Cobalt(II) Catalysts – Their Use in the Enantioselective Ring-opening of 1,2-Dioxines

A thesis submitted for the Degree of Doctor of Philosophy in the Faculty of Science

By

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Declaration of Originality

This work contains no material which has been accepted for the award of any other degree or diploma in any other university or other tertiary institution and, to the best of my knowledge and belief, this thesis contains no material previously published or written by any other person, except where due reference has been made in the text.

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Natalie Faye Jenkins

1st November 2003

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Abstract

A series of new cobalt(II) β-keto iminato complexes and cobalt(II) salens have been made and the effect of chirality in the northern, southern and peripheral quadrants of these catalysts, with respect to induced enantiomeric excess, during the ring-opening of 1,2-dioxines has been determined.

Synthesis of a series of cobalt β-keto iminato complexes was achieved after modification of literature procedures used for the synthesis of manganese β-keto iminato complexes and this procedure was applied to generate ligands with ethyl, *t*-butyl, (-)-bornyl, (+)-menthyl and (-)-menthyl esters and a methyl side chain. Synthesis of the cobalt salens was also achieved using a modified literature procedure, in respect to the more complex aldehydes made.

It was ascertained that chirality in the northern quadrant of these catalysts, obtained by the use of optically pure diamines, was of greatest importance in introducing enantiomeric excess into the products of ring-opening of 1,2-dioxines; namely γ-hydroxy enones, and chirality in the southern and peripheral quadrants was of lesser, although still significant, importance.

The reaction conditions were optimised and the conditions under which the highest enantiomeric excess was introduced were determined. The ideal solvent for the ring-opening was found to be THF with a catalyst concentration between 5 and 10 mol% at a temperature of $-15^{o}C$. These conditions were found to be applicable to all catalysts and 1,2-dioxines tested.

Enantiomeric excess as high as 76 % could be introduced when the optimised reaction conditions were used in large scale syntheses of cyclopropane **(61)**.

LC-MS studies indicate the presence of a solvent chelated species present in the reaction mixture when the solvent used is THF, however, the use of non-chelating solvents, such as dichloromethane, did not exhibit this same solvent chelated species. Catalyst dimers were also present in the mixture when analysed by LC-MS.

The presence of oxygen in the reaction mixture was found to inhibit rearrangement of the dioxine with catalyst oxygen dimers (two molecules of catalyst bound to a single molecule of oxygen) present when analysed by LC-MS, however, the catalyst could by 're-activated' by de-aeration of the solution and was able to introduce the same enantiomeric excess, as prior to the addition of oxygen was unaffected.

It was found that not only cobalt(II) tetradentate complexes were useful in the ring-opening of *meso* 1,2-dioxines. Achiral iron(II) salen and ruthenium(II) salen were also made and shown to be capable of ring-opening the dioxine. A purchased chiral manganese(III) salen was also shown to be capable of ring-opening the 1,2-dioxine, however, the time taken for the rearrangement to occur led to ring closure of the γ-hydroxy enone and dehydration of the cyclic hemiacetal.

The catalysts were also applied to the enantioselective ring-opening of epoxy-1,2-dioxines for the first time with a high level of success with enantiomeric excesses of between 60 and 90 % introduced with most of the catalysts.

To show that these catalysts have the potential for use in the synthesis of potentially bioactive cyclopropyl amino acids, amines, acids and alcohols a small number were prepared, including both racemic and optically enriched or optically pure cyclopropanes.

Abbreviations

Anal. Calculated	analysis calculated
Bn	benzyl
Bor	bornyl
Bu	butyl
Bu^t, *tert*-Bu, *t*-Bu	*tert*-butyl
DCM	dichloromethane
de	diastereomeric excess
DMAP	4-(*N,N*-dimethylamino)pyridine
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
ee	enantiomeric excess
EH	2,3-epoxy-4-hydroxynonanal
Et	ethyl
HPLC	high-performance liquid chromatography
IR	infra red
LC-MS	liquid chromatography – mass spectroscopy
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MHz	megahertz

Mn	menthyl
NMR	nuclear magnetic resonance
Pd/C	Palladium on carbon
Ph	phenyl
R_f	retention factor
TBDPS	*tert*-butyldiphenylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC, t.l.c.	thin layer chromatography
TMS	tetramethyl silane

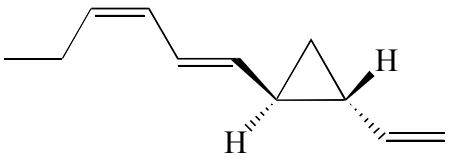
1. Introduction

1.1 Bioactive Natural and Synthetic Cyclopropanes

The cyclopropyl motif is a structural element found in many bioactive compounds, both natural and synthetic. They are found in diverse sources, including plants and both fungal and bacterial microorganisms, as stable components in secondary metabolites or transitional states between substrate and final product.[1,2]

The activity of these cyclopropyl-containing compounds is not, in most cases, generated by chemical reaction of the cyclopropyl group, but by the ability of the cyclopropane to provide conformational control producing tight enzyme-substrate interactions.[1]

Natural products containing the cyclopropyl motif include polyacetate-derived compounds such as Dictyopterene B **(1)**, a sex pheromone from the female brown algae *Dictyopteris plagiogramma* and *D. australis*, which is responsible for the characteristic smell of beaches.[3]



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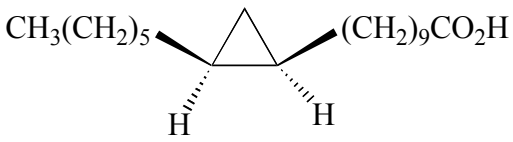
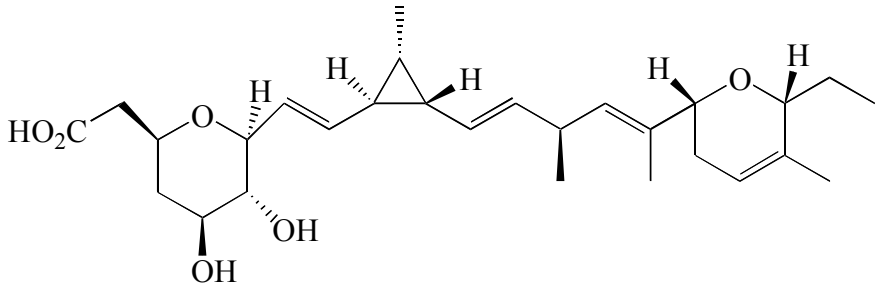


(2)

Fatty acids of biological importance in bacterial membranes are also known to contain cyclopropanes. Lactobacillic acid **(2)** is found in the cell membrane of *Lactobacillus arabinosus*.[4] Mycolic acids also contain the cyclopropyl motif and are an integral component in the cell membrane of *Mycobacterium tuberculosis*, responsible for the efficacy of the bacterium.[2,5]

Some cyclopropyl containing compounds are known to have potent anti-bacterial properties. Ambruticin **(3)**, from *Polyangium cellulosum var. fulvum*, is a polyether with anti-fungal and anti-biotic properties[6,7] and Cyclizidine **(4)**, from *Streptomyces NCIB 11649*, is an

alkaloid with anti-biotic and immunostimulatory properties also producing an effect parallel to that seen in β-blocking drugs.[1,2]



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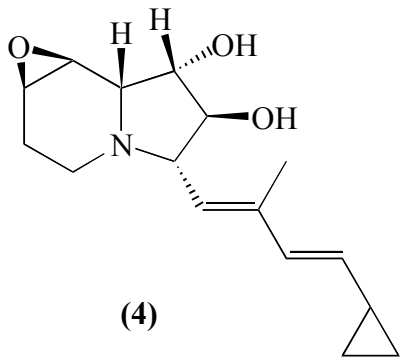
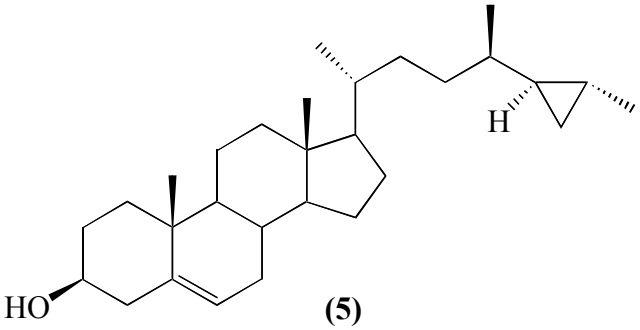


(4)

Sterol cyclopropanes have been found in the extracts obtained from marine sponges, Petrosterol **(5)** being a commonly detected metabolite of *Petrosia ficiformis*[8] and the Aragusterols **(6a-d)** found in *Xestospongia* with Aragusterols **6a-c** exhibiting anti-tumour activity.[9]



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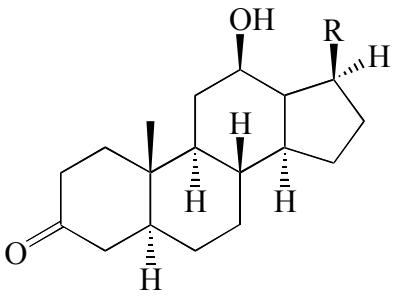

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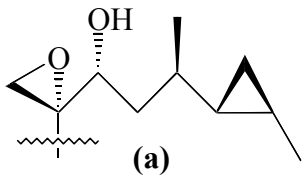

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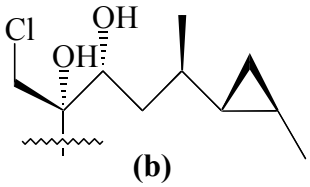

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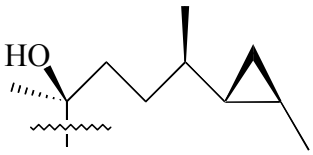

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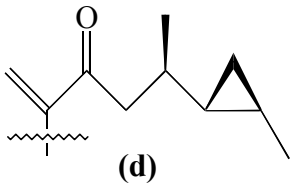
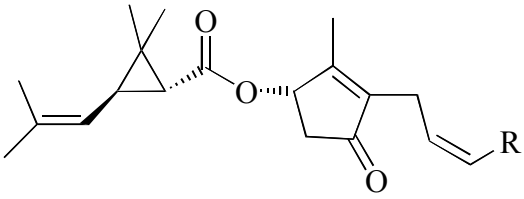


(d)

Pyrethrins **(7a, 8a)** found in the flowers of *Chrysanthemum cinerariaefolium*[2,10] along with crysamthemic acid **(9)**, pyrethric acid **(10)**, cinerins **(7b, 8b)** and jasmolins **(7c, 8c)** all show insecticidal activity. The pyrethrins, showing the highest activities of all the components, have been used as the basis for a series of insecticides.[1,10]



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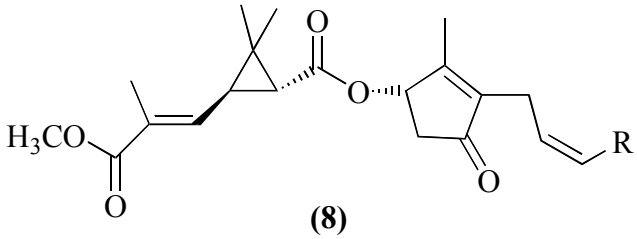
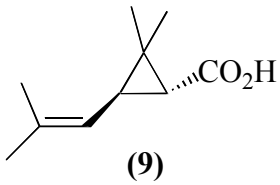


(8)

(7) & (8) **(a)** R = CH_3
(b) R = CH_2CH_3
(c) R = $CH{=}CH_2$



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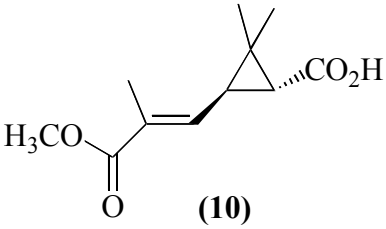
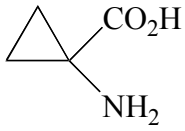


(10)

Of the many types of naturally occurring cyclopropane-containing compounds that have been mentioned above it is the cyclopropyl amino acids that exhibit a high tendency towards biological activity in plants, microorganisms and animals. 1-Aminocyclopropane carboxylic acid (ACPC) **(11)** is a ripening hormone in fruit[11,12] and coprine **(12)**, an adduct of glutamine (glutamic acid) found in the common ink cap mushroom, *Coprinus atramentarius*, is toxic in humans when consumed with alcohol due to its ability to inhibit aldehyde dehydrogenase.[1] Cyclopropyl amino acids are also discussed in more detail in **Chapter 5**.



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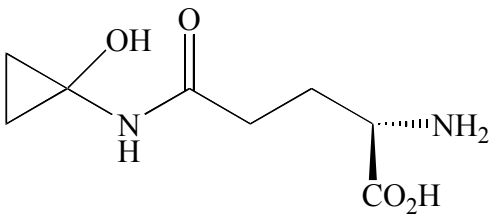
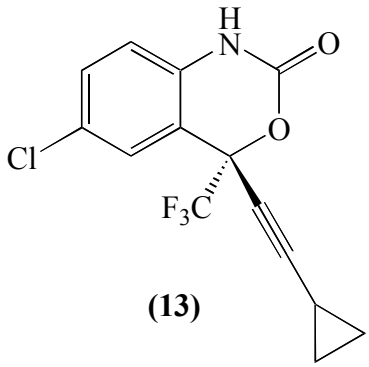


(12)

Development of synthetic compounds from a natural or theoretical lead has enabled the development of pharmaceuticals with varying social benefits. Therapeutic medications for use in combating both HIV and the symptoms it causes (AIDS) have been developed, a number of which contain a cyclopropyl motif.

The spread of HIV is a current concern worldwide and development of drugs that enable long-term inhibition of the virus or eradication of the virus gain huge sums of research time and money.

Efavirenz **(13)** is a non-nucleoside reverse transcriptase inhibitor (NNRTI)[13] and Abacavir **(14)** is a nucleoside analogue reverse transcriptase inhibitor (NRTI)[14] both of which are in current use in multi-drug regimes.



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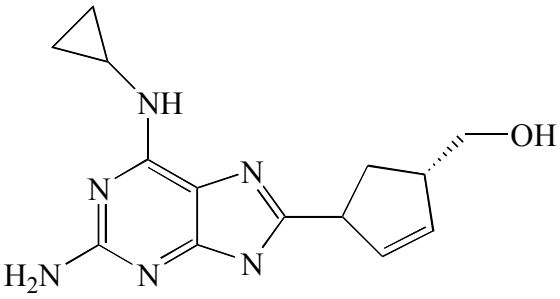
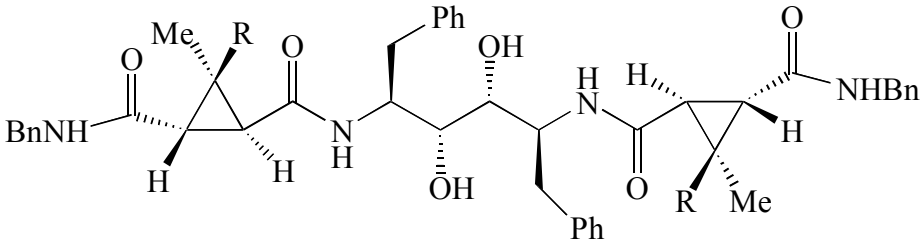


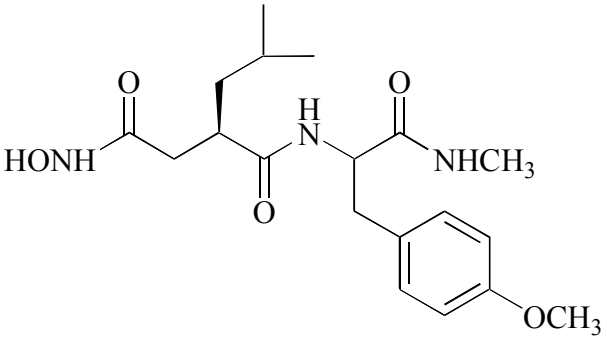
(14)

Work by Martin *et al.*[15] into cyclopropyl containing peptidomimetics has shown that peptide **(15 a-b)** is a potent sub-nanomolar HIV-1 protease inhibitor in experimental studies. Peptides containing related cyclopropanes may also be excellent inhibitors, however, as lead compounds towards the synthesis of pharmaceuticals they are poor candidates due to their vulnerability to proteolytic attack, their inability to cross the blood brain barrier and the high incidence of immunogenic responses to the peptide.[16]



(15) **(a)** R=H
(b) R=Me

In experimental models the potent collagenase inhibitor **(16)** has been shown to have reduced activity in synthetic derivatives containing a cyclopropane **(17a)** and no collagenase inhibitory activity for the isomeric cyclopropane **(17b)** indicating the dependence of free rotation on the activity of the peptide.



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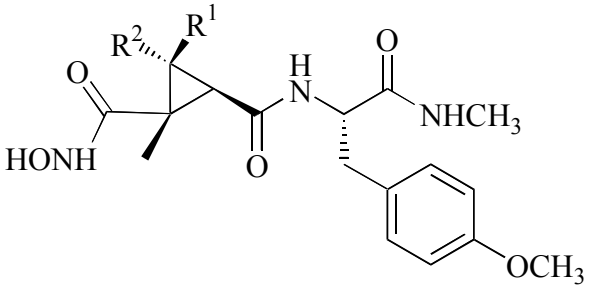


(17) **(a)** $R^1 = Pr^i$, $R^2 = H$
(b) $R^1 = H$, $R^2 = Pr^i$

1.2 Strategies for the Synthesis of Cyclopropanes

The ability to synthesise cyclopropanes of high enantiopurity is especially important in the production of compounds for use as pharmaceuticals. In many examples of bioactive compounds one enantiomer has greater activity, which can lead to either a beneficial or detrimental effect. This has led to the development of methods that enable the synthesis of the desired enantiomer in high excess.

For cyclopropanes there exists several methods for the generation of the cyclopropyl core: -

i.) 1,3-elimination of heteroatoms

ii.) carbene addition to olefins

iii.) nitrogen extrusion from pyrazolines

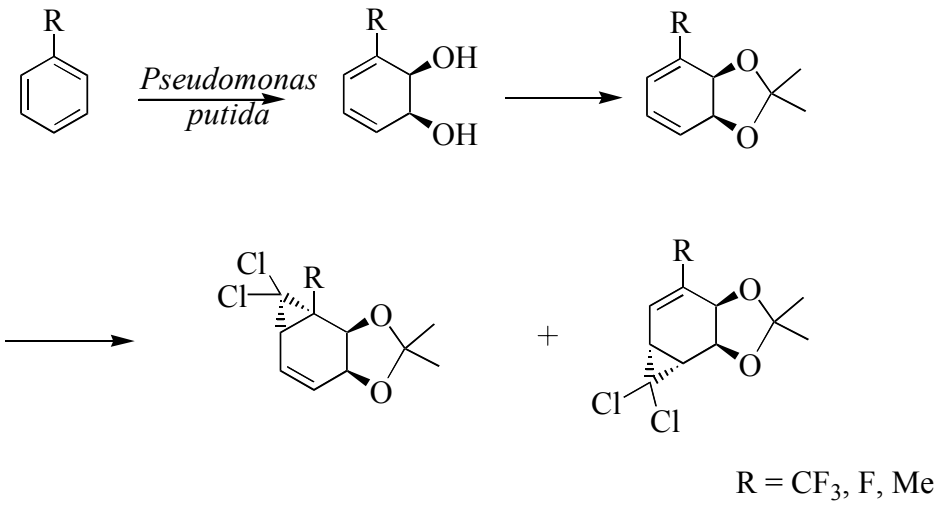
iv.) Michael induced ring closure (MIRC)

These methods have then been adapted to the synthesis of optically pure cyclopropanes by resolution of the final product, or precursor, or synthesis of the cyclopropane or cyclopropyl core by asymmetric means.

1.2.1 Resolution of the Cyclopropane or Precursor

Resolution and separation of enantiomers of a cyclopropane or cyclopropyl precursor can be attained either by indirect methods of chemical conversion to diastereomers, or enzymatic/microbial conversion,[17] or by the more direct method utilising chiral gas chromatography or HPLC.[18] Chemical conversion of the cyclopropane or precursor generally involves the use of enantiopure alcohols, amines, aldehydes and carboxylic acids to generate the corresponding diastereomers. Separation of the diastereomers can then be effected directly by chromatography (GC, HPLC, column chromatography) or by recrystallisation. Optically pure cyclopropanes and their precursors can also be attained by synthesis using asymmetric methods.

The microbial or enzymatic resolution of cyclopropanes and their precursors has been reported in a small number of specific examples.[17,18] Enzymes such as pig kidney acyclase and pig liver esterase have been used in the resolution of enantiomers of various systems.[17] Optically enriched cyclopropanes have been synthesised by the use of *cis*-1,2-dihydrocatechols generated by *Pseudomonas putida*. The catechols are synthesised with high enantiomeric excess by the bacterium from the corresponding aromatic precursors.[19] **(Scheme 1)**

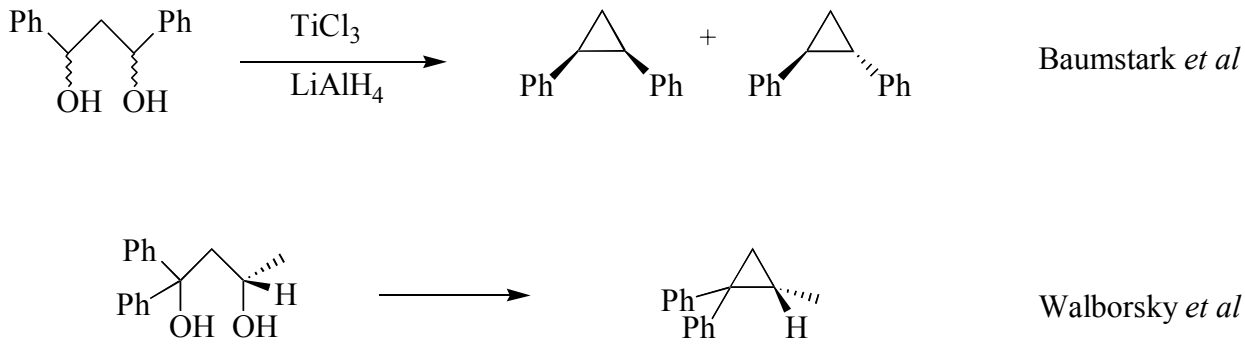


Scheme 1 Bacterial resolution of enantiomers.

The use of this bacterium in the synthesis of catechols with high enantiomeric excess has subsequently been adapted by Banwell *et al.* to the development of a partial synthesis of (*1R*)-*cis*-pyrethroids.[20]

1.2.2 1,3-Elimination of Heteroatoms

Baumstark *et al.* showed that the use of titanium trichloride and $LiAlH_4$ in reaction with 1,3-diols produced both *cis* and *trans* cyclopropanes in their synthesis of 1,2-diphenyl cyclopropane[21] and this was then further applied to the synthesis of an optically pure cyclopropane by Walborsky *et al.*.[22] **(Scheme 2)**



Scheme 2 Titanium 1,3-coupling of diols.

1,3-Dibromides and 1,3-diiodides have been coupled using zinc[23], sodium[24], magnesium[25] and $LiAlH_4$[26] to produce cyclopropanes by reductive 1,3-elimination of the halogens for primary, secondary and tertiary halides.[27]

1.2.3 Carbene Addition to Olefins

The addition of carbenes to olefins can be performed using two main methods:-

i.) Simmons-Smith carbene transfer utilising zinc intermediates[17,28,29]

ii.) transfer of carbene from transition metals using an alkyl diazoacetates precursor.[17,30]

The Simmons-Smith method relies on the *in situ* generation of an intermediate carbene species and can be performed by several methods. Three major methods utilised for cyclopropane synthesis are:-

i.) the Simmons-Smith reaction using a zinc-copper couple and a 1,1-dihaloalkane,[31]

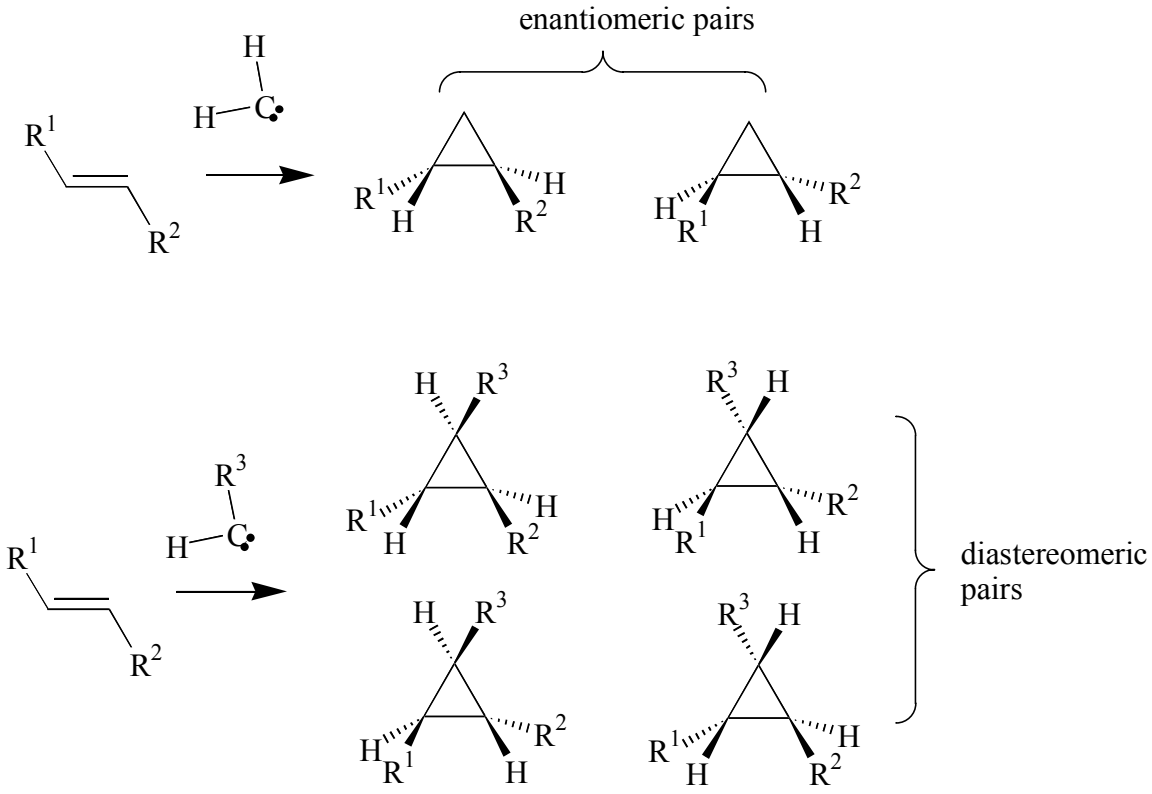
ii.) a method developed by Wittig utilising zinc(II) dihalide and alkyl diazoacetates[32]

iii.) the Furukawa method utilising dialkyl zinc and alkyl diazoacetates.[33]

After generation of the carbene species, a methylene or alkyl methylene addition across an olefinic bond produces the cyclopropane.

The addition of carbenes to olefins has been adapted to the synthesis of mono-, di- and tri-substituted cyclopropanes by the use of a suitably functionalised alkene and alkyl diazoacetate.[34]

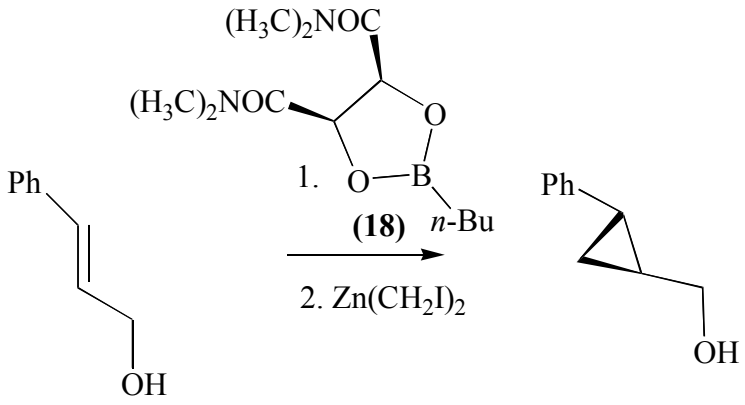
These syntheses produce only one diastereomer when methylene is added to the alkene, however, when a carbene of higher order is used in the synthesis both diastereomeric and enantiomeric pairs are possible, although only when R^1 is not equal to R^2 and hence the product is not *meso*. This can lead to synthetic problems when enantiomeric excess is required.[34,35] **(Scheme 3)**



Scheme 3 Diastereomeric and enantiomeric pairs formed in the addition of carbene to olefin**.**

By the use of suitable chiral ligands the Simmons-Smith reaction has been adapted to asymmetric synthesis of cyclopropanes by the addition of either a chiral compound that binds *in situ* to zinc enabling enantioselective carbene addition or a chiral auxiliary that is a component of the reactant alkene.[28,35,36]

The addition of chiral ligands to the reaction mixture in either catalytic or stoichiometric quantities leads to the introduction of enantiomeric excess. The use of a stoichiometric quantity of the chiral dioxaborolane **(18)** with allylic alcohols leads to the formation of cyclopropanes in high yield and high enantiomeric excess. The halomethylzinc reagent, which is preformed *in situ* by the reaction of diethylzinc and diiodomethane, interacts with the chiral dioxaborolane enabling synthesis of enantioenriched cyclopropanes. This reaction is catalytic and the chiral ligand can be recovered.[28,37] **(Scheme 4)**

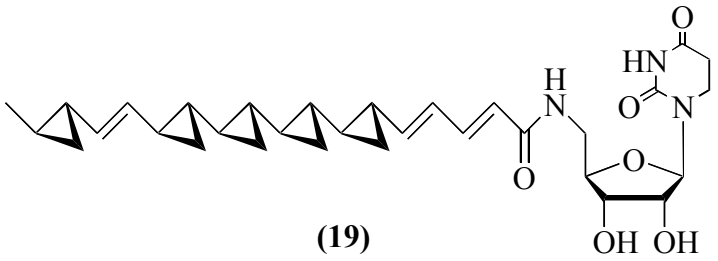


Scheme 4 Use of dioxaborolane ligands in enantioenriched cyclopropane synthesis**.**

Compounds are continually being developed for the catalytic synthesis of cyclopropanes with good enantiomeric excess. In the last decade new catalysts for the asymmetric synthesis of cyclopropanes from allylic alcohols have been developed which are utilised in a similar way to that shown in **Scheme 4**.[35,36]

The second method used in the Simmons-Smith reaction for the synthesis of chiral cyclopropanes utilises chiral auxiliaries that are a component of the olefin. These auxiliaries contain oxygen atoms that are free to bind, including alcohols, esters, ethers, ketals and boronates.[38] The cyclopropanation leads to the production of diastereomers that can then be separated by chromatography or recrystallisation, after which removal of the chiral auxiliary leads to cyclopropanes of high enantiomeric excess. The use of tartrate derivatives as the auxiliary has been shown to produce cyclopropanes with high enantiomeric excess.

The Simmons-Smith reaction has been applied to the asymmetric synthesis of biologically active polycyclopropyl compounds including a polycyclopropyl anti-biotic[39,40] **(19)** and a polycyclopropyl cholesteryl ester transfer protein reaction inhibitor[41] **(20)**.



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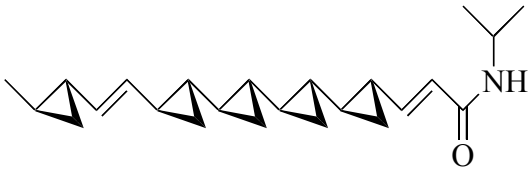
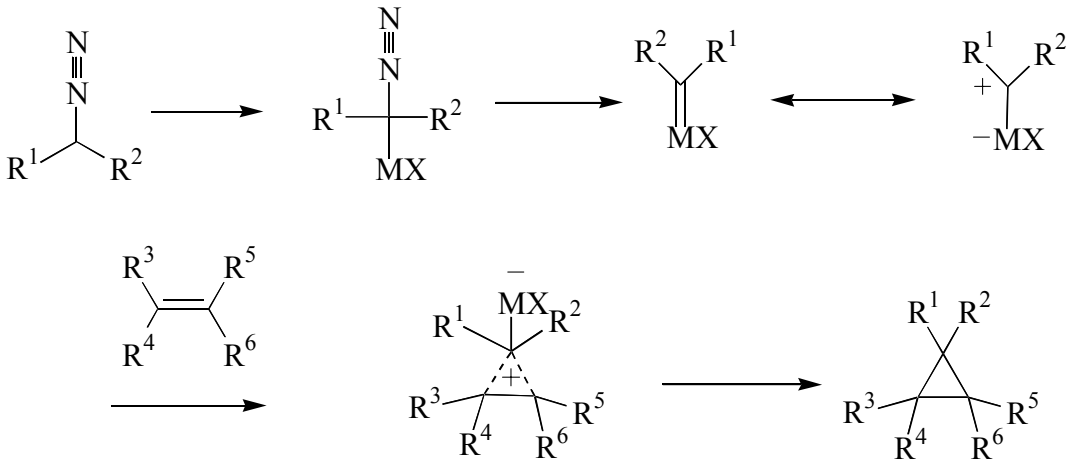


(20)

The second method utilised for the addition of carbene to olefins relies on the decomposition of alkyl diazoacetates by transition metal catalysts and the addition of the relatively stable carbene complex that results to the olefin.[17,30]

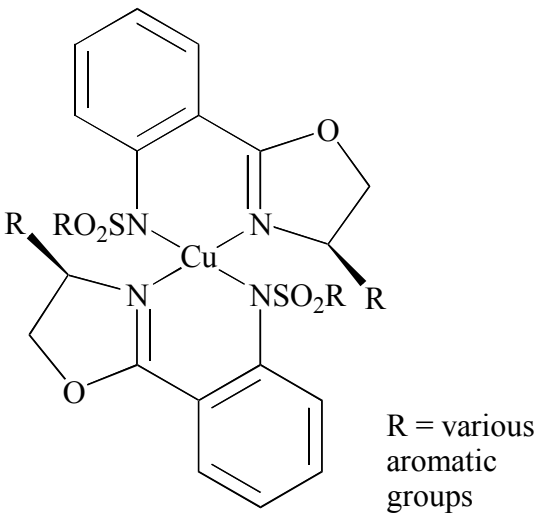
The reaction involves initial binding of the transition metal to the diazo compound. Expulsion of nitrogen produces the carbene complex which then complexes to the olefin. The orientation of this olefin complex determines the final configuration of the cyclopropane formed and determines the ratios of diastereomers and enantiomers. **(Scheme 5)**



Scheme 5 Synthesis of cyclopropanes from diazo precursors**.**

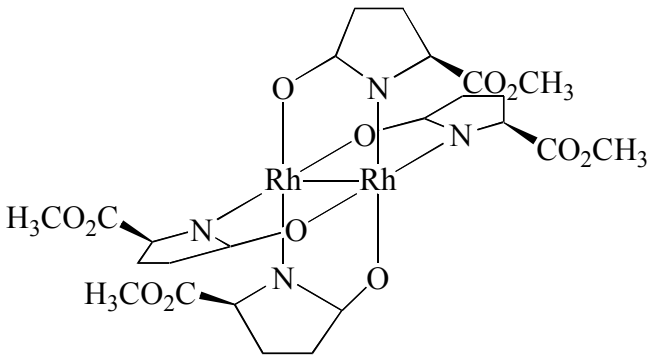
The use of transition metal-carbene complexes does not allow for high diastereoselection or the use of general chiral ligands, however, cyclopropanes of high enantioselectivity can be readily synthesised.[42]

Synthesis of cyclopropanes with moderate to high enantiomeric excess has been achieved by the use of a wide range of alkyl diazoacetates and chiral metal complexes. The use of *d*/*l* menthyl diazoacetates with chiral copper complexes leads to cyclopropanes of moderate to high enantiomeric excess **(21)**[43] and the use of di-rhodium catalysts enables synthesis of cyclopropanes with good enantioselectivity **(22)**.[44]



R = various aromatic groups

(21)



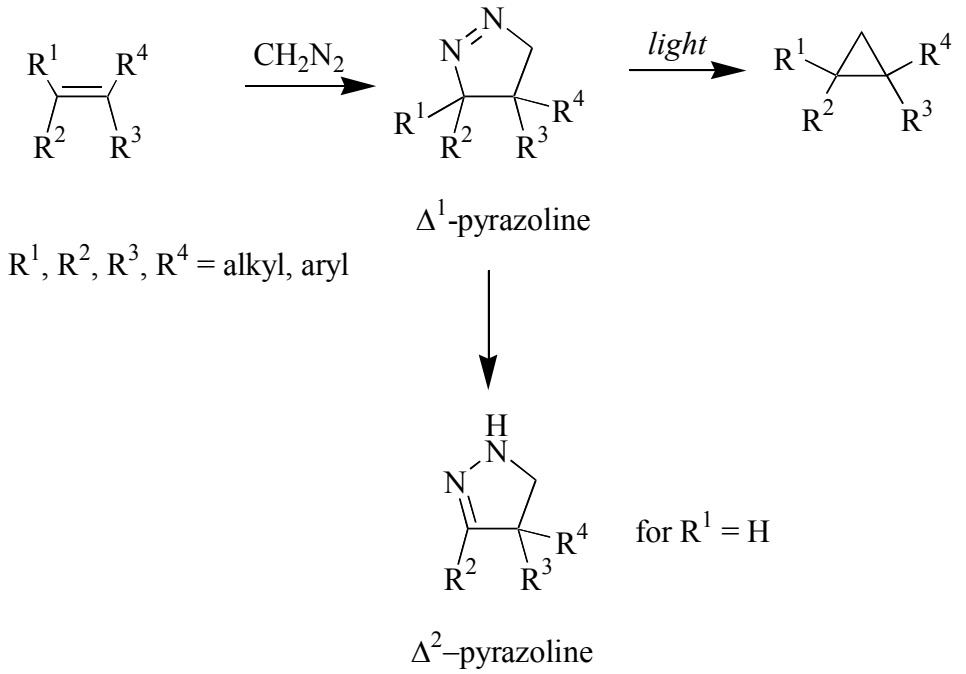
(22)

Simmons-Smith carbene transfer utilises the carbene in its highly reactive singlet state reacting with the olefin before decomposition to the triplet state. This leads to only *cis* addition to the olefin. Use of transition metals and diazomethane analogues produces the carbene in its more stable triplet state enabling both *cis* and *trans* cyclopropane formation.[45-47]

1.2.4 Nitrogen Extrusion from Pyrazolines

Cyclopropanes are formed when nitrogen is extruded photolytically from Δ^1-pyrazolines in a di-radical mechanism enabling retention of stereochemistry (**Scheme 6)**.[47] Δ^1-Pyrazolines can be synthesised by the addition of diazomethane, or a derivative, to the precursor olefin.

Introduction of optical activity by the use of chiral groups in the R^1-R^4 positions enables synthesis of the pyrazoline diastereoselectively from the olefin giving optically enriched or even optically pure cyclopropanes.[48-50] No loss of chirality occurs with the use of this method provided that tautomerisation to the corresponding Δ^2-pyrazoline is inhibited (**Scheme 6**) by the use of suitably designed precursor alkenes.



Scheme 6 Synthesis of cyclopropanes from pyrazolines by the extrusion of nitrogen.

The use of Δ^1-pyrazolines in the synthesis of cyclopropanes has been known for several decades[51] and its utility in the synthesis of highly strained systems **(Figure 1)** has been demonstrated.[52]

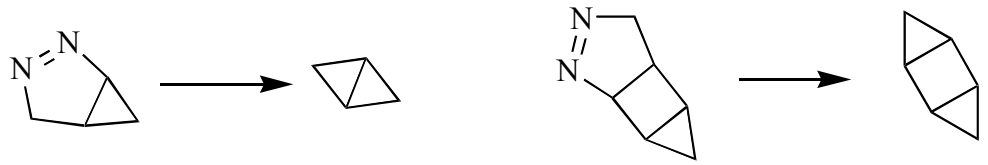
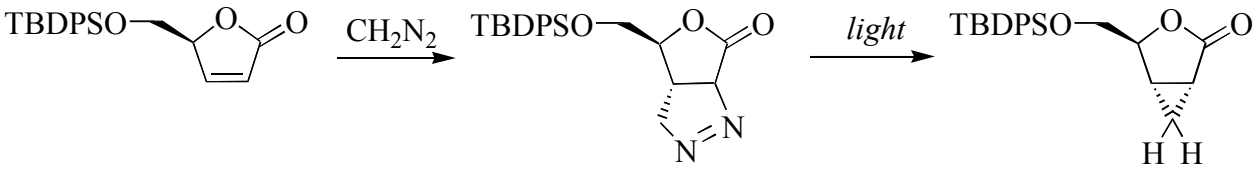


Figure 1

Enantiomerically pure precursors for cyclopropyl amino acids have been synthesised by the diastereoselective addition of diazomethane to enantio-pure furanone followed by the subsequent photolysis.[50] **(Scheme 7)**



Scheme 7 Synthesis of cyclopropanes from pyrazolines by the extrusion of nitrogen**.**

1.2.5 Michael Initiated Ring Closure (MIRC)

Michael initiated ring closure (MIRC) is the last of the commonly used methods for the synthesis of cyclopropanes and is the method by which cyclopropanes will be synthesised in this work.

MIRC is facilitated by the incorporation of an electron-withdrawing group in one of two ways:

i.) an electron withdrawing group and a leaving group on the carbanionic centre

ii.) an electron withdrawing-leaving group on the carbanionic centre.[53]

The presence of an electron withdrawing group and a leaving group in the arrangement shown below enables the formation of the cyclopropyl ring. **(Figure 2)**

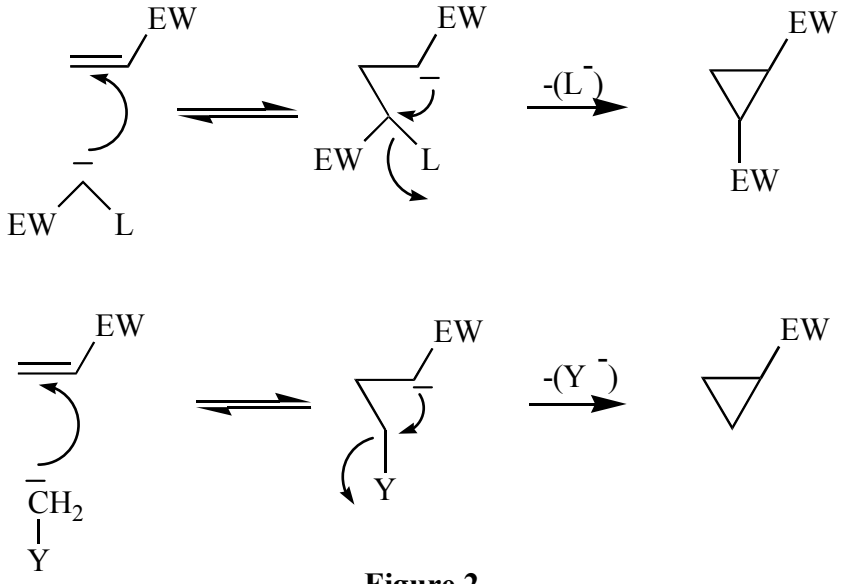
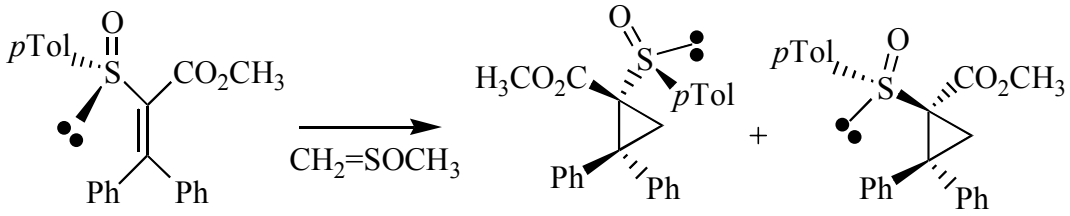


Figure 2

There are many variations of methods for the synthesis of cyclopropanes using MIRC's, however, only two of these approaches can be modified for the synthesis of enantiopure cyclopropanes. The use of chiral ylides, including sulphonium and sulphoxonium ylides, with achiral α,β-unsaturated olefins is in most cases unsuccessful,[54] the use of achiral ylides, including phosphorus ylides, with chiral α,β-unsaturated olefins leads to the introduction of enantiomeric excess with a moderate degree of success.[55-58] **(Scheme 8)**

Although good enantiomeric excess can be introduced into the cyclopropane the diastereomeric excess introduced is not necessarily sufficiently good for the reaction to be viable.

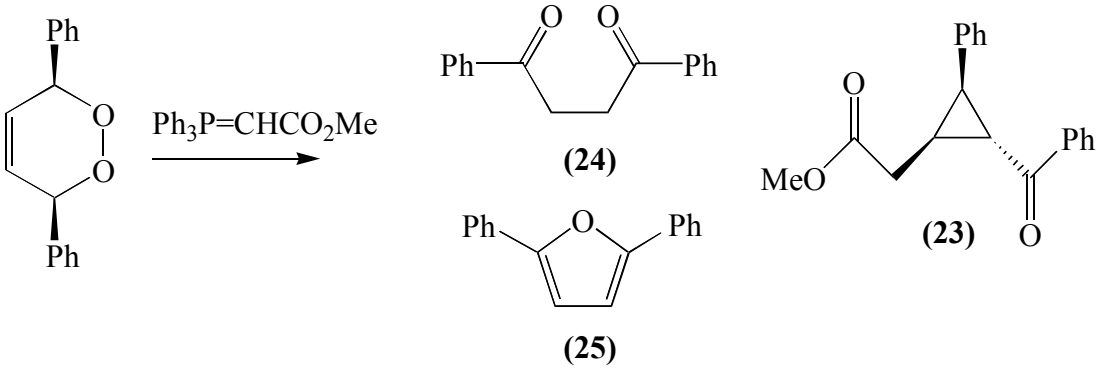


Scheme 8 Use of chiral alkenes in the synthesis of enantioenriched cyclopropanes**.**

Most of these syntheses rely on the addition of symmetrical anions and very few examples exist that enable the addition of non-symmetrical anions to the α,β-unsaturated olefins. Work within the *Taylor* group has enabled synthesis of cyclopropanes of high diastereomeric excess[59] and it is this work that enables the synthesis of cyclopropanes in both a high diastereomeric and enantiomeric fashion, as discussed in the forthcoming section.

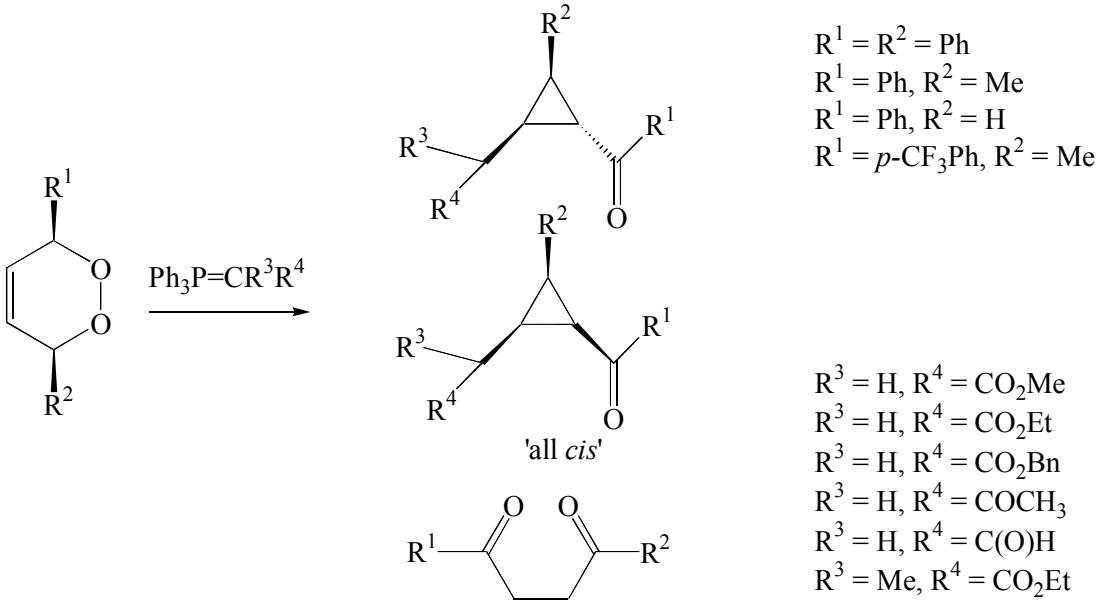
1.3 Previous Research

Work into the reactions of 1,2-dioxines and ylides, by the Taylor group, was begun several years ago in initial studies by T. Rathbone in which an excess of 1,2-dioxine was employed in reactions with various stabilised phosphorus ylides. In her work cyclopropane **(23)** was formed as only a minor product with diketone **(24)**, furan **(25)** and triphenylphosphine oxide isolated from the reaction mixture as the major components **(Scheme 9)**.[60]



Scheme 9 T. Rathbone synthesis of cyclopropanes.

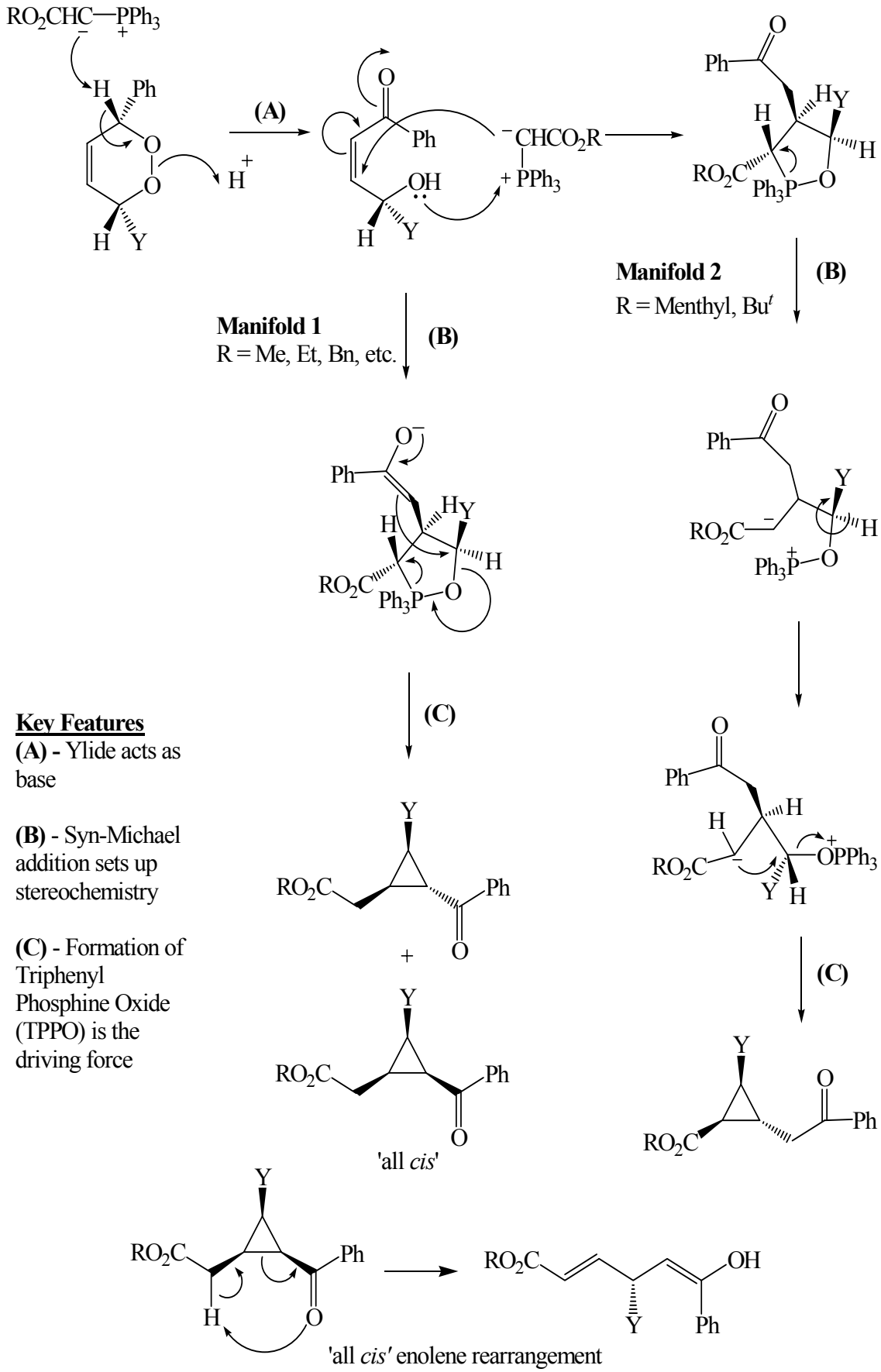
Due to time constraints the reaction conditions for the synthesis of cyclopropanes were not optimised in this initial work and it was not until the following year that studies into its optimisation and its applicability were performed,[61,62] and the stereochemistry of the cyclopropane products was determined **(Scheme 10)**.[62]



Scheme 10 Products in the cyclopropanation reaction.

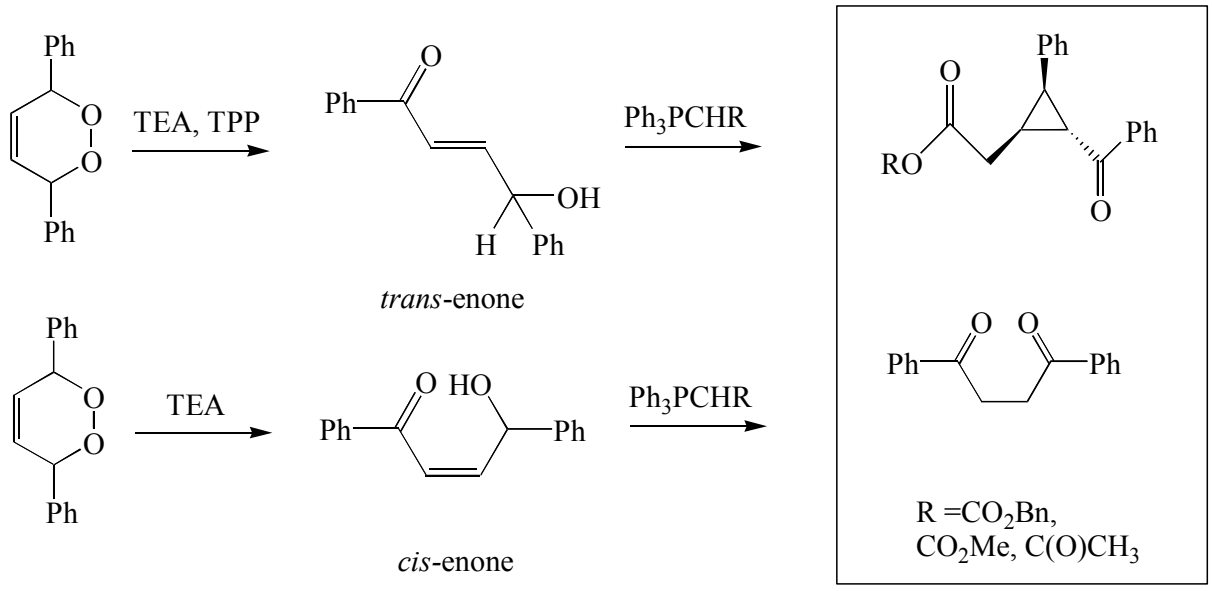
It was determined that high yields of cyclopropanes could be achieved when mono-substituted ylides were used and the reaction proceeded in a diastereoselective manner however the 'all *cis*' cyclopropane formed was unstable and would undergo facile enolene rearrangement **(Scheme 11)**. When di-substituted ylides were used in cyclopropanation a moderate yield of cyclopropane (40%) was produced enabling incorporation of another asymmetric centre into the cyclopropane.[62]

Cyclopropanation was found to produce two types of cyclopropane **(Scheme 11)** dependant on the ylide used and on any additives present in the reaction mixture. Manifold 1 predominated when ylides with 'non-bulky'esters (eg methyl, ethyl or benzyl) or bases such as triethylamine were added. Manifold 2 predominated when ylides with 'bulky' esters (eg *t*-butyl or adamantyl) or lithium bromide were added.



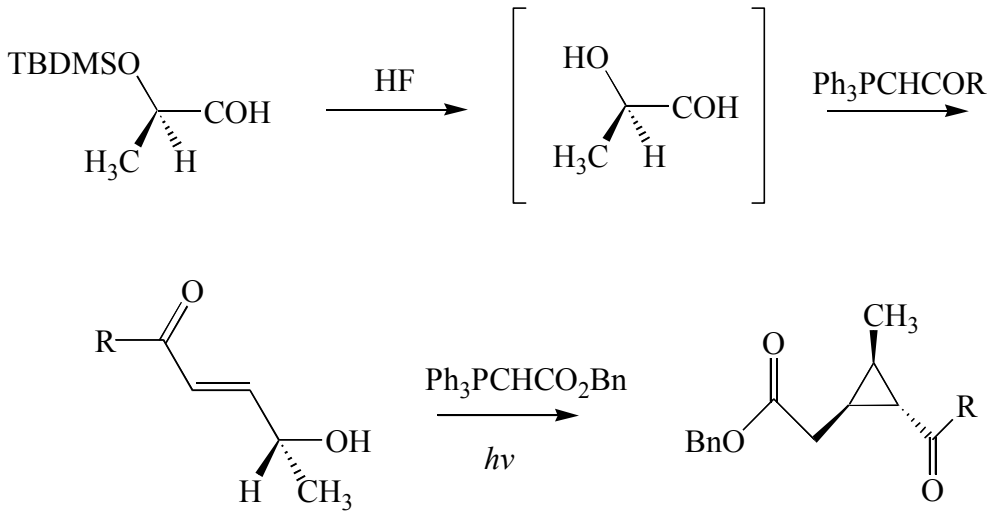
Scheme 11 Mechanism of cyclopropanation.

It was determined that the isomeric γ-hydroxyenone of the 1,2-dioxine was the compound responsible for reaction with the ylide, to produce the cyclopropane, however, it was unknown whether it was the *cis*- or *trans*-γ-hydroxyenone that participated in the reaction. Consequently, both the *cis* and *trans* enones were prepared. *Trans*-γ-hydroxyenones, formed by the addition of triethylamine and triphenylphosphine to dioxines, reacted with ylide to give cyclopropane as the minor product. *Cis*-γ-hydroxyenone, formed by the addition of triethylamine, produced cyclopropane in high yield when allowed to react with ylide and hence it was determined to be the enone responsible for the formation of cyclopropane in the reaction **(Scheme 12)**.[59,63-65]



Scheme 12 Synthesis of cyclopropanes from *cis* and *trans* enone**.**

Work was being performed concurrently into the synthesis of diastereo- and enantio-pure cyclopropanes using γ-hydroxyenones synthesised via mandelate and lactate esters.[66,67] Although work being performed by T. Avery and F. Palmer was showing that *trans*-γ-hydroxyenones were not the ideal starting material for the synthesis of cyclopropanes[59,63,64] the synthesis of optically pure cyclopropanes was achieved using *trans*-γ-hydroxyenones. Reaction of optically pure aldehydes with keto-ylides gave the *trans*-γ-hydroxyenones followed by reaction with an ester ylide in a one-pot reaction giving the cyclopropanes **(Scheme 13).**



R = CH_3, Ph, Bu^t, *p*-Br-Ph

Scheme 13 Synthesis of optically pure cyclopropane from optically pure aldehyde**.**

It was in 1989 that work into the ring-opening of 1,2-dioxines by cobalt(II) catalysts was reported by O'Shea and Foote and was the first reported example of the use of cobalt(II) in ring-opening monocyclic endoperoxides.[68]

Their work showed that 3,6-dimethyl- and 3,6-diphenyl-1,2-dioxines were ring-opened by cobalt(II) salen and cobalt(II) tetraphenylporphyrin, both 4-coordinate complexes. The 6-coordinate complexes investigated did not rearrange the dioxines, which suggested that it was the 4-coordinate geometry that was crucial in the ring-opening reaction. Of interest was their inability to detect any γ-hydroxyenone during the ring-opening of the 3,6-diphenyl-1,2-dioxine, evidence for the presence of γ-hydroxyenone only being present during the ring-opening of the 3,6-dimethyl-1,2-dioxine.[68] They did not study this reaction further, determining only its applicability to synthesise the 2,5-di-substituted furans.

The mechanism they proposed **(Figure 3)** involves the catalytic radical cleavage of the peroxide bond followed by a 1,5-hydrogen atom abstraction. The γ-hydroxyenone formed then closes to give the hemiacetal, which dehydrates to produce the furan.[68]

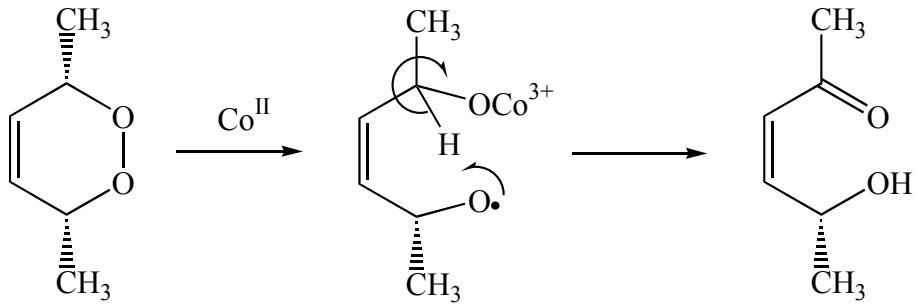


Figure 3 Mechanism of action of cobalt salen proposed by O'Shea and Foote**.**

It was this work by O'Shea and Foote that spurred interest into the use of tetradentate cobalt(II) complexes to ring-open 1,2-dioxines for use in the synthesis of cyclopropanes. Initial studies involved the use of achiral cobalt(II) salen and it was shown that cyclopropanes could indeed be formed from the enone produced.[63] The ring-opening was only applicable to symmetrical dioxines due to the fact that complex mixture of products formed when asymmetrical dioxines were employed. This is expected as the two regioisomers of the enone are both possible during the ring-opening of the 1,2-dioxine **(Figure 4)**.

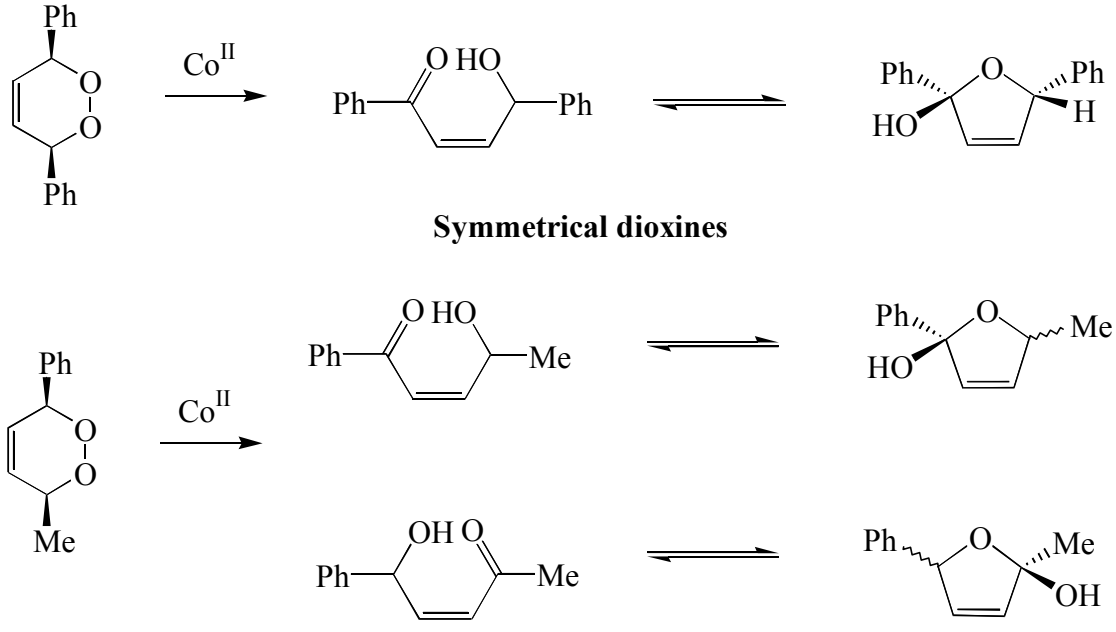


Figure 4 Rearrangement products when symmetrical and unsymmetrical dioxines are used**.**

Coupling the work by O'Shea and Foote with the new cyclopropanation reactions developed by the Taylor group, using 1,2-dioxines, suggested that if chiral ligands were employed for the catalysts then optically enriched enones would be produced. This enone could then be "trapped" by various ylides in a relatively simple synthesis of optically enriched cyclopropanes.

1.4 Catalysts in Asymmetric Synthesis

Catalysts have been used in organic chemistry for over 150 years. With slow beginnings from Faradays' use of platinum to induce the reaction of hydrogen and oxygen (published in the 1830's), and the first asymmetric reaction with Pasteurs' use of enzymatic resolution of ammonium tartrate using *Penicillium glauca* in the 1850's, the use of catalysts in organic synthesis has progressed in leaps and bounds to produce an area of synthesis that has become part of everyday chemistry.

Reactions that involve catalysis can be divided into one of three types:

i.) Enzymatic catalysis – which was discussed briefly in the previous section and is used either to selectively degrade one enantiomer preferentially or to facilitate an enantioselective reaction

ii.) Heterogenous chemical catalysis – such as the use of palladium on carbon in hydrogenation

iii.) Homogenous chemical catalysis – the use of which will be detailed in this section.

One of the first reported examples of asymmetric catalysis using a homogenous catalyst was work performed by Bredig in the early part of last century. His work involved the addition of HCN to benzaldehyde in the presence of an alkaloid that acted as the catalyst to produce mandelonitrile with limited enantioselectivity.[69]

For many years following few examples existed of the use of asymmetric synthesis. It was not until the 1930's that the oxidation of racemic 3,4-dioxy-phenylalanine by molecular oxygen in the presence of a chiral cobalt catalyst (*l*-diethylenediamine-monoammonio-monochloro-cobaltic bromide) was reported by Shibata.[70] Their research found that *l*-dioxy-phenylalanine was oxidised more rapidly than the *d*-form by the *l*-cobaltic salt, and vice versa when the *d*-cobaltic salt was employed.[71]

Some of the first examples of asymmetric synthesis, using an organometallic catalyst, that showed real promise occurred in the 1960's and were used in the synthesis of chiral polymers, cyclopropanes[72] and in asymmetric hydrogenation.[73-75] Further development of these early catalysts led to reactions capable of introducing useful levels of enantiomeric excess and further spurred research into chiral organometallic catalysts.

