PHD

Stereoselective synthesis of (E)-trisubstituted acid derivatives

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Stereoselective Synthesis
of \((E)\)-Trisubstituted Acid Derivatives

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Abstract

This PhD thesis describes on my progress towards the application of the aldol/retro-aldol reaction to the development of a novel concept for using chiral auxiliaries for the asymmetric synthesis of chiral aldehyde fragments. As a result of these investigations I have discovered synthetic methodology that employs syn-β-hydroxy-N-acyloxazolidin-2-ones as substrates for a novel intramolecular cyclisation/elimination reaction to afford trisubstituted (E)-α,β-unsaturated amides in high d.e. In Chapter 1 the range of strategies that are commonly employed to obtain chiral molecules in enantiopure form are described. The concept of directed reactions as a tool for introducing new chiral centres to a chiral synthon is explained, and a few relevant examples are described in a non-exhaustive fashion. In Chapter 2 the literature published on the synthesis of trisubstituted (E)- and (Z)-α,β-unsaturated carboxylic acids derivatives is comprehensively reviewed concentrating on examples that have been recently employed for natural product synthesis. In Chapter 3, the original chiral auxiliary concept based on the potential of the aldol/retro-aldol reaction to form/cleave stereogenic hydroxyl centres and the capacity of hydroxyl group to direct reactions at prochiral centres is discussed. The preliminary reactions that were carried out towards this aim that led to the discovery of novel methodology for the stereoselective synthesis of (E)-trisubstituted acid derivatives are also described. In Chapter 4 the scope and limitation of the methodology for affording trisubstituted (E)-α,β-unsaturated amides in 67-99% yield and in 90 to > 95% d.e. is described, although lower stereoselectivities were observed with syn-aldolates that contained γ,δ-unsaturation. A range of these (E)-amides were then cleanly transformed into their corresponding carboxylic acids and oxazolines in high yield. In Chapter 5 the mechanism of the novel elimination reaction is explored and found to occur via a tandem rearrangement/E1cB elimination reaction. 1,3-Oxazinane-2,4-dione intermediates were isolated, and the mechanism is discussed in the light of the results arising from Chapter 4. In Chapter 6, it was demonstrated that a series of syn- and anti-aldolates derived from chiral aldehyde fragments, heteroaryl aldehydes, and N-acyloxazolidine-2-ones that contain heteroatom substituents at their α-position, also undergo stereoselective elimination to afford (E)-amides However, products arising from a competing retro-aldol reaction were isolated in a number of cases. In Chapter 7, suitable aldolate substrates that undergo clean retro-aldol reaction were identified, thus establishing conditions that enabled a novel concept for employing chiral auxiliaries for the enantioselective synthesis of aldehydes to be realised.
Acknowledgements

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And a huge thanks to all of my friends, those I have met in England and the others, who all contributed to make these last few years as great as they could be. I don’t feel like naming but I’ll give it a go anyway: The French triplettes (Marie, Selma, Karine and Christelle, well they are 4!), Le Club des Cinq (Jérôme, Anthony, Steph and Julie), Olivier, Tim, Florence, Claire, Popi, Didier, Adem, Gerta, Yolanda, Mike and how could I have forgotten the ever so cheeky (!) Koko. This list is not exhaustive (© I am of course thinking about Carole who would go to such an extent to make me smile, Sylvie, David, ...).

And finally, last but not the least, ... à Maman, Papa et ma “petite” soeur Delphine. Cette thèse est dédiée à mes grands-parents.

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Publication
Abbreviations

Ac  acetyl
acac  acetylacetonate
aq.  aqueous
Ar  aryl
9-BBN  9-borabicyclo[3.3.1]nonanyl
BINAP  2,2’-bis-(diphenylphosphino)-1,1’-binaphthyl
Bn  benzyl
Boc  tert’butyloxy carbonyl
br  broad
”Bu, Bu  butyl
‘Bu  tert’butyl
cat  catalyst
Cbz  carboxybenzyl
CI  chemical ionisation
Cp  cyclopentadienyl
Cy  cyclohexyl
d  doublet
Δ  heat
DAST  diethylamino sulfur trifluoride
dba  dibenzylidene acetone
d.e.  diastereomeric excess
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
DCC  N,N-dicyclohexylcarbodiimide
DCM  dichloromethane
DIBAL-H  diisobutyraluminium hydride
DMF  N,N-dimethylformamide
DMSO  dimethylsulfoxide
EDC  1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee  enantiomeric excess
EI  electron impact
eq.  equivalent
ES  electrospray
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<td>infra-red</td>
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<td>KHMDS</td>
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<td>LHMDS</td>
<td>lithium hexamethyldisilazide</td>
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<td>m-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
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<td>Ms</td>
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<td>TMS</td>
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1.1 Introduction

The reactivity of organic compounds is closely related to their three-dimensional structure. For example, the biological properties of all chiral organic molecules depend on their stereochemistry, with important implications for drugs, insecticides, plant growth regulators, perfumery and flavouring compounds.\(^1\)

Thalidomide is a good example of the potential problems associated with the administration of racemic drugs. It was prescribed as a racemic mixture for many years in order to relieve pregnant women from pain and nausea, before it was realised in the 1960's that the desired activity resided in the \((R)\)-1 enantiomer, whilst the \((S)\)-1 enantiomer was teratogenic leading to tragically malformed infants (Figure 1).\(^2\)

![Figure 1](image)

Figure 1

One of the great challenges within organic chemistry lies in the synthesis of naturally occurring molecules that contain one or more stereogenic centres.\(^3\) As a consequence, a great deal of effort has been directed towards the development of methodology that allows chiral molecules to be constructed in a stereoselective manner.\(^4\) The syntheses of most complex molecules rely on a strategy where the stereogenic centres of one or more small chiral building blocks are used to control the introduction of new stereogenic centres into the target molecule \textit{via} a series of stereoselective reactions.\(^5\) Access to a wide range of these small chiral templates is therefore critical, and as a consequence a number of different approaches have been developed for their preparation.
1.2 Preparation of Enantiopure Synthons

There are a number of different strategies employed to obtain chiral molecules in enantiopure form. These different approaches may be conveniently divided into three main categories; (i) the use of molecules available from the chiral pool; (ii) the resolution of racemates; (iii) asymmetric synthesis.

1.3 The Chiral Pool

This approach employs naturally occurring enantiomerically pure substrates that are readily available from Nature as chiral templates for synthesis. For example, naturally occurring carbohydrates such as D-glucose 2, or α-amino acids such as L-valine 3 have been used widely in synthesis. Alternatively, chiral secondary metabolites such as the terpene limonene 4 are often available in multigram quantities (Figure 2).

![Figure 2](image)

There are problems with this approach however. Supply is often limited by availability, whilst only one enantiomeric series may occur naturally. For example, many α-amino acids are only available in their proteinogenic L-series, whilst carbohydrates are generally D-configured. Additionally, lengthy synthetic steps are often required to remove redundant functionality from naturally occurring substrates containing more than one stereogenic centre.

1.4 Resolution of Racemates

Techniques have been developed to obtain compounds as single enantiomers from racemic mixtures via resolution. This approach allows the use of racemic starting materials for the preparation of enantiopure compounds for synthesis. For example, the racemic α-methyl-α-amino acid 5 was treated with the sodium salt of enantiomerically pure menthol to give two diastereoisomers of the ester 6 and 7. Fractional crystallisation of the resulting mixture enabled one of the diastereoisomers 6 to be obtained in pure crystalline form, while the
other diastereoisomer 7 remained in solution. 7 could be obtained in isomerically pure form via subsequent recrystallisation of the mother liquors. Hydrolysis of either diastereoisomer 6 or 7 afforded either the (R)-8 or (S)-8 enantiomer of the parent α-amino acid in enantiopure form respectively (Scheme 1).⁶

Scheme 1

The key problem associated with resolution is the fact that the maximum theoretical yield of each pure enantiomer obtainable is 50%. A number of elegant dynamic kinetic resolution procedures have been developed to address this issue in which the racemic substrate rapidly racemises under the reaction conditions. For example, the stereogenic centre of racemic hydantoin 9 is acidic and rapidly racemises at pH 8.0, enabling hydantoinase enzyme to catalyse quantitative hydrolysis of the (R)-9 enantiomer to afford (R)-N-carbamoyl-α-amino-acid 10 in high e.e. (Scheme 2).⁷

Scheme 2
1.5 Asymmetric Synthesis

Asymmetric synthesis may be defined as the conversion of a prochiral unit into a chiral unit in such a way that the stereoisomeric products are formed in unequal amounts. To achieve asymmetric induction, one component of a reaction must be chiral. This ensures that the possible transition states of the reaction are diastereoisomeric, and potentially of different energies. If the diastereomeric transition states differ significantly in energy then high stereoselectivity should be observed for a given reaction. In the absence of a chiral component, the possible transition states are enantiomeric, thus of equal energy, and therefore lead to a racemate. Following this basic principle, the strategies for asymmetric induction may be conveniently classified into three main approaches, asymmetric catalysis, chiral reagents, and the use of chiral auxiliaries.

1.5.1 Asymmetric Catalysis

Chiral information is transferred in the transition state of a reaction using a chiral catalytic species that binds reversibly to both a substrate and an achiral reagent, thus facilitating reaction in a diastereoselective manner. For example, borane does not reduce ketones to alcohols in the absence of a catalyst, however with a catalytic amount (10%) of the CBS (Corey, Bakshi, and Shibita) oxazaborolidine catalyst 12, it can reduce acetophenone 11 to secondary alcohol 13 in high e.e. using a stoichiometric amount of achiral borane as hydride source (Scheme 3).8

Thus, when acetophenone 11 is complexed to the boron atom of oxazaborolidine 12, it becomes electrophilic enough to be reduced by a weak hydride source, which is delivered via the six-membered cyclic transition state 14. The observed facial selectivity arises from the preference of the larger phenyl group, to occupy a pseudoequatorial conformation in the transition state (Figure 3).
Figure 3
Whilst a large number of chiral catalysts have been developed, only a limited number have entered mainstream synthetic organic chemistry primarily due to problems associated with substrate selectivity and catalyst turnover. Thus, small changes in substrate structure can often lead to the catalyst forming mixtures of enantiomeric products that are difficult to purify to homogeneity.

1.5.2 Chiral Reagents
This approach is similar to the asymmetric catalytic approach described in Section 1.5.1 however in this case a stoichiometric quantity of a chiral reagent is used for the stereoselective transformation of an achiral substrate. For example, ketone 15 may be reduced by the chiral borane 16 to afford (R)-alcohol 17 in >99% e.e. (Scheme 4).9

Scheme 4
Whilst this approach is often a highly efficient one the cost of employing stoichiometric quantities of chiral reagents is often prohibitive.

1.5.3 The Chiral Auxiliary Approach
The chiral auxiliary approach relies on a strategy involving attachment of a chiral auxiliary CA to a prochiral substrate S resulting in the formation of a CA-S complex (Figure 4). Subsequent derivatisation of the CA-S complex, under the stereodirecting control of the chiral auxiliary fragment, results ideally in the formation of single diastereoisomer CA-P containing one or more new stereogenic centres. If stereocontrol is incomplete then any minor diastereoisomer must be removed via recrystallisation or chromatography. Finally,
the diastereoisomerically pure CA-P product is cleaved to afford the enantiomerically pure product P, and the chiral auxiliary fragment CA which may then be recycled as required.

\[
\begin{align*}
\text{CA} + S & \xrightarrow{\text{Couple together}} \text{CA-S} \\
\text{recycled} & \downarrow \downarrow \downarrow \\
\text{CA} + P & \xrightarrow{\text{1- Separate diastereoisomers}} \text{CA-P} \\
& \downarrow \downarrow \downarrow \\
& \text{2- Hydrolyse major diastereoisomer}
\end{align*}
\]

\textbf{Figure 4}
This principle may be illustrated by considering the use of Evans' oxazolidin-2-one 18 for the asymmetric synthesis of chiral α-substituted acid fragments. The oxazolidinone chiral auxiliary 18 is first attached to the achiral acid fragment 19 to afford N-propionyl-4-isopropyloxazolidin-2-one 20. Deprotonation of 20 with LHMDS in THF at -78°C affords a chelated (Z)-enolate that reacts with an incoming electrophile on the opposite face to the stereodirecting iso-propyl group to afford the major diastereoisomer 21 in > 95% d.e. Purification of 21 to homogeneity, followed by alkaline cleavage with lithium hydroperoxide, affords enantiopure (R)-benzylpropanoic acid 22 and the chiral auxiliary oxazolidin-2-one 18 (Scheme 5).\textsuperscript{10}

\textbf{Scheme 5}
Once again, the use of chiral auxiliaries for asymmetric synthesis is not without its problems however. These include the need to use stoichiometric quantities of expensive chiral auxiliaries; lengthy synthetic protocols for attaching and detaching the chiral auxiliary fragment; and the fact that on cleavage the chiral auxiliary must be separated from the chiral product.
1.6 Directed Reactions

Once a suitable route to a chiral synthon has been identified then it must be synthetically elaborated to afford the desired target chiral molecule via a series of stereoselective reactions that often rely on the presence of existing stereocentres to induce asymmetry. As a consequence of their natural abundance within the structure of a wide range of natural products, a significant number of ‘directed’ reactions have been developed that employ stereogenic hydroxyl groups to control the stereoselective functionalisation of sp\(^2\) centres in high d.e.\(^5\) These hydroxyl directed transformations include protocols for the stereoselective epoxidation, cyclopropanation and hydrogenation of allylic alcohols and these approaches are discussed in brief in the following section.

1.6.1 Hydroxyl directed epoxidations

The stereoselective epoxidation of allylic alcohols is commonly achieved in a diastereoselective manner using either meta-chloroperoxybenzoic acid (m-CPBA) or VO(acac)\(_2\)/H\(_2\)O\(_2\) as epoxidising agents. The hydroxyl group directs stereoselective epoxidation in both cases, however facial selectivity is achieved via a different mechanism in each case.

For example, m-CPBA epoxidised 1,2-disubstituted alkene 23 to afford \(\alpha,\beta\)-epoxyalcohol 24 in high d.e. (Scheme 6).\(^{11,12,13}\) The stereoselectivity of this directed epoxidation was rationalised through transition state 25 in which an electron lone pair on the peracid oxygen atom being transferred to the alkene forms a hydrogen bond with the hydrogen atom of the allylic hydroxyl functionality. As a result the oxygen atom was delivered on the same face as the hydroxyl group and the reaction affords a syn-epoxide in high d.e. (Figure 5).\(^{14}\)

\[
\text{Scheme 6}
\]
Figure 5
In a comparative study, VO(acac)$_2$ was also shown to catalyse efficiently the epoxidation of 1,1-disubstituted alkene 26 to afford the syn-α,β-epoxyalcohol 27 stereoselectively (Scheme 7). Unlike m-CPBA however, the mechanism of this epoxidation was proposed to proceed via transition state 28 in which initial coordination of the vanadium metal to the oxygen lone-pair of the allylic alcohol resulted in the oxygen atom of the coordinated 1$^t$BuOO- fragment being delivered to the olefin (Figure 6).

\[
\begin{align*}
\text{VO(acac)}_2 / \text{1$^t$BuOOH} & \rightarrow \text{OH} \\
(2R)-26 & \rightarrow (2R,3S)-27 \\
\text{diastereoselection} & > 95:5
\end{align*}
\]

Scheme 7

Figure 6

1.6.2 Cyclopropanation
A number of natural products and biologically active compounds contain cyclopropane rings, for example the antifungal antibiotic jawsamycin 29, which was first synthesised in 1996 (Figure 7).^{15}

Figure 7
The most important route for the introduction of the cyclopropane functionality was discovered by Simmons and Smith involving the use of Zn/Cu couple and CH$_2$I$_2$ 30 to generate a zinc carbenoid species for the functionalisation of alkenes.\textsuperscript{16} This procedure has been superseded by the use of diethylzinc to generate a carbenoid equivalent comprised of both the monomeric 31 and the dimeric species 32 that readily underwent addition to olefin 33 to produce a cyclopropane 34 (Scheme 8).\textsuperscript{17}

![Scheme 8](image)

Importantly, the presence of a hydroxyl group in the allylic position of the alkene increased the rate of cyclopropanation whilst also introducing diastereoccontrol into the reaction. This was achieved via coordination of the lone pair of the hydroxyl group to the zinc atom of the carbenoid thus delivering the carbene to the alkene according to the transition state model 35 described in Figure 8.

![Figure 8](image)

Charette \textit{et al.} demonstrated that Et$_2$Zn/CH$_2$I$_2$ affords the best results for these type of hydroxyl directed cyclopropanations.\textsuperscript{18} From an optimised 1:1 ratio of reagent and carbenoid they found that the cyclopropanation of allylic alcohols \textit{cis}-36 and \textit{trans}-38 afforded \textit{syn}-37 and \textit{syn}-39 as the major stereoisomers respectively (Scheme 9).
Scheme 9

Samarium-derived carbenoids offer a mild alternative to the Simmons-Smith reagent with the cyclopropanation reaction occurring at -60°C in a very stereoselective manner. The trans-allylic alcohol 40 yielded the syn-α,β-cyclopropane alcohol 41 with excellent diastereoselectivity (Scheme 10).

Scheme 10

1.6.3 Hydrogenation of acyclic olefins

Hydrogenation of allylic alcohols in the presence of rhodium catalyst 41 consistently affords chiral alcohols that contain new stereogenic centres at their α-position in high d.e. For example, hydrogenation of 1,1-disubstituted alkene 40 afforded an alcohol 42 in which the newly formed methyl group was anti to the pre-existing hydroxyl group (Scheme 11).

Scheme 11

The observed stereochemistry has been explained according to transition state 43 (Figure 9). The rhodium transition metal complexed to both the olefin and the oxygen functionality...
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of 40 to afford transition state 43, that reacted with molecular hydrogen to afford an octahedral complex that subsequently delivered hydrogen to the alkene functionality to afford anti-alcohol 42 in high d.e.

Figure 9

1.7 A new concept in chiral auxiliary design

I wished to devise a synthetic protocol that would combine the synthetic capacity of chiral auxiliaries to generate fragments that contain new stereogenic centres in high d.e. with the potential of directed reactions to control the stereoselective transformation of prochiral centres. The success of this project would afford a new concept in chiral auxiliary design, as well as providing novel methodology for the asymmetric synthesis of enantiopure aldehyde fragments. However, as a consequence of my studies directed towards this aim, a new diastereoselective approach to the synthesis of trisubstituted \((E)\)-\(\alpha,\beta\)-unsaturated amides has been discovered, and I will now review recent developments in methodologies that afford trisubstituted acid derivatives in high d.e.
CHAPTER 2. Review on the Stereoselective Synthesis of Electron-Deficient Alkenes

The importance of stereoselective methods to prepare unsaturated carbonyl compounds with either (E)- or (Z)- stereochemistry for natural product synthesis cannot be underestimated. Indeed, many natural products contain unsaturated carbonyl fragments whose (E)- or (Z)-geometry must be controlled if a successful synthesis is to be achieved. For example, (+)-geldanamycin 44 contains two trisubstituted (E)-alkene fragments and one disubstituted (Z)-alkene fragment (Figure 10).21

![Figure 10](image)

Given their importance, many procedures for the stereoselective synthesis of alkenes have been designed over the years for the stereoselective synthesis of natural products. Before describing specific approaches towards the synthesis of trisubstituted electron-deficient alkenes that are directly relevant to my research, it is instructive to consider briefly some established stereoselective protocols that have recently been employed for introducing highly functionalised alkene fragments into natural product targets.

2.1 General procedures towards the stereoselective synthesis of alkenes

2.1.1 The Wittig reaction

Katsumura et al. described a new route to peridinin in which a novel Wittig reagent 46 was successfully prepared from 3-furanmethanol and reacted with epoxyaldehyde 45 to afford the corresponding furan derivative (E)-47 in excellent yield and as a single isomer, which was subsequently employed for the synthesis of the carotenoid peridinin (Scheme 12).22
2.1.2 The Horner-Emmons reaction

Kibayashi et al. described the first synthesis of antifungal natural product (-)-stelletamide B 52, using reaction of the functionalised phosphonate ester 49 with \(\alpha\)-substituted aldehyde 50 to afford 51 with good (E)-stereocontrol and retention of stereochemistry at the stereogenic centre (Scheme 13).\(^\text{23}\)

\[
\begin{align*}
\text{EtOO} & \quad \text{P(OEt}_2\text{)} \\
\text{49} & \quad \text{BuLi} \\
\text{THF, -78°C} & \quad \text{EtOO} \\
\text{50} & \quad \text{O} \\
\text{51} & \quad \text{66% yield}
\end{align*}
\]

Scheme 13

2.1.3 The Peterson olefination

Chakraborty et al. reported in 2003 the facile diastereoselective Peterson elimination reaction of \(\beta\)-hydroxysilane 53 under basic conditions with (Z)-stereocontrol to afford (+)-croacin A 54 in good yield as the sole isomer (Scheme 14).\(^\text{24}\)
2.1.4 Dehydration of alcohols

Kalaus, Szántay et al. reported an interesting cyclisation reaction for the synthesis of alkaloid (+/-)-minovincine 58, involving dehydration of alcohol 55 to afford alkene 56, which cyclised in a [4+2] cycloaddition fashion to give a 1:1 mixture of the epimers 57a and 57b (Scheme 15).

2.1.5 The Corey-Winter olefination

Aoyama, Shioiri et al. reported the use of the Corey-Winter protocol to introduce unsaturation into a functionalised cyclohexane. syn-Diol 59 was treated with 1,1'-thiocarbonyldimidazole 60 to give thionocarbonate fragment 61 that smoothly gave diene 63 on treatment with the phospholidine 62 (Scheme 16).
2.1.6 The Ramberg-Backlund rearrangement

Taylor et al. reported the stereoselective synthesis of highly desirable exo-glycals via a tandem halogenation/Ramberg-Backlund rearrangement, in which glycosyl sulfone 64 was exposed to elimination conditions to afford (Z)-trisubstituted alkene 65 in high yield, which was subsequently converted to novel β-glycosidase inhibitor 66 (Scheme 17).

Scheme 17

2.1.7 Hydrogenation of alkynes

Winkler et al. has reported the hydrogenation of (E)-67, catalysed by Lindlar's catalyst to afford (E,Z)-alkene 68 quantitatively on his route towards the synthetically challenging polycyclic alkaloid manzamine A 69 (Scheme 18).
2.1.8 The Heck coupling
Kalesse et al. reported the enantioselective synthesis of callystatin A 74 in 2001, a key structural feature of which is the presence of the two-diene moieties. Treatment of alkyne 70 with Schwartz's reagent afforded an organozirconium species, which was quenched with I\(_2\) to give vinyl iodide (E)-71. Subsequent coupling of vinyl iodide 71 and terminal alkene 72 was then carried out under Heck conditions to afford (E,E)-diene 73 in 65% yield (Scheme 19).

2.1.9 Elimination of epoxides
Danishefsky et al. have proposed a novel route to taxol 77 in which an epoxy group was used to protect an alkene at C11 of the taxane skeleton 75 which was reductively removed with SmI\(_2\) to afford olefin (E)-76 in excellent yield (Scheme 20).
2.1.10 The Julia olefination reaction

Ruveda et al. reported in 2003 a one-pot coupling reaction between lithiated benzothiazolylsulfone 80 and lactol alkoxide 78 (in equilibrium with carboxylate aldehyde 79) to produce a synthon for the preparation of (+)-cassiol 82 as a single isomer (Scheme 21).\(^{32}\)

Scheme 20

Scheme 21
2.2 Stereoselective synthesis of trisubstituted electron-deficient alkenes

As described, a range of different procedures have been reported for the synthesis of \( \alpha,\beta \)-unsaturated acid derivatives in a stereoselective fashion. Much of the research described in this thesis is directed towards the stereoselective synthesis of \( (E) \)-trisubstituted \( \alpha,\beta \)-unsaturated amides, and as a consequence an in-depth review of the progress which has been made towards the stereoselective synthesis of trisubstituted acid derivatives is now described.

2.2.1 The Wittig reaction

The Wittig reaction has been the object of intense studies as a method of choice for the synthesis of trisubstituted \( \alpha,\beta \)-unsaturated esters, amides and carboxylic acids in a stereoselective manner. As will be described, the vast majority of \( \alpha,\beta \)-unsaturated acid derivatives prepared in this manner contain a methyl group at their \( \alpha \)-position due to the prevalence of this structural motif in natural product targets arising from biosynthetic pathways.

2.2.1.1 The mechanism of the Wittig reaction

After more than 40 years the mechanism of the Wittig reaction is still under active investigation and initially will be discussed in general terms for the synthesis of disubstituted alkenes.\(^{33,34}\) The reaction occurs \( \text{via} \) a three-step process, as drawn in Figure 11: first the phosphonium salt 83 is deprotonated \( \alpha \) to the phosphorus atom to give stabilised ylid 84 that can also be considered as phosphorane 85. This nucleophilic species then attacks the carbonyl group of the aldehyde 86, generating reversibly the four-membered ring oxaphosphetane intermediates \( \text{syn-87} \) and \( \text{anti-90} \), the ratio of which is highly dependent on the conditions of the reaction and the nature of the aldehyde employed as substrate. The oxaphosphetanes 87 and 90 then collapse \( \text{via} \) a final irreversible step to give alkenes \( (Z)-88 \) and \( (E)-91 \) with triphenylphosphine oxide as a by-product. The phosphorus-oxygen double bond is very strong (599.1 kJ.mol\(^{-1}\)),\(^{35}\) and this factor is a major element in driving the reaction to completion.
Oxaphosphetanes are very unstable species and for stabilised phosphoranes they have rarely been detected, even at temperatures as low as -80 to -100°C. However the unusually stable oxaphosphetane 93 has been isolated and characterised by X-ray crystallography. The resulting structure of oxaphosphetane 93, as shown in Figure 12, revealed that phosphorus was at the centre of a distorted trigonal bipyramid with oxygen atoms occupying the apical positions.

Vedejs et al. reported in 1973 the direct observation of oxaphosphetanes for the reaction between benzaldehyde 95 and an unstabilised phosphorane 94. The reaction was kept at -70°C and a sample was examined by $^{31}$P NMR spectroscopy. The proton noise-decoupled spectrum at -70°C consisted of a broad singlet at $\delta$ 62.7 ppm (width of half-height, $J = 15$Hz), which was consistent with a pentavalent phosphorus species, such as oxaphosphetane 96 (Scheme 22).
As a consequence oxaphosphetanes are currently favoured as true intermediates over another early contender, betaines 89 and 92 (Figure 11), which were considered for a few decades as intermediates in the Wittig reaction. Betaines have never been observed directly in any Wittig reaction under salt-free conditions, however they have been isolated in their complexed form with LiBr.\textsuperscript{39} For example, Vedejs et al. isolated betaine 98 from the reaction of phosphorane 97 and benzaldehyde 95 in the presence of LiBr.\textsuperscript{40} After dilute HBr workup, the hydroxyphosphonium salt 99 was isolated in good yield and reacted with KH at \(-40^{\circ}\text{C}\) in THF to obtain pure oxaphosphetane 100, since the \(^{31}\text{P}\) NMR spectrum showed a broad resonance at \(\delta -68\) ppm characteristic of pentavalent phosphorus. Furthermore, addition of LiBr to a solution of oxaphosphetane 100 was shown to regenerate the betaine-lithium halide adducts 98 (Scheme 23). Therefore it appears that betaines may not be true precursors of oxaphosphetanes, but instead reversible by-products of the reaction of intermediate oxaphosphetanes and lithium salts generated in situ.\textsuperscript{41}

![Scheme 23](image)

Finally, Eisenstein et al. demonstrated, with the help of \textit{ab initio} calculations under salt free conditions,\textsuperscript{42} that oxaphosphetanes are likely to be favoured over betaines as intermediates in the Wittig reaction. It is noteworthy that several mechanistic and kinetic studies have been conducted which led to the proposal of other potential mechanisms that are less widely accepted.\textsuperscript{43,44}

\subsection{2.2.1.2 Stereoselectivity considerations}

The oxaphosphetane is a short-lived intermediate which even at low temperature collapses to an alkene product \textit{via} a \textit{syn}-elimination pathway. Therefore, the stereochemical outcome
of the Wittig reaction is determined in the oxaphosphetane-forming step, as well as by the degree of reversibility of this reaction to afford starting materials. 

Maryanoff et al. have reported the rate study on the reaction of non-stabilised phosphorane 101 and benzaldehyde 95 in THF at -30°C in the presence of LiBr.45,46 The relative ratio of cis- and trans-oxaphosphetanes 102 and 104 formed was measured over 5 hours, the initial ratio was established to be 78:22, and compared to the final Z:E alkene ratio 103:105, 55:45 (Scheme 24). Maryanoff described this discrepancy as stereochemical drift and proposed it as a measure of the reversibility of the reaction. The salt-free reaction of phosphorane 101 and benzaldehyde 95 was monitored using the same procedure. The relative ratio of syn- and anti-oxaphosphetanes 102 and 104 remained constant throughout the reaction, affording a final Z:E ratio 103:105 of > 95:5. Therefore the formation of oxaphosphetanes from an unstabilised ylid under salt-free conditions appears to be essentially irreversible. The major intermediate is then the syn-oxaphosphetane and the reaction is said to be kinetically controlled, and will afford a (Z)-alkene (Scheme 24).

![Scheme 24](image)

The question arises as to why the syn-oxaphosphetane 87 is formed as the kinetic product in preference to the anti-oxaphosphetane 90. Conventional wisdom states that reaction of the phosphorane 85 and the aldehyde 86 occurs to afford a syn-oxaphosphetane 87 because this trajectory of attack minimises steric interactions between R1 of the phosphorane 85 and R2 of the aldehyde 86. In contrast the transition state leading to the anti-oxaphosphetane 90 requires that the R1 group of the phosphorane 85 and the R2 substituent of the aldehyde 86 are orientated in close proximity to each other, a situation which is clearly disfavoured relative to the syn-oxaphosphetane 87 transition state (Figure 13).
Unlike unstabilised ylids, the reaction of EWG-stabilised phosphorane 107 with aldehyde 106 affords the (E)-isomer 109 as the major diastereomer. The dominant explanation to account for this reversal in stereoselectivity is the potential reversibility in the formation of the oxaphosphetane intermediate. Clearly reversibility of this initial step facilitates equilibration of the anti- and syn-oxaphosphetane 108 and 110 intermediates, at a faster rate than their corresponding elimination to afford (E)- and (Z)-alkenes 109 and 111 respectively. This would ensure that the thermodynamically more stable anti-oxaphosphetane intermediate 108 predominates, and consequently the (E)-alkene 109 is formed as the major product (Figure 14).

