile and water.[38, 41, 42]

Since all of the iminium salt epoxidation catalysts used prior to Armstrong's work have the iminium bond as part of a ring (endocyclic iminiums), and are formed from condensation of an amine and a carbonyl compound, this places a limitation on the number of iminium salts, specifically chiral ones, that can be synthesized. He therefore examined iminium salts derived from intermolecular condensation reactions (acyclic iminium salts). This could allow a greater range of reagents to be used for condensation reactions and thus more catalyst possibilities.[42]

Table 11 Armstrong's Epoxidation
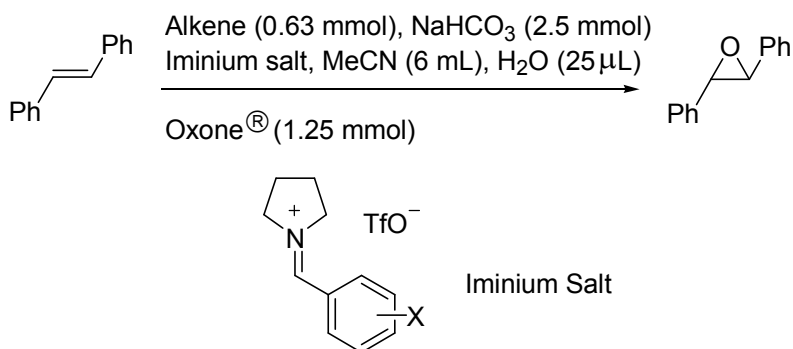
Entry	Iminium	Iminium (mol%)	Conversion[a] (%)
1	**24** X = p-MeO	100	0
2	**25** X = p-Cl	100	63
3	**26** X = o-Cl	25	100
4	**27** X = o-Cl	10	82
5	**28** X = o-CF$_3$	10	100

[a] conversion to epoxide determined by integration of proton signals on ^{1}H NMR spectra

Armstrong carried out epoxidation reactions using the same oxidizing coniditions described by Lusinchi and Hanquet, but where the iminium salts were derived from pyrrolidine and aromatic aldehydes with electron-withdrawing substituents in the *para-* or *ortho-* position. Substitution at the *ortho-* position gave catalysts that were more successful (Table 11, entries 3-5), with conversions of up to 100%. In comparison, the catalysts with substintuents in the *para-* position (Table 11, entries 1 and 2) gave a maximum of 63% conversion, with 100 mol% iminium salt present when a chloro group is in the *para* position. It is not known why the results are better for *ortho* substituents, but Armstrong believes that it may be related to the lower tendency for the aromatic ring to adopt planarity with respect to the iminium bond, resulting in the loss of conjugation.[42]

Further research by Armstrong using more hindered chiral amines was carried out, but was unsuccessful, perhaps due to hydrolysis of the iminium salts and/or the low reactivity of the oxaziridinium ions.[42] In the late 1990's, he went on to study intramolecular epoxidations in unsaturated oxaziridines, and was able to prove that it is possible to achieve high enantioselectivity (98% ee) with intramolecular epoxidations when using a chiral primary amine and an unsaturated aldehyde (Scheme 9).[43]
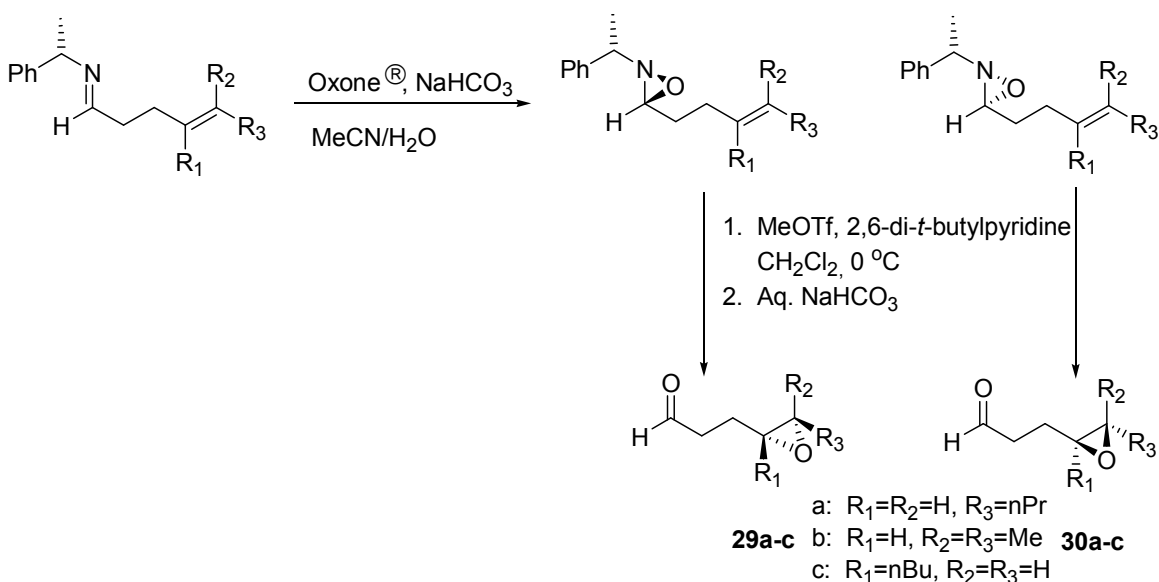
Scheme 9 Armstrong's Intramolecular Epoxides

1.2.6.3 Yang and Wong's Iminium Salts

Yang and Wong have also followed Armstrong in their development of an exocyclic iminium salt system that generates oxaziridinium salts *in situ,* from amines and aldehydes using Oxone® under slightly acidic conditions. Unfortunately, with this system, to achieve the best ee of 65%, a catalyst loading of 50 mol% is required. By altering these reaction conditions, Yang and Wong were able to improve this system giving them up to 65% ee (Figure 4).[44]
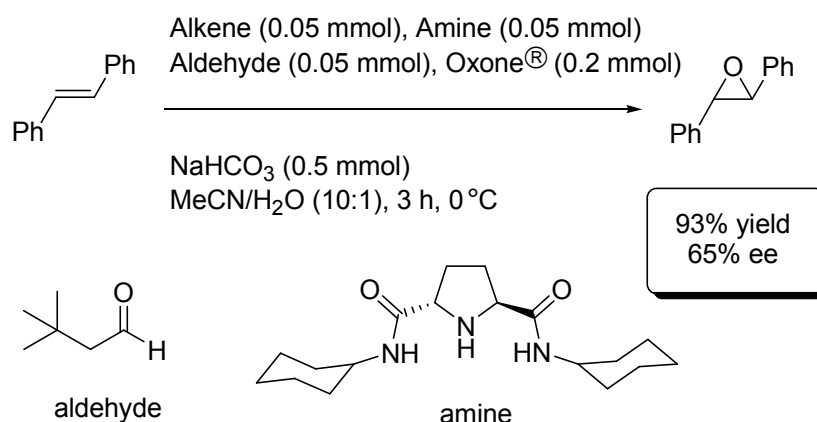
Figure 4 Yang and Wong's Epoxidation

1.2.6.4 Bohé's Iminium Salt Catalyst

In 2001 Bohé developed an improved achiral catalyst. He discovered that there were two main factors that gave a low catalytic efficiency during epoxidation with oxaziridinium salts; loss of oxygen from the active oxaziridinium intermediate, and hydrolysis of the iminium salt, in a reaction that does not regenerate the iminium salt. He then used a 3,3-disubstituted-dihydroisoquinolinium salt as the oxaziridinium salt precursor to reduce this, where the iminium salt (Scheme 8) was synthesized from the commercially available tertiary alcohol shown and the active oxaziridinium salt was then derived from this salt by the usual oxidation pathway (Oxone®/NaHCO$_3$).[44]
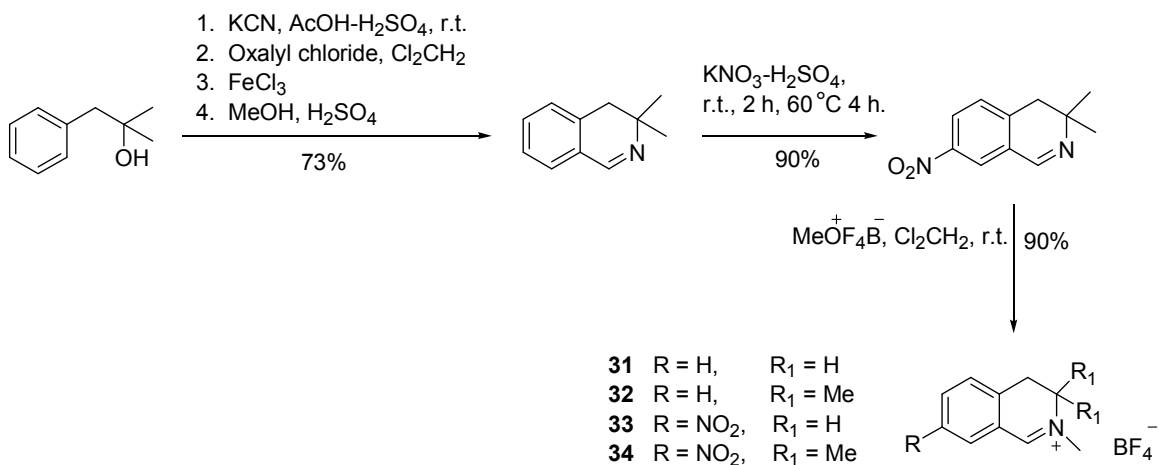
Scheme 10 Synthesis of Bohé's improved Catalyst

The epoxidation of this terminal alkene was slow, using 10 mol% of iminium salt **32** giving a low conversion of 40%, but repeating this using the same loading with catalyst **34** gave an increased conversion of 50%, and **34** showed great improvement with a conversion of 92% in six hours. Upon using catalyst **34** with monosubstituted olefins, high catalytic efficiency is also observed. Complete conversions were also achieved for di- and tri-substituted alkenes.[44]

1.2.6.5 Page's Iminium Salts

Page's group reported their first catalytic asymmetric epoxidation using iminium salt catalysts in 1997. They found that chiral iminium salts could be derived from a bromoaldehyde and primary amines (with chirality at the exocyclic nitrogen substituent), and that these could be used for catalytic asymmetric epoxidation of alkenes using Oxone® as the oxidant, although the more hindered the alkene the lower the conversion to epoxide. These reactions could be carried out at 0 °C, giving ees of up to 73%, and yields of up to 78%, with as little as 0.3 mol% of catalyst.[45, 46]
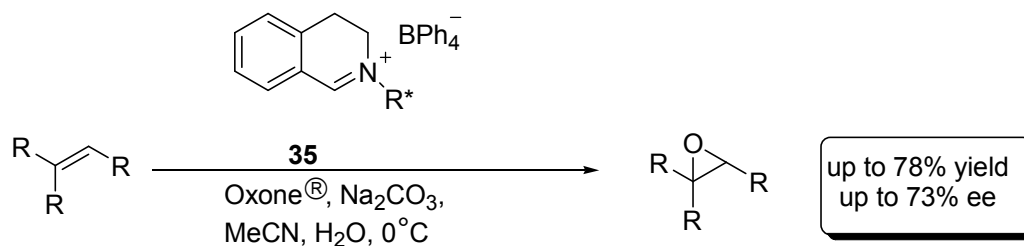
Scheme 11 Page's Epoxidation Conditions

In 2001 Page described a possible catalytic cycle (Scheme 12) for oxaziridinium ion-mediated epoxidation. The first step that occurs is a nucleophilic attack of persulfate on the iminium salt, to give a neutral nitrogen species, which then irreversibly loses sulfate to give the desired oxaziridinium. Oxygen can then be transferred to an olefin.[46]
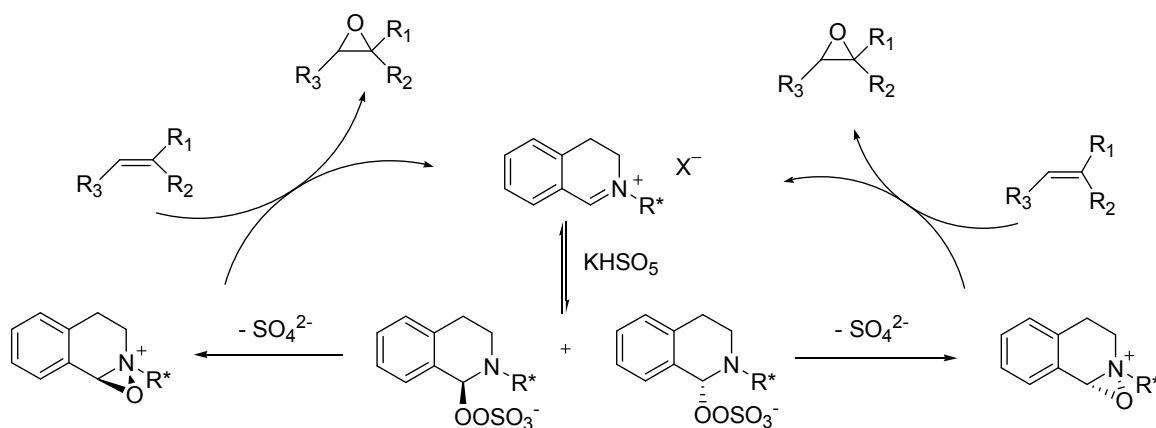
Scheme 12 Proposed Catalytic Cycle

In 2003 the group carried out a study to determine the best reaction conditions with a range of their catalysts (**36** and **37-39**), where catalysts **38** and **39** were members of a new family published by Page in 2002 (Figure 5).[46, 47]
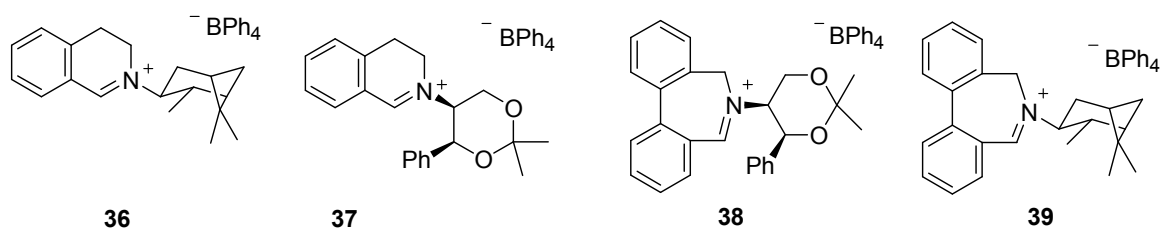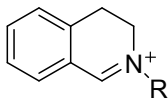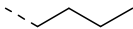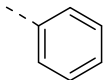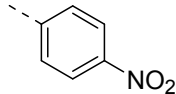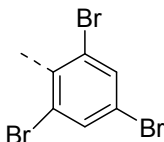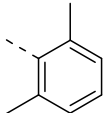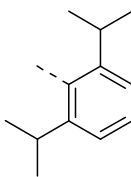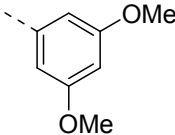
Figure 5 Page's Catalysts

The most recent work carried out by the Page group has focused on several new highly reactive iminium salt catalysts for epoxidation. The table below shows a selection of these catalysts.

Table 12 Synthesis of Iminium Salts

Entry	R group	Catalyst	Yield (%)
1		**40**	80
2		**41**	71
3		**42**	88
4		**43**	85
5		**44**	58
6		**45**	64
7		**46**	42
8		**47**	80

All the catalysts synthesized are air stable except **47**, which after several weeks decomposes. The iminium salts **40-46** were found to be active catalysts, and epoxidized 1-phenylcyclohexene to complete conversion, with reaction times varying between three and seventy minutes. Iminium salt **44** was the most reactive of the series, giving 68% yield in three minutes. It was also possible to lower catalyst loading to 0.5 mol%,

although this did increase the reaction time to ten minutes. It was also found that the addition of persulfate could be enhanced by the presence of electron-withdrawing substituents. These are present in all of the catalysts but **40** and **41**, which also lack the presence of an aryl group, which is inductively withdrawing, thus giving lower reactivity. Catalysts **43** and **44**, have *para-* nitro and tribromo groups, which would also increase the withdrawing nature of the aryl group, giving a more electrophilic C=N.[48]

Oxaziridinium formation would however be faster if there were more electron-donating groups present, which would increase the nitrogen lone pair's ability to attack and eliminate HSO_4^-.[48]

It was found that of this group catalyst **45** is the most reactive, epoxidizing 1-phenylcyclohexene in ten minutes with 0.5 mol% loading.
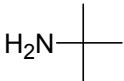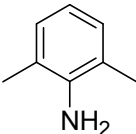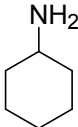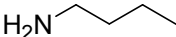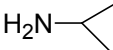
More recently in 2009 the Page group published new epoxidation reactions carried out with previously reported catalysts and sodium hypochlorite as the oxidant.[49]

Figure 6 Asymmetric Epoxidation

Sodium hypochlorite (6.0 eq.)
K_2CO_3 (0.25 eq.)
Catalyst (10 mol%), DCM

$0\,^\circ$C, 24 h.

$^-$BPh$_4$

38

68% yield
71% ee
(−)-(1*S*,2*S*)
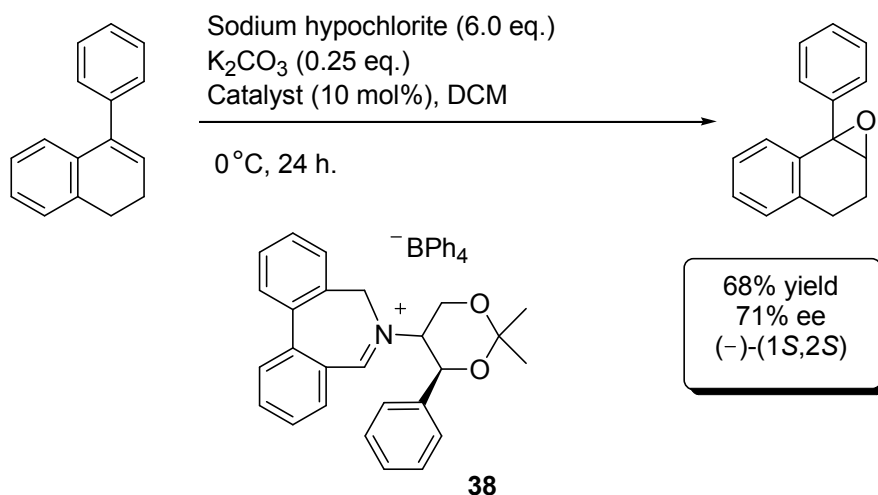
Page's group showed that it was possible to acheive to a 68% conversion and up to 71% ee for 2,3-dihydronaphthalene oxide (Figure 6), with similar enantioselectivities to the standard Oxone®-mediated conditions.

In 2007, Page reported his most recent results for epoxidations, this time using chiral binaphthalene-derived iminium salt organocatalysts. The binapthyl azepinium salts were prepared from the corresponding bromoaldehyde (Scheme 13).[50]

Catalyst	Amine	Yield (%)
48	H₂N⊥	60
49		71
50		72
51	H₂N~	59
52	H₂N<	79

Scheme 13 Synthesis of Page's Binapthyl azepinium salts

Using catalysts **48-52** to carry out epoxidation reactions with various alkenes, the best conversions to epoxide were seen using catalyst **50, 51** and **52**, where the yields were also best for these catalysts. The overall best catalyst was **52** under these conditions, achieving greater than 89% conversion for all the substrates (Table 13, entry 3), and moderate to good enantioselectivities (71-82%).[50]

Table 13 Asymmetric Epoxidation of Alkenes

Iminium salt (5 mol%)
Oxone® (2 eq.)

NaHCO$_3$ (5 eq.)
MeCN:H$_2$O (10:1), 0 °C 2 h.
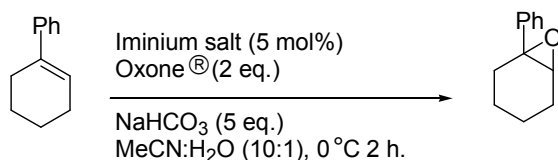
Entry	Catalyst	Conversion to Epoxide (%)[a]	Conversion to Diol (%)[a]	Epoxide yield (%)	ee (%)[b]	Configuration[c]
1	**50**	83	17	67	72	(−)-1S,2S
2	**51**	84	16	62	71	(−)-1S,2S
3	**52**	89	11	73	82	(−)-1S,2S

[a] conversions were evaluated from the ^{1}H NMR by integration of alkene/diol/epoxide signals
[b] enantiomeric excesses were determined by ^{1}H NMR spectroscopy with Eu(hfc)$_3$ (10 mol%) as chiral
   shift reagent, or by chiral HPLC on a Chiralcel OD column, or by chiral GC on a Chiraldex B-DM column
[c] the absolute configurations of the major enantiomers were determined by comparison with literature values

Catalyst **52** was used in a second study, epoxidizing alkenes with different electronic effects at the *para* position of the aromatic ring. These results showed excellent conversions (80-100%), and moderate enantiomeric excess (55-65%). Due to the acidic nature of the reaction mixture, hydrolysis of some of the epoxides to the corresponding diols was also observed. This problem was however overcome by altering the conditions to make them slightly more basic by using Oxone®, Na$_2$CO$_3$ and MeCN:H$_2$O (1:1).[50]

Tetraphenylphosphonium monoperoxybisulfate (TPPP), an organic soluble version of Oxone®, was prepared by cation exchange between Oxone® and tetraphenylphosphonium chloride, and then crystallised from dichloromethane and hexane, giving a colourless solid in 75% yield. TPPP was discovered by Di Furia in 1994, and was used for oxygen transfer.

TPPP was used in a number of reactions with catalysts **37** and **38** (Figure 2), to study the effects of the reaction conditions, as these have shown to be the most effective catalysts. In catalysts **38** and **39**, the dihydroisoquinolinium moiety has been replaced by a biphenyl backbone fused to a seven-membered cyclic azepinium salt.

Table 14 Asymmetric Epoxidation of 1-Phenylcyclohexene

Entry	Catalyst	Temperature (°C)	Time(min)	Conversion (%)	ee (%)
1	**37**	-40	60	42	43
2	**38**	-40	3	100	67

[a] conversion determined by ^{1}H NMR spectroscopy

These results showed that acetonitrile gives better enantioselectivities as a solvent and when the temperature of the reaction is lowered, the enantiomeric excess increases and the rate of conversion to epoxides is reduced. The highest ee obtained with catalyst **37** was 43% at –40 °C (Table 14, entry 1), and with catalyst **38** in a ee of 43% at –40 °C (Table 14, entry 2).[51]
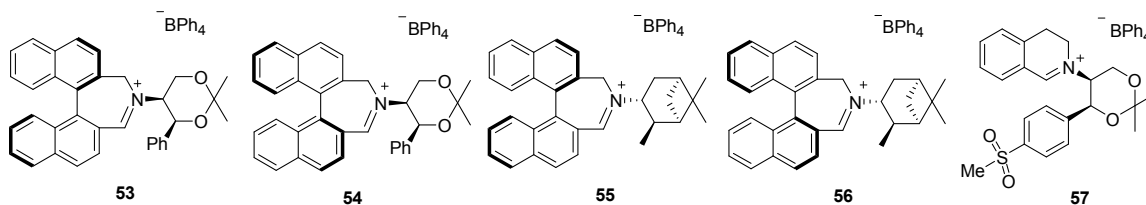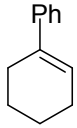
Figure 7 New Catalysts

Table 15 Asymmetric Epoxidation of Unfunctionalized Alkenes

Alkene	Catalyst	Time (h)	Yield (%)	ee(%)
Ph (1-phenylcyclohexene structure)	53	0.20	69	91
	54	2.0	54	78
	55	2.0	40	53
	56	2.0	44	58

Conditions: Iminium salt (5 mol%), Oxone $^{\circledR}$ (2 eq.), NaHCO$_3$ (4 eq.), MeCN/H$_2$O (1:1), 0 $^{\circ}$C

Using catalyst **53** with 1-phenylcyclohexene, the corresponding epoxide was formed in 69% yield with 91% ee in less than twenty minutes. (Table 15).[51]

Building on previous work using TPPP as the oxidant, in 2004 published work by the Page group, showed that using chloroform as a solvent instead of acetonitrile in the absence of water, asymmetric epoxidation of *cis*-alkenes can be carried out as well as high enantioselectivity in the synthesis of the antihypertensive agent levcromakalim.[52]

Using non-aqueous reaction conditions, it was possible for the Page group to carry out a ^{1}H and ^{13}C NMR spectroscopic investigation to look at the intermediates present during asymmetric epoxidation. It was also found that the amount of TPPP added had no effect on enantioselectivity, but temperature did.   Using catalyst **38** (Figure 5) and 1-phenylcyclohexene, the epoxide was formed in 50% ee at −78 °C, but at 0 °C in 26% ee. Mixing the catalyst and TPPP in the absence of the olefin was found to be exothermic. The optimum conditions for this reaction involved cooling a solution of TPPP in the reaction medium to the desired temperature, and separately cooling the catalyst and substrate in the desired solvent. The catalyst solution was then added dropwise to the oxidant, to give minimal temperature increase followed also by the dropwise addition of the substrate.**[52]**

In principle, nucleophilic attack could occur on either face of the iminium species, resulting in two diastereoisomeric oxaziridinium species.
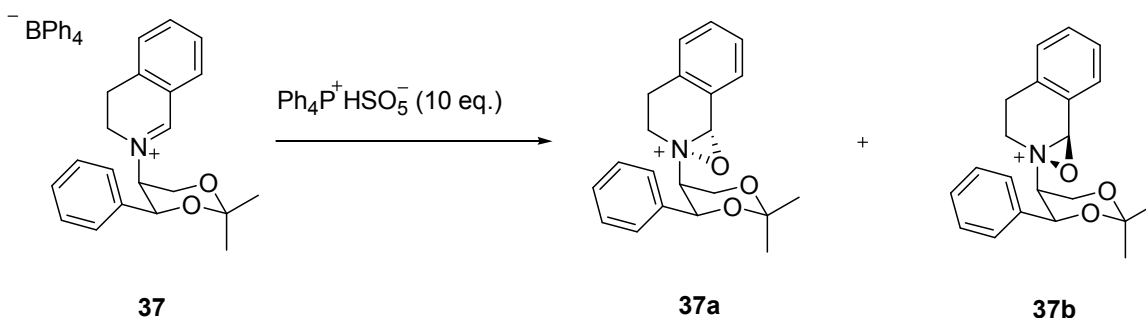
Figure 8 Diastereoisomeric oxaziridinium species

The most important discovery from this study was that the aromatic substituent present in the acetal moiety of the catalyst is vital for asymmetric induction during the epoxidation reaction.

In 2006, results were published for the mediation of asymmetric epoxidations using amines and/or iminium salts. The results showed that amines **58-60** (Figure 9) performed as well as the corresponding iminium for the enantioselective epoxidation of olefins in acetonitrile/water solvent systems. As the synthesis of the amines is a step shorter than the synthesis of the iminium salts, it may be advantageous to use these in synthetic applications.[53]
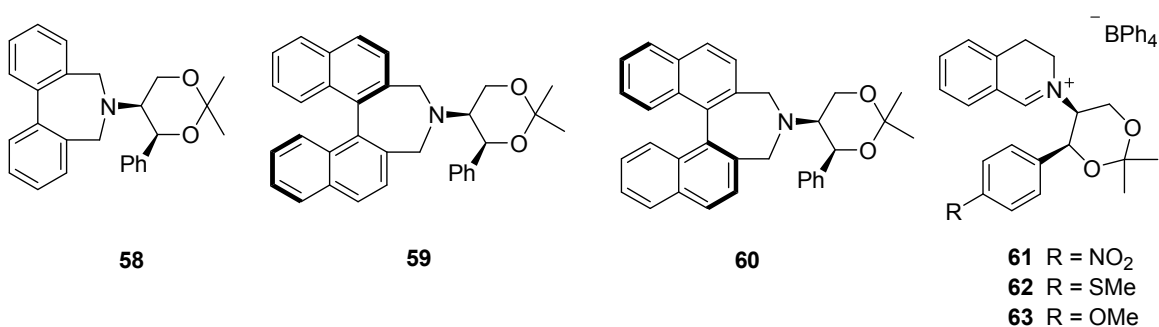
Figure 9 Page's Amines

1.2.7 Lacour Catalyts

In 2005 Lacour began to develop his own dibenzazepinium catalysts for asymmetric epoxidation. These combined a diphenylazepinium core, chiral exocyclic appendages, and chiral lipophilic counterions giving high ees of up to 80% (Table 16, entry 2) at 0 °C.[54]

Table 16 Epoxidation of 1-Phenylcyclohexene
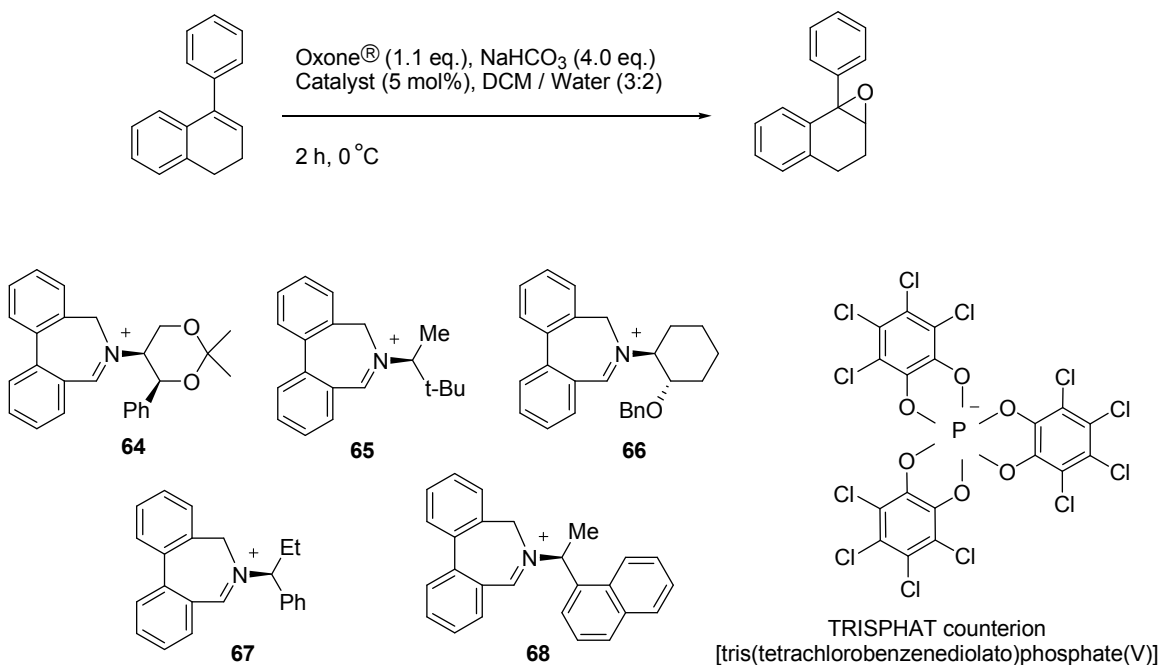
Entry	Catalyst	0°C		20°C	
		Conversion (%)[a]	ee (%)[b]	Conversion (%)[a]	ee (%)[b]
1	**64**	91	79	84	76
2	**65**	100	80	72	70
3	**66**	94	70	68	62
4	**67**	92	35	66	29
5	**68**	100	7	62	3

[a] conversion was calculated using an internal standard (naphthalene)
[b] determined by CSP-HPLC (Chiral OD-H)

Following on from this, in 2006, Lacour published a selection of novel biphenyl and binaphthyl azepines and azepinium salts.[55]

Table 17 Asymmetric Epoxidation of Olefins

TRISPHAT counterion
[tris(tetrachlorobenzenediolato)phosphate(V)]
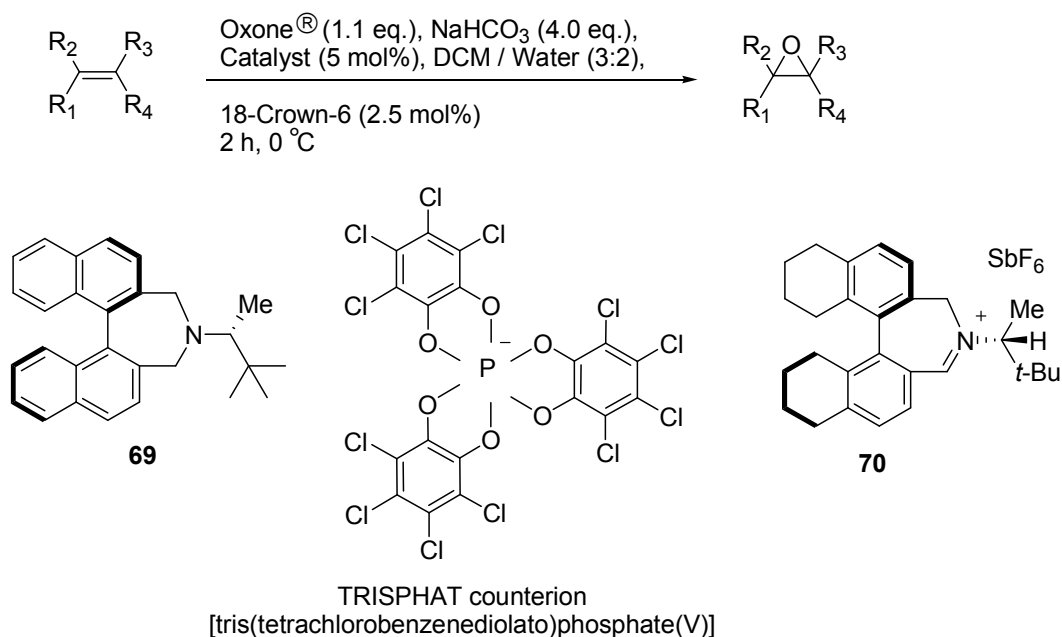
Entry	Alkene	Catalyst	Conversion (%)[a]	ee (%)[b]	Conf.[c]
1	Ph (cyclohexene)	**69**	48	86	(−)-(S,S)
2[d]		**70**	>99	92	(−)-(1S,2S)
3[e]		**70**	75	98	(+)

[a] conversion was calculated using an internal standard (naphthalene)
[b] determined by CSP-GC (Chiraldex Hydrodex β-3P) or CSP-HPLC
[c] the absolute configuration of the major enantiomer was determined by comparison of optical rotation with that reported in the literature
[d] catalyst (2.5 mol%), 24 h
[e] catalyst (20 mol%), 20 h

Table 17 shows that with iminium salt **75** it is possible to obtain ees of up to 86% for the oxide of 1-phenylcyclohexene (entry 1).

In 2008 and 2009, Lacour et al published novel iminium salt catalysts that combined (R_a)-dimethylbiphenyl or (R_a)-5,5',6,6',7,7',8,8'-octahydronaphthyl cores with chiral exocyclic appendages derived from commercially available (*S*)- or (*R*)-3-3,dimethylbutan-2-amine and (*S*) or (*R*)-1-phenylpropan-1-amine. These were shown to be effective asymmetric epoxidation catalysts for unfunctionalized alkenes, with improved ees of up to 98% (Table 17, entry 3).

Lacour proposed that the larger the dihedral angles θ and Φ around the central bond joining the aromatic rings (Figure 10) are, the stronger is the stereocontrol of the reaction by the biaryl axis over the exocyclic appendage. Having a larger θ and Φ angle means that the biaryl axis is predominant, whereas if the dihedral angles θ and Φ are smaller then the exocyclic appendage is predominant (Figure 10).[56]

Figure 10 Stereochemical Influence as a function of θ and Φ dihedral angles

A range of different catalysts were made by the group and then used for epoxidation of a range of alkenes. It was shown that the greater the dihedral angle within the central bond, then the higher the ee. This is perhaps due to the fact that if the dihedral angle is reduced then there is more clash between the protons on the backbone CH_2 groups. If the dihedral angle is reduced by in this instance using a backbone with CH groups on then there are less protons to clash and affect the structure of the catalyst.

Table 18 shows that with catalyst **71** an ee of 57% was obtained in comparison to 92% with catalyst **73**, which has the higher dihedral angle.

Table 18 Lacour's Asymmetric Epoxidation

Entry	Alkene	Catalyst **71** (ee)[a]	Catalyst **72** (ee)[a]	Catalyst **73** (ee)[a]	Configuration[b]
1	Ph (cyclohexene)	57	85	92	(+)-(1R,2S)

[a] determined by CSP-GC (Chiraldex Hydrodex β-3P) or CSP-HPLC
[b] the absolute configuration of major enantiomers was determined by comparison of optical rotation with that reported in the literature

1.3　Sulfoxidation

In asymmetric catalysis, there are a number of important factors to consider, other than high yields and enantioselectivity. Ideally procedures need to be easy and safe with environmentally friendly reagents and mild conditions. To meet these requirements, as mentioned above for other oxidation reactions, hydrogen peroxide is an ideal reagent, as it has been used for sulfoxidation, along with other non-metal and metal catalysts.

Chiral sulfoxides have important applications as auxiliaries in asymmetric synthesis, and in the pharmaceutical industry, although the majority of these to date have been catalysed by early transition metal complexes.[57]

Only a few of these methods to date, have been highly stereoselective towards a range of alkyl, aryl and dialkyl thioethers, and make use of chiral ligands. Other systems have been developed, with loading as low as 2 mol%, but these also use alkyl or aryl hydroperoxides as primary oxidants, which produce alcohols as by-products.[57, 58, 59]

Andersen reported the preparation of the first enantiopure sulfoxide, through substitution of chiral precursors, in the 1960's. He did this by nucleophilic displacement of a leaving group from a diastereopure sulfinate ester (Scheme 14). Despite obtaining high yields of enantiopure sulfoxides, the preparation was difficult and there was a limited availability of precursors. However, following on from this, Ruano and Senanayake used chiral auxillaries that could undergo two consecutive nucleophilic displacements to give an enantiopure sulfoxide.[60, 61, 62]
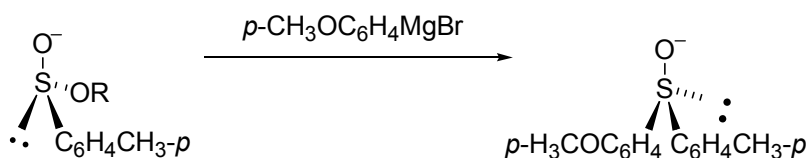
Scheme 14　Andersen's Nucleophilic Displacement

Although asymmetric sulfide oxidation has been of considerable interest over the years as a route to enantiopure sulfoxides, only efficient biological sulfoxidations have been reported using both whole cell systems and isolated enzymes.

1.3.1 Metal Catalysed Sulfoxidations

Metal catalysis for sulfide oxidation has been considered by a number of groups using various metals, including titanium-mediated[63] and vanadium-catalysed asymmetric sulfoxidation.[64] Other metals studied include manganese,[65] iron,[66] niobium,[67] zirconium,[68] tungsten,[69] molybdenum[70] and osmium,[71] which have all been used successfully to catalyse asymmetric sulfide oxidation.

One of the most widely used oxidation methods is the titanium-based Kagan oxidation method, first reported in 1980 and based on modified Sharpless reagents. This method was used to synthesize the drug esomeprazole (Scheme 15), the (S)-enantiomer of omeprazole, on a large scale.[72, 73]
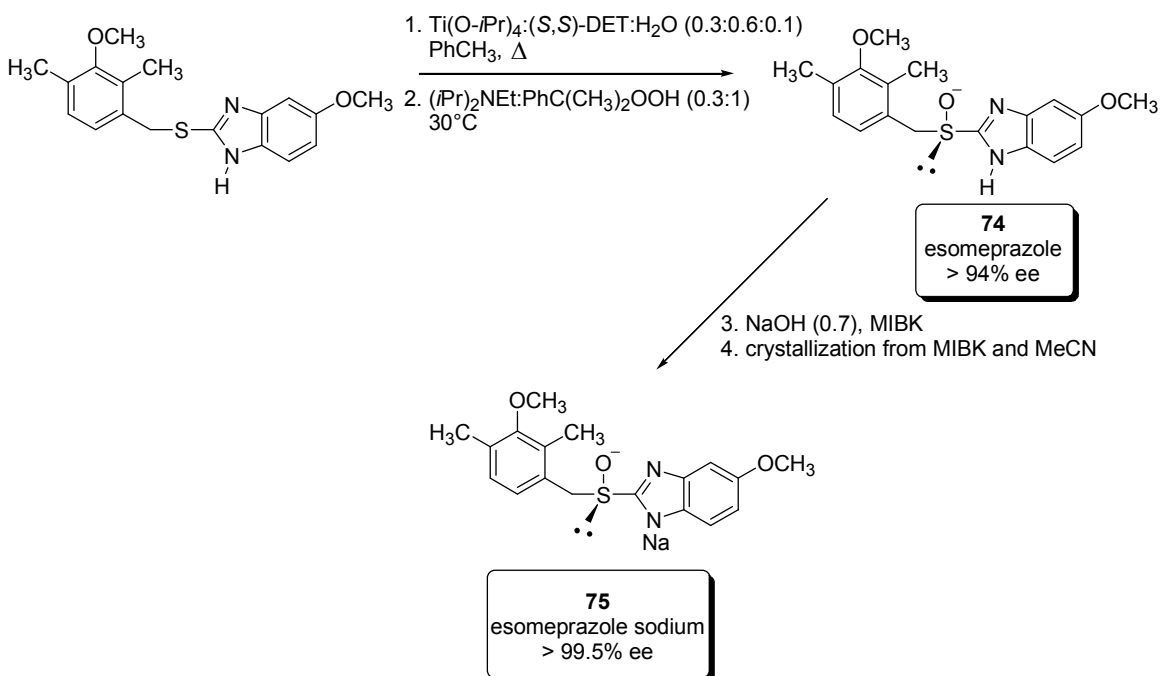
Scheme 15 Synthesis of Esomeprazole

51

In 1995, Bolm reported a robust oxidation method based on vanadium, which involved the *in-situ* formation of a catalyst from vanadyl acetylacetonate and a Schiff base, where the oxygen source was hydrogen peroxide. This reaction is not moisture-sensitive as was the case for of Kagan's oxidation, so therefore could be carried out in an open reaction vessel, giving high enantioselectivities of the sulfoxide product.[74]
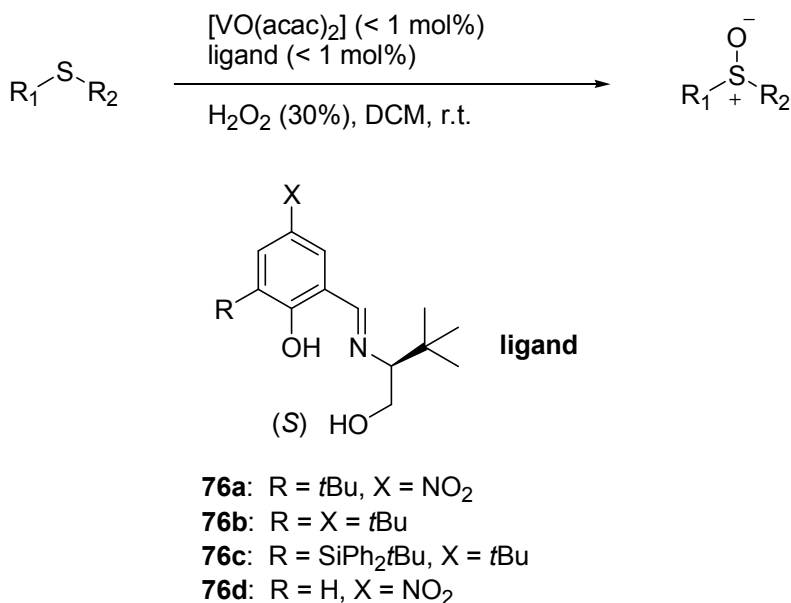
Figure 11 Bolm's Vanadyl acetylacetonate Sulfoxidation Conditions

There are a number of published examples of the kinetic resolution of sulfoxides (the reaction of two enantiomeric sulfoxides at different rates). In the 1980's Davis reported one of the first, obtaining sulfoxides in up to 28% ee using a multi-step oxidation (Scheme 16).[75]
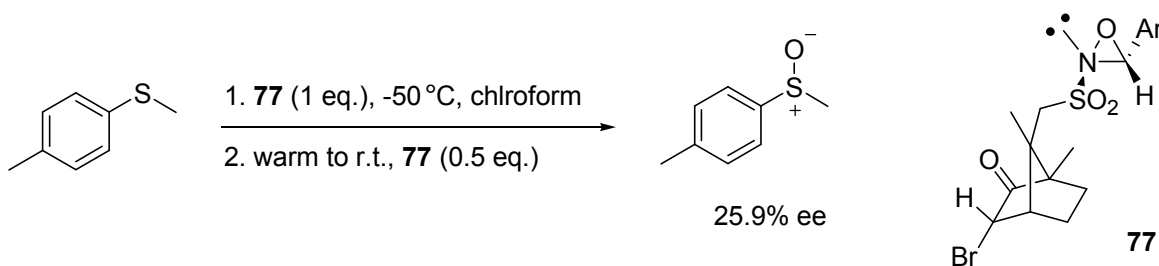
Scheme 16 Davis Sulfoxidation

Licini's group also carried out kinetic resolution reactions. Showing kinetic resolution accompanying a titanium chiral trialkanolamine-catalysed sulfoxidation, where the sulfoxide was derived from phenyl benzyl sulfide in 84% ee. Unfortunately overoxidation was also seen, giving 23% sulfone formation (Scheme 17).
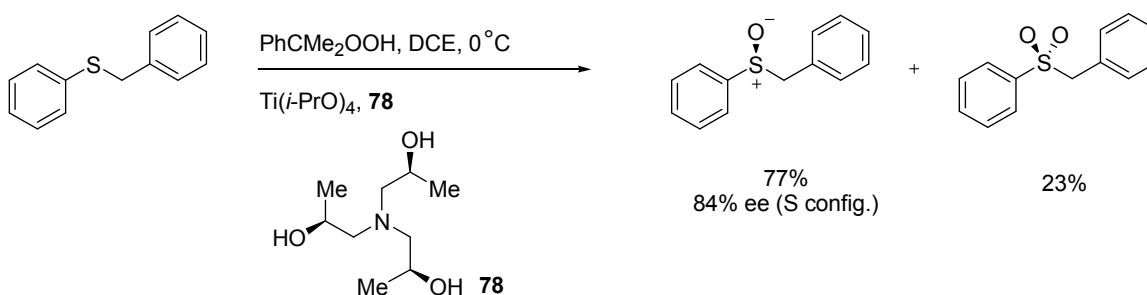
Scheme 17 Licini's Sulfoxidation

In 1998 both Rosini and Korb carried out sulfur oxidation reactions using titanium-based catalysis. Rosini's method allowed the group to isolate *p*-tolyl benzyl sulfoxide in 73% yield and 99% ee using titanium-diphenylethane-1,2-diol through a combination of asymmetric sulfur oxidation and kinetic resolution (Scheme 18).[76] Korb's oxidation used a titanium chiral hydroperoxide complex, but achieved a lower ee than Rosini of 39% ee (Scheme 19).[77]
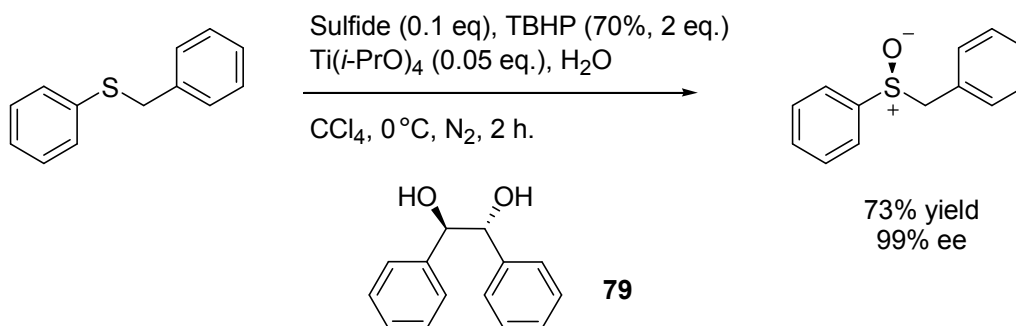
Scheme 18 Rosini's Sulfoxidation
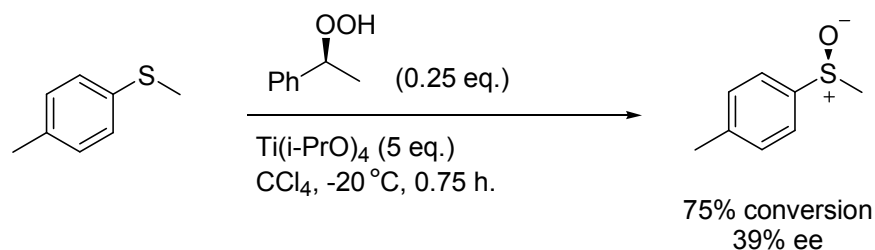
Scheme 19 Korb's Sulfoxidation

More recently in 2004 and 2005, Bolm reported highly enantioselective sulfide oxidations using hydrogen peroxide with an iron catalyst.   Iron complexes have advantages over other metals in that they are inexpensive, environmentally benign and relatively non-toxic in comparison.   Using a chiral iron catalyst, Bolm had previously reported asymmetric oxidations resulting in optically active sulfoxides with up to 90% ee. In 2003 he improved upon this by carrying out iron-catalysed asymmetric sulfoxidation, using 30% aqueous hydrogen peroxide and an iron complex (Fe[acac]$_3$ less than 4 mol%) at room temperature.   This enabled him to achieve optically active sulfoxides in up to 90% ee (Scheme 20).[78]
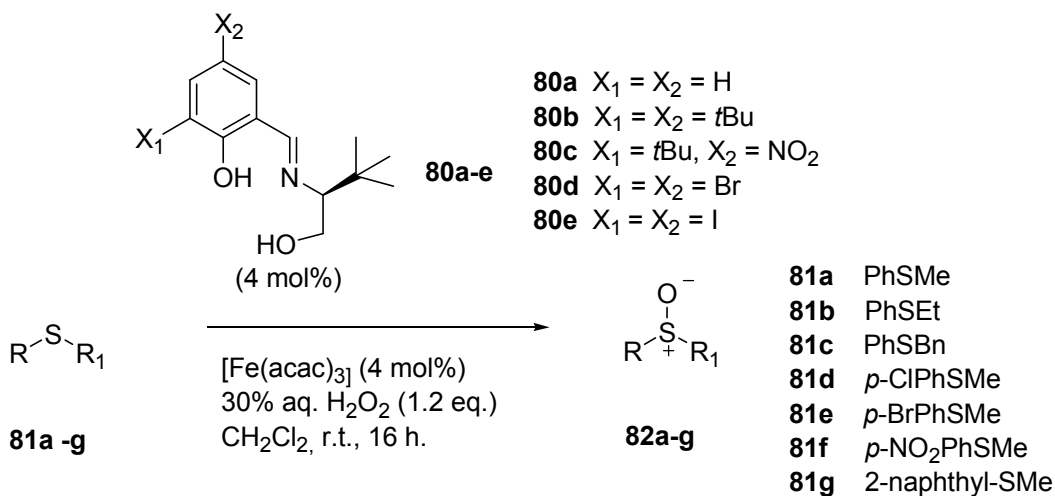
Scheme 20 Iron-catalysed asymmetric oxidation of sulfides

Bolm also showed that benzoic acid could be used for the sulfoxidation of methyl phenyl sulfide catalysed by an iron catalyst to improve enantiomeric excess from 59% with no additive to 73% ee (Scheme 21).[58]
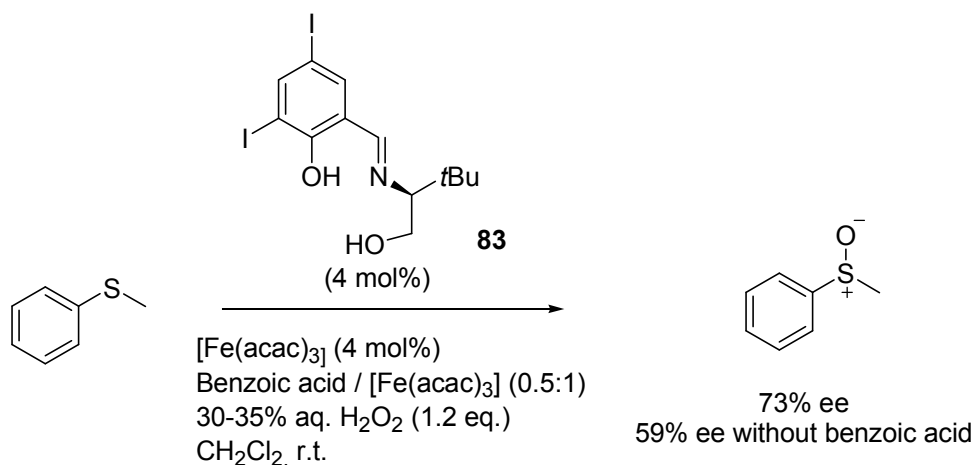
Scheme 21 Bolm's Additive Affect on Sulfoxidation

Sulfide oxidation has been successfully carried out using manganese-salen catalysts, but selectivity and yields are low. Katsuki achieved methyl phenyl sulfoxide in 95% ee, but with a yield of 5%, leading him to believe that kinetic resolution played only a minor role in asymmetric sulfoxidation when using his catalyst.[78] Following on from this in 2007, Katsuki reported a method for the highly enantioselective oxidation of sulfides with hydrogen peroxide, catalysed by a chiral Al(salalen) complex (Table 19). Chiral aluminium complexes have become well-established Lewis acid catalysts for a variety of asymmetric reactions. However asymmetric oxidation catalysis by aluminium complexes has not been much developed.[79, 80]

Table 19 Katsuki's Al(salalen) Sulfoxidation

Al (salalen) (2 mol%)
30% H$_2$O$_2$) (1.1 eq.)

phosphate buffer (pH 7.4)
MeOH, r.t., 24 h.