Many attempts have been made over the years to adapt organometallic catalysts enabling introduction of enantiomeric excess with varying success. The ability of catalysts to introduce chirality in more general reactions has provided much greater challenges than those of adapting the catalyst to one system. It was in the 1980's where the first major breakthroughs were discovered and it is these breakthroughs that still influence some areas of organometallic catalysis today.

Work by Sharpless in the early 1980's led to the development of methods for the asymmetric epoxidation of allylic alcohols. The method involved the use of titanium tartrate which was formed *in situ*, and used initially in stoichiometric quantities, however modification of the method with the addition of 3Å or 4Å molecular sieves enabled reduction of the quantity of catalyst (< 10% titanium(IV) isopropoxide) and improved the yields of the products and the enantiomeric excess introduced (from 39 – 80% *ee* using 5% titanium catalyst alone to 90 – 95% when molecular sieves are employed).[76]

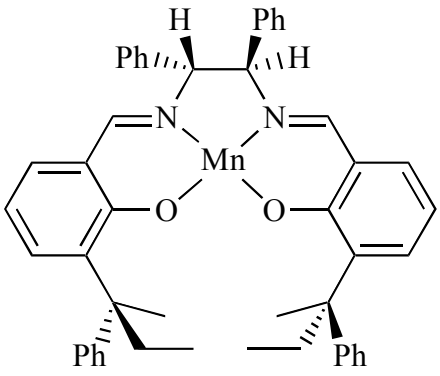
Further work by Sharpless in the 1980's in the area of asymmetric synthesis involved asymmetric dihydroxylation. Osmium tetroxide and derivatives of quinine were employed (quinine and quinidine act more like enantiomers than diastereomers) to introduce enantiomeric excess with varying success, stilbene having the highest *ee* introduced (78 – 88%) and alkyl alkenes and 1,1-disubstituted alkenes the lowest (20 – 46%).[77]

Some of the early examples of asymmetric synthesis involve the synthesis of cyclopropanes from alkenes and alkyl diazoacetates. This reaction has been discussed briefly in the previous section and the catalysts that have been employed will be discussed in more detail in **Chapter 2**.

Cobalt salen (or salcomine) was first synthesised in the 1930's by Pfeiffer, Breith and Lübbe[78] and the chemistry of the compound studied in the years following.[79] The synthesis was modified in 1950 by Audreith,[80] however, it was not until 1963 that work was published on its use in studies into the catalysed autooxidation of polyunsaturated fats.[81] In 1965 work was published detailing its use in the oxidation and autooxidation of *l*-limonene[82] and in 1967 work on the oxidation of cumene[83] and oxidation of phenols was published.[84] The use of cobalt salens in asymmetric synthesis will be discussed further in **Chapter 2**.

In the many years following the synthesis of cobalt salen many different metal salens have been synthesised for use in catalysis. Titanium salens,[85,86] copper salens,[87,88] chromium salens,[89,90] manganese salens,[91-93] palladium salens[94] and iron salens[95,96] have all been synthesised for their use as catalysts in organic synthesis.

In 1986 the use of achiral manganese salens in the epoxidation of olefins was reported.[91] Subsequently, in 1990 Irie *et al.* published work on the asymmetric epoxidation of olefins using a manganese salen **(26)**, which introduced enantiomeric excess into the epoxides of 1-phenyl-1-propene (44 – 50%).[92] In the same year Jacobsen *et al.* reported the first use of his manganese salens **(27)** for use in the epoxidation of unfunctionalised olefins.[93] The reactions utilised iodosylmesitylene as the oxygen donor to produce epoxides with varied enantiomeric excess, the lowest being for 1-phenyl-1-propene (20%) and highest for 1,1-ethylenedioxycyclohex-2-ene (93%).



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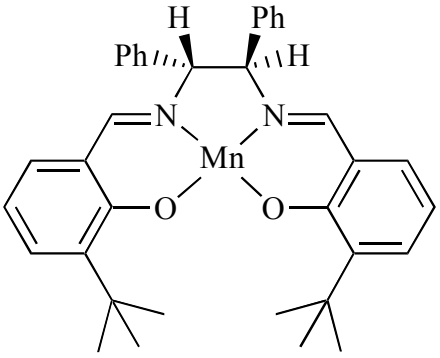


(27)

The use of metal salens in catalytic organic synthesis will be discussed further in subsequent chapters where appropriate.

Initial studies by other members of the Taylor group into the use of chiral cobalt(II) salen were performed using symmetrical dioxines and it was determined that enantiomeric excess could be introduced into the cyclopropanes synthesised, confirming the hypothesis. These early studies were only performed on a very limited range of catalysts and the reaction was yet to be optimised.[63]

It is these initial studies that the work contained within this thesis draws on with the synthesis of a wide range of catalysts, the introduction and optimisation of enantiomeric excess during the dioxine rearrangement and its application to the synthesis of cyclopropanes and other related molecules.

2. Cobalt β-Ketoiminato and Cobalt [Salen]$_2$ Complexes:- Synthesis and Use in Cyclopropanation

2.1 Introduction

2.1.1 Cobalt Salens

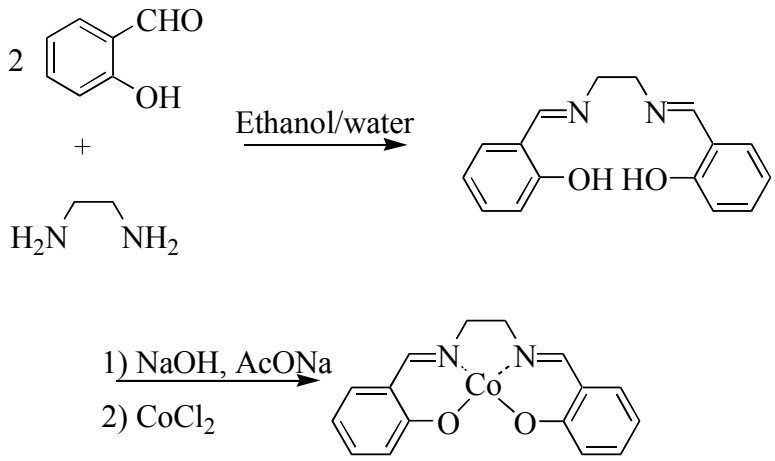
As was mentioned in **Chapter 1**, one of the very early chiral organometallic catalysts synthesised was a cobalt catalyst (*l*-diethylenediamine-monoammonio-monochloro-cobaltic bromide) that was used in the oxidation of 3,4-dioxy-phenylalanine by molecular oxygen.[70,71] It was around the same time that the synthesis of cobalt salen was first reported,[78] and in the following years the chemistry of the complex was studied,[79] the synthesis modified,[80] and its catalytic ability determined.[81-84]

The work of Shibata, mentioned above and discussed briefly in the previous chapter, is some of the earliest in which a chiral cobalt catalyst was employed, however, little work was done in the use of chiral cobalt catalysts for many years and it is not until the 1970's that further examples of their use were published.[97-99]

Cobalt salen was originally synthesised by the reaction of cobalt acetate, ethylene diamine and salicylaldehyde in aqueous ethanol in a one-pot reaction utilising the template method of catalyst formation (where the metal acts as a centre around which the reaction components bind and react to form the ligand).[78] This early method led to a mixture of products, due to the presence of oxygen and acid, which were inactive towards oxygen indicating they are already in a fully oxidised state.

The method by which Diehl[80] synthesised cobalt salen involved first synthesis of the ligand by the addition of ethylene diamine to a boiling solution of the aldehyde in ethanol. The crystalline material that resulted was then purified and allowed to react with sodium hydroxide and sodium acetate. A solution of cobalt(II) chloride was then added and the complex precipitated **(Scheme 14)**. This latter method led to fewer unreactive impurities and

it has been this method, with minor variations, which have been most useful in the synthesis of the cobalt(II) salens.



Scheme 14 Synthesis of Cobalt Salen.

Cobalt(II) and (III) salens have been used in asymmetric reactions involving: -

i.) hydroxylation, with only low yield (30%) and low enantiomeric excess (38%),[100]

ii.) cyclopropanation, using olefins and alkyl diazoacetates with varying success controlling the *cis* to *trans* ratio and a range of enantiomeric excess introduced,[101-104]

iii.) ring-opening of epoxides, using both monomeric and polymeric catalysts,[105,106]

iv.) kinetic resolution of racemic epoxides,[107,108]

v.) *S*-ylide formation by the asymmetric sigmatropic rearrangement of *trans*-cinnamyl phenyl sulphide and related compounds.[109]

Cobalt salens have also been used in several studies into the oxidation and autoxidation of phenols by molecular oxygen,[110-114] in the oxidation of 3-methylindole[115] and in the asymmetric reduction of ketones.[116]

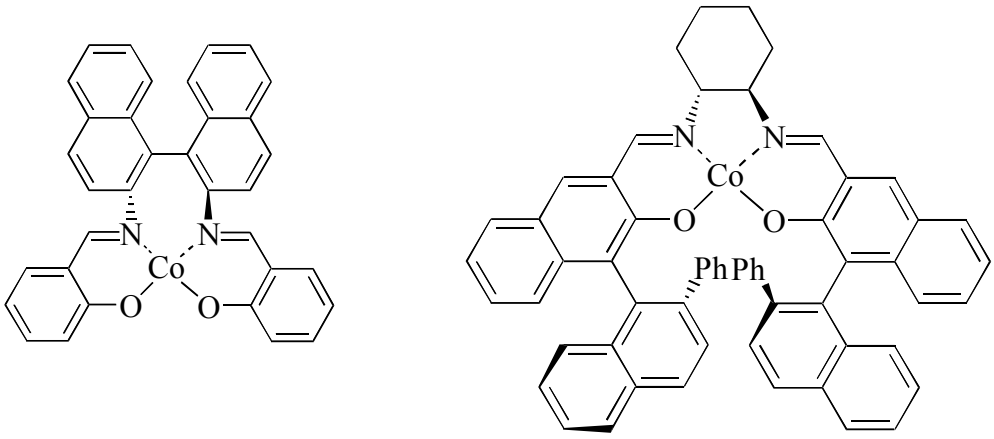
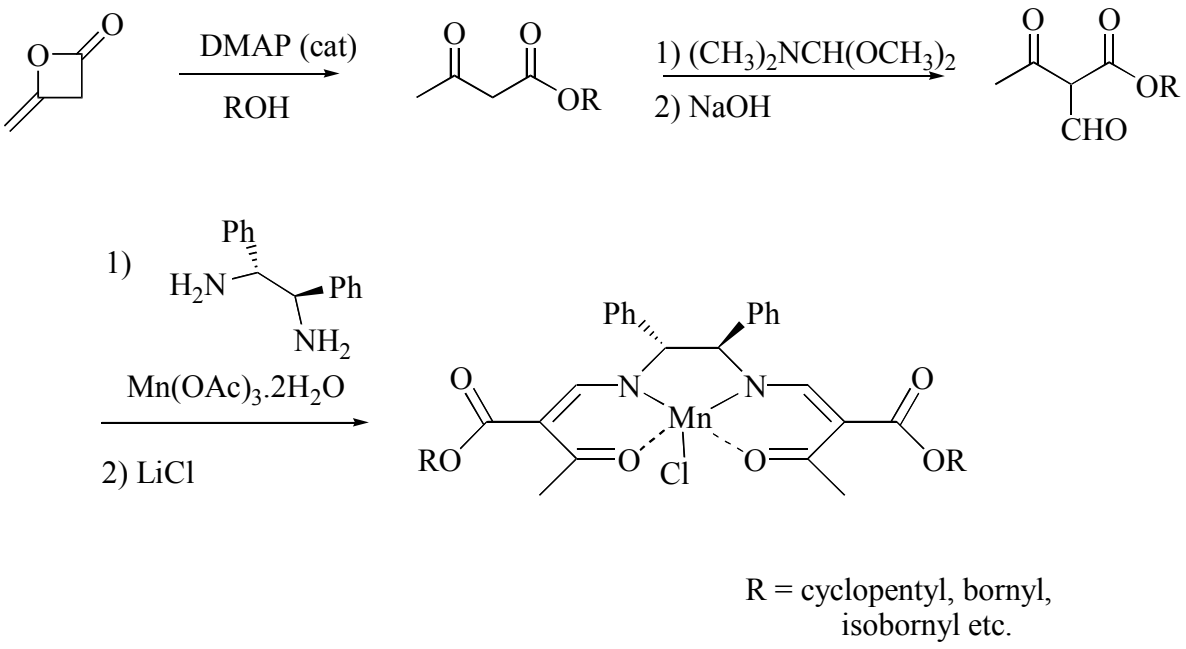


Figure 5 Examples of the types of ligands used for cobalt salens**.**

The chiral diamines used in the synthesis of the chiral ligands are often 1,2-diaminocyclohexane, 2,2'-diaminobinapthyl or 1,2-diphenyl diaminoethane, and the aldehydes employed in their synthesis are incredibly varied with substitution at the 3, 4, 5 and 6-positions with groups that can be small or bulky, chiral or achiral, napthyl and binapthyl systems included **(Figure 5)**. This variability provides complexes with an adaptable structure that enables determination of catalysts most suitable for a particular synthesis.

2.1.2 Cobalt β-Ketoiminato Complexes

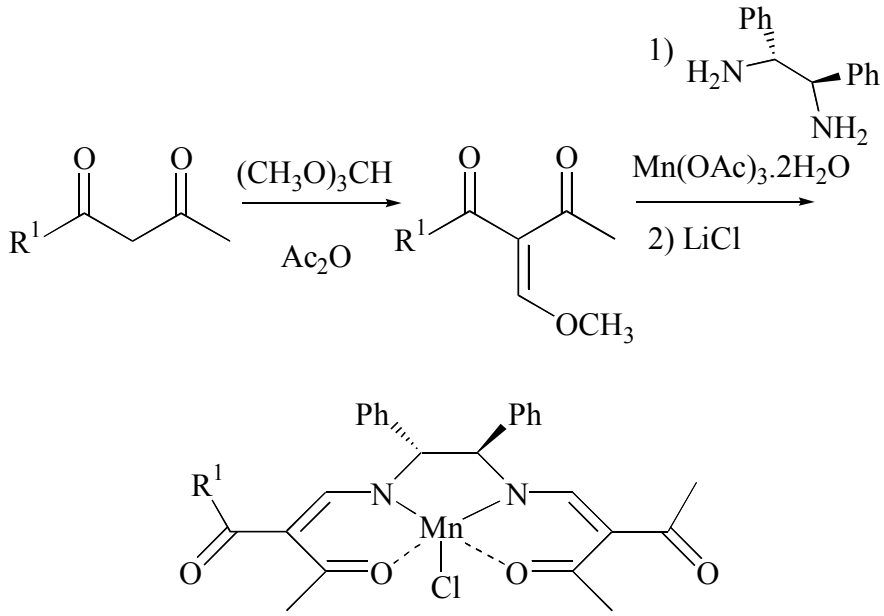
The β-ketoiminato ligands have been known for nearly a decade and were first used for manganese(III) complexes by Nagata *et al*.[117] The synthesis of the manganese complexes was performed using the template method, described above, to produce two types of the β-ketoiminato complexes **(Schemes 15 and 16).**[117]



Scheme 15 Method 1 for the synthesis of manganese (III) β-ketoiminato complexes.

The first type **(Scheme 15)** involved the use of diketene and the desired alcohol to give an alkyl acetoacetate. Reaction of the alkyl acetoacetate with dimethylformamide dimethyl acetal, followed by base hydrolysis, gave the aldehyde, which was allowed to react with diphenylethylene diamine and manganese(III) acetate to furnish the catalyst. (The catalysts were subsequently purified by chromatography.)[117]

The second type **(Scheme 16)** was synthesised using 2,4-pentanedione (acetylacetone) or a related compound, which was allowed to react with trimethyl orthoformate and acetic anhydride to furnish a protected aldehyde. The catalysts were then formed either by the template method or by synthesis of first the ligand followed by addition of manganese(III) acetate.[117]



R^1 = CH_3, 1-napthyl, 2-napthyl,
2,4,6-trimethylphenyl

Scheme 16 Method 2 for the synthesis of manganese (III) β-ketoiminato complexes**.**

These manganese catalysts were then used in epoxidation reactions of various olefins with the introduction of moderate to high enantiomeric excess introduced in the products.[117-119]

During the same period Nagata also synthesised cobalt(II) examples for use in the enantioselective reduction of ketones with sodium borohydride.[120] The complexes used in this work were synthesised by heating the ligand with sodium hydroxide and cobalt(II) chloride hydrate in aqueous methanol. These catalysts introduced moderate to high enantiomeric excess into the secondary alcohols produced.[120,121]

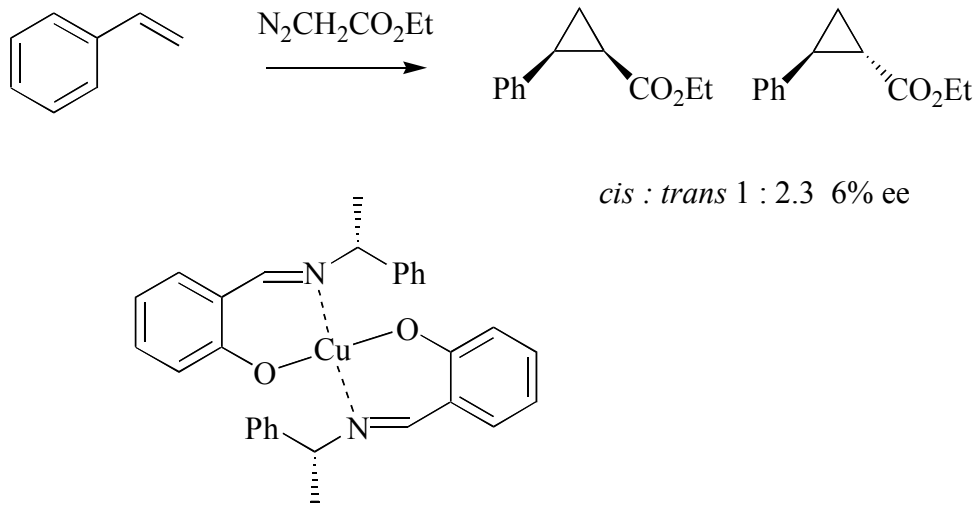
Several examples of the use of both cobalt(II) and (III) β-ketoiminato complexes in enantiomeric synthesis have been published over the last few years in reductions of ketones,[122-124] cyclisations[125,126] and in cyclopropanation using olefins and alkyldiazomethanes,[127,128] all of which report moderate to high introduction of enantiomeric excess into the products.

2.1.3 Metal Complexes in Cyclopropanation

Cyclopropanes play an important role in biological systems with many exhibiting biochemical activity, as was discussed in **Chapter 1**. It is not only natural cyclopropanes that play an important biochemical role; many synthetic cyclopropanes also produce complex biochemical interactions.

The methods used in the synthesis of cyclopropanes have been discussed in the previous chapter, with detail of some the catalysts used for asymmetric synthesis. The use of cobalt catalysts in asymmetric cyclopropanation will be discussed in more detail in the following section.

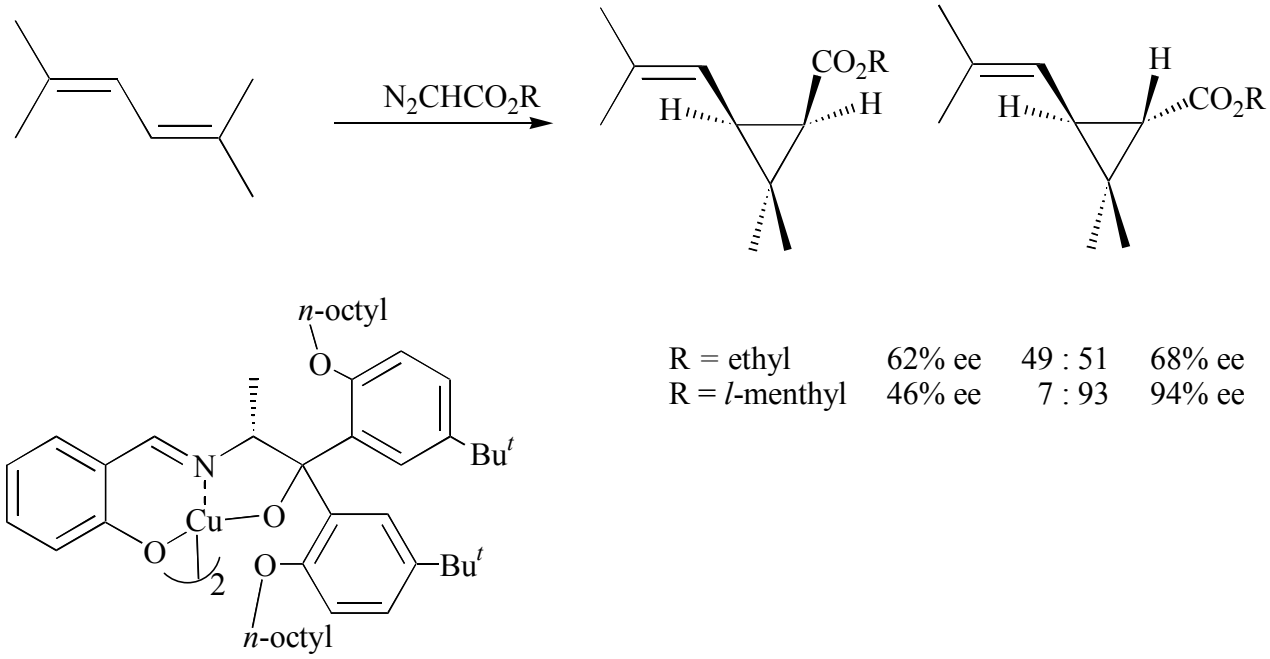
The first reported asymmetric synthesis of a cyclopropane, in 1966 by Nozaki *et al*, was one of the earliest examples of metal complex catalysed asymmetric synthesis.[72] Their work used a chiral copper catalyst in the decomposition of ethyl diazoacetate and the resultant carbene addition to styrene to give the cyclopropane in good yield (72%) as a mixture of *cis* and *trans* isomers (ratio of 1:2.3) and an enantiomeric excess of 6%. In comparison to more recent syntheses this enantiomeric excess is extremely low, however, in this early work it was a significant breakthrough **(Scheme 17)**.[129]



Scheme 17 Synthesis of cyclopropane using a chiral copper catalyst**.**

The above example was a significant development in the asymmetric synthesis of cyclopropanes, although for many years no further examples of this type were published.

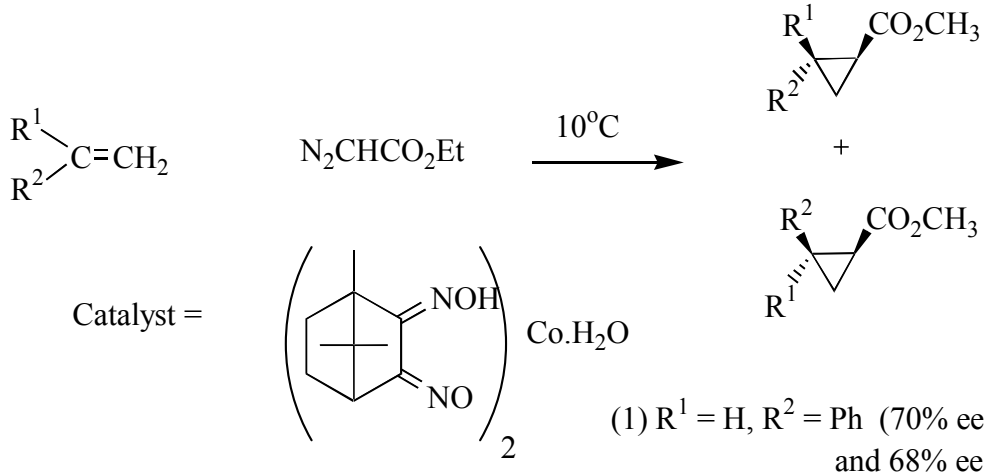
It was not until 1975 that further developments in asymmetric cyclopropanation were reported by Aratani *et al* who successfully used a chiral copper catalyst to introduce high enantiomeric excess (92%) into a simple cyclopropane.[130] The published work also includes an application of this reaction to the synthesis of Chrysanthemic acid, which is an important precursor for the synthesis of pyrethroid insecticides (the acid was produced with a *cis* to *trans* ratio of 48.6 : 51.4 and enantiomeric excesses of 62% and 68% respectively) **(Scheme 18)**.



Scheme 18 The synthesis of esters of Crysanthemic Acid using asymmetric catalysis**.**

The work of Shibata discussed previously is some of the earliest in which a chiral cobalt catalyst was employed, however, little work was done in the use of chiral cobalt catalysts for many years and it was not until the 1970's that further examples of their use were published.[97-99] Work by Tatsuno, reported in 1974, is the earliest example of the use of a chiral cobalt catalyst in the synthesis of cyclopropanes, from alkenes and diazoacetates, and

the method employed produced the cyclopropane with high enantiomeric excess **(Scheme 19)**.[99]

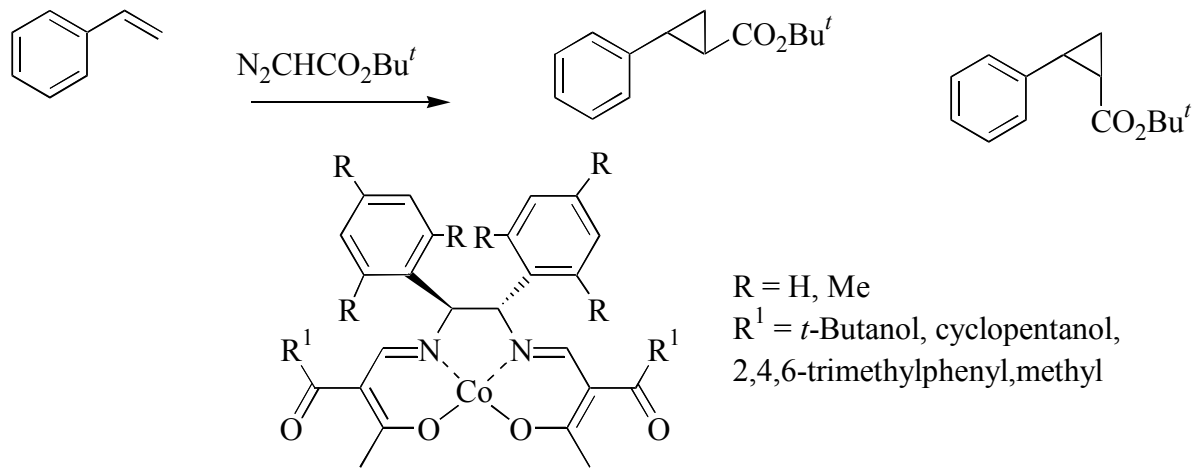


(1) R^1 = H, R^2 = Ph (70% ee for the *trans* isomer and 68% ee for the *cis* isomer)
(2) $R^1 = R^2$ = Ph

Scheme 19 Earliest reported use of a chiral cobalt catalyst in the synthesis of cyclopropanes**.**

Both cobalt(II) and (III) salens have been used in the addition of carbenes to olefins[101,102] the first example of which was reported in 1978 by Nakamura *et al*.[131] Cyclopropanes were synthesised in high yield with variable enantiomeric excesses, with a maximum optical yield of 88%.

The use of chiral cobalt(II) β-ketoiminato complexes in cyclopropanation has been reported only recently with their use by Ikeno *et al* in the reaction of styrenes and diazoacetates producing cyclopropanes with moderate to high enantioselectivity (61 – 96%) (**Scheme 20)**.[127,128]



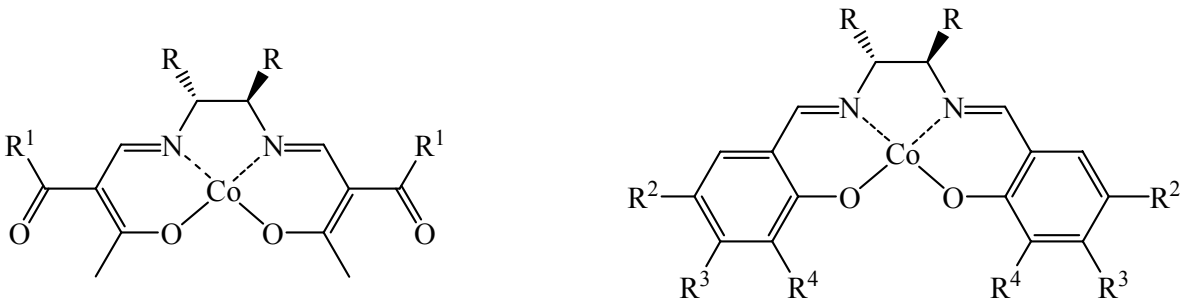
Scheme 20 Cyclopropanation utilising cobalt β–ketoiminato complexes.

The results published by Ikeno indicate that, in their application, increased bulk surrounding the cobalt centre leads to increased enantiomeric excess introduced into the cyclopropyl product.

The synthesis of cyclopropanes from olefins and alkyl diazoacetates has been reported using cobalt(II)[102,127,128,131] and (III)[101] complexes, copper(II) complexes,[132-134] rhodium(II) catalysts[135] and ruthenium(II) catalysts[136-139] along with palladium, nickel, molybdenum, rhenium, tungsten and iron complexes.[140]

The ability of cobalt(II) salens and cobalt(II) β-ketoiminato complexes to introduce enantiomeric excess into products has been demonstrated numerous times over the last 30 years in a wide range of syntheses. With the work by O'Shea and Foote[68] indicating that cobalt(II) in tetradentate complexes are able to ring-open 1,2-dioxines to give the corresponding racemic γ-hydroxy enone, and work within the Taylor group showing that enantio-pure γ-hydroxy enones can be utilised in the synthesis of enantio-pure cyclopropanes, it was of interest to synthesise a wide range of chiral cobalt(II) catalysts to determine whether previous observations can be applied to the asymmetric ring-opening of symmetrical (*meso*) 1,2-dioxines. As mentioned within the Introduction, if the resultant γ-hydroxy enones are produced in high enantiomeric excess then enantio-enriched cyclopropanes can then be synthesised from these 1,2-dioxines.

A broad range of salens and β-ketoiminato catalysts (**Figure 6**) were prepared and their efficacy examined. (Where the catalysts are denoted in the form of: R = -$(CH_2)_4$-, R^1 = Bu^t (*R,R* isomer) the chirality refers to the 'diamine' portion of the ligand).



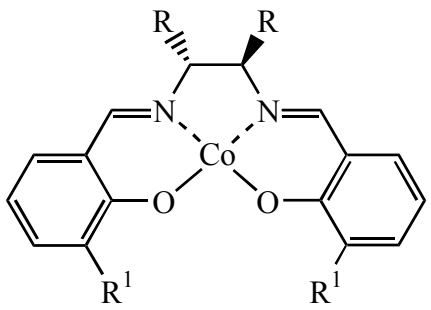
Cobalt β-ketoiminato complexes **Cobalt salens**

Figure 6 General form of the cobalt complexes to be prepared.

2.2 Results and Discussion

2.2.1 Synthesis of Cobalt Salens

The general method employed for the synthesis of the desired cobalt(II) salens followed that of Diehl,[80] published over 50 years ago, with only minor alterations. The synthesis of all of the cobalt salens involved, first, synthesis and purification of the ligand, by reaction of the aldehyde with the diamine in ethanol, followed by reaction with cobalt acetate tetrahydrate, in deairated ethanol. The precipitated catalyst was then collected, dried *in vacuo* and used without any further purification. The catalysts synthesised using this method, without the need for the synthesis of the aldehyde, are shown below **(28a-c, 29a-b & 30a-b)**.



28a: - R = -$(CH_2)_4$-, R^1 = OCH_3 (*R,R* isomer)
28b: - R = Ph, R^1 = OCH_3 (*R,R* isomer)
28c: - R = 2,2'-Binapthyl, R^1 = OCH_3 (*R* isomer)

29a: - R = -$(CH_2)_4$-, R^1 = *t*-Butyl (*R,R* isomer)
29b: - R = Ph, R^1 = *t*-Butyl (*R,R* isomer)

30a: - R = -$(CH_2)_4$-, R^1 = H (*R,R* isomer)
30b: - R = Ph, R^1 = H (*R,R* isomer)

To determine the effect of chirality in the southern quadrant **(Figure 7)** of the catalyst, chiral aldehydes were required. The aldehydes of interest, a benzaldehyde and a binapthaldehyde, had both been made previously and used in the synthesis of manganese salens.

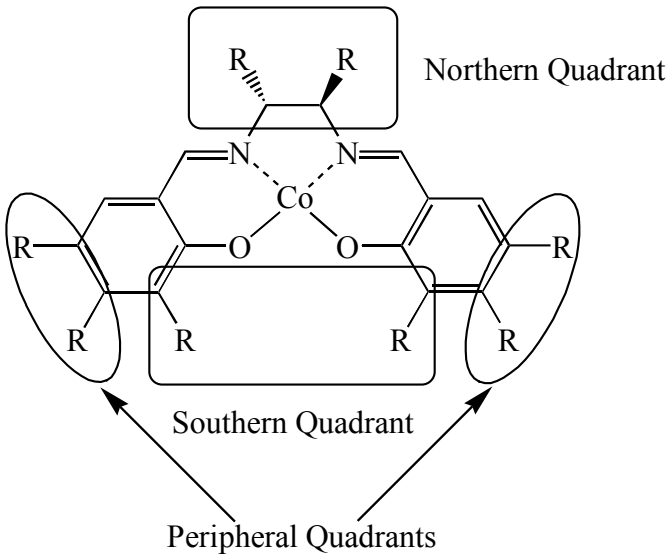
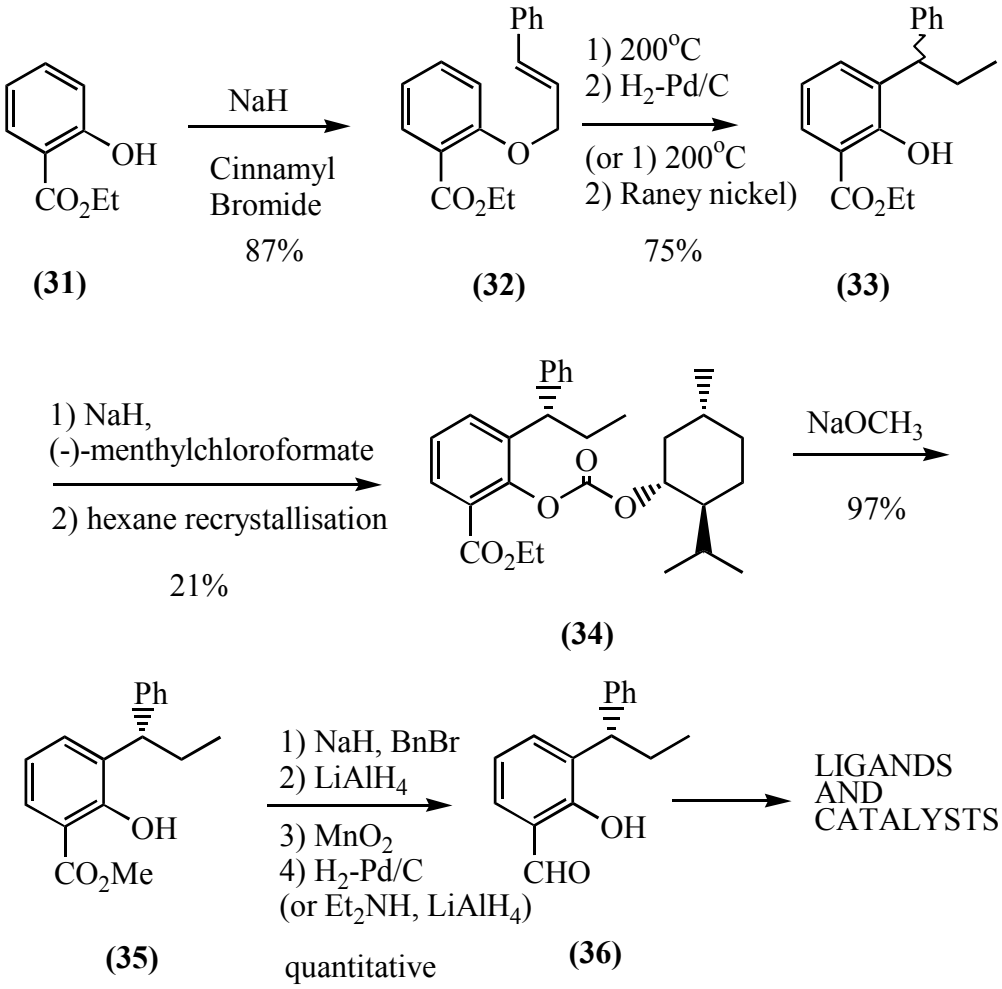


Figure 7 Division of the catalyst into quadrants.

A chiral benzaldehyde synthesised by Irie *et al*[141] for use in manganese catalysts was of interest in determining the effect of chirality in the southern quadrant. Irie *et al*[141] allowed ethyl salicylate **(31)** to react with sodium hydride and cinnamyl bromide to give the cinnamyl ether **(32),** which was heated at 200^{o}C, to enable Claisen rearrangement, and then hydrogenated to give the new salicylate **(33)**. Resolution of the enantiomers by use of the menthyloxycarbonyl derivative and hexane recrystallisation gave the optically pure compound **(34)** in low yield. The low yield produced is due to the numerous fractional recrystallisations needed, the remainder of the material was a mixture of diastereomers. The optically pure compound (**34**) was hydrolysed using methoxide to give the optically pure salicylate **(35)**. Protection, reduction, oxidation to the aldehyde and deprotection gave the requisite benzaldehyde **(36)** which was used to form the manganese catalysts using the template method **(Scheme 21)**.[141]

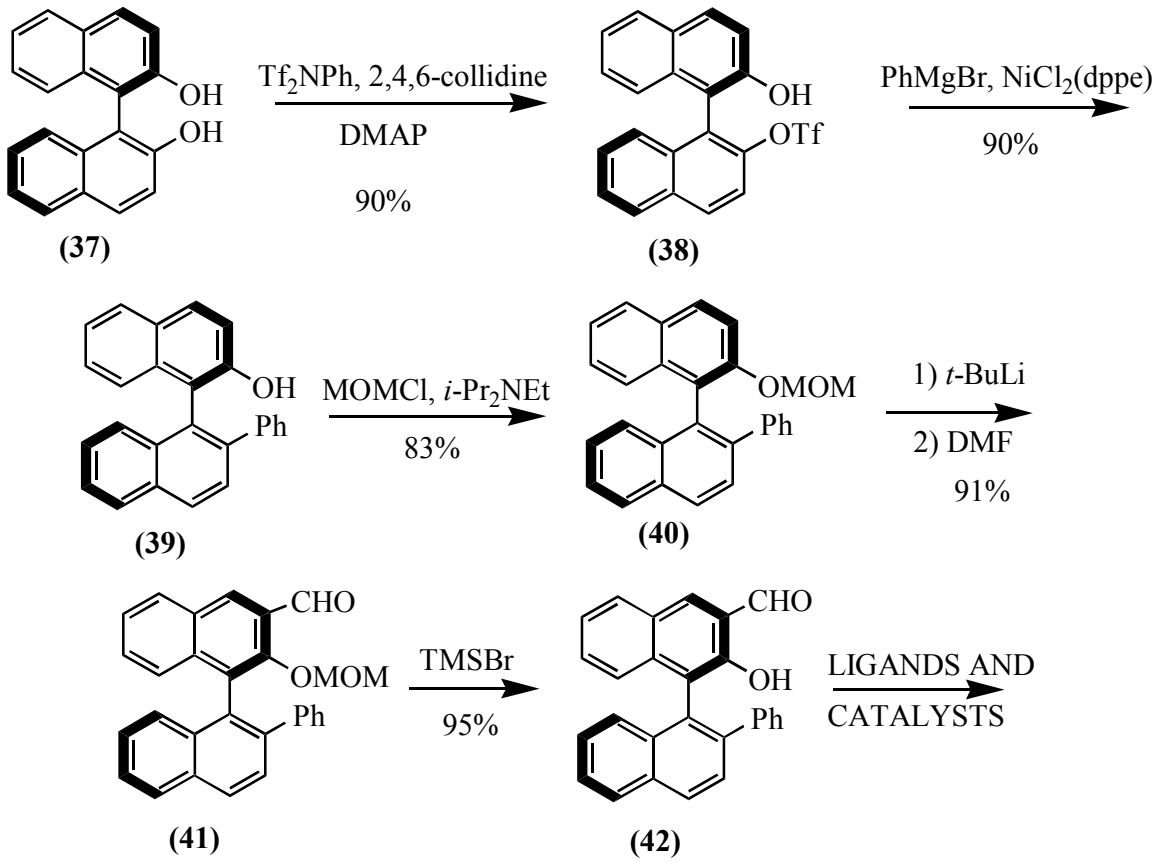


Scheme 21 Synthesis of chiral benzaldehyde used by Irie *et al.*

The method employed by Irie *et al*[141] was modified, although in slight detriment to the overall yield without optimisation of the modified steps. The first four steps in the synthesis were followed with only minor changes, Raney nickel was employed in place of palladium on carbon, only the last step was modified significantly using diethylamine and lithium aluminium hydride to produce the desired aldehyde directly without the need for protection, oxidation and deprotection.

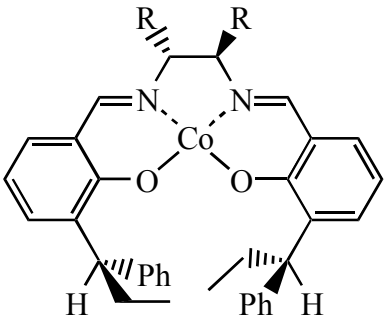
Two examples of the binapthaldehyde **(42)** desired for use in the catalysts had been reported in the literature, one with methoxy substituents in the 6 and 6′ positions, the other unsubstituted.[142,143] The aldehyde of interest was synthesised by monoprotection of optically pure binapthol **(37)** as the monotriflate **(38)**. Reaction of the monotriflate with phenyl magnesium bromide gave **(39)** which was protected as the MOM ether **(40)**. Formylation

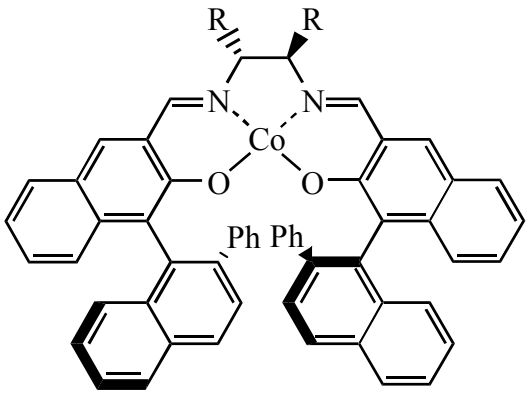
followed by deprotection produced the aldehyde **(42)**, which was then allowed to react with diamine to furnish the ligands and catalysts **(Scheme 22)**.[143] It was this method that was utilised in the synthesis of the binapthaldehyde, with the synthesis of **42** performed without purification of the MOM ether protected aldehyde.



Scheme 22 Synthesis of chiral binapthyl aldehyde.

From these chiral aldehydes the catalysts were synthesised by other members of the Taylor group, as for the other examples to give catalysts **(43a-c & 44a-c)** and their characterisation will be reported in the near future.





43a: - R = -$(CH_2)_4$- (*R,R* isomer)
43b: - R = Ph (*R,R* isomer)
43c: - R = Ph (*S,S* isomer)

44a: - R = -$(CH_2)_4$- (*R,R* isomer)
44b: - R = Ph (*R,R* isomer)
44c: - R = Ph (*S,S* isomer)

The catalysts thus made were used in the asymmetric ring-opening of *meso* 1,2-dioxines that will be discussed in subsequent sections.

2.2.2 Synthesis of Cobalt β-Ketoiminato Complexes

The cobalt(II) β-ketoiminato complexes were synthesised by modification of a procedure previously used by Nagata *et al*[117] in the synthesis of manganese(III) β-ketoiminato complexes. The cobalt(II) β-ketoiminato complexes were required to ascertain whether they were capable of ring-opening *meso*-1,2-dioxines in the same way as that of the cobalt(II) salens. β-Ketoiminato complexes with chirality in the Northern Quadrant and Peripheral Quadrants (**Figure** 8) were of interest to determine the effects these areas have on any introduced enantiomeric excess.

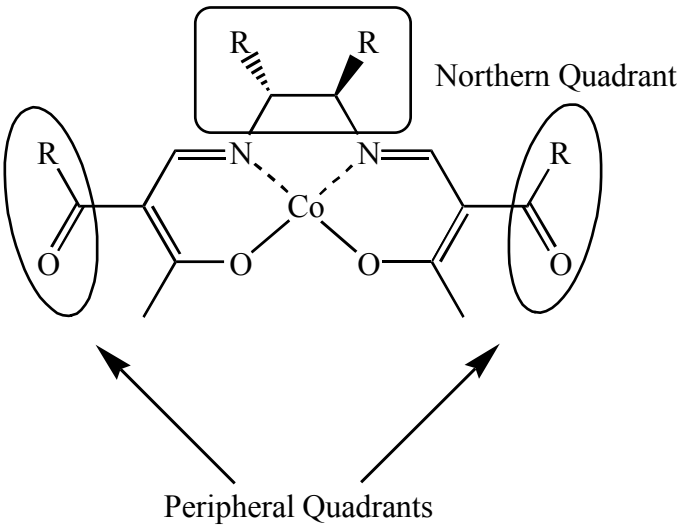


Figure 8 Division of the catalyst into quadrants.

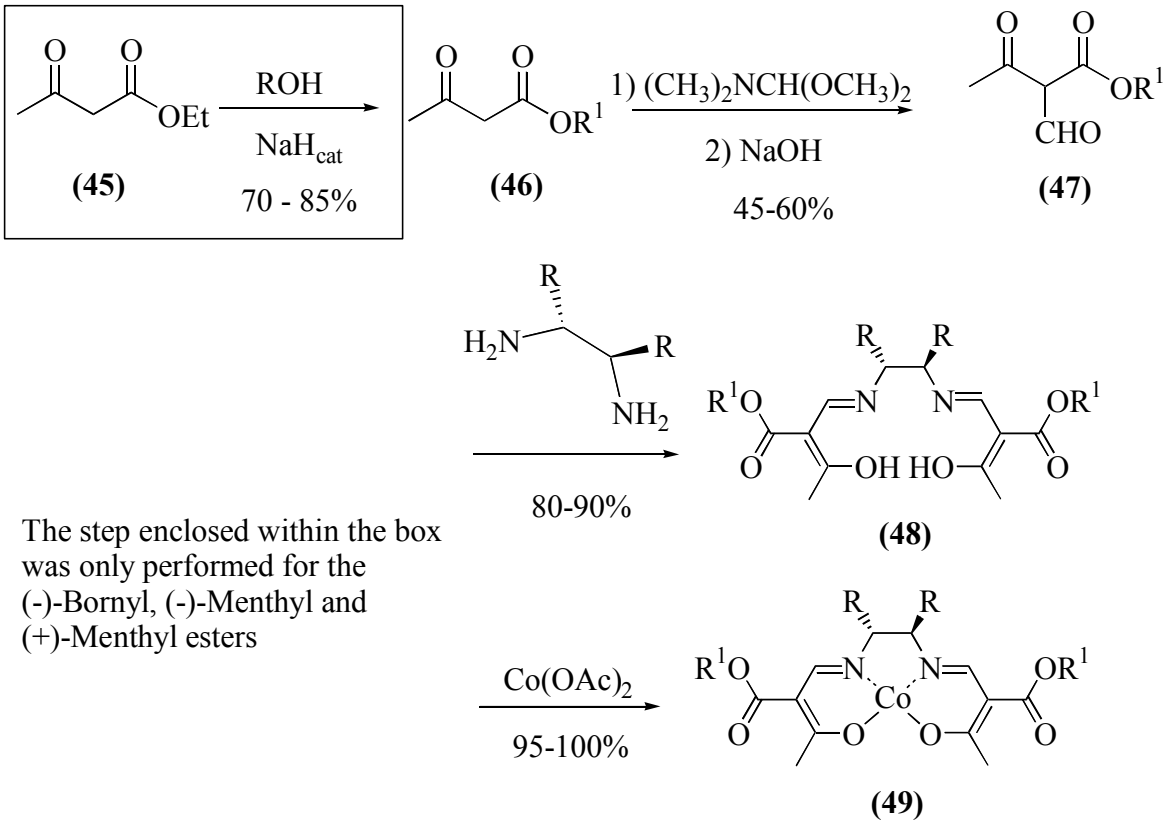
As was mentioned previously **(Scheme 15)** the previous method utilised in the synthesis of the alkyl acetoacetates used diketene as the precursor material. Due to an inability to obtain this compound, at the time that it was required, another method was required if the β-ketoiminato ligands were to be made.

Ethyl acetoacetate was readily available, as was *t*-butyl acetoacetate, hence the ethoxy and *t*-butoxy ester ligands could be readily synthesised using a literature method.[119] It was thought that ethyl acetoacetate would be an ideal substitute precursor for any other ligands required.

First attempts at synthesising the alkyl acetoacetates did not lead to the formation of any of the desired material. Hydrolysis of ethyl acetoacetate gave the corresponding acid, which was unstable if stored at room temperature for extended periods of time. Although the acid was unstable,[144] esterification was attempted several times with (-)-borneol using Dean and Stark conditions, in various solvents, catalysed by *p*-toluene sulphonic acid. This did not yield any of the desired starting material, 100 percent of the alcohol being recovered on each attempt.

With the failure of this first method a second was attempted. Transesterification of ethyl acetoacetate **(45)** with (-)-borneol, under Dean and Stark conditions with the catalytic addition of sodium hydride, produced the desired ester in moderate yield. This method was then applied to the synthesis of alkyl acetoacetates **(46)** from (-)-menthol and (+)-menthol **(Scheme 23)**.

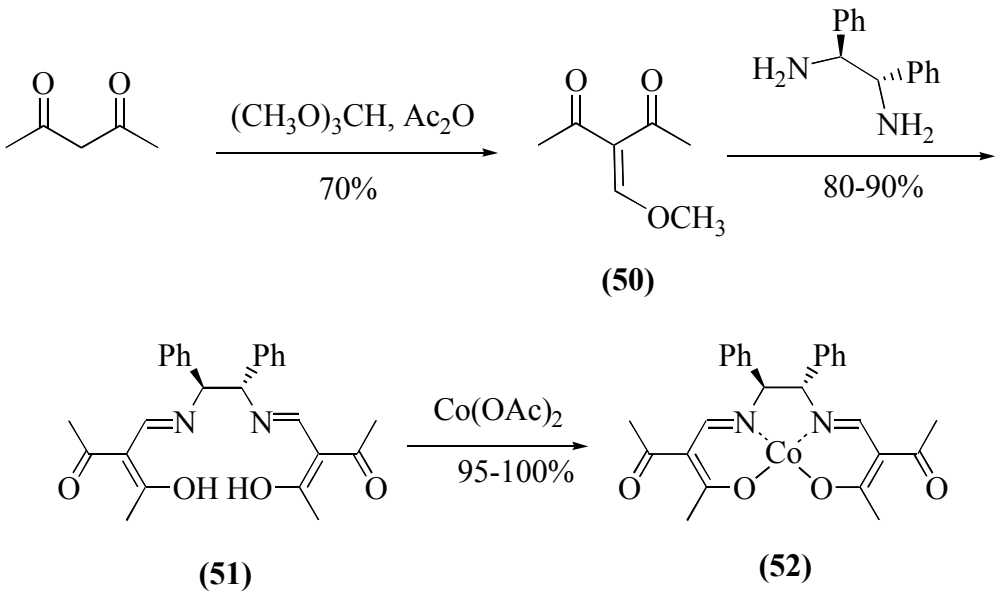
The remainder of the method used by Nagata *et al*[117] was then employed for the synthesis of each of the desired aldehydes **(47)**. The ligands of general structure **(48)** were then synthesised and purified before reaction with cobalt(II) acetate in deairated ethanol, under reflux, to give the catalysts of general structure **(49) (Scheme 23)**.



R^1 = Ethyl, *t*-Butyl, (-)-Bornyl, (-)-Menthyl, (+)-Menthyl
R = H, -$(CH_2)_4$- (*R,R* isomer), -$(CH_2)_4$- (*S,S* isomer), Ph (*R,R* isomer), Ph (*S,S* isomer)

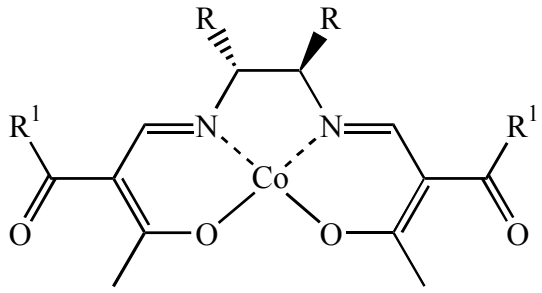
Scheme 23 Synthesis of Cobalt β-ketoiminato complexes from ethyl acetoacetate**.**

3-Methoxymethylene-2,4-pentane dione **(50**) was also required for additional catalysts with a methyl side chain rather than an ester. The dione was synthesised by the same method used by Nagata *et al*[117] **(Scheme 15)** to produce the ligand **(51)** for cobalt(II) complex **(52) (Scheme 24).**



Scheme 24 Synthesis of Cobalt β-ketoiminato complexes from 2,4-pentane dione.

The β-ketoiminato complexes synthesised **(52, 53a-c, 54, 55a-e, 56a & b & 57a & b)** were then used in the ring-opening of *meso* 1,2-dioxines.



52: - R = Ph, R^1 = Methyl (*S,S* isomer)

53a: - R = -$(CH_2)_4$-, R^1 = Ethoxy (*R,R* isomer)
53b: - R = Ph, R^1 = Ethoxy (*R,R* isomer)
53c: - R = Ph, R^1 = Ethoxy (*S,S* isomer)

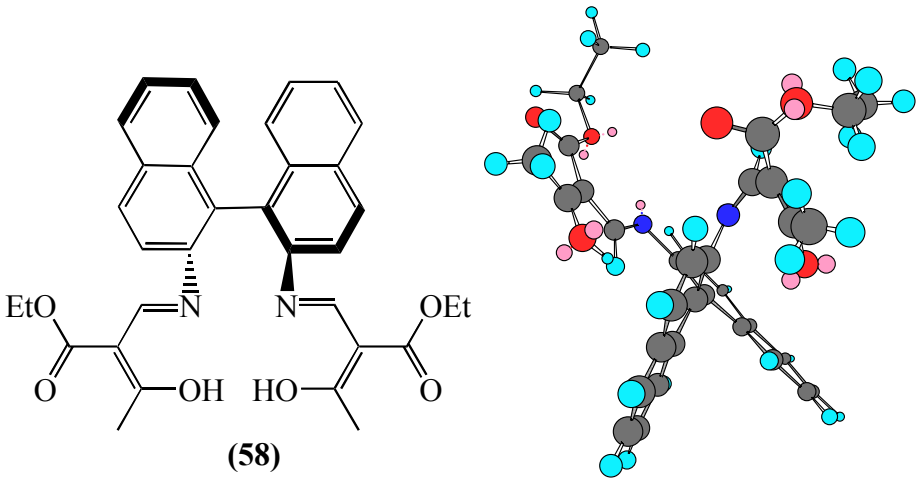
54:- R = Ph, R^1 = *t*-Butoxy (*S,S* isomer)

55a: - R = H, R^1 = (-)-Bornoxy
55b: - R = -$(CH_2)_4$-, R^1 = (-)-Bornoxy (*R,R* isomer)
55c: - R = -$(CH_2)_4$-, R^1 = (-)-Bornoxy (*S,S* isomer)
55d: - R = Ph, R^1 = (-)-Bornoxy (*R,R* isomer)
55e: - R = Ph, R^1 = (-)-Bornoxy (*S,S* isomer)

56a: - R = Ph, R^1 = (-)-Menthoxy (*R,R* isomer)
56b: - R = Ph, R^1 = (-)-Menthoxy (*S,S* isomer)

57a: - R = Ph, R^1 = (+)-Menthoxy (*R,R* isomer)
57b: - R = Ph, R^1 = (+)-Menthoxy (*S,S* isomer)

Of the ligands made the only ligand that did not complex with the cobalt(II) is shown below **(58)**. It is proposed that its inability to complex is due to the cavity shape and size being incorrect for adequate binding of the cobalt centre. The hydroxyl moieties of the enols directed away from the centre may also be inhibiting their ability to bind **(Figure 9)**. This ligand had not been made previously, however, the analogous salen had been made and was capable of binding metals without difficulty.[108]



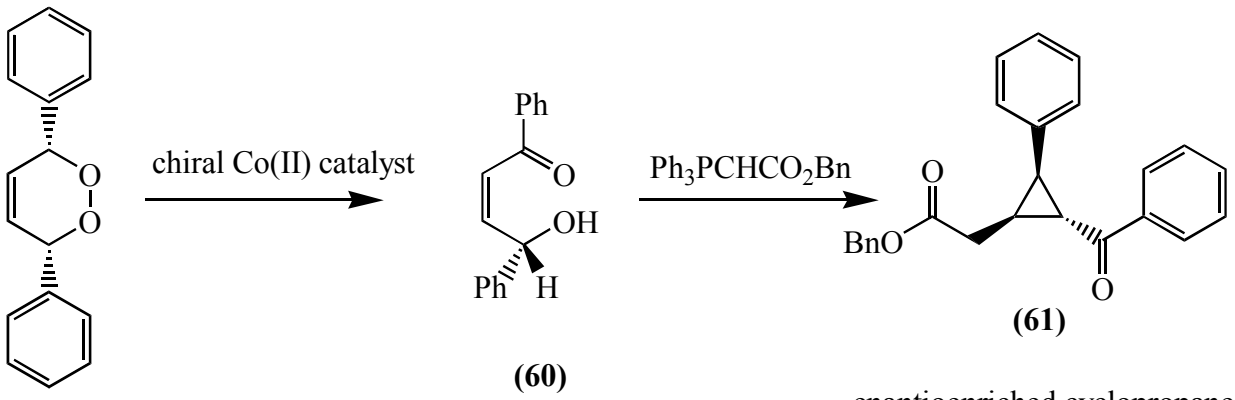
(58)

Figure 9 Ethyl ester binapthyl ligand schematic and MM2 minimised structure

Refer to fold out section **Appendix 3** for structures of Cobalt Salens mentioned from hereon and fold out section **Appendix 4** for structures of Cobalt β-Ketoiminato complexes mentioned hereon. These fold out sections are supplied to aid in the interpretation when catalysts are referred to hereafter.

2.2.3 Cobalt(II) Complexes in Cyclopropanation

As previous work by T. Avery[63] had shown that the yield of cyclopropane was maximised when dichloromethane was used as the solvent this was used as the starting point to test the catalysts made. The catalyst was first allowed to ring-open all of the dioxine (**59**), by t.l.c. analysis, before addition of the ylide (**Figure 10**). Moreover, the *meso* 1,2-dioxine **(59)** was employed in most of our optimisation studies.



(59)

'*Meso*'

(60)

(61)

enantioenriched cyclopropane

Figure 10 Reaction used for the majority of catalyst tests.

The enantiomeric excess of the cyclopropane (**61)** was measured using chiral shift NMR, in 1:4 d_6-benzene/carbon tetrachloride. Although there are many other methods available to measure enantiomeric excess this was deemed to be the most suitable for this system.

Initial studies into the use of the cobalt(II) salens provided useful insights into the regions of the catalysts that were important for the introduction of enantiomeric excess (**Table 1)**.

For catalysts **43b** and **44b** the diamine used in the synthesis of the catalyst is mismatched with the chiral amine used (i.e. the diamine introduces chirality in the opposite direction to that of the aldehyde), reducing the overall enantiomeric excess introduced. However, for each of the other examples in which a chiral aldehyde was utilised, the aldehyde and diamine are matched in their ability to introduce enantiomeric excess.

In several of the cases (**28a & b, 43a & c, 44a & c)** it was noted that the lesser steric bulk of the cyclohexyl diamine, and possibly its minimised freedom of rotation, led to a significant reduction in the enantiomeric excess introduced. This was not the case for all of the examples, the more electron poor systems containing the *t*-butyl and unsubstituted 'aldehydes' (**29a & b, 30a & b)** introducing a higher *ee* when the cyclohexyl catalyst was employed.

Using the standard conditions chirality in the Northern Quadrant **(Figure 7)** was determined to be essential to introduce enantiomeric excess with bulk in the Southern Quadrant less

important than the presence of an electron rich system. Chirality in the Southern Quadrant had virtually no effect on the enantiomeric excess introduced, under the reaction conditions utilised in these initial tests. (Compare entries **4** and **9, Table 1)**

Table 1 Enantiomeric excess introduced by the cobalt(II) salens[1]

Entry	Catalyst	Mol % cat.	*ee*[3]	Entry	Catalyst	Mol % cat.	*ee*[3]
1	**28a**	5	33	**8**	**43a**	5	36
2	**28b**	5	50	**9**	**43b**	5	34
3	**28c**	5	-[2]	**10**	**43c**	5	50
4	**29a**	5	38	**11**	**44a**	7.5	48
5	**29b**	5	28	**12**	**44b**	7.5	46
6	**30a**	5	38	**13**	**44c**	7.5	52
7	**30b**	5	24				

[1]Dichloromethane, 20°C, 0.08 M 3,6-diphenyl-3,6-dihydro-1,2-dioxine, Benzyl ester ylide (1.05 eq) added after full rearrangement of dioxine, rearrangement taking between 1 ½ and 2 hours. [2]No rearrangement after 10 days [3]The CH_2 of the benzyl was used for *ee* determinations, see **Appendix 1, Figure A1.2** for an example of the chiral shift results.

When rearrangement with catalyst **28c** using the standard conditions (dichloromethane, 20°C, 5 mol %) was attempted, no rearrangement occurred even after 10 days. An analogous cobalt(II) salen (no methoxy groups were present) had been used previously in the asymmetric hydroxylation of styrene.[108] The difference in the size of the reactant used may account for the catalysts inability to react with the dioxine. The reaction conditions were modified using THF as the solvent, however, this also did not result in the rearrangement of the dioxine. It was postulated that some form of steric interaction was occurring that may need a higher level of available system energy for the rearrangement to occur. Increasing the reaction temperature to 39°C, in dichloromethane, facilitated rearrangement of the dioxine,

with furan being the major product produced and only minor amounts of the enone present. Increasing the reaction temperature to 70^{o}C in carbon tetrachloride allowed the rearrangement to go to completion in 10 hours, however, only furan was obtained. The presence of furan suggests an enone intermediate. Previous work with diphenyl dioxine **(59)** has shown that at elevated temperatures, dehydration of the enone is more facile and results in furan formation in preference to cyclopropanation.[63] This suggests that the catalyst is capable of rearranging the dioxine, however, the elevated temperatures required to induce rearrangement preclude the use of this catalyst in these cyclopropanations.

The same reaction conditions were utilised for the initial tests of the cobalt(II) β-ketoiminato complexes and the results also provided useful insights into the regions of the catalyst important to introducing enantiomeric excess (**Table 2)**.

As for the cobalt(II) salens some of the diamines in the β-ketoiminato complexes were mismatched with the aldehyde used, reducing the enantiomeric excess introduced **(55c, 55d, 56b & 57a)**.

It was found for the cobalt(II) β-ketoiminato complexes that chirality in the Northern Quadrant (**Figure 8**) (Compare entries **6** and **7, Table 2**) was the most important for the introduction of enantiomeric excess. Chirality in the Peripheral Quadrants was also found to play an important role in the introduction of enantiomeric excess **(55a),** although to a lesser extent than the role played by chirality in the Northern Quadrant (Compare entries **3** and **11, Table 2**).

The catalysts found to introduce the highest enantiomeric excess were **56a** and **57b**. Although these catalysts introduced the higher *ee* they were not used in the further tests used to determine the ideal reactions conditions due to both the cost of the alcohols required and due to the instability of the aldehydes, decomposition occurring readily in the presence of any oxygen.

Table 2 Enantiomeric excess introduced by cobalt(II) β-ketoiminato complexes[1]

Entry	Catalyst	Mol % cat.	*ee*[2]	Entry	Catalyst	Mol % cat.	*ee*[2]
1	**52**	10	46	**8**	**55c**	7.5	28
2	**53a**	7.5	42	**9**	**55d**	7.5	34
3	**53b**	7.5	46	**10**	**55e**	7.5	44
4	**53c**	7.5	46	**11**	**56a**	7.5	60
5	**54**	7.5	46	**12**	**56b**	7.5	30
6	**55a**	7.5	14	**13**	**57a**	7.5	30
7	**55b**	7.5	46	**14**	**57b**	7.5	60

[1]Dichloromethane, 20°C, 0.08 M 3,6-diphenyl-3,6-dihydro-1,2-dioxine, Benzyl ester ylide (1.05 eq) added after full rearrangement of dioxine, rearrangement taking between 1 ½ and 2 hours. [2]The CH_2 of the benzyl was used for *ee* determinations, see **Appendix 1, Figure A1.2** for an example of the chiral shift results.