However, Vedejs et al. have questioned this assumed reversibility in the formation of these type of oxaphosphetane intermediates. He has reported on deprotonation studies of stabilised β-hydroxy phosphonium salts where for the case of an aliphatic aldehyde the erythro salt 112 was shown to produce a (Z)-alkene 113 stereoselectively, thus implying the absence of any reversibility in the (E)-selective addition of a stabilised ylid to an aliphatic aldehyde. In the case of β-hydroxyphosphonium salt 114 derived from an aromatic aldehyde some degree of reversibility in the formation of oxaphosphetane intermediate was observed, affording a significant amount of ester (E)-116 under thermodynamic control (Scheme 25).
2.2.1.3 The Wittig reaction of stabilised phosphoranes is (E)-selective

As we have seen the Wittig reaction of stabilised phosphoranes for the synthesis of disubstituted alkenes is (E)-selective and has proven very popular in research groups in both industry and academia due to its ease of application and its versatility, particularly for the synthesis of natural products.

In a landmark publication in 1961, House et al. reported that reaction of α-methyl phosphorane 117 and acetaldehyde 118 gave methyl (2S)-2-methyl-2-butenoate 119 in 92% d.e. (Scheme 26).47

Clearly from the discussion in the previous section this class of trisubstituted (E)-unsaturated ester is likely to be formed under thermodynamic control, due to the stabilising effect of the ester group. At first sight it is unclear if an (E)-ester of this type is more thermodynamically stable than its (Z)-isomer, however work by Marshall et al. has demonstrated this to be the case.49 They reported that treatment of (Z)-trisubstituted-α,β-unsaturated methyl ester 120 with sodium isopropylthiolate in DMF at high temperatures under equilibrating conditions afforded (E)-conjugated ester 122 as the major product. Likewise a 60:40 mixture of (E)- and (Z)-conjugated esters 120 and 122 under those conditions gave the same (E)-isomer 122 in a E:Z ratio of 93:7. Longer alkyl chains at the α-position (entries 3, 4) did shift the equilibrium, although the (E)-isomer 123 was still more stable than the (Z)-isomer 121 (Scheme 27, Table 1).
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Scheme 27

\[
\begin{array}{c}
\text{CH}_3(CH_2)_7 - O - Me \\
R = (CH_2)_9CH=CH_2
\end{array}
\]

**Table 1**

<table>
<thead>
<tr>
<th>( R_1 )</th>
<th>Time (hrs)</th>
<th>( T (^{\circ}C) )</th>
<th>initial</th>
<th>final</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH(_3)</td>
<td>0.5</td>
<td>90</td>
<td>4 / 96</td>
</tr>
<tr>
<td>2</td>
<td>CH(_3)</td>
<td>16</td>
<td>140</td>
<td>60 / 40</td>
</tr>
<tr>
<td>3</td>
<td>(CH(_2)_9CH=CH(_2))</td>
<td>18</td>
<td>140</td>
<td>7 / 93</td>
</tr>
<tr>
<td>4</td>
<td>(CH(_2)_9CH=CH(_2))</td>
<td>15</td>
<td>140</td>
<td>99 / 1</td>
</tr>
</tbody>
</table>

It appears therefore that the ester functionality in the reaction of \( \alpha \)-substituted stabilised Wittig reagent 117 must be more sterically demanding than the \( \alpha \)-methyl substituent such that formation of *anti*-oxaphosphetane 125 is favoured over formation of *syn*-oxaphosphetane 126 under thermodynamic control (Figure 15).

Figure 15

The use of \( \alpha \)-methyl stabilised Wittig reagents for the formation of trisubstituted (E)-\( \alpha \),\( \beta \)-unsaturated esters has been widely used in natural product synthesis. Its predictability has recently been elegantly demonstrated by Baldwin *et al.* who reported the iterative Wittig reaction of \( p \)-nitrobenzaldehyde 127 with phosphoranes 128 and 129 to access the sterically crowded (E,E,E,E)-tetraene 130, which was employed as a substrate for electrocyclic ring closure to afford the bicyclic core 131 of the novel immunosuppressant SNF 4435C (Scheme 28). 50
Scheme 28

Andersen et al. have reported the total synthesis of (-)-hemiasterlin 134, a structurally novel tripeptide that exhibits potent cytotoxic activity, involving reaction of aldehyde 132 with stabilised phosphorane 128 to afford (E)-α,β-unsaturated ethyl ester 133 as the only isomer in a highly stereoselective manner and with complete retention of the integrity of the stereogenic centre (Scheme 29).51

Scheme 29

A range of other groups have also used the Wittig reaction in their routes to complex natural products, such as (-)-acaterin 135 and (-)-delactonmycin 136 observing excellent diastereoselectivities, and no racemisation of neighbouring stereogenic centres (Scheme 30).52,53
Amos Smith III et al. undertook the total synthesis of the highly popular synthetic target (-)-callystatin A 74. Latent aldehyde equivalent 137 was reacted with stabilised phosphorane 128 to afford α,β-unsaturated ethyl ester 138 with retention of configuration of all the stereogenic centres (Scheme 31). The major (E)-isomer 138 was purified via conversion to its corresponding lactone.\(^5\)

This type of Wittig reaction has also been reported for other masked aldehyde substrates. Rein, Helquist et al. have reported the stereocontrolled synthesis of the C1-C11 fragment 141 of Iejimalide B and D which exhibits potent \textit{in vitro} antitumor activity. Thus, the reaction of hemiacetal 139 and phosphorane 128 afforded α,β-unsaturated ester 140 in good yield and as the sole isomer (Scheme 32).\(^5\)
Scheme 32

On their route towards the stereoselective synthesis of alkaloid (-)-pseudophrynaminol 144, Kawasaki et al. employed aminal 142 and α-substituted phosphorane 120 in a Wittig reaction to afford α,β-unsaturated ester 143 in good yield and selectivity (Scheme 33).\(^{56}\)

Scheme 33

2.2.2 The Horner-Wadsworth-Emmons (HWE) reaction

Due to difficulties arising from separation of reaction side-products (triphenylphosphine oxide) of the Wittig reactions and the general lack of reactivity of some stabilised ylides substituted with an electron-withdrawing group, another popular method of alkene formation is sometimes favoured: the HWE modification. This approach involves the use of phosphonate esters (or the corresponding nitriles or ketones) that can be deprotonated with sodium hydride or alkoxide anions to give enolate-type anions, which react well with aldehydes or ketones to give (E)-alkenes, and under certain specific conditions (Z)-alkenes.

2.2.2.1 The mechanism of the HWE reaction

Phosphonate anions are strongly nucleophilic and react readily with carbonyl compounds under mild conditions to form olefins and water-soluble phosphate esters. In the case of phosphonate esters the anions are doubly stabilised by the presence of the carbonyl group and the phosphonate group. It is widely accepted that the HWE reaction once again occurs under thermodynamic control to afford predominantly (E)-olefins via a mechanism similar to that of the Wittig reaction (Figure 16).\(^ {57}\) Thus the stabilised phosphonoester 145 attacks
the carbonyl of the aldehyde 146 and reversibly forms syn- and anti-oxaphosphetane 147 and 149 where the stereochemistry of the alkene is determined by the stereoselectivity in the initial carbon-carbon bond-forming step. Once again, the anti-oxaphosphetane 147 is generally considered to be more stable than the corresponding syn-oxaphosphetane 149 and collapses irreversibly to the (E)-isomer 148.

![Diagram](image)

**Figure 16**

### 2.2.2.2 The HWE reaction of stabilised phosphonates is (E)-selective
Hayashi *et al.* have employed the HWE reaction in their total synthesis of epolactaene 153. α-Methyl-phosphonate ester 151 reacted with triene aldehyde 150 in a stereoselective manner to afford (E)-α,β-unsaturated ester 152 as essentially the only stereoisomer formed in quantitative yield (Scheme 34).

![Scheme 34](image)

**Scheme 34**

Tan *et al.* have reported the facile condensation of p-methylthiobenzaldehyde 154 with phosphonate 155 to afford (E)-trisubstituted ethyl ester 156 quantitatively, once again as the sole isomer (Scheme 35).

28
Scheme 35
This theme is a general one, since many different groups in recent years have used the HWE reaction as a stereoselective tool to introduce efficiently unsaturated esters and amides into synthons for natural product synthesis, and a representative range of examples are described in Scheme 36.\textsuperscript{61,62}

Scheme 36
Mulzer et al. reported in 1995 a synthesis of $\alpha,\beta$-unsaturated $\gamma$-amino acid (R)-160 with excellent enantioselectivity.\textsuperscript{63} Attack of the phosphonate 158 onto electrophilic ketone 157 afforded (E)-$\alpha,\beta$-unsaturated ester 159 without racemisation of the stereogenic centre in the $\gamma$ position. Deprotection of the silyl ether 159, followed by inversion of the stereocentre using the aza-Mitsonobu reaction led to the $\alpha,\beta$-unsaturated $\gamma$-amino acid 160 (Scheme 37).
Yamada et al. reported an enantioselective route of (+)-dolabellatrienone 163 where they employed the HWE reaction for the synthesis of a late stage intermediate. Thus, reduction of ester 161 with DIBAL-H and reaction with phosphonate 155 in the presence of NaH afforded (E)-α,β-unsaturated amide 162 in a highly diastereoselective fashion (Scheme 38).

Finally, Wiemer et al. has reported on the HWE condensation of α-phosphonolactone 164 and acetaldehyde 125 to afford with modest stereoselectivity highly functionalised intergerrineic acid lactone 165, which was used as an intermediate for the synthesis of usaramin 166 (Scheme 39).

2.2.2.3 The modified HWE reaction in the presence of metal salts

So far we have described the successful preparation of (E)-α,β-unsaturated esters via HWE reaction, where the generation of the phosphonate carbanion is achieved using a relatively strong base such as "butyllithium, potassium "butoxide, or sodium hydride. Under certain
circumstances the aldehyde component may be sensitive to strong bases, and competing racemisation, aldol condensation, or decomposition of the aldehyde can occur, and thus milder conditions are preferable.

Seyden-Penne et al. described the formation of a tight complex 167 between a lithium cation and the carbanion derived from phosphonate 158 (Figure 17) and showed that in the presence of a lithium salt that phosphonates could be deprotonated with milder bases such as a tertiary amine.66

For example, in 1984, Masamune, Roush et al. reported that phosphonate 158, complexed with lithium cation could be deprotonated with mild base such as DBU or diisopropylethylamine to generate a reactive phosphonate carbanion.67 Addition of aldehyde 168 gave (E)-disubstituted α,β-unsaturated ester 169, thus avoiding epimerisation of the stereogenic centre, which had been previously reported for the same system in the presence of sodium hydride (Scheme 40).

In parallel studies to this work Rathke et al. reported that lithium or magnesium salts also facilitate the use of a weak base such as triethylamine, thereby extending the range of conditions introduced by Masamune, Roush et al. Thus, reaction of cyclohexanone 170, and benzaldehyde 95 with phosphonate 158 afforded the olefinated substrates (E)-171 and (E)-119 in a stereoselective fashion (Scheme 41).68
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Scheme 41
In 1999 West et al. reported the preparation of ethyl ester \((E)-173\) from methyl substituted phosphonate 155 in good yield and selectivity using the conditions developed by Masamune, Roush et al. (Scheme 42). Importantly no products arising from aldol condensation of aldehyde 172 with itself were observed.\(^6\)

Scheme 42
Paterson et al. have found that reaction of \(\beta\)-ketophosphonate 175 and labile aldehyde 174 under strongly basic conditions led to the epimerisation of the final product at the \(\alpha\)-position. However the milder protocol proposed by Masamune, Roush et al. was found to give a poor conversion to the final product \((E)-176\). Consequently he demonstrated that barium hydroxide was effective in this system for a range of functionalised \(\beta\)-ketophosphonates.\(^7\) Thus the reaction of phosphonate 175 and labile aldehyde 174 with barium hydroxide afforded \(\alpha,\beta\)-unsaturated ketone \((E)-176\) in 96% yield and > 95% d.e. (Scheme 43).
Scheme 43
This novel procedure has found further application in the synthesis of natural product synthesis using \( \alpha \)-substituted phosphonates. For example, Leahy et al. reported in 2003 an enantioselective synthesis of the popular target antitumor macrolide rhizoxin D. The olefination reaction involving oxazole-based aldehyde 177 and highly functionalised \( \beta \)-ketophosphonate 178 failed under the conditions proposed by Masamune and Roush. However the modification introduced by Paterson et al. proved to be highly successful in affording \((E)\)-trisubstituted-\( \alpha,\beta \)-unsaturated ketone 179 in 65% yield and as the only isomer (Scheme 44).
2.2.2.4 Progress towards the development of a (Z)-selective HWE reaction

As we have seen reaction of aldehydes with stabilised ylides such as 155 occurs with (E)-selectivity. However, it has been found that (Z)-selectivity may be obtained under certain conditions where formation of oxaphosphetanes and irreversible elimination to olefin products is quicker than their equilibration with starting materials.

In 1974 Seyden-Penne et al. reported on the influence of the counter cation and temperature in the reaction between stabilised phosphonitrile 181 and benzaldehyde 95 (Scheme 45).\(^7\) The use of 'BuOLi in the HWE reaction of ylide 181 and benzaldehyde 95 at +65°C afforded the thermodynamic product (E)-182 with 60% d.e.; whilst the same reaction using 'BuOK as a base at -78°C gave the (Z)-olefin 183 with 80% d.e., indicating that no equilibration was occurring at low temperature, and that (Z)-183 was being formed under kinetic control.

![Scheme 45](image)

In the HWE reaction, phosphonitriles were found to be even more sensitive to changes in metal cation and temperature. Kishi et al. reported in 1980 that whilst ester-stabilised phosphonate 185 reacted with aldehyde 184 to afford (E)-isomer 187 as the major product, the corresponding cyano conjugated phosphonate 186 gave the alternative (Z)-stereoisomer 188 under the same conditions (Scheme 46).\(^7\)

![Scheme 46](image)
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It is noteworthy that when this novel procedure was applied to the preparation of the related (Z)-α,β,γ,δ-bis-unsaturated cyanide 190 via reaction of aldehyde 189 with nitrile 186 the (Z)-stereoselectivity was 10:1 enabling a protected C15-C29 fragment 191 of rifamycin to be prepared (Scheme 47).

Scheme 47

Similarly, while designing an enantioselective route to naturally-occurring cancer chemopreventive agent sarcophytol A 197, Takayanagi et al. have reported that the Horner-Emmons reaction at -20°C between phosphonate ethyl ester 193 and aldehyde 192 afforded (2Z,4E)-diene 195 in 40% d.e. Although decreasing the reaction temperature tended to increase the (Z)-selectivity, the HWE reaction was found not to occur below -20°C. However the Horner-Emmons reaction of phosphonate nitrile 194 at -78°C produced (2Z,4E)-diene 196 in 94% d.e. (Scheme 48)

Scheme 48
In 1977 Breuer et al. and Seyden-Penne et al. proposed that the enolate 198 of a cyclic phosphonate in which the phosphorus atom was constrained within a five-membered ring would be forced to adopt a strained tetrahedral geometry.\textsuperscript{75,76} They reasoned that this strain would be released on reaction with an aldehyde, such as isobutyraldehyde 199, to form oxaphosphetane 200 where the phosphorus atom would now adopt a less strained trigonal bipyramidal geometry. Oxaphosphetane would then decompose rapidly under kinetic control to afford the (Z)-isomer 201 as the major product (Scheme 49).

Scheme 49

In 1991 Savignac et al. screened some oxygen and nitrogen-containing ring systems, and demonstrated that spirophosphoranes 202 reacted with a range of aliphatic aldehydes to afford (Z)-trisubstituted α,β-unsaturated ethyl ester 203 (Scheme 50).\textsuperscript{77}

Scheme 50

In 1983 Still et al. reported that the HWE reaction of electrophilic trifluoroethyl phosphonate 204 and benzaldehyde 95 produced (Z)-α,β-unsaturated methyl ester 205 in 66% d.e.\textsuperscript{78} They also reported that employing strongly dissociated base systems like KHMDS/18-crown-6 allowed the (Z)-selectivity to reach > 96% d.e. Under those optimised conditions, aromatic, saturated and unsaturated aliphatic aldehydes reacted successfully with phosphonate 204 to afford (Z)-esters 206a-c in a highly stereoselective fashion (Scheme 51).
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\[
\begin{align*}
\text{KHMDM/ 18-crown-6 THF, -78°C} \quad (Z)-205 \\
94\% \text{ d.e.} \\
>95\% \text{ yield}
\end{align*}
\]

\[
\begin{align*}
(Z)-206a \\
46\% \text{ d.e.} \\
18\% \text{ yield}
\end{align*}
\]

\[
\begin{align*}
(Z)-206b \\
>95\% \text{ d.e.} \\
79\% \text{ yield}
\end{align*}
\]

\[
\begin{align*}
(Z)-206c \\
>96\% \text{ d.e.} \\
80\% \text{ yield}
\end{align*}
\]

Scheme 51

As has been described, the HWE reaction is generally believed to proceed under thermodynamic control (see section 2.2.2.1). However, the electron-withdrawing capacity of the trifluoroethoxy group enhances the electrophilic character of the phosphorus atom of phosphonate 204, which Ando later proposed accelerates the ring-closing step to form the oxaphosphetane, therefore reducing the possibility for the kinetic syn-oxaphosphetane to equilibrate to the thermodynamically-favoured anti-oxaphosphetane.\(^7\)

In support of this hypothesis, Still \textit{et al.} has reported that (E)-isomer 207 was obtained from the reaction between benzaldehyde 95 and trimethyl phosphonate 151 under the same basic conditions used to produce (Z)-205, implying that the electron-withdrawing group of the phosphorus fragment is controlling the (Z)-stereochemistry of the product (Scheme 52).

\[
\begin{align*}
\text{KHMDM/ 18-crown-6 THF, -78°C} \quad (E)-207 \\
91\% \text{ d.e.} \\
83\% \text{ yield}
\end{align*}
\]

Scheme 52

Kobayashi \textit{et al.} has reported that reaction of new \(\alpha\)-ethyl HWE reagent 209 with \(\alpha\)-substituted aldehyde 208 gave (Z)-\(\alpha\beta\)-unsaturated methyl ester 210 in a stereoselective fashion (Scheme 53).\(^8\) This synthon was subsequently employed to determine the absolute stereochemistry of natural product callystatin A 74.
Scheme 53
Wiemer et al. experienced difficulties in carrying out a conventional HWE reaction using phosphonate 211 and aldehyde 212, which proceeded with no stereocontrol to afford a 1:1 mixture of (Z)- and (E)-isomers. They reasoned that reaction of aldehyde 212 with phosphonate 213 that contained a terminal acetal group would result in better selectivity via chelation of the acetal oxygen atoms to the lithium counteranion. Indeed, when phosphonate 213 was treated with lithium amide in the presence of LiCl at low temperature for 56 hours it gave selectively the (E)-isomer 215. The potential of the trifluoroethylphosphonate methodology was further demonstrated, since treatment of aldehyde 212 with phosphonate 214 resulted in the formation of (Z)-216 in 50% d.e. (Scheme 54).

Scheme 54
This modification of the original HWE procedure has proven to be exceptionally popular in recent years for the preparation of (Z)-α,β-unsaturated carboxylic acid derivatives in the total synthesis of natural products, such as (rac)-sterekunthal A 217, epothilone B 218, lasonolide A 219, and (+)-ratjadone 220 (Scheme 55).
Scheme 55. Selected recent examples of application of the (Z)-selective HWE in the synthesis of natural products.
Ando first reported on an alternative procedure for the preparation of 2-disubstituted ethyl esters (Z)-118 in a stereoselective manner using phosphonates in which the phosphorus atom is substituted with aryloxy groups. The reaction of diphenylphosphonate 222 and benzaldehyde 95 afforded \( \alpha,\beta \)-unsaturated ester (Z)-118 in quantitative yield and 90% d.e. (Scheme 56). Electron-withdrawing or electron-donating groups on the aromatic group of the phosphonate did not affect the d.e., or yield of the reaction, whilst the presence of a bulky alkyl group substituent (methyl, \( \text{\textsuperscript{6}} \)-butyl and \( \text{\textsuperscript{1}} \)-propyl) in the ortho position of the aryloxy group was shown to improve the overall diastereoselectivity of the reaction.

Scheme 56

Ando has subsequently employed this approach for the preparation of trisubstituted \( \alpha,\beta \)-unsaturated esters 224 (Scheme 57, Table 2). Substitution at the ortho position of the aryloxy substituent with a larger group once again improved the selectivity steadily from 90% d.e for \( \text{Ar} = \text{Ph} \) to 94% d.e. for \( \text{Ar} = \text{o-PrPh} \) (entry 1, 2), whilst aldehydes substituted at the \( \alpha \)-position also proceeded with good stereocontrol (entry 4, 5). However, there were some limitations using this approach since reaction of phosphonate 223 with trans-2-hexenal 225 gave no products at \(-78^\circ\text{C}\).

Scheme 57

Range of aldehyde substrates
Chatter 2

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<table>
<thead>
<tr>
<th>Base</th>
<th>Conditions</th>
<th>Ar</th>
<th>aldehyde</th>
<th>Yield (%)</th>
<th>Z:E ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>'BuOK -95 to -78°C</td>
<td>Ph</td>
<td>95</td>
<td>98</td>
<td>95:5</td>
</tr>
<tr>
<td>2</td>
<td>'BuOK -95 to -78°C</td>
<td>o-PrPh</td>
<td>95</td>
<td>100</td>
<td>97:3</td>
</tr>
<tr>
<td>3</td>
<td>Triton B -78 to 0°C</td>
<td>o-PrPh</td>
<td>225</td>
<td>95</td>
<td>89:11</td>
</tr>
<tr>
<td>4</td>
<td>NaH -78 to 0°C</td>
<td>o-PrPh</td>
<td>226</td>
<td>95</td>
<td>99:1</td>
</tr>
<tr>
<td>5</td>
<td>NaH -78 to 0°C</td>
<td>o-PrPh</td>
<td>227</td>
<td>79</td>
<td>98:2</td>
</tr>
</tbody>
</table>

Table 2

Ando has also reported on the reaction of α-butylyphosphonate 228 with a range of aldehydes (Scheme 58, Table 3). Lower selectivities were obtained using Triton B and 'BuOK, however use of NaH as base at -78°C improved the diastereoselectivity to 97% (Table 3, entry 1). Reaction with octyl aldehyde 229 was the least selective affording increasing amounts of the thermodynamic product, the (E)-isomer, as the temperature was lowered (entry 2-4).

\[
\text{EtO}_2\text{C}\&\text{P(O)O-PrPh}_2\xrightarrow{\text{1- NaH, DMSO}} \text{EtO}_2\text{C}\&\text{P(O)O-PrPh}_2\xrightarrow{\text{2- Bu}} \text{R}_1\text{CHO} \rightarrow \text{CO}_2\text{Et}
\]

Range of aldehyde substrates

Scheme 58

<table>
<thead>
<tr>
<th>Base</th>
<th>conditions</th>
<th>aldehyde</th>
<th>Yield (%)</th>
<th>Z:E ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH -78°C</td>
<td>95</td>
<td>95</td>
<td>97:3</td>
</tr>
<tr>
<td>2</td>
<td>NaH 0°C</td>
<td>229</td>
<td>94</td>
<td>83:17</td>
</tr>
<tr>
<td>3</td>
<td>NaH -20°C</td>
<td>229</td>
<td>88</td>
<td>82:18</td>
</tr>
<tr>
<td>4</td>
<td>NaH -40°C</td>
<td>229</td>
<td>58</td>
<td>69:31</td>
</tr>
<tr>
<td>5</td>
<td>'BuOK -78 to -40°C</td>
<td>229</td>
<td>69</td>
<td>12:88</td>
</tr>
</tbody>
</table>

Table 3

The sterically hindered ethyl-2-(diphenylphosphono)-3-methylbutanoate 231 was prepared by alkylation of ethyl (diphenylphosphono) acetate 230 with isopropyl iodide after treatment with NaH in DMSO (Scheme 59, Table 4). The reaction of the anion of 231 with benzaldehyde 95 initially gave poor yields of (Z)-232 but good selectivity, however reaction at higher temperature was more successful (entry 1). Optimisation of the reaction
of phosphonate 231 with octylaldehyde 229 (entry 2,3) or cyclohexanecarboxaldehyde 233 (entry 4) gave \((Z)-\)olefins 232 with excellent selectivities but modest yields.

![Scheme 59](image)

**Table 4**

The potential of this methodology to afford \((Z)-trisubstituted\) \(\alpha,\beta\)-unsaturated esters in high diastereoselectivity has also been demonstrated in natural product synthesis. For example, Dias et al. reported their efforts towards the enantioselective synthesis of C1-C11 fragment 237 of callystatin A. Thus, reaction of labile aldehyde 235 and \(\alpha\)-ethylphosphonoester 234 with sodium hydride afforded \((Z)-trisubstituted\) \(\alpha,\beta\)-unsaturated ester 236 in 93% yield and 90% d.e. (Scheme 60).

![Scheme 60](image)
Limitations of the Wittig and HWE reaction

The Wittig and HWE reactions are very versatile procedures and now constitute a powerful tool for organic chemists who are involved in the total synthesis of natural products.\(^8\)

There are however some cases where the HWE reaction affords trisubstituted \((E)-\alpha,\beta\)-unsaturated esters with modest or no selectivity. For example, Li et al. have reported that reaction of aldehyde 238 with phosphonate 239 afforded a 1:1 mixture of isomers \((E)-240\) and \((Z)-241\) (Scheme 61).\(^8\)

![Scheme 61](image)

Tius et al. have reported the use of intramolecular HWE methodology in the macrocyclisation of intermediate 242 in their route towards the enantioselective synthesis of cytotoxic (+)-desepoxyasperdiol 244.\(^9\) A variety of strong basic conditions (NaH, NaHMDS, Li(O\(\text{Pr}\))\(_3\) and K\(_2\)CO\(_3/18\)-crown-6) failed to produce olefin 243 in significant quantities. However treatment of 242 under conditions originally reported by Masamune et al. did result in cyclisation to afford a 2:1 isomeric mixture of \((E)-243\) and its \((Z)\)-isomer in a combined 30\% yield (Scheme 62).\(^6\)

![Scheme 62](image)
The nature of the base used for deprotonation of the phosphonate, and the presence of additives, can also affect the selectivity of the reaction. Roush et al. has reported the synthesis of intermediate 247 toward the synthesis of kijanolide, involving olefination of the advanced aldehyde 245 with 246. However reaction of phosphonate 246 with KHMDS or LHMDS in THF at -78°C, followed by addition of aldehyde 245 gave poor diastereoselectivities for 247 with $E:Z$ ratios ranging from 1:1 to 1.5:1. However the addition of lithium salts, as described by Masamune, Roush et al. enabled (E)-trisubstituted ester 247 to be obtained with much improved diastereocontrol (Scheme 63).

\[
\begin{align*}
\text{Scheme 63} \\
2.2.2.6 \text{ Asymmetric Wittig reaction} \\
\text{One of the major recent advances concerning the Wittig reaction has been made in studies of its asymmetric version. Several variations of this methodology have been described in order to induce asymmetry and these approaches have recently been reviewed by Rein et al.}^{92} \\
\text{The first strategy involves desymmetrisation of a ketone with a chiral phosphonate reagent. For example, Abiko, Masamune et al. reported that reaction of prochiral ketone 250 with phosphonate 249, containing a benzopyrano-[4,3-c]-iso-oxazolidine as chiral auxiliary afforded trisubstituted unsaturated amide 251 as a single enantiomer (Scheme 64).}^{93}
\end{align*}
\]
**Scheme 64**

Another strategy is kinetic resolution whereby a chiral reagent reacts selectively with only one enantiomer of a racemate. Reiser *et al.* have reported the use of 8-phenylmenthol-derived chiral auxiliary to selectively react with the (S)-enantiomer of aldehyde 252. Thus reaction of racemic aldehyde 252 and the anion of chiral phosphonate 253 afforded (S,Z)-α,β-unsaturated ester 254 in a diastereoselective manner (Scheme 65).

**Scheme 65**

The major drawback of kinetic resolution is the maximum yield obtainable that is 50%, therefore the racemic substrate needs to be present in at least a two-fold excess for complete conversion of the chiral reagent into the desired product. One solution is to carry out the reaction under conditions where the enantiomers of the aldehyde substrate can interconvert. Rein *et al.* recognised that α-amino aldehydes are easily racemised and proposed that under the basic conditions used for the HWE reaction that amino aldehyde (S)-255 would react preferentially with phosphonate 253 while enantiomer (R)-255 would be racemised. Thus, the reaction of 1 equivalent of racemic aldehyde 255 and 1.1 equivalent of chiral phosphonate 253 in the presence of 1 equivalent of KHMDS, afforded (S,Z)-olefin 256 as the major product in 56% yield and the “mismatched” (R,E)-olefin 257 in 13% yield (Scheme 66).
Scheme 66
An alternative strategy, which has also been used for the stereoselective synthesis of trisubstituted (E)-α,β-unsaturated esters was based on parallel kinetic resolution in which both enantiomers of a racemic aldehyde react with a different chiral reagent selectively to afford products that can be separated due to differences in physical properties imparted by their different chiral auxiliary fragments. Thus, Rein et al. have reported that reaction of 1 equivalent of racemic aldehyde 255 with 0.5 equivalent of (Z)-selective menthol-based phosphonate 253 and 0.5 equivalent of (E)-selective 1,2-diphenylaziridine-based phosphonate 258, resulted in a mixture of olefins (R,E)-259 and (S,Z)-256 which were easily separated via chromatography (Scheme 67).96

Scheme 67
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2.23 Elimination reactions

Another type of procedure for affording $\alpha,\beta$-unsaturated carboxylic acid derivatives is through the stereoselective elimination of $\beta$-hydroxyacid derivatives \textit{via} E2-type eliminations pathways under kinetic control, or \textit{via} E1-type mechanisms under thermodynamic control.