84

85	(a*R*,*R*,*R*,), R = H
86	(a*R*,*R*,*R*,), R = Me
87	(a*R*,*S*,*S*,), R = H
88	(a*R*,*S*,*S*,), R = Me
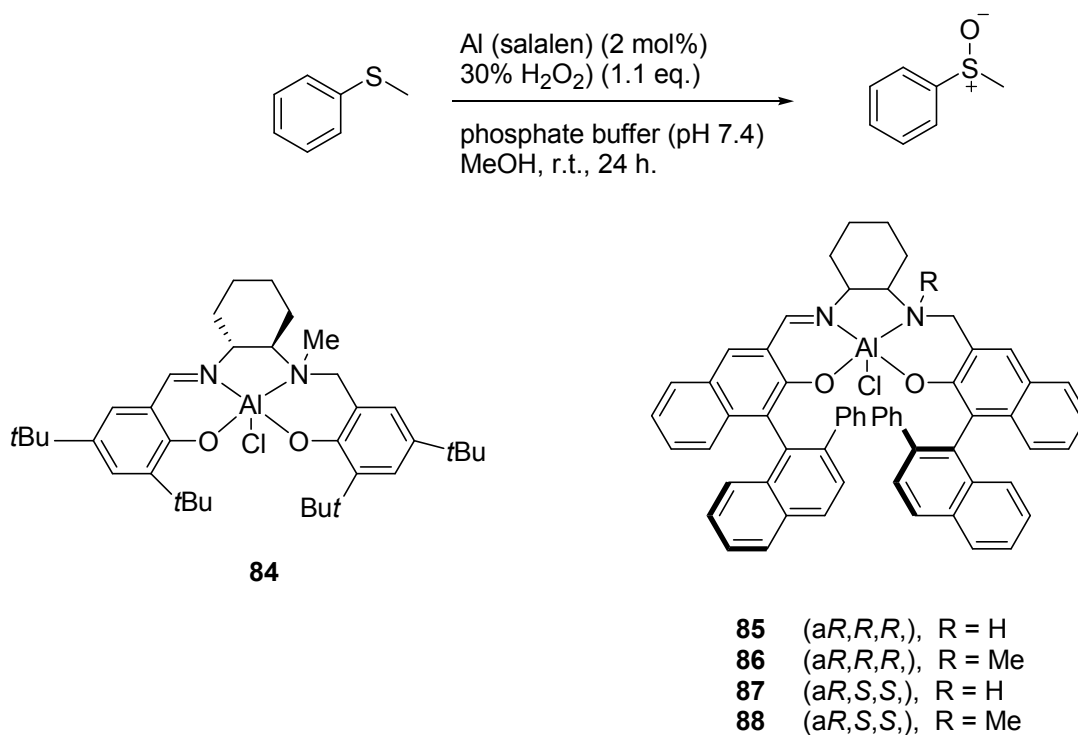
Entry	Catalyst	Conversion (%)[a]	Yield (%)[b]		ee (%)[c,d]	
			Sulfoxide	Sulfone		
1	**84**	40-60	40-60	2-10	20-60	(*S*)
2	**85**	70	64	6	46	(*S*)
2	**86**	55	51	4	10	(*R*)
2	**87**	86	78	8	89	(*S*)
2	**88**	99	90	9	98	(*S*)

[a] conversion determined by ^{1}H NMR spectroscopic analysis
[b] yields determined by ^{1}H NMR spectroscopic analysis
[c] ee value determined by HPLC analysis on chiral phase (Daicel Chiracel OB-H)
[d] absolute configuration determined by HPLC analysis by comparison of the elution order
of the enantiomers with that of an authentic sample

Copper catalysis is also possible for sulfoxidation reactions although prior to Maguire, copper catalysis in this field had received little attention over the years. Cross developed a copper-salen complex which oxidized thioanisole, but enantioselectivities were poor

(14% ee). Another group lead by Iglesias also studied copper catalysis reactions but using a different ligand to form the copper catalyst complex, and reported ees of up to 30%. Lastly, Kraemer also tried to carry out an enantioselective copper-salen catalysed sulfur oxidation, but unfortunately the catalyst complex he used was inactive.

The results obtained to date for metal-catalysed reactions show that Maguire's kinetic resolution study shows that dichloromethane is the best solvent when added portion-wise to the reaction, giving 21% yield, 86% ee, and a ratio of sulfoxide to sulfone of 28:72 (Table 20).

Table 20 Effect of solvents on the kinetic resolution

| | 89 | | 89 | 90 |
| | Racemic sulfoxide | | enantioenriched sulfoxide | sulfone |
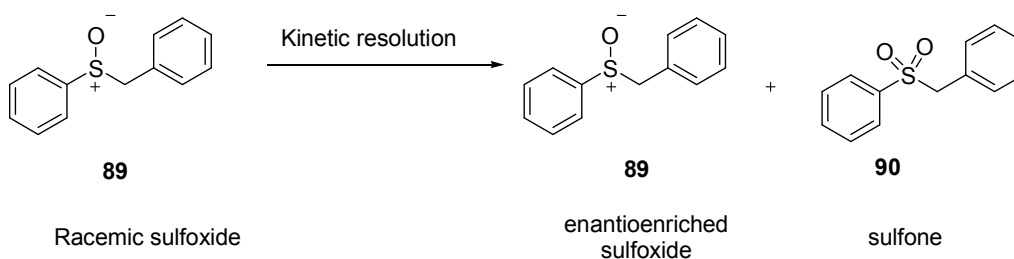
Entry	H$_2$O$_2$ eq.	rate of H$_2$O$_2$ addition	Solvent	Temperature (°C)	Ratio **89/90**	Yield (%)	ee (%)
1	0.8	portionwise	DCM	r.t.	28 : 72	21	86 (S)
2	0.6	single portion	DCM	0	46 : 54	23	44 (S)
3	0.6	single portion	CHCl$_3$	0	39 : 61	29	80 (S)
4	0.8	portionwise	CHCl$_3$	r.t.	38 : 62	33	78 (S)

After Maguire showed that dichloromethane is the best solvent for these kinetic resolution reactions, he investigated reactions using 4-methylmorpholine-*N*-oxide (NMO), obtaining the highest enantioselectivities to date for copper-catalysed asymmetric sulfide oxidation.[72]

1.3.2 Metal Free Sulfoxidations

Metal-free asymmetric sulfide oxidation has been reported using oxaziridines and hydroperoxides.

To achieve oxygen transfer, oxaziridines have been developed that have electron withdrawing substituents on the nitrogen atoms, or on both the nitrogen and carbon atom of the three-membered ring.

In 1988 Davis reported the synthesis and properties of (camphorylsulfonyl) ozaziridine, achieving a 77% yield, starting from inexpensive camphorsulfonic acid. The oxaziridine reported was the first optically active *N*-sulfonyloxaziridine to be obtained as a single enantiomer **91**.[81]
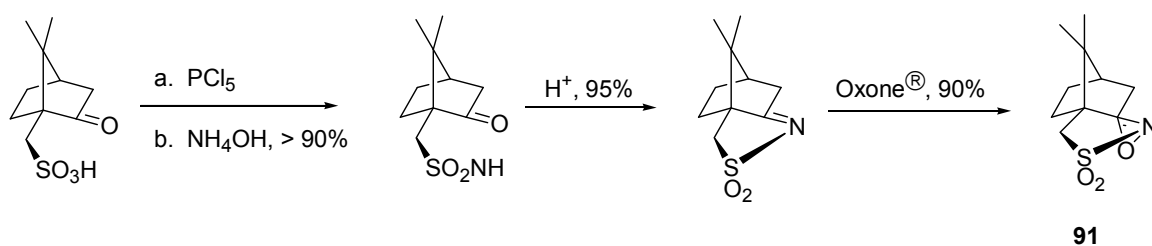
Scheme 22 Synthesis of Davis first N-sulfonyloxaziridine

Using **91**, Davis managed to obtain up to 73% ee (Scheme 23) carrying out his reactions in dichloromethane at room temperature.
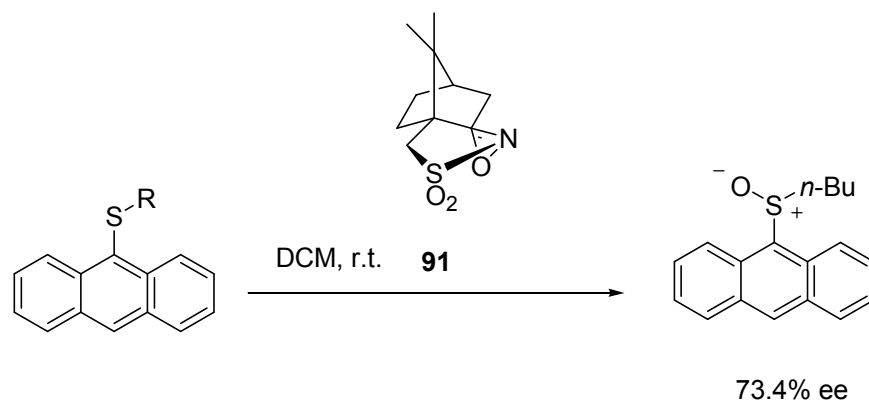
Scheme 23 Davis Sulfoxidation

In 1988, Jenning's phosphinoyloxaziridines were used for the oxidation of thioethers (Scheme 24), and also in 1988 Lusinchi reported the oxidation of weakly basic and

nucleophilic thioether substrates by oxaziridines. This can be performed if the oxygen transfer reaction is promoted by an acid.[82, 83, 84]
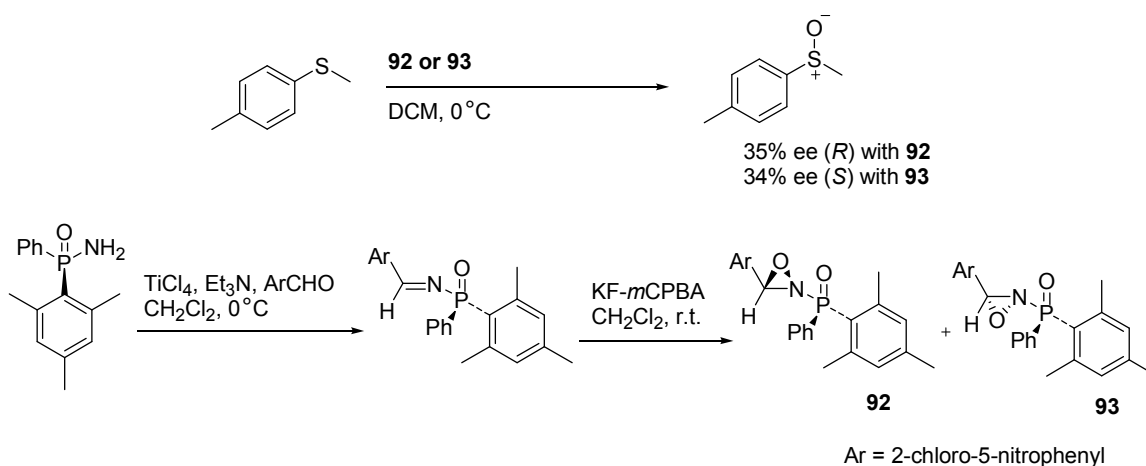
Scheme 24 Jenning's Sulfoxidation

In 1994, the oxidation of sulfides by perfluoro-*cis*-2,3-dialkyloxaziridines was reported by DesMarteau (Table 21).[85]

Table 21 Oxidation of Sulfides using the DesMarteau Protocol

Entry	R group	R_1 group	Oxaziridine	Sulfoxide yield (%)
1	C_6H_5	CH_3	**94**	97
2	C_6H_5	CH_2CO_2H	**94**	95
3			**95**	92
4	C_6H_5	CH_2N_3	**94**	95
5	C_6H_5	CH_2Cl	**94**	95
6			**95**	93
7	C_6H_5	$CH_3Si(CH_8)_3$	**94**	92

On using either of the fluorine-containing oxaziridines (**94** or **95**) high yields of the sulfoxide were obtained (90-97%).[85]

DesMarteau reported a number of useful syntheses (Scheme 25) using **94**. The hydrochlorides of promazine, chloropromazine, and promethazine (**95a**, **95b** and **95c** respectively), are three typical neuroleptic drugs commonly employed in human therapy. On treating the hydrochlorides with an equimolar amount of oxaziridine, in trifluoroethanol, the corresponding sulfinyl products **96a-c** have been obtained in 90-94% yields. The same reactions were also carried out on the free bases **95d-f** to form the corresponding sulfoxides **96d-f**.[85]

		R	X	n
a	Promazine HCl	H	H	1
b	Chlorpromazine HCl	H	Cl	1
c	Promethazine HCl	CH$_3$	H	0
d	Promazine	H	H	1
e	Chlorpromazine	H	Cl	1
f	Promethazine	CH$_3$	H	0
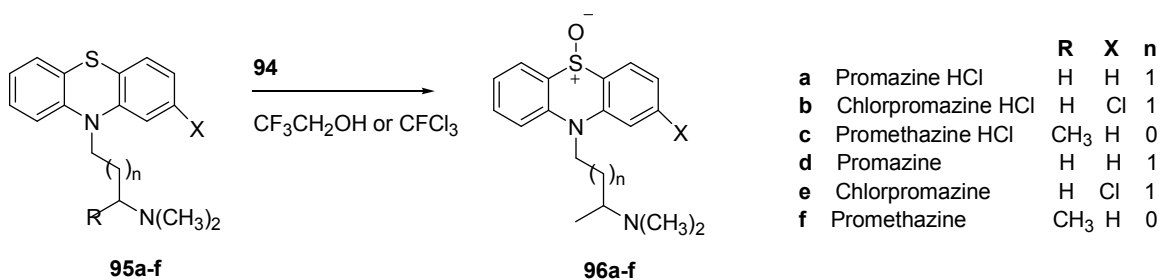
Scheme 25 Synthesis of neuroleptic drugs

More recently, in 2009 Russo carried out oxidation of sulfides, where catalyst loading was as low as 1 mol% of *N,N'*-Bis[3,5-bistrifluoromethyl)phenyl]thiourea using *tert*-butyl hydroperoxide (TBHP) as the oxidant at room temperature in dichloromethane (Table 22).[86]

Table 22 Sulfoxidation with a thiourea/TBHP system

N,N'-Bis[3,5-bistrifluoromethyl)phenyl]thiourea
(1 mol%)

$$R^{S}R' \xrightarrow[\text{r.t., DCM, TBHP (1.2 eq.)}]{} R \overset{+}{\underset{}{S}}_{R'}^{O^-}$$

Entry		Time (h)	Yield (%)[a]
1	S p-Tol	16	99
2	S Ph	22	99
3	Ph S	21	79

[a] isolated yields after flash chromatography

This particular thiourea used by Russo for sulfoxidation gives a catalytic turnover that competes well with the transition metal complexes generally used for sulfoxidation reactions. The effectiveness of the TBHP activation could be rationalized by a double hydrogen-bonding interaction of the thiourea with the proximal oxygen of TBHP. This should then enhance the elctrophilic character of the distal oxygen attacked by a sulfide.
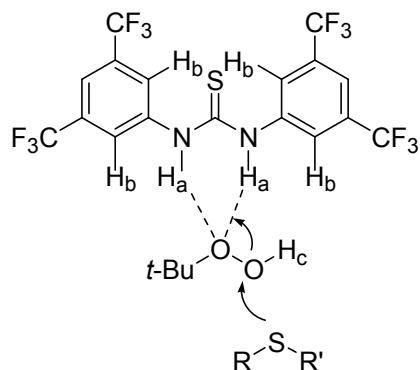
Figure 12 Proposed mode of activation of TBHP by thiourea complex

Formation of the TBHP and thiourea complex (Figure 12) was confirmed by ^{1}H NMR anaysis, where the chemical shift of H_a is downfield from 7.88 to 7.91 ppm, and proton H_c of TBHP also shifts downfield from 7.14 to 7.42 ppm.[86]

In 2009, Habibi showed that sulfoxidation reactions are possible with sodium perborate or sodium percarbonate with sulfuric acid in the presence of KBr, under mild heterogeneous conditions with moderate to good yields.[87]

Zolfigol's group showed that a bromine cation could effectively be applied to the oxidation of different types of organic compounds.[88] Following on from this Habibi tried to introduce a new catalytic medium, based on the in-situ generation of Br^+ using sodium percarbonate and/or sodium perborate and catalytic amounts of bromide in the presence of an activator for the effective oxidation of sulfides to sulfoxides.

Firstly, the group carried out a study that determined the best activator to be silica sulfuric acid giving 100% yield for the oxidation of benzyl phenyl sulfide to the sulfoxide, in DCM at room temperature using sodium perborate in the presence of catalytic amounts of KBr. Without KBr as the activator, these reactions do not work.[87]

Table 23 Oxidation of Sulfides to Sulfoxides

$$R\text{-}S\text{-}R^1 \xrightarrow[\substack{\text{Silica sulfuric acid (1.8 g)} \\ \text{KBr (0.3 mmol), wet SiO}_2 \text{ (50\% w/w), DCM, r.t.}}]{\substack{\text{2NaBO}_3.4H_2O \text{ (6 mmol) or} \\ \text{2Na}_2CO_3.3H_2O_2 \text{ (6 mmol)}}} R\text{-}\overset{O^-}{\underset{+}{S}}\text{-}R^1$$

Entry	Substrate	Oxidant	Time (h)	Yield (%)
1	Ph–S–Ph	Perborate	4.6	90
2		Percarbonate	7.5	88
3	S–OH	Perborate	4	80
4		Percarbonate	2	90

Table 23, shows that yields of up to 90% of sulfoxide could be obtained (entries 1 and 4).

In 1982, Davis carried out a sulfoxidation reaction using chiral 2-sulfonyloxaziridines, and found that the enantioselectivity for asymmetric oxidations of unfunctionalized substrates such as sulfides and disulfides could be increased. It is possible to achieve this by incorporating the active site of the oxidizing reagent into a rigid environment, such as in 2-sulfonyloxaziridines. From studies of asymmetric oxidations using these chiral oxidizing agents, factors important in controlling absolute configuration of the product appear to be steric in nature (Table 24).[89]

Table 24 Group size difference effect on the oxidation of Sulfides

Entry	Sulfide	Sulfoxide ee (%) / Configuration
1	PhCH$_2$-S-Me	1.1 (*S*)
2	Me$_3$C-S-S-CMe$_3$	13.8 (*S*)
3	2,4,5-*t*-Bu$_3$C$_6$H$_2$SMe	46.0 (*S*)

Ar = 2-chloro-5-nitrophenyl

(*S*,*S*)

97
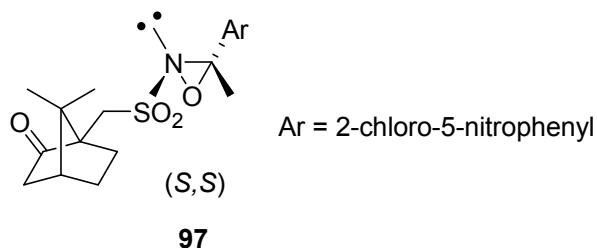
In 1987, Davis reported the asymmetric oxidation of non-functionalized sulfides using 2-sulfamyloxaziridine stereoisomers **98** and **99** (Figure 13) but only obtained ees ranging between 21-45% for the corresponding sulfoxides.[90]
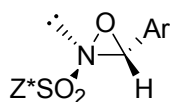
98a-g
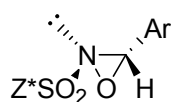
99a-g

a. Ar = 4-nitrophenyl
b. Ar = 3-nitrophenyl
c. Ar = 2-nitrophenyl
d. Ar = 2-chlorophenyl
e. Ar = 2-chloro-5-nitrophenyl
f. Ar = 3,5-dinitrophenyl
g. Ar = pentafluorophenyl
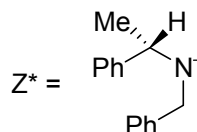
Figure 13 2-sulfamyloxaziridines

In 1995, Page reported asymmetric sulfoxidation using [(3,3-methoxycamphoryl)sulfonyl] oxaziridine **101**, and the corresponding imine **100**, as well as the dichloro derivatives **102** and **103**.[91, 92, 93]
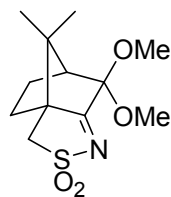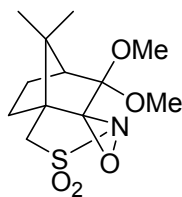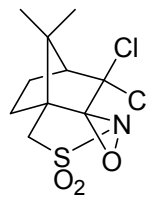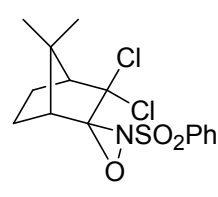
100   **101**   **102**   **103**

Scheme 26 Page's Imines and Oxaziridines

100 and **101** have been shown to be the most effective for sulfoxidation, where if **100** is used catalytically in the presence of a re-oxidant, then **101** can result. With oxaziridine **101** it is possible to obtain ees up to 98%, with yields of >99% (Table 25).[91]

Table 25 Enantioselective sulfoxidation

Entry	Sulfoxide	Yield (%)	ee (%)
1	H₃C–S(O)–tBu	100	85
2	Ph-dithiane sulfoxide	100	98

In 1994, Rozwadowska used non-racemic 3,4-dihydroisoquinolinium salts for the oxidation of sulfides where his best ee achieved was 42% (Scheme 27).[94]

Isoquinolinium salt (10 mol%)
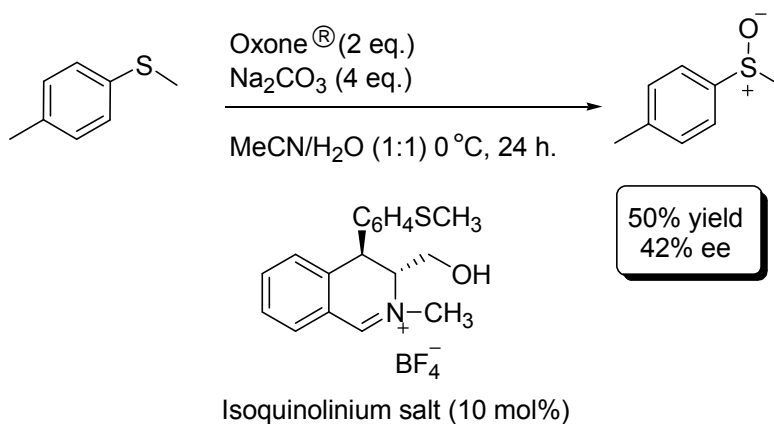
Scheme 27 Rozwadowska's Sulfoxidation

In 1998, Bohé and Lusinchi reported the oxygen atom transfer from a chiral *N*-alkyl oxaziridine promoted by acid, for the asymmetric oxidation of sulfides. The chiral

oxaziridine **102**, from the corresponding dihydroisoquinoline by *m*-CPBA oxidation was used to see if chiral *N*-alkyl oxaziridines would perform in the presence of acid.[95]
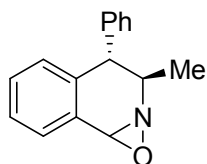
102

Figure 14 Oxaziridine 102

The results for the oxidation of *para*-tolylmethylsulfide using the oxaziridine **102**, using either TFA or methanesulfonic acid (MsOH) to promote oxygen transfer, are shown below. Both reactions were performed at room temperature, with 0.2 mmol of substrate and a slight excess of acid.[95]

Table 26 Sulfoxidation of para-tolylmethylsulfide

Entry	AH	**102**:AH	**102**:**103**	Time	Yield (%)	ee (%)
1	CF$_3$CO$_2$H	1:1.2	1:1.1	24 h	50	42 (*S*) configuration
2	MeSO$_3$H	0:1.05	1:1.1	1 min	64	44 (*S*) configuration

Using either TFA or MsOH made almost no difference on the ees (42% and 44% respectively). It can also be noted that the reaction takes much longer in TFA, in comparison to MsOH.

The proposed mechanism for this reaction (Scheme 28), suggests that equilibrium is established between oxaziridine **106**, and the two-protonated forms **108** and **109**. **109** is theoretically the most populated, owing to the greater basicity of the nitrogen, and is thus

able to transfer its oxygen onto the highly nucleophilic sulfide (DMS), resulting in the imine **109**. If DMS is not present, or any other sulfide, then the O-protonated form **107** will result in the corresponding nitrone **110**.[95]
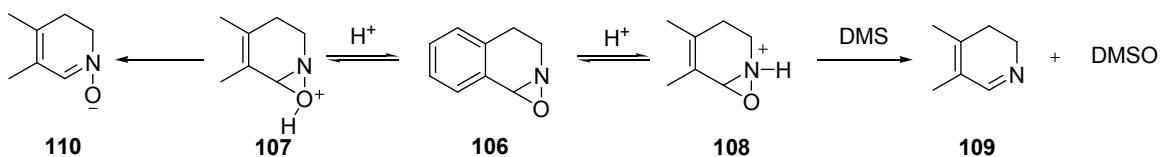
Scheme 28 Oxygen transfer

Bohé and Lusinchi also oxidized a series of arylmethylsulfides using 0.2 mmol of oxaziridine **102**, and methanesulfonic acid in dichloromethane at room temperature. These reactions are very fast, and finished within one minute.[95]

Oxygen transfer from electrophilic reagents to sulfides is thought to be similar to an S_N2 displacement, and can be rationalized in terms of two transition states, planar and spiro.

In a planar transition state, both electron pairs on the sulfur are in the plane of the electrophilic oxygen-containing functional group, whereas in the spiro one, the plane containing the two electron pairs on the sulfur is perpendicular to the plane of the electrophilic oxygen-containing functional group. Theoretical studies on the hypothetical oxidation of hydrogen sulfide by oxaziridines have shown that there are only slight energy differences between the two geometries, so that the asymmetric inductions seen maybe due to steric interactions from both the transition states.[96]

These results show that sulfides can be oxidized to the corresponding sulfoxides without over-oxidation to sulfones. The study of solvent effect showed that the three-component system is governed by subtle acid-base equilibria, which favour the oxygen transfer from the oxaziridine to the sulfide.[95]

In 2007, Bohé reported a new oxaziridinium salt (Figure 15) for enantioselective oxidation of sulfides, with up to 99% ee and good yields. [97]

111
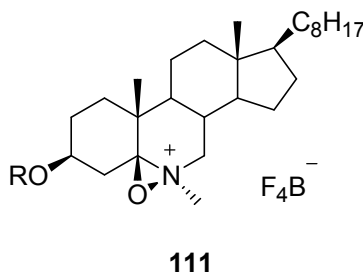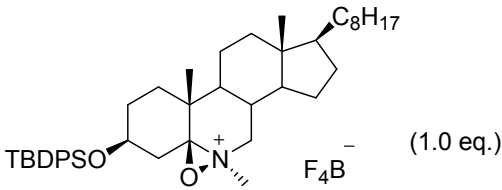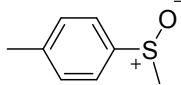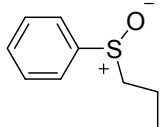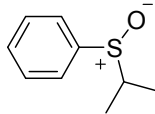
Figure 15 Bohé's Oxaziridinium salt

A series of sulfoxidations were performed using the new oxaziridinium salt (Figure 15). The sulfoxide shown in entry 1, under conditions A, was formed in a high ee of 92%, but not the best yield at only 69%. Bohé, also stated that no sulfone was present in this particular reaction, according to ^{1}H NMR spectroscopy.   On lowering the reaction temperature, ees were improved, with values higher than 99% (entry 1B), with a slight increase in yield to 88%.[96]

Table 27 Sulfoxidation with Bohe's new oxaziridinium

Entry	Sulfoxide	Conditions	Yield (%)	ee (%) (configuration)
1		A	69	92 (*R*)
		B	88	> 99 (*R*)
2		B	76	94 (*R*)
3		B	76	94 (*R*)

Conditions: (A) CH_2Cl_2, r.t. (B) CH_2Cl_2, - 70 °C to r.t.
(yields are not optimised)

Bohé carried out the same reactions using different R and R_1 groups, but did not see any improvement upon the results achieved for entry 1B. In most cases the reactions proceeded in high to excellent ees.

In 2010 Carbery published chemoselective oxidation reactions of a range of sulfides, catalysed by bridged, tetracyclic flavinium synthesized via a telescoped three-step process (Scheme 29).[97]

112a Y, Z=H, X=F
112b Z=H, Y=CF$_3$, X=Cl
112c Y=H, Z=Cl,X=Cl

113a Y, Z=H; 99%
113b Z=H, Y=CF$_3$; 98%
113c Y=H, Z=Cl; 31%

114a Y, Z=H; 80%
114b Z=H, Y=CF$_3$; 85%
114c Y=H, Z=Cl; 65%
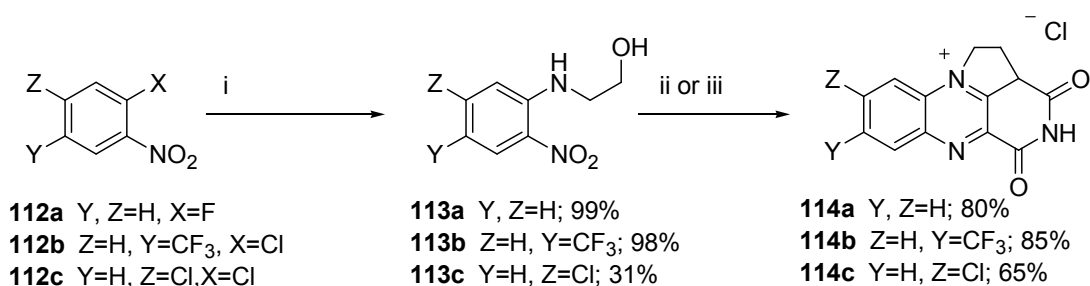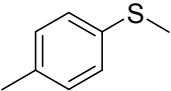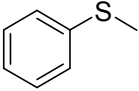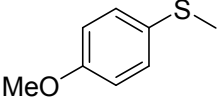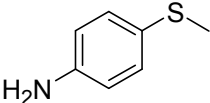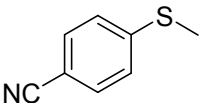
(i) 2-Aminoethanol (3 eq.), K$_2$CO$_3$ (1.2 eq.), EtOH, reflux, 5 h.; (ii) for **114a** and **114b**; HCO$_2$NH$_4$ (5 eq.), Pd/C (10% wt), MeOH, O °C to r.t., 1 h.; then alloxane monohydrate (1 eq.), B(OH)$_3$ (1.01 eq.), AcOH, 50 °C, dark, 18 h.; then SOCl$_2$, 50°C, dark, 18 h.; (iii) for **114c**; Sn (3 eq.), HCl (conc.), H$_2$O, 100 °C, 0.5 h.; then alloxane monohydrate (1 eq.), B(OH)$_3$ (1.01 eq.), AcOH, 50 °C, dark, 18 h.; then SOCl$_2$, 50°C, dark, 18h.

Scheme 29 Carbery's Catalysts

After a range of NMR experiments to test catalysts **114a-114c** for sulfoxidation reactions, catalyst **114c** was shown to give the best results in methanol, so was used to carry out sulfoxidation reactions on a range of substrates (Table 28), giving up to 99% yield (entry 1) with no over-oxidation to sulfone.[98]

Table 28 Carbery's Sulfoxidation

$$R_1\text{-S-}R_2 \xrightarrow[\text{25°C}]{\begin{array}{c}\text{H}_2\text{O}_2\ (1.2\ \text{eq.}),\ \text{MeOH}\\ \text{Catalyst }\textbf{114c}\ (1.8\ \text{mol\%})\end{array}} R_1\overset{\overset{\text{O}^-}{|}}{\underset{+}{\text{S}}}R_2$$

Entry	Substrate	Time (h)	Sulfoxide Yield (%)
1		5	>99
2[a]		5	25
3		3.5	95
4		2	99
5		0.5	93
6		3.5	97

[a] no catalyst

71

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2.0 <u>Results and Discussion</u>

Organic reactions, which can be carried out in or on water, are becoming more important today because of our concerns over safety and environmental impact.[1] Thus if an oxidation reaction can be carried out, where the oxidant is generated using electrolysis, this is advantageous over existing systems that use strong or large volumes of oxidant and solvent that cannot be recycled or transported.

Towards this end the Page group have been involved in developing novel stoichiometric oxidants for oxaziridinium ion mediated epoxidation. The initial aim of this project was to explore the use of electrosynthesis for the *in situ* develoment of a mild oxidant for asymmetric epoxidation, sulfoxidation and Baeyer-Villiger oxidation.

2.1 <u>Epoxidation</u>

Enantioselective epoxidation reactions, both driven by electrochemically generated oxidants and commercially available oxidants, have been studied. Previous work carried out using electrosynthesis, has been reported by Saha for the generation of peroxycarbonate, peroxydisulfuric acid and peroxydiphosphate.[2] Below is a brief background relating to these systems.

2.1.1 Peroxycarbonate

Peroxycarbonate can be formed from carbon dioxide by using a boron-doped diamond electrode (BDD) as the working electrode. Saha first demonstrated this in 2003, when he reported that experimental conditions such as current density, electrolyte concentration and the anode material all affect the formation of sodium peroxycarbonate.[2]

In 2003 Saha found the maximum current efficiency for producing sodium peroxycarbonate to be 82% at a current density of 0.05 A cm^{-2} , after electrolysis of a 1 M Na_2CO_3 solution for 30 minutes, in a divided cell.[2]

Looking at the effect of electrolyte concentration on the reaction, Saha concluded that a higher concentration gave both better current efficiency and higher peroxycarbonate concentrations (Table 29).[2]

Table 29 Influence of Electrolyte Concentration

Entry	Concentration Na_2CO_3 (M)	[sodium percarbonate] (mM)	Current efficiency (%)
1	0.1	4.40	9.6
2	1.0	33.8	72.5

Temperature: $0\,^{\circ}C$
Current density: 0.25 A cm^{-2}

Later in 2003, Saha showed that sodium peroxycarbonate could be prepared from a 1 M solution of sodium hydroxide (NaOH), with a platinum plate cathode, at 5 °C, where the carbon source comes from CO_2 in air, when a voltage was applied. On increasing the voltage within the cell, from 0.5 to 11.5 V an increase in current density was observed from 0.05 to 0.5 A cm^{-2}, and an increase in the concentration of peroxycarbonate formed was also seen. However on carrying out a study over time, Saha found that within up to 2 hours there was a steady increase in peroxycarbonate concentration, after which a maximum of 25 mM is reached.[3]

Temperature also has an effect on peroxycarbonate formation, with higher concentrations seemingly observed at lower temperature, however this is due to decomposition of peroxycarbonate at higher temperature. (Table 30).

Table 30 Temperature Influence on the conversion of CO_2 to Peroxymonocarbonate

Entry	Temperature (°C)	[peroxycarbonate] (mM)	Current efficiency (%)	Power Consumption (W h g^{-1})
1	5	5.0	53.6	3.28
2	25	3.1	33.5	3.53

Curent density: 0.05 A cm^{-2}; concentration of NaOH, 1 M and electrolysis time, 30 min.

The mechanism by which peroxycarbonate is formed is not entirely known. Saha postulated that it is formed *via* an active intermediate, perhaps electro-generated hydroxyl radicals, as hydroxyl radicals are formed by the electrochemical oxidation of water at the BDD anode surface (Equation 1).[3]

$$2H_2O \longrightarrow 2\overset{\bullet}{O}H \ + \ 2H^+ \ + \ 2e^- \qquad (1)$$
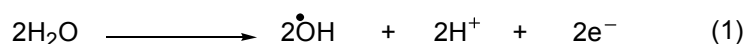
Equation 1 Hydroxyl Radicals in Peroxycarbonate Formation

Formation of peroxycarbonate is initiated by hydroxyl radicals and water is generated as the byproduct (Equation 2).

$$2HCO_3^- \ + \ 2\overset{\bullet}{O}H \longrightarrow C_2O_6^{2-} \ + \ 2H_2O \qquad (2)$$
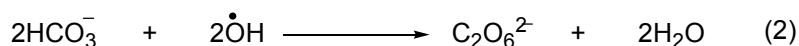
Equation 2 Proposed Peroxycarbonate Formation

2.1.2 Peroxodisulfuric Acid

Peroxodisulfuric acid ($H_2S_2O_8$) and its salts are strong oxidizing agents; used in a variety of applications for waste-water treatment, dye oxidation and fibre whitening. It is also an intermediate in electrochemical formation of hydrogen peroxide and is prepared by the electrolysis of sulfuric acid (H_2SO_4), using a BBD cathode and platinum anode.[4]

In 2000 the first formation of peroxodisulfuric acid using BDD electrodes was reported. Peroxodisulfuric acid was formed in a one-compartment, undivided cell using H_2SO_4 as

the electrolyte, with a diamond anode and zirconium cathode at 25 °C. This gave low conversions of less than 5% in under one hour.[5]

A study on electrolyte concentration (Equation 3), showed that the current efficiency increases with electrolyte concentration.[5]

Table 31 Influence of Electrolyte Concentration

Entry	$[H_2SO_4]$ (mol dm^{-3})	Current density (mA cm^{-2})	Current efficiency (%)
1	1.0	30	47
2	7.5	30	64
3	7.5	200	75

peroxodisulfuric acid formation at 25 °C

With the electrochemical generation of peroxodisulfuric acid, it is also possible that a number of side reactions occur at the anode site, such as; (**1**) oxygen evolution, (**2**) peroxodisulfate formation and (**3**) ozone production (Equation 3).[5]

$$2H_2O \longrightarrow O_2 + 4H^+ + 4e^- \quad (1)$$

$$2SO_4^{2-} \longrightarrow S_2O_8^{2-} + 2e^- \quad (2)$$

$$3H_2O \longrightarrow O_3 + 6H^+ + 6e^- \quad (3)$$
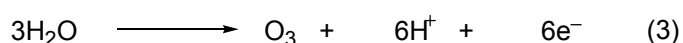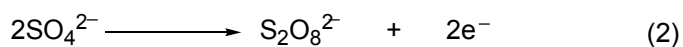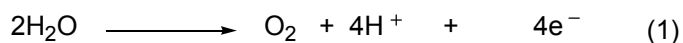
Equation 3 Side Reactions

It is also possible that peroxomonosulfuric acid (Caro's acid), and hydrogen peroxide are present in the electrolyte due to the hydrolysis of peroxodisulfuric acid (Equation 4).

$$H_2S_2O_8 \ + \ H_2O \longrightarrow H_2SO_5 \ + \ H_2SO_4$$

$$H_2SO_5 \ + \ H_2O \longrightarrow H_2SO_4 \ + \ H_2O_2$$
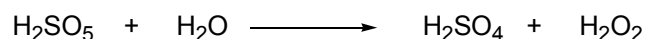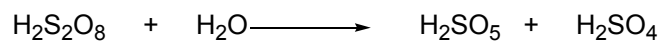
Equation 4 Hydrolysis of Peroxodisulfuric Acid

The proposed mechanism for the formation of peroxodisulfuric acid, involves a radical mechanism similar to that for peroxycarbonate, where water is discharged at the anode forming hydroxyl radicals (Equation 5).

$$H_2O \longrightarrow OH\bullet \ + \ H^+ \ + \ e^-$$

$$2HSO_4^- \ + \ 2OH\bullet \longrightarrow S_2O_8^{2-} \ + \ 2H_2O$$
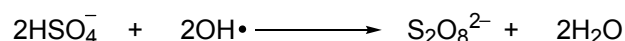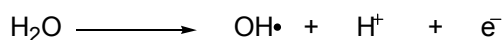
Equation 5 Proposed Mechanism for Peroxodisulfuric Acid Formation

In 2002, Serrano reported the electrochemical formation of peroxodisulfuric acid using BDD electrodes. Showing that high current efficiency could be achieved for sulfuric acid oxidation to peroxodisulfuric acid when concentrations of H_2SO_4 are greater than 2 M, with temperatures ranging between 8-10 °C.[6]

The oxidation rate of Caro's acid from hydrolysis of $S_2O_8^{2-}$ (Equation 6), according to Balej is higher than the rate of eventual formation of H_2SO_5, under general reaction conditions for electrosynthesis of $S_2O_8^{2-}$. This explains why the concentration of Caro's acid does not increase with an increase in temperature.[7]

Using a two-compartment cell, with a diamond anode and zirconium cathode, with electrolysis over 20 hours, Serrano showed that the influence of concentration on the experiment current efficiency at 9 °C, falls into two categories; (1) for concentration less than 2 M, the current efficiency increase with the concentration up to 90%, (2) for concentration greater than 2 M, the current efficiency is constant to a maximum value of 95%.[6]

In a separate study, Serrano found that peroxodisulfuric acid is unstable in aqueous solutions, decomposing in dilute sulfuric acid solutions with liberation of oxygen (Equation 6).[6]

$$S_2O_8{}^{2-} \ + \ H_2O \longrightarrow 2HSO_4^- \ + \ {}^1/_2O_2$$
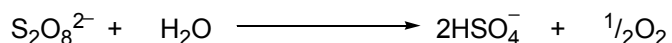
Equation 6 Decomposition

Kolthoff and Miller, previously reported the decomposition of persulfate in aqueous medium, in 1951. They stated that in alkaline, neutral and dilute acid solutions, persulfate decomposes**.**[8]

2.1.3   Peroxydiphosphate

Peroxodiphosphates are strong oxidizing agents used for numerous applications, including; cosmetic, agricultural, polluted water treatment and as bleaching agents in the detergent industry.

In 2005, Rodrigo reported the first electrochemical synthesis of peroxodiphosphate using a boron-doped diamond anode, achieving high current efficiencies. However, the current efficiencies strongly depend on pH, and reaction conditions such as temperature and current density.[9]

Rodrigo showed the optimum pH to be 12-13, with current densities over 1000 $A.m^{-2}$, and low temperatures, where the pH has the most effect upon the reaction. He also showed that high concentrations of phosphate in the raw materials increase the process efficiencies, but that they also seem to favour the corrosion of the electrode, hence concentrations below 1 M of $PO_4{}^{3-}$ are recommended.[9]

Potassium peroxodiphosphate ($K_4P_2O_8$), is prepared by electrolysis of potassium phosphate, with a platinum and BDD electrode, under alkaline conditions. Reagents such

as fluoride or thiocyanate are often added too. These work by promoting the blockage of oxygen evolution sites at the anode, promoting direct oxidation of phosphate to peroxodiphosphate, which is favoured over the water oxidation process, thus higher current efficiencies are obtained. Although it is possible to carry out the electrosynthesis without additives, the result is low efficiencies.[9]

In an experimental electrolysis of 1 M K_3PO_4, at 25 °C, in a two-compartment cell, the starting pH of the solution was adjusted to 12.5 by the additions of KOH. Over 300 minutes, the concentrations of oxidant synthesized increases.

It has been shown that the pH of the electrolytes changes as the reaction proceeds. This can be seen in a divided cell, where the pH decreased in the anolyte and increases in the catholyte. These changes are due to water oxidation and reduction. In the anodic compartment, the reaction generating oxidant on the anodic surface competes with the oxidation of water (Equation 7). Protons are also generated in a side reaction and cause a decrease of pH in the anolyte.[9]

$$H_2O + 2e^- \longrightarrow {}^1\!/_2O_2 + 2H^+$$
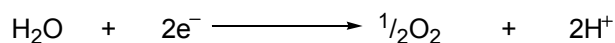
Equation 7 Water Oxidation

In the cathodic compartment, the reduction of water (Equation 8) occurs, and results in hydrogen and hydroxyl anions, hence the rise in pH.

$$H_2O + e^- \longrightarrow {}^1\!/_2H_2 + {}^-OH$$
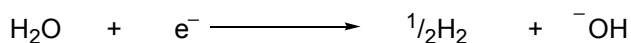
Equation 8 Water Reduction

If a single-compartment cell is used instead, the reduction of water competes with the oxidant formed, and thus the efficiency decreases.[9]

2.1.4 Previous Group Epoxidation Studies with Sodium Percarbonate

Previous work carried out by the Page group on enantioselective epoxidation reactions, shows that the same results are obtained with commercial sodium percarbonate and electrosynthesized sodium percarbonate (Scheme 30), using catalyst **38** (Page 35 of introduction, Figure 5).[10]
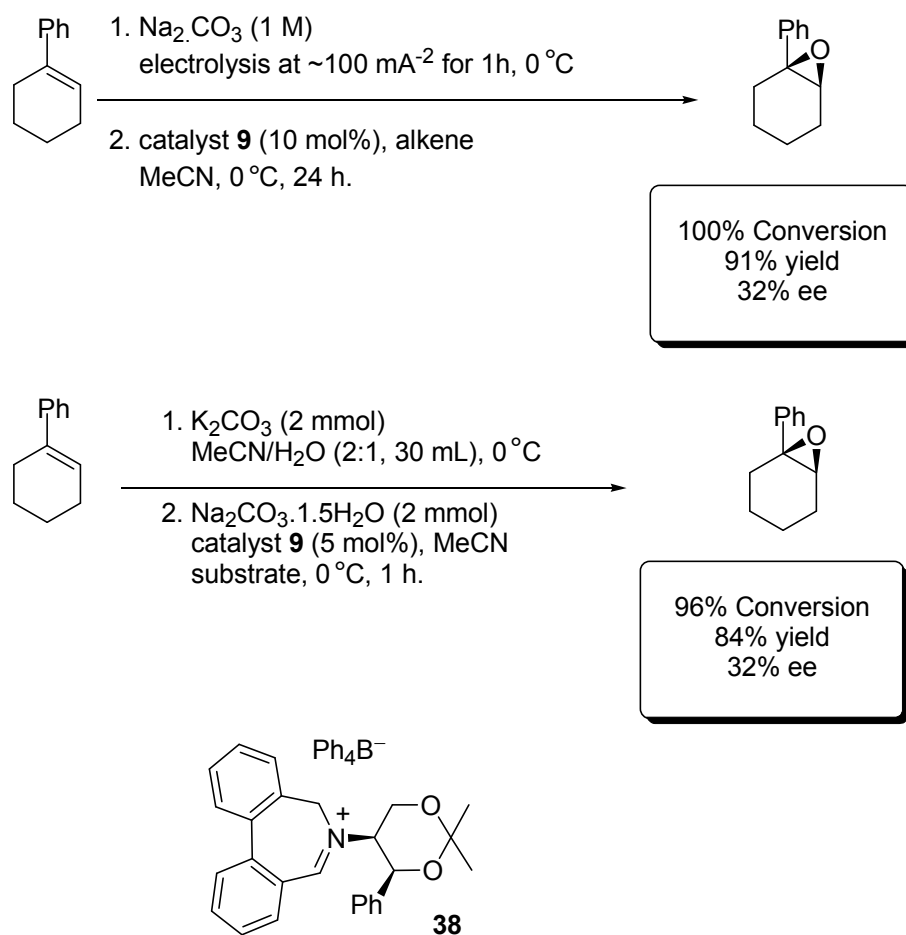
Scheme 30 Epoxidation with Catalyst 9

The work carried out showed that if a carbonate solution of less than 1.0 M is used, then epoxidation does not occur. This is also the case for any other solvent other than acetonitrile. Using dichloromethane, methanol and acetone resulted in no epoxide.