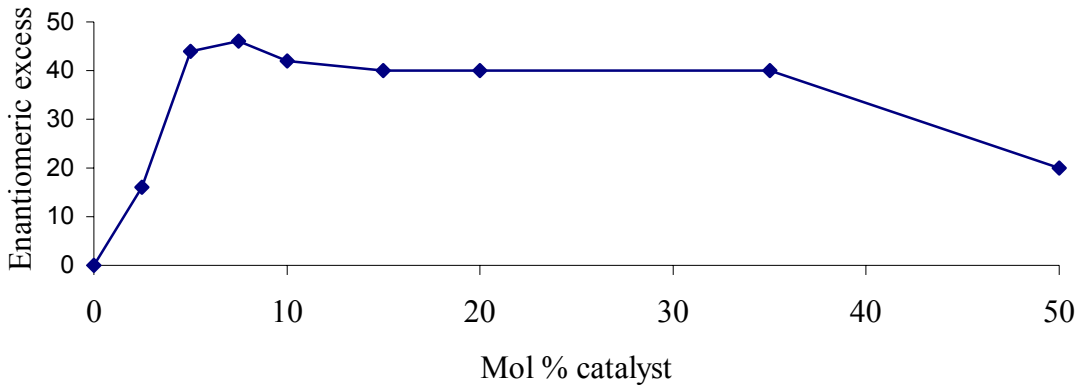
These initial tests determined conclusively that the cobalt β-ketoiminato complexes were capable of rearranging the *meso*-1,2-dioxines in the same way that cobalt(II) salens were shown to by O'Shea and Foote.[68] It also shows that although O'Shea and Foote did not observe the enone produced by the ring-opening of the diphenyl-1,2-dioxine it must have been present in their reaction mixture. Furthermore, the use of chiral cobalt catalysts allows for the asymmetric ring-opening of *meso*-1,2-dioxines and subsequent "trapping" with ylides affords cyclopropanes with enhanced enantiomeric excess.

It was determined that cobalt(II) acetate, cobalt(II) chloride and ligand on their own were not capable of rearranging the dioxine, with no reaction occurring over several weeks. This ruled out any rearrangement occurring with unreacted ligand or cobalt salt that could have potentially been present in the catalyst in minute quantities, affecting the enantiomeric excess

introduced. The presence of water in the mixture was found not to change the enantiomeric excess introduced hence it was unnecessary to completely exclude water from the reaction.

To determine effect of different variables on the enantiomeric excess introduced various catalyst concentrations, solvents and temperatures were assessed. Initial studies used dichloromethane as the standard solvent, as this had been shown in work by T. Avery to produce the best yield of cyclopropane, minimising any of the other by-products produced.[63] As initial tests of the catalyst had been performed at 20°C with between 5 and 10 mol % catalyst the standard conditions were taken to be dichloromethane at 20°C with 5 mol % catalyst for all of the following reactions series.

Chart 1 Effect of catalyst concentration of the enantiomeric excess introduced



The effect of the catalyst concentration on the enantiomeric excess introduced was somewhat counterintuitive (**Chart 1 and Table 3**). The percentage introduced increased up to a catalyst concentration of 7.5 mol % from which a small decrease in the enantiomeric excess was observed up to 15 mol %. The percentage then plateaued until 35 mol % after which the percentage observed dropped dramatically. This unexpected drop in the enantiomeric excess introduced is most likely due to slight temperature increases in the reaction mixture upon addition of the catalyst to the dioxine. As the catalyst is added in one portion to ensure that the overall catalyst concentration is kept constant, small but rapid temperature changes and inevitable and unavoidable. Even with careful control of the temperature of the reaction, due to the energy released when the oxygen-oxygen bond of the

1,2-dioxines is "broken", the enantiomeric excess with this concentration of catalyst could not be improved upon. This effect may also paly a role in the small decrease in going for 7.5 mol % to 10 mol % and may also explain the plateau with intermediate concentrations.

Table 3 Effect of catalyst concentration on the enantiomeric excess introduced[1]

Entry	Mol % cat.	*ee*[2]	Approx reaction time (hours)	Entry	Mol % cat.	*ee*[2]	Approx reaction time (hours)
1	**2.5**	16	4	**5**	**15**	40	1.4
2	**5**	44	2	**6**	**20**	40	1
3	**7.5**	46	1.8	**7**	**35**	40	0.75
4	**10**	42	1.6	**8**	**50**	20	0.5

[1]Catalyst **55e,** dichloromethane, 20°C, 0.08 M 3,6-diphenyl-3,6-dihydro-1,2-dioxine, Benzyl ester ylide (1.05 eq) added after full rearrangement of the dioxine. [2]The CH_2 of the benzyl was used for *ee* determinations, see **Appendix 1, Figure A1.2** for an example of the chiral shift results.

Although in most reported examples increase of the percentage catalyst is not detrimental to the enantiomeric excess that is introduced, in many cases producing no change, there are examples in which increase of the percentage of catalyst does reduce the enantiomeric excess introduced. Such an example exists in the use of a lanthanoid catalyst, the use of which exhibits small, yet significant, reductions in the enantiomeric excess with increase in the percentage catalyst.[145]

The influence of a solvent on the outcome of a reaction varies widely depending upon the solvent and also the reactants. The polarity of a solvent and whether it is protic or aprotic can dramatically affect both the yield of the products,[146,147] the mixture of the products[147] and any chirality introduced.[146,148] These types of effects have been exhibited numerous times and can be used to "steer" reactions in the desired direction.

The solvent utilised in the reaction was determined to have a dramatic effect on the enantiomeric excess introduced (**Table 4**). When the reaction was attempted in dioxane no rearrangement occurred, even after 7 days the dioxine was still intact and the full quantity of the dioxine was recovered from the solution.

Use of diethyl ether, toluene and carbon tetrachloride allowed introduction of the lowest level of enantiomeric excess (34 %) for all of the solvents tested (**Table 4**). Dichloromethane, at 44 %, introduced enantiomeric excess at the second lowest level, even though this had been used as the reaction standard.

It was when solvents with a potential ligand donor atom were used that variation in the enantiomeric excess began to show an improvement. Acetonitrile and acetone both enabled introduction of a moderate level of *ee* (52 %) and ethyl acetate slightly more (54 %).

An attempt to trial the reaction in hexanes showed just how insoluble both the dioxine and the catalyst were in non-polar solvent. To enable determination of whether the presence of a non-polar solvent, as part of a solvent mixture, would influence the *ee* introduced, the minimum percentage of ethyl acetate to dissolve both the dioxine and the catalyst was determined. The reaction produced cyclopropane with an enantiomeric excess similar to that when ethyl acetate was employed suggesting that the enantiomeric excess introduced is controlled more by the potential ligand donor than by the solvent polarity.

The solvent that showed the highest enantiomeric excess when used for the rearrangement was THF (68 %). This was in no way the most polar solvent employed but was the best potential donor solvent, of those trialed, to influence the *ee* introduced.

Table 4 Effect of solvent on the enantiomeric excess introduced[1]

Entry	Solvent	*ee*[3]	Approx r.t. (hours)	Entry	Solvent	*ee*[3]	Approx r.t. (hours)
1	Dioxane	-[2]	-[2]	**6**	Acetonitrile	52	1
2	Diethyl ether	34	2	**7**	Acetone	52	0.5
3	Toluene	34	2.5	**8**	Ethyl acetate	54	0.5
4	Carbon tetrachloride	34	2.5	**9**	1:1 Hexanes : Ethyl acetate	56	0.5
5	DCM	44	2	**10**	THF	68	0.25

[1]Catalyst **55e**, 5 mol % catalyst, 20°C, 0.08 M 3,6-diphenyl-3,6-dihydro-1,2-dioxine, Benzyl ester ylide (1.05 eq) added after full rearrangement of dioxine, [2]No rearrangement after 7 days. [3]The CH_2 of the benzyl was used for *ee* determinations, see **Appendix 1, Figure A1.2** for an example of the chiral shift results.

In using the different solvents it was noticed that the time taken to fully rearrange the dioxine varied dramatically, at 20°C. Rearrangements performed in dichloromethane, carbon tetrachloride and toluene were the slowest taking up to 3 ½ hours to complete. The same length of time was taken for most of the catalysts in dichloromethane, although several of the Co(II) salens were able to rearrange the dioxine **(59)** in much less time. In diethyl ether, acetonitrile, acetone and ethyl acetate (both 100% and 50%) the rate at which rearrangement occurred was faster taking up to 1 ½ hours. It was the rearrangement in THF which was the fastest taking only 15 minutes.

To determine if the use of THF was applicable to the other catalysts, to increase the enantiomeric excess introduced, a selection of the catalysts were again tested.

For most of the catalysts tested an increase in the enantiomeric excess, from slight to significant, was observed. For two of the catalysts (**29b** and **55b**) no change in the

enantiomeric excess introduced was observed and for another two (**28b** and **29a)** a slight decrease in the enantiomeric excess was observed. There is no obvious relationship between these four catalysts to be able to make any general statement as to why these results are the case and it would be inappropriate to make such generalisations without understanding the mechanistic implications that these variations imply.

For the remainder of the catalysts tested most exhibit a significant difference in their ability to introduce enantiomeric excess, the highest difference being for catalyst **55d** with a change from 34 to 64 %, and the highest enantiomeric excess observed, at 72 %, when catalyst **57b** was used. Although neither of these catalysts had been used as the standard the variation observed for catalyst **55e** is just as significant.

Table 5 Effect of solvent on the enantiomeric excess introduced for other catalysts[1]

Entry	Catalyst	Solvent	*ee*[2]	Solvent	*ee*[2]	Entry	Catalyst	Solvent	*ee*[2]	Solvent	*ee*[2]
1	**28a**	DCM	33	THF	35	**7**	**43c**	DCM	50	THF	64
2	**28b**	DCM	50	THF	48	**8**	**55b**	DCM	46	THF	46
3	**29a**	DCM	38	THF	32	**9**	**55d**	DCM	34	THF	64
4	**29b**	DCM	28	THF	28	**10**	**55e**	DCM	44	THF	68
5	**30a**	DCM	38	THF	44	**11**	**57a**	DCM	30	THF	50
6	**30b**	DCM	24	THF	46	**12**	**57b**	DCM	60	THF	72

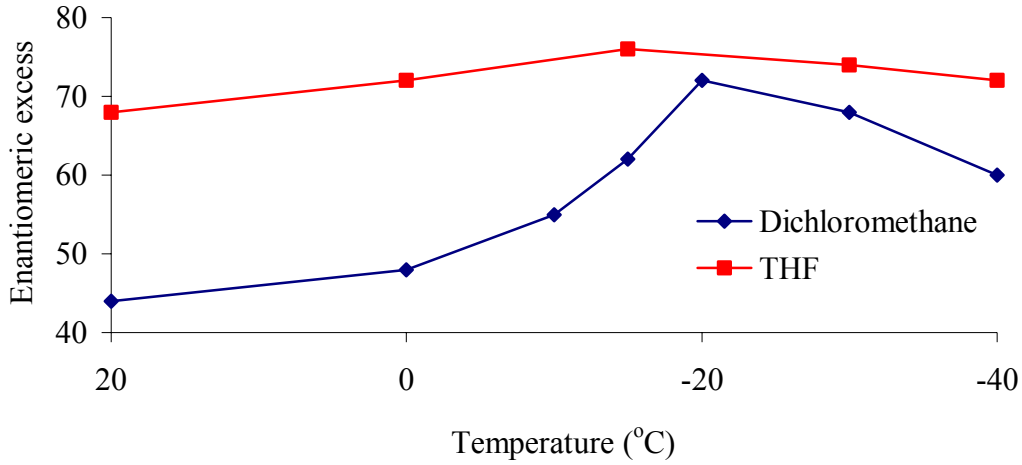
[1]Catalyst 5 mol %, 20°C, 0.08 M 3,6-diphenyl-3,6-dihydro-1,2-dioxine, Benzyl ester ylide (1.05 eq) added after full rearrangement of dioxine, in DCM rearrangement complete in approx 2 hours, in THF rearrangement complete in approx 15 min. [2]The CH_2 of the benzyl was used for *ee* determinations, see **Appendix 1, Figure A1.2** for an example of the chiral shift results.

The trend observed for the reaction time in THF was similar to that observed when dichloromethane was used. However, the faster rate of reaction observed in THF was not observed for all of the catalysts with **28b**, **29a & b** and **55b** taking considerably longer than

for the other catalysts. This suggests some interaction with the THF that occurs for the other catalysts does not occur, or only slightly occurs, for these four.

As with the solvent used for the reaction, the temperature at which a reaction is carried out can have a dramatic effect on the mixture of products and the enantiomeric excess introduced.[149] The effect of temperature on the outcomes of the reaction is variable, decrease in temperature can lead to either a steady increase or decrease in the enantiomeric excess introduced or in some cases the enantiomeric excess comes to a maximum at a temperature which is not the minimum at which the reaction can be performed.[150,151]

Chart 2 Effect of temperature on the enantiomeric excess introduced



For catalyst **55e** the temperature was found to have a dramatic effect on the enantiomeric excess introduced (**Chart 2** and **Table 6**). When the reaction was performed in dichloromethane using catalyst **55e** the variation in the enantiomeric excess introduced, with reducing temperature, showed an increase from 44 to 72 % (20°C to –20°C). When THF was used there was a slight increase in the enantiomeric excess introduced, increasing from 68 to 76 % (20°C to –15°C). For both THF and dichloromethane the enantiomeric excess was found to peak at a temperature much higher than that at which the reaction could still be performed. As mentioned above this is not an isolated occurrence, and has been reported when other catalysts have been used.

As was expected, the rate at which the rearrangement occurred was dramatically affected by the temperature used. For dichloromethane and THF the change from 20°C to –40°C resulted in a 10 fold increase in time required for complete rearrangement of the 1,2-dioxine. Although for both solvents this is significant, in dichloromethane the chance for decomposition of the enone was much higher taking 36 hours. For THF, with the longest reaction only taking 2 ½ hours, dehydration to furan was minimised.

Table 6 Effect of temperature on the enantiomeric excess introduced[1]

Entry	Solvent	Temperature (°C)	*ee*[2]	Approx r.t. (hrs)	Entry	Solvent	Temperature (°C)	*ee*[2]	Approx r.t. (hrs)
1	**DCM**	20	44	2	**8**	**THF**	20	68	0.25
2		0	48	3.5	**9**		0	72	0.75
3		-10	55	6	**10**		-15	76	1
4		-15	62	8	**11**		-30	74	3
5		-20	72	10	**12**		-40	72	5
6		-30	68	18					
7		-40	60	24					

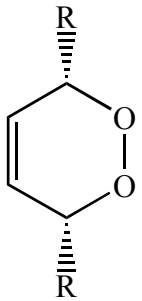
[1]Catalyst **55e**, 5 mol % catalyst, 0.08 M 3,6-diphenyl-3,6-dihydro-1,2-dioxine, Benzyl ester ylide (1.05 eq) added after full rearrangement of dioxine. [2]The CH_2 of the benzyl was used for *ee* determinations, see **Appendix 1, Figure A1.2** for an example of the chiral shift results.

When used at 20°C, catalyst **43c** did not exhibit any great ability to introduce enantiomeric excess, however, when tested in THF a significant difference in the enantiomeric excess was observed (50 to 64 %). To determine whether this catalyst would show more promise at a reduced temperature it was tested in THF at 4°C, using 7.5 mol %, giving an enantiomeric

excess of 78 %, which is comparable with results obtained for catalyst **55e** at much lower temperatures. When this catalyst was used at lower temperatures no further increase in the enantiomeric excess was observed, with no reduction in the enantiomeric excess either.

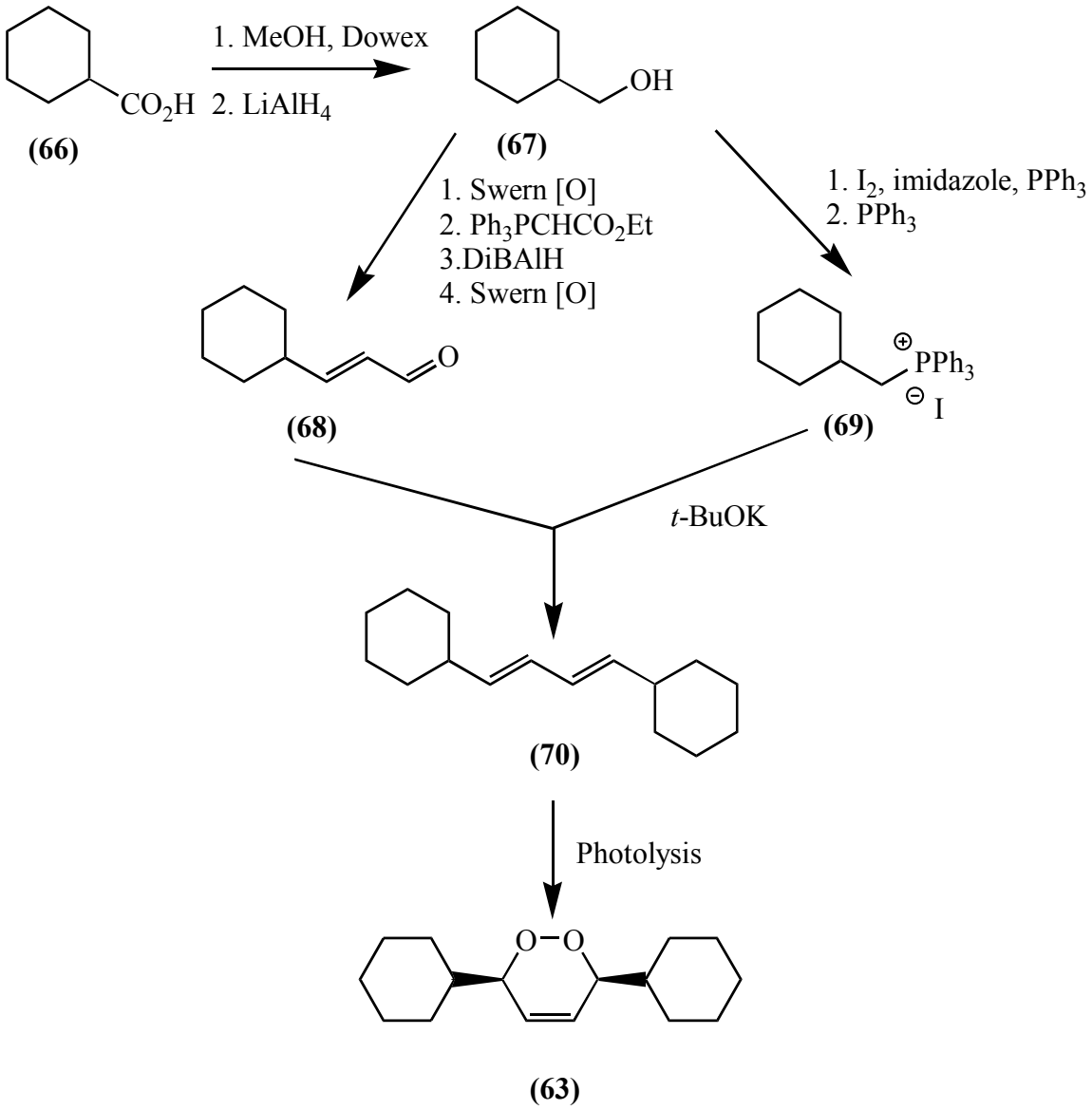
Now that the ideal conditions for the introduction of enantiomeric excess had been refined a large scale reaction was performed. A solution of the catalyst **55e** (0.12 g, 7.5 mol %) in THF and a solution of the 3,6-diphenyl-3,6-dihydro-1,2-dioxine **(59)** (0.5 g) in THF were pre-equilibrated to –15°C and then combined making sure that the temperature did not rise. The reaction mixture was left at –15°C until the consumption of the dioxine was complete then benzyl ester ylide (1.05 eq) was added and the reaction mixture allowed to slowly warm to ambient temperature. This gave the cyclopropane in a yield of 74 % with an enantiomeric excess of 76 %. Fractional recrystallisation of this cyclopropane from hexanes produced crystals with > 95 % enantiomeric excess which when compared to an authentic sample showed that the *trans* (-) benzyl 2-[(*1S,2S,3R*)-2-benzoyl-3-phenylcyclopropyl]acetate had been formed and hence mainly *R*-γ-hydroxy enone had been produced in the ring-opening of the *meso*-1,2-dioxines. This information could then be used to determine the enantiomer formed preferentially by each of the catalysts.

To determine whether these catalyst could be used in the asymmetric ring-opening of other *meso*-1,2-dioxines several were required. Three of the five symmetrical dioxines (**59 & 62 - 64**) that were necessary for this work had been prepared previously for use within the Taylor group, however, 3,6-dicyclohexyl-3,6-dihydro-1,2-dioxine (**63**) and 3,6-diisopropyl-3,6-dihydro-1,2-dioxine (**65**) had not been synthesised previously.



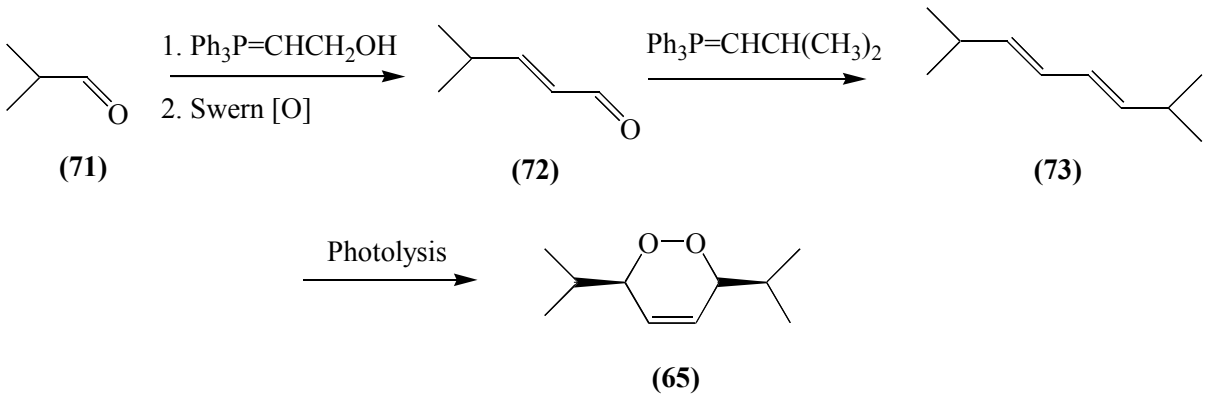
59:- R = Ph
62:- R = 1-napthyl
63:- R = cyclohexyl
64:- R = propyl
65:- R = isopropyl

To synthesise 3,6-dicyclohexyl-3,6-dihydro-1,2-dioxine the most readily available starting material was cyclohexane carboxylic acid (**66**). Conversion of the carboxylic acid (**66**) to its methyl ester and reduction to cyclohexyl methanol (**67**) produced the desired compound in high yield (95%). Reaction of the cyclohexyl methanol to form the halide and phosphonium salt (**69**) also occurred with high yields (>90%). Swern oxidation of the cyclohexyl methanol to the aldehyde followed by Wittig reaction, reduction of the ester and Swern oxidation gave the propenal (**68**) in good overall yield (70%) and Wittig reaction using the cyclohexyl phosphonium salt (**69**) gave the diene (**70**) in good yield (84%). Photolysis of the diene gave the dioxine (**63**) in low yield (16%), however, a considerable quantity of the diene (~40%) was recovered from the reaction (**Scheme 25**) and could be recycled.



Scheme 25 Synthesis of 3,6-dicyclohexyl-3,6-dihydro-1,2-dioxine **(63)**.

A similar method was used to synthesise the diisopropyl dioxine using isobutyraldehyde (**71)** and 2-hydroxyethyl triphenylphosphorane, followed by Swern oxidation, to give the propenal (**72**) in moderate yield (70%). Reaction with isobutyl triphenylphosphorane and photolysis gave the dioxine (**65**) in low yield (14%) with most of the unreacted diene (70%) recovered and recycled back into the photolysis reaction (**Scheme 26**).



(71) **(72)** **(73)** **(65)**

Scheme 26 Synthesis of 3,6-diisopropyl-3,6-dihydro-1,2-dioxine **(65)**.

Three of the cobalt(II) β-ketoiminato complexes were used to determine their applicability to rearrange other dioxines in an asymmetric fashion. Due to the instability of the dialkyl enones, and the inability of ylides to ring-open dialkyl dioxines, the ylide was added to the initial reaction mixture before rearrangement of the dioxine had taken place. It was observed that this increased the length of required for the rearrangement to go to completion possibly due to an interaction of the catalyst with the phosphorus of the ylide. This interaction between the ylide and catalyst may also account for the reduced enantiomeric excess introduced.

Catalyst **55e** was the only catalyst used for all five dioxines and exhibited more specificity for the diaromatic dioxines (**60** and **62**) than the dialkyl dioxines (**63, 64, 65**) and the same specificity was observed for the other two catalysts (**52** and **53c**) (**Table 7**). In general it can be concluded that the size of the aryl grouping has not effect on observed *ee* and that the ring-opening of dialkyl *meso* dioxines results in a slightly lower observed *ee*.

Table 7 Enantiomeric excess introduced with other 1,2-dioxines

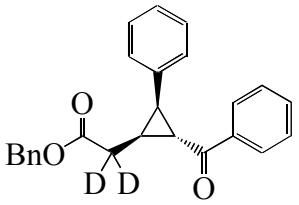
Entry	Catalyst	1,2-Dioxine	Mol % cat.	*ee*[4]	Entry	Catalyst	1,2-Dioxine	Mol % cat.	*ee*[4]
1	**52**	**59**[1]	10	46	**5**	**55e**	**59**[1]	7.5	44
2		**64**	10	30	**6**		**62**[1]	10	44
3	**53c**	**59**[1]	7.5	46	**7**		**63**[2,3]	7.5	36
4		**64**	10	32	**8**		**64**	10	34
					9		**65**	7.5	34

[1]Dichloromethane, 20°C, 0.08 M dioxine, Benzyl ester ylide (1.05 eq) added after full rearrangement of dioxine, reaction time approx 2 hours, [2]Dichloromethane, 20°C, 0.08 M dioxine, Benzyl ester ylide added prior to rearrangement of the dioxine, reaction time approx 5 days, [3]When cyclopropane was made from dicyclohexyl dioxine the chiral shift method used to determine *ee* was inadequate. Instead the cyclopropyl ester was hydrolysed and the corresponding acid converted to diastereomers (see **Chapter 5** for details on the method used). [4]The CH_2 of the benzyl was used for *ee* determinations, see **Appendix 1, Figure A1.2** for an example of the chiral shift results.

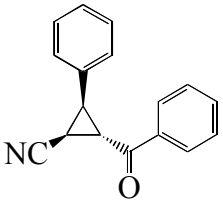
A small number of cyclopropanes were made with introduced enantiomeric excess (**74 – 78**) to determine the applicability of this reaction for other ylides. For each of the cyclopropanes, apart from (**78**), the optically enriched γ-hydroxy enone was taken from a batch, in dichloromethane, to rule out any variation of catalyst concentration affecting the *ee* introduced, enabling comparison of the results.

For three of the cyclopropanes the standard conditions could not be used without significant modification. The deuterated cyclopropane (**74**) was synthesised by addition of deuterium oxide and benzyl ester ylide to the γ-hydroxy enone. In a similar way cyclopropane (**77**) was synthesised by the addition of lithium bromide and *t*-butyl ester ylide to the γ-hydroxy enone. Cyclopropanes (**75** & **76**) were synthesised by the addition of cyano ylide and Weinreib

amide ylide respectively and cyclopropane (**78**) was synthesised by rearrangement in THF at –20^{o}C due to the use of trimethyl phosphonate in the place of a stabilised ylide.



(74)



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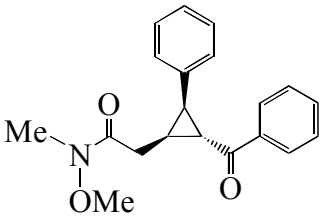
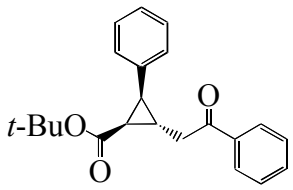


(76)



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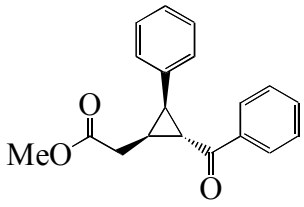


(78)

As can be seen (**Table 8**) the enantiomeric excess introduced is variable, with the *ee* for cyclopropanes (**74 – 77**) within experimental error. When the phosphonate was used in the cyclopropanation the *ee* is slightly lower (**Table 8, Entry 5**) than that found for the benzyl ester ylide (**Table 8, Entry 6**) although this is within experimental error. Each of the six reactions yield only around 75% of the cyclopropane expected with significant quantities of both diketone and furan also present. Consequently, it can be concluded that the ylide used has little or no effect on the enantiomeric excess that is introduced. This is as was expected as the enantiomeric excess is introduced into the enone prior to the addition of the ylide, the ylide hance having no effect on *ee*.

Table 8 Enantiomeric excess introduced with other ylides[1]

Entry	Solvent	Ylide	Cyclopropane	*ee*	Approx r.t. (hrs)
1	**DCM**	$Ph_3P=CHCO_2Bn$[2]	**74**	40[2]	2
2		$Ph_3P=CHCN$[3]	**75**	38[3]	2
3		$Ph_3P=CHC(O)N(OCH_3)CH_3$ (Weinreib amide)[4]	**76**	42[4]	2
4		$Ph_3P=CHCO_2t\text{-}Bu$[5]	**77**	38[5]	2
5	**THF**	$(CH_3O)_2P(O)=CHCO_2CH_3$[4,6] (trimethylphosphonoacetate)	**78**	66[4]	0.25
6		$PPh_3=CHCO_2Bn$	**61**	68[7]	0.25

[1]Catalyst **55e**, 5 mol % catalyst, 0.08 M 3,6-diphenyl-3,6-dihydro-1,2-dioxine, ylide (1.05 – 1.1eq) was then added after full rearrangement of dioxine. [2]D_2O added with the addition of ylide, the CH_2 of the benzyl was used for *ee* determinations. [3]The CH_2 next to the ketone was used for enantiomeric excess determinations. [4]The CH_3O signal was used for *ee* determinations. [5]LiBr added with the addition of ylide, the Bu^t signal was used for *ee* determinations. [6]Rearrangement and addition of ylide performed at –20°C. [7]The CH_2 of the benzyl was used for enantiomeric excess determinations. see **Appendix 1, Figure A1.2** for an example of the chiral shift results.

2.2.4 Mechanistic Studies

Although all of the results discussed above provided useful insights into the regions of the catalyst important for introducing enantiomeric excess, for both cobalt(II) salens and cobalt(II) β-ketoiminato complexes, and the conditions under which the enantiomeric excess could be maximised had been ascertained, no detail as to the mechanism of interaction and the active catalyst could be clearly gleaned.

There are two mechanisms possible for the ring-opening of the 1,2-dioxines by chiral cobalt(II) catalysts (**Figure 11**). Both mechanisms involve catalytic cleavage of the oxygen-oxygen bond. In one mechanism, the 1,5-hydrogen atom abstraction occurs with the cobalt still attached, leading to retention of the enantiomeric excess that has been introduced. The second mechanism involves loss of cobalt before the 1,5-hydrogen atom abstraction giving a diradical, which is capable of undergoing the 1,5-hydrogen atom abstration at either end of the molecule, leading to diminished enantiomeric excess. It is possible that both of these mechanisms are occurring during the ring-opening reaction. Changes to the reaction conditions, including temperature and solvent may help to stabilise the cobalt(III)-dioxine complex.

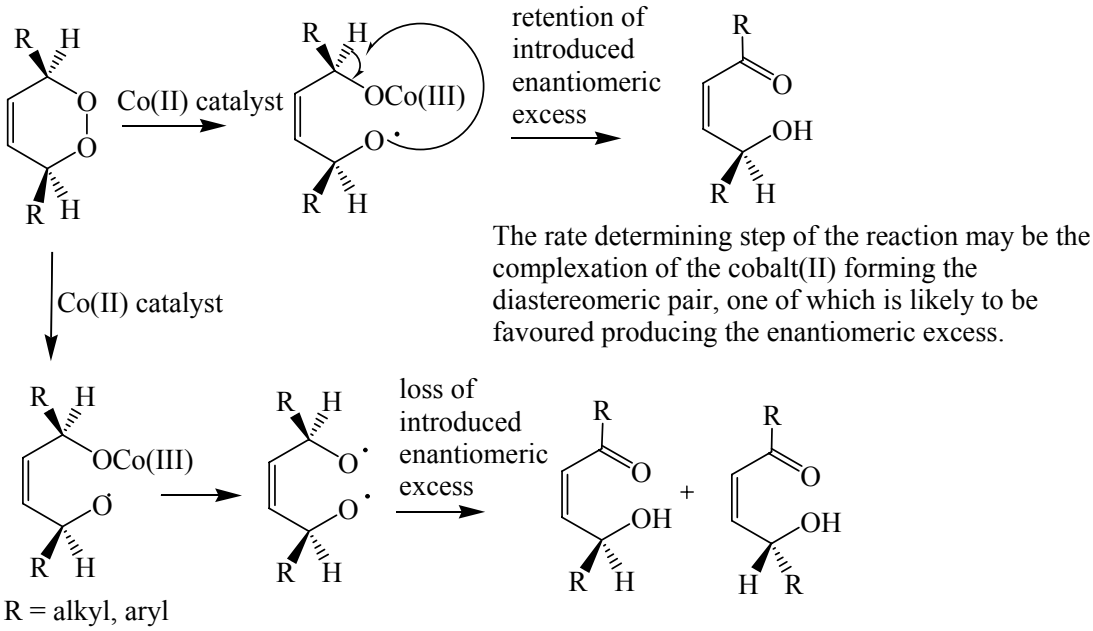


Figure 11 Possible mechanisms of Cobalt (II) ring-opening of 1,2-dioxine.

To enable some understanding into the mechanism of the ring-opening, studies were performed, including NMR and LC-MS.

It had already been observed that there was a dramatic difference in the time required for the catalysts to rearrange the dioxines. To be able to quantitatively analyse this, time variation NMR studies were carried out with a selection of catalysts. Due to the way in which cobalt(II) affects NMR spectra a minimum quantity of catalyst was used. Although this did mean that the rearrangement took longer than would normally be observed this would not pose a problem in comparing the reaction rates as all catalysts were used at the same molar percent.

The internal standard used was phenyltrimethyl silane, with its low volatility and clear methyl signal in the spectra, allowing calculation of the percentage conversion of the dioxine directly from the NMR spectra without the need for further analysis.

The reaction conditions used were 20 mg of 3,6-diphenyl-3,6-dihydro-1,2-dioxine **(59)** in 0.7 ml $CDCl_3$ with 2 mol % of catalyst. The experiments were run in duplicate, at 20^{o}C, to minimise any errors using the average results in **Chart 3**. There was minimal differences between the two runs.

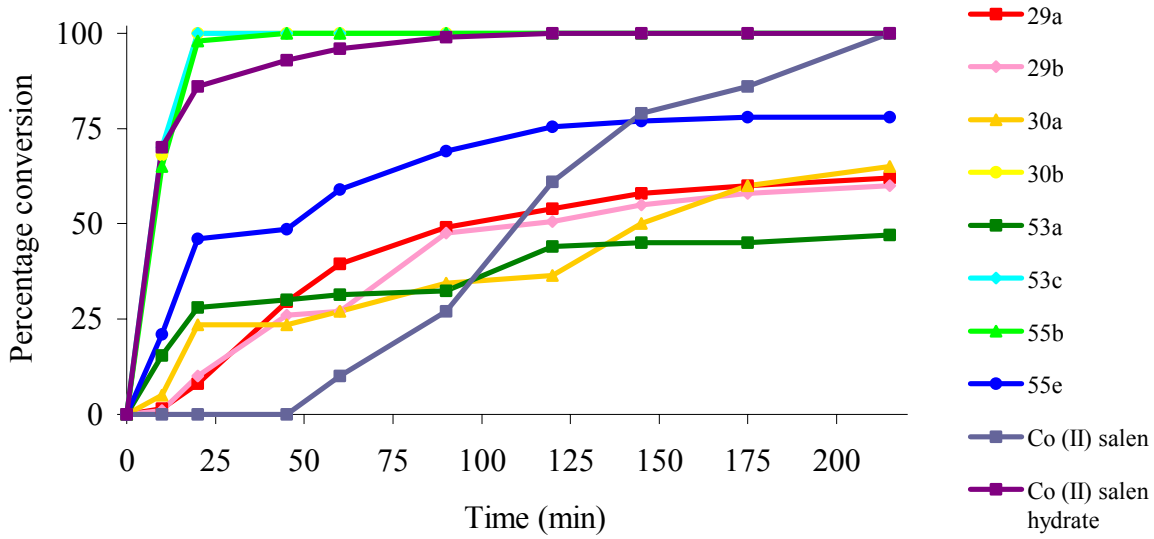
As can be seen in **Chart 3** the consumption of dioxine does not occur at a constant rate for all of the catalysts. Catalysts **30b**, **53c** and **55b** all rapidly rearrange the dioxine, even at the lower concentration of catalyst used. Catalysts **29a**, **29b**, **30a**, **53a**, and **55e** were much slower in rearranging the dioxine and did not occur at a constant rate, with the rearrangement stopping and starting during the reaction (although this is not obvious in the plot for catalyst **29a** it appears that the rearrangement is slowing, reaching a plateau).

As can be seen is **Chart 3**, catalysts **30b, 53c**, **55b** and the Co(II) salen hydrate, all show plots as would be expected in the use of a catalyst that does not undergo changes during the progress of the reaction. Although these four catalysts may also be exhibiting the unusual behaviour observed of the other five over a much shorter time frame, this is unlikely as **Chart 3** suggests that these changes in the catalyst take place over a lengthy period of time.

This unusual catalytic behaviour was not expected and suggests that changes to the catalysts occurs during the reaction, possibly binding to components of the reaction mixture. It is possible that the catalyst goes through a series of stages, first with water binding, then dioxine and then enone. These other species may then be responsible for altered introduction of enantiomeric excess.

There is no clear correlation between the "bulk" of the catalyst, the enantiomeric excess it is capable of introducing and this unusual behaviour, although the "bulkiest" of the catalysts with the least amount of rotational freedom around the carbon-carbon bond in the amine backbone appear to exhibit this unusual behaviour more often than the "non-bulky" examples.

Chart 3 Percentage conversion of dioxine[1]



[1]20 mg 3,6-diphenyl-3,6-dihydro1,2-dioxine and 2 mol % catalyst in $CDCl_3$ with 5 mg phenyltrimethyl silane

With the unusual results obtained from the NMR studies it was of interest to determine whether additives could have an effect on the enantiomeric excess introduced. To ascertain whether this was the case catalyst **55e** was allowed to interact with various compounds that are present / formed during the rearrangement reaction, and one compound thought to be able to mimic the portion of the enone containing the hydroxy group (benzyl alcohol).

For each additive the catalyst was dissolved in dichloromethane with one equivalent of the compound and allowed to interact for 4 hours. The solvent was then removed, the catalyst dried and then used in rearranging the dioxine.

When either the *cis* or *trans* 1,4-diphenyl-γ-hydroxy enone is incubated with the catalyst prior to use and then used in the rearrangement, the enantiomeric excess is increased significantly when used in dichloromethane, however, when THF is used as the solvent no increase results suggesting that THF binding to the catalyst is stronger, having a greater effect of the conformation of the catalyst and a more pronounced difference on its ability to introduce chirality (**Table 9)**.

Catalyst incubated with 1,4-diphenyl-1,4-diketone only showed a slight increase in the enantiomeric excess when used in dichloromethane and no increase was observed when THF was employed.

Table 9 Effect of additives on the enantiomeric excess introduced

Solvent	Additive[2]	*ee*[4]	Approx r.t. (hrs)
DCM	none	44	2
	cis and *trans* 1,4-diphenyl-γ-hydroxyenone	58	2
	diketone	46	2
	benzyl alcohol	44	2
THF	none	68	0.25
	cis 1,4-diphenyl-γ-hydroxyenone	68	0.25
	1,4-diphenyl-1,4-diketone	68	0.25

[1]Catalyst **55e**, 5 mol % catalyst, 0.08 M 3,6-diphenyl-3,6-dihydro-1,2-dioxine, Benzyl ester ylide (1.05 eq) added after full rearrangement of dioxine, [2]Catalyst combined with the additive for 3 hours in dichloromethane before removing the solvent *in vacuo*, all additives synthesised from 3,6-diphenyl-3,6-dihydro-1,2-dioxine, [3]The *ee* introduced when catalyst plus *cis* γ-hydroxyenone has the presence of the small amount of cyclopropane formed without optical enrichment taken into account. [4]The CH_2 of the benzyl was used for *ee* determinations.

As it now appeared that employing THF as the solvent had a greater impact on the reaction than previously thought, modification of the method that had been used previously for the rearrangement was revisited. NMR studies had suggested that another species of catalyst was present in the reaction as time progressed and mass spectral analysis of the reaction mixture had indicated that the complex bound strongly enough to THF to produce a signal peak in the LC-MS spectra (**Appendix 2, Figure A2.2**). To determine whether the solvent bound species played a role in either enhancing the enantiomeric excess a number of reactions were performed. Using 7.5 mol % of catalyst **55e**, equilibration of the catalyst in THF for ½ hour prior to use followed by addition of the dioxine increased the enantiomeric excess from 68 % to 72 %. The increase seen at lower temperature is not as significant (only a 2 % increase at –

15°C), and increasing the equilibration time did not increase the enantiomeric excess any further.

One additive that was found to have a detrimental effect on the catalytic ability of both the salens and β-ketoiminato complexes was oxygen. Its presence in the reaction hampered the rearrangement completely, with no reaction occurring when an oxygen atmosphere was used, irrespective of the time allowed. Of interest though was that the presence of oxygen did not destroy the catalyst. Upon deairation of the solution, with nitrogen, the reaction proceeded within the expected length of time and the catalyst introduced the same level of enantiomeric excess. Consequently, it was possible to stop/start these rearrangements by simply placing or removing an oxygen balloon.

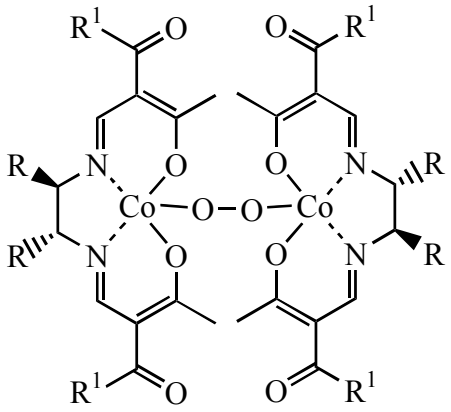


Figure 12 Oxygen dimer of a cobalt β-ketoiminato complex

To determine whether THF bound strongly to the catalyst and whether dichloromethane exhibited any binding LC-MS studies were performed. As can be seen in the spectra (**Appendix 2**) for catalyst **55e** in dichloromethane there is no peak suggestive of catalyst bound to solvent (**Figure A2.1**). However, when THF was used there is a definite peak suggestive of a solvent bound complex (835.9 mass units) (**Figure A2.2**) with both spectra exhibiting peaks suggestive of bound oxygen (1565 & 1566). This oxygen dimer disappears when the solution is fully deairated, and the amount can be increased by full oxygenation of the solution.

For catalyst **29b** in dichloromethane, as with catalyst **55e**, there is no discernable solvent bound peak (**Figure A2.3)**. In THF there is a small peak suggestive of solvent bound complex (658.2 mass units) (**Figure A2.4**).

Initial tests using catalyst **29b** showed that there was no difference in the enantiomeric excess introduced when THF was employed (**Table 5**). The small amount of THF bound material present in the mass spectrum may suggest that catalysts that do not strongly bind to THF cannot be influenced by the presence of the solvent and so solvent effects on the enantiomeric excess are reduced. However, as in the example of catalyst **56e**, when strong binding occurs a marked difference in the enantiomeric excess introduced results.

When the rearrangement of dioxine is analysed periodically by LC-MS, although no peak is observed for the dioxine or the ring-opened enone, changes are observed in the spectrum that suggest interactions between the catalyst and the enone. At time 0 (this is closer to being 30 sec) a small peak is observed with mass 1347 (**Figure A2.5**). This peak then steadily increases over the course of the reaction, the presence of which may be due to a complex formed with the catalyst, enone and THF.

2.3 Summary

A series of cobalt(II) salens (**28a-c**, **29a-b**, **30a-b, 43a-c** and **44a-c**) and cobalt(II) β-ketoiminato complexes (**52**, **53a-c**, **54**, **55a-e**, **56a-b**, **57a-b**) were made, using various chiral amines and aldehydes, and their ability to introduce enantiomeric excess during the ring-opening of *meso* 1,2-dioxines was determined.

For the cobalt(II) salens it was determined that chirality was of highest importance in the Northern Quadrant with lesser importance placed on chirality in the Southern Quadrant (**Figure 6**). For the cobalt(II) β-ketoiminato complexes chirality, as with the salens, was of highest importance in the Northern Quadrant and of significant importance in the Peripheral Quadrants (**Figure** 7).

With all of the initial tests using dichloromethane at 20^{o}C with between 5 and 10 mol % catalyst, tests to determine the ideal reaction conditions were performed. The concentration of catalyst in the reaction was found to have a significant effect with increasing *ee* for concentrations up to 7.5 mol %, followed by a small decrease and plateauing off to 35 %. Higher concentrations of catalyst showed dramatic reduction in the enantiomeric excess introduced during the ring-opening, possibly due to temperature changes in the reaction at higher concentrations.

Dichloromethane was found to be one of the poorest solvents for enabling the introduction of enantiomeric excess. Solvents with a group capable of acting as a fifth ligand were found to introduce higher enantiomeric excess, with THF enabling the highest excess to be introduced.

Increases were observed in the *ee* with decreasing temperature, for both dichloromethane and THF, with the ideal temperature determined to be between –15 and –20^{o}C. The catalyst concentration, solvent and temperature were found to be applicable to most of the cobalt(II) complexes with the highest enantiomeric excess introduced by catalyst **43c**.

Two new meso-1,2-dioxines were synthesised and the catalysts were determined to be applicable to a range of other *meso*-1,2-dioxines and ylides further expanding the uses of this reaction.

The rate at which the reactions occur for many of the catalysts has been determined to occur at an irregular rate, stopping at various time points, suggesting that there is more that one active form of the catalyst present in the reaction. The addition of enone and diketone to the catalyst prior to use was found to increase the enantiomeric excess introduced when dichloromethane was utilised as the solvent, however, when the reaction was performed in THF no increase was observed. THF thus has an overriding effect on the catalysts ability to introduce enantiomeric excess. Equilibration of the catalyst in THF prior to use enables increase of the enantiomeric excess, an effect that is not observed in dichloromethane.

Fully oxygenated reaction mixtures do not undergo rearrangement, but with deoxygenation the reaction proceeds introducing the same level of enantiomeric excess. THF can be observed to bind to the catalyst in LC-MS spectra and in solution oxygen dimers are also observed.

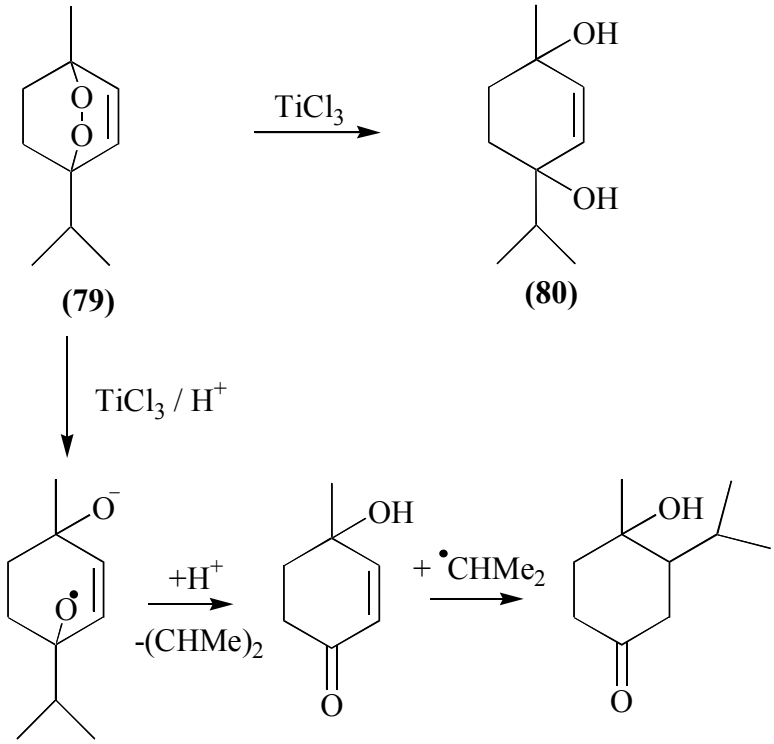
The catalysts were successfully tested, the ideal reaction conditions refined further and the effect of additives on the reaction analysed.

With the reaction conditions refined, as they have been in this work, utilising THF as the solvent with 7.5 mol% of catalyst at –15^{o}C, others within the Taylor group have applied the use of catalyst **55e** to the synthesis of other related systems producing *ee* of >76% consistently. (This work is yet to be published).

3. Other Metal Salens

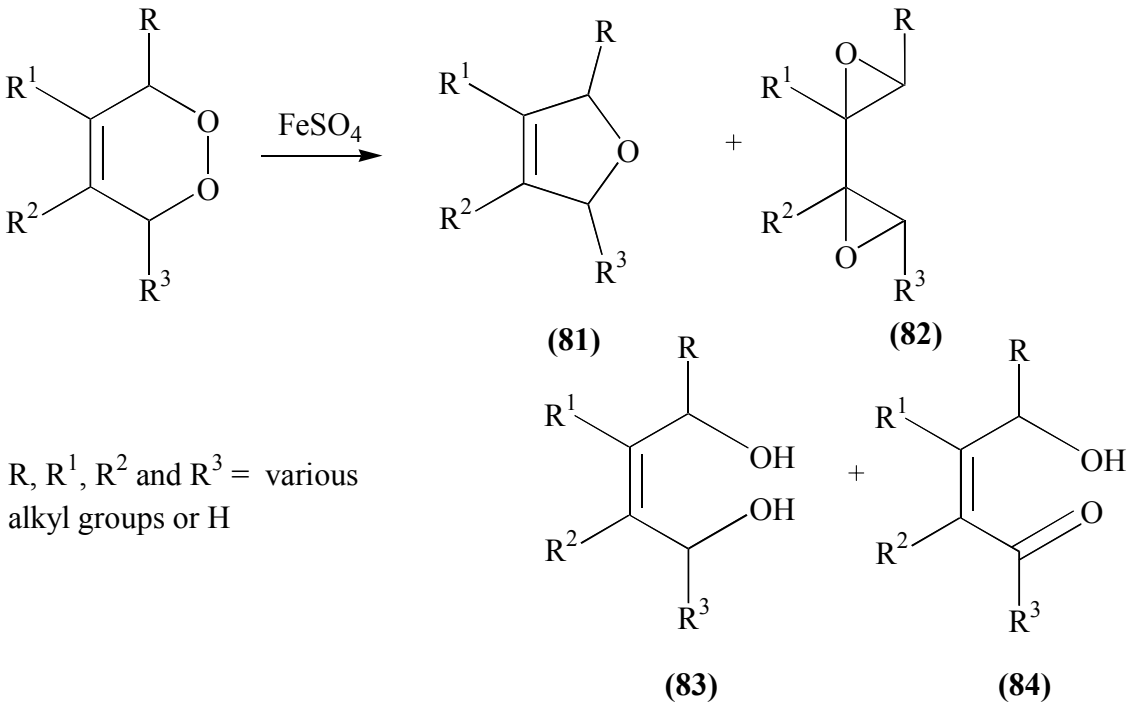
3.1 Introduction

It has been known since the 1930's that many metals capable of redox reactions are capable of ring-opening 1,2-dioxines. One of the earliest reported examples is the use of titanium(III) chloride in the ring-opening of ascaridole **(79)** to give the di-alcohol **(80)**.[152] Further work by Brown *et al* using titanium(III) chloride in the presence of acid produced an unusual major product indicative of a radical cleavage **(Scheme 27)**.[153]



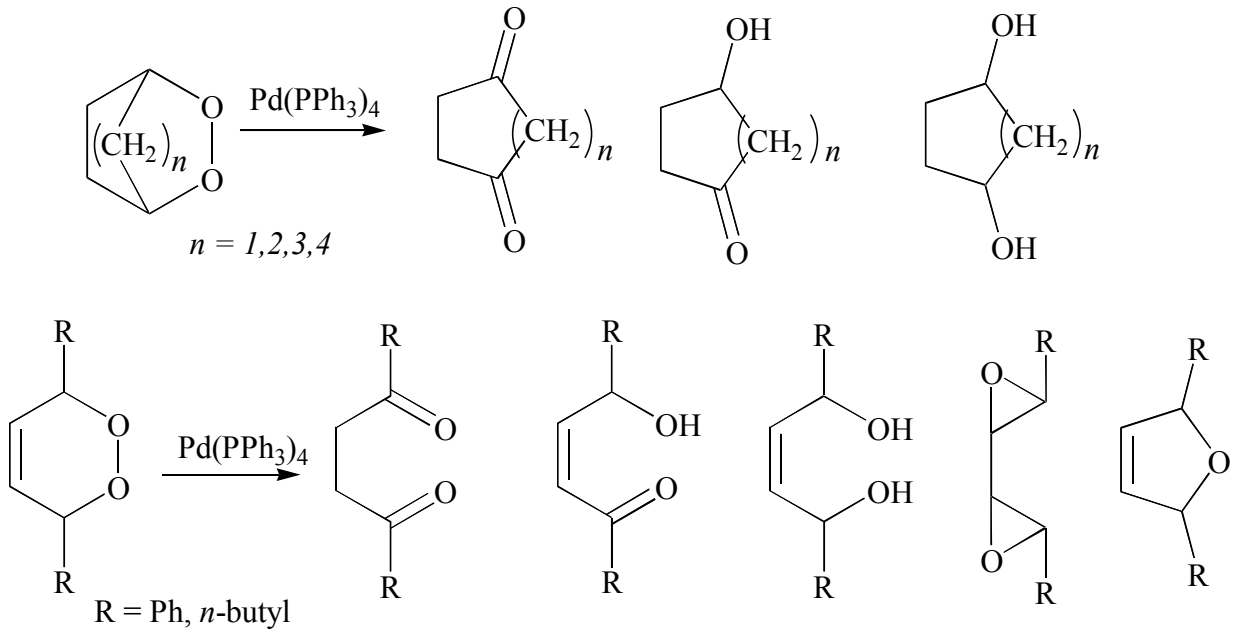
Scheme 27 Ring-opening of ascaridole with $TiCl_3$.

Subsequent work by Brown and co-workers showed that iron(II) was also capable of the same radical cleavage reaction.[154] Work in later years has shown that the use of iron(II) in the ring-opening of 1,2-dioxines was also applicable to other systems giving di-epoxides **(81),** furans **(82)**, di-alcohols **(83)** and γ-hydroxy enones **(84)** as products **(Scheme 28)**.[95,155-157]



Scheme 28 Ring-opening of dioxines with $FeSO_4$.

In 1952 Schenk published the use of lead(IV) acetate in the decomposition of a 1,2-dioxine to give the corresponding diketone.[158] Titanium(III), iron(II) and lead(IV) are not the only metals that have been utilised in the ring-opening of 1,2-dioxines. Cobalt(II),[68,159,160] copper(I) and copper(II),[161] palladium(0),[94,162] rhodium(I),[163,164] ruthenium(II)[165] and tin(II)[166] have also been used.



Scheme 29 $Pd(PPh_3)_4$ ring-opening of dioxines.

Palladium(0) has been used in the form of tetrakistriphenylphosphine palladium in the ring-opening of bicyclic 1,2-dioxines (**Scheme 29**), to give diketones, γ-hydroxy ketones and diols, and monocyclic 1,2-dioxines **(Scheme 29),** to afford diketones, γ-hydroxy enones, di-alcohols bisepoxides and furans in various ratios, via a Pd(0) to Pd(II) exchange mechanism.[94,162]

Work published using $RuCl_2(PPh_3)$[165] and $Rh_2(CO)_4Cl_2$[163,164] produce similar results to that of palladium(0) with varying ratios of the compounds depicted above.

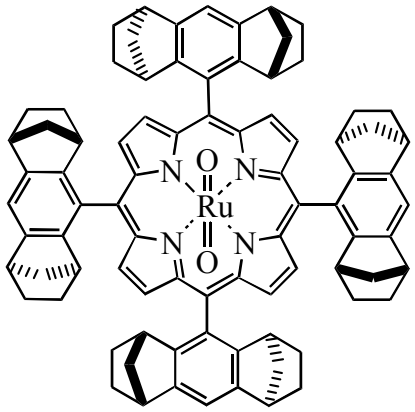
O'Shea and Foote, as has been discussed previously, reported their use of cobalt(II) tetraphenylporphyrin in the ring-opening of monocyclic 1,2-dioxines in 1989.[68] Work done prior to this by Foote used cobalt(II) tetraphenylporphyrin to ring-open bicyclic systems of varying complexity producing the di-epoxide, analogous to that shown above, in high yields.[159]

The work that has been published on the ring-opening of monocyclic and bicyclic 1,2-dioxines, both with and without a double bond, suggests that dioxines are readily ring-opened using metal catalysed radical cleavage. The compounds produced by this radical cleavage are less dependent on the metal used than on the complexity of the dioxine structure. The radical

cleavage can produce γ-hydroxyenone, diketone and furan, all of which are formed in the base catalysed ring-opening, along with di-epoxide and di-alcohol. The presence of γ-hydroxyenone when other metal complexes are used in the ring-opening of 1,2-dioxines suggests that other metal complexes could be useful in introducing enantiomeric excess into γ-hydroxy enones. The corresponding cyclopropanes could then be synthesised with enantiomeric excess when other metals are used in the ring-opening and this could be applied to metal salens.

3.2 Results and Discussion

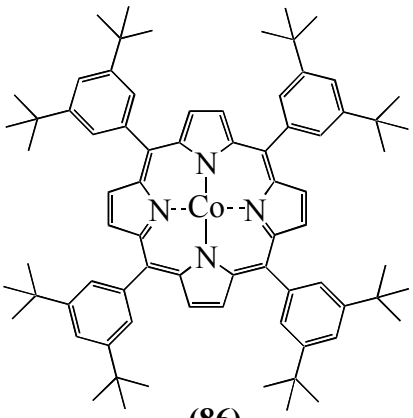
Catalysts in which the metal is bound by a porphyrin ligand (**87)** have been used previously in asymmetric epoxidation reactions (**Figure 10**).[167] The ability of porphyrin catalysts to bind metals in a tetradentate square planar arrangement is similar to that of the cobalt(II) salens and the cobalt(II) β-ketoiminato complexes and suggests that they may be capable of ring-opening 1,2-dioxines when bound to cobalt(II).



(85)

Figure 12 Porphyrin catalyst used in asymmetric epoxidation

Work into porphyrin complexes by Crossley *et al*, at The University of Sydney, had produced a series of porphyrin bound metals including cobalt(II).[168] A small amount of three of the cobalt(II) complexes (**86, 87, 88**) were donated to test in this work. The porphyrin cobalt(II) complexes were found to rearrange 3,6-diphenyl-3,6-dihydro-1,2-dioxine **(59)** as readily as any of the cobalt salens and cobalt β-ketoiminato complexes in both dichloromethane and THF. Cyclopropane was then readily synthesised for the γ-hydroxy enone formed without the need for removal of the catalyst. Although the complexes donated readily rearranged the dioxines they were racemic and so no tests on their ability to introduce enantiomeric excess could be tested.



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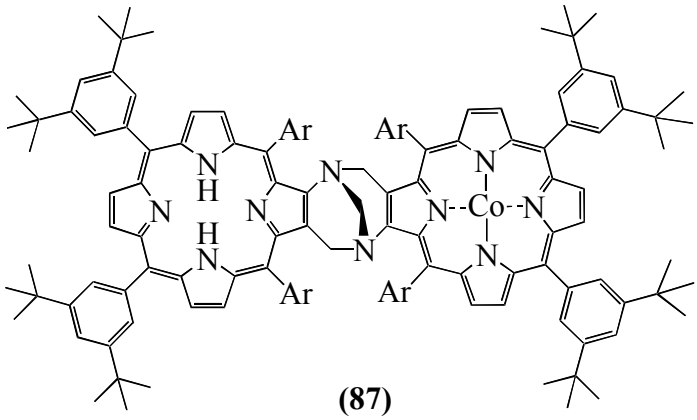

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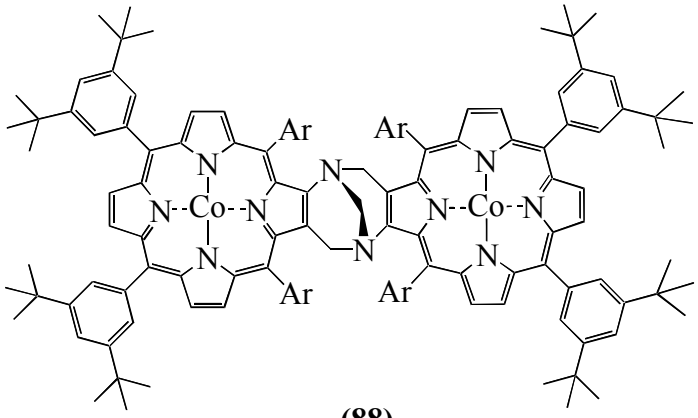

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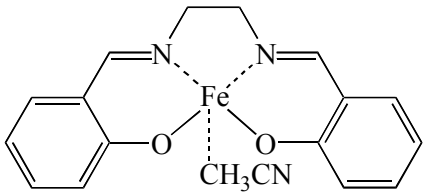
As it was known that other metals were capable of ring-opening 1,2-dioxines a small number of metal salens (**89, 90, 91)** were synthesised and tested.



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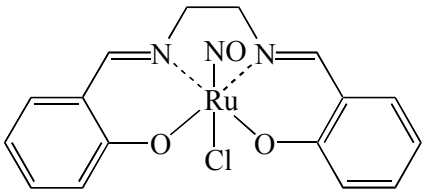

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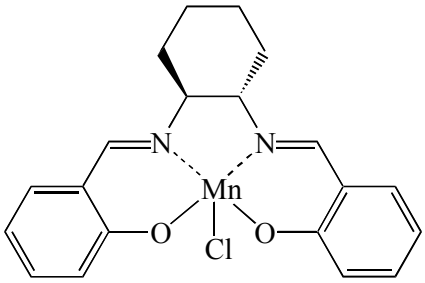


(91)

The synthesis of iron(II) salen (**89**) followed a literature method.[96] Addition of one molar equivalent of iron(II) acetate to the ligand, in hot acetonitrile, heating for 2 hrs, followed by cooling to room temperature produced the complex as a precipitate which was highly oxygen sensitive and required careful handling under nitrogen.[96] The precipitate was collected and use without further purification. The iron(II) salen was indeed capable of rearranging the dioxine to the enone from which cyclopropane could be synthesised using the crude rearrangement mixture.

The synthesis of ruthenium(II) salen (**90**)[169,170] also followed a literature method. The ligand was dissolved in DMF and treated with one molar equivalent of sodium hydride. Ruthenium nitrite trichloride hydrate[171-174] was then added and the reaction mixture stirred at 110^{o}C for 48 hrs. The residue was concentrated under reduced pressure, dissolved in dichloromethane, washed with water and dried *in vacuo*.[138] As with iron(II) salen the complex was used without further purification and found to rearrange the dioxine **(59)** in the same manner, with the enone formed used in the synthesis of cyclopropane (**61**).

For both the iron(II) and ruthenium(II) salen the rearrangement, in dichloromethane, took considerably longer than that found for the cobalt(II) complexes.

The manganese(III) catalyst, purchased from Aldrich Chemical Company, also rearranged the dioxine, although this rearrangement took place over such an extended time that when the rearrangement was eventually complete only small amounts of the enone were still present, most having ring closed and dehydrated to the furan.

For the iron(II), ruthenium(II) and manganese(III) complexes the reaction time was not decreased when THF was used as the solvent, with no significant difference in the reaction time.

3.3 Summary

It was found that the type of ligand does not significantly affect the ability of cobalt(II) to rearrange *meso*-1,2-dioxines. The presence of a tetradentate ligand that binds in a square planar configuration is one of the most important deciding factors on whether the catalyst will be capable of rearranging the dioxine.

Of the other metals tested, iron(II) and ruthenium(II) salen rearrange 1,2-dioxine within an acceptable length of time, with cyclopropane capable of being synthesised from the enone produced in the crude reaction mixture.

The manganese(III) salen will rearrange the dioxine, however, the length of time is prohibitive. Cyclopropane could not be synthesised due to decomposition of the enone.

The results obtained with the use of the porphyrin catalysts shows that there is ample opportunity for the synthesis of chiral templates that can incorporate metal ions, especially cobalt(II), for use in the asymmetric ring-opening of 1,2-dioxines.

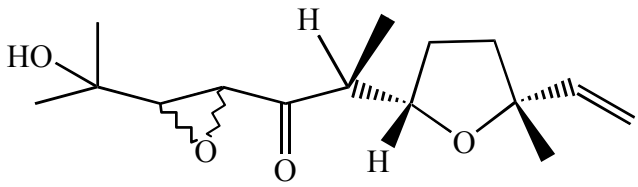
There is also ample opportunity for the synthesis of chiral iron(II) and ruthenium(II) salens and β-ketoiminato complexes for use in the ring-opening of *meso*-1,2-dioxines.

4. Epoxy Dioxines

4.1 Introduction

1,2-Dioxines have been known to be of biological importance for many years, with many biosynthetic pathways dependant on them as intermediates.[175] 4,5-Epoxy-1,2-dioxines and the isomeric 2,3-epoxy-4-hydroxyketones are known to have biological activity and significance in biosynthetic pathways, and have been used as intermediates in the synthesis of bioactive molecules.