2.2.3.1 Dehydration reactions

Ohmizu \textit{et al.} reported the highly stereoselective synthesis of (E)-$\alpha$-substituted cinnamate 261 \textit{via} treatment of \textit{anti}-aldolate 260 with 1-ethyl-3-(3-dimethylamino)propylcarbodiimide as a dehydrating agent.\textsuperscript{97} Alternatively the (Z)-$\alpha$-substituted cinnamate ester 263 was generated from dehydration of the corresponding \textit{syn}-aldolate 262 (Scheme 68). It should be noted that the selectivity observed in these elimination reactions is opposite to that expected if an E2 mechanism was in operation.

Scheme 68

Bartoli, Mercantoni \textit{et al.} have also developed an efficient procedure for the diastereoselective dehydration of aldolate compounds using a mixed CeCl$_3$.7H$_2$O/NaI system.\textsuperscript{98} For example $\beta$-hydroxy ester 264 was dehydrated to afford cinnamate ester (E)-265 in excellent yield and as the sole isomer. No mechanism has been proposed to explain the selectivity of this remarkable elimination reaction, however it should be noted that no reaction occurred in the absence of sodium iodide.
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Scheme 69

Nayak et al. reported the reductive dehydroxylation of Baylis-Hillman adducts which afforded the thermodynamically more stable (E)-cinnamate esters. Thus, aldolate 266 in the presence of the strong Lewis acid TiCl₃ and reducing agent LiAlH₄ in refluxing THF afforded (E)-α,β-unsaturated ester 267 in a stereoselective fashion but only in a modest yield (Scheme 70, Table 5).

<table>
<thead>
<tr>
<th>Ar</th>
<th>Yield (%)</th>
<th>E:Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>46</td>
<td>88:12</td>
</tr>
<tr>
<td>p-MeOPh</td>
<td>46</td>
<td>87:13</td>
</tr>
<tr>
<td>3,4-(CH₂O)Ph</td>
<td>41</td>
<td>92:8</td>
</tr>
<tr>
<td>2-furfuryl</td>
<td>50</td>
<td>96:4</td>
</tr>
</tbody>
</table>

Table 5

Titanium is oxophilic and will chelate between the β-hydroxyl group and the carbonyl oxygen of the ester inducing some selectivity into the reduction/elimination process. Transition state 270 results in a large steric crowding between the β-aromatic and alkoxy group of the ester, favouring transition state 268, which led to the formation of (E)-267 after rapid H-capture from radical 269 (Figure 18).

Figure 18
2.2.3.2 Elimination of thioalcohols

The elimination of syn-β-hydroxy-α-phenylthio esters to afford unsaturated esters via E2 elimination had been reported by a number of groups, however the starting syn-α-thioaldolates were not easily prepared. Shimagaki et al. reported that facile reduction of β-ketoester 271 afforded the desired syn-aldolate 272 in excellent yield and in a stereoselective fashion. E2 elimination of the thioester 272 then occurred readily to afford selectively the isomer (Z)-273 (Scheme 71).

\[
\text{Scheme 71}
\]

2.2.3.3 Aldol condensation and elimination

Verkade et al. have reported on the efficient preparation of (E)-α-methyl-α,β-unsaturated methyl esters 277 in the presence of pro-azaphosphatane 276 via aldol condensation of aromatic aldehydes 275 and methyl propionate 274 followed by in-situ dehydration of the resultant aldolate. Thus, this reaction afforded (E)-unsaturated esters 277 in excellent yield and as essentially single stereoisomers (Scheme 72, Table 6). It is noteworthy that Verkabe proved that the base 276 could be recovered at the end of the reaction in 81% yield, thereby demonstrating that the only by-product of this reaction is water.

\[
\text{Scheme 72}
\]
2.2.3.4 Elimination of halogen with $\text{SmI}_2$

Concellón et al. have reported that samarium iodide is a highly efficient reagent for promoting the $\beta$-elimination of a wide range of $\alpha$-halo-$\beta$-hydroxyesters 278 and 279, yielding high yields of trisubstituted unsaturated esters 280 with consistently high ($E$)-selectivities.$^{104}$ Aliphatic, unsaturated and aromatic aldehydes could be employed as substrates, whilst the size of the alkyl group on the carboxyl ester did not effect the selectivities. Better conversions were obtained when $\text{SmI}_2$ was formed in situ by adding diiodomethane (2.5 eq.) to a suspension of samarium metal (2.5 eq.) and 2-halo-3-hydroxyesters 278 and 279 in THF at room temperature (Scheme 73, Table 7).$^{105}$

Scheme 73

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Ph</td>
<td>93</td>
</tr>
<tr>
<td>2 $p$-ClPh</td>
<td>95</td>
</tr>
<tr>
<td>3 $p$-MeOPh</td>
<td>68</td>
</tr>
<tr>
<td>4 o-MeOPh</td>
<td>87</td>
</tr>
<tr>
<td>5 furyl</td>
<td>83</td>
</tr>
</tbody>
</table>

Table 6

2.2.3.4 Elimination of halogen with $\text{SmI}_2$

Concellón proposed a chelation-control model to account for the observed stereoselectivity in which a samarium enolate intermediate 281 is formed. Chelation of the oxophilic $\text{Sm}^{III}$
centre to the oxygen atom of the β-hydroxyl group produced a six-membered ring 281 thus increasing the leaving group ability of the hydroxyl group. In chair-like transition state A the bulky alkyl group R₁ occupies the more favoured equatorial position resulting in a cis relationship between R₂ and R₁ and consequently elimination affords (E)-α,β-unsaturated esters. This mechanism also explains why O-acetylated β-hydroxy ester (entry 1) was eliminated in poor yield in relatively low d.e. (Figure 20).

![Mechanistic proposal for the elimination of 2-halo-3-hydroxyesters with Sml₂](image)

**Figure 19.** Mechanistic proposal for the elimination of 2-halo-3-hydroxyesters with Sml₂

Using essentially the same methodology the reaction of 2-chloro-3-hydroxyamides syn-282 and anti-283 with Sml₂ afforded mixed results (Scheme 74, Table 8). Disubstituted unsaturated amides (E)-284 (entry 1) were prepared in good yield and with good (E)-selectivity. Lower diastereoselectivities and poorer conversions were observed in attempting to prepare trisubstituted unsaturated amides (E)-284 (entry 2) but an increase in the loading in the Lewis acid resulted in high to excellent (E)-selectivities (entries 3-5).

![Scheme 74](image)

**Scheme 74**

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>T (°C)</th>
<th>eq. Sml₂</th>
<th>d.e.</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCHPh</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>25</td>
<td>2.5</td>
<td>&gt;98</td>
</tr>
<tr>
<td>1</td>
<td>Ph</td>
<td>H</td>
<td>Me</td>
<td>Et</td>
<td>25</td>
<td>2.5</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>H</td>
<td>Me</td>
<td>Et</td>
<td>-25</td>
<td>4</td>
<td>&gt;98</td>
</tr>
<tr>
<td>3</td>
<td>p-MeOC₆H₄</td>
<td>H</td>
<td>Me</td>
<td>t'Pr</td>
<td>-25</td>
<td>4</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>cyclohexyl</td>
<td>H</td>
<td>Me</td>
<td>Et</td>
<td>-25</td>
<td>4</td>
<td>&gt;98</td>
</tr>
<tr>
<td>5</td>
<td>n-heptyl</td>
<td>H</td>
<td>Me</td>
<td>Et</td>
<td>-25</td>
<td>4</td>
<td>&gt;98</td>
</tr>
</tbody>
</table>

**Table 8**
Finally Concellón et al. reported last year that SmI$_2$ could be used to promote the elimination of epoxyesters syn-285 and anti-286 to yield $\alpha$$\beta$-unsaturated ester (E)-287 with high (E)-selectivities and good yields (Scheme 75).\textsuperscript{107}

\[ \text{syn-285 and anti-286} \rightarrow \text{(E)-287} \]

\[ \text{84\% yield} \quad >98\% \text{ d.e.} \]

Scheme 75

2.2.3.5 The Peterson olefination

The Peterson olefination is often seen as the silicon analogue of the Wittig reaction in which a silyl carbanion 288 attacks an electrophilic aldehyde 289 (or a ketone) to afford a mixture of $\beta$-hydroxysilanes 290 and 291, which can then eliminate to afford either olefins 292 and 293 (Figure 20).

\[ \text{288} + \text{289} \rightarrow \text{290, 291} \rightarrow \text{292, 293} \]

Figure 20

The elimination of $\beta$-hydroxysilane 294 is stereoselective and depends on the conditions employed for elimination. Acid-promoted elimination occurs via an anti-periplanar mechanism to afford olefin 292, while treatment of $\beta$-hydroxysilane 294 with base occurs via the 4-membered species 295 and affords olefin 293. Therefore, both geometric isomers can potentially be prepared from the same $\beta$-hydroxysilane 294, depending on the conditions employed for elimination (Figure 21).

\[ \text{294} \rightarrow \text{295} \rightarrow \text{292, 293} \]

Figure 21
For the specific cases of silyl carbanions stabilised with an electron-withdrawing group it has usually not been possible to isolate $\beta$-hydroxysilanes intermediates since they spontaneously eliminate to afford the $\alpha,\beta$-unsaturated acid derivatives.

Larson et al. reported that silylation of the lithium enolate of ester 296 afforded silyl ester 297. Further deprotonation, addition of benzaldehyde and syn-elimination afforded (Z)-unsaturated ester 298 in modest yield and selectivity (Scheme 76).

\[
\begin{align*}
\text{OEt} & \quad \text{OEt} \\
1\text{-LDA} & \quad 1\text{-LDA} \\
\text{SiPh}_2\text{Me} & \quad \text{PhCHO} \\
\text{THF, -78°C} & \quad \text{THF, -78°C} \\
296 & \quad 297 \\
\end{align*}
\]

\((Z)-298\)

65% yield

\(Z:E\) 77:23

Scheme 76

The length of the alkyl group on the phosphonate in the Wittig reaction and its variations can dramatically decrease the overall stereoselectivity (see section 2.2.2.5). Larson et al. found that the Peterson olefination of the lithium enolate of silyl ester 300 and aldehyde 299 afforded the unsaturated ethyl ester (Z)-301 once again with only modest selectivity (Scheme 77).

\[
\begin{align*}
\text{LDA} & \quad \text{LDA} \\
\text{SiMePh}_2 & \quad \text{THF, -78°C-reflux} \\
299 & \quad 300 \\
\text{THF, -78°C-reflux} & \quad \text{THF, -78°C-reflux} \\
\end{align*}
\]

\((Z)-301\)

62% yield

\(Z:E\) 71:29

Scheme 77

In 1996 Hart et al. prepared acetal-protected cyclohexanone 304 via Peterson olefination as a target on his route to terpenoid 305. Thus, the reaction of lithium enolate of $\alpha$-trimethylsilylethylester 303 and aldehyde 302 afforded unsaturated ester (Z)-304 in moderate yield and selectivity (Scheme 78).
Scheme 78

Finally in 1999 Evans et al. elected to use the Peterson reaction for olefination of ketone 306 as an alternative to the HWE reaction, which was found to afford the opposite (Z)-selectivity. 110 Thus, the reaction of cyclic ketone 306 and methyl (trimethylsilyl)acetate 307 with LDA in THF at -78°C gave α,β-unsaturated ester (E)-309 in 99% yield and 46% d.e. It is noteworthy that if NaHMDS was employed in THF the stereoselectivity was inverted and (Z)-308 was afforded in 64% d.e. (Scheme 79).

Scheme 79
2.2.4 Palladium coupling

2.2.4.1 The Heck reaction

Another means of preparing trisubstituted α,β-unsaturated esters containing β-aryl substituent is via the Heck reaction involving the coupling of an aryl halide or triflate and a disubstituted α,β-unsaturated ester in the presence of palladium catalyst and a base.

The Heck reaction is initiated by oxidative addition of halide 311 to a palladium Pd(0) species 310, the resulting vinyl (or aryl) palladium Pd(II) intermediate 312 then forms a π-complex with the alkene 313, which rearranges to σ-complex 314 resulting in carbon-carbon bond formation. σ-Complex 314 decomposes by β-elimination to afford the coupled product 316 and the Pd(II) catalyst species 315 which is eliminated by a base to regenerate Pd(0) species 310 (Figure 22).

Figure 22

Unlike the preparation of disubstituted α,β-unsaturated carboxylic acid derivatives, using this methodology, reports on the stereo and regioselective synthesis of trisubstituted esters are relatively rare. Moreno-Manas et al. have reported that β,β-diarylpropenamides (E)-318 could be prepared using the Heck reaction, affording (E)-esters as major products for both electron-donating and electron-withdrawing aryl iodides 317 (Scheme 80, Table 9). A palladium-iodo complex added to alkene 119 in a stereoselective fashion to afford (E)-318, although E/Z isomerisation was observed as the temperature of the reaction was increased (entry 2). With electron-withdrawing substituents in the para-position some biaryl products 319 were also observed (entry 4).

55
Scheme 80

<table>
<thead>
<tr>
<th>X</th>
<th>Time (days)</th>
<th>T (°C)</th>
<th>Yield (%)</th>
<th>E:Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe</td>
<td>8</td>
<td>60</td>
<td>73</td>
<td>83:17</td>
</tr>
<tr>
<td>OMe</td>
<td>2</td>
<td>120</td>
<td>81</td>
<td>64:33</td>
</tr>
<tr>
<td>Me</td>
<td>2</td>
<td>80</td>
<td>67</td>
<td>100:0</td>
</tr>
<tr>
<td>CF₃</td>
<td>9</td>
<td>60</td>
<td>19ᵃ</td>
<td>100:0</td>
</tr>
</tbody>
</table>

ᵃ 4,4’Bis(trifluoromethyl)biphenyl (6% yield) was also isolated.

Table 9

Moreno-Manas et al. reported a year later that the equivalent nitrile (E)-321 could also be obtained in improved yield and stereoselectivity using cinnaminitrile 320 as a coupling partner under related conditions (Scheme 81, Table 10).

Scheme 81

<table>
<thead>
<tr>
<th>X</th>
<th>Yield (%)</th>
<th>% recovered 320</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH₂</td>
<td>78</td>
<td>-</td>
</tr>
<tr>
<td>CH₃</td>
<td>80</td>
<td>9</td>
</tr>
<tr>
<td>Cl</td>
<td>55</td>
<td>29</td>
</tr>
</tbody>
</table>

Table 10

The same research group has also reported on the alternative preparation of (Z)-β,β-diarylpropenacids via addition of iodobenzene 324 to substituted cinnamate substrates 322 and 323, however they once again found that cinnaminitriles 323 were more stable under the reaction conditions affording (Z)-α,β-unsaturated nitrile 326 in improved yield and selectivity (Scheme 82, Table 11).
Cacchi et al. have recently reported improved stereoselectivity and yields for the preparation of this type of trisubstituted acid derivatives using a molten \textsuperscript{6}Bu\textsubscript{4}NOAc/\textsuperscript{6}Bu\textsubscript{4}NBr mixture. Thus, the Heck reaction of methyl cinnamate ester 327 and aryl iodide 317 afforded coupling product \((E)-328\) (Scheme 83, Table 12).\textsuperscript{113}

\begin{table}[h]
\centering
\begin{tabular}{cccc}
\hline
\textbf{X} & \textbf{Time (hours)} & \textbf{Yield (\%)} & \textbf{E:Z} \\
\hline
1 & \textsuperscript{p}-OMe & 3 & 80 & >99:1 \\
2 & \textsuperscript{p}-Me & 3.5 & 82 & 99:1 \\
3 & \textsuperscript{m}-Me & 7 & 80 & 99:1 \\
4 & \textsuperscript{p}-COOEt & 9 & 38 & 98:2 \\
\hline
\end{tabular}
\caption{Time and yield of product formation.}
\end{table}

Under the same conditions the reaction of 3-arylacrylates 329 and iodobenzene 324 was also shown to afford \((Z)-\beta,\beta\text{-diarylpropenester 330 in a diastereoselective fashion (Scheme 84, Table 13).}
Table 13

Coupling of disubstituted unsaturated esters with vinyl triflates has also been shown to afford (E)-esters in high d.e.\textsuperscript{114} Cacchi \textit{et al.} have reported the application of this approach to the preparation of substituted coumarin 333 via coupling reaction of cinnamo ester 331 and vinyl triflate 332 (Scheme 85).\textsuperscript{115}

Scheme 85

There are few examples where the Heck reaction between methacrylate esters and aryl halide has been successfully realised despite the potential of α-methyl-substituted cinnamic acid derivatives as a building block for organic synthesis. Beller \textit{et al.} attempted to carry out this transformation using butyl methacrylate ester 334 and aryl bromides 335 as substrates (Scheme 86, Table 14).\textsuperscript{116} Reaction using sodium acetate as a base afforded no selectivity between the formation of 336 and 337, whilst longer reaction times (entry 1) resulted in the formation of disubstituted 338. However, reaction with tributylamine was shown to afford the desired trisubstituted α,β-unsaturated ester (E)-336 with improved
selectivity (entry 2), whilst higher catalyst loading also afforded better conversion of substrates to product (entry 3). Other electron withdrawing aryl halides afforded trisubstituted ester \((E)-336\) in a selective fashion and in good yield (entries 4 and 6), however, whilst the reaction with electron-donating aryl halides was both stereo and regioselective, it did not go to completion with 75\% of starting material being recovered, for \(R = \text{OCH}_3\) (entry 5).

![Scheme 86](image)

**Table 14.**

<table>
<thead>
<tr>
<th>R</th>
<th>(336 : 337 : 338)</th>
<th>Yield ((336 + 337))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(1.4 : 1 : 1.2)</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>(3.9 : 1 : 0.2)</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>(9.3 : 1 : 1.5)</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>(11.5 : 1 : 2.1)</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>(4.9 : 1 : &lt;0.1)</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>(8.1 : 1 : 0.7)</td>
<td>75</td>
</tr>
</tbody>
</table>

\(^a\)Pd cat at 0.01\%; \(^b\)base used NaOAc.

Kozlowski et al. reported in 2001 on the synthesis of the isocoumarin portion of the rubromycins, a class of natural products that exhibits antibiotic properties.\(^{117}\) The isocoumarin ring system 341 was formed *via* Heck coupling of a masked pyruvate synthon 340, and iodo-terephthalic acid derivative 339 with good d.e. followed by an intramolecular acid-catalysed cyclisation (Scheme 87).
2.2.4.2 Cross-coupling of organostannanes

\(\alpha,\beta\)-Unsaturated esters that contain stannane substituents at either their \(\alpha\)- or \(\beta\)-positions are versatile synthons for the preparation of aryl substituted \(\alpha,\beta\)-unsaturated esters via Stille coupling protocols. For example the Stille reaction of tributyl stannane (\(Z\))-343 and allylic chloride 344 in the presence of a palladium catalyst afforded (\(E\))-trisubstituted \(\alpha,\beta\)-unsaturated ester 345 (Scheme 88).\(^{118}\) Alternatively, \(\beta\)-stannyl ester 344 has been employed for the synthesis of a range of \(R\)-amino ester derivatives 345 in good yield.\(^{119}\)

Scheme 87

\[
\begin{align*}
\text{MeO} & \quad \text{CO}_{2}\text{Me} \\
\text{TBSO} & \quad \text{MeO} \\
339 & \quad \text{H} \\
+ & \quad \text{MeO} \\
\text{OMe} & \quad \text{CO}_{2}\text{Me} \\
340 & \quad \text{OMe}
\end{align*}
\]

\[
\begin{align*}
\text{Pd}(\text{PPh}_3)_4 & \quad \text{K}_2\text{CO}_3 \\
\text{TBSO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{CO}_{2}\text{Me} \\
(Z)-341 & \quad \text{71\% yield} \\
(23\% \text{recovered 339}) \\
\text{OH} & \quad \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{isocoumarin}
\end{align*}
\]

Scheme 88

Consequently the stereoselective preparation of \(\alpha\)- or \(\beta\)-substituted esters has been widely investigated. For example, Piers et al. have reported that treatment of acetylenic esters 346 with stannyl cuprate reagents afforded (\(E\))-3-trimethylstannylalkenoate 347 as the sole isomers (Scheme 89, Table 15).\(^{120}\)
Scheme 89

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>Yield (%)</th>
<th>E:Z*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Me</td>
<td>Et</td>
<td>76</td>
<td>&gt; 95:5</td>
</tr>
<tr>
<td>2 'Pr</td>
<td>Me</td>
<td>77</td>
<td>&gt; 95:5</td>
</tr>
<tr>
<td>3 Br(CH₂)₄</td>
<td>Me</td>
<td>84</td>
<td>&gt; 95:5</td>
</tr>
<tr>
<td>4 'BuMe₂SiOCH₂</td>
<td>Et</td>
<td>80</td>
<td>95:5</td>
</tr>
</tbody>
</table>

*Product ratios are determined by GLC analyses.

Table 15

Remarkably a reversal in E:Z stereoselectivity was observed if this reaction was allowed to warm up to -48°C prior to hydrolytic work-up. This variation of the procedure afforded in a stereoselective fashion the corresponding alkenoates (Z)-348 (Scheme 90, Table 16).

Scheme 90

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>Yield (%)</th>
<th>Z:E</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Me</td>
<td>Et</td>
<td>78</td>
<td>&gt; 1:99a</td>
</tr>
<tr>
<td>2 Me</td>
<td>Et</td>
<td>76</td>
<td>98:2b</td>
</tr>
<tr>
<td>3 'Bu</td>
<td>Et</td>
<td>86</td>
<td>98:2</td>
</tr>
<tr>
<td>4 'BuMe₂SiO(CH₂)₂</td>
<td>Me</td>
<td>81</td>
<td>96:4</td>
</tr>
<tr>
<td>5 Br(CH₂)₄</td>
<td>Me</td>
<td>74</td>
<td>95:5</td>
</tr>
</tbody>
</table>

*The reaction is quenched at -78°C;  
b The reaction is quenched at -48°C.

Table 16

Piers proposed that the trimethylstannane copper(I) reagent initially adds syn to the triple bond to form intermediate 349, which on hydrolysis at -78°C afforded (E)-3-trimethylstannyl-2-alkenoates 347. On warming to -48°C adduct 349 isomerised to the thermodynamically more stable allenoate 320 which on hydrolysis was protonated to afford (Z)-348 (Figure 23).
Rossi et al. have reported an elegant alternative stereo and regioselective preparation of $\alpha$-aryl-2-alkenoate \((Z)-353\).\(^{121}\) The reaction of acetylenic esters 346 with tributylstannane reagent in the presence of a palladium catalyst afforded \((E)-351\) in a regioselective and stereoselective fashion. Instead of employing a direct Stille coupling, \((E)-351\) was converted to their 2-aryl-$\alpha,\beta$-unsaturated esters \((Z)-353\) via substitution of the stannyl group with iodide, and cross-coupling with organozinc reagents (Scheme 91, Table 17).

<table>
<thead>
<tr>
<th>$R_1$</th>
<th>$R_2$</th>
<th>Yield (%)</th>
<th>351:352</th>
<th>$E:Z$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^7$C$<em>2$H$</em>{11}$</td>
<td>Me</td>
<td>85</td>
<td>92:8</td>
<td>98:2</td>
</tr>
<tr>
<td>Ph</td>
<td>Et</td>
<td>71</td>
<td>90:10</td>
<td>99:1</td>
</tr>
<tr>
<td>$^t$BuMe$_2$SiOCH$_2$</td>
<td>Et</td>
<td>84</td>
<td>91:9</td>
<td>99:1</td>
</tr>
<tr>
<td>$(S)$-$^t$Bu</td>
<td>Et</td>
<td>93</td>
<td>98:2</td>
<td>&gt;99:1</td>
</tr>
</tbody>
</table>

2.2.5 Lithium ynlolates

In the past twenty years several methods for the generation of ynlolates or ketene anions have been developed, making them more synthetically accessible thus, allowing the study of their reactivity. In 1982, Kowalski et al. observed that when α-bromo lithium enolate anion 354 was treated with base, rearrangement afforded ynlolate anion 355. This reaction is an analogue of the Hofmann rearrangement where N-bromoamide 356 is deprotonated with sodium hydroxide followed by migration of the alkyl substituent R to nitrogen with loss of bromide to afford isocyanate 357 (Figure 24).

Figure 24

For example, dibromoketone 358 was deprotonated by action of LHMDS to afford dibromoenoate 359, which on addition of t-butyl lithium underwent an elimination/migration reaction to afford lithium ynlolate 360. Alkynolate 360 underwent subsequent nucleophilic addition to benzaldehyde 95 to yield (E)-α,β-unsaturated carboxylic acid 362. Kowalski proposed that the key reaction that determines (E)-selectivity occurred via elimination of CO$_2$ from a β-lactone intermediate 361 (Scheme 92).

Scheme 92

Mulzer et al. previously reported that treatment of β-lactone 363 with LDA produced an enolate 364 that was stable at -78°C. On warming to room temperature the expected
\( \beta \)-elimination reaction occurred and the acrylic acid (E)-365 was formed in quantitative yield, thus supporting the 4-membered intermediate 361 that Kowalski had proposed to explain the outcome of the addition of ynolates to aldehydes (Scheme 93).

**Scheme 93**

Murai et al. became interested in this type of ketenylation reaction 15 years later and designed an efficient procedure to convert lithiosilyldiazomethane 366 into lithium silyl ynolate 367 under one atmosphere of carbon monoxide and reported its reactivity towards a number of electrophilic substrates such as epoxides or aldimines. For example, lithium ynolate 367 reacted with aldimine 368 to afford amide (E)-370 as the sole geometric isomer, whereby the stereochemistry was explained via rearrangement to the \( \beta \)-lactam enolate 369 and subsequent ring-opening (Scheme 94).

**Scheme 94**

Shindo et al. subsequently reported that this reaction showed good versatility for the reaction of a range of ynolates 371 and aldimines 372 affording (E)-unsaturated esters 373 with excellent selectivities (entries 1-3). However, this reaction did suffer from some limitations; imines containing electron-withdrawing aromatic ring did not react (entry 4) whilst neither did bulky lithium ynolate (entry 5) (Scheme 95, Table 18).
Scheme 95

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>%Yield</th>
<th>E:Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>88</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>52</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>3</td>
<td>Cyclohexyl</td>
<td>83</td>
<td>85:15</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>'Bu</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 18

Shindo et al. have reported that treatment of dibromoester 374 with two equivalents of 'BuLi and two equivalents of aldehyde gave a trisubstituted β-lactone 375. They reported that further treatment of this lactone 375 with an extra equivalent of 'BuLi resulted in formation of an unsaturated carboxylic acid (E)-377 via a tandem retro-aldol reaction, followed by ring-opening of a cyclobutene enolate intermediate 376 (Scheme 96).

Scheme 96

Shindo has reported a related one-pot modification of this synthesis in which treatment of dibromoketone 378 with base, followed by addition of an excess of benzaldehyde yielded a mixture of lactones 379 and 380 that collapsed in a stereoselective manner to afford (E)-acid 381 (Scheme 97).
Finally, Kowalski et al. proposed a novel olefination procedure to prepare \((E)\)-trisubstituted unsaturated esters in two steps.\(^\text{130}\) They reported the formation of silyloxyacetylene 383 from ethyl ester 382, which was subsequently reacted with a range of aldehydes with good \((E)\)-stereocontrol to afford \((E)\)-384 in good d.e. (Scheme 98, Table 19).

### Table 19

<table>
<thead>
<tr>
<th>(R)</th>
<th>(R_1)</th>
<th>% yield</th>
<th>(E:Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C_5H_{11})</td>
<td>((CH_2)_2Ph)</td>
<td>65</td>
<td>&gt; 95:5</td>
</tr>
<tr>
<td>(C_5H_{11})</td>
<td>(Ph)</td>
<td>64</td>
<td>84:16</td>
</tr>
<tr>
<td>(Ph)</td>
<td>(C_6H_{11})</td>
<td>65</td>
<td>&gt; 95:5</td>
</tr>
<tr>
<td>(C_6H_{11})</td>
<td>((CH_2)_2Ph)</td>
<td>63</td>
<td>&gt; 95:5</td>
</tr>
</tbody>
</table>

### 2.2.6 Miscellaneous

#### 2.2.6.1 Hydrocarboxylation of alkynes

Hydrocarboxylation of acetylene is a major industrial process for the large scale production of acrylic acid derivatives, however, hydrocarboxylation of unsymmetrical alkynes often affords mixtures of geometric stereoisomers.\(^\text{131}\) Kocienski et al. have reported the use of this type of methodology for the stereoselective synthesis of anti-fertility agent zoapatanol 387.\(^\text{132}\) In order to achieve selective carboxylation, alkyne 385 was subjected to addition of Grignard reagent \(^\text{t}BuMgCl\) in the presence of \(\text{Cp}_2\text{TiCl}_2\) to afford after quenching with
carbon dioxide \((E)-\alpha\)-substituted-\(\alpha,\beta\)-unsaturated carboxylic acid 386 in modest yield and in a regio and diastereoselective fashion (Scheme 99).

\[ \text{Scheme 99} \]

An original approach to this chemistry was proposed by Periasamy et al. who reported on the regio and stereoselective synthesis of \(\alpha,\beta\)-unsaturated carboxylic acid 389 and 392.\(^{133}\) Reaction of alkyne 388 with NaHFe(CO)\(_4\) and CH\(_2\)Cl\(_2\) in THF afforded a metal carbonyl complex that decomposed to give a 3:1 mixture of \(\alpha,\beta\)-unsaturated carboxylic acid \((E)-389\) and cyclobutenedione 390. Under these conditions, alkyne 391 afforded \(\alpha,\beta\)-unsaturated carboxylic acid \((E)-392\) as the sole product in > 95% d.e. (Scheme 100). No intermediate or mechanism has yet been proposed for this reaction although an excess of CH\(_2\)Cl\(_2\) was essential to optimise conversion since low yields were obtained in its absence.

\[ \text{Scheme 100} \]

Matsuda et al. have reported on a one-pot procedure to condense an alkyne 393, hydrosilane 394, amine 395 and carbon monoxide in the presence of a rhodium Rh(0) catalyst, to afford \(Z\)-\(\alpha,\beta\)-unsaturated amides 396 in good d.e. (Scheme 101, Table 20).\(^{134}\)
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Introduction

Scheme 101

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>Z:E</th>
</tr>
</thead>
<tbody>
<tr>
<td>pentyl</td>
<td>82</td>
<td>96:4</td>
</tr>
<tr>
<td>cyclohexyl</td>
<td>73</td>
<td>96:4</td>
</tr>
<tr>
<td>phenyl</td>
<td>44</td>
<td>100:0</td>
</tr>
</tbody>
</table>

Table 20

A related route towards trisubstituted α,β-unsaturated carboxylic acid has been described involving Pd(0) mediated carbonylation of alkenes that are substituted with halide or triflate substituents. For example, in 1998, Ortar et al. reported the preparation of primary (E)-amides and applied this approach to the synthesis of cholest-2-en-yl amide 398. Thus, vinyl triflate 397 was treated with HMDS and a catalytic amount of PdCl2/4PPh3 under a CO atmosphere to afford trisubstituted α,β-unsaturated amide 398 in excellent yield (Scheme 102).