Upon using the best conditions which gave complete conversion of the alkene substrate, where the conditions were; acetonitrile, 0 °C and 10 mol% of catalyst, with percarbonate that has been generated electrochemically by applying 10.0 V to a 1 M $Na_2CO_3.10H_2O$ solution for one hour. A series of substrates were tested under these conditions. However ees obtained for the epoxidation of 1-phenylcyclohexene with catalyst **38**, were lower (32% ee) than those obtained using Oxone® (60% ee, Scheme 31).
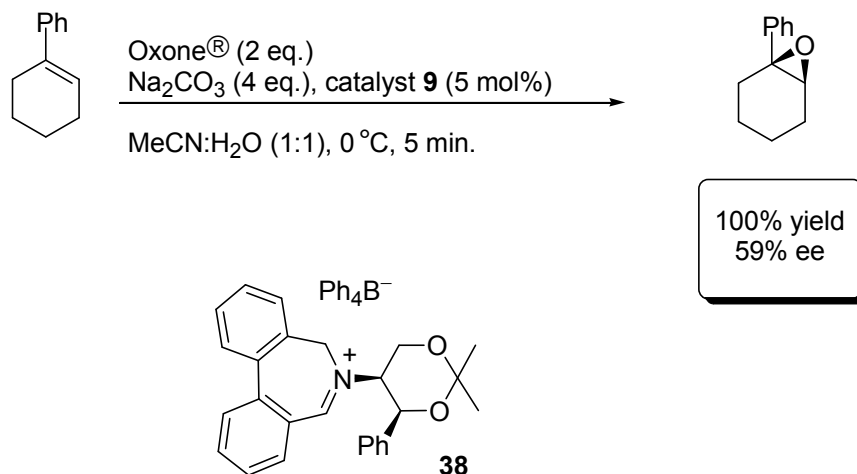
Scheme 31 Epoxidation with Oxone®

2.1.5   New Electrochemical Systems for Asymmetric Epoxidation

Using cyclic voltammetry, it was possible to determine the concentration of an electrochemically produced percarbonate solution. This was carried out by electrolysing a 1 M aqueous solution of $Na_2CO_3.10H_2O$ in an undivided cell using a BDD working electrode, and a platinum counter electrode, where a potential of 10.0 V was applied for one hour. The solution was kept cold in an ice bath, and emulsified using an ultra-turrax (6500 rpm). At regular intervals over the hour period, cyclic voltammetry was run (Figure 16), which plots current and potential. After an hour 1 mmol of sodium percarbonate was added to the solution and a cyclic voltammogram obtained. This then allows the amount of percarbonate generated in the hour period to be calculated from the voltammogram, by comparison in the difference between percarbonate concentration before and after the addition of 1 mmol sodium percarbonate. This shows the

concentration of percarbonate solution to be 20-30 mM, with a current efficiency of approximately 30%.
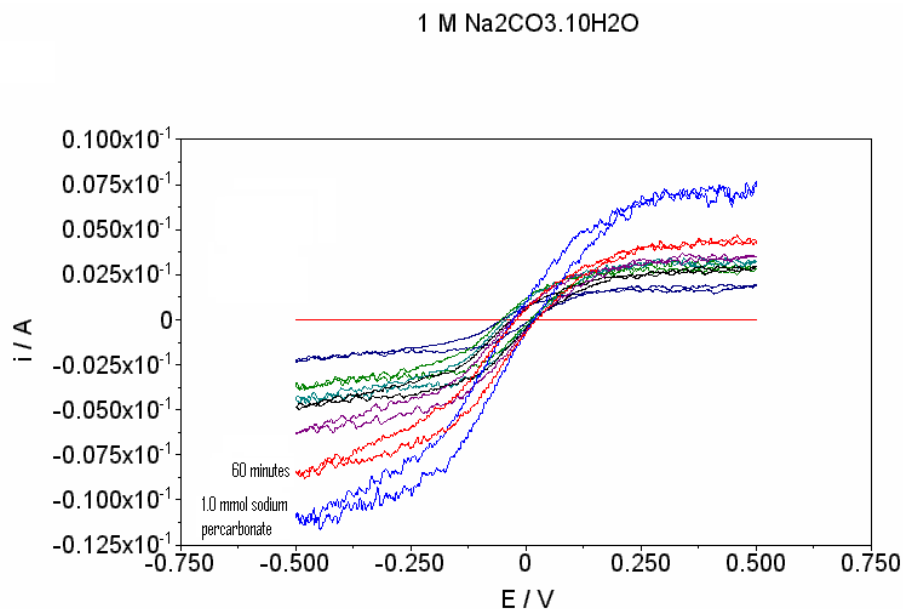
Figure 16 Titration of 1 M Na₂CO₃.10H₂O

Continuing on from previous work on enantioselective epoxidation reactions, both driven by electrochemically generated percarbonate, and using sodium percarbonate, the effects of a number of additives to the reaction were studied, where catalysts **9**, **10** and **13** were used (Scheme 35).

The synthesis of five of the Page group catalysts was carried out (Scheme 35), which were then used for ongoing chiral oxidation studies. The backbone for catalysts **9-11** (Scheme 35), is identical, synthesized from 2,2'-biphenyl dimethanol refluxed in hydrobromic acid (48%), giving 2,2'-bis-bromomethylphenyl backbone **2** (77%) (Scheme 32).
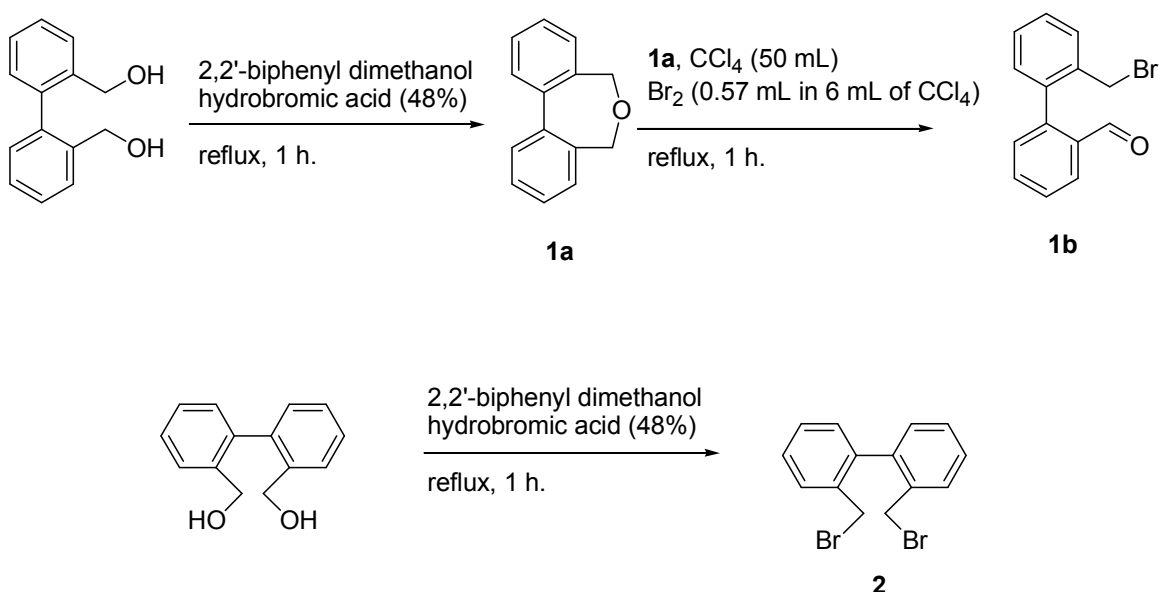
Scheme 32 Synthesis of Catalyst Backbone 1b and 2

The 2-(2-Bromoethyl) benzaldehyde backbone for catalysts **12** and **13** is synthesized from isochroman, by treatment with bromine in cyclohexene for one hour under reflux, giving an intermediate compound that on heating in hydrobromic acid for approximately ten minutes gave bromoaldehyde **3** (67%) (Scheme 33).
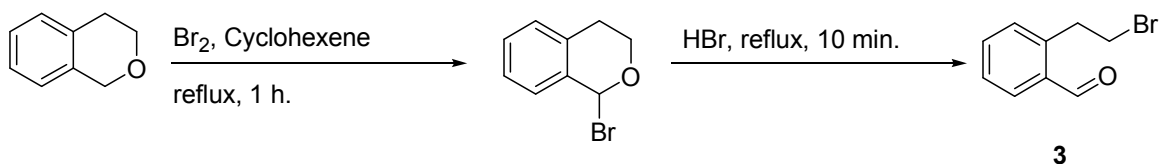
Scheme 33 Synthesis of Catalyst Backbone 3

Synthesis of the amine section of each catalyst was from the relevant propandiol stirred at room temperature in the presence of methyl formate (1.1 eq.) and sodium methoxide (10 mol%) in methanol (Scheme 34, **5**). After amine protection by the addition of the formate group, the diol can also be protected. This is done with 2,2'-dimethyloxypropane (10 eq.) and *para*-toluenesulfonic acid (10 mol%) in acetone at room temperature, giving compound **6** (53%) (Scheme 34).
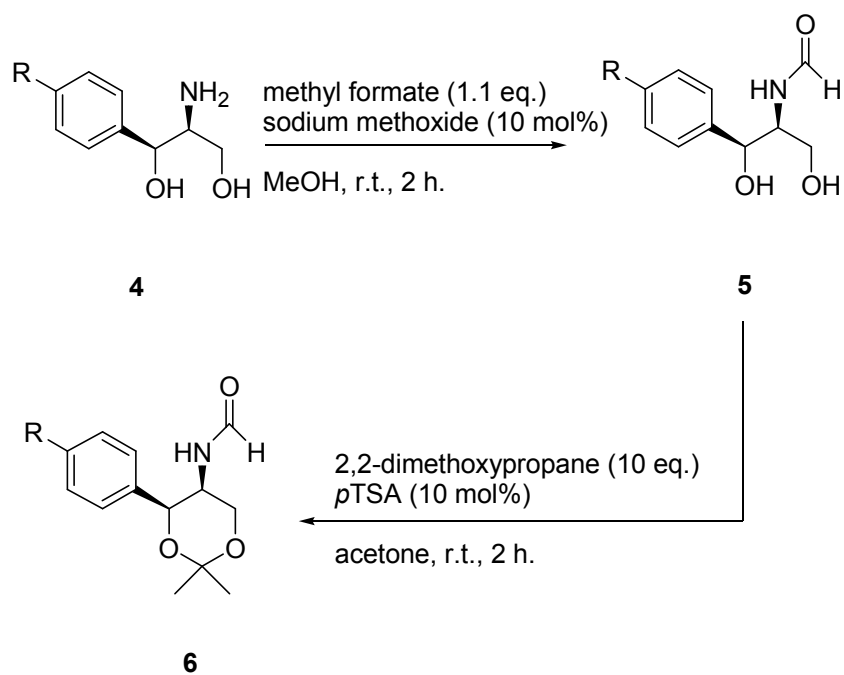
Scheme 34 Synthesis of Amine 6

Once the diol group is protected, the formate protection is removed by refluxing **6** in hydrazine hydrate (for compounds **9** and **12**), or for compounds **10**, **11** and **13** an oxidation is done with *m*CPBA (3 eq.) in DCM first, before removing the formate protecting group with hydrazine hydrate, giving **7** (95%) (Scheme 35).
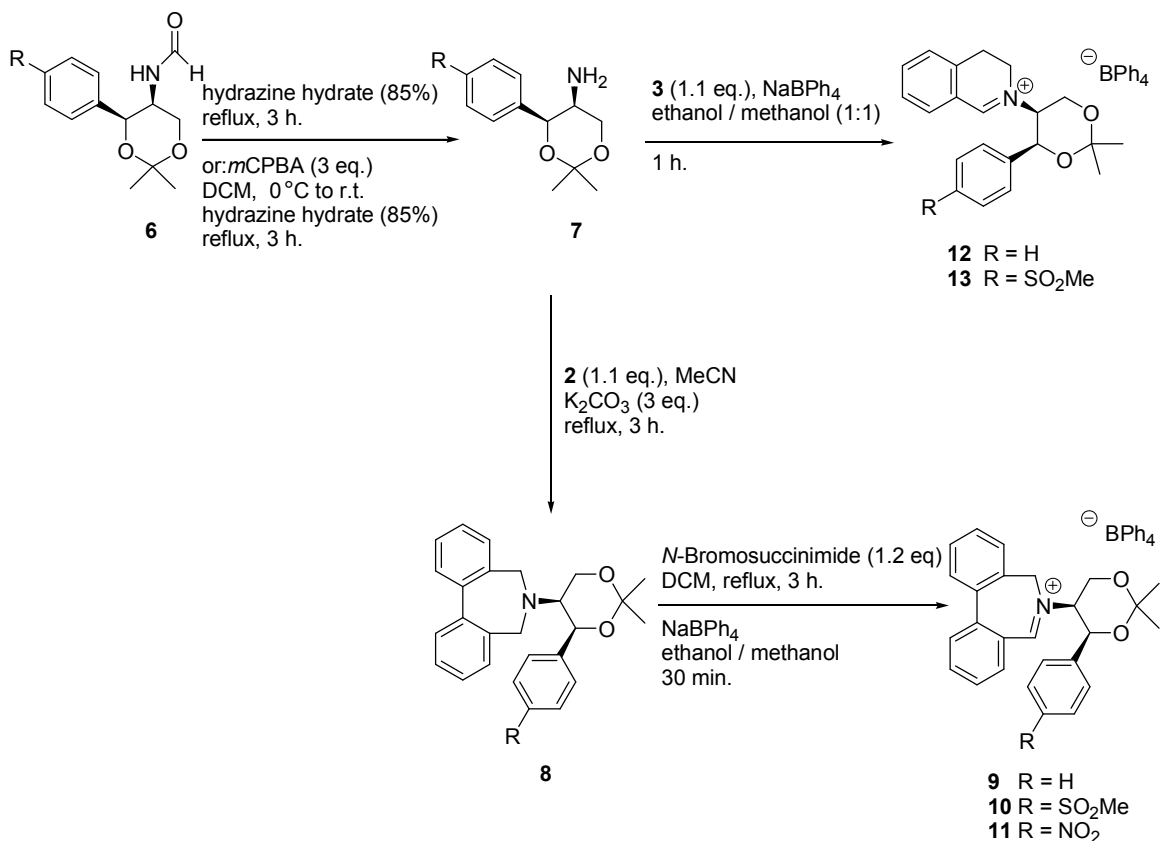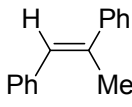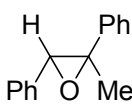
Scheme 35 Catalyst Synthesis

For compounds **9-11**, the diol-protected amine **7** undergoes reaction with backbone **2** (1.1 eq.), in the presence of potassium carbonate (3 eq.) in MeCN under reflux, giving **8** (93%). The last step in the synthesis is the addition of the counterion, this is carried out by refluxing compound **8** in DCM with *N*-bromosuccinimide (1.2 eq.), the solution is then reduced to a viscous consistency and ethanol added. Stirring the solution after the addition of sodium tetraphenylborate (1.1 eq.) in the minimal amount of MeCN followed and after work-up gave compounds **9-11** (Scheme 35).

Compounds **12** and **13** (Scheme 35) are synthesized again from amine **7** reacted with bromoaldehyde **3** (1.1 eq.) in ethanol at 0 ºC, before the addition of sodium tetraphenylborate (1.1 eq.) in the minimum amount of acetonitrile, the reaction was then stirred at room temperature. After work-up this gave compound **12** in a yield of 90% and **13** in 85% yield.

Firstly, epoxidation reactions were carried out using catalysts **9**, **10** and **13**, with different oxidants, in acetonitrile/water (Table 32).

Table 32 Epoxidation of trans-α-methylstilbene

Catalyst (10 mol%)

Na$_2$CO$_3$ (4 eq.), Oxone$^®$ (2 eq.)
MeCN / H$_2$O (2:3), 0 °C

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Entry	Catalyst	Time (h)	Conversion (%)[b]	ee (%)[c]
1	**9**	3	72	23
2[a]	**9**	24	100	21
3	**10**	3	44	13
4[a]	**10**	32	65	12
5	**13**	3	22	21

[a] reaction conditions: catalyst (10 mol%), Na$_2$CO$_3$.1.5H$_2$O$_2$ (10 eq.), MeCN / H$_2$O (2:3), 0 °C
[b] conversion determined by ^{1}H NMR spectroscopy by integration of alkene / epoxide signals
[c] enantiomeric excesses determined by chiral HPLC

These results show that after three hours catalyst **9** gives a higher conversion (72%) (entry 1) to the epoxide, whereas catalysts **10** and **13** (entries 3 and 5) give much lower conversions (44% and 22%, respectively). Increasing the reaction time, catalyst **9** gives 100% conversion, with 21% ee. Overall catalyst **9** gives the greater conversion and higher ees, with catalyst **13** giving the lowest ee values of 12% and 13% (entries 3 and 4).

Using catalyst **13**, an electrochemically driven catalytic epoxidation was carried out as a one-pot reaction. This was attempted by adding the organic phase (acetonitrile) with the catalyst, and the substrate into the cell with the 1 M sodium carbonate decahydrate solution, whilst stirring with an ultra-turrax at 6500 rpm, in an undivided cell, fitted with a BDD working electrode, and a Pt wire counter electrode, in an ice bath. A potential of

10.0 V was applied for one hour. After an hour no oxidation had occurred, and 100% substrate was retrieved. This could be because the electrolysis is only left for an hour whereas in other results (Table 32), the reactions have been left for longer. However, we believe that decomposition of the catalyst occurs by oxidation at the anode as we were unable to re-isolate the catalyst.

2.1.6   Epoxidation with Sodium Perborate

The conversion achieved using electro-synthesized percarbonate is higher than the conversion achieved using sodium perborate as the oxidant (Table 33, entries 3 and 4). Although slightly higher conversions were observed, when a different alkene is epoxidized (entries 1 and 2).

Table 33 Epoxidation using Sodium Perborate

Catalyst **9** (10 mol%)

MeCN / H_2O (2:3), 0°C

Entry	Alkene	Time (h)	Oxidant	Conversion (%)[a]	ee (%)
1[b]	Ph **15**	18	$NaBO_3.4H_2O$ (10 eq.)	24	33
2[b]		30	$NaBO_3.4H_2O$ (20 eq.)	63	31
3[c]	H, Ph **14** Ph, Me	18	$NaBO_3.4H_2O$ (10 eq.)	14	19
4[c]		30	$NaBO_3.4H_2O$ (20 eq.)	44	23

[a] conversion determined by ^{1}H NMR spectroscopy by integration of alkene / epoxide signals
[b] enantiomeric excesses determined by ^{1}H NMR spectroscopy with Eu(hfc)$_3$ as a chiral shift reagent
[c] enantiomeric excesses determined by chiral HPLC

With sodium perborate as the oxidant, the conversions achieved are not as good as those of 72% and 100% (Table 32, entries 1 and 2 respectively), obtained using Oxone®, and the Oxone® reaction takes less time than when sodium perborate is used as the oxidant, even with up to twenty equivalents (Table 33, entries 2 and 4).

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Leaving the reaction for longer (30 hours compared to 18), and doubling the equivalents of oxidant (entries 2 and 4), results in higher conversions of 63% and 44% (entries 2 and 4) to the corresponding epoxides, with similar ee values. For 1-phenylcyclohexene the epoxide is obtained in 31% ee after 30 hours with 20 equivalents of oxidant (33% after 18 h with 10 equivalents), and for *trans*-α-methylstilbene 23% ee (entry 4) is obtained after 30 hours (19% after 18 h).

The experiment was also attempted using perborate that had been generated by electrolysis. This was achieved by electrolysing a 1 M aqueous solution of boric acid whilst stirring with an ultra-turrax at 6500 rpm. This was carried out in an undivided cell, fitted with a BDD working electrode, and a Pt wire counter electrode, in an ice bath. A potential of 10.0 V was applied for one hour. Unfortunately, according to CV data obtained we were unsuccessful in actually preparing the perborate solution electrochemically.

2.1.7   Additive Affect on Epoxidations

In 2005 Bolm and Legros reported enantioselective sulfide oxidation reactions, involving a chiral iron catalyst and aqueous hydrogen peroxide as the oxidant. These conditions gave good yields and enantioselectivities.[11]

The use of additives is both a common and convenient method for increasing the efficiency of metal-catalysed reactions. The process of discovering which additive will prove most effective often requires trial and error. Bolm and Legros showed that the reaction outcome was highly dependent on the position of the substituent on the aryl ring of the additive. This could be fine tuned by using various commericially available substituted benzoic acids.

Using a *para*-substituted electron rich derivative such as benzoic acid led to the best results, increasing the yield of sulfoxidation from 36% to 63% (ee 59% to 80%) (Table 34, entries 1 and 2).[11]

Table 34 Bolm's Additive Affect on Sulfoxidation

H$_2$O$_2$ (35%, 1.2 eq.)
[Fe(acac)$_3$] (2 mol%)
4-methoxybenzoic acid (1 mol%)

DCM, r.t., 0 °C, 16 h.

(4 mol%)
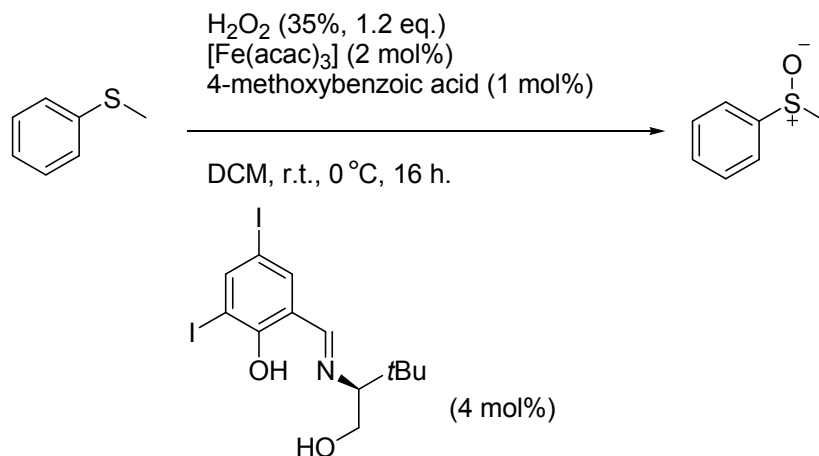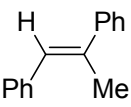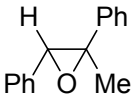
Entry	Yield (%)	ee (%)[a]
1[b]	36	59
2	63	80

[a] enantiomer ratios were determined by HPLC using chiral stationary phase
[b] without 4-methoxybenzoic acid

With the success of the Bolm and Legros system we decided to apply this to the epoxidation of α-methylstilbene using the iminium salt catalyst **9**. We have shown that without catalyst present no background epoxidation occurs with the additives (Table 35, entries 3, 5 and 7). Where the role of the additives is to assist in the epoxidation process *via* oxygen transfer.

Table 35 Additive Affect on Epoxidation

Catalyst **9** (10 mol%)
Additive (0.05 eq.)

$Na_2CO_3.1.5H_2O_2$ (20 eq.)
MeCN / H_2O (2:1), 0 °C

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Entry	Additive	Time (h)	Catalyst	Conversion (%)[a]	ee (%)[b]
1	-	20	Yes	84	15
2	4-methoxybenzoic acid	20	Yes	93	17
3	4-methoxybenzoic acid	20	No	0	-
4	2-biphenylcarboxylic acid	4	Yes	100	16
5	2-biphenylcarboxylic acid	4	No	0	-
6	diphenyl diselenide	4	Yes	100	17
7	diphenyl diselenide	4	No	0	-
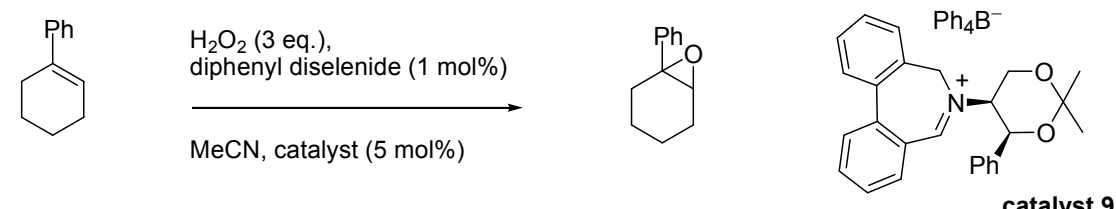
[a] conversion determined by ^1H NMR spectroscopy by integration of alkene / epoxide signals
[b] enantiomeric excesses determined by chiral HPLC

Initial results (Table 35) show that by using an additive in the reaction the conversion is improved from 84% (entry 1) without additive to 93-100% with additive (entries 2, 4, and 6). Although none of the additives appear to increase the ee values, as far as conversion is concerned both 2-biphenylcarboxylic acid (entry 4) and diphenyl diselenide (entry 6), give complete conversion within 4 hours, which is better than the 93% achieved with 4-methoxybenzoic acid in 20 hours (entry 2). Due to the low ee values the effect of additives in epoxidation reactions, where the oxidant is generated electrochemically has yet to be investigated.

2.1.8 Epoxidation using Hydrogen Peroxide

Mlochowski showed that it was possible to increase reaction rates by using diphenyl diselenide during oxidation reactions.[12] Therefore, following on from our own findings (Table 35), we looked at the effect of adding diphenyl diselenide into reactions with hydrogen peroxide.

Table 36 Epoxidation with H_2O_2 Temperature Study
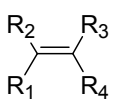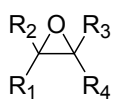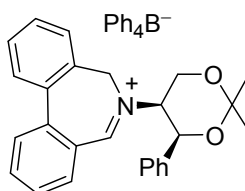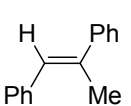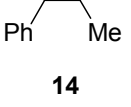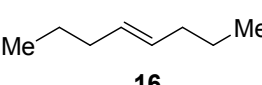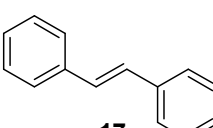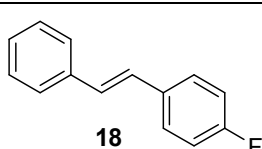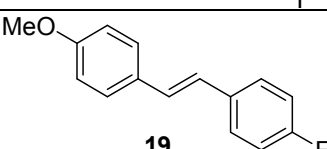
Entry	Temperature (°C)	Time (minutes)	Conversion[a] (%) (Yield (%))	ee (with TPPP) (%)
1	40	10	100 (97)	31 (50)
2	r.t.	35	100 (77)	50
3	0	90	100 (60)	47 (58)
4	-20	240	17 (13)	39
5	-40	240	12 (10)	34 (67)

[a] conversions determined by integration of proton signals on ^1H NMR spectra

Table 36 shows that we have been able to achieve ees of up to 47% (entry 3), when carrying out epoxidation of 1-phenylcyclohexene with hydrogen peroxide in the presence of diphenyl diselenide. Epoxidations carried with TPPP at 0 ºC (entry 3), where ees of 58% have been obtained, are almost comparable with those obtained with hydrogen peroxide at 47% (entry 3). Looking at the range of temperatures studied between 40 ºC and minus 40 ºC, the highest ees were obtained at 0 ºC (entry3), therefore it was decided to take 0 ºC as the optimum temperature for future reactions (Table 37).

Table 37 Epoxidation with H_2O_2

$$R_2R_3C=R_1R_4 \xrightarrow[\text{MeCN, 0 °C, catalyst (5 mol\%)}]{\substack{H_2O_2 \text{ (3 eq.),} \\ \text{diphenyl diselenide (1 mol\%)}}} R_2R_3\text{(epoxide)}R_1R_4$$

catalyst 9 (Ph_4B^-)

Entry	Substrate	Time (minutes)	Conversion[a] (%) (Yield(%))	ee (%)
1[b,c]	H, Ph / Ph, Me **14**	20	100 (68)	12
2[b]		120	100 (96)	15
3		240	79 (73)	18
4	Me ~~~ Me **16**	90	100 (85)	racemic
5	**17**	150	100 (78)	12
6	**18** (F)	240	100 (90)	30
7	MeO— **19** (F)	150	100 (78)	21

[a] conversions determined by integration of proton signals on ^1H NMR spectra
[b] DCM used in place of MeCN
[c] reaction carried out at r.t.

Table 37 shows that excellent conversions can be obtained when carrying out epoxidation reactions with hydrogen peroxide, diphenyl diselenide and catalyst in acetonitrile at 0 ºC. However, the ees that were obtained for these reactions were low at between 12% (entry 1) and 30% (entry 6) with the tested catalyst.

Although Table 37 shows good conversions, the ees obtained are low. This led us to develop a new catalyst based on previous research by Lacour's group.

In 2008 and 2009, Lacour et al published novel iminium salt catalysts that combined (R_a)-dimethylbiphenyl or (R_a)-5,5',6,6',7,7',8,8'-octahydronaphthyl cores with chiral exocyclic appendages derived from commercially available (*S*)- or (*R*)-3-3,dimethylbutan-2-amine and (*S*) or (*R*)-1-phenylpropan-1-amine. These were shown to be effective asymmetric epoxidation catalysts for unfunctionalized alkenes, with improved ees of up to 98% (Table 17, entry 3).

Lacour proposed that the larger the dihedral angles θ and Φ around the central bond joining the aromatic rings (Figure 10) are, the stronger is the stereocontrol of the reaction by the biaryl axis over the exocyclic appendage. Having a larger θ and Φ angle means that the biaryl axis is predominant, whereas if the dihedral angles θ and Φ are smaller then the exocyclic appendage is predominant (Figure 10). This should allow us stronger stereocontrol over the reactions.

In 2006, Lacour et al showed that both amines and iminium ions behaving as effective catalysts for the enantioselective epoxidation of unfunctionalized olefins, achieving up to 83% ee.[13]

Catalyst **25** (Scheme 37) was synthesized from binaphthol, where the first step was triflate protection of the alcohol groups, carried out by reacting the diol with triflic anhydride (2.2 eq.) and pyridine (2.5 eq.) in DCM at 0 °C for twenty hours, giving the bistriflate **20** (74%) (Scheme 36). Following this with a carbonylation on compound **20** under carbon monoxide at 80 °C, 30 psi, in the presence of palladium acetate (15 mol%), 1,3-bis(diphenylphosphino)propane (15 mol%) and diisopropylethylamine (4.4 eq.) in methanol and dimethyl sulfoxide, a 82% yield of 21 is achieved (Scheme 36).

A reduction of **21** with lithium aluminium hydride (4 eq.) in ethanol, gives **22** (96%), which is then refluxed in hydrobromic acid (48%), giving **23** (72%) (Scheme 36).

The new catalyst backbone **23**, then forms a new amine **24** (Scheme 37) on reactions with amine **7** (1.1 eq.) and potassium carbonate (3 eq.) in MeCN under reflux. The last step to obtaining the new catalyst reacts **24** firstly with N-bromosuccinimide (1.2 eq.) in DCM under reflux, before being reduced and dissolved in ethanol. Sodium tetraphenylborate (1.1 eq.) is then added in the minimum amount of MeCN to the solution and stirred at room temperature, after work-up resulting in catalyst **25** (76%).
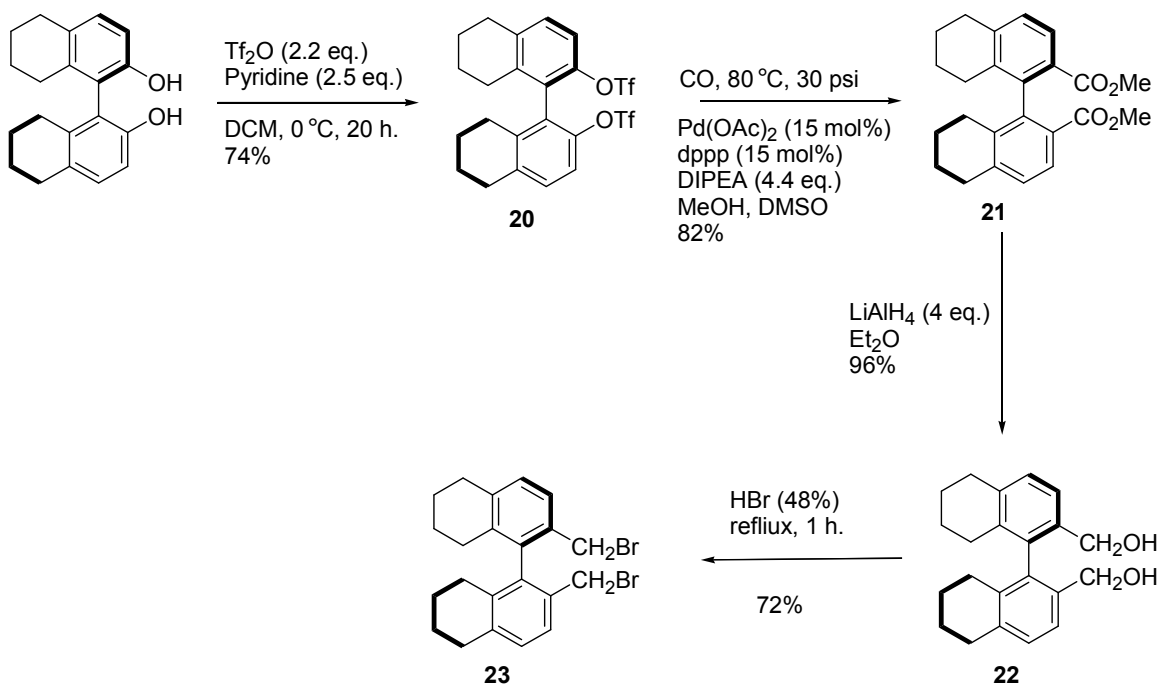
Scheme 36 Novel Catalyst Synthesis, Part 1
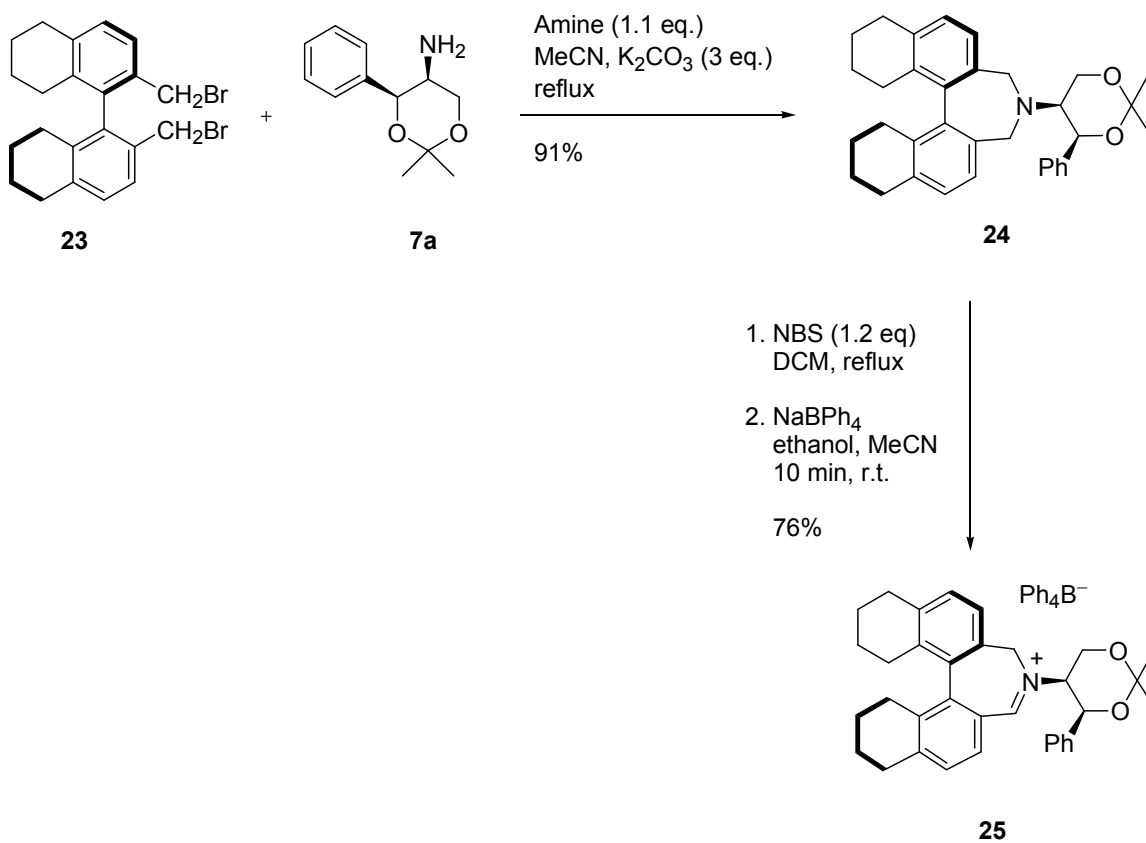
Scheme 37 Novel Catalyst Synthesis, Part 2
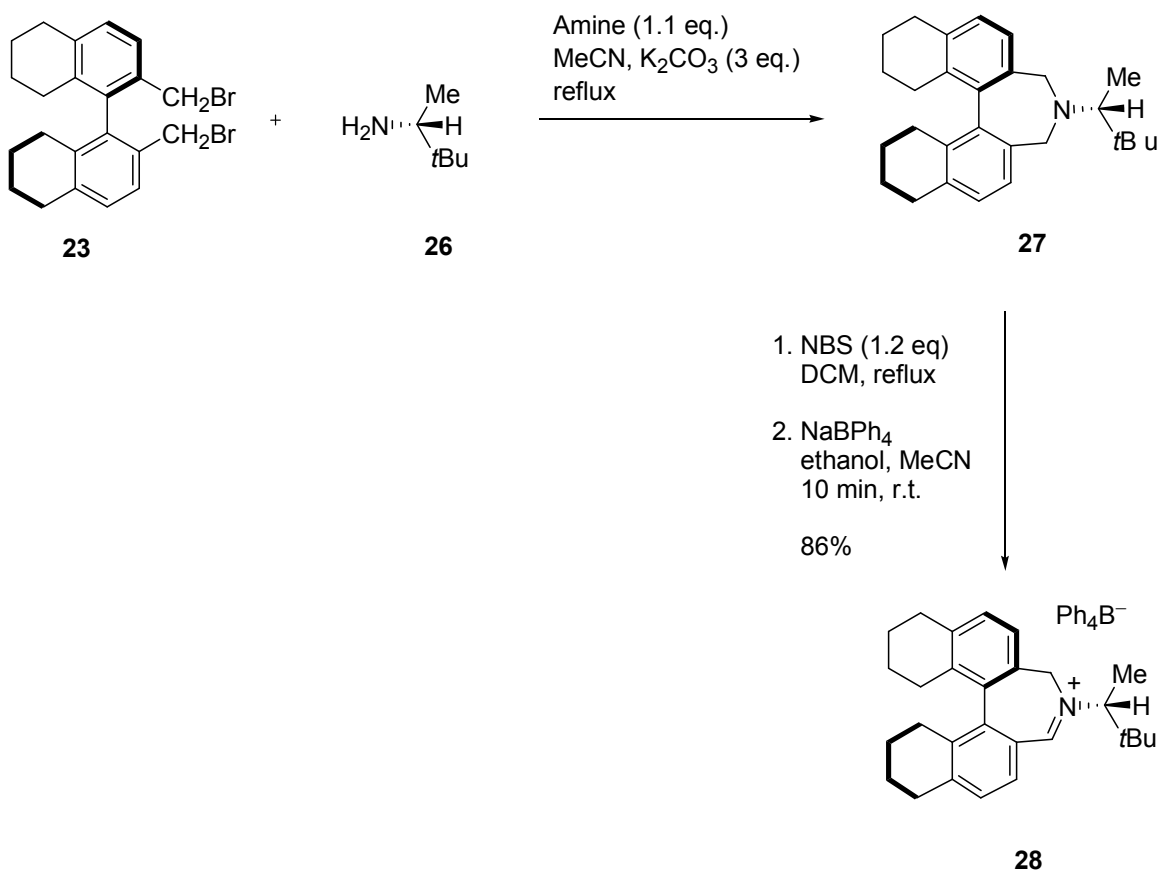
Scheme 38 Synthesis of Novel Catalyst 28

A study is reported in which a range of amines and directly related iminium cations were synthesized, and tested as catalysts for enantioselective epoxidation of olefins (Table 38).[13]

Table 38 Lacour's Counterion Study
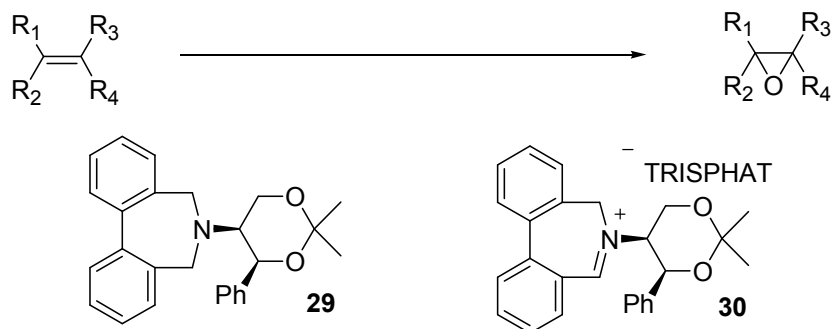
Entry	Substrate	Conditions	Time (minutes)	Catalyst	Conversion (%)	ee (%)
1[c]	Ph	A[a]	15	**29**	90	53
2		B[b]	120	**29**	78	26
3[c]		A[a]	15	**30**	75	54
4		B[b]	120	**30**	81	54
5[c]	Ph	A[a]	15	**29**	50	51
6		B[b]	120	**29**	66	23
7[c]		A[a]	15	**30**	36	57
8		B[b]	120	**30**	85	68

[a] conditions A: catalyst 1 (5 mol%), Oxone $^{®}$(2 eq.), NaHCO$_3$ (5 eq.), MeCN/H$_2$O (10:1), 0 °C
[b] conditions B: catalyst 2 (5 mol%), 18-crown-6 (2.5 mol%), Oxone $^{®}$(1.1 eq.), NaHCO$_3$ (4 eq.), DCM/H$_2$O (3:2), 0 °C
[c] complete conversion was observed in 2 h along with product decomposition

Two different sets of epoxidation conditions (A: CH$_3$CN/NaHCO$_3$/H$_2$O, B: CH$_2$Cl$_2$/NaHCO$_3$/18-Crown-6/H$_2$O) and a number of different prochiral trisubstituted unfunctionalized alkenes were studied.   Amine **29** performed better in terms of conversion and enantiomeric excesses in CH$_3$CN/H$_2$O and iminium salt **30** gave better overall results in biphasic CH$_2$Cl$_2$/H$_2$O. Up to 51% ee (Table 38, entry 5) and 68% ee (Table 38, entry 8), were obtained for the epoxide of 4-phenyl-1,2-dihydronaphthalene with amine **29** and iminium salt **30** respectively.

As making the amines requires less synthetic steps than the preparation of the iminium salts, it is therefore advantageous to perhaps use these reagents for oxidation reactions.

Overall, Lacour reported that all three amines tested performed as well as their iminium salts as catalysts for the enantioselective epoxidation of alkenes, particularly in MeCN/H_2O.

Based on Lacour's catalysts with (Ra)-5,5',6,6',7,7',8,8'-octahydronaphthyl cores and the study by Lacour in 2006, we developed and tested a new iminium catalyst and amine.

With the newly developed catalyst **25** (Scheme 37) under the same reaction conditions as used in Table 37 it was possible to obtain 76% conversion to epoxide in 85% ee. This result is superior to that achieved with the biphenyl catalyst **9** under the same reaction conditions using H_2O_2, giving 100% conversion to epoxide but with a 47% ee. The same reaction conditions but using Oxone® as the oxidant, gave a 58% ee.
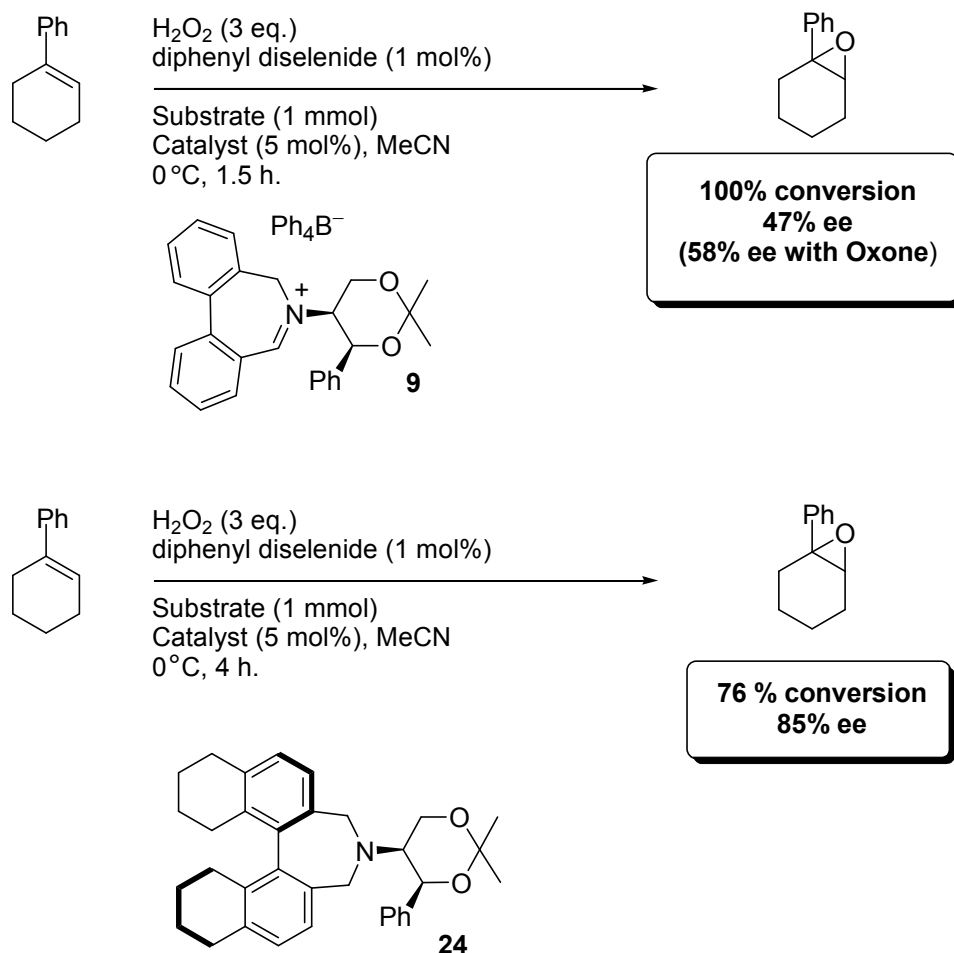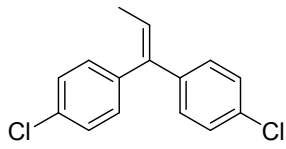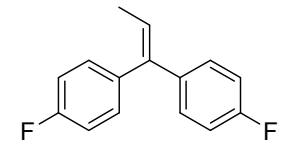
Figure 17 Epoxidation with H$_2$O$_2$ and New Catalyst

After obtaining increased enantioselectivity with the newly developed catalyst, a number of other catalysts with the same structural backbone were also synthesized and used for the epoxidation of 1-phenylcyclohexene with Oxone® (Table 40).