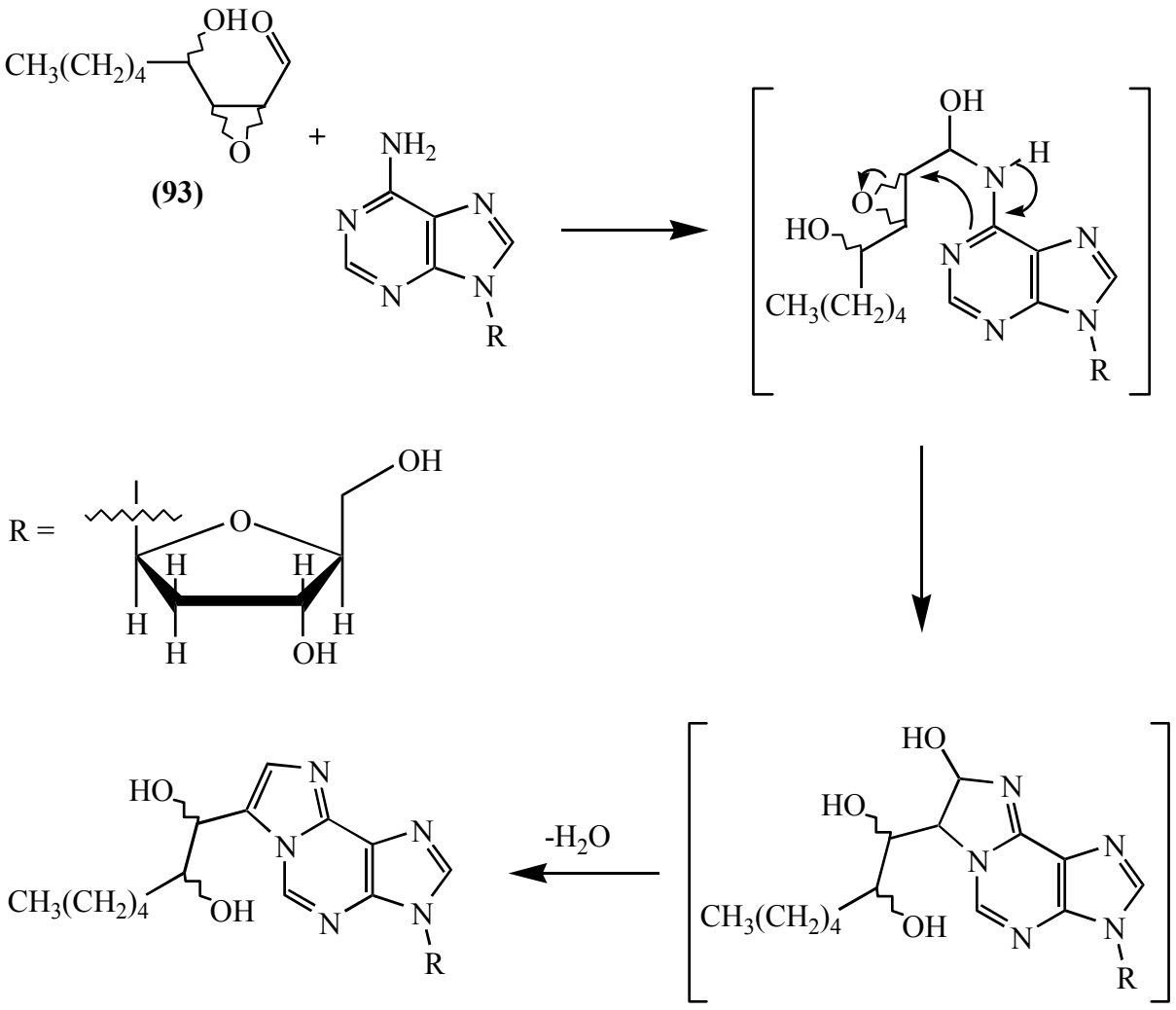
The essential oil from *Artemisia Pallens* (davana oil) contains several compounds, including sesquiterpenes and flavones. The non-steam volatile component of the oil contains a large number of compounds including **(92)**.[176]



(92)

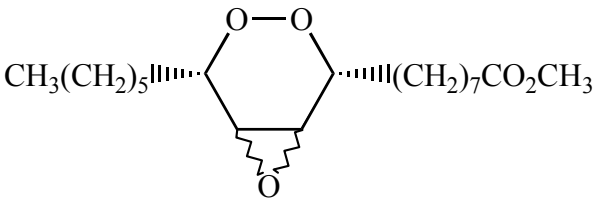
2,3-Epoxy-4-hydroxynonanal (EH) **(93)** is a known mutagen, carcinogen and tumourigen, that causes irreversible DNA damage, in *in vitro* studies when reaction at guanosine and adenosine occurs **(Scheme 30)**.[177-182]

EH is a potential metabolite of *trans*-4-hydroxy-2-nonenal, which is generated by lipid peroxidation of ω-6 polyunsaturated fatty acids. Under normal circumstances it is detoxified by the action of epoxide hydrolase, however, when this enzyme is defective buildup of the EH enables reaction with DNA. This damage leads to mutations, tumours and cancers.



Scheme 30 Mechanism of formation of DNA adducts with adenosine.

Bascetta *et al* synthesised an epoxy dioxine **(94)**[183] from a long chain conjugated ester for use in studies of the reactivity of fatty acids. Epoxy dioxines have been used to mask double bonds in systems where the double bond causes degradation of the intermediates to undesirable compounds. Nakano *et al* used an epoxy dioxine in this way in the synthesis of natural (+)-isodrimenin **(95)**[184] to prevent decomposition of one of the intermediates, which was inhibiting the synthesis of **(95) (Scheme 31)** and epoxy dioxines have been used as a starting material for the synthesis of cyclitols **(96 & 97)** (cyclohexanetriols) **(Scheme 32)**.[185]



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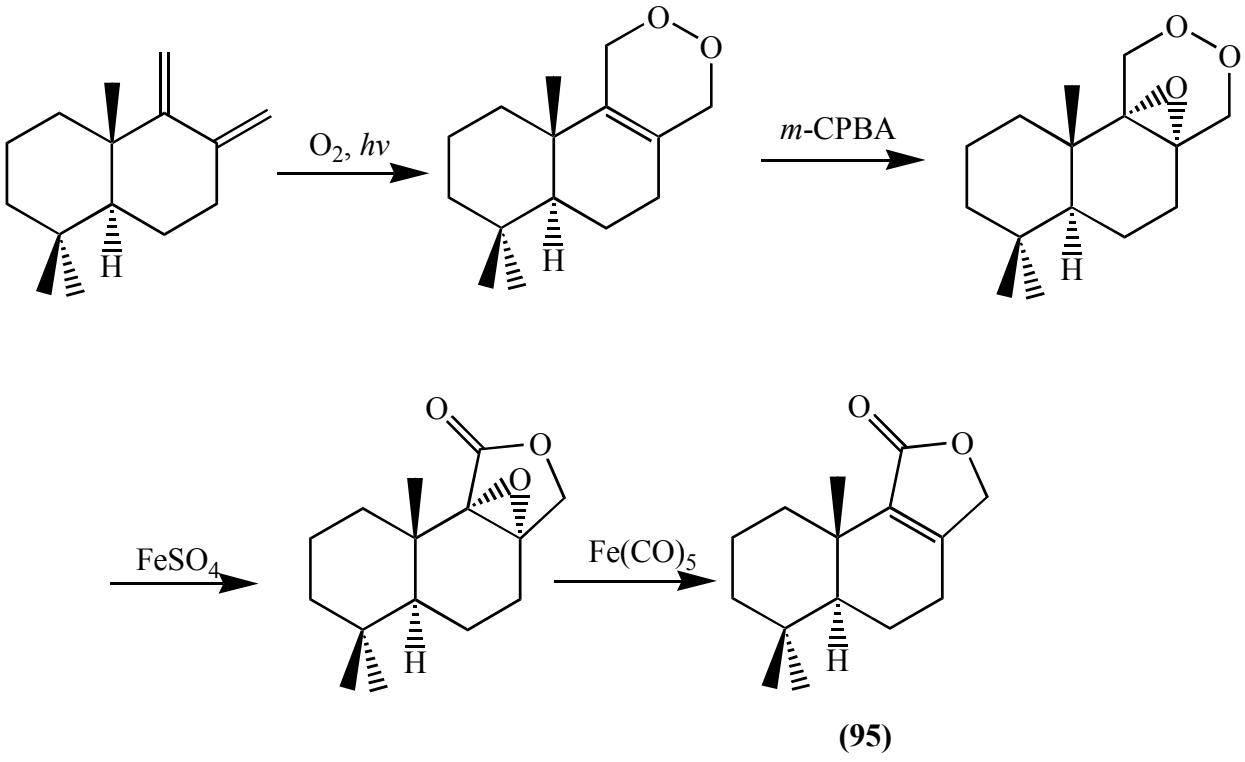

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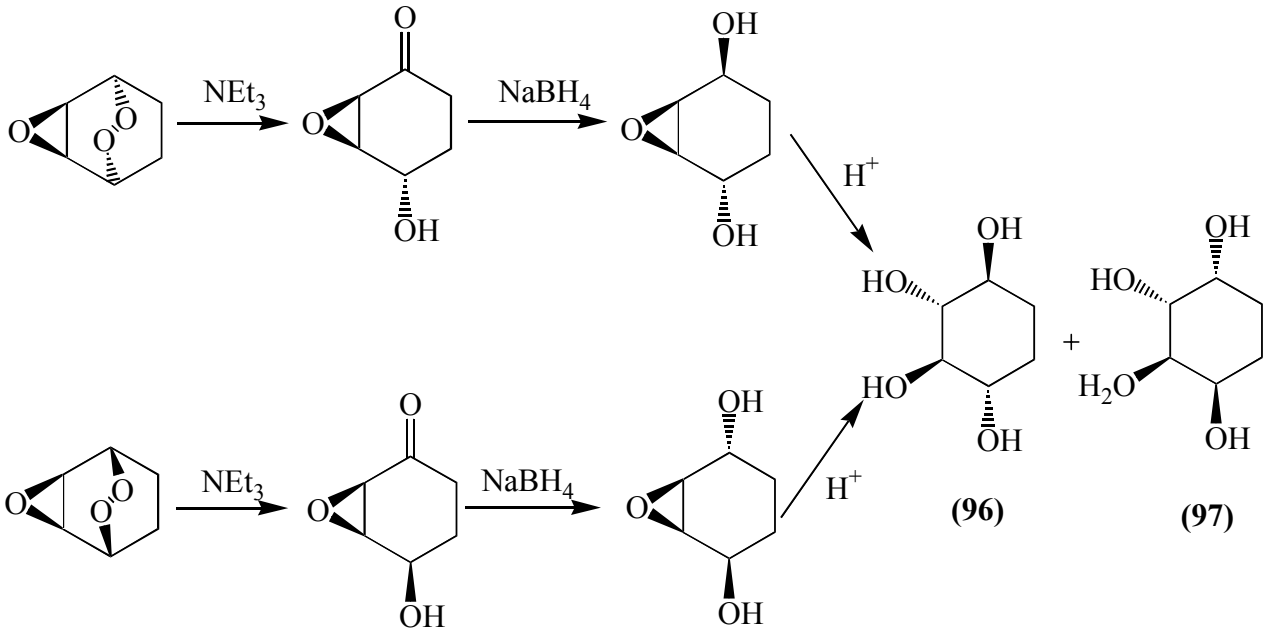
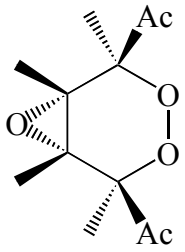
Scheme 31 Synthesis of (+)-Isodrimenin.



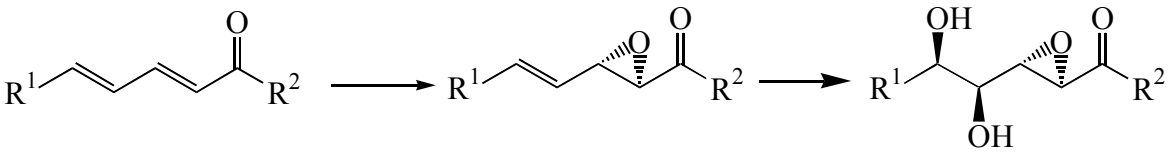
Scheme 32 Synthesis of cyclitols from epoxy dioxines.

There are several examples of the synthesis of epoxydioxines in varied systems including tetrahydronapthalene,[186] naphthalenes,[187] arenes,[188] and the epoxidation of a natural dioxine, ascaridole, see **Chapter 3**.[189] An unusual synthesis of an epoxydioxine uses hexamethylbenzene which is treated with activated oxygen to give the epoxydioxine **(98).** [190]



(98)

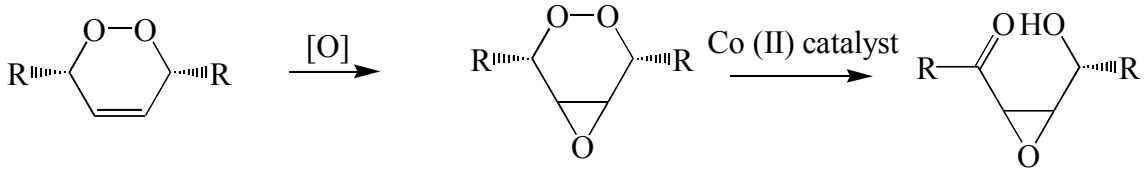
There are fewer examples of the synthesis of the 2,3-epoxy-4-hydroxyketones. One method that has been utilised by Allen *et al* involved the asymmetric epoxidation of a dieneone followed by the asymmetric dihydroxylation **(Scheme 33)**.[191,192]



$R^1 = CO_2Me$, $R^2 = Ph$
$R^1 = CO_2Bu^t$, $R^2 = Ph$

Scheme 33 Synthesis of epoxyketones from dieneones

The potential bioactivity of the 2,3-epoxy-4-hydroxyketones suggests that the ability to synthesise optically pure compounds will benefit studies in this area. The application of the cobalt(II) β-ketoiminato complexes and cobalt(II) salens in the ring-opening of *meso* epoxydioxines should enable the synthesis of enantioenriched epoxyketones, as depicted below, that may have biological activity **(Scheme 34)**.



Parent 1,2-dioxine system

Meso epoxy dioxine

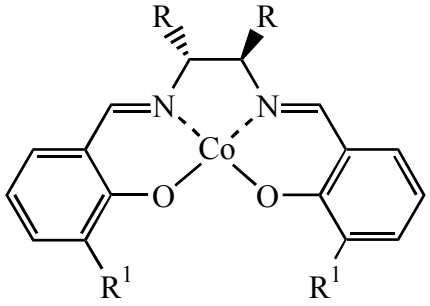
Optically enriched epoxyketone

R = alkyl, aryl, etc

Scheme 34 Synthesis and ring-opening of epoxy dioxines.

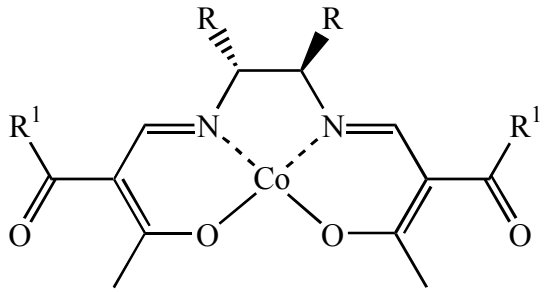
4.2 Results and Discussion

A significant amount of work has been performed, in the Taylor group, into the synthesis and reactivity of epoxy dioxines. To determine whether the cobalt(II) complexes, that have been used in the ring-opening of parent 1,2-dioxines, were also capable of enantioselectively ring-opening *meso* 4,5-epoxy-1,2-dioxines a small selection of catalysts (**29a & b, 30a & b, 53c, 55d & e, 56a, 57b)** were trialed and are depicted below.



29a: - R = -$(CH_2)_4$-, R^1 = *t*-Butyl (*R,R* isomer)
29b: - R = Ph, R^1 = *t*-Butyl (*R,R* isomer)

30a: - R = -$(CH_2)_4$-, R^1 = H (*R,R* isomer)
30b: - R = Ph, R^1 = H (*R,R* isomer)



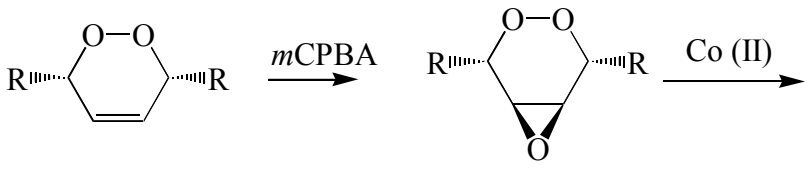
53c: - R = Ph, R^1 = Ethoxy (*S,S* isomer)

55d: - R = Ph, R^1 = (-)-Bornoxy (*R,R* isomer)
55e: - R = Ph, R^1 = (-)-Bornoxy (*S,S* isomer)

56a: - R = Ph, R^1 = (-)-Menthoxy (*R,R* isomer)

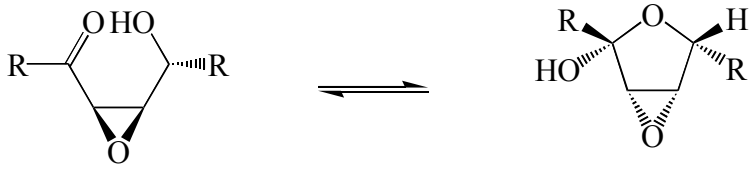
57b: - R = Ph, R^1 = (+)-Menthoxy (*S,S* isomer)

Synthesis of the epoxydioxines (**99a-c**) involved epoxidation of the starting dioxine with *m*-chloro perbenzoic acid. In the same way in which the catalysts ring-open the 1,2-dioxines, the 4,5-epoxy-1,2-dioxines were ring-opened to give the hydroxy ketones (**100a-c**), analogous to the γ-hydroxy enones and in equilibrium with the ring closed hemiacetal (**101a-c**) **(Scheme 35)**.



(59) R = Ph
(63) R = cyclohexyl
(64) R =*n*- propyl
(65) R = isopropyl

(99a) R = Ph
(99b) R = cyclohexyl
(99c) R = *n*-propyl
(99d) R = isopropyl



cis/trans

(100a) R = Ph
(100b) R = cyclohexyl
(100c) R = *n*-propyl
(100d) R = isopropyl

(101a) R = Ph
(101b) R = cyclohexyl
(101c) R = *n*-propyl
(101d) R = isopropyl

Scheme 35 Synthesis and ring opening of epoxy dioxines.

The conditions determined to introduce enhanced enantiomeric excess, for the 1,2-dioxines, were employed in the ring-opening of the epoxy dioxines (**Table 10**). The enantiomeric excesses was determined by the use of the same europium complex utilised previously, using the chemical shift of the CH attached to the alcohol, to determine the *ee*. Catalysts **29a & b** were both much more selective for the epoxydioxine system as was catalyst **30b** and **55e**. Catalysts **30a** and **55d** introduced substantially less enantiomeric excess than that observed for the cyclopropyl system under the same reaction conditions and catalyst **57b** introduced a comparable level of enantiomeric excess. Of the catalysts tested **56a** and **57b** introduced the equal and opposite enantiomeric excess.

Table 10 Enantiomeric excess introduced the ring-opened product with various catalysts[1]

Entry	Catalyst	*ee* (Epoxy dioxine)[3]	*ee* (Dioxine)[4]	Entry	Catalyst	*ee* (Epoxy dioxine)[3]	*ee* (Dioxine)[4]
1	**29a**	66	32	**6**	**55d**	76	64
2	**29b**	68	28	**7**	**55e**	58	68
3	**30a**	30	44	**8**	**56a**	68	-[2]
4	**30b**	60	46	**9**	**57b**	68	72
5	**54c**	30	-[2]				

[1]5 mol % catalyst, THF, 20°C, 0.08 M 3,6-diphenyl-3,6-dihydro-3,6-epoxy-1,2-dioxine, reaction time approx 30 min, [2]Not used in THF for the parent 1,2-dioxine system. [3]CH attached to the hydroxyl moiety used for *ee* determination. [4] The CH_2 of the benzyl was used for enantiomeric excess determinations.

As with the 1,2-dioxines it was necessary to determine whether or not the reaction conditions used for the initial tests were ideal for this system. The percentage catalyst, temperature and solvent were all modified, using 5 mol % catalyst in THF at 20°C as the standard.

Using catalyst **57b** it was found that 7.5 mol % of catalyst introduced the highest enantiomeric excess (higher amounts of catalyst, up to 20 mol %, did not improve the enantiomeric excess introduced) (**Table 11**) with no difference between 2.5 and 5 mol %. When cooler temperatures were used with 5 mol % catalyst the highest enantiomeric excess was introduced at 0°C with no further increase with decreasing temperature. Employing 7.5 mol % catalyst at 0°C did not increase the enantiomeric excess any further from that at 20°C suggesting that a limit had been reached for the enantiomeric excess that the catalyst was capable of introducing. Performing the rearrangement in dichloromethane produced only a minimal difference in the enantiomeric excess and was not significant.

The greater specificity of several of the catalysts for the epoxy dioxines suggests that the epoxide functionality greatly influences the way in which the catalyst binds, potentially acting as a loosely bound ligand during the rearrangement.

Table 11 Temperature and solvent effects on the enantiomeric excess introduced for the diphenyl epoxy dioxine[1]

Entry	Mol % catalyst	Solvent	Temperature (^oC)	*ee*[2]
1	2.5	THF	20	68
2	5	THF	20	68
3	7.5	THF	20	84
4	5	THF	0	78
5	5	THF	-15	78
6	7.5	THF	0	84
7	5	CH_2Cl_2	20	72

[1]Catalyst **57b**, THF, 20^{o}C, 0.08 M 3,6-diphenyl-3,6-dihydro-3,6-epoxy-1,2-dioxine, rearrangement time approx 30 min in THF, rearrangement time approx 2 hours in DCM. [2]CH attached to the hydroxyl moiety used for *ee* determination.

The use of catalysts with dialkyl dioxines had proven to be less specific for the parent 1,2-dioxine system. When catalysts **53c** and **57b** were used with diisopropyl epoxy dioxine **(99c)** the enantiomeric excess introduced is very similar to that found for diphenyl epoxy dioxine **(99a)** (**Table 12**). Dipropyl epoxy dioxine **(99c)** and dicyclohexyl epoxy dioxine **(99b)** (the dicyclohexyl epoxy dioxine and its ring-opened form were provided by a member of the Taylor group) were also rearranged to the hydroxy ketone in high yield, however, attempts to determine the enantiomeric excess failed, chiral shift NMR being inappropriate for these

compounds due to overlapping signals and the lack of any discernable single peak once any europium complex was added.

Table 12 Catalyst effect on the enantiomeric excess introduced for the diisopropyl epoxy dioxine[1]

Catalyst	***ee***	**Catalyst**	***ee*[2]**
54c	34	**58b**	64

[1]THF, 20°C, 0.08 M 3,6-diisopropyl-3,6-dihydro-3,6-epoxy-1,2-dioxine, rearrangement time approx 30 min.

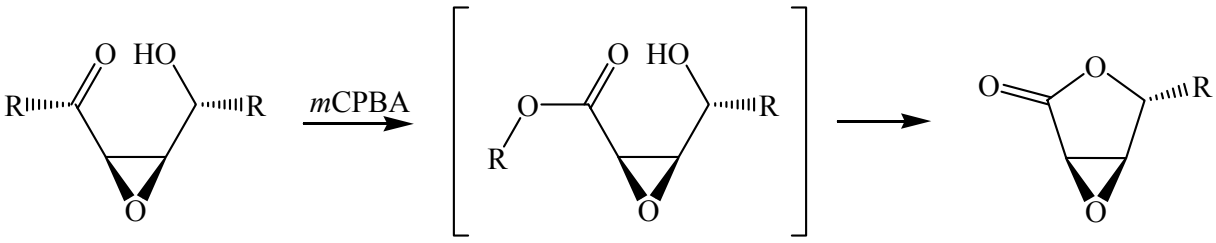
[2]CH attached to the hydroxyl moiety used for *ee* determination.

4.3 Summary

The catalysts tested in the ring-opening of the epoxydioxines were found to readily introduce enantiomeric excess, with 30% enantiomeric excess being the lowest and most between 64 and 84%. It is not possible to use data from the ring-opening of the parent 1,2-dioxines to predetermine the amount of enantiomeric excess that may be introduced. Some of the catalysts tested are much more selective for the epoxydioxines than the 1,2-dioxines.

Modification of the conditions found that 7.5 mol % of catalyst in THF was ideal at 20°C. With decrease in temperature 7.5 mol % catalyst, in THF, exhibited no further increase in the enantiomeric excess introduced. Enantiomeric excess as high as 84% could be introduce using the ideal conditions (7.5 mol% catalyst, 0°C, THF).

With the ability to synthesise these epoxy dioxines and produce their ring-opened isomer in high yield and with high enantiomeric excess it seems practicable that these reactions could be applied to the synthesis of a series of chiral epoxy lactones **(102)**. These types of compounds are known to have antimicrobial activity[193-195] in their racemic form and this may provide a route by which the enantiomerically pure form can be synthesised **(Scheme 36)** utilising a Baeyer-Villiger oxidation.



R = alkyl, aryl **(102)**

Scheme 36 Baeyer-Villiger and cyclisation of epoxy ketone.

5. Cyclopropyl Amino Acids, Amines, Acids and Alcohols

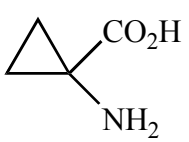
5.1 Introduction

5.1.1 Cyclopropyl Amino Acids

Of the many general types of naturally occurring cyclopropane-containing compounds, the cyclopropyl amino acids are of interest because of their high tendency to have biological activity in plants, microorganisms and especially animals.

1-Aminocyclopropane carboxylic acid (ACPC) **(103)** was discovered in the 1950's and is the first naturally occurring cyclopropyl amino acid whose structure was determined.[196] It is found in fruits such as apples and pears and is metabolised to ethylene, a phytohormone involved in many metabolic processes in plants.[11,12]

Cyclopropane containing amino acids, such as Hypoglycine A **(104)** and its glutamate amide analogue Hypoglycine B, both found in unripe akee arils (fruit) of *Blighia sapida Kon.* cause Jamaican vomiting sickness and hypoglycemia,[197-199] and (1*S*,2*S*)-Coronamic acid **(105)**, a component of Coronatine which induces chlorosis (in rye grass and potatoes).[200-202] Each of these compounds are known to have biological activity in animals and plants and all contain the cyclopropyl functionality.



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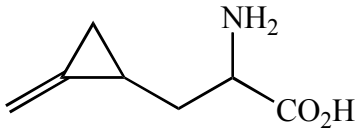

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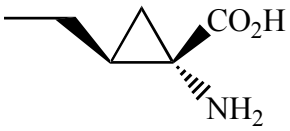
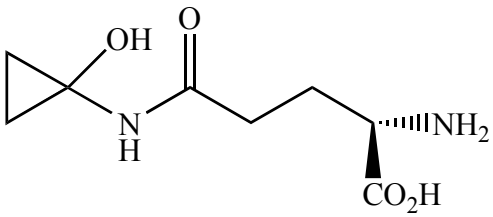


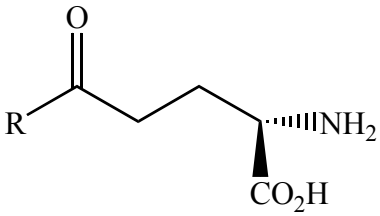
(105)

A few of the examples of cyclopropyl amino acids are known to be toxic, due to their ability to inhibit the action of certain enzymes.[203-208] An excellent example of such a cyclopropyl

amino acid is coprine **(106)**, an adduct of glutamic acid **(107a)** found in the common ink cap mushroom, *Coprinus atramentarius*,[1] which has been found to be toxic when taken with alcohol. The cyclopropane produced from its hydrolysis inhibits aldehyde dehydrogenase causing a buildup of acetaldehyde, leading to the toxic side effects attributed with its co-consumption with alcohol.[1]

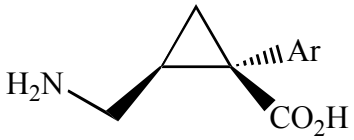


(106)



(107) **(a)** R = OH
(b) R = NH_2

Some cyclopropyl amino acids have been shown to have the potential to act as anti-depressants **(108)**, acting as γ-aminobutyric acid (GABA) analogues.[209]



Ar = various aromatic groups

(108)

Many of the cyclopropanes that are structurally analogous to L-glutamate **(107b)**, or contain L-glutamate within their structure, are known to have neurological activity.[1,210]

Communication between cells within the central nervous system (CNS) is brought about by release of chemicals at synapses producing either excitation or inhibition of the target cell. At approximately half of these synapses the chemical released is nitric oxide,[211] the communication at the other half of these synapses is the amino acid L-glutamate that binds and activates a range of receptors.[212,213]

Glutamate induced pathogenesis occurs due to the neurotoxicity of the amino acid.[214] When under or over activation of the receptors or a defect in the cellular mechanism occurs neurological disorders including epilepsy, cerebral ischaemia, CNS trauma, schizophrenia and

chronic neurodegenerative diseases, such as Alzheimer's, are often the result.[214] It is of interest in many scientific areas to find compounds that can act to block this activation or circumvent any defect to prevent this neurological damage.[213]

Glutamate receptors are present in two main forms, ionotropic glutamate receptors, that form ligand gated channels and directly control electrical signals between nerve cells, and metabotropic glutamate receptors ($mGluR^c$), that have only an indirect influence on the regulation of electrical signalling via intracellular metabolic processes.[213]

It has been proposed that glutamate binds to its receptors using a three point method **(Figure 13)** and rather than tight binding, as in the case of many receptor sites, a looser less specific binding occurs enabling a wider range of compounds to bind.[210]

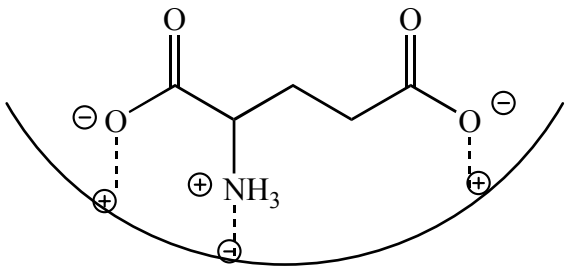
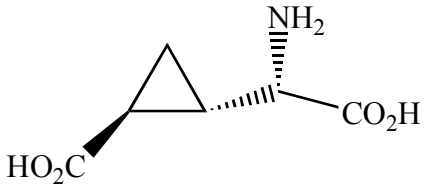


Figure 13 3 point binding model for interaction of glutamate and mGluRc.

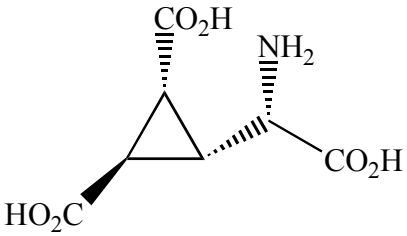
$mGluR^c$ are divided into three subgroups (by their amino acid content) and 8 main classes.[213,215] Subgroup 1 contains class 1, that mediates excitation, and class 5, found in many areas within the brain. Subgroup 2 contains class 2, which is found in the accessory olfactory bulb (nasal passages) and mediates depression, and class 3, which is found in neurons. Subgroup 3 contains the remaining classes, namely 4, 6, 7 and 8.[213,216] All of these subtypes are potential targets for drug development.

Drugs that target class 1 receptors in an antagonistic manner and class 2 and 3 in an agonistic manner have the potential for use as anti-epilepsy drugs. Compounds that are selective agonists for class 2 receptors, such as L-2-(carboxycyclopropyl)glycine–I (L-CCG–I) **(109)** and 2-(3,4-dicarboxycyclopropyl)glycine (DCG–IV) **(110)**, have been shown to

protect neurons from cerebral ischaemia, a process in which neurons are destroyed due to the excessive action of glutamate.[213,217]

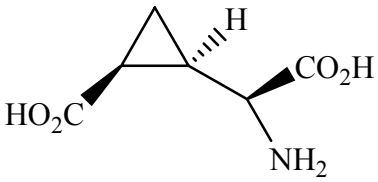


(109)

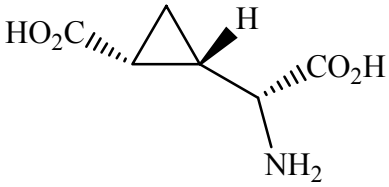


(110)

There are several known cyclopropyl amino acid agonists and antagonists for glutamate receptors, many of which are extremely potent. The agonists include: L-CCG-IV **(111)**, D-CCG-IV **(112)** and D-CCG-II **(113)** and the antagonists include: **(114 a-d)**.[210]



(111)



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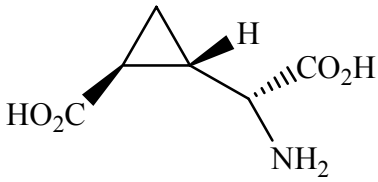
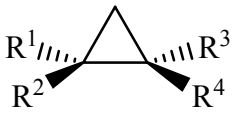


(113)



(114)

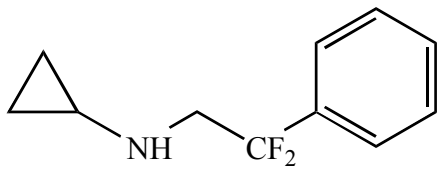
	R^1	R^2	R^3	R^4
114a	$CH(NH_2)CO_2H$	H	$CH_2PO_3H_2$	H
114b	H	$CH(NH_2)CO_2H$	$CH_2PO_3H_2$	H
114c	NH_2	CO_2H	H	$(CH_2)_2PO_3H_2$
114d	CO_2H	NH_2	H	$(CH_2)_2PO_3H_2$

5.1.2 Cyclopropyl Amines, Acids and Alcohols

There are also many natural and synthetic cyclopropyl amines, acids and alcohols known, many of which are biologically active.

One of the best examples of a cyclopropyl amine with biological effects is that of Coprine **(98)** discussed above. Although classed as an amino acid it is the cyclopropyl amine produced by its hydrolysis that is the compound responsible for the inhibition of aldehyde dehydrogenase, and the subsequent toxicity when consumed with alcohol.[12,218]

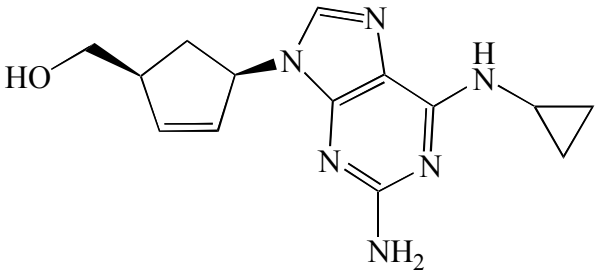
Cyclopropyl amines are known suicidal inhibitors of Cytochrome P450 enzyme, a crucial system in the biosynthesis of steroid hormones and well as the metabolism of drugs. In model studies the cyclopropane **(115)** has been found to inhibit the system up to 90 percent.[219,220]



(115)

Cyclopropyl amines are also inhibitors of mitochondrial monoamine oxidase and plasma amine oxidase,[220] and the exploitation of this activity has enabled them to be used as antidepressants and as useful therapies in the treatment of Parkinson's disease.[12]

A potent inhibitor of HIV reverse transcriptase, 1592U89 **(116)**, capable of reducing the viral load by more than 99 percent contains a cyclopropyl amine. It is only the presence of the cyclopropyl amine that differs it from its parent compound, Carbovir **(117)**.[221]



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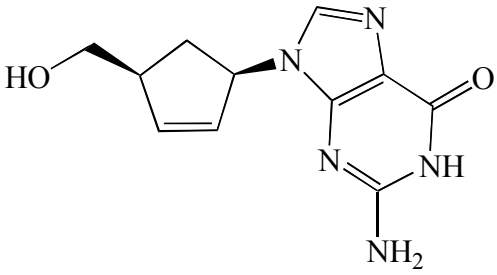
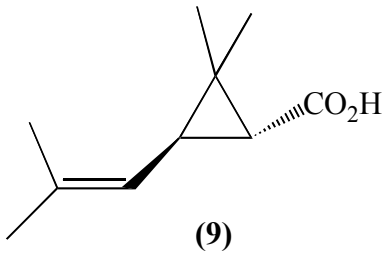


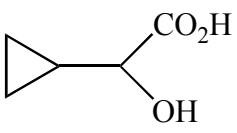
(117)

One of the better known examples of a cyclopropyl acid is Chrysanthemic acid **(9) (see Chapter 1)**, the (*R*) configuration of which shows the higher bioactivity and has a diverse use as an insecticide.[222]

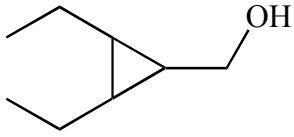


(9)

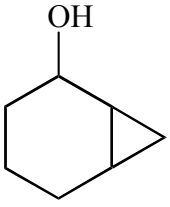
Lactic acid analogues **(118)**, containing a cyclopropane, have been shown to inhibit lactate dehydrogenase and cyclopropyl methanols **(119-122)** have been shown to inhibit alcohol dehydrogenase with the lowest level of inhibition exhibited when the 2,2,3,3-tetramethyl compound **(122)** is used.[223-225]



(118)



(119)



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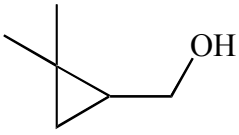

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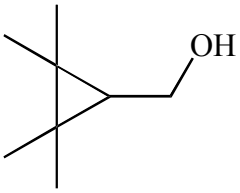


(122)

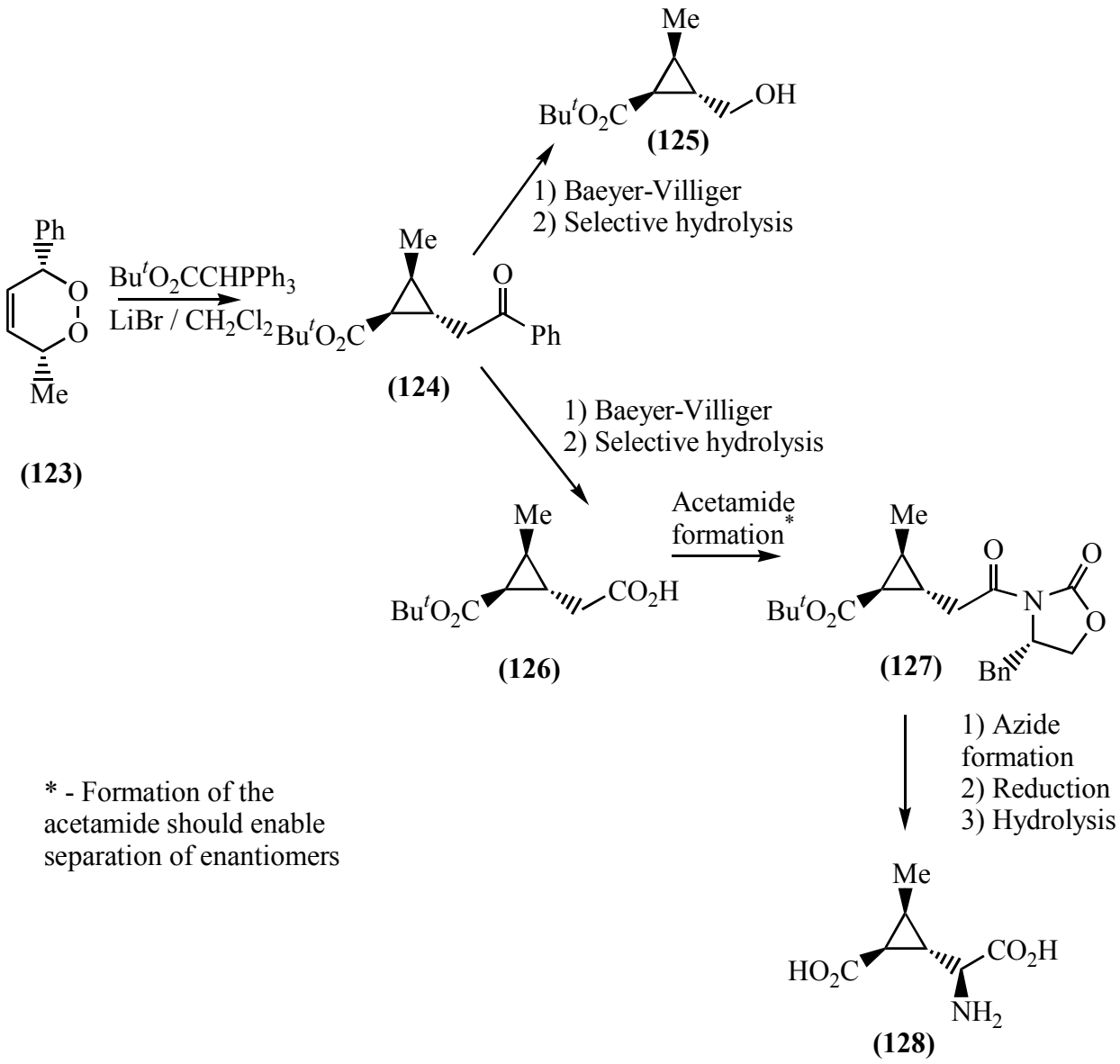
There are only a small number of syntheses available for the synthesis of cyclopropyl amines. The methods that are known are widely applicable to the synthesis of 1-, 1,2- and 1,1-substituted cyclopropanes.[226,227] Of the synthetic methods available for the synthesis of cyclopropyl amines, one of the methods has been applied to the synthesis of cyclopropanols as well as cyclopropyl amines.[227] It is the cyclopropyl methanols that have been synthesised most frequently for use in enzyme inhibition studies.[224,225]

The cyclopropyl moiety is a component in many other groups of compounds including pesticides, insecticides, antiviral and antibacterial compounds, cardiovascular stimulating agents, antihypertensives, diuretics, hypnotics, anti-inflammatory agents, analgesics and anticonvulsives.[12]

The ability to synthesise optically pure cyclopropyl amino acids, amines, acids and alcohols has the potential to be applied to studies into enzyme inhibition but more importantly to the synthesis of new drugs that may be crucial in the treatment of disease.

5.2 Results and Discussion

The retrosynthetic proposal for the synthesis of cyclopropyl amino acids involved the reaction of the unsymmetrical 3-methyl-6-phenyl dioxine (**123**) with a 'bulky' ester ylide, such as *t*-butyl, to produce the *trans* cyclopropane (**124**) as the major product. Baeyer–Villiger oxidation of the cyclopropane with conditions specific to the formation of either of the desired diesters and subsequent selective hydrolysis would then yield either the cyclopropyl methanol (**125**) or the cyclopropyl acetic acid (**126**). (**Scheme 37**)

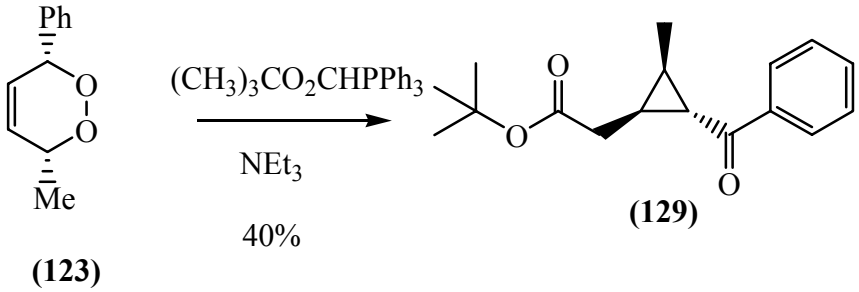


Scheme 37 Proposed synthesis of cyclopropyl amino acids.

The cyclopropyl acetic acid could then be converted to the acetamide (**127**) via the acid chloride with further reaction to the amino acid (**128**) through the azide.

Reaction of the dioxine with *t*-butyl ester ylide and lithium bromide produced the major *trans* isomer of the cyclopropane (**124**) in high yield (70%), with the cyclopropane (**124**) formed preferentially when lithium bromide is present.[228] Baeyer-Villiger oxidation using *m*-CPBA, for 4 days, gave a 1:1 mixture of the two diesters, the precursor esters to compounds **(126 & 127)** that were inseparable by column chromatography. Basic hydrolysis of this mixture enabled separation of the cyclopropyl methanol (**125**) readily, in high purity, however, the cyclopropyl acetic acid (**126**) was part of a mixture of the cyclopropane with benzoic acid that could not be separated by sublimation or chromatography.

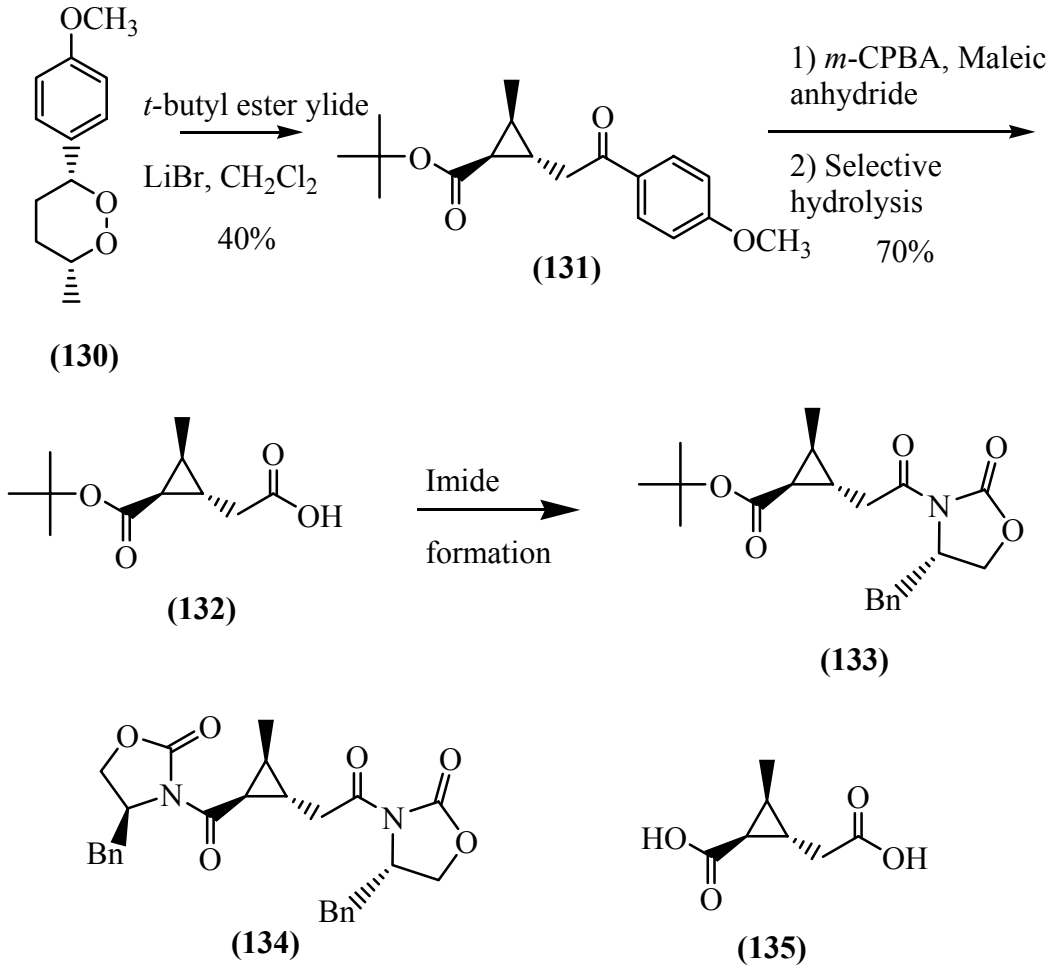
As cyclopropane (**124**), and its isomer (**129**), had not been made previously, for completeness the structural isomer of cyclopropane (**124),** made above, was synthesised. Phenyl methyl dioxine (**123**) was allowed to react with triethylamine, to produce the *cis* γ-hydroxyenone, followed by *t*-butyl ester ylide to form the desired cyclopropane (**129**) (**Scheme 38)**.



Scheme 38

With the Baeyer-Villiger product from cyclopropane (**124)** being part of a mixture of two inseparable esters the ability to selectively produce either of the two isomeric cyclopropyl esters was needed. The synthesis of the cyclopropyl compound containing the 4-methoxyphenyl ketone from the reaction of 3-methyl-6-(4-methoxyphenyl) dioxine (**130**) with *t*-butyl ester ylide and lithium bromide produced the major *trans* cyclopropane (**131**) in moderate yield (40%). Baeyer-Villiger oxidation of the cyclopropane with *m*-CPBA and

maleic anhydride gave only the one isomer and basic hydrolysis gave a mixture of the acid (**132**) and the 4-methoxyphenol (**Scheme 39**), which were separated by fractional recrystallisation from heptane. Conversion of the acid to imide (**133**) failed, with hydrolysis of the *t*-butyl ester due to the presence of anhydrous hydrochloric acid. Both the diacetamide (**134**) and the diacid (**135**) were formed under the reaction conditions. The formation of the diacetamide (**134**) was confirmed by the synthesis of a genuine sample, although the diastereomers could not be separated by chromatography or crystallisation. Due to this failure another approach was necessary for the synthesis of the cyclopropyl amino acids.

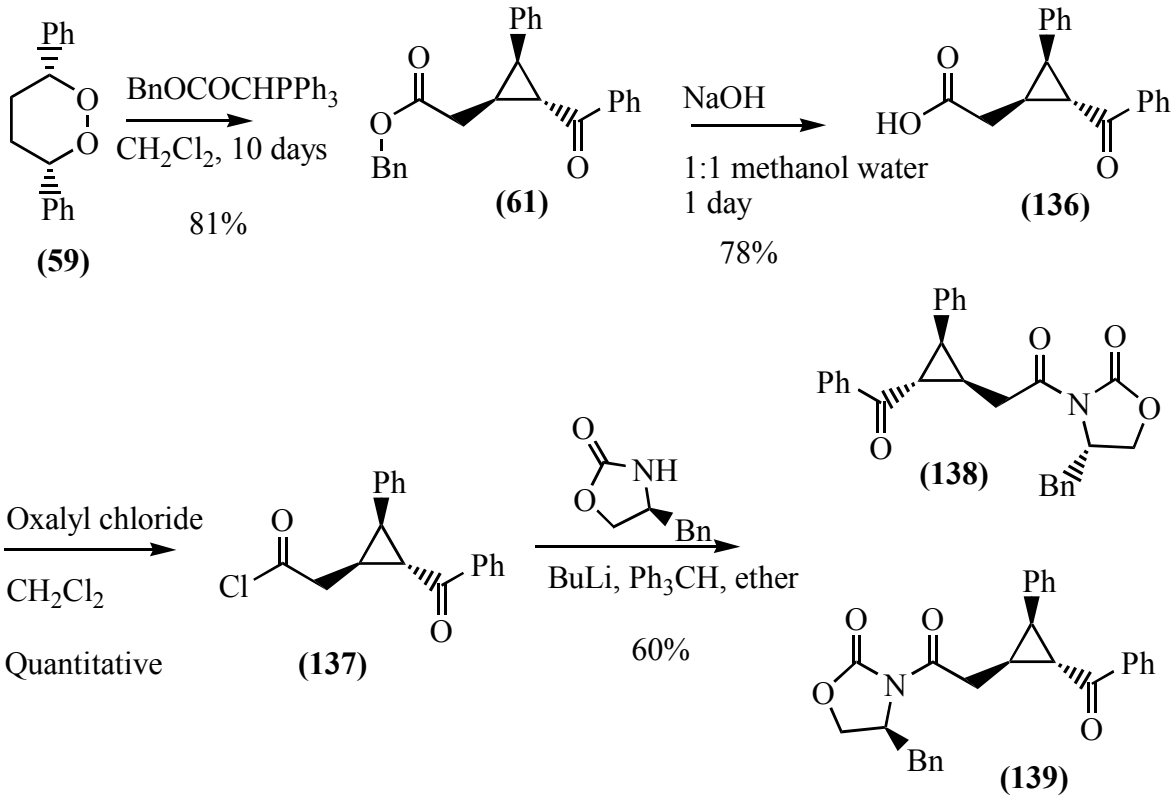


Scheme 39

To determine whether the initial proposed reactions could be modified to a related cyclopropyl system cyclopropane (**61**) was synthesised. Moreover, as the precursor dioxine is

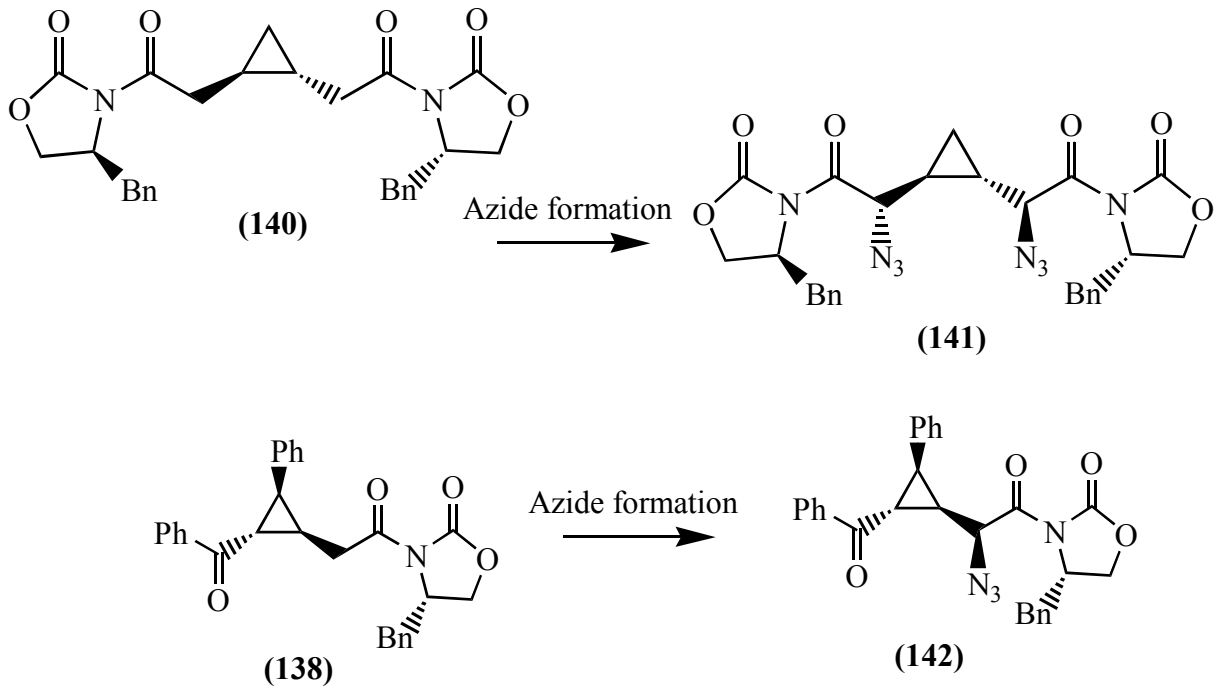
meso there would be the possibility to introduce enantiomeric excess into the cyclopropane by the use of chiral cobalt catalysts.

Reaction of 3,6-diphenyl dioxine (**60**) with benzyl ester ylide produced the major *trans* cyclopropane (**61**) in excellent yield. Without the need for Baeyer-Villiger oxidation the potential for hydrolysis of the second ester, in the formation of the acetamide, is avoided. Hydrolysis of the benzyl ester gave the cyclopropyl acetic acid (**136**) (78%), which was allowed to react to form the acetamide, via the acid chloride (**137**). The diastereomers thus formed could be separated chromatographically to give the optically pure imides (**138 & 139**) (**Scheme 40**).



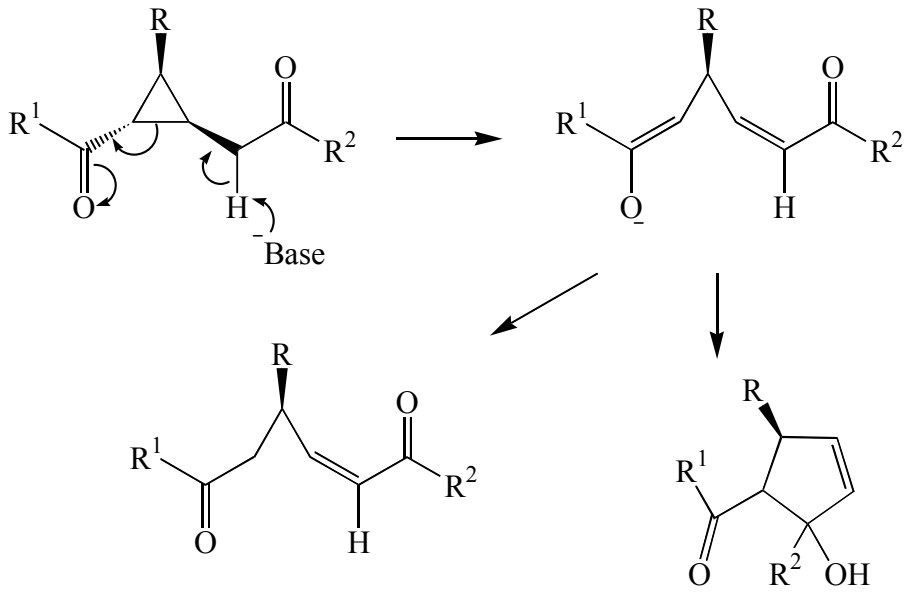
Scheme 40

Neset *et al.* published their synthesis of a cyclopropyl diazide **(141)** from the cyclopropane **(140)**[229] Attempts to form the azide **(142)**, following published methods,[229,230] from either of the acetamides (**138 & 139**) resulted in complex mixtures of products, none of which was the azide (**142**).



Scheme 41

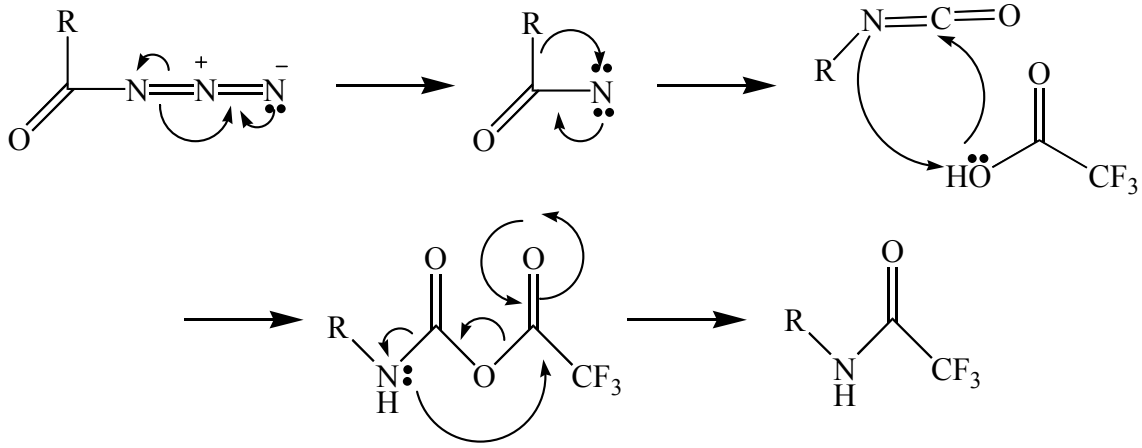
Recent work within the Taylor group has suggested that formation of the azide is not possible in the system being used, due to the ability of the cyclopropane to ring-open (**Scheme 42**).[231] Although the same reaction conditions were used in the attempt to synthesise azide **(142)** the α-ketone of the cyclopropane inhibits the reaction. This explains why the literature procedure to form **(141)** is successful where the attempted synthesis of (**142**) is unsuccessful.



Scheme 42

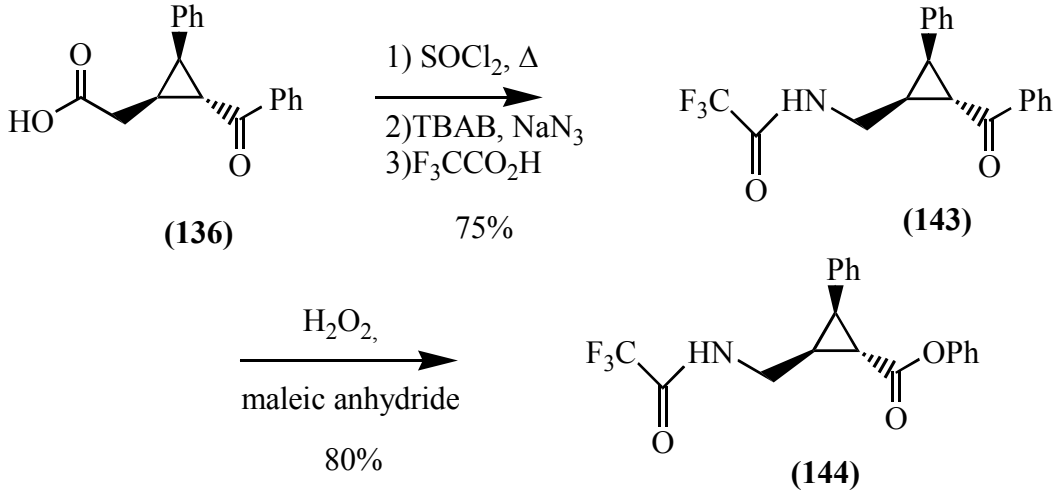
Although this reaction pathway was found to be incompatible with the cyclopropyl system, the 1,2-dioxine used lent this reaction pathway to the synthesis and use of chiral cyclopropanes. Catalyst **55e** was used in a large scale reaction of cyclopropane (**61**) with an enantiomeric excess of 76%. Hydrolysis to the acid and conversion to the acetamide produced a mixture of the two diastereomers **(138 & 139)** with the diastereomer with lower R_f in 76% excess, exactly that found by chiral shift for the starting cyclopropane.

With the incompatibility of the cyclopropyl systems with this reaction series, another method was required suitable for the synthesis of cyclopropyl amino acids. Whilst a range of new cyclopropanes have been prepared there had been no success towards the synthesis of a cyclopropyl amino acid. With the cyclopropyl systems available for use in this work it was thought that using some old chemistry first developed in the 1920's would be of use in the synthesis of a cyclopropyl amino acid. The use of the Curtius rearrangement in the synthesis of protected amines, from carboxylic acids, had been shown previously to be applicable to a variety of systems.[232] The mechanism involves the pyrolytic rearrangement of an acyl azide to form an isocyanate (**Scheme 43**). Treatment of the isocyanate with trifluoroacetic acid then yields the trifluoroacetamide.[47]



Scheme 43

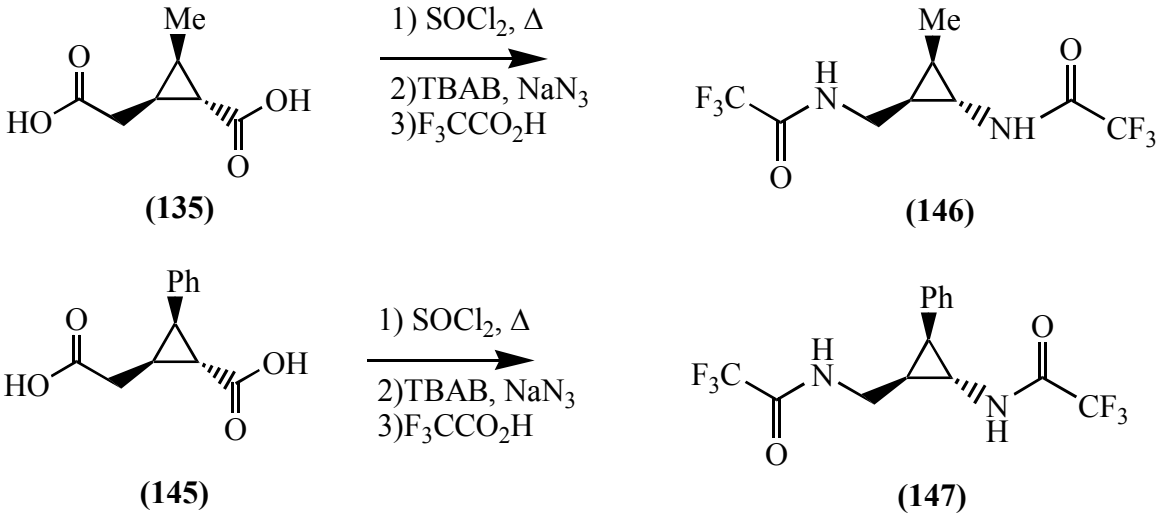
Racemic cyclopropyl acid (**136**) was converted to the protected amine (**143**) via the azide using the Curtius rearrangement. Baeyer-Villiger oxidation using hydrogen peroxide and maleic anhydride gave the protected amino acid (**144**). The hydrolysis of one of the optically pure acetamides (**138 or 139**) to give the acid enabled the synthesis of an optically pure cyclopropyl amine (**143**) (**Scheme 44)**.



Scheme 44

It was thought that this rearrangement could be applied to the synthesis of protected cyclopropyl diamines, both chiral and racemic. Diacids were synthesised by the Baeyer-Villiger oxidation of either cyclopropane (**133** , for diacid (**135**)) or cyclopropane (**61** , for diacid (**145**)), followed by hydrolysis using trifluoroacetic acid. Attempts to convert both the methyl diacid (**135**) and the phenyl diacid (**145**) to their requisite protected amines (**146 &**

147) did not achieve the desired compound, with a complex mixture of inseparable products (**Scheme 45)**. Mass spectral analysis of the mixture did not indicate the presence of any of the protected cyclopropyl diamide or any other recognisable products.



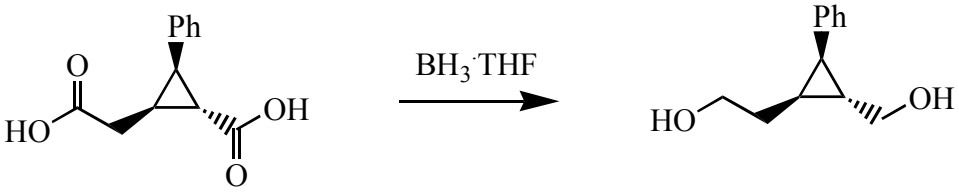
(135) **(146)**

(145) **(147)**

Scheme 45

Work in the 1950's and 60's suggests that the inability to synthesise the cyclopropyl diamines is due to the ready hydrolysis of the diacid chloride to the mono acid chloride in the phase transfer conditions used.[233,234]

Cyclopropyl diol (**148**) was synthesised from diacid (**144**) readily using borane-THF complex. The diol was made in high yield and its synthesis could be applied to other diols and to chiral systems (**Scheme 46**).



(144) **(148)**

Scheme 46

With the results presented above the Curtius rearrangement can be applied to the synthesis of protected amines and amino acids, and provided the 1,2-dioxine used in the synthesis of the cyclopropane is symmetrical, optically enriched cyclopropyl amines and amino acids can be

synthesised. The synthesis of diols should also be readily applied to the synthesis of chiral systems.

5.3 Summary

Initial attempts into the synthesis of α-amino acids showed that the compounds being utilised were incompatible with reaction conditions. *t*-Butyl ester protected acids were hydrolysed during the formation of acid chlorides and cyclopropanes were ring-opened in azide formation reactions.