Scheme 102

2.2.6.2 Cross metatheses

Grubbs et al. described a new route towards the synthesis of trisubstituted electron-poor alkenes, using their powerful ring-closing metathesis procedure to form the alkene functionality. Thus, terminal olefin 399 participated in cross-metatheses reaction with methyl methacrylate 400 in the presence of ruthenium catalyst 401 to generate the trisubstituted unsaturated ester 402 in moderate yield but with excellent stereoselectivity (Scheme 103).
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Scheme 103

It was known that ester-α-carbene complexes were highly unstable, whilst α-substitution of the ester would hinder the approach of the ruthenium catalyst. Therefore Grubbs proposed that the (E)-trisubstituted ester formed in this reaction was derived from the ruthenium-terminal olefin complex 403 (Figure 25).

Figure 25

Grubbs et al. proposed though that changing the substitution pattern of the participating olefin fragments might also change the course of the metathesis reaction. Indeed, substitution of a disubstituted olefin 404 hindered its complexation to the ruthenium catalyst 401, which made formation of acid-carbene complex 406 more kinetically favoured. Thus, the reaction afforded the β-isomer (E)-403 in good yield but with only modest diastereoselectivity (Scheme 104).

Scheme 104

2.2.6.3 Addition of carbanions to Baylis-Hillman adducts

In section 2.2.3.1 it was described how the reductive elimination of a Baylis-Hillman adduct affords α-methyl cinnamate esters, however Basavaiah et al. have reported an
alternative strategy whereby addition of a Grignard reagent to an allylic acetate offered wide versatility for substitution at the \( \alpha \)-position. For example, Baylis-Hillman adduct 408 reacted with a range of Grignard reagents to afford \((E)\)-\(\alpha\)-substituted alkenoates 409 as the sole isomers (Scheme 105, Table 21).

\[
\begin{array}{c}
\text{R}_1 \\
\text{OAc} \\
\rightarrow \\
\text{R}_2 \text{MgX} \\
\text{THF, reflux} \\
\text{OMe}
\end{array}
\rightarrow
\begin{array}{c}
\text{R}_1 \\
\text{OAc} \\
\rightarrow \\
\text{R}_2 \text{MgX} \\
\text{THF, reflux} \\
\text{OMe}
\end{array}
\]

**Scheme 105**

<table>
<thead>
<tr>
<th>( \text{R}_1 )</th>
<th>( \text{R}_2 )</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Ph</td>
<td>75</td>
</tr>
<tr>
<td>( \text{n} ^{\text{C}<em>6\text{H}</em>{13}} )</td>
<td>( \text{n} ^{\text{Bu}} )</td>
<td>62</td>
</tr>
<tr>
<td>Ph</td>
<td>( \text{n} ^{\text{Bu}} )</td>
<td>70</td>
</tr>
</tbody>
</table>

**Table 21**

The \((E)\)-selectivity was rationalised by invoking a chelated structure 410 in which the magnesium cation forms a six-membered ring, which collapses to afford the \((E)\)-isomer 409 stereoselectively (Figure 26).

\[
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{Me} \\
\text{OAc} \\
\rightarrow \\
\text{R}_2 \text{MgX} \\
\text{THF, reflux} \\
\text{OMe}
\end{array}
\rightarrow
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{Me} \\
\text{OAc} \\
\rightarrow \\
\text{R}_2 \text{MgX} \\
\text{THF, reflux} \\
\text{OMe}
\end{array}
\]

**Figure 26**

This rationale was supported by the observation that the addition of Grignard reagents to nitriles 411 under the same conditions was \((Z)\)-selective. Thus, the addition of Grignard reagents to 3-acetoxy-2-methylenealkanenitrile 411 under the same reaction conditions afforded 2-substituted alk-2-ene nitriles \((Z)\)-412 as the major isomers in fair to good d.e. (Scheme 106, Table 22).

\[
\begin{array}{c}
\text{OAc} \\
\rightarrow \\
\text{R}_2 \text{MgX} \\
\text{THF, reflux} \\
\text{CN}
\end{array}
\rightarrow
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{CN} \\
\text{OAc}
\end{array}
\]

**Scheme 106**
Marson et al. have reported the use of a variant of this procedure for the synthesis of aza analogues 415 of the ABC ring system of phorbol, via treatment of allylic alcohol 413 with HBraq to afford allylic bromide 414 (Scheme 107).139

![Scheme 107](image)

**Scheme 107**

**2.2.6.4 Metal insertion into alkynes**

Takai, Utimoto et al. have reported on the insertion of an aldehyde 418 into a tantalum-carbon bond in a regioselective manner to afford Baylis-Hillman-like α-substituted α,β-unsaturated esters (Z)-419 via intermediate 417 (Scheme 108, Table 23).140 Electronic effects appear to control the α,β-regioselectivity for ethyl esters (entries 1-3) with the ester substituent polarising the alkene to favour the formation of intermediate 421, with alkaline hydrolysis of 421 subsequently affording the desired trisubstituted unsaturated ester 419.

![Scheme 108](image)

**Scheme 108**

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>Yield (%)</th>
<th>419:420</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&quot;C10H21</td>
<td>OEt</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>C6H11</td>
<td>OEt</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>OEt</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>&quot;C6H13</td>
<td>NMe2</td>
<td>79a</td>
</tr>
</tbody>
</table>

* The reaction was carried out at 50°C.

**Table 22**

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Yield (%)</th>
<th>Z:E</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Bu</td>
<td>&quot;Bu</td>
<td>73</td>
<td>82:18</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>75</td>
<td>80:20</td>
</tr>
<tr>
<td>Ph</td>
<td>p-MeOPh</td>
<td>81</td>
<td>&gt; 95:5</td>
</tr>
</tbody>
</table>

**Table 23**
In contrast to acetylenic esters, reaction of a tantalum-acetylenic amide complex (entry 4) yielded predominantly the β-regioisomer 420. It was shown that complexation of tantalum to electron-poor alkyne 416 proceeded exceptionally fast while the reactivity of the resultant complex 417 with butyraldehyde 418 was slower. β-Selectivity in this case was therefore attributed to coordination between the nitrogen lone pair of the amide fragment and low-valent tantalum, preferentially affording intermediate 422 (Figure 27).

Figure 27
CHAPTER 3. A novel Concept for the Asymmetric Synthesis of Aldehydes

The remainder of this thesis describes the discovery and development of synthetic methodology that employs syn-β-hydroxy-N-acyloxazolidin-2-ones as substrates for a novel intramolecular cyclisation/elimination reaction to afford trisubstituted (E)-α,β-unsaturated amides in high d.e. As is often the case, this novel methodology was discovered as part of another research program directed towards employing chiral auxiliaries for asymmetric synthesis in a novel manner using concepts that are still under active investigation within the SDB research group. Consequently, I will first discuss this original chiral auxiliary concept, and the preliminary reactions that were carried out that led to the discovery of this novel methodology for the stereoselective synthesis of (E)-trisubstituted acid derivatives.

3.1 A new concept for using chiral auxiliaries for asymmetric synthesis

3.1.1 The use of chiral auxiliaries for asymmetric synthesis

To recap, chiral auxiliaries are widely used in asymmetric synthesis for the stereoselective synthesis of a wide range of enantiopure compounds. Conventional chiral auxiliaries operate according to a general strategy in which a chiral auxiliary fragment CA is covalently attached to a prochiral substrate S to afford a covalent complex CA-S; which is then transformed stereoselectively (under the control of the chiral auxiliary fragment CA) to afford a new product CA-P which contains one or more new stereocentres (NS). The product CA-P is then cleaved to afford an enantiopure product P and the chiral auxiliary CA which is then recycled as required (Figure 28).

![Figure 28](image-url)
Chapter 3 Results and Discussion

Perhaps the most widely used chiral auxiliaries to date are chiral oxazolidin-2-ones such as (S)-18 described originally by Evans et al. which have been used for stereocontrol in a wide range of reaction scenarios including asymmetric aldol reactions,\(^{141}\) conjugate additions,\(^{142}\) and Diels-Alder reactions.\(^{143}\) For example, Evans’ oxazolidin-2-one was used as a chiral auxiliary for the asymmetric synthesis of chiral acid fragments according to the enolate alkylation protocol described in Scheme 109. Thus, the chiral oxazolidin-2-one (S)-18 was attached to an achiral acyl chloride fragment 19 to afford N-acyl-oxazolidin-2-one 20, which was deprotonated with LHMDS to afford a lithium (Z)-enolate that reacted with electrophiles such as benzyl bromide to afford an α-benzylated-N-acyl-oxazolidin-2-one (S,α-R)-21 in high d.e. Subsequent hydrolysis of (S,α-R)-21 then afforded the desired chiral acid (R)-22 in enantiopure form, and the chiral auxiliary fragment 18 which could be recycled as required.\(^{10}\)

![Scheme 109](image)

**Scheme 109**

3.1.2 A new approach to the use of chiral auxiliaries

An alternative strategy for using chiral auxiliaries in asymmetric synthesis may be proposed, in which the chiral auxiliary fragment CA reacts with the achiral functionality (A\(_1\)) of a substrate S to afford a complex CA-S that contains a new ‘temporary’ stereogenic centre (TS\(_1\)). The newly formed temporary stereocentre (TS\(_1\)) of CA-S may then be employed to subsequently control facial selectivity during stereoselective transformation of prochiral functionality A\(_2\) (contained within CA-S), to afford a transformed product CA-P containing a second new stereogenic centre (NS\(_2\)). Subsequent cleavage of product CA-P would result in destruction of the temporary stereocentre TS\(_1\) (regenerating achiral functionality A\(_1\)) to afford a product P containing a new stereocentre NS\(_2\), and the chiral auxiliary fragment CA, which could then be recycled as required (Figure 30).
Clearly, for this novel approach towards chiral auxiliary use to be successful it required that the newly formed 'temporary' stereocentre (TS\textsubscript{i}) of CA-S should contain functionality that was capable of carrying out directed stereoselective transformations. It was well known that stereogenic hydroxyl groups have the capacity to carry out directed chemical reactions for a wide range of stereoselective transformations in high d.e. (see section 1.6) Given the capacity of the aldol/retro-aldol reaction to form/cleave stereodefined \(\beta\)-hydroxy-aldolate fragments, it was proposed that this combination of synthetic transformations would be ideally suited for the design of this new class of chiral auxiliary.

### 3.1.3 Evans' \(N\)-acyl-oxazolidin-2-ones as a prospective chiral auxiliary fragment

In order to develop a working model of the novel chiral auxiliary concept described in Figure 30, we required a chiral auxiliary fragment that would not only afford aldolates in high d.e., but that would also afford aldolates that underwent \textit{retro}-aldol reaction under controlled conditions.

An extensive review of the literature revealed that a working system based on the use of chiral Evans' \(N\)-acyl-oxazolidin-2-ones might be ideally suited to these purposes. Firstly, boron enolates of \(N\)-acyloxazolidin-2-ones were well known to undergo stereoselective aldol reactions with a wide range of aldehydes. For example, aldol reaction between the boron enolate of \(N\)-propionyl-(4\textsubscript{S})-benzyl-oxazolidin-2-one 423 and crotonaldehyde was known to afford quantitatively a \textit{syn}-aldolate 424 in > 99% d.e. (Scheme 110).\textsuperscript{144}

![Scheme 110](image)
Secondly, it was well established that directed hydrogenation reactions of chiral allylic alcohols in the presence of certain transition metal catalysts occurred in a highly stereoselective manner to afford chiral alcohols that contained new stereogenic centres in high d.e. More specifically, Evans et al. had reported that directed hydrogenation of the chiral allylic alcohol functionality of N-acyl-oxazolidin-2-one 425 afforded a saturated alcohol (4S)-426 product in high d.e., where hydrogen had been delivered to the alkene functionality from the same face as the β-hydroxyl group (Scheme 111).

![Scheme 111](image)

Thirdly, a survey of the literature revealed that a single example of a base-promoted retro-aldol cleavage of a β-hydroxy-N-acyl-oxazolidin-2-one had already been reported. Thus, Bartroli et al. demonstrated that kinetic deprotonation of the hydroxyl functionality of ketolate 427 with LDA at -40°C did not afford the desired epoxide 428 as expected, but instead underwent clean retro-aldol fragmentation to afford the parent N-acyl-oxazolidin-2-one 423 and α-chloro-ketone 429 (Scheme 112).

![Scheme 112](image)

It was proposed that combining these three literature precedents would enable us to realise the novel concept for using chiral auxiliaries for asymmetric synthesis as described in Scheme 113. Thus, reaction of the boron enolate of N-propionyl-2-oxazolidin-2-one 423 with 2-phenyl propenal 430 would afford syn-aldolate 431 (step 1); directed hydrogenation of syn-aldolate 431 with Crabtree’s catalyst 432 under the control of the stereogenic hydroxyl group would afford syn-aldolate 433 containing a new stereocentre (step 2); retro-aldol reaction of aldolate 433 would afford (S)-2-phenyl-propionaldehyde 434, and
the chiral auxiliary fragment 423 which could be recycled as required. This protocol would therefore result in an overall transformation in which the achiral \( \alpha,\beta \)-unsaturated aldehyde 430 had been stereoselectively hydrogenated to afford chiral aldehyde (\( R \))-434 that contained a new stereocentre at its \( \alpha \)-position.

![Scheme 113](image)

Alternatively, it was proposed that the readily available \( \text{syn-aldolate product 435 could also be subjected to the same type of hydrogenation/retro-aldol protocol to afford the corresponding (\( S \))-\( \alpha \)-methyl aldehyde 434 (Scheme 114), thus enabling the same enantiomer of (\( S \))-4-benzyl-\( N \)-propionyloxazolidin-2-one 423 to be employed for the preparation of either enantiomer of 2-phenylpropionaldehyde via a stereodivergent approach (Scheme 114).

![Scheme 114](image)

Once the aldol/directed hydrogenation/retro-aldol methodology described had been optimised then it was my intention to further explore the capacity of the \( \beta \)-hydroxyl functionality of aldolates such as 437 and 440 to control other directed stereoselective
transformations such as cyclopropanations,\textsuperscript{19} or epoxidations.\textsuperscript{11,12,13} These reactions would result in aldolate products 438 and 441 that could potentially undergo retro-aldol reactions to afford chiral aldehyde products such as 439 and 442 that contain cyclopropyl or epoxide functionality respectively (Scheme 115).

\begin{center}
\includegraphics[width=\textwidth]{Scheme_115.png}
\end{center}

\textbf{Scheme 115}

It was reasoned therefore that applying this type of aldol/directed reaction/retro-aldol strategy to a wide range of aldolate substrate, for a range of different types of hydroxyl directed reaction, would enable the development of versatile methodology for the asymmetric synthesis of libraries of chiral aldehyde fragments that contained a diverse range of functionality. It should be noted that there are currently few methods available for the direct asymmetric synthesis of chiral aldehyde fragments, which are a class of compound that are highly prized in synthesis.

\section*{3.2 Development of an effective \textit{syn}-aldol reaction using boron enolates of \textit{N}-acyl-oxazolidin-2-ones}

My first goal was to develop an effective and robust protocol for carrying out stereoselective reactions between boron enolates of \textit{N}-acyloxazolidin-2-one and \(\alpha,\beta\)-unsaturated aldehydes to afford \textit{syn}-aldolates in high d.e. A great deal of literature precedent exists for this type of \textit{syn}-selective aldol reaction and relevant reports will now be discussed in brief.

\subsection*{3.2.1 Literature precedent}

\((Z)\)-Enolates derived from \textit{N}-acyloxazolidin-2-ones have been widely employed for the asymmetric synthesis of enantiopure aldolate products containing a diverse range of functionality in high d.e. Pioneering work carried out by Evans \textit{et al.} resulted in the development of methodology that enables the stereoselective formation of \textit{syn}-aldolate fragments.\textsuperscript{148} Thus, while lithium enolates of \textit{N}-acyloxazolidin-2-ones generally exhibit
low levels of control in aldol reactions, the corresponding boron (Z)-enolates 443 afford remarkably high stereochemical control for kinetic aldol reactions with a wide range of aldehydes to afford syn-aldolates 444 in high d.e (Scheme 116).

Scheme 116
The stereochemistry of the resulting syn-aldolate product 444 may be rationalised by invoking a boron chelated chair transition state in which the R1 substituent of the aldehyde substrate prefers to occupy an equatorial environment. Consideration of the relative energies of the chelated chair transition states S1 and S2 revealed that formation of ‘Non-Evans’ syn-aldolate 445 was disfavoured by steric interactions between the isopropyl stereodirecting group of the oxazolidin-2-one and the chelated boracycle fragment. Thus, the alternative ‘Evans’ syn-aldolate 444 was formed in high d.e. under these conditions (Figure 31).

Figure 31
Heathcock et al. later introduced an alternative protocol for the formation of ‘non-Evans’ syn-aldolates 445 in high d.e. in which the aldehyde substrate was precomplexed to a strong Lewis acid TiCl4 before addition to the boron enolate 443 in the usual manner.149 It was proposed that this aldol reaction proceeded via an ‘open’ transition state 446 in which steric interactions between the R-alkyl group of the (Z)-enolate 443 and the R1 alkyl group of the aldehyde were minimised (Scheme 117).
3.2.2 Achiral \( N \)-acyl-oxazolidin-2-ones as substrates for optimising \( \text{syn} \)-selective aldol reactions

As described, the synthesis of \( \text{syn} \)-aldolate products employing aldol reaction between (Z)-boron enolates of \( N \)-acyl-oxazolidin-2-ones and achiral aldehydes is well-established, with over 100 reports having been described to date on its use for stereoselective synthesis.\(^{150}\) Despite this popularity however, it is well known within the synthetic community that this stereoselective aldol methodology can be highly capricious and that the yields and diastereoselectivities of aldolate products are highly dependent on the quality of the boron Lewis acid employed for reaction. In order to optimise the conditions employed for the aldol reactions I initially concentrated on the preparation of racemic \( \text{syn} \)-449 aldolate products derived from condensation of the boron enolate of an achiral \( N \)-acyl-oxazolidin-2-one 447 with an \( \alpha \beta \)-unsaturated aldehyde 448. The decision to carry out initial optimisation studies using this model system was taken in order to help simplify \( ^1 \)H NMR spectroscopic analysis of crude product mixtures. Thus, for any ‘unsuccessful’ stereoselective aldol reaction carried out using the enolate of achiral \( N \)-acyl-oxazolidin-2-one 447, only two new compounds \( \text{syn} \)-aldolate \( (\text{rac})-449 \) and \( \text{anti} \)-aldolate \( (\text{rac})-450 \) would be observed in the \( ^1 \)H NMR spectrum of the crude reaction products (Scheme 118).
Chapter 3 Results and Discussion

Scheme 118
This simplicity compares with the potential difficulties in analysing the $^1$H NMR spectrum of crude reaction products in which the enolate of a chiral $N$-acyl-oxazolidin-2-one such as 451 had been used for optimisation studies, where an 'unsuccessful' stereoselective aldol reaction would potentially afford four possible aldolate diastereoisomers products, syn-452, syn-453, anti-454, and anti-455, all of which would afford their own set of distinct signals in the $^1$H NMR spectrum (Scheme 119).

Scheme 119

3.2.3 Preparation of achiral $N$-acyl-oxazolidin-2-ones
Therefore, my first synthetic target was to prepare a range of achiral $N$-acyl-oxazolidin-2-ones 457-460 (Scheme 120, Figure 32) as substrates for carrying out optimisation studies of the syn-selective aldol reaction. $N$-acyl-oxazolidin-2-ones 457-460 were prepared via treatment of the parent achiral oxazolidin-2-one 456 with $^8$BuLi in THF at $-78^\circ$C, followed by addition of the appropriate acid chloride and warming to room temperature.$^{151}$ Purification of the crystalline $N$-acyl-oxazolidin-2-ones was afforded in fair to good yield, via recrystallisation from ethyl acetate, or via chromatography over silica.
Figure 32

3.2.4 Syn-aldol reactions using dialkylboron triflates as Lewis acids

Initially, the aldol reaction between achiral N-phenylacetyl-oxazolidin-2-one 459 and trans-cinnamaldehyde was investigated employing commercially available dibutylboron triflate (Aldrich, 1M in dichloromethane) as a stoichiometric Lewis acid, under the range of conditions described in Table 24. The overall yield of aldolate product formed in these reactions was disappointing however, with the best results being obtained using 1.5 equivalents of dibutylboron triflate in CH$_2$Cl$_2$ at 0°C, which afforded syn-461 in only 38% yield after exhaustive chromatographic purification. Analysis of the $^1$H NMR spectrum of this crude reaction mixture revealed that whilst syn-aldolate 461 had been formed in high d.e., the poor overall yield was a result of large amounts of unreacted starting material 459. However, syn-aldolate 461 was fully characterised. The $^1$H NMR spectrum revealed a strong coupling of $J$=7 Hz between $\alpha$-CHPh (5.24 ppm, d) and $\beta$-CHOH (4.95 ppm, app t). The infra-red spectrum of this compound showed two bands of absorption in the carbonyl region at 1694 and 1778 cm$^{-1}$ whilst the correct molecular ion at 337 (M$^+$, Cl$^+$) was also observed.
Results and Discussion

\[ \text{Bu}_2\text{BOTf, Et}_3\text{N} \]

\[ \text{CH}_2\text{C}_2, -78°C \]

\[ \rightarrow \]

\[ \text{459} \]

\[ \rightarrow \]

\[ \text{syn-461} \]

\[ \text{anti-462} \]

Scheme 121

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0: 1.2: 1.1</td>
<td>53 &gt; 45 &lt; 2</td>
</tr>
<tr>
<td>1.0: 1.6: 1.5</td>
<td>28 &gt; 68 &lt; 4</td>
</tr>
<tr>
<td>1.0: 2.1: 2</td>
<td>54 &gt; 41 &gt; 5</td>
</tr>
</tbody>
</table>

Ratios were calculated by measurement of the integrals in the \( ^1\text{H} \) NMR of the crude reaction mixture.

Table 24

It was reasoned that the low yield of syn-aldolate product 461 observed in this aldol reaction might be a consequence of potential stability problems associated with \( \text{trans-cinnamaldehyde} \) (stabilised via conjugation to aryl ring), and with the enolate of \( N\)-phenylacetyl-oxazolidin-2-one 459 (stabilised by presence of \( \alpha \)-phenyl substituent). As a consequence it was decided to carry out the aldol reaction using achiral \( N\)-acyl-oxazolidin-2-one 458 and \( \text{trans-crotonaldehyde} \). However, under optimal conditions (Table 24, entry 2), only marginal improvement was observed with a disappointing 42% yield of the desired syn-aldolate product 463 being obtained after chromatographic purification.

\[ \text{Scheme 122} \]

As indicated, it was well known that the quality of boron triflate reagent used for carrying out this type of syn-aldolate reaction was an important factor in the yield of aldolate product obtained. Consequently, it was decided to freshly prepare my own sample of Et\(_2\)BOTf for reaction, which would then be used immediately for a stereoselective syn-aldol reaction. Thus, a solution of Et\(_2\)BOTf in CH\(_2\)Cl\(_2\) was prepared by addition of triflic acid to triethylborane, warming to 40°C, followed by cooling to \(-78°C\). This solution of boron reagent was then transferred to a solution of \( N\)-acyl-oxazolidin-2-one 458 in dichloromethane at 0°C followed by addition of crotonaldehyde (Scheme 123). Analysis of the crude \( ^1\text{H} \) NMR spectrum of this reaction revealed that the desired syn-aldolate 463 had been formed in approximately 70% conversion, with approximately 30% of the starting \( N\)-acyl-oxazolidin-2-one 458 still remaining. This reaction mixture was then purified via...
chromatography to afford the desired syn-aldolate 463 in 60% yield, which was fully characterised.

![Scheme 123](image)

Repeated attempts to optimise this syn-aldol procedure were unsuccessful in my hands however, with no more than 75% conversion of reactants to aldolate product being observed. Thus, whilst using freshly prepared Et₂BOTf as a reagent enabled access to the desired syn-aldolate product 463, the necessity to carry out a tedious chromatographic preparation to remove starting material after each reaction, was clearly unsatisfactory. As a consequence it was decided to explore the use of other boron reagents to facilitate this syn-aldol reaction.

3.2.5 9-BBN-Triflate as an effective Lewis Acid for syn-selective aldol reactions

A review of the literature revealed that Caddick et al. had reported that treatment of the related N-acetyl-imidazolidin-2-one 465 with 9-BBN.OTf and base afforded a boron enolate that reacted with benzaldehyde to afford syn-aldolate 466 in 84% yield and > 95% d.e. (Scheme 124).¹⁵²

![Scheme 124](image)

Repeating this chemistry using N-acetyl-oxazolidin-2-one 458 and crotonaldehyde with a commercially available solution of 9-BBN triflate in hexanes, resulted in the formation of the desired syn-aldolate product 463 in 72% yield in very high d.e., and with < 5% of starting material remaining. After carrying out a series of syn-aldol reactions using 9-BBN.OTf, optimised reaction conditions were established as follows. The enolate of 458 was prepared in CH₂Cl₂ via successive addition of 9-BBN triflate and ¹Pr₂NEt at 0°C. The
colour of the solution changed from colourless to yellow on addition of 9-BBN triflate, and then back to colourless after the addition of Hüning's base. After a few minutes the reaction vessel was cooled to -78°C, and crotonaldehyde added, the reaction was left at this temperature for one hour, then warmed up to 0°C (Scheme 125).

Scheme 125
Having optimised the preparation of syn-aldolate 463 I wanted to confirm the relative stereochemistry of the syn-aldolate product that had been prepared using this methodology. Thus, reaction of the boron enolate of N-propionyloxazolidin-2-one 457 and benzaldehyde was carried out to afford the known syn-aldolate 467 in 69% yield (Scheme 126). This syn-aldolate 467 was fully characterised and compared to authentic spectroscopic data available in the literature. Both \(^1\)H and \(^13\)C NMR spectra reported by Ito et al. for syn-aldolate 467 matched my spectroscopic data, notably the coupling constant between \(\alpha\)-CHCH\(_3\) and \(\beta\)-CHOH was consistent with that reported in the literature of \(J = 3.5 \text{ Hz}\). This value is in marked contrast to the coupling constant reported for the corresponding anti-aldolate 468 of \(J = 8.5 \text{ Hz}\).\(^{153}\) It was concluded therefore that these conditions had proven successful in establishing an optimised procedure for the preparation of syn-aldolates in a diastereoselective fashion.

Scheme 126

3.2.6 Asymmetric syn-aldol reactions using chiral oxazolidin-2-ones
Since these optimisation studies had established that 9-BBN triflate was the reagent of choice for the preparation of model syn-aldolates (rac)-449 in high d.e., my attention next turned to preparing a chiral syn-aldolate product using these conditions via reaction of the boron enolate of a chiral-\(N\)-acyl-oxazolidin-2-one 471 with an \(\alpha\),\(\beta\)-unsaturated aldehyde substrate.
3.2.6.1 Preparation of chiral-$N$-acyl-oxazolidin-2-ones

Since enantiopure 4-benzyl-oxazolidin-2-one had previously been shown to afford the best diastereoselectivities for the formation of both syn- and anti-aldolates,\textsuperscript{148,154,149} access to multigram quantities of (S)-4-benzyl-oxazolidin-2-one 471 was required. Initial attempts to prepare the precursor amino-alcohol (S)-470 via reduction of L-phenylalanine methyl ester with LiAlH$_4$ were only partially successful affording amino-alcohol (S)-470 in only 35% yield. The use of a commercially available solution of BH$_3$.Me$_2$S in THF for reduction of the parent $\alpha$-amino acid 469 was successful however, affording the desired amino-alcohol (S)-470 in 74% yield.\textsuperscript{155} Subsequent treatment of (S)-470 with diethylcarbonate as a carbonyl equivalent under basic conditions afforded the 4-benzyl-oxazolidin-2-one (S)-471 in 83% yield whose identity was confirmed via spectroscopic comparison with an authentic commercial sample (Scheme 127).

