A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

Designing new chiral hydroxamic acid ligands for the asymmetric epoxidation reaction in water.

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For my family

Acknowledgements:

I would like to start by saying a huge thank you to Professor Andrei Malkov for all his kind support and encouragement over the past three years. I am extremely grateful for the opportunity to work at Glasgow University.

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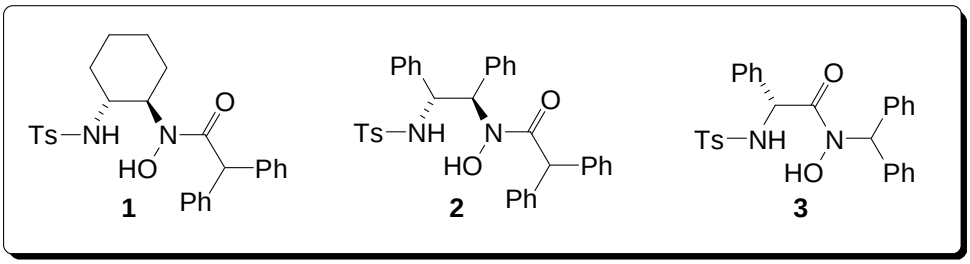
Finally, I would like to say a huge thank you to my family for all their support and encouragement over the years. Mum, Dad, Jenni you made me the person I am today.

Abstract:

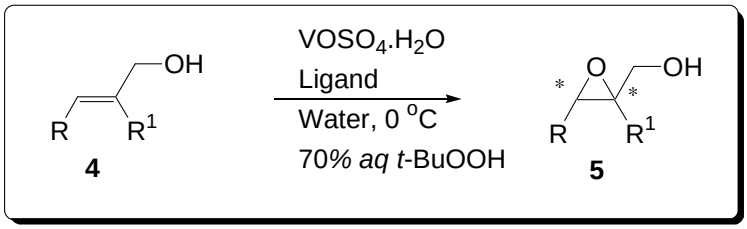
Herein, we report the synthesis of new chiral hydroxamic acid ligands for the V-catalysed asymmetric epoxidation reaction in aqueous solution (Figure 1).

Figure 1: New ligands for the asymmetric epoxidation reaction.



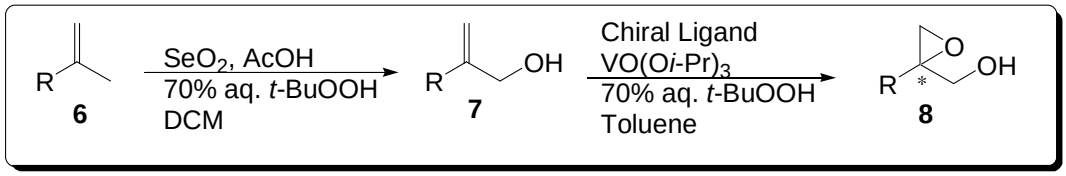
During the course of this project, a wide range of allylic alcohols were epoxidised under mild reaction conditions. The target epoxides were isolated in good-to-excellent yields with up to 94% ee (Scheme 1).

Scheme 1: General reaction conditions for the asymmetric epoxidation.



To further develop the project, we also report that the range of substrates has been extended to unfunctionalised alkenes. These materials have been successfully converted to the corresponding allylic alcohols in the presence of SeO_2 and acetic acid. Asymmetric epoxidation was then achieved under anhydrous conditions in good-to-moderate yields with up to 76% ee (Scheme 2).

Scheme 2:



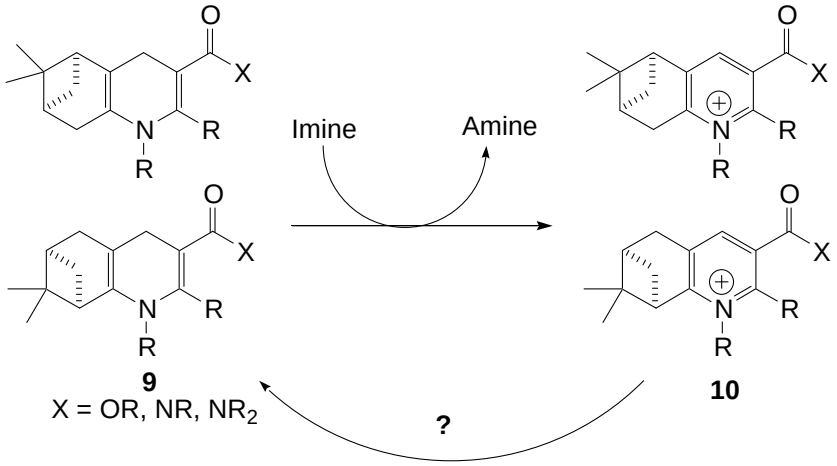
In certain cases, the overall transformation can occur as a one-pot process.

A brief investigation into the development of organocatalytic transfer hydrogenation mediated by chiral pyridines has also been carried out. In this project, a range of chiral quarternary ammonium salts have been prepared as precursors to the corresponding dihydropyridines.

It was our initial intention to utilise these chiral dihydropyridines in the enantioselective reduction of imines. This would result in the formation of the desired chiral amine and a quaternary pyridinium salt, which could then be reduced to reform the dihydropyridine in a catalytic cycle (Scheme 3).

However, with all pyridinium salts formed we were unable to produce the target dihydropyridines and this project was consequently abandoned.

Scheme 3: Organocatalytic transfer hydrogenation mediated by chiral pyridines



Contents:

Abbreviations:

Ac	acetate
aq	aqueous
Bn	benzyl
b.p.	boiling point
Bu	butyl
bs	broad singlet
c	concentration
CHP	cumene hydroperoxide
CI	chemical ionisation
Config	configuration
CV	cyclic voltammogram
^{o}C	degrees centigrade
DCM	dichloromethane
d	doublet
dd	doublet of doublets
DIBAL-H	diisobutyl aluminium hydride
DMAP	dimethyl amino pyridine
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
dt	doublet of triplets
ee	enantiomeric excess
EI	electron impact
Et	ethyl
EtOAc	ethyl acetate
eq	equivalent
FAB	fast atom bombardment
FGI	functional group interconversion
g	grams
GC	gas chromatography
h	hour(s)
HPLC	high pressure liquid chromatography

HRMS	high resolution mass spectroscopy
Hz	hertz
i	iso
IR	infrared
LUMO	lowest unoccupied molecular orbital
M	molar
m	multiplet
m-CPBA	3-chloroperbenzoic acid
mbar	millibar
Me	methyl
mg	milligram
MHz	megaHertz
mins	minutes
mL	millilitres
mmol	millimole
MeOTf	methyl triflate
m.p.	melting point
MS	mass spectroscopy
NADH	nicotinamide adenine dinucleotide
naphth	naphthyl
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
OTf	triflate
p	para
Ph	phenyl
ppm	parts per million
Pr	propyl
py	pyridine
q	quartet
r.t.	room temperature
s	singlet
sat.	saturated
t	tertiary
t	triplet

T	temperature
TBHP	*tert*-butyl hydroperoxide
TCA	trichloroacetate
TFA	trifluoroacetate
THF	tetrahydrofuran
TIPS	tri-*iso*-propyl silyl
TLC	thin layer chromatography
TMS	trimethyl silyl
TMSCl	chloro trimethyl silane
TPP	*meso*-tetra phenyl porphine
TrOOH	trityl hydroperoxide
Ts	tosyl
UV	ultraviolet

Part A: Designing new chiral liagnds for the asymmetric epoxidation reaction

1.0 Introduction to asymmetric epoxidation of allylic alcohols:

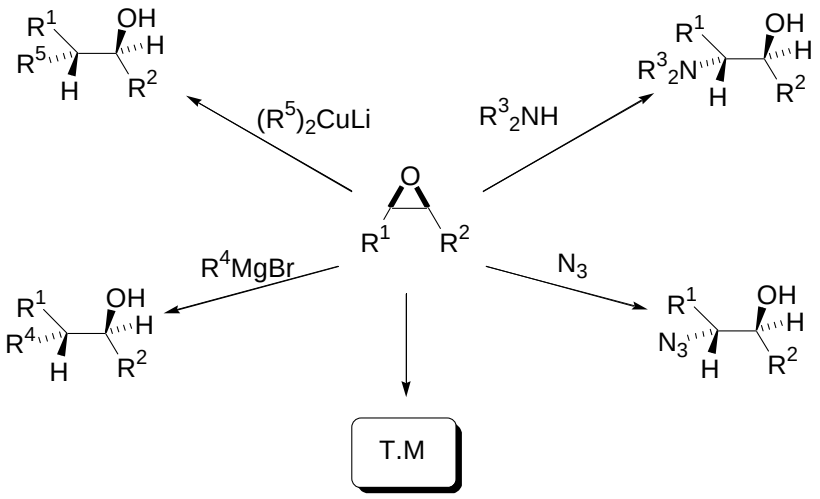
1.1 Introduction:

In this literature review, the development of the vanadium-catalysed asymmetric epoxidation of allylic alcohols will be discussed. This will include the ground-breaking work carried out by Sharpless and Yamamoto; as well as the results previously achieved within our laboratories. A brief overview of the Sharpless titanium system will also be described.

1.1.1 Epoxides as powerful intermediates for organic synthesis:

The formation of a chiral epoxide is a very powerful tool for organic synthesis. These important intermediates provide endless opportunities for further functionalisation, and synthetic development (Scheme 1.1).[1, 2, 3]

Scheme 1.1:



Therefore, it is not surprising that the asymmetric epoxidation reaction is frequently used as a key method for introducing chirality into a synthetic pathway.

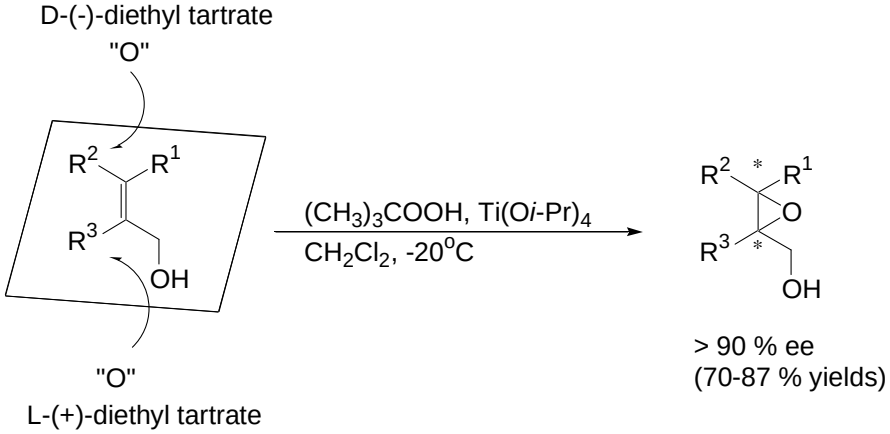
1.2 The Sharpless asymmetric epoxidation reaction:

1.2.1 Introduction:

The Sharpless asymmetric epoxidation procedure is currently the leading method for preparing a chiral epoxide. The system uses (+) or (–) diethyl tartrate, Ti(O*i*-Pr)$_4$ and *t*-BuOOH, all of which are commercially available.[4]

This system has been very successful. An extremely high yield and excellent selectivity is nearly always observed.[4] However, what is most exciting about this process is that it is applicable to a wide range of substrates. It would appear that the substitution pattern of the starting allylic alcohol does not dictate the chiral induction.[4] Scheme 1.2 highlights how this reaction works.[4]

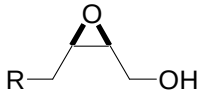
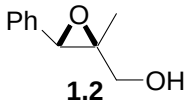
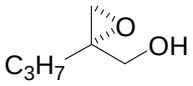
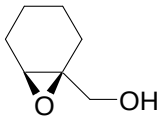
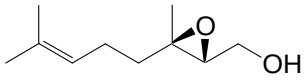
Scheme 1.2:



The enantiofacial discrimination is entirely dependant on the enantiomer of diethyl tartrate used.[4] If (–) diethyl tartrate is utilised, then the source of oxygen is always delivered from the top face when the allylic alcohol is orientated as shown in Scheme 1.2. Likewise, when (+) diethyl tartrate is employed, then the source of oxygen is always delivered from the bottom face.[4]

Originally, the process utilised a stoichiometric amount of titanium, although epoxidation of more reactive substrates could be carried out at 10 mol% catalyst.[5] However, the process was modified in 1986 when the Sharpless group realised that the addition of molecular sieves allowed the catalyst loading to be lowered to 5-10 mol % for all substrates.[6] Table 1.1 shows a sample of the results achieved in this highly successful process.[5]

Table 1.1: Results obtained by Sharpless et al.

Entry	**Product**	**Sieves**	**Catalyst, mol% Ti/tartrate**	**Yield (%)**	**ee (%)**
	 **1.1**				
1	R = C_3H_7	4A	5/6.0	85	94
2	R = C_8H_{17}	4A	5/6.0	78	94
3	R = p-nitrophenyl	4A	5/7.5	82	>98
4	 **1.2**	4A	5/7.5	79	>98
5	 **1.3**	3A	4.7/5.9	88	95
6	 **1.4**	4A	5/7.3	77	93
7	 **1.5**	4A	5/7.4	95	91

The results indicate that for a wide range of substrates, the corresponding epoxides were obtained in high yields (>77 %) and excellent selectivities (>91 % ee).[5] The consistently good results produced for substrates with diverse substitution patterns make the Sharpless epoxidation an extremely desirable procedure.

1.2.2 Disadvantages of the Sharpless system:

Nevertheless, there are drawbacks associated with this process.

(i) The catalyst requires ageing prior to use.[5]

The titanium-tartrate complex is not stable at room temperature. Attempted reactions carried out with a pre-mixed stock solution of the catalyst were not successful.[5] In order to form the catalyst, Ti(O*i*-Pr)$_4$, diethyl tartrate and the allylic alcohol are stirred at –20 ^{o}C for 30 minutes. The *t*-BuOOH is then introduced to the system. After this 'ageing period', the temperature is adjusted according to the substrate.[5]

(ii) The catalyst is extremely moisture sensitive.[5]

As little as one equivalent of water is enough to completely decompose the catalyst. However, the addition of molecular sieves helps overcome this problem. It was therefore suggested that water initially reacts with the titanium catalyst in a reversible manner, as the addition of molecular sieves can revive most of the catalytic activity.[5] However, this does eventually become an irreversible problem and the catalyst will be completely destroyed.[5]

(iii) The procedure has a long and tedious work-up associated with the formation of colloid suspensions of titanium hydroxides.

(iv) The process requires a high catalyst loading. The majority of substrates require at least 5-10 mol% Ti/tartrate complex, and in the absence of molecular sieves a stoichiometric amount is required.[4,5]

1.3 Vanadium-catalysed epoxidations:

1.3.1 Initial Studies carried out by the Sharpless group:

Vanadium catalysis represents an alternative methodology capable of overcoming these problems (section 1.2.2). Vanadium-based protocols tolerate the presence of moisture; the associated work-up is also much simpler, as the reaction mixture only requires an aqueous quench followed by extraction with organic solvent. However, the most important point in vanadium catalysis is that the reaction works consistently well with catalyst loading as low as 1 mol%.[7]

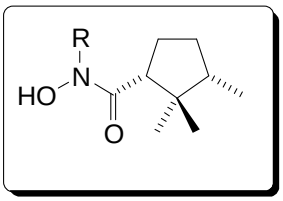
This system was first investigated by Sharpless and co-workers in 1977.[8,9] Initial studies focussed on the formation of new chiral ligands based on β-diketones.[10] However, these ligands produced poor results as the β-diketone was not stable under the reaction conditions.[10]

The Sharpless group examined many different compounds as ligands for the asymmetric epoxidation reaction and found that hydroxamic acids had the greatest potential as they not only bind well to vanadium, but are also resistant to oxidation under the reaction conditions.[9]

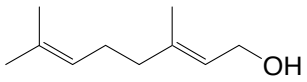
The following three compounds **1.6a-c** were employed as ligands for the epoxidation of allylic alcohols **1.7**, **1.8**, and **1.9**. However, the selectivities obtained were disappointingly low.

A selection of the best results achieved with these ligands are shown in Table 1.2.[9]

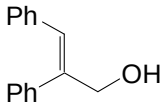
Table 1.2: Vanadium Catalysed Epoxidations:



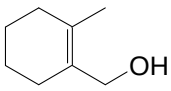
1.6a, R = CH_3
1.6b, R = Ph
1.6c, R = 2,6-Me_2Ph



1.7



1.8



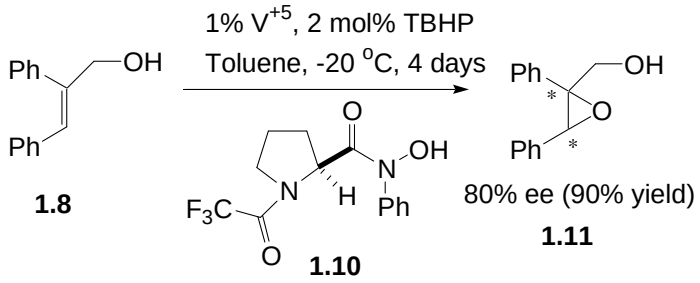
1.9

Entry	Ligand (eq)	Substrate	Temp (^{o}C)	Conversion(%)	ee (%)
1	1.6a (5)	1.8	-78 to 25	80	21
2	1.6a (10)	1.8	-78 to 25	22	18
3	1.6b (4)	1.7	-78 to 25	100	19
4	1.6b (5)	1.7	25	86	30
5	1.6b (3)	1.8	-78 to 25	100	22.5
6	1.6b (5)	1.8	-78 to 25	30	50
7	1.6b (5)	1.8	25	84	40
8	1.6b (5)	1.9	25	87	40
9	1.6b (5)	1.9	-10	75	44
10	1.6c (4)	1.7	0	55	19

The highest selectivity was obtained with ligand **1.6b** at –78 ^{o}C (entry 6). Table 1.2 highlights a sample of the best results obtained in this study. The overall selectivities were low, ranging from just 5 - 50 % ee.[9] Therefore, a better ligand was clearly desired.

However, an extensive search for new, more efficient ligands failed to emerge.[11] The best selectivity was observed by Sharpless in the epoxidation of α-phenylcinnamyl alcohol **1.8** to give **1.11** (80% ee) using chiral ligand **1.10** derived from proline (Scheme 1.3).[11]

Scheme 1.3:

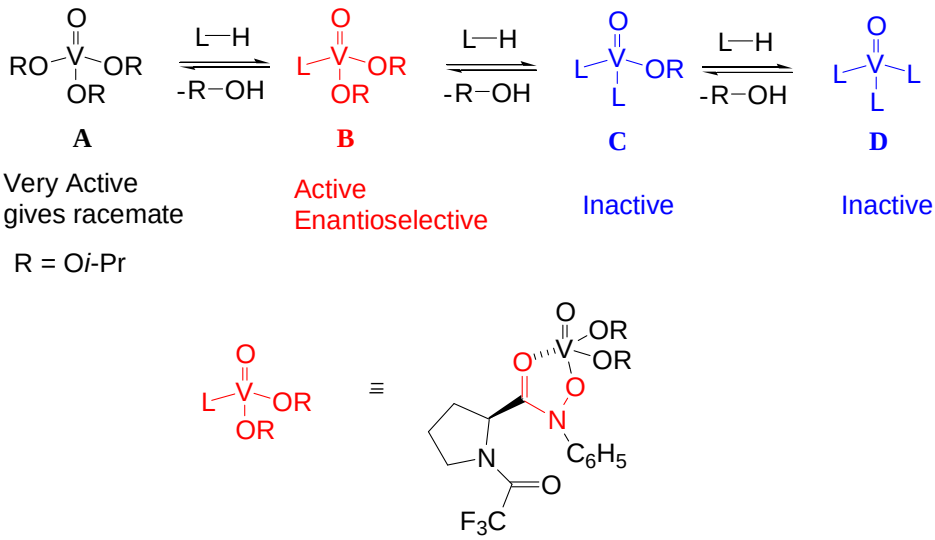


However, **1.8** was the only substrate that showed a high level of asymmetric induction, as other substrates produced much lower selectivities.[11] The process was also extremely slow. In this particular example, four days were required for the reaction to occur.[11] When compared to a racemic epoxidation carried out under the same reactions conditions, epoxide formation was complete in just a few hours in the absence of a chiral ligand.[1] Therefore it was deduced that the presence of a ligand was responsible for this notable decrease in the rate of reaction.

1.4 The Ligand Deceleration Effect:

When a ligand is bound to a metal, the rate of product formation can either a) increase, b) decrease or c) stay the same.[1] In section 1.3 we saw that co-ordination of a hydroxamic acid ligand to the vanadium catalyst substantially reduced the rate of epoxidation. However, increasing the concentration of ligand leads to the formation of more than one species in solution (Scheme 1.4).[1]

Scheme 1.4:



Scheme 1.4 illustrates that the vanadyl trialkoxide species **A** is very reactive. As there is not any steric bias, which is normally created by a co-ordinated ligand, the resulting epoxide will be, naturally, racemic. When a chiral ligand is introduced into the system, a labile alkoxide group is exchanged for one equivalent of ligand. This results in the formation of species **B**, which is now capable of performing a selective reaction.

However, species **B** reacts much slower than species **A**, as the vanadium has been partially deactivated by the addition of a Lewis basic chiral liagnd. Nevertheless, this is the key selective species that we want to produce in solution.

As the concentration of ligand is further increased, inactive species **C** and **D** begin to dominate in solution.[1, 12] Therefore, the resultant rate of reaction would be significantly lower.[1] However, an increased concentration of ligand is required in order to achieve a selective reaction, as the presence of species **A** would result in a significantly lower ee.

By using a high concentration of ligand, we rely on shifting the equilibrium away from non-chiral species **A** towards inactive species **C** and **D,** which could occasionally disproportionate into active species **B,** but at the same time avoiding the presence of species **A** in the reaction mixture.

These key points can be summarised in the following diagram (Figure 1.1).[1]

Figure 1.1:

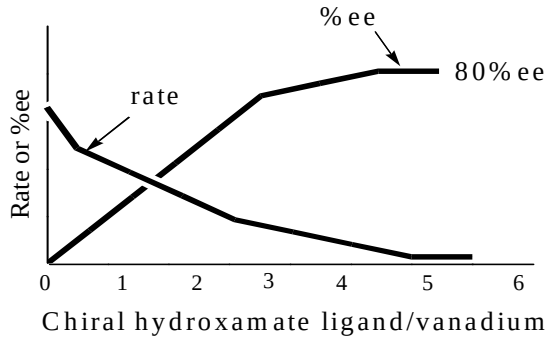


Figure 1.1 demonstrates that increasing the concentration of ligand, increases the selectivity up to 80% ee. Once this value is achieved, the selectivity reaches a plateau. Increasing the concentration further has no additional effect on the ee observed.

Regarding the rate of reaction, the opposite is true. As the concentration of ligand increases, the rate of reaction dramatically drops and continues to decrease as more ligand is utilised.

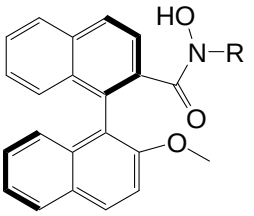
Because of this massive reduction in reactivity, for many years the vanadium-catalysed epoxidation reaction was thought to be impractical. It would take another twenty years before a feasible method was developed.[13]

1.5 The New Generation of V-Catalysts

1.5.1 Outstanding developments in the field:

In 1999, the first real breakthrough in vanadium catalysis was reported.[14] This pioneering work was carried out by the Yamamoto group, who developed a new range of hydroxamic acid ligands for the asymmetric epoxidation reaction (Figure 1.2).[14,15]

Figure 1.2: Yamamoto's Chiral Ligands.

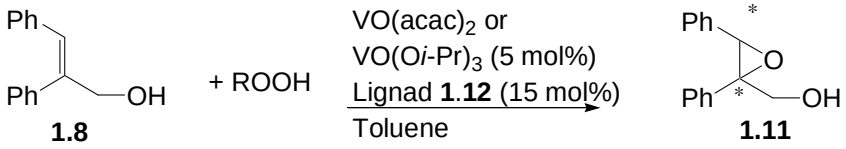


1.12

1.12a, R = cyclohexyl
1.12b, R = Bn
1.12c, R = $CHPh_2$

These three ligands were tested on model substrate **1.8** with both $VO(acac)_2$ [vanadium (IV)] and $VO(O\textit{i}\text{-}Pr)_3$ [vanadium (V)]. Different alkyl peroxides and temperatures were also assessed. The results are summarised in Table 1.3.[14]

Table 1.3:



1.8 **1.11**

Entry	Catalyst	ROOH	Conditions (^{o}C/h)	ee (%)
1	$VO(acac)_2$/**1.12a**	CHP	0, 6 days	25
2	$VO(acac)_2$/**1.12b**	CHP	0, 8 days	54
3	$VO(acac)_2$/**1.12c**	CHP	0, 19	65
4	$VO(OPr^{i})_3$/**1.12c**	CHP	0, 3	68
5	$VO(OPr^{i})_3$/**1.12c**	TBHP	-40, 10	40
6	$VO(OPr^{i})_3$/**1.12c**	TrOOH	-20, 68	86
7	$VO(OPr^{i})_3$/**1.12c**	TrOOH	-20, 24	83

Note: CHP = cumenehydroperoxide, TrOOH = triphenylmethylhydroperoxide.

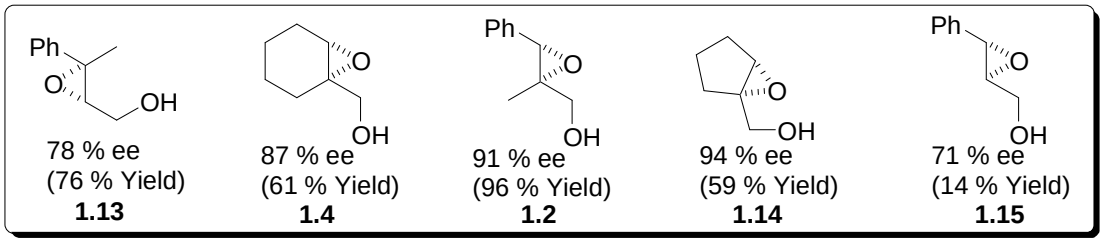
The results show that the rate of reaction is dependant on various factors; including the steric bulk of the ligand, peroxide employed and the oxidation state of vanadium.[14]

From Table 1.3, we can see that the reaction is much faster when vanadium (V) is employed as a catalyst. The source of peroxide and temperature also have a dramatic effect on the selectivity. Cumenehydroperoxide at 0 ^{o}C produced a much lower selectivity when compared with results obtained using TrOOH (entries 5-7). However, all of these examples were carried out at a much

lower temperature. Optimum results were achieved using $VO(O\textit{i}\text{-}Pr)_3$ and TrOOH at - 20 ^{o}C (entry 6).

Under the optimised reaction conditions, a wide range of allylic alcohols were epoxidised.[14] Overall selectivities ranged from 38 – 94 % ee on a variety of cyclic and acyclic substrates.[14] A selection of the best results obtained are shown in Figure 1.3, highlighting the potential power of this new procedure.[14]

Figure 1.3:



With these results achieved by the Yamamoto group we can see the revival of vanadium catalysis. The vanadium-catalysed asymmetric epoxidation is now well on it's way to becoming a practical method for selective epoxide formation.

1.5.2 Combinatorial approach to ligand design.

After this discovery, Yamamoto went on to synthesise a library of chiral ligands based on α-amino acids.[16] In this study, three structural components were independently varied:

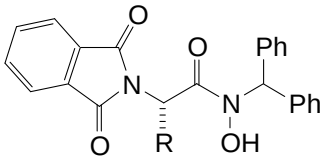
(i) the α-amino acid part

(ii) the imido part

(i) the aromatic part of hydroxylamine.

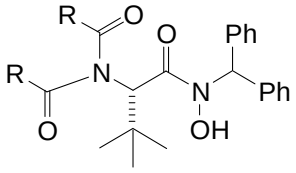
All twenty-eight ligands prepared in this iterative study are shown in Figure 1.4.[16]

Figure 1.4: Yamamoto's library of ligands



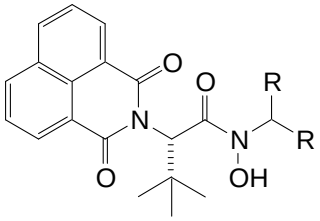
Amino Acid part:

1.16a, R = Ala
1.16b, R = Abu
1.16c, R = Val
1.16d, R = lle
1.16e, R = Leu
1.16f, R = Tie
1.16g, R = Phe
1.16h, R = Trp
1.16i, R = Lys(Pht)
1.16j, R = Met



Imido part:

1.16k, R = 4(Me)Pht
1.16l, R = tetra(F)Pht
1.16m, R = tetra(Cl)Pht
1.16n, R = 2,3-di(Me)maleoyl
1.16o, R = 2,3-di(Ph)maleoyl
1.16p, R = 2,3-Nap
1.16q, R = 1,8-Nap
1.16r, R = 4-Br, 1,8-Nap
1.16s, R = Ant

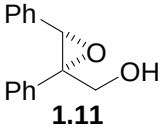
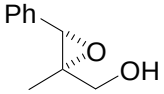
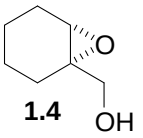
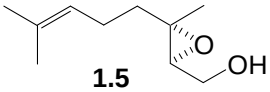
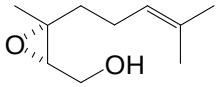
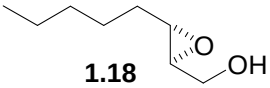
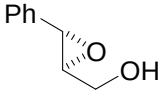
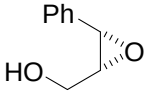
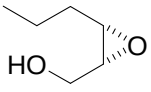


Ar or Ar-Ar part:

1.16t, R = o-Tol
1.16u, R = o-(iPr)Ph
1.16v, R = m,m-di(tBu)$_2$Ph
1.16w, R = 1-naphthyl
1.16x, R = 2-(Meo)naphth-1-yl
1.16y, R = fuluorenyl
1.16z, R = dibenzosuberyl
1.16A, R = (R)-Phenethyl
1.16B, R = (S)-Phenethyl

The above ligands were tested using model substrate **1.8** (Table 1.3). The best results were obtained with ligand **1.16w**, which was then employed in the epoxidation of a wide range of allylic alcohols. These ground-breaking results are shown in Table 1.4.[16]

Table 1.4: Asymmetric epoxidation of various allylic alcohols in the presence of $VO(O\textit{i}\text{-}Pr)_3$ (1 mol%) and hydroxamic acid **1.16w** (1.5 mol%).

Entry	Epoxy alcohol	Time (h)	Yield (%)	ee (%)
1	 **1.11**	6	96	95
2		15	99	86
3	 **1.2**	6	97	95
4	 **1.4**	5	82	93
5	 **1.5**	6	95	81
6	 **1.17**	3	97	78
7	 **1.18**	70	94	83
8	 **1.15**	80	58	87
9	 **1.19**	1 week	71	76
10	 **1.20**	24	80	82

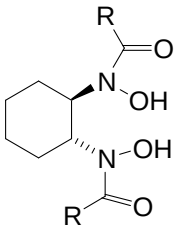
Epoxidations were performed under mild reaction conditions (0 ^{o}C) using just 1 mol % of vanadium. Table 1.4, demonstrates that the vanadium catalysed epoxidation reaction is now both extremely high yielding and highly selective on a wide range of substrates.

This important work shows that vanadium catalysis can now match the performance of the Sharpless titanium system in terms of both reactivity and selectivity.

1.5.3 Current leading vanadium-catalysed system:

Further ligand modification and optimisation of reaction conditions has resulted in what is currently the leading method for the vanadium catalysed epoxidation of allylic alcohols. This impressive system makes use of a bishydroxamic acid ligand **1.21** (Figure 1.5).[17]

Figure 1.5: Bishydroxamic acid **1.21**.



1.21

1.21-a, R = $CHPh_2$
1.21-b, R = CH_2CPh_3
1.21-c, R = $CH(3,5\text{-dimethylphenyl})_2$

This ligand was designed to overcome some issues associated with the ligand deceleration effect.[17] Design features include an additional binding site resulting in a bis-hydroxamic acid ligand and the utilisation of large R groups.

In theory, a bis-hydroxamic acid ligand should form a chiral vanadium/ligand complex with greater efficiency than the corresponding mono-hydroxamic acid ligand.[17]

In addition, steric hinderance from R groups should prevent the co-ordination of a second ligand to the metal to avoid formation of inactive species, which would reduce the overall rate of reaction (Scheme 1.4, Section 1.4).[17]

In initial studies, all three ligands formed epoxides in both a high yield and selectivity.[17] However, optimum results were observed with ligand **1.21a** which was then employed in the epoxidation of a wide range of allylic alcohols (Figure 1.6).[17] Reactions were performed on a 1 mmol scale with 1 mol% vanadium loading at –20 ^{o}C.

Figure 1.6: Epoxides produced.

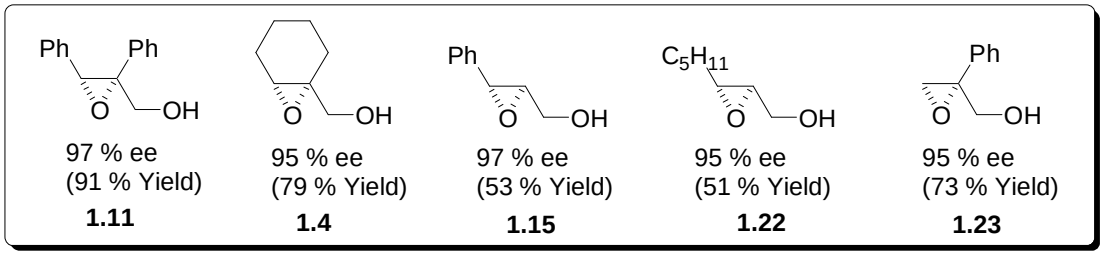


Figure 1.6 shows a selection of the results obtained by the Yamamoto group using ligand **1.21a**.[17] High selectivities in the range of 95 – 97 % ee were attained for all compounds tested in this study.[17]

With the development of these new ligands by the Yamamoto group, vanadium epoxidation methodology can now successfully compete with the Sharpless titanium systems in terms of practicality, enantioselectivity and the substrate range. Issues of reactivity, though, remain to be resolved since in vanadium-catalysis epoxidation on average requires more than 24 h compared to 2-4 h for Ti. However, by employing vanadium as a catalyst, the Yamamoto group has overcome many of the disadvantages associated with titanium chemistry (Section 1.2.2): catalyst loading was substantially reduced (1 mol%) and aqueous peroxide can be used as an oxidant. Though, in order to fully understand these concepts, a better understanding of the reaction mechanism is still required.

1.5.4 Epoxidation of homoallylic alcohols:

Yamamoto has also applied this methodology to the asymmetric epoxidation of homoallylic alcohols.[18] The following liagnds **1.24a-f** (Figure 1.7) were screened in the epoxidation of model substrate **1.25** (Table 1.5). The reaction conditions employed and results obtained are highlighted in Table 1.5.[18]

Figure 1.7: Range of ligands developed by the Yamamoto group.

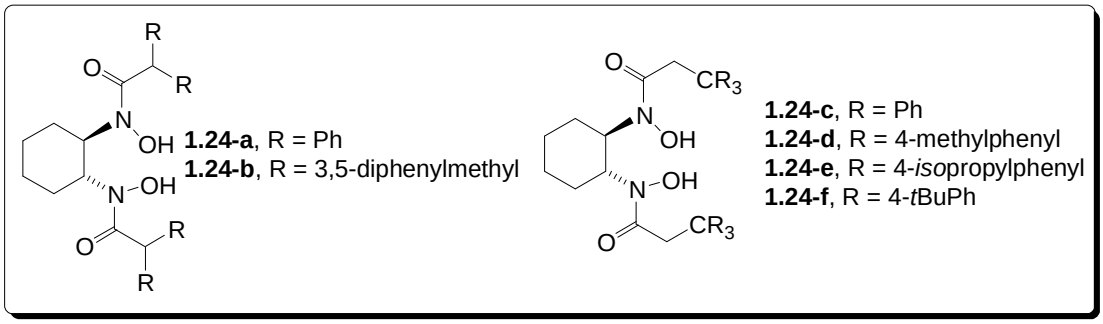
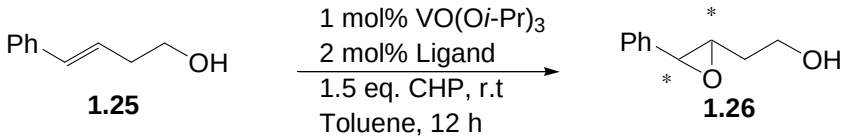


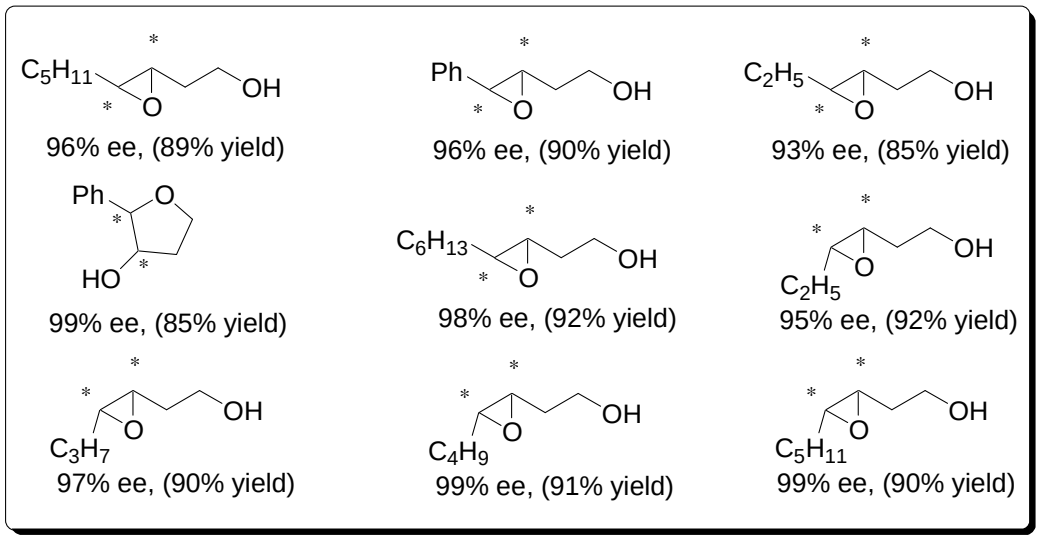
Table 1.5: Asymmetric epoxidation of homoallylic alcohols.



Entry	Ligand	Yield(%)	ee (%)
1	**1.24a**	23	10
2	**1.24b**	48	53
3	**1.24c**	52	71
4	**1.24d**	56	90
5	**1.24e**	60	92
6	**1.24f**	61	96

Optimum results were obtained using chiral ligand **1.24f**, (Entry 6, Table 1.5) which was then tested on a wide range of homoallylic alcohols (Figure 1.8.).[18]

Figure 1.8:



Therefore, the Yamamoto group has demonstrated that a wide range of both *cis* and *trans* homoallylic alcohols can be epoxidised in a good yield and excellent selectivity.

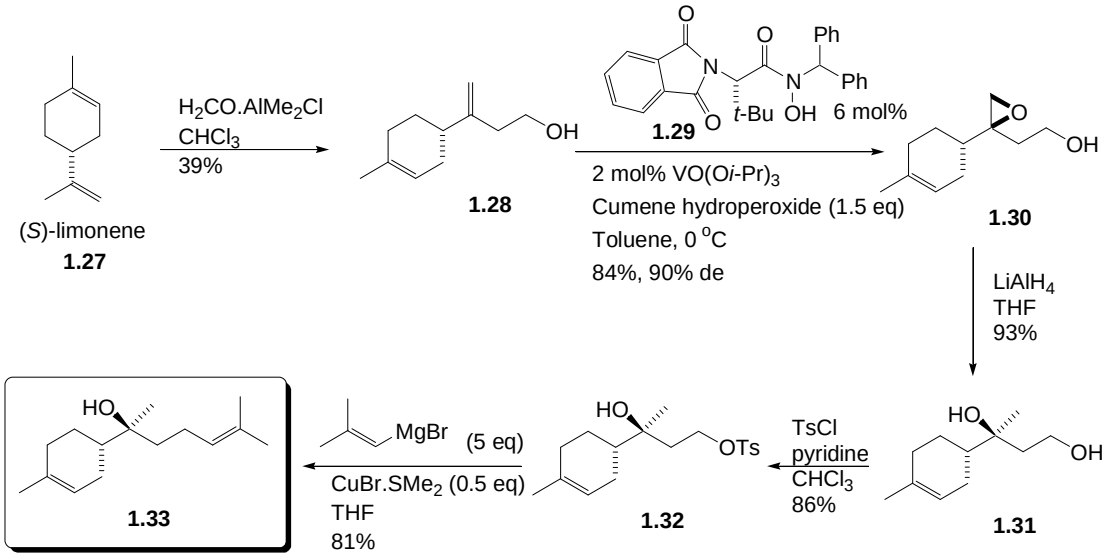
1.5.5 Applications:

Chiral epoxides have many applications in synthetic chemistry. Selective epoxidation can be used as a method for formation of an extremely useful synthetic intermediate, as well as a method for resolution.

(a) Epoxidation in total synthesis:

To demonstrate the synthetic potential of the developed methods, Yamamoto carried out the total synthesis of (−)-α and (−)-8-epi-α-bisabolol using asymmetric epoxidation in the key selectivity determining step (Scheme 1.5).[19]

Scheme 1.5:

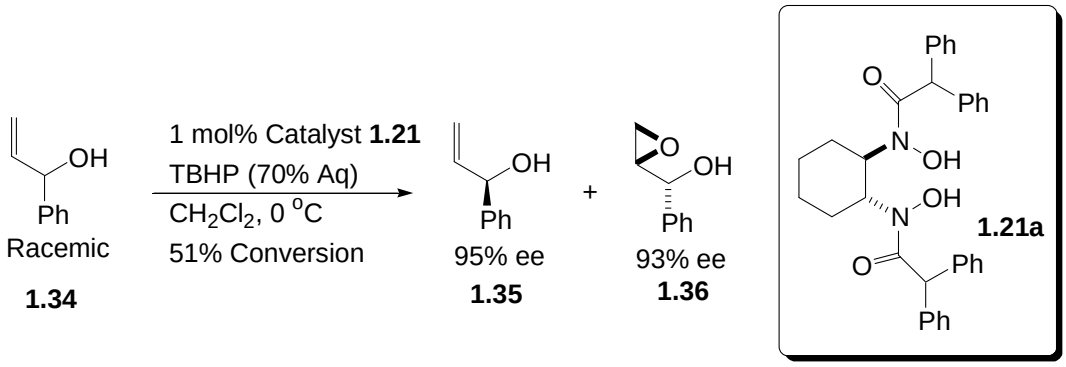


The known fragrance (−)-(4*S*,8*S*)-α-bisabolol **1.33**[20] was synthesised as shown in Scheme 1.5**.** The synthesis started with (*S*)-limonene **1.27**, which underwent the dimethyl aluminium chloride catalysed ene reaction using formaldehyde, to give the hydroxy methylated product **1.28** following a method by the Cordova group.[21] The resulting homoallylic alcohol **1.28** was then epoxidized in 90 % d.e. under mild reaction conditions.[19] To complete the synthetic sequence, epoxide **1.30** was then reduced with $LiAlH_4$, tosylated and alkylated to produce (-)-α-bisabolol **1.33** in an 81% yield. Through this synthesis, Yamamoto demonstrated that incorporation of a chiral epoxide is a quick and efficient method for preparing compounds of this type.