The Curtius rearrangement was found to be ideal in synthesising protected cyclopropyl amines and with subsequent Baeyer-Villiger oxidation the amino acid could be synthesised. Provided the starting acid was optically enriched, the catalysts discussed in Chapter 2 ideal for this use, or optically pure, amino acids of the same optical purity can be produced.

Attempts to synthesis protected diamines form the diacids using the Curtius rearrangement did not produce the desired products with only a complex mixture resulting. However the synthesis of a cyclopropyl diol occurred readily using Borane-THF complex. This reaction could then be applied to the synthesis of chiral diols.

6. Experimental

6.1 General Experimental

^{1}H and ^{13}C NMR spectra were measured using a 300 MHz spectrometer in deuterochloroform as the solvent for all compounds unless otherwise stated. Resonances are in parts per million (ppm).

^{1}H NMR spectra are referenced to tetramethylsilane (TMS: δ 0.0). ^{13}C NMR spectra are referenced to chloroform (δ 77.0). Multiplicities are assigned as follows: s :- singlet, d :- doublet, q :- quartet, quin :- quintet, m :- multiplet, and combinations thereof. All coupling constants are in Hz.

Infrared spectra were measured using a ATI Mattson Genesis Series FTIR as solutions in an appropriate solvent or in the case of oils as the neat compound.

Electron Impact (EI) mass spectra were carried out using a VG ZAB 2HF mass spectrometer operating at 70eV.

Accurate mass spectra were performed by the Organic Mass Spectrometry Facility, Central Science Laboratory, University of Tasmania.

Microanalyses were performed by the Chemistry Department, University of Otago for Organic compounds or the Chemical and Micro Analytical Services, Belmont, Victoria for Cobalt catalysts.

Thin layer chromatography was performed on Merck silica gel 60 F_{254} on aluminium backed silica sheets using redistilled solvents. T.l.c plates were visualised using vanillin-sulphuric acid dip[235] or under UV 253 nm.

Flash chromatography was performed using Merck silica gel 60 (230 – 400 mesh) grade silica and redistilled solvents.

Melting points were carried out on a Reichert hot stage melting point apparatus and are uncorrected.

Optical rotations were performed using a Polaar 21 optical activity automatic polarimeter with a sodium lamp. Concentration (c) is g/100 mL in the solvent indicated and the specific rotations ($[\alpha]_D$) are reported with the temperature used.

Solutions were dried using anhydrous sodium sulphate unless otherwise stated. All solvents were distilled prior to use.

Unless otherwise stated all reactions utilising air or moisture sensitive reagents were performed under a nitrogen atmosphere.

The following compounds were purchased from Aldrich Chemical Company, Inc. and used without further purification. *N,N'*-bis(salicylidene)-ethylenediaminocobalt(II); *N,N'*-bis-(salicylidene)-ethylenediaminocobalt(II) hydrate; (*S,S)*-(+)-bis(3,5-di-*t*-butyl-salicylidene)-1,2-cyclohexanediaminocobalt(II); (*R,R)*-(+)-bis(3,5-di-*t*-butylsalicylidene)-1,2-cyclohexane-diaminocobalt(II); (1*R*,2*R*)-(-)-1,2-diaminocyclohexane; (*1S,2S*)-(+)-1,2-diaminocyclo-hexane; (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine; (*1S,2S*)-(-)-1,2-diphenylethylenediamine; *trans,trans*-1,4-diphenyl-1,3-butadiene; rose bengal, bis(triethylammonium)salt; europium tris[3-(heptafluoropropylhydroxymethylene)]-(+)-camphorate; (*S*)-4-benzyl-2-oxazolidinone; *N,N*-dimethylformamide dimethylacetal; (+)-menthol; (-)-menthol; *o*-vanillin; lithium bromide.

A small number of compounds, the synthesis of which is not described in the main text, were synthesised routinely for use in this work, the synthesis of which is detailed below.

Resolution of (±) 1,2-Diamino-1,2-diphenylethane[236]

5-Spirocyclohexyl-2,3-diphenylisoimidazole[236]

A mixture of benzil (31.5 g, 0.15 mol), cyclohexanone (16 mL, 15.15 g, 0.0154 mol), ammonium acetate (120 g, 1.56 mol) and glacial acetic acid (300 mL) was heated at reflux for

one hour. The mixture was then slowly poured into rapidly stirring water (450 mL), stirred for a further 2 hours and the reaction mixture left overnight. The resulting precipitate was collected by vacuum filtration, washed with water and dried. The crude crystals were then recrystallised from methanol water (4:1) to give colourless crystals. (36 g, 83 %) m.p. = 105 – 107°C (lit.[236] 105 – 106°C). ^{1}H NMR: δ = 1.64 – 2.05 (m, 10H), 7.20 – 7.55 (m, 10H). ^{13}C NMR: δ = 24.00, 25.58, 34.60, 103.97, 128.12, 128.74, 129.80, 133.03, 163.87.

(±) 1,2-Diamino-1,2-diphenylethane[236]

To a stirred solution of 5-spirocyclohexyl-2,3-diphenylisoimidazole (36 g, 0.125 mol) in dry THF (175 mL) and ammonia (250 mL) at –78°C was added lithium (3.4 g, 0.486 mol) in small pieces. The dark solution was stirred for 2 hours during which time the dark colour persisted. TLC analysis showed the presence of starting material and hence ethanol (14.4 mL, 11.4 g, 0.248 mol) was added and the reaction mixture stirred for a further 2 hours. Solid ammonium chloride (35 g, 0.655 mol) was then added at –78°C and the cooling bath removed. The ammonia was allowed to evaporate overnight. Water (175 mL) was then added and the phases separated. The aqueous phase was then extracted with diethyl ether (3 x 175 mL), the organic extracts combined and then washed with brine and dried and concentrated *in vacuo* to 150 mL. The solution was cooled to 0°C then treated with hydrochloric acid (2M, 200 mL) and the biphasic mixture was stirred vigorously for 1 hour. The phases were separated and the organic phases were washed with water. The combined aqueous phases were washed with dichloromethane (200 mL) and then treated with sodium hydroxide (2N, 200 mL). The aqueous phase was then extracted with dichloromethane (4 x 100 mL) and the organic phase dried and the solvent removed *in vacuo* to give white crystals. (26 g, 98 %) m.p. = 82 – 83°C (lit.[237]83°C). ^{1}H NMR: δ = 1.64 (bs, 4H), 4.09 (s, 2H), 7.28 (m, 10H). Enantiomers were then separated via their tartrate salts and fractional crystallisation from hexane (x 6).[236]

t-Butyl trichloroacetimidate[238]

To a solution of trichloroacetonitrile (75 mL, 108 g, 0.748 mol) in dry *t*-butanol (55.5 g, 0.75 mol), under nitrogen, was added dropwise sodium *t*-butoxide (12.13 g, 0.126 mol) in *t*-butanol (60 mL) and the resulting orange solution was stirred for 16 hours. After distillation of the residual *t*-butanol the compound was distilled from the crude reaction mixture as a clear colourless oil. b.p. = 65°C/11mm (lit.[238] 65°C/11mm).

t-Butyl bromoacetate[239]

To a solution of bromoacetic acid (14.5 g, 0.104 mol) in dry dichloromethane (200 mL), under nitrogen, was added, dropwise, a solution of *t*-butyl trichloroacetimidate (45 mL, 54.95 g, 0.252 mol) and $BF_3 \cdot OEt_2$ (2.1 mL, 2.35 g, 0.0166 mol) in dry cyclohexane (400 mL) and the resulting solution stirred for 16 hours. Solid sodium hydrogen carbonate (20 g, 0.24 mol) was then added in one portion, the mixture filtered through a plug of silica and the solvent removed *in vacuo* to give a clear colourless oil. (20 g, 98 %) ^{1}H NMR: δ = 1.48 (s, 9H), 3.75 (s, 2H).[240]

(t-Butoxycarbonylmethylene)triphenylphosphorane

To a solution of triphenylphosphine (30 g, 0.115 mol) in dry toluene (100 mL) was added *t*-butyl bromoacetate (20 g, 0.108 mol) and the reaction mixture stirred at ambient temperature for 2 days after which time the precipitate was collected, washed with dry toluene and dried *in vacuo*. (40 g, 85 %).

To a vigorously stirred solution of the salt (40 g, 0.089 mol) in methanol (75 mL) and water (75 mL) was added sodium hydroxide (1N, 75 mL) until no further precipitation occurred. The crystals were then collected, washed with water until the washings were neutral and dried *in vacuo* to give pale cream powder. (32 g, 98 %) ^{1}H NMR: δ = 1.22 (bs, 9H), 2.68 (bs, 1H), 7.41 – 7.67 (m, 15H).[240]

Benzyl 2-(triphenylphosphanylidene)acetate

Bromoacetic acid (20.05 g, 0.144 mol), benzyl alcohol (14.16 g, 0.131 mol) and *p*-toluenesulfonic (100 mg, 0.58 mmol) acid were combined in benzene (100 mL) and heated to reflux under Dean and Stark conditions for 2 days. The reaction was then cooled and washed with sodium bicarbonate solution (saturated) and the organic phase dried. R_f = 0.5 (hexanes : ethyl acetate = 1:4).

To the solution of benzyl bromoacetate (33 g, 0.131 mol (assumed to be 100 %) in benzene (100 mL) was added triphenyl phosphine (34.3 g, 0.131 mol) and the reaction mixture stirred at ambient temperature for 2 days. The resultant precipitate was collected and washed with cold hexanes and dried *in vacuo*.

The salt was dissolved in methanol / water (1:1) and stirred while sodium hydroxide solution (1M) was added in small portions, and the precipitate formed was collected and washed with water until the washings were neutral. The ylide was then dried *in vacuo* to give a pale cream powder. (51 g, 95 %) ^{1}H NMR: δ = 5.06 (bs, 2H), 7.26 – 7.80 (m, 20H).[240]

6.2 Compounds Described in Chapter 2

Synthesis of catalysts 28a-c, 29a-b, 30a-b

General method for the synthesis of ligands for cobalt salens 28a-c, 29a-b, 30a-b[80,101,118]

The benzaldehyde (2 mol. equivalents) was combined in absolute ethanol (15 mL per mol of substrate) with the diamine (1 mol. equivalent) and allowed to react for 2 days, the solvent was then removed *in vacuo* and the residue purified by chromatography.

Ligands from *o*-vanillin and the appropriate diamine for catalysts 28a-c

2-Methoxy-6-({[(*1R,2R*)-2-({1-[3-methoxy-2-hydroxyphenyl]methylidene}amino)cyclo-hexyl]imino}methyl)phenol (for catalyst 28a using (*1R,2R*)-1,2-diaminocyclohexane)

Purification by chromatography (dichloromethane : acetone = 19:1) afforded yellow crystals. (74 mg, 85 %). R_f = 0.83 (dichloromethane : acetone = 93 :7). $[\alpha]_D^{23}$ = -437.50 (c = 0.432, CH_2Cl_2). IR: 1464, 1550, 1631, 1713, 2304, 2684, 2862, 2986, 3055 cm^{-1}. ^1H NMR: δ = 1.43 – 2.05 (m, 18H), 3.29 – 3.34 (m, 2H), 3.86 (s, 6H), 6.68 – 6.88 (m, 6H), 8.22 (s, 2H). ^{13}C NMR: δ = 23.99, 32.97, 55.97, 72.36, 113.83, 117.83, 118.34, 123.13, 124.52, 148.21, 151.55. MS: *m/z* = 382 (M^+, 35 %), 231 (100 %), 152 (44 %). HRMS: calculated for $C_{22}H_{26}N_2O_4$ requires 382.1892, found *m/z* 382.1897.

2-Methoxy-6-({[(*1R,2R*)-2-({1-[3-methoxy-2-hydroxyphenyl]methylidene}amino)–1,2-diphenylethyl]imino}methyl)phenol (for catalyst 28b using (*1R,2R*)-1,2-diphenyl-1,2-diaminoethane)

Purification by chromatography (dichloromethane : acetone = 19:1) to give yellow crystals. (85 mg, 91 %). R_f = 0.76 (dichloromethane : acetone = 93:7). $[\alpha]_D^{23}$ = 5.24 (c = 0.420, CH_2Cl_2). IR: 1467, 1629, 1712, 2305, 2684, 2836, 2987, 3054 cm^{-1}. ^1H NMR: δ = 3.87 (s,

6H), 6.74 (t, *J* = 7.8 Hz, 2H), 6.79 (dd, *J* = 2.1, 7.8 Hz, 2H), 6.87 (dd, *J* = 2.1, 7.8 Hz, 2H), 8.36 (s, 2H), 13.84 (s, 2H). ^{13}C NMR: δ = 55.95, 80.16, 114.09, 118.15, 118.35, 123.34, 127.57, 127.82, 128.82, 138.99, 148.06, 151.04, 166.03. MS: *m/z* = 480 (M^+, 2 %), 240 (100 %), 225 (12 %), 152 (8 %). HRMS: calculated for $C_{30}H_{28}N_2O_4$ requires 480.2049, found 480.2058.

2-Methoxy-6-[({(*R*)-1-[2-({1-[3-methoxy-2-hydroxyphenyl]methylidene}amino)-1-napthyl]-2-napthyl}imino)methyl]phenol (for catalyst 28c using (*R*)-2,2′-diaminobinapthyl)

Purification by chromatography (dichloromethane : acetone = 19:1) to give orange crystals. (65 mg, 94 %). R_f = 0.90 (dichloromethane : acetone = 93:7). $[\alpha]_D^{23}$ = -377.05 (c = 0.366, CH_2Cl_2). IR: 1462, 1608, 2305, 2684, 2833, 2987, 3055 cm^{-1}. ^{1}H NMR: δ = 3.75 (s, 6H), 6.71 (t, *J* = 9.0 Hz, 2H), 6.78 – 6.83 (m, 4H), 7.15 – 7.25 (m, 4H), 7.41 (t, *J* = 9.0 Hz, 2H), 7.56 (d, *J* = 9.0 Hz, 2H), 7.91 (d, *J* = 9.0 Hz, 2H), 8.04 (d, *J* = 9.0 Hz, 2H), 8.59 (s, 2H), 12.34 (s, 2H). ^{13}C NMR: δ = 25.55, 55.93, 67.90, 114.49, 117.60, 118.08, 119.25, 123.88, 125.66, 126.36, 126.80, 128.28, 128.67, 130.08, 132.43, 133.13, 144.28, 147.99, 150.84, 162.81. MS: *m/z* = 552 (M^+, 38 %), 402 (100 %), 280 (84 %), 40 (30 %). HRMS: calculated for $C_{36}H_{28}N_2O_4$ requires 552.2049, found 552.2049.

Ligands from 3-(*t*-butyl)-2-hydroxybenzaldehyde and the appropriate diamine for catalysts 29a-c

2-(*t*-Butyl)-6-({[(*1R,2R*)-2-({1-[3-(*t*-butyl)-2-hydroxyphenyl]methyldiene}amino)cyclo-hexyl]imino}methyl)phenol (for catalyst 29a using (*1R,2R*)-1,2-diaminocyclohexane)[85]

Purification by chromatography (dichloromethane : acetone = 19:1) to give yellow crystals. (82 mg, 69 %). R_f = 0.92 (dichloromethane : acetone = 19:1). $[\alpha]_D^{23}$ = -395.27 (c = 0.465, CH_2Cl_2). ^{1}H NMR: δ = 0.82 – 1.27 (m, 2H), 1.42 (s, 18H), 1.55 – 2.04 (m, 4H), 3.29 – 3.34 (m, 2H), 6.71 (t, J = 7.0 Hz, 2H), 6.99 (d, J = 7.0 Hz, 2H), 7.24 (d, J = 7.4 Hz, 2H), 7.46 (dd, J

= 7.8, 27.8 Hz, 2H), 8.27 (s, 2H). ^{13}C NMR: δ = 24.27, 29.18, 29.32, 33.09, 34.72, 72..32, 117.71, 118.58, 122.09, 129.21, 129.76, 137.06, 160.30, 165.49.[85]

2-(*t*-Butyl)-6-({[(*1R,2R*)-2-({1-[3-(*t*-butyl)-2-hydroxyphenyl]methyldiene}amino)-1,2-diphenylethyl]imino}methyl)phenol (for catalyst 29b using (*1R,2R*)-1,2-diphenyl-1,2-diaminoethane)[101]

Purification by chromatography (dichloromethane : acetone = 19:1) to give yellow crystals. (132 mg, 89 %). R_f = 0.90 (dichloromethane : acetone = 19:1). $[\alpha]_D^{23}$ = -102.13 (c = 0.658, CH_2Cl_2). ^{1}H NMR: δ = 1.42 (s, 18H), 4.72 (s, 2H), 6.69 (dt, *J* = 0.6, 7.4 Hz, 2H), 6.95 – 6.99 (m, 2H), 7.10 – 7.27 (m, 12H), 8.34 (s, 2H). ^{13}C NMR: δ = 29.18, 29.31, 34.77, 80.14, 117.83, 118.53, 127.51, 127.99, 128.31, 129.59, 130.07, 137.12, 139.49, 160.24, 166.85.[101]

Ligands from salicylaldehyde and the appropriate diamine for catalysts 30a-b

2-({[(*1R,2R*)-2-({1-(-2-hydroxyphenyl)methyldiene]amino}cyclohexyl)imino]methyl} phenol (for catalyst 30a using (*1R,2R*)-1,2-diaminocyclohexane)[85]

Purification by chromatography (dichloromethane : acetone = 19:1) to give yellow crystals. (81 mg, 66 %). R_f = 0.68 (dichloromethane : acetone = 19:1). $[\alpha]_D^{23}$ = -393.51 (c = 0.370, CH_2Cl_2). ^{1}H NMR: δ = 1.41 = 1.97 (m, 8H), 3.28 – 3.33 (m, 2H), 6.74 – 6.90 (m, 4H), 7.12 - 7.27 (m, 4H), 8.25 (s, 2H). ^{13}C NMR: δ = 24.12, 33.04, 72.56, 97.69, 102.34, 116.69, 118.53, 131.41, 137.09, 160.90, 164.64.[85]

2-({[(*1R,2R*)-2-({1-(-2-hydroxyphenyl)methyldiene]amino}-1,2-diphenylethyl)imino] methyl}phenol (for catalyst 30b using (*1R,2R*)-1,2-diphenyl-1,2-diaminoethane)[88]

Purification by chromatography (dichloromethane : acetone = 19:1) to give yellow crystals. (126 mg, 73 %). R_f = 0.79 (dichloromethane : acetone = 19:1). $[\alpha]_D^{23}$ = -4.75 (c = 0.632, CH_2Cl_2). ^{1}H NMR: δ = 4.72 (s, 2H), 6.76 (dt, *J* = 1.2, 7.4 Hz, 2H), 6.92 – 6.98 (m, 2H), 7.09

– 7.29 (m, 16H), 8.28 (s, 2H). ^{13}C NMR: δ = 80.13, 116.83, 117.53, 118.53, 118.68, 127.57, 127.80, 128.31, 131.69, 132.51, 139.33, 160.87, 166.15.[88]

General method to cobalt salens 28a-c, 29a-b, 30a-b[101]

A mixture of ligand (0.203 mmol) was combined with cobalt acetate tetrahydrate (50.6 mg, 0.20 mmol) in deairated ethanol (4 mL) and heated under reflux for 4 hours. The solvent was then removed *in vacuo* till dryness of the complex resulted. The complex was used without further purification. All complexes made have melting points of >350^{o}C.

Ligands synthesised from O-vanillin and the appropriate diamine

[(*8R,8R'*)-3,3′-Bismethoxy-8,8′-cyclohexylsalen]cobalt(II) (28a using (*1R,2R*)-1,2-diaminocyclohexane)

Complex synthesised was red/brown in colour. IR: (CH_2Cl_2) = 1452, 1473, 1565, 1604, 1640, 1690, 1715, 2864, 2945 cm^{-1}. Anal. calculated for $C_{22}H_{24}N_2O_6Co$ requires C: 67.02, H: 4.88, N: 5.21, found C: 67.27, H: 5.01, N: 5.82.

[(*8R,8R'*)-3,3′-Bismethoxy-8,8′-diphenylsalen]cobalt(II) (28b using (*1R,2R*)-1,2-diphenyl-1,2-diaminoethane)

Complex synthesised was red/brown in colour. IR: (CH_2Cl_2) = 1453, 1474, 1559, 1605, 1638, 1714, 1758, 2865, 2944 cm^{-1}. Anal. calculated for $C_{30}H_{26}N_2O_6Co$ requires C: 60.12, H: 5.51, N: 6.38, found C: 60.08, H: 5.62, N: 7.30.

[(*R*)-3,3′-Bismethoxy-8,8′-binapthylsalen]cobalt(II) (28c using (*R*)-2,2′-diaminobinapthyl)

Complex synthesised was red/brown in colour. IR: (CH_2Cl_2) = 1437, 1458, 1505, 1543, 1590, 1607, 1655, 1714, 1758, 2865, 2944 cm^{-1}.

Ligands synthesised from 3-(*t*-butyl)-2-hydroxybenzaldehyde and the appropriate diamine

[(*8R,8R'*)-3,3′-Bis(*t*-butyl)-8,8′-cyclohexylsalen]cobalt(II) (29a using (*1R,2R*)-1,2-diaminocyclohexane)

Complex synthesised was red/brown in colour. IR: (CH_2Cl_2) = 1410, 1466, 1536, 1597, 2866, 2947 cm^{-1}.

[(*8R,8R'*)-3,3′-Bis(*t*-butyl)-8,8′-diphenylsalen]cobalt(II) (29b using (*1R,2R*)-1,2-diphenyl-1,2-diaminoethane)

Complex synthesised was red/brown in colour. IR: (CH_2Cl_2) = 1403, 1453, 1466, 1493, 1532, 1595, 3054 cm^{-1}.

Ligands synthesised from salicylaldehyde and the appropriate diamine

[(*8R,8R'*)-Bis-8,8′-cyclohexylsalen]cobalt(II) (30a using (*1R,2R*)-1,2-diaminocyclohexane)

Complex synthesised was red/brown in colour. IR: (CH_2Cl_2) = 1450, 1470, 1533, 1566, 1603, 1648, 2872, 2753 cm^{-1}

[(*8R,8R'*)-Bis-8,8′-diphenylsalen]cobalt(II) (30b using (*1R,2R*)-1,2-diphenyl-1,2-diaminoethane)

Complex synthesised was red/brown in colour. IR: (CH_2Cl_2) = 1448, 1494, 1527, 1586, 1604, 1640, 2871, 2750 cm^{-1}.

Synthesis of catalysts 43a-c, 44a-c

General method for the synthesis of ligands for cobalt salens 43a-c, 44a-c[80,101,118]

The benzaldehyde (2 mol. equivalents) was combined in absolute ethanol (3 mL) with the diamine (1 mol. equivalent) and allowed to react for 2 days, the solvent was then removed *in vacuo* and the residue purified by chromatography.

Ligands from 3-[(*S*)-1-Phenylpropyl]salicylaldehyde and the appropriate diamine for catalysts 43a-c

Ethyl O-cinnamyl salicylate (32)[141]

To a suspension of sodium hydride (0.17 g, 7.08 mmol) in DMPU (3 mL), at 0°C, under nitrogen, was added ethyl salicylate (1.0 g, 6.02 mmol) in THF (3 mL), at such a rate that evolution of hydrogen was controlled. The reaction mixture was warmed to ambient temperature and cinnamyl bromide (1.18 g, 5.99 mmol) in THF (3 mL) was then added in one portion and the reaction mixture stirred for 4 hours. The reaction mixture was then diluted with aqueous H_3PO_4 (5 %, 1 mL), ether (30 mL) and water (30 mL) and the phases separated. The aqueous phase was extracted with ether and the combined organic phases were washed with brine and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue purified by chromatography (hexanes : ethyl acetate = 9:1) to give a colourless oil (1.52 g, 90 %). R_f 0.16 (hexanes : ethyl acetate = 9:1). ^{1}H NMR: δ1.37 (t, *J* = 7.2 Hz, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.79 (dd, *J* = 1.5, 5.4 Hz, 2H), 6.53 (dt, *J* = 5.4, 16.2 Hz, 1H,), 6.79 (d, *J* = 15.9 Hz, 1H), 6.97 – 7.03 (m, 2H), 7.22 – 7.47 (m, 6H), 7.81 (dd, *J* = 1.2, 7.8 Hz, 1H). ^{13}C NMR: δ 14.25, 60.71, 69.45, 113.82, 120.41, 121.17, 124.11, 126.45, 127.72, 128.47, 131.46, 132.57, 133.07, 136.44, 157.97, 166.28.[141]

Ethyl 3-[(*R,S*)-1-phenyl-2-propyl]salicylate (33)[141]

Ethyl O-cinnamyl salicylate (20 g, 0.0709 mol) was heated at 195°C for 3 hours after which time the reaction was cooled and diluted with ethyl acetate (50 mL). Raney nickel (5 g, wet with ethanol) was added to the solution and hydrogenated under atmospheric pressure for 24 hours. The catalyst was then filtered off and the filtrate concentrated *in vacuo* to give a colourless oil. (20 g, 100 %). ^{1}H NMR: δ = 0.91 (t, *J* = 6.9 Hz, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 2.04 (quin, *J* = 7.5 Hz, 2H), 4.34 (t, *J* = 7.8 Hz, 1H), 4.37 (q, *J* = 6.9 Hz, 2H), 6.84 (t, *J* = 7.8 Hz, 1H), 7.11 – 7.43 (m, 6H), 7.71 (dd, *J* = 1.8, 8.1 Hz, 1H), 11.21 (s, 1H). ^{13}C NMR: 12.59, 14.12, 27.73, 44.65, 61.27, 117.39, 118.49, 125.75, 127.60, 128.28, 128.38, 133.48, 135.86,

144.40, 159.56, 170.59. MS: *m/z* 284 (32 %, M^+), 255 (70 %), 209 (100 %), 181 (12 %), 153 (23 %), 152 (40 %), 91 (50 %).[141]

Ethyl O-((-)-menthyloxycarbonyl)-3-[(*S*)-1-phenylpropyl]salicylate (34)[141]

To a suspension of sodium hydride (129 mg, 5.375 mmol) in THF (8 mL), at 0°C, under nitrogen, was added ethyl 3-[(*R,S*)-1-phenyl-2-propyl]salicylate (1.0 g, 3.54 mmol) in THF (12 mL) at such a rate that the evolution of hydrogen gas was controlled. (-)-Menthylchloroformate (0.77 g, 3.52 mmol) in THF (2 mL) was then added to the cooled solution and the reaction mixture stirred at ambient temperature for 3 hours. The reaction mixture was then diluted with H_3PO_4 (5 %, 0.4 mL), ether (20 mL) and water (20 mL) and the phases separated. The organic phase was then washed with brine and dried ($MgSO_4$) and the solvent removed *in vacuo.* The residue was then purified by chromatography (hexanes : dichloromethane = 7:3) and the viscous oil allowed to crystallise, the crystals collected and recrystallised from hexanes twice to give the enantiomerically pure compound as colourless crystals. (0.58 g, 35 %). R_f 0.42 (hexanes : dichloromethane = 3:1). ^{1}H NMR: δ = 0.8 – 1.0 (m, 13H), 1.05 – 1.21 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 3H (S)), 1.34 (t, *J* = 7.2 Hz, 3H (*R*)), 1.45 – 1.57 (m, 2H), 1.99 – 2.23 (m, 4H), 4.16 (t, *J* = 7.8 Hz, 1H), 4.33 (m, 2H), 4.59 (m, 1H), 7.08 – 7.36 (m, 6H), 7.45 (ddd, *J* = 1.5, 7.5, 23.1 Hz, 1H), 7.83 (ddd, *J* = 0.9, 1.5, 7.8 Hz, 1H). MS: *m/z* 466 (5 %, M^+), 367 (5 %), 328 (10 %), 283 (35 %), 254 (100 %), 208 (25 %), 83 (60 %).[141]

Methyl 3-[(*S*)-1-phenylpropyl]salicylate (35)[141]

To a solution of sodium methoxide (0.945 g, 17.7 mmol) in methanol (5 mL) was added a solution of ethyl O-((-)-menthyloxycarbonyl)-3-[(RS)-1-phenylpropyl]salicylate (1.23 g, 2.63 mmol) in THF (5 mL) and the reaction mixture allowed to stir for 16 hours at 20°C. The reaction was then acidified to pH = 1 with HCl (1M) and the aqueous mixture extracted with dichloromethane, dried and the solvent removed *in vacuo*. The residue was purified by chromatography (hexanes : ethyl acetate = 19:1) to give a colourless oil. (0.675g, 95 %). ^{1}H NMR: δ = 0.90 (t, *J* = 7.8 Hz, 3H), 2.04 (quint, *J* = 7.8 Hz, 2H), 3.91 (s, 3H), 4.34 (t, *J* = 7.8

Hz, 1H), 6.83 (t, *J* = 7.8 Hz, 1H), 7.14 – 7.31 (m, 5H), 7.41 (dd, *J* = 2.1, 7.8 Hz, 1H), 7.68 (dd, *J* = 2.1, 7.8 Hz, 1H), 11.05 (s, 1H).[141]

3-[(*S*)-1-Phenylpropyl]salicylaldehyde (36)

To a solution of $LiAlH_4$ (0.134 g, 3.514 mmol) and diethylamine (0.728 g, 7.029 mmol) in hexanes (20 mL) was added methyl 3-[(S)-1-phenylpropyl]salicylate (0.95g, 3.514 mmol) in hexanes (10 mL) and the reaction allowed to stir for 1 hour at 20°C. The reaction mixture was quenched with hydrochloric acid (1M, 10 mL) and extracted with hexanes. The solvent was removed *in vacuo* and the residue purified by chromatography (hexanes : ethyl acetate = 9:1) to give a colourless oil. (0.19g, 23 %). ^{1}H NMR: δ = 0.92 (t, *J* = 7.3 Hz, 3H), 2.06 (quint, *J* = 7.3 Hz, 2H), 4.34 (t, *J* = 7.3 Hz, 1H), 6.99 (t, *J* = 7.3 Hz, 1H), 7.15 – 7.32 (m, 5H), 7.39 (dd, *J* = 1.5, 7.3 Hz, 1H), 7.50 (dd, *J* = 1.5, 7.3 Hz, 1H), 9.84 (s, 1H), 11.29 (s, 1H)[141]

2-((*S*)-1-Phenylpropyl)-6-({[(*1R,2R*)-2-({1-[3-((*S*)-1-phenylpropyl)-2-hydroxyphenyl] methylidene}amino)cyclohexyl]imino}methyl)phenol (for catalyst 43a using (*1R,2R*)-1,2-diaminocyclohexane)

Purification by chromatography (dichloromethane : acetone = 19:1) to give yellow crystals. (19 mg, 39 %). R_f = 0.24 (hexanes : ethyl acetate = 9:1). ^{1}H NMR: δ = 0.89 (t, *J* = 7.4 Hz, 6H), 1.22 – 1.86 (m, 8H), 2.01 (quint, *J* = 7.6 Hz, 4H), 3.26 – 3.30 (m, 2H), 4.31 (t, *J* = 7.8 Hz, 2H), 6.70 – 6.98 (m, 2H), 7.01 – 7.13 (m, 2H), 7.15 – 7.28 (m, 12H), 8.23 (s, 2H).

2-((*S*)-1-Phenylpropyl)-6-({[(*1R,2R*)-2-({1-[3-((*S*)-1-phenylpropyl)-2-hydroxyphenyl] methylidene}amino)-1,2-diphenylethyl]imino}methyl)phenol (for catalyst 43b using (*1R,2R*)-1,2-diphenyl-1,2-diaminoethane)

Purification by chromatography (dichloromethane : acetone = 19:1) to give yellow crystals. (29 mg, 35 %). R_f = 0.32 (hexanes : ethyl acetate = 9:1). ^{1}H NMR: δ = 0.91 (t, *J* = 7.4 Hz, 6H), 2.04 (quint, *J* = 7.2 Hz, 4H), 4.39 (t, *J* = 7.6 Hz, 2H), 4.69 (s, 2H), 6.74 (t, *J* = 7.8 Hz, 2H), 6.97 (dd, *J* = 1.4, 7.6 Hz, 2H), 7.15 – 7.33 (m, 22H), 8.33 (s, 2H).

2-((*S*)-1-Phenylpropyl)-6-({[(*1S,2S*)-2-({1-[3-((S)-1-phenylpropyl)-2-hydroxyphenyl] methylidene}amino)-1,2-diphenylethyl]imino}methyl)phenol (for catalyst 43c using (*1S,2S*)-1,2-diphenyl-1,2-diaminoethane)

Purification by chromatography (dichloromethane : acetone = 19:1) to give yellow crystals. (26 mg, 29 %). R_f = 0.37 (hexanes : ethyl acetate = 9:1). ^{1}H NMR: δ = 0.89 (t, *J* = 7.2 Hz, 6H), 2.03 (quint, *J* = 7.6 Hz, 4H), 4.36 (t, *J* = 7.6 Hz, 2H), 4.64, (s, 2H), 6.66 – 6.73 (m, 4H), 7.17 – (m, 22H), 8.24 (s, 2H).

Ligands from (*R*)-3-Formyl-2-hydroxy-2′-phenyl-1,1′-binapthyl and the appropriate diamine for catalysts 44a-c

(*R*)-2-Hydroxy-2′-trifluoromethanesulfonyloxy-1,1′-binapthyl (38)[143]

To a solution of (*R*)-binapthol (286 mg, 1 mmol) in dichloromethane (4 mL) was added 2,4,6-collidine (121 mg, 1 mmol), 4-(*N,N*-dimethylamino)pyridine (15 mg, 1.23 mmol) and *N*-phenyltrifluoromethanesulfonimide (357 mg, 1 mmol) and the reaction mixture heated at reflux for 12 hours. The solvent was then removed *in vacuo* and the residue purified by chromatography (hexanes : ethyl acetate = 9:1) to give a clear viscous oil. (0.202 g, 46 %). R_f 0.15 (hexanes : ethyl acetate = 9:1). ^{1}H NMR: δ = 7.00 (d, *J* = 8.0 Hz, 1H), 7.23 – 7.38 (m, 3H), 7.42 (d, *J* = 3.8 Hz, 2H), 7.58 (t, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 9 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.91 (d, *J* = 9.2 Hz, 1H), 7.99 (d, *J* = 9 Hz, 1H), 8.10 (d, *J* = 9.2 Hz, 1H). ^{13}C NMR: 22.67, 112.11, 115.01, 117.87, 119.73, 123.34, 123.68, 124.22, 125.42, 126.50, 126.96, 127.15, 127.43, 128.16, 128.41, 129.04, 129.51, 131.27, 131.38, 132.87, 133.31.[143]

(*R*)-2-Hydroxy-2′-phenyl-1,1′-binapthyl (39)[143]

To a solution of (*R*)-2-hydroxy-2′-trifluoromethanesulfonyloxy-1,1′-binapthyl (0.202 g, 0.483 mmol) and $NiCl_2(PPh_3)_2$ (0.016g) in dry THF (2 mL) was added phenyl magnesium bromide (1.93 mL, 1M) in THF and the solution heated under reflux for 2 hours. The reaction mixture was quenched with NH_4Cl (sat. aq., 50 mL), the aqueous phase extracted with dichloromethane. The organic phase was washed with $NaHCO_3$ (sat. aq.), brine, dried and the

solvent removed *in vacuo*. The residue was purified by chromatography (hexanes : ethyl acetate = 1:1) to give a clear viscous oil. (0.184 g, 99 %). ^{1}H NMR: δ = 7.05 – 7.33 (m, 11H), 7.53 (dt, *J* = 2.4, 10.2 Hz, 1H), 7.72 (d, *J* = 8.7 Hz, 1H), 7.77 (d, *J* = 9.3 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H). [143]

(*R*)-2-Methoxymethoxy-2′-phenyl-1,1′-binapthyl (40)[143]

To a solution of (*R*)-2-Hydroxy-2′-phenyl-1,1′-binapthyl (0.188 g, 0.543 mmol) in dry dichloromethane (5 mL) was added triethylamine (0.207 mL, 1.48 mmol) followed by chloromethyl methyl ether (0.113 mL, 1.48 mmol) and the reaction allowed to stir for 16 hours. The reaction was quenched with water and the aqueous layer extracted with dichloromethane, the organic layer dried and the solvent removed *in vacuo* to give a clear viscous oil. The residue was purified by chromatography (hexanes : ethyl acetate = 1:19). (0.174 g, 82 %). ^{1}H NMR: δ = 3.11 (s, 3H), 4.85 (AB_q, *J* = 10.1 Hz, 2H), 7.00 – 8.22 (m, 17H).[143]

(*R*)-3-Formyl-2-hydroxy-2′-phenyl-1,1′-binapthyl (42)[143]

t-Butyllithium (1.7M, 1.68 mL) was added to a solution of (*R*)-2-methoxymethoxy-2′-phenyl-1,1′-binapthyl in THF at –78^{o}C and the mixture was stirred at –78^{o}C for 3 hours. *N,N*-dimethylformamide (0.495 mL, 6.404 mmol) was added and the reaction mixture was allowed to warm to ambient temperature and stirred for 1 hour. The reaction mixture was quenched with NH_4Cl and the aqueous phase extracted with diethyl ether, washed with brine, dried and the solvent removed *in vacuo*.

Bromotrimethylsilane (0.684 g, 5.18 mmol) was added to a solution of the residue dissolved in dichloromethane with MS: 4Å and stirred for 1 hour. The mixture was quenched with $NaHCO_3$ (aq.) and extracted with dichloromethane, dried and the solvent removed *in vacuo*. The residue was purified by chromatography (ethyl acetate hexanes = 3:2) to give a clear viscous oil. (0.324 g, 68 %). ^{1}H NMR δ = 7.00 – 7.02 (m, 3H), 7.12 (d, *J* = 9.3 Hz, 1H), 7.19

(m, 6H), 7.49 (d, *J* = 3.4 Hz, 1H), 7.64 (d, *J* = 8.31 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 8.31 Hz, 1H), 8.05 (d, *J* = 8.31 Hz, 1H), 8.17 (s, 1H), 10.10 (s, 1H), 10.40 (s, 1H).[143]

2-((1′-Phenyl)napthyl)-10-({[(*1R,2R*)-2-{[1-((*R*)-2-hydroxy-2′-phenyl-1,1′-binapthyl methyldiene]amino}cyclohexyl]imino}methyl)napthol (for catalyst 44a using (*1R,2R*)-1,2-diaminocyclohexane)

Purification gave yellow crystals. ^{1}H NMR: δ = 1.27 - 2.06 (m, 8H), 3.22 - 3.36 (m, 2H), 6.74 - 6.83 (m, 2H), 6.97 – 7.40 (m, 20H), 7.58 – 7.68 (m, 4H), 7.92 – 8.04 (m, 4H), 8.38 (s, 2H).

2-((1′-Phenyl)napthyl)-10-({[(*1R,2R*)-2-{[1-((*R*)-2-hydroxy-2′-phenyl-1,1′-binapthyl) methyldiene]amino}-1,2-diphenylethyl]imino}methyl)napthol (for catalyst 44b using (*1R,2R*)-1,2-diphenyl-1,2-diaminoethane)

Purification gave yellow crystals. ^{1}H NMR: δ = 6.35 – 6.54 (m, 4H), 6.98 – 7.33 (m, 30H), 7.41 - 7.49 (m, 2H), 7.69 (d, *J* = 8.0 Hz, 4H), 7.71 – 8.10 (m, 4H), 8.27 (s, 2H).

2-((1′-Phenyl)napthyl)-10-({[(*1S,2S*)-2-{[1-((*R*)-2-hydroxy-2′-phenyl-1,1′-binapthyl) methyldiene]amino}-1,2-diphenylethyl]imino}methyl)napthol (for catalyst 44c using (*1S,2S*)-1,2-diphenyl-1,2-diaminoethane)

Purification gave yellow crystals. ^{1}H NMR: δ = 6.35 – 6.54 (m, 4H), 6.98 – 7.33 (m, 30H), 7.41 – 7.49 (m, 2H), 7.69 (d, *J* = 8.0 Hz, 4H), 7.71 – 8.10 (m, 4H), 8.27 (s, 2H).

General method to cobalt salens 43a-c, 44a-c[101]

A mixture of ligand (0.203 mmol) was combined with cobalt acetate tetrahydrate (50.6 mg, 0.20 mmol) in deairated ethanol (4 mL) and heated under reflux for 4 hours. The solvent was then removed *in vacuo* till dryness of the complex resulted. The complex was used without further purification. All complexes made have melting points of >350^{o}C.

Catalysts 43a-c and 44a-c and their corresponding ligands were synthesised by another member of the Taylor group and as such their characterisation is not mentioned here. The details of the characterisation of the ligands and catalysts will be published at a later date.

Attempted preparation of (-)-Bornyl 3-oxobutanoate (46 (-)-Bornyl)

3-Oxobutanoic acid[144]

To a solution of ethyl acetoacetate (30 g, 0.231 mol) in water (250 mL) was added sodium hydroxide (9.7 g, 0.243 mol) and the solution was stirred overnight. Diethyl ether (230 mL) was added and the reaction mixture was saturated with ammonium sulphate. Sulfuric acid (10%, 85 mL) was then added and the phases separated. The organic phase was dried and the solvent removed *in vacuo*. (12 g, 49%) and the colourless crystalline product was stored at –15^{o}C. ^{1}H NMR: δ = 2.33 (s, 3H), 3.54 (s, 2H).[144]

(-)-Bornyl 3-oxobutanoate (46 (-)-Bornyl)

(-)-Borneol (2.72 g, 0.0147 mol), 3-oxobutanoic acid (2 g, 0.0196 mol) and *p*-toluene sulfonic acid (100 mg, 5.81 x 10^{-4} mol) were combined in benzene (15 mL) and heated at reflux under Dean and Stark conditions for 10 hours after which time the solvent was removed. No desired product resulted and the original amount of (-) borneol was recovered from the reaction residue.

General method to alkyl acetoacetates

To a solution of ethyl acetoacetate (4.5 g, 0.0346 mol) in *n*-heptane (70 mL) was added the appropriate alcohol (0.0346 mol) and sodium hydride (50 mg) and the reaction mixture heated at reflux under Dean and Stark conditions for 2 days. The solvent was then removed *in vacuo* and the residue purified by chromatography (hexanes : ethyl acetate = 9:1) to afford the following alkyl acetoacetates.

(-)-Bornyl 3-oxobutanoate (46 (-)-Bornyl)

Purification gave a colourless oil. (6.16 g, 70 %). R_f = 0.32 (hexanes : ethyl acetate = 9:1). ^{1}H NMR: δ = 0.85 (s, 3H), 0.88 (s, 3H), 0.91 (s, 3H), 0.94 – 1.43 (m, 4H), 1.64 – 2.00 (m, 3H), 2.85 (s, 3H), 3.47 (s, 2H), 4.95 (ddd, *J* = 3.3, 5.1, 15 Hz, 1H). ^{13}C NMR: δ = 13.35, 18.71, 19.57, 26.96, 27.89, 29.99, 36.51, 44.76, 47.77, 48.76, 50.29, 81.07, 90.10, 167.30. MS: *m/z* = 238 (42 %, M^+), 154 (11 %), 137 (100 %), 121 (10 %), 95 (23 %).

(-)-Menthyl 3-oxobutanoate (46 (-)-Menthyl)

Purification gave a colourless oil. (5.10 g, 85 %). R_f = 0.31 (hexanes : ethyl acetate = 9:1). ^{1}H NMR: δ = 0.77 (d, *J* = 6.9 Hz, 6H), 0.88 – 2.06 (m, 12H), 2.27 (s, 3H), 3.44 (s, 2H), 4.74 (dt, *J* = 4.2, 11.1 Hz, 1H). ^{13}C NMR: δ = 16.00, 20.53, 21.78, 23.19, 26.05, 29.78, 31.23, 34.03, 40.56, 46.75, 50.32, 75.26, 89.98, 166.51. MS: *m/z* = 240 (100 %, M^+), 139 (20 %), 103 (22 %), 81 (18 %), 43 (25 %).

(+)-Menthyl 3-oxobutanoate (46 (+)-Menthyl)

Purification gave a colourless oil. (4.98 g, 83 %). R_f = 0.31 (hexanes : ethyl acetate = 9:1). ^{1}H NMR: δ = 0.77 (d, *J* = 7.2 Hz, 6H), 0.88 – 2.08 (m, 12H), 2.27 (s, 3H), 3.44 (s, 2H), 4.74 (dt, *J* = 4.2, 10.8 Hz, 1H). ^{13}C NMR: δ = 16.00, 20.52, 21.78, 23.20, 26.05, 29.78, 34.02, 40.56, 46.75, 50.32, 75.26, 89.99, 166.51. MS: *m/z* = 240 (100 %, M^+), 139, (20 %), 103 (22 %), 81 (18 %), 43 (25 %).

***General method to 2-formyl-3-oxobutanoates*[117]**

To the alkyl acetoacetate (8.4 x 10^{-3}moles) was added *N,N*-dimethylformamide dimethyl acetal (2 g, 1.68 x 10^{-2}moles) and the mixture stirred at ambient temperature for 2 hours, then cooled to 0^{o}C and methanolic sodium hydroxide (1M, 14 mL 1:1 methanol: water) and stirred for a further 2 hours. The reaction mixture was cooled to 0^{o}C and hydrochloric acid (1M) added till pH 3-4. The mixture was extracted with diethyl ether, dried and the solvent removed *in vacuo*.

Ethyl 2-formyl-3-oxobutanoate (47 Ethyl)

The crude aldehyde was present as part of a mixture in a yellow oil. R_f 0.17 (hexanes : ethyl acetate = 9:1) Due to the instability of the aldehyde it was used directly in the next reaction to form the ligand. ^{1}H NMR: δ = 1.33 (t, *J* = 7.2 Hz, 3H), 2.56 (s, 3H), 4.26 (q, *J* = 6.9 Hz, 2H), 9.20 (d, *J* = 6.0 Hz, 1H).

***t*-Butyl 2-formyl-3-oxobutanoate (47 *t*-Butyl)**

The crude aldehyde was present as part of a mixture in a yellow oil. R_f 0.20 (hexanes : ethyl acetate = 9:1) Due to the instability of the aldehyde it was used directly in the next reaction to form the ligand. ^{1}H NMR: δ = 0.9 (s, 9H), 2.58 (s, 3H), 9.21 (d, *J* = 6.2 Hz, 1H).

(-)-Bornyl 2-formyl-3-oxobutanoate (47 (-)-Bornyl)

The crude aldehyde was present as part of a mixture in a yellow oil. R_f 0.6 (hexanes : ethyl acetate = 9:1) Due to the instability of the aldehyde it was used directly in the next reaction to form the ligand. ^{1}H NMR: δ = 0.88 (s, 3H), 0.90 (s, 3H), 0.94 (s, 3H), 1.00 – 1.48 (m, 1H), 1.12 – 1.48 (m, 4H), 2.32 – 2.54 (m, 1H), 2.57 (s, 3H), 4.96 – 5.05 (m, 1H), 9.25 (d, *J* = 9.0 Hz, 1H).

(-)-Menthyl 2-formyl-3-oxobutanoate (47 (-)-Menthyl)

The crude aldehyde was present as part of a mixture in a yellow oil. R_f 0.45 (hexanes : ethyl acetate = 9:1) Due to the instability of the aldehyde it was used directly in the next reaction to form the ligand. ^{1}H NMR: δ = 0.76 – 2.55 (complex multiplets, 22H), 4.77 – 4.90 (m, 1H), 9.20 (bs, 1H).

(+)-Menthyl 2-formyl-3-oxobutanoate (47 (+)-Menthyl)

The crude aldehyde was present as part of a mixture in a yellow oil. R_f 0.45 (hexanes : ethyl acetate = 9:1). Due to the instability of the aldehyde it was used directly in the next

reaction to form the ligand. ^{1}H NMR: δ = 0.76 – 2.55 (complex multiplets, 22H), 4.77 – 4.90 (m, 1H), 9.20 (bs, 1H).

3-(Methoxymethylene)-2,4-pentanedione (50)[117]

A mixture of acetyl acetone (4.0 g, 0.04 mol), trimethyl orthoformate (7.4 g, 0.07 mol) and acetic anhydride (12.2 g, 0.12 mol) was heated at reflux for 5 hours. Unreacted starting material was then removed *in vacuo* and the residue distilled under reduced pressure to give a red/orange oil. b.p. 120^{o}C / 15mm. ^{1}H NMR: δ = 2.34 (s, 3H), 2.40 (s, 3H), 4.05 (s, 3H), 7.63 (s, 1H).[117]

General method to ligands for cobalt β-keto iminato complexes

Ligand for catalyst 52

3-Methoxymethylene-2,4-pentanedione (0.5 g, 3.52 mmol) was combined in ethanol (4 mL) with the diamine (1.65 mmol) and allowed to react for 2 days. The solvent was then removed *in vacuo* and the residue purified by chromatography.

Methyl side chain

3-{[((*1S,2S*)-2-[[2-acetyl-3-hydroxy-2-butenylidene]amino}-1,2-diphenylethyl)imino] methyl}-4-hydroxy-3-penten-2-one (for catalyst 52 using (*1S,2S*)-1,2-diphenyl-1,2-diaminoethane)

Purification by chromatography (dichloromethane) to give colourless crystals. (0.66 g, 93 %). R_f 0.53 (dichloromethane : acetone = 9:1). $[\alpha]_D^{23}$ = 201.39 (c = 0.432, CH_2Cl_2). IR: (CH_2Cl_2) = 1025, 1195, 1274, 1311, 1357, 1419, 1496, 1579, 1629, 2304, 2987, 3060 cm^{-1}. ^{1}H NMR: δ = 2.09 (s, 6H), 2.49 (s, 6H), 4.63 (dd, *J* = 2.0, 4.6 Hz, 2H), 7.08 – 7.15 (m, 4H), 7.28 – 7.33 (m, 6H), 7.58 (d, *J* = 12.4 Hz, 2H), 11.95 (dd, *J* = 7.0, 11.8 Hz, 2H). ^{13}C NMR: δ = 22.64, 26.85, 31.74, 70.26, 112.25, 126.94, 128.88, 129.13, 135.61, 159.03, 194.33. MS:

m/z = 432 (M^+, 12 %), 404 (32 %), 364 (33 %), 322 (24 %), 188 (34(5) 43 (100 %). HRMS: calculated for $C_{26}H_{28}N_2O_4$ + H requires 433.2127; found 433.2145.

General method to cobalt β-keto iminato complex 52[101]

A mixture of ligand (0.203 mmol) was combined with cobalt acetate tetrahydrate (50.6 mg, 0.20 mmol) in deairated ethanol (4 mL) and heated under reflux for 4 hours. The solvent was then removed *in vacuo* till dryness of the complex resulted. The complex was used without further purification. All complexes made have melting points of >350^oC.

Ligands synthesised from 3-(methoxymethylene)-2,4-pentanedione and the appropriate diamine

[N, N′-Bis(2-methyl-3-oxobutylidene)-(*1S,2S*)-diphenylethylenediaminato]cobalt(II) (52)

Complex synthesised was brown in colour. IR: (CH_2Cl_2) = 896, 1253, 1278, 1421, 1565, 2304, 2987, 3050 cm^{-1}. Anal. calculated for $C_{26}H_{26}N_2O_6Co$ requires C: 63.78, H: 5.36, N: 5.73, Co: 12.05, found C: 63.41, H: 5.41, N: 5.78, Co: 12.54.

General method for the ligands for catalysts 53a-c, 54, 55a-e, 56a-b, 57a-b

The crude 3-formyl alkyl acetoacetate (2 mol. equivalents) was combined in ethanol (3 mL) with the diamine (1 mol. equivalent) and allowed to react for 2 days, the solvent was then removed *in vacuo* and the residue purified by chromatography.

Ethyl ester

Ethyl 2-{[((*1R,2R*)-2-{[2-(ethoxycarbonyl)-3-hydroxy-2-butenylidene]amino}cyclohexyl)imino]methyl}-3-hydroxy-2-butenoate (for catalyst 53a using (*1R,2R*)-1,2-diaminocyclohexane)

Purification by chromatography to give a colourless wax. (dichloromethane : acetone = 9:1). (0.159 g, 85 %). R_f = 0.55 (dichloromethane : acetone = 9:1). $[\alpha]_D^{23}$ = -396.15 (c =

0.364, CH_2Cl_2). IR: (CH_2Cl_2) = 1070, 1143, 1199, 1236, 1309, 1365, 1417, 1573, 1635, 1697, 2863, 2944, 2983 cm^{-1}. ^1H NMR: δ = 1.26 (t, *J* = 7 Hz, 6H), 1.34 – 1.64 (m, 4H), 1.85 – 1.91 (m, 2H), 2.12 (bs, 2H), 2.17 (s, 2H), 2,45 (s, 6H), 2.95 – 3.11 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 4H), 7.82 (d, *J* = 13.4 Hz, 2H), 10.94 – 11.03 (m, 2H). ^{13}C NMR: δ = 14.22, 24.02, 30.59, 31.92, 59.35, 64.10, 100.49, 158.82, 166.62, 199.57. MS: *m/z* = 394 (M^+, 74 %), 348 (100 %), 237 (67 %), 43 (88 %). HRMS: calculated for $C_{20}H_{30}N_2O_6$ + H requires 395.2182; found 395.2161.

Ethyl 2-{[((1R2R)-2-{[2-(ethoxycarbonyl)-3-hydroxy-2-butenylidene]amino}-1,2-diphenylethyl)imino]methyl}-3-hydroxy-2-butenoate (for catalyst 53b using (*1R,2R*)-1,2-diphenyl-1,2-diaminoethane)

Purification by chromatography to give a colourless wax. (dichloromethane : acetone = 9:1). (0.206 g, 88 %). R_f = 0.62 (dichloromethane : acetone = 9:1). $[\alpha]_D^{23}$ = -112.45 (c = 0.482, CH_2Cl_2). IR: (CH_2Cl_2) = 1072, 1199, 1253, 1278, 1297, 1365, 1384, 1419, 1573, 1633, 1697, 2304, 2985, 3050 cm^{-1}. ^1H NMR: δ = 1.24 (t, *J* = 7.2 Hz, 6H), 2.47 (s, 6H), 4.12 (q, *J* = 7.2 Hz, 4H), 4.59 (dd, *J* = 2.0, 6.8 Hz, 2H), 7.01 – 7.06 (m, 4H), 7.25 – 7.30 (m, 6H), 7.85 (d, *J* = 12.8 Hz, 2H), 11.75 – 11.90 (m, 2H). ^{13}C NMR: δ = 2.92, 14.37, 30.80, 59.60, 69.77, 101.53, 127.07, 128.72, 128.94, 135.67, 159.04, 166.64. MS: *m/z* = 492 (M^+, 37 %), 446 (21 %), 245 (100 %), 199 (95 %), 157 (33 %). HRMS: calculated for $C_{28}H_{32}N_2O_6$ + H requires 493.2338; found 493.2354.

Ethyl 2-{[((*1S,2S*)-2-{[2-(ethoxycarbonyl)-3-hydroxy-2-butenylidene]amino}-1,2-diphenylethyl)imino]methyl}-3-hydroxy-2-butenoate (for catalyst 53c using (*1S,2S*)-1,2-diphenyl-1,2-diaminoethane)

Purification by chromatography to give a colourless wax. (dichloromethane : acetone = 9:1). (0.203 g, 87 %). R_f = 0.62 (dichloromethane : acetone 9:1). $[\alpha]_D^{23}$ = 112.10 (c = 0.471, CH_2Cl_2). IR: (CH_2Cl_2) = 1072, 1199, 1253, 1278, 1297, 1365, 1384, 1419, 1573, 1633, 1697, 2304, 2985, 3050 cm^{-1}. ^1H NMR: δ = 1.24 (t, *J* = 7.2 Hz, 6H), 2.47 (s, 6H), 4.12 (q, *J* = 7.2

Hz, 4H), 4.59 (dd, *J* = 2.0, 6.8 Hz, 2H), 7.01 – 7.06 (m, 4H), 7.25 – 7.30 (m, 6H), 7.85 (d, *J* = 12.8 Hz, 2H), 11.75 – 11.90 (m, 2H). ^{13}C NMR: δ = 14.37, 30.80, 59.60, 69.77, 101.53, 127.07, 128.72, 128.94, 135.67, 159.04, 166.64. MS: *m/z* = 492 (M^+, 37 %), 446 (21 %), 245 (100 %), 199 (95 %), 157 (33 %). HRMS: calculated for $C_{28}H_{32}N_2O_6$ + H requires 493.2338; found 493.2354.

***t*-Butyl ester**

(*t*-Butyl) 2-{[((*1S,2S*)-2-{[2-(*t*-butylcarbonyl)-3-hydroxy-2-butenylidene]amino]-1,2-diphenyl ethyl)imino}methyl}-3-hydroxy-2-butenoate (for catalyst 54 using (*1S,2S*)-1,2-diphenyl-1,2-diaminoethane)

Purification by chromatography to give a colourless wax. (dichloromethane : acetone = 93:7). (45 mg, 36 %). R_f = 0.45 (dichloromethane : acetone = 93:7). $[\alpha]_D^{23}$ = 78.46 (c = 0.448, CH_2Cl_2). IR: (CH_2Cl_2) = 1253, 1306, 1367, 1414, 1455, 1572, 1630, 1694, 2337, 2932, 2979 cm^{-1}. ^{1}H NMR: δ = 1.46 (s, 18H), 2.47 (s, 6H), 4.58 (dd, *J* = 2.1, 6.9 Hz, 2H), 7.04 – 7.07 (m, 4H), 7.27 – 7.31 (m, 6H), 7.77 (d, *J* = 12.6 Hz, 2H), 11.85 (dd, *J* = 6.6, 12.0 Hz, 2H). ^{13}C NMR: δ = 28.36, 31.00, 69.71, 79.71, 102.79, 127.08, 128.63, 128.88, 135.77, 159.03, 166.19. MS: *m/z* = 549 ([M+H^+], 13 %), 419 (54 %), 274 (30 %), 218 (100 %). HRMS: calculated for $C_{32}H_{40}N_2O_6 + H^+$ 549.3051; found 549.2956.

(-)-Bornyl ester

(-)-Bornyl 2-{[(2-{[(2-((-)-bornoxycarbonyl)-3-hydroxy-2-butenylidene]amino}ethyl) imino]methyl}-3-hydroxy-2-butenoate (for catalyst 55a using 1,2-diaminoethane)

Purification by chromatography to give a colourless wax. (dichloromethane : acetone = 9:1). (0.176 g, 92 %). R_f = 0.74 (dichloromethane : acetone = 9:1). $[\alpha]_D^{23}$ = -19.86 (c = 0.554, CH_2Cl_2). IR: (CH_2Cl_2) = 1060, 1126, 1193, 1253, 1274, 1375, 1419, 1579, 1635, 1691, 2304, 2879, 2958, 2987, 3052 cm^{-1}. ^{1}H NMR: δ = 0.86 (s, 6H), 0.89 (s, 6H), 0.93 (s, 6H), 1.03 – 1.41 (m, 4H), 1.69 – 1.97 (m, 6H), 2.31 – 2.46 (m, 2H), 2.48 (s, 6H), 3.53 – 3.58

(m, 4H), 4.96 (d, J = 8.2 Hz, 2H), 7.90 (d, J = 13.2 Hz, 2H), 11.11 – 11.18 (m, 2H). ^{13}C NMR: δ = 13.68, 18.85, 19.70, 27.70, 28.09, 31.05, 37.01, 44.98, 47.74, 48.79, 50.31, 80.34, 101.83, 159.95, 167.19, 199.71. MS: *m/z* = 556 (M^+, 8 %), 403 (14 %), 267 (44 %), 246 (39 %), 200 (32 %), 137 (42 %), 95 (100 %). HRMS: calculated for $C_{32}H_{49}N_2O_6$ + H requires 557.3590; found 557.3625.

(-)-Bornyl 2-{[((*1R,2R*)-2-{[2-((-)-bornoxycarbonyl)-3-hydroxy-2-butenylidene]amino} cyclohexyl)imino]methyl}-3-hydroxy-2-butenoate (for catalyst 55b using (*1R,2R*)-1,2-diaminocyclohexane)

Purification by chromatography to give a colourless wax. (dichloromethane : acetone = 9:1). (0.235 g, 89 %). R_f = 0.57 (dichloromethane : acetone = 9:1). $[\alpha]_D^{23}$ = -218.53 (c = 0.464, CH_2Cl_2). IR: (CH_2Cl_2) = 1064, 1112, 1143, 1201, 1236, 1307, 1390, 1415, 1452, 1573, 1635, 1691, 2250, 2871, 2954 cm^{-1}. ^{1}H NMR: δ = 0.80 – 0.96 (m, 20H), 1.01 – 1.60 (m, 10H), 1.65 – 1.98 (m, 10H), 2.08 – 2.22 (m, 2H), 2.29 – 2.46 (m, 8H), 4.88 – 4.99 (m, 2H), 7.83 (dt, J = 3.2, 13.2 Hz, 2H), 11.15 (bs, 2H). ^{13}C NMR: δ = 13.58, 18.83, 19.70, 24.12, 27.64, 28.11, 31.01, 32.03, 36.96, 44.87, 47.71, 48.76, 64.22, 79.31, 101.01, 158.63, 167.13, 199.67. MS: *m/z* = 612 (6 %, $[M + 2H]^+$), 458 (12 %), 322 (24 %), 278 (10 %), 137 (21 %), 95 (100 %), 67 (30 %), 39 (31 %). HRMS: calculated for $C_{36}H_{54}N_2O_6$ + H requires 611.4060; found 611.4054.

(-)-Bornyl 2-{[((*1S,2S*)-2-{[2-((-)-bornoxycarbonyl)-3-hydroxy-2-butenylidene]amino} cyclohexyl)imino]methyl}-3-hydroxy-2-butenoate (for catalyst 55c using (*1S,2S*)-1,2-diaminocyclohexane)

Purification by chromatography to give a colourless wax. (dichloromethane : acetone = 9:1). (0.14 g, 86 %). R_f = 0.55 (dichloromethane : acetone = 9:1). $[\alpha]_D^{23}$ = 11.92 (c = 1.25, CH_2Cl_2). IR: (CH_2Cl_2) = 1060, 1110, 1141, 1197, 1236, 1255, 1311, 1413, 1579, 1635, 1702, 2251, 2871, 2956 cm^{-1}. ^{1}H NMR: δ = 0.80 – 0.97 (m, 18H), 1.10 – 1.60 (m, 10H), 1.65 – 1.98 (m, 8H), 2.08 – 2.22 (m, 4H), 2.29 – 2.46 (m, 6H), 3.01 – 3.09 (m, 2H), 4.93 (dm, J = 9.6 Hz,

2H), 7.83 (dt, *J* = 3.2, 13.2 Hz, 2H), 11.16 (bs, 2H). ^{13}C NMR: δ = 13.52, 18.64, 19.52, 23.96, 27.52, 27.83, 30.64, 31.82, 36.70, 44.63, 47.55, 48.56, 64.03, 79.01, 100.79, 158.47, 166.91, 199.35. MS: *m/z* = 610 (11 %, M^+), 457 (48 %), 321 (98 %). HRMS: calculated for $C_{36}H_{54}N_2O_6$ requires 610.3981, found 610.3982.

(-)-Bornyl 2-{[((*1R,2R*)-2-{[2-((-)-bornoxycarbonyl)-3-hydroxy-2-butenylidene]amino}-1,2-diphenylethyl)imino]methyl}-3-hydroxy-2-butenoate (for catalyst 55d using (*1R,2R*)-1,2-diphenyl-1,2-diaminoethane)

Purification by chromatography to give a colourless wax. (dichloromethane : acetone = 9:1). (0.247 g, 85 %). R_f 0.64 (dichloromethane : acetone = 9:1). $[\alpha]_D^{23}$ = -63.20 (c = 0.481, CH_2Cl_2). IR: (CH_2Cl_2) = 1068, 1113, 1201, 1242, 1306, 1367, 1417, 1454, 1574, 1631, 1691, 2250, 2881, 2956 cm^{-1}. ^{1}H NMR: δ = 0.79 (s, 6H), 0.86 (s, 6H), 0.90 (s, 6H), 0.96 – 1.32 (m, 4H), 1.60 – 1.82 (m, 6H), 2.28 – 2.49 (m, 2H), 2.51 (s, 6H), 4.67 (d, *J* = 7.8 Hz, 2H), 4.89 (dm, *J* = 8.2 Hz, 2H), 7.10 – 7.15 (m, 4H), 7.27 – 7.33 (m, 6H), 7.79 (d, *J* = 12.8 Hz, 2H), 11.93 – 12.02 (m, 2H). ^{13}C NMR: δ = 13.63, 18.84, 19.70, 27.64, 28.03, 31.02, 36.92, 44.84, 47.74, 48.74, 69.53, 79.48, 102.05, 135.68, 158.96, 167.09, 199.71. MS: *m/z* = 710 ([M + 2H]$^+$, 4 %), 555 (22 %), 447 (19 %), 354 (14 %), 200 (31 %), 137 (33 %), 95 (100 %). HRMS: calculated for $C_{44}H_{56}N_2O_6$ + H requires 709.4216; found 709.4208.