![Scheme 127](image)

**Scheme 127**

Two chiral $N$-acyl-oxazolidin-2-ones 423 and 472 (Scheme 128, Figure 33) were then prepared in fair to good yields via treatment of the chiral 4-benzyl-oxazolidin-2-one (S)-471 with n-BuLi in THF at $-78^\circ$C, followed by addition of the appropriate acid chloride and warming the reaction mixture to room temperature. Purification of crystalline (S)-423 was afforded via recrystallisation from ethyl acetate in 96% yield, whilst (S)-472 was purified via silica gel chromatography in 57% yield.

![Scheme 128](image)
3.2.6.2 Use of chiral N-acyl-oxazolidin-2-ones for stereoselective syn-aldol reactions

Applying the 9-BBN triflate aldol procedure to (4S)-4-benzyl-N-propionyloxazolidin-2-one 423 and methacrolein as substrates resulted in the successful formation of syn-aldolate 440 in 69% yield and in > 95% d.e. (Scheme 129).

Scheme 129

In order to confirm that the 9-BBN.O Tf procedure was indeed affording chiral syn-aldolates with the expected stereochemistry, a chiral syn-aldolate 473 was prepared that had already been reported and fully characterised in the literature. Thus, the boron enolate of (S)-4-benzyl-N-propionyloxazolidin-2-one 423 was reacted with benzaldehyde to afford syn-aldolate 473 in 82% yield and > 95% d.e. (Scheme 130). The compound was fully characterised and the spectroscopic data was shown to be consistent with those reported previously for syn-aldolate 473.151

Scheme 130

87
3.3 Initial attempts to develop an effective \textit{retro-}aldol reaction

3.3.1 Strategy for developing an efficient \textit{retro-}aldol reaction

Having demonstrated that I could reproducibly prepare \textit{syn-}aldolates containing an allylic alcohol functionality in good yield and in high d.e. it was clear that Step 1 of the novel strategy for using chiral auxiliaries for asymmetric synthesis had been achieved (Scheme 131). Since there was ample literature precedent for carrying out directed reactions on substrates that contained allylic alcohol functionality in high d.e. (Step 2), my attention next turned to the development of effective \textit{retro-}aldol methodology that would enable Step 3 of the protocol described in Scheme 131 to be achieved. Thus, I attempted to identify conditions that would enable \textit{N-}acyl-oxazolidin-2-one-\textit{syn-}aldolates such as 475 to cleanly undergo a \textit{retro-}aldol reaction to afford the parent chiral auxiliary 423 and a chiral aldehyde 434 product.

Scheme 131

3.3.2 Preparation of a suitable \textit{syn-}aldolate substrate for the \textit{retro-}aldol reaction

Syw-aldolate 476 was chosen as a substrate for developing an efficient \textit{retro-}aldol reaction because it was similar in structure to the type of \textit{syn-}aldolate product 475 that would be afforded by the directed hydrogenation reaction (Step 2). Consequently, \textit{syn-}aldolate 476 was prepared in 58% yield from \textit{N-}acyl-oxazolidin-2-one 458 and cyclohexane carboxaldehyde using the 9-BBN triflate protocol described in the previous section (Scheme 132).
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3.3.3 A Failed retro-aldol reaction

As described in Section 2.1.3, Bartroli et al. had described that deprotonation of ketolate 427 with LDA resulted in a lithium alkoxide that underwent retro-aldol reaction to afford \(N\)-acyl-oxazolidin-2-one 423 and \(\alpha\)-chloro ketone 429 in good yield (Scheme 133).

In light of this precedent, it was reasoned that deprotonation of syn-aldolate 476 with a strong base should result in an alkoxide intermediate that would undergo a similar retro-aldol reaction. KHMDS was initially chosen as a base for this study because it would result in a potassium alkoxide whose counterion was unlikely to chelate to the oxazolidin-2-one carbonyl, thus ensuring the formation of a highly reactive alkoxide species. Treatment of 476 with KHMDS did not result in the desired retro-aldol reaction however, since analysis of the crude \(^1\)H NMR spectrum revealed no evidence of resonances corresponding to either the \(N\)-acyloxazolidin-2-one 458 or aldehyde 477. Instead, this crude \(^1\)H NMR spectrum revealed that this attempted retro-aldol reaction had in fact afforded a single new compound A in very high yield (Scheme 134).
3.3.4 Structural determination of the unknown product A

Analysis of the $^1$H NMR spectrum of the unknown product A formed in the attempted retro-aldol reaction revealed a well-resolved alkene doublet at 5.59 ppm with a coupling constant of $J = 7.0$ Hz that was coupled to a proton multiplet at 2.25-2.39 ppm. Another feature in the $^1$H NMR spectrum was a broad peak of low intensity at 6.08 ppm, which was coupled to a methylene resonance appearing as an apparent quartet at 3.44 ppm. Acquisition of the $^{13}$C NMR spectrum revealed a single carbonyl resonance at 173 ppm and two olefinic carbon resonances at 138 and 142 ppm. The infra-red spectra of this compound showed three bands of absorption values at 1541, 1619 and 1652 cm$^{-1}$ in the carbonyl region consistent with the formation of an $\alpha\beta$-unsaturated secondary amide fragment. Finally, the molecular ion of A was measured at 239 (M$,^+$, EI), indicating a product resulting from loss of CO$_2$ from the syn-aldolate 476.

With this spectroscopic data in hand, it was proposed that the potassium alkoxide of syn-aldolate 476 had undergone an elimination reaction to afford a trisubstituted $\alpha\beta$-unsaturated amide fragment in a diastereoselective fashion. As has been discussed earlier in this thesis, when this type of trisubstituted acid fragment is formed under thermodynamic control the resulting alkene fragment is normally formed with an (E)-geometry. Consequently, it was proposed that the potassium alkoxide of syn-aldolate 476 had undergone a stereoselective elimination reaction to afford an (E)-$\alpha\beta$-unsaturated amide 478 in 77% yield and > 95% d.e. after purification through column chromatography (Scheme 135).

Scheme 135

Fortunately it was found that (E)-$\alpha\beta$-unsaturated amide 478 was a crystalline solid which was recrystallised from a 1:2 mixture of ethyl acetate and petrol, to afford crystals that were submitted to X-ray analysis. As can be seen from Figure 34 this structural determination clearly confirmed the proposed structure of amide (E)-478, with the cyclohexane moiety in its chair conformation trans to the amide carbonyl and cis to the iso-propyl group (Figure 34, Appendix 1).
Figure 34. X-ray crystal structure of (E)-478

This new and fascinating route to α,β-unsaturated amides from syn-aldolates appeared to afford a highly stereoselective route to synthetically desirable (E)-trisubstituted acid derivatives. As a consequence, it was decided to postpone further investigation into optimising the retro-aldol reaction, in favour of investigating the scope and limitation of this novel elimination reaction for a range of achiral syn-aldolate substrates.
CHAPTER 4. A New Route to trisubstituted \( (E) \)-\( \alpha,\beta \)-Unsaturated Acid Derivatives

It was decided to investigate further the base-mediated elimination reaction of a range of syn-aldolate substrates in order to fully determine the potential of this procedure for the stereoselective synthesis of trisubstituted \( (E) \)-unsaturated amides.

4.1 Preparation of \( (E) \)-\( \alpha,\beta \)-unsaturated amides

4.1.1 Preparation of a range of syn-aldolate substrates

Firstly, a range of syn-aldolate substrates were prepared using 9-BBN-triflate under our optimised conditions in 31-74% yield after purification by chromatography. The low yield obtained for the preparation of 479 (Table 25, entry 1) is due to an observed lack of reactivity in the reaction of the boron enolate of \( N \)-propionyloxazolidin-2-one 457 with propionaldehyde, since significant amounts of starting material 457 were recovered. In all cases no evidence of any \( anti \)-aldolate products, was observed in the \( ^1H \) NMR spectra of the crude reaction product with all aldolates being purified \textit{via} chromatography and fully characterised.

![Scheme 136](image)

**Scheme 136**

<table>
<thead>
<tr>
<th>( R )</th>
<th>( R_1 )</th>
<th>aldolate</th>
<th>( % ) yield</th>
<th>( \delta \ CHR^a )</th>
<th>( IR (cm^{-1})^b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( CH_3 )</td>
<td>( CH_2CH_3 )</td>
<td>479</td>
<td>31</td>
<td>3.79-3.89 (m)</td>
</tr>
<tr>
<td>2</td>
<td>( ^4Pr )</td>
<td>( CH_2CH_3 )</td>
<td>480</td>
<td>48</td>
<td>3.83 (app t)</td>
</tr>
<tr>
<td>3</td>
<td>( CH_3 )</td>
<td>( Ph )</td>
<td>467</td>
<td>69</td>
<td>4.12 (qd)</td>
</tr>
<tr>
<td>4</td>
<td>( ^4Pr )</td>
<td>( Ph )</td>
<td>481</td>
<td>50</td>
<td>4.48 (dd)</td>
</tr>
<tr>
<td>5</td>
<td>( ^4Pr )</td>
<td>( p-MeOPh )</td>
<td>482</td>
<td>60</td>
<td>4.48 (dd)</td>
</tr>
<tr>
<td>6</td>
<td>( CH_2Ph )</td>
<td>( (CH_2)_(CH_3) )</td>
<td>483</td>
<td>74</td>
<td>4.33-4.40 (m)</td>
</tr>
</tbody>
</table>

\(^a\) Chemical shifts and multiplicity of \( CHR \) in the \( ^1H \) NMR spectra; \(^b\) Frequencies correspond to the carbonyl C=O stretches from oxazolidin-2-one and amide, respectively.

Table 25
4.1.2 Elimination of the potassium alkoxides of syn-aldolates to afford (E)-amides in high d.e.

Each syn-aldolate was then treated with 1.5 equivalents of KHMDS in THF at -78°C for 2 hours, after which time the reaction was quenched with saturated NH₄Claq. Examination of the crude ¹H NMR spectra of these reactions indicated that trisubstituted (E)-α,β-unsaturated amides 484-489 had been formed in high d.e. and good yield in each case. Each (E)-amide was purified to homogeneity via chromatography and fully characterised. The (E)-stereochemistry of each of these products was confirmed via comparison of their spectroscopic data with that of (E)-478 whose structure had previously been established via X-ray crystallography, and via subsequent hydrolysis to their corresponding acids (vide supra) (Scheme 137, Table 26). For amides 484-486 (Table 26, entry 1-3) no evidence for the presence of any (Z)-isomer was present in the ¹H NMR spectra of the crude reaction mixtures. For amides 487-489 (Table 26, entry 4-6), diastereomeric excess was assigned via integration of the peaks corresponding to the NH peak of both the (E)- and (Z)-isomers, where the NH resonance of the (Z)-isomer always appeared downfield to the NH resonance of the (E)-isomer.

\[
\text{Scheme 137}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>R₁</th>
<th>(E)-amide</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CH₃</td>
<td>CH₂CH₃</td>
<td>484</td>
</tr>
<tr>
<td>2 iPr</td>
<td>CH₂CH₃</td>
<td>485</td>
</tr>
<tr>
<td>3 CH₃</td>
<td>Ph</td>
<td>486</td>
</tr>
<tr>
<td>4 CH₃</td>
<td>Ph</td>
<td>486</td>
</tr>
<tr>
<td>5 iPr</td>
<td>Ph</td>
<td>487</td>
</tr>
<tr>
<td>6 iPr</td>
<td>p-MeOPh</td>
<td>488</td>
</tr>
<tr>
<td>7 Bn</td>
<td>(CH₂)₆CH₃</td>
<td>489</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(E)-amide</th>
<th>% d.e.</th>
<th>% yield</th>
<th>δ CH₃</th>
<th>IR (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>484</td>
<td>&gt;95</td>
<td>67</td>
<td>6.19 (br s), 6.38 (t)</td>
<td>1538, 1615, 1701</td>
</tr>
<tr>
<td>485</td>
<td>&gt;95</td>
<td>99</td>
<td>5.77 (t), 6.26 (br s)</td>
<td>1534, 1617, 1653</td>
</tr>
<tr>
<td>486</td>
<td>&gt;95</td>
<td>91</td>
<td>6.48 (s), 7.19 (br s)</td>
<td>1575, 1620, 1644</td>
</tr>
<tr>
<td>486</td>
<td>80ᵇ</td>
<td>Not isol.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>487</td>
<td>92</td>
<td>94 (69)</td>
<td>6.33 (br s), 6.79 (s)</td>
<td>1538, 1612, 1641</td>
</tr>
<tr>
<td>488</td>
<td>90</td>
<td>95 (64)</td>
<td>6.38 (br s), 6.73 (s)</td>
<td>1542, 1620, 1645</td>
</tr>
<tr>
<td>489</td>
<td>92</td>
<td>95 (73)</td>
<td>6.17 (br t), 6.54 (t)</td>
<td>1537, 1620, 1656</td>
</tr>
</tbody>
</table>

* Yields in bracket correspond to yields afforded after chromatographic purification for characterisation purposes; ‡ Reaction was carried out at 0°C. The crude reaction product was not purified.

Table 26
During investigations into the scope and limitation of this novel methodology a significant limitation of this elimination procedure was discovered for syn-aldolate substrates that derived from α,β-unsaturated aldehydes. Thus, treatment of syn-aldolate 463 previously prepared for optimisation studies of the aldol reaction (see section 3.2.5) with KHMDS afforded a crude reaction product with a complex 1H NMR spectrum arising from the presence of two compounds that were assigned as the (E,E)-α,β,γ,δ-unsaturated amide 490, and its geometric isomer (Z,E)-491 in 60% d.e. (Scheme 138). The d.e. of this elimination reaction was determined via integration of the resonances of the iso-propyl methyl protons in the 1H NMR spectrum of the crude reaction mixture. Attempted chromatographic purification of this mixture of geometric isomers through silica gel did not result in any separation, however these (E,E)- and (Z,E)-isomers could be separated via chromatography over a stationary phase derived from silica gel that had been coated with silver nitrate. Indeed this purification technique allowed isolation of both the major (E,E)-isomer and the minor (Z,E)-isomer which were independently characterised via 1H NMR spectroscopy. These (E,E)-490 and (Z,E)-491 isomers were found to isomerise on standing however, so they could not be fully characterised in a conventional manner, however the mass spectra of the resultant mixture of isomers 490 and 491 did reveal a molecular ion peak of 197 (M+, EI) (Scheme 138). Since these samples darkened significantly over time it was suspected that they contained residual traces of silver nitrate that had catalysed the observed (E)/(Z) isomerisation in the presence of light.

\[
\text{Scheme 138}
\]

In order to determine if this lack of stereoselectivity during the elimination of syn-aldolates derived from α,β-unsaturated aldehydes was a general trend, syn-aldolate 492 was next prepared via reaction of the boron enolate of N-propionyloxazolidin-2-one 457 with trans-cinnamaldehyde in 88% yield and in > 95% d.e. This syn-aldolate 492 was then treated with 1.5 equivalents of KHMDS in THF at -78°C in the usual manner to afford a mixture of (E)- and (Z)-unsaturated amides 493 and 494 once again in only 60% d.e. (Scheme 139). Fractional recrystallisation of this mixture of geometric isomers from ethyl acetate was
successful in affording the major diastereoisomer in 64% yield, which was assigned as trisubstituted \((E,E)-\alpha,\beta\)-unsaturated amide 493 by analysis of its spectroscopic data and subsequent cleavage to its parent acid (vide supra). It should be noted that the first time this reaction was carried out \(^1\)H NMR spectroscopic analysis of the crude product appeared to indicate that \((E,E)-493\) had been formed in > 95% d.e. However, this d.e. could not be repeated and as a consequence it appears that this value was incorrect and must have arisen from unintentional fractional recrystallisation of the crude reaction product.

![Scheme 139](image)

In conclusion, the base mediated elimination of \(\gamma,\delta\)-unsaturated-\(\text{syn-aldolates}\) 463 or 492 was not as stereoselective as the other \(\text{syn-aldolates}\) 430, 467, 479-483 employed as substrates in this study.

4.2 Preparation of \((E)-\alpha,\beta\)-unsaturated carboxylic acids and \((E)-\alpha,\beta\)-unsaturated oxazolines

Having demonstrated that this elimination methodology afforded an excellent general route to \((E)-\text{trisubstituted} \ \alpha,\beta\)-unsaturated amides, their conversion to other carboxylic acid derivatives was next explored in order to expand the synthetic versatility of this methodology.

4.2.1 Hydrolysis of trisubstituted \((E)-\alpha,\beta\)-unsaturated amides to afford their corresponding \((E)-\text{acids}\)

Conditions were next investigated that would enable aqueous hydrolysis of \((E)-\text{amides}\) to afford their corresponding carboxylic acids \((E)-495-499\) in good yield. Thus, five representative \((E)-\alpha,\beta\)-unsaturated amide 478, 484, 486, 489 and 493 were refluxed in 6M HCl\(_{aq}\) for 6 hours. Problems were initially encountered in extracting the water soluble \((E)-\text{acid}\) products 495-499 from aqueous solution, however a work-up protocol involving saturating the aqueous solution with sodium chloride prior to extraction into ethyl acetate.
Chapter 4 Results and discussion

gave the corresponding \((E)\)-acids 495-499 in excellent yield. Importantly, care had to be taken during removal of organic solvent from some of these \((E)\)-acids because of their volatility, leading to significant loss in mass on exposure to reduced pressure over time (Scheme 140, Figure 35).

![Scheme 140](image)

Figure 35

Importantly, examination of the crude \(^1\)H NMR spectra of these hydrolysis reactions revealed that all of these \(\alpha,\beta\)-unsaturated acids had been formed as single isomers with no evidence of any alkene migration having occurred under the strong acid conditions used for hydrolysis. Finally, the structures and stereochemistry of \((E)\)-acids 495 and 497 were confirmed via comparison with commercially available samples of \((E)\)-2-methylpentenoic acid and \((E)\)-2-methyl-3-phenylpropenoic acid, whilst spectroscopic data of \((E)\)-496 and \((E)\)-498 were compared with known literature values.\(^{156,157}\) It should be noted that these structural assignments for \((E)\)-acids 495-499 provide further evidence for the original assignment of \((E)\)-stereochemistry to amides 484-489 discussed in section 4.1.2.

4.2.2 Conversion of trisubstituted \((E)\)-\(\alpha,\beta\)-unsaturated amides into their corresponding \((E)\)-oxazolines.

The synthetic versatility of this methodology was further demonstrated via cyclisation of the \(N\)-hydroxyamide fragment of the \((E)\)-amides to afford their corresponding trisubstituted \((E)\)-\(\alpha,\beta\)-unsaturated oxazolines. It was reasoned that access to synthetically versatile \((E)\)-oxazolines 500 would allow future combinatorial access to a range of \((E)\)-acids 501,
(E)-alcohols 502, or even (E)-aldehydes 503 using the range of hydrolytic reductive protocols described in Scheme 141.\textsuperscript{158,159}

\[ \text{Scheme 141} \]

A number of different approaches were attempted to achieve this aim before an effective protocol was identified for the conversion of tiglate derived (E)-amide to its corresponding (E)-oxazoline. For example, treatment of (E)-\(\alpha,\beta\)-unsaturated amide 484 with mesylchloride and triethylamine in CH\(_2\)Cl\(_2\) at 0°C, followed by washing with sodium hydroxide, gave a single product in 60% yield which was tentatively assigned as chloride 504 (Scheme 142).\textsuperscript{160}

\[ \text{Scheme 142} \]

An alternative protocol by Vorbruggen et al.,\textsuperscript{161} involving treatment of amide (E)-484 with triphenylphosphine, carbon tetrachloride and triethylamine in acetonitrile was partially successful, affording (E)-oxazoline 505 in only 40% yield after purification by column chromatography (Scheme 143). The structure of oxazoline 505 was confirmed via analysis of the \(^1\text{H} \) NMR spectrum which no longer showed the broad peaks characteristics of OH and NH resonances of amide (E)-484, whilst the four methylene protons from the \(\text{N-hydroxyamide in amide 484} \) had shifted to a higher frequency. The infrared spectra of this compound showed two bands of absorption values at 1653 and 1700 cm\(^{-1}\) consistent with the presence of an unsaturated oxazoline fragment. Finally, the mass spectrum of 505 was
measured at 139 (M⁺, EI), indicating a product consistent with loss of H₂O from amide 484.

Scheme 143
Alternatively, a procedure by Curran et al. was carried out involving treatment of (E)-484 with the expensive reagent diethyl ammonium sulfur trifluoride DAST (1.3 eq.) at -78°C for 6 hours, followed by stirring at room temperature overnight, which once again resulted in formation of trisubstituted (E)-oxazoline 505, but in only 45% isolated yield (Scheme 144).³⁶²

Scheme 144
In an attempt to address these low yields I next refluxed α,β-unsaturated amide 484 with 2.5 equivalents of SOCl₂ for 2 hours to afford a crude reaction mixture which contained a 3:2 mixture of the oxazoline (E)-505 and chloride (E)-504 (Scheme 145).³⁶³ Reasoning that the reaction was proceeding via a mechanism in which (E)-amide 484 was first converted to chloride 504, followed by cyclisation of chloride 504 to afford the desired (E)-oxazoline 505, the length of the reaction was increased to 48 hours. Surprisingly, this did not lead to an increase in the amount of (E)-oxazoline product 505 formed, but instead gave a 20:1 mixture of chloride 504 to (E)-oxazoline 505.

Scheme 145
This result clearly indicated that the initially low yield observed in this reaction was not a consequence of the parent (E)-amide 484 failing to cyclise to afford the (E)-oxazoline 505, but instead was due to attack of adventitious chloride ion on the (E)-oxazoline (as its HCl
Chapter 4 Results and discussion

salt 506) to afford its corresponding (E)-chloride 504 via the mechanism described in Figure 36.

![Figure 36](image)

With this information in hand, thionyl chloride (5 eq.) was added in a dropwise fashion to an ice-cold solution of unsaturated amide 484 in CH$_2$Cl$_2$ followed by stirring at 0°C for 2 hours before work-up via slow addition of sodium hydroxide (5M), to afford the desired (E)-oxazoline 505 in 88% yield (Scheme 146).

![Scheme 146](image)

These conditions were then applied to a second trisubstituted (E)-$\alpha$-$\beta$-unsaturated amide 486 to afford (E)-trisubstituted $\alpha$-$\beta$-unsaturated oxazoline 507 in 97% yield, thus demonstrating the general applicability of this protocol for the cyclisation of (E)-amide substrates arising from my novel elimination methodology (Scheme 147).

![Scheme 147](image)

Whilst time considerations restricted the range of (E)-oxazolines that have been prepared using this methodology, as well as preventing me from demonstrating the potential of these type of oxazolines (E)-500 to afford acids (E)-503, alcohols (E)-504 or aldehydes (E)-505 (see Scheme 141), there is ample literature precedent to suggest that these type of trisubstituted (E)-oxazolines will prove to be versatile synthons. Indeed, a more complete
study on the potential of these type of α-substituted unsaturated oxazolines for the
development of novel asymmetric protocols is currently being carried out by a member of
the SDB research group.
Since treatment of a range of syn-aldolates with KHMDs had been shown to afford (E)-α,β-unsaturated amides in a highly stereoselective manner, the mechanism of this elimination reaction was next explored.

5.1 Mechanistic Hypothesis

It is well known that sterically unhindered N-acyl oxazolidin-2-ones can undergo endocyclic ring cleavage via either inter- or intramolecular attack of oxygen nucleophiles at their oxazolidin-2-one carbonyl groups.\textsuperscript{164,165} For example, reaction of Diels-Alder adduct 508 and lithium benzylxide had been shown to afford the endocyclic cleavage product 510 as the major product, as well as the desired benzylester 509 in 46% conversion (Scheme 148).

\begin{equation}
\text{Scheme 148}
\end{equation}

Consequently, it was proposed that the stereochemical outcome of the elimination reaction of the potassium alkoxides of syn-aldolates 511 could be explained by invoking an intramolecular endocyclic cleavage mechanism. Thus, a potassium alkoxide 512 would initially undergo intramolecular attack at the oxazolidin-2-one carbonyl resulting in O-O carbonyl migration, to afford a 1,3-oxazinane-2,4-dione alkoxide intermediate 513. Subsequent anion equilibration of alkoxide 513 to afford enolate 514 would then enable
stereoselective elimination of carbon dioxide to occur to afford the trisubstituted secondary amide (E)-515 in high d.e. (Figure 37).

![Reaction Scheme]

Figure 37. Intramolecular cyclisation/elimination mechanism for the formation of (E)-α,β-unsaturated amides 515.

Whilst this mechanism appeared perfectly feasible it was important to obtain clear proof that the formation of an oxazinanedione intermediate was responsible for stereocontrol in this reaction, and I therefore attempted to find conditions that would enable selective conversion of syn-aldolate 511 into its corresponding oxazinane-2,4-dione, which would then be employed for elimination studies.

5.2 Isolation of a possible intermediate

5.2.1 Literature precedent for rearrangement of syn-aldolates to oxazinane-2,4-diones

A review of the literature revealed two previous examples where alkoxides of β-hydroxy-N-acyloxazolidin-2-ones had selectively rearranged to afford products containing an oxazinane-2,4-dione skeleton. Ito et al. had reported that reaction of a zinc enolate prepared from α-bromo-N-acyl-oxazolidin-2-one 516 with benzaldehyde at 0°C had not afforded the expected adolate products but instead had given a mixture of rearranged 1,3-oxazinane-2,4-dione diastereoisomers 517 and 518 in good yield but in poor d.e. (Scheme 149).
5.2.2 An effective protocol for the rearrangement of syn-aldolates to afford oxazinane-2,4-diones

Since these observations implied that titanium or zinc alkoxides of \( \beta \)-hydroxy-\( N \)-acyloxazolidin-2-ones could undergo facile rearrangement to their corresponding 1,3-oxazinane-2,4-diones, it was decided to investigate whether generating zinc alkoxides of \( N \)-acyl-oxazolidin-2-one-syn-aldolates 511 would result in selective rearrangement to afford 1,3-oxazinane-2,4-dione products. Thus, treatment of a solution of syn aldolate 479 with a stoichiometric amount of \( \text{Et}_2\text{Zn} \) in \( \text{CH}_2\text{Cl}_2 \) cleanly afforded a single product A which was tentatively assigned as the desired oxazinane-2,4-dione 522 using the following spectroscopic arguments (Scheme 151). Analysis of the \(^1\text{H} \) NMR spectrum revealed that unlike syn-aldolate 479, the \( \text{CHCH}_3 \) and \( \text{CHEt} \) protons of product A were well-resolved and appeared respectively at \( \delta \) 2.79 ppm as a quartet of doublets and \( \delta \) 4.34 ppm as a doublet of doublets of doublets. Likewise the \(^{13}\text{C} \) NMR spectrum revealed that the corresponding carbon resonances appeared at \( \delta \) 39.6 and \( \delta \) 40.8 ppm in syn-aldolate 479 whilst in product A they were respectively shifted downfield at \( \delta \) 38.0 ppm and upfield at \( \delta \) 48.1 ppm. Both carbonyl absorptions at 1750 and 1695 cm\(^{-1}\) were similar to those of the starting aldolate 479 (1752, 1696 cm\(^{-1}\)), with no difference in the chemical shift of the
carbonyl resonances in $^{13}$C NMR, whilst the molecular ion of A was measured at 202 (MH$^+$, CI$^+$), confirming the molecular formula of the product as C$_{9}$H$_{16}$NO$_{4}$. Whilst the spectroscopic data described for product A was consistent with the formation of the desired oxazinane-2,4-dione skeleton, this data was also consistent with the structure of an alternative anti-aldolate 523 product that could potentially have been formed from the zinc alkoxide of syn-aldolate 479 undergoing a reversible retro-aldol/aldol reaction.

Scheme 151

This potential assignment problem was solved by carrying out a long range carbon-hydrogen NMR correlation experiment that demonstrated coupling between carbon and proton resonances that were connected to each other by up to three bonds. Thus, carrying out this long range coupling correlation experiment on product A (Figure 38) revealed coupling between the $^{13}$C resonance of the C2 carbonyl and $^1$H resonances corresponding to H5, H6, 2xH7, 2xH1' and 2-CH2'OH protons (for oxazinane-2,4-dione 522); whilst the C4 carbonyl $^{13}$C resonance was coupled with H5, H6, 2xH7, 2xH1' and 2xCH2'OH and the C5-CH$_3$ protons (for oxazinane-2,4-dione 522). This connectivity pattern was clearly incompatible with the structure of anti-aldolate 523, which whilst demonstrating the same type of coupling pattern between its C4 carbonyl and its 2xH2, 2xH3, H5, H6, H7 and H9 protons, would only have afforded three cross-peaks between its C1 carbonyl and its 2xH2, 2xH3 and H5 resonances. This NMR correlation spectra clearly revealed therefore, that the structure of rearranged product A was consistent with the oxazinane-2,4-dione skeleton syn-522, and not with the structure of anti-aldolate product 523.

Since this approach appeared to provide a facile route from $N$-acyl-oxazolidin-2-one-syn-aldolates to afford oxazinane-2,4-diones, it was decided to explore further this rearrangement reaction. Optimisation studies on syn-aldolate 479 revealed that the rearrangement reaction could be initiated using a catalytic amount of Et$_2$Zn affording the same oxazinane-2,4-dione product 522 in an essentially identical 58% yield (Scheme 152).
Possible structures for A:

- Aldolate product
- Antipode (anti)

Oxazinane-1,4-dione

Figure 38
5.2.3 Elimination of syn-oxazinane-2,4-diones affords trisubstituted (E)-α,β-unsaturated amides in high d.e.

With an authentic sample of syn-oxazinane-2,4-dione 522 in hand it was explored whether treatment with KHMDS would result in a stereoselective elimination reaction to form (E)-amide 484 in high d.e. Thus, treatment of syn-oxazinane-2,4-dione 522 with KHMDS in THF at -78°C resulted in clean elimination to afford trisubstituted (E)-α,β-unsaturated amide 484 in > 95% d.e. (Scheme 154). It should be noted that the d.e. obtained for the formation of amide (E)-484 in this reaction was identical to that obtained previously for elimination of syn-aldolate 479, thus providing compelling evidence that oxazinane-2,4-dione alkoxide is a common intermediate responsible for the excellent levels of stereocontrol observed in both types of stereoselective elimination reactions.
5.3 Probing the mechanism of the elimination reaction

Having established that oxazinane-2,4-diones were plausible intermediate in the base mediated stereoselective elimination reaction of syn-aldolates to afford (E)-amides, it was necessary to establish whether the key elimination reaction of CO$_2$ from this oxazinane-2,4-dione intermediate 522 was likely to occur via a stepwise ElcB-type pathway, or via a concerted E2 elimination pathway (Figure 39).