(b) Kinetic resolution:

The Yamamoto group have demonstrated that V-catalysed epoxide formation can also be used as a method for kinetic resolution of chiral racemic secondary allylic alcohols (Scheme 1.6).[17]

Scheme 1.6:



Chiral ligand **1.21a** can be used to epoxidise (*S*)-**1.34** in 93% ee, while leaving the (*R*)-**1.34** enantiomer unreacted. The process effectively removes the undesired enantiomer from the initial racemic mixture.

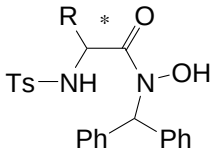
These two enantiopure compounds can then be easily separated by column chromatography and used as required.[17]

1.6 Previous work carried out by the group:

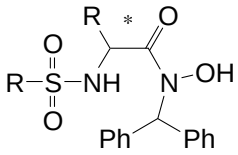
1.6.1 Asymmetric epoxidation reaction in organic solvent:

Initial studies were carried out by Dr Zaina Bourhani, who synthesised a wide range of chiral hydroxamic acids based on α-amino acids for the asymmetric epoxidation of allylic alcohols (Figure 1.9).[22]

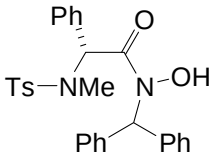
Figure 1.9: Range of new chiral ligands prepared by the Malkov group.



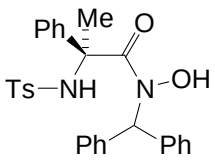
1.37a, R = (R)-Ph
1.37b, R = (S)-*i*-Pr
1.37c, R = (S)-$PhCH_2$
1.37d, R = (S)-*t*-BU



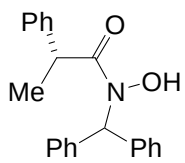
1.38a, R = Me
1.38b, R = 2,4,6-$Me_3C_6H_2$
1.38c, R = 3,5-$Me_2C_6H_3$
1.38d, R = 4-Ph-C_6H_4



1.39



1.40



1.41

In this study, three structural features were investigated:

(i) The amino acid backbone (**1.37a – d** + **1.40**)

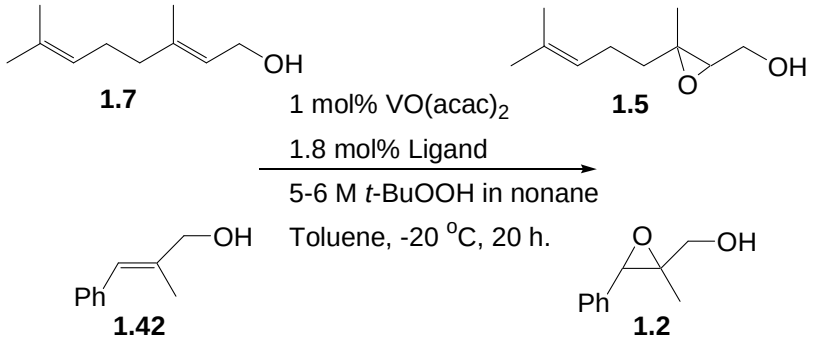
(ii) The sulfonyl group (**1.38a** – **d**)

(iii) The substitution pattern at the stereogenic centre (**1.37a**, **1.39**, **1.41**)

The diphenylmethane hydroxylamine functionality remained constant throughout the study; as literature data has shown that if a smaller group is used in this position, then a lower selectivity is observed.[15]

These new ligands were tested in two model reactions, which were carried out on a 1 mmol scale, in toluene at – 20 ^{o}C. An overview of the results obtained and the reaction conditions employed are shown in Table 1.6.[22]

Table 1.6: Model Reactions



		1.7		1.42	
Entry	**Ligand**	**Yield (%)**	**ee (%)**	**Yield (%)**	**ee (%)**
1	**1.37a**	95	64	90	62
2	**1.37b**	84	15	79	17
3	**1.37c**	95	<5	88	<5
4	**1.37d**	93	66	87	51
5	**1.40**	87	32	-	-
6	**1.41**	<5	43	-	-
7	**1.38a**	86	4	69	8
8	**1.38b**	55	41	52	39
9	**1.38c**	62	61	85	48
10	**1.38d**	95	64	76	56
11	**1.39**	96	7	93	14

It has to be noted that the catalytic systems based on ligands **1.37a**, **1.37c** and **1.37d** (entries 1,3 and 4) reacted very fast. The average yield obtained in these three experiments was > 87% after just 20 h, which was close to the reaction rate shown by $VO(acac)_2$ alone, meaning that these ligands did not show the typical ligand deceleration effect.[22]

The best results were observed with ligand **1.37a** (entry 1). In general, the selectivities obtained were only slightly lower than those observed with the earlier generation Yamamoto systems.[14-16,19] Entry 6 on the other hand, highlights the importance of the sulfonamide group. Ligand **1.41** does not contain a sulfonamide side-chain; and as a result, the model epoxidations

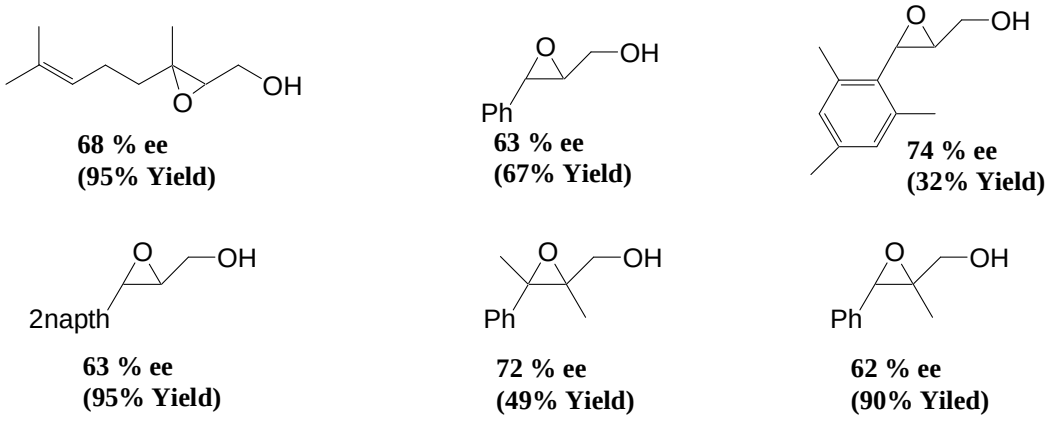
proceeded extremely slow. Therefore, the sulfonamide group was incorporated into all further ligand design.[22,23]

It is interesting to note that increasing the bulk on the sulfonamide group does not increase the observed selectivity (entries 8 – 10).

Entry 11 highlights another important point. Alkylation at the sulfonamide nitrogen, resulted in a dramatic drop in selectivity giving nearly racemic products. This suggests that the sulfonamide group is likely to be involved in the coordination to vanadium, and is another key feature which should be incorporated into future ligand design.

Ligand **1.37a** produced the best results in the model reactions and was therefore tested on a wide range of allylic alcohols. Figure 1.10 highlights a selection of the best results obtained.[22]

Figure 1.10: Range of epoxides formed.



Overall results were very promising. With chiral ligand **1.37a**, selectivity of 62 – 74 % ee was attained. However, further optimisation of the ligand structure is required to bring the enantioselectivity in line with the current standards.

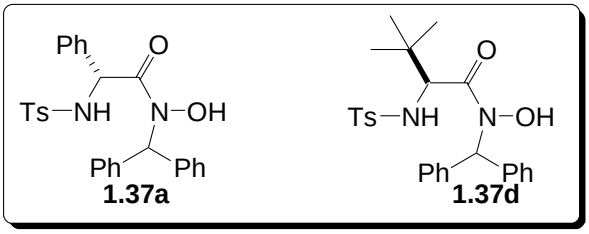
1.6.2 Asymmetric epoxidation in aqueous solution:

In section 1.4 we showed that co-ordination of a chiral ligand to the vanadium catalyst results in a notable deactivation of the catalyst. This is the major drawback associated with vanadium catalysis. One way to overcome this problem is to carry out an aqueous epoxidation.

Using water as a solvent has many benefits. The reagents employed are cheaper and are much more environmentally friendly. By using an aqueous system, the experimental procedure is also much simpler. The Sharpless titanium system is extremely sensitive to the slightest traces of moisture and, in addition, the process requires a very long and tedious work-up. For our aqueous V-system this is not the case. Simple extraction with an organic solvent is all that is required.[23]

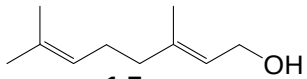
Figure 1.11 shows the two ligands which were used in the aqueous system,[23] both of which have already been employed in organic solvents (section 1.6.1.).

Figure 1.11: Chiral ligands **1.37a** and **1.37d**

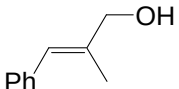


The results of aqueous epoxidation were compared with the respective results obtained under anhydrous conditions using model substrates **1.7** and **1.42** (Table 1.7).[23]

Table 1.7: Comparison of epoxidations in either toluene or water.



1.7



1.42

		Toluene		**Water**	
Entry	**Liagnd**	**Yield (%)**	**ee (%)**	**Yield (%)**	**ee (%)**
Geraniol(1.7)					
1	**1.37a**	95	64	73	60
2	**1.37d**	93	66	52	32
Alcohol(1.42)					
3	**1.37a**	90	62	79	59
4	**1.37d**	87	51	73	46

The original epoxidations were carried out in a 1.8:1 ligand/vanadium ratio, in toluene at –20 ^{o}C while the aqueous epoxidations were performed at 0 ^{o}C with just 10% excess of ligand over vanadium.[23]

Table 1.7 shows that the rate of epoxidation in the aqueous system is slightly slower. Nevertheless, the products are obtained in acceptable yields. But what was really important, was that the enantioselectivity produced in the aqueous system was equal to results obtained under anhydrous conditions.[23] Therefore, the aqueous method represents a promising new technique for asymmetric epoxidations.

Investigation into the influence of ligand/vanadium ratio using geraniol **1.7** as a model substrate uncovered a very surprising result (Table 1.8).[23]

Conversion without a ligand (entry 1) turned out to be extremely slow. This is the opposite to what has been observed in an organic solvent reaction.[22] Previously, in section 1.4, we have seen that under anhydrous conditions racemic epoxidation catalysed by VO(O*i*-Pr)$_3$ proceeds very fast. As more ligand is added to the reaction mixture, the rate of reaction begins to rapidly drop.[1]

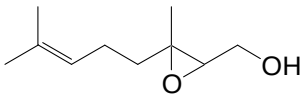
Table 1.8: Effect of the ligand **1.37a**:vanadium ratio on epoxidation of geraniol **1.7**

Entry	Ligand/mol%	V/mol%	T/^{o}C	Conversion (%)	ee (%)
1	0	1	0	18	-
2	1	0	0	<1	-
3	0.5	1	0	84	57
4	1	1	0	93	60
5	1.1	1	0	73	60
6	1.1	1	20	100	-
7	1.1	1	-20	69	69
8	1.5	1	0	76	61
9	2.5	1	0	47	61

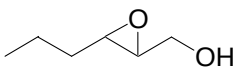
However, the exact opposite trend is observed in the aqueous system: presence of a hydroxamic acid ligand is required in order to produce a reasonable rate of reaction (entry 3). When as little as 0.5 mol% ligand is used, an 84% yield is recorded. Now it appears that the presence of a ligand is necessary for the reaction to occur. Therefore, the vanadium-catalysed epoxidation has now become a ligand accelerated process when carried out in an aqueous solution.[23]

Ligand **1.37a** once again produced the highest enantioselectivity, it was therefore employed to assess the efficacy of the new method using a range of allylic alcohols (Figure 1.12).[23]

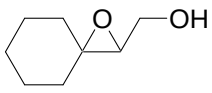
Figure 1.12: Range of epoxides formed.



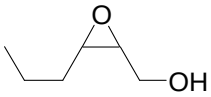
69% ee
(69% Yield)



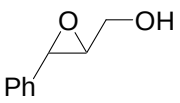
70% ee
(61% Yield)



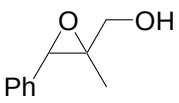
72% ee
(92% Yield)



63% ee
(41% Yield)



57% ee
(55% Yield)



59% ee
(79% Yield)

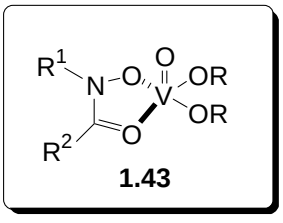
Figure 1.12 demonstrates the very promising results that have been achieved in the new ligand accelerated system. This exciting work inspired the development of a new range of hydroxamic acid ligands for the asymmetric epoxidation in aqueous solution.

1.7 Proposed reaction mechanism:

The exact mechanism for the asymmetric epoxidation reaction in organic solvent is not yet fully established. In an attempt to get a deeper insight into the process, a number of kinetic and multinuclear NMR studies have been carried out using ^{51}V, ^{13}C and ^{17}O NMR.[24-27] The following evidence obtained from these studies, allowed to formulate the reaction mechanism for simple bidentate hydroxamic acid ligands.

$VO(O\textit{n}\text{-}Bu)_3$ gives a single peak in ^{51}V NMR at δ = -594 ppm.[24] Bryliakov *et al* found that when 1 equivalent of chiral hydroxamic acid is mixed with $VO(O\textit{n}\text{-}Bu)_3$, the signal at -594 ppm disappears and a new signal at -508 ppm appears.[24] This suggests the formation of a new vanadium species **1.43**, in which the hydroxamic acid is now co-ordinated to the vanadium (Figure 1.13).[24]

Figure 1.13: Formation of new Vanadyl species.



1.43

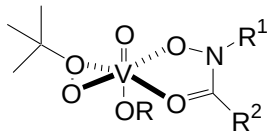
This implies that the alkoxide groups surrounding the vanadium (V) are labile and can be easily exchanged for 1 equivalent of hydroxamic acid.[22]

However, this single vanadium species is only observed at a ligand:vanadium ratio of 1:1.[24] When the ratio is increased to 1.73:1 the concentration of this single species at -508 ppm decreases and four new signals

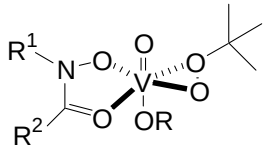
at ~ -440 ppm appear,[24] implying the formation of four new different vanadium species.

When an excess of *t*-BuOOH was added to **1.43**, four separate vanadium signals were once again observed.[22] It can be assumed that if one labile alkoxide group can be exchanged with one equivalent of ligand, then in a similar manner, one of the other alkoxide groups can also be replaced by *t*-BuOOH.

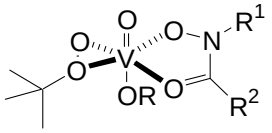
Figure 1.14: Diastereomeric pairs.



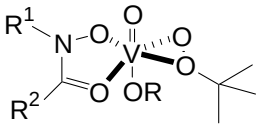
1.44



1.45



1.46

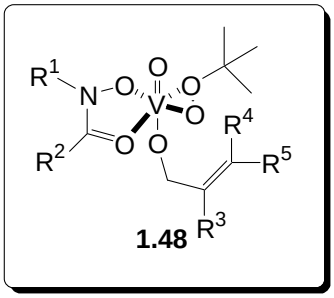


1.47

When a chiral hydroxamic acid is employed, two sets of diastereomeric pairs **1.44 – 1.47** (Figure 1.14) could represent the four signals observed in the ^{51}V NMR spectra.[22] The relative reactivity and the ratios of these diastereomers are likely to contribute to the overall selectivity.[22]

Once the ligand and peroxide have co-ordinated to the vanadium, the axial labile alkoxide group can then be replaced by the substrate allylic alcohol (Figure 1.15).[22]

Figure 1.15: In situ Chiral Catalyst.



1.48

Once complex **1.48** is formed, an oxygen atom can be easily transferred from the co-ordinated peroxide onto the closest face of the allylic alcohol.[22]

This mechanism for the asymmetric epoxidation reaction was investigated using only bidentate hydroxamic acids. In the case of the ligands developed by Yamamoto and in our group, which have groups capable of additional coordination, the mechanism, and particularly in the step of enantiodifferentiation, may differ substantially.

1.8 Conclusions:

From this literature review we can see that vanadium catalysis has come a long way over the past thirty years. For decades, the Sharpless titanium system dominated the field, but this process was not without its disadvantages.

Pioneering work by the Yamamoto group has shown that vanadium-catalysed epoxidations can not only match the Sharpless system in terms of selectivity; but can also overcome many of the associated problems.

For many years, vanadium catalysed epoxidations were considered to be impractical due to the deleterious ligand decelerating effect. However, as this literature review has shown, with careful ligand design and the use of an aqueous system, a highly successful ligand-accelerated process can be achieved.

1.9 Aims of the project:

To optimise the vanadium-catalysed epoxidation, we aimed to develop a new range of hydroxamic acid ligands for the aqueous system. The new catalysts should be highly reactive and capable of producing selectivity of the practically acceptable level.

Previous investigations from our laboratories found that in aqueous solution, the vanadium-catalysed epoxidation becomes a ligand-accelerated process. However, previous ligands synthesised within the group only achieved a maximum of 72% ee.

Nevertheless, this iterative study highlighted the importance of two key functional groups. Therefore, the sulfonaimde and hydroxmic acid functional groups shall be incorporated into all future ligand design.

The main target of this project was to improve the observed selectivity through careful ligand design. Previous ligands were all based on the α-amino acid scaffold, where the sulfonamide and hydroxamic acid functional groups were separated by just one carbon atom.

We aim to extend this separation to two carbon atoms while varying the backbone. These new ligands shall be synthesised from the corresponding chiral 1,2-diamines, and both their reactivity and slectivity will be compared within our model systems.

Once an optimum ligand is found, the reaction conditions of the aqueous system can then be optimised accordingly, and tested on a much wider range of allylic alcohols.

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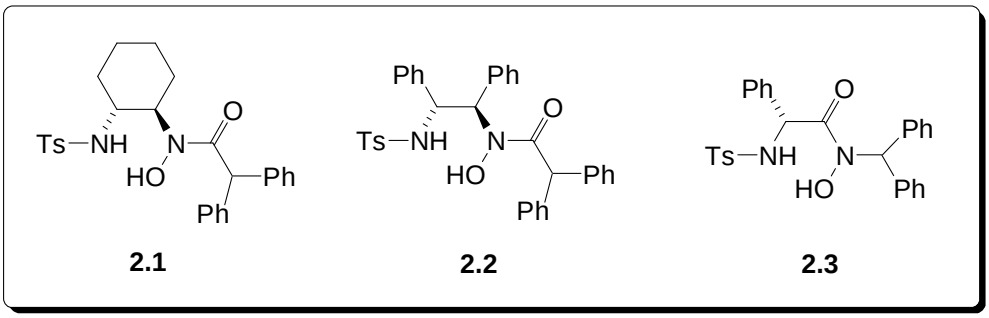
2.0 Results and Discussion:

2.1 Design and structure of hydroxamic acid ligands for an aqueous epoxidation

2.1 Design and structure of hydroxamic acid ligands for an aqueous epoxidation.

2.1.1 Target Ligands:

Figure 2.1: Chiral ligands for the asymmetric epoxidation reaction.



2.1 **2.2** **2.3**

2.1.2 Ligand design:

All ligands prepared for the vanadium catalysed epoxidation reaction are based on chiral hydroxamic acids. Ligands of other types were less successful in our aqueous system.

Previous work carried out in the group has highlighted the importance of the sulfonamide group.[1] It proved to be the key feature responsible for attaining the high reactivity of the catalytic systems, therefore any new design of the chiral ligand should incorporate both sulphonamide and hydroxamate functionalities.

Previously, the general ligand structure was based on α-amino acids where the sulfonamide and the hydroxamic acid functional group were separated by just one carbon atom (Figure 2.1, ligand **2.3**). In an attempt to further improve selectivity, we decided to move the chelating sulphonamide group from the acid fragment onto the hydroxylamine moiety (Figure 2.1, ligands **2.1** and **2.2**).

Therefore, compounds **2.1** and **2.2** were chosen as new target ligands as they can both be prepared from simple commercial diamines.

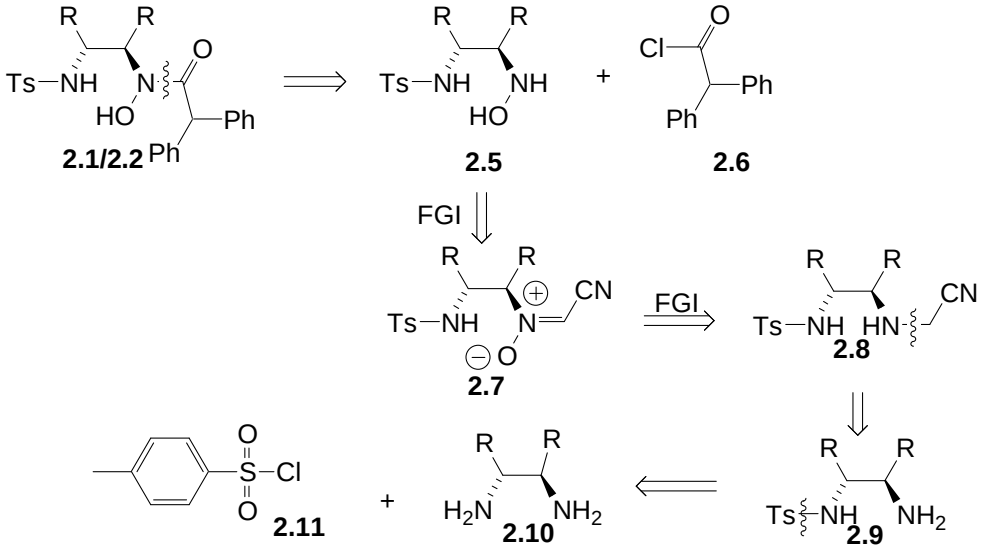
The retrosynthetic analysis of all three chiral ligands are discussed in section 2.1.3.

2.1.3 Retrosynthetic analysis:

General retrosynthetic routes are shown in Schemes 2.1 and 2.2. Scheme 2.1 highlights disconnections of hydroxamic acids with a diamine backbone, while Scheme 2.2 focuses on the retrosynthesis of the ligand derived from an α-amino acid.

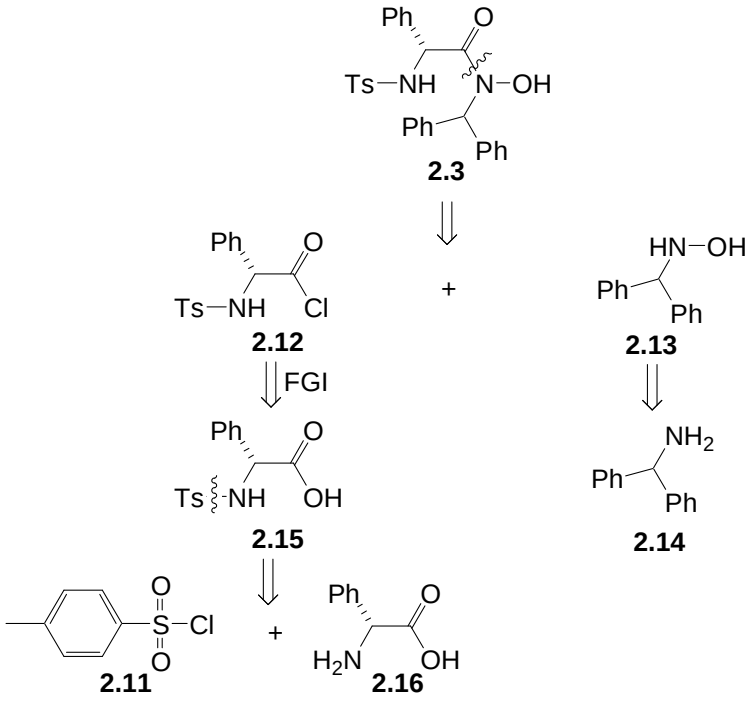
Following a traditional route for hydroxamic acids, ligands **2.1** and **2.2** can be disconnected to give the corresponding hydroxylamine **2.5** and commercial diphenyl acetyl chloride (Scheme 2.1). Functional group interconversion of the hydroxylamine affords the nitrone **2.7**, which can be produced from the corresponding cyanomethylated diamine **2.8**. This can then be further disconnected to the mono-tosylated diamine **2.9**, which can be produced from commercial diamine **2.10** and tosyl chloride.

Scheme 2.1: Retrosynthetic analysis of ligands **2.1** and **2.2**.



In a similar fashion, disconnection of the hydroxamic acid functional group in **2.3** (Scheme 2.2) gives the acid chloride **2.12** and benzhydryl hydroxylamine **2.13**, which can be easily prepared from commercial benzhydrylamine. Functional group interconversion of the acid chloride **2.12** produces the tosyl protected amino acid **2.15** which can be prepared from commercial phenyl glycine and tosyl chloride.

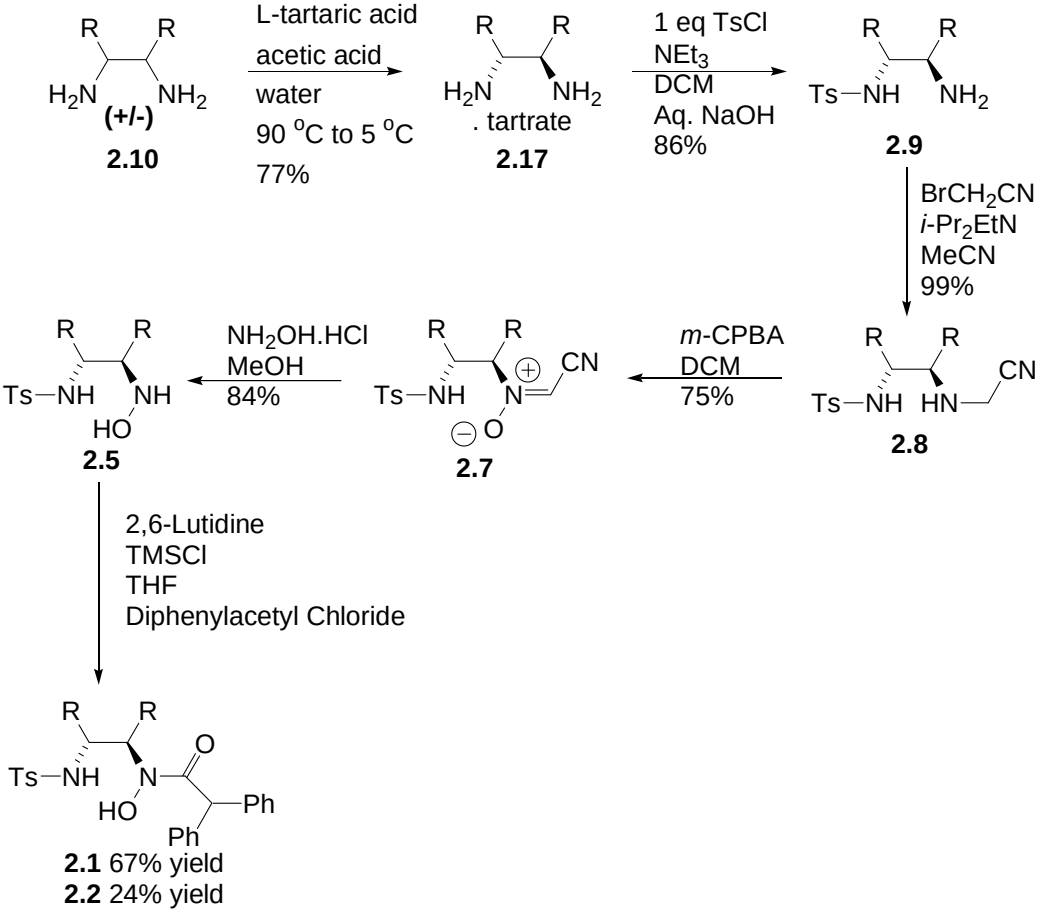
Scheme 2.2: Retrosynthetic analysis of ligand **2.3**.



2.1.4 Ligand Synthesis:

The general synthetic pathways towards hydroxamic acids **2.1** – **2.3** are illustrated in Schemes 2.3 and 2.5.

Scheme 2.3: Synthesis of ligands **2.1**/**2.2** (Yields shown for synthesis of **2.1**).

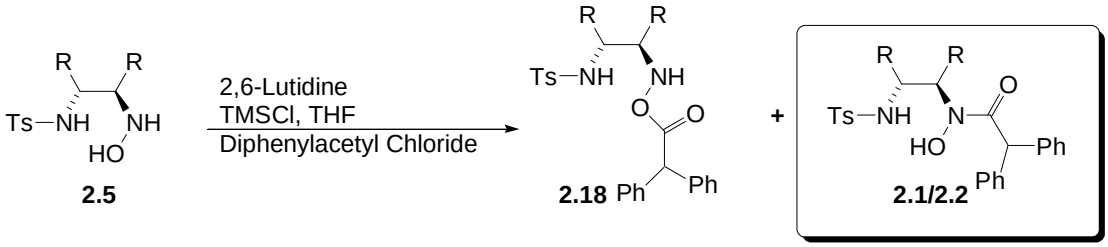


Ligands **2.1** and **2.2** were prepared as shown in Scheme 2.3. Initially the synthesis of **2.1** was carried out using commercial enantiomerically pure (*R,R*)-cyclohexyl diamine. However, due to its high cost, we switched to a much cheaper racemic diamine **2.10**, which was resolved using L-tartaric acid to form the (*R,R*)-diamine tartrate salt **2.17** as described by Jacobsen.[2] This was then mono-tosylated following a literature protocol.[3] Next, compound **2.9** was cyanomethylated using bromoacetonitrile, followed by oxidation with *m*-CPBA to give the corresponding nitrone **2.7** as described by Fukuyama.[4] Nitrone **2.7** was then hydrolysed using hydroxylamine hydrochloride,[4] to produce the desired hydroxylamine **2.5**.

Initially, a direct coupling method was undertaken to produce the desired hydroxamic acid, in which the corresponding hydroxylamine was mixed with diphenyl acetyl chloride in DCM. However, the yield of ligand obtained in this

way was very low (~ 20%). The ^{1}H NMR of the crude reaction mixture revealed that a mixture of products was forming. These compounds proved very difficult to separate by column chromatography, so we were unable to get a clear picture of what was going on. However, based on the previous experience in the group,[1] formation of the *O*-acylated product **2.18** can be suggested (Scheme 2.4).

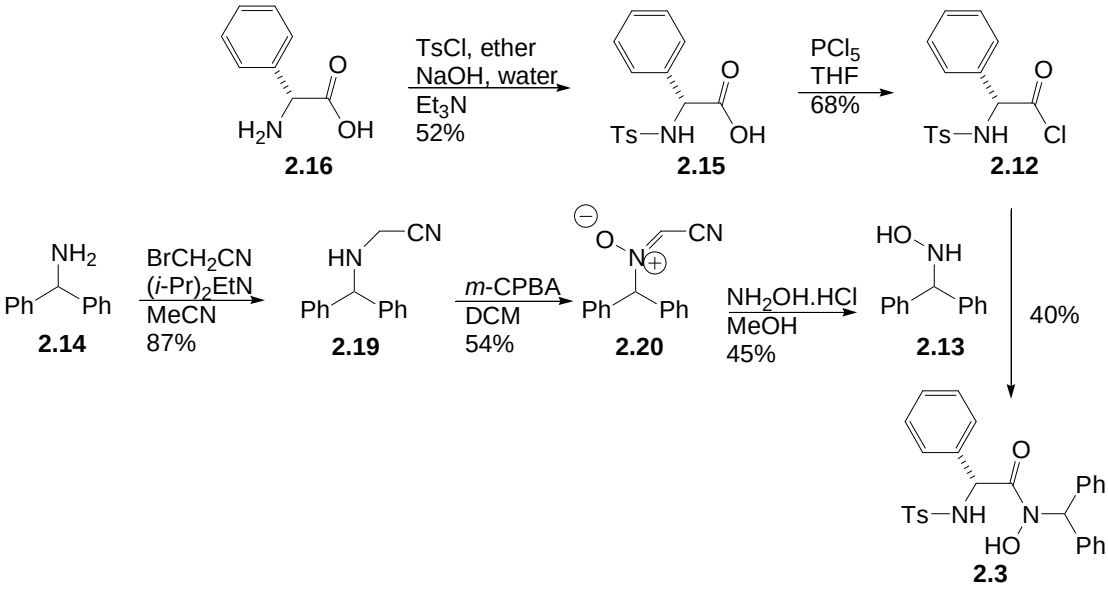
Scheme 2.4: Possible competing side reaction.



In order to prevent this from happening, TMS protection was employed as described by Kim[5], where the TMS group specifically protects the hydroxyl group due to the high affinity of silicon for oxygen. This would then leave the nitrogen free to react as desired.

This new coupling procedure allowed us to obtain the target ligand **2.1** in a much improved yield (67%).

Scheme 2.5: Synthesis of ligand **2.3**.



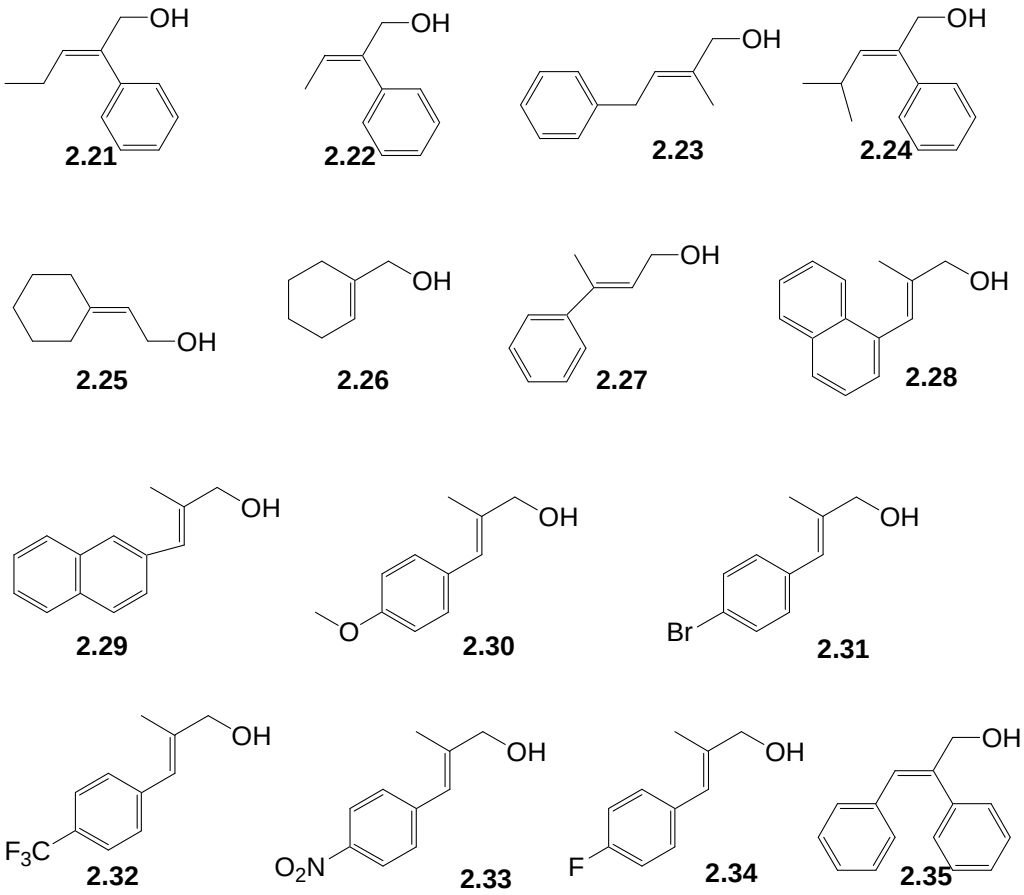
Ligand **2.3** was prepared as shown in scheme 2.5 following a procedure developed earlier in the group.[1] The synthesis begins with the commercial α-amino acid phenyl glycine **2.16** which was tosylated at the nitrogen using tosyl chloride. Compound **2.15** was converted to the acid chloride **2.12** by treatment with PCl_5, and then coupled with benzhydryl-hydroxylamine **2.13**. The latter was prepared in parallel from benzhydryl amine **2.14** as described by Fukuyama.[6]

The coupling step produced the target ligand **2.3** in a 40% yield. However, unlike in the synthesis of **2.1** and **2.2**, TMS protection did not bring any increase in the yield.

2.1.5 Synthesis of allylic alcohols:

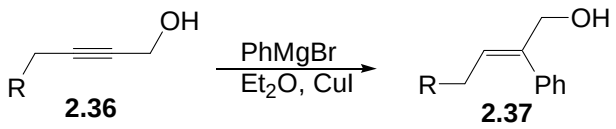
In order to fully test our new chiral ligands, a wider range of substrates were required. From previous investigations carried out in the group, it was found that epoxidation reaction was highly selective when the substrate allylic alcohol had a *cis* orientation of the vicinal substituents. Therefore, compounds **2.21** – **2.35** (Figure 2.2) were chosen as new substrates for our aqueous system.

Figure 2.2: Range of new allylic alcohols synthesised.



Two main procedures were used in the preparation of the above allylic alcohols. The synthesis of compounds **2.21** and **2.22** involved the addition of a mixed copper Grignard reagent to the corresponding commercial alkyn-1-ol (Scheme 2.6). Only *syn*-products as shown in Scheme 2.6 were formed, no traces of the *anti*-product were detected by ^{1}H NMR.

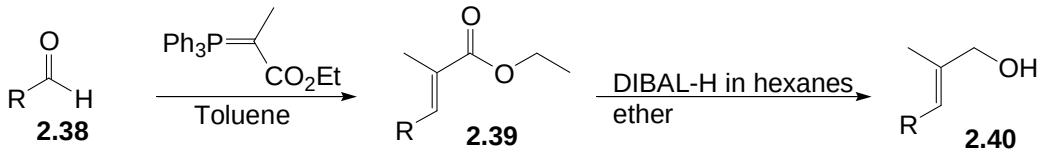
Scheme 2.6: General synthesis of **2.21** and **2.22**



Allylic alcohols **2.23**, **2.25** and **2.27 – 2.34** (Figure 2.2) were all prepared from their corresponding aldehydes or ketones. These underwent Wittig

reaction under reflux conditions followed by DIBAL-H reduction to form the desired allylic alcohol (Scheme 2.7). All Wittig reagents were acquired from commercial sources.

Scheme 2.7: General synthesis of **2.23**, **2.25** and **2.27 – 2.34**



2.1.6 Conclusions:

In conclusion, new chiral ligands for the asymmetric epoxidation reaction in aqueous solution have been synthesised. We have shown that the optimisation of the synthetic pathway is highly ligand dependant, and TMS protection prior to coupling is of great benefit in the case of ligands of type **2.1**/ **2.2**.

Application of all new ligands in V-catalysed asymmetric epoxidation is discussed in the next chapter.

2.2 Optimisation of the asymmetric epoxidation reaction in aqueous solution:

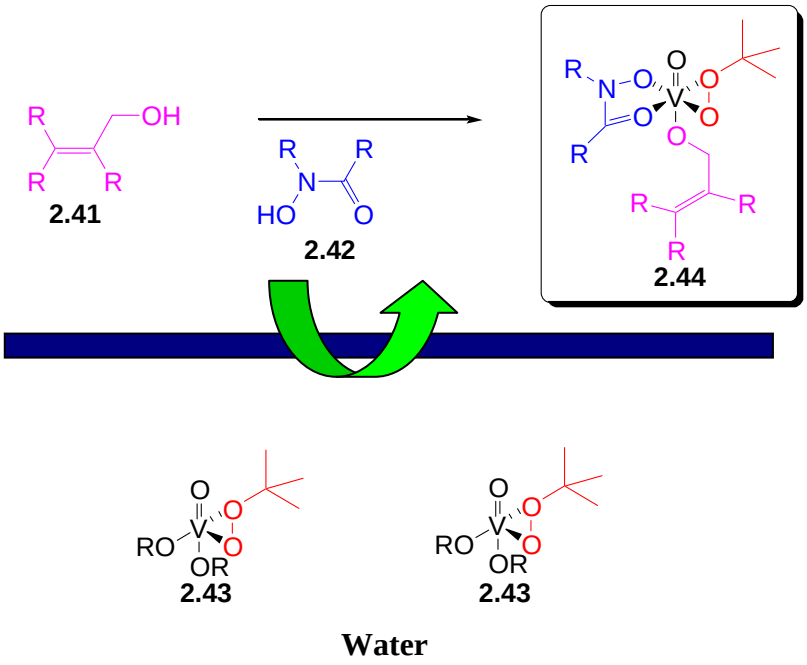
2.2.1 Advantages of aqueous conditions:

In chapter one, we showed that the Sharpless titanium system is very sensitive to trace amounts of water.[8] Therefore strict anhydrous conditions must be employed. Similar strict anhydrous conditions are seen in the earlier vanadium-based protocols carried out in an organic solvent.[9] However, as previously stated, the greatest drawback associated with vanadium catalysis is the ligand decelerating effect observed in organic solvents. One way to overcome both of these problems is to carry out the epoxidation in aqueous solution. This not only results in a much simpler experimental procedure, but also gives rise to a highly desirable ligand accelerated process (Section 1.6.2).

2.2.2 Proposed reaction mechanism:

In Chapter 1, we summarised the current hypothesis on the mechanism of the asymmetric epoxidation catalysed by V(V) based on the evidence collected to date for the process performed in an organic solvent. However, when the epoxidation reaction is carried out in aqueous solution, a bi-phasic system is formed (Figure 2.3).

Figure 2.3: Schematic of bi-phasic aqueous system.



It is important to note that in the aqueous method we are using an inorganic source of vanadium ($VOSO_4.H_2O$) and a 70 % aqueous solution of *t*-BuOOH. Both of these reagents are much cheaper than the respective $VO(O$*i*$-Pr)_3$ and anhydrous *t*-BuOOH previously used in the organic systems.[7]

Figure 2.3 gives a schematic presentation on how catalysis may operate in this bi-phasic aqueous system.

Both the vanadium salt and aqueous peroxide are dissolved in the aqueous layer. The allylic alcohol substrate is not soluble in water and forms the organic layer of our bi-phasic system. The chiral ligand dissolves in the allylic alcohol, so that a mixture of ligand and allylic alcohol is floating on top of an aqueous solution containing the vanadium and alkyl peroxide.

Within the aqueous layer, the alkyl peroxide reacts with vanadium to form peroxo complex **2.43** as shown in Figure 2.3. At the interface, the chiral ligand present in the organic layer is capable of co-ordinating to the vanadium peroxo complex and thus transferring it up into the organic layer where finally, the allylic alcohol co-ordinates to the vanadium, producing the active reaction complex **2.44** (Figure 2.3).

Once everything is held together, an oxygen atom can be selectively transferred from the co-ordinated peroxide onto the closest face of the allylic alcohol to form the corresponding chiral epoxide.