(-)-Bornyl 2-{[((*1S,2S*)-2-{[2-((-)-bornoxycarbonyl)-3-hydroxy-2-butenylidene]amino}-1,2-diphenylethyl)imino]methyl}-3-hydroxy-2-butenoate (for catalyst 55e using (*1S,2S*)-1,2-diphenyl-1,2-diaminoethane)

Purification by chromatography to give a colourless wax. (dichloromethane : acetone = 9:1). (0.262 g, 90 %). R_f = 0.64 (dichloromethane : acetone = 9:1). $[\alpha]_D^{23}$ = 14.14 (c = 0.481, CH_2Cl_2). IR: (CH_2Cl_2) = 1068, 1113, 1201, 1242, 1306, 1367, 1417, 1454, 1574, 1631, 1691, 2250, 2881, 2956 cm^{-1}. ^{1}H NMR: δ = 0.79 (s, 6H), 0.86 (s, 6H), 0.90 (s, 6H), 0.96 – 1.32 (m, 4H), 1.60 – 1.82 (m, 6H), 2.28 – 2.49 (m, 2H), 2.51 (s, 6H), 4.67 (d, *J* = 7.8 Hz, 2H), 4.89 (dm, *J* = 8.2 Hz, 2H), 7.10 – 7.15 (m, 4H), 7.27 – 7.33 (m, 6H), 7.79 (d, *J* = 12.8 Hz, 2H),

11.93 – 12.02 (m, 2H). ^{13}C NMR: δ = 13.63, 18.84, 19.70, 27.64, 28.03, 31.02, 36.92, 44.84, 47.74, 48.74, 69.53, 79.48, 102.05, 135.68, 158.96, 167.09, 199.71. MS: *m/z* = 710 ([M + 2H]$^+$, 4 %), 555 (22 %), 447 (19 %), 354 (14 %), 200 (31 %), 137 (33 %), 95 (100 %). HRMS: calculated for $C_{44}H_{56}N_2O_6$ + H requires 709.4216; found 709.4208.

(-)-Menthyl ester

(-)-Menthyl 2-{[((*1R,2R*)-2-{[2-((-)-menthoxycarbonyl)-3-hydroxy-2-butenylidene] amino}-1,2-diphenylethyl)imino]methyl}-3-hydroxy-2-butenoate (for catalyst 56a using (*1R,2R*)-1,2-diphenyl-1,2-diaminoethane)

Purification by chromatography to give a colourless wax. (dichloromethane : acetone = 9:1). (0.290 g, 86 %). R_f 0.79 (dichloromethane : acetone = 9:1). $[\alpha]_D^{23}$ = -80.53 (c = 0.529, CH_2Cl_2). IR: (CH_2Cl_2) = 1199, 1253, 1278, 1421, 1573, 1629, 1689, 2304, 2686, 2871, 2960, 2987, 3056 cm^{-1}. ^{1}H NMR: δ = 0.73 (d, *J* = 6.9 Hz, 6H), 0.87 (s, 6H), 0.89 (s, 6H), 0.92 – 2.05 (m, 18H), 2.50 (s, 6H), 4.73 (dt, *J* = 4.5, 10.8 Hz, 2H), 7.08 – 7.12 (m, 4H), 7.31 – 7.35 (m, 6H), 7.77 (d, *J* = 12.6 Hz, 2H), 11.97 (dd, *J* = 8.1, 12.0 Hz, 2H). ^{13}C NMR: δ = 16.33, 20.68, 21.95, 23.49, 26.32, 30.34, 31.33, 34.25, 41.15, 47.14, 69.54, 73.14, 101.70, 127.07, 128.66, 128.86, 135.61, 158.86, 166.06, 199.97. MS: *m/z* = 712 (M$^+$, 8 %), 500 (12 %), 473 (14 %), 446 (31 %), 169 (29 %), 112 (46 %). HRMS: calculated for $C_{44}H_{60}N_2O_6$ + H requires 713.4616; found 713.4552.

(-)-Menthyl 2-{[((*1S,2S*)-2-{[2-((-)-menthoxycarbonyl)-3-hydroxy-2-butenylidene] amino}-1,2-diphenylethyl)imino]methyl}-3-hydroxy-2-butenoate (for catalyst 56b using (*1S,2S*)-1,2-diphenyl-1,2-diaminoethane)

Purification by chromatography to give a colourless wax. (dichloromethane : acetone = 9:1). (0.304 g, 90 %). R_f = 0.83 (dichloromethane : acetone = 9:1). $[\alpha]_D^{23}$ = -6.84 (c = 0.468, CH_2Cl_2). IR: (CH_2Cl_2) = 1068, 1201, 1253, 1278, 1421, 1573, 1631, 1691, 2304, 2960, 2985, 3050 cm^{-1}. ^{1}H NMR: δ = 0.73 (d, *J* = 6.9 Hz, 6H), 0.87 (s, 6H), 0.89 (s, 6H), 0.92 – 2.05 (m,

18H), 2.50 (s, 6H), 4.73 (dt, *J* = 4.5, 10.8 Hz, 2H), 7.08 – 7.12 (m, 4H), 7.31 – 7.35 (m, 6H), 7.77 (d, *J* = 12.6 Hz, 2H), 11.97 (dd, *J* = 8.1, 12.0 Hz, 2H). ^{13}C NMR: δ = 16.33, 20.68, 21.95, 23.49, 26.32, 30.34, 31.33, 34.25, 41.15, 47.14, 69.54, 73.14, 101.70, 127.07, 128.66, 128.86, 135.61, 158.86, 166.06, 199.97. MS: *m/z* = 712 (M^+, 8 %), 500 (12 %), 473 (14 %), 446 (31 %), 169 (29 %), 112 (46 %). HRMS: calculated for $C_{44}H_{60}N_2O_6$ + H requires 713.4616; found 713.4561.

(+)-Menthyl ester

(+)-Menthyl 2-{[(*1R,2R*)-2-{[2-((+)-menthoxycarbonyl)-3-hydroxy-2-butenylidene] amino}-1,2-diphenylethyl)imino]methyl}-3-hydroxy-2-butenoate (for catalyst 57a using (*1R,2R*)-1,2-diphenyl-1,2-diaminoethane)

Purification by chromatography to give a colourless wax. (dichloromethane : acetone = 9:1). (0.308 g, 91 %). R_f = 0.82 (dichloromethane : acetone = 9:1). $[\alpha]_D^{23}$ = 9.57 (c = 0.606, CH_2Cl_2). IR: (CH_2Cl_2) = 1068, 1201, 1253, 1278, 1421, 1573, 1631, 1691, 2304, 2960, 2985, 3050 cm^{-1}. ^{1}H NMR: δ = 0.72 (d, *J* = 6.8 Hz, 6H), 0.85 (d, *J* = 7.0 Hz, 6H), 0.91 (d, *J* = 6.6 Hz, 6H), 1.03 – 2.24 (m, 16H), 2.50 (s, 6H), 4.74 (dt, *J* = 4.4, 10.8 Hz, 2H), 7.04 – 7.11 (m, 4H), 7.26 – 7.31 (m, 6H), 7.83 (d, *J* = 12.8 Hz, 2H), 11.90 (dd, *J* = 7.0, 12.0 Hz, 2H). ^{13}C NMR: δ = 16.33, 20.68, 21.95, 23.49, 26.32, 30.34, 31.33, 34.25, 41.15, 47.14, 69.54, 73.14, 101.70, 127.07, 128.66, 128.86, 135.61, 158.86, 166.06, 199.97. MS: *m/z* = 712 (M^+, 8 %), 500 (12 %), 473 (14 %), 446 (31 %), 169 (29 %), 112 (46 %). HRMS: calculated for $C_{44}H_{60}N_2O_6$ + H requires 713.4616; found 713.4603.

(+)-Menthyl 2-{[(*1S,2S*)-2-{[2-((+)-menthoxycarbonyl)-3-hydroxy-2-butenylidene] amino}-1,2-diphenylethyl)imino]methyl}-3-hydroxy-2-butenoate (for catalyst 57b using (*1S,2S*)-1,2-diphenyl-1,2-diaminoethane)

Purification by chromatography to give a colourless wax. (dichloromethane : acetone = 9:1). (0.281 g, 83 %). R_f = 0.80 (dichloromethane : acetone = 9:1). $[\alpha]_D^{23}$ = 68.93 (c = 0.676,

CH_2Cl_2). IR: (CH_2Cl_2) = 1199, 1253, 1278, 1421, 1573, 1629, 1689, 2304, 2686, 2871, 2960, 2987, 3056 cm^{-1}. ^1H NMR: δ = 0.72 (d, *J* = 6.8 Hz, 6H), 0.85 (d, *J* = 7.0 Hz, 6H), 0.91 (d, *J* = 6.6 Hz, 6H), 1.03 – 2.24 (m, 16H), 2.50 (s, 6H), 4.72 (dt, *J* = 4.5, 10.7 Hz, 2H), 7.04 – 7.11 (m, 4H), 7.26 – 7.31 (m, 6H), 7.77 (d, *J* = 12.8 Hz, 2H), 11.97 (dd, *J* = 7.0, 12.0 Hz, 2H). ^{13}C NMR: δ = 16.33, 20.68, 21.95, 23.49, 26.32, 30.34, 31.33, 34.25, 41.15, 47.14, 69.54, 73.14, 101.70, 127.07, 128.66, 128.86, 135.61, 158.86, 166.06, 199.97. MS: *m/z* = 712 (M^+, 8 %), 500 (12 %), 473 (14 %), 446 (31 %), 169 (29 %), 112 (46 %). HRMS: calculated for $C_{44}H_{60}N_2O_6$ + H requires 713.4616; found 713.4608.

General method to cobalt β-keto iminato complexes 53a-c, 54, 55a-e, 56a-b, 57a-b[101]

A mixture of ligand (0.203 mmol) was combined with cobalt acetate tetrahydrate (50.6 mg, 0.20 mmol) in deairated ethanol (4 mL) and heated under reflux for 4 hours. The solvent was then removed *in vacuo* till dryness of the complex resulted. The complex was used without further purification. All complexes made have melting points of >350°C.

Ligands synthesised from ethyl 2-formyl-3-oxobutanoate and the appropriate diamine

[N, N′-Bis(2-ethoxycarbonyl-3-oxobutylidene)-(*1R,2R*)-cyclohexyldiaminato]cobalt(II) (53a)

Complex synthesised was brown in colour. IR: = 896, 1070, 1143, 1199, 1238, 1278, 1413, 1573, 1637, 1697, 2254, 2341, 2358, 2865, 2940, 2979 cm^{-1}. Anal. calculated for $C_{20}H_{28}N_2O_6Co$ requires C: 53.20, H: 6.26, N: 6.21, found C: 53.41, H: 6.74, N: 6.31.

[N, N′-Bis(2-ethoxycarbonyl-3-oxobutylidene)-(*1R,2R*)-diphenylethylenediaminato] cobalt(II) (53b)

Complex synthesised was brown in colour. IR: (CH_2Cl_2) = 896, 1091, 1253, 1274, 1423, 1552, 1608, 1697, 2306, 2987, 3052 cm^{-1}. Anal. calculated for $C_{28}H_{30}N_2O_6Co$ requires C: 61.78, H: 5.51, N: 5.09, Co: 10.73, found C: 61.21, H: 5.51, N: 5.04, Co: 10.64.

[N, N′-Bis(2-ethoxycarbonyl-3-oxobutylidene)-(*1S,2S*)-diphenylethylenediaminato] cobalt(II) (53c)

Complex synthesised was brown in colour. IR: (CH_2Cl_2) = 896, 1091, 1253, 1274, 1423, 1552, 1608, 1697, 2306, 2987, 3052 cm^{-1}.

Ligands synthesised from *t*-butyl 2-formyl-3-oxobutanoate and the appropriate diamine

[N, N′-Bis(2-(*t*-butylcarbonyl)-3-oxobutylidene)-(*1R,2R*)-diphenylethylenediaminato] cobalt(II) (54)

Complex synthesised was brown in colour. IR: (CH_2Cl_2) = 1084, 1172, 1296, 1367, 1404, 1427, 1454, 1608, 1695, 1757, 2980 cm^{-1}. Anal. calculated for $C_{32}H_{38}N_2O_6Co$ requires C: 63.45, H: 6.33, N: 4.63, found C: 63.20, H: 7.16, N: 4.05.

Ligands synthesised from (-)-bornyl 2-formyl-3-oxobutanoate and the appropriate diamine

[N, N′-Bis(2-(-)-bornoxycarbonyl-3-oxobutylidene)-ethylenediaminato]cobalt(II) (55a)

Complex synthesised was brown in colour. IR: (CH_2Cl_2) = 896, 1253, 1276, 1423, 1577, 1635, 1691, 2306, 2987, 3058 cm^{-1}. Anal. calculated for $C_{32}H_{42}N_2O_6Co$ requires C: 62.62, H: 7.56, N: 4.57, found C: 62.38, H: 7.51, N: 4.85.

[N, N′-Bis(2-(-)-bornoxycarbonyl-3-oxobutylidene)-(*1R,2R*)-cyclohexyldiaminato] cobalt(II) (55b)

Complex synthesised was brown in colour. IR: (CH_2Cl_2) = 896, 1058, 1087, 1153, 1253, 1253, 1278, 1423, 1616, 1695, 2306, 2987, 3050 cm^{-1}. Anal. calculated for $C_{36}H_{52}N_2O_6Co$ requires C: 64.74, H: 7.85, N: 4.20, found C: 64.32, H: 7.79, N: 3.86.

[N, N′-Bis(2-(-)-bornoxycarbonyl-3-oxobutylidene)-(*1S,2S*)-cyclohexyldiaminato] cobalt(II) (55c)

Complex synthesised was brown in colour. IR: (CH_2Cl_2) = 1085, 1423, 1569, 1614, 1693, 2871, 2956, 3056 cm^{-1}. Anal. calculated for $C_{36}H_{52}N_2O_6Co$ requires C: 64.74, H: 7.85, N: 4.20, found C: 64.73, H: 7.69, N: 4.27.

[N, N′-Bis(2-(-)-bornoxycarbonyl-3-oxobutylidene)-(*1R,2R*)-diphenylethylene diaminato]cobalt(II) (55d)

Complex synthesised was brown in colour. IR: (CH_2Cl_2) = 896, 1081, 1253, 1278, 1423, 1567, 1610, 1695, 2306, 2987, 3052 cm^{-1}. Anal. calculated for $C_{42}H_{54}N_2O_6Co$ requires C: 68.99, H: 7.11, N: 3.66, found C: 68.84, H: 7.25, N: 3.66.

[N, N′-Bis(2-(-)-bornoxycarbonyl-3-oxobutylidene)-(*1S,2S*)-diphenylethylene diaminato]cobalt(II) (55e)

Complex synthesised was brown in colour. IR: (CH_2Cl_2) = 896, 1087, 1195, 1278, 1301, 1390, 1454, 1575, 1606, 1693, 2879, 2956 cm^{-1}. Anal. calculated for $C_{44}H_{54}N_2O_6Co$ requires C: 68.99, H: 7.11, N: 3.66, Co: 7.70, found C: 69.16, H: 6.97, N: 3.71, Co: 7.94.

Ligands synthesised from (-)-menthyl 2-formyl-3-oxobutanoate and the appropriate diamine

[N, N′-Bis(2-(-)-menthoxycarbonyl-3-oxobutylidene)-(*1R,2R*)-diphenylethylene diaminato]cobalt(II) (56a)

Complex synthesised was brown in colour. IR: (CH_2Cl_2) = 896, 1083, 1253, 1278, 1423, 1552, 1608, 1695, 2304, 2987, 3050 cm^{-1}. Anal. calculated for $C_{44}H_{58}N_2O_6Co$ requires C: 68.48, H: 7.52, N: 3.63, Co: 7.65, found C: 68.57, H: 7.59, N: 3.71, Co: 7.74.

[N, N′-Bis(2-(-)-menthoxycarbonyl-3-oxobutylidene)-(*1S,2S*)-diphenylethylene diaminato]cobalt(II) (56b)

Complex synthesised was brown in colour. IR: (CH_2Cl_2) = 896, 1081, 1182, 1253, 1278, 13591423, 1456, 1562, 1608, 1625, 1695, 2304, 2960, 2987, 3056 cm^{-1}. Anal. calculated for $C_{44}H_{58}N_2O_6Co$ requires C: 68.63, H: 7.59, N: 3.64, found C: 68.68, H: 8.02, N: 3.25.

Ligands synthesised from (+)-menthyl 2-formyl-3-oxobutanoate and the appropriate diamine

[N, N′-Bis(2-(+)-menthoxycarbonyl-3-oxobutylidene)-(*1R,2R*)-diphenylethylene diaminato]cobalt(II) (57a)

Complex synthesised was brown in colour. IR: (CH_2Cl_2) = 896, 1081, 1182, 1253, 1278, 13591423, 1456, 1562, 1608, 1625, 1695, 2304, 2960, 2987, 3056 cm^{-1}. Anal. calculated for $C_{44}H_{58}N_2O_6Co$ requires C: 68.63, H: 7.59, N: 3.64, found C: 68.37, H: 7.97, N: 3.53.

[N, N′-Bis(2-(+)-menthoxycarbonyl-3-oxobutylidene)-(*1S,2S*)-diphenylethylene diaminato]cobalt(II) (57b)

Complex synthesised was brown in colour. IR: (CH_2Cl_2) = 896, 1083, 1253, 1278, 1423, 1552, 1608, 1695, 2304, 2987, 3050 cm^{-1}.

Ethyl 2-({[(*R*)-1-(2-{[2-(ethoxycarbonyl)-3-hydroxy-3-butenylidene]amino}-1-napthyl)-2-napthyl]imino}methyl)-3-hydroxy-2-butenoate (58 using (*R*)-2,2′-diaminobinapthyl)

The crude 3-formyl alkyl acetoacetate (2 mol. equivalents) was combined in ethanol (15 mL per mol of substrate) with the diamine (1 mol. equivalent) and allowed to react for 2 days, the solvent was then removed *in vacuo* and the residue purified by chromatography.

Purification by chromatography to give yellow crystals. (dichloromethane : acetone = 9:1). (0.241 g, 90 %). R_f = 0.78 (dichloromethane : acetone = 9:1). $[\alpha]_D^{23}$ = -239.43 (c = 0.558, CH_2Cl_2). IR: (CH_2Cl_2) = 1070, 1213, 1253, 1295, 1363, 1411, 1467, 1513, 1563, 1594, 1633,

1700, 293, 2983, 3056 cm^{-1}. ^{1}H NMR: δ = 1.34 (t, *J* = 4.6 Hz, 6H), 2.20 (s, 6H), 4.23 (q, *J* = 4.8 Hz, 4H), 7.10 (d, *J* = 5.4 Hz, 2H), 7.15 – 7.34 (m, 4H), 7.49 (tt, *J* = 0.6, 4.6 Hz, 2H), 7.51 – 7.87 (m, 2H), 7.95 - 8.11 (m, 4H), 8.24 (d, *J* = 6 Hz, 2H), 8.62 (d, *J* = 8.6 Hz, 2H), 12.38 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR: δ = 14.35, 30.80, 59.75, 103.19, 114.97, 119.97, 125.14, 125.79, 127.80, 128.56, 131.44, 131.51, 132.90, 135.83, 150.99, 166.61, 199.26. MS: *m/z* = 564 (M^{+}, 16 %), 362 (10 %), 267 (12 %), 143 (11 %), 98 (48 %). HRMS: calculated for $C_{34}H_{32}N_2O_6$ requires 564.2347; found 564.2245.

(3R,6S)-3,6-Diphenyl-3,6-dihydro-1,2-dioxine (59)

1,4-Diphenyl-1,3-butadiene (10 g, 0.0485 mol) was combined with rose bengal *bis* triethylammonium salt (130mg, 0.1105 mmol) in dichloromethane (85 mL) and irradiated with 3 x 500W tungsten halogen lamps, at a distance of 15cm from the reaction vessel, in a Pyrex flask fitted with an external cooling jacket in the presence of oxygen for 6 hours. The solvent was then removed *in vacuo* and the residue purified by chromatography (hexanes : ethyl acetate = 1:9) to give colourless crystals. (6.5 g, 56 %). ^{1}H NMR: δ = 5.64 (s, 2H), 6.35 (s, 2H), 7.35 – 7.46 (m, 10H).

Racemic trans (±) Benzyl 2-[(1S,2R,3R)]-2-benzoyl-3-phenylcyclopropyl]acetate (61)[62]

(±) (*3R,6S*)-3,6,diphenyl-3,6-dihydro-1,2-dioxine (1.9 g, 7.98 mmol) was combined with (benzylcarbonylmethylene)triphenylphosphorane (3.6 g, 8.78 mmol) in dichloromethane (50 mL) and stirred at ambient temperature for 7 days. The solvent was then removed *in vacuo* and the residue purified by chromatography (hexanes : ethyl acetate = 17:1) to give colourless crystals. (2.01 g, 81 %). R_f = 0.17 (hexanes : ethyl acetate = 9:1). ^{1}H NMR: (1:4 benzene : carbon tetrachloride) δ = 1.99 (dd, *J* = 7.8, 15.0 Hz, 1H), 2.21 (m, 1H), 2.29 (dd, *J* = 6.0, 15.0 Hz, 1H), 2.95 (t, *J* = 4.8 Hz, 1H), 3.06 (dd, *J* = 5.1, 9.0 Hz, 1H), 4.94 (AB_q, *J* = 15.6 Hz, 2H), 7.08 - 7.45 (m, 13H), 7.98 - 8,01 (m, 2H).

General method for introducing and determining enantiomeric excess used for most of the studies performed (Tables 1-6)

The cobalt catalyst (5 mol%) was dissolved in the desired solvent (1 mL) (in the case of **Table 4**, Entry 9, 2 mL of the 1:1 mixture of hexanes : ethyl acetate was used) and allowed to equilibrate at the desired temperature for the reaction. Symmetrical 3,6-disubstituted-3,6-dihydro-1,2-dioxine (20 mg) was added and the reaction left until such time as complete rearrangement of the dioxine had occurred (t.l.c.). (Benzylcarbonylmethylene) triphenylphosphorane (1.05 equivalents) was then added and the reaction mixture left for 10 hours. The solvent was then removed and the residue purified by column chromatography (hexanes : ethyl acetate = 17:3).

The cyclopropane (5mg) was then dissolved in 1:4 d^6-benzene : carbon tetrachloride and enantiomeric excess determined by chiral shift n.m.r using europium tris[3-(heptafluoropropylhydroxymethylene)]-(+)-camphorate.

Enantioenriched (±) benzyl 2-[(*1S,2S,3R*)-2-benzoyl-3-phenylcyclopropyl]acetate (61) using optimised conditions

A solution of 3,6-diphenyl-3,6-dihydro-1,2-dioxine (0.5 g, 2.10 mmol) in THF (20mL) and a solution of catalyst **55e** (120mg, 0.156 mmol) in THF (5mL) were equilibrated at –15°C for 30 minutes after which time the two solutions were combined and the temperature maintained at –15°C. The rearrangement to the γ-hydroxyenone was monitored by t.l.c. and when complete benzyl 2-(triphenylphosporanylidene)acetate (1.0 g, 2.20 mmol) was added and the reaction mixture stirred overnight. The solvent was then removed *in vacuo* and the residue purified by chromatography (hexanes : ethyl acetate = 17:3). Spectral data as above.

Fractional recrystallisation of the cyclopropane from hexanes (x 6) gave the major enantiomer in >95% optical purity enabling comparison to an authentic sample of the enantiomer[66]. It was ascertained that the major enantiomer formed when this catalyst was utilised was the *trans* (-) benzyl 2-[(*1S,2S,3R*)-2-benzoyl-3-phenylcyclopropyl]acetate and hence the *R*-γ-hydroxy enone was generated from the *meso*-1,2-dioxine **(59)**.

(3R,6S)-3,6-Di(1-napthyl)-3,6-dihydro-1,2-dioxine (62)

The dinapthyl-1,2-dioxine was synthesised by another member of the Taylor group and was donated for used in this work. The details of the characterisation of the dioxine **(62)** will be published at a later date.

(±) Benzyl 2-[(*1S,2R,3R*)-2-napthoyl-3-napthylcyclopropyl]acetate (from dioxine 62)[241]

The cobalt catalyst **55e** (5 mol%) was dissolved in the dichloromethane (1 mL) and allowed to equilibrate at the desired temperature for the reaction. Symmetrical 3,6-di(1-napthyl)-3,6-dihydro-1,2-dioxine (20 mg) was added and the reaction left until such time as complete rearrangement of the dioxine had occurred (t.l.c.). (Benzylcarbonylmethylene) triphenylphosphorane (1.05 equivalents) was then added and the reaction mixture left for 10 hours. The solvent was then removed and the residue purified by column chromatography (hexanes : ethyl acetate = 17:3). ^{1}H NMR: (1:4 benzene: carbon tetrachloride) δ = 1.88 (dd, 1H, *J* = 9.6, 16.8 Hz), 2.44 (dd, 1H, *J* = 5.1, 11.4 Hz), 2.71 – 2.80 (dquin, 1H, *J* = 4.5, 9.3 Hz), 3.20 (t, 1H, *J* = 4.5 Hz), 3.63 (dd, 1H, *J* = 3.8, 4.2 Hz), 4.97 (s, 2H), 7.14 – 7.6 (m, 12H), 7.86 – 8.13 (m, 5H), 8.29 – 8.32 (m, 1H), 8.54 – 8.57 (m, 1H).

The complete characterisation of this cyclopropane was performed by another member of the Taylor group and will be published at a later date.

The cyclopropane (5 mg) was then dissolved in 1:4 d^6-benzene : carbon tetrachloride and the enantiomeric excess determined by chiral shift n.m.r. using the europium complex listed in the general experimental section.

(3R,6S)-3,6-Dicyclohexyl-3,6-dihydro-1,2-dioxine (63)

Methyl cyclohexane carboxylate

To a solution of cyclohexane carboxylic acid (30.0 g, 0.234 mol) in methanol (300 mL) was added DOWEX cation exchange resin (18.0 g) and the reaction mixture heated under reflux for 10 hours. Water (100 mL) was added to the cooled solution and the aqueous solution

extracted with diethyl ether (3 x 250 mL). The combined organic phases were then washed with sodium bicarbonate (sat. 2 x 150 mL), the organic phase dried and the solvent removed *in vacuo* to give a clear colourless oil. (31.9 g, 96 %). ^{1}H NMR: (200 MHz) δ = 1.17 – 1.54 (m, 5H), 1.59 – 1.81 (m, 3H), 1.84 – 1.94 (m, 2H), 2.3 (tt, *J* = 3.8, 10.8 Hz, 1H), 3.66 (s, 3H). ^{13}C NMR: (200MHz) δ = 25.27, 25.60, 28.85, 42.92, 51.13, 176.24.[240]

Cyclohexylmethanol (67)

To a solution of methyl cyclohexane carboxylate (10.0 g, 0.0704 mol) in dry diethyl ether (120 mL), under nitrogen, was added $LiAlH_4$ (4.0 g, 0.105 mol) in small portions and the reaction mixture heated under reflux overnight. The excess $LiAlH_4$ was quenched with addition of water dropwise (50 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (100 mL) and the combined organic phases were dried and the solvent removed *in vacuo* to give a clear colourless oil. (6.71 g, 84 %). ^{1}H NMR: δ = 0.80 – 1.04 (m, 3H), 1.17 – 1.35 (m, 1H), 1.38 – 1.57 (m, 1H), 1.68 – 1.80 (m, 6H), 2.41 (bs, 1H), 3.41 (d, *J* = 6.4 Hz, 2H). ^{13}C NMR: δ = 25.75, 26.50, 29.50, 40.35, 68.40.[240]

Cyclohexane carboxaldehdye

To a solution of oxalyl chloride (9.30 g, 0.073 mol) in dichloromethane (110 mL) at –78^{o}C was added dropwise dimethylsulfoxide (8.25 g, 0.106) in dichloromethane (22 mL), at such a rate that the reaction temperature was kept below –65^{o}C, and the reaction mixture then stirred for 5 minutes. Cyclohexylmethanol (5.0 g, 0.0439 mol) was then added dropwise, keeping the temperature below –65^{o}C and the mixture stirred at –78^{o}C for 25 minutes. Triethylamine (30.7 mL, 22.28 g, 0.220 mol) was then added and the reaction mixture stirred for 5 minutes after which time the reaction was warmed to ambient temperature. Water (150 mL) was then added and the reaction mixture separated and the aqueous phase extracted with dichloromethane (3 x 20 mL). The combined organic extracts were then dried ($MgSO_4$) and the solvent removed *in vacuo* to give a clear colourless oil. ^{1}H NMR: δ = 1.19 – 1.43 (m, 5H), 1.64 – 1.93 (m, 5H), 2.13 – 2.27 (m, 1H), 9.62 (d, *J* = 1.5 Hz, 1H).[240]

Ethyl 3-cyclohexyl-2-propenoate[242]

To a suspension of sodium hydride (1.17 g, 60 % in oil, 0.029 mol) in THF (7 mL) was added trimethylphosphonoacetate (6.55 g, 0.029 mol) dropwise and the reaction mixture then stirred for 5 minutes. The reaction mixture was cooled to –78°C and cyclohexane carboxaldehyde (3.28 g, 0.029 mol) was added dropwise after which the reaction mixture was allowed to warm to ambient temperature and then allowed to stir overnight. The reaction mixture was quenched with aqueous ammonium chloride (saturated, 30 mL) and extracted with diethyl ether (2 x 30 mL), washed with water (2 x 30 mL) and brine (2 x 30 mL) and dried and the solvent removed *in vacuo* to give a clear colourless oil. (5.21 g, 98 %). ^{1}H NMR: δ = 1.05 – 1.25 (m, 5H), 1.22 (t, 3H, *J* = 7.1 Hz), 1.6 – 1.7 (m, 5H), 2.07 (m, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 5.70 (d, 1H, *J* = 15.8 Hz), 6.85 (dd, *J* = 6.8, 15.8 Hz, 1H).[242]

3-Cyclohexyl-2-propen-1-ol[242]

To a solution of ethyl 3-cyclohexyl-2-propenoate (4.8 g, 0.0264 mol) in dichloromethane (130 mL), at –78°C, was added DIBAl-H (1.5 M, in toluene, 35 mL). The reaction mixture was allowed to stir for 1 ½ hours after which time ethanol (50 mL) and aqueous sodium sulfate solution (saturated, 40 mL) was added and the reaction mixture allowed to warm to ambient temperature. The reaction mixture was filtered through a pad of Celite and the solvent then removed *in vacuo* to give a clear colourless oil. (2.9 g, 78 %). ^{1}H NMR: δ = 1.0 – 1.4 (m, 5H), 1.6 – 1.8 (m, 5H), 2.07 (m, 1H), 4.05 (d, *J* = 4.4 Hz, 2H), 5.6 (m, 2H).[242]

3-Cyclohexyl-2-propenal (68)[242]

To a solution of oxalyl chloride (3.8 g, 0.030 mol) in dichloromethane (100 mL), at –78°C, was added a DMSO (4.73 g, 0.061 mol) in dichloromethane (15 mL) at such a rate that the reaction temperature did not rise above –65°C. The reaction mixture was then allowed to stir for ½ hour then 3-cyclohexyl-2-propen-1-ol (2.8 g, 0.02 mol) in dichloromethane (25 mL) was added keeping the reaction temperature below –65°C. After stirring for a further hour trimethylamine (17 mL) was added and the reaction mixture allowed to warm to 0°C. Water (100 mL) was then added, the phases separated and the aqueous phase extracted with diethyl

ether (100 mL). The combined organic extracts were washed with water (100 mL), dried and the solvent removed *in vacuo* to give a clear colourless oil. (2.7 g, 98 %). ^{1}H NMR: δ = 1.1 – 1.4 (m, 5H), 1.6 – 1.85 (m, 5H), 2.27 (m, 1H), 6.10 (dd, *J* = 7.8, 15.7 Hz, 1H), 6.79 (dd, *J* = 6.6, 15.7 Hz, 1H), 9.46 (d, *J* = 7.8 Hz, 1H).[242]

(Iodomethyl)cyclohexane[243]

To a solution of cyclohexyl methanol (5.0 g, 0.0439 mol) in dry dichloromethane (200 mL) was added triphenyl phosphine (17.25 g, 0.0658 mol) in one portion, followed by imidazole (3.0 g, 0.044 mol) in one portion. Iodine (16.73 g, 0.066 mol) was then added in small portions and the bright yellow reaction stirred overnight. Sodium thiosulphate (1 M, 100 mL) was then added in small portions and the phases separated. The aqueous phase was extracted with dichloromethane (100 mL) and the combined organic phases dried and the solvent removed *in vacuo*. The residue was extracted with diethyl ether (50 mL) and the organic phase dried and the solvent removed *in vacuo* to furnish the product as a clear colourless oil (9.6 g, 98 %). ^{1}H NMR: δ = 0.94 (dq, *J* = 3.6, 12.3 Hz, 2H), 1.07 – 1.33 (m, 2H), 1.35 – 1.48 (m, 1H), 1.59 – 1.65 (m, 1H), 1.67 – 1.74 (m, 2H), 1.75 – 1.89 (m, 2H), 3.09 (d, *J* = 6.6 Hz, 2H) ^{13}C NMR: δ = 16.10, 25.87, 26.06, 33.42, 39.98.[244]

Cyclohexylmethyl triphenylphosphonium iodide (69)[245]

To a solution of (iodomethyl)cyclohexane (9.2 g, 0.041 mol) in benzene (30 mL) was added triphenyl phosphine (11.20 g, 0.0427 mol) in small portions and the reaction mixture stirred at ambient temperature for 5 days. The solvent was then removed *in vacuo* and the residue triturated with diethyl ether to afford the title compound as pale cream crystals. (18.4 g, 92 %) m.p. = 274^{o}C (lit.[245]275^{o}C).

1-(4-Cyclohexyl-1,3-butadienyl)cyclohexane (70)

To a suspension of cyclohexylmethyl triphenylphosphonium iodide (9.0 g, 0.0185 mol) in diethyl ether (100 mL) was added potassium *t*-butoxide (2.10 g, 0.0188 mol) in small portions and the reaction mixture allowed to stir for 10 minutes. 3-Cyclohexyl-2-propenal (2.0 g,

0.0144 mol) in diethyl ether (10 mL) was then added dropwise and the reaction mixture allowed to stir over night. The reaction mixture was diluted with hexane (100 mL) and filtered through a pad of silica. The solvent was then removed *in vacuo* and the residue purified by chromatography (hexanes) to give the title compound as a clear colourless oil. (2.65 g, 84 %). ^{1}H NMR: δ = 0.83 – 0.98 (m, 4H), 1.08 – 1.34 (m , 10H), 1.52 – 1.75 (m, 8H), 5.15 (t, *J* = 10.2 Hz, 1H), 5.60 (dd, *J* = 7.2, 15.0 Hz, 1H), 5.84 (t, *J* = 10.5 Hz, 1H), 6.27 (dd, *J* = 10.8, 15.0 Hz, 1H).[246]

(*3R,6S*)-3,6-Dicyclohexyl-3,6-dihydro-1,2-dioxine (63)

Method used as for (±) (3R,6S)-3,6-diphenyl-3,6-dihydro-1,2-dioxine **(59)** using 1-(4-cyclohexyl-1,3-butadienyl)cyclohexane to give the title compound as a clear colourless oil (2 g, 9.17 mmol). (376 mg, 16 %, most of the unreacted diene was recovered). IR: (CH_2Cl_2) = 650, 754, 893, 1450, 2856, 2929 cm^{-1}. ^{1}H NMR: δ = 0.81 – 0.90 (m, 4H), 1.07 – 1.29 (m, 10H), 1.50 – 1.60 (m, 2H), 1.63 – 1.76 (m, 6H), 4.18 (d, *J* = 5.4 Hz, 2H), 5.97 (s, 2H). ^{13}C NMR: δ = 26.04, 26.15, 26.41, 28.87, 28.90, 426.04, 26.15, 26.41, 28.87, 28.90, 41.36, 82.42, 126.77. Further characterisation was not possible due to the instability of the dioxine at elevated temperatures.

(±) Benzyl 2-[(*1S,2R,3R*)-2-cyclohexoyl-3-cyclohexylcyclopropyl]acetate (from dioxine 63)

The cobalt catalyst (5 mol%) was dissolved in dichloromethane (1 mL) and allowed to equilibrate at the temperature of the reaction. Symmetrical 3,6-dicyclohexyl-3,6-dihydro-1,2-dioxine and benzyl 2-(triphenylphosphoranylidene)acetate (1.05 equivalents) were added and the reaction left until such time as complete rearrangement of the dioxine and consumption of the γ-hydroxy enone had occurred (t.l.c.). The solvent was then removed and the residue purified by column chromatography (hexanes : ethyl acetate = 9:1) to give the desired compound as a clear colourless oil. (0.85 g, 79 %). R_f = 0.21 (hexanes : ethyl acetate = 9:1). ^{1}H NMR: δ = 0.83 – 0.98 (m, 2H), 1.08 – 1.38 (m, 11H), 1.58 – 1.91 (m, 12H), 2.30 (dd, *J* = 6.2, 10.6 Hz, 1H), 2.63 (dd, *J* = 4.0, 10.6 Hz, 1H), 5.12 (AB_q, *J* = 6.4 Hz, 2H), 7.32 – 7.41

(m, 5H). ^{13}C NMR: δ = 25.05, 25.41, 25.53, 25.68, 25.73, 25.95, 27.98, 28.40, 31.82, 32.61, 32.72, 33.00, 36.06, 36.89, 128.03, 128.32, 135.65, 171.79. MS: *m/z* = 382 (M^+, 2 %), 291 (20 %), 233 (15 %), 91 (100 %), 55 (23 %). HRMS: calculated for $C_{25}H_{34}O_3$ requires 382.2508; found 382.2506.

For cyclopropane (from dioxine **63**) there was no discernable separation of peaks using chiral shift n.m.r. The ester was hydrolysed, reacted to give the acid chloride and a chiral auxiliary reacted with the acid chloride produce diastereomers that were used as a crude mixture to determine the enantiomeric excess by ^{1}H n.m.r.

(±) 2-[(*1S,2R,3R*)-2-Cyclohexoyl-3-cyclohexylcyclopropyl]acetic acid

(±) Benzyl 2-[(*1S,2R,3R*)-2-cyclohexoyl-3-cyclohexylcyclopropyl]acetate (0.41 g, 1.073 mmol) with introduced enantiomeric excess was dissolved in THF (10 mL) and water (4 mL). NaOH (2M, 7 mL) was then added and the reaction mixture stirred at ambient temperature for 5 hours. The reaction mixture was diluted with water (15 mL) and then washed with dichloromethane. The aqueous phase was acidified to pH 1 then extracted with dichloromethane (2 x 15 mL), dried and the solvent removed *in vacuo* to give the desired compound as colourless crystals. (261 mg, 83 %). ^{1}H NMR: δ = 0.93 – 1.42 (m, 12H), 1.63 – 1.91 (m, 13H), 2.29 (dd, *J* = 8.8, 16.2 Hz, 1H), 2.62 (dd, *J* = 5.8, 16.4 Hz, 1H), 9.40 (bs, 1H). ^{13}C NMR: δ = 25.01, 25.47, 25.54, 25.62, 25.84, 26.04, 28.28, 28.48, 32.04, 32.50, 32.73, 33.12, 36.29, 37.08, 51.47, 52.61, 65.08, 67.79, 177.94. MS: *m/z* = 292 (M^+, 21 %), 233 (16 %), 209 (9 %), 83 (84 %), 55 (100 %), 41 (77 %). HRMS: calculated for $C_{18}H_{28}O_3$ requires 292.2038; found 292.2040.

(*4S*) 3-{2-[(*1S,2R,3R*)-2-Cyclohexoyl-3-cyclohexylcyclopropyl]acetyl}-4-benzyl-1,3-oxazolan-2-one and (*4S*) 3-{2-[(*1R,2S,3S*)-2-cyclohexoyl-3-cyclohexylcyclopropyl] acetyl}-4-benzyl-1,3-oxazolan-2-one

Oxalyl chloride was added to a solution of (±) 2-[(*1S,2R,3R*)-2-cyclohexoyl-3-cyclohexylcyclopropyl]acetic acid (80 mg, 0.27 mmol) and DMF (1 drop) in

dichloromethane, at 0°C. The reaction mixture was stirred at 0°C for 1 hour then ambient temperature for 1 hour after which time the solvent was removed.[247]

n-BuLi (2M in hexanes) was added to a solution of (*S*)-4-benzyl-2-oxazolidinone (53.5 mg, 0.30 mmol) and triphenylmethane (5 mg) in THF (2 mL), at –78°C, until an orange colour persisted, and the reaction mixture stirred for 30 minutes. The acid chloride was then added via cannula and the reaction mixture stirred for 2 hours after which time the reaction mixture was quenched with saturated ammonium chloride then extracted with dichloromethane (2 x 10 mL) to give the mixture of enantiomers as a white wax. R_f = 0.1 (hexanes : ethyl acetate = 9:1). ^{1}H NMR: δ = **major isomer** 0.92 – 0.98 (m, 2H), 1.10 – 1.44 (m, 10H), 1.44 – 1.97 (m, 10H), 2.29 (dd, *J* = 8.4, 16.2 Hz, 1H), 2.43 – 2.49 (m, 2H), 2.60 (dd, *J* = 6.0, 16.8 Hz, 1H), 2.74 – 3.02 (m, 2H), 3.30 (dt, *J* = 3.6, 12.0 Hz, 1H), 3.50 (dd, *J* = 4.2, 13.2 Hz, 1H), 4.61 – 4.71 (m, 2H), 7.12 – 7.41 (m, 5H), **minor isomer** 0.92 – 0.98 (m, 2H), 1.10 – 1.44 (m, 10H), 1.44 – 1.97 (m, 10H), 2.26 (dd, *J* = 9.0, 16.2 Hz, 1H), 2.40 – 2.46 (m, 2H), 2.56 (dd, *J* = 6.0, 15.6 Hz, 1H), 2.74 – 3.02 (m, 2H), 3.36 (dt, *J* = 3.6, 13.8 Hz, 1H), 3.69 (dd, *J* = 3.0, 13.8 Hz, 1H), 4.79 – 4.83 (m, 2H), 7.12 – 7.41 (m, 5H). MS: *m/z* = 451 (M^+, 5 %), 368 (20 %), 233 (55 %), 178 (60 %), 117 (60 %), 83 (100 %). HRMS: calculated for $C_{28}H_{37}N_1O_4$ requires 451.27226, found *m/z* 451.27341.

(3R,6S)-3,6-Dipropyl-3,6-dihydro-1,2-dioxine (64)

The dipropyl-1,2-dioxine was synthesised by another member of the Taylor group and was donated for used in this work. The details of the characterisation of the dioxine **(64)** will be published at a later date.

(±) Benzyl 2-[(*1S,2R,3R*)-2-propoyl-3-propylcyclopropyl]acetate (from dioxine 64)[241]

The cobalt catalyst (5 mol%) was dissolved in dichloromethane (1 mL) and allowed to equilibrate at the temperature of the reaction. Symmetrical 3,6-dipropyl-3,6-dihydro-1,2-dioxine and benzyl 2-(triphenylphosphoranylidene)acetate (1.05 equivalents) were added and the reaction left until such time as complete rearrangement of the dioxine and consumption of the γ-hydroxy enone had occurred (t.l.c.). The solvent was then removed and the residue

purified by column chromatography (hexanes : ethyl acetate = 9:1) to give the title comound as a clear colourless oil. ^{1}H NMR: (1:4 benzene : carbon tetrachloride) δ = 0.77 – 0.83 (m, 6H), 1.04 – 1.23 (m, 1H), 1.19 – 1.28 (m, 4H), 1.36 – 1.48 (m, 3H), 1.63 – 1.67 (m, 1H), 2.08 (dd, *J* = 9.0, 16.2 Hz, 1H), 2.23 (t, *J* = 7.2 Hz, 2H), 2.35 (dd, *J* = 6.6, 16.2 Hz, 1H), 4.96 (s, 2H), 7.16 (m, 5H).

The cyclopropane synthesised from dioxine **(64)** was characterised by another member of the Taylor group and the details of the characterisation will be published at a later date.

The cyclopropane (5 mg) was then dissolved in 1:4 d^{6}-benzene : carbon tetrachloride and the enantiomeric excess determined by chiral shift n.m.r. using the europium complex listed in the general experimental section.

(3R,6S)-3,6-Diisopropyl-3,6-dihydro-1,2-dioxine (65)

(2-Hydroxyethyl)triphenylphosphonium bromide

2-Bromoethanol (21.16 g, 0.169 mol) and triphenylphosphine (46.1 g, 0.176 mol) were combined and heated at 100^{o}C for 2 hours then allowed to cool. The solid was then collected, washed with diethyl ether (2 x 50 mL) and dried *in vacuo* to give pale cream crystals. (60.5g, 92 %). ^{1}H NMR: δ = 3.77 (dt, *J* = 5.6, 12.2 Hz, 2H), 4.05 (dt, *J* = 5.6, 18.8 Hz, 2H), 4.52 (bs, 1H), 7.63 – 7.84 (m, 15H). ^{13}C NMR: δ = 26.67 (d, *J* = 201.8 Hz), 54.95 (d, *J* = 19.6 Hz), 118.17 (d, *J* = 344.6 Hz), 129.95 (d, *J* = 51.6 Hz), 133.45 (d, *J* = 41.0 Hz), 134.57 (d, *J* = 12.0 Hz).[248]

4-Methyl-2-penten-1-ol

To a suspension of (2-hydroxyethyl)triphenylphosphonium bromide (32.2 g, 83.3 mmol) in THF (100 mL) at –20^{o}C was added *n*-BuLi (30 mL, 1.8M, in hexanes) and the reaction mixture stirred at –20^{o}C for 30 minutes, then allowed to sit without stirring for 30 minutes. The reaction mixture was then added, via cannula, to a solution of isobutyraldehyde (5.0 g, 69.3 mmol) in diethyl ether (100 mL) at –20^{o}C. The reaction mixture was then stirred for 1 hour at –20^{o}C then allowed to warm to ambient temperature. Ethanol (10 mL) was then

added and the reaction mixture allowed to sit overnight. The mixture was then diluted with hexanes (50 mL) and filtered through a pad of Celite. The solvent was removed *in vacuo* and the residue was purified by chromatography (hexanes : ethyl acetate = 17:3) to give the desired compound as a clear colourless oil. (3.98 g, 74 %). R_f = 0.09 (hexanes : ethyl acetate = 9:1). ^{1}H NMR: δ = 1.0 (d, *J* = 3.5 Hz, 6H), 2.31 (m, 1H), 3.33 (bs, 1H), 4.02 (d, *J* = 2.0 Hz), 5.60 (m, 2H).[249]

Isobutyltriphenylphosphonium bromide

Isobutyl bromide (40.0 g, 0.292 mol) and triphenyl phosphine (76.56 g, 0.292 mol) were combined in toluene (200 mL) and heated under reflux for 7 days. The resulting precipitate was collected washed with cold toluene (3 x 30 mL), hexanes (2 x 30 mL) and dried *in vacuo* for 4 hours to give pale cream crystals. (84.1 g, 72 %). ^{1}H NMR: δ = 1.03 (d, *J* = 6.9 Hz, 6H), 2.05 (m, 1H), 3.70 (dd, *J* = 6.9, 12.2 Hz), 7.6 – 7.9 (m, 15H).[250]

4-Methyl-2-penten-1-al (72)

To a solution of oxalyl chloride (5.43 g, 42.8 mmol) in dichloromethane (150 mL), at –78^{o}C, was added a solution of DMSO (6.68 g, 85.5 mmol) in dichloromethane (30 mL) at such a rate that the temperature of the reaction did not rise above –65^{o}C. The mixture was allowed to stir for 30 minutes, after which time 4-methyl-2-penten-1-ol (2.85 g, 28.5 mmol) in dichloromethane (20 mL) was added at such a rate that the reaction temperature did not rise above –65^{o}C and the reaction mixture then stirred at –78^{o}C for 1 hour. Triethyl amine (24 mL) was then added and the reaction slowly warmed to ambient temperature. Water (100 mL) was added, the phases separated, the aqueous phase extracted with dichloromethane (2 x 50 mL) and the combined organic extracts washed with water, dried and the solvent removed *in vacuo* to give a clear colourless oil. (2.65 g, 95 %). R_f = 0.31 (hexanes : ethyl acetate = 9:1). ^{1}H NMR: δ = 1.11 (d, *J* = 6.5 Hz, 6H), 2.59 (m, 1H), 6.07 (m, 1H), 6.81 (dd, *J* = 6.2, 15.8 Hz, 1H), 9.50 (d, *J* = 8.2 Hz, 1H).[251]

2,7-Dimethyl-3,5-octadiene (73)

To a suspension of isobutyl triphenylphosphonium bromide (12.52 g, 31.4 mmol) in diethyl ether (100 mL) was added potassium *t*-butoxide (3.52 g, 31.4 mmol) in small portions and the reaction mixture allowed to stir for 30 minutes. 4-Methyl-2-penten-1-al (2.79 g, 28.5 mmol) in diethyl ether (10 mL) was then added and the reaction mixture stirred overnight. The reaction mixture was diluted with hexanes (100 mL), filtered through a pad of silica and the solvent removed *in vacuo*. The residue was purified by chromatography (hexanes) to give a colourless oil. (1.68 g, 43 %). R_f = 0.6 (hexanes). ^{1}H NMR: δ = 0.98 (d, *J* = 5.4 Hz, 6H), 1.01 (d, *J* = 6.6 Hz, 6H), 2.26 – 2.40 (m, 1H), 2.71 – 2.83 (m, 1H), 5.14 (t, *J* = 10.2 Hz, 1H), 5.62 (dd, *J* = 6.6, 15.0 Hz, 1H), 5.83 (t, *J* = 11.1 Hz, 1H), 6.21 – 6.32 (m, 1H).[252]

(*3R,6S*)-3,6-Diisopropyl-3,6-dihydro-1,2-dioxine (65)

Method used as for (±) (3R,6S)-3,6-diphenyl-3,6-dihydro-1,2-dioxine **(59)** using 1-(4-cyclohexyl-1,3-butadienyl)cyclohexane (1.68 g, 12.2 mol) and cobalt catalyst **55e**. The solvent was then removed *in vacuo* and the residue purified by chromatography (hexanes) to give a colourless oil. (298 mg, 14 %, most of the unreacted diene was recovered). R_f = 0.07 (hexanes). IR: ($CDCl_3$) = 1369, 1385, 1467, 2872, 2930, 2962 cm^{-1}. ^{1}H NMR: δ = 0.95 (d, *J* = 6.9 Hz, 6H), 1.0 (d, *J* = 6.9Hz, 6H), 1.96 (octet, *J* = 6.9 Hz, 2H), 4.16 (d, *J* = 5.4 Hz, 2H), 5.99 (s, 2H). ^{13}C NMR: δ = 18.31, 18.63, 31.55, 82.88, 126.85. Further characterisation was not possible due to the instability of the dioxine at elevated temperatures.

(±) Benzyl 2-[(*1S,2R,3R*)-2-isopropoyl-3-isopropylcyclopropyl]acetate (from dioxine 65)

The cobalt catalyst (5 mol%) was dissolved in dichloromethane (1 mL) and allowed to equilibrate at the temperature of the reaction. Symmetrical 3,6-diisopropyl-3,6-dihydro-1,2-dioxine and benzyl 2-(triphenylphosphoranylidene)acetate (1.05 equivalents) were added and the reaction left until such time as complete rearrangement of the dioxine and consumption of the γ-hydroxy enone had occurred (t.l.c.). The solvent was then removed and the residue purified by column chromatography (hexanes : ethyl acetate = 9:1) as a colourless oil. (254

mg, 82 %). R_f = 0.10 (hexanes : ethyl acetate = 9:1). IR: 1081, 1095, 1168, 1228, 1258, 1288, 1365, 1383, 1464, 1692, 1752, 2870, 2932, 1961 cm^{-1}. ^1H NMR: δ = 0.84 – 0.91 (m, 1H), 0.94 (d, *J* = 6.0 Hz, 3H), 1.0 (d, *J* = 6.0 Hz, 3H), 1.05 (d, *J* = 6.0 Hz, 6H), 1.21, 1.27 (m, 2H), 1.32 – 1.44 (m, 1H), 2.32 (dd, *J* = 8.7, 15.9 Hz, 1H), 2.59 – 2.68 (m, 2H), 5.11 – 5.12 (m, 2H), 7.32 – 7.38 (m, 5H). ^{13}C NMR: δ =17.99, 18.27, 21.86, 25.76, 31.82, 37.81, 41.55, 66.46, 115.67, 128.34, 128.58, 144.98, 151.04, 172.06. MS: *m/z* = 302 (M^+, 2 %), 259 (25 %), 211 (40 %), 91 (100 %). HRMS: calculated for $C_{19}H_{26}O_3$ requires 302.1882, found *m/z* 302.1876.

The cyclopropane (5 mg) was then dissolved in 1:4 d^6-benzene : carbon tetrachloride and the enantiomeric excess determined by chiral shift n.m.r. using the europium complex listed in the general experimental section.

(±) Benzyl 2,2-dideutero-2-[(*1S,2R,3R*) 2-benzoyl-3-phenylcyclopropyl]acetate (74)

A solution of catalyst **55e** (12 mg, 1.56 x 10^{-5} mol) in dichloromethane (0.1 mL) was added to an equilibrated solution of 3,6-diphenyl-3,6-dihydro-1,2-dioxine **(59)** (50 mg, 0.210 mmol) in dichloromethane (2.9 mL) at 20°C. After rearrangement of the dioxine was complete deuterium oxide (1 mL) was added, and allowed to stir vigorously for 1 hour, followed by benzyl 2-(triphenylphosphoranylidene)acetate (100 mg, 0.24 mol) and the reaction mixture stirred vigorously for 5 days. The deuterium oxide was pipetted off and the reaction mixture dried. The solvent was removed *in vacuo* and the residue purified by chromatography (hexanes : ethyl acetate = 17:3) to give the pure cyclopropane (49.9mg, 67 %) as colourless crystals. ^1H NMR: (1:4 d^6-benzene: carbon tetrachloride) δ = 2.12 (dd, 1H, *J* = 4.5, 9.3 Hz), 2.86 (t, 1H, *J* = 4.8 Hz), 2.98 (dd, 1H, *J* = 4.8, 9.3 Hz), 6.99 – 7.33 (m, 8H), 7.90 – 7.93 (m, 2H).[253]

The cyclopropane synthesised from dioxine **(64)** was characterised by another member of the Taylor group and the details of the characterisation will be published at a later date.

The cyclopropane (5 mg) was then dissolved in 1:4 d^6-benzene : carbon tetrachloride and the enantiomeric excess determined by chiral shift n.m.r. using the europium complex listed in the general experimental section.

(±) Cyano (*1R,2R,3S*) 2-(2-oxo-2phenylethyl)-3-phenylcyclopropane (75)

A solution of catalyst **55e** (4.0 mg, 5.2 μmol) in dichloromethane (0.1 mL) was added to an equilibrated solution of 3,6-diphenyl-3,6-dihydro-1,2-dioxine **(59)** (20 mg, 0.084 mmol) in dichloromethane (2.0 mL) at 20°C. After rearrangement of the dioxine was complete (cyanomethylene)triphenylphosphorane (25 mg, 0.084 mol) was added and the reaction mixture stirred vigorously for 16 hours. The solvent was removed *in vacuo* and the residue purified by chromatography (hexanes : ethyl acetate = 17:3) to give the pure cyclopropane (17.4 mg, 87 %) as colourless crystals. ^{1}H NMR (1:4 d^6-benzene: carbon tetrachloride) : δ = 2.29 – 2.39 (m, 3H), 3.11 – 3.19 (m, 2H), 7.26 -7.40 (m, 5H), 7.51 – 7.65 (m, 3H), 8.07 - 8.10 (m, 2H).[254]

The cyclopropane synthesised from dioxine **(59)** was characterised by another member of the Taylor group and the details of the characterisation will be published at a later date.[254]

The cyclopropane (5 mg) was then dissolved in 1:4 d^6-benzene : carbon tetrachloride and the enantiomeric excess determined by chiral shift n.m.r. using the europium complex listed in the general experimental section.

(±) *N*-Methyl-*N*-methoxy (*1R,2R,3S*) 2-(2-oxo-2phenylethyl)-3-phenyl cyclopropane-1-acetamide (76)

A solution of catalyst **55e** (4.1 mg, 5.35 μmol) in dichloromethane (0.1 mL) was added to an equilibrated solution of 3,6-diphenyl-3,6-dihydro-1,2-dioxine **(59)** (20 mg, 0.084 mmol) in dichloromethane (2.0 mL) at 20°C. After rearrangement of the dioxine was complete (*N*-methyl-*N*-methoxy) 2-(triphenylphosphanylidene)acetamide (30.5 mg, 0.084 mol) was added and the reaction mixture stirred vigorously for 16 hours. The solvent was removed *in vacuo* and the residue purified by chromatography (hexanes : ethyl acetate = 17:3) to give the pure

cyclopropane (22 mg, 82 %) as colourless crystals. ^{1}H NMR (1:4 d^6-benzene: carbon tetrachloride) : δ = 1.91 (dd, 1H, *J* = 5.4, 10.2 Hz), 2.05 – 2.14 (m, 1H), 2.32 (dd, 1H, *J* = 4.6, 10.4), 2.85 (s, 3H), 2.97 (t, 1H, *J* = 3.4 Hz), 3.05 (t, 1H, *J* = 4.2 Hz), 3.14 (s, 3H), 6.97 – 7.06 (m, 2H), 7.09 – 7.14 (m, 2H), 7.23 – 7.31 (m, 4H), 7.95 – 7.98 (m, 2H).[254]

The cyclopropane synthesised from dioxine **(59)** was characterised by another member of the Taylor group and the details of the characterisation will be published at a later date.[254]

The cyclopropane (5 mg) was then dissolved in 1:4 d^6-benzene : carbon tetrachloride and the enantiomeric excess determined by chiral shift n.m.r. using the europium complex listed in the general experimental section.

(±) *t*-Butyl (*1R,2R,3S*) 2-(2-oxo-2phenylethyl)-3-phenylcyclopropane-1-carboxylate (77)

A solution of catalyst **55e** (12 mg, 1.56 x 10^{-5} mol) in dichloromethane (0.1 mL) was added to an equilibrated solution of 3,6-diphenyl-3,6-dihydro-1,2-dioxine **(59)** (50 mg, 0.210 mmol) in dichloromethane (2.9 mL) at 20^{o}C. After rearrangement of the dioxine was complete lithium bromide (19 mg, 0.218 mmol) was added, and allowed to stir for 5 minutes, followed by (*t*-butoxycarbonylmethylene)triphenylphosphorane (100 mg, 0.266 mol) and the reaction mixture stirred vigorously for 5 days. The reaction mixture was filtered and the solvent was then removed *in vacuo*. Purification by chromatography (hexanes : ethyl acetate = 17:3) gave the pure cyclopropane (40.1 mg, 57 %) as colourless crystals. ^{1}H NMR: (1:4 benzene : carbon tetrachloride) δ = 1.14 (s, 9H), 1.72 (dd, 1H, *J* = 5.4, 9.6 Hz), 2.20 (dd, 1H, *J* = 6.6, 9.3 Hz), 2.34 – 2.42 (m, 1H), 2.51 (dd, 1H, *J* = 8.7, 17.4 Hz), 3.12 (dd, 1H, *J* = 4.8, 17.4 Hz), 7.08 – 7.41 (m, 8H), 7.81 – 7.84 (m, 2H).[253]

The cyclopropane (5 mg) was then dissolved in 1:4 d^6-benzene : carbon tetrachloride and the enantiomeric excess determined by chiral shift n.m.r. using the europium complex listed in the general experimental section.

(±) Methyl (*1R,2R,3S*) 2-(2-oxo-2phenylethyl)-3-phenylcyclopropane-1-carboxylate (78)

To a solution of trimethylphosphonoacetate (1.0 g, 5.49 mmol), at –78^{o}C, was added a solution of methyl lithium in ether (3.9 mL) and the reaction mixture allowed to stir at –78^{o}C for 30 minutes.

In a parallel reaction, cobalt catalyst **55e** was equilibrated, at –78^{o}C, in THF (1 mL) followed by the addition of dioxine (**59)** (60 mg, 0.252 mmol). After complete rearrangement of the dioxine the lithium phosphonate solution (0.4 mL) was added and the reaction mixture allowed to stir for 30 minutes at –78^{o}C followed by stirring at room temperature for 16 hours. The solvent was then removed *in vacuo* and the residue purified by chromatography (hexanes : ethyl acetate 17 3) to give the title compound as colourless crystals. (60.1 mg, 81 %). ^{1}H NMR: δ = 1.87 (dd, 1H, *J* = 4.8, 10.0 Hz), 2.01 – 2.17 (m, 2H), 2,85 – 2.88 (m, 1H), 2.95 – 3.00 (m, 1H), 3.36 (s, 3H), 6.99 – 7.11 (m, 5H), 7.23 – 7.34 (m, 3H), 7.91 – 7.94 (m, 2H).[63]

The cyclopropane (5 mg) was then dissolved in 1:4 d^{6}-benzene : carbon tetrachloride and the enantiomeric excess determined by chiral shift n.m.r. using the europium complex listed in the general experimental section.

General method for NMR rate studies

To dioxine **(59)** (20 mg, 0.084 mmol) in $CDCl_3$ (0.7 mL), with phenyl trimethyl silane (5 mg) present as a standard, was added the catalyst (2 mol%) and the reaction monitored by n.m.r for 4 hours or until rearrangement of the dioxine was complete.

General method for the introduction of additives to the cobalt catalyst (55e)

The catalyst **(55e)** (50 mg, 0.065 mmol) was combined with the desired additive (0.065 mmol) in dichloromethane (5 mL) and allowed to stir at room temperature for 3 hours. The solvent was then removed *in vacuo* to dryness of the residue. These catalysts were then used as previously described in the ring-opening of dioxine **(59)**.

6.3 Compounds Described in Chapter 3

Iron(II) salen acetonitrile (89)[96]

To refluxing acetonitrile (5 mL) was added $SalenH_2$ (100 mg, 0.373 mmol) and iron(II) chloride (47.4 mg, 0.373 mmol) and the mixture allowed to reflux for 2 hours. The solvent was then removed *in vacuo* to give the title compound as brown crystals and the complex used without further purification. m.p. >350°C (lit.[255] m.p. >350°C). Anal. calculated for $C_{16}H_{14}N_2O_2$ requires: C: 59.6, H: 4.4, N: 8.7, found C: 59.5, H:, 4.2, N: 8.6.[255]

Ruthenium(II) salen [NO] Cl (90)[169,170]

Nitroso Ruthenium(III) trichloride[172]

To degassed hydrochloric acid (2M, 3 mL) was added ruthenium trichloride trihydrate (0.50 g, 1.91 mmol) and the reaction mixture heated to reflux. Sodium nitrite (0.396 g, 5.74 mmol) in water (2 mL) was then added dropwise over 30 minutes and the resultant red/brown solution was allowed to reflux for a further 2½ hours. The solvent was then removed *in vacuo* and the residue dissolved in absolute ethanol (5 mL), the solution filtered and the ethanol removed *in vacuo*. The residue was then dissolved in hydrochloric acid (2M, 2 mL) and the residue dried thoroughly *in vacuo*. The red residue was then dissolved in water (1 mL) and the solvent removed *in vacuo*, with this last step repeated an additional two times. The solid was then taken to dryness *in vacuo* to give red crystals and desiccated until required. (300 mg, 54%). IR: 1915 cm^{-1}.[172]

Ruthenium(II) salen [NO] Cl (90)[169,170]

Sodium hydride (33 mg, 60 % dispersion in mineral oil) was washed with dry hexanes. The $SalenH_2$ (100 mg, 0.373 mmol) in DMF (3 mL) was then added at such a rate that the evolution of hydrogen gas was controlled. The reaction mixture was then stirred at room temperature for 1 hour. Nitroso ruthenium trichloride hydrate (105 mg, 0.410 mmol) was then added and the reaction mixture heated at 110°C for 48 hours. The reaction mixture was

allowed to cool prior to removal of the solvent *in vacuo*. The residue was then washed with water and dried *in vacuo* to give the desired compound as brown crystals. m.p. >350°C (lit.[169,170] m.p. >350°C). IR: 1829 cm^{-1}.[169]

General method for the use of metal salens in the ring-opening of dioxine (59)

A solution of catalyst (5 mol%) in the appropriate solvent (0.1 mL) was added to an equilibrated solution of 3,6-diphenyl-3,6-dihydro-1,2-dioxine (59) (50 mg, 0.210 mmol) in the appropriate solvent (2.9 mL) at 20°C. After rearrangement of the dioxine was complete (t.l.c.) benzyl ester ylide (100 mg, 0.24 mol) was added and the reaction mixture allowed to stir for 10 hours. The solvent was then removed *in vacuo* and the residue analysed by ^{1}H NMR to determine whether cyclopropane had been formed in the reaction mixture. (In the case of the manganese catalyst no ylide was added due to the near absence of enone in the reaction mixture).

6.4 Compounds Described in Chapter 4

General method to epoxy dioxines[241]

The dioxine (0.420 mmol) was combined with *m*-CPBA (79 mg, 0.628 mmol) in dichloromethane (4 mL) and the reaction stirred at ambient temperature protected from light for 7 days. The solvent was then removed *in vacuo* and the residue purified by chromatography.

(*1aR,2R,5S,5aS*)-2,5-Diphenylperhydrooxireno*/2,3-d/*[1,2]dioxine (99a)[241]

Purification by chromatography (hexanes : ethyl acetate = 9:1) gave the title compound as colourless crystals. (68 mg, 64%). R_f = 0.25 (hexanes : ethyl acetate = 9:1). ^{1}H NMR: δ = 3.73 (s, 2H), 5.43 (s, 2H), 7.37 – 7.49 (m, 10H).[241]

(*1aR,2S,5S,5aS*)-2,5-Dipropylperhydroxooxireno*/2,3-d/*[1,2]dioxine (99c)[241]

Purification by chromatography (hexanes : ethyl acetate = 9:1) gave the title compound as colourless crystals. (68 mg, 64%). R_f = 0.31 (hexanes : dichloromethane = 1:1). ^{1}H NMR: δ = 0.96 (t, *J* = 6.9 Hz, 6H), 1.44 – 1.57 (m, 6H), 1.60 – 1.82 (m, 2H), 3.19 (d, *J* = 0.6 Hz, 2H), 4.24 (dd, *J* = 4.2, 7.8 Hz, 2H).[241]

(*1aR,2S,5R,5aS*)-2,5-Diisopropylperhydroxooxireno*/2,3-d/*[1,2]dioxine (99d)[241]

Purification by chromatography (hexanes : ethyl acetate = 9:1) gave the title compound as colourless crystals. (68 mg, 64%). R_f = 0.15 (hexanes : dichloromethane = 1:1). ^{1}H NMR: δ = 1.03 (d, *J* = 6.9 Hz, 12H), 2.02 (oct, *J* = 6.9 Hz, 2H), 3.30 (d, *J* = 0.9 Hz, 2H), 3.91 (d, *J* = 6.9 Hz, 2H).[241]

Compounds **99a, 99c-d** were characterised by another member of the Taylor group. Their characterisation is published in the *J. Org. Chem*. paper attached in the Appendices at the back of this thesis.