Using amine catalyst **24** with H$_2$O$_2$ (Figure 17), gives us a high epoxidation conversion of 97% in 2 hours with a 88% ee (Table 40, entry 2). If the same reaction is carried out with the iminium salt catalyst present (Table 40, entry 1), then the ee is the same at 88% in two hours with a conversion of 75% to epoxide.

As the test reaction with our newly developed catalyst gave us a good ee (85%) for the epoxidation of 1-phenylcyclohexene, it was also tried with two other substrates (Table 39). In both instances (Table 39, entries 1 and 2), we see complete conversions in under two hours, with ees of 80% for the epoxide of 1,1-di(4-chlorophenyl)prop-1-ene (entry 1) and a ee of 86% for the epoxide of 1,1-di(4-fluorophenyl)prop-1-ene (entry 2).

Table 39 Epoxiation with H_2O_2 and Catalyst 25

Entry	Substrate		Time (minutes)	Conversion[a] (%) (Yield(%))	ee (%)
1		**31**	90	100 (97)	80
2		**32**	100	100 (98)	86

[a] conversions determined by integration of proton signals on ^{1}H NMR spectra

If a catalyst with a different group attached to the backbone (Table 40, entry 3) is used with Oxone®, then a high ee of 85% in four hours is achieved. Although we have shown the best ee obtained for one-pot epoxidation reactions of 1-phenylcyclohexene to be 44%, the new Page group catalysts based on Lacours catalysts, give us better ees with Oxone® as the oxidant (Table 40). The new Page group catalysts (Table 40) give us up to 88% ee (entry 1) in 2 hours with Oxone® (2 eq.), Na_2CO_3 (4 eq.) and catalyst (5 mol%) in MeCN/H_2O at 0 °C, if the catalysts have a BINAP based backbone. Results also show that the catalyst works as well if we do not have the counter ion present on the catalyst

(entry 2) giving us 88% ee with an epoxide conversion of 97% in 2 hours. Changing the substituents on the nitrogen to a more bulky group also gives us good conversion (76%) and an ee of 85% (entry 3).

The presence of bulky groups off the backbone of these catalysts could possibly enable high ees by helping to direct the angle of epoxidation.

Table 40 Oxone® Epoxidation

Oxone® (2 eq.), Na$_2$CO$_3$ (4 eq.)
Catalyst (5 mol%)

MeCN/H$_2$O (1:1), 0°C
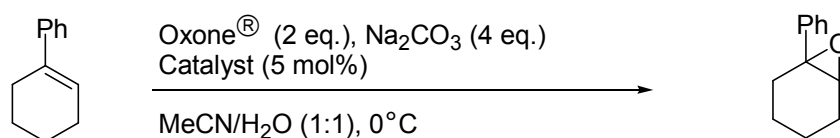
Entry	Catalyst	Time (h)	Conversion (%)[a]	ee (%)
1	**25**	2	75	88
2	**24**	2	97	88
3	**28**	4	76	85

[a] conversions determined by integration of proton signals on ^{1}H NMR spectra

2.1.9 Electrochemical Epoxidation

Following on from the epoxidation work using commercial sources of hydrogen peroxide, epoxidation reactions were carried out to see if the generation of an oxidant electrochemically would enable successful oxidation.

Table 41 shows that by using a 1 M solution of $Na_2CO_3.10H_2O$, where the pH has been lowered to pH 6 by slow addition of hydrochloric acid before being placed into a undivided cell fitted with a BDD anode and platinum wire counter electrode, alkene (1 mmol) and diphenyl diselenide (1 mol%) that after 2.5 hours complete conversion to the epoxide is observed (entry 3), when 10.0 V is passed through the cell, at 0 °C.

A study carried out for sulfoxidation reactions showed that the lower the pH the higher the conversion to the sulfoxide. Although the reactions are successful at pH 6, better results are actually obtained at even lower pH, however pH 6 was used for these reactions as the conditions are mild and allow for a range of substrates to be tested at a future date.

Although previous epoxidation studies have shown that diphenyl diselenide increases the alkene to epoxide conversion rate, in the case of electrochemical reactions, the difference in conversion after two hours with diphenyl diselenide (77%, entry 2), and without (67%, entry 3) is minimal.

Table 41 shows that if we increase the surface area of the BDD electrodes then this produces more oxidant and enables the reaction to proceed faster, giving 100% epoxide in two hours.

Table 41 One-Pot Epoxidation Study

1. 1 M $Na_2CO_3.10H_2O$ (50 mL)
   pH adjusted to pH 6

2. substrate (1 mmol), MeCN,
   diphenyl diselenide (1 mol%)
3. 0°C, 10.0 V
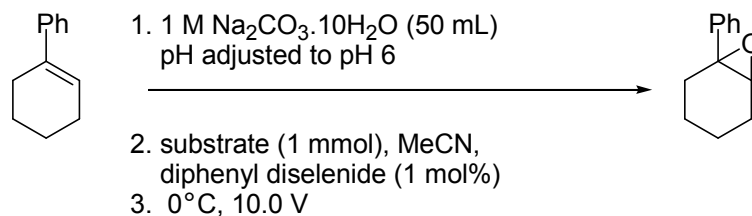
Entry	Time (minutes)	Conversion (%)[a]
1	60	37
2	120	77
3	150	100
4[b]	120	100
5[c]	120	67
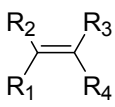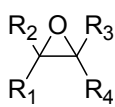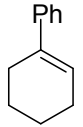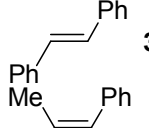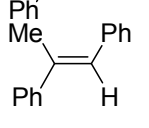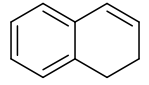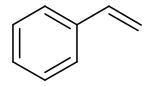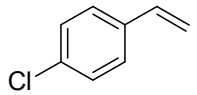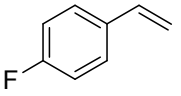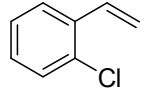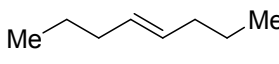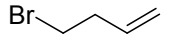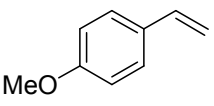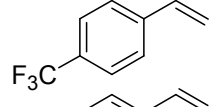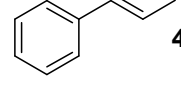
[a] conversions determined by integration of proton signals on ^{1}H NMR spectra
[b] larger surface on BDD electrode
[c] background reaction without diphenyl diselenide

The electrochemical reactions, although slow, do give us conversion to the epoxide.   The same conditions were applied to the epoxidation of a range of olefins.

Table 42 shows that it is possible to apply these conditions to different alkenes, and still achieve 100% conversion to epoxides, using styrene with different electron-withdrawing (entries 6 and 7), electron-donating (entry 11) groups and terminal alkenes (entry 10).

Table 42 One-Pot Epoxidation

R₂R₃C=CR₁R₄ alkene →

1. 1 M $Na_2CO_3 \cdot 10H_2O$ (100 mL)
   pH adjusted to pH 6
2. substrate (1 mmol), MeCN
3. 10.0 V, 0 °C

→ epoxide R_2-R_3 / R_1-R_4 with O

Entry	Substrate	Time (minutes)	Conversion (%)[a]	Yield (%)[b]
1	Ph-cyclohexene **30**	180	100	>99
2	stilbene (Ph, Ph) **33**	180	98	95
3	(Me, Ph, Ph, H) **15**	180	100	95
4	dihydronaphthalene **34**	<5	100 (diol)	>99 (diol)
5	styrene **35**	30	100	92
6	4-Cl-styrene **36**	15	100	95
7	4-F-styrene **37**	15	100	96
8	2-Cl-styrene **38**	15	100	98
9	Me...=...Me **16**	5	100	98
10	Br-...-= **39**	60	100	91
11	MeO-styrene **40**	15	100	95
12	F_3C-styrene **41**	<5	(100% diol)	88% (diol)
13	β-methylstyrene **42**	25	100	94

[a] conversion determined by integration of proton signals on ^1H NMR spectra
[b] isolated yield

109

Having observed complete conversion for a range of alkenes to epoxides under out newly developed one-pot epoxidation, the same reaction conditions were used with a selection of the Page group catalyst. Table 43 entry 1 shows that the best ees are obtained with the biphenyl based catalyst gave a 90% epoxide conversion in 7 hours with a 44% ee, if the same reaction is carried out without the diphenyl diselenide (entry 2) then we do not see any change in the ee at 46%. The other catalysts tested gave either lower ees or racemic compounds.

Table 43 Chiral One-Pot Epoxidation

Reaction scheme:

1. 1 M $Na_2CO_3 \cdot 10H_2O$ (50 mL)
   pH adjusted to pH 6

2. substrate (1 mmol)
   catalyst (5 mol%) in MeCN (10 mL)

3. 0°C, 10.0 V, 2 h
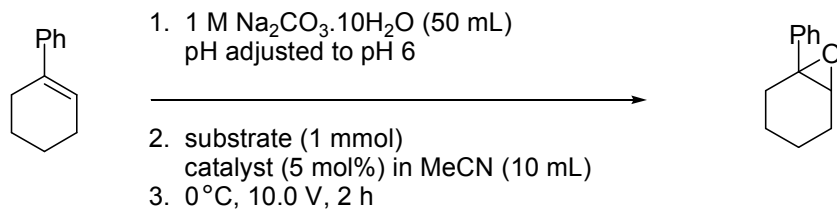
Entry	Catalyst	Conversion (%)[a]	ee (%)
1	**9**	90	44
2[b]	**9**	89	46
3[c]	**12**	42	15
4	**12**	89	20
5	**13**	50	9
6	**28**	100	racemic

[a] conversions determined by integration of proton signals on ^1H NMR spectra

[b] background reaction without diphenyl diselenide

[c] catalyst not dissolved in acetonitrile

2.2 <u>Baeyer-Villiger Oxidation</u>

To date, the main methodology used to carry out the Baeyer-Villiger reaction, requires corrosive acids such as trifluoroacetic acid, that are not 'green' or acetic acid (Figure 18).[14, 15]
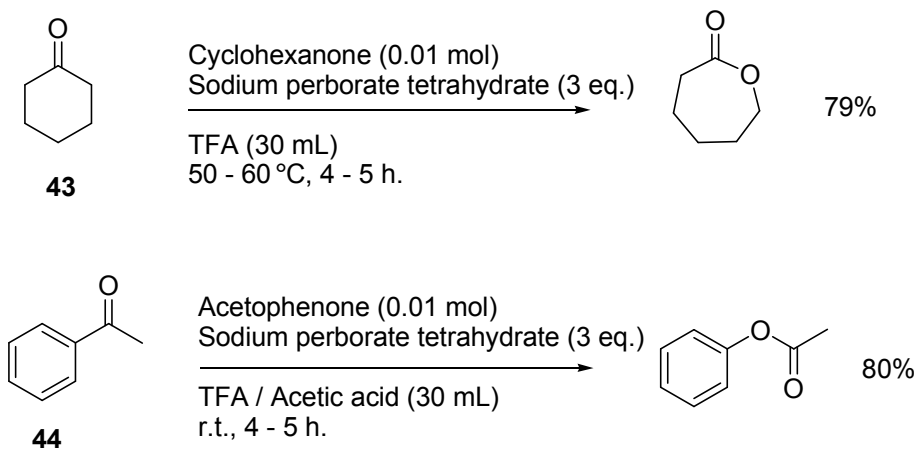
Figure 18 Baeyer-Villiger Reaction Conditions

We started our study using sodium percarbonate as the oxidant, but the possibility of the reaction proceeding in the presence of water and solvent seems to be a problem when the reactions are repeated. With an aqueous / organic phase (1:1), the Baeyer-Villiger reaction yields only starting material when trying an oxidation on cyclohexanone (Table 44), in either diethyl ether and water, or acetonitrile and water.

Table 44 Baeyer-Villiger Oxidation in Different Solvent / Water systems

Reaction scheme: cyclohexanone → ε-caprolactone; conditions: $Na_2CO_3.1.5H_2O_2$ (4 eq.), X, solvent / H_2O (1:1), 4 h.
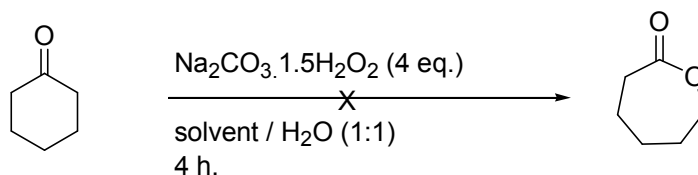
Entry	Solvent system	Temperature (°C)	Conversion (%)[a]
1	$Et_2O : H_2O$	0	0
2	$Et_2O : H_2O$	r.t.	0
3	$MeCN : H_2O$	0	0
4	$MeCN : H_2O$	r.t.	0

[a] conversion determined determined by ^1H NMR spectroscopy by integration of proton peaks.

A further study, involved screening various solvents for the Baeyer-Villiger oxidation, including: dichloromethane, water, dilute sulfuric acid, acetonitrile and methanol, however these experiments gave no conversion to the corresponding esters.

Other than TFA and potassium perborate tetrahydrate, the only other reaction conditions to date that work for Baeyer-Villiger oxidations are with Oxone® or *m*CPBA (Figure 19). Unfortunately, TFA is not considered a green reagent, so therefore is not useful in a system where the aim is to make the reaction conditions more environmentally friendly. It also does not work if water is added into the reaction, so is therefore no good if the oxidant is generated using electrolysis, because the solution contains water. As TFA only works with potassium perborate as the oxidant, these conditions are unsuitable for electrochemistry, because as previously mentioned we were unsuccessful in our attempted to generate perborate using electrolysis.
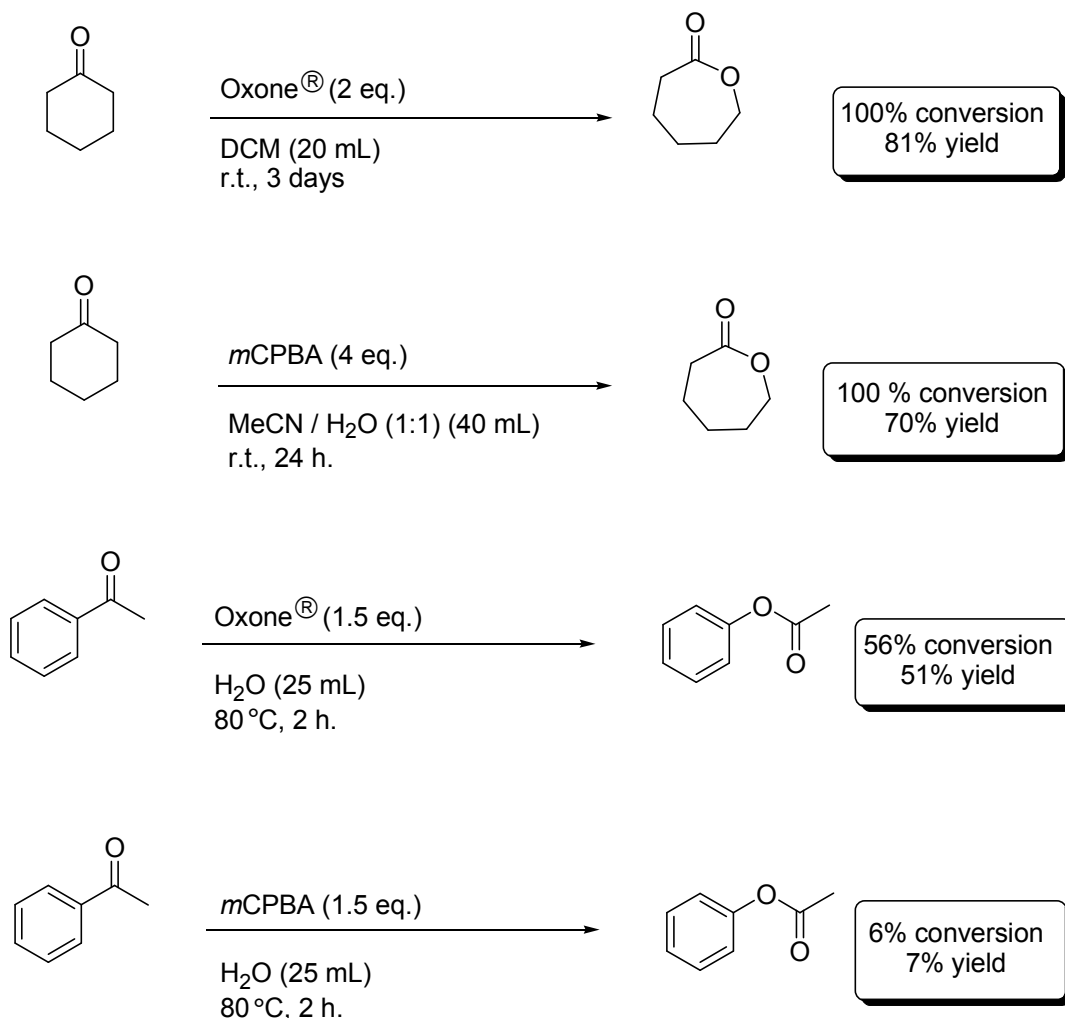
Figure 19 Successful Baeyer-Villiger Oxidations

Further studies, looking at solvent / water mixtures for the reaction, showed that some conversion was seen after 3 days, so a series of experiments were carried out under the same conditions where the pH of the sodium percarbonate solution was altered by adding dilute hydrochloric acid, before the addition of the organic phase and substrate to find the optimum condition under which the reaction would proceed (Table 45).

Table 45 Baeyer-Villiger Oxidation at pH 3-12

Cyclohexanone (5 mmol)
Na$_2$CO$_3$.1.5H$_2$O$_2$ (4 eq.)

MeCN / H$_2$O (1:1) (40 mL)
r.t., 3 days
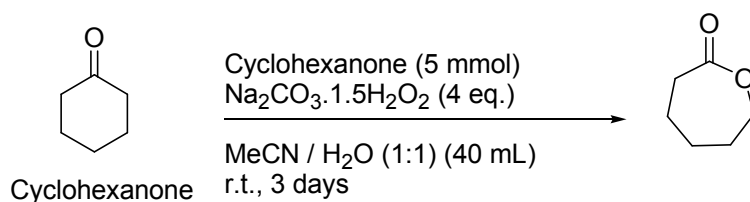
Entry	pH	Conversion (%)[a]
1	3	2
2	4	6
3	5	10
4	6	4
5	7	1
6	8	1
7	9	14
8[b]	9	11
9[b,c]	9	0
10	10	5
11[d]	12	10

[a] conversion determined determined by ^{1}H NMR spectroscopy by
  integration of proton peaks
[b] reaction left for 7 days
[c] reaction conditions: acetophenone (5 mmol), Na$_2$CO$_3$.1.5H$_2$O$_2$ (4 eq.),
  MeCN / H$_2$O (1:1) (40 mL), r.t., 7 days
[d] reaction left for 8 days

After a minimum of three days, conversions for the Baeyer-Villiger were still low (Table 45), but the highest conversion of 14% was seen at pH 9 (entry 7), so the reaction was repeated at this pH, but left for seven days (entry 8), and tried with another substrate

(entry 9). However it appears that the conversion is not improved on leaving the reaction longer and acetophenone was not converted to the ester (entry 9), with only starting material present at the end of the reaction.
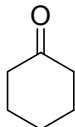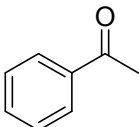
Although the Baeyer-Villiger oxidation has yet to be tried under any of the reported conditions, using electrochemically derived percarbonate as the oxidant. A one-pot synthesis has been attempted, in which the organic phase with the catalyst (in acetonitrile), and the substrate have been added into the cell with the 1 M sodium carbonate solution, and then 10.0 V applied for one hour. However, no oxidation occurs, and 100% substrate is retrieved at the end of the reaction. This could be because the electrolysis is only left for one hour, whereas in other results (e.g.Table 45), the reactions were left for three days.

Continuing on with reactions using commercially available sodium percarbonate, where the solution has been adjusted to pH 9 by the slow addition of hydrochloric acid, with 18-Crown-6 acting as a phase transfer catalyst. After 3 days, conversion of 82% with a 72% yield (Table 46, entry 1) for formation of caprolactone via a Baeyer-Villiger reaction was obtained. Leaving the reaction for a longer time period (Table 46, entry 4) 88% conversion and a 74% yield were obtained, however it has not been possible to improve upon this result, even after 12 days (Table 46, entry 6) no further improvement is seen. If the same reaction is carried out without adjusting the pH (Table 46, entry 2) then no conversion is seen, this is also the case if dichloromethane is used as the solvent instead of acetonitrile (Table 46, entry 3).

It is possible that the percarbonate decomposes after a certain time, therefore the same reaction was repeated but starting with only two equivalents of sodium percarbonate, and after seven days four more equivalents of percarbonate were added. This again gives the same conversion and yield (Table 46, entry 7) even after 14 days. Readjusting the pH again after the second addition of percarbonate also showed no improvement (Table 46, entry 8).

Similar reactions have also been carried out using acetophenone, but changing the solvent, not adjusting the pH and adding more percarbonate after seven days, showed no improvement in conversion or yield (Table 46, entries 9-12).

Table 46 Baeyer-Villiger Reaction Condition Study

Entry	Substrate	Reaction Time (Days)	Conversion (%)[a]	Yield (%)
1		3	82	72
2[b]		3	0	-
3[c]		3	0	-
4		6	88	74
5[c,d]		6	0	-
6		12	88	75
7[e]		14	88	74
8[f]		14	88	73
9		3	15	12
10[c]		3	0	-
11		6	19	15
12[c,d]		6	0	-

[a] conversion determined by ^{1}H NMR spectroscopy by integration of proton peaks
[b] no pH change
[c] DCM used instead of MeCN
[d] 18-Crown-6 (10mol%) added in MeCN (10 mol%)
[e] $Na_2CO_3.1,5H_2O_2$ (2 eq.) added after 7 days, and again after 4 more days
[f] $Na_2CO_3.1,5H_2O_2$ (2 eq.) added after 7 days, and again after 4 more days, and pH adjusted to pH9 after each addition by adding HCl
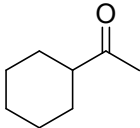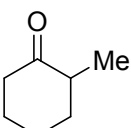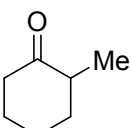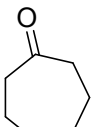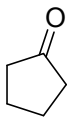
The best conditions found to date for the Baeyer-Villiger reaction were used for a number of other substrates (Table 47, entries 1-5), although unfortunately the reaction only appears to work under these conditions for cyclohexanone and acetophenone.
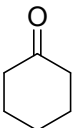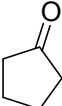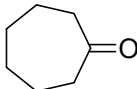
Table 47 Baeyer-Villiger Reaction of Cyclic Substrates
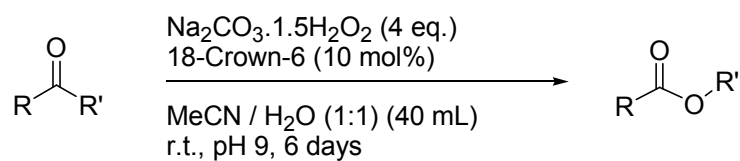
Entry	Substrate	Conversion (%)[a]	Yield (%)
1		25	20
2		53	43
3		5	-
4		0	-
5		0	-

[a] conversion determined by ^{1}H NMR spectroscopy by integration of proton peaks

Carrying out the reaction with a solution of electrochemically generated percarbonate, where the solvent is added with the substrate and 18-Crown-6 after adjusting the pH of the solution, only starting material is recovered after 7 days. Trying the reaction as a one-pot system has also proven to be unsuccessful in forming the corresponding lactone.

Table 48 Baeyer-Villiger without Organic Phase
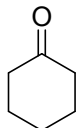
$$R \overset{O}{\underset{}{\underset{}{\parallel}}} R' \xrightarrow[\substack{H_2O\ (20\ mL)\\ r.t.,\ pH\ 9}]{\substack{Na_2CO_3.1.5H_2O_2\ (4\ eq.)\\ 18\text{-Crown-6}\ (10\ mol\%)}} R \overset{O}{\underset{}{\underset{}{\parallel}}} O^{\diagup R'}$$

Entry	Substrate	Reaction Time (Hours)	Conversion (%)[a]	Yield (%)
1		24	0	-
2[b]		24	0	-
3		24	0	-
4		24	0	-

[a] conversion determined by ^{1}H NMR spectroscopy by integration of proton peaks
[b] no 18-Crown-6

The reaction has been tried without solvent, both with and without 18-Crown-6 (Table 48, entries 1 and 2), and with other substrates (Table 48, entries 3 and 4), but has been unsuccessful in twenty-four hours.

Table 49 One-pot Baeyer-Villiger with Electrochemically Generated Persulfate

$$R \overset{O}{\underset{}{\wedge}} R' \xrightarrow[\text{0 °C, 1.0 A applied}]{\text{2.5 M } H_2SO_4 \text{ (100 mL)}} R \overset{O}{\underset{O}{\wedge}} R'$$

Entry	Substrate	Reaction Time (Hours)	Conversion (%)[a]	Yield (%)
1		6	0	-
2[b]		6	0	-

[a] conversion determined by ^{1}H NMR spectroscopy by integration of proton peaks
[b] persulfate generated and neutralised before addition of substrate

As the percarbonate system has been unsuccessful for the Baeyer-Villiger reaction, it was decided to try with an electrochemically generated solution of persulfate, where this is achieved by applying a potential of 1.0 A to 100 mL of a 2.5 M solution of sulfuric acid at 0 °C for one hour. The solvent then is or isn't added depending on the reaction conditions with the substrate. These reactions are then stirred at 0 °C.

Table 49 shows that if the reaction is carried out as a one-pot system (Table 49, entry 1), or by generation of the persulfate solution first (Table 49, entry 2), then without any solvent no conversion is seen under any of these conditions after six hours.

The reaction has been tried using electrochemically generated persulfate both with 18-Crown-6 acting as a phase transfer catalyst, as this has shown improvement compared to the results obtained using the percarbonate system, and diphenyl diselenide has also been tried. But no conversion is seen after six days at room temperature, even in the presence of solvent (Table 50, entries 1-3).

Table 50 Baeyer-Villiger with Electrochemically Generated Persulfate

1. 2.5 M H_2SO_4
   0 °C, 1 h, 1.0 A applied

2. MeCN / H_2O (1:1) (100 mL:100 mL)
   r.t. , 6 days
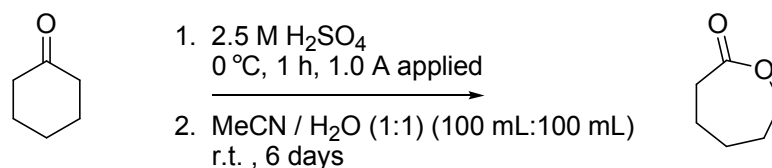
Entry	Additive (10 mol%)	Conversion (%)[a]
1	18-Crown-6	0
2[b]	18-Crown-6	0
3	diphenyl diselenide	0

[a] conversions determined by integration of proton signals on ^{1}H NMR spectra
[b] one-pot reaction

Carrying out a one-pot Baeyer-Villiger reaction, where the persulfate oxidant is generated electrochemically from 2 M sulfuric acid, in the presence of solvent at room temperature and no phase transfer catalyst, again results in only starting material being recovered after 7 days.

Of all the conditions tried to date, it has yet not been possible to find a suitable environment for carrying out these reactions or for applying it to a number of different substrates.

2.3 <u>Sulfoxidation</u>

2.3.1 Sulfoxidations with Sodium Percarbonate

Although our previous work has been concerned with electrochemical epoxidation reactions, no studies for sulfoxidation reactions have been attempted under similar conditions. Therefore our study looked at the optimum conditions for these reactions using the Page catalysts previously described. To begin with, the achiral catalyst **45** was employed (Figure 20).
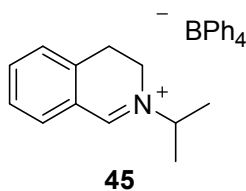
Figure 20 Achiral Iminium Salt 45

Table 51 Optimising Sulfoxidation Conditions
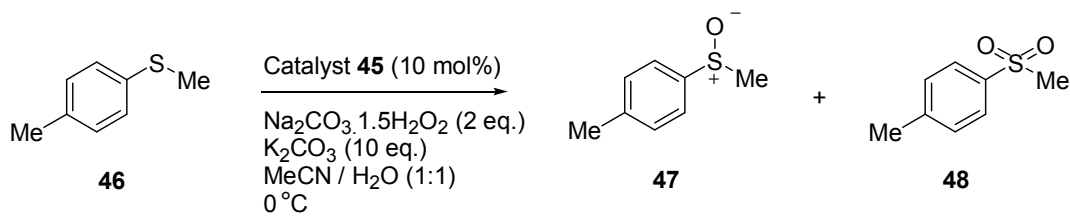
Entry	Time (h)	Ratio (%)[d]		
		MePhSMe 46	MePhSO$_2$Me 48	MePhSOMe 47
1[a]	20	-	100	-
2[a,b]	20	-	100	-
3[c]	4	70	12	18
4[b,c]	4	-	-	100
5	4	97	-	3
6[b]	4	87	-	13
7	24	86	3	9
8[b]	24	87	-	13

[a] reaction conditions: catalyst **45** (10 mol%), Na$_2$CO$_3$.1.5H$_2$O$_2$ (5 eq.), MeCN / H$_2$O (1:1), 0°C
[b] background reaction carried out under same conditions without catalyst
[c] reaction conditions: catalyst (10 mol%), Na$_2$CO$_3$.1.5H$_2$O$_2$ (2 eq.), K$_2$CO$_3$ (5 eq.), MeCN / H$_2$O (1:1), 0°C
[d] conversions determined by integration of proton signals on ^{1}H NMR spectra

Table 51 shows that without any base present in the reaction (entries 1 and 2), 100% conversion to sulfone is observed, and none of the desired sulfoxide is formed. On addition of five equivalents of K$_2$CO$_3$ (entries 3 and 4), the background reaction (entry 3) shows 18% sulfoxide is present without any catalyst which is relatively high, although under the same conditions with catalyst 100% conversion to the desired sulfoxide is observed (entry 4). On increasing the levels of base to 20 equivalents (entries 5 and 6), a much lower background reaction occurs (only 3%, entry 5), although the conversion with catalyst is also very low at 13%. As only 13% was obtained after four hours, the reaction

was left for twenty-four hours (entries 7 and 8). This shows the same sulfoxide conversion of 13%, with a higher background of 9% to the sulfoxide as well as 3% of the sulfone. Therefore it is possible that the reaction goes no further after four hours, and the optimum conditions are outlined in entry 4, although the background sulfoxidation is also at its highest under these conditions.

Using the optimum conditions (Table 51, entry 4), the same reaction was carried out with electrochemically-produced percarbonate. This was achieved in the same way as previously described for epoxidation. Once the percarbonate solution (100 mL) had been obtained, it was split into two equal portions, 50 mL of which was added to a separate solution of catalyst in acetonitrile at 0 °C, followed by the addition of the sulfide. The remaining 50 mL of percarbonate solution was used to carry out a background reaction without catalyst. Upon leaving this reaction stirring for twenty-four hours at 0 °C, the results in Table 52 were obtained. Under these conditions it was possible to obtain a conversion of 30% to the sulfoxide (entry 2) without any over oxidation to the sulfone. If the same reaction is carried out without any catalyst (entry 1), then we see a much lower conversion (6%).

Table 52 Sulfoxidation with Electrochemically-Produced Percarbonate
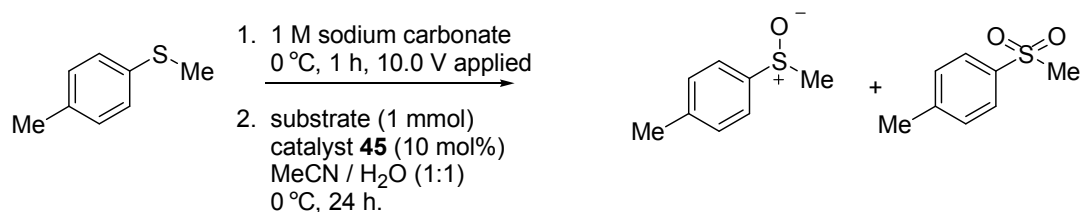
Entry	Conversion (%)[a]		
	MePhSMe	MePhSOMe	MePhSO$_2$Me
1[b]	94	6	-
2	70	30	-

[a] conversions determined by integration of proton signals on ^{1}H NMR spectrum
[b] background reaction carried out under the same conditions without catalyst

Although for epoxidation reactions it is known that electrochemically-generated percarbonate will not transfer the oxygen to the iminium salt in any solvent other than acetonitrile, a range of other solvents such as; dichloromethane, chloroform, methanol and toluene under the same conditions as used previously (Table 52, entry 2) were tried, but no sulfoxide or sulfone was observed after twenty-four hours.

The optimum conditions (Table 51, entry 4) so far, were used with various chiral catalysts to improve the enantioselectivity and evaluate reactivity. Table 53 shows sulfoxidations carried out using commercially available sodium percarbonate, with catalysts **9** and **13**. Using catalyst **13** a good conversion to sulfoxide is possible of 51% but only in 4% ee (Table 53, entry 2). In comparison to this, catalyst **9**, gives 80% conversion in eighteen hours with 9% of sulfone present, and in 20% ee (entry 1). Using catalyst **49**, again under the same reaction conditions but for twenty-four hours, only 16% of sulfoxide is seen in 21% ee, but no sulfone, this is also promising but the conversion is very low.

Table 53 Enantioselective Sulfoxidation with Catalysts 9, 13 and 49

Entry	Catalyst	Time (h)	Ratio (%)[a]			ee (%)
			MePhSMe	MePhSO$_2$Me	MePhSOMe	
1	**9**	18	11	9	80	20
2	**13**	4	40	9	51	4
3	**49**	24	84	0	16	21

[a] conversions determined by integration of proton signals on ^{1}H NMR spectra

These are promising results for initial attempts. Using a range of chiral catalysts, the sulfur oxidation was tried using a solution of percarbonate that had been generated by electrolysis of a 1 M solution of Na$_2$CO$_3$.10H$_2$O for one hour (Table 54). The results in Table 54 show that the best ee of 20% was achieved using catalysts **9** and **13** (entries 2 and 3), where the conversions were 11% and 30% respectively. Conversions using catalyst **49** and **11** were 11% and 15%, respectively (entries 4, and 5).

If the reaction is only left for five hours instead of fifteen (entries 1 and 2), then a drop in conversion occurs (from 29% to 11%, and results in a 20% ee). Because of this, other sulfoxidations (entries 2-5) were carried out with only 25 mL of the percarbonate solution instead of 100 mL, to lower the amount of percarbonate present in the reaction solution, and hence reduce over oxidation to the sulfone.

In the shorter time period (entry 1), 10% of the sulfone was also present, whereas in the case of all the other reactions tried no sulfone was detected. Catalyst **11** gave a conversion of 15% in 15% ee (entry 5), which was not as good as catalyst **13** (entry 3), and catalyst **49** (entry 4) gave a low conversion of 15%, and resulted in racemic product.

Overall, with these studies using electrochemically-generated percarbonate the best reaction conditions are those in Table 54 (entry 3), which give the highest conversion with no sulfone, and the highest ee.

In carrying out the reaction with percarbonate solution that has resulted from electrolysis of 1 M $Na_2CO_3.10H_2O$ (100 mL), it has been shown previously that in one hour the concentration of peroxide present is approximately 20-30 mM, with a current efficiency of approximately 30% (Figure 16). However on using this solution for sulfoxidation (e.g.Table 54, entry 1), there is a maximum of 3 equivalents of percarbonate in the reaction. In comparison to this, when using commercially available sodium percarbonate only two equivalents are used (e.g. Table 53). Hence 25 mL of the solution in later examples, however this gives approximately 0.75 equivalents of percarbonate in the solution, which is perhaps not enough, and thus the conversions are lower (Table 54), than those achieved using the commercial percarbonate (Table 53).

Table 54 Sulfoxidation with Chiral Catalysts

1. 1 M sodium carbonate
   0 °C, 1 h, 10.0 V applied

2. Catalyst (10 mol%)
   MeCN / H₂O (1:1)
   0 °C, 15 h.

Entry	Catalyst	Ratio (%)[a]			ee (%)
		MePhSMe	MePhSO₂Me	MePhSOMe	
1[b]	9	61	10	29	20
2[c]	9	89	0	11	20
3[c]	13	70	0	30	20
4[c]	49	85	0	15	racemic
5[c]	11	85	0	15	15

[a] conversions determined by integration of proton signals on ¹H NMR spectra
[b] reaction time 5 h.
[c] 25 mL of percarbonate solution used instead of 100 mL

Having found the optimum conditions for the reaction, but then been unsuccessful applying them electrochemically, a range of different iminium salts were tested with the

reaction, but using commercially available sodium percarbonate rather than electrochemically generated percarbonate.

Table 55 Chiral Sulfoxidation Reactions of methyl _p_-tolyl sulfide

Entry	Catalyst	Ratio (%)[a]			ee (%)
		MePhSMe	MePhSO$_2$Me	MePhSOMe	
1[b]	**50**	62	12	26	9
2		62	13	25	3
3	**10**	35	31	34	11
4	**12**	24	24	52	racemic
5	**13**	32	17	51	13

[a] conversions determined by integration of proton signals on ^{1}H NMR spectra
[b] no 18-Crown-6

Table 55 shows the results, but unfortunately of all the catalysts tested with methyl *p*-tolyl sulfide the best conversion to sulfoxide of 51% and 52% (entries 4 and 5), but these resulted in a racemic compound (entry 4) and a low ee of 13% (entry 5), after twenty-four hours. It was thought that the phase-transfer catalyst 18-Crown-6, might help the migration across the phase barrier in these reaction, but with or without it the conversions and ees of 9% and 3% (entries 1 and 2) respectively are almost indentical when used in sulfoxidation reactions with the binaphthyl azepinium salt **50**.

After being unsuccessful with sulfoxidation reactions using methyl *p*-tolyl sulfide, we decided to try a different substrate but under the same reaction conditions (Table 56). With thiochroman-4-one as the substrate, the ees were also very low, where 13% ee (entry 1) was the best, using the binaphthyl azepinium salt **50**, but with a very low conversion of only 8% sulfoxide and mostly sulfone (52%). The best conversion seen was 41% (entry 2) using the biphenyl iminium salt, but this reaction also showed high levels of sulfone conversion (21%), and a low 5% ee.

Table 56 Chiral Sulfoxidation Reactions

Reaction scheme: **51** → Catalyst (10 mol%), 18-Crown-6 (10 mol%), $Na_2CO_3 \cdot 1.5H_2O_2$ (2 eq.), K_2CO_3 (5 eq.), MeCN / H_2O (1:1), 0 °C, 24 h. → **52** + **53**

Entry	Catalyst		Ratio (%)[a]		ee (%)
		Sulfide	Sulfone	Sulfoxide	
1	**25**	40	52	8	13
2	**10**	38	21	41	5
3	**12**	52	25	23	9
4	**13**	4	26	25	6
5	**54**	69	12	19	racemic
6	**9**	74	11	15	9

[a] conversions determined by integration of proton signals on ^{1}H NMR spectra

Table 57 Chiral Sulfoxidation of Thiochroman-4-one Electrochemically

1. 1 M sodium carbonate
0 °C, 1 h, 10.0 V applied

2. substrate (1 mmol%), catalyst (10 mol%)
MeCN / H$_2$O (1:1) (50 mL : 50 mL)
0 °C, 24 h.

Entry	Catalyst	Conversion (%)[a]			ee (%)
		MePhSMe	MePhSO$_2$Me	MePhSOMe	
1[b]	**25**	47	48	5	11
2[c]		84	0	16	24
3[d]	**9**	27	28	45	22
4[c]		80	6	14	24
5	**10**	69	14	17	19
6[d]		41	53	6	22
7[b,c]	**12**	22	25	53	racemic
8[b,c]	**13**	32	30	38	6
9		42	44	14	3

[a] conversions determined by integration of proton signals on ^{1}H NMR spectra
[b] (100 mL : 100 mL) electrochemical percarbonate / MeCN
[c] reaction time 24 h
[d] reaction time 4 days
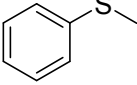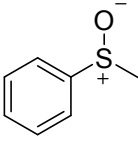
After being unsuccessful in finding conditions with a chiral catalyst under which the sulfoxidation reaction would result in good ees, it was decided to try the catalysts in the electrochemical reactions, after the application of a 10.0 V current to a 1 M solution of sodium percarbonate at 0 ºC for one hour, the organic phase was added after being cooled to 0 ºC with the iminium salt (10 mol%), and methyl *p*-tolyl sulfide and the reaction stirred at 0 ºC for twenty four hours. These reactions were carried out only using 50 mL of the electrochemically generated percarbonate solution and 50 mL of solvent, (which corresponds to 1.5 equivalents of oxidant). This was thought to perhaps give better results than using only 25 mL of the solution where only 0.75 equivalents of peroxide were being used (Table 54), which meant the results obtained were not comparable with those obtained using two equivalents of commercially available sodium percarbonate.

Unfortunately these reactions have not been successful either, with the best catalyst being one of the biphenyl salts and giving 24% ee (Table 57, entry 4), with a very low conversion of 14% after four days, although the conversion to the sulfone is also low in this instance. If the same reaction is left for a shorter period of time (Table 57, entry 5) a 17% conversion is observed, but the ee is lower at 19%.

As the sulfoxidation reactions were proving to be unsuccessful, an electrochemical study was carried out using additives in the reaction. We have shown that when diphenyl diselenide is used as an additive during sulfoxidation with H_2O_2 as the oxidant, then sulfoxide yields are increased. Therefore it was decided to try this under different conditions for electrochemical sulfoxidation reactions (Table 58). The results show that during the initial period (Table 58, entries 1 and 2) no sulfone is obtained when using 1 mol% of diphenyl diselenide, however the conversions are again low at a maximum of 18% (entry 11).

Table 58 Sulfoxidation with Electrochemically Generated Percarbonate

1. 1M $Na_2CO_3 \cdot 10H_2O$ (50 mL), 0 °C, 1 h, 10.0 V

2. diphenyl diselenide (1 mol%) substrate, r.t.

55

Entry	Reaction Time (hours)	Conversion (%)[a] (Yield (%))
1	1	0 (-)
2[b]	1	0 (-)
3	8	0 (-)
4[b]	8	0 (-)
5[c]	24	0 (-)
6[c]	24	0 (-)
7	120	0 (-)
8[b]	120	0 (-)
9	120	18 (12)
10[d]	120	0 (-)
11[e]	120	18 (15)
12[b]	120	15 (11)
13[e, f]	120	4
14[b, e, f]	120	3
15[f, g]	120	4
16[b, f, g]	120	7

[a] conversions determined by integration of proton signals on ^{1}H NMR spectra
[b] benzeneselenic anhydride (1 mol%) used instead of diphenyl diselenide
[c] reactions carried out at 0 °C
[d] organic phase (50 mL) added to reaction
[e] 100 mL of percarbonate solution used instead of 50 mL
[f] -10.0 V applied for 1 h instead of 10.0 V
[g] organic phase (50 mL) added to the reaction

The electrochemically-mediated oxidation reactions were still slow even though some conversion is observed with diphenyl diselenide as an additive. Temperature and solvent studies have already been carried out for these reactions, so the next variable to consider was the pH of the reaction.

2.3.2 Electrochemical Sulfoxidation

Table 59 shows the results of sulfoxidation reactions carried out using 100 mL of electrochemically generated percarbonate solution. Once the solution has been obtained from appling a 10.0 V potential to a 1 M solution of $Na_2CO_3.10H_2O$ for one hour at 0 ºC, hydrochloric acid is added to the solution to achieve a range of pH values between 2 and 10. Entry 1 (Table 59) shows that if the pH of the solution is lowered to 2, and then diphenyl diselenide (1 mol%), and substrate are added, that after stirring this reaction at room temperature for 5 days then 100% conversion and a 92% yield is achieved. Using a slightly higher pH (Table 59, entry 5) we can see that a high conversion (90%) to the sulfoxide is still seen after 5 days, with a yield of 85%.

These reactions have given the reported conversion in 5 days, but continuous monitoring by ^{1}H NMR shows that sulfoxide conversion is occurring steadily over the time period rather than all at once.

Although the optimum conversions are observed when the reactions are run at pH 2. In order for this system to be widely applicable and therefore show high functional group tolerance, we opted to use less acidic conditions at pH 6.

Table 59 pH study of Electrochemically Generated Oxidant for Sulfoxidation

1. 1M Na$_2$CO$_3$.10H$_2$O (100 mL), 0 °C, 1 h, 10.0 V

2. pH adjustment
3. diphenyl diselenide (1 mol%) substrate, r.t., 5 days
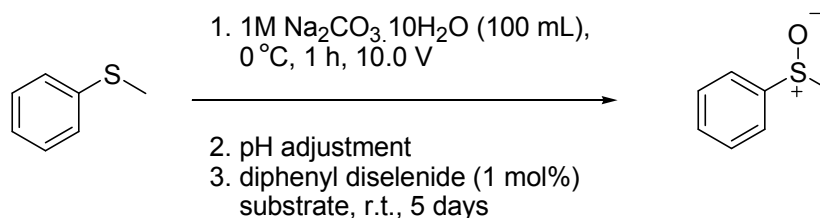
Entry	pH of solution	Conversion[a] (%) (Yield(%))
1	2	100 (92)
2[b]	2	46 (42)
3	4	94 (91)
4[b]	4	24 (15)
5	6	90 (85)
6[b]	6	18 (13)
7	8	59 (58)
8	10	41 (39)

[a] conversions determined by integration of proton signals on ^{1}H NMR spectra
[b] reaction carried out for 2 days

For standard experiments carried out electrochemically, we have shown through cyclic voltammetry experiments, that taking a solution of 1 M Na$_2$CO$_3$.10H$_2$O and applying 10.0 V for a given time period at 0 °C, it is possible to form sodium percarbonate as an oxidant in solution.

If the pH of the same 1 M Na$_2$CO$_3$.10H$_2$O solution is lowered by the slow addition of hydrochloric acid before applying a potential, then it is possible to form sodium

hypochlorite as the oxidant in solution instead. This is due to a shift in equilibrium of the species in solution.

As pH 6 is the optimum from previous studies, a range of other substrates have been tested electrochemically under these conditions. To a 1 M solution of $Na_2CO_3.10H_2O$ in an undivided cell fitted with a BDD anode and Pt counter electrode, 10.0 V was applied to the solution at 0 °C whilst stirring (6500 rpm, ultra-turrax) for one hour. After this time the pH of the solution was adjusted by slow adition of HCl, before adding substrate and diphenyl diselenide to the solution. This was then stirred at room temperature, giving 96% conversion for the oxidation of 4-fluorothioanisole (Table 60, entry 4) in 65 hours, 92% conversion for oxidation of thioanisole (Table 60, entry 1) in 24 hours and high conversions for other substrates (Table 60).

Table 60 Electrochemical Sulfide Oxidation

R'–S–R"

1. 1.0 M Na$_2$CO$_3$.10H$_2$O (100 mL)
   0 °C, 10.0 V, 1 h.
2. pH adjustment to pH 6
3. substrate (1 mmol),
   diphenyl diselenide (1 mol%), r.t.

→ R'–S(=O)$^-$–R"$^+$
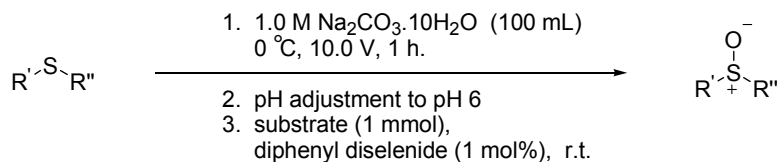
Entry	Substrate	Time (h)	Unreacted Sulfide (%)[a]	Sulfoxide Conversion (%)[a]	Sulfoxide Yield (%)[b]	Sulfone Conversion (%)
1	**55**	24	-	98	92	2
2[c]		24	2	98	90	-
3[d]		24	25	75	72	-
4	**56**	65	-	>99	96	-
5[c]		65	-	85	79	-
6		20	~1	98	89	~1
7[c]	**57**	20	-	59	49	-
8	**58**	72	-	>99	92	-
9	**59**	30	-	>99	91	-

[a] conversion evaluated by comparison of the methylene ^{1}H NMR shift a to sulfur in both the sulfide and sulfoxide
[b] isolated yield
[c] reaction carried out in the absence of Ph$_2$Se$_2$
[d] reaction carried out at -10.0 V
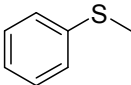
After achieving high conversions for a range of substrates, we also carried out experiments to see if it is possible to recycle the aqueous electrolyte solution. We tried first to recycle the aqueous phase after electrolysis by extracting the sulfoxide, and using the aqueous solution to carry out another sulfoxidation by addition of more substrate, but this only resulted in a 10% conversion the 2nd time after 24 hours, when we had complete conversion to the oxide the 1st time.

More successful was repeating the electrolysis of the aqueous phase (Table 61). So after the 1st reaction had been worked-up and the sulfoxide extracted, the aqueous phase is placed back into the undivided cell after reducing the pH back to pH 6, and 10.0 V were applied for a further 1 hour. Adding sulfide to this solution, afforded complete conversion to the sulfoxide after 22 hours (Table 61). Repeating this cycle a number of times gave complete conversion to the sulfoxide, with the reaction rate increasing each time, presumably due to the fact that there is an increase in concentration of oxidant in the solution each time the reaction is carried out.