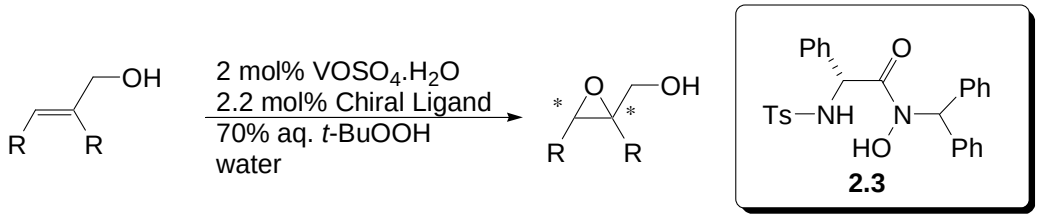
In this way, only coordinated metal species are present in the organic phase, while the ligand-free metal species cannot cross the interface, thus preventing the non-selective pathway from occurring.

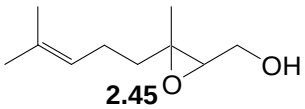
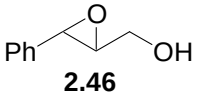
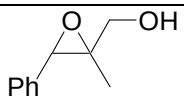
2.2.3 Optimisation of the asymmetric epoxidation reaction in aqueous solution:

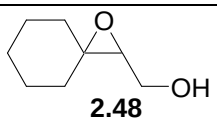
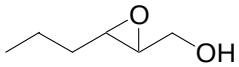
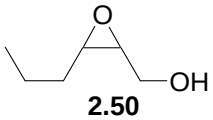
a) Catalyst loading:

Initial investigations in the group[7] were carried out using 2 mol% of the catalyst prepared from ligand **2.3** and $VOSO_4.H_2O$. It was found that only a slight excess of chiral ligand was necessary (2.2 mol%) and on average, the process required at least 60 h to react at 0 ^oC. A summary of these conditions and the results obtained are highlighted in Table 2.1.

Table 2.1: Previous results obtained in the group.

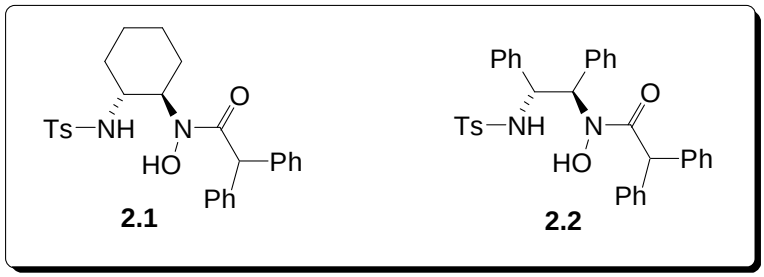


Entry	Epoxide	T/ ^oC	t/h	Yield (%)	Ee (%) (config)
1	 **2.45**	- 20	20	69	69 (*S*,*S*)
2	 **2.46**	0	60	55	57 (*R*,*R*)
3	 **2.47**	0	60	79	59 (*S*,*S*)

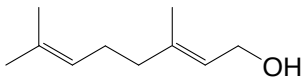
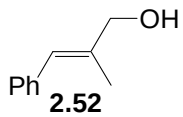
4	 **2.48**	- 20	60	92	72 (+)
5	 **2.49**	0	60	61	70 (*R*,*R*)
6	 **2.50**	0	60	41	63 (*S*,*R*)

To allow a direct comparison with the earlier results, we have chosen two commercially available allylic alcohols **2.51,** and **2.52** as model substrates. The results of the epoxidations using the two new chiral ligands **2.1** and **2.2** are shown in Table 2.2. Epoxidations were carried out at 0 ^{o}C at 2 mol% catalyst loading over 48 h unless otherwise stated.

Table 2.2: Model reactions using **2.1** and **2.2.**



2.1 **2.2**

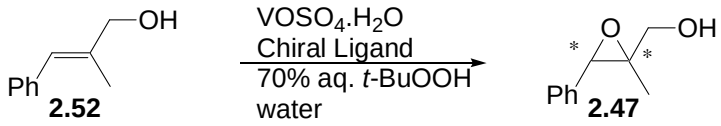
Substrate	**Ligand 2.1** Yield (%), ee (%), Configuration	**Ligand 2.2** Yield (%), ee (%), Configuration
 **2.51**	-, 69 (*S*,*S*) *	59, 33 (*S*,*S*)
 **2.52**	73, 82 (*S*,*S*)	63, 66 (*S*,*S*)

* Result obtained at –20 ^{o}C in a 3:1 mixture of water/methanol.

The results in Table 2.2 show that hydroxamic acid **2.1** derived from cyclohexyl diamine proved to be a much more effective ligand for the asymmetric epoxidation. These results highlight an important structural feature. Ligand **2.1** has a rigid cyclohexyl backbone, with little potential to rotate, whereas the diphenyl backbone of ligand **2.2** allows more rotational flexability.

As ligand **2.1** produced higher enantioselectivities, all further optimisation from this point onwards focussed primarily on **2.1**. A brief investigation into the effect of the catalyst loading was then carried out using allylic alcohol **2.52** as a model substrate. The results are shown in Table 2.3.

Table 2.3: Effect of catalyst loading (ligand **2.1**).



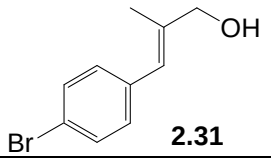
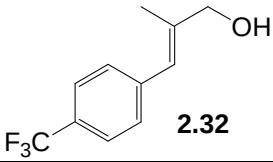
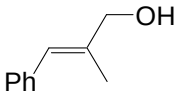
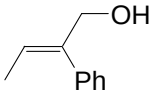
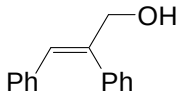
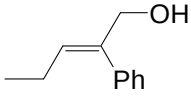
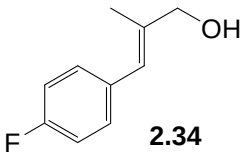
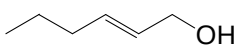
Catalyst Loading	t/h	Yield (%)	ee (%)
2 mol %	48	72	82
5 mol %	12	95	85
7 mol %	12	94	87

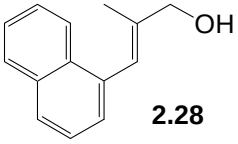
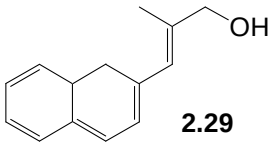
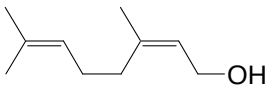
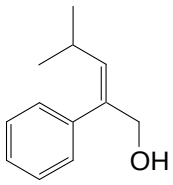
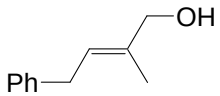
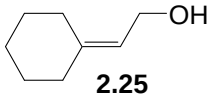
A slight increase in selectivity is observed when catalyst loading is increased from 2 mol% up to 5 mol%. However, a much bigger effect is seen on both the yield and the time required for completion of the reaction. At 5 mol%, a complete conversion was obtained overnight, while previously 48 h were required to give a maximum yield of 73 %.

When the catalyst loading was further increased to 7 mol %, the overall improvement was marginal. Although the selectivity does go up from 85 % ee to 87 % ee, it is not large enough to justify increasing the catalyst loading any further. Therefore, optimum conditions were set at 5 mol %, for 12 h at 0 ^{o}C.

Table 2.4 shows the results obtained under these optimum conditions for a wider range of allylic alcohols.

Table 2.4: Epoxidation reaction at 5 mol % V using ligand **2.1**.

Entry	Allylic Alcohol	Yield (%)	ee (%)	Config.
1	 **2.31**	40	87	(+)
2	 **2.32**	61	87	(+)
3	 **2.52**	74	85	*S,S*
4	 **2.22**	84	85*	(+)
5	 **2.35**	8	84	*S,S*
6	 **2.21**	71	78	(+)
7	 **2.34**	49	77	(+)
8	 **2.53**	42	70	*R,R*

9	 **2.28**	66	58	(-)
10	 **2.29**	63	60	(+)
11	 **2.54**	7	20**	*S,R*
12	 **2.24**	73	46*	*R,R*
13	 **2.23**	52	56	(+)
14	 **2.25**	61	38	(-)

* Reactions carried out at catalyst loading 2 mol%.

** Reaction carried out at catalyst loading 2 mol% in a 3:1 water/methanol mixture at –20 ^{o}C

Table 2.4 shows some very promising results. Selectivities in entries 1-8 ranged from 70 – 87 % ee. However, the yields of the epoxy alcohols varied from just 7% up to a maximum of 84%.

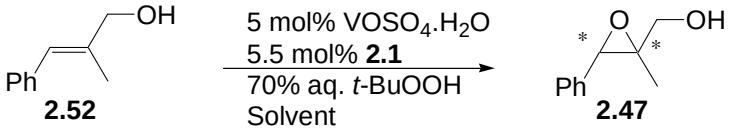
The lowest yield was observed with nerol (entry 11). This reaction was carried out at –20 ^{o}C, so it was not surprising that at a lower temperature the reaction proceeded much slower. However, the diphenyl allylic alcohol **2.35** (entry 5) was reacted at 0 ^{o}C and produced only 8 % yield. The reason for such

poor conversion might be that this compound is one of the few solid allylic alcohols tested. It is much more difficult for this allylic alcohol to effectively mix with the chiral ligand and vanadium in an aqueous solution, thus resulting in a much slower rate of reaction. Therefore, in order to achieve a more homogeneous mixture, addition of small quantities of organic solvents were investigated.

b) Organic solvent additives:

Table 2.5 shows the effect of different organic solvent additives. The reactions were carried out at 5 mol% vanadium, using cyclohexyl ligand **2.1** and allylic alcohol **2.52** as a model substrate. In the original aqueous method[1] the epoxidation is taking place in the organic phase consisting predominantly of the starting alcohol, however, alcohols were shown[1] to be poor solvents for this process. On the other hand, toluene and dichloromethane (DCM) had a proven record in successful V-catalysed epoxidation reactions,[9,10] therefore they were chosen as additives. The reactions were performed in a 3:1 water/organic solvent mixture.

Table 2.5: Effect of organic solvent additives.



Entry	Solvent System	Yield (%)	ee (%)
1	Water	74	82
2	Water/DCM (3:1)	97	80
3	Water/Toluene (3:1)	97	90

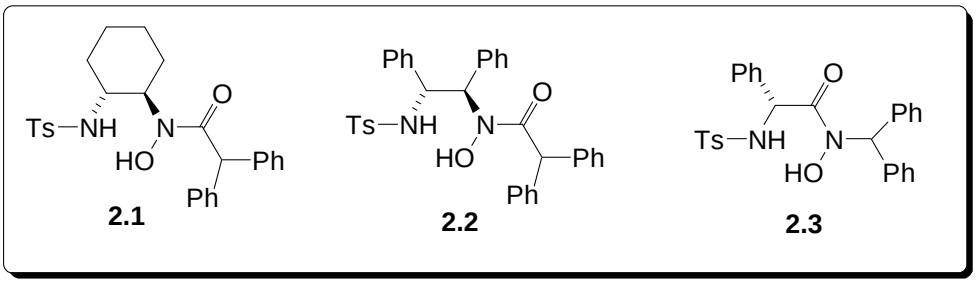
Epoxidation carried out in water alone produced epoxide **2.47** in 82% ee (Entry 1).

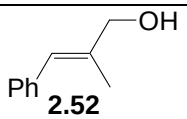
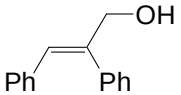
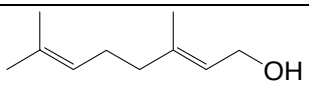
Addition of DCM to the reaction mixture (entry 2) increased the yield of the product, however, it had a very little effect on the selectivity. At the same

time, a dramatic increase in selectivity and yield were observed when small amounts of toluene were added into the aqueous mixture (entry 3).

Thus, the previous reactions employing model substrates were repeated with all three chiral ligands under the new optimised conditions using a 3:1 mixture of water/toluene as the solvent system. The results are given in Table 2.6.

Table 2.6: Model reactions at 5 mol% in water/toluene mixture using ligands **2.1**, **2.2** and **2.3**

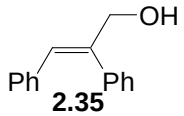
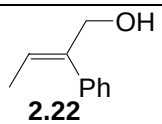
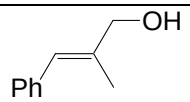
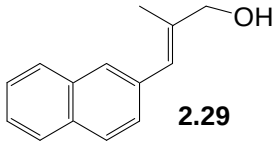
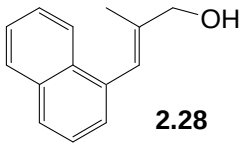
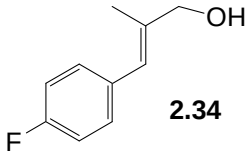
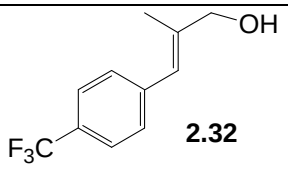
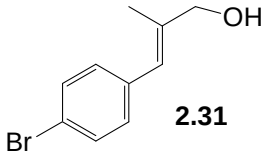
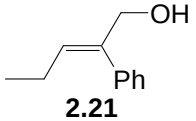
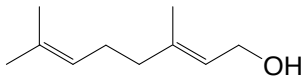
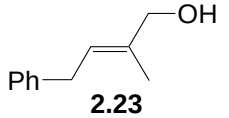


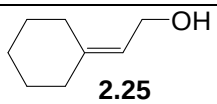
Substrate	**Ligand 2.1** Yield (%), ee (%)	**Ligand 2.2** Yield (%), ee (%)	**Ligand 2.3** Yield (%), ee (%)
 **2.52**	98, 90	89, 78	41, 58
 **2.35**	92, 94	90, 86	40, 26
 **2.51**	65, 50	72, 32	-, -

It is worth noting that not all ligands benefited from the addition of an organic solvent. Thus, ligand **2.3**, which has already been synthesised in the group[1] did not produce improved selectivities under the new optimised reaction conditions. In fact, results obtained were identical to those already achieved at just 2 mol % in water alone.[7]

The results collected in Table 2.6 confirm that hydroxamic acid **2.1** still remained the best ligand under the new optimised reaction conditions. Therefore, the catalyst based on this ligand was tested on a wider range of allylic alcohols. The results are shown in Table 2.7.

Table 2.7: Epoxidation results at 5 mol% in a 3:1 water/toluene mixture.

Entry	Allylic Alcohol	Yield (%)	Ee (%)	Config.
1	 **2.35**	98	94	*S,S*
2	 **2.22**	97	91	(+)
3	 **2.52**	98	90	*S,S*
4	 **2.29**	90	85*	(+)
5	 **2.28**	75	83*	(–)
6	 **2.34**	65	84	(+)
7	 **2.32**	48	87	(+)
8	 **2.31**	60	87	(+)
9	 **2.21**	80	72	(+)
10	 **2.51**	65	50	*S,S*
11	 **2.23**	77	48	(+)

12	 **2.25**	67	37	(–)

* - epoxidations carried out with a 2:1 Ligand/Vanadium ratio

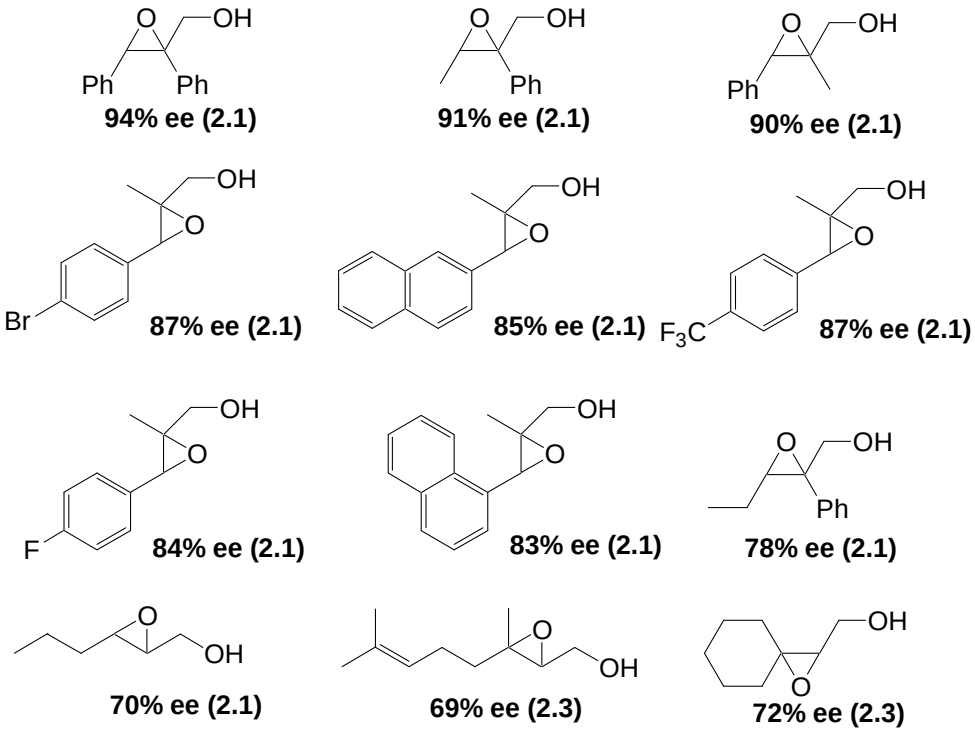
Good-to-excellent selectivities (up to 94% ee) have been achieved for geminal allylic alcohols (Entries 1-8). Table 2.7 shows that a water/toluene mixture is most beneficial for bigger, bulkier substrates which are relatively sluggish in the aqueous mixture (entries 1- 8). This is particularly beneficial for solid allylic alcohols (entry 1) as the presence of toluene allows the reactants to fully mix.

In the case of epoxides derived from 1- and 2-naphthalene (entries 4 and 5), it was found that an increased quantity of ligand was required. In all other cases, epoxidation was carried out using a ligand/vanadium ratio of 1.1 to 1. For naphthyl derivatives, the standard conditions gave only 60% ee. Therefore, the epoxidations of these substrates was carried out with a ligand/vanadium ratio of 2:1.

It is worth noting that not all substrates showed a higher selectivity in the water/toluene mixture. In fact, allylic alcohols in entries 7 and 8 produced identical results to those obtained in water alone, while alcohols in entries 9 –12 all produced better results in water alone.

In summary, we have demonstrated that by using a combination of different ligands and the addition of small quantities of toluene for larger, bulky substrates, a wide range of epoxides can be produced in both a high yield and high selectivity (Figure 2.4).

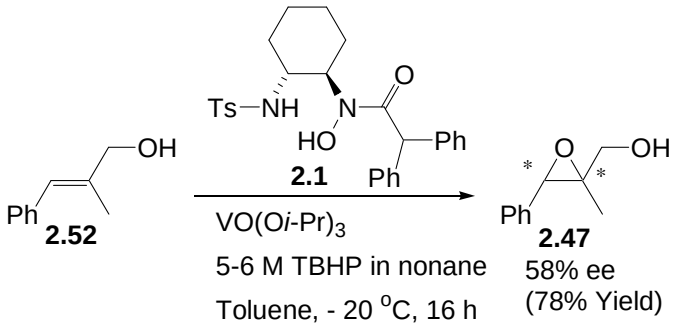
Figure 2.4: The highest enantioselectivities achieved to date (ligand is shown in parenthesis).



2.2.4: Performance of ligand 2.1 under anhydrous conditions.

Next, we briefly tested the performance of ligand **2.1** in a model epoxidation under anhydrous conditions using allylic alcohol **2.52** as a model substrate (Scheme 2.8).[1]

Scheme 2.8: Anhydrous epoxidation of model substrate **2.52**.



In organic solvent alone, epoxy alcohol **2.47** was obtained in only 58 % ee (ligand/vanadium ratio of 1.1:1). In our optimised aqueous system, 90 % ee was achieved (Table 2.7). This experiment demonstrates two important points:

(i) Utilisation of an aqueous system has overcome the problematic ligand deceleration effect. Under anhydrous conditions, epoxide **2.47** was formed in a 78 % yield after 12 h at –20 ^{o}C. Equal length of reaction in the aqueous system provided epoxide **2.47** in a 98 % yield. However, the aqueous reaction was performed at 0 ^{o}C, so this vast improvement in the yield can also be attributed to the temperature of reaction.

(ii) For substrate **2.52** a much higher selectivity is achieved in the aqueous system.

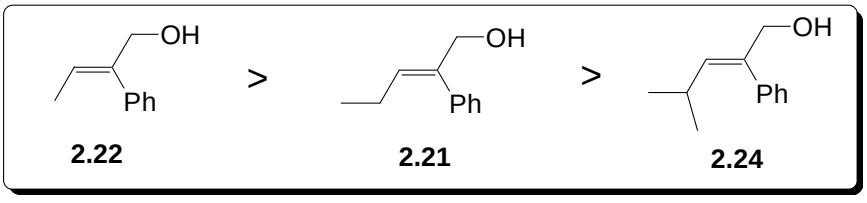
Therefore, with careful ligand design and the use of the optimised aqueous system, higher yields and better selectivities can be produced using simpler methodology and more affordable reagents.

2.2.5:Effect of structural variations in substrate alcohols:

a) **Effect of the steric size of substituents in allylic alcohols.**

The effect of the steric size of substituents at allylic alcohols was investigated next. Figure 2.5 highlights the expected trend in enantioselectivity for allylic alcohols **2.22**, **2.21 and 2.24**.

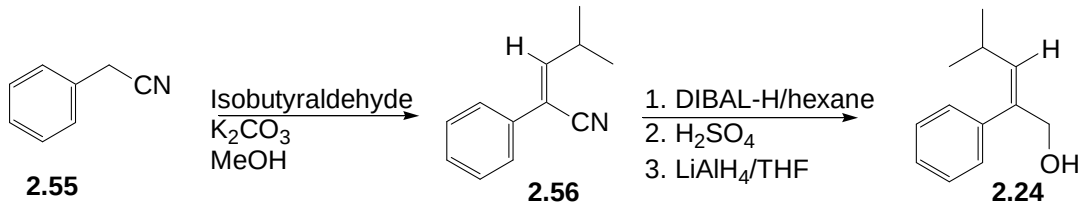
Figure 2.5: Series of decreasing selectivites of substrates with increasing bulk.



Under the optimised reaction conditions, compound **2.22** produced 91 % ee. With a slight increase in the steric size to an ethyl group (**2.21**), we observed a drop in selectivity to 78 % ee. Further increase to an *i*-propyl group (**2.24**) caused the selectivity to plummet to just 46% ee. This result seemed uncharacteristically low considering the high enantioselectivity obtained in the epoxidation of the diphenyl substrate (Table 2.7, entry 1).

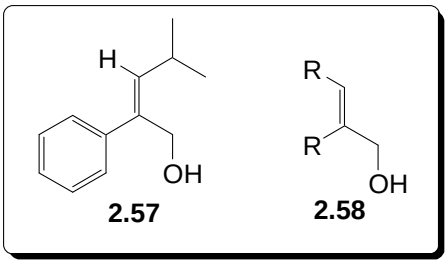
Alcohol **2.24** was prepared following a literature protocol (Scheme 2.9).[12,13] First, benzylcyanide **2.55** was converted to **2.56**. Kimura et al[13] claimed that on reduction of the nitrile, the isopropyl group flipped over to the other side of the double bond to become *cis* to the phenyl group.

Scheme 2.9: Synthesis of alcohol **2.24**.



If no isomerisation was occurring during the reduction step, this would result in the formation of a different allylic alcohol **2.57**, which would no longer have the required *cis* orientation of the vicinal substituents shown in compound **2.58** (Figure 2.6)

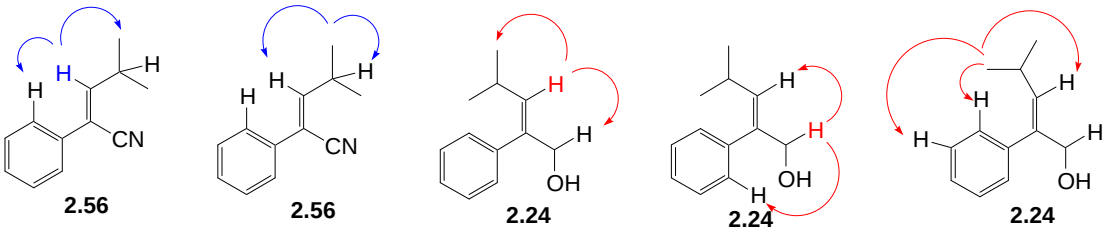
Figure 2.6: Possible structure after reduction **2.57** and general structure for substrates **2.58**.



In order to confirm the structure of the reduced alcohol, we carried out NOE studies on compounds **2.24** and **2.56**, to establish the position of the *i*-propyl group both before and after the reduction step. The results are illustrated in

Figure 2.7. The NOE studies confirmed that, indeed, isomerisation of the double bond was taking place during the reduction.

Figure 2.7: NOE studies on compounds **2.24** and **2.56**.



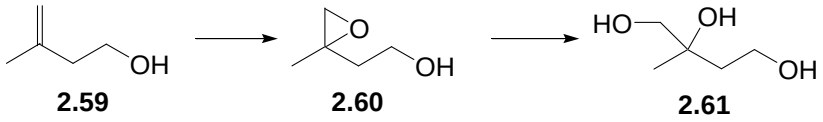
b) **Epoxidation of homo-allylic alcohols.**

To extend the range of substrates, vanadium catalysed epoxidation of homoallylic alcohols in aqueous solutiuon was attempted, however, it was unsuccessful. After work-up, only the chiral ligand was isolated suggesting that any product formed in the reaction remained in the aqueous layer.

Two possible explanations to account for the results can be proposed.

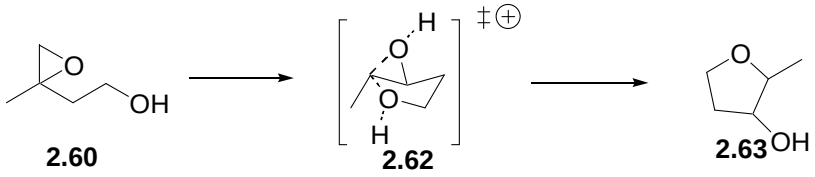
1. Hydrolytic opening of the epoxide produced the highly water-soluble triol **2.61,** which after work-up stayed in the aqueous phase (Scheme 2.10)

Scheme 2.10: Formation of water-soluble triol **2.61**.



2. Jamison et al[14] have found evidence that under aqueous conditions, homo-allylic alcohols can cyclise to form the corresponding tetrahydrofurans (Scheme 2.11).

Scheme 2.11: Cyclisation of homo-allylic alcohols under aqueous conditions.



Both of these reactions result in a highly water-soluble product which cannot be extracted from the aqueous layer. It is clear that substrates with large lipophilic groups should be investigated before any conclusion can be made regarding applicability of this method to homoallylic alcohols.

2.2.6 Conclusions:

In conclusion, we have developed a range of new chiral ligands for the asymmetric epoxidation reaction in water. The aqueous system employed has been extensively optimised and selectivities of up to 94 % ee have been achieved. We have also demonstrated that for certain substrates the addition of a small quantity of toluene is extremely beneficial.

2.3 Asymmetric epoxidation in organic solvent:

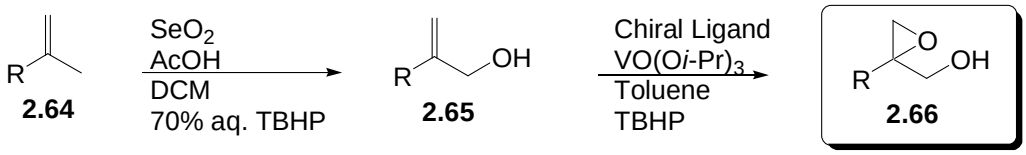
2.3 Asymmetric epoxidation in organic solvent:

2.3.1 Aims:

To further develop the project, we were interested in extending the range of substrates to unfunctionalised alkenes. For the success of this protocol, the starting alkenes would need to be initially converted to the corresponding allylic alcohols, which are traditional substrates for the V-catalysed epoxidation.

One of the possible methods for this transformation utilises selenium dioxide in the presence of acetic acid (Scheme 2.12). The conditions of this allylic oxidation seem compatible with V-mediated epoxidation.

Scheme 2.12:

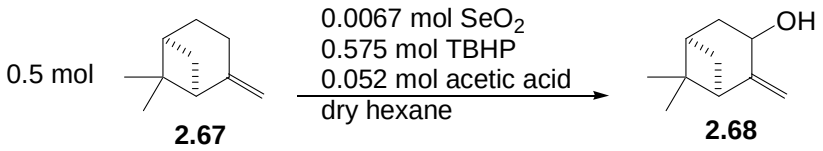


Once these two steps have been individually optimised, development of a one-pot process could be envisioned, as both selenium and vanadium are able to co-exist within the same reaction vessel.

2.3.2 Introduction: Selenium catalysed ene reaction:

Selenium dioxide is a very reliable reagent for inserting an oxygen atom into an allylic C-H bond.[15] In 1977, Sharpless et al[15] found that highly active alkenes such as β-pinene can be oxidized to the corresponding allylic alcohols in the presence of H_2O_2 and catalytic amounts of SeO_2 (Scheme 2.13).

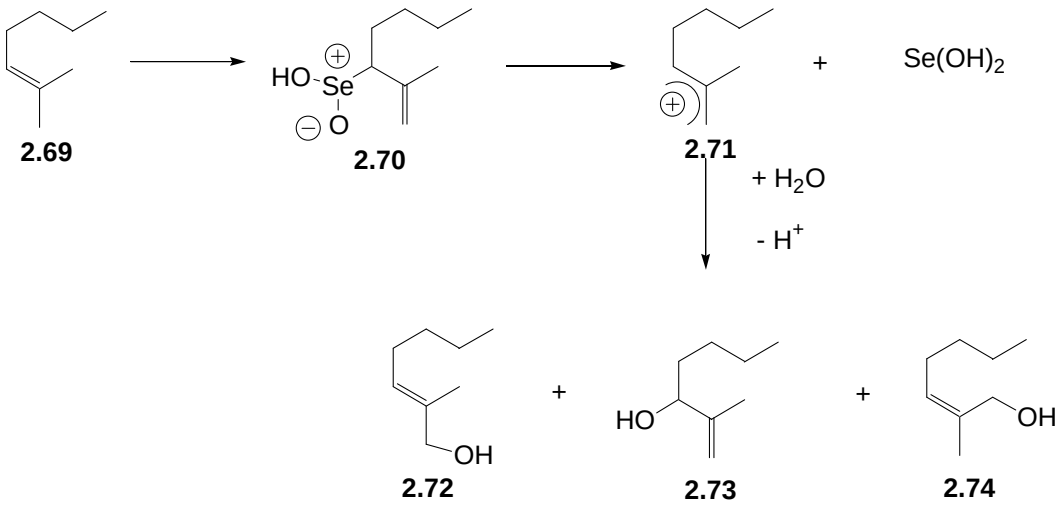
Scheme 2.13: Oxidation of β-pinene.



However, there are several drawbacks associated with this process. Sharpless found that less reactive alkenes produced a complex mixture of products.[15] In combination with the problems of removal of the resulting organoselenium by-products, these are the major difficulties associated with selenium chemistry.[15]

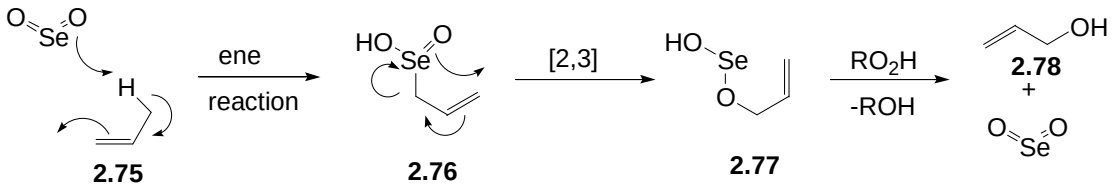
A variety of mechanisms have been proposed for the process. Wiberg and Nielson suggest that an allylselenic acid **2.70** is produced, which then undergoes solvolysis to form a complex mixture of products[16] (Scheme 2.14).

Scheme 2.14: Mechanism proposed by Wiberg and Nielson.



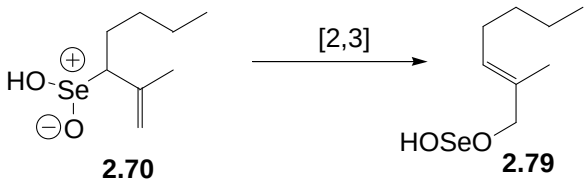
However, Sharpless[17,18] has reported evidence that the process occurs by the selenium catalysed ene reaction followed by a 2,3-sigmatropic rearrangement (Scheme 2.15).

Scheme 2.15: Mechanism proposed by Sharpless.[17,18]



If the proposed reaction pathway is correct, then the 2,3-sigmatropic rearrangement of the allyl selenic acid **2.70** (Scheme 2.14) would result in the stereoselective formation of (*E*)-ester **2.79** (Scheme 2.16).[17]

Scheme 2.16:

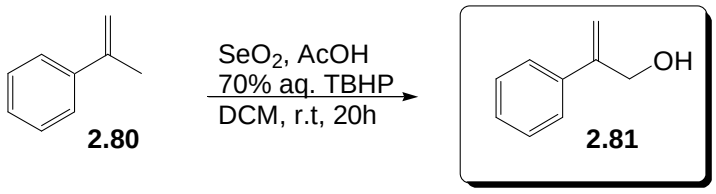


In order to test this theory, a range of alkyl phenyl selenides were prepared.[17] Then, under the same reaction conditions (for the conditions, see Scheme 2.13) all the selenides prepared were successfully rearranged to the corresponding allylic alcohols.[17]

Therefore, these results confirm that ene reaction followed by 2,3-sigmatropic rearrangement is the most likely mechanism of allylic oxidation by SeO_2.

2.3.3 Optimisation of reaction conditions:

Scheme 2.17: Oxidation of the model substrate with selenium dioxide.



Compound **2.80** was chosen as a model substrate for the two-step oxidation sequence. Scheme 2.17 shows the reaction conditions in which α-methyl styrene **2.80** can be converted into the corresponding allylic alcohol **2.81** by treatment with selenium dioxide.

Initial investigations focussed on the catalyst loading. Sheldon et al[18] have shown that only catalytic amounts of SeO_2 (2 mol%) are required for the formation of allylic alcohols. However, in our model system only 8% conversion was observed under these reaction conditions. Table 2.8 highlights the effect of catalyst loading on conversion. The results show that in order to achieve complete conversion of the starting material within 20 h, the catalyst loading needs to be increased to at least 10 mol%.

Table 2.8 – Optimisation of catalyst loading for Se oxidation.

Entry	SeO_2 (mol %)	Acetic Acid (mol %)	t/h	Conversion (%)
1	1.3	0.8	0.5	<5
2	1.3	0.8	20	8
3	4.0	6	20	35
4	10	10	20	68
5	10	15	20	100

Complete conversion was deemed necessary in order to immediately carry out a successful epoxidation reaction. Therefore, 10 mol% was chosen as the optimal catalyst loading.

The epoxidation of allylic alcohol **2.81** was then investigated. Originally, the initial aim was to develop an aqueous one-pot procedure for the oxidation of an alkene followed by asymmetric epoxidation. However, two major problems were encountered.

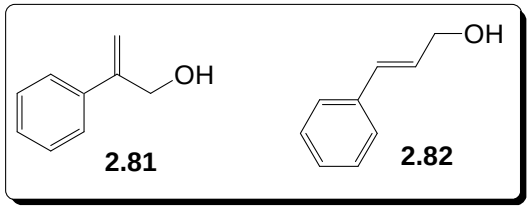
(i) The selenium oxidation does not occur in aqueous solution.

(ii) Allylic alcohol **2.81** does not undergo epoxidation in aqueous solution.

Inspection of the ^{1}H NMR spectrum of the product mixture obtained after the aqueous epoxidation revealed that the formation of the corresponding aldehyde was more favourable than epoxide formation. Therefore, the epoxidation step was carried out in organic medium.

A brief investigation into the vanadium catalyst loading was then carried out using positional isomers **2.81** and **2.82** as model substrates. The results are shown in Table 2.9.

Table 2.9: Optimisation of vanadium catalyst loading using ligand **2.2** in toluene at –20 ^{o}C for 16 h.



2.81 **2.82**

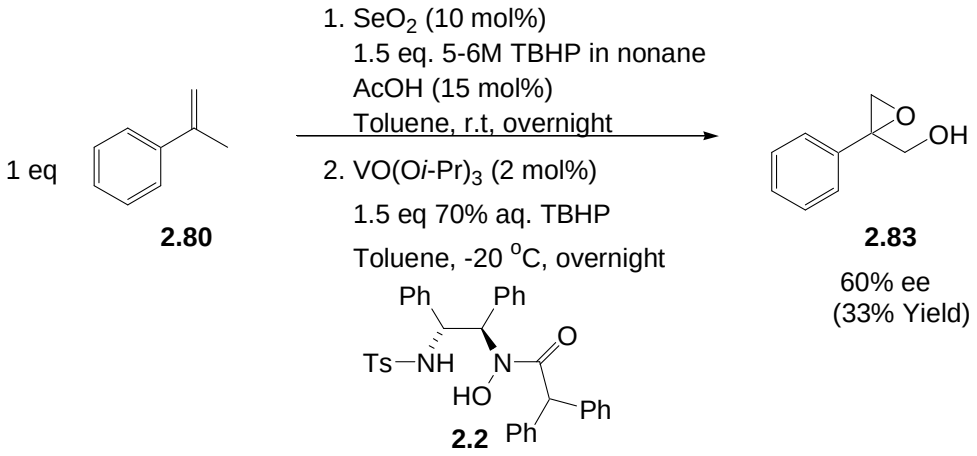
Entry	Substrate	V (mol %)	L:V ratio	Conversion(%)	ee (%)
1	**2.81**	1	1:1	57	58
2	**2.81**	1	1.8:1	40	73
3	**2.81**	2	1.8:1	50	76
4	**2.82**	1	1.8:1	42	58
5	**2.82**	2	1.8:1	33	66

From Table 2.9, we can see that optimum selectivities were achieved at 2 mol% catalyst loading at a ligand/vanadium ratio of 1.8:1. As expected, increasing the

ligand concentration resulted in a dramatic drop in the rate of reaction due to the ligand decelerating effect, which was reflected in reduced conversions. (Table 2.9). Nonetheless, a reasonable compromise between reactivity and selectivity had been achieved at 2 mol% catalyst loading.

Once the optimum conditions for each individual step were established, we went on to combine them into a one-pot process. Once again α-methylstyrene **2.80** was employed as a model substrate. The reaction conditions are shown in Scheme 2.18.

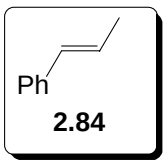
Scheme 2.18: One-pot oxidation/epoxidation procedure.



The target epoxide **2.83** was isolated in a 33% yield. In the one-pot process, a slight decrease in selectivity was observed. For comparison, when the process was carried out over two separate steps, **2.83** was isolated in 76% ee.

The one-pot process was also investigated using *trans*-β-methylstyrene **2.84** (Figure 2.8).

Figure 2.8: Substrate **2.84**.



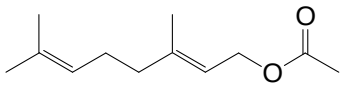
However, no epoxide was formed. Taking into account that cinnamyl alcohol **2.82** (Table 2.9) does undergo epoxidation under these reaction conditions, it

was assumed that the problem must lie within the selenium dioxide oxidation step.

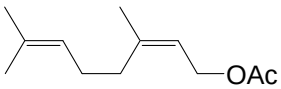
Therefore, this first step was investigated separately using the optimised reaction conditions (step 1, Scheme 2.18). At 10 mol% selenium dioxide, no reaction was taking place and 100 % of starting **2.84** was recovered. When the process was attempted under reflux conditions, no reaction occurred in DCM, whereas in toluene a complex mixture of products was detected by ^{1}H NMR. The reaction in toluene was repeated at a lower temperature (65 ^{o}C) but with no success. It would appear that compound **2.84** is not reactive at room temperature; while at increased temperatures it undergoes polymerisation. Therefore **2.84** was deemed an unsuitable substrate for our two-step oxidation protocol.

Consequently, a range of new substrates were prepared (Figure 2.9).

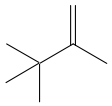
Figure 2.9: Substrates for hydroxylation/epoxidation sequence



2.85



2.86

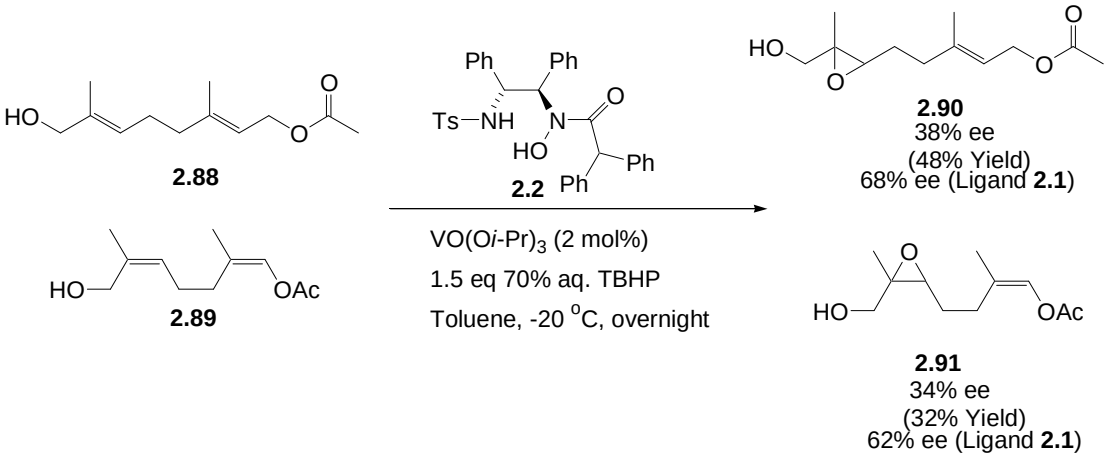


2.87

Compounds **2.85** and **2.86** were successfully oxidised to the corresponding allylic alcohols following a literature protocol employing 1.3 mol% SeO_2.[20] The conditions optimised for **2.80** (10 mol%) were less satisfactory in these instances.

The new substrates were then tested in the epoxidation step. The reaction conditions and results are shown in Scheme 2.19. With ligand **2.2**, both epoxides **2.90** and **2.91** were formed in low-to-moderate yield and with disappointing ee's. The selectivities were improved by employing cyclohexyl ligand **2.1** (Scheme 2.19).

Scheme 2.19: Epoxidation of geranyl and neryl acetate with ligands **2.1** and **2.2**.

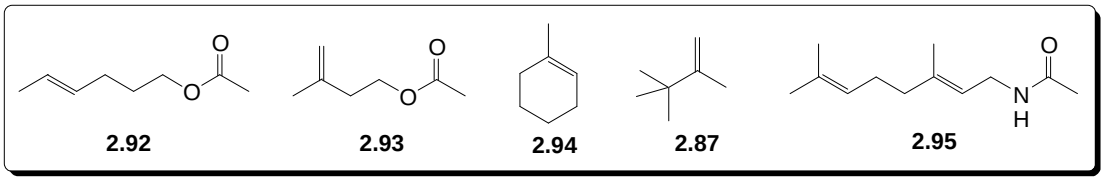


It would appear that in order to achieve a successful one-pot process, each substrate needs to be individually optimised in both reaction steps; including which chiral ligand is employed in the epoxidation step.