General method to oxiranyl methanones[241]

The cobalt catalyst (5 mol %, 0.0196 mmol) was dissolved in dichloromethane (2 mL) and allowed to equilibrate at ambient temperature for 1 hour after which time the epoxy dioxine (0.393 mmol) was added. After rearrangement of the epoxy dioxine was complete the reaction mixture was diluted with hexanes (2 mL) and filtered through silica to give the pure oxiranyl methanone, which was analysed by chiral shift n.m.r using europium tris[3-(hepta-fluoropropylhydroxymethylene)]-(+)-camphorate in chloroform.

From (*1aR,2R,5S,5aS*)-2,5-diphenylperhydrooxireno*[2,3-d]*[1,2]dioxine

{(*2S,3S*)-3-(1-Hydroxy-1-phenylmethyl)oxiran-2-yl}(phenyl)methanone (100a)[241]

Purification by chromatography (hexanes : ethyl acetate = 4:1) gave the title compound as colourless crystals. R_f = 0.50 (hexanes : ethyl acetate = 3:2). ^{1}H NMR: (600 MHz) δ = 2.34 (br d, *J* = 3.0 Hz, 1H), 3.59 (dd, *J* = 4.5, 6.6 Hz, 1H), 4.26 (d, *J* = 4.5 Hz, 1H), 4.57 (dd, *J* = 3.0, 6.6 Hz, 1H), 7.30 – 7.68 (m, 8H), 8.01 – 8.09 (m, 2H).[241]

(*1aR,2S,4R,4aS*)-2,4-diphenyltetrahydrooxireno*[2,3-c]*furan-2-ol (Major Anomer) (101a)

^{1}H NMR: (600 MHz) δ = 3.05 (br s, 1H), 3.98 (s, 2H), 5.42 (s. 1H), 7.29 – 7.69 (m, 10H).

From (*1aR,2S,5S,5aS*)-2,5-dipropylperhydroxooxireno*[2,3-d]*[1,2]dioxine

(*1aR,2S,4R,4aS*)-2,4-dipropyltetrahydrooxireno*[2,3-c]*furan-2-ol[241] **(Major Anomer) (101c)**

Purification by chromatography (hexanes : ethyl acetate = 7:3) gave the title compound as colourless crystals. R_f = 0.50 (hexanes : ethyl acetate = 7:3). ^{1}H NMR: δ = 0.93 – 0.99 (m, 6H), 1.35 – 1.85 (m, 8H), 2.28 (s, 1H), 3.61 (d, *J* = 3.0 Hz, 1H), 4.09 (dd, *J* = 5.7, 8.4 Hz, 1H).[241]

From (*1aR,2S,5R,5aS*)-2,5-diisopropylperhydroxooxireno*[2,3-d]*[1,2]dioxine

(*1aR,2S,4R,4aS*)-2,4-diisopropyltetrahydrooxireno*[2,3-c]*furan-2-ol[241] (Major Anomer) (101d)

Purification by chromatography (hexanes : ethyl acetate = 3:2) gave the title compound as colourless crystals. R_f = 0.52 (hexanes : ethyl acetate = 3:2). ^{1}H NMR: (600 MHz) δ = 1.0 (d, *J* = 6.6 Hz, 6H), 1.05 (d, *J* = 6.6 Hz, 6H), 1.81 (d sept, *J* = 6.6, 9.0 Hz, 1H), 2.04 (sept, *J* = 6.6 Hz, 1H), 2.11 (s, 1H), 3.63 (d, *J* = 3.0 Hz, 1H), 3.67 (d, *J* = 3.0 Hz, 1H), 3.68 (d, *J* = 9.0 Hz, 1H).[241]

Compounds **100a, 101a, 101c-d** were characterised by another member of the Taylor group. Their characterisation is published in the *J. Org. Chem*. paper attached in the Appendices at the back of this thesis.

Determination of enantiomeric excess for the ring-opened epoxy dioxines

The cyclopropane (5 mg) was then dissolved in d-chloroform and the enantiomeric excess determined by chiral shift n.m.r. using the europium complex listed in the general experimental section.

6.5 Compounds Described in Chapter 5

Benzyl triphenylphosphonium bromide

To a solution of triphenylphosphine (30.4 g, 0.116 mol) in dry toluene (100 mL), under nitrogen, was added benzyl bromide (15.82 g, 0.093 mol) dropwise over 5 minutes. The resulting solution was then stirred at ambient temperature for 48 hours after which time the white precipitate was collected and washed with dry toluene (2 x 50 mL) and the remaining solvent removed *in vacuo* to give pale cream crystals. (32 g, 80 %) m.p. = 292 – 298 ^{o}C (lit.[240] 295 – 298 ^{o}C)

1-Phenyl-1,3-propanediene

To a rapidly stirred suspension of benzyl triphenylphosphonium bromide (16.08 g, 0.037 mol) in dry diethyl ether (130 mL), under nitrogen, was added potassium *t*-butoxide (4.16 g, 0.037 mol) portion wise over 10 minutes and the reaction mixture then stirred for a further 20 minutes. Crotonaldehyde (2 g, 0.029 mol) in diethyl ether (10 mL) was then added dropwise over 10 minutes and the reaction mixture stirred for 3 hours. The reaction mixture was then diluted with hexanes (100 mL) and filtered. The solvent was removed *in vacuo* and the crude product purified by chromatography (hexanes) to give a clear colourless oil. (3.7 g, 90 %) R_f = 0.55 (hexanes) as a mixture of two isomers. ^{1}H NMR: δ = 1.78 (m, 3H), 5.85 (m, 1H), 6.18 – 6.81 (m, 3H), 7.15 – 7.38 (m, 5H).[62]

(±) (3R,6R)-3-Methyl-6-phenyl-3,6-dihydro-1,2-dioxine (123)

1-Phenyl-1,3-propanediene (3.5 g, 0.024 mol) was combined with rose bengal *bis* triethylammonium salt (130 mg, 0.1105 mmol) in dichloromethane (85 mL) and irradiated with 3 x 500W tungsten halogen lamps, at a distance of 15cm from the reaction vessel, in a Pyrex flask fitted with an external cooling jacket in the presence of oxygen for 6 hours. The solvent was then removed *in vacuo* and the residue purified by chromatography (hexanes : ethyl acetate = 1:9) to give a clear colourless oil. (1.6 g, 40 %). R_f = 0.45 (hexanes : ethyl

acetate = 9:1). ^{1}H NMR: δ = 1.35 (d, *J* = 10.2 Hz, 3H), 4.76 (s, 1H), 5.47 (s, 1H), 6.06 (s, 2H), 7.34 – 7.41 (m, 5H).[62]

(±) t-Butyl 2-methyl-3-(2-oxo-2-phenylethyl)cyclopropane-1-carboxylate (124)

(*3R,6R*)-3-Methyl-6-phenyl-3,6-dihydro-1,2-dioxine (2.5 g, 0.014 mol) was combined with (*t*-butoxycarbonylmethylene)triphenylphosphorane (7.56 g, 0.20 mol) and lithium bromide (1.5 g, 0.17 mol) in dry dichloromethane (250 mL) and stirred under nitrogen for 3 days. The reaction mixture was filtered and the solvent was then removed *in vacuo*. The residue was purified by chromatography (hexanes : ethyl acetate = 9:1) to give the major *trans* product (2.56 g, 70 %). R_f = 0.25 (hexanes : ethyl acetate = 9:1). and a minor *cis* product (40 mg, 1 %). R_f = 0.3 (hexanes : ethyl acetate = 9:1) and the products recrystallised from *n*-heptane as colourless crystals. ***trans* (±) *t*-butyl (*1R,2S,3S*)-2-methyl-3-(2-oxo-2-phenylethyl) cyclopropane-1-carboxylate** IR: (CH_2Cl_2) 1551, 1581, 1598, 1690, 1715, 2306, 2411, 2522, 2686, 2934, 2986, 3055, 3693 cm^{-1}. ^{1}H NMR: (600 MHz) δ = 1.14 – 1.18 (m, 1H), 1.23, (d, 3H, *J* = 6.0 Hz), 1.45 (s, 9H), 1.50 (dd, *J* = 5.4, 9 Hz, 1H), 1.60 – 1.64 (m, 1H), 2.75 (dd, *J* = 7.8, 16.6 Hz, 1H), 3.16 (dd, *J* = 6.0, 16.2 Hz, 1H), 7.46 (tt, *J* = 1.2, 9.0 Hz, 2H), 7.56 (tt, *J* = 1.2, 7.2 Hz, 1H), 7.92 (dt, *J* = 1.8, 7.8 Hz, 2H). ^{13}C NMR: (600 MHz) δ = 11.68, 22.81, 22.84, 26.58, 28.20, 42.12, 80.27, 128.09, 128.65, 133.11, 136.75, 171.29, 198.78. Anal. calculated for $C_{17}H_{22}O_3$ requires: C: 74.4, H: 8.08, found C: 74.46, H:, 8.02. MS: *m/z* = 275 (12 %, M^+), 219 (23 %), 201 (100 %), 105 (51 %), 77 (18 %), 57 (31 %), 41 (20 %). ***cis* (±) *t*-butyl (*1S,2S,3S*)-2-methyl-3-(2-oxo-2-phenylethyl)cyclopropane-1-carboxylate** ^{1}H NMR: (600 MHz) δ = 1.16 (d, *J* = 6.0 Hz, 3H), 1.26 – 1.31 (m, 1H), 1.40 (s, 9H), 1.42 – 1.49 (m, 1H), 1.55 (dd, *J* = 1.8, 4.8 Hz, 1H), 4.95 (dd, *J* = 7.2, 10.8 Hz, 1H), 3.35 (dd, *J* = 6.6, 18 Hz, 1H), 7.44 (tt, *J* = 0.9, 8.4 Hz, 2H), 7.54 (tt, *J* = 2.7, 7.2 Hz, 1H), 7.94 (dt, *J* = 0.6, 7.2 Hz, 2H). ^{13}C NMR: δ = 17.61, 21.77, 24.30, 26.86, 28.08, 36.31, 80.25, 128.00, 128.53, 137.07, 172.39, 199.74.

Trans (±) [(1R,2S,3S)-2-(t-butoxycarbonyl)-3-methylcyclopropyl]methyl benzoate and trans (±) t-butyl (1R,2S,3R)-2-methyl-3-(2-oxo-2-phenoxyethyl)cyclopropane-1-carboxylate

To a solution of (±) *t*-butyl-2-methyl-3-(2-oxo-2-phenylethyl)cyclopropane carboxylate (0.997 g, 3.63 mmol) in dichloromethane (50 mL) was added *m*-chloroperbenzoic acid (0.63 g, 3.63 mmol) and the reaction mixture stirred for 4 days in the absence of light. Saturated sodium sulfite solution (10 mL) was then added and the reaction mixture stirred for 1 hour. The phases were separated and the aqueous phase extracted with dichloromethane (2 x 50 mL). The organic phases were washed with sodium bicarbonate solution (saturated) and the organic phase dried. The solvent was removed *in vacuo* to give a 1:1 mixture of two inseparable diesters.(1.05 g, 100 %) in a waxy oil. ***trans* (±) [(*1R,2S,3S*)-2-(*t*-butoxycarbonyl)-3-methylcyclopropyl]methyl benzoate** ^{1}H NMR: δ = 1.20 – 1.27 (m, 3H), 1.30 – 1.39 (m, 10H), 1.65 – 1.78 (m, 2H), 4.21 (dd, *J* = 6.6, 12.3 Hz, 1H), 4.26 (dd, *J* = 5.7 11.4 Hz, 1H), 7.44 (tt, *J* = 1.2, 8.1Hz, 2H), 7.56 (tt, *J* = 1.5, 6.0 Hz, 1H), 8.04 (dt, *J* = 1.2, 7.5 Hz, 2H). ***trans* (±) *t*-butyl (*1R,2S,3R*)-2-methyl-3-(2-oxo-2-phenoxyethyl)cyclopropane-1-carboxylate** ^{1}H NMR: δ = 1.13 – 1.29 (m, 4H), 1.38 – 1.50 (m, 10H), 1.54 – 1.66 (m, 1H), 2.44 (dd, *J* = 7.8, 16.2 Hz, 1H), 2.67 (dd, *J* = 6.0, 15.6Hz, 1H), 7.06 – 7.12 (m, 2H), 7.21 – 7.27 (m, 1H), 7.36 – 7.42 (m, 2H).

trans (±) t-Butyl (1S,2R,3S)-2-(hydroxymethyl)-3-methylcyclopropane-1-carboxylate (125) and trans (±) 2-[(1R,2R,3S)-2-(t-butoxycarbonyl)-3-methylcyclopropyl]acetic acid (126)

The mixture of *trans* (±) [(*1R,2S,3S*)-2-(*t*-butoxycarbonyl)-3-methylcyclopropyl]methyl benzoate and *trans* (±) *t*-butyl (*1R,2S,3R*)-2-methyl-3-(2-oxo-2-phenoxyethyl) cyclopropane-1-carboxylate (1.05 g, 3.61 mmol) was dissolved in methanolic sodium hydroxide (1 M, 1:1 methanol: water, 100 mL) and stirred at ambient temperature overnight. The reaction mixture was extracted with dichloromethane, dried and the solvent removed *in vacuo*. The aqueous phase was acidified to pH = 1 with dilute hydrochloric acid (1M) and extracted with

dichloromethane (2 x 40 mL), dried and the solvent removed *in vacuo*. The cyclopropyl acetic acid could not be separated from the phenol and benzoic acid and hence further characterisation was not possible. ***trans (±) t-butyl (1S,2R,3S)-2-(hydroxymethyl)-3-methylcyclopropane-1-carboxylate*** ^{1}H NMR: δ = 1.18 (s, 3H), 1.21 – 1.27 (m, 1H), 1.44 (s, 9H), 1.49 – 1.60 (m, 2H), 2.83 (bs, 1H), 3.46 (dd, *J* = 6.3, 11.7 Hz, 1H), 3.52 (dd, *J* = 6.0, 11.4 Hz, 1H). ^{13}C NMR: δ = 11.54, 20.33, 24.84, 28.13, 29.36, 64.43, 80.32, 171.36. MS: *m/*z = 187 (50 %, M + H$^+$), 131 (70 %), 113 (100 %), 99 (24 %), 57 (78 %). ***trans (±) 2-[(1R,2R,3S)-2-(t-butoxycarbonyl)-3-methylcyclopropyl]acetic acid*** ^{1}H NMR: δ = 1.11 – 1.21 (m, 1H), 1.22 (s, 3H), 1.45 (s, 9H), 1.50 – 1.60 (m, 2H), 2.25 (dd, *J* = 6.9, 16.8 Hz, 1H), 2.52 (dd, *J* = 6.3, 10.8 Hz, 1H).

trans (±) t-Butyl 2-[(1S,2R,3R)-2-benzoyl-3-methylcyclopropyl]acetate (129)

To a solution of (*3R,6R*) 3-methyl-6-phenyl-3,6-dihydro-1,2-dioxine **(123)** (0.68 g, 3.86 mmol) in dichloromethane (10 mL) was added triethylamine (10 drops) and stirred for 30 minutes at ambient temperature after which time some rearrangement to the γ-hydroxyenone had occurred (t.l.c.). (*t*-Butoxycarbonyl-methylene)triphenylphosphorane (1.7 g, 4.52 mmol) was then added and the reaction mixture stirred at ambient temperature for 2 days. The solvent was then removed and purified using chromatography (hexanes : ethyl acetate = 17:3) to give the title compound as colourless crystals. (0.4 g, 40 %). R_f = 0.28 (hexanes : ethyl acetate = 9:1). ^{1}H NMR: δ = 1.23 (d, *J* = 6.0 Hz, 3H), 1.40 (s, 9H), 1.84 – 1.89 (m, 1H), 1.99 – 2.04 (m, 1H), 2.23 (t, *J* = 4.2 Hz, 1H), 2.39 (dd, *J* = 7.8, 15.6 Hz, 1H), 2.45 (dd, *J* = 7.2, 15.6 Hz, 1H), 7.47 (tt, *J* = 1.2, 7.2 Hz, 2H), 7.46 (tt, *J* = 1.2, 7.5 Hz, 1H), 7.97 (dt, *J* = 1.8, 6.9 Hz, 2H). ^{13}C NMR: δ = 12.42, 24.53, 27.17, 27.96, 32.64, 34.23, 80.66, 128.03, 128.40, 132.65, 138.11, 171.60, 199.42. MS: *m/z* = 274 (19 %, M$^+$), 218, (80 %), 158 (55 %), 104 (100 %), 76.8 (32 %), 57 (82 %), 41 (38 %).

4-Methoxybenzyl triphenylphosphonium bromide

4-Methoxybenzyl bromide

To a solution of carbon tetrabromide (7.54 g, 0.0238 mol) in dry diethyl ether (10 mL), under nitrogen, was added dropwise triphenylphosphine (5.98 g, 0.0238 mol) in diethyl ether (25 mL). 4-Methoxybenzyl alcohol (3 g, 0.0217 mol) in diethyl ether (10 mL) was then added dropwise over 10 minutes and the reaction mixture stirred for 2 hours. The reaction mixture was then filtered and the solvent removed *in vacuo.* The residue was then purified by distillation to give a clear colourless oil. (4.4 g). b.p. = 143 – 149°C (lit.[256] 145 – 148°C).

4-Methoxybenzyl triphenylphosphonium bromide

To a solution of triphenylphosphine (5.98 g, 0.0228 mol) in dry toluene (50 mL) was added 4-methoxybenzyl bromide (4.4 g, 0.0217 mol) and the reaction mixture stirred under nitrogen for 3 days. The precipitate was then collected, washed with dry toluene (2 x 20 mL) and dried *in vacuo* to give pale cream crystals. (8 g, 78 %). m.p. = 205 – 207°C (lit.[257] 206 – 207°C).

Crotyl triphenylphosphonium bromide

To a solution of triphenylphosphine (13.2 g, 0.0504 mol) in dry toluene (80 mL) was added crotyl bromide (6.8 g, 0.0504 mol) and the resulting mixture stirred at ambient temperature for 3 days. The precipitate was collected, washed with dry toluene (2 x 50 mL) and dried *in vacuo* to give pale cream crystals. (19.8 g, 99 %). m.p. = 242 – 244°C (lit.[258] 241 – 243°C). ^{1}H NMR: δ = 1.62 (t, 3H), 4.62 (dd, J = 7.0, 14.6 Hz, 2H), 5.20 – 5.40 (m, 1H), 5.80 – 6.10 (m, 1H), 7.65 – 7.91 (m, 15H).

1-Methoxy-4-(1,3-pentadienyl)benzene

From 4-methoxybenzyl triphenylphosphonium bromide and crotonaldehyde

To a stirred suspension of 4-methoxybenzyl triphenylphosphonium bromide (6.4 g, 0.0138 mol) in dry diethyl ether (50 mL) was added potassium *t*-butoxide (1.55 g, 0.0138 mol) portion wise over 10 minutes and the reaction mixture then stirred for a further 10 minutes.

Crotonaldehyde (0.88 g, 0.0126 mol) in diethyl ether (5 mL) was then added dropwise and the reaction mixture stirred for 16 hours. The reaction mixture was then diluted with hexanes (60 mL) and filtered through a 1cm plug of silica. The solvent was removed *in vacuo* and the residue purified by chromatography (hexanes) to give the title compound as a clear colourless oil. (1.6 g, 73 %). R_f = 0.63 (hexanes : ethyl acetate = 9:1). ^{1}H NMR: δ = 1.76 – 1.85 (m, 3H), 3.76 (s, 3H), 5.57 – 5.80 (m, 1H), 6.05 – 6.68 (m, 3H), 6.77 – 6.96 (m, 2H), 7.17 – 7.35 (m, 2H).[259]

From crotyl triphenylphosphonium bromide and anisaldehyde[260]

To a suspension of crotyl triphenylphosphonium bromide (10 g, 0.0252 mol) in diethyl ether (50 mL) was added potassium *t*-butoxide (2.8 g, 0.025 mol) portion wise over 10 minutes and the reaction mixture was stirred for a further 10 minutes. Anisaldehyde (2.85 g, 0.021 mol) in diethyl ether (5 mL) was then added dropwise and the reaction mixture then stirred for 16 hours. The reaction mixture was then diluted with hexanes (100 mL) and filtered through a plug of silica. The solvent was removed *in vacuo* and the residue purified by chromatography (hexanes) to give the title compound as a clear colourless oil. (3.6 g, 99 %). R_f = 0.62 (hexanes : ethyl acetate = 9:1). Spectral data as above.

(±) (3R, 6R)-3-methyl-6-(4-methoxyphenyl)-3,6-dihydro-1,2-dioxine (130)

1-(4-Methoxyphenyl)-1,3-propanediene (1.6 g, 9.19 mmol) was combined with rose bengal *bis* triethylammonium salt (100mg, 8.50 x 10^{-5} mol) in dry dichloromethane (85 mL) and irradiated with 4 x 500W tungsten halogen lamps, at a distance of 15cm from the reaction vessel, in a Pyrex flask, fitted with an external cooling jacket, in the presence of oxygen for 7 hours. The solvent was then removed and the residue purified by chromatography (hexanes : ethyl acetate = 9:1) to give the title compound as a clear colourless oil. (0.66 g 35 %) R_f = 0.44 (hexanes : ethyl acetate = 4:1). ^{1}H NMR: δ = 1.35 (d, *J* = 6.8 Hz, 3H), 3.80 (s, 3H), 4.71 – 4.75 (m, 1H), 5.44 (s, 1H), 6.01 – 6.10 (m, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H).[261]

trans (±) t-Butyl (1R,2R,3S)-2-[2-(4-methoxyphenyl)-2-oxoethyl]-3-methylcyclo-propane-1-carboxylate (131)

(±) (*3R,6R*)-3-methyl-6-(4-methoxyphenyl)-3,6-dihydro-1,2-dioxine (1.32 g, 6.41 mmol) was combined with (*t*-butoxycarbonylmethylene)triphenylphosphorane (3.4 g, 9.04 mmol) and lithium bromide (0.66 g, 7.59 mmol) in dry dichloromethane (80 mL) and stirred under nitrogen for 4½ days. The reaction mixture was filtered and the solvent was then removed *in vacuo*. The residue was purified by chromatography (hexanes : ethyl acetate = 9:1) to give the major *trans* product (0.7 g, 40 %) R_f = 0.11 (hexanes : ethyl acetate = 9:1) and a minor *cis* product (40 mg, 3 %) and the product recrystallised from *n*-heptane as colourless crystals. ^{1}H NMR: δ = 1.10 – 1.18 (m, 1H), 1.22 (d, *J* = 6.0 Hz, 3H), 1.45 (s, 9H), 1.49 (dd, *J* = 5.4, 9.6 Hz, 1H), 1.56 – 1.64 (m, 1H), 2.68 (dd, *J* = 7.8, 16.2 Hz, 1H), 3.13 (dd, *J* = 6.0, 16.2 Hz, 1H), 3.87 (s, 3H), 6.98 (d, *J* = 8.7 Hz, 2H), 7.95 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR: δ = 11.72, 22.88, 23.09, 26.60, 28.23, 55.43, 80.25, 113.80, 129.85, 130.41, 163.55, 171.34, 197.36. MS: *m/z* = 304 (5 %), 248 (15 %), 231 (10 %), 218 (18 %), 159 (25 %), 135 (100 %), 105 (51 %), 77 (22 %), 57 (60 %). HRMS: calculated for $C_{17}H_{24}O_4$ requires 292.1675; found 292.1702.

trans (±) t-Butyl (1R,2R,3S)-2-[2-(4-methoxyphenoxy)-2-oxoethyl]-3-methylcyclo-propane-1-carboxylate

To *trans* (±) *t*-butyl (*1R,2R,3S*)-2-[2-(4-methoxyphenyl)-2-oxoethyl]-3-methyl-cyclopropane-1-carboxylate (0.943 g, 3.10 mmol) in dichloromethane (50 mL) was added *m*-chloroperbenzoic acid (1.456 g, 8.44 mmol) and maleic anhydride (0.29 g, 2.96 mmol) and the reaction mixture stirred away from light for 4 days. Sodium sulfite (saturated, 10 mL) was then added and the reaction mixture stirred for 1 hour. The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were then washed with sodium bicarbonate solution (saturated), the organic phases dried and the solvent removed *in vacuo*. The residue was purified by chromatography (hexanes : ethyl acetate = 9:1) as colourless crystals. (0.92 g, 93 %) R_f = 0.10 (hexanes : ethyl acetate = 9:1). ^{1}H NMR: δ = 1.10 – 1.23 (m, 1H), 1.25 (d, *J* = 10.0 Hz, 3H), 1.56 (s,

9H), 1.53 – 1.66 (m, 2H), 2.41 (dd, *J* = 7.2, 15.8 Hz, 1H), 2.64 (dd, *J* = 6.0, 15.8 Hz, 1H), 3.79 (s, 3H), 6.87 (m, 2H), 7.01 (m, 2H). ^{13}C NMR: δ = 11.63, 22.61, 22.91, 26.54, 28.23, 37.72, 55.55, 80.38, 114.43, 122.19, 144.17, 157.25, 170.91. MS: *m/z* = 320 (10 %), 247 (71 %), 231 (12 %), 124 (100 %), 109 (28 %), 57 (53 %), 41 (37 %). HRMS: calculated for $C_{17}H_{24}O_5$ requires 308.1624; found 308.1638.

trans (±) 2-[(1R,2R,3S)-2-(t-Butoxycarbonyl)-3-methylcyclopropyl]acetic acid (132)

trans (±) *t*-Butyl (*1R,2R,3S*)-2-[2-(4-methoxyphenoxy)-2-oxoethyl]-3-methylcyclo propane-1-carboxylate (0.5 g, 1.56 mmol) was dissolved in methanolic sodium hydroxide (1 M, 20 mL, 1:1 methanol : water) and stirred overnight. The reaction mixture was washed with dichloromethane (20 mL). The aqueous phase acidified to pH 1 with HCl (1 M) and extracted with dichloromethane (2 x 20 mL) and the organic phase dried and the solvent removed *in vacuo*. The residue contained both the desired cyclopropyl acid and 4-methoxyphenol, which was separated by crystallisation (slow evaporation of heptane) as colourless crystals. (251 mg, 75 %). ^{1}H NMR: δ = 1.20 (s, 3H), 1.43 – 1.57 (m, 1H), 1.46 (s, 9H), 2.21 (dd, *J* = 7.2, 16.2 Hz, 1H), 2.49 (dd, *J* = 6.3, 16.2 Hz, 1H). ^{13}C NMR: δ = 11.60, 22.43, 22.50, 26.52, 28.24, 37.35, 55.76, 171.04, 177.86. HRMS: calculated for $C_{11}H_{18}O_4$ requires 214.1205; found 214.1196.

Attempted synthesis of t-Butyl (1R,2S,3S)-2-{2-[(4S)-4-benzyl-2-oxo-1,3-oxazolan-3-yl]-2-oxoethyl}-3-methylcyclopropane-1-carboxylate (133)

***t*-Butyl (*1R,2S,3S*)-2-(2-chloro)-2-oxoethyl)-3-methylcyclopropane-1-carboxylate**

To a cooled solution of *trans* (±) 2-[(*1R,2R,3S*)-2-(*t*-butoxycarbonyl)-3-methylcyclopropyl]acetic acid (251 mg, 1.17 mmol) in dichloromethane (8 mL), with DMF (2 drops), was added a solution of oxalyl chloride (200 mg, 1.57 mmol) in dichloromethane (4 mL) and the reaction mixture allowed to stir for 4 hours. The volatiles were then removed and the acid chloride used without further purification

Attempted synthesis of *t*-Butyl (*1R,2S,3S*)-2-{2-[(*4S*)-4-benzyl-2-oxo-1,3-oxazolan-3-yl]-2-oxoethyl}-3-methyl cyclopropane-1-carboxylate

To a solution of (*S*) 4-benzyl 2-oxazolidinone (207 mg, 1.17 mmol) in THF (4 mL), with triphenylmethane (5 mg, 0.02 mmol), at –78°C was added *n*BuLi (2.5 M in hexanes) until an orange colour persisted. The reaction mixture was then stirred at –78°C for 30 minutes. The acid chloride (1.17 mmol, assumed to be 100% from the last reaction) in THF (3 mL) was then added via a cannula and the reaction mixture allowed to stir at –78°C for 4 hours. The mixture was then poured onto ammonium chloride solution (saturated, 5 mL), diluted with water (5 mL) and extracted with dichloromethane (4 x 10 mL). The organic phase was dried and the solvent removed *in vacuo*.

None of the desired compound was present in the mixture, only diacetimide **(134)** and diacid **(135)** being produced.

(1S,2R,3R)-2-(Carboxymethyl)-3-methylcyclopropane-1-carboxylic acid (135)

Trifluoroacetic acid (0.5 mL) and water (1 mL) were added to a solution of *trans* 2-[(*1R,2R,3S*)-2-*t*-Butoxycarbonyl)-3-methylcyclopropyl]acetic acid (0.19 g, 0.89 mmol) dissolved in dichloromethane (5 mL) and the reaction mixture vigorously stirred for 2 days at ambient temperature. The organic phase was then extracted with water (3 x 20 mL), the aqueous phase washed with dichloromethane (2 x 10 mL) and the water removed *in vacuo*. The residue was then recrystallised from acetone as colourless crystals. m.p. 110 – 112°C. ^{1}H NMR: δ = 1.25 (d, *J* = 6.8 Hz, 3H), 1.27 – 1.30 (m, 1H), 1.53 – 1.65 (m, 2H), 2.35 (dq, *J* = 1.6, 16.5 Hz, 2H). ^{13}C NMR: δ = 11.61, 24.08, 25.13, 37.41, 178.31, 178.60. Anal calculated for $C_7H_{10}O_4$ requires C: 53.15, H: 6.38, found C: 53.15, H: 6.13. MS: *m/z* = 158 (4%), 157 (23%), 156 (20%), 139, 40%, 91 (100%), 65 (56%).

(±) (4S)-4-Benzyl-3-[((1S,2R,3S)-2-{2-[(4S)-4-benzyl-2-oxo-1,3-oxalonan-3-yl]-2-oxoethyl}-3-methylcyclopropyl)carbonyl]-1,3-oxazolan-2-one (134)

(±) (*1R,2R,3S*)-2-(2-Chloro-2-oxoethyl)-3-methylcyclopropane-1-carbonyl chloride

To a cooled solution of (*1S,2R,3R*)-2-(carboxymethyl)-3-methylcyclopropane-1-carboxylic acid (150 mg, 0.95 mmol) combined with DMF (1 drop) in dichloromethane (5 mL) was added oxalyl chloride (700 mg, 5.6 mmol) in dichloromethane (2 mL) and the reaction mixture allowed to stir for 4 hours. The volatiles were then removed and the acid chloride used without further purification.

(±) (*4S*)-4-Benzyl-3-[((*1S,2R,3S*)-2-{2-[(*4S*)-4-benzyl-2-oxo-1,3-oxalonan-3-yl]-2-oxo ethyl}-3-methylcyclopropyl)carbonyl]-1,3-oxazolan-2-one

To a solution of (*S*) 4-benzyl 2-oxazolidinone (369 mg, 2.09 mmol) in THF (8 mL), with triphenylmethane (15 mg, 0.06 mmol), at –78^{o}C was added *n*BuLi (2.5 M in hexanes) until an orange colour persisted. The reaction mixture was then stirred at –78^{o}C for 30 minutes. The acid chloride (0.95 mmol, assumed to be 100% from the last reaction) in THF (5 mL) was then added via a cannula and the reaction mixture allowed to stir at –78^{o}C for 4 hours. The mixture was then poured onto ammonium chloride solution (saturated, 10 mL), diluted with water (10 mL) and extracted with dichloromethane (4 x 15 mL). The organic phase was dried, the solvent removed *in vacuo* and the residue purified by chromatography (hexanes : ethyl acetate = 1:1) (135 mg, 81 %) The diastereomers were inseparable by chromatography and recrystallisation. ^{1}H NMR: (600 MHz) δ = 1.23 (d, *J* = 6.0 Hz, 3H), 1.49 (dquin, *J* = 6.6, 9.0 Hz, 1H), 1.92 (dq, *J* = 5.4, 6.6 Hz, 1H), 2.78 (dd, *J* = 9.6, 13.2 Hz, 1H), 2.83 (dd, *J* = 9.0, 13.2 Hz, 1H), 2.96 (dd, *J* = 7.2, 18.0 Hz, 1H), 3.02 (dd, *J* = 5.4, 9.0 Hz, 1H), 3.12 (dd, *J* = 6.6, 18.0 Hz, 1H), 3.16 (d br t, *J* = 2.4, 13.8 Hz, 2H), 4.13 – 4.23 (m, 4H), 4.67 (ddt, *J* = 3.0, 10.8, 12.6 Hz, 11H), 4.71 (ddt, *J* = 3.0, 7.8, 9.6 Hz, 1H), 7.18 – 7.33 (m, 10H). ^{13}C NMR: δ = 11.73, 24.21, 25.29, 25.60, 37.83, 37.90. 38.98, 55.11, 55.28, 65.83, 66.29, 127.23, 127.35, 128.89, 128.95, 129.40, 129.53, 135.18, 135.32. 153.49, 153.85, 170.86, 171.49. Anal

calculated for $C_{27}H_{27}N_2O_6$ requires C: 68.04, H: 5.93, N: 5.88, found C: 68.03, H: 6.07, N: 5.84. MS: *m/z* = 475 (8%), 300 (42%), 258 (60%), 178 (98%), 43 (100%).

(4S) 3-{2-[(1S,2R,3R)-2-benzoyl-3-phenylcyclopropyl]acetyl}-4-benzyl-1,3-oxazolan-2-one and (4S) 3-{2-[(1R,2S,3S)-2-benzoyl-3-phenylcyclopropyl]acetyl}-4-benzyl-1,3-oxazolan-2-one (138 and 139)[229]

trans (±) 2-[(*1R,2R,3S*)-2-benzoyl-3-phenylcyclopropyl]acetic acid (136)

(±) Benzyl 2-[(*1S,2R,3R*)]-2-benzoyl-3-phenylcyclopropyl]acetate (1.076 g, 2.908 mmol) was dissolved in methanolic sodium hydroxide (1 M, 50 mL, 1:1 methanol: water) and methanol (30 mL) and the reaction mixture stirred overnight. The reaction mixture was then extracted with dichloromethane (30 mL). The aqueous phase acidified to pH = 1 with HCl (1 M) and then extracted with dichloromethane (2 x 30 mL), the organic phase washed with brine, dried and the solvent removed *in vacuo* to give the title compound as colourless crystals. (0.66 g, 78 %).

trans (±) 2-[(*1R,2R,3S*)-2-benzoyl-3-phenylcyclopropyl]acetyl chloride (137)[247]

To a solution of *trans* (±) 2-[(*1R,2R,3S*)-2-benzoyl-3-phenylcyclopropyl]acetic acid (0.394 g, 1.41 mmol) in dry dichloromethane (8 mL) and DMF (1 drop), at 0°C under nitrogen, was added oxalyl chloride (0.291 g, 2.29 mmol) in dichloromethane (4 mL) dropwise over 5 minutes. The reaction mixture was then stirred at 0°C for 2 ½ hours and a further 2 hours at ambient temperature. The volatiles were then removed.

(*4S*) 3-{2-[(*1S,2R,3R*)-2-benzoyl-3-phenylcyclopropyl]acetyl}-4-benzyl-1,3-oxazolan-2-one and (*4S*) 3-{2-[(*1R,2S,3S*)-2-benzoyl-3-phenylcyclopropyl]acetyl}-4-benzyl-1,3-oxazolan-2-one (138 and 139)

To a solution of (S)-4-benzyl-2-oxazolidinone (0.252 g, 1.43 mmol) in THF (4 mL) with triphenylmethane (indicator, 5 mg, 2.05 x 10^{-5} mol), at –78°C under nitrogen, was added *n*-BuLi (1.9 M in hexanes) until an orange colour persisted. The reaction mixture was then

stirred at –78°C for ½ hour after which time the acid chloride in THF (3 mL) was added via a cannula. The reaction was then stirred at –78°C for 4 hours then poured into NH_4Cl (sat. 10 mL) immediately, diluted with water (10 mL) and extracted with dichloromethane (2 x 30 mL). The combined organic phases were dried and the solvent removed *in vacuo*. The residue was purified by chromatography (hexanes : ethyl acetate = 3:1) with separation of the diastereomers. (0.371 g, 60 % total yield, 1:1 mixture of the diastereomers). **Diasteromer 1 (top spot).** Colourless crystals. R_f 0.20 (hexanes : ethyl acetate = 5:1). m.p. = 177 – 178°C. $[\alpha]_D^{23}$ = -39.24 (c = 2.064, CH_2Cl_2). IR: (CH_2Cl_2) 1668, 1703, 1780 cm^{-1}. ^1H NMR: (600MHz) δ = 2.42 – 2.46 (m, 1H), 2.67 (dd, *J* = 9.6, 13.2 Hz, 1H), 2.93 (dd, *J* = 7.2, 17.4 Hz, 1H), 2.99 (dd, *J* = 7.8, 17.4 Hz, 1H), 3.16 (dd, *J* = 4.8, 9.6 Hz, 1H), 3.23 (dd, *J* = 4.8, 9.6 Hz, 2H), 4.06 (t, *J* = 8.4 Hz, 1H), 4.08 (dd, *J* = 9.3 Hz, 1H), 4.51 – 4.55 (m, 1H), 7.15 (d, *J* = 7.2 Hz, 2H), 7.22 – 7.26 (m, 2H), 7.28 – 7.34 (m, 6H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.61 (tt, *J* = 1.2, 7.2 Hz, 1H), 8.08 – 8.10 (m, 2H). ^{13}C NMR: δ = 27.16, 29.01, 33.60, 33.83, 37.81, 55.08, 66.18, 126.93, 127.36, 128.19, 128.43, 128.69, 128.79. 128.94, 129.35, 133.05, 135.11, 135.88, 137.72, 171.61. Anal calculated for $C_{28}H_{25}NO_4$ requires C: 76.51, H: 5.74, found C: 76.63, H: 5.65. MS: *m/z* 440.2 (42 %, $[M+H]^+$), 422.2 (8 %), 263.1 (100 %), 221.1 (37 %). HRMS: $C_{28}H_{25}NO_4$ + H requires 440.1861, found 440.1875 ($[M+H]^+$). **Diastereomer 2 (bottom spot)**. Colourless crystals. m.p. 168.5 – 169.5°C. R_f 0.13 (hexanes : ethyl acetate = 5:1). $[\alpha]_D^{23}$ = 97.87 (c = 0.891, CH_2Cl_2). IR: (CH_2Cl_2) 1668, 1703, 1782 cm^{-1}. ^1H NMR: (600MHz) δ = 2.46 (tt, *J* = 6.6, 7.8Hz, 1H), 2.59 (dd, *J* = 9.0, 13.8 Hz, 1H), 2.93 (dd, *J* = 6.6, 18 Hz, 1H), 2.99 (dd, *J* = 7.8, 17.4 Hz, 1H), 3.05 (dd, *J* = 3.6, 13.8 Hz, 1H), 3.21 (d, *J* = 6.0 Hz, 2H), 4.09 (dd, *J* = 3, 9 Hz, 1H), 4.13 (t, *J* = 7.8 Hz, 1H), 4.60 – 4.64 (m, 1H), 7.02 (dd, *J* = 1.8, 7.8 Hz, 2H), 7.24 – 7.28 (m, 4H), 7.33 (d, *J* = 4.2 Hz, 4H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.59 (tt, *J* = 1.8, 7.8 Hz, 1H), 8.09 – 8.10 (m, 2H). ^{13}C NMR: (600MHz) δ = 26.94, 28.81, 33.75, 34.31, 37.47, 54.75, 66.09, 127.02, 127.34, 128.16, 128.48, 128.67, 128.88, 128.92, 129.35, 133.04, 134.87, 135.88, 137.72, 153.30, 171.45, 198.39. Anal. calculated for $C_{28}H_{25}NO_4$ requires: C: 76.51, H: 5.74, found C: 76.49, H: 5.68. MS: *m/z* 440.1 (45 %,

$[M+H]^+$), 422.1 (10 %), 263.1 (100 %), 221.1 (34 %). HRMS: $C_{28}H_{25}NO_4$ + H requires 440.1861, found 440.1871 ($[M+H]^+$).

Attempted synthesis of (4S)-3-{(2R)-2-Azido-2-[(1R,2R,3S)-2-benzoyl-3-phenylcyclopropyl]ethanoyl}-4-benzoyl-1,3-oxazolan-2-one (142)

To a solution of potassium *bis*(TMS)amide (1.4 mL, 0.5 M in hexanes), diluted in THF (6 mL), at –78°C was added the cyclopropane in THF (12 mL) at –78°C via a Teflon™ cannula and the reaction mixture stirred at –78°C for 20 minutes.

A solution of the 2,4,6-triisopropylbenzene sulphonyl azide in THF (3 mL) at –78°C was then added via a Teflon™ cannula and the reaction mixture stirred for 30 minutes at –78°C. The reaction mixture was immediately warmed to 30°C and stirred for 2 hours. The mixture was diluted with ethyl acetate (10 mL) and brine (10 mL), the phases separated and the aqueous phase extracted with ethyl acetate (2 x 10 mL). The combined organic phases were washed with sodium bicarbonate solution (10%), dried and the solvent removed *in vacuo*. The residue did not contain any of the desired product.

Racemic trans-(±)-[((1R,2R,3S)-2-Benzoyl-3-phenylcyclopropyl)methyl]-2,2,2-trifluoro-acetimide (143)

trans (±) 2-[(*1R,2R,3S*)-2-Benzoyl-3-phenylcyclopropyl]acetic acid (342 mg, 1.22 mmol) was combined with thionyl chloride (435 mg, 3.66 mmol) in dichloromethane (10 mL) and heated at reflux for 4 hours. The volatiles were then removed, the residue redissolved in dichloromethane (5 mL) with tetrabutylammonium bromide (10 mg, 0.03 mmol) and then cooled to 0°C. Sodium azide (95 mg, 1.46 mmol) in water (0.1 mL) was then added and the reaction mixture stirred vigorously at 0°C for 2 hours. The reaction mixture was diluted with dichloromethane (5 mL)) and water (5 mL)), the phases separated and the organic layer dried ($MgSO_4$). After standing for 16 hours trifluoroacetic acid (200 mg) was added to the filtered solution and the reaction mixture allowed to reflux for 6 hours. The cooled reaction mixture was washed with sodium bicarbonate solution (saturated), dried ($MgSO_4$), and the solvent

removed *in vacuo*. The residue was purified by chromatography (hexanes : ethyl acetate = 4:1) (320 mg, 75 %) as colourless crystals. R_f = 0.33 (hexanes : ethyl acetate = 4:1). m.p. = 144 – 145°C. IR: = 705, 745, 1045, 1165, 1309, 1377, 1458, 1551, 2360, 3355 cm^{-1}. ^1H NMR: δ = 2.24 – 2.29 (m, 1H), 3.11 (dd, *J* = 5.1, 9.3 Hz, 1H), 3.22 (ddd, *J* = 5.6, 5.7, 14.1 Hz, 1H), 3.31 (t, *J* = 4.5 Hz, 1H), 3.44 (m, 1H), 6.67 (bs, 1H), 7.26 – 7.51 (m, 5H), 7.52 – 7.54 (m, 2H), 7.61 – 7.63 (m, 1H), 8.05 – 8.07 (m, 2H). ^{13}C NMR: δ = 28.47, 29.56, 33.26, 38.76, 127.39, 128.12, 128.46, 128.75, 128.83, 133.34, 135.04, 137.25, 157.26 (q, *J* = 36.7 Hz, $\underline{C}(O)CF_3$), 197.87, CF_3 too broad to be observed. MS: *m/*z = 347 (M^+, 1 %), 234 (8 %), 221 (50 %), 157 (82 %), 129 (59 %), 105 (100 %), 77 (36 %), 51 (11 %). HRMS: calculated for $C_{19}H_{16}NO_2F_3$ requires 347.1133, found 347.1182.

Enantiopure trans-(±)-[((1R,2R,3S)-2-Benzoyl-3-phenylcyclopropyl)methyl]-2,2,2-trifluoro-acetimide (143)

Enantiopure trans (±) 2-[(*1R,2R,3S*)-2-benzoyl-3-phenylcyclopropyl]acetic acid (136)

To a solution of the enantiopure cyclopropane **(138 or 139)** (0.357 g, 1.22 mmol) in a 3:1 mixture of THF and water (25 mL), at 0°C, was added aqueous hydrogen peroxide (30%, 1 mL) and lithium hydroxide (0.21 g, 8.77 mmol) and the reaction mixture allowed to stir for 30 minutes at room temperature. The reaction mixture was quenched with sodium sulfite (2.04g) and the THF removed *in vacuo*. The aqueous solution was washed with dichloromethane (20 mL), cooled to 0°C, acidified to pH 1 with hydrochloric acid (10%) then extracted with dichloromethane (2 x 20 mL). The organic phase was dried and the solvent removed *in vacuo*. (0.34 g, 99%)

Enantiopure trans-(±)-[((*1R,2R,3S*)-2-Benzoyl-3-phenylcyclopropyl)methyl]-2,2,2-trifluoro-acetimide (143)

The method used for the synthesis of the optically pure example was exactly that used for the racemic example (above) with all data identical for the two samples. For the optically pure example synthesised $[\alpha]_D^{23}$ = 11.14 (c = 0.678, CH_2Cl_2)

Phenyl (1R,2R,3S)-2-phenyl-3-{[(2,2,2-trifluoroacetyl)amino]methyl}-1-cyclo-propane carboxylate (146)

To a solution or maleic anhydride (29 mg, 0.296 mmol) in dichloromethane (3 mL) at 0°C was added hydrogen peroxide (30 %, 0.5 mL) and the reaction mixture allowed to stir at 0°C for 10 minutes. trans-(±)-[((*1R,2R,3S*)-2-Benzoyl-3-phenylcyclopropyl)methyl]-2,2,2-trifluoroacetimide (104.7 mg, 0.302 mmol) in dichloromethane (5 mL) was then added and the reaction mixture vigorously stirred at 0°C for 8 hours. The reaction was quenched by the addition of potassium hydroxide solution (2 %, 5 mL), the phases separated and the aqueous phase extracted with dichloromethane. The combined organic extracts were dried, the solvent removed *in vacuo* and the residue purified by chromatography (hexanes : ethyl acetate = 4:1) as colourless crystals. (87.6 mg, 80 %). R_f = 0.30 (hexanes : ethyl acetate = 4:1). m.p. = 98 – 99°C. IR: = 702, 1172, 1377, 1456, 1697, 1731, 3075, 3340 cm^{-1}. ^1H NMR: δ = 2.19 – 2.23 (m, 1H), 2.44 (t, *J* = 5.0 Hz, 1H), 3.11 (ddd, *J* = 5.2, 7.8, 17 Hz, 1H), 3.45 (m, 1H), 6.38 (bs, 1H), 7.04 – 7.41 (m, 10H). ^{13}C NMR: δ = 23.98, 27.16, 30.98, 38.39, 113.78, 121.36, 125.99, 127.58, 128.89, 129.44, 134.10, 157.11 (q, *J* = 36.75, $\underline{C}(O)CF_3$) 171.08. MS: *m/z* = 363 (M^+, 1 %), 270 (4 %), 234 (12 %), 221 (54 %), 157 (20 %), 129 (20 %), 105 (100 %), 77 (28 %). HRMS: calculated for $C_{19}H_{16}NO_3F_3$ requires 363.1082, found 363.1071.

trans (±) Phenyl-2-[2-benzyloxy)-2-oxoethyl]-3-phenylcyclopropane-1-carboxylate

(±) Benzyl 2-[(*1S,2R,3R*)]-2-benzoyl-3-phenylcyclopropyl]acetate (1.0 g, 2.7 mmol) was dissolved in dichloromethane (11 mL). *m*CPBA (1.65 g, 65%, 6 mmol) and hydrogen peroxide (10 mL, 30 %) were added and the reaction mixture stirred, protected from light, for 4 weeks. The reaction mixture was filtered, the solution washed with sodium bicarbonate solution (saturated), dried and the solvent removed *in vacuo*. The residue was purified by chromatography (hexanes : ethyl acetate = 4:1) as colourless crystals. (0.99 g, 94%). R_f = 0.50 (benzene ether = 19:1). ^1H NMR: δ = 2.26-2.29 (m, 4H), 3.05 (dd, *J* = 5.7, 8.9 Hz), 5.09 and 5.11 (AB_q, *J* = 12.4 Hz, 2H), 7.08 – 7.11 (m, 2H), 7.20 – 7.40 (m, 13H).[63]

(1S,2R,3R)-2-(Carboxyphenyl)-3-phenylcyclopropane-1-carboxylic acid (145)

(±) Phenyl-2-[2-benzyloxy)-2-oxoethyl]-3-phenylcyclopropane-1-carboxylate (0.99 g, 2.56 mmol) was dissolved in methanol (15 mL). Potassium hydroxide solution (2 M, 15 mL) was then added and the reaction mixture stirred at ambient temperature for 16 hours. The reaction mixture was diluted with water (15 mL) and washed with dichloromethane (3 x 15 mL). The aqueous phase was acidified to pH = 1 and extracted with dichloromethane (3 x 15 mL). The organic phase was dried and the solvent removed *invacuo* to give the crude diacid which was recrystallised from acetone as colourless crystals. (0.42 g, 74%). m.p. = 184 – 185°C (lit.[63] 185 – 187°C). ^{1}H NMR: δ = 1.98 (dd, *J* = 9.0, 16.8 Hz, 1H), 2.07 (dd, *J* = 4.8, 4.7 Hz, 1H), 2.18 (dddd, *J* = 4.8, 5.4, 9.0, 9.6 Hz, 1H), 2.36 (dd, *J* = 5.4, 16.8 Hz, 1H), 2.96 (dd, *J* = 4.8, 9.6 Hz, 1H), 7.16 – 7.32 (m, 5H).[63]

Attempted synthesis of (±) N 1-({(1S,2R,3R)-2-methyl-3-[(2,2,2-trifluoroacetyl)amino]cyclopropyl} methyl)-2,2,2-trifluoroacetamide (146)

(*1S,2R,3R*)-2-(Carboxymethyl)-3-methylcyclopropane-1-carboxylic acid (200 mg, 1.27 mmol) was combined with thionyl chloride (0.9 g, 7.6 mmol) in dichloromethane (5 mL) and heated at reflux for 5 hours. The reaction mixture was cooled to ambient temperature and the volatiles removed. The residue was dissolved in dichloromethane (5 mL) with tetrabutylammonium bromide (10 mg) and cooled to 0°C. Sodium azide (199 mg, 3.01 mmol) in water (0.1 mL) was then added and the reaction mixture stirred vigorously for 3 hours at 0°C. The mixture was washed with water (10 mL) and dried ($MgSO_4$) over 24 hours. Trifluoroacetic acid (0.5 mL) was then added and the mixture refluxed for 5 hours. After cooling to ambient temperature the mixture was washed with water, dried and the solvent removed *in vacuo*. The complex mixture could not be purified by chromatography and did not contain any compound resembling the diamine.

Attempted synthesis of (±) N 1-({(1R,2S,3S)-2-Phenyl-3-[(2,2,2-trifluoroacetyl)amino]cyclopropyl} methyl)-2,2,2-trifluoroacetamide (147)

(*1S,2R,3R*)-2-(Carboxyphenyl)-3-phenylcyclopropane-1-carboxylic acid (145 mg, 0.66 mmol) was combined with thionyl chloride (0.6 g, 5.1 mmol) in dichloromethane (4 mL) and heated at reflux for 5 hours. The reaction mixture was cooled to ambient temperature and the volatiles removed. The residue was dissolved in dichloromethane (5 mL) with tetrabutylammonium bromide (10 mg) and cooled to 0°C. Sodium azide (170 mg, 2.61 mmol) in water (0.1 mL) was then added and the reaction mixture stirred vigorously for 3 hours at 0°C. The mixture was washed with water (10 mL) and dried ($MgSO_4$) over 24 hours. Trifluoroacetic acid (0.5 mL) was then added and the mixture refluxed for 5 hours. After cooling to ambient temperature the mixture was washed with water (10 mL), dried and the solvent removed *in vacuo*. The complex mixture could not be purified by chromatography and did not contain any compound resembling the diamine.

(±) 2-[(1S,2R,3R)-2-(Hydroxymethyl)-3-phenylcyclopropyl]-1-ethanol (148)

Borane-THF complex (1.5M in THF, 5 mL) was added to a solution of (*1S,2R,3R*)-2-(carboxyphenyl)-3-phenylcyclopropane-1-carboxylic acid (350 mg, 1.6 mmol) in THF (5 mL) and the reaction mixture allowed to stir for 3 days. HCl (10 %, 10 mL) was then added at such a rate that the evolution of hydrogen gas was controlled. The mixture was diluted with dichloromethane (30 mL) and the phases separated. The organic phase was washed with sodium bicarbonate solution (saturated), dried and the solvent removed *in vacuo*. The residue was purified by chromatography (dichloromethane) as a clear colourless oil. (285 mg, 92 %). R_f = 0.10 (hexanes : ethyl acetate = 4:1). IR: (neat) = 911, 1025, 1196, 1455, 1495, 1601, 1743, 2933, 3030, 3402 cm^{-1}. ^1H NMR: δ = 1.32 – 1.46 (m, 2H), 1.50 – 1.60 (m, 3H), 3.64 (t, *J* = 6.6 Hz, 2H), 3.65 (t, *J* = 6.6 Hz, 2H), 7.20 – 7.41 (m, 5H). ^{13}C NMR: δ =24.84, 26.60, 30.29, 31.64, 61.60, 64.89, 128.24, 128.31, 128.61, 129.25. MS: *m/z* = 192 (M^+, 6%), 115 (60%). HRMS: calculated for $C_{12}H_{16}O_2$ requires 192.1150; found 192.1152.

References

(1) Suckling, C. J. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 537.

(2) Liu, H. W.; Walsh, C. T. In *The Chemistry of the Cyclopropyl group*; Rappoport, Z., Ed.; Wiley: New York, 1987.

(3) Pettus, J. J. A.; Moore, R. E. *J. Chem. Soc.* **1970**, 1093.

(4) Hofmann, K.; Lucas, R. A. *J. Am. Chem. Soc.* **1950**, *72*, 4328.

(5) Marques, M. A. M.; Chitale, S.; Brennan, P. J.; Pessolani, M. C. V. *Infection and Immunity* **1998**, *66*, 2625.

(6) Connor, D. T.; Greenough, R. C.; Strandtmann, M. v. *J. Org. Chem.* **1977**, *42*, 3664.

(7) Connor, D. T.; Strandtmann, M. v. *J. Org. Chem.* **1978**, *43*, 4606.

(8) Ravi, B. N.; Kokke, W. C. M. C.; Delseth, C.; Djerassi, C. *Tetrahedron Lett.* **1978**, 4379.

(9) Mitome, H.; Miyaoka, H.; Nakano, M.; Yamada, Y. *Tetrahedron Lett.* **1995**, *36*, 8231.

(10) Cottens, S.; Schlosser, M. *Tetrahedron* **1988**, *44*, 7127.

(11) Burroughs, L. F. *Nature* **1957**, *179*, 360.

(12) Vilsmaier, E. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987.

(13) Ruiz, N. *International Journal of Clinical Practice* **1999**, *Supplement 103*, 3.

(14) Staszewski, S.; Morales-Ramirez, J.; Tashima, K. T.; Rachlis, A.; Skiest, D.; Stanford, J.; Stryker, R.; Johnson, P.; Labriola, D. F.; Farina, D.; Manion, D. J.; Ruiz, N. M. *The New England Journal of Medicine* **1999**, *341*, 1865.

(15) Martin, S. F.; Dwyer, M. P.; Hartmann, B.; Knight, K. S. *J. Org. Chem.* **2000**, *65*, 1305.

(16) Weiner, D. B.; Williams, W. V., Eds. *Biological Approaches to Rational Drug Design*; CRC Press:, 1995.

(17) Salaun, J. *Chem. Rev.* **1989**, *89*, 1247.

(18) *Drug Stereochemistry Analytical Methods and Pharmacology*; Second ed.; Marcel Dekker: New York, 1993.

(19) Carless, H. A. J. *Tetrahedron: Asymm.* **1992**, *3*, 795.

(20) Banwell, M. G.; Forman, G. S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2565.

(21) Baumstark, A. L.; McCluskey, C. J.; Tolsom, T. J. *Tetrahedron Lett.* **1977**, *35*, 3003.

(22) Walborsky, H. M.; Murari, M. P. *J. Am. Chem. Soc.* **1980**, *102*, 427.

(23) Rippoll, J. L.; Lamasset, J. C.; Conia, J.-M. *Tetrahedron* **1971**, *27*, 2431.

(24) Wiberg, K. B.; Burgmaier, G. J. *J. Am. Chem. Soc.* **1972**, *94*, 7396.

(25) Sicjaa, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 130.

(26) Newman, M. S.; LeBlanc, J. R.; Karnes, H. A.; Axelrad, G. *J. Am. Chem. Soc.* **1964**, *86*, 868.

(27) Tsuji, T.; Nishida, S. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987.

(28) Charette, A. B.; Lebel, H.; Gagnon, A. *Tetrahedron* **1999**, *55*, 8845.

(29) Denmark, S. E.; Edwards, J. P.; Wilson, S. R. *J. Am. Chem. Soc.* **1992**, *114*, 2592.

(30) Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*, 7919.

(31) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323.

(32) Wittig, G.; Schwarzenbach, K. *Angew. Chem.* **1959**, *71*, 652.

(33) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, *28*, 3353.

(34) Nishimura, J.; Kawabata, N.; Furukawa, J. *Tetrahedron* **1969**, *25*, 2647.

(35) Denmark, S. E.; Christenson, B. L.; O'Connor, S. P. *Pure and Appl. Chem.* **1996**, *68*, 23.

(36) Charette, A. B.; Brochu, C. *J. Am. Chem. Soc.* **1995**, *117*, 11367.

(37) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651.

(38) Charette, A. B.; Marcoux, J.-F. *Synlett* **1995**, 137.

(39) Falck, J. R.; Mekonnen, B.; Yu, J.; Lai, J.-Y. *J. Am. Chem. Soc.* **1996**, *118*, 6096.

(40) Barrett, A. G. M.; Kasdorf, K. *J. Am. Chem. Soc.* **1996**, *118*, 11030.

(41) Charette, A. B.; Lebel, H. *J. Am. Chem. Soc.* **1996**, *118*, 10327.

(42) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.

(43) Ichiyanagi, T.; Shimizu, M.; Fujisawa, T. *Tetrahedron* **1997**, *53*, 9599.

(44) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763.

(45) Skell, P. S. *Tetrahedron* **1985**, *41*, 1427.

(46) Skell, P. S.; Woodworth, R. C. *J. Am. Chem. Soc.* **1956**, *78*, 4496.

(47) March, J. *Advanced Organic Chemistry*; 4th ed.; John Wiley and Sons: New York, 1991.

(48) Alcarez, C.; Fernandez, M.; Frutos, M. P. d.; Marlo, J. L.; Bernabe, M. *Tetrahedron* **1994**, *1994*, 43.

(49) Rispens, M. T.; Keller, E.; de Lange, B.; Zijlstra, R. W. J.; Feringa, B. L. *Tetrahedron: Asymm.* **1994**, *5*, 607.

(50) Martin-Vila, M.; Hanafi, N.; Jimenez, J. M.; Alvarez-Larena, A.; Piniella, J. F.; Brandchadell, V.; Oliva, A.; Ortuna, R. M. *J. Org. Chem.* **1998**, *63*, 3581.

(51) van Auken, T. V.; Rinehart, K. C. *J. Am. Chem. Soc.* **1962**, *14*, 3736.

(52) Adam, W.; de Lucchi, O. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 762.

(53) Thebtaranonth, C.; Thebtaranonth, Y. *Cyclization Reactions*; CRC Press: Boca Raton, 1994.

(54) Li, A.-H.; Dai, L.-X. *Chem. Rev.* **1997**, *97*, 2351.

(55) Romo, D.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 6265.

(56) Calmes, M.; Daunis, J.; Escale, F. *Tetrahedron: Asymm.* **1996**, *7*, 395.

(57) Krief, A.; Provins, L.; Froidbise, A. *Tetrahedron Lett.* **1998**, *39*, 1437.

(58) Hamdouchi, C. *Tetrahedron Lett.* **1992**, *33*, 1701.

(59) Avery, T. D.; Taylor, D. K.; Tiekink, E. R. T. *J. Org. Chem.* **2000**, *65*, 5531.

(60) Rathbone, T. J. In *Dept. of Chem.*; Monash University: Melbourne, 1996.

(61) Haselgrove, T. In *Dept. of Chem.*; University of Adelaide: Adelaide, 1997.

(62) Avery, T. D. In *Dept. of Chem.*; University of Adelaide: Adelaide, 1997.

(63) Avery, T. D. In *Dept. of Chem.*; University of Adelaide: Adelaide, 2001.

(64) Avery, T. D.; Fallon, G.; Greatrex, B.; Pyke, S. M.; Taylor, D. K.; Tiekink, E. R. T. *J. Org. Chem.* **2001**, *66*, 7955.

(65) Avery, T. D.; Haselgrove, T. D.; Rathbone, T. J.; Taylor, D. K.; Tiekink, E. R. T. *Chem. Commun* **1998**, 333.

(66) Palmer, F. N. In *Dept. of Chem.*; University of Adelaide: Adelaide, 2000.

(67) Palmer, F. N.; Taylor, D. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1323.

(68) O'Shea, K. E.; Foote, C. S. *J. Org. Chem.* **1989**, *54*, 3475.

(69) Bredig, G.; Fiske, P. S. *Biochem Z* **1912**, *46*, 7.

(70) Shibata, Y.; Tsuchida, R. *Bull. Chem. Soc. Jpn.* **1929**, *4*, 142.

(71) Shibata, Y.; Tanaka, Y.; Goda, S. *Bull. Chem. Soc. Jpn.* **1931**, *6*, 210.

(72) Nozaki, H.; Moruiti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, *22*, 5239.

(73) Osborn, J. A.; Jardine, F. S.; Young, J. F.; Wilkinson, G. *J. Chem. Soc.* **1966**, 1711.

(74) Horner, L.; Siegel, H.; Buthe, H. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 942.

(75) Knowles, W. S.; Sabacky, M. J. *J. Chem. Soc., Chem. Commun.* **1968**, 1445.

(76) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

(77) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

(78) Pfeiffer, P.; Breith, E.; Lubbe, E.; Tsumaki, T. *Annales* **1933**, *503*, 84.

(79) Tsumaki, T. *Bull. Chem. Soc. Jpn.* **1938**, *13*, 252.

(80) Diehl, H.; Hach, C. C. In *Inorganic Syntheses*; Audrieth, L. F., Ed.; M^{c}Graw-Hill: New York, 1950; Vol. 3, p 196.

(81) Fedeli, E.; Capella, P.; Livraghi, G.; Acampora, G.; Jacini, G. *Riv. Ital. Sostanze Grasse* **1963**, *40*, 300.

(82) Garnier, M.; Pallaud, R. *Compt. Rend.* **1965**, *261*, 3154.

(83) Rouchard, J. *Bull. Soc. Chimiques* **1967**, *76*, 171.

(84) van Dort, H. M.; Geursen, H. J. *Recueil* **1967**, *86*, 520.

(85) Belokon, Y.; Ikonnikov, N.; Moscalenko, M.; North, M.; Orlova, S.; Tararov, V.; Yashkina, L. *Tetrahedron: Asymm.* **1996**, *7*, 851.

(86) Belokon, Y. N.; Caveda-Cepas, S. *J. Am. Chem. Soc* **1999**, *121*, 3968.

(87) Belokon, Y. N.; North, M. *Tetrahedron Lett.* **1999**, *40*, 6105.

(88) Zolezzi, S.; Decinti, A.; Spodine, E. *Polyhedron* **1999**, *18*, 897.

(89) Samsel, E. G.; Srinivasan, K.; Kochi, J. K. *J. Am. Chem. Soc.* **1985**, *107*, 7606.

(90) Schaus, S. E.; Larrow, J. F. *J. Org. Chem.* **1997**, *62*, 4197.

(91) Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309.

(92) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345.

(93) Zhang, W.; Leobach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801.

(94) Suzuki, M.; Oda, Y.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 4413.

(95) Turner, J. A.; Herz, W. *J. Org. Chem.* **1977**, *42*, 1895.

(96) Mukherjee, R. N.; Abrahamson, A. J.; Patterson, G. S.; Stack, T. D. P.; Holm, R. H. *Inorg. Chem.* **1988**, *27*, 2137.

(97) Ogho, Y.; Takeuchi, S.; Natori, Y.; Yoshimura, J. *Chem. Lett.* **1974**, 33.

(98) Ohgo, Y.; Natori, Y.; Takeuchi, S.; Yoshimura, J. *Chem. Lett.* **1974**, 709.

(99) Tatsuno, Y.; Konishi, A.; Nakamura, A.; Otsuka, S. *J. Chem. Soc., Chem. Commun.* **1974**, 588.

(100) Nishinaga, A.; Yamato, H.; Abe, T.; Maruyama, K.; Matsuura, T. *Tetrahedron Lett.* **1988**, *29*, 6309.

(101) Fukuda, T.; Katsuki, T. *Tetrahedron* **1997**, *53*, 7201.

(102) Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3647.

(103) Fukuda, T.; Katsuki, T. *Synlett* **1995**, 825.

(104) Ito, Y. N.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 603.

(105) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 2687.

(106) Jacobsen, E. N.; Kakiuch, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, *38*, 773.

(107) Brandes, B. D.; Jacobsen, E. N. *Tetrahedron: Asymm.* **1997**, *8*, 3927.

(108) Canali, L.; Sherrington, D. C. *Chem. Soc. Rev.* **1999**, *28*, 85.

(109) Fukuda, T.; Irie, R. *Tetrahedron* **1999**, *55*, 649.