Table 61 Recycling of the Electrolyte Solution

Entry	Substrate	Time (h)	Sulfoxide Conversion (%)[a,b]
1		22	100
2[c]		18	100
3[c]		14	100
4[c]		11	100

[a] Conversion evaluated by comparison of the methylene ^{1}H NMR shift in both the sulfide and sulfoxide

[b] monitored by LC-MS

[c] electrolyte solution after work-up was re-adjusted to pH 6 with HCl and 10.0 V applied for 1h prior to addition of sulfide

Using cyclic voltammetry, it was possible to determine the concentration of an electrochemically produced hypochlorite solution. This was carried out by electrolysing a 1 M aqueous solution of $Na_2CO_3.10H_2O$ that had been adjusted to pH 6 by slow addition of conc. HCl (37%, 15 mL), in an undivided cell, using a BDD working electrode and a platinum counter electrode, where a potential of 10.0 V was applied for one hour. The solution was kept cold in an ice bath, and emulsified using an ultra-turrax (6500 rpm). At regular intervals over the hour period, cyclic voltammetry was run (Figure 21), which plots current and potential. After an hour 200 μL of commercial bleach is added to the solution and a cyclic voltammogram obtained. This then allows

the amount of ⁻OCl generated in the hour period to be calculated from the voltammogram, by comparison in the difference between ⁻OCl concentration before and after the addition of commercial bleach. Figure 21 shows that the difference in the CV curves after 0 and 60 minutes is the same as the distance between the curves after 60 minutes and after the addition of 200 µL. Therefore as we know the amount of ⁻OCl added we can calcuate the concentration we produce after 1 hour of electrolysis. This gives us 0.25 mmol of ⁻OCl after 1 hour of electrolysis, and a concentration of 2.5 mmol/L, with a current efficiency of 4.5%.
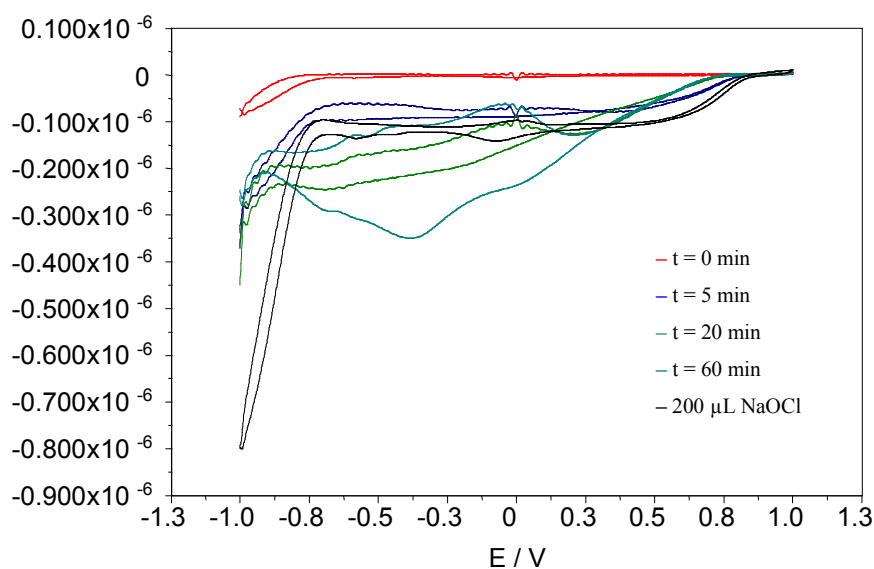
Figure 21 Titration of 1M Na₂CO₃.H₂O at pH 6

Once we had determined the oxidant that is being formed under these reaction conditions, a number of studies were carried out to find the optimum time and potential for the reactions.

Firstly looking at a positive potential (Figure 22), It can be seen that over time the concentration of hypochlorite in solution increases when 10.0 V is applied at 0 ºC, to a solution of 1 M Na₂CO₃.10H₂O that has had its pH lowered to 6, until approximately

1200 seconds when the amount does not then increase. The maximum concentration of hypochlorite in solution at 1200 seconds is 2.90 mmol/L.
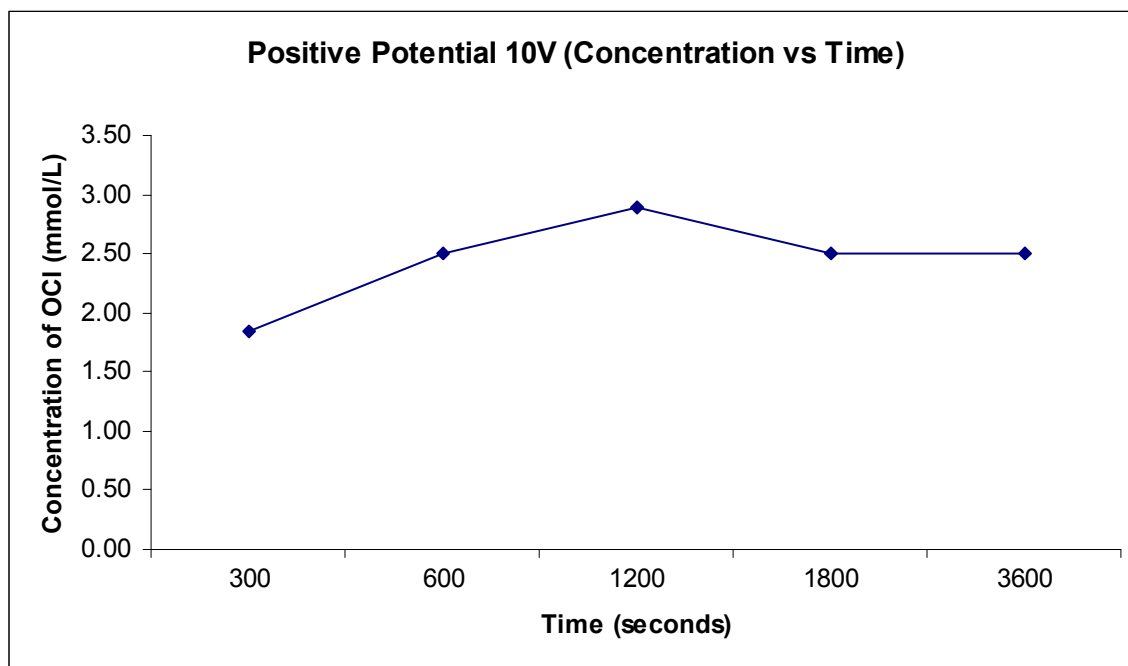
Figure 22 Concentration vs Time at a Positive Potential

Looking at the same reaction under a negative potential (Figure 23), then the optimum concentration of hypochlorite is achieved after applying -10.0 V to the solution for 1800 seconds, giving 2.50 mmol/L. This is close to the concentration at a positive potential of 2.90 mmol/L, however at a negative potential the concentration takes a more rapid drop after 1800 seconds.
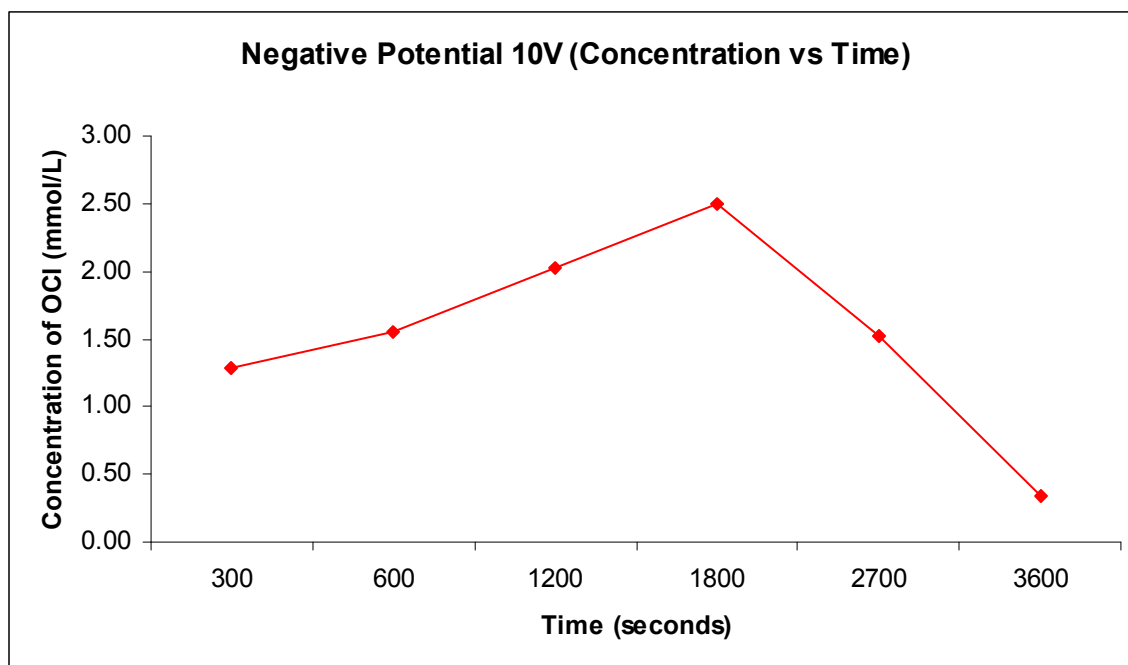
Figure 23 Concentration vs Time at Negative Potential

Figure 24 and Figure 25 show us that at both negative and positive potential the concentration of hypochlorite in solution increases with increase in potential. In both instances at 25 V and –25 V we see concentrations of 6.49 mmol/L and 7.00 mmol/L respectively.
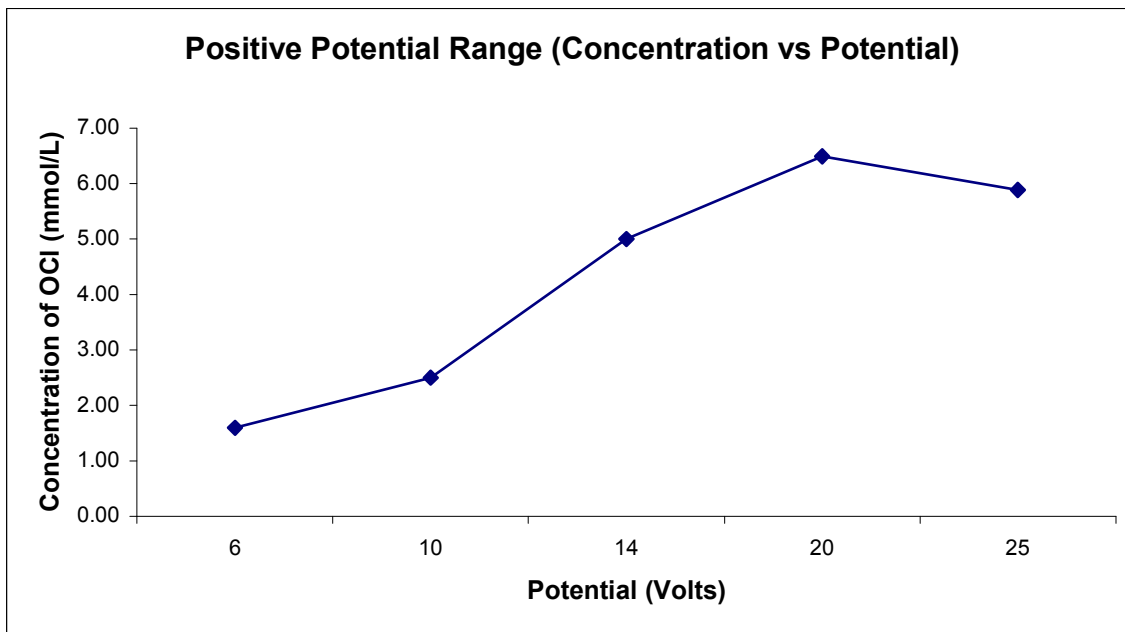
Figure 24 Concentration vs Potential over a Positive Potential Range
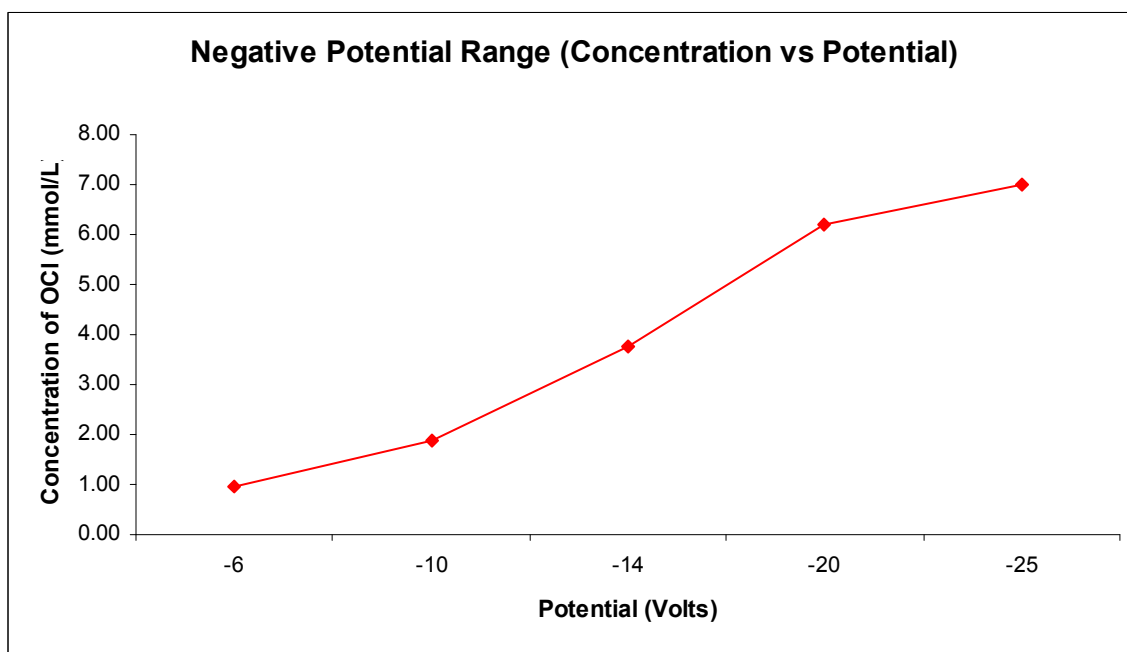
Figure 25 Concentration vs Potential over a Negative Potential Range

Although Figure 24 and Figure 25 show that as we alter potential we can alter the concentration of oxidant in solution, Figure 26 shows that over a positive potential range the percentage yield of hypochlorite in solution decreases from 25.7% at 6 V to 10.0% as

the current is increased to 25 V. The same is seen in Figure 27, where the percentage yield decreases from 25.3% at –6 V to 9.2% at –25 V.
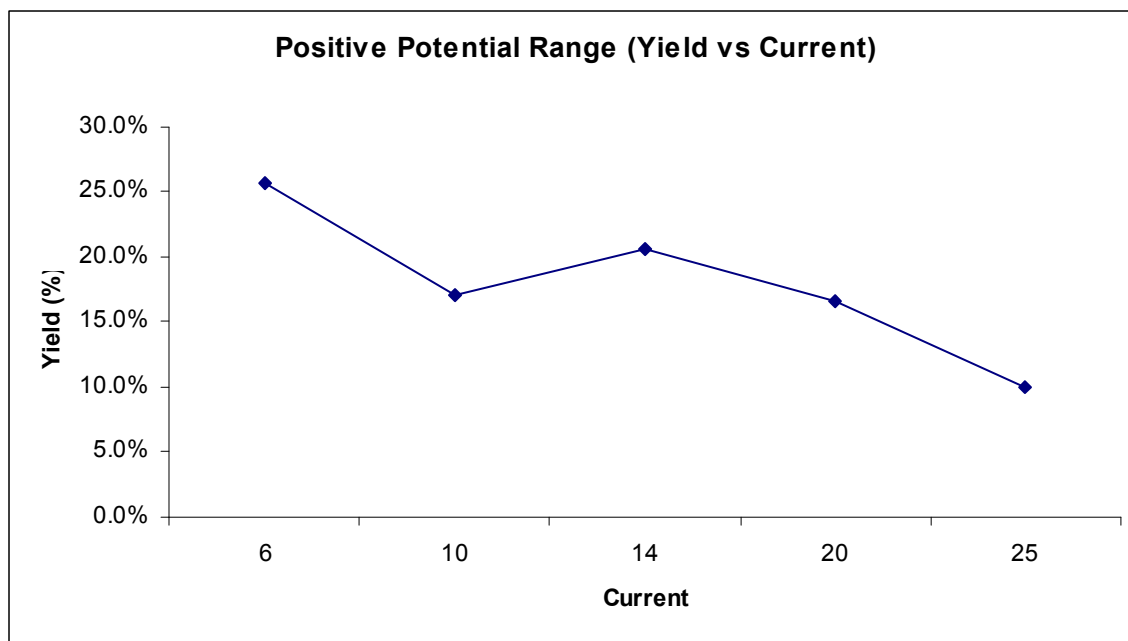
Figure 26 Yield vs Current over a Positive Potential Range
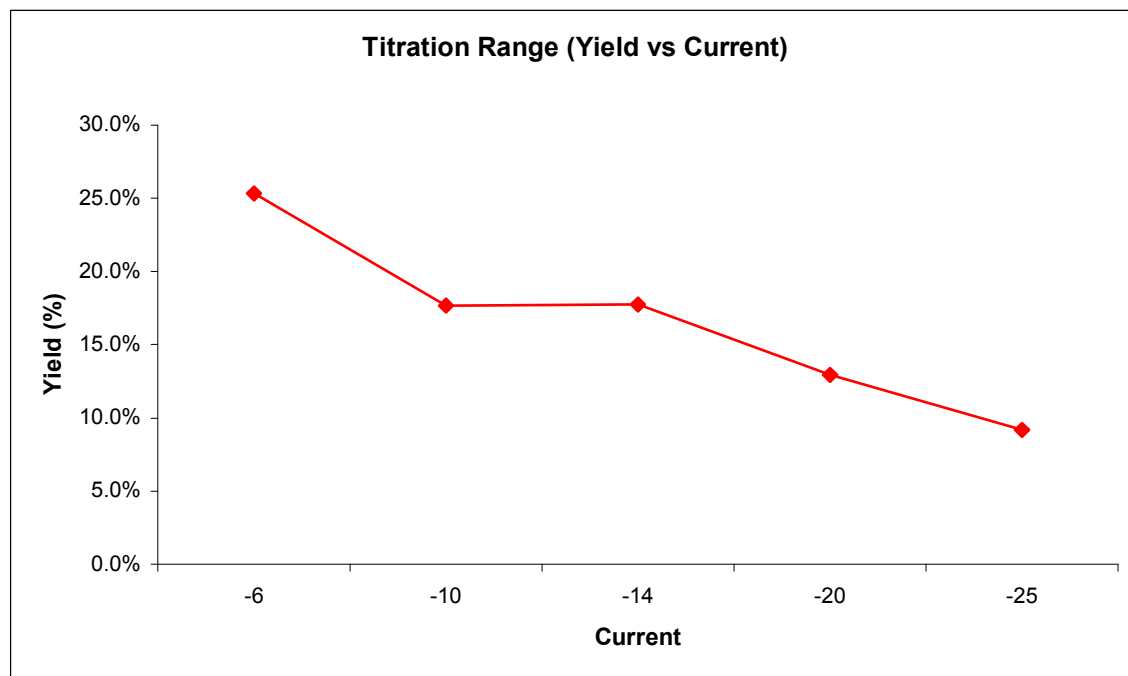
Figure 27 Yield vs Current over a Negative Potential Range

Results in Table 62 have shown that pH adjustment gives successful sulfoxide conversions. So following on from this study, a range of one-pot epoxidation reactions were carried out, where the pH of a 1 M solution of $Na_2CO_3.10H_2O$ is adjusted to pH 6 before the addition of diphenyl diselenide (1 mol%) and substrate in a undivided cell fitted with a BDD cathode and Pt counter electrode. -10.0 V was then applied to the solution at 0 ºC whilst stirring with an ultra-turrax (6500 rpm).

Entry 1, Table 62 shows that after one hour over oxidation is seen, resulting in 100% sulfone and after 30 minutes the same reaction affords 43% sulfoxide but 51% sulfone (entry 5). However, if the quantity of sulfide added into the reaction is increased (entry 8), then 46% sulfoxide is seen, as there is more sulfide to react with the oxidant instead of it reacting with sulfoxide resulting in a lower amount of sulfone at 16%.

Entry 6, Table 62 shows the same reaction but carried out at a positive potential. This gives 25% sulfoxide conversion after 30 minutes and 18% sulfone, which are both lower than those achieved at a negative potential.

Table 62 One-pot Sulfoxidation

1. 1M $Na_2CO_3 \cdot 10H_2O$ (50 mL)
   pH adjustment to pH 6

2. substrate (1 mmol)
   diphenyl diselenide (1 mol%)
3. 0 °C, -10.0 V
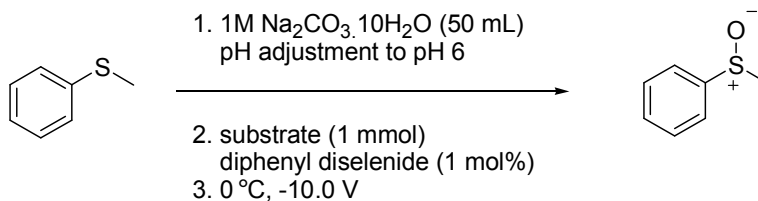
Entry	Time (minutes)	Ratio[a] (%)		
		Sulfoxide	Sulfone	Sulfide
1	360	0	100	0
2[b]	60	22	78	0
3	60	0	100	0
4[c]	60	28	52	20
5	30	43	51	6
6[d]	30	25	18	57
7[d]	60	0	100	0
8[e]	30	46	16	38
9[e]	45	22	31	37
10[f]	30	47	15	38
11[g]	30	12	8	80
12[h]	30	16	78	6

[a] conversions determined by integration of proton signals on ^{1}H NMR spectra
[b] 1 M $Na_2CO_3 \cdot 10H_2O$ (50 mL) adjusted to pH 4
[c] 1 M $Na_2CO_3 \cdot 10H_2O$ (50 mL) adjusted to pH 8
[d] + 10.0 V potential applied to the reaction
[e] twice as much sulfide added into the reaction
[f] three times as much sulfide added into the reaction
[g] slow addition of sulfide over 30 min
[h] larger BDD electrode used
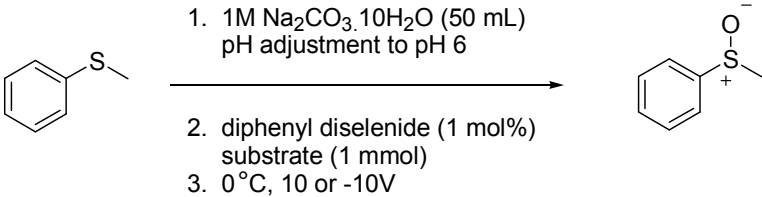
We have shown that one-pot sulfoxidation reactions are possible if either a negative or positive potential is applied to the solution. However, a positive potential is favourable because under these conditions the oxidant is generated at the BDD electrode, with the smaller Pt counter electrode being too small to increase the rate of oxidant decomposition. Under a negative potential, the oxidant is generated at the smaller Pt electrode and the larger BDD electrode surface facilitates electrochemical decomposition of the oxidant, according to the redox equations.

Table 63 shows that at a negative potential after 30 minutes (entry 2) 43% sulfoxide is obtained compared to only 25% sulfoxide (entry 5) at a positive potential.

Table 63 One-pot Sulfoxidation Potential Study

1. 1M $Na_2CO_3.10H_2O$ (50 mL) pH adjustment to pH 6
2. diphenyl diselenide (1 mol%) substrate (1 mmol)
3. 0 °C, 10 or -10V
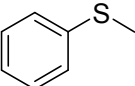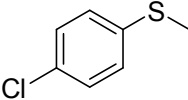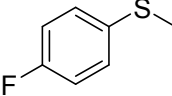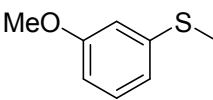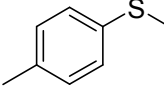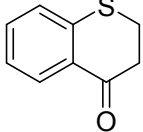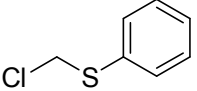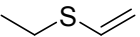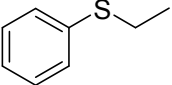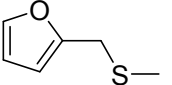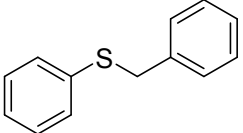
Entry	Potential	Time (minutes)	Ratio[a] (%)		
			Sulfide	Sulfoxide	Sulfone
1	negative	60	0	0	100
2		30	6	43	51
3[b]		30	33	48	19
4	positive	60	0	0	100
5		30	57	25	18
6[b]		30	17	46	37

[a] conversions determined by integration of proton signals on ^{1}H NMR spectra
[b] background reaction without diphenyl diselenide

Table 63 shows that the reactions give better conversions overall at a negative potential, so these conditions were applied to the oxidation of a range of sulfides. With electron-withdrawing groups *para* to the sulfide on thioanisoles, conversions of 14% for 4-chlorothioanisole sulfoxide (entry 2), and 26% for 4-fluorothioanisole (entry 3) were achieved. Conversion to sulfoxide for sulfides containing a terminal alkene / ethyl vinyl sulfide was achieved (entry 12) giving 17% conversion after 5 minutes. The majority of the reactions under these conditions, are very fast and result in over-oxidation to the sulfone.

Table 64 One-pot Sulfoxidation

R'–S–R"

1. Na$_2$CO$_3$.10H$_2$O (50 mL), adjusted to pH 6
2. substrate (1 mol%)
   diphenyl diselenide (1 mol%)
3. 0 °C, -10.0 V, 30 min

→ R'–S$^+$(O$^-$)–R"

Entry	Substrate		Conversion (%)		
---	---	---	Sulfoxide	Sulfone	Sulfide
1[a]		55	46	16	38
2		60	14	45	41
3		56	26	29	45
4[b]			0	100	0
5		57	92	8	0
6		46	44	8	48
7[b]		50	23	26	51
8[c]			46	49	5
9		61	12	0	88
10			0	100	0
11[d]		59	11	89	0
12[e]			17	73	10
13[c]			0	100	0
14		62	70	0	30
15[c]			72	0	28
16		58	60	0	40
17[d]			0	100	0
18[e]		63	0	10	90

[a] twice as much sulfide added; [b] reaction left for 2h; [c] reaction left for 1h; [d] reaction left for 15 min; [e] reaction left for 5 min

2.3.3 Sulfoxidation with Hydrogen Peroxide

Another oxidant studied for oxidation reactions has been hydrogen peroxide. Previously we showed that using hydrogen peroxide as an oxidant for epoxidation reactions gave us excellent conversions to epoxides (Table 37), this is also the case for sulfoxidation (Table 65), giving us a 100% conversion and 94% yield after 192 hours with H_2O_2 (1 eq.) and diphenyl diselenide (1 mol%) at room temperature in water (entry 4). If the same reaction is carried out with benzeneselenic anhydride (1 mol%) instead of diphenyl diselenide, then the reaction is quicker, giving a 98% conversion and 89% yield in 72 hours (entry 5, Table 65). Under these reaction conditions, no sulfone is present after any of the reactions.

Table 65 Sulfoxidation with H_2O_2
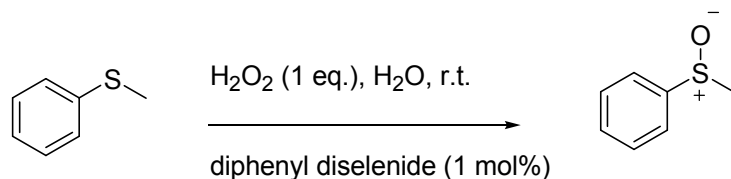
Entry	Time (hours)	Conversion (%)[a] (Yield%)
1	24	25 (20)
2	72	59 (56)
3	120	92 (85)
4	192	100 (94)
5[b]	72	98 (89)
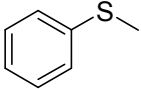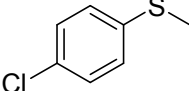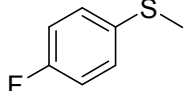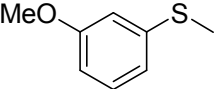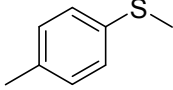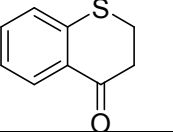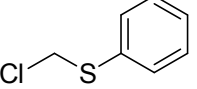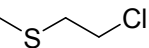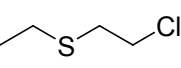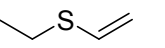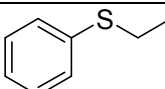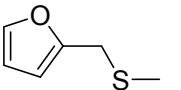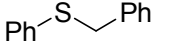
[a] conversion determined by integration of proton signals on ^{1}H NMR spectra
[b] reaction carried out with benzeneselenic anhydride (1mol%) not diphenyl diselenide

2.3.4 Sulfoxidations with Urea Hydrogen Peroxide

Using urea hydrogen peroxide, as the oxidant source has also proven to be more successful than those reactions using sodium percarbonate as the oxidant.

Using commercially available urea hydrogen peroxide (1 eq.), in dichloromethane at room temperature with diphenyl diselenide (1 mol%), has given both excellent conversions and yields for a range of substrates within twenty-four hours (Table 66).

Table 66 Racemic Sulfoxidation reactions using Urea Hydrogen Peroxide

R'—S—R" →[Urea Hydrogen Peroxide (1 eq.) / diphenyl diselenide (1 mol%) / DCM, r.t., 24 h] R'—S(+)(O⁻)—R"

Entry	Substrate		Conversion (Yield) (%)
1[a]		**55**	100 (97)
2			100 (98)
3[b]			100 (99)
4[c]			5 (3)
5		**60**	97 (80)
6		**50**	100 (96)
7		**57**	96 (90)
8		**46**	100 (66)
9		**50**	73 (68)
10		**61**	96 (68)
11		**64**	100 (89)
12		**65**	100 (74)
13		**59**	100 (92)
14		**62**	95 (73)
15		**58**	99 (74)
16		**63**	92 (69)

[a] reaction time 7 h; [b] diphenyl diselenide (0.01 mol%); [c] background reaction - no diphenyl diselenide

Without the presence of diphenyl diselenide in the reaction, the background formation of sulfoxide is minimal at a conversion of only 5% (Table 66, entry 4) after twenty-four hours. Adding diphenyl diselenide results in 100% conversion to the sulfoxide, and a 97% yield (Table 66, entry 1) after twenty-four hours. The reaction will also give comparable results with a minimal amount of diphenyl diselenide used (0.1 mol%) (Table 66, entry 3), giving 100% conversion after twenty-four hours and 99% yield, with no presence of sulfone.

A range of other sulfides have also been used under the same reaction conditions, starting with different substituents on thioanisole (Table 66, entries 5-8), all with conversions to the sulfoxides being greater than 95%, with good yields. Of the other sulfides tested (Table 66, entries 9-16) they all show excellent conversions too, being greater than 90% except for thiochroman-4-one at 73% (Table 66, entry 9), but all within twenty-four hours.

The reaction was monitored over a period of 420 minutes to see how the reaction progresses (Figure 28). If the same reaction is carried out with benzeneselenic anhydride instead of diphenyl diselenide then formation of the sulfoxide begins earlier, this can be seen for thioanisole and 4-chlorothioanisole (Figure 28). Looking at the 4-chlorothioanisole reaction after 120 minutes only trace amounts of sulfoxide are detected by ^{1}H NMR spectroscopy, and conversion is not complete (at 96% after 430 minutes). However, if benzeneselenic anhydride is used instead conversion is seen almost instantly within the first minute, and 100% conversion is seen after only 60 minutes.

This led to the conclusion that in the case where diphenyl diselenide was being used as the additive, there is an initial period during which no sulfoxide is formed, probably because the diphenyl diselenide firstly reacts with the urea hydrogen peroxide to form benzeneselenic anhydride, which is then oxidizing the sulfides.

The formation of benzeneselenic anhydride from diphenyl diselenide has been proven by a number of experiments. Firstly it is possible to see the presence of both diphenyl

diselenide and benzeneselenic anhydride on the ^{1}H NMR spectrum after the reaction is complete, and both are also evident by TLC. Using urea hydrogen peroxide, and diphenyl diselenide it is possible to synthesize benzeneselenic anhydride, which can then be used for sulfoxidation reactions. Doing this gives identical results to the thioanisole reaction carried out (Figure 28) with benzeneselenic anhydride.
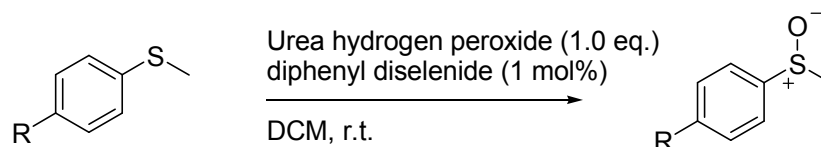
Time (min)	Thioanisole Conversion (%)[a]	Thioanisole Conversion (%)[a, b]	Methyl p-tolyl sulfide Conversion (%)[a]	4-Chlorothioanisole Conversion (%)[a]	4-Chlorothioanisole Conversion (%)[a, b]
1	0	0	10	0	11
5	0	0	78	0	19
10	0	0	82	0	65
20	0	0	100	0	76
30	0	3	100	0	83
60	6	10	100	0	100
120	12	100	100	1	100
180	91	100	100	94	100
240	96	100	100	95	100
360	98	100	100	96	100
420	100	100	100	96	100

[a] conversion determined using ^{1}H NMR spectroscopy by integration of proton signals.

[b] benzeneselenic anhydride (1 mol%) used instead of diphenyl diselenide.
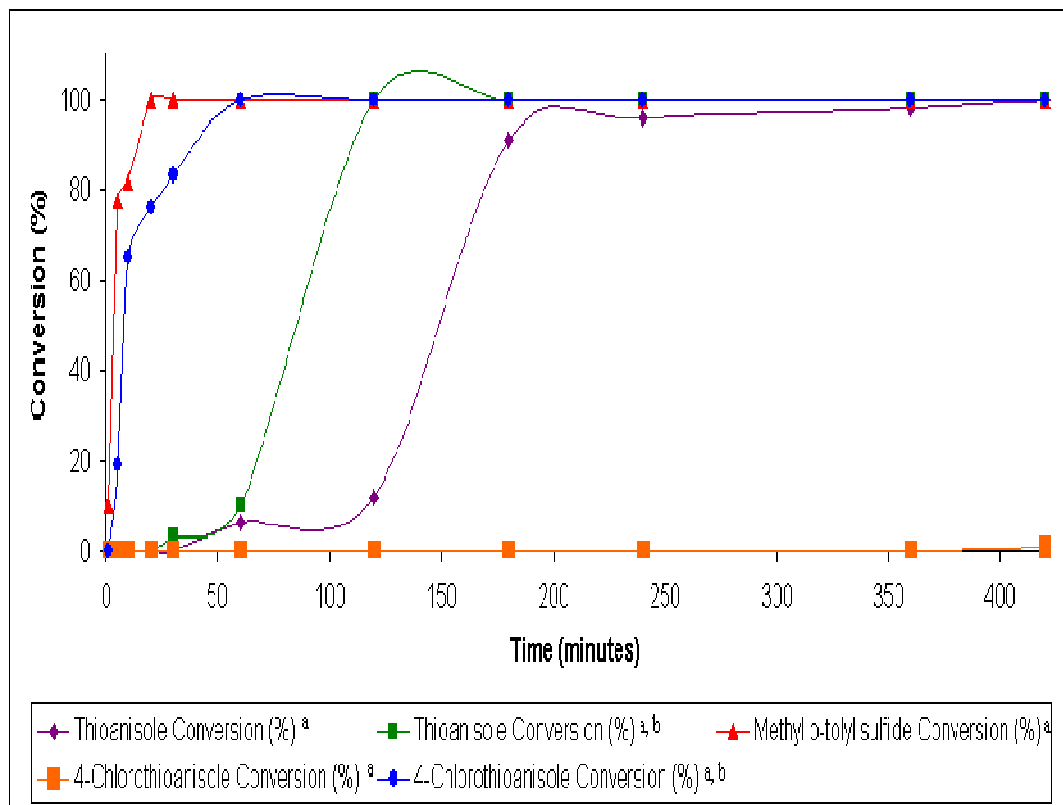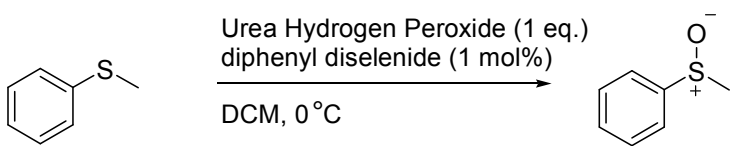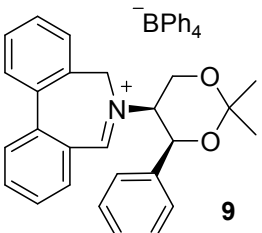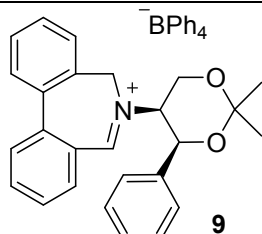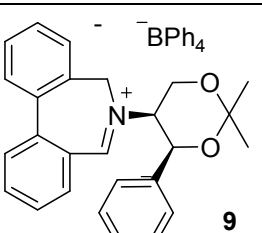
Figure 28 Sulfoxidation over time with Urea Hydrogen Peroxide and Benzeneselenic Anhydride

Having achieved good results for the formation of racemic sulfoxides using urea hydrogen peroxide at room temperature the reaction was tried at different temperatures. If the temperature is changed to −78 ºC (Table 67, entry 3) then only starting material is retrieved after ten hours. Trying the reaction with benzeneselenic anhydride instead of diphenyl diselenide also results in no sulfoxide after ten hours (Table 67, entry 5). Carrying out the same reaction but at −40 ºC with benzeneselenic anhydride (Table 67, entry 7), then trace amounts of sulfoxide are seen by ^{1}H NMR. Changing the solvent to acetonitrile in place of dichloromethane has not improved the results (Table 67, entry 9). These results are positive, as we will therefore get no background oxidation using asymmetric catalysts at low temperatures.

Using catalysts to try and form chiral sulfoxides so far has given minimal conversion and only trace amounts of sulfoxide are seen when the reaction was carried out at −78 °C (Table 67, entries 4, 6 and 8) after ten hours.

Table 67 Sulfoxidation Work at Different Temperatures with Various Catalysts

Entry	Catalyst	Time (hours)	Temperature (°C)	Conversion (Yield) (%)
1[a]	-	24	r.t.	97 (71)
2[b]	-	24	r.t.	66 (64)
3	-	10	-78	0
4	**9**	10	-78	11
5[b]	-	10	-78	0
6[b]	**9**	10	-78	0
7[b]	-	10	-40	0
8[b]	-	10	-40	6
9[b,c]	**9**	10	-40	0

[a] diphenyl diselenide (50 mol%)
[b] no diphenyl diselenide, benzeneselenic anhydride (1 mol%) instead
[c] no dichloromethane as solvent, reaction carried out in acetonitrile

2.4   References

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3.0   Conclusion and Future Work

A wide variety of conditions and methods for producing enantiomerically enriched epoxides and sulfoxides have been reported using both electrochemically generated percarbonate and hypochlorite.

We have reported a range of successful oxidation reactions both as one-pot reaction and with the oxidant generated in a batch process.

3.1   'Batch' Electrochemical Oxidation

Reported results show that is has been possible to generated 20-30mM of percarbonate by electrolysis of a 1 M $Na_2CO_3.10H_2O$ (100 mL) solution. Carrying out sulfoxidation reactions as a batch process with this solution it is possible to obtain ees of 20% (Table 54) with catalyst **9** for the sulfoxidation of 2-methyoxythioanisole.

3.2   One-Pot Electrochemical Oxidation

Using 1 M $Na_2CO_3.10H_2O$ (100 mL) solution, after adjusting its pH via the slow addition of HCl to pH 6 it is possible to successfully carry out oxidation reactions in an undivided cell electrochemically by producing 1.38 mmol/L of hypochlorite in solution after 20 minutes. Under these conditions we have carried out asymmetric sulfoxidation where a range of good conversions to the sulfoxide are possible. This enabled up to 98% conversion and 92% yield in 24 hours (for the sulfoxide of Thioanisole) (Table 60).

Under the same conditions it has been possible to achieve >99% conversion to oxides for a range of tested alkenes, and carry out successful chrial epoxidation reactions obtaining up to 44% ee for the epoxide of 1-phenylcyclohexene after two hours (Table 43), with catalyst **9**.

With the newly developed electrochemical systems, it is also possible to recycle the electrolyte a number of times and still obtain complete conversion to the corresponding oxide, with the reaction rate increasing with each repeated cycle.

To develop this system further, the novel catalysts **24** and **25**, which gave successful ees for electrochemical sulfoxidation reactions can be tried with our one-pot electrochemical epoxidation system and our 'batch' epoxidation conditions, where percarbonate is formed electrochemically before the addition of substrate, solvent and catalyst.

3.3   New Electrochemical Systems

We have developed a new cell, where the BDD electrode is at the base of the cell rather than the side. This gives us the ability to carry out reactions as a two-phase system, in which the oxidation occurs at the interface only. This would allow the aqueous layer to sit at the bottom of the cell, directly in contact with the BDD electrode, with the organic layer on top of the aqueous. When applying a current the electrolysis can then occur only in the bottom aqueous phase. However, test reactions with this cell have so far been unsuccessful. Future reactions could involve the use of our one-pot bleach system, where the pH of the 1 M $Na_2CO_3.10H_2O$ solution is lowered to pH6 before being placed into the bottom of the cell. This may give more promising results with oxidation occurring at the interface of the two phases.

Oxidation might work better in a two-phase system, because unlike the one-pot system with an emulsion, the two-phase system means that the catalyst cannot decompose, because the decomposition occurs at the anode and in my first attempts the catalyst did decompose, probably due to the miscibility of acetonitrile and water. So if this is in the bottom of the cell in the aqueous phase then electro-oxidation of it is not possible, as it will sit in the organic phase and interact at the interface to transfer oxygen onto the substrate.

3.4   Hydrogen Peroxide Reactions

Other than electrochemical oxidations, we have reported successful enantioselective epoxidation reactions using H_2O_2 as the oxidant with 1 mol% diphenyl diselenide and 5 mol% of catalyst in MeCN, giving up to 47% ee for the epoxide of 1-phenylcyclohexene using catalyst **9** (Table 36, entry 3). This is almost comparable with results obtained with

Oxone$^{®}$ (58% ee). Using a novel amine catalyst **25** we have achieved ees up to 85% with H$_2$O$_2$ and 88% with Oxone$^{®}$ (Figure 17).

3.5 Urea Hydrogen Peroxide Reactions

As well as carrying out sulfoxidation reactions using sodium percarbonate and hypochlorite, successful achiral oxidation reactions have also been achieved using urea hydrogen peroxide (1 equivalent), in dichloromethane in the presence of diphenyl diselenide in DCM at room temperature. This has afforded greater than 95% conversion with high yields for a wide range of substrates. It has been proven that in these reactions the diphenyl diselenide reacts first with urea hydrogen peroxide to form benzeneselenic anhydride, which then in turn reacts with a sulfide.

Carrying out achiral oxidation reactions with urea hydrogen peroxide in the presence of diphenyl diselenide in DCM at room temperature has also afforded conversions >99% for a wide range of sulfoxides.

3.6 Baeyer-Villiger Oxidation

The Baeyer-Villiger reaction has shown some promising results with commercial percarbonate, with the best conditions to date being at pH 9, at room temperature, in three days giving a conversion of 14% from cyclohexanone to caprolactone. After seven days under the same conditions no improvement was seen. This could be due to the decomposition of the oxidant, and it is possible that the 14% conversion seen after three days is in fact present in a shorter time period, but it is difficult to follow the progression of the reaction *via* TLC, because the product does not absorb in the UV wavelength.

Since it is possible that the oxidant decomposes, resulting in low conversions, addition of the oxidant batch-wise rather than in one portion over a period of time was attempted, but this also showed no improvement in the conversions being observed for formation of caprolactone from cyclohexanone.

Addition of 18-Crown-6 to the reaction, which acts as a phase transfer catalyst at the interface between the water and organic phase, gives an increased conversion of 82% in three days, and 88% after six days for the formation of caprolactone. These are promising results, but we were unable to convert other ketones to the corresponding lactones using this methodology.

Electrochemically the Baeyer-Villiger reaction has also been unsuccessful, as it has not been possible to obtain comparable results to those using commercially available percarbonate source, either as a one-pot reaction generating the percarbonate *in-situ*, or by generation of the percarbonate before addition of the organic phase and substrate.

4.0 __Experimental__

Commercially available reagents were used as supplied, without any further purification, unless stated otherwise and stored according to the manufacturer's recommendations.

Flash chromatography was carried out using glass columns packed with Merck Kiesekgel 60-45. Thin layer chromatography was carried out on aluminium-backed plates coated with Merck Kieselgel 60 GF_{254}. Plates were visulised under UV light and developed by staining using ethanolic phosphomolybdic acid, followed by heated.

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

All ^{1}H and ^{13}C NMR spectra were measured at 400.13 and 100.62 MHz with a Bruker DPX 400 / Advance 400 MHz spectrometer, in deuteriochloroform solution unless otherwise stated, using TMS (tetramethylsilane) as the internal reference.

Mass spectra were recorded using a Jeol-SX102 instrument utilising electron-impact(EI) and fast atom bombardment (FAB) or at the EPSRC National Mass Spectrometry Service, Swansea.

Melting points were recorded using an Electrothermal-IA 9100 melting point instrument.

Optical rotation values were measured using an Optical Activity-polAAr 2001 instrument, operating at λ=598 nm, corresponding to the sodium D line, at the temperatures indicated.

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

Enantiomeric excesses were determined by either proton nuclear magnetic resonance (^{1}H-NMR), or by chiral HPLC.

The proton nuclear magnetic resonance spectra were recorded in deuteriated chloroform, in the presence of europium (III) tris [3-(hepta-fluoropropylhydroxymethylene)-(+)-camphorate], [(+)-Eu(hfc)$_3$], as the chiral shift reagent and tetramethylsilane as the internal standard.

The chiral column used for the determination of enantiomeric excesses (ee), of non-racemic mixtures by chiral HPLC, was Chiracel OD on a TSP Thermo-Separating-Products Spectra Series P200 instrument, with TSP Spectra Series UV100 ultra-violet absorption detector set at 254 nm and a Chromojet integrator. Both solvents used to gain measurements (hexane and isopropanol), were of HPLC grade.

All compounds once made were dried under vacuum at room temperature unless otherwise stated.

DCM and toluene were distilled from calcium hydride before use. All reactions were carried out using Pyrex or equivalent glass round-bottomed flasks.

Electrochemical experiments were carried out in a two-electrode undivided cell fitted with a boron-doped diamond (Diafilm, Windsor Scientific, UK) electrode (3 cm^2) and a small platinum wire electrode as the counter electrode.

4.1 Catalyst Synthesis

4.1.1 *N*-[(4*S*,5*S*)-2,2-Dimethyl-4- phenyl-1,3-dioxan-5-yl]formamide (6)[2]
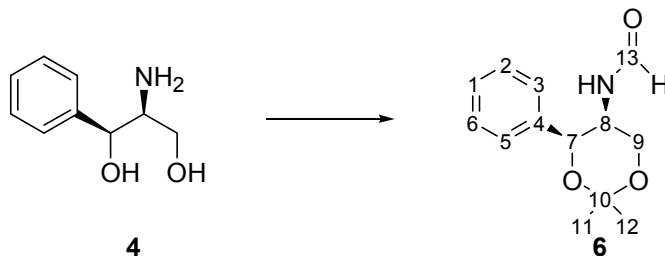
(1*S*,2*S*)-(+)-2-Amino-phenyl-1,3-propandiol (1.00 g, 5.98 mmol) was dissolved in methanol (10 mL). Methyl formate (0.4 mL, 6.58 mmol, 1.1 eq.) and sodium methoxide (0.03 mL, 0.59 mmol, 10 mol%) were then added and the reaction was left to stir at room temperature and monitored by TLC for 2 h. The solvent was then removed under reduced pressure. The resulting crude yellow solid was dissolved in acetone (50 mL) with *para*-toluenesulfonic acid (0.2 g, 0.59 mmol, 10 mol%) and 2,2-dimethoxypropane (7.5 mL, 59.8 mmol, 10.0 eq.). The reaction was then stirred at room temperature and monitored by TLC for 2 h. Solvents were removed under reduced pressure and the residue re-dissolved in dichloromethane and washed with saturated aqueous sodium hydrogen carbonate. Organic phases were dried (MgSO$_4$), filtered and solvents removed under reduced pressure to give the product as a yellow oil (0.27 g, 53%); ν_{max} (film)/cm^{-1} 3289, 2900, 1664, 1381, 1199, 1087; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.32 (3 H, s, C*H$_3$* at C11), 1.33 (3 H, s, C*H$_3$* at C12), 3.50 (1 H, dd, *J* 9.6, 17.2 Hz, 1H of C*H$_2$* at C9), 3.62 (1 H, dd, *J* 9.6, 10.0 Hz, 1H of C*H$_2$* at C9), 4.29 (1 H, m, C*H* at C8), 5.00 (1 H, d, *J* 4.0 Hz, C*H* at C7), 6.49 (1 H, d, *J* 8.4 Hz, -N*H*), 7.22 – 7.35 (5 H, m, 5 x C*H* arom. at C1, C2, C3, C5 & C6), 8.03 (1 H, s, -NHCO*H* at C13) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 18.52 (CH$_3$, C12), 29.70 (CH$_3$, C11), 45.49 (CH, C8), 64.60 (CH$_2$, C9), 71.63 (CH, C7), 99.70 (C, C10), 125.11 (2 x CH, arom CH), 128.14 (1 x CH, arom CH), 128.87 (2 x CH, arom CH), 137.99 (C, C4), 160.50 (C=O, C13); *m/z* (FAB) 236.1289; C$_{13}$H$_{17}$NO$_2$ [M+H$^+$] requires 236.1287, 258 (28), 236 (44) & 178 (100).