2.3.4: Future work for the project:

Further investigation into the selenium dioxide hydroxylation step is clearly required. Out of the chosen substrates for this reaction, the compounds shown in Figure 2.10 did not produce the desired allylic alcohols.

Figure 2.10: Range of substrates tested in Se oxidation step.

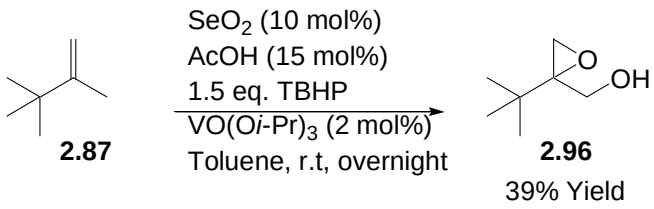


Nevertheless, reaction of compound **2.87** requires special comments. When selenium dioxide oxidation was attempted using previously described conditions, a complex mixture of products was obtained. Because of this, the corresponding allylic alcohol could not be identified, nor isolated from the reaction mixture.

It became apparent that the selenium dioxide oxidation was occurring too fast, resulting in the decomposition of the resulting allylic alcohol. Therefore, we reasoned that all the reagents required for both steps should be introduced at once. This would allow for epoxidation to occur the very instance allylic alcohol is produced.

Preliminary investigations were carried out without a chiral ligand. Reactions were conducted at room temperature to ensure a faster rate of epoxidation, removing any trace of allylic alcohol from solution before it decomposes. Conditions for this racemic one-pot process are illustrated in Scheme 2.20.

Scheme 2.20: Racemic one-pot epoxidation of **2.87**.



Under these new reaction conditions, target epoxide **2.96** was isolated in a 39% yield. This exciting result proves that not only is a one-pot process possible for this transformation, but in some cases it is necessary in order for the reaction to occur.

2.3.5 Conclusions: In conclusion, we have carried out the preliminary work for the development of a new one-pot process comprising selenium dioxide catalysed oxidation of an alkene to the corresponding allylic alcohol followed by vanadium-catalysed epoxidation. We have shown that this process can occur in a reasonable yield with good selectivity. However, further investigation is still required to develop a reliable protocol applicable to a wider range of substrates. We have also demonstrated that the utilisation of a rapid one-pot process can be extremely beneficial for some substrates.

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Part B:

Development of organocatalytic transfer hydrogenation mediated by chiral pyridines.

3.1 Introduction:

3.0 Introduction:

At present, there are three main methods for selectively reducing an imine. These are:

(i) Transition metal catalysed high-pressure hydrogenations.[1]

(ii) Hydrosilylations.[2]

(iii) Transfer hydrogenations.[3]

As stated above, transition metal catalysed hydrogenations can sometimes require extremely harsh reaction conditions in order to achieve a high yield and selectivity.[1] Hydrosilylations, although highly selective, are extremely moisture sensitive.[2] Therefore, our attention was drawn to transfer hydrogenations, where we aimed to develop a mild, organocatalytic process.

At present, metal-free transfer hydrogenations are mainly used in the following three reactions:

(i) Reduction of α,β-unsaturated aldehydes.[4-7]

(ii) Reduction of ketimines[9] and a closely related reductive aminiation.[8]

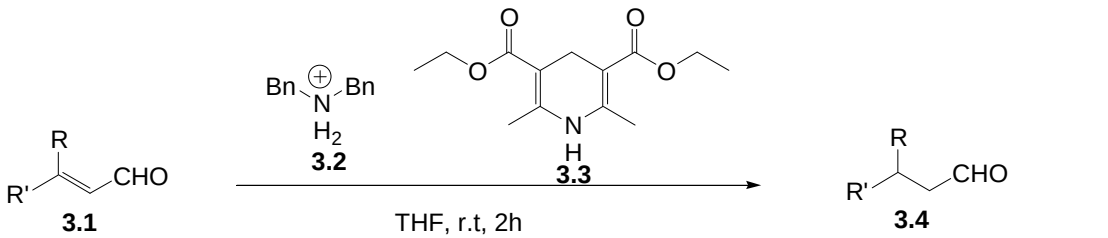
Each of these reactions has been carried out in the presence of an organocatalyst where the Hantzsch dihydropyridine was used as a hydride source. This exciting work was the inspiration for the development of our new organocatalytic system. A detailed overview of these key reactions are given in sections 3.1 and 3.2.

3.1: Reduction of α,β-unsaturated aldehydes

The reduction of imines and α,β-unsaturated compounds through selective hydrogen transfer reactions is currently a challenging and thought provoking area of organic synthesis. At present, the majority of hydrogenation processes rely heavily on the use of a transition metal catalyst.[1] However, the complete removal of any residing metal particles can be both a time consuming and expensive process.[4]

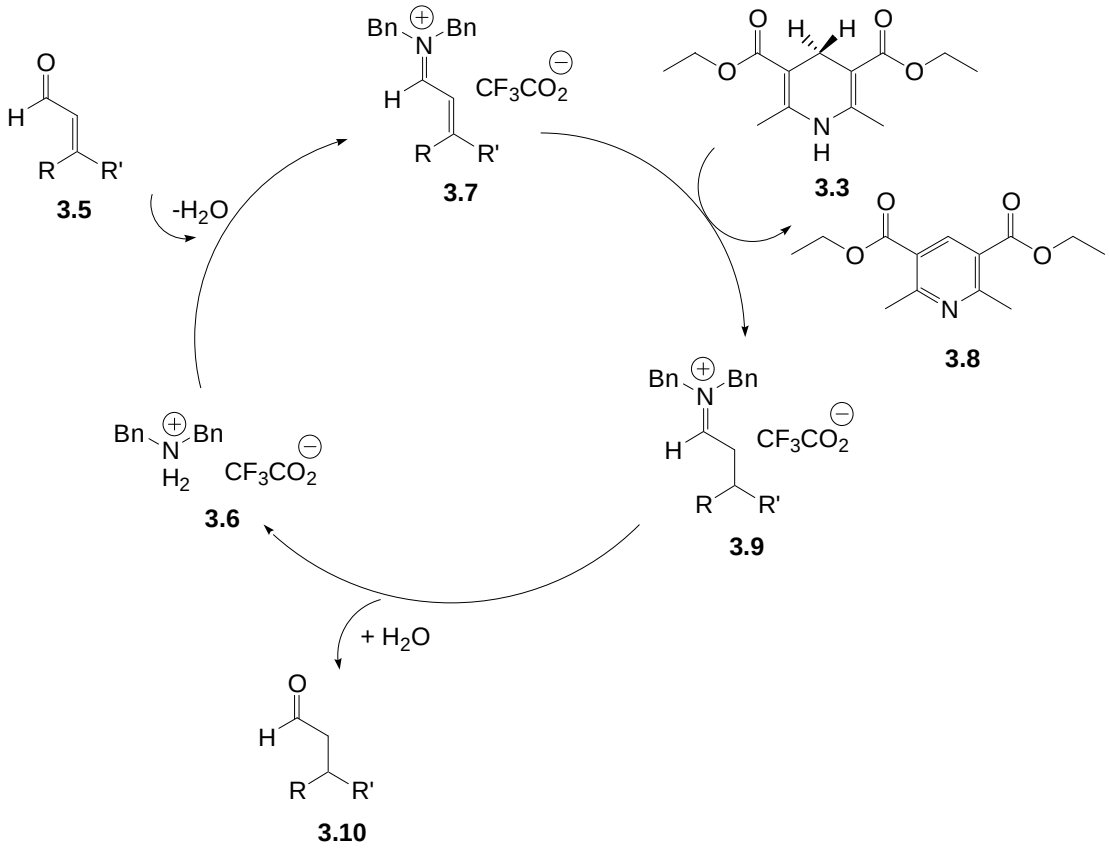
Looking to nature for inspiration, many researchers, such as List and MacMillan, observed that organic co-factors such as nicotinamide adenosine dinucleotide (NADH) can carry out these processes in the presence of a metalloenzyme.[4-6,10,11] They have since shown that a metal-free organocatalyst can be used in combination with diethyl Hantzsch ester to perform a highly chemoselective reduction of α,β-unsaturated aldehydes (Scheme 3.1)[4]

Scheme 3.1: Reduction of α,β-unsaturated aldehydes performed by List.[4]



In general, transition metal catalysed hydrogenations of α,β-unsaturated aldehydes usually have a low chemoselectivity, and are also intolerant of certain functional groups such as benzyloxy, nitro and nitrile groups.[5] This is not the case for the organocatalytic processes developed by the groups of List and MacMillan, which are compatible with these functional groups while still retaining a high standard of chemoselectivity.[5] Scheme 3.2 shows the catalytic cycle proposed by List *et al*.[5]

Scheme 3.2: Catalytic cycle proposed by List et al.

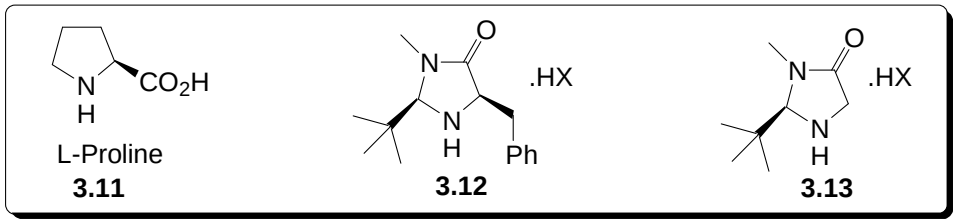


The α,β-unsaturated aldehyde **3.5** can reversibly bind to the amine catalyst **3.6** to form the iminium ion **3.7**. Formation of ion **3.7** lowers the energy of the LUMO compared with the starting aldehyde, allowing a hydrogen to be easily transferred from the Hantzsch ester **3.3**. On addition of water, the now reduced iminium ion **3.9** quickly reverts back to the corresponding aldehyde **3.10**, recycling the amine catalyst **3.6** which can then be used again.[5]

This process has proven to be extremely successful. Results to date are best achieved using a chiral binaphthol-derived phosphoric acid catalyst, which has delivered consistently high yields and selectivities of > 96% ee.[12]

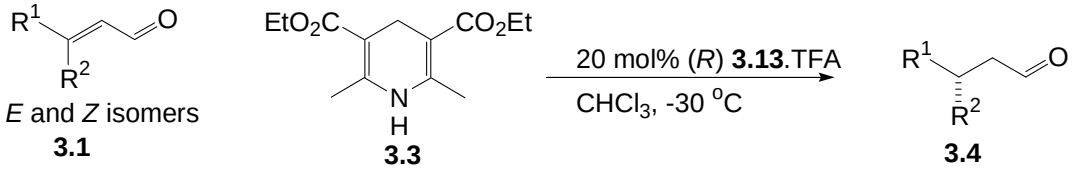
The MacMillan group have developed a highly enantioselective reduction of α,β-unsaturated aldehydes using chiral amine catalysts such as L-proline **3.11** and imidazolidinones **3.12** and **3.13** (Figure 3.1), in the presence of the Hantzsch dihydropyridine.[6]

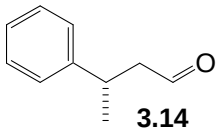
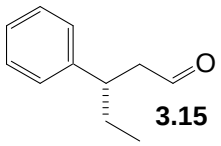
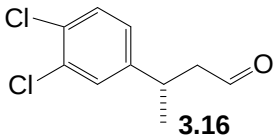
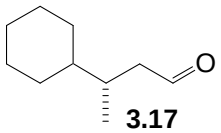
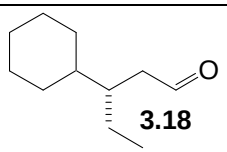
Figure 3.1: Chiral amine catalysts developed by the MacMillan group.

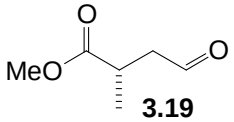
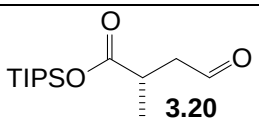
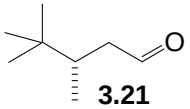


The reaction proceeds via a similar mechanism as shown in Scheme 3.2, where the aldehyde is activated to the corresponding chiral iminium ion prior to reduction. The results obtained are highlighted in Table 3.1.[6]

Table 3.1: Selective reduction of α,β-unsaturated aldehydes.

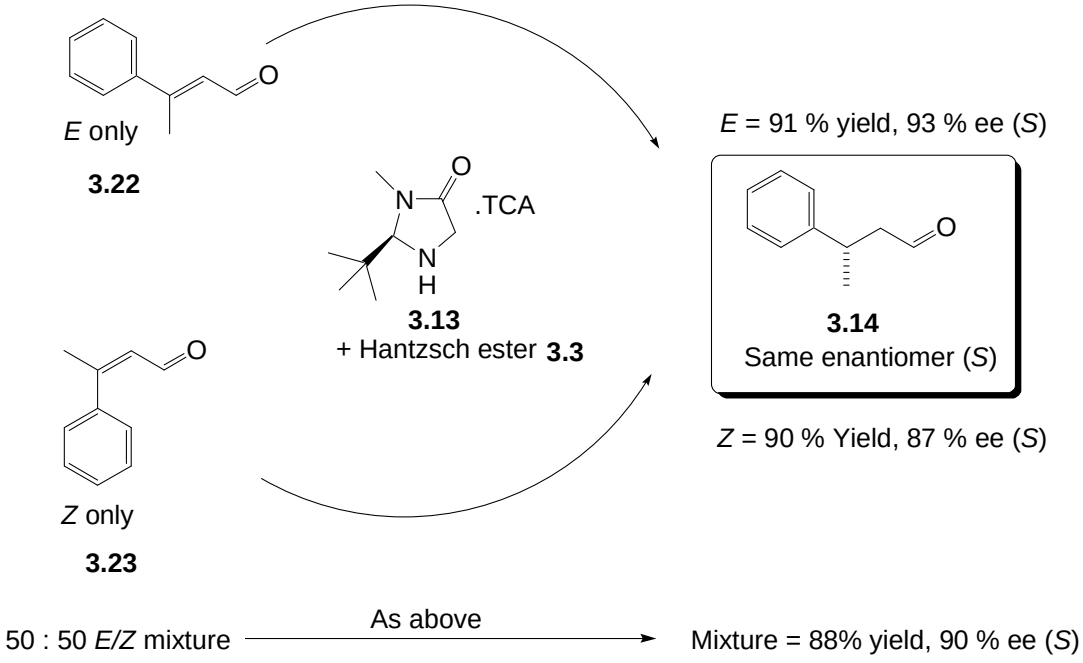


Entry	Product	Time (h)	Yield (%)	ee (%)
1	 **3.14**	23	91	93
2	 **3.15**	16	74	94
3	 **3.16**	16	92	97
4	 **3.17**	10	91	96
5	 **3.18**	23	95	91

6	 **3.19**	26	83	91
7	 **3.20**	72	74	90
8	 **3.21**	0.5	95	97

All products were formed in a very good yield and showed excellent enantioselectivity. However, the most exciting result from these experiments is that only the (*S*)-product is formed irrespective of the geometry of the starting double bond (Table 3.1).[6] Scheme 3.3 highlights this result.[6]

Scheme 3.3: Configuration of products obtained by MacMillan et al.



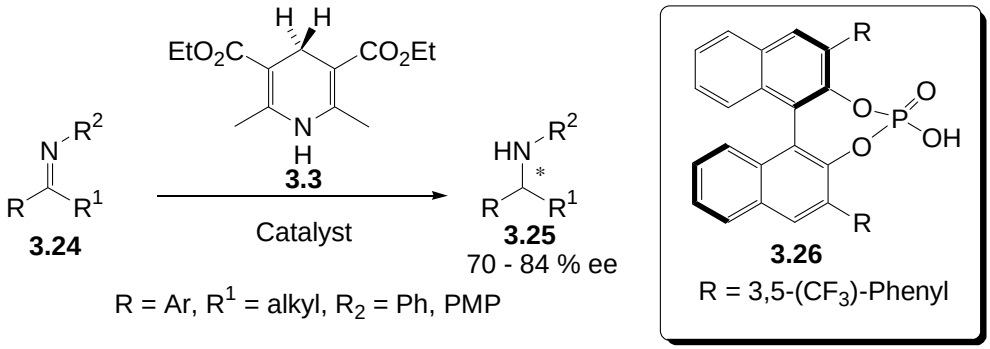
When a single isomer (*E* or *Z*) is used, only the (*S*)-product is formed. If the reaction is performed on a 50:50 *E/Z* mixture, again only the (*S*)-enantiomer is formed. Therefore the MacMillan group came to the conclusion that under their reaction conditions, the two isomers are in equilibrium so that the geometry of the alkene substrate does not dictate the stereoselectivity of the product.

3.2 Reduction of ketimines and reductive amination:

3.2.1 Reduction of Ketimines:

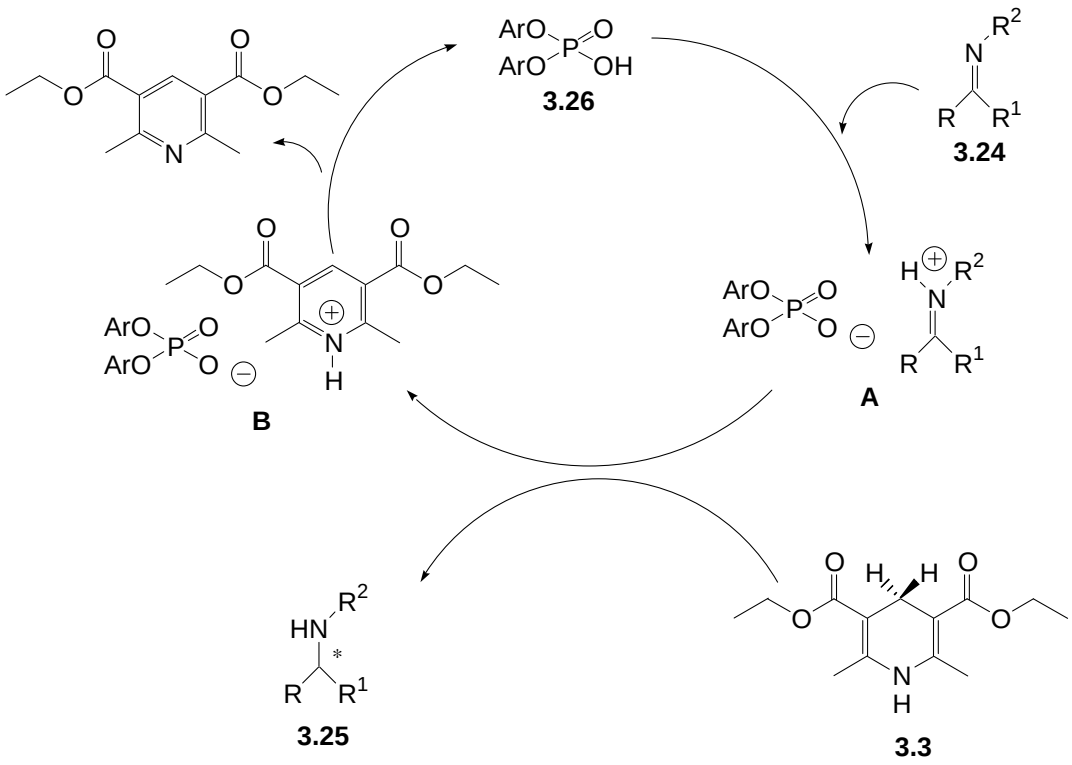
The reduction of ketimines has also been achieved using an organocatalytic/Hantzsch ester transfer hydrogenation. Rueping et al have developed a highly selective process for the reduction of ketimines in the presence of a phosphoric acid catalyst[13] (Scheme 3.4).

Scheme 3.4: Ketimine reductions carried out by Rueping et al**.**



The mechanism is similar to the one shown in Scheme 3.2, only this time the ketimine **3.24** is activated by formation of iminium ion pair species **A** (Scheme 3.5).

Scheme 3.5: Mechanism proposed by Rueping et al.[13]

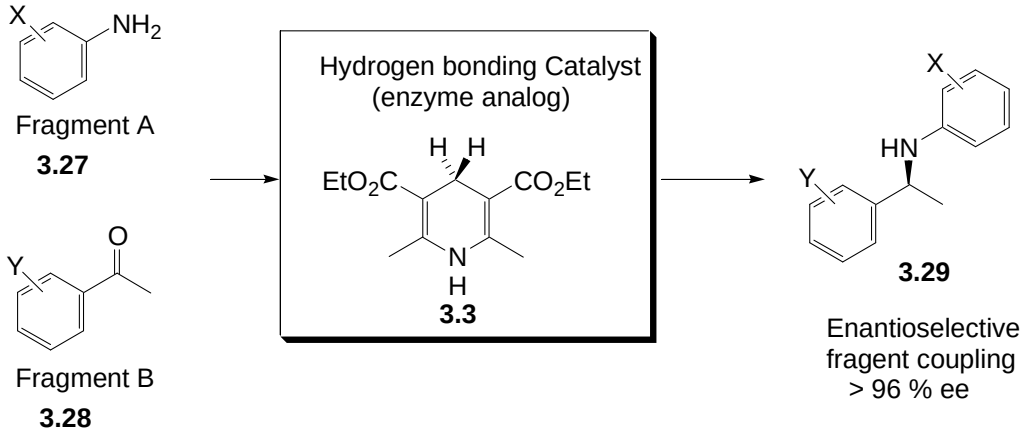


This is then delivered a hydride from Hantzsch dihydropyridine **3.3** resulting in the formation of chiral amine **3.25** and the pyridinium ion pair species **B**. This can then be used to regenerate the starting phosphoric acid catalyst **3.26**. However, as in the case of conjugated reduction mechanism, the Hantzsch dihdropyridine **3.3** is not reformed and has to be used in stoichiometric quantities.

3.2.2 Reductive amination:

MacMillan and co-workers extended this concept to the process of reductive amination of ketones (Scheme 3.6).[8]

Scheme 3.6: General reductive amination carried out by MacMillan et al.

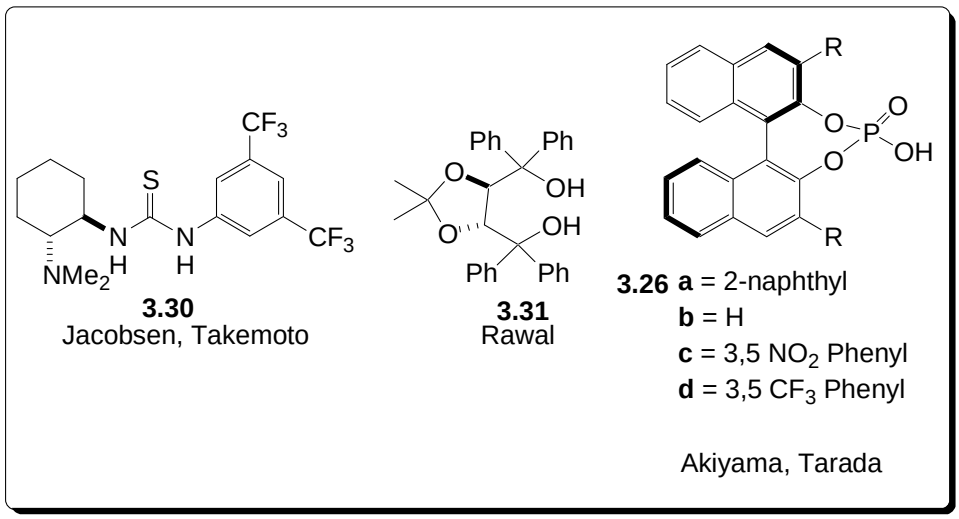


Following essentially the same route as described in section 3.1, the two fragments can combine to form an iminium species which is then reduced by the Hantzsch dihydropyridine.[8]

In nature, reductive amination has been shown to occur in the presence of a transferase enzyme, which uses hydrogen bonding to activate an iminium species. A hydride can then be selectively delivered from NADH.[8] As the dihydropyridine is acting as a NADH mimic, it was therefore assumed that a hydrogen bonding catalyst would be most beneficial in this system.[8]

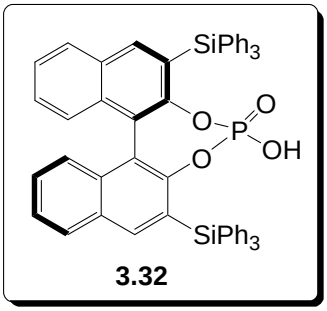
Recent advances in hydrogen bonding catalysts[14-18] led to the investigation of the following three compounds in the MacMillan system (Figure 3.2).

Figure 3.2: Hydrogen bonding catalysts.



The group found that both catalysts **3.30** and **3.31** showed no catalytic activity, where as catalyst **3.26d** afforded 65 % ee in their trial studies. Optimisation of the catalyst structure by varying the R groups of compound **3.26** resulted in catalyst **3.32** (Figure 3.3) which achieved selectivities of up to 94 % ee.[8]

Figure 3.3: Optimum hydrogen bonding catalyst.



3.32

Reductive amination is a very important reaction as it allows for the reduction of imines which are not stable to isolation. By developing this mild, selective reduction, the MacMillan group have paved the way to selectively reduce a much wider range of substrates.

3.3 Conclusions:

Many research groups have demonstrated that organocatalysts can be used in combination with the Hantzsch dihydropyridine to carry out a highly selective transfer hydrogenation reaction. Particularly high enantioselectivities have been observed in:

(i) The reduction of α,β-unsaturated aldehydes.[4,5,6]

(ii) Reductions of ketimines[13] and reductive amination of ketones.[8]

By carrying out these organocatalytic reductions using Hantzsch dihydropyridine, new highly selective protocols have been developed, which tolerate the presence of other functional groups sensitive to hydrogenation, and furthermore have avoided the many drawbacks associated with transition metal catalysed processes.

4.0 Results and Discussion:

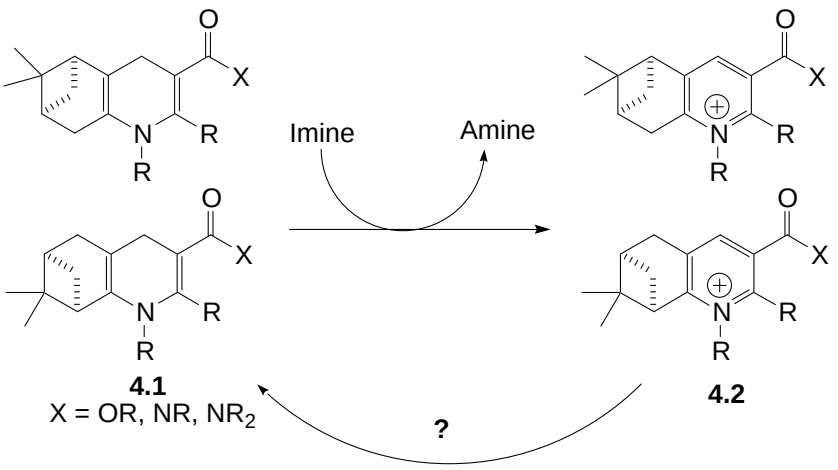
4.1 Design and Synthesis of New Chiral Pyridines:

4.1 Design and Synthesis of new chiral pyridines:

4.1.1 Aims:

From the literature overview, we have seen that Hantzsch dihydropyridine in the presence of an organocatalyst can be used to perform highly selective reductions. The drawback of these processes is that a stoichiometric amount of heavy dihydropyridine is required, which adversely affects the overall atom efficiency. The aim of this project was (i) to develop a reaction where dihydropyridine can be used in catalytic quantity and (ii) to combine the source of chirality and the dihydropyridine functionality in the same molecule (Scheme 4.1).

Scheme 4.1:

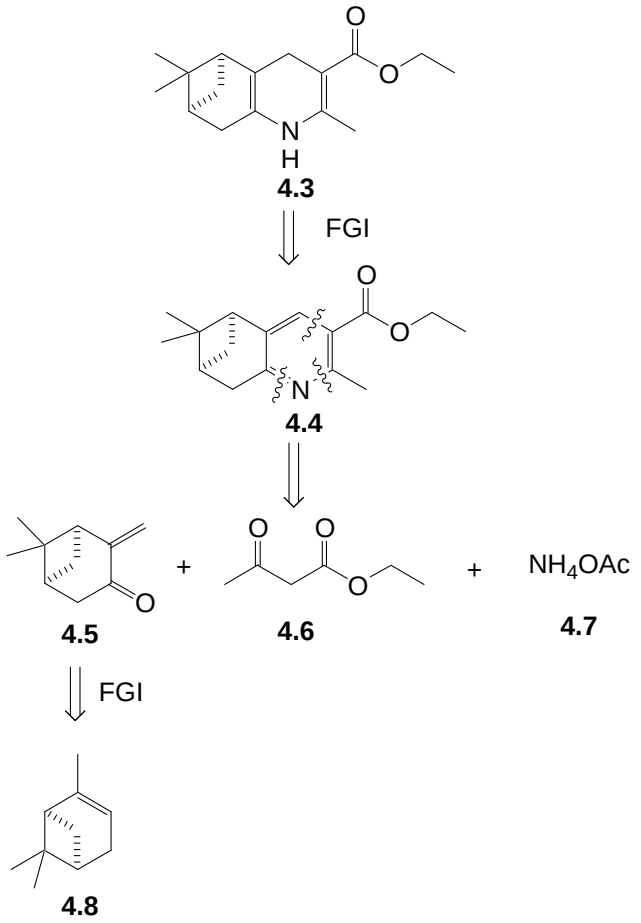


To accomplish these tasks, we needed to develop a catalytic cycle in which the pyridinium ion **4.2** resulting from the reduction of an imine is regenerated in-situ to the initial chiral dihydropyridine **4.1**.

4.1.2 Retrosynthetic analysis:

The retrosynthetic analysis for target compound **4.3** is shown in Scheme 4.2.

Scheme 4.2: Retrosynthetic analysis.

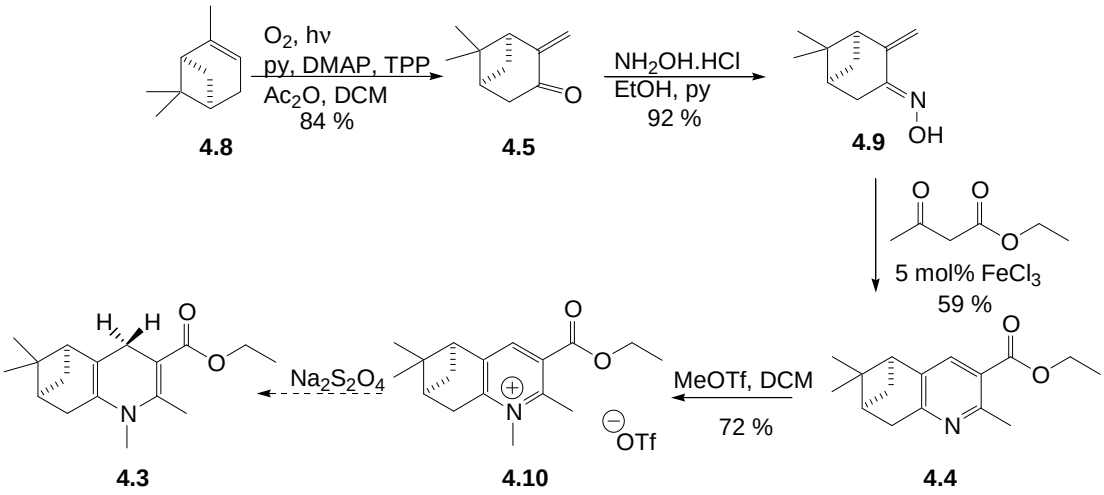


Target dihydropyridine **4.3** can be formed from the corresponding pyridine **4.4**. Disconnection of **4.4** produces pinocarvone **4.5**, ethyl acetoacetate and ammonium acetate. Pinocarvone can be obtained from the commercially available (+)-α-pinene **4.8** by functional group interconversion.

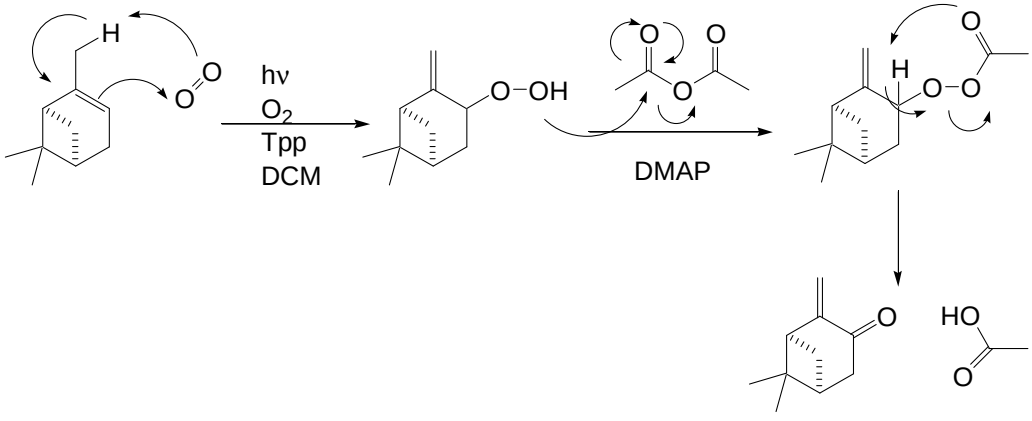
4.1.3 Synthesis of dihydropyridines:

The synthesis of dihydropyridine **4.3** is shown in Scheme 4.3. The sequence commenced with the ene reaction of α-pinene **4.8** with singlet oxygen generated by UV irradiation to form pinocarvone **4.5**, following a literature protocol.[19] The mechanism is highlighted in Scheme 4.4.

Scheme 4.3: Synthesis of dihydropyridine **4.3**.



Scheme 4.4: Mechanism for the formation of pinocarvone **4.5.**



Pinocarvone **4.5** was converted to the corresponding oxime **4.9** using hydroxylamine hydrochloride and then cyclised into pyridine **4.4** using ethyl acetoacetate in the presence of 5 mol% $FeCl_3$. Chiral pyridine **4.4** was then

converted to the quaternary ammonium salt **4.10** by treatment with methyl triflate.

The final stage was then to reduce the triflate salt **4.10** with sodium dithionite to produce the target dihydropyridine. However, this proved to be a major problem. Various reducing agents and techniques were screened in an attempt to produce the target dihydropyridine. These are summarised in Table 4.1.

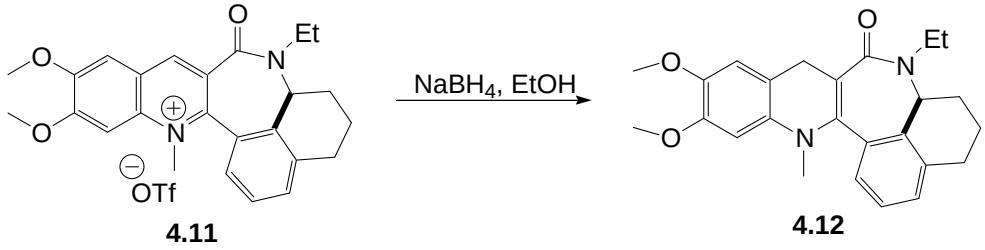
Table 4.1: Summary of various reducing agents and conditions employed.

Entry	**Reagent**	**Solvent**	**Time (h)**	**Temp (^{o}C)**
1	NaS_2O_4	EtOAc/H_2O	3	50
2	NaS_2O_4	H_2O	Overnight	Room temp
3	NaS_2O_4	DCM	Overnight	60
4	Hantzsch ester	DCM	2.5	Room temp
5	Hantzsch ester	DCM	Overnight	60
6	$NaBH_4$	EtOH	1	Room temp
7	$NaBH_4$	THF	1	Room temp
8	Et_3SiH	EtOH	Overnight	Reflux
9	Et_3SiH	Toluene	Overnight	Reflux
10	Ph_2SiH	Toluene	Overnight	Reflux
11	$Na(OAc)_3BH$	EtOH	Overnight	Room temp
12	$Na(OAc)_3BH$	EtOH	Overnight	60
13	$Na(OAc)_3BH$	THF	Overnight	Room temp

Unfortunately, none of these procedures produced the target dihydropyridine.

From the literature, there are very few examples of dihyrdopyridines with a structure similar to our models. Only one example of a triflate salt **4.11** was found, which was synthesised by Vasse et al (Scheme 4.5).[20] Pyridinium salt **4.11** was reduced to **4.12** using sodium borohydride in ethanol. When these same conditions were used for our pyridinium salt (entries 6 and 7, Table 4.1), no reduction was observed.

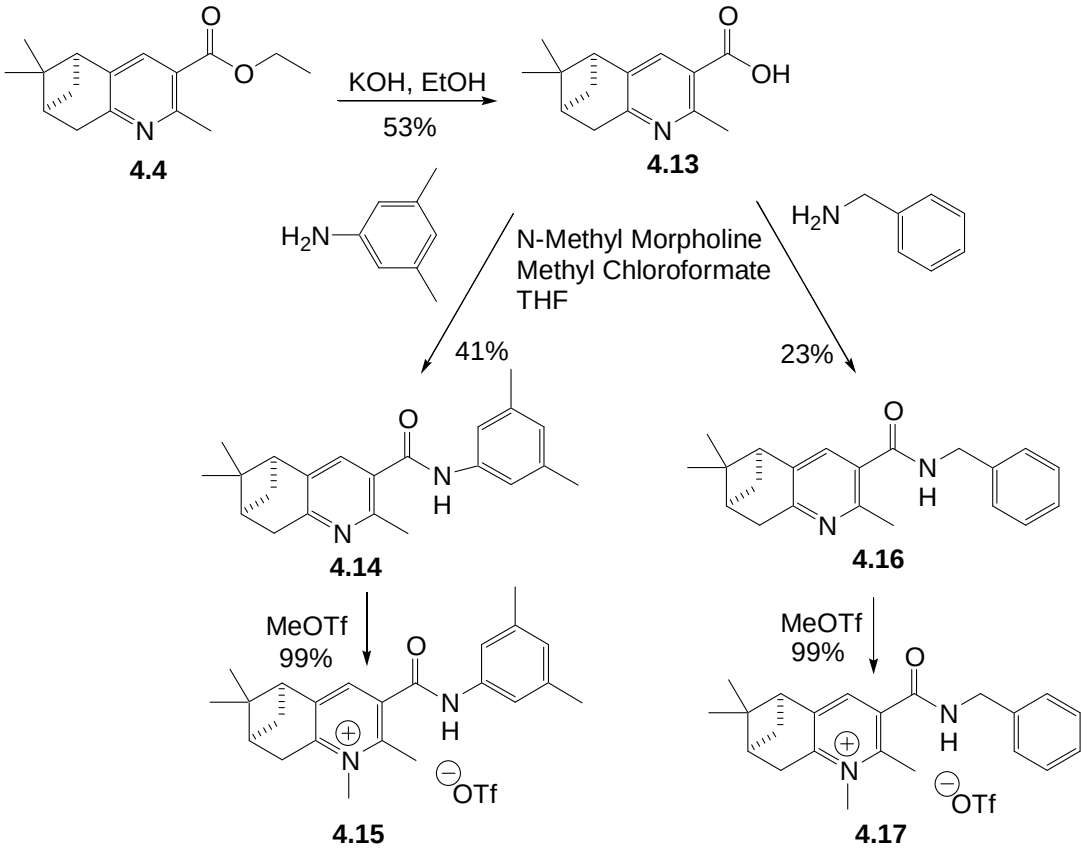
Scheme 4.5: Reduction of pyridinium salt by Vasse et al**.**



4.11 **4.12**

However, the basic structure of Vasse's pyridine is quite different to ours. There are two functionalities in particular which might be affecting their reduction potential: (i) the presence of a quinoline ring system[21] and (ii) a tertiary amide group.[22] Due to the structural features of our systems, only the option of functionalising the nicotinamide group is available to us. Therefore, two corresponding amides were synthesised as shown in Scheme 4.6.

Scheme 4.6: Synthesis of chiral pyridines with an amide side group.

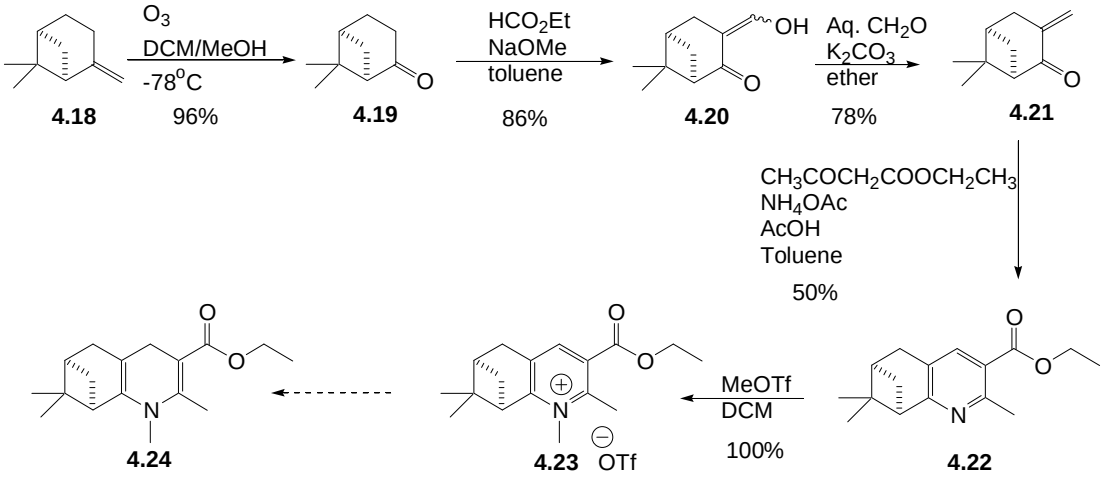


4.4 **4.13** **4.14** **4.16** **4.15** **4.17**

Ester **4.4** prepared according to Scheme 4.3 was hydrolysed to the corresponding acid using aqueous KOH. Acid **4.13** was then coupled to the corresponding amine in the presence of methyl chloroformate and *N*-methyl morpholine. The resulting pyridines **4.14** and **4.16** were then converted to the respective triflate salts **4.15** and **4.17** using methyl triflate.

It was also thought that the position of the bridging group may be interfering with the attempted reduction step. Therefore the positional isomer **4.24** was prepared in parallel as shown in Scheme 4.7.

Scheme 4.7: Synthesis of dihydropyridine **4.24**.