In order to probe which of these two elimination mechanisms was occurring, it was decided to compare the stereoselectivity of elimination of potassium alkoxides of a syn-aldolate with its corresponding anti-aldolate substrates, since changing the relative stereochemistry of the aldolates would have important stereochemical consequences depending on whether an ElcB or E2 elimination pathway was in operation. Thus, for an
ElcB reaction pathway, it was predicted that elimination of both syn- and anti-aldolate substrates would proceed via a common enolate-like intermediate that would eliminate CO$_2$ to afford the same (E)-$\alpha$$\beta$-unsaturated amide 484 (Figure 40). Alternatively, for a concerted E2 elimination reaction, it would be expected that the stereochemistry of both aldolate substrates would be conserved throughout, with antiperiplanar elimination of syn-oxazinane-2,4-dione intermediate 522 affording an (E)-$\alpha$$\beta$-unsaturated amide 484, whilst anti-526 would afford the corresponding (Z)-$\alpha$$\beta$-unsaturated amide 527.

![Chemical Structure](image)

ElcB elimination of an anti-oxazinane-2,4-dione 526 will result in a (E)-amide 484

![Chemical Structure](image)

E2 elimination of an anti-oxazinane-2,4-dione 526 will result in a (Z)-amide 527

**Figure 40**

It was therefore necessary to develop an efficient protocol for the preparation of an anti-aldolate substrate that would enable these comparative elimination reactions to be carried out.

### 5.3.1 The anti-stereoselective aldol reaction using N-acyl oxazolidin-2-ones

#### 5.3.1.1 Background

Heathcock *et al.* have reported previously on a protocol that enables selective access to anti-aldol diastereoisomers. Thus, treatment of the boron (Z)-enolate of an (S)-N-acyl-oxazolidin-2-one with an aldehyde precoordinated to Et$_2$AlCl had resulted in the formation of the (2S,3S)-anti-aldolate 529 in high d.e. It was proposed that Et$_2$AlCl acts as a bulky Lewis acid due to a relatively short O-Al bond, which results in a transition state 528 that
minimizes steric interaction between the Et₂AlCl and both the R-alkyl group of the enolate and the R₁-alkyl group of the aldehyde, thus affording anti-aldolate 529 in high d.e. (Scheme 155).

Scheme 155

During the course of my investigation, Evans et al. described an alternative method to obtain the alternative anti-aldolate of N-acyl-oxazolidin-2-ones. He reported that treatment of (R)-4-benzyl-N-acyl-oxazolidin-2-one 530 with a catalytic amount of magnesium chloride and an excess of triethylamine and chlorotrimethylsilane gave anti-aldolate 532 with good conversion rates and selectivity under very mild conditions at room temperature.¹⁶⁷¹⁵⁴ The catalytic reaction was limited by a narrow substrate specificity profile however, with only aromatic and conjugated aldehydes affording good yields of anti-aldolate products, whilst bulky R-substituents at the α-position of the N-acyl-oxazolidin-2-one 530 were not well tolerated (Scheme 156).

Scheme 156

The mechanism of this reaction has not been yet elucidated, although Evans has ruled out the possibility of a Mukaiyama aldol pathway in which an enolsilane is formed and attacks the electrophilic aldehyde complexed to a Lewis acid species.¹⁶⁸ Indeed, the independently prepared enolsilane of 530 was shown not to react with benzaldehyde in the presence of MgCl₂ in ethyl acetate. Instead, Evans proposed that a nucleophilic magnesium enolate 531
reversibly attacked the aldehyde to form a magnesium aldolate product 533. Silylation of aldolate 533 displaces the magnesium counterion from the alkoxide fragment, irreversibly affording the silyl-aldolate 534. The magnesium catalyst is then displaced by another molecule of N-acyl-oxazolidin-2-one 530, thereby completing the catalytic cycle (Figure 41).  

Evans proposed that the aldol reaction of magnesium enolate gave anti-aldolate 535 via a six-membered transition state. Computational calculations predicted that formation of the alternative anti-aldolate 536 was disfavoured due to steric interaction between the benzyl stereodirecting group and the incipient aldehyde. Thus, the alternative anti-aldolate 536 was formed in high d.e. under these conditions (Figure 42).

5.3.1.2 Preparation of anti-aldolate substrates for stereospecific elimination studies
My attempts to repeat Heathcock's anti-aldolate chemistry were universally unsuccessful. Repeated attempts involving addition of the boron enolate of N-acyloxazolidin-2-one 458 in CH₂Cl₂, to a solution of propionaldehyde pre-complexed with Et₂AlCl never afforded
any of the desired anti-aldolate product 537, instead giving either recovered starting material 458, or the corresponding Evans’ syn-aldolate product 480 (Scheme 157).

![Scheme 157]

The alternative Evans’ procedure involving addition of the magnesium enolate of N-acyloxazolidin-2-one 457 to benzaldehyde was successful however, affording the desired anti-aldolate 468 as a single stereoisomer, albeit in a low 33% yield (Scheme 158). The stereochemistry of the anti-aldolate 468 was confirmed via examination of its $^1$H NMR spectra which revealed a large coupling constant between $\alpha$-CHCR$^2$ and $\beta$-CHOH of $J = 8.5$ Hz. This compares with the smaller coupling constant of $J = 3.5$Hz for the corresponding syn-aldolate 467 which was also prepared in 69% yield using the 9-BBN triflate syn-aldol protocol described previously (see section 3.2.5).

![Scheme 158]

5.3.2 Elimination of the potassium alkoxide of N-acyl-oxazolidin-2-one aldolates is non-stereospecific

With both syn-aldolate 467 and anti-aldolate 468 in hand, the key elimination reactions involving separate treatment of each of the syn-467 and anti-468 diastereoisomers with 1.5 equivalents of KHMDS in THF at -78°C were carried out. As expected, the potassium alkoxide of syn-aldolate 467 cleanly eliminated to afford (E)-N-(2-hydroxyethyl)-2-
methyl-3-phenyl-2-propenamide 486 in a good 90% yield and in > 95% d.e. Under the same conditions the potassium alkoxide of anti-aldolate 468 also underwent stereoselective elimination reaction, affording the same (E)-N-(2-hydroxyethyl)-2-methyl-3-phenyl-2-propenamide 486 in similar yield and in identical d.e. (Scheme 159), thus providing good evidence that these reactions occur via E1cB-type reactions that proceed through a common oxazinane-2,4-dione-intermediate.

Scheme 159

In order to provide further proof that a common oxazinane-2,4-dione enolate intermediate was responsible for stereocontrol in both these elimination reaction, syn-aldolate 467 and anti-aldolate 468 were treated with a catalytic amount of diethylzinc in CH$_2$Cl$_2$ at room temperature, to afford syn-oxazinane-2,4-dione 517 in 90% d.e. and anti-oxazinane-2,4-dione 518 in > 95% d.e. respectively. The $^1$H NMR spectra of oxazinanediones syn-517 and anti-518 revealed coupling constants between CHCH$_3$ and CHPh of 3.5 and 11.5 Hz respectively. Both syn- and anti-oxazinanedione 517 and 518 were then separately treated with 1.5 equivalents of KHMDS in THF at -78°C, with both substrates once again affording (E)-$\alpha$,$\beta$-unsaturated amide 486 in good yield and in the same > 95% d.e. (Scheme 160).
5.3.3 Mechanistic rationale

The series of experiments described in this chapter are clearly consistent with the potassium alkoxides of syn-aldolates and anti-aldolates undergoing stereoselective elimination to afford the same \( (E)\)-\( \alpha\beta \)-unsaturated amide via a common oxazinane-2,4-dione intermediate according to the original reaction mechanism described in Figure 39 and 40. Thus, deprotonation of either syn-aldolate 467 or anti-aldolate 468 will afford alkoxides that rearrange stereoselectively to afford the potassium alkoxides of syn-oxazinane-2,4-dione 538 and anti-oxazinane-2,4-dione 540 respectively, each of which is in equilibrium with a common oxazinane-2,4-dione enolate intermediate 539 (Figure 42). Thus, in this mechanism, the stereochemistry that originates from the C1 stereocentre of each aldolate substrate is always destroyed, with the stereochemistry of the \( (E)\)-\( \alpha\beta\)-unsaturated amide being controlled during irreversible elimination of CO\(_2\) from enolate 539 via an E1cB type pathway.

![Diagram](image.png)

Figure 42

Previously in this thesis it has been described that the potassium alkoxide of syn-aldolate 463 eliminated to afford a mixture of unsaturated \( (E)\)- and \( (Z)\)-amides in only 60% d.e. I wished to probe whether this loss of stereocontrol occurred during rearrangement of syn-aldolate 463 to its oxazinane-2,4-dione intermediate 541, or during the resulting elimination of this oxazinane-2,4-dione 541 to afford the amide products. Treatment of
Chapter 5 Results and Discussion

*syn*-aldolate 463 with KHMDS resulted in a zinc alkoxide, which cleanly rearranged to afford oxazinane-2,4-dione 541 as a single isomer (Scheme 161).

![Scheme 161](image)

Scheme 161

The oxazinanedione 541 (> 95% d.e.) was then treated with KHMDS under the same conditions used previously to eliminate *syn*-aldolate 463 to α,β-unsaturated amide, and was shown to afford the same ratio of (E)- and (Z)-α,β-unsaturated amide 490 and 491 in 60% d.e. (Scheme 162).

![Scheme 162](image)

Scheme 162

Thus, for this particular type of *syn*-aldolate substrate 463, rearrangement to the corresponding *syn*-oxazinanedione 541 appears to be completely stereoselective, with any loss in stereocontrol occurring during the resulting elimination reaction of CO₂ to form a mixture of (E)- and (Z)-α,β-unsaturated amides 490 and 491 (Figure 43).

![Figure 43](image)
5.3.4 Molecular modelling studies on the elimination of oxazinane-2,4-dione enolates

The mechanistic investigations in this chapter have clearly revealed that the (E)- or (Z)-stereochemistry of the trisubstituted amide products produced via base mediated elimination of syn- or anti-aldolates was determined during the E1cB elimination step of oxazinane-2,4-dione enolate 514 (Figure 45).

![Figure 45](image)

As has been described previously in this thesis, (E)-trisubstituted esters are normally formed in preference to (Z)-trisubstituted esters when elimination reactions occur under thermodynamic control. However in this case it appears likely that the elimination reaction was occurring under kinetic control via concerted elimination of oxazinane-2,4-dione 514. In order to further understand the reasons why this E1cB reaction was preferentially affording (E)-amides in high d.e., I have collaborated with Dr David Fox of the University of Cambridge who has carried out preliminary molecular modelling studies on the transition states of simplified models leading to the formation of amides (Z)-542 and (E)-543 (Figure 46).

![Figure 45](image)
Calculations were performed using the Windows PC version of GAMESS using the MP2 method and a 6-31(d,p)++ basis set, which revealed that transition state TS 1 leading to the (Z)-amide 542 was 16 kJ mol⁻¹ greater in energy than transition state TS 2 leading to the (E)-amide 543. This transition state energy difference is very large, and at -78°C represents a large difference in relative reaction rates, thus providing good evidence in support of the selective formation of (E)-amides under kinetically controlled conditions.
CHAPTER 6. Broadening the Range of Aldolate Substrates employed for Elimination

The novel elimination reaction of N-acyl-oxazolidin-2-one aldolates that has been described appeared to be attractive methodology that could potentially rival the Wittig or Horner-Wadsworth-Emmons procedures for the preparation of (E)-trisubstituted acid derivatives. It was therefore decided to explore the versatility of this methodology to demonstrate that aldolates derived from chiral aldehydes, or heteroaryl aldehydes, would also undergo stereoselective elimination reactions.

6.1 Elimination of syn-aldolates derived from chiral aldehydes

Since most natural products of interest are derived from (E)-trisubstituted α,β-unsaturated acid fragments (or derivatives) containing a methyl group at their α-position, I concentrated on the preparation of three chiral trisubstituted (E)-amides containing this functionality.

Reaction of the boron enolate of achiral N-propionyl-oxazolidin-2-one 457 with (R)-perillaldehyde 544 (90% pure) resulted in a mixture of two diastereoisomers in 64% yield. Attempted purification of this mixture of diastereoisomers via exhaustive chromatography was unsuccessful and did not afford any enhancement in diastereoisomeric purity, and as a consequence this reaction was characterised as a mixture of diastereoisomers. The $^1$H NMR spectrum of the mixture was too complex to reveal the d.e., however the relative heights of the resonances for the two diastereoisomers in the $^{13}$C NMR spectrum showed clearly that the two diastereoisomers 545:546 had been formed in essentially equal amounts. Treatment of this mixture of diastereomers 545 + 546 with KHMDSS in CH$_2$Cl$_2$ at -78°C resulted in stereoselective elimination to afford the novel α,β-unsaturated amide 547 in a disappointing 50% d.e., and the major diastereomer was purified easily via chromatography. This poor diastereoselectivity is consistent with that observed previously for other α,β-unsaturated aldehydes. Pertinent NMR spectroscopic details for 547 include the presence of a singlet at δ 1.95 ppm corresponding to the allylic methyl protons at the α-position, whilst the new olefinic proton at the β-position appeared as a singlet at δ 6.66 ppm (Scheme 163). Since the stereogenic centres arising from the (S)-citronellal fragment in aldolate 545 and 546, and hence the corresponding (E)-amide
547, were not acidic, and unlikely to racemise, it was assumed that \((E)-547\) \((\alpha)_{25}^\text{D} = -72.2,\) c 0.90, CH$_2$Cl$_2$) had been formed with no loss of stereochemical integrity.

![Chemical structure](image)

**Scheme 163**

Encouraged by this reaction the boron enolate of \(N\)-propionyl-oxazolidin-2-one 457 was next treated with \((S)\)-citronellal 548 (96% pure), which contains a long chain alkyl group containing a stereogenic centre at its β-position. This reaction once again afforded an inseparable mixture of diastereoisomeric \(\text{syn-aldolates} \ 549:550\) in a combined yield of 93% yield and in a ratio of 1:1 as measured via integration of the singlet resonances of the hydroxyl protons of the two diastereoisomers in the crude \(^1\text{H} \ NMR\) spectrum at δ 2.73 and δ 2.80 ppm. This mixture of \(\text{syn-aldolates} \ 549 + 550\) was then treated with KHMDS to afford potassium alkoxides that cleanly eliminated to afford \(\text{novel} \ \alpha,\beta\)-unsaturated \((E)\)-amide 551 in 60% d.e., which was purified via chromatography to give \((E)\)-amide 551 in 55% yield. The allylic methyl protons of \((E)-551\) at the α-position appeared as a singlet at δ 1.85 ppm in the \(^1\text{H} \ NMR\) spectra, while the olefinic proton at the β-position appeared as a triplet at δ 6.44 ppm. Once again, given the non-acidic nature of the stereocentre of \((S)\)-citronellal 548 and \((E)\)-amide 551, it was assumed that it had been formed in enantiopure form, which was substantiated by the observation of a specific rotation of +2.7 (c 2.61, CH$_2$Cl$_2$) (Scheme 164).
Scheme 164
It should be noted that the diastereoselectivity observed for the formation of (E)-551 was somewhat disappointing however, when compared with achiral (E)-amide 489, which also contains a long alkyl chain that was formed in 92% d.e. under identical conditions (Figure 47).

Figure 47
Finally, we proposed to test this elimination methodology using (R)-(+)−2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde 552 as an aldehyde substrate that contained a potentially racemisable stereogenic centre at its α-position. Reaction of the boron enolate of N-propionyl-oxazolidin-2-one 457 and 1.1 equivalents of aldehyde (R)-552 afforded a mixture of diastereoisomers 553:554 which was isolated by chromatography over silica in 58% yield. Once again the complexity of the $^1$H NMR spectrum of this reaction prevented the diastereomeric excess from being determined. However, analysis of the $^{13}$C NMR spectrum revealed that partial kinetic resolution had occurred since a consistent 2:1 enhancement of resonances for one diastereoisomer (unassigned) was observed. Generation of the potassium alkoxide of this mixture of syn-aldolates 553 + 554 using KHMDS as base afforded a novel (E)-amide in 80% d.e., which after purification via chromatography gave pure (E)-amide 555 in 42% isolated yield (Scheme 165). The $^1$H
NMR spectrum of the pure diastereoisomer 555 revealed the allylic methyl group at the α-position as a distinct doublet at 1.93 ppm, $J = 1.2$ Hz and the olefinic proton at the β-position as a doublet of quartets at 6.25 ppm, $J = 8.0, 1.2$ Hz.

**Scheme 165**

The specific rotation of 555 was measured as +4.5 (c 1.54, CH$_2$Cl$_2$) indicating that it had been formed in enantiomerically enriched form, but there was some concern that partial racemisation might have occurred during the elimination reaction. It was well known that aldol reaction between the boron enolate of an N-acyl-oxazolidin-2-one and chiral aldehydes that contain an acidic α-stereogenic centre occurs with no loss in stereochemical integrity (Scheme 166).$^{170}$

**Scheme 166**

Thus, it was reasoned that if any racemisation had occurred then it would have happened during the subsequent KHMDS mediated elimination reaction of $\text{syn}$-aldolates 553:554. If the structure of the intermediates formed during this elimination reaction are considered, it can be deduced that it is only the final (E)-amide product 555 that has the potential to racemise, because it is the only compound that contains a potentially acidic stereocentre due to conjugation to the carbonyl group of the amide functionality. Consequently, it was reasoned that if exposure of a purified sample of (E)-amide 555 to KHMDS in THF at -78°C, followed by work-up, resulted in recovery of 555 with an unchanged specific
rotation, then it would be unlikely that racemisation was a problem during the elimination reaction.

Therefore 1.5 equivalents of KHMDS was added to a solution of the (E)-amide 555 in THF at -78°C and the reaction left stirring for 1.5 hours. Addition of saturated NH₄Cl in H₂O at -78°C and work up afforded recovered (E)-amide 555 in > 95% d.e., whose specific rotation was remeasured in CH₂Cl₂ at +4.8° (c 0.62, CH₂Cl₂), confirming that the elimination reaction conditions were not racemising the stereocentre of (E)-amide 555.

6.2 Elimination of syn-aldolates derived from heteroaryl aldehydes

As has been described in the introduction to this thesis, a large amount of effort has been directed towards the stereoselective synthesis of (E)-trisubstituted acid derivatives containing aromatic or heteroaryl substituents at their β-position. As described in section 3.1.2 it had been demonstrated that potassium alkoxides of aldolate products containing aromatic groups at the β-position readily eliminated to give α,β-unsaturated amides in a diastereoselective fashion. For example, the reaction of syn-aldolate 467 with KHMDS afforded under standard conditions (E)-amide 486 in 91% yield and > 95% d.e. (Scheme 167).

![Scheme 167](image)

In order to investigate whether similar diastereoselective elimination reactions would occur for syn-aldolates derived from heteroarylaldehydes it was decided to investigate the elimination reaction of a syn-aldolate derived from a furylaldehyde substrate. It was reasoned that elimination of syn-aldolate 557 derived from a furyl fragment with an oxygen substituent at its 2-position would prove to be the most challenging substrate, since problems might arise from coordination of the lone pair of the oxygen atom to the potassium counterion during the elimination process.

Reaction of 2-furylaldehyde 556 and the boron enolate of N-acyl oxazolidin-2-one 457 using our standard protocol afforded syn-aldolate 557 in good d.e. but in only 38% yield with most of the mass loss occurring during chromatographic purification of the crude reaction mixture (Scheme 168).
Treatment of the pure aldolate syn-557 with KHMDS resulted in a clean elimination reaction to afford a diastereoisomeric mixture of (E)- and (Z)-amides 558 and 559 in a very poor ratio of 70:30, which could not be separated by chromatographic purification (Scheme 169). Once again the stereochemistry of (E)- and (Z)-amides 558 and 559 were assigned in the $^1$H NMR spectrum by the relative position of the NH peaks, at $\delta$ 6.52 ppm and 6.38 ppm respectively.

It was argued that this loss in diastereoselectivity might be a result of steric interactions between the relatively large isopropyl group and the furyl substituent in the transition state leading to (E)-558, and as a consequence the same reaction was investigated using a syn-aldolate containing a smaller methyl group at its $\alpha$-position. Thus, reaction of the boron enolate of $N$-propionyl-oxazolidin-2-one 457 with 2-furaldehyde 556 was carried out to give a mixture of syn- and anti-aldolate diastereoisomers that were separated after exhaustive chromatography to afford syn-aldolate 560 in only a poor 19% yield (and its anti-isomer 561 in 4% yield). The products were assigned according to the coupling constants between $\alpha$-CHCH$_3$ and $\beta$-CHOH: for the syn-isomer, $J = 4.5$ Hz whilst for the anti-isomer $J = 8.5$Hz (Scheme 170).

Since this aldol reaction had occurred to afford syn-aldolate 560 in relatively poor d.e. and very poor yield, it was decided to use the Evans’ magnesium enolate procedure to prepare the corresponding anti-aldolate 561 since it had already been demonstrated that potassium
alkoxides of both syn- and anti-aldolates eliminated to afford \((E)-\alpha\beta\)-unsaturated amides in essentially the same d.e. Thus, the magnesium enolate of \(N\)-propionyl-oxazolidin-2-one 457 was reacted with 2-furaldehyde under Evans’ conditions to afford anti-aldolate 561 in 80% d.e. and 77% isolated yield (Scheme 171).

\[
\begin{align*}
\text{457} & \quad \text{+} \quad \text{556} \\
\text{1- MgCl}_2, \text{Et}_3\text{N} & \quad \text{2-} \text{TMSCl} \quad \text{EtOAc, rt} \\
\text{anti-561} & \quad \text{77\% yield} \\
& \quad \text{80\% d.e.}
\end{align*}
\]

Scheme 171

Treatment of anti-aldolate 561 with KHMDS in THF at -78°C resulted in a clean elimination reaction to afford \((E)-\alpha\beta\)-unsaturated amide 562 in >95% d.e. and in 61% yield (Scheme 172). It is clear therefore that the presence of bulky substituents at the \(\alpha\)-position of syn-aldolate substrates can result in a loss in diastereocntrol in the subsequent KHMDS-mediated elimination reaction.

\[
\begin{align*}
\text{anti-561} & \quad \text{KHMD (1.5 eq.)} \\
\text{THF, -78°C} & \quad \text{HO} \quad \text{N} \quad \text{O} \\
& \quad \text{(E)-562} \\
& \quad 61\% \text{ yield} \\
& \quad \text{>95\% d.e.}
\end{align*}
\]

Scheme 172

Having demonstrated that an anti-aldolate derived from an oxygen heterocyclic derivative could be successfully eliminated it was next decided to study the elimination of an aldolate substrate derived from 2-pyridine-carboxaldehyde 563. Thus, reaction of 2-pyridinecarboxaldehyde 563 with the boron enolate of \(N\)-propionyl-oxazolidin-2-one 457 afforded a crude reaction product containing the desired syn-aldolate 564 in good d.e. The recovered yield of the crude product was lower than expected, which in hindsight was due to the protocol employed for work-up: the boron alkoxide was quenched with a phosphate buffer solution (pH 7) which may have allowed partial protonation of the pyridine ring and loss into water. Initial purification through silica gel chromatography was only partially successful, since the product appeared to decompose on silica affording the desired syn-aldolate 564 in < 10% yield. Purification of the crude reaction product through a column of alumina was more successful however affording syn-aldolate 564 in 27% yield, which was fully characterised (Scheme 173).
Chapter 6 Results and Discussion

Scheme 173

Unfortunately, attempts to address this yield problem using Evans’ alternative magnesium enolate protocol to prepare the corresponding anti-aldolate were unsuccessful affording only recovered starting \(N\)-propionyl-oxazolidin-2-one 457. Nevertheless, reaction of \(\text{syn-}\)aldolate 564 with KHMDS under standard conditions afforded a crude reaction product, which \(^1\text{H NMR}\) spectroscopy revealed to be a mixture of \((E)-\alpha\beta\)-unsaturated amide 565 and the parent oxazolidin-2-one 456. Chromatographic purification of this mixture of products over silica or alumina was unsuccessful due to the polarity of the products, which appeared to result in decomposition of the desired \((E)-\text{amide}\) 565. The mixture was therefore partially characterised as a mixture of \((E)-\text{amide}\) 565 and oxazolidin-2-one 456 via \(^1\text{H NMR}\) spectroscopy, by subtracting the resonances arising from oxazolidin-2-one 456 (Scheme 174). This partial characterisation of 565 was entirely consistent with the spectroscopic data previously afforded for \((E)-\text{amides}\) 562 and 486 (Table 27). In hindsight, it is clear that it would have been better to attempt to purify 565 via extraction into acid, however time constraints prevented this from being carried out.

Scheme 174

Table 27

It was noteworthy that for the first time in my studies the potassium alkoxide of \(\text{syn-}\beta\)-hydroxy-\(N\)-acyloxadolidin-2-one 564 appeared to be collapsing via a competing retro-aldol pathway with oxazolidin-2-one 456 presumably arising via ketene.

| \(\delta\) CH₂ | 2.28 | 2.17 | 2.04 |
| \(\delta\) NH | 7.02 | 6.44 | 6.48 |
| \(\delta\) CH=O | 7.29 | 7.12 | 7.19 |

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decomposition of the resulting enolate 566 (Figure 48). It is well known that enolates of N-acyl-oxazolidin-2-ones can decompose via ketene-like intermediates to afford their parent oxazolidin-2-one 456, whilst pyridine carboxaldehyde 563 was volatile enough to have been removed under reduced pressure during work-up.

![Image of chemical structures](image)

**Figure 48**

Finally, the use of 3-indole carboxaldehyde 567 as a substrate was explored as part of this investigation into the elimination of heterocyclic aldolates. Unfortunately, aldehyde 567 was poorly soluble in most solvents, and in particular CH$_2$Cl$_2$, the solvent that was commonly used in our procedure to afford syn-aldolates. Therefore, aldehyde 567 was dissolved in dry THF and added to a stirred solution of the boron enolate of N-propionyloxazolidin-2-one 457 in CH$_2$Cl$_2$. The reaction was stirred at $-78^\circ$C, then allowed to warm to 0°C to afford syn-aldolate 568 in 46% yield after purification via recrystallisation from ethyl acetate (Scheme 175). Generation of the potassium alkoxide of syn-aldolate 568 afforded a complex untractable mixture which $^1$H NMR spectroscopy revealed contained at least 6 compounds and as a consequence this experiment was not pursued further.

![Image of reaction scheme](image)

**Scheme 175**

6.3 Elimination studies of aldolates containing heteroatoms at their $\alpha$-position

It was next decided to determine whether aldolates that contained heteroatom substituents at their $\alpha$-position would also undergo stereoselective elimination reactions on treatment with KHMDS.
6.3.1 Synthesis of masked α-keto-amides
The application of the rearrangement/elimination methodology to α-benzyloxy-aldolate substrates would enable an efficient protocol to be developed for the synthesis of α-keto acid fragments, that would be of great interest to the synthetic community since 1,2-diketo functionalities are present in peptidic natural products, such as proteasome inhibitor TMC-95A and anti-HIV agent chloropeptin (Figure 49).

In this regard, it was proposed that treatment of syn-aldolate with KHMDS would result in formation of an (E)-α,β-unsaturated amide that also contained a benzylic enol-ether fragment. Subsequent hydrogenation of (E)- would then remove the benzyl protecting group to cleanly afford the desired (E)-α-ketoamide product under mild conditions (Scheme 176).

Therefore, reaction of the sodium anion of oxazolidin-2-one with benzyloxyacetylchloride cleanly afforded N-acyl oxazolidin-2-one containing a benzyloxy-substituent at its α-position, which was purified via recrystallisation from ethyl acetate in 79% yield. The boron enolate of N-acyl oxazolidin-2-one was then generated via treatment with 9-BBN-OTf and 'PrNEt, and reacted with propionaldehyde to afford a mixture of two diastereoisomers (Scheme 177).
Chapter 6 Results and Discussion

Scheme 177

Purification by exhaustive chromatography gave two aldolate products A (major) and B (minor) in 52 and 10% yield respectively. The coupling constants between β-CHOH and α-CHOCPh for A were $J = 2.5$ Hz, and for B $J = 7.0$ Hz, and as a consequence they were tentatively assigned as the syn-572 and anti-575 aldolates respectively. The syn-geometry of A was subsequently confirmed by growing suitable crystals from ethyl acetate and petroleum ether, which were subjected to X-ray crystallographic analysis (Figure 50).

Figure 50. X-ray crystal structure of syn-aldolate 572

The potassium alkoxide of syn-aldolate 572 rearranged and eliminated to afford α,β-unsaturated amide (E)-576 in an unoptimised 18% isolated yield after silica gel chromatography (Scheme 178), with the representative olefinic and amidic protons appearing as a triplet at 6.24 ppm and a broad singlet at 6.76 ppm. The loss in mass is at least partly due to a side-reaction that afforded a product whose identity was not
determined, because it could not be found after chromatography, but was tentatively assigned as the syn-oxazinane-2,4-dione from analysis of the crude $^1$H NMR spectrum.