4.1.2   *N*-[(4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-amine (7)[2]

6   **7**
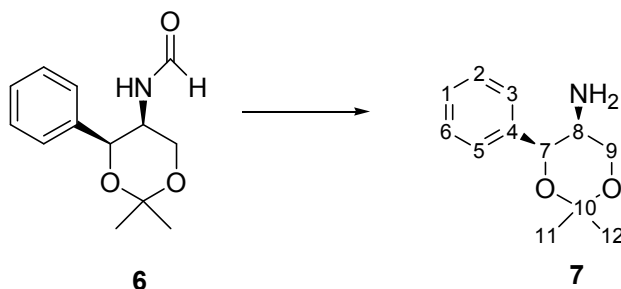
Formate protected acetonide (**6**) (0.26 g, 1.22 mmol) was dissolved in a mixture of hydrazine / water (85:15) (20 mL) and the reaction was heated under reflux for 3 h. The solution was then allowed to cool to room temperature before being extracted with ethyl acetate (3 x 20 mL). The organic layers were then combined and washed with brine (2 x 20 mL), dried (MgSO$_4$), filtered and the solvent removed under reduced pressure to give the desire product as a yellow oil (0.04 g, 13%); Found: C, 59.96; H, 8.08; N, 11.59. C$_{12}$H$_{17}$NO$_2$ requires C, 59.54; H, 8.27; N, 6.76 %; ν_{max} (film)/cm^{-1} 3364, 2990, 2141, 1653, 1498, 1379, 1198, 1087, 944; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.33 (3 H, s, C*H*$_3$ at C11), 1.33 (3 H, s, C*H*$_3$ at C12), 3.06 (1 H, s, C*H* at C8), 3.34 (1 H, dd, *J* 9.2, 9.6 Hz, 1H of C*H*$_2$ at C9), 3.46 (1 H, dd, *J* 9.2, 9.6 Hz, 1H of C*H*$_2$ at C9), 4.61 (1 H, d, *J* 5.2 Hz, C*H* at C7), 7.26 – 7.34 (5 H, s, 5 x C*H* arom. at C1, C2, C3, C5 & C6) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 18.58 (CH$_3$, C12), 29.75 (CH$_3$, C11), 49.64 (CH, C8), 60.01 (CH$_2$, C9), 73.74 (CH, C7), 99.17 (C, C10), 125.67 (2 x CH, arom CH), 127.42 (1 x CH, arom CH), 128.43 (2 x CH, arom CH),   139.49 (C, C4); *m/z* (FAB) 208.1336; C$_{12}$H$_{17}$NO$_2$ [M+H$^+$] requires 208.1337, 150 (62) & 208 (100).

4.1.3 2,2'-Bis-bromomethylphenyl (2)[3]

2
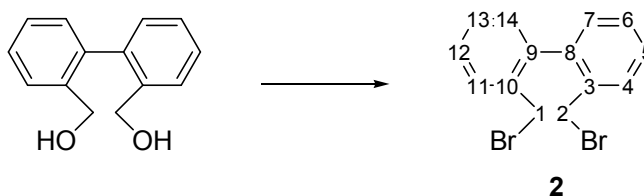
A suspension of 2,2'-biphenyl dimethanol (1.00 g, 4.66 mmol) in hydrobromic acid (20 mL, 48% in H_2O), was heated to 100 $^{\circ}$C for 1 h. The solution was then allowed to cool to room temperature before being extracted with diethyl ether (3 x 20 mL). The organic phases were then combined and washed with saturated aqueous sodium hydrogen carbonate (20 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure yielding a colourless solid (0.74 g, 77%); Found: C, 49.51; H, 3.57. $C_{14}H_{12}Br_2$ requires C, 49.45; H, 3.56 %; ν_{max} (film)/cm^{-1} 3442, 1643, 1475, 1443, 1220, 759, 606; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 4.20 (2 H, AB, J 10.0 Hz, CH_2 at C1), 4.35 (2 H, AB, J 10.0 Hz, CH_2 at C2), 7.26 (1 H, d, J 1.6 Hz, arom. CH at C14), 7.28 (1 H, d, J 1.2 Hz, arom. CH at C7), 7.40 (4H, ddt, J 1.6, 7.4, 18.4 Hz, 4 x arom. CH at C5, C6, C12 & C13), 7.40 (1 H, d, J 1.6 Hz, arom. CH at C11), 7.55 (1 H, d, J 1.6 Hz, arom. CH at C4) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 31.94 (2 x CH$_2$, C1 & C2), 128.30 (2 x arom. CH, C6 & C13), 128.6 (2 x CH arom. C5 & C12), 130.1 (2 x arom. CH, C7 & C14), 130.66 (2 x arom. CH, C4 & C11), 135.83 (2 x C quat. arom., C3 & C10), 139.28 (2 x C quat. arom., C8 & C9); m/z (EI) 337.9312; $C_{14}H_{12}Br_2$ (cation) requires 337.9306, 259 (54), 165 (67) & 179 (100).

4.1.4 5,7-dihydrodibenzo[*c,e*]oxepine (1a)[3]

1a
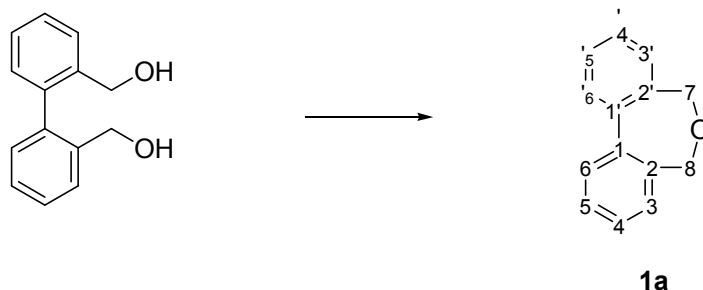
A suspension of 2,2'-biphenyl dimethanol (4.22 g, 19.7 mmol), in hydrobromic acid (60 mL, 24% in H_2O), was heated at 100 °C for 40 min. The cloudy beige solution was allowed to cool, and the aqueous phase extracted with diethyl ether (3 x 50 mL). The organic layers were combined and washed with saturated aqueous sodium hydrogen carbonate (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and the solvents removed under reduced pressure yielding a colourless solid that was re-dissolved in hot ethyl acetate / light petroleum, giving colourless crystals which were collected by suction filtration filtration (3.71 g, 96 %), mp 70-71 °C; Found: C, 84.89; H, 6.16. $C_{14}H_{12}O$ requires C, 85.68; H, 6.16 %; ν_{max} (film)/cm^{-1} 1566, 1196, 1073, 1042, 903, 892, 756, 601; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 4.36 (4 H, s, 2 x C*H*$_2$ at C7 & C7'), 7.39-7.45 (4 H, m, 4 x arom. C*H* at C4, C4', C5 & C5'), 7.48-7.52 (2 H, m, 2 x arom. C*H* at C3 & C3'), 7.55-7.57 (2 H, m, 2 x arom. C*H* at C6 & C6') ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 67.53 (CH$_2$, C7 & C7'), 127.47 (2 x arom. CH, C6 & C6'), 128.26 (2 x arom. CH,, C4 & C4'), 128.92 (2 x arom. CH, C3 & C3'), 129.70 (2 x arom. CH, C5 & C5'), 135.13 (2 x quat. C, C1 & C1'), 141.18 (2 x quat. C, C2 & C2'); *m/z* 196.0886; $C_{14}H_{12}O$ (cation) requires 196.0888, 195 (36), 165 (47), 196 (58) & 167 (100).

4.1.5   2-[2-(bromomethyl)phenyl]benzene carbaldehyde (1b)[3]

1a   **1b**
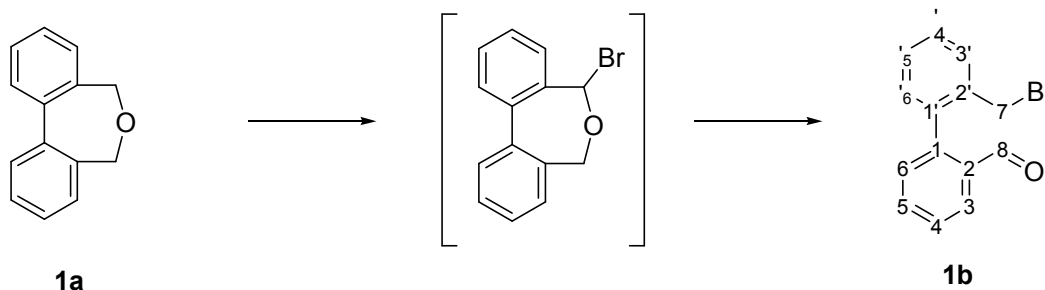
To an ice cooled solution of **1a** (2.00 g, 10.2 mmol), in carbon tetrachloride (50 mL), in a round bottom flask fitted with a reflux condenser bromine (0.57 mL, 11 mmol) was added in carbon tetrachloride (6 mL), dropwise over 5 min causing the reaction to turn deep red. The cooling bath was removed and the reaction mixture heated under reflux until pale yellow and liberation of HBr ceased (~1 h.). The solvent was removed under reduced pressure, and the resulting product dissolved in diethyl ether (100 mL), washed with saturated aqueous sodium hydrogen carbonate (50 mL) and brine (50 mL), dried (MgSO$_4$), filtered and the solvents removed under reduced pressure yielding a pale yellow oil (1.40 g, 50 %); ν_{max} (film)/cm^{-1} 1692, 1593, 1255, 1221, 1194, 761; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 4.19 (2 H, dd, J 10.4, 11.2 Hz, CH_2 at C7), 7.18-7.71 (8 H, m, 8 x arom. CH at C3, C3', C4, C4', C5, C5', C6 & C6')), 9.71 (1 H, s, -CHO at C8) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 31.04 (CH$_3$, C7), 127.53 (2 x arom. CH, C6 & C6'), 129.03 (2 x arom. CH, C4 & C4'), 129.11 (2 x arom. CH, C3 & C3'), 129.92 (2 x arom. CH, C5 & C5'), 140.38 (2 x quat. C, C1 & C1'), 140.14 (2 x quat. C, C2 & C2'), 190.75 (C8, CHO).

4.1.6   (−)-2-[(4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl]-5*H*-dibenzo[*c*,*e*]azepinium tetraphenylborate (9)[3]
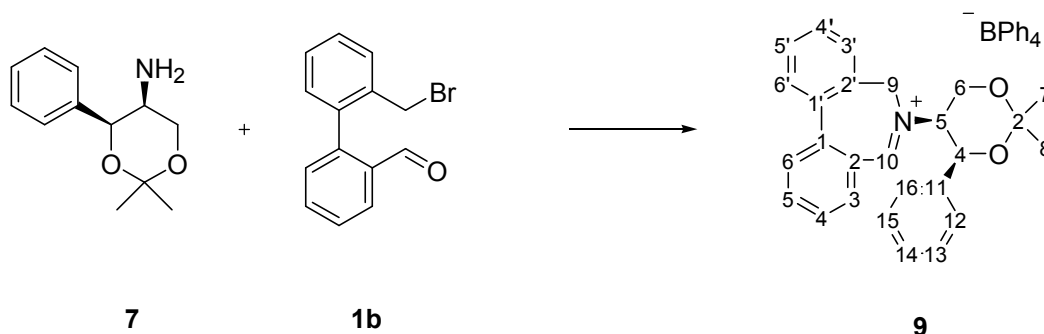
A solution of the amine **7** (0.12 g, 0.60 mmol) in ethanol (10 mL per g of amine, 1 eq.), was added dropwise to a pre-cooled solution of 2-[2-(bromoethyl)phenyl] benzene carbaldehyde (**1b**) (0.18 g, 0.66 mmol, 1.1 eq.), in ethanol (10 mL per g) at 0 °C.   The reaction mixture was stirred overnight at room temperature.   Sodium tetraphenylborate (0.23 g, 0.66 mmol, 1.1 eq.), was added in one protion in the minimum amount of acetonitrile and the reaction mixture stirred for 5 min.   Solvents were removed under reduced pressure and the resulting residue dissolved in ethanol, followed by the slow addition of H_2O.   Pale yellow crystals were then collected by suction filtration and washed with cool ethanol (0.38 g, 90%), m.p. 186 – 187 °C (lit.[3] m.p. 187 – 188 °C); $[\alpha]^{20}_D$ − 38.5° (*c* 1.3, MeCN) (lit.[3] $[\alpha]^{20}_D$ − 44.0 (*c* 1.01, MeCN)); Found: C, 85.21; H, 4.54; N, 1.99. $C_{26}H_{25}NO_2$ requires C, 85.22; H, 6.72; N, 1.99 %; ν_{max} (film)/cm^{-1} 3053, 3036, 3000, 1631, 1578, 1478, 1449, 1383, 1202, 1113, 848, 733, 703; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ$_H$ 1.73 (3 H, s C*H*$_3$ at C7), 1.75 (3 H, s, C*H*$_3$ at C8), 4.06 – 4.09 (1 H, m, 1H of C*H*$_2$ at C9), 4.21 – 4.28 (1 H, m, 1H of C*H*$_2$ at C9), 4.61 – 4.73 (2 H, m, C*H*$_2$ at C6), 5.61 – 5.78 (1 H, m, -NC*H* at C5), 5.91 (1 H, d, *J* 1.2 Hz, -PhC*H* at C4), 6.77-6.80 (4 H, m, 4 x arom. C*H para* in BPh$_4$), 6.90-6.94 (8 H, m, 8 x arom. C*H ortho* in BPh$_4$), 7.41-7.72 (8 H, m, 8 x arom. C*H meta* in BPh$_4$), 7.75-8.05 (13 H, m, 13 x arom. C*H* at C3, C3', C4, C4', C5, C5', C6, C6', C12, C13, C14, C15 & C16), 9.0 (1 H, s, C*H* at C10) ppm; ^{13}C NMR (100 MHz, CD$_3$CN): δ$_C$ 18.05 (CH$_3$, C8), 28.41 (CH$_3$, C7), 55.77 (CH$_2$, C9), 60.81 (CH$_2$, C6), 66.12 (CH, C5), 70.49 (C, C4), 99.87 (quat. C, C2), 120.42 (8 x

CH arom., *ortho* in BPh$_4$ gp.), 124.10 (4 x CH arom., *para* in BPh$_4$ gp.), 124.16 (2 x CH arom., C13 & C15), 124.19 (2 x CH arom., C12 & C16), 124.39 (CH arom., C14), 127.59 (CH arom., C4'), 127.69 (CH arom., C6'), 128.19 (CH arom., C3'), 128.26 (CH arom., C5'), 129.00 (CH arom., C4), 129.31 (CH arom., C6), 129.39 (CH arom., C3), 132.58 (C quat. arom., C1'), 133.57 (CH arom., C5), 134.95 (8 x CH arom., *meta* in BPh$_4$ gp.), 135.23 (C quat. arom., C1), 140.46 (C quat. arom., C2), 160.30 (4 x C quat., arom., q, C-B in BPh$_4$ gp.), 170.11 (C=N, C10); *m/z* 384.1964; C$_{26}$H$_{26}$NO$_2$ (cation) requires 384.1964.

4.1.7   *N*-[(4*S*,5*S*)-2,2-Dimethyl-4-[4-(methylsulfanyl)-phenyl]-1,3-dioxan-5-yl]formamide (6)[1,2]

4   **6**
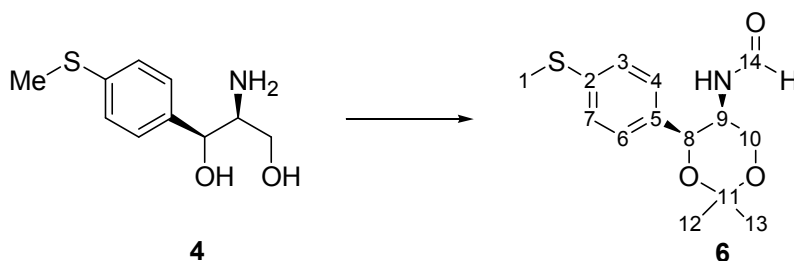
(1*S*,2*S*)-2-Amino-1-(4-(methylthio)phenyl)-1,3-propanediol (1.50 g, 7.03 mmol) was dissolved in methanol (10 mL). Methyl formate (0.49 mL, 7.14 mmol, 1.1 eq.) was then added, followed by sodium methoxide solution (0.04 mL, 0.70 mmol, 10 mol%). The reaction was then stirred at room temperature for 3 h. The solvents were removed under reduced pressure to yield a yellow oil. The crude oil was dissolved in acetone (75 mL) and 2,2-dimethoxypropane (8.64 mL, 70.32 mmol, 10 eq.) and *para*-toluenesulfonic acid (0.13 g, 0.70 mmol, 10 mol%) added. The reaction was then stirred at room temperature for 16 h. The solvents were then removed under reduced pressure and the residue re-dissolved in ethyl acetate, washed with saturated aqueous sodium hydrogen carbonate (2 x 30 mL), brine (30 mL), dried (MgSO$_4$) and the solvents removed under reduced pressure to give a colourless oil (1.74 g, 88%), [α]^{20}$_D$ + 1.2 (*c* 1.3, CHCl$_3$); ν$_{max}$ (film)/cm$^-$^{1} 3301, 2987, 2260, 1684, 1495, 1380, 1197, 1084, 950; ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ 1.55 (3 H, s, C*H$_3$* at C12), 1.58 (3 H, s, C*H$_3$* at C13), 2.47 (3 H, s, C*H$_3$* at C1), 3.87 (1 H,

dd, J 12.0, 12.4 Hz, 1H of CH_2 at C10), 4.26 (1 H, dd, J 12.0, 12.0 Hz, 1H of CH_2 at C10) 4.27 – 4.32 (1 H, m, CH at C9), 5.17 (1 H, d, J 1.2 Hz, CH at C8), 6.28 (1 H, d, J 8.8 Hz, -NH), 7.22 (4 H, s, arom CH at C3, C4, C6 & C7), 7.97 (1 H, s, NHCOH at C11) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 15.74 (CH$_3$, C13), 18.52 (CH$_3$, C12), 29.67 (SO$_2$CH$_3$, C1), 45.30 (CH, C9), 64.56 (CH$_2$, C10), 71.37 (CH, C8), 99.71 (C, C11), 125.76 (2 x CH, arom CH), 126.43 (2 x CH, arom CH), 134.88 (C, C2), 138.47 (C, C5), 160.53 (C=O, C14); m/z 281.1083; C$_{14}$H$_{19}$NO$_3$S (cation) requires 281.1083.

4.1.8 N-[(4S,5S)-2,2-Dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-yl]formamide[2]

6
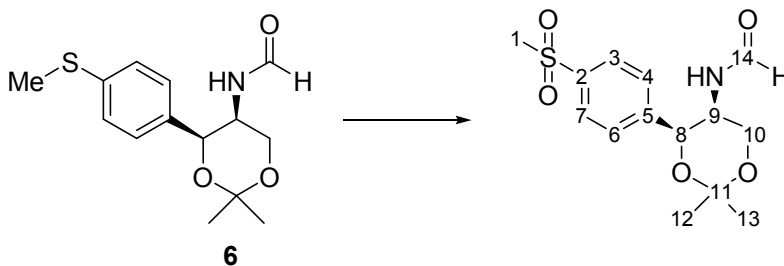
Formate protected acetonide (**6**) (1.74 g, 6.81 mmol) was dissolved in dichloromethane and cooled to 0 °C. m-CPBA (4.58 g, 20.44 mmol, 3 eq.) was then added and the reaction stirred at room temperature for 16 h. The organic phases were then washed with saturated sodium hydrogen carbonate (2 x 30 mL), brine (30 mL), dried (MgSO$_4$), filtered and the solvents removed under reduced pressure to give the dried compound as colourless crystals (2.13 g, 99%), mp 146 - 149 °C; $[\alpha]^{20}_D$ – 10.6 (c 1.5, CHCl$_3$); ν_{max} (film)/cm^{-1} 3052, 2990, 1678, 1514, 1380, 1300, 1239, 1200, 1151, 1085, 948; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.58 (3 H, s, CH_3 at C12), 1.61 (3 H, s, CH_3 at C13), 3.04 (3 H, s, CH_3 at C1), 3.89 (1 H, dd, J 4.2, 12.2 Hz, 1H of CH_2 at C10), 4.34 (1 H, d, J 12.0 Hz, 1H of CH_2 at C10), 4.42 (1 H, d, J 10.4 Hz, CH at C9), 5.29 (1 H, s, CH at C8), 6.51 (1 H, d, J 9.6 Hz, -NH), 7.90 (2 H, d, J 8.4 Hz, 2 x arom. CH at C3 & C7), 7.98 (2 H, d, J 6.4 Hz, 2 x arom. CH C4 & C6) 8.06 (1 H, s, CH at -HHCHO) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 18.50 (CH$_3$, C13), 29.56 (CH$_3$, C12), 44.48 (SO$_2$CH$_3$, C1), 45.31 (CH, C9), 64.48 (CH$_2$, C10), 71.51 (CH, C8), 100.34 (C, C11), 127.57 (2 x CH, arom CH), 127.72

(2 x CH, arom CH), 139.66 (CH, C2), 144.31 (CH, C5), 161.06 (C=O, C14); *m/z* 314.1068; $C_{14}H_{19}NO_5S$ [M+H$^+$] requires 314.1062.

4.1.9 *N*-[(4*S*,5*S*)-2,2-Dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-amine (7)[3]

7
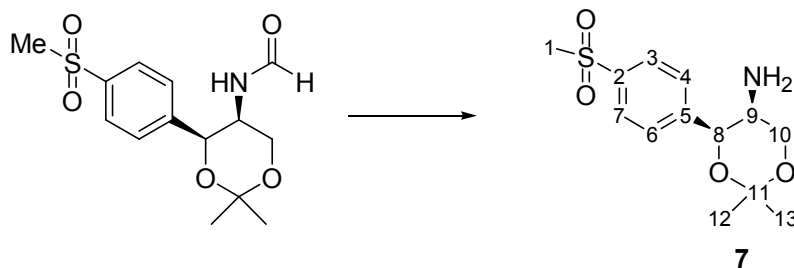
Amine (**5**) (1.83 g, 6.36 mmol) was dissolved in a mixture of hydrazine / water (85:15) (30 mL) and the solution heated under reflux for 3 h. The reaction mixture was allowed to cool to room temperature and extracted with ethyl acetate (3 x 20mL). Organic phases were combined, washed with water (2 x 20mL), dried (MgSO₄), filtered and the solvents removed under reduced pressure to give colourless crystals (0.64 g, 38%), m.p. 124 – 126 °C (lit.[3] m.p. 120 – 122 °C); $[\alpha]^{20}_D$ + 47.1 (*c* 1.7, CHCl₃) (lit.[3] $[\alpha]^{20}_D$ + 50.0° (*c* 1.0, CHCl₃)); ν_{max} (film)/cm^{-1} 3367, 2991, 1599, 1380, 1148, 1077, 949; ^{1}H NMR (400 MHz, CDCl₃): δ_H 1.56 (6 H, s, C*H*₃ at C12), 2.85 (1 H, s, C*H*₃ at C12), 3.06 (3 H, s, C*H*₃ at C1), 3.89 (1H, dd, *J* 12.0, 12.0 Hz, 1H of C*H*₂ at C10), 4.33 (1 H, dd, *J* 12.0, 11.6 Hz, 1H of C*H*₂ at C10), 5.18 (1 H, s, C*H* at C8), 7.55 (2 H, d, *J* 8.0 Hz, 2 x arom. C*H* at C4 & C6), 7.96 (2 H, d, *J* 8.4 Hz, 2 x arom. C*H* at C3 & C7) ppm; ^{13}C NMR (100 MHz, CDCl₃): δ_C 18.56 (CH₃, C13), 29.66 (CH₃, C12), 44.55 (SO₂CH₃, C1), 49.38 (CH, C9), 66.29 (CH₂, C10), 73.43 (CH, C8), 99.51 (C, C11), 127.31 (2 x CH, arom CH), 127.52 (2 x CH, arom CH), 139.45 (CH, C2), 145.11 (CH, C5); *m/z* (FAB) 286.1117; $C_{13}H_{19}NO_4S$ [M+H$^+$] requires 286.1113, 136 (61), 154 (62), 228 (83), & 286 (100).

4.1.10 (−)-2-[4S,5S)-2,2-Dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-yl]-5H-dibenzo[c,e] amine (8)[3]
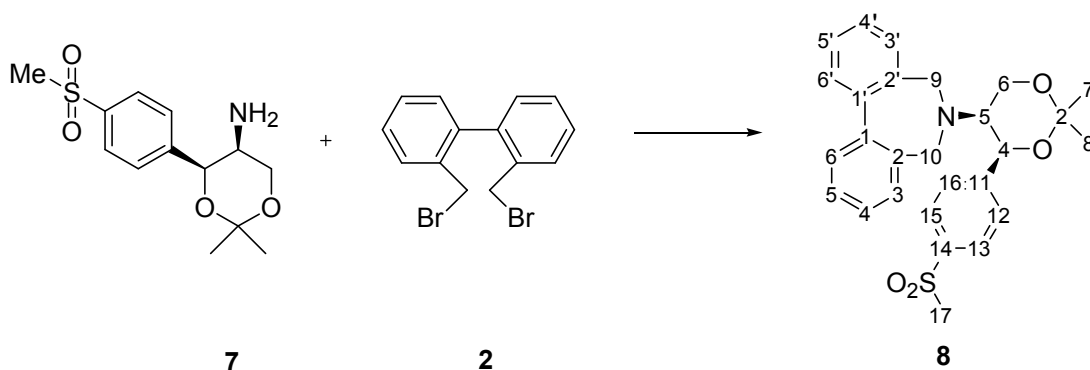
Amine (**7**) (0.55 g, 1.93 mmol) was dissolved in acetonitrile (40 mL) and dibromo compound (**2**) (0.60 g, 1.75 mmol, 1.0 eq.) and potassium carbonate (0.73 g, 5.25 mmol, 3.0 eq.) were added. The resulting solution was then heated under reflux for 3 h. After being allowed to cool to room temperature, the solid yellow product was re-dissolved in dichloromethane (40 mL) and washed with water (2 x 30mL), dried (MgSO$_4$), filtered and the solvents removed under reduced pressure yielding a pale yellow crystalline solid (0.75 g, 93%), mp 118 − 121 °C; ν$_{max}$ (film)/cm^{-1} 3052, 2997, 1636, 1599, 1511, 1477, 1454, 1385, 1308, 1200, 1147, 1085, 947, 840; ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ 1.59 (3 H, s, CH_3 at C7), 1.59 (3 H, s, CH_3 at C8), 3.05 (1 H, s, CH at C5), 3.06 (3 H, s, CH_3 at C17), 3.43 (2 H, AB, J 12.6 Hz, 1H of 2 x CH_2 at C9 & C10), 3.68 (2 H, AB, J 12.6 Hz, 1H of 2 x CH_2 at C9 & C10), 4.23 − 4.24 (2 H, m, CH_2 at C6), 5.30 (1 H, s, CH at C4), 7.18 (2 H, t, J 3.8 Hz, 2 x arom. CH at C3 & C3'), 7.27 (2 H, t, J 5.4 Hz, 2 x arom. CH at C6 & C6'), 7.36 − 7.42 (4 H, m, 4 x arom. CH at C4, C4', C5 & C5'), 7.65 (2 H, d, J 8.0 Hz, 2 x arom. CH at C12 & C16), 7.92 (2 H, d, J 8.4 Hz, 2 x arom. CH at C13 & C15) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ$_C$ 19.10 (CH$_3$, C7), 19.11 (CH$_3$, C8), 30.15 (SO$_2$CH$_3$, C17), 44.68 (CH, C5), 53.95 (NCH, C10), 60.09 (CH$_2$, C6), 61.58 (CH$_2$, C9), 74.22 (CH, C4), 98.50 (quat. C, C2), 126.75 (2 x CH arom., C13 & C15), 127.09 (2 x CH arom., C12 & C16), 127.44 (arom. CH, C14), 127.69 − 129.19 (8 x CH arom., C3, C3', C4, C4', C5, C5', C6 & C6'), 136.16 (C quat. arom., C11), 140.0 (2 x C quat. arom., C1

& C1'), 140.82 (2 x C quat. arom., C2 & C2'); m/z (FAB) 464.1888; $C_{27}H_{29}NO_4S$ [M+H$^+$] requires 464.1896, 462 (34), 237 (69), 221 (90) & 179 (100).

4.1.11 (−)-2-[4S,5S)-2,2-Dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-yl]-5H-dibenzo[c,e]azepinium tetraphenylborate (10)[3]

8   **10**
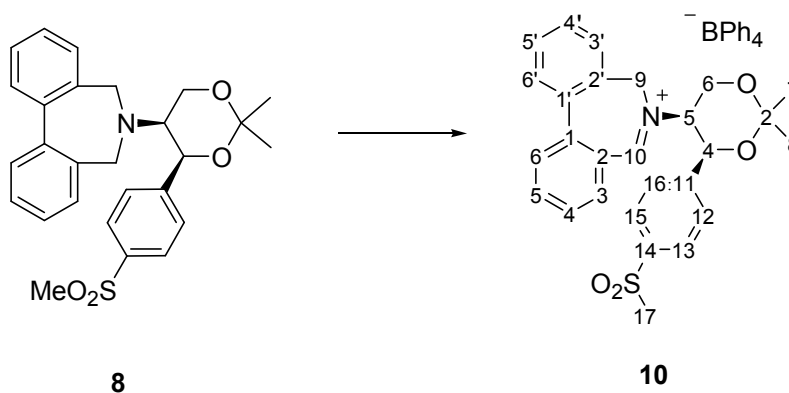
Compound (**8**) (0.74 g, 1.60 mmol) was dissolved in dichloromethane (40 mL) and *N*-bromosuccinimide (0.34 g, 1.92 mmol, 1.2 eq.) added. The mixture was then heated under reflux for 4 h, after which the reaction was allowed to cool to room temperature and the solvent removed under reduced pressure. The crude yellow oil was re-dissolved in ethanol and sodium tetraphenylborate (0.60 g, 1.76 mmol, 1.1 eq.) dissolved in the minimum amount of acetonitrile was added in one portion to the reaction mixture and stirred for 5 min. The solvents were then removed under reduced pressure to yield a yellow residue that was re-dissolved in hot ethanol, and yellow crystals were collected by suction filtration, washed with cold ethanol and diethyl ether (0.87 g, 70%), m.p. 120 – 123 ^{o}C (lit.[3] m.p. 162 – 165 ^{o}C); $[\alpha]^{20}_D$ – 46.7° (*c* 1.1, acetone) (lit.[3] $[\alpha]^{20}_D$ – 50.3 (*c* 1.09, acetone)); ν_{max} (film)/cm^{-1} 3000, 2999, 2301, 1500, 1311, 1149, 1075, 949; ^{1}H NMR (400 MHz, CD$_3$CN): δ_H 1.73 (3 H, s, CH_3 at C7), 1.76 (3 H, s, CH_3 at C8), 3.00 (1 H, s, -NCH at C5), 3.12 (3 H, s, CH_3 at C17), 4.12 – 4.18 (1 H, m, 1H of CH_2 at C9), 4.26 – 4.34 (1 H, m, 1H of CH_2 at C9), 4.68 – 4.72 (2 H, m, CH_2 at C6), 5.77 (1 H, s, CH at C4), 6.79 (4 H, t, *J* 7.2 Hz, 4 x arom. CH in BPh$_4$), 6.92 (8 H, t, *J* 7.2 Hz, 8 x arom. CH in BPh$_4$), 7.16-7.18 (8 H, m, 8 x arom. CH in BPh$_4$), 7.56-8.00 (12 H, m, 12 x arom. CH at C3, C3', C4, C4', C5, C5', C6, C6', C12, C13, C15 & C16), 9.12 (1 H, s) ppm; ^{13}C NMR

(100 MHz, DMSO-d_6): δ_C 19.28 (CH$_3$, C7), 29.67 (CH$_3$, C8), 44.23, (SCH$_3$, C17), 57.04 (CH$_2$, C9), 62.07 (CH$_2$, C6), 66.80 (NCH, C5), 71.35 (CH, C4), 101.34 (C quat., C2), 121.77 (4 x CH arom., *para* in BPh$_4$ gp.), 122.3 (8 x CH arom., *ortho* in BPh$_4$ gp.), 126.43 (C quat. arom., C2), 126.79 (2 x CH arom., C13 & C15), 127.39 (2 x CH arom., C12 & C16), 128.64 (C quat. arom., C14), 129.02 (CH arom., C5'), 129.45 (CH arom., C4), 129.59 (CH arom., C6), 130.35 (CH arom., C6'), 130.61 (CH arom., C4'), 130.80 (CH arom., C3), 135.06 (CH arom., C5), 126.19 (8 x CH arom., *meta* in BPh$_4$ gp.), 136.66 (CH arom., C3'), 137.06 (C quat. arom., C2'), 141.48 (C quat. arom., C1), 141.68 (C quat. arom., C1'), 142.01 (C quat. arom., C11), 164.1 (4 x C quat. arom., q, C-B in BPh$_4$ gp.), 171.63 (C=N, C10); *m/z* (FAB) 462.1734; C$_{27}$H$_{29}$NO$_4$S [M+H$^+$] requires 462.1039, 220 (29), 136 (46), 154 (57) & 462 (100).

4.1.12 2-(2-Bromoethyl) benzaldehyde (3)[5]
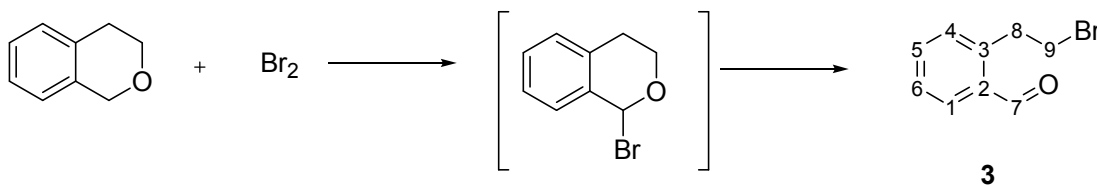
Isochroman (9.3 mL, 74.5 mmol) was dissolved in cyclohexane (30 mL) and cooled to 0 °C. Bromine (4.1 mL, 81.9 mmol, 1.1 eq.) was then added slowly, and the reaction heated under reflux until a pale yellow colour is observed. Reaction was then allowed to cool to room temperature and the solvents removed under reduced pressure. The crude residue was re-dissolved in hydrobromic acid (20 mL), and the reaction heated under reflux for 10 minutes, the reaction was then allowed to cool to room temperature. Extraction was carried out with diethyl ether (3 x 100 mL), and the organics washed with water (2 x 100 mL) and a saturated sodium hydrogen carbonate solution (100 mL), dried (MgSO$_4$), filtered and the solvents removed under reduced pressure yielding a dark green residue, distillation under vacuum yielded the desired compound as a deep red oil (10.60 g, 67%); ν_{max} (film)/cm^{-1} 2742, 1697, 1600, 1575, 1260, 1193, 755; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 3.55-3.65 (4 H, m, 2 x C*H$_2$* at C8 & C9), 7.32-7.36 (1 H, m, arom. C*H* at

C4), 7.49 (1 H, dt, *J* 7.6, 1.6 Hz, arom. C*H* at C6), 7.56 (1 H, dt, *J* 7.6, 1.6 Hz, arom. C*H* at C5), 7.88 (1 H, dd, *J* 7.6, 1.6 Hz, arom. C*H* at C1), 10.15 (1 H, s, C*H*O at C9) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 31.25 & 36.27 (2 x CH$_2$, C8 & C9), 127.67 (arom. CH, C6), 132.09 (arom. CH, C4), 133.72 (arom. CH, C5), 133.88 (arom. CH, C1), 140.30 (2 x CH quat. arom., C2 & C3), 193.0 (CHO, C9) ; *m/z* (FAB) 211.9835; C$_9$H$_9$BrO (cation) requires 211,9837, 213 (18), 149 (42) & 133 (100).

4.1.13 (+)-*N*-[(4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl]-3,4-dihydroisoquino-linium tetraphenylborate (12)[3]
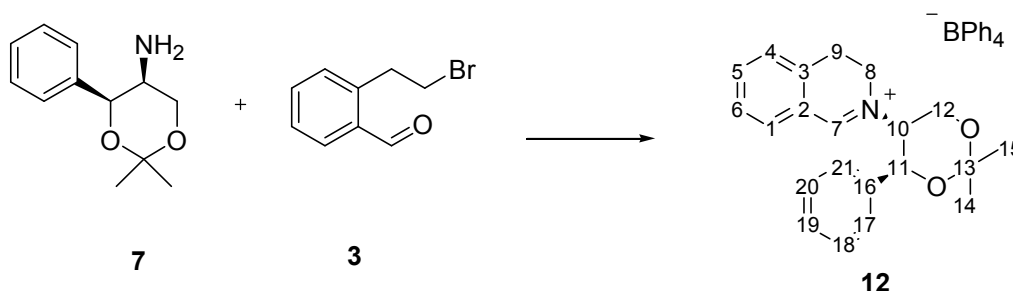
A solution of amine (**7**) (1.00 g, 4.83 mmol) in ethanol (10 mL) was added to a solution of bromoaldehyde (**3**) (1.13 g, 5.31 mmol, 1.1 eq.) in ethanol (10 mL) at 0 °C. The solution was then stirred at room temperature for 15 h, giving a yellow solution. Sodium tetraphenylborate (1.82 g, 5.31 mmol, 1.1 eq.) in a minimum amount of acetonitrile was added in one portion to the reaction mixture and stirred for 10 minutes at room temperature. Solvents were then removed under reduced pressure to yield a yellow residue that was re-dissolved in dichloromethane (40 mL), washed with water (2 x 30 mL) and brine (2 x 30 mL), dried (MgSO$_4$), filtered and the solvents removed under reduced pressure to yield a yellow solid. Recrystallisation from hot ethanol yielded the desired compound as yellow solid (1.21 g, 33%), m.p. 167 – 169 °C (lit.[3] m.p. 169 – 170 °C); $[\alpha]^{20}_D$ + 39.2 (*c* 1.5, MeCN) (lit.[3] $[\alpha]^{20}_D$ + 38.6 (*c* 2.70, MeCN); ν_{max} (film)/cm^{-1} 1634, 1602, 1571, 1478, 1265, 1201, 1164, 1112, 1083; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.53 (3 H, s, C*H*$_3$ at C14), 1.57 (3 H, s, C*H*$_3$ at C15), 2.24 – 2.35 (1 H, m, 1H of C*H*$_2$ at C9), 2.39 – 2.46 (1 H, m, 1H of C*H*$_2$ at C9), 2.89 – 2.94 (2 H, m, C*H*$_2$ at C8), 3.53 (1 H,

dd, J 14.0, 14.4 Hz, 1H of CH_2 at C12), 3.72 (1 H, dd, J 14.0, 14.4 Hz, 1H of CH_2 at C12), 5.02 (1 H, d. J 3.0 Hz, -NCH at C10), 5.16 (1 H, d, J 2.4 Hz, PhCH at C11), 6.91 (4 H, t, J 7.2 Hz, 4 x arom. CH *para* in BPh$_4$), 7.06 (8 H, t, J 7.2 Hz, 8 x arom. CH *ortho* in BPh$_4$), 7.28 – 7.34 (8 H, m, 8 x arom. CH *meta* in BPh$_4$), 7.36 (1 H, t, J 7.5 Hz, arom. CH), 7.69 (1 H, s, arom. CH), 7.72 – 7.80 (3 H, m, 3 x arom. CH), 7.90 (2 H, d, J 8.2 Hz, 2 x arom. CH in phenyl group), 7.95 (2 H, d, J 8.2 Hz, 2 x arom. CH in phenyl group), 8.08 (1 H, s, -N=CH at C7) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 18.80 (CH$_3$, C14), 25.42 (CH$_3$, C15), 29.45 (CH$_2$, C8), 52.49 (CH$_2$, C9), 62.79 (CH$_2$, C12), 66.74 (CH, C10), 71.76 (C, C11), 101.0 (quat C, C13), 122.25 (8 x CH arom., *ortho* in BPh$_4$ gp.), 125.99 (2 x CH arom., C20 & C18), 126.02 (2 x CH arom., C21 & C17), 126.43 (CH arom., C19), 129.23 (2 x CH arom., *para* in BPh$_4$ gp.), 129.86 (2 x CH arom., *para* in BPh$_4$ gp.), 135.31 (8 x CH arom., *meta* in BPh$_4$ gp.), 137.04, 137.40 (4 x CH arom., C4, C5, C6 & C1), 137.90 (C quat. arom., C3), 139.51 (C quat. arom., C2), 143.0 (C quat. arom., C16), 164.90 (4 x CH, quat. arom. in BPh$_4$), 169.20 (C=N, C7); *m/z* (EI) 322.1809; C$_{45}$H$_{44}$BrNO$_2$ (cation) requires 322.1807.

4.1.14 (+)-*N*-{(4*S*,5*S*)-2,2-Dimethyl-4-[4-(methylsulfonyl)phenyl]-1,3-dioxan-5-yl}-3,4-dihydroisoquinolinium tetraphenylborate (13)[3]
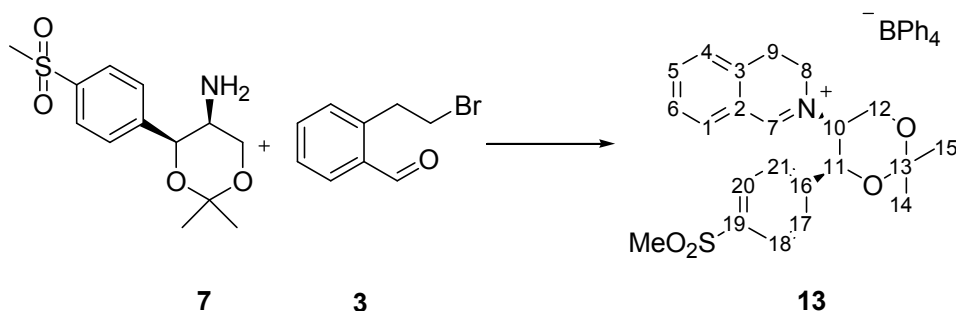
A solution of amine (**7**) (1.00 g, 4.83 mmol) in ethanol (10 mL) was added to a solution of bromoaldehyde (**3**) (1.13 g, 5.31 mmol, 1.1 eq.) in ethanol (10 mL) at 0 °C. The solution was then stirred at room temperature for 15 h, giving a yellow solution. Sodium tetraphenylborate (1.82 g, 5.31 mmol, 1.1 eq.) was dissolved in the minimum amount of acetonitrile, then added in one portion to the reaction mixture and stirred for 10 minutes

at room temperature. The solvents were then removed under reduced pressure to yield a yellow residue that was re-dissolved in dichloromethane (40 mL), washed with water (2 x 30 mL) and brine (2 x 30 mL), dried (MgSO$_4$), filtered and the solvents removed under reduced pressure to yield a yellow solid. This was re-dissolved in hot ethanol, and a pale yellow solid collected by suction filtration (1.21 g, 33%), m.p. 200 – 202 °C (lit.[3] m.p. 199 – 201 °C); $[\alpha]^{20}_D$ + 125.8° (*c* 1.2, acetone) (lit.[3] $[\alpha]^{20}_D$ + 126.7 (*c* 1.2, acetone)); ν_{max} (film)/cm^{-1} 1635, 1602, 1573, 1478, 1382, 1313, 1266, 1202, 1148, 1076, 1031, 955; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.70 (3 H, s, C*H*$_3$ at C14), 1.75 (3 H, s, C*H*$_3$ at C15), 3.02 (3 H, s, C*H*$_3$ at C22), 3.76-3.84 (1 H, m, 1H of C*H*$_2$ at C9), 3.90-4.12 (2 H, m, C*H*$_2$ at C8), 4.27-4.34 (1 H, m, 1H of C*H*$_2$ at C9), 4.62 (1 H, dd, *J* 13.6, 14.7 Hz, 1H of C*H*$_2$ at C12), 4.73-4.80 (1 H, m, -NC*H* at C10), 4.86 (1 H, dd, *J* 13.6, 14.7 Hz, 1H of C*H*$_2$ at C12), 6.14 (1 H, d, *J* 2.8 Hz, PhC*H* at C11), 6.77 (4 H, t, *J* 7.2 Hz, 4 x arom. C*H para* in BPh$_4$), 6.92 (8 H, t, *J* 7.2 Hz, 8 x arom. C*H ortho* in BPh$_4$), 7.31-7.35 (8 H, m, 8 x arom. C*H meta* in BPh$_4$), 7.54 (1 H, t, *J* 7.6 Hz, arom. C*H*), 7.65-7.81 (3H, m, 3 x arom. C*H*), 7.87 (2 H, d, *J* 8.0 Hz, 2 x arom. C*H* in phenyl group), 7.97 (2 H, d, *J* 8.0 Hz, 2 x arom. C*H* in phenyl group), 9.39 (1 H, s, -N=C*H* at C7) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 18.82 (CH$_3$, C14), 29.27 (CH$_3$, C17), 29.47 (CH$_2$, C8), 44.30 (SCH$_3$, C22), 52.10 (CH$_2$, C9), 62.81 (CH$_2$, C17), 66.24 (CH, C10), 71.60 (CH, C11), 101.31 (C quat., C18), 122.26 (8 x CH arom., *ortho* in BPh$_4$ gp), 126.0 (2 x CH arom., C18 & C20), 127.60 (2 x CH arom., C17 & C21), 128.91 (CH arom., C19), 129.40 (2 x CH arom., *para* in BPh$_4$ gp.), 130.20 (2 x CH arom., *para* in BPh$_4$ gp.), 135.57 (8 x CH arom., *meta* in BPh$_4$ gp.), 137.04, 137.90 (4 x CH arom., C4, C5, C6 & C1), 139.71 (C quat. arom., C2), 142.10 (C quat. arom., C16), 165.0 (4 x C quat. arom., in BPh$_4$ gp.), 169.80 (C=N, C7); *m/z* (EI) 400.1586; C$_{45}$H$_{44}$BrNO$_2$ (cation) requires 400.1583.

4.1.15 (R)-(4S,5S)-2,2-dimethyl-4-phenyl-1,3-dioxane-5-yl]-3H-4-azapinium-cyclohepta[2,1-a;3,4-a']dinaphthalene tetraphenylborate (50)[4]
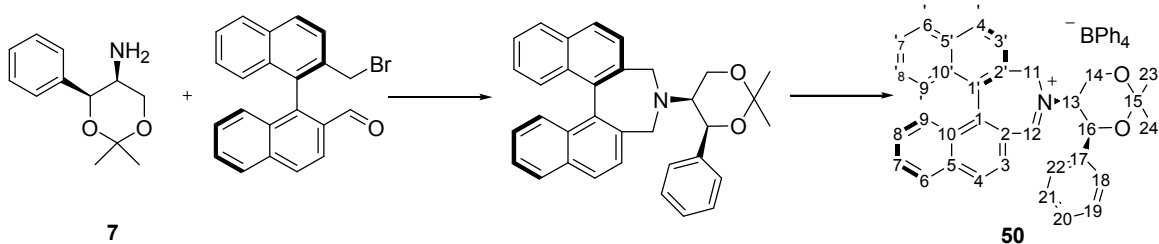
A solution of the amine (**7**) (0.55 g, 2.67 mmol) in ethanol (10 mL per g of amine) was added dropwise to a solution of aldehyde (1.00 g, 2.94 mmol, 1.1 eq.) in ethanol (10 mL per g of carboxaldehyde) at 40 °C. The reaction mixture was stirred at 40 °C overnight. The yellow mixture was left to cool to room temperature before the addition of a solution of sodium tetraphenylborate (1.01 g, 2.94 mmol, 1.1 eq.) in the minimum amount of acetonitrile in one portion. The reaction mixture was stirred for a further 5 minutes, and the solvents removed under reduced pressure. The resulting yellow residue was dissolved in dichloromethane (20 mL) (40 mL per g of amine), and washed with water (2 x 20 mL), brine (2 x 20 mL), the organic phase dried (Na$_2$SO$_4$), and the solvents removed under reduced pressure resulting in a yellow solid. The solid was recrystallised from ethanol, and washed with cold ethanol before being dried (1.40 g, 85%), m.p. 112-114 °C (lit.[4] m.p. 111-113 °C); $[\alpha]^{20}_D$ – 98.8 (c 1.4, acetone) (lit.[4] $[\alpha]^{20}_D$ – 98.5 (c 1.04, acetone); ν_{max} (film)/cm^{-1} 3052, 2989, 1683, 1609, 1557, 1506, 1456, 1426, 1380, 1264, 1201, 1109, 961, 815, 733, 702; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.82 (3 H, s, CH$_3$ at C23), 1.87 (3 H, s, CH$_3$ at C24), 4.47 (1 H, d, J 14.4 Hz, upfield portion of ABX N-CHCHH-O at C14), 4.57 (1 H, d, J 13.6 Hz, downfield portion of ABX N-CHCHH-O at C14), 4.87-4.91 (1 H, m, PhCH at C16), 6.02-6.05 (1 H, m, NCH at C13), 6.78 (4 H, t, J 7.2 Hz, 4 x arom. CH para in BPh$_4$), 6.93 (8 H, t, J 7.6 Hz, 8 x arom. CH ortho in BPh$_4$), 6.96-7.14 (5 H, m, 5 x arom. CH at C18, C19, C20, C21 & C22), 7.17-7.22 (2 H, m, 2 x arom. CH), 7.34-7.37 (8 H, m, 8 x arom. CH meta in BPh$_4$), 7.42-7.49 (3 H, m, 3 x arom. CH), 7.53-7.62 (2H, m, 2 x arom. CH), 7.78-7.82 (1 H, m, arom. CH), 7.88 (1 H, d, J 6.8 Hz, arom. CH), 8.10 (1 H, d, J 8.8 Hz, arom. CH), 8.20 (1 H, d, J 5.6 Hz, arom. CH), 8.25 (1 H, d, J

8.4 Hz, arom. C*H*), 9.68 (1 H, s, *H*C=N at C12) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 19.32 (CH$_3$, C23), 29.20 (CH$_3$, C24), 57.10, 62.23, 68.43, 72.81, 102.56, 120.52, 122.65 (8 x CH arom., *ortho* in BPh$_4$), 126.30, 126.60, 126.70, 127.70, 128.12, 128.20, 128.40, 129.05, 129.20, 129.90, 130.05, 130.30, 130.60, 130.70, 131.80, 132.20, 132.58, 134.00, 134.20, 135.10 (8 x CH arom., *meta* in BPh$_4$), 136.62 & 137.83 (4 x CH arom., *para* in BPh$_4$), 143.75, 165.25 (4 x CH quat. arom., quat. in BPh$_4$), 172.40 (C=N, C12); *m/z* (EI) 484.2279; C$_{58}$H$_{50}$BNO$_2$ (cation) requires 484.2277, 320 (14) & 484 (100).