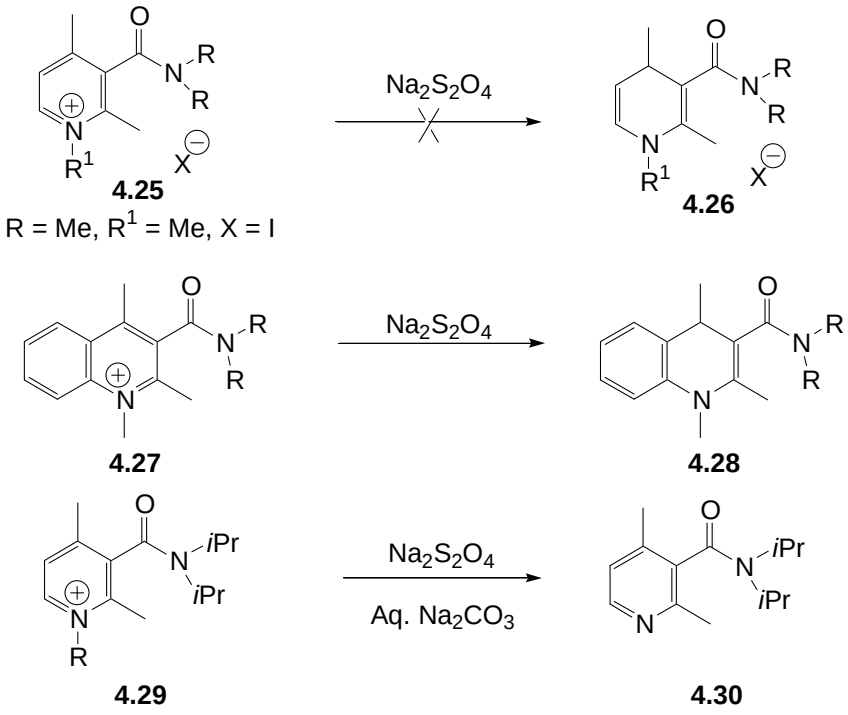


The synthesis began with the ozonolysis of β-pinene **4.18** to give nopinone **4.19**.[23] This was then converted to the 1,3-dicarbonyl compound **4.20** using ethyl formate in the presence of sodium methoxide, which was then reacted with an aqueous solution of formaldehyde to produce the α,β-unsaturated compound **4.21**.[24] A direct cyclisation resulted in the formation of pyridine **4.22**, so there was no longer any need to form the corresponding oxime prior to cyclisation. Pyridine **4.22** was then converted to the quaternary ammonium salt as previously described.

These three new pyridine salts **4.15**, **4.17** and **4.23** were then screened against a wide range of reducing agents and conditions as before, and once again no trace of dihydropyridine was observed.

On further consultation of the literature, our attention was drawn to a report by Mikata et al[21] who carried out a detailed investigation into the reduction of pyridinium salts (Scheme 4.8).

Scheme 4.8: Reduction of pyridinium salts carried out by Mikata.[21]

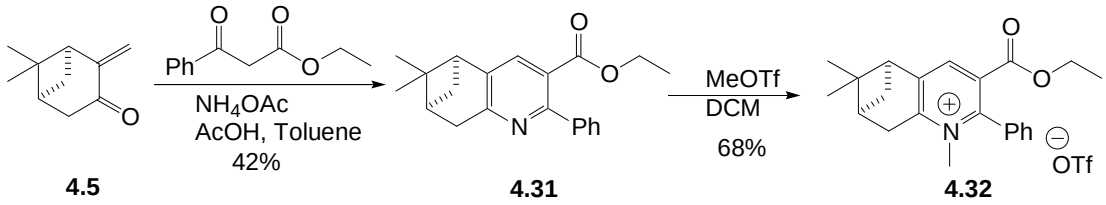


Compounds **4.25** and **4.29**, which are close in structure to our novel pyridinium salts, did not undergo reduction to the corresponding target dihydropyridines. On the other hand, **4.27**, did undergo the desired reduction.

From their results it appears that the presence of a quinoline ring is crucial for a successful reduction of derivatives featuring an α–methyl group. Without this added stability, it was thought that this α–methyl group was in some way hindering the desired reduction.

With this in mind, we then set out to make two new pyridinium salts, one with a phenyl group in place of the methyl group (**4.32**) and unsubstituted derivative **4.38** (Schemes 4.9 and 4.10, respectively).

Scheme 4.9: Synthesis of phenyl substrate.

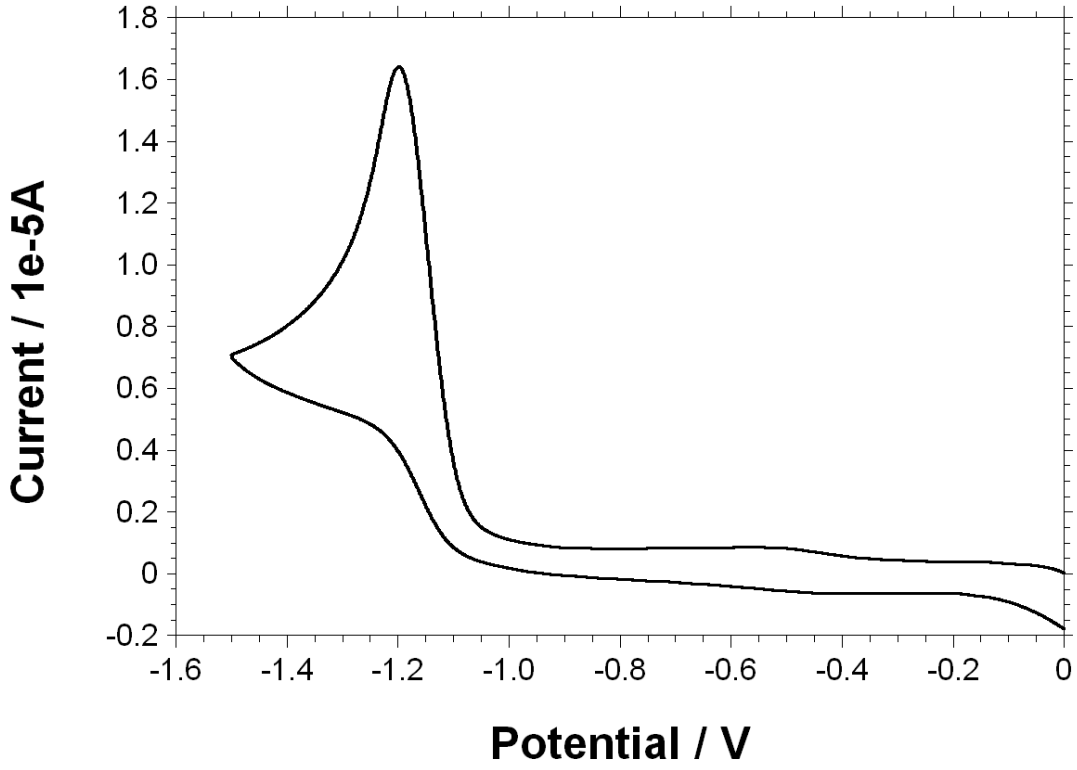


4.5 **4.31** **4.32**

The phenyl substrate **4.32** was prepared in a similar manner as previously described (Scheme 4.3), only this time, pinocarvone **4.5** was directly cyclised with ethyl benzoyl acetate and ammonium acetate to produce pyridine **4.31**, which was converted to the triflate salt **4.32.** As before, the phenyl substrate was screened against a wide range of reductants and once again, no formation of dihydropyridine was observed.

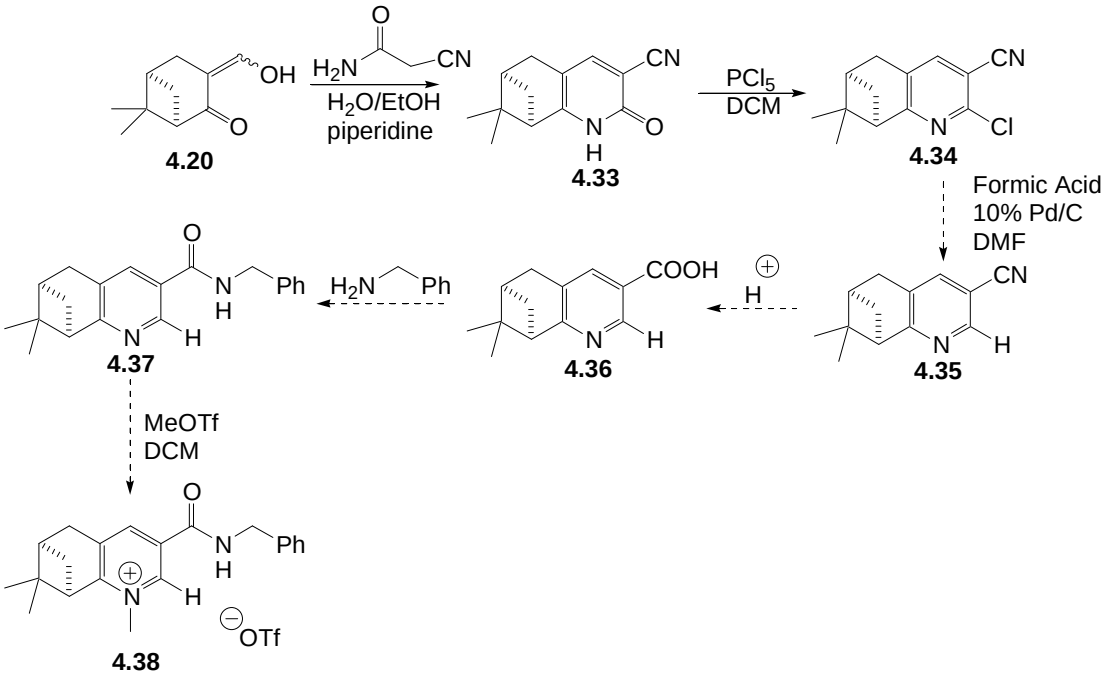
In order to get a better understanding of what was going on during the reduction step, a CV analysis was carried out on the phenyl derivative **4.32**. The results (Figure 4.1) showed that the initial one-electron reduction was occurring, however, it was irreversible suggesting that the resulting pyridinium radical is unstable under these conditions and is consumed (decomposed) before the second electron can be delivered to give the target dihydropyridine.

Figure 4.1: Cyclic voltammogram (4.1 mg in 6ml of acetonitrile). Scan rate 100 mVs^{-1}. Reference electrode: Ag/AgCl; Working electrode: Pt disk; Counter electrode: Pt wire



The final pyridinium salt **4.38** was prepared as shown in Scheme 4.10.

Scheme 4.10: Synthesis of compound **4.38**.



Synthesis of compound **4.38** started with 1,3-dicarbonyl compound **4.20** prepared according to Scheme 4.7. It was cyclised with cyanoacetamide to form pyridone **4.33**, which was converted to chloro-pyridine **4.34** using PCl_5.

Purification of pyridone **4.33** proved extremely difficult, furthermore chloropyridine **4.34** was extremely unstable and even trace amounts of moisture resulted in its hydrolysis. Therefore, we were unable to progress beyond this step.

The difficulties encountered during the synthesis of **4.38** in combination with the disappointing results obtained from CV analysis of other terpene-derived pyridinium salts led us to abandon this project.

4.1.4 Conclusions:

In conclusion, we have synthesised a range of chiral pyridinium salts as precursors to chiral dihydropyridines which were intended for use in enantioselective reduction of imines or ketones.

However, under a wide variety of conditions, the key reduction step to produce dihydropyridines did not occur. Electrochemical CV analysis of compound **4.32** confirmed that the intermediates in the reduction of our pyridinium salts are too unstable and decomposes before the target dihydropyridines can be formed. Therefore, this project was not investigated any further. In future development, the structure of chiral NADH analogues should be based on chiral quinolines to ensure facile generation of dihydropyridine fragment from pyridinium salt.

References:

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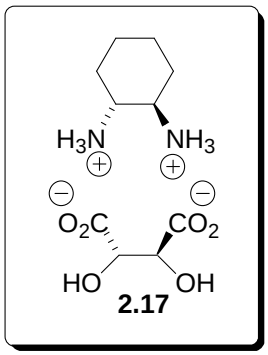
Chapter 5.0 Experimental:

General Methods. Melting points were determined on a Kofler block and are uncorrected. Boiling points (bp) of compounds obtained by Kugelrohr (bulb-to-bulb) distillation correspond to uncorrected air bath temperatures. Optical rotations were recorded in $CHCl_3$ at 25 °C unless otherwise indicated with an error of $<\pm 0.1$. The $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. The NMR spectra were recorded in $CDCl_3$, ^1H at 400 MHz and ^{13}C at 100.6 MHz on a Bruker spectrospin 400 (400 MHz) spectrometer with chloroform-d_1 (δ 7.26, ^1H; δ 77.0, ^{13}C) as internal standard unless otherwise indicated. Various 2D-techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra were recorded for a thin film between NaCl plates or for $CHCl_3$ solutions or in a solid by the Golden Gate technique. The mass spectra (EI and/or CI) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. All reactions were performed under an atmosphere of dry, oxygen-free nitrogen (or argon where specified) in oven-dried glassware twice evacuated and filled with the nitrogen. Solvents and solutions were transferred by syringe-septum and cannula techniques. All solvents for the reactions were of reagent grade and were dried and distilled immediately before use as follows: diethyl ether from lithium aluminium hydride; tetrahydrofuran (THF) from sodium/benzophenone; dichloromethane from calcium hydride. Standard workup of an ethereal solution means washing 3 × with 5% HCl (aqueous), water, and 3 × with 5% $KHCO_3$ (aqueous) and drying with $MgSO_4$. Petroleum ether refers to the fraction boiling in the range of 40-60 ^oC. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR, IR, and MS data and by the TLC behaviour. The chiral GC and HPLC methods were calibrated with the corresponding racemic mixtures.

Allylic alcohols **2.51**, **2.52**, **2.53**, **2.54** and **2.82** were purchased from Sigma-Aldrich and used as received.

5.1 Synthesis of hydroxamic acids:

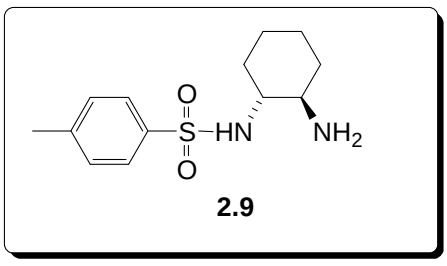
5.1.1 Synthesis of cyclohexyl ligand 2.1:



2.17

Cyclohexane-1,2-diamine tartrate salt (R,R): Following a procedure by Jacobsen et al[1] distilled water (23 mL) and L-tartaric acid (6.57 g, 43. 79 mmol) were added to a 100 mL beaker and warmed to 30 ^{o}C until the solid dissolved. Cyclohexyldiamine (10.5 mL, 87.57 mmol) was then added dropwise, followed by acetic acid (4.4 mL) making sure the temperature did not rise above 90 ^{o}C. The mixture was warmed to 80 ^{o}C, then allowed to cool slowly, over 2 h, to room temperature. Then it was placed in an ice bath (5 ^{o}C) for a further 2h.The precipitate was collected by filtration, washed with cold water (10 mL) and a few pipettes of methanol. The salt was dried under reduced pressure to give a white solid (8.86 g, 77%) which was used immediately in the next step.

$[\alpha]_D$ 12.2 (c = 1, water) in accordance with literature data.[2]

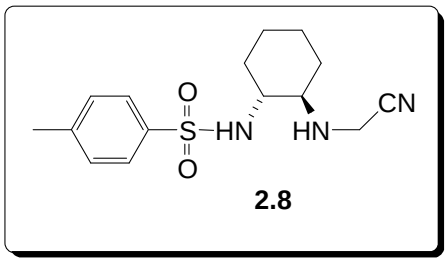


2.9

N-(2-Amino-cyclohexyl)-4-methyl-benzenesulfonamide. (R,R): Following a procedure by Ng et al[3] to a stirred solution of L-tartrate salt **2.17** (4 g, 15.14 mmol) in 2M aqueous NaOH (18 mL) was added Et_3N (2.80 mL, 38.11 mmol) and DCM (130 mL). The mixture was cooled to 0 ^{o}C and a solution of TsCl

(3.17 g, 16.65 mmol) in DCM (90 mL) was added dropwise over 30 mins. The mixture was warmed to room temperature and stirred for 12 h. The resulting reaction mixture was washed with 2 M Aq HCl (3 x 50 mL) and the organic phase was removed. The aqueous phase was collected and adjusted to pH 9 by addition of 6M NaOH. The basic aqueous solution was extracted with DCM (3 x 50 mL). The combined DCM layers were dried over $MgSO_4$ and evaporated in vacuo to give a pale yellow solid (3.5 g, 86 %). A small sample was recrystallised from ethyl acetate: yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99-1.21 (m, 4H), 1.57-1.66 (m, 3H), 1.86-1.95 (m, 1H), 2.37 (s, 3H), 2.42 (dt, *J* = 10.3 Hz, 3.7 Hz, 1H), 2.66 (dt, *J* = 10.3 Hz, 3.7 Hz, 1H), (bs, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.5 (CH_3), 24.7 (CH_2), 25.0 (CH_2), 32.4 (CH_2), 34.9 (CH_2), 54. 7 (CH), 60.4 (CH), 127.0 (aromatic CH), 129.7 (aromatic CH), 138.2 (C), 143.1 (C).

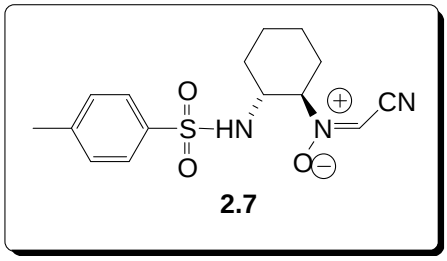
In accordance with literature data.[4]



2.8

N-[2-(Cyanomethyl-amino)-cyclohexyl]-4-methyl-benzenesulfonamide. (R,R): Following a procedure by Fukuyama et al[5] diisopropylethylamine (2.30 mL, 23.67 mmol), was added to a solution of monotosyl diamine **2.9** (1.8 g, 6.72 mmol), in acetonitrile (30 mL) and was stirred for 5 mins. Bromoacetonitrile (0.51 mL, 7.39 mmol) was then added via syringe over 10 mins and the mixture was left with stirring overnight at room temperature. Then the mixture was concentrated on a rotary evaporator to give a yellow oil, which was treated with sat aqueous $NaHCO_3$ (50 mL). The suspension was extracted with DCM (50 mL), the organic phase was washed with brine (50 mL) and the combined aqueous phases were extracted with DCM (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo to give a yellow solid

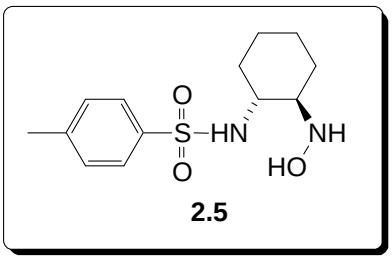
(1.98 g, 99 %). This was used in the next step without further purification. A small sample was recrystallized from ethyl acetate: yellow solid; m.p = 104 – 105 ^{o}C (petroleum ether/ethyl acetate); $[\alpha]_D$ –9.3 (c = 1, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90-1.20 (m, 4H), 1.38-1.64 (m, 4H), 1.93-2.01 (m, 1H), 2.36 (s, 3H), 2.40 (dt, *J* = 10.8 Hz, 3.9 Hz, 1H), 2.77-2.87 (m, 1H), 3.50 (d, *J* = 17.7 Hz, 1H), 3.63 (d, *J* = 17.7 Hz, 1H), 5.10 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.7 (CH_3), 21.6 (CH_2), 24.2 (CH_2), 30.4 (CH_2), 32.4 (CH_2), 34.5 (CH_2), 57.4 (CH), 59.5 (CH), 118.1 (C), 126.8 (aromatic CH), 129.8 (aromatic CH), 137.6 (C), 143.6 (CN); IR (NaCl) 3353.6 (NH), 2940.9 (C-H), 2253.4 (CN), 1062.6 (O=S=O); MS (FAB), *m/z* (%) 281.2 (100), 308.3 ($(M + H)^+$ 55), 153.1 (29), 92.9 (25); HRMS (FAB) 308.1430 ($C_{15}H_{22}N_3O_2S$ requires 308.1433).



2.7

Nitrone (R,R): Following the procedure of Fukuyama et al,[5] a flask containing a solution of cyanodiamine **2.8** (1.52 g, 4.95 mmol) in DCM (23 mL) under argon was cooled in an ice bath. Followed by addition of *m*-CPBA (2.14 g, 12.38 mmol) in small portions over 30 mins. After completion of addition, the ice bath was removed and the mixture was stirred at room temperature for 2h. It was then diluted with DCM (20 mL), washed with conc. $Na_2S_2O_3$ (30 mL) and, sat $NaHCO_3$ (3 x 30 mL). The aqueous phases were extracted with DCM (2 x 30 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated to give a white solid (1.19 g, 75 %). It was used in the next step without further purification. A small sample was recrystallized from DCM: white solid; m.p = 152 – 155 ^{o}C (petroleum ether/ethyl acetate); $[\alpha]_D$ –27.3 (c = 1, Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14-1.40 (m, 4H), 1.62-2.04 (m, 4H), 2.38 (s, 3H), 3.50-3.59 (m, 1H), 3.82 (td, *J* = 11.2 Hz, 4.4 Hz, 1H), 5.10 (bs, 1H), 6.60 (s, 1H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H); ^{13}C

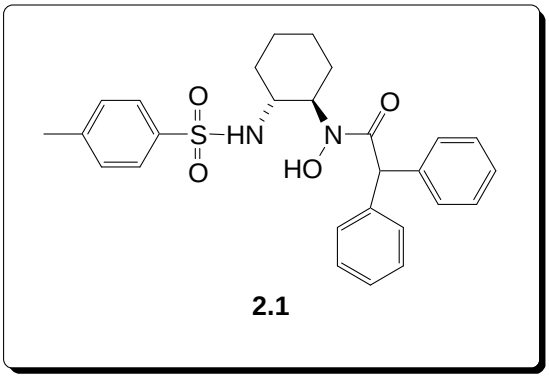
NMR (100.6 MHz, $CDCl_3$) δ 23.6 (CH_2), 24.3 (CH_2), 30.3 (CH_2), 33.1 (CH_2), 54.5 (CH_3), 77.3 (CH), 79.4 (CH), 107.4 (CH), 111.9 (C), 127.3 (aromatic CH), 129.9 (aromatic CH), 137.5 (C), 144.2 (CN); IR (NaCl) 3303.5 (NH), 2949.6 (C-H), 2253.4 (CN), 1087.7 (O=S=O), 911.2 (N^+- O^-); MS (CI), *m/z* (%) 322.3 ($(M + H)^+$ 12), 306.3 (50), 281.3 (40), 125.2 (31); HRMS (CI) 322.1224 ($C_{15}H_{20}N_3O_3S$ requires 322.1225).



2.5

N-(2-Hydroxyamino-cyclohexyl)-4-methyl-benzenesulfonamide. (R,R):
Following a procedure by Fukuyama et al,[5] hydroxylamine hydrochloride (1.29 g, 18.5 mmol) was added to a solution of nitrone **2.7** (1.19 g, 3.70 mmol) in methanol (32 mL) and the mixture was heated at 60 ^oC for 2h. After that time, the reaction mixture was cooled to room temperature and diluted with DCM (50 mL). After stirring for 5 mins, the resulting precipitate was collected by filtration and the filter cake was washed with DCM. The filtrate was neutralised with $NaHCO_3$ (30 mL) and the organic layer separated. The aqueous phase was extracted with DCM (25 mL). The organic phase was washed with brine (30 mL) and the combined aqueous phases were back-extracted with DCM (3 x 30 mL). The organic extracts were then dried over $MgSO_4$ and concentrated to give a pale yellow solid (0.88 g, 84%). It was used in the next step without further purification. A small sample was recrystallized from DCM: pale yellow solid; m.p = 100 – 102 ^oC (petroleum ether/ethyl acetate); $[\alpha]_D$ –28.9 (c = 1, Acetone); ^1H NMR (400 MHz, $CDCl_3$) δ 0.99-1.18 (m, 4H), 1.45-1.84 (m, 4H), 2.34 (s, 3H), 2.43 (td, *J* = 11.3 Hz, 3.9 Hz, 1H), 3.0 (m, 1H), 4.74 (bs, 1H), 5.92 (bs, 1H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.6 (CH_3), 24.4 (CH_2), 24.7 (CH_2), 29.3 (CH_2), 33.2 (CH_2), 54.4 (CH), 64.2 (CH), 127.1 (aromatic CH), 127.3 (aromatic CH), 129.8 (aromatic CH), 136.9 (aromatic CH), 137.7 (C), 143.6 (C); IR (NaCl) 3263.9 (NH),

3155.0 (OH), 2938.0 (C-H), 2253.4 (C=C), 1026.9 (O=S=O); MS (FAB), *m/z* (%) 285.2 ($(M + H)^+$ 100), 92.9 (16), 130.4 (15), 92.9 (13); HRMS (FAB) 285.1274 ($C_{13}H_{21}N_2O_3S$ requires 285.1273); IR (NaCl) 3263.9 (NH), 3155.0 (OH), 2938.0 (C-H), 2253.4 (C=C), 1026.9 (O=S=O).

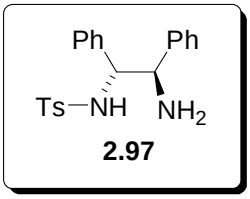


2.1

N-Hydroxy-2,2-diphenyl-N-[2-(toluene-4-sulfonylamino)-cyclohexyl]-acetaminde. (R,R): Following a procedure by Kim et al,[6] 2,6-Leutidine (0.58 mL, 4.94 mmol) and TMSCl (0.63 mL, 4.94 mmol) were added to a solution of hydroxylamine **2.5** (0.7 g, 2.47 mmol), in THF (21 mL) at 0 ^oC and the resulting mixture was stirred for 6 h at room temperature. The mixture was cooled to 0 ^oC and diphenyl acetyl chloride (0.57 g, 2.47 mmol) in THF (5.5 mL) was added dropwise. The mixture was stirred at room temperature overnight. Water (0.9 mL) was added and the resulting solution was stirred for 1 h at room temperature. Volatile organics were evaporated in vacuo. Ethyl acetate (20 mL) was added to the residue and the organic layer was washed successively with 10% citric acid (30 mL), then 5% $NaHCO_3$ (30 mL), then water (30 mL). Organic phase was then dried over $MgSO_4$ and concentrated to give a yellow sticky oil which was recrystallised in methanol to give a white solid (0.80 g, 67%). White solid: m.p. 183 - 186 ^oC (petroleum ether/ethyl acetate). $[\alpha]_D$ + 4.8 (c = 0.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.90-1.20 (m, 4H), 1.30-1.74 (m, 4H), 2.35 (s, 3H), 3.10 (m, 1H), 4.30 (td, *J* = 11.0 Hz, 3.6 Hz, 1H), 4.76 (d, *J* = 9.6 Hz, 1H), 5.62 (s, 1H), 7.14-7.31 (m, 12H), 7.61 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.6 (CH_3), 23.3 (CH_2), 24.0 (CH_2), 27.1 (CH_2), 31.1 (CH_2), 52.1 (CH), 52.8 (CH), 58.2 (CH), 125.6 (aromatic CH), 125.7 (aromatic CH), 125.8 (aromatic CH), 126.2 (aromatic CH), 126.3 (aromatic

CH), 127.3 (aromatic CH), 127.5 (aromatic CH), 127.6 (aromatic CH), 127.7 (aromatic CH), 128.2 (aromatic CH), 128.7 (aromatic CH), 136.5 (C), 138.4 (C), 138.5 (C), 142.5 (C), 172.5 (C=O). IR (NaCl) 3154.0 (OH), 2940.9 (C-H), 2253.4 (C=C), 1709.6 (C=O), 1093.4 (O=S=O); HRMS (EI) *m/z* 478.1929 ($C_{27}H_{30}N_2O_4S$ requires 478.1926).

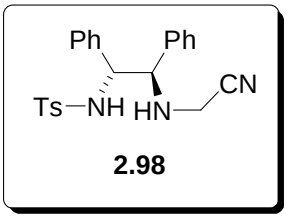
5.1.2 Synthesis of diphenyl ligand 2.2:



2.97

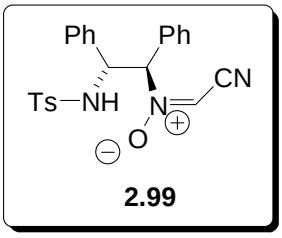
N-1,2-diphenyl-ethyl]-4-methyl-benzenesulfonamide. (R,R): Tosyl chloride (0.09 g, 0.47 mmol) was added to a solution of diamine (0.1 g, 0.47 mmol) in DCM (2 mL) and Et_3N (0.13 mL, 0.94 mmol). This was stirred at room temperature overnight. The reaction mixture was then diluted with water (10 mL) and neutralised with 1 M HCl (20 mL). The organic layer was then dried over $MgSO_4$ and concentrated in vacuo. The resulting solid was then recrystallised in H_2O/EtOH to give a white solid (0.067 g, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (bs, NH_2), 2.36 (s, 3H), 4.15 (d, *J* = 5.2 Hz, 1H), 4.40 (d, *J* = 5.2 Hz, 1H), 6.05 (bs, NH), 7.00 (d, *J* = 8.2 Hz, 2H), 7.12 – 7.24 (m, 10 H), 7.34 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.5 (CH_3), 60.5 (CH), 63.1 (CH), 126.5 (aromatic CH), 126.9 (aromatic CH), 127.0 (aromatic CH), 127.4 (aromatic CH), 127.5 (aromatic CH), 128.3 (aromatic CH), 128.5 (aromatic CH), 129.2 (aromatic CH), 137.1 (C), 139.3 (C), 141.4 (C), 142.5 (C).

In accordance with commercial data.[7]



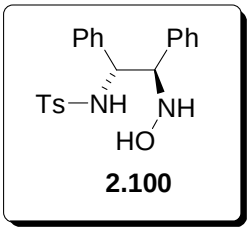
2.98

N-[2-(Cyanomethyl-amino)-1,2-diphenyl-ethyl]-4-methyl-benzenesulfonamide. (R,R): Following a procedure by Fukuyama et al.[5] Diisopropylethyl amine (1.90 mL, 10.92 mmol) was added to a solution of commercial diamine **2.97** (2.00 g, 5.46 mmol), in MeCN (14 mL) and was stirred for 5 mins. Bromoacetonitrile (0.42 mL, 6.01 mmol) was then added over 10 mins and the mixture was stirred at room temperature overnight. The mixture was then concentrated on a rotary evaporator to give a yellow oil, to which was added sat $NaHCO_3$ (50 ml). The suspension was extracted with DCM (50 mL), the organic phase was washed with Brine (30 mL) and the combined aqueous phases were back-extracted with DCM (2 x 20 mL). Combined organics were then dried over $MgSO_4$ and concentrated in vacuo to give a yellow oil which was then purified by column chromatography on silica gel (15 x 3 cm) with a petroleum ether-ethyl acetate mixture (2:1) to give a white solid (1.54 g, 70%): m.p = 107 - 108 ^oC (petroleum ether/ethyl acetate); $[\alpha]_D$ – 49.5 (c = 1, DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.60-2.68 (m, 1H), 3.22 (dd, *J* = 17.5 Hz, 11.1 Hz, 1H), 3.65 (dd, *J* = 17.5 Hz, 4.2 Hz, 1H), 4.06 (d, *J* = 6.8 Hz, 1H), 4.40 (t, *J* = 8.3 Hz, 1H), 5.48 (d, *J* = 8.3 Hz, 1H), 6.81 (d, *J* = 6.8 Hz, 2H), 6.99-7.19 (m, 10H), 7.40 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.4 (CH_3), 33.8 (CH_2), 62.7 (CH), 65.2 (CH), 116.6 (C), 126.3 (CH), 127.1 (CH), 127.2 (CH), 127.4 (CH), 127.6 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 135.7 (C), 135.8 (C), 136.3 (C), 141.9 (C); IR (NaCl) 3259.1 (NH), 2254.4 (CN), 1599.7 (C=C), 1161.9 (S=O); MS (CI), *m/z* (%) 379.1 (99), 106.1 (59), 223.2 (49), 157.1 (23), 260.1 (20), 406.1 ($(M + H)^+$ 13); HRMS (CI) 406.1587 ($C_{23}H_{24}O_2N_3S$ requires 406.1589).



2.99

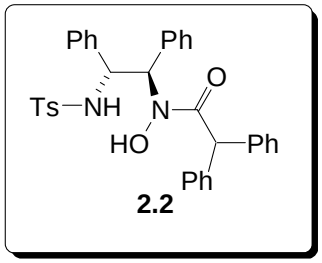
Nitrone (R,R): Following a procedure by Fukuyama et al.[5] Cyanomethylated diamine **2.98** (1.54 g, 3.80 mmol) was dissolved in DCM (25 mL). To this was added *m*-CPBA (1.64 g, 9.50 mmol) portion-wise over 10 mins at 0 ^{o}C. This was then stirred at room temperature for 4.5 h. The reaction mixture was diluted with DCM (30 mL), then washed with NaS_2O_3 (2 x 20 mL), followed by $NaHCO_3$ (4 x 20 mL). Combined aqueous layers were then back-extracted with DCM (2 x 20 mL). Combined organics were then dried over $MgSO_4$ and concentrated in vacuo to give a white solid (1.47 g, 92%) This was used immediately in the next step; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 5.13 (dd, *J* = 8.8 Hz, 6.5 Hz, 1H), 5.21 (d, *J* = 6.5 Hz, 1H), 6.21 (d, *J* = 8.8 Hz, 1H), 6.49 (s, 1H), 6.95-7.35 (m, 14H).



2.100

N-(2-Hydroxyamino-1,2-diphenyl-ethyl)-4-methyl-benzenesulfonamide. (R,R): Following a procedure by Fukuyama et al.[5] Nitrone **2.99** (1.47 g, 3.50 mmol) was dissolved in methanol (19 mL). Hydroxylamine hydrochloride (1.22 g, 17.50 mmol) was then added and the mixture was warmed to 60 ^{o}C for 2 h. The reaction mixture was cooled to room temperature and diluted with DCM (50 mL). After stirring for 5 mins, the resulting precipitate was collected by filtration and the filter cake was washed with DCM. The filtrate was neutralised with $NaHCO_3$ (100 mL) and partitioned. The aqueous phase was then extracted with DCM (50 mL), washed with brine (50 mL), and the combined aqueous phases were back-extracted with DCM (2 x 50 mL). The combined organics

were then dried over $MgSO_4$ and concentrated in vacuo to give a yellow solid which was then purified by column chromatography on silica gel (15 x 3 cm) with a petroleum ether-ethyl acetate mixture (2:1) to give a pale yellow solid (0.98 g, 73%): m.p = 45 – 48 ^oC (petroleum ether/ethyl acetate); $[\alpha]_D$ – 8.2 (c = 1, DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3H), 4.14 (d, *J* = 8.5 Hz, 1H), 4.65 (m, 1H), 5.71 (bs, 1H), 6.14 (d, *J* = 6.4 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 2H), 6.86-7.11 (m, 10H), 7.35 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.5 (CH_3), 60.8 (CH), 70.4 (CH), 127.1 (CH), 127.4 (CH), 127.5 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), 129.2 (CH), 137.2 (C), 137.3 (C), 137.6 (C), 142.9 (C); IR (NaCl) 3370.0 (OH), 2924.5 (C-H), 1599.7 (C=C), 1160.9 (S=O); MS (FAB), *m/z* (%) 383.3 ($(M + H)^+$ 100), 212.5 (92), 107.7 (58), 350.3 (50), 92.9 (46), 194.7 (39), 260.2 (19); HRMS (FAB) 383.1434 ($C_{21}H_{23}O_3N_2S$ requires 383.1429).

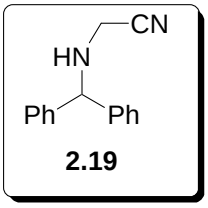


2.2

N-[1,2-Diphenyl-2-(toluene-4-sulfonylamino)-ethyl]-N-hydroxy-2,2-diphenyl-acetamide. (R,R): Following a procedure by Kim et al,[6] To a solution of hydroxylamine **2.100** (0.5 g, 1.31 mmol) in dry THF (8 mL) was added 2,6-Leutidine (0.31 mL, 2.62 mmol) and TMSCl (0.33 mL, 2.62 mmol) at 0 ^oC and the resulting mixture was stirred at room temperature for 6 h. The mixture was cooled to 0 ^oC and diphenyl acetyl chloride (0.16 g, 0.7 mmol) was added drop-wise with stirring and the solution was stirred at room temperature overnight. 0.4 mL water was added and resulting solution was stirred for 1 h at room temperature, THF was then evaporated in vacuo. Ethyl acetate was added to the residue and the organic layer was washed successively with 10% citric acid solution (30 mL), 5% $NaHCO_3$ (30 mL), then water (30 mL). Organics were then dried over $MgSO_4$ and concentrated in vacuo to give a yellow oil which was then purified by column chromatography on silica gel (15 x 3 cm) with a petroleum ether-ethyl acetate mixture (4:1) to give a pale yellow solid (0.18 g,

24%): m.p = 65 – 68 ^{o}C (petroleum ether/ethyl acetate); $[\alpha]_D$ – 70.3 (c = 1, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3H), 4.69 (dd, *J* = 11.2 Hz, 9.8 Hz, 1H), 5.61 (s, 1H), 5.93 (d, *J* = 9.8 Hz, 1H), 6.04 (d, *J* = 11.2 Hz, 1H), 6.60-7.34 (m, 23H), 7.63 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.9 (CH_3), 52.6 (CH), 56.7 (CH), 61.8 (CH), 125.0 (C), 125.3 (CH), 125.5 (CH), 125.6 (CH), 125.7 (CH), 125.8 (CH), 126.1 (CH), 126.3 (CH), 126.6 (CH), 126.8 (CH), 126.9 (CH), 127.1 (CH), 127.3 (CH), 127.4 (CH), 127.7 (CH), 172.7 (C=O); IR (NaCl) 3299.6 (OH), 1715.4 (C=O), 1599.7 (C=C), 1186.0 (S=O); MS (FAB), *m/z* (%) 577.2 ($(M + H)^+$ 100), 350.2 (96), 167.9 (94), 194.6 (82), 107.7 (67), 260.2 (61), 92.9 (44); HRMS (FAB) 577.2155 ($C_{35}H_{33}O_4N_2S$ requires 577.2161).

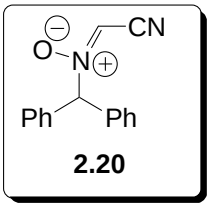
5.1.3 Synthesis of Benzhydryl hydroxylamine 2.13:



2.19

(Benzhydrylamino)-acetonitrile: Following a procedure by Fukuyama et al.[8] Bromoacetonitrile (3.10 mL, 45.00 mmol) was added to a stirred suspension of Na_2CO_3 (6.36 g, 60.00 mmol) in a solution of aminodiphenylmethane (5.20 mL, 30.00 mmol) in anhydrous acetonitrile (26 mL) in a 100 mL flask and the mixture was stirred at 60 ^{o}C for 24 h. The reaction mix was then filtered through celite and the filtrate was concentrated to give an orange liquid. This was recrystallised in a 4:1 mixture of petroleum ether/ethyl acetate to give a white solid (2.72 g, 41%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, NH), 3.51 (s, 2H), 5.12 (s, 1H), 7.25-7.55 (m, 10H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 35.3 (CH_2), 65.8 (CH_2), 117.8 (C), 127.1 (CH), 128.1 (CH), 128.9 (CH), 141.9 (C).

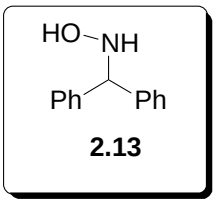
In accordance with literature data.[8]



2.20

Nitrone: Following a procedure by Fukuyama et al.[8] A solution of cyanomethylated amine **2.19** (2.72 g, 12.24 mmol), in dry DCM (20 mL), in a 250 mL flask was cooled to 0 ^{o}C in an ice bath. In another 250 mL flask, 70% *m*-CPBA (5.28 g, 30.60 mmol) was dissolved in dry DCM (40 mL), then $MgSO_4$ (2.70 g) was added and the mixture was stirred for 10 mins. The solid was removed by filtration and washed with dry DCM. The organic solution was then transferred to a dropping funnel and slowly added to the mixture containing the cyanomethylated amine at 0 ^{o}C. After all of the solution had been added, the flask was stirred at room temperature for 2 h. Reaction mixture was then washed with sat. sodium thiosulfate (2 x 50 mL), sat. $NaHCO_3$ (2 x 50 mL) and water (2 x50 mL). Aqueous layer was then extracted with DCM (50 mL). Combined organics were then dried over $MgSO_4$ and concentrated in vacuo to give a yellow solid (1 57 g, 91%), which was used immediately in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (s, 1H), 6.68 (s, 1H), 7.15-7.40 (m, 10H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 83.3 (CH), 107.2 (CH), 127.7 (CH), 129.5 (CH), 133.8 (C), 138.4 (C).

In accordance with literature data.[8]



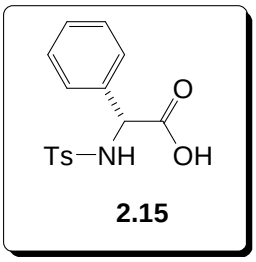
2.13

N-Benzhydryl-hydroxylamine: Following a procedure by Fukuyama et al.[8] Hydroxylamine hydrochloride (3.02 g, 43.40 mmol) was added to a stirred solution of nitrone **2.20** (2.05 g, 8.68 mmol), in methanol (30 mL) and the mixture was stirred at 60 ^{o}C for 24 h. The solution was allowed to cool to room

temperature and then concentrated in vacuo. DCM (20 mL) was added and the solution was filtered through celite. The filtrate was washed with $NaHCO_3$ (2 x 30 mL) and the aqueous layer was extracted with DCM (50 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give a yellow oil which was then purified by column chromatography on silica gel (15 x 3 cm) with a petroleum ether-ethyl acetate mixture (4:1) to give a pale yellow oil (0.46 g, 35%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (s, 1H), 5.65 (NH), 7.29-7.45 (m, 10H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 70.7 (CH), 127.4, (CH), 127.5 (CH), 129.0 (CH), 140.6 (C).

In accordance with literature data.[8]

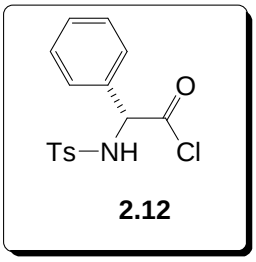
5.1.4 Synthesis of ligand 2.3:



2.15

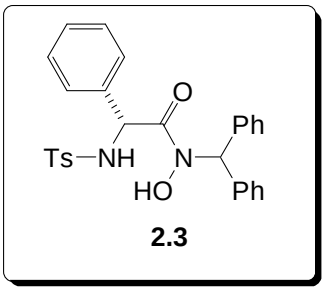
Phenyl-(toluene-4-sulfonylamino)-acetic acid: Following a procedure by Malkov et al,[9] A solution of tosyl chloride (1.37 g, 7.20 mmol) in ether (12 mL) was added drop-wise to a solution of amino acid (0.9 g, 6.0 mmol) and NaOH (0.6 g, 15 mmol) in water (12 mL) at room temperature. The mixture was stirred for 16 h and then acidified to pH ~ 2 with 12 M HCl to produce a white precipitate. Precipitate was then separated by filtration and washed with water to give a white solid. (0.88 g, 48%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.38 (s, 3H), 4.92 (d, J = 9.1 Hz, 1H), 7.29-7.35 (m, 7H), 7.66 (d, J = 8.2 Hz, 2H), 8.68 (d, J = 9.1 Hz, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 20.9 (CH_3), 59.5 (CH), 126.5 (CH), 127.3 (CH), 127.9 (CH), 128.3 (CH), 129.2 (CH), 136.6 (C), 138.2 (C), 142.4 (C), 171.0 (C).