Scheme 178

Whilst the overall yield of this elimination reaction was clearly unsatisfactory, the benzyl-protected enol-ether 576 was dissolved in CH$_2$Cl$_2$ in the presence of a catalytic amount of Pd/C and the reaction mixture stirred under one atmosphere of hydrogen. $^1$H NMR spectroscopic analysis of the crude reaction mixture did not afford the expected $\alpha$-keto-amide 574, but instead revealed the presence of two new products A and B that had been formed in a ratio of 1:1. Analysis of the $^1$H NMR spectrum of this mixture of compounds A and B revealed that A displayed resonances with a methyl triplet at $\delta$ 0.88 ppm, a sextet at $\delta$ 1.39 ppm and a broad singlet (NH) at $\delta$ 6.97 ppm. These three peak multiplicities were mirrored for unknown compound B by a triplet at $\delta$ 0.89 ppm, a sextet at $\delta$ 1.58 ppm and a broad singlet (NH) at $\delta$ 7.31 ppm, indicating that these compounds were likely to be structurally related isomers. This assumption was confirmed by thin-layer chromatographic analysis which revealed a single spot by tlc indicating that compounds A and B were co-eluting. With this data in hand it was concluded that the hydrogenolytic deprotection had been successful to afford the desired $\alpha$-keto-amide 574 which had then undergone further reaction to afford a mixture of 6-membered hemi-acetals 577 and 578, via intramolecular attack of the $\omega$-hydroxyl group onto the $\alpha$-keto group. Unsurprisingly, this mixture of hemi-acetals could not be separated via chromatography, and were partially characterised as a mixture via $^1$H NMR and $^{13}$C NMR spectroscopy and low resolution mass spectrometry (Scheme 179).

Scheme 179
6.3.2 Attempted elimination of α-bromo-aldoles

It was next decided to target the preparation of α-bromo-syn-aldoles as a substrate for elimination studies, since it could be employed as a versatile substrate for the preparation of a wide range of other syn-aldoles via simple displacement of the α-bromo substituent using a range of different nucleophiles. For example, a similar procedure had been employed by Caddick et al. for the synthesis of enantiopure α-amino acid 579 according to the strategy described in Scheme 180.152

\[
\begin{align*}
\text{Scheme 180} \\
\text{Attempts to prepare α-bromo-N-acetyl-oxazolidin-2-one 580 via treatment of the parent oxazolidin-2-one 456 with NaH followed by addition of α-bromo-acetyl chloride were unsuccessful in my hands. Modification of these reaction conditions in which the parent oxazolidin-2-one 456 was refluxed with excess NaH in THF for two hours, followed by cooling to 0°C, and addition of bromoacetylbromide resulted in formation of the desired N-acloyloxazolidin-2-one 580 in a good 73% isolated yield (Scheme 181).173}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 181} \\
\text{The aldol reaction between α-bromo-N-acetyl-oxazolidin-2-one 580 and propionaldehyde was then carried out under standard conditions, to afford the desired syn-aldoles in only 19% yield after purification through silica gel chromatography. Indeed, Evans et al. had reported previously that reaction of the boron enolate of the parent chiral N-chloroacetyloxazolidin-2-one with benzaldehyde in CH₂Cl₂ had also not proceeded to completion, affording a 70:30 mixture of syn-aldoles and unreacted starting material.174 However, the same reaction carried out in Et₂O as solvent had afforded the desired}
\end{align*}
\]
syn-aldolate in 9% yield, and as a consequence I employed these conditions for reaction to afford syn-aldolate 581 in an improved 37% yield (Scheme 182).

Scheme 182
The potassium alkoxide of syn-aldolate 581 was generated in the usual manner, which resulted in the formation of the parent oxazolidin-2-one 456 as the only product, thus completely favouring the retro-aldol pathway over the E1cB elimination (Scheme 183).

Scheme 183

6.3.3 Synthesis of vinyl azides
With α-bromo-syn-aldolate 581 in hand I next attempted to displace the α-bromo-substituent with azide, reasoning that this would potentially afford access to α,β-unsaturated amides containing a vinyl-azide fragment, a functionality that had been shown previously to afford good potential for further synthesis. For example, treatment of azidocinnamate 582 with Al-Hg amalgam was shown to afford aminoester 583 in 71% yield, whilst indole 585 and isoquinoline derivative 586 are readily available from decomposition of azidocinnamate 584 (Scheme 184).

Scheme 184
Treatment of α-bromo-N-acyl-oxazolidin-2-one-syn-aldolate 581 with a large excess of sodium azide in DMF over a period of 2 hours resulted in the formation of two novel products A and B in a 1:1 ratio, which were separated by chromatography. The $^1$H NMR spectrum of A was very similar to the $^1$H NMR spectra of syn-aldolate 581, however the doublet resonance corresponding to the CHBr of syn-aldolate 581 at 5.63 ppm had been shifted upfield to 4.94 ppm. The infra-red spectra of A also revealed the presence of a sharp and strong absorption at 2108 cm$^{-1}$, characteristic of an azido group and as a consequence product A was assigned as the target α-azido-N-acyl-oxazolidin-2-one-anti-aldolate 587 that had been formed via $S_N2$-type nucleophilic substitution. $^1$H NMR spectroscopic analysis of product B revealed a broad singlet at 6.76 ppm and a triplet at 6.18 ppm, and a strong and sharp absorption in the infra-red spectra at 2117 cm$^{-1}$ for an azide group, that was clearly indicative of formation of (E)-α-azido-trisubstituted-α,β-unsaturated amide 588. The isolation of (E)-amide 588 as a product from this reaction is somewhat surprising however, since it implied that sodium azide was functioning as a base to afford the sodium alkoxide of syn-aldolate 581, which had then undergone elimination via the usual pathway to afford (E)-588 (Scheme 185).

![Scheme 185](image)

In an attempt to drive this elimination reaction to completion, the reaction was then repeated under the same conditions over a longer 24 hour period, however essentially the same 1:1 ratio of products was obtained from this reaction. However, increasing the temperature of the reaction to 70°C over a period of 12 hours did result in total conversion to the unsaturated (E)-amide 588 as the only observable product in the crude $^1$H NMR spectrum, but only in a low 50% yield due to difficulties associated with its extraction from DMF into organic solvent during aqueous work-up of the reaction. In order to address this isolation problem the azide displacement reaction was repeated using acetone as a solvent instead of DMF from which any (E)-amide product would be more easily recoverable. Thus, the reaction of syn-aldolate 581 with sodium azide in acetone at reflux afforded cleanly a 85:15 mixture of anti- and syn-aldolate 587 and 589 in an unoptimised yield of 50% (Scheme 186).
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Scheme 186

Treatment of the α-aza-anti-aldolate 587 with KHMDS in THF at -78°C in the usual manner resulted in the formation of the α-aza-α,β-unsaturated amide (E)-588, and oxazolidin-2-one 456 (from retro-aldol pathway) in a ratio of 4:1 (Scheme 186). The mixture was separated via chromatography to afford (E)-α-aza-amide 588 in 36% isolated yield.

Scheme 187

Conclusion This chapter has described some promising preliminary investigations into the elimination of N-acyl-oxazolidin-2-one aldolates derived from chiral aldehydes and heteroaryl aldehydes, as well as aldolates that contain α-heteroatom substituents. Results arising from these investigations clearly reveal that the rearrangement/elimination protocol described has great potential for the synthesis of (E)-α,β-unsaturated carboxylic acid derivatives of use in natural product synthesis, medicinal chemistry and organic synthesis and. Further investigations to optimise both the yields and range of substrates employed in these eliminations reactions are currently underway within the SDB research group.
CHAPTER 7. Optimising the \textit{retro}-Aldol Reaction for Chiral $N$-acyl-oxazolidin-2-one-\textit{syn}-Aldolates

7.1 Introduction

Whilst the decision to employ achiral $N$-acyl-oxazolidin-2-one-\textit{syn}-aldolates had been fruitful, resulting in the discovery of a \textit{novel} elimination reaction, if the original concept of employing a chiral auxiliary in a \textit{novel} manner was to be realised then conditions that would result in a facile \textit{retro}-aldol reaction (Scheme 131, Step 3) still needed to be developed. In the preceding chapters there was clearly evidence that elimination of certain aldolate substrates to afford (E)-amides had been accompanied by the formation of products arising from a competing \textit{retro}-aldol reaction. It was therefore necessary to find conditions or substrates (or both) that would efficiently repress the elimination pathway, which in turn would enable the \textit{retro}-aldol pathway to predominate.

![Scheme 131](image)

7.2 Exploring the reactivity of alkoxides of $N$-acyl-oxazolidin-2-one-\textit{syn}-aldolates containing an $\alpha$-aryl group

It was reasoned that elimination of \textit{syn}-aldolate 590 derived from $N$-phenylacetyl-oxazolidin-2-one 459 might favour the \textit{retro}-aldol pathway, since the resultant enolate would be stabilised by the capacity of the $\alpha$-phenyl substituent to afford extra conjugation (Figure 51).
Indeed, to my delight, treatment of syn-aldolate 460 with a series of alkali metal bases (LHMDS, KHMDS and NaHMDS) in THF at -78°C resulted in the desired retro-aldol reaction to afford a mixture of $N$-phenylacetylloxazolidin-2-one 459 and trans-cinnamaldehyde. Comparison of the crude $^1$H NMR spectra indicated that deprotonation of syn-aldolate 460 with KHMDS had afforded the cleanest reaction product with the resultant potassium alkoxide cleanly undergoing a retro-aldol reaction to afford the best overall yield of $N$-phenylacetylloxazolidin-2-one 459. Reaction of 460 with LHMDS gave a more complex mixture of products, whilst reaction with NaHMDS afforded some (E)-amide product via the elimination pathway (Scheme 188).

Scheme 188

It should be noted that the observed retro-aldol reaction for syn-aldolate 460 containing an $\alpha$-phenyl group is in direct contrast to syn-aldolate 492, that contains an $\alpha$-methyl group, which I had shown previously had undergone a clean elimination reaction to afford (E)-493 (Scheme 189).

Scheme 189
Whilst these results clearly indicated that potassium alkoxides of an \( N \)-phenylacetyl-\( \text{syn} \)-aldolate derived from an \( \alpha \beta \)-unsaturated aldehyde had undergone a clean *retro*-aldol reaction, it was still necessary for our chiral auxiliary approach to develop conditions that would enable \( \text{syn} \)-aldolates derived from saturated aldehydes to undergo the same reaction. Since electronic factors were clearly important in determining whether the alkoxides of \( \text{syn} \)-aldolates underwent elimination or *retro*-aldol reaction, deprotonation of a saturated \( \text{syn} \)-aldolate 591 containing a phenyl substituent at its \( \alpha \)-position was next investigated. Thus, the \( \text{syn} \)-aldolate 591 derived from \( N \)-phenylacetyl-oxazolidin-2-one 459 and propionaldehyde was prepared using 9-BBN.OTf in the usual manner in a poor 37% yield. Treatment of this \( \text{syn} \)-aldolate 591 with KHMDS in THF at -78°C resulted in the formation of a crude reaction product which \(^1\)H NMR spectroscopic analysis revealed contained (E)-amide 592 arising from an elimination reaction in >95% d.e., and \( N \)-phenylacetyl-oxazolidin-2-one 459 as a product of the *retro*-aldol reaction, in a ratio of 2:1. The crude reaction mixture was purified to homogeneity to afford (E)-amide 592 in 47% yield, which was fully characterised (Scheme 190).

\[
\text{Scheme 190}
\]

In order to confirm that the introduction of a phenyl substituent at the \( \alpha \)-position of the \( \text{syn} \)-aldolate 460 and 591 was indeed responsible for the increase in the amount of \( N \)-phenylacetyl-oxazolidin-2-one 459 arising from the *retro*-aldol pathway, a \( \text{syn} \)-aldolate substrate containing a \( \text{para} \)-methoxy substituent at its \( \alpha \)-position was next prepared. It was reasoned that this class of aldolate substrate should afford more (E)-amide product arising from the elimination pathway, because the enolate of \( N-p \)-methoxyphenyl-oxazolidin-2-one 593 would be destabilised by the electron rich \( \text{para} \)-methoxy substituent, resulting in the *retro*-aldol pathway being disfavoured.

Acylation of the parent oxazolidin-2-one 456 with 4-methoxyphenylacetylchloride proved to be quite challenging, since reaction with the lithium salt of oxazolidin-2-one 456 in THF under standard conditions gave no product. Matsumura et al. had described previously that
deprotonation of oxazolidin-2-one with sodium hydride in THF at 0°C, followed by addition of an acid chloride had afforded good yields of \( N \)-acyl-oxazolidin-2-ones.\(^{177}\) Thus, under these conditions the desired \( N \)-acyloxazolidin-2-one 593 was successfully prepared in 69% yield. With \( N \)-\( p \)-methoxyphenylacetyl-oxazolidin-2-one 593 in hand its boron enolate was reacted with propionaldehyde under standard conditions, to afford the desired \( \text{syn} \)-aldolate 594 in 77% yield (Scheme 191).

\[
\begin{array}{c}
\text{456} \\
\begin{array}{c}
\text{1-NaH} \\
\text{2-\( p \)-MeOC_6H_4COCl}
\end{array}
\end{array}
\xrightarrow{\text{THF, 0°C}}
\begin{array}{c}
\text{593} \\
\begin{array}{c}
\text{9-BBN.OTf, } \text{Pr}_3\text{NEt} \\
\text{propionaldehyde}
\end{array}
\end{array}
\xrightarrow{\text{CH}_2\text{Cl}_2, 0 \text{ to } -78°C}
\begin{array}{c}
\text{sym-594} \\
\begin{array}{c}
\text{OMe}
\end{array}
\end{array}
\]

Scheme 191
Treatment of \( \text{syn} \)-aldolate 594 with KHMDS in THF at \(-78°C\) resulted in a crude reaction product which \(^1\)H NMR spectroscopic analysis revealed contained \((E)\)-amide 595 in 75% d.e. and \( N \)-\( p \)-methoxyphenyl-oxazolidin-2-one 593 in a ratio of 4:1. \((E)\)-amide 595 was subsequently purified to homogeneity via chromatography and fully characterised in 39% yield (Scheme 192). Thus, the argument that electronic factors were important in determining the ratio of products arising from the competing elimination/\( \text{retro} \)-aldol reaction appeared to be a valid one, since \( \alpha \)-\( p \)-methoxybenzyl-\( \text{syn} \)-aldolate 594 had afforded less \( \text{retro} \)-aldol product 593 than the corresponding \( \alpha \)-phenyl-\( \text{syn} \)-aldolate 591 as predicted by the enolate stabilisation argument.

\[
\begin{array}{c}
\text{594} \\
\xrightarrow{\text{KHMD (1.5 eq.)}}
\begin{array}{c}
\text{THF, -78°C}
\end{array}
\end{array}
\xrightarrow{1}
\begin{array}{c}
\text{593} \\
\begin{array}{c}
\text{OMe}
\end{array}
\end{array}
\xrightarrow{4}
\begin{array}{c}
\text{OMe}
\end{array}
\]

Scheme 192
In an attempt to confirm this theory, it was proposed to carry out studies on the alkoxide of a \( \text{syn} \)-aldolate derived from \( \alpha \)-\( p \)-nitrophenylacetyl-oxazolidin-2-one 596, since the presence of the highly electron deficient nitro-aryl group would add additional stabilisation to the enolate arising from the \( \text{retro} \)-aldol pathway. However, all attempts to prepare the desired \( \text{syn} \)-aldolate substrate under standard conditions using 9-BBN.OTf as Lewis acid were unsuccessful, affording only starting material 596 in each case (Scheme 193).
7.3 Investigating what effect changing the base used for deprotonation of syn-aldolate substrates has on the outcome of the reaction

Since it was possible that the ratio of products arising from the elimination/retro-aldol pathway might be affected by the nature of the base used for deprotonation of the syn-aldolate, the effect of changing the nature of the base in this reaction was next investigated. Reaction of the lithium alkoxide of syn-aldolate 594 resulted in a crude reaction product that contained a number of unknown compounds (<10%), as well as unsaturated (E)-amide 595 and N-p-methoxyphenyl-oxazolidin-2-one 593 in a ratio of 9:1. Alternatively, reaction of syn-aldolate 594 with NaHMDS in THF at -78°C gave a crude reaction product containing (E)-amide 595 and N-p-methoxyphenylacetyl-oxazolidin-2-one 593 in a ratio of 77:23 similar to that previously observed for KHMDS. Attempts to screen alternative bases for elimination were initially unsuccessful, since treatment of syn-aldolate 594 with sodium hydride or potassium tert-butoxide in THF at -78°C resulted in no reaction, with starting material being recovered in each case. Repeating these reactions at 0°C did result in reaction of syn-aldolate 594 however, with sodium hydride affording products 595:593 arising from the elimination/retro-aldol pathway in a ratio of 67:33, whilst reaction with potassium tert-butoxide resulted in the same mixture in a ratio of 80:20 (Scheme 194, Table 28). Thus, whilst these results clearly indicated that the ratio of products arising from the elimination/retro-aldol reaction could be ‘fine-tuned’ by varying the base, it appeared unlikely that simply changing the nature of the base would be sufficient to result in a reversal in the reaction manifold so that the retro-aldol reaction would dominate over the elimination reaction.
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<table>
<thead>
<tr>
<th>base</th>
<th>temperature</th>
<th>Ratio 595:593</th>
<th>% d.e. of (E)-amide 595</th>
</tr>
</thead>
<tbody>
<tr>
<td>KHMDS</td>
<td>-78°C</td>
<td>80:20</td>
<td>75</td>
</tr>
<tr>
<td>LHMDS</td>
<td>-78°C</td>
<td>90:10</td>
<td>78</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>-78°C</td>
<td>77:23</td>
<td>60</td>
</tr>
<tr>
<td>NaH</td>
<td>-78°C</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NaH</td>
<td>0°C</td>
<td>67:33</td>
<td>68</td>
</tr>
<tr>
<td>'BuOK</td>
<td>-78°C</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>'BuOK</td>
<td>0°C</td>
<td>80:20</td>
<td>72</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Complex mixture with more than two products; \textsuperscript{b} Under the reaction conditions \textit{N}-acyl oxazolidin-2-one 595 decomposed to the parent oxazolidin-2-one 456.

Table 28

7.4 Studying the reactivity of the alkoxides of chiral-\textit{N}-acyl-oxazolidin-2-ones

These studies had clearly demonstrated that potassium alkoxides of \textit{syn}-aldolates derived from \textit{achiral} \textit{N}-acyl-oxazolidin-2-ones could react \textit{via} competing elimination/\textit{retro}-aldol pathways, and that the introduction of an aryl group at the \textit{α}-position of the aldolate maximised the potential for formation of products arising from the \textit{retro}-aldol pathway. It was therefore decided to explore the reactivity of alkoxides of chiral \textit{syn}-aldolates derived from (\textit{S})-4-benzyl-oxazolidin-2-one 530. In this regard it was reasoned that elimination of the alkoxide of this type of chiral \textit{syn}-aldolate 597 to form (\textit{E})-amides 599 would be less likely than for the corresponding elimination of achiral \textit{syn}-aldolates, because introduction of a chiral substituent at the 4-position would help to block intramolecular attack of the \textit{β}-alkoxide at the carbonyl of the oxazolidin-2-one fragment. This, in turn would suppress the formation of the oxazinane-2,4-dione intermediate 598, which was necessary for the unwanted elimination pathway to occur (Figure 52).
7.4.1 Synthesis of chiral \textit{N}-acyl-oxazolidin-2-one-\textit{syn}-aldolates

Soon after optimising the formation of achiral aldolates I had shown that the 9-BBN triflate methodology was suitable for the formation of chiral aldolates 473 and 440 in an enantioselective fashion (see section 2.2.6.2). Reaction of the boron enolate of chiral \textit{N}-acyl-oxazolidin-2-one 472 with benzaldehyde was also carried out to afford \textit{syn}-aldolate 600 in 65\% yield and \textgreater{} 95\% d.e. (Scheme 195). The characterisation of \textit{syn}-aldolate 600 was consistent with spectroscopic data of previously prepared and fully characterised \textit{syn}-aldolates 473 and 440 (Figure 53).

\textbf{Scheme 195}

Figure 53
7.4.2 Alkoxides of chiral \( N \)-acyl-oxazolidin-2-one-\( \alpha \)-\( \alpha \)-aldolates undergo clean retro-aldol reaction

Treatment of \( \textit{syn} \)-aldolates 473 and 600 with KHMDS in THF at \(-78^\circ\text{C}\) both resulted in a clean reaction to afford the parent 4-benzyl-oxazolidin-2-one 471 and benzaldehyde, with no evidence of any of the corresponding (\(E\))-amide product having been formed. It was reasoned therefore that the potassium alkoxides of both \( \textit{syn} \)-aldolates 473 and 600 had undergone clean retro-aldol reaction to afford their corresponding unstable enolates 423 and 472 (and benzaldehyde) that had decomposed \textit{in situ} via a retro-ketene like mechanism to afford the parent oxazolidin-2-one 471 (Scheme 196).

\[
\text{Scheme 196}
\]

It was demonstrated earlier in this chapter that alkoxides of achiral \( N \)-acyl-oxazolidin-2-ones \( \textit{syn} \)-aldolate 460 containing \( \gamma \delta \)-unsaturation in the achiral series had collapsed \textit{via} a retro-aldol pathway. Likewise generation of the potassium alkoxide of chiral \( \textit{syn} \)-aldolate 440 resulted in a clean retro-aldol reaction affording the parent 4-benzyloxazolidin-2-one 471 (Scheme 197).

\[
\text{Scheme 197}
\]

7.4.3 Attempted rearrangement of chiral \( \textit{syn} \)-aldolates to afford chiral oxazinane-2,4-dione using diethylzinc as base

These results had demonstrated that the presence of the chiral substituent at C4 of the oxazolidin-2-one fragment had suppressed intramolecular cyclisation/elimination reaction of the potassium enolates of a range of chiral \( \textit{syn} \)-aldolates. Consequently, I investigated whether a rearranged chiral oxazinane-2,4-dione 601 could be formed \textit{via} treatment of \( \textit{syn} \)-aldolate 600 with \( \text{Et}_2\text{Zn} \). Carrying out this reaction in the usual manner, treatment of
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the syn-aldolate 600 with diethylzinc in THF, resulted in formation of a crude reaction product, that $^1$H NMR spectroscopic analysis revealed contained $N$-acyl-oxazolidin-2-one 472, syn-aldolate 600, and one major unidentified compound A as the major product (Scheme 198).

![Scheme 198](image)

Exhaustive chromatographic purification of this reaction enabled the unknown product A to be isolated in a low 40% yield, which was fully characterised in the usual manner. Examination of the spectroscopic data of A led me to propose a structure that was consistent with the formation of a new $N$-acyl-oxazolidin-2-one aldolate diastereoisomer, but not with the formation of an oxazinane-2,4-dione 601. The primary piece of evidence that enabled the oxazinane-2,4-dione skeleton to be discounted was the observed doublet between the $\beta$-C-H and the OH of $J = 9.5$ Hz which was consistent with the formation of an aldolate, but not with the structure of the corresponding oxazinane-2,4-dione syn-601 skeleton which had been shown previously to afford distinctive resonances as either a triplet, or broad singlet. Close examination of the $^1$H NMR spectrum of A also revealed a coupling constant between $\alpha$-H and the $\beta$-H of $J = 4.5$ Hz, which was consistent with the formation of an anti-aldolate structure, since the corresponding coupling constant for the syn-aldolate starting material 600 was $J = 8.5$ Hz. I was therefore left with a choice of two anti-aldolates 603 and 604 for the structure of A (Figure 54).
Of the two anti-aldolates, \textit{anti-603} had been prepared previously by Evans \textit{et al.}, however there was no spectroscopic data published in the literature\textsuperscript{154}. After contacting Professor Evans by personal correspondence, I obtained the unpublished spectroscopic data for his \textit{anti-aldolate 603}, which on comparison was clearly different from that of product A. Thus, by a process of elimination, the structure of the unknown compound A was assigned as \textit{anti-aldolate 604} (Scheme 199).

It was clear therefore that the presence of the benzyl substituent at the 4-position of the chiral oxazolidin-2-one \textit{syn-aldolate 600} was sufficient to ‘shut-down’ the intramolecular rearrangement pathway to afford oxazinane-2,4-dione \textit{601}. It appears therefore that equilibration of the zinc alkoxide of \textit{syn-aldolate 600} to its corresponding \textit{anti-aldolate 604} must have occurred via \textit{retro-aldol} cleavage to afford a zinc enolate \textit{605}, which then undergoes reversible reaction with benzaldehyde to afford the \textit{anti-aldolate 604} as the major product, presumably under thermodynamic control (Figure 55).
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Figure 55
There are three pieces of evidence in support of this reversible retro-aldol/aldol mechanism to explain the epimerisation of the β-stereocentre of syn-aldolate 600. Firstly, the corresponding N-phenyl-oxazolidin-2-one 472 was identified as a product of this reaction, the enolate 605 of which would be an intermediate on this reversible retro-aldol/aldol reaction pathway. Secondly, Ito et al. had shown that reaction of the zinc enolate of N-acyl-oxazolidin-2-one 516 with benzaldehyde afforded a mixture of anti-oxazinane-2,4-dione 518 and syn-oxazinane-2,4-dione 517 as products, with the anti-diastereoisomer 518 having been formed as the major diastereoisomer (Scheme 149). Since these oxazinane-2,4-diones must have been formed via rearrangement of their corresponding anti- and syn-aldolates, it appears that zinc enolates of N-acyl-oxazolidin-2-ones preferentially afford anti-aldolates.

Scheme 149
Finally, Bertrand et al. prepared a zinc enolate from the reaction of chiral N-enoyloxazolidin-2-one 606 with Et₂Zn, which on reaction with benzaldehyde gave a
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diastereomeric mixture of aldolates 607, thereby demonstrating that zinc enolates readily afford aldolate products (Scheme 200).  

Scheme 200

7.4.4 Stereochemical leakage in the rearrangement of achiral \( \beta \)-aryl-syn-aldolates

In parallel to this work, and following the study of the mechanism and the isolation of oxazinanediones a series of achiral syn-\( \beta \)-arylaldolates were treated with a catalytic amount of diethylzinc in \( \text{CH}_2\text{Cl}_2 \) at room temperature. Unlike the previous achiral substrates, which afforded the corresponding oxazinanediones in high d.e. the zinc alkoxides of syn-aldolates 467, 481 and 482 afforded syn-oxazinanediones 517, 608 and 610 in the presence of significant amounts of the corresponding anti-isomers 518, 609 and 611. The syn-oxazinanediones 608 and 610 were purified through flash chromatography and fully characterised, COSY correlation revealing the characteristic coupling between \( \text{OH} \) and \( \text{C}^2 \) (Scheme 201).

Scheme 201
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This study revealed a clear discrepancy with the results obtained previously for the KHMDS-mediated elimination of syn-481, which had afforded (E)-amide 487 in 92% d.e. (Scheme 202).

Scheme 202

In order to determine if this lack of stereoselectivity during the rearrangement of syn-aldo1ates derived from aromatic aldehydes was a general trend, syn-aldo1ate 609 was next prepared via reaction of the boron enolate of N-acyl-oxazolidine-2-one 458 and p-nitrobenzaldehyde 612 in 70% yield (Scheme 203). This syn-aldo1ate 609 was then treated with 1.5 equivalents of KHMDS in THF at -78°C in the usual manner but failed to afford the desired amide, affording instead the starting material syn-613, along with product of the retro-aldol reaction N-acyl-oxazolidin-2-one 458 and unknown compounds.

Scheme 203

Treatment of syn-aldo1ate 609 with Et₂Zn at room temperature afforded a 85:15 mixture of oxazinane-2,4-diones syn-613 and anti-614. Purification via column chromatography afforded syn-oxazinane-2,4-dione 613 in 51% yield and > 95% d.e. (Scheme 204).
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Scheme 204
Clearly, these reactions demonstrated that the base-catalysed rearrangement of aldolates derived from aromatic aldehydes was not as stereoselective as the other syn-aldolates 476, 479, 480 and anti-468 described in Chapter 5. In the light of the observation of a reversible retro-aldol/aldol pathway for the zinc alkoxide of chiral syn-aldolate 600, it is proposed that equilibration of syn-oxazinane-2,4-diones to anti-oxazinane-2,4-diones (X = H) under these conditions is occurring via the retro-aldol mechanism described in Figure 56.

Figure 56

7.5 Conclusion and further developments
Given that the retro-aldol reaction of a chiral syn-aldolate derived from N-phenylacetyloxazolidin-2-one would afford an enolate stabilised by the presence of the α-aryl group, it was decided to next investigate the retro-aldol reaction of syn-aldolate 615. Unfortunately, time considerations have prevented me from investigating this approach any further, however Matthew Cheeseman, another member of the SDB group, has found that treatment of syn-aldolate 615 with KHMDS in THF at -78°C, followed by dropwise
addition of saturated NH₄Cl₉q solution at -78°C, resulted in clean retro-aldol reaction to afford N-phenylacetyl-oxazolidin-2-one 616 and aldehyde 617 (not isolated) as the only products (Scheme 205). It is noteworthy that slow addition of NH₄Cl₉q was found to be crucial for avoiding decomposition of the enolate of N-phenylacetyl-oxazolidin-2-one 616 into its parent oxazolidin-2-one 471.

Scheme 206

Thus, a suitable N-acyl-oxazolidine-2-one-syn-aldolate substrate has been identified that undergoes a clean retro-aldol reaction to occur on deprotonation with KHMDS at -78°C, a situation that would enable Step 3 of our original concept using chiral auxiliaries in a novel manner to be realised (see scheme 131).