4.1.16 Synthesis of (R)-2,2'-bis(trifluoromethanesulfonate)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl (20)[6]

20

(R)-(+)-5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol (3.00 g, 10.19 mmol) and pyridine (2.07 mL, 25.48 mmol, 2.5 eq.), were dissolved in dichloromethane (50 mL), and the solution was cooled to 0 °C. Then triflic anhydride (4.65 mL, 22.41 mmol, 2.2 eq.) was added dropwise to the solution, and the solution was stirred at room temperature for 20 h. 2 M hydrochloric acid (25 mL) was then added to the reaction mixture and washed. The organic layer was washed three times with water (100 mL) and brine (100 mL). Organic phase was then dried (MgSO$_4$), filtered and solvents removed under reduced pressure giving a brown residue as a crude product. The crude product was recrystallised from hexanes giving the product as a brown solid (4.20 g, 74%); Found: C, 48.68; H, 3.79. C$_{22}$H$_{20}$F$_6$O$_6$S$_2$ requires C, 47.31; H, 3.61 %; ν_{max} (film)/cm^{-1} 2938, 1416, 1211, 1140, 933, 836, 736; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.68-1.76 (4 H, m, 2 x C*H*$_2$ at C8 & C8'), 1.77-1.85 (4 H, m, 2 x C*H*$_2$ at C7 & C7'), 2.28 (2 H, *dt*, *J* 6.4, 6,8, 17.2 Hz, 2 x C*H* at C9 & C9'), 2.42 (2 H, *dt*, *J* 6.0, 6,2, 16.8 Hz, 2 x C*H* at C9 & C9'), 2.85 (4 H, *t*, *J* 6.0

Hz, 2 x CH_2 at C6 & C6'), 7.16 (2 H, *d*, *J* 8.8 Hz, 2 x C*H* arom. at C3 & C3'), 7.22 (2 H, *d*, *J* 8.4 Hz, 2 x C*H* arom. at C4 & C4') ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 22.32 (2 x CH$_2$, C7 & C7'), 22.37 (2 x CH$_2$, C8 & C8'), 27.49 (2 x CH$_2$, C9 & C9'), 29.41 (2 x CH$_2$, C6 & C6'), 118.10 (2 x CH arom., C3 & C3'), 127.04 (2 x C quat. arom., C1 & C1'), 130.09 (2 x CH arom., C4 & C4'), 138.26 (2 x C quat., C5 & C5'), 139.27 (2 x C quat., C10 & C10'), 144.76 (2 x C quat. arom., C2 & C2'); *m/z* (EI) 560.0757; C$_{22}$H$_{22}$F$_6$O$_6$S$_2$ [M+H]$^+$ requires 560.0752.

4.1.17 Synthesis of (R)-2,2'-bis(carbomethoxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl (21)[6]
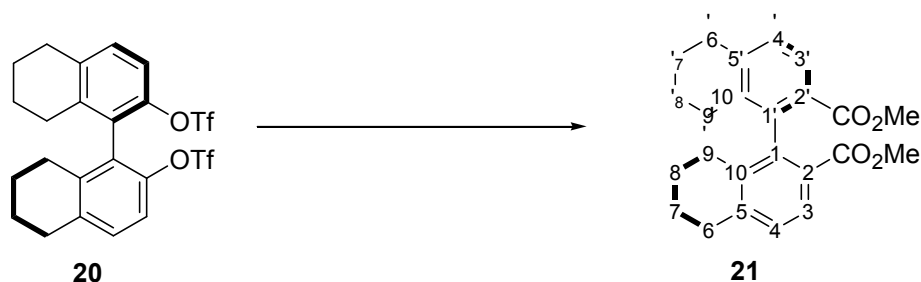
Bistriflate (3.00 g, 5.37 mmol), methanol (10.88 mL, 268.5 mmol, 50 eq.) and diisopropylethylamine (4.11 mL, 23.63 mmol, 4.4 eq.) were dissolved in 20 mL of dimethyl sulfoxide. The solution was transferred to a Parr 50 mL stainless steel reactor, fitted with a sealed magnetic stirrer drive unit, then Pd(OAc)$_2$ (0.18 g, 0.81 mmol, 0.15 eq.) and dppp (0.33 g, 0.81 mmol, 0.15 eq.) were added. Under an atmosphere of argon, the vessel was sealed and quickly cycled three times between a vacuum and an atmosphere of CO. The CO pressure in the flask was increased to 30 psi and heated to 80 °C. The reaction was followed by LC-MS at roughly 12 h intervals following the release of pressure and removal from the heat. After complete consumption of all starting material (48 h) the reaction was purged with nitrogen and cooled to room temperature. The contents were transferred to a flask and the majority of the solvent was removed *in vacuo*. The reduced mixture was diluted with ethyl acetate (60 mL), washed with water (3 x 30 mL) and brine (30 mL). Organic phase was then dried (MgSO$_4$), filtered, and solvents removed under reduced pressure. The resulting residue was purified by flash

column chromatography (5:1 hexanes:EtOAc) giving a yellow oil (1.66 g, 82%); $[\alpha]^{20}_D$ − 2.0 (*c* 0.8, CDCl$_3$) (lit.[6] $[\alpha]^{20}_D$ − 1.6 (*c* 1.00, CDCl$_3$)); Found: C, 75.73; H, 6.97. C$_{24}$H$_{26}$O$_4$ requires C, 76.17; H, 6.92 %; ν_{max} (film)/cm^{-1} 2931, 2858, 1727, 1590, 1432, 1291, 1189, 1134, 836; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.62-1.67 (4 H, m, 2 x C*H*$_2$ at C8 & C8'), 1.69-1.76 (4 H, m, 2 x C*H*$_2$ at C7 & C7'), 1.97-2.04 (2 H, m, 2 x C*H* at C9 & C9'), 2.12-2.21 (2 H, m, 2 x C*H* at C9 & C9'), 2.82-2.87 (4 H, m, 2 x C*H*$_2$ at C6 & C6'), 3.55 (6 H, s, 2 x C*H*$_3$ at C12 & C12'), 7.12 (2 H, d, *J* 7.6 Hz, 2 x arom. C*H* at C4 & C4'), 7.75 (2 H, d, *J* 8.0 Hz, 2 x arom. C*H* at C3 & C3') ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 22.53 (2 x CH$_2$, C7 & C7'), 23.19 (2 x CH$_2$, C8 & C8'), 27.34 (2 x CH$_2$, C9 & C9'), 30.34 (2 x CH$_2$, C6 & C6'), 51.57 (2 x CH$_3$, C12 & C12'), 126.52 (2 x C quat. arom., C2 & C2'), 127.05 (2 x CH arom., C3 & C3'), 127.97 (2 x CH arom., C4 & C4'), 135.32 (2 x C quat., C10 & C10'), 141.69 (2 x C quat. arom., C1 & C1'), 141.83 (2 x C quat., C5 & C5'), 167.50 (2 x C=O, C11 & C11'); *m/z* (EI) 401.1725; C$_{24}$H$_{26}$O$_4$ [M+Na]$^+$ requires 401.1728.

4.1.18 Synthesis of (R$_a$)-5,5',6,6',7,7',8,8'-Octahydro-1,1'-binaphthyl-2,2'-dimethanol (22)[7]

21   **22**
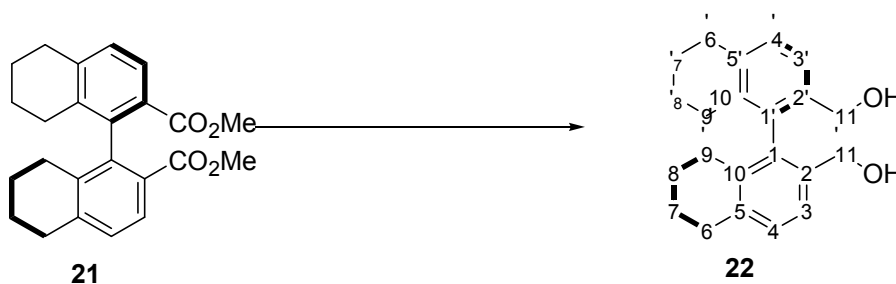
To a suspension of LiAlH$_4$ (0.43 g, 11.24 mmol, 4 eq.) in diethyl ether (50 mL), **21** (1.06 g, 2.81 mmol) in diethyl ether (50 mL) was added dropwise at 0 °C under nitrogen. After the addition, the reaction mixture was stirred at room temperature for 30 min, refluxed for 30 min and recooled to 0 °C. Water (50 mL) was added carefully via an addition funnel and concentrated HCl was added slowly until the mixture became homogeneous. Diethyl ether (50 mL) was then added and the resulting mixture separated. The aqueous layer was extracted with ether (2 x 50 mL). The combined organic layers were washed with 10%

aqueous solution of NaHCO$_3$ (50 mL) and brine (50 mL). The organic layers were then dried (MgSO$_4$), filtered and solvents removed under reduced pressure. The crude product was purified by flash column chromatography (5:1 hexanes:EtOAc) to give octahydrodiol as a white solid (0.87 g, 96 %); $[\alpha]^{20}_D$ + 94.5 (c 1.1, CH$_2$Cl$_2$) (lit.[7] $[\alpha]^{20}_D$ + 91.6 (c 1.0, CH$_2$Cl$_2$)); Found: C, 81.08; H, 8.00. C$_{22}$H$_{26}$O$_2$ requires C, 81.95; H, 8.13 %; ν_{max} (film)/cm^{-1} 3305, 2929, 2858, 1730, 1593, 1450, 1408, 1071, 823; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.66-1.69 (4 H, m, 2 x CH$_2$ at C8 & C8'), 1.70-1.76 (4 H, m, 2 x CH$_2$ at C7 & C7'), 1.96-2.02 (2 H, m, 2 x CH$_2$ at C9 & C9'), 2.04-2.07 (2 H, m, 2 x CH$_2$ at C9 & C9'), 2.81 (4 H, m, 2 x CH$_2$ at C6 & C6'), 4.01 (2 H, d, J 11.2 Hz, CH$_2$ at C11 or C11'), 4.20 (2 H, d, J 11.2 Hz, CH$_2$ at C11 or C11'), 7.10 (2 H, d, J 8.0 Hz, 2 x arom. CH at C4 & C4'), 7.23 (2 H, d, J 7.6 Hz, 2 x arom. CH at C3 & C3') ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 22.83 (2 x CH$_2$, C7 & C7'), 23.32 (2 x CH$_2$, C8 & C8'), 27.53 (2 x CH$_2$, C9 & C9'), 29.97 (2 x CH$_2$, C6 & C6'), 62.91 (2 x CH$_2$, C11 & C11'), 127.19 (2 x CH arom., C3 & C3'), 129.56 (2 x CH arom., C4 & C4'), 134.67 (2 x C quat., C10 & C10'), 135.60 (2 x C quat., C2 & C2'), 136.86 (2 x C quat., C5 & C5'), 137.88 (2 x C quat., C1 & C1'); m/z 645.3936 (EI); C$_{44}$H$_{53}$O$_4$ [M+H]$^+$ (dimer) requires 645.3938.

4.1.19 Synthesis of Octahydrodibromide (23)[8]

22   **23**
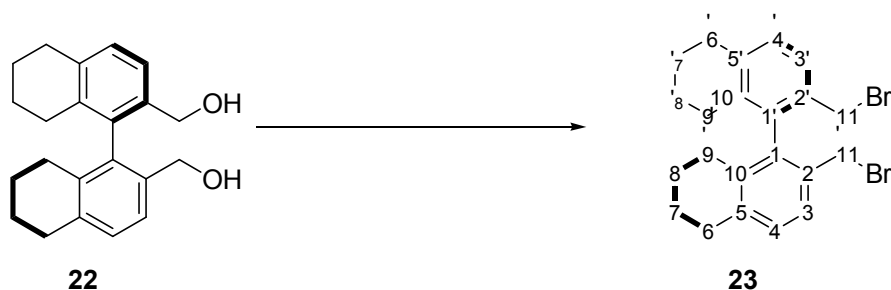
A suspension of the octahydrodiol **22** (0.40 g, 1.25 mmol) in hydrobromic acid (40 mL, 46% in H$_2$O), was heated under reflux for 1 h. The solution was then allowed to cool to room temperature before being extracted with diethyl ether (3 x 20 mL). The organic layers were combined, dried (MgSO$_4$), filtered and solvents removed under reduced pressure. The resulting residue was purified by column flash chromatography (10:1

hexanes:EtOAc), resulting in a yellow residue (0.40 g, 72%); $[\alpha]^{20}_D$ − 2.0 (*c* 0.8, CDCl$_3$) (lit.[8] $[\alpha]^{20}_D$ − 1.6 (*c* 1.00, CDCl$_3$)); Found: C, 59.33; H, 5.58. C$_{22}$H$_{24}$Br$_2$ requires C, 58.95; H, 5.40 %; ν_{max} (film)/cm^{-1} 2920, 2854, 1591, 1433, 1205, 907, 816, 732; ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ 1.60-1.69 (4 H, m, 2 x C*H$_2$* at C8 & C8'), 1.72-1.79 (4 H, m, C*H$_2$* at C7 & C7'), 2.04-2.17 (2 H, m, 2 x C*H* at C9 & C9'), 2.81-2.84 (4 H, m, 2 x C*H$_2$* at C6 &C6'), 4.12 (4 H, q, *J* 10.0 Hz, 2 x C*H$_2$* at C11 & C11'), 7.13 (2 H, d, J 8.0 Hz, 2 x arom. C*H* at C4 & C4'), 7.33 (2 H, d, *J* 8.0 Hz, 2 x arom. C*H* at C3 & C3') ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ$_C$ 22.89 (2 x CH$_2$, C7 & C7'), 23.09 (2 x CH$_2$, C8 & C8'), 27.69 (2 x CH$_2$, C9 & C9'), 30.05 (2 x CH$_2$, C6 & C6'), 35.01 (2 x CH$_2$, C11 & C11'), 128.05 (2 x CH arom., C3 & C3'), 130.25 (2 x CH arom., C4 & C4'), 132. 29 (2 x C quat., C10 & C10'), 135.51 (2 x C quat., C2 & C2'), 137.80 (2 x C quat., C5 & C5'), 138.58 (2 x C quat., C1 & C1').

4.1.20 (R)-(4S,5S)-2,2-dimethyl-4-phenyl-1,3-dioxane-5-yl]-3H-4-azapinium-cyclohepta[2,1-a;3,4-a'] 5,5',6,6',7,7',8,8'-octahydrobinaphthyl amine (24)
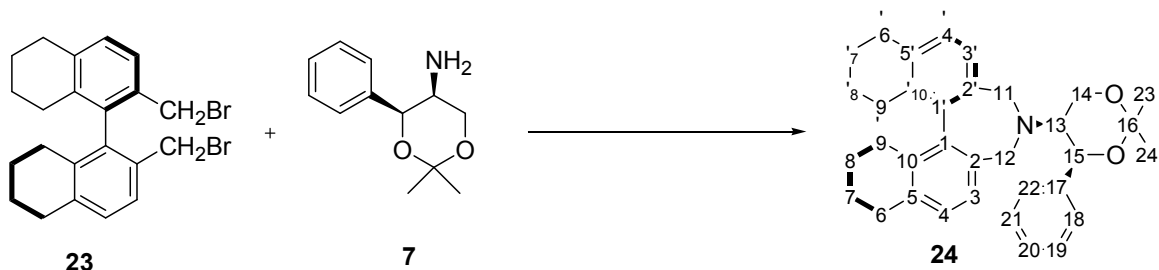
Amine **7** (0.10 g, 0.49 mmol, 1.1 eq.) was dissolved in acetonitrile (30 mL) and octohydrodibromide compound **23** (0.20 g, 0.45 mmol) was added along with potassium carbonate (0.185 g, 1.34 mmol). The resulting solution was then stirred with heating under reflux for 4 h. After being allowed to cool to room temperature, solvent was removed under reduced pressure. Resulting product was redissolved in dichloromethane (30 mL), washed with water (2 x 30 mL), dried (MgSO$_4$), filtered and solvents removed under reduced pressure; m.p. 170-171 °C; $[\alpha]^{20}_D$ − 8.4 (*c* 0.9, CH$_2$Cl$_2$); Found: C, 82.52; H, 7.66. C$_{34}$H$_{39}$NO$_2$ requires C, 82.72; H, 7.96; N, 2.84 %; ν_{max} (film)/cm^{-1} 3052, 2932, 1633, 1599, 1449, 1443, 1388, 1300, 1200, 1142, 1109, 950, 850, 731; ^{1}H NMR (400

MHz, CDCl$_3$): δ$_H$ 1.59 (3 H, s, CH_3 at C23), 1.64 (3 H, s, CH_3 at C24), 1.74-1.78 (8 H, m, 4 x CH_2 at C7, C7', C8 & C8'), 2.12-2.19 (2 H, m, 2 x CH of CH_2 at C9 & C9'), 2.62-2.65 (3 H, m, 2 x CH of CH_2 at C9 & C9'& CH at C13), 2.85 (4 H, t, J 6.8 Hz, 2 x CH_2 at C6 & C6'), 3.10 (2 H, d, J 12.4 Hz, CH_2 at C11), 3.50 (2 H, d, J 12.0 Hz, CH_2 at C12), 4.11-4.23 (3 H, m, CH_2 at C14 & CH at C15), 6.90 (2 H, d, J 7.2 Hz, 2 x arom. CH at C4 & C4'), 6.99 (2 H, d, J 7.2 Hz, 2 x arom. CH at C3 & C3') ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ$_C$ 19.22 (2 x CH$_3$, C23 & C24), 22.69, 22.83, 22.96, 23.05 (4 x CH$_2$, C7, C7', C8 & C8'), 27.58, 27.71 (2 x CH$_2$, C9 & C9'), 29.50, 29.63 (2 x CH$_2$, C6 & C6'), 52.82 (2 x CH$_2$, C11 & C12), 59.86 (CH, C13), 61.32 (CH, C15), 125.90 (2 x CH arom., C4 & C4'), 126.66 (4 x CH arom., C18, C19, C21 & C22), 127.55 (CH arom., C20), 128.02 (2 x CH arom., C3 & C3'), 132.28, 133.51, 134.85, 137.78, 138.13, 138.57 (10 x C quat. arom., C1, C1', C2, C2', C5, C5', C10, C10', C16 & C17).

4.1.21 (*R*)-(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxane-5-yl]-3*H*-4-azapinium-cyclohepta[2,1-*a*;3,4-*a*'] 5,5',6,6',7,7',8,8'-octahydrobinaphthyl tetraphenylborate (25)

24   **25**
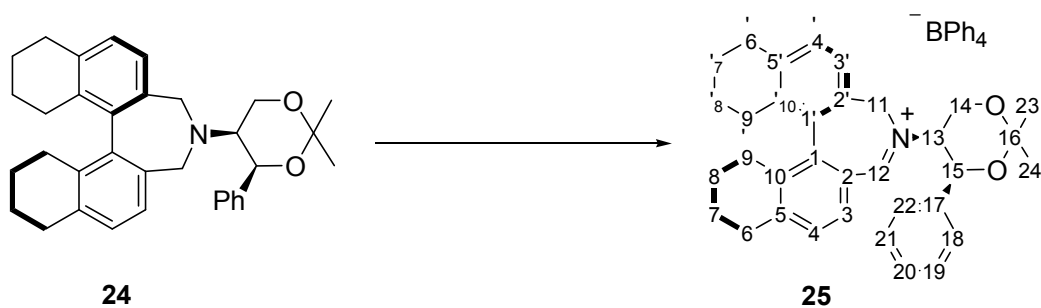
Compound **24** (0.08 g, 0.16 mmol) was dissolved in dichloromethane (20 mL) and N-bromosuccinimde (0.04 g, 0.19 mmol, 1.2 eq.) added. The resulting solution was heated under reflux for 4 h. After being allowed to cool to room temperature the solvent was removed under reduced pressure. The resulting residue was re-dissolved in ethanol and sodium tetraphenylborate (0.06 g, 0.018 mmol, 1.1 eq.) dissolved in the minimum amount of acetonitrile was added in one portion to the reaction mixture and stirred for 5 min. The solvents were then removed under reduced pressure to yield a yellow residue

that was re-dissolved in hot ethanol, and yellow crystals were collected by suction fitration, washed with cold ethanol and diethyl ether (0.10 g, 76%), m.p. 130-135 °C; $[\alpha]^{20}_{D} - 10.0$ (*c* 0.8, CH_2Cl_2); Found: C, 85.45; H, 6.82 ; N 1.63. $C_{58}H_{58}BNO_2$ requires C, 85.80; H, 7.20; N, 1.73 %; ν_{max} (film)/cm^{-1} 3053, 2936, 1619, 1575, 1488, 1427, 1382, 1202, 1111, 838, 733, 703; ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ 1.55-1.62 (6 H, d, 2 x C*H*$_3$ at C23 & C24), 1.76-2.27 (12 H, m, 6 x C*H*$_2$ at C7, C7', C8, C8', C9 & C9'), 2.53-2.99 (6 H, m, 3 x C^H$_2$ at C6, C6' & C11), 3.45-3.71 (3 H, m, C*H*$_2$ at C14 and C*H* at C13), 5.00-5.05 (1 H, m, C*H* at C15), 6.73-6.78 (4 H, m, 4 x C*H* at C3, C3', C4 & C4'), 6.84-7.11 (10 H, m, 4 x C*H para* in BPh$_4$, 5 x arom. C*H* at C18, C19, C20, C21, C22 and CH at C12), 7.20-7.28 (8 H, m, 8 x C*H ortho* in BPh$_4$), 7-29-7.36 (8 H, m, 8 x C*H meta* in BPh$_4$) ppm; ^{13}C NMR (100 MHz, CDCl$_3$); δ$_C$ 18.92 (2 x CH$_3$, C23 & C24), 22.53, 22.84, 22.93, 23.29 (4 x CH$_2$, C7, C7', C8 & C8'), 27.82, 27.95 (2 x CH$_2$, C9 & C9'), 29.49, 29.57 (2 x CH$_2$, C6 & C6'), 55.18 (CH$_2$, C11), 60.49 (CH, C15), 63.17, 66.38, 71.68, 73.76, 99.12, 100.38, 122.28, 124.13, (8 x CH arom., *ortho* in BPh$_4$), 125.91 (2 x CH arom., C4 & C4'), 127.12 (4 x CH arom., C18, C19, C21 & C22), 127.99 (CH arom., C20), 128.18 (2 x CH arom., C3 & C3'), 128.36, 128.64, 128.77, 128.86, 128.99, 129.65, 130.54, 130.78 (8 x CH arom., *meta* in BPh$_4$), 131.72, 133.81, 134.14, 135.95 & 136.14 (4 x CH arom., *para* in BPh$_4$), 137.74, 138.81, 139.81 (10 x C quat. arom., C1, C1', C2, C2', C5, C5', C10, C10', C16 & C17), 140.38, 140.45, 144.01, 144.59 (4 x CH quat. in BPh$_4$) & 187.0 (C=N, C12); *m/z* (EI) 492.2897; $C_{34}H_{38}NO_2$ [M$^+$] requires 492.2895 (100).

4.1.22 5,5',6,6',7,7',8,8'-octahydrobinaphthyl (R)-(-)-3,3-Dimethyl-2-butylamine (27)[9]

23   **26**   **27**
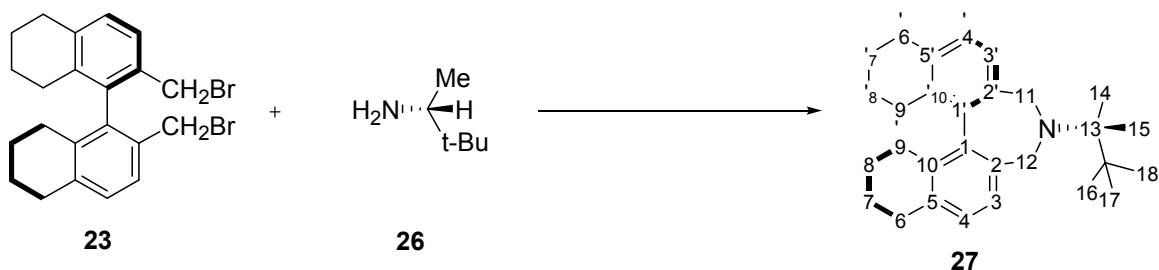
(R)-(-)-3,3-Dimethyl-2-butylamine (amine **26**) (0.10 g, 0.49 mmol, 1.1 eq.) was dissolved in acetonitrile (30 mL) and octohydrodibromide **23** (0.20 g, 0.48 mmol) was added along with potassium carbonate (0.19 g, 1.34 mmol). The resulting solution was then stirred with heating under reflux for 4 h. After being allowed to cool to room temperature, solvent was removed under reduced pressure. Resulting product was redissolved in dichloromethane (30 mL), washed with water (2 x 30 mL), dried (MgSO$_4$), filtered and solvents removed under reduced pressure yielding white/yellow crystals (0.14 g, 82%); ν_{max} (film)/cm^{-1} 2930, 2860, 1689, 1620, 1450, 1379, 1335, 1300, 1245, 1202, 1076, 908, 832, 731; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 0.78 (3 H, d, *J* 7.2 Hz, C*H*$_3$ at C14), 0.90 (9 H, s, 3 x C*H*$_3$ at C16, C17 & C18), 1.53-1.58 (6 H, m, 3 x C*H*$_2$ at C7, C7', C8 or C8'), 1.71-1.83 (2 H, m, C*H*$_2$ at C7, C7', C8 or C8'), 2.16-2.26 (2 H, m, C*H*$_2$ at C9 or C9'), 2.61-2.72 (2 H, m, C*H*$_2$ at C9 or C9'), 2.79-2.86 (5 H, m, 2 x C*H*$_2$ at C6 & C6', C*H* at C15), 3.26 (4 H, s, 2 x C*H*$_2$ at C11 & C12), 7.03 (4 H, s, 4 x arom. C*H* at C3, C3', C4 & C4') ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 18.22 (CH$_3$, C14), 20.55 (3 x CH$_3$, C16, C17, C18), 23.69, 23.45, 23.96, 23.05 (4 x CH$_2$, C7, C7', C8 & C8'), 27.59, 27.98 (2 x CH$_2$, C9 & C9'), 29.44, 29.63 (2 x CH$_2$, C6 & C6'), 51.82 (2 x CH$_2$, C11 & C12), 59.55 (CH, C13), 125.88 (2 x CH arom., C4 & C4'), 129.02 (2 x CH arom., C3 & C3'), 132.55, 133.21, 133.85, 136.58 (8 x C quat. arom., C1, C1', C2, C2', C5, C5', C10, C10').

4.1.23 5,5',6,6',7,7',8,8'-octahydrobinaphthyl   (R)-(-)-3,3-Dimethyl-2-butylamine tetraphenylborate (28)

27   **28**

Compound **27** (0.08 g, 0.16 mmol) was dissolved in dichloromethane (20 mL) and N-bromosuccinimde (0.04 g, 0.19 mmol, 1.2 eq.) added. The resulting solution was heated under reflux for 4 h. After being allowed to cool to room temperature the solvent was removed under reduced pressure. The resulting residue was re-dissolved in ethanol and sodium tetraphenylborate (0.06 g, 0.018 mmol, 1.1 eq.) dissolved in the minimum amount of acetonitrile was added in one portion to the reaction mixture and stirred for 5 min. The solvents were then removed under 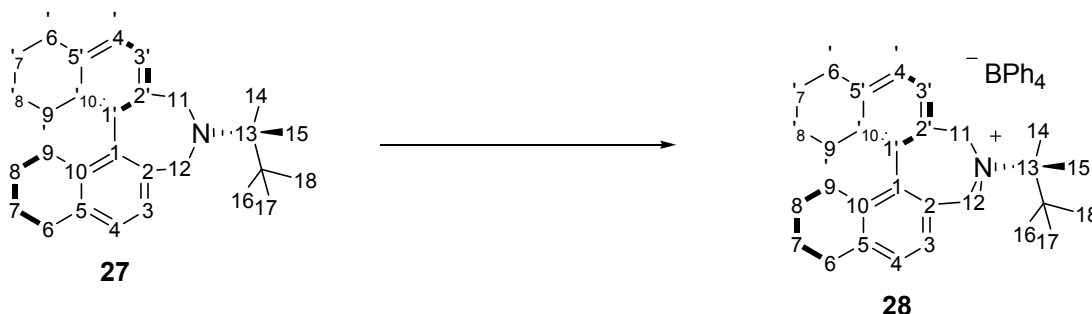reduced pressure to yield a yellow residue that was re-dissolved in hot ethanol, and yellow crystals were collected by suction fitration, washed with cold ethanol and diethyl ether yielding a yellow solid (0.13 g, 94; ν_{max} (film)/cm^{-1} 2936, 2866, 1698, 1593, 1435, 1367, 1365, 1240, 1282, 1220, 1189, 833, 818, 739, 701; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 0.76-0.94 (12 H, m, 4 x CH_3 at C4, C16, C17 & C18), 1.56-1.88 (8 H, m, 4 x CH_2 at C7, C7', C8 & C8'), 2.68-2.89 (5 H, m, 2 x CH_2 at C6, C6', C9, C9' & CH at C15), 6.86 (1 H, d, J 3.2 Hz, arom. CH), 6.89 (1 H, d, J 3.2 Hz, arom. CH), 6.98 (1 H, d, J 3.2 Hz, arom. CH), 7.00 (1 H, d, J 3.2 Hz, arom. CH), 7.08-7.28 (20 H, m, CH at C15, 8 x arom. CH *ortho* in BPh$_4$, 8 x arom. CH *meta* in BPh$_4$ & 4 x arom. CH *para* in BPh$_4$) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 18.27 (CH$_3$, C14), 21.55 (3 x CH$_3$, C16, C17, C18), 23.69, 23.58, 23.86, 24.05 (4 x CH$_2$, C7, C7', C8 & C8'), 27.69, 27.77 (2 x CH$_2$, C9 & C9'), 29.22, 29.44 (2 x CH$_2$, C6 & C6'), 61.55 (CH, C13), 124.5 (8 x CH arom., *ortho* in BPh$_4$), 126.67 (4 x CH arom., *para* in BPh$_4$), 127.0 (2 x CH arom., C4 & C4'), 129.45 (2 x CH arom., C3 & C3'), 130.32 (8 x CH arom., *meta* in BPh$_4$), 131.50, 133.56, 133.99, 136.34 (8 x C quat. arom., C1, C1', C2, C2', C5, C5', C10, C10'); *m/z* (EI) 386.2840; C$_{28}$H$_{36}$N [M+H]$^+$ requires 386.2842.

4.2   Epoxidation

4.2.1   Alkene Synthesis

4.2.2   1,1-Di(4-methylphenyl)prop-1-ene[9]
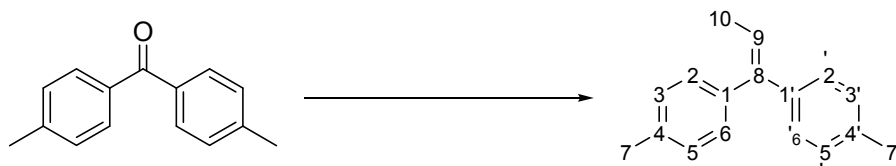
Ethyl-triphenylphosphonium bromide (7.06 g, 19.02 mmol, 2.0 eq.) in THF (10 mL/g salt) was added under nitrogen to a solution of sodium hydride (0.72 g, 19.02 mmol, 2.0 eq.) in THF (20 mL) over a period of 20 minutes. The resulting solution was stirred under nitrogen at room temperature for 1 h, resulting in a yellow solution. The ketone (2.00 g, 9.51 mmol) in THF was then added via cannula, before stirring the reaction at room temperature overnight. The resulting solution was quenched with water (40 mL) and ethyl acetate (50 mL) was then added and the resulting mixture separated. The aqueous layer was extracted with ethyl acetate (2 x 50 mL) and the combined organic layers were then dried (MgSO$_4$), filtered and solvents removed under reduced pressure. The crude product was purified by flash column chromatography (100% petroleum ether) to give the alkene as a white solid (1.98 g, 94%); ν_{max} (film)/cm^{-1} 3021, 2921, 2854, 1656, 1608, 1511, 1276, 806; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.74 (3 H, d, *J* 6.8 Hz, C*H*$_3$ at C10), 2.29 (3 H, s, C*H*$_3$ at C7), 2.35 (3 H, s, C*H*$_3$ at C7'), 6.09 (1 H, q, *J* 7.2 Hz, C*H* at C9), 7.03 (2 H, d, *J* 8.0 Hz, 2 x arom. C*H* (part of AA'BB') at C2' & C6'), 7.06 (2 H, d, *J* 8.4 Hz, 2 x arom. C*H* (part of AA'BB') at C2 & C6), 7.10 (2 H, d, *J* 8.4 Hz, 2 x arom. C*H* (part of AA'BB') at C3' & C5'), 7.15 (2 H, d, *J* 7.6 Hz, 2 x arom. C*H* (part of AA'BB') at C3 & C5) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 15.66 (CH$_3$, C10), 21.01 (CH$_3$, C7), 21.21 (CH$_3$, C7'), 123.36, (CH, C9), 127.84 (2 x CH arom., C3' & C5'), 129.43 (2 x CH arom., C2 & C6), 129.56 (2 x CH arom., C3 & C5), 129.56 (2 x CH arom., C3 & C5), 130.64 (2 x CH arom., C2' & C6'), 137.20 (C quat. arom., C4'), 137.30 (C quat. arom., C4), 138.05 (C quat. arom., C1), 141.19 (C quat. arom., C1'), 143.25 (C quat., C8).

4.2.3   1,1-Di(4-chlorophenyl)prop-1-ene[9]
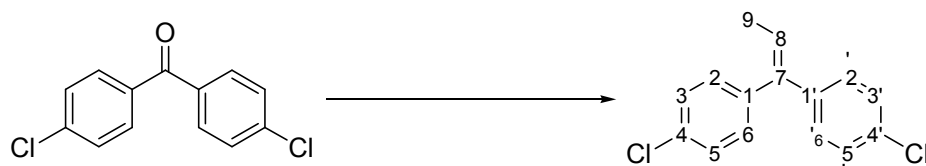
Ethyl-triphenylphosphonium bromide (5.91 g, 15.93 mmol, 2.0 eq.) in THF (10 mL/g salt) was added under nitrogen to a solution of sodium hydride (0.61 g, 15.93 mmol, 2.0 eq.) in THF (20 mL) over a period of 20 minutes. The resulting solution was stirred under nitrogen at room temperature for 1 h, resulting in a yellow solution. The ketone (2.00 g, 7.96 mmol) in THF was then added via cannula, before stirring the reaction at room temperature overnight. The resulting solution was quenched with water (40 mL) and ethyl acetate (50 mL) was then added and the resulting mixture separated. The aqueous layer was extracted with ethyl acetate (2 x 50 mL) and the combined organic layers were then dried ($MgSO_4$), filtered and solvents removed under reduced pressure. The crude product was purified by flash column chromatography (100% petroleum ether) to give the alkene as a white solid (1.91 g, 91%); ν_{max} (film)/cm^{-1} 3028, 2923, 2852, 1662, 1590, 1490, 1462, 1091, 1018, 851, 815; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.14 (3 H, d, J 6.8 Hz, CH_3 at C9), 6.15 (1 H, q, J 7.2 Hz, CH at C8), 7.07 (2 H, d, J 5.2 Hz, 2 x arom. CH (part of AA'BB') at C2' & C6'), 7.09 (2 H, d, J 8.4 Hz, 2 x arom. CH (part of AA'BB') at C2 & C6), 7.21 (2 H, d, J 11.6 Hz, 2 x arom. CH (part of AA'BB') at C3' & C5'), 7.34 (2 H, d, J 8.8 Hz, 2 x arom. CH (part of AA'BB') at C3 & C5) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 15.71 (CH_3, C9), 125.25 (CH, C8), 128.41 (2 x CH arom., C3' & C5'), 128.53 (2 x CH arom., C2 & C6), 128.68 (2 x CH arom., C2' & C6'), 131.07 (2 x CH arom., C3 & C5), 132.66 (C quat arom., C4'), 132.78 (C quat. arom.,C4), 137.92 (C quat arom., C1), 140.34 (C quat., C7), 140.98 (C quat, C1').

4.2.4 1,1-Di(4-fluorophenyl)prop-1-ene[9]
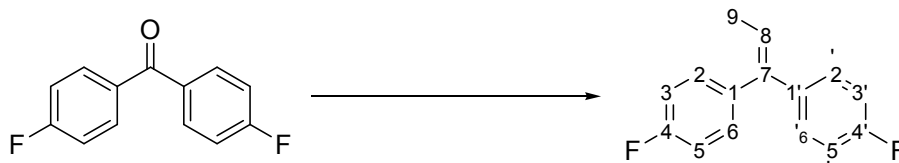

Ethyl-triphenylphosphonium bromide (6.81 g, 18.34 mmol, 2.0 eq.) in THF (10 mL/g salt) was added under nitrogen to a solution of sodium hydride (0.70 g, 18.34 mmol, 2.0 eq.) in THF (20 mL) over a period of 20 minutes. The resulting solution was stirred under nitrogen at room temperature for 1 h, resulting in a yellow solution. The ketone (2.00 g, 9.17 mmol) in THF was then added via cannula, before stirring the reaction at room temperature overnight. The resulting solution was quenched with water (40 mL) and ethyl acetate (50 mL) was then added and the resulting mixture separated. The aqueous layer was extracted with ethyl acetate (2 x 50 mL) and the combined organic layers were then dried (MgSO$_4$), filtered and solvents removed under reduced pressure. The crude product was purified by flash column chromatography (100% petroleum ether) to give the alkene as a white solid (2.00 g, 95%); ν_{max} (film)/cm^{-1} 3042, 2924, 2854, 1601, 1509, 1222, 838, 822; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.73 (3 H, d, J 6.8 Hz, CH_3 at C9), 6.08 (1 H, q, J 6.8 Hz, CH at C8), 6.91 (2 H, t, J 8.8 Hz, 2 x arom. CH (part of AA'BB') at C3' & C5'), 7.03 (2 H, t, J 8.8 Hz, 2 x arom. CH (part of AA'BB') at C3 & C5), 7.09 (2 H, d, J 8.4 Hz, 2 x arom. CH (part of AA'BB') at C2 & C6), 7.13 (2 H, d, J 8.4 Hz, 2 x arom. CH (part of AA'BB') at C2' & C6') ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 15.67 (CH$_3$, C9), 115.01 (2 x CH arom., $^2J_{CF}$ 21.3 Hz, C3' & C5'), 115.09 (2 x CH arom., $^2J_{CF}$ 21.3 Hz, C3 & C5), 124.35 (quat C, C8), 128.73 (2 x CH arom., $^3J_{CF}$ 7.8 Hz, C2' & C6'), 131.62 (2 x CH arom., $^3J_{CF}$ 8.0 Hz, C2 & C6), 135.70 (C quat arom., C1), 139.04 (C quat., C7), 140.59 (C quat. arom., C1'), 162.06 & 167.27 (2 x C quat. arom., C4 & C4').

### 4.2.5   5-Ethylidene-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene[9]

Ethyl-triphenylphosphonium bromide (7.13 g, 19.2 mmol, 2.0 eq.) in THF (10 mL/g salt) was added under nitrogen to a solution of sodium hydride (0.73, 19.2 mmol, 2.0 eq.) in THF (20 mL) over a period of 20 minutes. The resulting solution was stirred under nitrogen at room temperature for 1 h, resulting in a yellow solution. The ketone (2.00 g, 9.6 mmol) in THF was then added via cannula, before stirring the reaction at room temperature overnight. The resulting solution was quenched with water (40 mL) and ethyl acetate (50 mL) was then added and the resulting mixture separated. The aqueous layer was extracted with ethyl acetate (2 x 50 mL) and the combined organic layers were then dried (MgSO$_4$), filtered and solvents removed under reduced pressure. The crude product was purified by flash column chromatography (100% petroleum ether) to give the alkene as a colourless oil (2.01 g, 95%); v_{max} (film)/cm^{-1} 3058, 3015, 2921, 2853, 1484, 1440, 1358, 1264, 908, 767, 736; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.82 (3 H, d, J 6.8 Hz, CH_3 at C10), 2.85 (1 H, m, CH of CH_2 at C7'), 3.04 (1 H, m, CH of CH_2 at C7), 3.39 (1 H, m, CH of CH_2 at C7), 3.48 (1 H, m, CH of CH_2 at C7') 6.05 (1 H, q, J 6.8 Hz, CH at C9), 7.12-7.15 (1 H, m, arom. CH at C5'), 7.20-7.32 (6 H, m, 6 x arom.. CH at C2, C3, C3', C4, C4' & C5), 7.35-7.36 (1 H, m, arom. CH at C2') ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 15.83 (CH$_3$, C10), 32.04 (CH$_2$, C7), 33.82 (CH$_2$, C7'), 128.81 (CH arom., C4), 126.16 (CH arom., C3'), 126.56 (CH arom., C8), 127.08 (CH arom., C4'), 127.89 (CH arom., C3), 128.19 (CH arom., C5), 128.78 (CH arom., C2), 128.91 (CH arom., C2'), 130.19 (CH arom., C5'), 137.22 (C quat. arom., C6'), 139.61 (C quat. arom., C6), 139.97 (C quat. arom., C1), 141.44 (C quat. arom., C1'), 142.65 (C quat. arom., C9).

4.2.6 General Procedure for Epoxidation of Alkenes
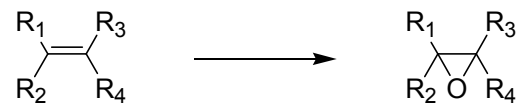
Alkene (0.5 mmol) and catalyst (10 mol%) were dissolved in acetonitrile (0.2 mL). The reaction was cooled to 0 °C with stirring. A separate solution of sodium percarbonate (4 eq.) in water (2 mL) was also cooled to 0 °C, and added to the acetonitrile solution. The mixture was stirred at 0 °C until complete conversion of the alkene was observed by TLC.

4.2.7 General Procedure for Epoxidation of Alkenes with Electrochemically-Generated Percarbonate

In an undivided cell fitted with a boron-doped diamond anode (3 cm^2) as the working electrode and a platinum wire cathode (0.1 cm^2) as the counter electrode, a solution of $Na_2CO_3.10H_2O$ (100 mL, 1 M) was stirred (6500 rpm, ultra-turrax) whilst being cooled to 0 °C in an ice bath. A fixed potential of 10.0 V was applied for 1 h, after which time the electrodes were removed. The organic phase consisting of acetonitrile (20 mL), catalyst (10 mol%) and olefin (1 mmol) were then added to the electrochemically-derived percarbonate (100 mL), and the mixture was stirred at 0 °C and monitored by TLC until complete conversion was observed. Extraction was carried out with diethyl ether (3 x 50 mL), and the combined organic phases washed with brine (50 mL), dried ($MgSO_4$), filtered and the solvents removed under reduced pressure.

4.2.8 General Procedure for Epoxidation of Alkenes with Electrochemically-Generated Hypochlorite as a One-Pot System

An aqueous 1.0 M $Na_2CO_3.10 H_2O$ (100 mL) solution was almost neutralized to pH 6 by slow addition of aq. HCl (37%, ~15 mL), this was then placed into an undivided cell fitted with a boron-doped diamond anode (3.0 cm^2) as the working electrode and a

platinum wire cathode (0.1 cm^2) as the counter electrode. Alkene (1.0 mmol) and diphenyl diselenide (1.0 mol%) were then added. The solution was stirred (6500 rpm, ultra-turrax) whilst being cooled to 0 °C in an ice bath while applying a fixed potential of 10.0 V for 1 h, which resulted in a constant current of 30 A. Extraction was carried out with dichloromethane (3 x 50 mL), and the organics washed with brine (50 mL), dried (MgSO$_4$), filtered and the solvents removed under reduced pressure.

4.2.9 *trans*-α-methylstilbene oxide[1]

14
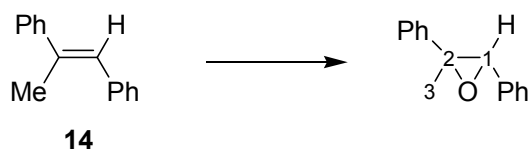
Colourless oil; ν_{max} (cm^{-1}) 3061, 1602, 1495, 1449, 1381, 1279, 1157, 1118, 1065, 1027, 980; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.46 (3 H, s, C*H*$_3$ at C3), 3.96 (1 H, s, C*H* at C1), 7.23-7.46 (10 H, m, 10 x arom. C*H*) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 16.67 (CH$_3$, C3), 63.05 (C, C2), 67.09 (CH, C1), 125.66, 126.88, 127.80, 127.90, 128.44, 129.02 (10 x CH, arom. CH), 135.88 (C, arom.), 142.28 (C, arom.). The ee values were determined by HPLC on a chiral stationary phase; 25 °C; flow rate 1.0 mL min^{-1}. Retention times [min]: (*S,S*)-**12** 4.2 min, (*R,R*)-**12** 6.9 min, (Chiralcel OD; hexane/IPA, 8:2).

4.2.10 1-Phenylcyclohexene oxide[1]

15
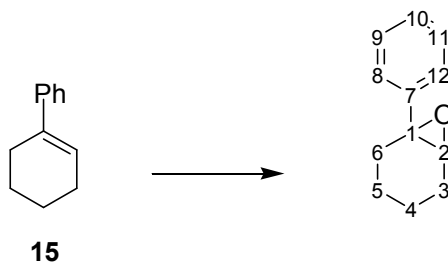
Colourless oil; ν_{max} (cm^{-1}) 3084, 1602, 1495, 1446, 1359, 1249, 1173, 1132, 1079, 1030, 993, 974; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.62-1.66 (2 H, m, C*H*$_2$ at C4), 1.73-1.77 (2

H, m, CH_2 at C3), 2.19 (2 H, d, *J* 2.4 Hz, CH_2 at C5), 2.39 (2 H, d, *J* 2.0 Hz, CH_2 at C6), 3.97 (1 H, s, C*H* at C2), 7.13-7.16 (1 H, m, arom. C*H* at C10), 7.25-7.29 (2 H, m, 2 x arom. C*H* at C9 & C11), 7.34-7.36 (2 H, m, 2 x arom. C*H* at C8 & C12) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 19.8, 20.1, 24.7, 28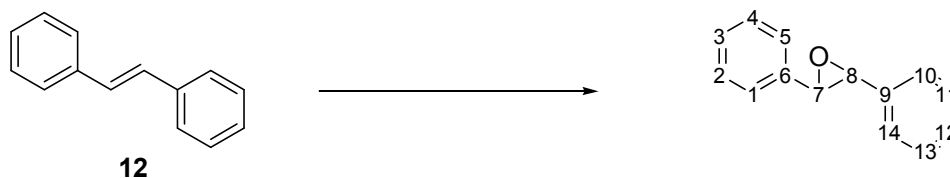.2 (4 x CH$_2$, C3, C4, C5 & C6), 60.1 (C, C1), 61.8 (CH, C2), 125.3 (2 x CH, C8 & C12), 127.1 (CH, C10), 128.2 (2 x CH, C9 & C11), 142.8 (C, C7). The ee values were determined by ^{1}H NMR spectroscopy with (+)-Eu(hfc)$_3$ as a chiral shift reagent, configuration (1*S*,2*S*).