In accordance with literature data.[9]



2.12

(R)-(-)-Phenyl-(toluene-4-sulfonylamino)-acetyl chloride: Following a procedure by Malkov et al,[9] PCl_5 (0.40 g, 1.90 mmol) was added portion-wise to a stirred solution of N-protected acid **2.15** (0.50 g, 1.60 mmol) in dry THF (5 mL). After stirring at room temperature for 2 h, n-hexane (18 mL) was added and the mixture was left in a freezer overnight. The precipitated crystals were quickly separated by filtration, washed with n-hexane and used immediately in the next step.



2.3

(R)-(-)-N-Benzhydryl-N-hydroxy-2-phenyl-2-(toluene-4-sulfonylamino)-acetamide: Following a procedure by Malkov et al,[9] Acid Chloride **2.12** (0.35 g, 1.09 mmol) in dry THF (4 mL) was added to a solution of hydroxylamine **2.13** (0.22 g, 1.09 mmol) in dry THF (3 mL) at 0 ^{o}C. This was then warmed to room temperature and stirred for 2 h. Reaction was quenched by a 10 % Na_2CO_3 solution (150 μL). A sat. solution NH_4Cl (20 mL) was then added and mixture was extracted with DCM (2 x 30 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give a yellow oil which was then purified by column chromatography on silica gel (15 x 3 cm) with a petroleum ether-ethyl acetate mixture (4:1) to give a pale yellow solid (0.21 g, 40%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 5.57 (d, *J* = 7.3 Hz, 1H), 6.04 (d, *J* = 8.3 Hz,

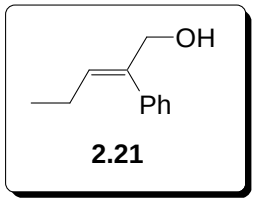
1H), 6.77 (d, *J* = 7.3 Hz, 1H), 6.96-7.28 (m, 17 H), 7.47 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.6 (CH_3), 57.5 (CH), 63.1 (CH), 127.1 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 128.6 (CH), 128.8 (CH), 128.9 (CH), 129.5 (CH), 136.0 (C), 137.0 (C), 137.2 (C), 143.2 (C), 169.2 (C).

In accordance with literature data.[9]

5.2 Synthesis of allylic alcohols:

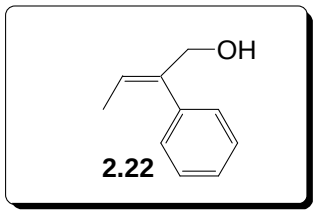
General procedure for copper grignard addition to alkynes:

Mg turnings (0.72 g, 29.73 mmol) and 4 crystals of iodine were added to a three-neck flask. This was then heated gently until the iodine sublimed producing a purple vapour. Into a dropping funnel was added 6 mL of dry ether and bromobenzene (3.10 mL, 29.73 mmol). This was then added slowly to the magnesium and was warmed with the palm of the hand until reaction started. 9 mL of dry ether was then added slowly and reaction was refluxed for 15 mins. The reaction mixture was then cooled over an ice bath. A solution alkyne-1-ol (1.1 mL, 11.89 mmol) in ether (6 mL) was added to the dropping funnel and then added dropwise to a cooled reaction mixture followed by addition of copper iodide (0.23 g, 1.19 mmol). The reaction mixture was then warmed to room temperature and stirred for 48 h. Then it was hydrolysed with saturated NH_4Cl (20 mL) at 0 ^{o}C and the two layers were separated. The organic layer was washed with 4M HCl solution (2 x 20 mL) and the combined organic phase was dried over $MgSO_4$ and concentrated to give a brown liquid which was purified by column chromatography on silica gel (15 x 3 cm) with a petroleum ether-ethyl acetate mixture (10:1).



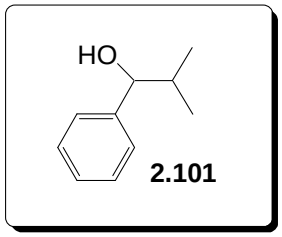
2.21

2-Phenyl-pent-2-en-1-ol: Alcohol **2.21** was prepared from 2-pentyne-1-ol (1.1 mL, 11.89 mmol) and bromobenzene (5.30 mL, 50.13 mmol) as a yellow oil (1.34 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t , *J* = 7.5 Hz, 3H), 1.73 (bs, OH), 2.00-2.10 (dt, *J* = 7.5 Hz, 7.5 Hz, 2H), 4.34 (d, *J* = 1.0 Hz, 2H), 5.72-5.77 (m, 1H), 7.23-7.41 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.4 (CH3), 22.0 (CH2), 68.1 (CH2), 127.3 (CH), 127.9 (CH), 128.5 (CH), 130.9 (CH), 138.5 (C) 139.6 (C); IR (NaCl) 3602.4 (OH), 3022.9 (C=C-H), 2965.9 (C-H), 1599.7 (C=C); MS (EI), *m/z* (%) 162.1 (M^+ 11), 145.1 (43), 129.1 (54), 105.1 (100), 91.1 (88), 77.1 (60).



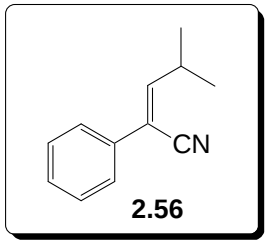
2.22

2-Phenyl-but-2-en-1-ol: Alcohol **2.22** was prepared as above from 2-butyne-1-ol (1.5 mL, 20.05 mmol) and bromobenzene (5.30 mL, 50.13 mmol) as a yellow oil (0.40g, 14%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68 (dt, *J* = 6.9 Hz, 1.2 Hz, 3H), 4.35 (s, 2H), 5.87 (q, *J* = 6.9 Hz, 1H), 7.25-7.44 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.4 (CH_3), 68.1 (CH_2), 123.5 (CH), 127.5 (aromatic CH), 128.4 (aromatic CH), 128.8 (aromatic CH), 138.3 (C), 141.0 (C); IR (NaCl) 3263.9 (NH), 3401.8 (OH), 2917.8 (C-H), 2253.4 (C=C); MS (EI), *m/z* (%) 148.1 (M^+ 48), 137.1 (78), 105.1 (100), 51.0 (66).



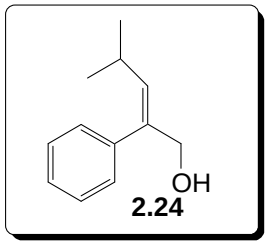
2.101

2-Methyl-1-phenyl-propan-1-ol: Compound **2.101** was prepared from Isobutyraldehyde (1.80 mL, 20.05 mmol) and bromobenzene (5.30 mL, 50.13 mmol) as a yellow oil (1.97g, 66%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.92-2.03 (m, 1H), 2.12 (bs, OH), 4.35 (dd, *J* = 6.8 Hz, 1.8 Hz, 1H), 7.27-7.39 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.4 (CH_3), 19.2 (CH_3), 35.3 (CH), 80.1 (CH), 126.7 (aromatic CH), 127.3 (aromatic CH), 128.2 (aromatic CH), 143.7 (C).
In accordance with literature data.[10]



2.56

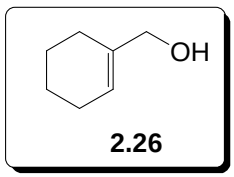
4-Methyl-2-phenyl-pent-2-enenitrile: Following a procedure by El Gharbi et al,[11] a mixture of phenylacetonitrile (0.23 mL, 117.10 mmol), potassium carbonate (0.3 g, 138.21 mmol), methanol (5 mL) and isobutyraldehyde (0.18 mL, 72.11 g) was stirred vigorously at 65 ^{o}C for 4 h. After completion of reaction, the mixture was filtered and solvent was evaporated to give an orange oily solid (0.36 g, 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, *J* = 6.7 Hz, 6H), 3.06-3.16 (m, 1H), 6.67 (d, *J* = 10.1 Hz, 1H), 7.35-7.45 (m, 3H), 7.55-7.58 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.2 (2 x CH_3), 32.0 (CH), 113.6 (C), 116.6 (C), 125.7 (CH), 129.1 (2 x CH), 133.2 (C), 153.5 (CH); IR (NaCl) 3032.5 (C=C-H), 2968.9 (C-H), 2253.4 (CN); MS (CI), *m/z* (%) 172.2 ((M + H)$^{+}$ 100), 69.11 (24); HRMS (CI) 172.1124 ($C_{12}H_{14}N$ requires 172.1126).



2.24

4-Methyl-2-phenyl-pent-2-en-1-ol: Following a procedure by Kimura et al,[12] a 1M solution of DIBAL-H in hexanes (1.60 mL, 1.60 mmol) was added to a solution of phenylisopropylacrylonitrile **2.56** (0.3 g, 1.75 mmol), in hexane (2 mL) at –30 ^{o}C over 20 mins. After 2h at 0 ^{o}C, the reaction mixture was poured into ice-cold 3M H_2SO_4 ensuring the mixture remained below 10 ^{o}C. The resulting solution was stirred at 0 ^{o}C for 42 mins and then at 60 ^{o}C for 19 h. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (50 mL). The combined organic layers were washed with saturated $NaHCO_3$ (3 x 30 mL), Organics were then dried over $MgSO_4$ and concentrated to give a yellow oil which was purified by column chromatography on silica gel (15 x 3 cm) with a petroleum ether-ethyl acetate mixture (4:1) to give a yellow oil (0.13g, 74%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.6 Hz, 6H), 1.45 (bt, *J* = 5.0 Hz, OH), 2.25-2.35 (m, 1H), 4.20 (d, *J* = 4.5 Hz, 2H), 5.44 (dt, *J* = 10.1 Hz, 1.1 Hz, 1H), 7.11-7.31 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.2 (2 x CH_3), 27.6 (CH), 68.2 (CH_2), 127.1 (aromatic CH), 128.4 (aromatic CH), 128.5 (aromatic CH), 136.2 (CH), 137.9 (C), 138.9 (C).

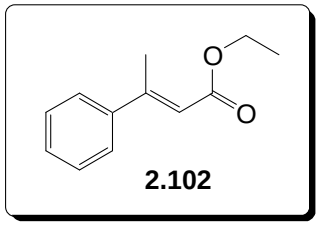
In accordance with literature data.[12]



2.26

Cyclohex-1-enyl-methanol: A 1M solution of DIBAL-H in hexanes (4.50 mL, 4.50 mmol) was added to a solution of cyclohexene-1-carboxaldehyde (0.52 mL, 4.54 mmol) in dry ether (3.5 mL) at 0 ^{o}C. The mixture was allowed to warm to room temperature and was stirred for 20 h. Then, the mixture was diluted with ether (6.5 mL), cooled to 0 ^{o}C, and quenched by a careful addition

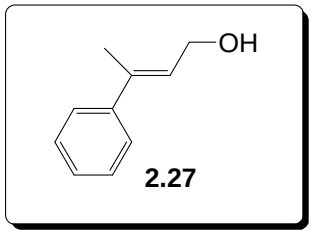
of Brine (6.5 mL), followed by a dropwise addition of 4M HCl (6.5 mL). The aqueous layer was extracted with ether (3 x 20 mL), the combined organic phase was dried over $MgSO_4$ and concentrated to give a yellow oil. (0.5 g, 98%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47-1.62 (m, 4H), 1.91-1.99 (m, 4H), 3.90 (s, 2H), 5.60 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.5 (CH_2), 22.5 (CH_2), 24.9 (CH_2), 25.6 (CH_2), 67.7 (CH_2), 123.0 (CH), 137.6 (C).
In accordance with literature data.[13]



2.102

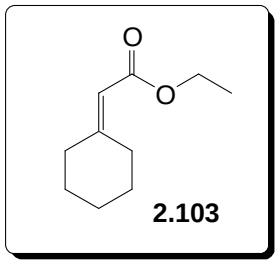
3-Phenyl-but-2-enoic acid ethyl ester: Following a procedure by Kakinuma et al[14], to a solution of ethyl(triphenylphosphoranyl)acetate (8.70 g, 25.0 mmol), in dry toluene (25 mL) was added acetophenone (1.40 mL, 12.30 mmol) in dry toluene (13 mL). The mixture was stirred at 70 ^{o}C for 10 days. The solvent was then removed under reduced pressure. The residue was purified by column chromatography on silica gel (15 x 3 cm) with a petroleum ether-ethyl acetate mixture (50:1 to 20:1) to give a colourless oil (0.40g, 17%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.2 Hz, 3H), 2.60 (s, 3H), 4.25 (q, *J* = 7.2 Hz, 2H), 6.19 (s, 1H), 7.34-7.54 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.0 (CH_3), 27.2 (CH_3), 59.8 (CH_2), 117.8 (CH), 126.8 (aromatic CH), 127.8 (aromatic CH), 127.9 (aromatic CH), 140.9 (C), 155.5 (C), 166.0 (C); MS (EI), *m/z* (%) 190.1 ((M^+) 79), 145.1 (99), 115.1 (65) 91 (29); HRMS (EI) 190.0993 ($C_{12}H_{14}O_2$ requires 190.0994).

In accordance with literature data.[15]



2.27

3-Phenyl-but-2-en-1-ol: A 1M solution of DIBAL-H in hexanes (4.20 mL, 4.20 mmol) was added to a solution of ester **2.102** (0.4 g, 2.09 mmol) in dry ether (2 mL) at 0 ^{o}C. The mixture was allowed to warm to room temperature and was stirred for 20 h. Then, the mixture was diluted with ether (6.5 mL), cooled to 0 ^{o}C, and quenched by careful addition of brine (6.5 mL), followed by a dropwise addition of 4M HCl (6.5 mL). The aqueous layer was extracted with ether (3 x 20 mL) and the combined organics were dried over $MgSO_4$ and concentrated to give a sticky white oil. (0.23 g, 74%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (s, 3H), 2.43 (s, OH), 4.23 (d, *J* = 6.5 Hz, 2H), 5.86 (dd, *J* = 6.5 Hz, 5.7 Hz, 1H), 7.11-7.32 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.9 (CH_3), 58.7 (CH_2), 124.7 (CH), 125.6 (CH), 126.2 (CH), 127.2 (CH), 136.4 (C), 141.8 (C).
In accordance with literature data.[16]

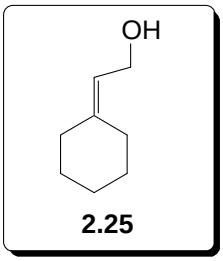


2.103

Cyclohexylidene-acetic acid ethyl ester: Following a procedure by Kulkarni et al,[17] a solution of cyclohexanone (1.30 mL, 13.99 mmol) was added to a solution of ethyl(triphenylphosphoranyl)acetate (4.40 g, 12.70 mmol) in *p*-xylene (10 mL) and the mixture was heated at reflux for 24 h. The solvent was then removed under reduced pressure. The residue was purified by column chromatography on silica gel (15 x 3 cm) with a petroleum ether-ethyl acetate mixture (10:1) to give a colourless oil (1.54g, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.1 Hz, 3H), 1.55-1.68 (m, 6H), 2.15-2.22 (m, 2H), 2.80-2.85 (m, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 5.58 (s, 1H); ^{13}C NMR (100.6 MHz,

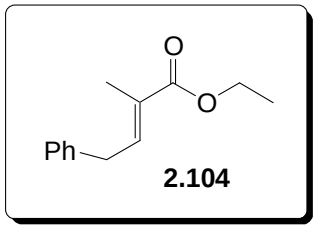
$CDCl_3$) δ 14.2 (CH_3), 26.0 (CH_2), 27.8 (CH_2), 28.6 (CH_2), 29.8 (CH_2), 38.0 (CH_2), 59.4 (CH_2), 113.0 (CH), 163.5 (C), 166.8 (C); MS (EI), *m/z* (%) 168.15 ((M^+) 100), 140.10 (47), 123.10 (80) 105.09 (74), 83.96 (83), 80.07 (36); HRMS (EI) 168.1154 ($C_{10}H_{16}O_2$ requires 168.1150).

In accordance with literature data.[17]



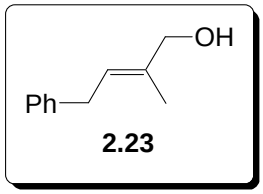
2.25

2-2Cyclohexylidene-ethanol: A 1M solution of DIBAL-H in hexanes (18.30 mL, 18.30 mmol) was added to a solution of ester **2.103** (1.54 g, 9.16 mmol) in dry ether (8.80 mL) at 0 ^oC. The mixture was allowed to warm to room temperature and was stirred for 20 h. Then, the mixture was diluted with ether (10 mL), cooled to 0 ^oC, and quenched by careful addition of Brine (18 mL), followed by a dropwise addition of 4M HCl (18 mL). The aqueous layer was extracted with ether (3 x 50 mL) and the combined organics were dried over $MgSO_4$ and concentrated to give a sticky yellow oil. (0.94 g, 81%): ^1H NMR (400 MHz, $CDCl_3$) δ 1.41-1.51 (m, 6H), 2.00-2.05 (m, 2H), 2.07-2.13 (m, 2H), 2.49 (bs, OH), 4.04 (d, *J* = 7.1 Hz, 2H), 5.26 (tt, 7.1 Hz, 1.1 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.9 (CH_2), 26.8 (CH_2), 27.2 (CH_2), 27.6 (CH_2), 35.9 (CH_2), 57.0 (CH_2), 119.3 (CH), 142.9 (C); MS (EI), *m/z* (%) 126.1 ((M^+) 21), 108.1 (96), 93.1 (74) 55.1 (41), 54.1 (25); HRMS (EI) 126.1048 ($C_8H_{14}O$ requires 126.1045). In accordance with literature data.[17]



2.104

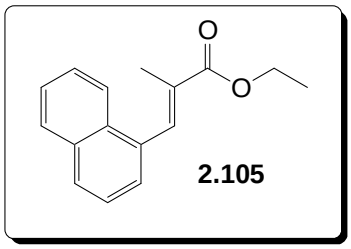
2-Methyl-4-phenyl-but-2-enoic acid ethyl ester: Phenylacetaldehyde (1.16 mL, 10.4 mmol) was added to a solution of (carbethoxyethylidene)triphenylphosphorane (3.77 g, 10.4 mmol) in dry toluene (10 mL) and was heated to reflux overnight. Reaction mixture was then evaporated. This was then purified by column chromatography on silica gel (15 x 3 cm) with a petroleum ether-ethyl acetate mixture (20:1) to give a pale yellow liquid (0.84 g, 40%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.1 Hz, 3H), 1.99 (s, 3H), 3.52 (d, *J* = 7.6 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 6.96 (td, 7.6 Hz, 1.3 Hz, 1H), 7.22-7.37 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.6 (CH_3), 14.3 (CH_3), 34.9 (CH_2), 60.6 (CH_2), 126.4 (CH), 128.6 (C), 128.6 (CH), 128.7 (CH), 139.1 (C), 140.1 (CH), 168.1 (C); IR (NaCl) 3029.6 (C=C-H), 2984.3 (C-H), 1704.8 (C=O), 1257.4 (C-O); MS (EI), *m/z* (%) 131.1 (100), 91.1 (75), 204.1 ($(M + H)^+$ 68), 129.1 (50), 159.1 (33); HRMS (EI) 204.1149 ($C_{13}H_{16}O_2$ requires 204.1150).



2.23

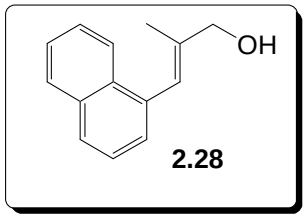
2-Methyl-4-phenyl-but-2-en-1-ol: A 1M solution of DIBAL-H in hexanes (8.30 mL, 8.30 mmol) was added to a solution of ester **2.104** (0.84g, 4.13 mmol) in dry ether (4 mL) at 0 ^{o}C. The mixture was allowed to warm to room temperature and stirred for 20 h. Then, the mixture was diluted with ether (12 mL), cooled to 0 ^{o}C and quenched by careful addition of brine (12 mL), followed by a drop-wise addition of 4M HCl (12 mL). The aqueous layer was extracted with ether (3 x 20 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. This was then purified by column chromatography on silica gel (15 x 3 cm) with a petroleum ether-ethyl acetate mixture (4:1) to give a colourless

liquid (0.23 g, 82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (s, 3H), 2.05 (bs, OH), 3.46 (d, *J* = 7.3 Hz, 2H), 4.08 (s, 2H), 5.67 (d, *J* = 7.3 Hz, 1H), 7.22-7.38 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.9 (CH_3), 34.0 (CH_2), 70.0 (CH_2), 124.7 (CH), 126.0 (CH), 128.5 (CH), 128.6 (CH), 135.7 (C), 141.0 (C); IR (NaCl) 3378.7 (OH), 3028.7 (R-C=CH), 2917.8 (C-H), 1602.6 (C=C); MS (EI), *m/z* (%) 131.1 (100), 91.0 (70), 83.9 (47), 129.0 (34), 162.1 ($(M + H)^+$ 26).



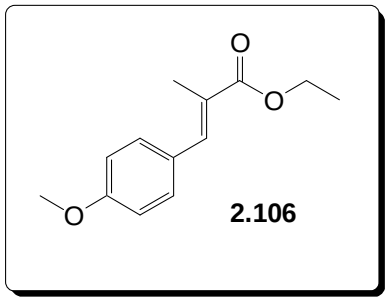
2.105

2-Methyl-3-naphthalen-1-yl-acrylic acid ethyl ester: 1-naphthaldehyde (1.30 mL, 9.60 mmol) was added to a solution of (carbethoxyethylidene)triphenylphosphorane (3.48 g, 9.60 mmol) in dry toluene (10 mL) and was heated to reflux overnight. Reaction mixture was then evaporated. This was then purified by column chromatography on silica gel (15 x 3 cm) with a petroleum ether-ethyl acetate mixture (20:1) to give a yellow liquid (2.30 g, 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.2 Hz, 3H), 1.89 (d, *J* = 1.5 Hz, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 7.31 – 7.43 (m, 4H), 7.69 – 7.87 (m, 3H), 8.10 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.3 (CH_3), 14.4 (CH_3), 61.0 (CH_2), 124.8 (CH), 125.0 (CH), 126.1 (CH), 126.4 (CH), 126.7 (CH), 127.0 (CH), 128.3 (CH), 133.3 (C), 133.4 (C), 137.3 (CH), 168.4 (C), 193.6 (C); IR (NaCl) 3061.4 (C=C-H), 2938.0 (C-H), 1702.8 (C=O), 1638.2 (C=C). 1272.8 (C-O); MS (EI), *m/z* (%) 240.0 (M^+ 53), 195.0 (22), 167.1 (100), 165.0 (65), 152.0 (40); HRMS (EI) 240.1147 ($C_{16}H_{16}O_2$ requires 240.1150).



2.28

2-Methyl-3-naphthalen-1-prop-2-en-1-ol: A 1M solution of DIBAL-H in hexanes (19.20 mL, 19.20 mmol) was added to a solution of ester **2.105** (2.30 g, 9.58 mmol) in dry ether (9 mL) at 0 ^{o}C. The mixture was allowed to warm to room temperature and stirred for 20 h. Then, the mixture was diluted with ether (20 mL), cooled to 0 ^{o}C and quenched by careful addition of brine (20 mL), followed by a drop-wise addition of 4M HCl (20 mL). The aqueous layer was extracted with ether (3 x 30 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give a cloudy white oil, which was used without further purification. (1.37 g, 69%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67 (d, *J* = 1.3 Hz, 3H), 1.79 (t, *J* = 6.1 Hz, OH), 4.23 (d, *J* = 5.3 Hz, 2H), 6.98 (s, 1H), 7.21 – 7.49 (m, 4H), 7.64 – 7.92 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.4 (CH_3), 68.5 (CH_2), 122.8 (CH), 125.3 (CH), 125.4 (CH), 125.8 (CH), 127.2 (CH), 127.5 (CH), 128.4 (CH), 132.0 (C), 133.6 (C), 134.8 (C), 139.5 (C); IR (NaCl) 3376.8 (OH), 3060.5 (R-C=CH), 2985.3 (C-H), 1663.3 (C=C); MS (EI), *m/z* (%) 198.0 (M^+ 50), 167.0 (33), 165.0 (65), 141.0 (100), 128.0 (40), 115.0 (16); HRMS (EI) 198.1047 ($C_{14}H_{14}O$ requires 198.1045).

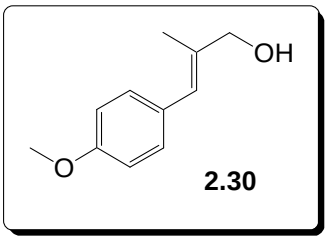


2.106

3-(4-Methoxy-phenyl)-2-methyl-acrylic acid ethyl ester: Anisaldehyde (0.50 mL, 4.14 mmol) was added to a solution of (carbethoxyethylidene)triphenylphosphorane (1.50 g, 4.14 mmol) in dry toluene (6 mL) and was heated to reflux overnight. Reaction mixture was then evaporated. This was then purified by column chromatography on silica gel (15

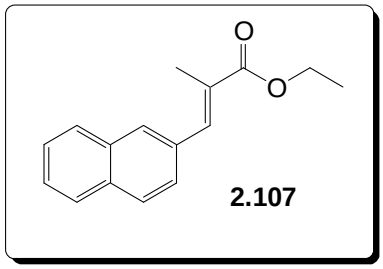
x 3 cm) with a petroleum ether-ethyl acetate mixture (20:1) to give a colourless liquid (0.88 g, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.1 Hz, 3H), 2.14 (d, *J* = 1.4 Hz, 3H), 3.84 (s, 3H), 4.28 (q, *J* = 7.1 Hz, 2H), 6.91 – 6.96 (m, 2H), 7.37 – 3.42 (m, 2H), 7.66 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.0 (CH_3), 14.4 (CH_3), 55.2 (CH_3), 60.8 (CH_2), 114.1 (CH), 126.4 (C), 128.6 (C), 131.4 (CH), 138.4 (CH), 159.6 (C), 168.9 (C).

In accordance with literature data.[18]



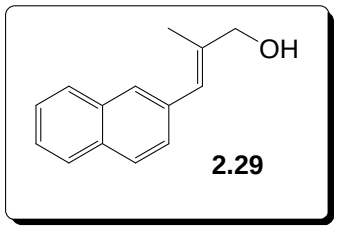
2.30

3-(4-Methoxy-phenyl)-2-methyl-prop-2-en-1-ol: A 1M solution of DIBAL-H in hexanes (8.00 mL, 8.0 mmol) was added to a solution of ester **2.106** (0.88 g, 4.01 mmol) in dry ether (4 mL) at 0 ^{o}C. The mixture was allowed to warm to room temperature and stirred for 20 h. Then, the mixture was diluted with ether (10 mL), cooled to 0 ^{o}C and quenched by careful addition of brine (10 mL), followed by a drop-wise addition of 4M HCl (10 mL). The aqueous layer was extracted with ether (3 x 20 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give a white solid, which was used without further purification (0.58 g, 81%): white solid, m.p = 35 – 38 ^{o}C (ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (t, *J* = 6.2 Hz, OH), 1.84 (d, *J* = 1.3 Hz, 3H), 3.74 (s, 3H), 4.10 (d, *J* = 5.5 Hz, 2H), 6.38 (s, 1H), 6.79 – 6.83 (m, 2H), 7.13 – 7.18 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.7 (CH_3), 53.6 (CH_3), 67.7 (CH_2), 112.0 (CH), 123.2 (CH), 128.4 (CH), 128.5 (C), 134.4 (C), 156.5 (C); IR (NaCl) 3414.4 (OH), 3004.6 (R-C=CH), 2956.3 (C-H), 1607.4 (C=C), 1442.5 (C-O); MS (EI), *m/z* (%) 178.0 (M^+ 38), 121.0 (100), 108.0 (22), 91.0 (16); HRMS (EI) 178.0993 ($C_{11}H_{14}O_2$ requires 178.0994).



2.107

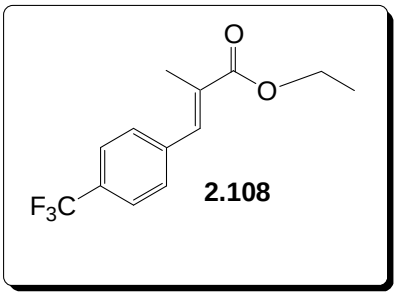
2-Methyl-3-naphthalene-2-yl-acrylic acid ethyl ester: 2-naphthaldehyde (1.50 g, 9.60 mmol) was added to a solution of (carbethoxyethylidene)triphenylphosphorane (3.48 g, 9.60 mmol) in dry toluene (10 mL) and was heated to reflux overnight. Reaction mixture was then evaporated. This was then purified by column chromatography on silica gel (15 x 3 cm) with a petroleum ether-ethyl acetate mixture (20:1) to give a yellow oil (2.15 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.2 Hz, 3H), 2.26 (d, *J* = 1.5 Hz, 3H), 4.35 (q, *J* = 7.1 Hz, 2H), 7.50 – 7.57 (m, 3H), 7.84 – 7.92 (M, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.3 (CH_3), 14.4 (CH_3), 61.0 (CH_2), 126.2 (CH), 126.5 (CH), 126.6 (CH), 127.9 (CH), 128.1 (CH), 128.6 (CH), 129.4 (CH), 132.7 (C), 133.0 (C), 133.2 (C), 138.5 (CH), 168.7 (C), 192.3 (C); IR (NaCl) 3059.5 (R-C=CH), 2983.3 (C-H), 1699.0 (C=O), 1632.5 (C=C), 1446.4 (C-O); MS (CI), *m/z* (%) 241.2 ((M + H)$^{+}$ 100), 240.2 (8); HRMS (CI) 241.1227 ($C_{16}H_{17}O_2$ requires 241.1229).



2.29

2-Methyl-3-naphthalen-2-yl-prop-2en-ol A 1M solution of DIBAL-H in hexanes (18.00 mL, 18.00 mmol) was added to a solution of ester **2.107** (2.15 g, 8.95 mmol) in dry ether (8 mL) at 0 ^{o}C. The mixture was allowed to warm to room temperature and stirred for 20 h. Then, the mixture was diluted with ether (20 mL), cooled to 0 ^{o}C and quenched by careful addition of brine (20 mL), followed by a drop-wise addition of 4M HCl (20 mL). The aqueous layer was extracted with ether (3 x 30 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give a white solid, which was used without further

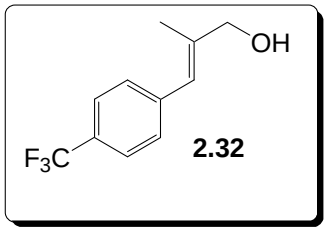
purification (1.31 g, 74%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 – 1.52 (m, OH), 1.92 (s, 3H), 4.18 (d, *J* = 5.1 Hz, 2H), 6.61 (s, 1H), 7.33 – 7.43 (m, 3H), 7.66 (s, 1H), 7.71 – 7.77 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.5 (CH_3), 69.1 (CH_2), 125.1 (CH), 125.2 (CH), 125.7 (CH), 127.4 (CH), 127.6 (CH), 127.6 (CH), 127.6 (CH), 127.9 (CH), 132.1 (C), 133.4 (C), 135.1 (C), 138.2 (C).
In accordance with literature data.[19]



2.108

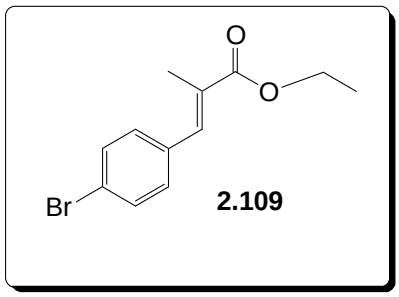
2-Methyl-3-(4-trifluoromethyl-phenyl)-acrylic acid ethyl ester: 4-(trifluoromethyl) benzaldehyde (1.20 mL, 5.41 mmol) was added to a solution of (carbethoxyethylidene)triphenylphosphorane (3.12 g, 8.61 mmol) in dry toluene (9 mL) and was heated to reflux overnight. Reaction mixture was then evaporated. This was then purified by column chromatography on silica gel (15 x 3 cm) with a petroleum ether-ethyl acetate mixture (20:1) to give a yellow liquid (2.09 g, 94%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, *J* = 7.1 Hz, 3H), 2.12 (s, 3H), 4.31 (q, *J* = 7.1 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.71 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.0 (CH_3), 14.3 (CH_3), 61.1 (CH_2), 125.2 (CH), 125.3 (C), 129.7 (CH), 130.9 (C), 136.9 (CH), 139.5 (C), 168.2 (C).

In accordance with literature data.[20]



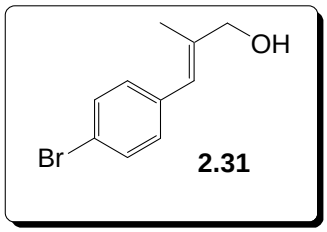
2-Methyl-3-(4-trifluoromethyl-phenyl)-prop-2-en-1-ol: A 1M solution of DIBAL-H in hexanes (16.20 mL, 16.20 mmol) was added to a solution of ester **2.108** (2.09 g, 8.09 mmol) in dry ether (9 mL) at 0 ^{o}C. The mixture was allowed to warm to room temperature and stirred for 20 h. Then, the mixture was diluted with ether (20 mL), cooled to 0 ^{o}C and quenched by careful addition of brine (20 mL), followed by a drop-wise addition of 4M HCl (20 mL). The aqueous layer was extracted with ether (3 x 30 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give a yellow cloudy oil, which was used without further purification (1.17 g, 67%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (s, 3H), 4.13 (s, 2H), 6.47 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (CH_3), 67.4 (CH_2), 122.4 (CH), 124.0 (C), 124.1 (CH), 128.0 (CH), 138.9 (C), 140.2 (C).

In accordance with literature data.[20]



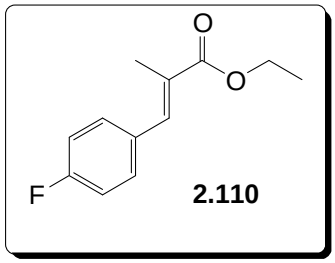
3-(4-Bromo-phenyl-2-methyl-acrylic acid ethyl ester: 4-bromobenzaldehyde (1.5 g, 8.10 mmol) was added to a solution of (carbethoxyethylidene)triphenylphosphorane (2.94 g, 8.10 mmol) in dry toluene (10 mL) and was heated to reflux overnight. Reaction mixture was then evaporated. This was then purified by column chromatography on silica gel (15 x 3 cm) with a petroleum ether-ethyl acetate mixture (20:1) to give a yellow liquid (2.04 g, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.0 Hz, 3H),

2.11 (d, *J* = 1.5 Hz, 3H), 4.29 (q, *J* = 7.0 Hz, 2H), 7.25 – 7.30 (m, 2H), 7.51 – 7.56 (m, 2H), 7.62 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1 (CH_3), 14.3 (CH_3), 61.0 (CH_2), 122.4 (C), 129.4 (C), 131.2 (CH), 131.6 (CH), 134.9 (C), 137.3 (CH), 168.4 (C); IR (NaCl) 3154.0 (R-C=CH), 2984.3 (C-H), 1701.9 (C=O), 1635.3 (C=C), 1446.4 (C-O); MS (EI), *m/z* (%) 268.0 (M^+ 43), 196.0 (28), 160.1 (15), 115.1 (100), 83.9 (21); HRMS (EI) 268.0101 ($C_{12}H_{13}O_2Br$ requires 268.0099).



2.31

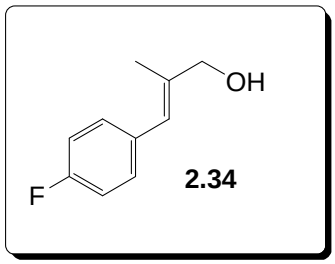
3-(4-Bromo-phenyl)-2-methyl-prop-2-en-1-ol: A 1M solution of DIBAL-H in hexanes (15.20 mL, 15.20 mmol) was added to a solution of ester **2.109** (2.04 g, 7.58 mmol) in dry ether (8 mL) at 0 ^{o}C. The mixture was allowed to warm to room temperature and stirred for 20 h. Then, the mixture was diluted with ether (20 mL), cooled to 0 ^{o}C and quenched by careful addition of brine (20 mL), followed by a drop-wise addition of 4M HCl (20 mL). The aqueous layer was extracted with ether (3 x 30 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give a white solid, which was used without further purification (1.14 g, 66%). White solid; m.p = 44 – 46 ^{o}C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (d, *J* = 4.9 Hz, OH), 1.80 (s, 3H), 4.10 (s, 2H), 6.39 (s, 1H), 7.07 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (CH_3), 67.7 (CH_2), 119.2 (C), 122.7 (CH), 129.5 (CH), 130.2 (CH), 135.4 (C), 137.5 (C); IR (NaCl) 3451.0 (OH), 3154.0 (R-C=CH), 2918.7 (C-H), 1588.1 (C=C); MS (EI), *m/z* (%) 226.0 (M^+ 87), 211.0 (30), 169.0 (100), 115.1 (97), 91.0 (68), 77.0 (40), 43.0 (23); HRMS (EI) 225.9990 ($C_{10}H_{11}OBr$ requires 225.9993).



2.110

3-(4-Fluoro-phenyl)-2-methyl-acrylic acid ethyl ester: 4-Fluorobenzaldehyde (1.5 g, 12.08 mmol) was added to a solution of (carbethoxyethylidene)triphenylphosphorane (4.38 g, 12.08 mmol) in dry toluene (15 mL) and was heated to reflux overnight. Reaction mixture was then evaporated. This was then purified by column chromatography on silica gel (15 x 3 cm) with a petroleum ether-ethyl acetate mixture (20:1) to give a yellow liquid (2.08 g, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3H), 2.00 (d, *J* = 1.4 Hz, 3H), 4.17 (q, *J* = 7.1 Hz, 2H), 6.95 – 7.01 (m, 2H), 7.25 – 7.31 (m, 2H), 7.55 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1 (CH_3), 14.5 (CH_3), 60.9 (CH_2), 115.5 (CH), 115.9 (CH), 128.4 (C), 131.2 (CH), 131.4 (CH), 137.5 (CH), 161.2 (C), 163.7 (C), 168.5 (C=O).

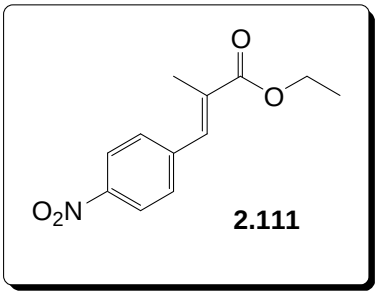
In accordance with literature data.[21]



2.34

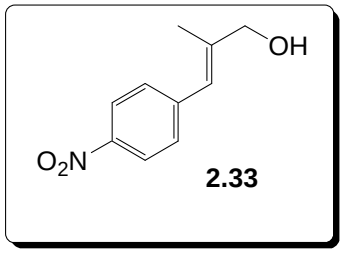
3-(4-Fluoro-phenyl)-2-methyl-prop-2-en-1-ol: A 1M solution of DIBAL-H in hexanes (20.00 mL, 20.00 mmol) was added to a solution of ester **2.110** (2.08 g, 9.99 mmol) in dry ether (10 mL) at 0 ^{o}C. The mixture was allowed to warm to room temperature and stirred for 20 h. Then, the mixture was diluted with ether (20 mL), cooled to 0 ^{o}C and quenched by careful addition of brine (20 mL), followed by a drop-wise addition of 4M HCl (20 mL). The aqueous layer was extracted with ether (3 x 30 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give a colourless liquid, which was used without

further purification (0.99 g, 60%): ^{1}H NMR (400 MHz, $CDCl_3$) δ1.76 (s, 3H), 2.38 (s, OH), 4.06 (s, 2H), 6.38 (s, 1H), 6.87 – 6.95 (m, 2H), 7.09 – 7.14 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.4 (CH3), 68.7 (CH2), 114.9 (CH), 115.1 (CH), 124.1 (CH), 130.4 (CH), 130.7 (CH), 133.6 (C), 137.5 (C), 161.1 (C); IR (NaCl) 3155.0 (OH), 3040.2 (R-C=CH), 2984.3 (C-H), 1601.6 (C=C), 1379.8 (C-F); MS (EI), *m/z* (%) 166.1 (M^+ 90), 151.1 (53), 133.1 (75), 109.1 (100), 96.1 (48), 95.0 (19); HRMS (EI) 166.0790 ($C_{10}H_{11}OF$ requires 166.0794).



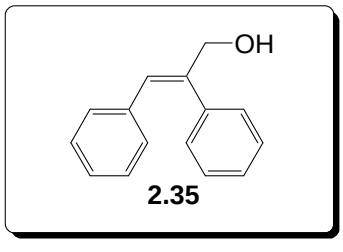
2.111

2-Methyl-3-(4-nitro-phenyl)-acrylic acid ethyl ester: p-nitrobenzaldehyde (1.5 g, 9.99 mmol) was added to a solution of (carbethoxyethylidene)triphenylphosphorane (3.62 g, 9.99 mmol) in dry toluene (12 mL) and was heated to reflux overnight. Reaction mixture was then evaporated. This was then purified by column chromatography on silica gel (15 x 3 cm) with a petroleum ether-ethyl acetate mixture (20:1) to give a yellow solid (2.06 g, 88%): Yellow solid; m.p = 40 – 44 ^{o}C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.2 Hz, 3H), 2.05 (s, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 7.44 – 7.48 (m, 2H), 7.62 (s, 1H), 8.16 – 8.20 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (CH_3), 14.3 (CH_3), 61.4 (CH_2), 123.7 (CH), 130.2 (CH), 132.3 (C), 136.0 (CH), 142.6 (C), 147.2 (C), 168.5 (C); IR (NaCl) 3155.0 (R-C=CH), 2985.3 (C-H), 1707.7 (C=O), 1640.2 (C=C), 1475.3 (C-O); MS (EI), *m/z* (%) 235.0 (M^+ 32), 190.0 (39), 161.0 (22), 117.9 (26), 115.0 (62), 84.9 (100), 47.0 (96); HRMS (EI) 235.0843 ($C_{12}H_{13}O_4N$ requires 235.0845).



2.33

2-Methyl-3-(4-nitro-phenyl)-prop-2-en-1-ol: A 1M solution of DIBAL-H in hexanes (17.50 mL, 17.50 mmol) was added to a solution of ester **2.111** (2.06 g, 8.76 mmol) in dry ether (9 mL) at 0 ^{o}C. The mixture was allowed to warm to room temperature and stirred for 20 h. Then, the mixture was diluted with ether (20 mL), cooled to 0 ^{o}C and quenched by careful addition of brine (20 mL), followed by a drop-wise addition of 4M HCl (20 mL). The aqueous layer was extracted with ether (3 x 30 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give a red oil, which was used without further purification (0.98 g, 58%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85 (s, 3H), 4.17 (s, 2H), 6.55 (s, 1H), 7.33 – 7.37 (m, 2H), 8.11 – 8.16 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.5 (CH_3), 68.2 (CH_2), 122.6 (CH), 123.6 (CH), 129.5 (CH), 141.9 (C), 144.5 (C), 146.1 (C); IR (NaCl) 3413.4 (OH), 3154.9 (R-C=CH_2), 2983.3 (C-H), 1650.8 (C=C), 1518.7 (C-NO_2); MS (CI), *m/z* (%) 194.1 ((M + H)$^{+}$ 100), 193.1 (20), 130.1 (10).