(110) Frostin-Rio, M.; Pujol, D.; Bied-Charreton, C.; Perree-Fauvet, M.; Gaudemer, A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1971.

(111) Hassanein, M.; Abdel-Hay, F. L.; El-Hefnawy El-Esawy, T. *Eur. Polym. J.* **1994**, *30*, 335.

(112) Sasaki, I.; Pujol, D.; Gaudemer, A. *Inorgan. Chim. Acta* **1987**, *134*, 53.

(113) Yamada, M.; Araki, K.; Shiraishi, S. *J. Chem. Soc., Chem. Commun.* **1988**, 530.

(114) Musie, G. T.; Wei, M.; Subramaniam, B.; Busch, D. H. *Inorg. Chem.* **2001**, *40*, 3336.

(115) Goto, M.; Koyama, M.; Usui, H.; Mouri, M.; Mori, K.; Sakai, T. *Chem. Pharm. Bull.* **1985**, *33*, 927.

(116) Halle, R. t.; Breheret, A.; Schulz, E.; Pinel, C.; Lemaire, M. *Tetrahedron: Asymm.* **1997**, *8*, 2101.

(117) Nagata, T.; Imagawa, K.; Yamada, T. *Inorgan. Chim. Acta* **1994**, *220*, 283.

(118) Nagata, T.; Imagawa, K.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1994**, 1259.

(119) Nagata, T.; Imagawa, K.; Yamada, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1455.

(120) Nagata, T.; Yorozu, K. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2145.

(121) Yamada, T.; Nagata, T.; Ikeno, T.; Ohtsuka, Y.; Sagara, A.; Mukaiyama, T. *Inorgan. Chim. Acta* **1999**, *296*, 86.

(122) Ohtsuka, Y.; Miyazaki, D.; Ikeno, T.; Yamada, T. *Chem. Lett.* **2002**, 24.

(123) Ohtsuka, Y.; Ikeno, T.; Yamada, T. *Tetrahedron: Asymm.* **2000**, *11*, 3671.

(124) Ohtsuka, Y.; Kiichirou, K.; Ikeno, T.; Yamada, T. *Org. Lett.* **2001**, *3*, 2543.

(125) Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Org. Lett.* **2002**, *4*, 2457.

(126) Kezuka, S.; Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Chem. Lett.* **2000**, 824.

(127) Ikeno, T.; Nishizuka, A.; Sato, M.; Yamada, T. *Synlett* **2001**, *3*, 406.

(128) Ikeno, T.; Sato, M.; Yamada, T. *Chem. Lett.* **1999**, 1345.

(129) Nozaki, H.; Takaya, H.; Moriuti, S. *Tetrahedron* **1968**, *24*, 3655.

(130) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1975**, 1707.

(131) Nakamura, A.; Konishi, A.; Tsujitani, R.; Kudo, M.; Otsuka, S. *J. Am. Chem. Soc.* **1978**, *100*, 3449.

(132) Fritschi, H.; Leutenegger, U.; A., P. *Angew. Chem. Int. Ed. Engl.* **1986**, *11*, 1005.

(133) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726.

(134) Jommi, G.; Pagliarin, R. *Synlett* **1993**, 833.

(135) Kitagaki, S.; Matsuda, H.; Watanabe, N.; Hashimoto, S. *Synlett* **1997**, 1171.

(136) Uchida, T.; Irie, R. *Synlett* **1999**, 1163.

(137) Uchida, T.; Irie, R. *Synlett* **1999**, 1793.

(138) Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron* **2000**, *56*, 3501.

(139) Yao, X.; Qiu, M.; Lu, W.; Chen, H.; Zheng, Z. *Tetrahedron: Asymm.* **2001**, *12*, 197.

(140) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds. *Comprehensive Asymmetric Catalysis*; Springer-Verlag: Berlin, 2000.

(141) Irie, R.; Noda, K. *Tetrahedron: Asymm.* **1991**, *2*, 481.

(142) Hamada, T.; Fukuda, T. *Tetrahedron* **1996**, *52*, 515.

(143) Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T. *Tetrahedron* **1994**, *30*, 11827.

(144) Grayson, D. H.; Tuite, M. R. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2137.

(145) Groger, H.; Saida, Y.; Sasai, H.; Yamaguchi, K.; Martens, J.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*.

(146) Flood, T. C.; Campbell, K. D. *J. Am. Chem. Soc.* **1984**, *106*, 2853.

(147) Mamai, A.; Madalengoita, J. S. *Tetrahedron Lett.* **2000**, *41*, 9009.

(148) Inoue, Y.; Ikeda, H.; M.Kaneda; Sumimura, T.; Everitt, S. R. L. *J. Am. Chem. Soc.* **2000**, *122*, 406.

(149) Inoue, Y.; Matsushima, E.; Wada, T. *J. Am. Chem. Soc.* **1998**, *120*, 10687.

(150) Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188.

(151) Avdagic, A.; Lesac, A.; Majer, Z.; Hollosi, M.; Sunjic, V. *Helv. Chim. Acta* **1998**, *81*, 1567.

(152) Paget, H. *J. Chem. Soc.* **1938**, 829.

(153) Brown, D.; Davis, B. T.; Halsall, T. G.; Hands, A. R. *J. Chem. Soc.* **1962**, 4492.

(154) Brown, D.; Davis, B. T.; Halsall, T. G. *J. Chem. Soc.* **1963**, 1095.

(155) Kanno, H.; Schuller, W. H.; Lawrence, R. V. *J. Org. Chem.* **1966**, *31*, 4138.

(156) Herz, W.; Juo, R.-R. *J. Org. Chem.* **1985**, *50*, 618.

(157) Turner, J. A.; Herz, W. *J. Org. Chem.* **1977**, *42*, 1900.

(158) Schenk, G. O. *Angew. Chem.* **1952**, *64*, 12.

(159) Boyd, J. D.; Foote, C. S.; Imagawa, D. K. *J. Am. Chem. Soc.* **1980**, *102*, 3641.

(160) Sutbeyaz, Y.; Secen, H.; Balci, M. *J. Org. Chem.* **1988**, *53*, 2312.

(161) Porter, N. A.; Nixon, J. R.; Gilmore, D. W. *ACS Symp. Ser.* **1978**, *69*, 89.

(162) Suzuki, M.; Noyori, R.; Hamanaka, N. *J. Am. Chem. Soc.* **1981**, *103*, 5606.

(163) Hagenbuch, J.-P.; Birbaum, J.-L.; Metral, J.-l.; Vogel, P. *Helv. Chim. Acta* **1982**, *65*, 887.

(164) Hagenbuch, J.-P.; Vogel, P. *J. Chem. Soc., Chem. Commun.* **1980**, 1062.

(165) Suzuki, M.; Ohtake, H.; Kameya, Y.; Hamanka, N.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 5292.

(166) Natsume, M.; Muratake, H. *Tetrahedron Lett.* **1979**, 3477.

(167) Lai, T.-S.; Kwong, H.-L.; Zhang, R.; Che, C. M. *J. Chem. Soc., Dalton Trans.* **1998**, 3559.

(168) Crossley, M. J.; Waern, J. B., University of Sydney, Cobalt (II) complexes provided for use in this work.

(169) Odenkirk, W.; Rheingold, A. L.; Bosnich, B. *J. Am. Chem. Soc.* **1992**, *114*, 6392.

(170) Hollis, T. K.; Odenkirk, W.; Robinson, N. P.; Whelan, J.; Bosnich, B. *Tetrahedron* **1993**, *49*, 5415.

(171) Fletcher, J. M.; Jenkins, I. L.; Lever, F. M.; Martin, F. S.; Powell, A. R.; Todd, R. *J. Inorg. and Nuclear Chem.* **1955**, *1*, 378.

(172) Muller, J. G.; Takeuchi, K. J. *Inorg. Chem.* **1990**, *29*, 2185.

(173) Ishiyama, T.; Matsumura, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 619.

(174) Slocik, J. M.; Shepherd, R. E. *Inorgan. Chim. Acta* **2000**, *311*, 80.

(175) Baldwin, J. E.; Basson, H. H.; Krauss jr., H. *J. Chem. Soc., Chem. Commun.* **1968**, 984.

(176) Catalan, C. A. N.; Cuenca, M. D. R.; Verghese, J.; Joy, M. T.; Gutierrez, A. B.; Herz, W. *Phytochemistry* **1990**.

(177) Sodum, R. S.; Chung, F.-L. *Cancer Research* **1991**, *51*, 137.

(178) Chen, H.-J. C.; Gonzalez, F. J.; Shou, M.; Chung, F.-L. *Carcinogenesis* **1998**, *19*, 939.

(179) Chen, H.-J. C.; Zhang, L.; Cox, J.; Cunningham, J. A.; Chung, F.-L. *Chem. Res. Toxicol.* **1998**, *11*, 1474.

(180) Sodum, R. S.; Chung, F.-L. *Chem. Res. Toxicol.* **1989**, *2*, 23.

(181) Rindgen, D.; Lee, S. H.; Nakajima, M.; Blair, I. A. *Chem. Res. Toxicol.* **2000**, *13*, 846.

(182) Chen, H.-J. C.; Chiang, L.-C.; Tseng, M.-C.; Zhang, L. L.; Ni, J.; Chung, F.-L. *Chem. Res. Toxicol.* **1999**, *12*, 1119.

(183) Bascetta, E.; Gunstone, F. D.; Scrimgeour, C. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2199.

(184) Nakano, T.; Aguero, M. E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1164.

(185) Akbulut, N.; Balci, M. *J. Org. Chem.* **1988**, *53*, 3338.

(186) Atasoy, B.; Bayramoglu, F.; Hokelek, T. *Tetrahedron* **1994**, *50*, 5753.

(187) Sasaoka, M.; Hart, H. *J. Org. Chem.* **1979**, *44*, 368.

(188) Foster, C. H.; Berchtold, G. A. *J. Org. Chem.* **1975**, *40*, 3743.

(189) Turner, J. A.; Herz, W. *J. Org. Chem.* **1977**, *42*, 2006.

(190) Zadok, E.; Rubinraut, S.; Frolow, F.; Mazur, Y. *J. Org. Chem.* **1985**, *50*, 2647.

(191) Allen, J. V.; Bergeron, S.; Griffiths, M. J.; Mukherjee, S.; Roberts, S. M.; Williamson, N. M.; Wu, L. E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3171.

(192) Allen, J. V.; Cappi, M. W.; Kary, P. D.; Roberts, S. M.; Williamson, N. M.; Wu, L. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3297.

(193) Jakubowski, A. A.; Guziec, F. S.; Sugiura, M.; Tam, C. C.; Tishler, M. *J. Org. Chem.* **1982**, *47*, 1221.

(194) Boeckman, R. K.; Thomas, E. W. *J. Am. Chem. Soc.* **1979**, *101*, 987.

(195) Boeckman, R. K.; Thomas, E. W. *Tetrahedron Lett.* **1976**, *45*, 4045.

(196) Wagner, I.; Musso, H. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 816.

(197) Hassell, C. H.; Reyle, K.; Feng, P. *Nature* **1954**, *173*, 356.

(198) Ropp, R. S. d.; meter, J. C. V.; Renzo, R. C. d.; McKerns, K. W.; Pidacks, C.; Bell, P. H.; Ullman, E. F.; Safir, S. R.; Fanshawe, W. J.; Davis, S. B. *J. Am. Chem. Soc.* **1958**, *80*, 1004.

(199) Fowden, L.; Lea, P. J.; Bell, E. A. In *Advances in Enzymology*; Meister, A., Ed.; Wiley: New York, 1979; p 117.

(200) Ichihara, A.; Shiraishi, K.; Sakamura, S. *Tetrahedron Lett.* **1977**, 269.

(201) Ichihara, A.; Shiraishi, K.; Sakamura, S. *Tetrahedron Lett.* **1979**, 365.

(202) Stammer, C. H. *Tetrahedron* **1990**, *46*, 2231.

(203) Fujimoto, Y.; Irreverre, F.; Karle, J. M.; Karle, I. L.; Witkop, B. *J. Am. Chem. Soc.* **1971**, *93*, 3471.

(204) Fowden, L.; MacGibbon, C. M.; Mellon, F. A.; Sheppard, R. C. *Phytochemistry* **1972**, *11*, 1105.

(205) Fowden, L.; Smith, A.; Millington, D. S.; Sheppard, R. C. *Phytochemistry* **1969**, *8*, 437.

(206) Ichihara, A.; Shiraishi, K.; Sato, H.; Sakamura, S.; Nishiyama, K.; Sakai, R.; Furusaki, A.; Matsumoto, T. *J. Am. Chem. Soc.* **1977**, *99*, 636.

(207) Wakamiya, T.; Shiraishi, K.; Sakamura, S. *Tetrahedron Lett.* **1984**, *25*, 4411.

(208) Wakamiya, T.; Oda, Y.; Fujita, H.; Shiba, T. *Tetrahedron Lett.* **1986**, *27*, 2143.

(209) Bonnaud, B.; Cousse, H.; Mouzin, G.; Briley, M.; Stenger, A.; Fauran, F.; Couzinier, J.-P. *J. Med. Chem* **1987**, *30*, 824.

(210) Collingridge, G. L.; Watkins, J. C., Eds. *The NMDA Receptor*; 2nd ed.; Oxford University Press: Great Britain, 1994.

(211) Lincoln, J.; Hoyle, C. H. V.; Burnstock, G. In *Nitric Oxide in Health and Disease*; Cambridge University Press, 1997; p 42.

(212) Farber, N. B.; Newcomer, J. W.; Olney, J. W. In *The Glutamate Synapse as a Therapeutic Target: Molecular Organization and Pathology of the Glutamate Synapse*; Ottersen, O. P., Langmoen, I. A., Gjerstad, L., Eds.; Elsevier Science: Amserdam, 1998; Vol. 116, p 421.

(213) Knopfel, T.; Kuhn, R.; Allgeier, H. *J. Med. Chem.* **1995**, *38*, 1417.

(214) Berg-Johnsen, J.; Haugstad, T. S.; Langmoen, I. A. In *The Glutamate Synapse as a Therapeutic Target: Molecular Organization and Pathology of the Glutamate Synapse*; Ottersen, O. P., Langmoen, I. A., Gjerstad, L., Eds.; Elsevier Science: Amsterdam, 1998; Vol. 116, p 287.

(215) Hayashi, Y.; Momiyama, A.; Takahashi, T.; Ohishi, H.; Ogawa-Meguro, R.; Shigemoto, R.; Mizuno, N.; Nakanishi, S. *Nature* **1993**, *366*, 687.

(216) Bruno, V.; Battaglia, G.; Copani, A.; Casabona, G.; Storto, M.; Gerevini, V. D. G.; Ngomba, R.; Nicoletti, F. In *The Glutamate Synapse as a Therapeutic Target: Molecular Organization and Pathology of the Glutamate Synapse*; Ottersen, O. P., Langmoen, I. A., Gjerstad, L., Eds.; Elseveir Science: Amsterdam, 1998; Vol. 116, p 209.

(217) Attwell, P. J. E.; Singh-Kent, N.; Jane, D. E.; Croucher, M. J.; Bradford, H. F. *Brain Research* **1998**, *805*, 138.

(218) Hanzlik, R. P.; Tullman, R. H. *J. Am. Chem. Soc.* **1982**, *104*, 2048.

(219) Tullman, R. H.; Hanzlik, R. P. *Drug Metab. Reviews* **1984**, *15*, 1163.

(220) Macdonald, T. L.; Zirvi, K.; Burka, L. T.; Peyman, P.; Guengerich, F. P. *J. Am. Chem. Soc.* **1982**, *104*, 2050.

(221) Crimmins, M. T.; King, B. W. *J. Org. Chem.* **1996**, *61*, 4192.

(222) Mulzer, J.; Kappert, M. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 63.

(223) Suckling, C. J. *Biochem. Soc. Trans.* **1986**, 402.

(224) MacInnes, I.; Nonhebel, D. C.; Orszulik, S. T.; Suckling, C. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2771.

(225) MacInnes, I.; Nonhebel, D. C.; Orszulik, S. T.; Suckling, C. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2777.

(226) Chaplinski, V.; de Meijere, A. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 413.

(227) Winsel, H.; Gazizova, V.; Kulinkovich, O.; Pavlov, V.; de Meijere, A. *Synlett* **1999**, *12*, 1999.

(228) Avery, T. D.; Greatrex, B. W.; Taylor, D. K.; Tiekink, E. R. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1319.

(229) Neset, S.; Hope, H.; Undheim, K. *Tetrahedron* **1997**, *53*, 10459.

(230) Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881.

(231) Greatrex, B.; Taylor, D. K.; Tiekink, E. R. T. *Org. Lett.* **2002**, *4*, 221.

(232) Curtius, T.; Ehrhart, G. *Ber. (Chem. Ber.)* **1922**, *55B*, 1559.

(233) Wasley, W. L.; Whitfield, R. E.; Miller, L. A.; Kodani, R. Y. *Textile Res. J* **1963**, *33*, 1029.

(234) Bunton, C. A.; Lewis, T. A. *Chemistry and Industry* **1956**, 180.

(235) Casen, M.; Procter, G.; Leonard, J.; Lygo, B. *Advanced Practical Organic Chemistry*; Blackie and Sons, Ltd.: London, 1990.

(236) Corey, E. J.; Imwinkelriea, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493.

(237) Williams, O. F.; Bailar, J. C. *J. Am. Chem. Soc.* **1959**, *81*, 4464.

(238) Cramer, F.; Pawelzik, K.; Baldauf, H. J. *Chem. Ber.* **1958**, 1049.

(239) Armstrong, A.; Brackenridge, I.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron Lett.* **1988**, *29*, 2483.

(240) Pouchert, C. J.; Behnke, J. *The Aldrich Library of ^{13}C and ^{1}H NMR Spectra*; 1st ed., 1993.

(241) Greatrex, B. *Personal Communication* **2000**.

(242) Barrett, A. G. M.; Doubleday, W. W.; Tustin, G. J. *Tetrahedron* **1996**, *52*, 15325.

(243) Lange, G. L.; Goltardo, C.; Merica, A. *J. Org. Chem.* **1999**, *64*, 6738.

(244) Kropp, P. J.; Pienta, N. J. *J. Org. Chem.* **1983**, *48*, 2084.

(245) Rosen, T.; Taschner, M. J.; Heathcock, C. H. *J. Org. Chem.* **1984**, *49*, 3994.

(246) Larock, R. C.; Bernhardt, J. C. *J. Org. Chem.* **1977**, *42*, 1680.

(247) Murphy, C. F.; Koehler, R. E. *J. Org. Chem.* **1970**, *35*, 2429.

(248) Kitahara, T.; Horiguchi, A.; Mori, K. *Tetrahedron* **1988**, *44*, 4713.

(249) Gorthey, L.-A.; Vairamani, M.; Djerassi, C. *J. Org. Chem.* **1984**, *49*, 1511.

(250) Gannett, P. M.; Nagel, D. L.; Reilly, P. J.; Lawson, T.; Sharpe, J.; Toth, B. *J. Org. Chem.* **1988**, *53*, 1064.

(251) Cameron, D. W.; Heisey, R. M. *Aust. J. Chem* **2000**, *53*, 109.

(252) Huang, J.; Goedken, V.; Walborsky, H. M. *J. Org. Chem.* **1988**, *53*, 4128.

(253) Avery, T. D. *Personal Communication* **2001**.

(254) Kimber, M. C. *Personal Communication* **2002**.

(255) Earshaw, A.; King, E. A.; Larkworthy, L. F. *J. Chem. Soc.* **1968**, 1048.

(256) Aizpurua, J. M.; Palomo, C. *Tetrahedron Lett.* **1984**, *25*, 1103.

(257) Zaslona, A. T.; Hall, C. D. *J. Chem. Soc., Perkin Trans. 1* **1981**, *12*, 3059.

(258) Dilbeck, G. A.; Morris, D. L.; Berlin, K. D. *J. Org. Chem.* **1975**, *40*, 1150.

(259) Mitsudo, T.; Fischetti, W.; Heck, R. F. *J. Org. Chem.* **1984**, *49*, 1640.

(260) Vedejs, E.; Bershas, J. P.; Fuchs, P. L. *J. Org. Chem.* **1973**, *38*, 3625.

(261) Motoyoshiya, J.; Okuda, Y.; Matsuoka, I.; Hayashi, S. *J. Org. Chem.* **1999**, *64*, 493.

Appendices

Appendix 1 ^{1}H NMR spectra of chiral shift studies.

Figure A1.1 ^{1}H NMR of the cyclopropane used to test the ability of the catalysts to introduce enantiomeric excess

Figure A1.2 Chiral Shift of cyclopropane (^{1}H NMR shown above) CH_2 of the benzyl group used for the chiral shift studies.

Appendix 2 LC-MS plots of catalyst 29b and 56e in dichloromethane and THF.

Figure A2.1 LC-MS of catalyst **56e** (0.02 g/mL) in dichloromethane showing absence of solvent bound peak and oxygen dimer at 1565.1.

Figure A2.2 LC-MS of catalyst **56e** (0.02 g/mL) in THF showing solvent bound peak at 835.8 mass units and oxygen dimer at 1566.0.

Figure A2.3 LC-MS of catalyst **29b** (0.02 g/mL) in dichloromethane showing absence of solvent bound and oxygen dimer.

Figure A2.4 LC-MS of catalyst **29b** (0.02 g/mL) in THF showing small solvent bound peak at 658.2 and small oxygen dimer peak (not labelled) at approx 1210.

Figure A2.5 LC-MS analysis of rearrangement of 3,6-dihydro-3,6-diphenyl-1,2-dioxine with catalyst **56e**

Appendix 3 Cobalt Salens Synthesised and Used (Fold out Section).

Figure 7 Division of the catalyst into quadrants.

Appendix 4 Cobalt β-ketoiminato Complexes Synthesised and Used (Fold out Section).

Figure 8 Division of the catalyst into quadrants.

Appendix 1 ^{1}H NMR spectra of chiral shift.

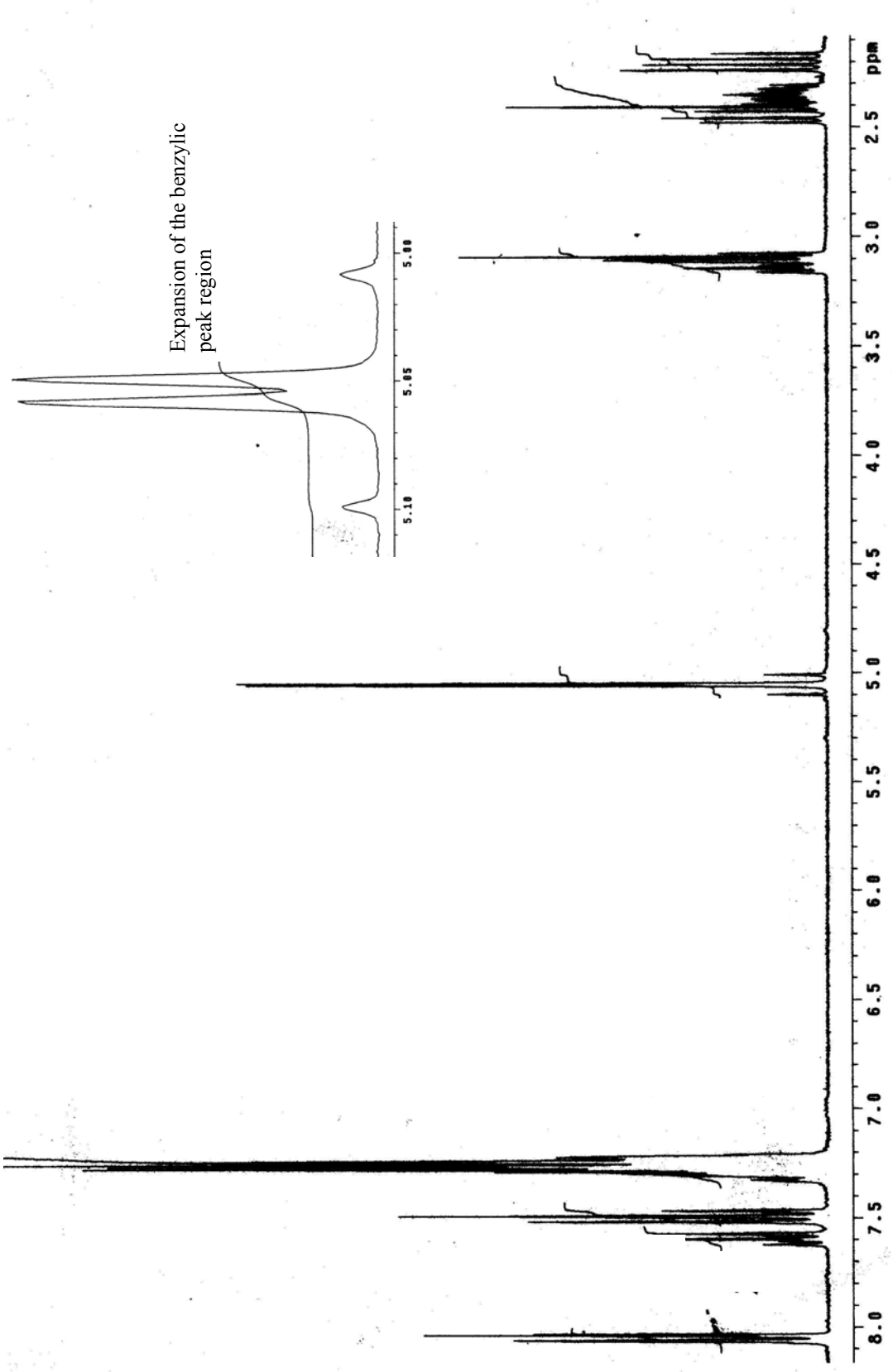


Figure A1.1 ^{1}H NMR of the cyclopropane **(61)** used to test the ability of the catalysts to introduce enantiomeric excess.

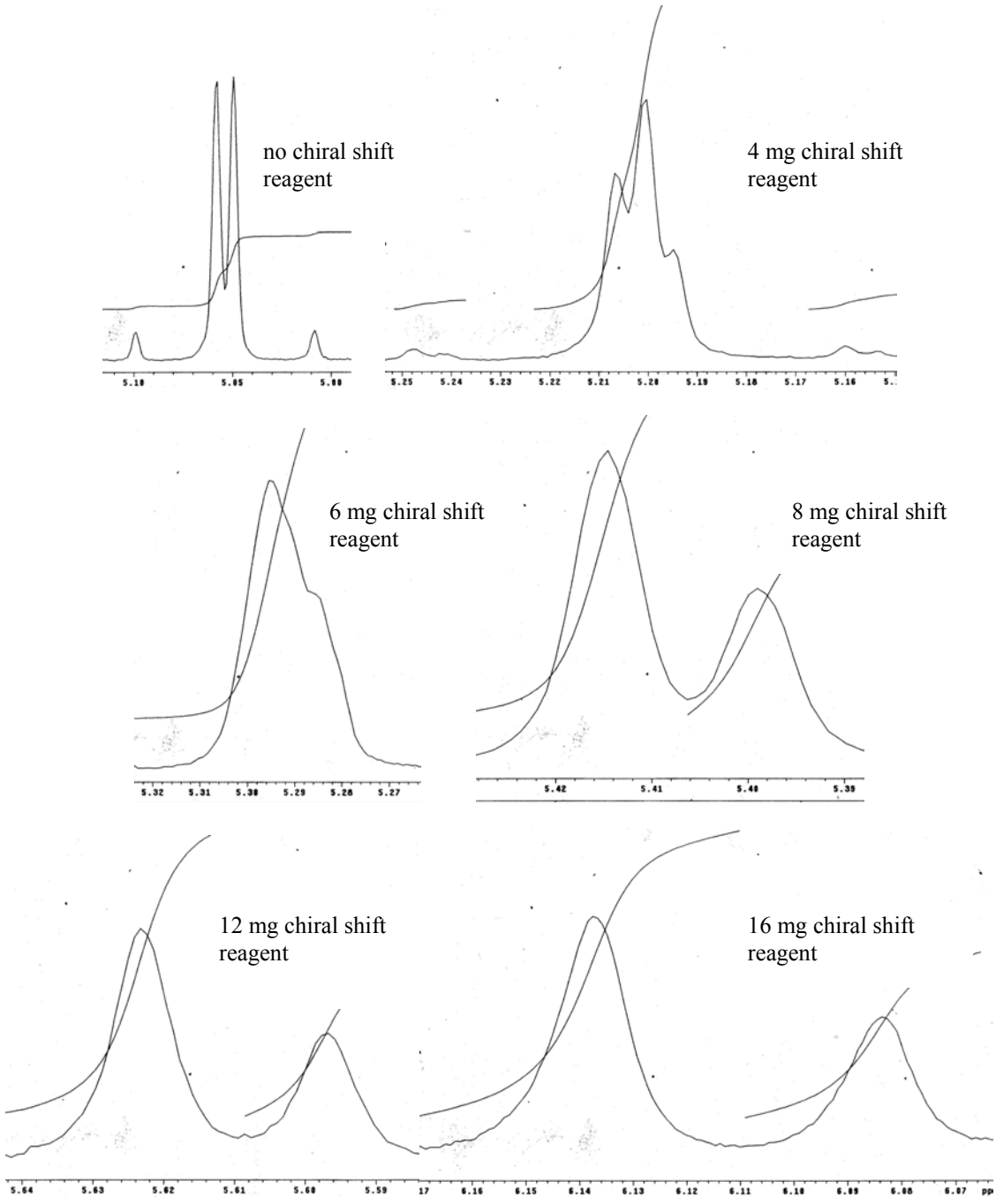


Figure A1.2 Chiral Shift of cyclopropane **(61)** (^{1}H NMR shown above) CH_2 of the benzyl group used for the chiral shift.

Appendix 2 LC-MS plots of catalyst **29b** and **55e** in dichloromethane and THF.

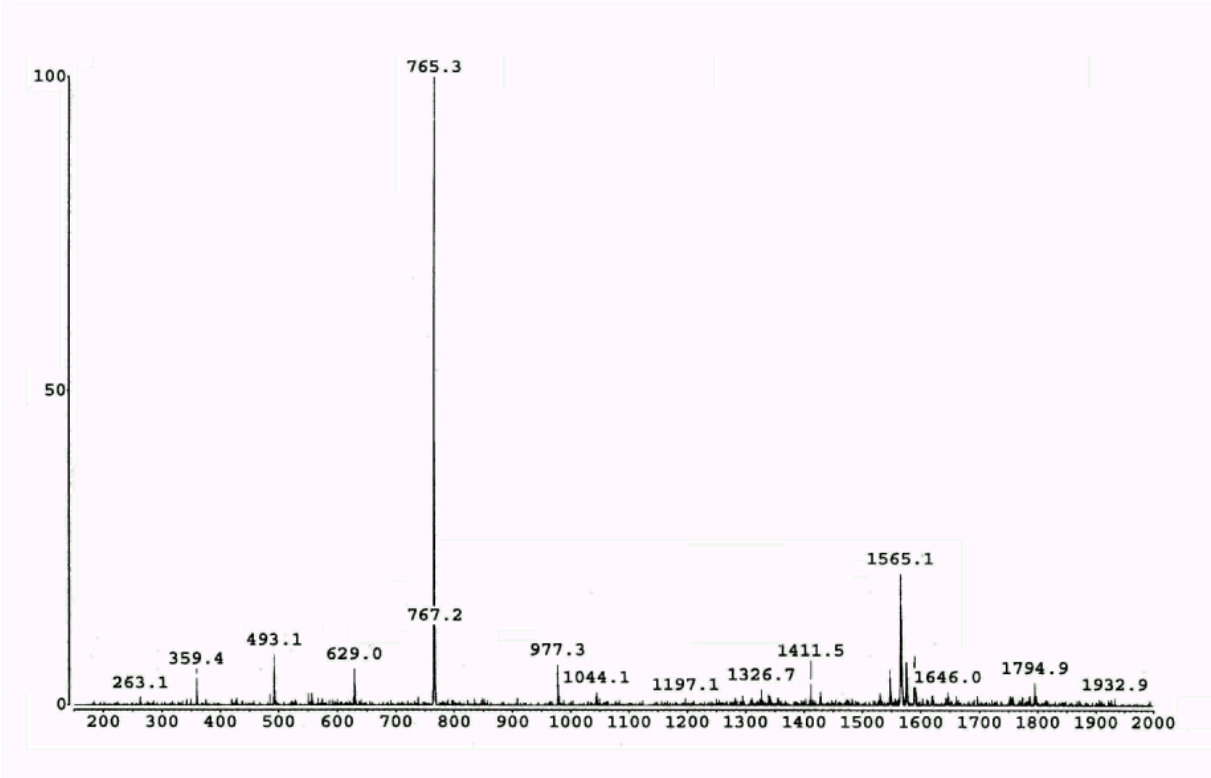


Figure A2.1 LC-MS of catalyst **55e** (0.02 g/mL) in dichloromethane showing absence of solvent bound peak and oxygen dimer at 1565.1.

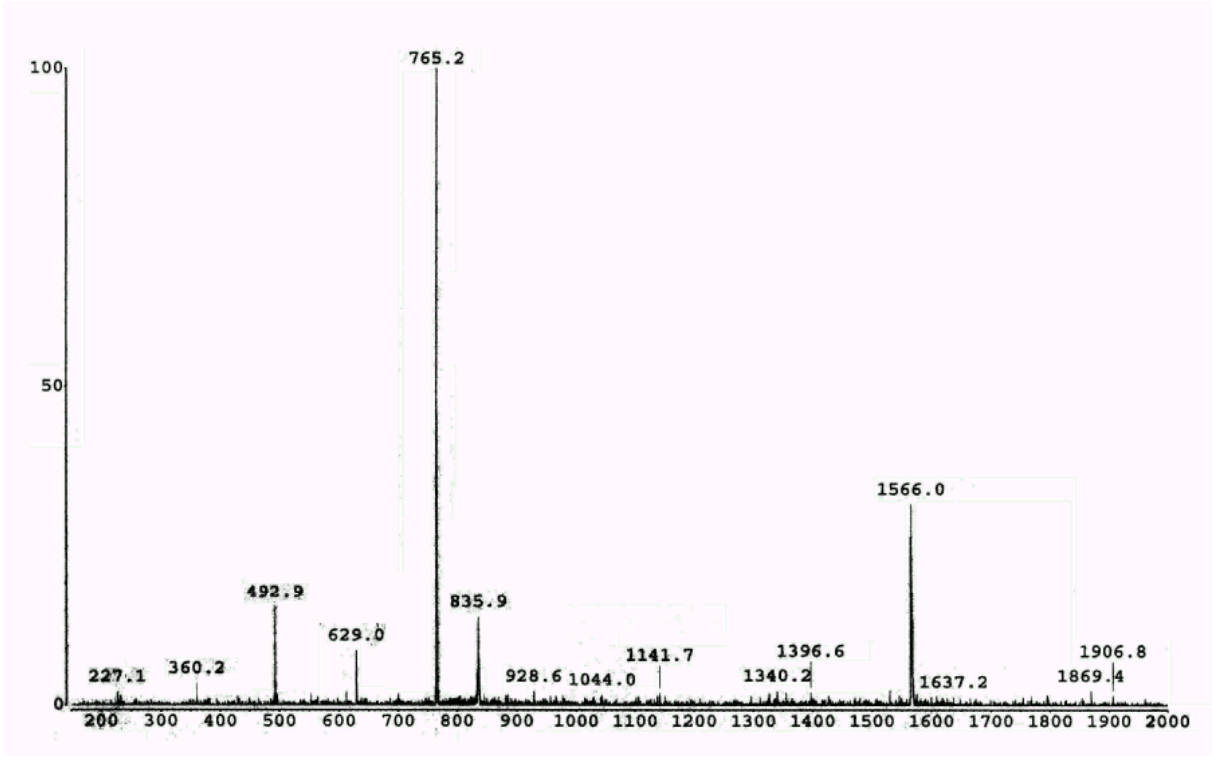


Figure A2.2 LC-MS of catalyst **55e** (0.02 g/mL) in THF showing solvent bound peak at 835.8 mass units and oxygen dimer at 1566.0.

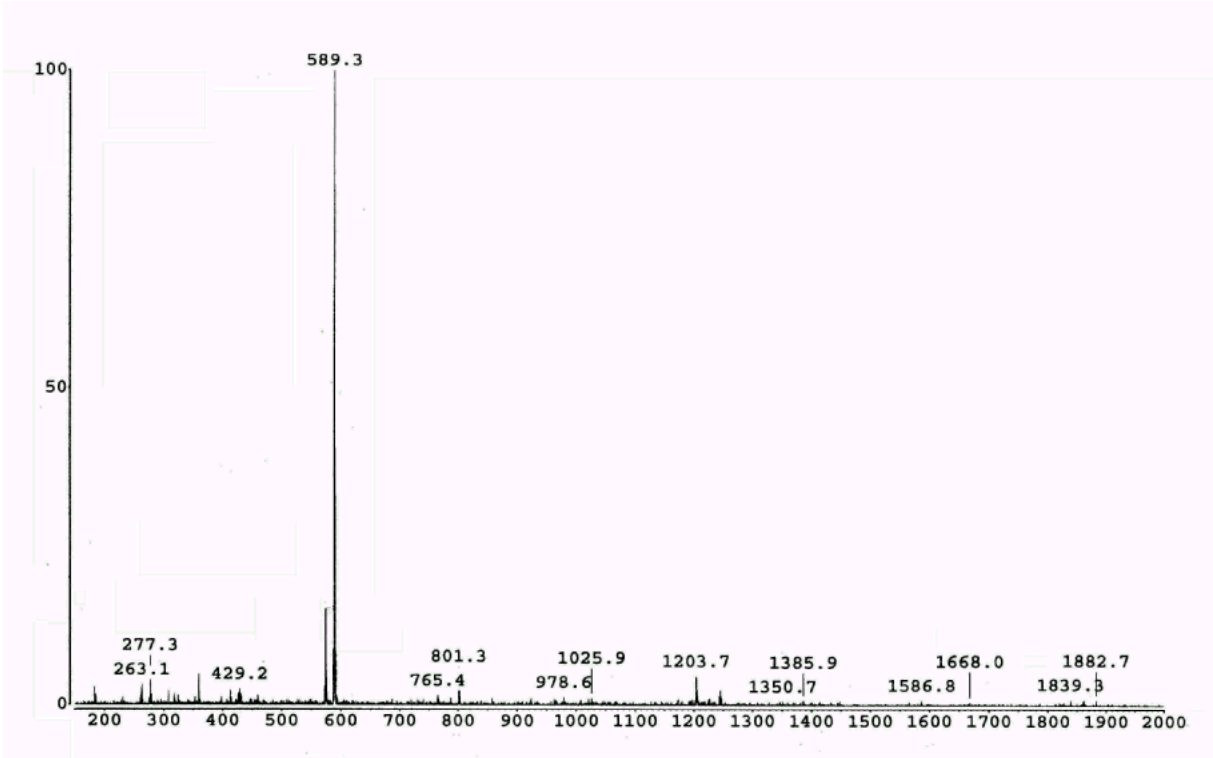


Figure A2.3 LC-MS of catalyst **29b** (0.02 g/mL) in dichloromethane showing absence of solvent bound and oxygen dimer.

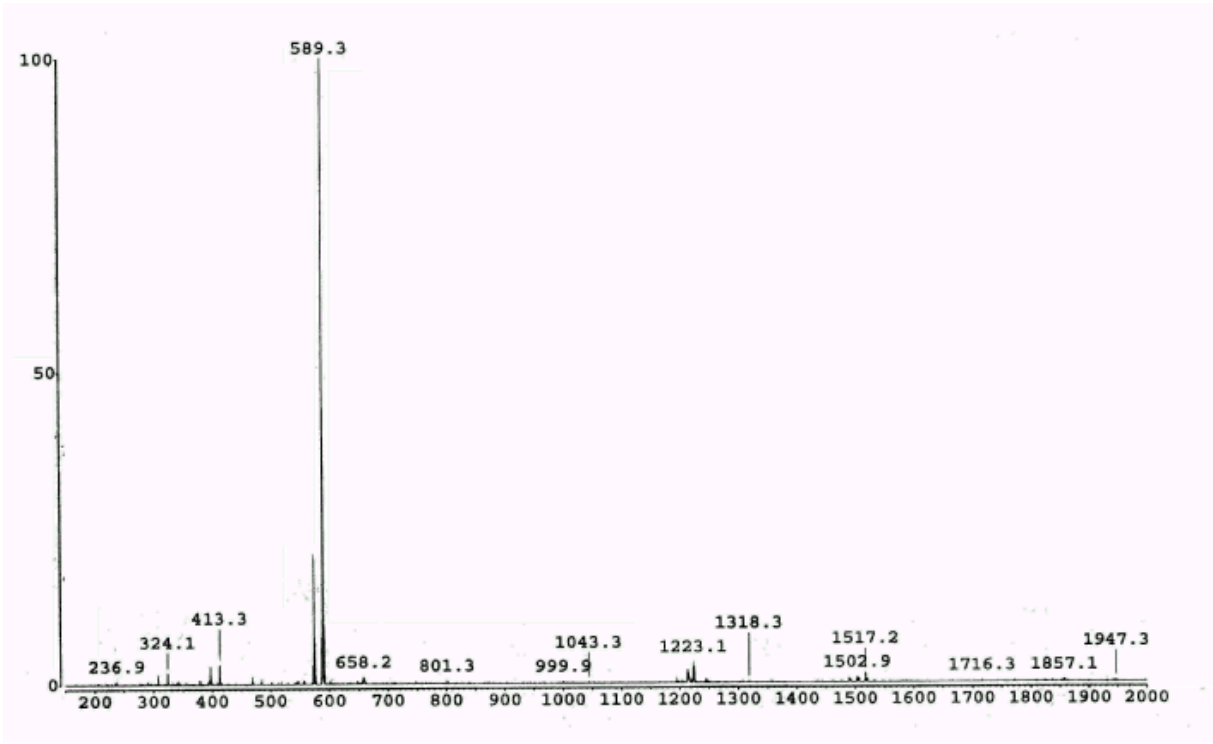


Figure A2.4 LC-MS of catalyst **29b** (0.02 g/mL) in THF showing small solvent bound peak at 658.2 and small oxygen dimer peak (not labelled) at approx 1210.

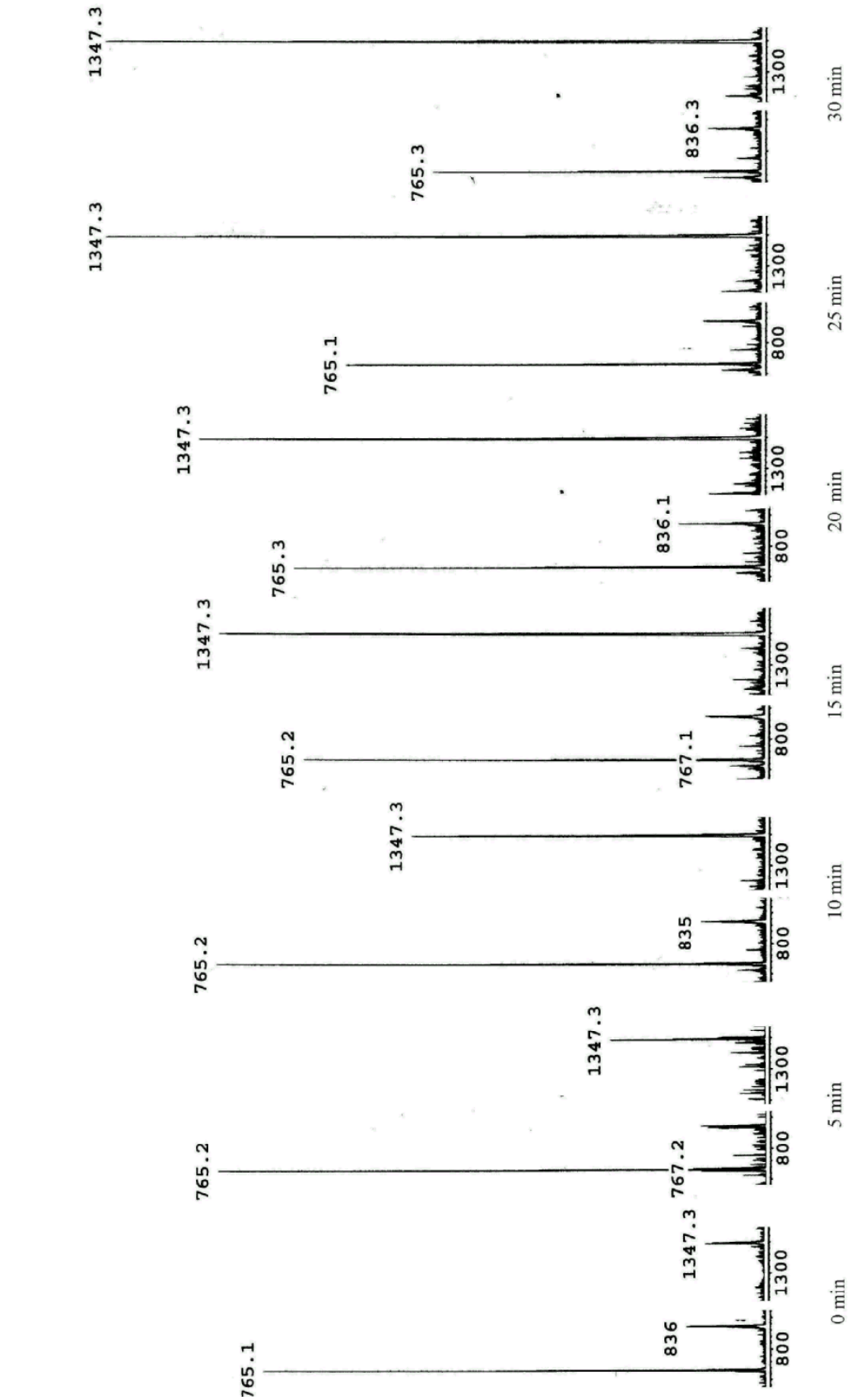


Figure A2.5 LC-MS analysis of rearrangement of 3,6-dihydro-3,6-diphenyl-1,2-dioxine **(59)** with catalyst **55e.**

Appendix 3 Cobalt Salens Synthesised and Used.

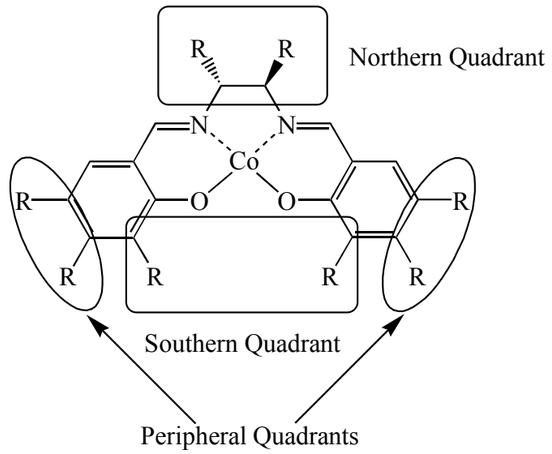
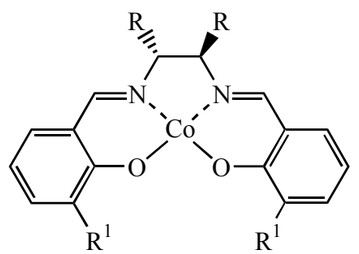


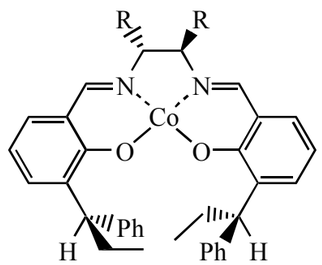
Figure 7 Division of the catalyst into quadrants.



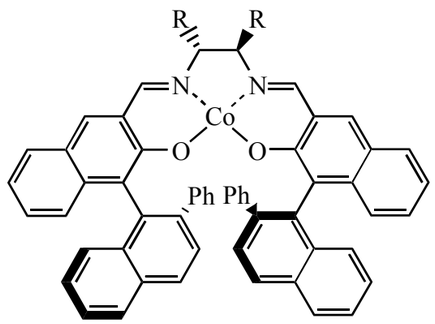
28a: - R = -$(CH_2)_4$-, R^1 = OCH_3 (*R,R* isomer)
28b: - R = Ph, R^1 = OCH_3 (*R,R* isomer)
28c: - R = 2,2'-Binapthyl, R^1 = OCH_3 (*R* isomer)

29a: - R = -$(CH_2)_4$-, R^1 = *t*-Butyl (*R,R* isomer)
29b: - R = Ph, R^1 = *t*-Butyl (*R,R* isomer)

30a: - R = -$(CH_2)_4$-, R^1 = H (*R,R* isomer)
30b: - R = Ph, R^1 = H (*R,R* isomer)



43a: - R = -$(CH_2)_4$- (*R,R* isomer)
43b: - R = Ph (*R,R* isomer)
43c: - R = Ph (*S,S* isomer)



44a: - R = -$(CH_2)_4$- (*R,R* isomer)
44b: - R = Ph (*R,R* isomer)
44c: - R = Ph (*S,S* isomer)

Appendix 4 Cobalt β-Ketoiminato Complexes Synthesised and Used

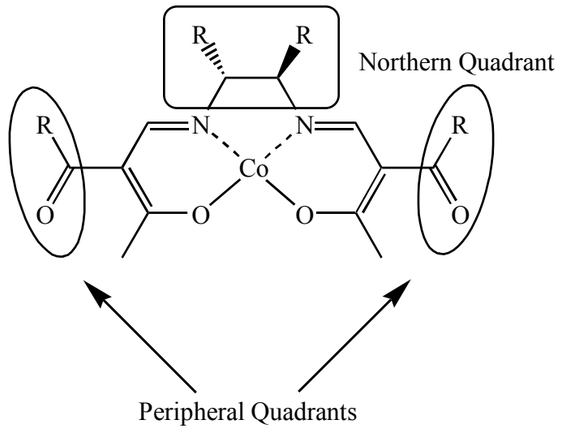
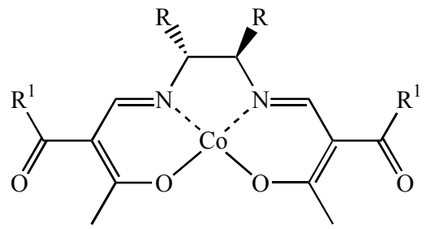


Figure 8 Division of the catalyst into quadrants.



52: - R = Ph, R^1 = Methyl (*S,S* isomer)

53a: - R = -$(CH_2)_4$-, R^1 = Ethoxy (*R,R* isomer)
53b: - R = Ph, R^1 = Ethoxy (*R,R* isomer)
53c: - R = Ph, R^1 = Ethoxy (*S,S* isomer)

54:- R = Ph, R^1 = *t*-Butoxy (*S,S* isomer)

55a: - R = H, R^1 = (-)-Bornoxy
55b: - R = -$(CH_2)_4$-, R^1 = (-)-Bornoxy (*R,R* isomer)
55c: - R = -$(CH_2)_4$-, R^1 = (-)-Bornoxy (*S,S* isomer)
55d: - R = Ph, R^1 = (-)-Bornoxy (*R,R* isomer)
55e: - R = Ph, R^1 = (-)-Bornoxy (*S,S* isomer)

56a: - R = Ph, R^1 = (-)-Menthoxy (*R,R* isomer)
56b: - R = Ph, R^1 = (-)-Menthoxy (*S,S* isomer)

57a: - R = Ph, R^1 = (+)-Menthoxy (*R,R* isomer)
57b: - R = Ph, R^1 = (+)-Menthoxy (*S,S* isomer)

Publications

First examples of the catalytic asymmetric ring-opening of *meso* 1,2-dioxines utilising cobalt(II) complexes with optically active tetradentate Schiff base ligands: formation of enantio-enriched cyclopropanes. Thomas D. Avery, Natalie F. Jenkins, Marc C. Kimber, David W. Lupton and Dennis K. Taylor,. *Chemical Communication.* **2002**, *1,* 28

Base- and Co(II)-Catalysed Ring-Opening Reactions of Perhydrooxireno[2,3-*d*][1,2]dioxines: An Efficient Route to 4-Hydroxy-2,3-epoxy-ketones, Ben W. Greatrex, Natalie F. Jenkins, Dennis K. Taylor, Edward R. T. Tiekink,. *J. Org. Chem.* **2003**, *ASAP article published on the Web June 3rd, 2003*

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First examples of the catalytic asymmetric ring-opening of *meso* 1,2-dioxines utilising cobalt(II) complexes with optically active tetradentate Schiff base ligands: formation of enantio-enriched cyclopropanes

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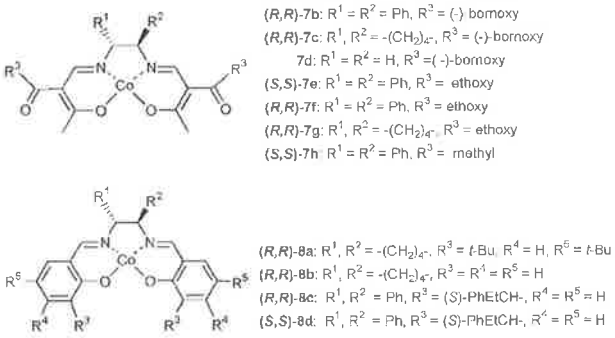
The combination of chiral cobalt β-ketoiminato or cobalt salen complexes and *meso* 1,2-dioxines leads to catalytic asymmetric ring-opening affording enantio-enriched *cis* γ-hydroxy enones; subsequent capture by an ylide affords enantio-enriched cyclopropanes.

Functionalised cyclopropanes have proven to be exceedingly useful building blocks for the synthesis of natural and non-natural products.[1] Although there exists many excellent ways for the construction of the cyclopropyl core,[2,3] there is currently a deficiency in diastereoselectively efficient methods for the construction of diversely functionalised optically-pure cyclopropanes that contain greater than di-substitution. Our efforts have focussed on exploiting 1,2-dioxines **1** and stabilised phosphorus ylides **2** (*e.g.* R^1 = Me, Bn, Bu^t *etc.*) as precursors for the construction of diversely functionalised cyclopropanes **5** or **6**, Scheme 1. The ylides act as a mild base inducing ring-opening of the 1,2-dioxine **1** in a regiochemical fashion to produce the isomeric *cis* γ-hydroxy enones **3**, route A. Capture of this latter isomer by the ylide ultimately affords the observed cyclopropanes and is widely applicable to both symmetrical and non-symmetrical 1,2-dioxines.[4,5] We have also shown that cobalt salen can be utilised as a catalyst, which accelerates the ring-opening process affording *cis* γ-hydroxy enones **3** through the intermediacy of species **4**, route B.[4,5] This latter process is currently restricted to the ring-opening of symmetrical 1,2-dioxines **1** as only one regioisomer of enone **3** can be formed.

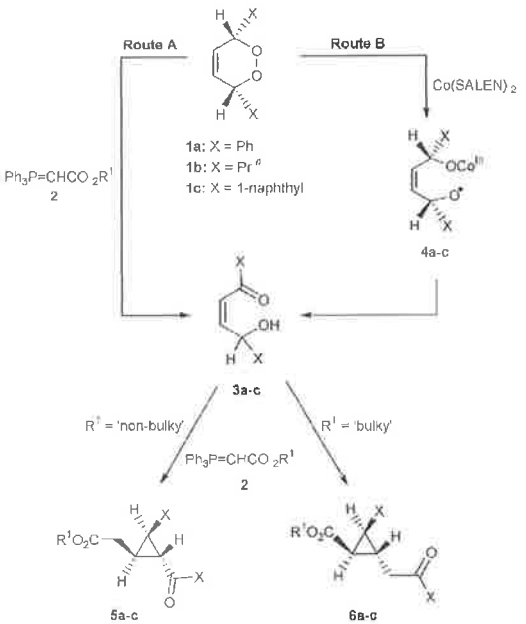
A logical extension to these latter findings was to investigate the use of cobalt(II) complexes with optically-active tetradentate Schiff base ligands. The hypothesis being that the chirality of the cobalt complex would induce enantioselectivity during the ring-opening process. We have previously shown that if the *cis* γ-hydroxy enone **3** is optically-pure then the resultant cyclopropanes formed on addition of ylide are also optically-pure.[6] We therefore report here the first examples of a catalytic asymmetric ring-opening of *meso* 1,2-dioxines which relies on the use of chiral cobalt β-ketoiminato or cobalt salen complexes; subsequent capture by an ylide affords enantio-enriched cyclopropanes.[7]

Three *meso* 1,2-dioxines (**1a–c**)[4,5] and twelve chiral cobalt catalysts (**7a–h** and **8a–d**) were chosen to be evaluated. It is worthy of mention that while cobalt catalysts (**8a** and **b**) are



known, only the synthesis of the chiral ligands for some of the remaining catalysts have previously been reported.[8] In particular, chiral cobalt β-ketoiminato complexes of types (**7a–h**) represent a new class of chiral cobalt complexes.

Table 1 contains examples of the formation of optically-enriched cyclopropane **5a**[9] utilizing 1,2-dioxine **1a**, catalyst **7a** (5 mol%) and the benzyl ester ylide.[10] The results confirm our hypothesis that the chirality of the cobalt complex would induce enantioselectivity during the ring-opening process of *meso* 1,2-dioxines. Additionally, it can be seen that the solvent of choice for this particular ring-opening process from those currently trialled is THF. The effect of temperature on observed *ee* in both CH_2Cl_2 (entries 1–5) and THF (entries 11–14) was also probed and revealed that ee is maximized for the ring-opening of **1a** by the catalyst **7a** at *ca.* −15 to −20 °C. Based on these initial observations it is now possible to highlight the practical potential of this new catalytic asymmetric cyclopropanation reaction under semi-optimized conditions. Thus, a solution of 1,2-dioxine **1a** 0.5 g in THF 20 mL and a solution of catalyst **7a** 120 mg in THF 5 mL were equilibrated at −15 °C for 0.5 h after which time the two solutions were combined whilst maintaining the temperature at −15 °C. The rearrangement of **1a** into **3a** was monitored by TLC and when complete, (0.5 h) benzyl ester ylide 1.0 g added and the reaction mixture allowed to attain ambient temperature overnight. Workup and measurement of ee resulted in cyclopropane **5a** being isolated in 78% yield and displaying a 76% ee.



Scheme 1

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Table 1 Preparation of optically-enriched cyclopropane **5a** from *meso* 1,2-dioxine **1a** with chiral cobalt β-ketoiminato complex **7a**[a]

Entry	Solvent	Temp./°C)	Ee (%)[b]	Entry	Solvent	Temp./°C)	Ee (%)[b]
1	CH_2Cl_2	20	38	8	CCl_4	20	34
2	CH_2Cl_2	0	48	9	Acetone	20	52
3	CH_2Cl_2	−10	56	10	CH_3CN	20	52
4	CH_2Cl_2	−20	72	11	THF	20	68
5	CH_2Cl_2	−40	60	12	THF	0	74
6	Et_2O	20	34	13	THF	−15	76
7	Toluene	20	34	14	THF	−40	72

[a] Carried out utilising 20 mg **1a** in the appropriate solvent (1 mL) at the specified temperature. The catalyst **7a** (5 mol% with respect to 1,2-dioxine concentration) was then added and the ring-opening monitored by TLC. After complete rearrangement the benzyl ester ylide 1 equiv. was added and the mixture allowed to attain ambient temperature overnight. Cyclopropane **5a** was then isolated by column chromatography. [b] Determined according to ref. 9.

Table 2 Effect of chiral cobalt β-ketoiminato complexes of type **7a–h** and cobalt salen catalysts **8a–d** on observed ee utilising 1,2-dioxines **1a–c**[a]

Entry	1,2-Dioxine	Catalyst	Ee (%)[b]	Entry	1,2-Dioxine	Catalyst	Ee (%)[b]
1	**1a**	**7a**	44	11	**1b**	**7h**	30
2		**7b**	34	12	**1c**	**7a**	44
3		**7c**	46	13	**1a**	**8a**	30
4		**7d**	14	14[c]			34
5		**7e**	46	15		**8b**	38
6		**7f**	46	16[c]			44
7	**1a**	**7g**	42	17		**8c**	34
8		**7h**	46	18		**8d**	50
9	**1b**	**7a**	34	19[c]			64
10		**7e**	32	20[c,d]			78

[a] Reactions were carried out utilising 20 mg of 1,2-dioxine in CH_2Cl_2 (1 mL) at 20 °C except where noted. The appropriate amount of catalyst (entries 1–3, 7.5 mol%; entries 4–12, 10 mol%; entries 13–20, 5 mol% with respect to 1,2-dioxine concentration) was then added and the ring-opening monitored by TLC. After complete rearrangement the benzyl ester ylide 1 equiv. was added and the mixture left overnight. Cyclopropanes **5a–c** were then isolated by column chromatography and the isolated yields varied between 70–88%. [b] Determined according to ref. 9. [c] Performed in THF. [d] Performed at 4 °C.

A diverse range of chiral cobalt β-ketoiminato complexes **7a–h** and cobalt salen catalysts **8a–d** were prepared next in order to probe in which quadrant(s) sterics and/or chiral group positioning is important on observed ee, Table 2. In addition, these catalysts were examined for a range of di-alkyl and di-aryl *meso* 1,2-dioxines **1a–c** in order to probe the generality of this transformation. Overall, the results summarised within Table 2 indicate that useful enantioselectivities can be incorporated for a wide range of chiral cobalt β-ketoiminato catalysts **7a–h** (entries 1–12) and that the catalytic asymmetric cyclopropanation is widely applicable to a range of *meso* 1,2-dioxines. Comparison of entries 1 and 4 indicate that chirality located within the northern hemisphere of these β-ketoiminato complexes is important in inducing the high enantioselectivities. Moreover, analysis of the use of chiral cobalt salen catalysts **8a–d** (entries 13–20) also reveals that these catalysts induce useful ee's into the cyclopropanation sequence. Indeed, the matched salen catalyst **8d** led to an impressive 89 : 11 enantiomeric ratio when the reaction was carried out in THF at 4 °C (entry 20).

A full study encompassing a wide range of catalyst types is the focus of current studies and will be reported in full shortly along with a model depicting how the enantioselectivity is induced.

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Notes and references

1 See for example: H. W. Lin and C. T. Walsh, 'Biochemistry of the Cyclopropyl Group'. *In The Chemistry of the Cyclopropyl Group*, ed. S. Patai and Z. Rappoport, Wiley, New York, 1987, Chapter 16; J. Martel, 'The Development and Manufacture of Pyrethroid Insecticides'. *In Chirality in Industry*, ed. A. N. Collins, G. N. Sheldrake and J. Crosby, Wiley, Chichester, 1992, Chapter 4 and references cited therein; J. R. Falck, B. Mekonnen, J. Yu and J. Y. Lai, *J. Am. Chem. Soc.*, 1996, **118**, 6096; A. G. M. Barrett and J. Kasdorf, *J. Am. Chem. Soc.*, 1996, **118**, 11030.

2 For recent examples of the direct carbene transfer (both stoichiometric and catalytic) from a diazo precursor to an olefin utilizing transition metals see: S. E. Denmark, B. L. Christenson, S. P. O'Conner and N. Murase, *Pure Appl. Chem.*, 1996, **68**, 23; V. K. Singh, A. DattaGupta and G. Sekar, *Synthesis*, 1997, 137; T. Ichiyanagi, M. Shimizu and T. Fujisawa, *Tetrahedron*, 1997, **53**, 9599; H. M. L. Davies and S. A. Panaro, *Tetrahedron Lett.*, 1999, **40**, 5287.

3 For examples of the Michael addition of nucleophiles to α,β-unsaturated ketones and esters followed by intramolecular cyclisation see: M. Calmes, J. Daunis and F. Escale, *Tetrahedron: Asymmetry*, 1996, **7**, 395; A.-H. Li, L.-X. Dai and V. K. Aggarwal, *Chem. Rev.*, 1997, **97**, 2341.

4 T. D. Avery, T. D. Haselgrove, T. J. Rathbone, D. K. Taylor and E. R. T. Tiekink, *Chem. Commun.*, 1998, 333; T. D. Avery, D. K. Taylor and E. R. T. Tiekink, *J. Org. Chem.*, 2000, **65**, 5531.

5 T. D. Avery, B. W. Greatrex, D. K. Taylor and E. R. T. Tiekink, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1319; T. D. Avery, G. Fallon, B. W. Greatrex, S. M. Pyke, D. K. Taylo and E. R. T. Tiekink, *J. Org. Chem.*, 2001, in press.

6 F. N. Palmer and D. K. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1323.

7 The overall concept is by no means limited to cyclopropane formation. We will describe shortly the formation of enantio-enriched lactones which is also reliant on the catalytic asymmetric ring-opening of *meso* 1,2-dioxines by these chiral cobalt catalysts.

8 (*a*) For general procedures to prepare the β-ketoiminato ligands see: T. Nagata, K. Imagawa and T. Yamada, *Inorg. Chim. Acta*, 1994, **220**, 283; K. D. Sugi, T. Nagata, T. Yamada and T. Mukaiyama, *Chem.Lett.*, 1997, 493; T. Nagata, K. Imagawa, T. Yamada and T. Mukaiyama, *Chem. Lett.*, 1994, 1259; (*b*) For general procedures to prepare cobalt salen catalysts see: T. Fukuda and T. Katsuki, *Tetrahedron*, 1997, **53**, 7201; R. Irie, K. Noda, Y. Ito, N. Matsumoto and T. Katsuki, *Tetrahedron: Asymmetry*, 1991, **2**, 481.

9 Racemic **5a** has previously been characterized, see ref. 4. The ee was determined by dissolving cyclopropane **5a** (5 mg) in a 1 : 4 benzene-d_6 : CCl_4 solution and employing the chiral shift reagent europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] complex. The benzyl protons at *ca.* δ 5.2 ppm displayed baseline separation.

10 It should be noted that a wide range of bulky and non-bulky ester ylides including chiral ester ylides can be employed. See refs. 4 and 5 for examples.

B.W. Greatrex, N.F. Jenkins, D.K. Taylor, and E.R.T. Tiekink (2003) Base- and Co(II)-Catalyzed Ring-Opening Reactions of Perhydrooxireno[2,3-d][1,2]dioxines: An Efficient Route to 4-Hydroxy-2,3-epoxy-ketones.
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