4.2.11 *trans*-Stilbene oxide[5]

12

Colourless solid, m.p. 66-67 °C (lit.[5] m.p. 61-63 °C); ν_{max} (film)/cm^{-1} 3020, 2924, 1658, 1597, 1450, 1381, 1273, 1172, 1072, 1126; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 3.84 (2 H, s, 2 x CH at C7 & C8), 7.28-7.37 (10 H, m, 10 x arom. CH at C1, C2, C3, C4, C5, C10, C11, C12, C13 & C14) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 62.94 (2 x CH, C7 & C8), 125.61 (4 x CH arom., C1, C5, C10, C14), 128.54 (2 x CH arom., C3 & C12), 128.66 (4 x CH arom., C2, C4, C11, C12), 137.19 (2 x C quat. arom., C6, C9).

4.2.12 1-Fluoro-3-[(*E*)-2-(4-methoxyphenyl)vinyl]benzene oxide

18
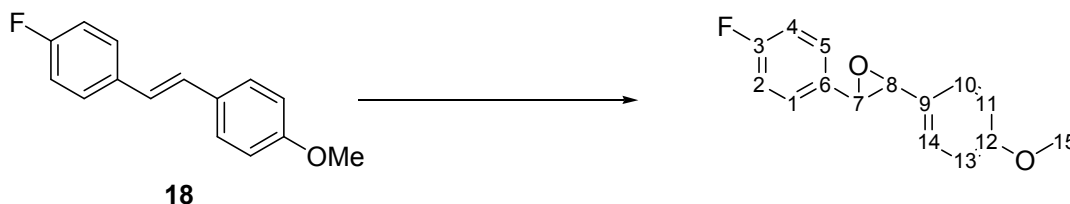
Yellow solid; Found: C, 78.30; H, 5.63. C$_{15}$H$_{13}$FO$_2$ requires C, 78.93; H, 5.74 %; ν_{max} (film)/cm^{-1} 2970, 1606, 1511, 1246, 1033, 834; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 3.75 (1

H, d, J 2.0 Hz, C*H* at C7), 3.82 (3 H, s, C*H*$_3$ at C15), 3.84 (1 H, d, *J* 2.0 Hz, C*H* at C8), 6.91 (2 H, d, *J* 14.4 Hz, 2 x arom. C*H* at C11 & C13), 7.06 (2 H, d, *J* 14.4 Hz, 2 x arom. C*H* at C2 & C4) 7.24-7.27 (2 H, m, 2 x arom. C*H* at C12 & C14), 7.28-7.34 (2 H, m, 2 x arom C*H* at C1 & C5) ppm; $^{1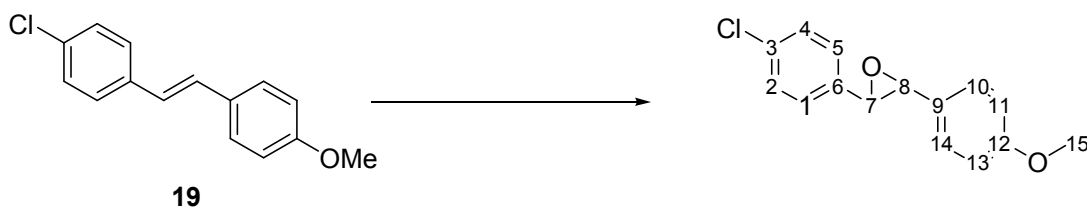3}$C NMR (100 MHz, CDCl$_3$): δ$_C$ 55.35 (CH$_3$, C15), 62.07 (CH, C7), 62.74 (CH, C8), 114.06 (2 x CH arom., C11 & C13), 115.42 & 115.64 (2 x CH arom., C1 & C5), 127.09 & 127.17 (2 x CH arom., C10 & C14), 128.85 (C quat. arom., C9), 132.98 & 133.01 (C quat. arom., C6), 159.84 (C quat. arom., C12), 163.95 (C quat. arom., C3); *m/z* (FAB) 245.098; C$_{15}$H$_{13}$FO$_2$ [*M*+H$^+$] requires 245.097, 245 (31), 136 (53), 154 (67), 55 (84) & 57 (100).

4.2.13 1-Chloro-3-[(*E*)-2-(4-methoxyphenyl)vinyl]benzene oxide

19

Yellow solid; Found: C, 68.72; H, 4.70. C$_{15}$H$_{13}$ClO$_2$ requires C, 69.10; H, 5.03 %; ν$_{max}$ (film)/cm^{-1} 2931, 1604, 1512, 1249, 825, 734; ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ 3.76 (1 H, d, *J* 2.0 Hz, C*H* at C7), 3.80 (3 H, s, C*H*$_2$ at C15), 3.82 (1 H, d, *J* 1.6 Hz, C*H* at C8), 6.90 (2 H, d, *J* 8.4 Hz, 2 x arom. C*H ortho* to OMe at C11 & C13), 7.24 (2 H, d, *J* 3.6 Hz, 2 x arom. C*H meta* to OMe at C10 & C14), 7.26 (2 H, d, *J* 2.8 Hz, 2 x arom. C*H meta* to Cl at C1 & C5), 7.31-7.35 (2 H, m, 2 x arom. C*H* to Cl at C2 & C4) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ$_C$ 50.33 (CH$_3$, C15), 61.99 (CH, C8), 62.87 (CH, C7), 114.06 (2 x CH arom., C11 & C13), 126.79 (4 x CH arom., C1, C5, C10 & C14), 128.79 (2 x CH arom., C2 & C4), 133.96 (c quat. arom., C9), 135.77 (C quat. arom., C6), 156.99 (C quat. arom., C3), 159.95 (C quat. arom., C12) *m/z* (FAB) 261.07; C$_{16}$H$_{13}$ClO$_2$ [*M*+H]$^+$ requires 261.07.

4.2.14 1,2-Dihydronaphthalene oxide[10]

34
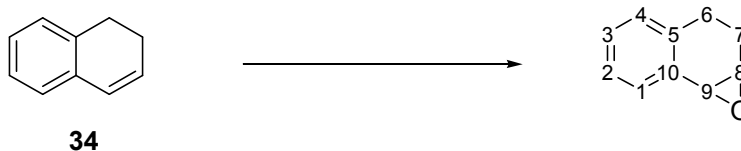
Colourless oil; Found: C, 81.50; H, 6.48. $C_{10}H_{10}O$ requires C, 82.16; H, 6.89 %; ν_{max} (film)/cm^{-1} 3052, 3022, 2931, 2849, 1655, 1495, 1315, 1127, 936; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.66-1.75 (1 H, m, 1H of C*H*$_2$ at C7), 2.32-2.39 (1 H, m, 1H of C*H*$_2$ at C7), 2.47-2.52 (1 H, m, 1H of C*H*$_2$ at C6), 2.70-2.79 (1 H, m, 1H of C*H*$_2$ at C6), 3.68 (1 H, t, *J* 4.0 Hz, C*H* at C9), 3.80 (1 H, d, *J* 4.0 Hz, C*H* at C8), 7.05 (1 H, d, *J* 7.2 Hz, arom. C*H* at C4), 7.13-7.24 (2 H, m, 2 x arom. C*H* at C2 & C3), 7.33-7.37 (1 H, dd, *J* 16.0 & 7.2 Hz, arom. C*H* at C1) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 21.73 (CH$_2$, C7), 24.16 (CH$_2$, C6), 53.44 (CH, C8), 55.06 (CH, C9), 126.05 (arom. CH, C4), 128.14 (2 x CH arom., C2 & C3), 129.73 (CH arom., C1), 132.45 & 136.60 (2 x C quat. arom., C5 & C10); *m/z* (FAB) 147.0812; $C_{10}H_{10}O$ [M+H$^+$] requires 147.0899, 147 (84), 130 (82) & 117 (60).

4.2.15 *trans*-4-Octene oxide[11]

16
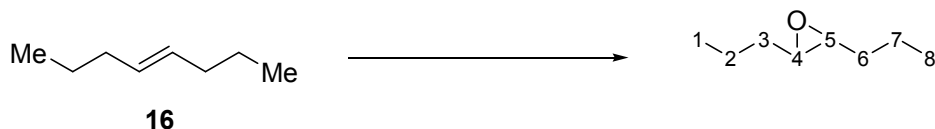
Colourless Oil; ν_{max} (film)/cm^{-1} 2958, 1771, 4463, 1215, 910; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 0.86-0.90 (6 H, m, 2 x C*H*$_3$ at C1 & C8), 1.41-1.55 (8 H, m, 4 x C*H*$_2$ at C2, C3, C6 & C7), 2.63-2.67 (2 H, m, 2 x C*H* at C4 & C5) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 13.97 (2 x CH$_3$, C1 & C8), 19.37 (2 x CH$_2$, C2 & C7), 34.20 (2 x CH$_2$, C3 & C6), 58.48 (2 x CH, C4 & C5); *m/z* (EI) 129.1270; $C_8H_{16}O$ [M+H$^+$] requires 129.1274, 129 (100).

4.2.16 1,1-Di(4-chlorophenyl)prop-1-ene oxide[9]
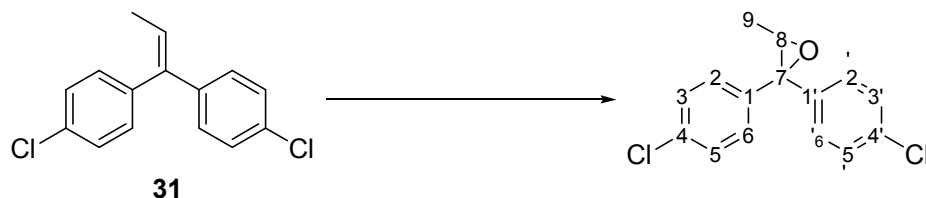
Colourless oil; ν_{max} (film)/cm^{-1} 3063, 2925, 2855, 1662, 1595, 1490, 1452, 1092, 905, 829, 760, 780, 631; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.05 (3 H, d, J 5.6 Hz, CH_3 at C9), 3.34 (1 H, q, J 5.6, 10.8 Hz, CH at C8), 7.10 (2 H, d, J 8.8 Hz, 2 x arom. CH (part of AA'BB') at C2' & C6'), 7.15 (2 H, d, J 8.8 Hz, 2 x arom. CH (part of AA'BB') at C3' & C5'), 7.20 (2 H, d, J 8.4 Hz, 2 x arom. CH (part of AA'BB') at C2 & C6), 7.24 (2 H, d, J 8.4 Hz, 2 x arom. CH (part of AA'BB') at C3 & C5) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 15.43 (CH$_3$, C9), 62.61 (CH, C9), 65.06 (C quat., C7), 128.27 (2 x CH arom., C2' & C6'), 128.56 & 128.58 (4 x CH arom., C3, C3', C5 & C5'), 129.56 (2 x CH arom., C2 & C6), 133.80 & 133.85 (2 x C quat. arom., C4 & C4'), 135.54 (C quat. arom., C1), 139.20 (C quat. arom., C1').

4.2.17 1,1-Di(4-fluorophenyl)prop-1-ene oxide[9]
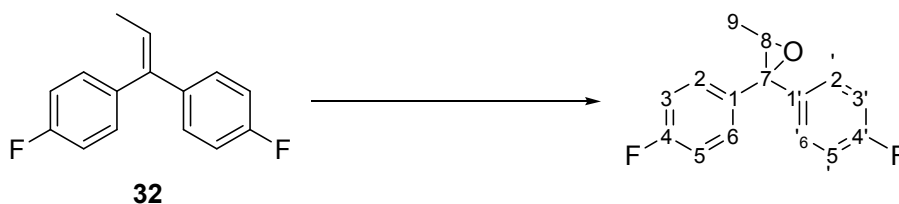
Colourless oil; ν_{max} (film)/cm^{-1} 3071, 2925, 2855, 1603, 1506, 1222, 1158, 1125, 902, 836; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.16 (3 H, d, J 5.6 Hz, CH_3 at C9), 3.45 (1 H, q, J 5.6, 10.8 Hz, CH at C8), 6.97 (2 H, t, J 8.8 Hz, 2 x arom. CH at C3' & C5'), 7.06 (2 H, t, J 8.8 Hz, 2 x arom. CH at C3 & C5), 7.25 (2 H, dd, J 5.6, 8.8 Hz, 2 x arom. CH (part of AA'BB'X) at C2' & C6'), 7.35 (2 H, dd, J 5.6, 8.8 Hz, 2 x arom. CH (part of AA'BB'X) at C2 & C6) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 17.95 (CH$_3$, C9), 62.56 (CH, C8),

65.10 (C quat. arom., C7), 115.13 (2 x CH arom., $^2J_{CF}$ 3.08 Hz, C3' & C5'), 115.34 (2 x CH arom., $^2J_{CF}$ 3.08 Hz, C3 & C5), 127.64 (2 x CH. arom., $^3J_{CF}$ 8.28 Hz, C2' & C6'), 128.63 (2 x CH arom., $^3J_{CF}$ 8.28 Hz, C2 & C6), 132.57 & 136.83 (2 x C quat. arom., C1 & C1'), 161.08 & 163.53 (2 x C quat. arom., J_{CF} 246.60, 246.80 Hz, C4 & C4').

4.2.18 Styrene oxide[12]

35
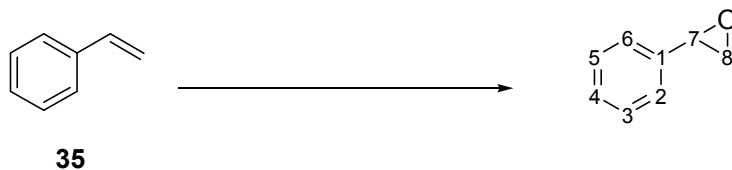
Colourless oil; ν_{max} (film)/cm^{-1} 3034, 2916, 1600, 1494, 1452, 1390, 1255, 1199, 875, 699; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 2.78 (1 H, dd, J 2.8, 5.6 Hz, 1H of CH$_2$ at C8), 3.12 (1 H, dd, J 4.0, 5.6 Hz, 1H of CH$_2$ at C8), 3.84 (1 H, dd, J 2.4, 4.0 Hz, CH at C7), 7.25-7.35 (5 H, m, 5 x arom. CH at C2, C3, C4, C5 & C6) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 51.20 (CH$_2$, C8), 52.39 (CH, C7), 125.48 (2 x CH arom., C2 & C6), 127.92 (CH arom., C4), 129.75 (2 x CH arom., C3 & C5), 137.49 (C quat. arom., C1).

4.2.19 2-Chlorostyrene oxide[13]

38

Colourless oil; ν_{max} (film)/cm^{-1} 3061, 2997, 1698, 1593, 1475, 1437, 1153, 1250, 1125, 1055, 1033, 879, 750; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 2.66 (1 H, dd, J 2.4, 5.6 Hz, 1H of CH$_2$ at C8), 3.19 (1 H, dd, J 4.4, 5.6 Hz, 1H of CH$_2$ at C8), 4.21 (1 H, dd, J 2.4, 4.0 Hz, CH at C7), 7.15-7.30 (4 H, m, 4 x CH arom. at C3, C4, C5 & C6) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 50.08 (CH, C7), 50.74 (CH2, C8), 125.68 (2 x arom. CH, C5 &

C6), 126.42 (2 x arom. CH, C3 & C4), 133.84 (C quat. arom., C2), 135.56 (C quat. arom., C1).

4.2.20 4-Chlorostyrene oxide[14]

36
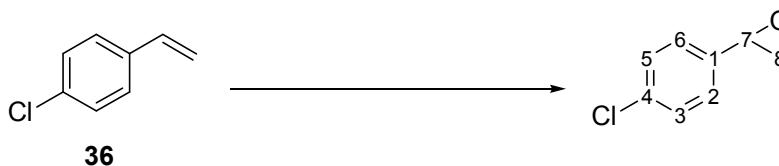
Colourless oil; ν_{max} (film)/cm^{-1} 3034, 2916, 1600, 1494, 1452, 1390, 1255, 1199, 1072, 875, 757, 699; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 2.74 (1 H, dd, J 2.8, 5.6 Hz, 1H of CH_2 at C8), 3.13 (1 H, dd, J 4.0, 5.2 Hz, 1H of CH_2 at C8), 3.82 (1 H, dd, J 4.0, 6.8 Hz, CH at C7), 7.19 (2 H, d, J 8.4 Hz, 2 x arom. CH at C2 & C6), 7.30 (2 H, d, J 8.4 Hz, 2 x arom. CH at C3 & C5) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 51.24 (CH$_2$, C8), 51.78 (CH, C7), 127.38 (2 x arom. CH, C2 & C6), 128.86 (2 x arom. CH, C3 & C5), 130.90 (C quat. arom., C1), 136.17 (C quat. arom., C4).
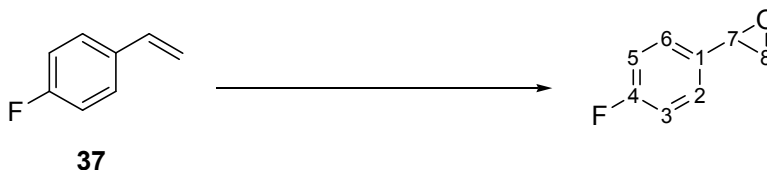
4.2.21 4-Fluorostyrene oxide[14]

37

Colourless oil; ν_{max} (film)/cm^{-1} 3034, 2916, 1601, 1494, 1453, 1391, 1256, 1200, 1072, 876, 756, 699; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 2.75 (1 H, dd, J 2.4, 5.2 Hz, 1H of CH_2 at C8), 3.13 (1 H, dd, J 4.0, 5.6 Hz, 1H of CH_2 at C8), 3.84 (1 H, dd, J 2.8, 3.6 Hz, CH at C7), 7.03 (2 H, dd, J 2.0, 8.8 Hz, 2 x arom. CH at C3 & C5), 7.24 (2 H, dd, J 2.0, 8.8 Hz, 2 x arom. CH at C2 & C6) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 51.18 (CH$_2$, C8), 51.56 (CH, C7), 115.38 & 115.59 (2 x arom. CH, C3 & C5), 127.16 & 127.24 (y2 x

arom. CH, C2 & C6), 163.93 (C quat. arom., d, J_{CF} 86.3 Hz, C1), 164.79 (C quat. arom., C4).

4.2.22 4-Methyoxystyrene oxide[15]

40
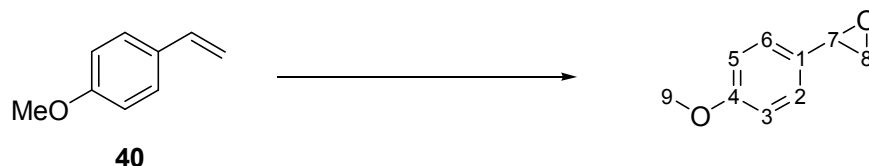
Colourless oil; ν_{max} (film)/cm^{-1} 3002, 2956, 1611, 1461, 1248, 872, 835, 738, 702; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 3.65 (1 H, dd, J 3.6, 11.2 Hz, 1 H of CH_2 at C8), 3.69 (1 H, dd, J 3.6, 11.2 Hz, 1 H of CH_2 at C8), 3.80 (3 H, s, CH_3 at C9), 4.84 (1 H, dd, J 3.6, 8.8 Hz, CH at C7), 6.90 (2 H, d, J 8.8 Hz, 2 x arom. CH at C3 & C5), 7.30 (2 H, d, J 8.8 Hz, 2 x arom. CH at C2 & C6) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 50.88 (CH$_2$, C8), 55.31 (CH$_3$, C9), 73.71 (CH, C7), 114.04 (2 x CH arom., C3 & C5), 127.33 (2 x CH arom., C2 & C6), 132.04 (C quat. arom., C1), 159.66 (C quat. arom., C4).
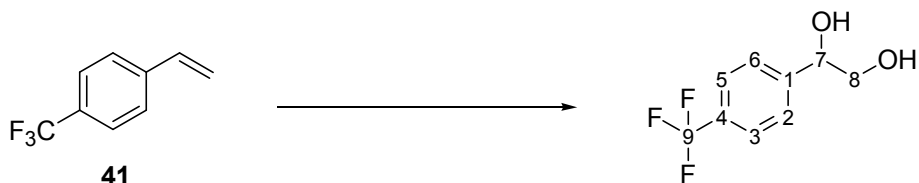
4.2.23 4-(Trifluoromethyl) Styrene diol[16]

41

Yellow oil; ν_{max} (film)/cm^{-1} 3404, 1620, 1327, 1166, 1126, 1069, 846; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 3.64 (1 H, dd, J 8.4, 11.2 Hz, 1 H of CH_2 at C8), 3.77 (1 H, dd, J 3.6, 11.6 Hz, 1 H of CH_2 at C8), 4.98 (1 H, dd, J 3.2, 8.4 Hz, CH of C7), 7.52 (2 H, d, J 8.4 Hz, 2 x arom. CH at C2 & C6), 7.64 (2 H, d, J 8.4 Hz, 2 arom. CH at C2 & C5) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 50.61 (CH$_2$, C8), 73.37 (CH, C7), 122.61 (C quat., C9), 125.69 (2 x CH arom., C3 & C5), 126.45 (2 x CH arom., C2 & C6), 130.80 (C quat. arom., C1), 143.72 (C quat. arom., C4).

4.2.24 *trans*-β-methylstyrene oxide[17]

42
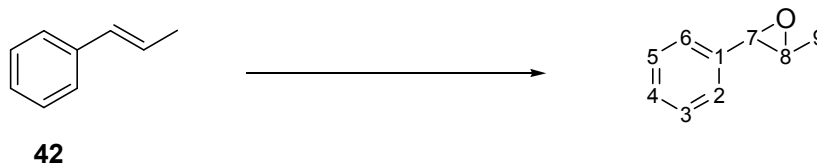
Colourles oil; ν_{max} (film)/cm^{-1} 3062, 2984, 1600, 1496, 1459, 1250, 1020, 952, 858, 743, 697; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.44 (3 H, d, J 4.2 Hz, CH_3 at C9), 3.03 (1 H, dq, J 2.0, 4.8 Hz, CH at C8), 3.57 (1 H, d, J 2.0 Hz, CH at C7), 7.17-7.33 (5 H, m, 5 x arom. CH at C2, C3, C4, C5 & C6) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 17.90 (CH$_3$, C9), 59.02 (CH, C8), 59.51 (CH, C7), 125.54 (2 x CH arom., C2 & C6), 128.26 (CH arom., C4), 128.45 (2 x CH arom., C3 & C5), 137.74 (C quat. arom., C1).

4.2.25 4-Bromobutene oxide[18]

39
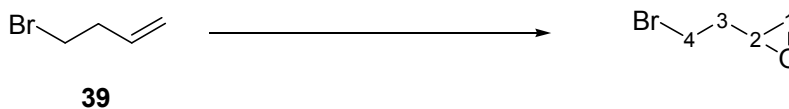
Colourless oil; ν_{max} (film)/cm^{-1} 3052, 2994, 1725, 1431, 1262, 1217, 1073, 909; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 2.00-2.10 (1 H, m, CH of CH_2 at C1), 2.10-2.21 (1 H, m, CH of CH_2 at C1), 2.61 (1 H, dd, J 2.8, 4.8 Hz, CH of CH_2 at C3), 2.85 (1 H, t, CH of CH_2 at C3), 3.08-3.12 (1 H, m, CH of C2), 3.52 (2 H, dd, J 6.0, 7.2 Hz, CH_2 at C4) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 28.99 (CH$_2$, C4), 35.68 (CH$_2$, C1), 47.08 (CH$_2$, C3), 50.76 (CH, C2).

4.3 Baeyer-Villiger Oxidation
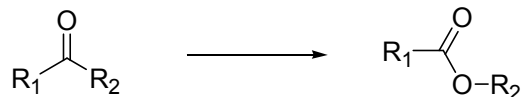
Sodium percarbonate (3.14 g, 20 mmol) in water (20 mL) was stirred at room temperature. Acetonitrile (20 mL) was added followed by the slow addition of hydrochloric acid to give an acidic pH (~9). Cyclohexanone (0.52 mL, 5 mmol) was then added, and the reaction stirred at room temperature until TLC observed conversion.

### 4.3.1 General Procedure for the Baeyer-Villiger Reaction with Electrochemically-Generated Percarbonate

In an undivided cell fitted with a boron-doped diamond anode (Diafilm, Windsor Scientific, UK) (3 cm^2) as the working electrode and a platinum wire (0.2 cm^2) cathode as the counter electrode, 1.0 M Na$_2$CO$_3$.10H$_2$O (100 mL) was stirred (6500 rpm, ultra-turrax) whilst being cooled to 0°C in an ice bath. A fixed potential of 10.0 V was applied for 1 h, after which time the electrodes were removed. The organic phase consisting of acetonitrile (50 mL) and substrate were then added to the electrochemically-derived percarbonate (50 mL), and the mixture was stirred at 0 ^{o}C and monitored by TLC until complete conversion was observed. Extraction was carried out with diethyl ether (3 x 50 mL), and the combined organic phases washed with brine (50 mL), dried (MgSO$_4$), filtered and the solvents removed under reduced pressure.

4.3.2 General Procedure for the Baeyer-Villiger Reaction with Electrochemically-Generated Persulfate

2.5 M Aqueous sulfuric acid (100 mL) was placed into a undivided cell fitted with a boron-doped diamond (Diafilm, Windsor Scientific, UK) working electrode (3 cm^2), and a small platinum wire (0.2 cm^2) countrer electrode. The cell was placed in a ice bath for one hour at 0 ºC, and a 1.0 A current was applied resulting in a potential of 5.0 V, whilst

being stirred at 6500 rpm using a ultra-turrax. After this time the solution was basified using potassium carbonate until the pH of the mixture reached pH 8-9. Substrate was then dissolved in the organic phase and cooled to 0 ºC, then added to the peroxymonosulfate solution and the reaction mixture stirred at 0 ºC, whilst being monitored by TLC until conversion was observed. Extraction was carried out with diethyl ether (3 x 50 mL), and the organics washed with brine (50 mL), dried (MgSO₄), filtered and the solvents removed under reduced pressure.

4.5.1 Baeyer-Villiger Oxidation of Cyclohexanone[19]

43
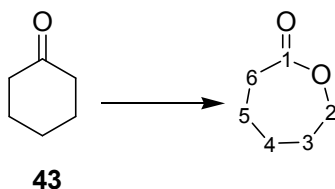
Yellow oil; ν_{max} (cm⁻¹); 2934, 2861, 1730, 1327, 1291, 1167; ¹H NMR (400 MHz, CDCl₃): δ_H 1.76-1.79 (4 H, m, 2 x CH_2 at C3 & C5), 1.84-1.87 (2 H, m, CH_2 at C4), 2.66 (2 H, t, J 2.0 Hz, CH_2 at C6), 4.23 (2 H, t, J 4.8 Hz, CH_2 at C2) ppm; ¹³C NMR (100 MHz, CDCl₃): δ_C 23.01 (CH₂, C5), 28.91 (CH₂, C3), 29.20 (CH₂, C4), 34.46 (CH₂, C6), 69.07 (CH₂, C2), 176.25 (C=O, C1)

4.5.2 Baeyer-Villiger Oxidation of Acetophenone[20]

44
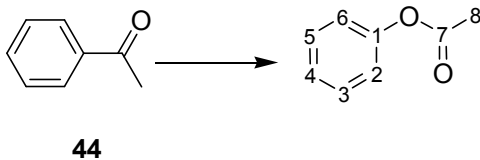
Yellow oil; ¹H NMR (400 MHz, CDCl₃): δ_H 2.09 (3 H, s, CH_3 at C8), 6.98-7.06 (3 H, m, arom.), 7.07-7.10 (2 H, m, arom.) ppm; ¹³C NMR (100 MHz, CDCl₃): δ_C 20.8 (CH₃, C8), 121.3 (2 x CH, C2 & C6), 125.5 (CH, C4), 129.2 (2 x CH, C3 & C5), 150.5 (C, C1), 169.1 (C=O, C7).

4.4   Sulfoxidation

4.4.1   General Procedure for Sulfoxidation using Sodium Percarbonate

A solution of sodium percarbonate (2.0 eq.) in water (2 mL) was cooled to 0 $^{\circ}$C with stirring. A separate solution of catalyst (10 mol%) in acetonitrile (2 mL) was cooled to 0 $^{\circ}$C and added to the percarbonate solution, along with potassium carbonate (5.0 eq.) and the sulfide (1.0 mmol). Resulting solution was then stirred at 0 $^{\circ}$C and monitored by TLC for 4 h. Dichloromethane (10 mL), and water (5 mL) were then added, and the organic layer separated, dried (MgSO$_4$), filtered and solvents removed under reduced pressure.

4.4.2   General Procedure for Sulfoxidation with Electrochemically-Generated Percarbonate

In an undivided cell fitted with a boron-doped diamond anode (3 cm^2) as the working electrode and a platinum wire cathode (0.2 cm^2) as the counter electrode, 1.0 M Na$_2$CO$_3$.10H$_2$0 (100 mL) was stirred (6500 rpm, ultra-turrax) whilst being cooled to 0 $^{\circ}$C in an ice bath. A fixed potential of 10.0 V was applied for 1 h, after which time the electrodes were removed. The organic phase consisting of acetonitrile (50 mL), a non-chiral catalyst (10 mol% wrt to sulfide) and sulfide were then added to the electrochemically-derived percarbonate (50 mL), and the mixture was stirred at 0 $^{\circ}$C and monitored by TLC until conversion was observed. Extraction was carried out with diethyl ether (3 x 50 mL), and the organics washed with brine (50 mL), dried (MgSO$_4$), filtered and the solvents removed under reduced pressure.

4.4.3 General Procedure for Sulfoxidation of Sulfides with Electrochemically-Generated Hypochlorite as a 'Batch' System

In an undivided cell fitted with a boron-doped diamond anode (3.0 cm^2) as the working electrode and a platinum wire cathode (0.2 cm^2) as the counter electrode. Aqueous 1 M Na$_2$CO$_3$.10 H$_2$O (100 mL) was stirred (6500 rpm, ultra-turrax) whilst being cooled to 0 ^{o}C in an ice bath. A fixed potential of 10.0 V was applied for 1 h, which resulted in a constant current of 30 A. After this time, solution was almost neutralized to pH 6 by slow addition of aq. HCl (37%, 40 mL). Sulfide (1.0 mmol) and diphenyl diselenide (1.0 mol%) were added and the reaction mixture was stirred at room temperature. Extraction was carried out with dichloromethane (3 x 50 mL), and the organics washed with brine (50 mL), dried (MgSO$_4$), filtered and the solvents removed under reduced pressure.

4.4.4 General Procedure for Sulfoxidation of Sulfides with Electrochemically-Generated Hypochlorite as a One-Pot System

An aqueous 1.0 M Na$_2$CO$_3$.10H$_2$O (100 mL) solution was almost neutralized to pH 6 by slow addition of aq. HCl (37%, ~15 mL), this was then placed into an undivided cell fitted with a boron-doped diamond anode (3.0 cm^2) as the working electrode and a platinum wire cathode (0.2 cm^2) as the counter electrode. Sulfide (1.0 mmol) and diphenyl diselenide (1.0 mol%) were then added. The solution was stirred (6500 rpm, ultra-turrax) whilst being cooled to 0 ^{o}C in an ice bath while applying a fixed potential of 10.0 V for 1 h, which resulted in a constant current of 30 A. Extraction was carried out with dichloromethane (3 x 50 mL), and the organics washed with brine (50 mL), dried (MgSO$_4$), filtered and the solvents removed under reduced pressure.

4.4.5   General Procedure for Sulfoxidation using Urea Hydrogen Peroxide

Urea hydrogen peroxide (1 eq.) was dissolved in dichloromethane (2 mL), and the solution stirred at room temperature. A separate solution of diphenyl diselenide (1 mol%) and sulfide (2 mmol) in dichloromethane (2 mL) was also stirred at room temperature, and added to the urea hydrogen peroxide solution. The mixture was stirred at room temperature until complete conversion was observed by TLC. Extraction was carried out with dichloromethane (3 x 5 mL), after the addition of water (5 mL) and the organics washed with brine (50 mL), dried (MgSO$_4$), filtered and the solvents removed under reduced pressure.

## 4.4.6   Sulfoxidation from methyl *p*-tolyl sulfide[21]

46   **47**   **48**
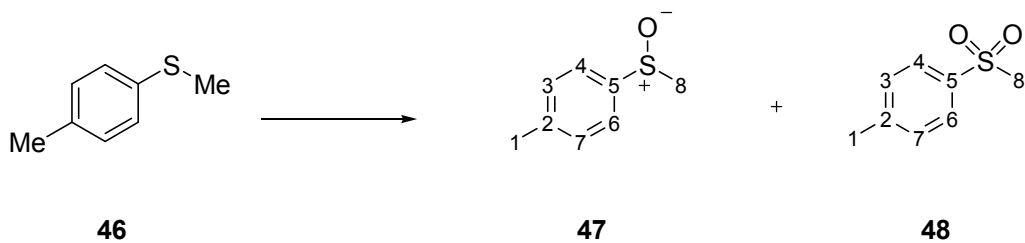
4.4.6.1 Sulfoxidation from 4-methoxythioanisole

Yellow oil; ν_{max} (cm^{-1}) 3050, 2918, 1665, 1035, 958; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 2.41 (3 H, s, C*H*$_3$ at C1), 2.70 (3 H, s, -SOC*H*$_3$ at C8), 7.33 (2 H, d, *J* 8.0 Hz, 2 x arom. C*H* at C3 & C7), 7.54 (2 H, d, *J* 8 Hz, 2 x arom. C*H* at C4 & C6) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 21.40 (CH$_3$, C8), 21.62 (CH$_3$, C1), 123.53 (2 x arom. CH, C4 & C6), 130.67 (2 x arom. CH, C3 & C7), 141.52 (C quat. arom., C5), 142.42 (C quat. arom., C2. The ee values were determined by HPLC on a chiral stationary phase; 25 °C; flow rate 0.5 mL min^{-1}.   Retention times [min]: (*R*)-17 18.7, (*S*)-17 21.1, (Chiralcel OD; hexane/IPA, 9:1).

4.4.6.2 Sulfone 48

Colourless oil; ν_{max} (cm^{-1}) 3048, 2915, 1665, 1639, 1250, 960; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 2.45 (3 H, s, CH_3 at C1), 3.04 (3 H, s, -SO$_2$CH_3 at C8), 7.82 (2 H, d, J 8.4 Hz, 2 x arom. CH at C3 & C7), 7.34 (2 H, d, J 12.6 Hz, 2 x arom. CH at C4 & C6); ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 21.64 (2 x CH3, C1 & C8), 127.39 (2 x arom.CH, C4 & C6), 130.29 (2 x arom. CH, C3 & C7), 137.63 (C quat. arom., C5), 144.73 (C quat. arom., C2).

4.4.7 Sulfoxidation from Thioanisole[22]

55
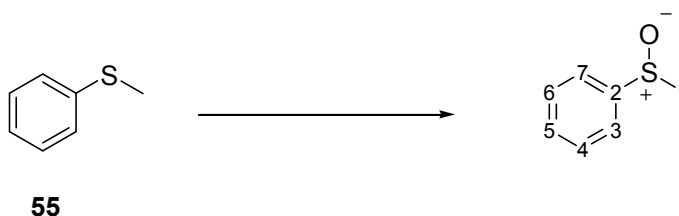
Yellow oil; ν_{max} (cm^{-1}) 3054, 2996, 2911, 1657, 1581, 1038 (S=O), 956; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 2.71 (3 H, s, CH_3 at C1), 7.48-7.54 (3 H, m, 3 x arom. CH at C4, C5 & C6), 6.64 (2 H, dd, J 10.4, 9.6 Hz, 2 x arom. CH at C3 & C7) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 43.86 (CH$_3$, C1), 123.38 (2 x arom. CH, C3 & C7), 129.27 (2 x arom. CH, C4 & C6), 133.64 (C quat. arom., C5), 145.63 (C quat. arom., C2).

4.4.8 Sulfoxidation from 4-chlorothioanisole[23]

60
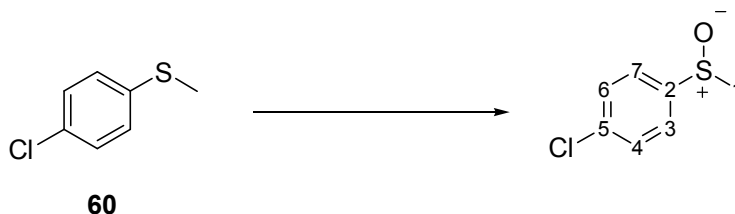
Yellow oil; ν_{max} (cm^{-1}) 3078, 2996, 2910, 1656, 1640, 1050 (S=O), 740 (C-Cl); ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 2.72 (3 H, s, CH_3 at C1), 7.39 (2 H, d, J 13.2 Hz, 2 x arom. CH at

C3 & C7), 7.49 (2 H, d, *J* 13.2 Hz, 2 x arom. C*H* at C4 & C6) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ$_C$ 43.95 (CH$_3$, C1), 124.62 (2 x arom. CH, C4 & C6), 129.54 (2 x arom. CH, C3 & C7), 137.04 (C quat. arom., C5), (C quat. arom., C2).

4.4.9 Sulfoxidation from 4-fluorothioanisole[24]

56

Yellow oil; ν$_{max}$ (cm^{-1}) 3096, 3062, 2996, 1655, 1641, 1046 (S=O), 958, 834 (C-F); ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ 2.73 (3 H, s, C*H*$_3$ at C1), 7.21-7.26 (2 H, m, 2 x arom. C*H* at C3 & C7), 7.66-7.69 (2 H, m, 2 x arom. C*H* at C4 & C6) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ$_C$ 44.03 (CH$_3$, C1), 116.69 (2 x arom. CH, C3 & C7), 125.54 (2 x arom. CH, C4 & C6), 130.14 (C quat. arom., C5), 141.16 (C quat. arom., C2).
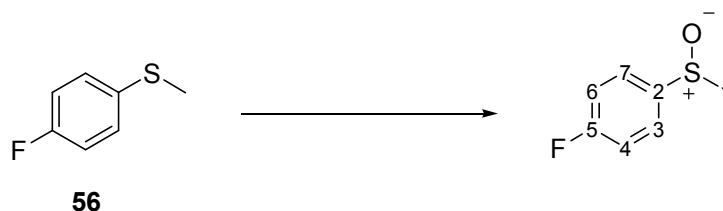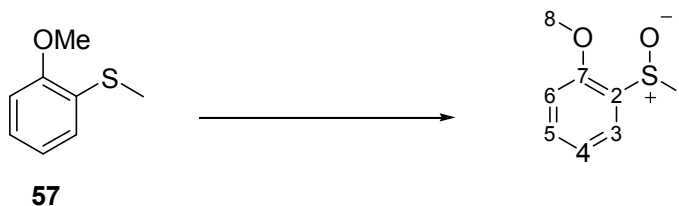
### 4.4.10 Sulfoxidation from 2-methoxythioanisole[25]

57

Yellow oil; ν$_{max}$ (cm^{-1}) 3009, 2941, 2918, 2841, 1161, 1037 (S=O), 960, 758; ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ 2.76 (3 H, t, *J* 2.12 Hz, C*H*$_3$ at C1), 3.87 (3 H, t, *J* 2.12 Hz, C*H*$_3$ at C8), 6.92 (1 H, dd, *J* 0.8, 8.4 Hz, arom. C*H* at C6), 7.16 (1 H, ddd, *J* 0.8, 7.6, 14.8 Hz, arom. C*H* at C4), 7.44 (1 H, ddd, *J* 2.0, 8.4, 16.0 Hz, arom. C*H* at C5), 7.80 (1 H, dd, *J* 1.6, 7.6 Hz, arom. C*H* at C3) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ$_C$ 41.10 (CH$_3$, C1), 55.62 (CH$_3$, C8), 110.60 (arom. CH, C6), 121.46 (arom. CH, C4), 124.28 (arom. CH, C3), 131.93 (arom. CH, C5), 132.85 (C quat. arom., C7), 154.68 (C quat. arom., C2).

4.4.11 Sulfoxidation from Thiochroman-4-one[26]

51
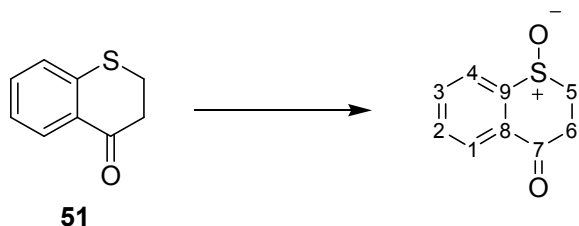
Yellow oil; v_{max} (cm^{-1}) 1694 (C=O), 1585, 1325, 1282, 1237, 1182, 1120, 1080 (S=O), 1039 (S=O), 854; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 2.86-2.97 (1 H, m, 1H of CH_2 at C5), 3.43-3.56 (3 H, m, 1H of CH_2 at C5 & CH_2 at C6), 7.65-7.68 (1 H, m, arom CH at C2), 7.75-7.79 (1 H, m, arom. CH at C3), 7.87 (1 H, dd, J 8.1, 7.6 Hz, arom. CH at C4), 8.14 (1 H, dd, J 8.0, 7.6 Hz, arom. CH at C1) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 30.28 (CH$_2$, C5), 46.62 (CH$_2$, C6), 128.47 (arom. CH, C4), 128.86 (arom. CH, C1), 132.13 (arom. CH, C3), 134.60 (arom. CH, C2), 145.49 (2 x C quat. arom., C8 & C9), 192.09 (C=O, C7).

4.4.12 Sulfoxidation from Chloromethyl phenyl sulfide[27]

61
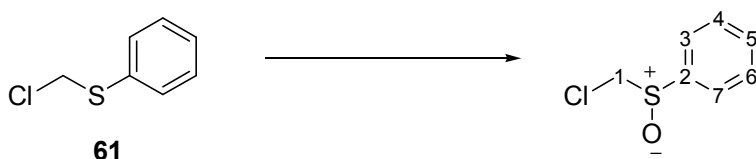
Yellow oil; v_{max} (cm^{-1}) 3056, 3001, 2932, 1657, 1640, 1443, 1053 (S=O), 997, 740 (C-Cl); ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 4.42 (2 H, dd, J 10.4, 31.2 Hz, ClCH_2 of anti and syn isomers at C1), 7.52-7.59 (3 H, m, 3 x arom. CH at C4, C5 & C6), 7.67-7.69 (2 H, m, 2 x arom. CH at C3 & C4) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 61.51 (CH$_2$, C1), 124.78 (2 x arom. CH, C3 & C7), 129.34 (2 x arom. CH, C4 & C6), 132.13 (arom. CH, C5), 140.82 (C quat. arom., C2).

4.4.13 Sulfoxidation from 2-chloroethyl methyl sulfide[28]

64
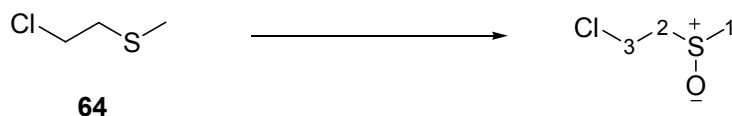
Yellow oil; ν_{max} (cm^{-1}) 3003, 2914, 1424, 1409, 1302, 1023 (S=O), 743 (C-Cl); ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 2.67 (3 H, s, CH_3 at C1), 3.05-3.12 (2 H, m, ClCH$_2$CH_2 at C2), 3.90-3.98 (2 H, m, ClCH_2 at C3) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 36.14 (CH$_2$, C1), 38.85 (CH$_3$, C3), 56.83 (CH$_2$, C2).

4.4.14 Sulfoxidation from 2-chloroethyl ethyl sulfide[28]

65
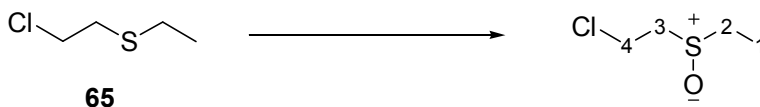
Yellow oil; ν_{max} (cm^{-1}) 1653, 1455, 1301, 1127, 1020 (S=O), 864 (C-Cl); ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.37 (3 H, t, J 7.6 Hz, CH_3 at C1), 2.76-2.86 (2 H, m, CH_2 at C2), 3.04-3.08 (2 H, m, CH_2 at C3), 3.89-4.00 (2 H, m, CH_2 at C4) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 6.70 (CH$_3$, C1), 37.01 (CH$_2$, C4), 45.97 (CH$_2$, C2), 54.00 (CH$_2$, C3).

4.4.15 Sulfoxidation from Ethyl vinyl sulfide[29]

59
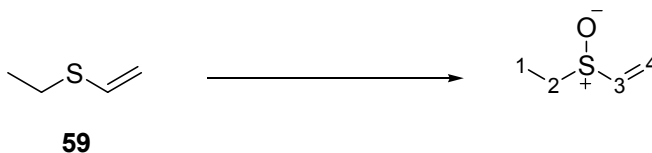
Yellow oil; ν_{max} (cm^{-1}) 2950, 2891, 1657, 1438, 1019 (S=O), 743; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.29 (3 H, t, J 7.2 Hz, CH_3 at C1), 2.65 (1 H, dq, J 7.4 Hz, 1H of CH_2 at C2), 2.85 (1 H, dq, J 7.4 Hz, 1H of CH_2 at C2), 5.99 (1 H, d, J 10.0 Hz, CH *cis* at C4), 6.10 (1 H, d, J 16.8 Hz, CH *trans* at C4), 6.58 (1 H, dd, J 10.0 & 16.8 Hz, CH at C3) ppm; ^{13}C

NMR (100 MHz, CDCl$_3$): δ$_C$ 5.65 (CH$_3$, C1), 46.46 & 48.55 (2 x CH, C2), 122.56 (CH$_2$, C4), 139.83 (CH, C3).

4.4.16 Sulfoxidation from Ethyl phenyl sulfide[22]

62
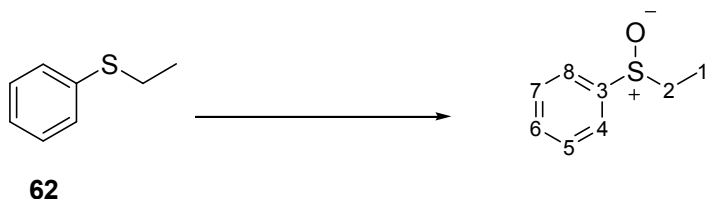
Yellow oil; ν$_{max}$ (cm^{-1}) 3057, 2978, 2933, 2918, 2874, 1643, 1581, 1043 (S=O), 968; ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ 1.18 (3 H, t, J 7.4 Hz, CH_3 at C1), 2.70-2.79 (1 H, m, 1H of CH_2 at C2), 2.88-2.95 (1 H, m, 1H of CH_2 at C2), 7.47-7.52 (3 H, m, 3 x arom. CH at C5, C6 & C7), 7.59-7.62 (2 H, m, 2 x arom. CH at C4 & C8) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ$_C$ 5.78 (CH$_3$, C1), 50.08 (CH$_2$, C2), 124.01 (2 x arom. CH, C4 & C8), 129.02 (2 x arom. CH, C5 & C7), 130.53 (arom. CH, C6), 143.20 (C quat. arom., C2).

4.4.17 Sulfoxidation from Furfuryl methyl sulfide[30]

58
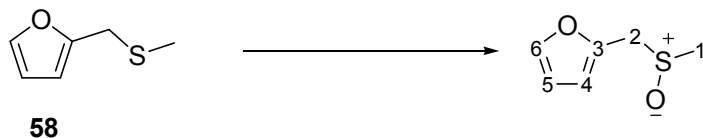
Yellow oil; ν$_{max}$ (cm^{-1}) 2972, 2916, 1423, 1033 (S=O), 933, 744; ^{1}H NMR (400 MHz, CDCl$_3$): δ$_H$ 2.52 (3 H, s, CH_3 at C1), 4.06 (2 H, q, J 13.92 Hz, CH_2 at C2), 6.40 (2 H, m, 2 x CH at C4 & C5), 7.39 (1 H, dd, J 2.0 Hz, arom. CH at C6) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ$_C$ 37.99 (CH$_3$, C1), 52.22 (CH$_2$, C2), 111.17 (2 x CH, C4 & C5), 143.52 (CH, C6), 143.92 (C quat., C3).

4.4.18 Sulfoxidation from Benzyl phenyl sulfide[22]

63
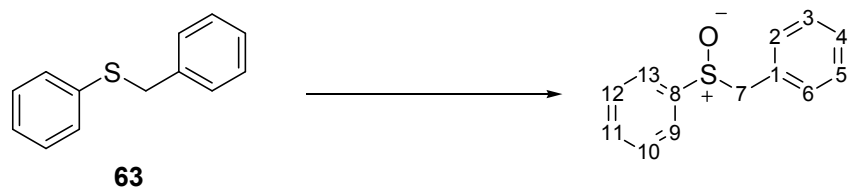
Yellow oil; ν_{max} (cm^{-1}) 3040, 2980, 2917, 1648, 1630, 1081 (S=O), 866; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 4.00 (2 H, q, J 12.4 Hz, CH_2 at C7), 6.96 (2 H, dd, J 8.0 Hz, 2 x arom. CH at C2 & C6), 7.18-7.24 (3 H, m, 2 x arom. CH at C3, C4 & C5), 7.34-7.41 (5 H, m, 5 x arom. CH at C8, C9, C10, C11, C12 & C13) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 63.44 (CH$_2$, C7), 124.38 (2 x arom. CH, C9 & C13), 128.21 (arom. CH, C4), 128.28 (2 x arom. CH, C3 & C5), 128.89 (2 x arom. CH, C10 & C12), 130.82 (2 x arom. CH, C2 & C6), 131.14 (arom. CH, C11), 142.78 (2 x C quat. arom., C1 & C8).

4.5　References

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