2.35

2,3-Diphenyl-prop-2-en-1-ol: Following a procedure by Rodriguez et al[22] $LiAlH_4$ (2.03 g, 53.5 mmol) was dissolved in dry diethyl ether (40 mL) and cooled to 0 ^{o}C. A solution of aluminium chloride (2.37 g, 17.80 mmol) in dry diethyl ether (30 mL) was then added to the mixture at 0 ^{o}C and stirred for 20 mins at this temperature before the addition in small portions of α-phenyl cinnamic acid (4.0 g, 17.8 mmol) at 0 ^{o}C. After the addition, the solution was allowed to warm to room temperature and was stirred overnight at this

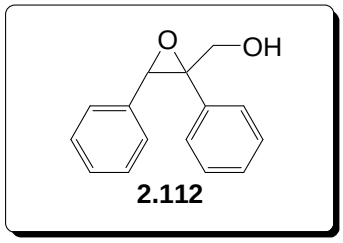
temperature. Then the reaction was quenched by the addition of small portions of $Na_2SO_4.10H_2O$. Then the mixture was filtered through celite and the residue washed with diethyl ether. The filtrate was concentrated in vacuo to afford a brown oil. Purification of the products was accomplished by column chromatography on silica gel (15 x 3 cm) with a 10:1 mixture of petroleum ether-ethyl acetate yielded a white solid (1.38 g, 37%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70 (t, *J* = 6.2 Hz, OH), 4.36 (dd, *J* = 6.2 Hz, 1.3 Hz, 2H), 6.60 (s, 1H), 6.90 – 7.28 (m, 10H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 68.5 (CH_2), 126.5 (CH), 126.9 (CH), 127.7 (CH), 128.2 (CH), 128.7 (CH), 129.1 (CH), 136.5 (C), 138.6 (C), 141.6 (C).

In accordance with literature data.[23]

5.3 Asymmetric epoxidations in aqueous solution:

General procedure for asymmetric epoxidation in water/toluene mixture:

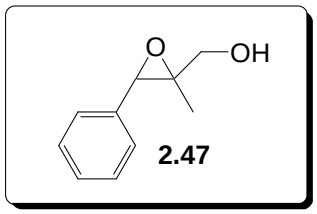
Following a procedure by Malkov et al,[24] ligand **2.1** (5.5 mol%) and vanadyl sulfate (5.0 mol%) were added to distilled water (2.25 mL) and toluene (0.75 mL) and stirred at room temperature. Allylic alcohol (1 mmol) was then added in one portion and the mixture was stirred at room temperature for 30 mins and then cooled to 0 ^{o}C. A 70% aqueous solution of *t*-BuOOH (0.15 mL) was added and the mixture was stirred at 0 ^{o}C overnight. The reaction mixture was then quenched with a concentrated solution of Na_2SO_3 (10 mL) and after stirring for 1 h at 0 ^{o}C it was extracted with DCM (3 x 20 mL), the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give a brown oil. Purification of the products was accomplished by column chromatography on silica gel (15 x 3 cm) with a 4:1 mixture of petroleum ether-ethyl acetate. The absolute configuration of the epoxide products was assigned by comparison of their optical rotations with the literature data; the enantiomeric excess was determined using analysis by chiral GC or HPLC.



2.112

(2,3-Diphenyl-oxiranyl)-methanol: Epoxide was isolated as a white solid: m.p = 73 – 75 ^{o}C (petroleum ether/ethyl acetate); $[\alpha]_D$ –65.2 (c = 1, DCM); chiral HPLC (Chiracel IB; 0.75 mL/min; hexane/2-propanol 90:10, $t_{R,R}$ = 9.27, $t_{S,S}$ = 9.99) showed 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (t, *J* = 6.2 Hz, OH), 3.96 (d, *J* = 6.2 Hz, 2H), 4.44 (s, 1H), 6.94-7.15 (m,10H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 60.8 (CH), 64.9 (CH_2), 69.2 (C), 126.6 (aromatic CH), 127.6 (aromatic CH), 127.7 (aromatic CH), 127.8 (aromatic CH), 127.9 (aromatic CH), 128.1 (aromatic CH), 134.3 (C), 134.7 (C).

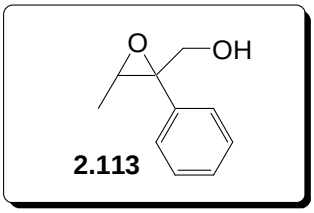
In accordance with literature data.[1]



2.47

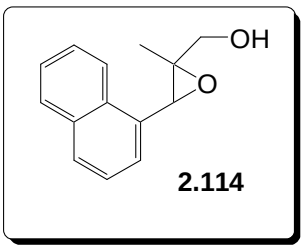
(2-Methyl-3-phenyl-oxiranyl)-methanol: Epoxide was isolated as a pale orange solid: m.p = 35 – 37 ^{o}C (petroleum ether/ethyl acetate); $[\alpha]_D$ + 9.4 (c = 1, DCM); chiral GC (Supelco α-Dex 120 column, oven temp. 110 ^{o}C for 2 mins, then 1 ^{o}C/min to 200 ^{o}C $t_{R,R}$ = 31.96, $t_{S,S}$ = 33.42) showed 90% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 3H), 2.10 (bs, OH), 3.68 (dd, *J* = 12.4 Hz, 6.6 Hz, 1H), 3.79 (d, *J* = 12.4 Hz, 1H), 4.14 (s, 1H), 7.18-7.32 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.5 (CH_3), 60.3 (CH), 63.9 (C), 65.0 (CH_2), 126.5 (aromatic CH), 127.6 (aromatic CH), 128.2 (aromatic CH), 135.3 (C).

In accordance with literature data.[1]



2.113

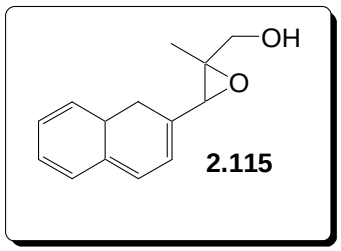
(3-Methyl-2-phenyl-oxiranyl)-methanol: Epoxidation of alcohol **2.22**: was isolated as a yellow oil; $[\alpha]_D$ + 33.5 (c = 1, DCM); chiral GC (Supelco β-Dex 120 column, oven temp. 110 ^oC for 2 mins, then 1 ^oC/min to 200 ^oC $t_{R,R}$ = 22.65, $t_{S,S}$ = 23.44) showed 91% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, *J* = 5.5 HZ, 3H), 2.02 (bq, *J* = 4.2 Hz, OH), 3.53 (q, *J* = 5.5 Hz, 1H), 3.91-4.02 (m, 2H), 7.31-7.42 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1 (CH_3), 56.9 (CH), 64.6 (CH_2), 66.0 (C), 127.0 (aromatic CH), 127.9 (aromatic CH), 128.4 (aromatic CH), 135.7 (C); IR (NaCl) 3449.1 (OH), 2966.0 (C-H), 2252.5 (C=C); MS (CI), *m/z* (%) 165.2 ($(M + H)^+$ 14), 147.2 (100), 121.1 (94), 85.2 (31), 69.1 (50); HRMS (CI) 165.0915 ($C_{10}H_{13}O_2$ requires 165.0916).



2.114

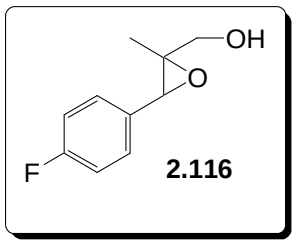
(2-Methyl-3-naphthalene-1-yl-oxiranyl)-methanol: Epoxidation of alcohol **2.28**: was isolated as a red solid, m.p = 62 – 65 ^oC (petroleum ether/ethyl acetate); $[\alpha]_D$ – 73.40 (c = 0.5, DCM); chiral HPLC (Chiracel IB; 0.70 mL/min; hexane/2-propanol 95:5, t(–) = 15.30, t(+) = 22.35) showed 83% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 3H), 2.02 (dd, *J* = 8.2 Hz, 4.9 Hz, OH), 3.91 – 3.93 (m, 2H), 4.61 (s, 1H), 7.39 – 7.48 (m, 4H), 7.71 – 7.75 (m, 1H), 7.80 – 7.88 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.9 (CH_3), 59.1 (CH), 63.8 (C), 64.9 (CH_2), 123.0 (CH), 124.1 (CH), 125.4 (CH), 126.0 (CH), 126.4 (CH), 127.8 (CH), 128.7 (CH), 130.9 (C), 131.9 (C), 133.2 (C); IR (NaCl) 3588.9 (OH), 3062.4 (epoxide-H), 2929.3 (C-H), 1598.7 (C=C); MS (EI), *m/z* (%)

214.1 (M^+ 16), 183.1 (66), 181.0 (19), 141.1 (29), 140.1 (100), 83.9 (26); HRMS (EI) 214.0990 ($C_{14}H_{14}O_2$ requires 214.0994).



2.115

[3-(1,8a-Dihydro-naphthalen-2-yl)-2-methyl-oxiranyl]-methanol: Epoxide **2.115** was isolated as an orange/red solid m.p = 78 – 80 ^oC (petroleum ether/ethyl acetate); $[\alpha]_D$ + 14.50 (c = 2, DCM); chiral Europium tris[3-(heptafluoro-propylhydroxymrthylene)-(+)-camphorate] showed 85% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 3H), 2.04 (dd, *J* = 8.7 Hz, 4.0 Hz, OH), 3.73 (dd, *J* = 12.4 Hz, 8.7 Hz, 1H), 3.82 (dd, *J* = 12.4 Hz, 4.0 Hz, 1H), 4.30 (s, 1H), 7.32 – 7.43 (m, 3H), 7.69 (s, 1H), 7.72 – 7.77 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.6 (CH_3), 60.4 (CH), 64.1 (C), 65.0 (CH_2), 124.3 (CH), 125.4 (CH), 126.0 (CH), 126.4 (CH), 127.8 (CH), 127.9 (CH), 127.9 (CH), 133.0 (C), 133.1 (C), 133.2 (C); IR (NaCl) 3585.0 (OH), 3060.5 (epoxide-H), 2929.3 (C-H), 1602.6 (C=C); MS (CI), *m/z* (%) 215.1 ($(M+H)^+$ 70), 197.1 (100), 185.1 (86), 157.1 (31), 69.1 (27); HRMS (CI) 215.1070 ($C_{14}H_{15}O_2$ requires 215.1072).



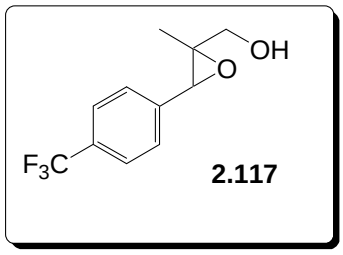
2.116

[3-(4-Fluoro-phenyl)-2-methyl-oxiranyl]-methanol: Epoxide **2.116** was isolated as a red oil; $[\alpha]_D$ + 8.40 (c = 1, DCM); chiral GC (Supelco β-Dex 120 column, oven temp. 110 ^oC for 2 mins, then 1 ^oC/min to 200 ^oC t(–) = 31.01, t(+) = 31.77) showed 84% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 3H), 2.40 (bs, OH), 3.67 (d, *J* = 12.5 HZ, 1H), 3.77 (d, *J* = 12.5 Hz, 1H), 4.11 (s, 1H), 6.93 – 6.99 (m, 2H), 7.16 – 7.21 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.4

(CH_3), 58.7 (CH), 62.8 (C), 63.8 (CH_2), 114.1 (CH), 114.2 (CH), 126.9 (CH), 127.0 (CH), 160.1 (C), 162.5 (C); IR (NaCl) 3626.5 (OH), 3155.0 (epoxide-H), 2965.0 (C-H), 1609.3 (C=C); MS (CI), *m/z* (%) 183.2 ($(M+H)^+$ 83), 165.2 (100), 157.1 (18), 125.1 (40), 69.1 (31); HRMS (CI) 183.0818 ($C_{10}H_{12}O_2F$ requires 183.0821).

General procedure for the asymmetric epoxidation in water:

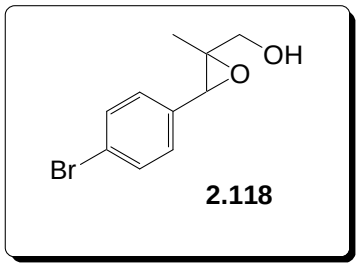
Following a literature protocol,[24] ligand **2.1** (5.5 mol%) and vanadyl sulfate (5.0 mol%) were added to distilled water (3 mL) and stirred at room temperature. Allylic alcohol (1 mmol) was then added in one portion and the mixture was stirred at room temperature for 30 mins and then cooled to 0 ^oC or – 20 ^oC. A 70% aqueous solution of *t*-BuOOH (0.15 mL) was added and the mixture was stirred at the same temperature for 2 d. The reaction mixture was then quenched with a concentrated solution of Na_2SO_3 (10 mL) and after stirring for 1 h at 0 ^oC it was extracted with DCM (3 x 20 mL), the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give a brown oil. Purification of the products was accomplished by column chromatography on silica gel (15 x 3 cm) with a 4:1 mixture of petroleum ether-ethyl acetate. The absolute configuration of the epoxide products was assigned by comparison of their optical rotations with the literature data; the enantiomeric excess was determined using analysis by chiral GC or HPLC.



2.117

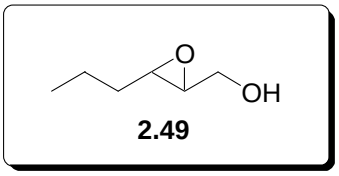
[2-Methyl-3-(4-trifluoromethyl-phenyl)-oxiranyl]-methanol: Epoxide was isolated as a white solid: m.p = 34 – 36 ^oC (petroleum ether/ethyl acetate); $[\alpha]_D$ + 7.80 (c = 0.5, DCM); chiral HPLC (Chiracel IB; 0.75 mL/min; hexane/2-

propanol 95:5, t(+) = 13.37, t(–) = 14.27) showed 87% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.88 (dd, *J* = 9.1 Hz, 4.1 Hz, OH), 3.71 (dd, *J* = 12.6 Hz, 9.1 Hz, 1H), 3.81 (dd, *J* = 12.6 Hz, 4.1 Hz, 1H), 4.19 (s, 1H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.5 (CH_3), 60.5 (CH), 64.0 (C), 64.6 (CH_2), 125.1 (CH), 125.1 (C), 125.2 (C), 126.8 (CH), 139.9 (C); IR (NaCl) 3566.7 (OH), 3154.0 (epoxide-H), 2999.7 (C-H), 1620.9 (C=C), 1325.8 (C-F); MS (CI), *m/z* (%) 233.1 ($(M + H)^+$ 100), 215.1 (72), 203.1 (40), 175.1 (9); HRMS (CI) 233.0788 ($C_{11}H_{12}O_2F_3$ requires 233.0789).



2.118

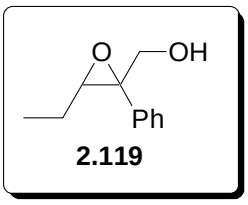
[3-(4-Bromo-phenyl)-2-methyl-oxiranyl]-methanol: Epoxide was isolated as a white solid: m.p = 73 – 75 ^{o}C (petroleum ether/ethyl acetate); $[\alpha]_D$ = 10.60 (c = 1, DCM); chiral HPLC (Chiracel IB; 0.75 mL/min; hexane/2-propanol 99:1, t(+) = 44.10, t(–) = 48.07) showed 87% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.90 (dd, *J* = 9.0 Hz, 4.3 Hz, OH), 3.67 (dd, *J* = 12.5 Hz, 9.0 Hz, 1H), 3.78 (dd, *J* = 12.5 Hz, 4.3 Hz, 1H), 4.10 (s, 1H), 7.09 – 7.13 (m, 2H), 7.40 – 7.43 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.5 (CH_3), 59.6 (CH), 63.8 (C), 64.7 (CH_2), 121.6 (C), 128.2 (CH), 131.3 (CH), 134.7 (C); IR (NaCl) 3599.5 (OH), 3155.0 (epoxide-H), 2987.2 (C-H), 1597.7 (C=C); MS (CI), *m/z* (%) 245.0 ($(M + H)^+$ 14), 227.0 (41), 185.0 (66), 107.1 (32), 94.1 (92); HRMS (CI) 243.0015 ($C_{10}H_{12}O_2Br$ requires 243.0021).



2.49

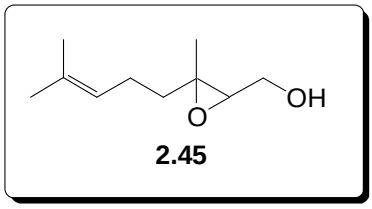
(3-Propyl-oxiranyl)-methanol: Epoxidation of trans-hexene-1-ol: was isolated as a red oil; $[\alpha]_D$ + 31.7 (c = 1, $CHCl_3$); the product was converted into the trifluoroacetate derivative for GC analysis; chiral GC (Supelco β-Dex 120 column, oven temp. 70 ^oC for 2 mins, then 1 ^oC/min to 200 ^oC $t_{S,S}$ = 14.66, $t_{R,R}$ = 15.00) showed 70% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.2 Hz, 3H), 1.33-1.52 (m, 4H), 1.78 (bs, OH), 2.84-2.92 (m, 2H), 3.56 (d, *J*= 12.5 Hz, 1H), 3.85 (d, *J* = 12.5 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.9 (CH_2), 19.3 (CH_3), 33.6 (CH), 55.9 (CH_2), 58.5 (CH_2), 61.7 (CH).

In accordance with literature data.[25]



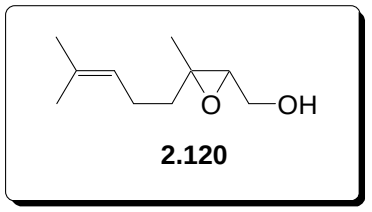
2.119

(3-Ethyl-2-phenyl-oxiranyl)-mathanol: Epoxidation of alcohol **2.21**: was isolated as a yellow oil; $[\alpha]_D$ + 28.9 (c = 1, CH_2Cl_2); chiral GC (Supelco β-Dex 120 column, oven temp. 110 ^oC for 2 mins, then 1 ^oC/min to 200 ^oC t(–) = 28.29, t(+) = 29.09) showed 78% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.5 Hz, 3H), 1.07-1.28 (m, 2H), 2.09 (dd, *J* = 8.2 Hz, 5.0 Hz, OH), 3.25 (t, *J* = 6.3 Hz, 1H), 3.82-3.92 (m, 2H), 7.20-7.35 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.1 (CH_3), 21.7 (CH_2), 62.3 (CH), 64.7 (CH_2), 66.2 (C), 126.9 (CH), 127.9 (CH), 128.3 (CH), 135.9 (C); IR (NaCl) 3459.7 (OH), 2972.7 (C-H); MS (CI), *m/z* (%) 161.2 (100), 121.2 (82), 179.2 ($(M + H)^+$ 60), 120.2 (16); HRMS (CI) 179.1074 ($C_{11}H_{15}O_2$ requires 179.1072).



2.45

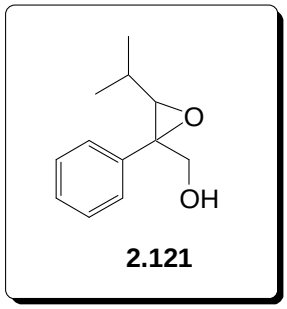
[3-Methyl-3-(4-methyl-pent-3-enyl)-oxiranyl]-methanol: Epoxidation of geraniol: was isolated as an orange oil; $[\alpha]_D$ = -2.1 (c = 1, DCM); chiral GC (Supelco α-Dex 120 column, oven temp. 100 ^oC for 2 mins, then 1 ^oC/min to 200 ^oC $t_{S,S}$ = 26.99, $t_{R,R}$ = 27.46) showed 50% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.40 (ddd, *J* = 16.5 Hz, 9.2 Hz, 7.6 Hz, 2H), 1.55 (s, 3H), 1.62 (s, 3H), 2.02 (q, *J* = 7.6 Hz, 2H), 2.91 (dd, *J* = 6.8 Hz, 4.2 Hz, 1H), 3.62 (dd. *J* = 12.1 Hz, 6.8 Hz, 1H), 3.77 (dd, *J* = 12.1 Hz, 4.2 Hz, 1H), 5.00 (t, *J* = 5.7 Hz, 1H). In accordance with literature data.[1]



2.120

[3-Methyl-3-(4-methyl-pent-3-enyl)-oxiranyl]-methanol: Epoxidation of nerol: was isolated as a pale yellow oil; $[\alpha]_D$ + 7.3 (c = 1, $CHCl_3$); the product was converted into the trifluoroacetate derivative for GC analysis; chiral GC (Supelco β-Dex 120 column, oven temp. 70 ^oC for 2 mins, then 1 ^oC/min to 200 ^oC $t_{S,R}$ = 39.23, $t_{R,S}$ = 39.50) showed 20% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.33-1.46 (m, 2H), 1.55 (s, 3H), 1.62 (s, 3H), 1.94-2.13 (m, 2H), 2.90 (dd, *J*= 6.8 Hz, 4.5 Hz, 1H), 3.75 (ddd, *J* = 11.7 Hz, 6.8 Hz, 4.5 Hz, 1H), 3.60 (ddd, *J* = 11.7 Hz, 6.8 Hz, 4.5 Hz, 1H), 5.00-5.06 (m, 1H).

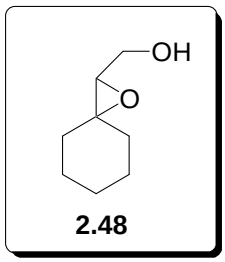
In accordance with literature data.[1]



2.121

(3-Isopropyl-2-phenyl-oxiranyl)-methanol: Epoxidation of alcohol **2.24**: was isolated as a red/brown oil; $[\alpha]_D$ + 14.3 (c = 1, $CHCl_3$); chiral GC (Supelco β-Dex 120 column, oven temp. 110 ^oC for 2 mins, then 1 ^oC/min to 200 ^oC t(–) = 35.06, t(+) = 36.27) showed 46% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 0.70 (d, *J* = 6.7 Hz, 3H), 0.92-0.99 (m, 1H), 0.96 (s, 3H), 1.90 (bs, OH), 2.92-3.40 (m, 1H), 3.90 (s, 2H), 7.22-7.30 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.8 (CH_3), 18.8 (CH_3), 26.1 (CH), 63.6 (CH_2), 65.4 (C), 65.8 (CH), 125.7 (aromatic CH), 126.8 (aromatic CH), 127.2 (aromatic CH), 135.0 (C).

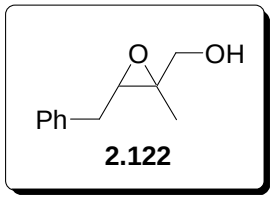
In accordance with literature data.[12]



2.48

(1-Oxa-spiro[2,5]oct-2-yl)-methanol: Epoxidation of alcohol **2.25**: was isolated as a colourless oil; $[\alpha]_D$ – 2.80 (c = 1, DCM); chiral GC (Supelco β-Dex 120 column, oven temp. 110 ^oC for 2 mins, then 1 ^oC/min to 200 ^oC t(–) = 18.37, t(+) = 18.75) showed 37 % ee; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (m, 8H), 1.60-1.72 (m, 2H), 2.92 (bs, OH), 2.90 (dd, *J* = 6.9 Hz, 4.3 Hz, 1H), 3.63 (dd, *J*= 12.1 Hz, 6.9 Hz, 1H), 3.79 (dd, *J* = 12.1 Hz, 4.3 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.9 (CH_2), 24.5 (CH_2), 28.5 (CH_2), 34.4 (CH_2), 60.0 (CH2), 62.3 (CH), 63.1 (C).

In accordance with literature data.[26]



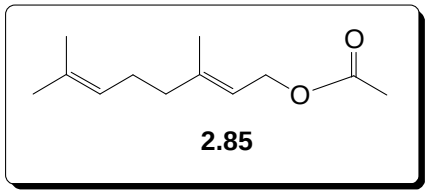
2.122

(3-Benzyl-2-methyl-oxiranyl)-methanol: Epoxidation of alcohol **2.23**: was isolated as a yellow oil; $[\alpha]_D$ + 12.5 (c = 1, CH_2Cl_2); chiral HPLC (Chiracel IB; 0.75 mL/min; hexane/2-propanol 90:10, t(+) = 10.58, t(–) = 11.30) showed 56% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.77 (dd, *J* = 8.5 Hz, 4.6 Hz, OH), 2.80 (dd, *J* = 14.7 Hz, 6.2 Hz, 1H), 2.89 (dd, *J* = 14.7 Hz, 6.5 Hz, 1H), 3.22 (t, *J* = 6.3 Hz, 1H), 3.52 (dd, *J* = 12.3 Hz, 8.5 Hz, 1H), 3.63 (dd, *J* = 12.3 Hz, 4.5 Hz, 1H), 7.15-7.28 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.5 (CH_3), 34.7 (CH_2), 60.3 (CH), 61.3 (C), 65.3 (CH_2), 126.7 (CH), 128.7 (CH), 128.8 (CH), 137.6 (C); IR (NaCl) 3446.2 (OH), 3030.6 (epoxide-H), 2928.4 (C-H); MS (EI), *m/z* (%) 91.0 (100), 103.0 (75), 121.1 (63), 78.0 (33), 147.1 (31), 43.0 (23), 178.1 ($(M + H)^+$ 12); HRMS (EI) 178.0997 ($C_{11}H_{14}O_2$ requires 178.0994).

5.4 Acetylation of homoallylic alcohols:

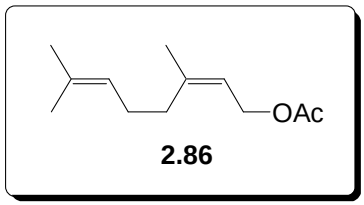
General procedure for acetylation of homo-allylic alcohols:

Following a procedure by Watson et al,[27] Et_3N (2.70 mL, 19.04 mmol) was added to a solution of alcohol (3.00 mL, 17.04 mmol) in dry DCM (15 mL) and mixture was cooled over an ice bath. Acetic anhydride (1.80 mL, 19.04 mmol) was then added and the resulting mixture was stirred at room temperature overnight. The solution was transferred to a separating funnel and washed with water (20 mL) and $NaHCO_3$ (2 x 20 mL). Combined aqueous layers were then extracted with DCM (20 mL). Combined organic extracts were then dried over $MgSO_4$ and concentrated in vacuo.



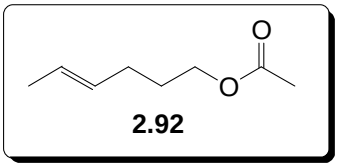
2.85

Geranyl acetate: Following the general procedure compound **2.85** was prepared from geraniol (3 mL, 17.04 mmol) as a pale yellow liquid (2.35 g, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 3H), 1.60 (s, 3H), 1.63 (s, 3H), 1.97 (s, 3H), 1.95-2.07 (m, 4H), 4.52 (d, *J* = 7.1 Hz, 2H), 4.99-5.04 (m, 1H), 5.27 (t, *J* = 7.1 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.4 (CH_3), 17.7 (CH_3), 21.0 (CH_3), 26.3 (CH_3), 26.6 (CH_2), 39.5 (CH_2), 61.4 (CH_2), 118.2 (CH_2), 123.4 (CH), 131.8 (CH), 142.2 (C), 171.1(C).
In accordance with literature data.[27]



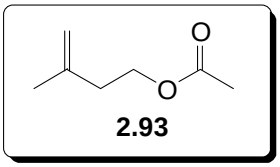
2.86

Neryl acetate: Following the general procedure, compound **2.86** was prepared from nerol (3 mL, 17.04 mmol) as a colourless liquid (2.31 g, 69 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 3H), 1.61 (s, 3H), 1.70 (s, 3H), 1.97 (s, 3H), 1.98-2.08 (m, 4H), 4.48 (dd, *J* = 7.2 Hz, 0.7 Hz, 2H), 4.98-5.05 (m, 1H), 5.29 (td, *J* = 7.3 Hz, 1.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.7 (CH_3), 21.1 (CH_3), 23.5 (CH_3), 25.7 (CH_3), 26.3 (CH_2), 32.2 (CH_2), 61.1 (CH_2), 119.1 (CH), 123.6 (CH), 132.2 (C), 142.7 (C), 171.1 (C).
In accordance with literature data.[28]



2.92

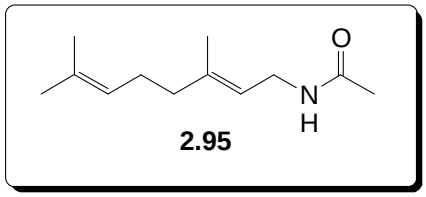
Acetic acid hex-4-enyl ester: Following the general procedure, compound **2.92** was prepared from 4-hexen-1-ol (3 mL, 25.46 mmol) as a colourless oil (2.59 g, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 – 1.65 (m, 5H), 1.94 – 1.99 (m, 5H), 3.98 (t, *J* = 6.70 Hz, 2H), 5.27 – 5.43 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.7 (CH_3), 19.9 (CH_3), 27.4 (CH_2), 27.9 (CH_2), 63.0 (CH_2), 124.8 (CH), 128.9 (CH), 170.2 (C); IR (NaCl) 3023.8 (R-C=CH), 2939.0 (C-H), 1741.4 (C=O), 1450.2 (C=C), 1041.4 (C-O); MS (CI), *m/z* (%) 143.2 ($(M + H)^+$ 100), 101.2 (12), 83.2 (83), 69.1 (22); HRMS (CI) 143.1069 ($C_8H_{15}O_2$ requires 143.1072).



2.93

Acetic acid 3-methyl-but-3-enyl ester: Following the general procedure, compound **2.93** was prepared from 3-methyl-3-butene-1-ol (1 mL, 9.86 mmol) as a yellow oil (0.36 g, 28%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68 (s, 3H), 1.95 (s, 3H), 2.26 (t, *J* = 6.9 Hz, 2H), 4.10 (t, *J* = 6.9 Hz, 2H), 4.65 (s, 1H), 4.72 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.2 (CH_2), 20.8 (CH_2), 35.5 (CH_3), 61.2 (CH_3), 110.8 (2 x CH), 140.5 (C), 169.5 (C); IR (NaCl) 3078.8 (R-C=CH), 2972.7 (C-H), 1734.7 (C=O), 1456.0 (C=C), 1044.3 (C-O); MS (CI), *m/z* (%) 129.3 ($(M + H)^+$ 100), 69.14 (93); HRMS (CI) 129.0911 ($C_7H_{13}O_2$ requires 129.0916).

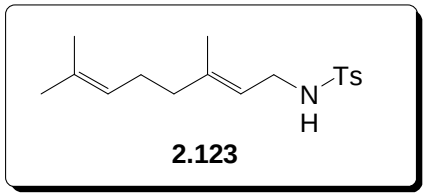
In accordance with literature data.[29]



2.95

Geranylamine acetate: Following the general procedure, compound **2.95** was prepared from geranylamine (0.5 mL, 2.70 mmol) as a yellow liquid (0.48g, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 3H), 1.66 (s, 3H), 1.68 (s, 3H), 1.97 (s, 3H), 1.98 – 2.12 (m, 4H), 3.84 (t, *J* = 6.1 Hz, 2H), 5.07 (t, *J* = 6.7 Hz, 1H), 5.19 (t, *J* = 6.7 Hz, 1H), 5.70 (bs, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.2 (CH_3), 17.7 (CH_3), 23.2 (CH_3), 25.7 (CH_3), 26.4 (CH_2), 37.6 (CH_2), 39.5 (CH_2), 119.9 (CH), 123.8 (CH), 131.7 (C), 139.9 (C), 169.9 (C); MS (CI), *m/z* (%) 196.5 ($(M + H)^+$ 100), 195.5 (7); HRMS (CI) 196.1703 ($C_{12}H_{22}ON$ requires 196.1701).

In accordance with literature data.[30]



2.123

N-(3,7-Dimethyl-octa-2,6-dienyl)-4-methyl-benzenesulfonamide: A solution of Et_3N (0.3 mL) in DCM (14 mL) was added toa stirred solution of geranylamine (0.3 mL, 1.63 mmol) in aq. 2M NaOH (2 mL). The mixture was cooled to 0 ^{o}C and a solution of tosyl chloride (0.31 g, 1.63 mmol) in DCM (9 mL) was added dropwise over 30 mins. This was then allowed to warm to room temperature and was stirred for 12 h. The resulting mixture was washed with 2M HCl (3 x 30 mL). Organic phase was dried over $MgSO_4$ and concentrated in vacuo to give an orange oil (0.45g, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 3H), 1.49 (s, 3H), 1.59 (s, 3H), 1.80 – 1.95 (m, 4H), 2.35 (s, 3H), 3.48 (t, *J* = 6.43 Hz, 2H), 4.38 (t, *J* = 5.7 Hz, 1H), 4.90 – 5.00 (m, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.3 (CH_3), 17.7 (CH_3), 21.6 (CH_3), 25.7 (CH_3), 26.2 (CH_2), 39.3 (CH_2), 41.0 (CH_2), 118.6 (CH),

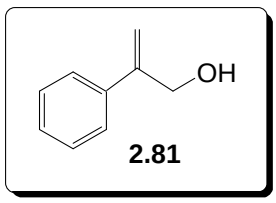
123.7 (CH), 127.2 (aromatic CH), 129.8 (aromatic CH), 131.9 (C), 137.1 (C), 141.0 (C), 143.4 (C); MS (EI), *m/z* (%) 307.3 (M^+ 8), 224.2 (11), 184.1 (56), 155.1 (61), 91.1 (100), 69.1 (74), 68.1 (33); HRMS (EI) 307.1609 ($C_{17}H_{25}O_2NS$ requires 307.1606).

In accordance with literature data.[31]

5.5 Formation of allylic alcohols using SeO_2:

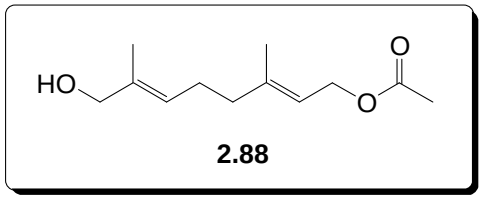
General procedure for Selenium oxidation:

Following a modified procedure by Sheldon et al,[32] *t*-BuOOH (1.20 mL, 14.31 mmol), SeO_2 (0.094 g, 085 mmol) and acetic acid (0.07 mL, 1.27 mmol) were stirred in DCM (13.2 mL) at room temperature for 30 mins. Substrate alkene (8.46 mmol) was then added and reaction mixture was stirred at room temperature for 20 h. After removal of solvent at reduced pressure, the residue was purified by column chromatography on silica gel (15 x 3 cm) with a 2:1 or 4:1 petroleum ether-ethyl acetate mixture.



2.81

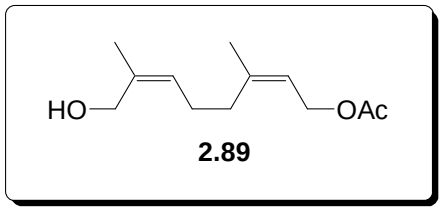
2-Phenyl-prop-2-en-1-ol: Compound **2.81** was prepared from α-methyl styrene as a colourless oil (1.10 mL, 8.46 mmol): ^1H NMR (400 MHz, $CDCl_3$) δ 1.97 (bs, OH), 4.55 (s, 2H), 5.37 (s, 1H), 5.50 (s, 1H), 7.30-7.51 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 64.9 (CH_2), 112.6 (CH_2), 126.1 (aromatic CH), 128.0 (aromatic CH), 128.6 (aromatic CH), 138.6 (C), 147.3 (C); IR (NaCl) 3375.8 (OH), 3058.6 (R-C=CH_2), 2925.5 (C-H), 1632.5 (C=C); MS (CI), *m/z* (%) 135.19 ($(M + H)^+$ 100), 117.17 (72), 69.11 (17); HRMS (CI) 135.0811 ($C_9H_{11}O$ requires 135.0810).



2.88

Acetic acid 8-hydroxy-3,7-dimethyl-octa-2,6-dienyl ester: Following a procedure by Kato et al,[33] compound **2.88** was prepared from *t*-BuOOH (0.60 mL, 7.15 mmol), selenium dioxide (0.005 g, 0.05 mmol), acetic acid (15 μL, 0.26 mmol) and geranyl acetate **2.85** (0.2 g, 3.85 mmol) as a colourless liquid (0.098 g, 45%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 3H), 1.64 (s, 3H), 1.97 (s, 3H), 1.97-2.15 (m, 4H), 3.91 (s, 2H), 4.52 (d, *J* = 7.1 Hz, 2H), 5.24-5.32 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.7 (CH_3), 16.4 (CH_3), 21.2 (CH_3), 25.7 (CH_2), 39.1 (CH_2), 61.4 (CH_2), 68.8 (CH_2), 118.4 (CH), 125.2 (CH), 135.3 (C), 141.8 (C), 171.3 (C).

In accordance with literature data.[33]



2.89

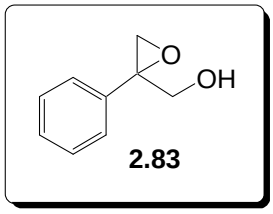
Acetic acid 8-hydroxy-3,7-dimethyl-octa-2,6-dienyl ester: Following a procedure by Kato et al,[33] compound **2.89** was prepared from *t*-BuOOH (0.60 mL, 7.15 mmol), selenium dioxide (0.005 g, 0.05 mmol), acetic acid (15 μL, 0.26 mmol) neryl acetate **2.86** (0.2 g, 3.85 mmol) as a colourless liquid (0.70 g, 32%): ^{1}H NMR (400 MHz, $CDCl_3$) δ1.59 (s, 3H), 1.70 (s, 3H), 1.88 (s, 3H), 2.06-2.11 (m, 4H), 3.92 (s, 2H), 4.50 (d, *J* = 7.2 Hz, 2H), 5.26-5.35 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.6 (CH_3), 20.1 (CH_3), 22.4 (CH_3), 24.9 (CH_2), 30.7 (CH_2), 60.2 (CH_2), 67.7 (CH_2), 118.5 (CH), 123.8 (CH), 134.6 (C), 140.9 (C), 170.2 (C).

In accordance with literature data.[34]

5.6 Asymmetric epoxidation in organic solvent:

General procedure for epoxidation in organic solvent:

Following a procedure by Malkov et al,[9] ligand **2.1** (1.8 mol%) and $(i\text{-PrO})_3VO$ (4.0 μL, 20 μmol) were dissolved in dry toluene (3 mL) under a nitrogen atmosphere and the resulting deep brown solution was stirred at room temperature for 30 mins. Allylic alcohol (1 mmol) was then added in one portion and the mixture was stirred at room temperature for a further 10 mins and then cooled to –20 ^{o}C. A 5M solution of *t*-BuOOH in nonane (0.3 mL) was added and the mixture was stirred at –20 ^{o}C overnight. The solution was then washed with water (10 mL), the aqueous phase was extracted with DCM (3 x 20 mL), the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give a red oil. Purification of the products was accomplished by column chromatography on silica gel (15 x 3 cm) with a 4:1 petroleum ether-ethyl acetate mixture. The absolute configuration of the epoxides were assigned by comparison of their optical rotations with the literature data; the enantiomeric excess was determined using chiral GC, HPLC or Europium tris[3-(heptafluoro-propylhydroxymrthylene)-(+)-camphorate .

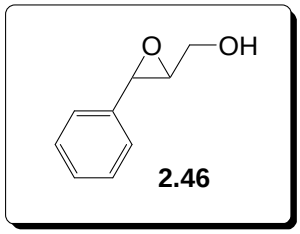


2.83

(2-Phenyl-oxiranyl)-methanol: Epoxidation of alcohol **2.81**: was isolated as a red/brown oil; $[\alpha]_D$ = +7.1 (c = 1, DCM); chiral GC (Supelco β-Dex 120 column, oven temp. 110 ^{o}C for 2 mins, then 1 ^{o}C/min to 200 ^{o}C t(–) = 31.60, t(+) = 33.12) showed 76% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99 (bs, OH), 2.75 (d, *J* = 5.3 Hz, 1H), 3.19 (d, *J* = 5.3 Hz, 1H), 3.93 (d, *J* = 12.6 Hz, 1H), 4.03 (d, *J* = 12.6 Hz, 1H), 7.20-7.34 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ

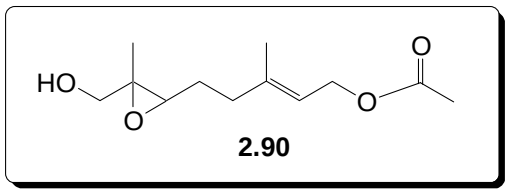
50.2 (CH_2), 58.1 (C), 60.7 (CH_2), 123.7 (CH), 125.9 (CH), 126.3 (CH), 137.1 (C).

In accordance with literature data.[35]



2.46

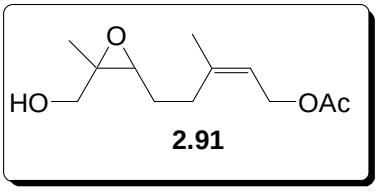
(3-Phenyl-oxiranyl)-methanol: Epoxide **2.46** was isolated as an orange solid mp = 29 - 31 ^{o}C: (petroleum ether/ethyl acetate); $[\alpha]_D$ + 10.2 (c = 1, DCM); chiral HPLC (Chiracel IB; 0.75 mL/min; hexane/2-propanol 95:5, $t_{S,S}$ = 23.70, $t_{R,R}$ = 25.87) showed 66% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (dd, *J* = 7.0 Hz, 5.6 Hz, OH), 3.15 (dt, *J* = 3.9 Hz, 2.3 Hz, 1H), 3.73 (ddd, *J* = 12.7 Hz, 4.8 Hz, 2.3 Hz, 1H)) , 3.86 (d, *J* = 2.1 Hz, 1H), 3.70-3.78 (m, 1H)), 7.18-7.30 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 54.5 (CH), 60.2 (CH_2), 61.4 (CH), 124.7 (CH), 127.3 (CH), 127.5 (CH), 135.6 (C). In accordance with literature data.[36]



2.90

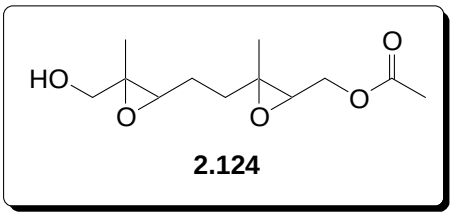
Acetic acid 5-(3-hydroxymethyl-3-oxiranyl)-3-methyl-pent-2-enyl ester: Epoxide **2.90** was isolated as a red oil; $[\alpha]_D$ – 8.80 (c = 0.5, DCM); chiral Europium tris[3-(heptafluoro-propylhydroxymrthylene)-(+)-camphorate] showed 50% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.65 (s, 3H), 1.58-1.70 (m, 2H), 1.99 (s, 3H), 2.03-2.23 (m, 2H), 2.95 (t, *J* = 6.2 Hz, 1H), 3.50 (d, *J* = 12.2 Hz, 1H), 3.60 (d, *J* = 12.2 Hz, 1H), 4.53 (d, *J* = 7.0 Hz, 2H), 5.35 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.3 (CH_3), 15.4 (CH_3), 20.0 (CH_3), 25.3 (CH_2), 35.1 (CH_2), 58.7 (CH), 60.0 (C), 60.2 (CH_2), 64.3 (CH_2), 118.1 (CH), 140.0 (C), 170.1 (C).

In accordance with literature data.[37]



2.91

Acetic acid 4-(3-hydroxymethyl-3-methyl-oxiranyl)-but-1-enyl ester: Epoxide **2.91** was isolated as a red oil; $[\alpha]_D$ – 6.40 (c = 0.25, DCM); chiral Europium tris[3-(heptafluoro-propylhydroxymrthylene)-(+)-camphorate] showed 62% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 3H), 1.55 – 1.69 (m, 2H), 1.72 (s, 3H), 1.98 (s, 3H), 2.17-2.23 (m, 2H), 2.96 (t, *J* = 6.3 Hz, 1H), 3.52 (d, *J* = 12.1 Hz, 1H), 3.60 (d, *J* = 12.1 Hz, 1H), 4.52 (d, *J* = 7.3 Hz, 2H), 5.34 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.2 (CH_3), 20.0 (CH_3), 22.3 (CH_3), 25.6 (CH_2), 27.7 (CH_2), 58.5 (CH), 59.9 (CH_2), 60.0 (C), 64.3 (CH_2), 119.1 (CH), 140.2 (C), 170.1 (C). In accordance with literature data.[38]



2.124

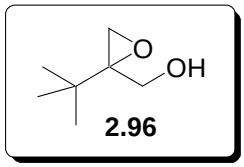
Acetic acid 3-[2-(3-hydroxymethyl-3-methyl-oxiranyl)-ethyl]-3-methyl-oxiranylmethyl ester: *m*-CPBA (0.045 g, 0.26 mmol) was added portionwise over 10 mins to a cooled to 0 ^{o}C solution of allylic alcohol **2.88** (0.05 g, 0.24 mmol) in DCM (4 mL). The reaction mixture was allowed to warm to room temperature and was stirred for 3 h. Reaction mixture was then diluted with DCM (50 mL), washed with a saturated solution of sodium thiosulfate (2 x 30 mL) and sat $NaHCO_3$ (3 x 30 mL). The combined aqueous layers were then back-extracted with DCM (2 x 30 mL) and combined organics were then dried over $MgSO_4$ and concentrated in vacuo to give a colourless oil (0.018 g, 31%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, *J* = 3.8 Hz, 3H), 1.27 (d, *J* = 5.3 Hz,

3H), 1.60 – 1.66 (m, 4H), 2.04 (s, 3H), 2.94 – 3.00 (m, 2H), 3.56 (t, *J* = 12.7 Hz, 2H), 3.97 (dt, *J* = 12.1 Hz, 6.5 Hz, 1H), 4.28 (ddd, *J* = 14.3 Hz, 12.2 Hz, 4.2 Hz, 1H).

One pot procedure for selenium oxidation followed by vanadium catalysed asymmetric epoxidation:

A 5-6 M solution of *t*-BuOOH in nonane (1.5 mmol) was added to dry toluene (3 mL) followed by addition of solid SeO_2 (0.1 mmol) and acetic acid (0.15 mmol). After stirring the resulting mixture for 30 mins at room temperature, substrate was added (1 mmol) and reaction mixture was stirred at room temperature overnight. Chiral ligand (6 mol%) and $VO(O\textit{i}\text{-}Pr)_3$ (2 mol%) were then added to the mixture and stirring continued for a further 30 mins. Then, the reaction mixture was cooled to –20 ^{o}C and 5 - 6 M *t*-BuOOH in nonane was added (1.5 mmol). The mixture was stirred at –20 ^{o}C for 48 h. Then, the mixture was allowed towarm to room temperature, quenched with water (10 mL) and extracted with DCM (3 x 25 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give a red oil. Purification of the products was accomplished by column chromatography on silica gel (15 x 3 cm) with a 4:1 mixture of petroleum ether-ethyl acetate. The absolute configuration of the epoxide products was assigned by comparison of their optical rotations with the literature data; the enantiomeric excess was determined using chiral GC, HPLC or Europium tris[3-(heptafluoro-propylhydroxymrthylene)-(+)-camphorate.

One-pot procedure for oxidation of compound 2.87:

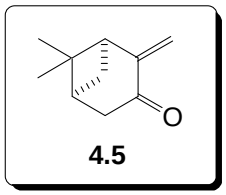


2.96

(2-tert-Butyl-oxiranyl)-methanol: A 5-6 M solution of *t*-BuOOH in nonane (0.3 mL, 1.5 mmol), SeO_2 (0.011 g, 0.1 mmol) and acetic acid (8 μL, 0.15 mmol) were added in succession to a solution of 2,3,3-trimethyl-1-butene (0.14 mL, 1 mmol) in dry toluene (4 mL), followed by addition of $VO(Oi\text{-}Pr)_3$ (4 μL, 20μmol) and a second portion of 5-6 M *t*-BuOOH in nonane (0.3 mL, 1.5 mmol). The reaction mixture was stirred overnight at room temperature. Then it was quenched with water (10 mL) and extracted with DCM (3 x 15 mL). Combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give the racemic product as a yellow oil. (0.051 g, 39%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.9 (s, 9H), 2.74 (d, *J* = 4.5 Hz, 1H), 2.82 (d, *J* = 4.5 Hz, 1H), 3.70 (d, *J* = 12.1 Hz, 1H), 3.84 (d, *J* = 12.1 Hz, 1H).

In accordance with literature data.[39]

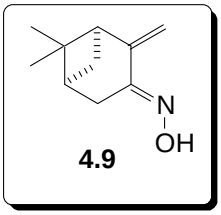
5.7 Synthesis of chiral pyridines:



4.5

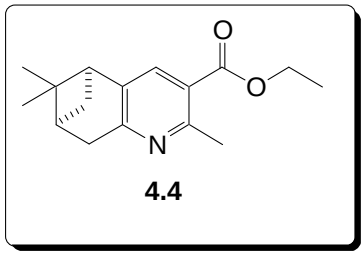
(+) Pinocarvone: Following a procedure by Bell et al,[40] a solution of (-)α-pinene (10.4 mL, 66.6 mmol) in DCM (150 mL) was charged with acetic anhydride (6.3 mL, 66.6 mmol), pyridine (3.4 mL, 44.4 mmol), DMAP (2.17 g, 17.77 mmol) and TPP (5 mg, 0.009 mmol) turning the solution purple. Oxygen was bubbled through the solution and a UV lamp (546 nm) provided the irradiation. The process continued for 24 h to give a light brown solution. The reaction mixture was diluted with DCM (50 mL) and washed with saturated

$NaHCO_3$ until basic (3 x 50 mL). Then, the organic layer was washed with 1M HCl (2 x 30 mL) turning the solution green followed with washing with saturated $CuSO_4$ (2 x 50 mL) and brine (2 x 50 mL). Organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a red/brown oil (8.39 g, 55.9 mmol, 83.9 %), which was used immediately in the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (s, 3H), 1.23 (d, *J* = 10.3 Hz, 1H), 1.30 (s, 3H), 2.11 – 2.17 (m, 1H), 2.46 (dd, *J* = 19.2 Hz, 3.1 Hz, 1H), 2.57 - 2.66 (m, 2H), 2.70 (t, *J* = 5.8 Hz, 1H), 4.95 (s, 1H), 5.90 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.1 (CH_3), 25.9 (CH_3), 32.4 (CH_2), 38.5 (CH), 40.7 (C), 42.5 (CH_2), 48.2 (CH), 117.4 (CH_2), 149.1 (C), 199.9 (C).
In accordance with literature data.[41]



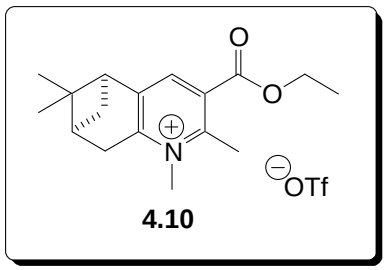
4.9

(+)-Pinocarvoxime: Hydroxylamine hydrochloride (1.39 g, 20.03 mmol) was added to a solution of pinocarvone **4.5** (1.82 g, 12.11 mmol) in ethanol (30 mL) and pyridine (0.9 mL) and the mixture was heated to reflux for 2h. This was then immediately diluted with water (100 mL) and extracted with DCM (3 x 100 mL). The combined organic extracts were washed with 1M HCl (2 x 100 mL) and water (100 mL), then dried over $MgSO_4$ and concentrated in vacuo to give a dark green oil (1.83 g, 11.08 mmol, 92 %), which was used immediately in the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (s, 3H), 1.10 (d, *J* = 10.1 Hz, 1H), 1.23 (s, 3H), 2.01 – 2.07 (m, 1H), 2.43 – 2.49 (m, 1H), 2.51 (t, *J* = 5.7 Hz, 1H), 2.63 (dt, *J* = 19.0 Hz, 3.0 Hz, 1H), 2.73 (dd, *J* = 19.0 Hz, 3.0 Hz, 1H), 4.66 (s, 1H), 5.52 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.1 (CH_3), 26.1 (CH_3), 29.1 (CH_2), 31.3 (CH_2), 37.7 (CH), 40.6 (C), 49.9 (CH), 108.2 (CH_2), 145.4 (C), 154.7 (C).
In accordance with literature data.[42]



4.4

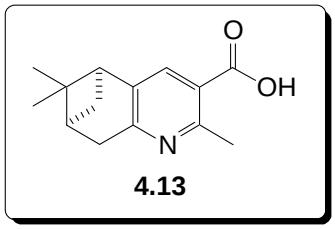
***5,10,10-Trimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]*undeca-2(7),3,5-triene-4-carboxylic acid ethyl ester:** Pinocarvoxime **4.9** (1.38 g, 8.36 mmol), ethyl acetoacetate (3.6 mL, 28.17 mmol) and 5% $FeCl_3$ (0.07 g, 0.42 mmol) were mixed together in a 50 mL round-bottom flask. The mixture was heated under vigorous stirring at 110 ^oC overnight. The reaction mixture was then transferred to Kuglerohr apparatus and excess ethyl acetoacetate was distilled off at 100 ^oC under reduced pressure. The pure product **4.4** was then distilled off bulb-to-bulb at 175 ^oC to give a pale yellow oil (1.28 g, 4.9 mmol, 59%), which was sufficiently pure for the next step: Yellow oil, $[\alpha]_D$ + 17.8 (c = 1.0, DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 0.62 (s, 3H), 1.24 (d, *J* = 9.7 Hz, 1H), 1.40 (t, 7.2 Hz, 3H), 1.41 (s, 3H), 2.28 – 2.33 (m, 2H), 2.70 (dt, *J* = 9.7 Hz, 5.9 Hz, 1H), 2.72 – 2.76 (m, 3H), 3.11 (d, *J* = 2.8 Hz, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 7.71 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.3 (CH_3), 21.3 (CH_3), 24.3 (CH_3), 25.9 (CH_3), 32.0 (CH_2), 36.7 (CH_2), 39.5 (C), 40.0 (CH), 45.8 (CH), 61.0 (CH_2), 122.2 (C), 134.9 (aromatic CH), 139.2 (C), 156.8 (C), 159.9 (C), 167.0 (C); IR (NaCl) υ 2977.6 (C-H), 1717.3 (C=O) 1560.1 (C=C), 1189.9 (C-O); MS (EI), *m/z* (%) 259.1 ($M^{\cdot+}$, 81), 244.1 (60), 216.1 (90), 215.1 (29), 172.1 (24), 144.1 (56), 143.1 (12), 77.0 (11); HRMS (EI) 259.1573 ($C_{16}H_{21}NO_2$ requires 259.1572).



4.10

4-Ethoxycarbonyl-5,6,10,10-tetramethyl-6-azonia-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene triflate salt: Methyl triflate (0.2 mL, 1.7 mmol) was added to a

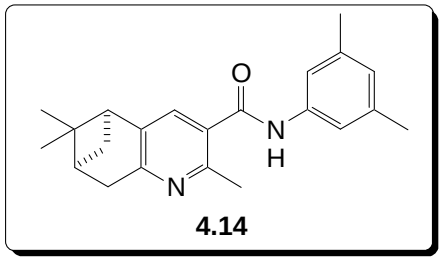
solution of ester **4.13** (0.3 g, 1.2 mmol) in DCM (1 mL) and the reaction mixture was stirred for 1 h. The solvent was evaporated to give the pyridinium salt **4.10** as a pale yellow oil (0.35 g, 0.8 mmol, 72%) which was used in the next step without any further purification: $[\alpha]_D$ 12.8 (c = 0.25, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.6 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 2H), 1.38 (s, 3H), 1.45 (d, *J* = 10.4 Hz, 1H), 2.47 – 2.52 (m, 1H), 2.70 (dt, *J* = 10.4 Hz, 5.7 Hz, 1H), 2.95 – 3.01 (m, 4H), 3.22 (dd, *J* = 19.0 Hz, 3.0 Hz, 1H), 3.42 (dd, *J* = 19.0 Hz, 3.0 Hz, 1H), 4.13 (s, 3H), 4.35 (q, *J* = 7.2 Hz, 3H), 8.15 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.0 (CH_3), 18.4 (CH_3), 21.1 (CH_3), 25.2 (CH), 30.3 (CH_2), 34.8 (CH_2), 38.9 (C), 39.3 (CH), 40.7 (CH), 46.3 (CH_3), 63.1 (CH_2), 128.6 (C), 140.8 (aromatic CH), 145.2 (C), 154.5 (C), 157.9 (C), 163.7 (C=O); IR (NaCl) υ 3449.1 (aromatic C-H), 2961.2 (C-H), 1733.7 (C=O), 1475.3 (C=C), 1198.5 (C-O) cm^{-1}; MS (FAB), *m/z* (%) 274.2 ($M^{\cdot+}$, 100); HRMS (FAB) 274.1806 ($C_{17}H_{24}NO_2$ requires 274.1807).



4.13

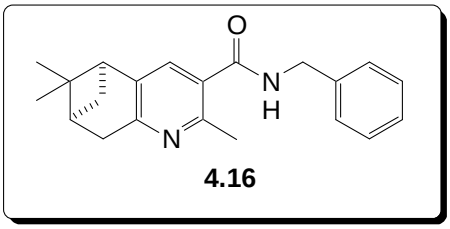
5,10,10-Trimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene-4-carboxylic acid: A 1M solution of KOH (9.5 mL) was added to a solution of ethyl ester **4.4** (2.2 g, 8.6 mmol) in ethanol (10.8 mL) and the mixture was heated at reflux for 2 h. The reaction mixture was then diluted with water (100 mL), pH was adjusted to 6.0 with 1M HCl followed by extraction with DCM (3 x 50 mL). Collected organic extracts were dried over $MgSO_4$ and evaporated in vacuo to give crude **4.13** which was recrystallised from ethyl acetate to give **4.13** (1.1 g, 4.6 mmol, 53%) as pale yellow crystals: m.p = 145 – 148 ^oC (ethyl acetate); $[\alpha]_D$ + 27.40 (c = 0.5, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.69 (s, 3H), 1.31 (d, *J* = 10 Hz, 1H), 1.48 (s, 3H), 2.20 (s, 2H), 2.42 – 2.50 (m, 1H), 2.77 – 2.83 (m, 1H), 2.90 – 2.95 (m, 1H), 3.05 (s, 2H), 3.34 – 3.40 (m, 1H), 8.15(s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.4 (CH_3), 23.7 (CH_3), 25.9 (CH_3), 31.9 (CH_2), 36.1 (CH_2), 39.5 (C), 39.9 (CH), 45.8 (CH), 122.6 (C), 136.3 (aromatic CH),

139.8 (C), 157.1 (C), 159.9 (C), 170.9 (C=O); IR (NaCl) υ 2935.1 (OH), 1698.0 (C=O); MS (EI), *m/z* (%) 83.9 (100), 47.0 (31), 35.0 (13), 231.09 ($M^{\cdot+}$, 8); HRMS (EI) 231.1256 ($C_{14}H_{17}NO_2$ requires 231.1259).



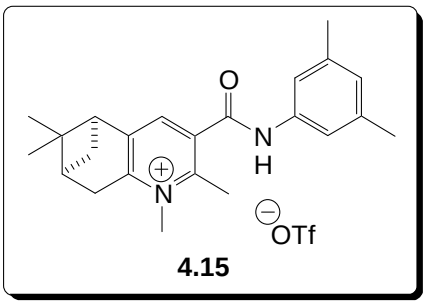
4.14

5,10,10-Trimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene-4-carboxylic acid(3,5-dimethyl-phenyl)-amide: *N*-methyl morpholine (0.6 mL, 5 mmol) and methyl chloroformate (0.2 mL, 2.8 mmol) were successively added to a solution of acid **4.13** (0.5 g, 2.2 mmol) in dry THF (5 mL). The mixture was stirred for 1 hour at room temperature. Then, 3,5-dimethyl aniline (0.3 mL, 3.6 mmol) was added and the reaction mixture was stirred for a further 72 h at 40 ^{o}C. After this time, the mixture was carefully diluted with water (100 mL) and extracted with DCM (2 x 70 mL). Combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo to give crude **4.14** (0.7 g, 2.4 mmol). The resulting oil was purified by column chromatography on silica gel (15 x 3 cm) with a 1:2 petroleum ether-ethyl acetate mixture to give **4.14** as pale a yellow solid (0.3g, 41%): m.p = 60 – 63 ^{o}C (petroleum ether/ethyl acetate); $[\alpha]_D$ + 11.60 (c = 1, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.68 (s, 3H), 1.26 (d, *J* = 9.6 Hz, 1H), 1.43 (s, 3H), 2.35 (s, 6H), 2.38 - 2.43 (m, 1H), 2.70 (s, 3H), 2.71 – 2.81 (m, 2H), 3.12 (s, 2H), 7.27 (bs, NH), 7.31 (s, 3H), 7.42 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.4 (CH_3), 22.8 (CH), 26.0 (CH), 32.0 (CH_2), 36.6 (CH_2), 39.5 (C), 40.1 (CH_3), 46.0 (CH_3), 117.7 (CH), 126.5 (CH), 128.4 (C), 131.5 (CH), 137.6 (C), 139.0 (C), 139.2 (C), 153.0 (C), 158.4 (C), 167.1 (C); IR (NaCl) υ 3154.9 (NH), 1673.9 (amide C=O), 2932.2 (C-H), 1559.2 (C=C) cm^{-1}; MS (CI), *m/z* (%) 335.3 ($(M + H)^+$, 100), 334.3 (55), 164.2 (10); HRMS (CI) 335.2138 ($C_{22}H_{27}ON_2$ requires 335.2123).



4.16

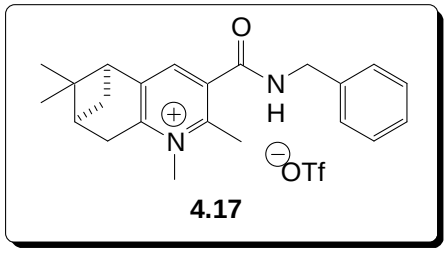
5,10,10-Trimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene-4-carboxylic acid benzyamide: Compound **4.16** was prepared from acid **4.13** (0.8 g, 3.5 mmol), *N*-methyl morpholine (0.9 mL, 8 mmol), methyl chloroformate (0.4 mL, 4.5 mmol) and benzylamine (0.6 mL, 5.7 mmol) and dry THF (7.5 mL). The resulting oil was purified by column chromatography on silica gel (15 x 3 cm) with a 1:2 petroleum ether-ethyl acetate mixture to give **4.16** as pale a yellow oil (0.3g, 0.8 mmol, 23%): $[\alpha]_D$ + 42.80 (c = 0.5, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (s, 3H), 1.14 (d, *J* = 9.6 Hz, 1H), 1.32 (s, 3H), 2.26 – 2.31 (m, 1H), 2.59 (s, 3H), 2.58 - 2.64 (m, 1H), 2.67 (t, *J* = 5.7 Hz, 1H), 3.12 (s, 2H), 4.56 (d, *J* = 5.7 Hz, 2H), 6.0 (broad s, NH), 7.14 (s, 1H), 7.17 - 7.31 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.4 (CH_3), 22.7 (CH_3), 26.0 (CH_3), 32.0 (CH_2), 36.5 (CH_2), 39.5 (C), 40.1 (CH), 44.1 (CH_2), 45.9 (CH), 127.8 (CH), 127.9 (C), 128.0 (CH), 128.9 (CH), 131.7 (CH), 137.9 (C), 139.0 (C), 152.8 (C), 158.1 (C), 169.0 (C); IR (NaCl) υ 3437.5 (aromatic CH), 1655.6 (amide C=O), 2934.2 (C-H), 1509.9 (C=C) cm^{-1}; MS (EI), *m/z* (%) 320.2 ($M^{\cdot+}$, 100), 277.1 (75), 170.1 (27), 144.1 (35), 91.0 (90), 77.0 (18) ; HRMS (EI) 320.1886 ($C_{21}H_{24}ON_2$ requires 320.1889).



4.15

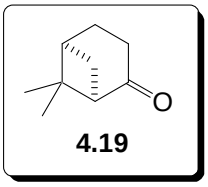
4-(3,5-Dimethyl-phenylcarbamoyl)-5,6,10,10-tetramethyl-6-azonia-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene triflate salt: Compound **4.15** was prepared from amide **4.14** (0.15 g, 0.45 mmol) and methyl triflate (0.08 mL, 0.68 mmol) in DCM (1 mL) to yield the quaternary ammonium salt **4.15** as a

pale yellow solid (0.23 g, 99%): m.p = 255 – 258 ^{o}C (ethyl acetate); $[\alpha]_D$ + 7.80 (c = 0.5, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.69 (s, 3H), 1.36 – 1.41 (m, 4H), 2.24 (s, 6H), 2.43 – 2.49 (m, 1H), 2.67 – 2.74 (m, 1H), 2.77 (s, 3H), 2.96 (t, *J* = 5.7 Hz, 1H), 3.15 (dd, *J* = 18.4 Hz, 2.8 Hz, 1H), 3.26 (dd, *J* = 18.4 Hz, 2.8 Hz, 1H), 4.02 (s, 3H), 6.75 (s, 1H), 7.26 (s, 2H), 7.77 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.1, (CH3), 21.2 (CH), 21.4 (CH), 25.2 (CH3), 30.6 (CH2), 34.4 (CH2), 39.2 (CH3), 39.7 (C), 39.8 (CH3), 46.3 (CH3), 117.9 (CH), 118.7 (C), 121.9 (CH), 136.3 (C), 137.5 (C), 138.8 (C), 139.0 (CH), 145.9 (C), 150.0 (C), 154.6 (C), 163.1 (C); IR (NaCl) υ 3269.7 (NH), 1681.6 (amide C=O), 1563.0 (C=C); MS (FAB), *m/z* (%) 349.4 (M^+, 100), 348.4 (60), 305.3 (25), 201.7 (37), 159.0 (13); HRMS (FAB) 349.2273 ($C_{23}H_{29}ON_2$ requires 349.2280).



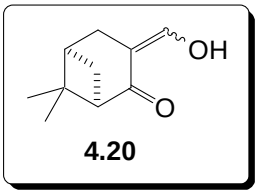
4.17

4-Benzylcarbamoyl-5,6,10,10-tetramethyl-6-azonia-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene triflate salt: Compound **4.17** was prepared from amide **4.16** (0.2 g, 0.6 mmol) and methyl triflate (0.1 mL, 0.8 mmol) in DCM (4 mL) to yield the ammonium salt **4.17** as a yellow oil (0.3 g, 99%): $[\alpha]_D$ + 34.8 (c = 0.5, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64 (s, 3H), 1.38 – 1.40 (m, 1H), 1.39 (s, 3H), 2.45 (s, 1H), 2.65 (s, 3H), 2.65 - 2.72 (m, 1H), 2.91 - 2.96 (m, 1H), 3.10 (d, *J* = 18.4 Hz, 1H), 3.25 (d, *J* = 18.4 Hz, 1H), 3.98 (s, 3H), 4.50 (d, *J* = 5.7 Hz, 2H), 7.18-7.35 (m, 5H), 7.70 (s, 1H), 8.48 (broad s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.8 (CH_3), 20.1 (CH_3), 24.2 (CH_3), 29.5 (CH_2), 33.2 (CH_2), 37.9 (CH), 38.2 (CH), 38.5 (C), 42.9 (CH_2), 45.1 (CH_3), 126.8 (CH), 126.9 (CH), 127.7 (CH), 135.0 (C), 136.4 (C), 137.9 (CH), 144.6 (C), 149.1 (C), 153.3 (C), 164.2 (C); IR (NaCl) υ 3295.8 (NH), 1664.3 (amide C=O), 1475.3 (C=C); MS (CI), *m/z* (%) 335.2 ($M^{\cdot+}$, 3), 321.2 (100); HRMS (CI) 335.2124 ($C_{22}H_{27}ON_2$ requires 335.2123).



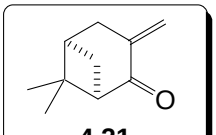
4.19

(+) Nopinone: Following a procedure by Malkov et al,[43] a solution of (–)-β-pinene **4.18** (17.2 mL, 108.60 mmol) in a mixture of methanol (30 mL) and DCM (30 mL) was cooled to –78 ^{o}C in a 3-neck round bottomed flask. Ozone, was bubbled through the solution by means of a sinter-glass-ended tube for 20 h, while maintaining the same temperature, until the blue colour persisted. The reaction progress was monitored by TLC (95:5 petroleum ether/ethyl acetate). After completion, nitrogen was bubbled through the reaction mixture for 30 mins, and it was allowed to warm to 0 ^{o}C. Zinc powder and acetic acid were than added carefully in small portions at 0 ^{o}C over a 1 h period. (Caution! Reaction mixture tends to foam so effective stirring is required.) The resulting suspension was filtered and the solid material was washed with DCM repeatedly. The organic layer was carefully washed with saturated aqueous $NaHCO_3$ solution. The aqueous layer
was extracted with DCM (3 x 60 mL). The combined organic extracts were washed with water (3 x 100 mL) and dried over $MgSO_4$ and the solvent was evaporated in vacuo to give crude nopinone **4.19** (14. 4 g, 104 mmol, 96%) as a colourless liquid, which was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 3H), 1.28 (s, 3H), 1.55 (d, *J* = 10.1 Hz, 1H), 1.87 - 2.07 (m, 2H), 2.18 - 2.24 (m, 1H), 2.27 - 2.35 (m, 1H), 2.46 - 2.61 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.2 (CH_2), 21.5 (CH_3), 25.2 (CH_2), 25.9 (CH_3), 32.8 (CH_2), 40.2 (CH), 41.2 (C), 57.9 (CH), 214. 9 (C=O); MS (EI), *m/z* (%) 138.1 ($M^{\cdot+}$, 36), 123.1 (38), 95.0 (79), 83 (100), 39.1 (69); HRMS (EI) 138.1036 ($C_9H_{14}O$ requires 138.1035).
In accordance with literature data.[43]



4.20

(+) 3-Hydroxymethylene-6,6-dimethyl-bicyclo[3.1.1]heptan-2-one: Following a procedure by Kwong et al,[44] a solution of ethyl formate (7.3 mL, 90.3 mmol) in toluene (7.5 mL) was added to a suspension of NaOMe (4.9 g, 90.3 mmol) in toluene (45 mL) under Ar. The reaction mixture was stirred for 5 mins at room temperature. A solution of nopinone **4.19** (4.16g, 30.1 mmol) in dry toluene (7.5 mL) was added and the mixture was stirred overnight at 35 ^{o}C. (Caution! Reaction mixture solidified, so an extra 20-30 mL of dry toluene was added) The reaction mixture was quenched with water (50 mL), the aqueous phase was separated and the organic phase was extracted with 1M NaOH solution (2 x 50 mL). The combined aqueous extracts were acidified to pH 1 with concentrated HCl, then extracted with DCM (3 x 50 mL). The DCM extracts were dried over $MgSO_4$ and the solvent was evaporated in vacuo to give crude **4.20** as a yellow solid (4.3 g, 25.9 mmol, 86%), which was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.34 (s, 3H), 1.42 (d, *J* = 10.4 Hz, 1H), 2.24 - 2.29 (m, 1H), 2.47 (t, *J* = 5.4 Hz, 1H), 2.51 - 2.60 (m, 3H), 7.2 (s, 1H), 13.35 (bs, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.1 (CH_3), 26.0 (CH_2), 26.2 (CH_3), 27.4 (CH_2), 39.5 (CH), 40.0 (C), 54.6 (CH), 107.1 (C), 163.9 (alkene CH), 209.5 (C=O); MS (CI), *m/z* (%) 167.2 ($M^{\cdot+}$, 100), 153.2 (15) ; HRMS (CI) 167.1069 ($C_{10}H_{15}O_2$ requires 167.1072)
In accordance with literature data.[45]

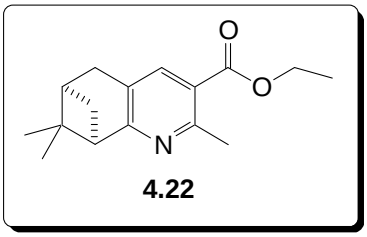


4.21

(+) 6,6-Dimethyl-3-methylene-bicyclo[3.1.1]heptan-2-one: Following a procedure by Kwong et al,[44] aldehyde **4.20** (4 g, 24.1 mmol) was mixed together with 37% formaldehyde (27.3 mL), water (24.1 mL), diethyl ether (56 mL) and

potassium carbonate (8.03 g). The mixture was stirred under reflux overnight under a nitrogen atmosphere. The organic phase was separated and the aqueous layer was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with 1M NaOH (2 x 50 mL), then water (50 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo to give **4.21** as a yellow liquid (2.8 g, 18.7 mmol, 78%), which was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.8 (s, 3H), 1.29 (s, 3H), 1.37 (d, *J* = 10.2 Hz, 1H), 2.14 - 2.2 (m, 1H), 2.49 - 2.56 (m, 2H), 2.6 - 2.73 (m, 1H), 5.31 (s, 1H), 6.24 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.6 (CH_3), 26.2 (CH_3), 26.9 (CH_2), 30.4 (CH_2), 39.2 (CH), 41.0 (C), 55.8 (CH), 122.5 (alkene CH_2), 140.6 (C), 202.7 (C=O); MS (EI), *m/z* (%) 150.1 ($M^{\cdot+}$, 77), 135.1 (73), 95 (79), 83 (100), 41.1 (69), 39.1 (35).

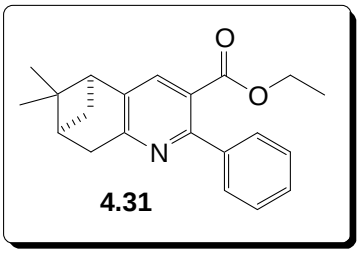
In accordance with literature data.[45]



4.22

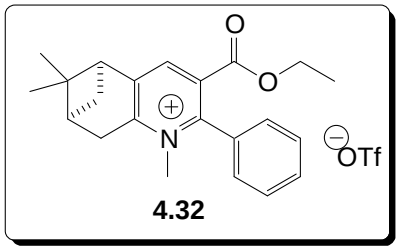
(-)4,10,10-Trimethyl-3-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene-5-carboxylic acid ethyl ester: α,β-unsaturated compound **4.21** (0.5 g, 3.3 mmol) was added to a solution of ethyl acetoacetate (0.5 mL, 3.9 mmol) and ammonium acetate (0.26 g, 3.3 mmol) in acetic acid (1 mL) and toluene (5 mL). The mixture was heated at reflux overnight. The resulting mixture was then diluted with DCM (50 mL), washed with $NaHCO_3$ (3 x 20 mL), water (1 x 20 mL), dried over $MgSO_4$ and evaporated in vacuo. The residue was transferred to Kuglerohr apparatus and excess ethyl acetoacetate was removed under reduced pressure at 100 ^{o}C and then the pure product **4.22** was distilled bulb-to-bulb under vacuum at 200 ^{o}C to give a yellow oil (0.43 g, 1.7 mmol, 50%): $[\alpha]_D$ – 22.30 (c = 1, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.59 (s, 3H), 1.19 (d, *J* = 9.8 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.35 (s, 3H), 2.24 - 2.29 (m, 1H), 2.64 (dt, *J* = 9.8 Hz, 5.8 Hz, 1H), 2.70 (s, 3H), 2.89 (s, 2H), 2.93 (t, *J* = 5.5 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 7.86 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.3 (CH_3),

21.2 (CH_3), 25.0 (CH_3), 26.0 (CH_3), 30.5 (CH_2), 30.7 (CH_2), 39.1 (CH), 40.0 (C), 50.4 (CH), 60.9 (CH_2), 123.1 (C), 127.2 (C), 137.3 (aromatic CH), 155.9 (C), 167.0 (C), 169.2 (C=O); IR (NaCl) υ 2977.6 (C-H), 1717.3 (C=O), 1560.1 (C=C), 1157.1 (C-O) cm^{-1}; MS (CI), *m/z* (%) 260.2 ($M^{\cdot+}$, 100), 216.2 (13); HRMS (CI) 260.1649 ($C_{16}H_{22}NO_2$ requires 260.1651).



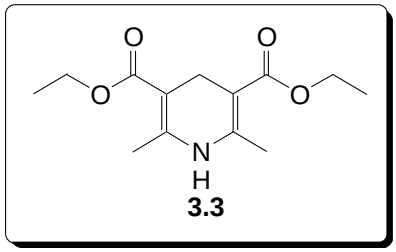
4.31

(+) 10,10-Dimethyl-5-phenyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene-4-carboxylic acid ethyl ester: A solution of pinocarvone **4.5** (0.3 g, 1.99 mmol) ethyl benzoyl acetate (0.41 mL, 2.34 mmol) and ammonium acetate (0.15 g, 1.99 mmol) in toluene (3 mL) and acetic acid (0.6 mL), was heated at reflux overnight. The mixture was then diluted with DCM (50 mL), washed with $NaHCO_3$ (3 x 20 mL), water (1 x 20 mL), dried over $MgSO_4$ and evaporated to give a red/brown oil, which was then transferred to Kuglerohr apparatus and after bulb-to-bulb distillation under vacuum at 250 ^oC afforded pure product **4.31** as a yellow oil (0.27 g, 0.85 mmol, 42%): $[\alpha]_D$ + 29.0 (c = 1.0, DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 0.62 (s, 3H), 0.95 (t, *J* = 7.1 Hz, 3H), 1.23 (d, *J* = 9.8 Hz, 1H), 1.38 (s, 3H), 2.33 (septuplet, *J* = 2.9 Hz, 1H), 2.66 (dt, *J* = 9.8 and 5.7 Hz, 1H), 2.80 (t, *J* = 5.7 Hz, 1H), 3.12 (d, *J* = 2.8 Hz, 2H), 4.04 (q, *J* = 7.1 Hz, 2H), 7.31 - 7.36 (m, 3H), 7.44 (dd, 1.6 Hz and 7.5 Hz, 2H), 7.56 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.6 (CH_3), 20.4 (CH_3), 24.9 (CH_3), 30.9 (CH_2), 35.9 (CH_2), 38.5 (C), 39.1 (CH), 45.0 (CH), 60.2 (CH_2), 122.8 (C), 127.2 (aromatic CH), 127.5 (aromatic CH), 133.2 (aromatic CH), 139.1 (C), 139.7 (C), 155.4 (C), 158.6 (C), 167.6 (C=O); IR (NaCl) ν 2036 (C-H), 1714 (C=O), 15.52 (C=C), 1163 (C-O); MS (EI), *m/z* (%) 321.1 ($M^{\cdot+}$, 100), 278.1 (48), 248.1 (23), 204.1 (20), 77.0 (9);HRMS (EI) 321.1725 ($C_{21}H_{23}NO_2$ requires 321.1729).



4.32

(+) 4-Ethoxycarbonyl-6,10,10-trimethyl-5-phenyl-6-azonia-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene triflate salt: Compound **4.32** was prepared from ester **4.31** (0.09 g, 0.28 mmol) and methyl triflate (0.05 mL, 0.41 mmol) in DCM (0.5 mL) to give the pyridinium salt **4.32** as a thick white oil (0.086 g, 0.19 mmol, 68%): $[\alpha]_D$ + 22.1 (c = 1, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (s, 3H), 0.96 (t, *J* = 7.4 Hz, 3H), 1.52 (s, 3H), 1.77 (d, *J* = 10.6 Hz, 1H), 2.58 - 2.7 (m, 1H), 2.85 (dt, *J* = 10.5 and 5.7 Hz, 1H), 3.17 (t, *J* = 5.7 Hz, 1H), 3.34 (dd, *J* = 19.0 and 2.3 Hz, 1H), 3.73 (dd, *J* = 19.2 and 3.1 Hz, 1H), 4.01 (s, 3H), 4.07 (q, *J* = 7.1Hz, 2H), 7.41 (d, *J* = 8.3, 1H), 7.55 - 7.71 (m, 3H), 7.67 - 7.71 (m, 1H), 8.21 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.4 (CH_3), 20.4 (CH_3), 24.2 (CH_3), 28.9 (CH_2), 33.6 (CH_2), 38.1 (C), 38.2 (CH), 41.4 (CH_3), 45.6 (CH), 61.6 (CH_2), 127.4 (aromatic CH), 127.9 (aromatic CH), 128.2 (aromatic CH), 128.3 (aromatic CH), 128.6 (C), 129.8 (aromatic CH), 130.3 (C), 139.5 (aromatic CH), 146.2 (C), 152.4 (C), 157.6 (C), 162.2 (C=O); IR (NaCl) ν 2927.6 (C-H), 1638 (C=O); MS (FAB), *m/z* (%) 336.2 ($M^{\cdot+}$, 100), 307.1 (16), 155.0 (58), 137.2 (36); HRMS (FAB) 336.1967 ($C_{22}H_{26}NO_2$ requires 336.1964).



3.3

2,6-Dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester: Following the procedure of Perumal et al,[46] aqueous formaldehyde (0.09 mL, 3.33 mmol), ethyl acetoacetate (0.85 mL, 6.66 mmol) and ammonium acetate (0.26 g, 3.33 mmol) in ethanol (10 mL) were placed in a conical flask and

subjected to microwave irradiation for 45 seconds in a domestic microwave oven with a pulse of 15 seconds each and then allowed to stand at room temperature. The Hantzsch ester **3.3** was then separated by filtration to give a yellow solid (0.27 g, 0.9 mmol, 27%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.1 Hz, 6H), 2.10 (s, 6H), 3.20 (s, 2H), 4.10 (q, *J* = 7.1 Hz, 4H), 5.05 (bs, 1H) In accordance with literature data.[46]

General procedure for $Na_2S_2O_4$ reductions:

Following the procedure of Combret et al,[47] pyridinium salt (0.05 g, 0.11 mmol) was dissolved in degassed ethyl acetate (0.25 mL). A solution of $NaHCO_3$ (0.05g, 0.55 mmol) in degassed water (0.45 mL) at 40 – 50 ^{o}C was added to the mixture under argon in the dark. Then, a solution of $Na_2S_2O_4$ (0.15 g, 0.88 mmol) in degassed water (0.45 mL) was added dropwise with stirring. After 1h (or overnight) the mixture was extracted with DCM (3 x 20 mL) and the organic phase was washed with water (30 mL), dried, concentrated and the crude dihydropyridine was stored under argon in the dark.

General procedure for borohydride reductions:

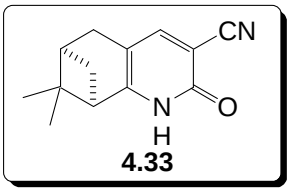
Following a procedure of Vasse et al,[48] $NaBH_4$ (0.033g, 0.88 mmol) was added in small portions to a solution of ester salt (0.05 g, 0.11 mmol) in ethanol (1 mL) at 0 ^{o}C under argon in the dark. The mixture was stirred at room temperature for 1h (or overnight). Then, the reaction mixture was quenched with degassed water and extracted with DCM (3 x 20 mL), washed with water (30 mL), dried, concentrated and stored in the dark.

General procedure for silane reduction:

Triethylsilane (0.03 mL, 0.17 mmol) was added to a solution of ester salt (0.05g, 0.11 mmol) in toluene (1 mL) and was heated at reflux overnight. The reaction mixture was then diluted with DCM (50 mL), washed with water (30 mL), dried and concentrated.

General procedure for Hantzsch ester reduction:

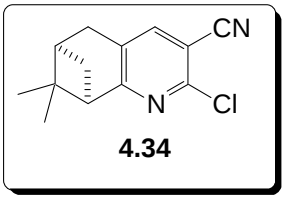
Hantzsch ester (0.03g, 0.11 mmol) was added to a solution of salt (0.05g, 0.11 mmol) in DCM (1 mL) and stirred at room temperature (or 60 ^{o}C) for 2.5h (or overnight). The reaction mixture was then diluted with DCM (50 mL), washed with water (30 mL), dried and concentrated.



4.33

10,10-Dimethyl-4-oxo-3-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),5-diene-5-carbonitrile: Following the procedure by Baxendale et al,[49] 1,3- dicarbonyl compound (0.44 g, 2.67 mmol) and piperidine (0.11 mL) were added to a solution of cyanoacetamide (0.22 g, 2.67 mmol) in ethanol (0.9 mL) and water (0.9 mL) and the mixture was heated at 85 ^{o}C overnight. After cooling the reaction mixture, ethanol was removed under reduced pressure. The aqueous residue was extracted with DCM (3 x 20 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was remover under reduced pressure to give **4.33** as a brown oil which was recrystallised from ether to give an orange/brown powder (0.108g, 20%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 3H), 1.42 (d, *J* = 9.7 Hz, 1H), 1.49 (s, 3H), 2.36 - 2.41 (m, 1H), 2.74 - 2.85 (m, 4H), 6.09 (bs, NH), 8.45 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.1 (CH_3), 25.8 (CH_3), 29.3 (CH_2), 30.4 (CH_2), 39.8 (C), 40.2 (CH), 45.7 (CH), 112.6 (C), 116.3 (C), 145.9 (aromatic CH), 159.2 (C), 162.9 (C), 166.6 (C); MS (CI), *m/z* (%) 215.2 ($(M + H)^+$ 100), 178.2 (10)); HRMS (CI) 215.1187 ($C_{13}H_{15}N_2O$ requires 215.1184).

In accordance with literature data.[43]



4.34

4-Chloro-10,10-dimethyl-3-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene-5-carbonitrile: Following the procedure of Nishikawa et al,[50] a mixture of pyridone (0.108 g, 0.51 mmol) and phosphorous pentachloride (0.106g, 0.51 mmol) were heated in DCM (2 mL) at reflux for 1h with stirring. The mixture was then poured into 5 mL of ice water. The solution was adjusted to pH 7 with $NaHCO_3$ and extracted with DCM (3 x 15 mL). The combined extracts were then dried over $MgSO_4$ and the solvent was removed under reduced pressure to give an orange solid which was then recrystallised from ether to give **4.34** as a yellow/orange solid (0.046 g, 39%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (s, 3H), 1.28 (d, *J* = 9.9 Hz, 1H), 1.39 (s, 3H), 2.27 (bs, 1H), 2.63 - 2.75 (m, 3H), 2.90 (t, *J* = 5 Hz, 1H), 7.60 (s, 1H).

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Appendix: Publication