The only step left to be realised in this protocol was therefore Step 2, which was to identify a suitable conditions that would enable a directed reaction to be carried out under the control of the β-hydroxyl-functionality of syn-aldolate with good stereocontrol. Building on the results described in this thesis, Matthew Cheeseman prepared syn-aldolate 620 using the 9-BBN.OTf boron enolate protocol in > 95% d.e. This syn-aldolate 620 was employed for a modified Simmons-Smith reaction, where the β-hydroxy group was used to direct the cyclopropanation of the allylic alcohol functionality to afford cyclopropane-syn-aldolate 621 in > 95% d.e. Subsequent purification of cyclopropane 621 to homogeneity via chromatography, followed by treatment with KHMDS in THF at -78°C and quenching at -78°C with NH₄Cl₉q, resulted in a clean retro-aldol reaction to afford N-phenylacetyl-oxazolidin-2-one 623, and the diastereoisomerically pure aldehyde 622 in 85% yield (Scheme 206).
Therefore, it is particularly gratifying that all of the hard-work that has been carried out in this thesis in optimising methodology for carrying out efficient aldol and retro-aldol reactions on N-acyl-oxazolidin-2-one syn-aldolate substrates, has finally been successful in ultimately realising the original strategy for using chiral auxiliaries to prepare enantiopure aldehyde fragments in high d.e.
CHAPTER 8. Experimental

8-1 General conditions

Melting points were measured on a Büchi 535 melting point apparatus and are uncorrected. Optical rotations were recorded on an Optical Activity Ltd AA-10 automatic polarimeter. Infra red spectra were recorded in the range of 4000-600 cm\(^{-1}\) on a Perkin Elmer FT 1000 spectrometer with internal calibration. Absorption in the carbonyl region are presented in the following manner:

- carbon-hydrogen stretch in methoxy group, \((\text{C-H})_{\text{MeO}}\)
- carbonyl stretch in the oxazolidin-2-one, \((\text{C=O})_{\text{ox}}\)
- carbonyl stretch in the side chain, \((\text{C=O})_{\text{am}}\)
- carbon-carbon double bond stretch, \((\text{C=C})\)
- carbon-carbon double bond stretch in an aromatic ring, \((\text{C=C})_{\text{ar}}\)
- nitro group conjugated with a \(\pi\) system, \((\text{N=O})_{\text{conj}}\)

\(^{1}\text{H}\) NMR spectra were recorded on Bruker AM-300 spectrometers at 300 MHz. Chemical shifts (\(\delta\)) are expressed in parts per million (ppm), and are relative to residual protic solvent \(\text{CHCl}_3\) (\(\delta_{\text{H}} = 7.26\) ppm), \(\text{CH}_3\text{COCH}_3\) (\(\delta_{\text{H}} = 2.12\) ppm) or TMS (\(\delta_{\text{H}} = 0\) ppm). The multiplicities are presented in the following manner:

- singlet, \(s\)
- broad singlet, \(\text{br}\ s\)
- doublet, \(d\)
- doublet of doublets, \(\text{dd}\)
- doublet of doublets of doublets, \(\text{ddd}\)
- doublet of quartets of doublets, \(\text{dqd}\)
- apparent doublet of triplets, \(\text{app}\ dt\)
- triplet, \(t\)
- apparent triplet, \(\text{app}\ t\)
- quartet, \(q\)
- quartet of doublets, \(\text{qd}\)
- apparent quartet, \(\text{app}\ q\)
- apparent pentet, \(\text{app}\ pentet\)
- septet of doublets, \(\text{septet of d}\)
- apparent octet, \(\text{app}\ octet\)
- apparent nonet, \(\text{app}\ nonet\)

Coupling constants (\(J\)) were measured in Hz. Diastereomeric excess were estimated from the relative intensities of the relevant peaks in the \(^{1}\text{H}\) NMR. \(^{13}\text{C}\) spectra were recorded in \(\text{CDCl}_3\) or \(\text{CD}_3\text{COCD}_3\), unless otherwise stated, at 75 MHz using the resonance of \(\text{CDCl}_3\) (\(\delta_{\text{C}} = 77\) ppm, \(t\)) or \(\text{CD}_3\text{COCD}_3\) (\(\delta_{\text{C}} = 30.1\) ppm, septet) as the internal reference.
Experimental

Mass spectra were carried out either at the University of Bath (Finnigan MAT 8340 instrument) or at the University of Wales, Swansea (Finnigan MAT 900 XLT instrument) using techniques such as electron ionisation (EI, 70 eV), chemical ionisation (CI), fast atomic bombardment (FAB) and electrospray (ES). Ionisation gas for chemical ionisation will be specified between brackets for each analysis. Elemental analyses were performed using an Exeter Analytical Inc CE-440 Elemental analyser.

Single crystal X-ray diffraction data was collected on a Nonius Kappa CCD machine. Structural determination and refinement were achieved using the SHELZ suite of programmes; drawings were produced using ORTEX.

Analytical thin layer chromatography was performed on pre-coated aluminium-backed silica gel (Merck Kieslegel 60 F<sub>254</sub>) plates or pre-coated aluminium-backed aluminium oxide gel (Merck Kieslegel 60 F<sub>254</sub>). Plates were visualised under ultra-violet light (at 254 nm) or by staining with potassium permanganate or vanillin followed by heating. Column chromatography was carried out using Merck Kieselgel 60H silica gel or Acros Organics aluminium oxide gel, neutral, 50-200 μm. Samples were added on top of the column as pre-absorbed on silica or as concentrated solutions.

Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl, and dichloromethane from CaH<sub>2</sub> all under nitrogen. Petrol refers to light petroleum, bp 40-60 °C, ether refers to diethyl ether.

Unless otherwise stated, commercially available starting materials were used throughout without any further purification. Reactions requiring anhydrous conditions were performed under nitrogen or argon in oven or flame dried apparatus.
8.2 Preparation of acylated oxazolidin-2-ones

Procedures for the preparation of N-acyl oxazolidin-2-ones:

**General protocol A**

A solution of "butyllithium in hexanes (1.1 eq.) was added dropwise via syringe to a stirred solution of oxazolidin-2-one 457 (1 eq.) in THF at -78°C under a nitrogen atmosphere and the mixture was allowed to stir for 15 minutes. Acyl chloride (1.1 eq.) was added at -78°C. The reaction was stirred at this temperature for 2 hours and allowed to warm to room temperature over a 1-hour period. Saturated NH₄Cl was added and the reaction extracted with CH₂Cl₂ (x 3). The combined organic extracts were washed with NaHCO₃aq and brine, dried (MgSO₄), and concentrated *in vacuo* to afford N-acyl oxazolidin-2-one 460.

**General protocol B**

A 60% dispersion of sodium hydride in mineral oil (1.5 eq.) was added to a stirred solution of oxazolidin-2-one 456 (1 eq.) in THF at 0°C under a nitrogen atmosphere and the mixture allowed to stir for 2 hours. Acyl chloride (1.55 eq.) was added at 0°C and the reaction was stirred for 3 hours at this temperature. Saturated NH₄Cl was added and the reaction extracted with CH₂Cl₂ (x 3). The combined organic extracts were washed with brine, dried (MgSO₄), and concentrated *in vacuo* to afford N-acyl oxazolidin-2-one 624.

**General protocol C**

A 60% dispersion of sodium hydride in mineral oil (1.1 eq.) was added to a stirred solution of oxazolidin-2-one 456 (1 eq.) in THF at 0°C under a nitrogen atmosphere. The reaction was refluxed for one hour and then cooled to 0°C. Acyl chloride (1.05 eq.) was added at 0°C and the reaction stirred for 3 hours at this temperature. Saturated NH₄Cl was added and the reaction extracted with CH₂Cl₂ (x 3). The combined organic extracts were washed
with brine, dried (MgSO₄), and concentrated in vacuo to afford N-acyl oxazolidin-2-one 624.

3-propionyl-1,3-oxazolidin-2-one 457₁⁶₄

![457]

Reaction of oxazolidin-2-one 456 (5.000 g, 57.47 mmol) with a 2.5M solution of "butyllithium in hexanes (25.30 mL, 63.2 mmol) and propionyl chloride (5.16 g, 63.2 mmol) in THF (250 mL), according to general protocol A, afforded after recrystallisation from hot ethyl acetate the title compound 457 (5.940 g, 41.54 mmol) in 72% yield as a white crystalline solid, mp 77-79°C (lit., 164 80-81°C); \( \nu_{\text{max}} \) (KBr disc)/cm⁻¹ 1773 (C=O), 1700 (C=O)₉⁻; \( \delta_H \) (300MHz, CDCl₃, Me₄Si) 1.17 (3H, t, \( J = 7.5 \), CH₂CH₃), 2.94 (2H, q, \( J = 7.5 \), CH₂CH₃), 4.02 (2H, app t, \( J = 8.0 \), CH₂N), 4.42 (2H, app t, \( J = 8.0 \), CH₂O); \( \delta_C \) (CDCl₃) 8.7, 29.1, 62.4, 154.0, 174.6; \( m/z \) (EI⁺) 143 (49, \( M^+ \)), 57 (100%, CH₃CH₂CO⁺); (Found (EI⁺) \( M^+ \) 143.0574 C₆H₉NO₃ requires 143.0577).

3-(3-methylbutanoyl)-1,3-oxazolidin-2-one 458₁⁸₀

![458]

Reaction of oxazolidin-2-one 456 (9.905 g, 113.85 mmol) with a 2.5M solution of "butyllithium in hexanes (50.10 mL, 125.23 mmol) and iso-valeryl chloride (21.50 mL, 125.23 mmol) in THF (500 mL), according to general protocol A, afforded after purification through silica gel chromatography (40% ethyl acetate/petrol) the title compound 458 (14.408 g, 84.26 mmol) in 74% yield as a colourless oil, \( \nu_{\text{max}} \) (neat)/cm⁻¹ 1779 (C=O)₉⁻, 1699 (C=O)₉⁻; \( \delta_H \) (300MHz, CDCl₃, Me₄Si) 0.99 (6H, d, \( J = 7.0 \), CH(CH₃)₂), 2.18 (1H, app nonet, \( J = 7.0 \), CH(CH₃)₂), 2.81 (2H, d, \( J = 7.0 \), CH₂Pr), 4.03 (2H, app t, \( J = 8.0 \), CH₂N), 4.42 (2H, app t, \( J = 8.0 \), CH₂O); \( \delta_C \) (CDCl₃) 22.7, 22.8, 25.3, 42.9, 43.9, 62.3, 153.9, 173.2; \( m/z \) (CI⁺, iso-butane) 172 (85, \( M^+ \)), 129 (82, \( M^+ - CH(CH₃)₂ \)), 85 (100%); (Found (FAB⁺) \( M^+ \) 172.0974 C₈H₁₄NO₃ requires 172.0974).
3-(2-phenylacetyl)-1,3-oxazolidin-2-one 459

Reaction of oxazolidin-2-one 456 (9.900 g, 113.79 mmol) with a 1.6M solution of n-butyllithium in hexanes (78.20 mL, 125.17 mmol) and phenyl acetyl chloride (21.50 mL, 125.17 mmol) in THF (500 mL), according to general protocol A, afforded after purification through silica gel chromatography (20% ethyl acetate/petrol) the title compound 459 (14.404 g, 70.26 mmol) in 62% yield as a white solid, mp 61-63°C (lit., 64-65°C); νmax (KBr disc)/cm⁻¹ 3010 (C-H)ar, 1773 (C=O)ox, 1696 (C=O)am, 1599 (C=C)ar, 1507 (C=C)ar; δH (300MHz, CDCl3, Me4Si) 3.92 (2H, app t, J 8.0, CH2N), 4.25 (2H, s, CH2Ph), 4.29 (2H, app t, J 8.0, CH2O), 7.26-7.31 (5H, m, Ph-H); δC (CDCl3) 12.2, 13.8, 63.2, 128.1, 129.4, 130.0, 131.6, 154.7, 172.3; m/z (EI⁺) 205 (30, M⁺), 118 (100), 91 (60%, PhCH2⁺); (Found (EI⁺) M⁺ 205.0742 C11H11NO3 requires 205.0739).

3-(3-phenylpropanoyl)-1,3-oxazolidin-2-one 460

Reaction of oxazolidin-2-one 456 (1.496 g, 17.20 mmol) with a 2.5M solution of n-butyllithium in hexanes (7.60 mL, 18.91 mmol) and phenylpropionyl chloride (2.80 mL, 18.91 mmol) in THF (90 mL), according to general protocol A, afforded after purification through silica gel chromatography (20% ethyl acetate/petrol) the title compound 460 (2.765 g, 12.63 mmol) in 73% yield as a white solid, mp 100-101°C; νmax (KBr disc)/cm⁻¹ 3008 (C-H)ar, 1765 (C=O)ox, 1692 (C=O)am, 1602 (C=C)ar, 1484 (C=C)ar; δH (300MHz, CDCl3, Me4Si) 2.91 (2H, t, J 7.5, CH2CH2Ph), 3.17 (2H, t, J 7.5, CH2CH2Ph), 3.90 (2H, app t, J 8.0, CH2N), 4.29 (2H, app t, J 8.0, CH2O), 7.09-7.24 (5H, m, Ph-H); δC (CDCl3) 30.6, 37.2, 42.9, 62.5, 126.6, 128.8, 128.9, 140.9, 153.9, 172.9; m/z (EI⁺) 219 (55, M⁺), 132 (27, PhCH2CH2CO⁺), 104 (100), 88 (87, M⁺-PhCH2CH2CO⁺); (Found (ES⁺) M⁺NH₄⁺ 237.1237 C12H17N2O₃ requires 237.1234).
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3-[2-(benzyloxy)acetyl]-1,3-oxazolidin-2-one 571

![Chemical Structure](image)

Reaction of oxazolidin-2-one 456 (0.500 g, 5.74 mmol) with a 60% dispersion of sodium hydride in mineral oil (0.345 g, 8.61 mmol) and benzyloxyacetyl chloride (1.40 mL, 8.90 mmol) in THF (25 mL), according to general protocol B, afforded after recrystallisation from hot ethyl acetate the title compound 571 (1.071 g, 4.56 mmol) in 79% yield as a white solid, $mp$ 128-130°C; $\nu_{max}$ (KBr disc)/cm$^{-1}$ 1761 (C=O)$_{\text{ox}}$, 1718 (C=O)$_{\text{am}}$, 1607 (C=C)$_{\text{ar}}$, 1498 (C=C)$_{\text{ar}}$, 1144 (C-O); $\delta_{H}$ (300MHz, CDCl$_3$, Me$_4$Si) 3.96 (2H, app t, $J$ 8.0, CH$_2$O), 4.39 (2H, app t, $J$ 8.0, CH$_2$N), 4.60 (2H, s, CH$_2$OCH$_2$Ph), 4.62 (2H, s, CH$_2$OCH$_2$Ph), 7.23-7.34 (5H, m, Ph-$H$); $\delta_{C}$ (CDCl$_3$) 42.4, 63.5, 69.8, 73.8, 128.4, 128.5, 128.9, 137.5, 153.9, 170.6; $m/z$ (EI$^+$) 253 (100, MNH$_4^+$), 236 (60%, M$^+$); (Found (ES$^+$) M$^+$ 236.0918 C$_{12}$H$_{14}$NO$_4$ requires 236.0917).

3-(2-bromoacetyl)-1,3-oxazolidin-2-one 580

Reaction of oxazolidin-2-one 456 (1.500 g, 17.24 mmol) with a 60% dispersion of sodium hydride in mineral oil (0.792 g, 19.85 mmol) and bromoacetyl bromide (1.60 mL, 18.10 mmol) in THF (90 mL), according to general protocol C, afforded after purification through silica gel chromatography (40% ethyl acetate/petrol) the title compound 580 (2.61 g, 12.63 mmol) in 73% yield as a colourless oil, $\nu_{max}$ (neat)/cm$^{-1}$ 1777 (C=O)$_{\text{ox}}$, 1712 (C=O)$_{\text{am}}$, 758 (C-Br); $\delta_{H}$ (300MHz, CDCl$_3$) 4.07 (2H, app t, $J$ 8.5, CH$_2$N), 4.48 (2H, app t, $J$ 8.5, CH$_2$O), 4.50 (2H, s, CH$_2$Br); $\delta_{C}$ (CDCl$_3$) 28.1, 43.1, 63.0, 153.5, 166.5; $m/z$ (EI$^+$) 207-209 (7, M$^+$), 128 (100%, M$^+$-Br); (Found (ES$^+$) MNH$_4^+$ 224.9871 C$_5$H$_{10}$N$_2$O$_3$Br requires 224.9869).
3-[2-(4-methoxyphenyl)acetyl]-1,3-oxazolidin-2-one 593

Reaction of oxazolidin-2-one 456 (0.500 g, 5.74 mmol) with a 60% dispersion of sodium hydride in mineral oil (0.344 g, 8.61 mmol) and p-methoxyphenylacetyl chloride (1.40 mL, 8.90 mmol) in THF (30 mL), according to general protocol B, afforded after purification through silica gel chromatography (gradient, 15-30% ethyl acetate/petrol) the title compound 593 (1.112 g, 4.72 mmol) in 69% yield as a white solid, mp 114-115°C; \( \nu_{\text{max}} \) (KBr disc)/cm\(^{-1}\) 3017 (C-H)ar, 2832 (C-H)MeO, 1769 (C=O)ox, 1709 (C=O)am, 1614 (C=C)ar, 1585 (C=C)ar, 1519 (C=C)ar; \( \delta_h \) (300MHz, CDCl\(_3\), Me\(_4\)Si) 3.72 (3H, s, ArOC\(_{\text{Me}3}\)), 3.94 (2H, app t, J 8.0, CH\(_2\)O), 4.14 (2H, s, CH\(_2\)Ar), 4.32 (2H, app t, J 8.0, CH\(_2\)N), 6.79 (2H, d, J 9.0, Ar-H), 7.16 (2H, d, J 9.0, Ar-H); \( \delta_c \) (CDCl\(_3\)) 40.6, 43.1, 55.6, 62.4, 114.3, 125.9, 131.2, 153.9, 159.1, 172.0; m/z (EI\(^+\)) 235 (23, ArCH\(^{\text{O}^+}\)), 148 (100%, ArCH\(_2\)CO\(^+\)); (Found (ES\(^+\)) MNH\(_4^+\) 253.1186 \( \text{C}_{12}\text{H}_{17}\text{N}_2\text{O}_4 \) requires 253.1183); (Found: C, 60.9; H, 5.43; N, 5.84 \( \text{C}_{12}\text{H}_{13}\text{NO}_4 \) requires C, 61.3; H, 5.57; N, 5.95%).

\( p \)-nitrophenylacetyl chloride 626

A solution of \( p \)-nitrophenyl acetic acid 625 (3.327 g, 18.33 mmol) was refluxed for 3 hours in thionyl chloride (20 mL). Evaporation of the solvent afforded the title compound 626 (2.912 g, 14.61 mmol) in 80% yield as a yellow solid, \( \delta_h \) (300MHz, CDCl\(_3\), Me\(_4\)Si) 4.21 (2H, s, CH\(_2\)Ar), 7.40 (2H, d, J 9.0, Ar-H), 8.18 (2H, d, J 9.0, Ar-H); \( \delta_c \) (CDCl\(_3\)) 52.7, 124.5, 131.0, 138.6, 148.2, 171.2.
3-[2-(4-nitrophenyl)acetyl]-1,3-oxazolidin-2-one 596

Reaction of oxazolidin-2-one 456 (0.500 g, 5.74 mmol) with a 60% dispersion of sodium hydride in mineral oil (0.330 g, 8.21 mmol) and p-nitrophenylacetyl chloride 626 (1.702 g, 8.52 mmol) in THF (25 mL), according to general protocol B, afforded after separation through silica gel chromatography (gradient: 20-30% ethyl acetate/petrol) the title compound 626 (0.343 g, 1.37 mmol) in 24% yield as a yellow solid, mp 154-156°C; \( \nu_{\text{max}} \) (KBr disc)/cm\(^{-1}\) 3111 (C-H)\(_{\text{ar}}\), 1776 (C=O)\(_{\text{ox}}\), 1695 (C=O)\(_{\text{uns}}\), 1606 (C=C)\(_{\text{ar}}\), 1516 (N=O)\(_{\text{conj}}\), 1348 (N=O)\(_{\text{conj}}\); \( \delta \)\(_{\text{H}}\) (300MHz, CDCl\(_3\), Me\(_4\)Si) 3.99 (2H, app t, J 8.0, CH\(_2\)N), 4.32 (2H, s, CH\(_2\)Ar), 4.39 (2H, app t, J 8.0, CH\(_2\)O), 7.41 (2H, d, J 9.0, Ar-H), 8.11 (2H, d, J 9.0, Ar-H); \( \delta \)\(_{\text{C}}\) (CDCl\(_3\)) 41.4, 43.0, 62.6, 124.2, 131.2, 141.3, 147.6, 153.9, 170.2; \( m/z \) (Cl\(^{+}\), iso-butane) 251 (29, M\(^{+}\)), 182 (100%); (Found (ES\(^{+}\)) M\(^{+}\) 251.0657 C\(_{11}\)H\(_{11}\)N\(_2\)O\(_5\) requires 251.0662).

(2S)-2-amino-3-phenyl-1-propanol 470

Boron trifluoride-etherate (15.30 mL, 121.20 mmol) was added dropwise to a solution of (S)-phenylalanine 469 (20.000 g, 121.01 mmol) in THF (60 mL) in a flame-dried, 250-mL, 3-necked, round-bottomed flask equipped with a pressure equalising addition funnel and an 18-inch Vireux column with a distillation head. The reaction was refluxed for 1 hour, after which the solid material had completely dissolved. Reaction temperature was adjusted to just below the reflux point, and BH\(_3\).Me\(_2\)S (12.70 mL, 133.30 mmol) was added dropwise over 20 min. During the addition, hydrogen evolved, and methyl sulphide was allowed to distil as it was liberated. The reaction was then refluxed for 6 hours and cooled to room temperature. A 1:1 mixture of THF/water (15 mL) followed with 5M NaOH\(_{\text{aq}}\) (90 mL) was added carefully and reaction mixture was refluxed for additional 12 hours. The remaining THF was removed in vacuo, and the resulting slurry extracted with CH\(_2\)Cl\(_2\) (5 x 20 mL). The combined organic extracts were washed with brine, dried (Na\(_2\)SO\(_4\)) and concentrated under reduced pressure to afford the title compound 470. Recrystallisation from hot ethyl acetate afforded (2S)-2-amino-3-phenyl-1-propanol 470 (13.600 g, 90.10
mmol) in 74% yield as white needles, $[\alpha]_{D}^{25} = -23.5$ (c 1.03, ethanol) [lit. $^{181}$ -22.4 (c 1.03, ethanol)]; mp 89-91°C (lit. $^{181}$ 88.5-91°C); $v_{\text{max}}$ (KBr disc)/cm$^{-1}$ 3393 (br, OH, NH), 1602 (C=C)$_{ar}$, 1494 (C=C)$_{ar}$; $\delta_{H}$ (300MHz, CDCl$_3$, Me$_4$Si) 1.80 (3H, br s, OH, NH$_2$), 2.52 (1H, dd, J 13.5, 8.5, CH$_3$H$_2$Ph), 2.80 (1H, dd, J 13.5, 5.0, CH$_3$H$_2$Ph), 3.08-3.17 (1H, m, CHNH$_2$), 3.38 (1H, dd, J 10.5, 7.5, CH$_3$H$_2$OH), 3.64 (1H, dd, J 10.5, 4.0, CH$_3$H$_2$OH), 7.18-7.34 (5H, m, Ph-H); $\delta_{C}$ (CDCl$_3$) 41.2, 54.6, 66.3, 126.9, 129.0, 129.6, 138.8.

(4S)-4-benzyl-1,3-oxazolidin-2-one 471$^{181}$

Potassium carbonate (1.250 g, 9.01 mmol), and diethyl carbonate (21.300 g, 180.10 mmol) were added to (S)-phenylalaninol 456 (13.602 g, 90.10 mmol) in a dry, 100mL, 3-necked, round-bottomed flask equipped with a thermometer, an 18-inch Vigreux column with a distillation head. The reaction was heated to 135-140°C, and ethanol was allowed to distil as it was formed for 2 hours. The reaction was cooled to room temperature, diluted with CH$_2$Cl$_2$, and filtered to remove most of the remaining potassium carbonate. The reaction was washed with NaHCO$_3$aq and brine, dried (MgSO$_4$), and concentrated in vacuo to afford the title compound 471. Recrystallisation from a mixture of ethyl acetate and petrol afforded (4S)-4-benzyl-1,3-oxazolidin-2-one 471 (13.305 g, 75.1 mmol) in 83% yield as a white crystalline solid, $[\alpha]_{D}^{25} +5.5$ (c 1.09, ethanol) [lit. $^{181}$ +4.9 (c 1.10, ethanol)]; mp 84-86°C (lit. $^{181}$ 84.5-86.5°C); $v_{\text{max}}$ (KBr disc)/cm$^{-1}$ 3281 (s, NH), 1748 (C=O)$_{am}$, 1711 (C=O)$_{amll}$, 1602 (C=C)$_{ar}$, 1496 (C=C)$_{ar}$; $\delta_{H}$ (300MHz, CDCl$_3$, Me$_4$Si) 2.84 (1H, dd, J 13.5, 7.0, CH$_3$H$_2$Ph), 2.91 (1H, dd, J 13.5, 7.0, CH$_3$H$_2$Ph), 4.04-4.17 (2H, m, CH$_3$H$_2$O, CHNH), 4.42 (1H, app t, J 8.0, CH$_3$H$_2$O), 6.12 (1H, br s, NH$_2$), 7.15-7.37 (5H, m, Ph-H); $\delta_{C}$ (CDCl$_3$) 41.8, 54.2, 66.3, 126.9, 129.0, 129.6, 138.8. C$_{10}$H$_{11}$NO$_2$ requires C, 67.8; H, 6.26; N, 7.90%.
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(4S)-4-benzyl-3-propionyl-1,3-oxazolidin-2-one 423

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\begin{align*}
\text{O} & \quad \text{N} \\
\text{423} & \quad \text{O} \\
\end{align*}
\]

Reaction of (S)-4-benzyl-oxazolidin-2-one 471 (5.001 g, 28.25 mmol) with a 2.5M solution of n-butyllithium in hexanes (12.40 mL, 31.08 mmol) and propionyl chloride (2.70 mL, 31.08 mmol) in THF (120 mL), according to general protocol A, afforded after recrystallisation from hot ethyl acetate the title compound 423 as a white crystalline solid (6.322 g, 27.13 mmol) in 96% yield, \([\alpha]_D^{25} +100.0 \text{ (c 1.02, ethanol)} [\text{lit.}^{151} +99.5, \text{ (c 1.01, ethanol)}] \); mp 43-45°C (lit.\(^{141}\) 44-46°C); \(\nu_{\text{max}} \text{(KBr disc)/cm}^{-1}\) 1786 (C=O)\(_{ox}\), 1701 (C=O)\(_{am}\), 1602 (C=C)\(_{ar}\), 1496 (C=C)\(_{ar}\); \(\delta_{\text{H}} \text{(300MHz, CDCl}_3, \text{Me}_4\text{Si})\) 1.13 (3H, t, J 7.5, CH\(_3\)), 2.70 (1H, dd, J 13.5, 9.5, CH\(_{2}\text{H}_3\)), 2.78-2.99 (2H, m, CH\(_2\)), 3.23 (1H, dd, J 13.5, 3.0, CH\(_3\)HPh), 4.07-4.16 (2H, m, CH\(_2\)), 4.56-4.64 (1H, m, CAN), 7.13-7.30 (5H, m, Ph-t); \(\delta_{\text{C}} \text{(CDCl}_3)\) 8.7, 29.6, 38.3, 55.6, 66.6, 127.7, 129.3, 129.8, 135.7, 153.9, 174.5; \(m/z \text{(Cl}^+, \text{NH}_3)\) 251.2 (100, \(\text{MNH}_4^+\)), 234 (55, \(\text{MH}^+\)), 91 (51%, PhCH\(_2\)).

(4S)-4-benzyl-3-(3-methylbutanoyl)-1,3-oxazolidin-2-one 472

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\begin{align*}
\end{align*}
\]

Reaction of (S)-4-benzyl-oxazolidin-2-one 471 (3.995 g, 22.57 mmol) with a 1.6M solution of n-butyllithium in hexanes (15.50 mL, 24.83 mmol) and iso-valeryl chloride (4.30 mL, 24.83 mmol) in THF (120 mL), according to general protocol A, afforded after purification through silica gel chromatography (30% ethyl acetate/petrol) the title compound 472 (3.392 g, 13.00 mmol) in 57% yield as a white crystalline solid, \([\alpha]_D^{23} +61.5 \text{ (c 1.04, CHCl}_3)\); mp 50-51°C; \(\nu_{\text{max}} \text{(KBr disc)/cm}^{-1}\) 3032 (C-H)\(_{ar}\), 1787 (C=O)\(_{ox}\), 1694 (C=O)\(_{am}\), 1604 (C=C)\(_{ar}\), 1491 (C=C)\(_{ar}\); \(\delta_{\text{H}} \text{(300MHz, CDCl}_3)\) 1.01 (3H, d, J 6.5, CH\(_3\)), 1.03 (3H, d, J 6.5, CH\(_3\)), 2.22 (1H, app nonet, J 6.5, CH(CH\(_3\)_2)), 2.75 (1H, dd, J 13.0, 9.5, CH\(_3\)HPh), 2.78 (1H, dd, J 16.0, 6.5, CH\(_3\)HPhCH(CH\(_3\)_2)), 2.90 (1H, dd, J 16.0, 6.5, CH\(_3\)HPhCH(CH\(_3\)_2)), 3.31 (1H, dd, J 13.0, 3.0, CH\(_3\)HPh), 4.17 (2H, m, CH\(_2\)), 4.68 (1H,
m, CHN), 7.15-7.40 (5H, m, Ph-H); δC (CDCl₃) 22.8, 22.9, 25.4, 38.4, 44.4, 55.5, 66.5, 127.7, 129.3, 129.8, 135.7, 153.8, 173.1; m/z (Cl⁺, NH₃) 279 (100, M+H⁺), 262 (62%, M+H⁺); (Found: C, 68.9; H, 7.31; N, 5.42. C₁₅H₁₉N₃O₃ requires C, 68.9; H, 7.33; N, 5.36%).
8.3 Preparation of aldol products

Procedures to prepare syn-aldolate products:

General protocol D\textsuperscript{151}

Triethylamine (1.6 eq.) was added via syringe to a stirred solution of N-acyloxazolidin-2-one 624 (1 eq.) in CH\textsubscript{2}Cl\textsubscript{2} at -78°C under a nitrogen atmosphere and the mixture allowed to stir for 5 minutes. A 1.0M solution of Bu\textsubscript{2}BOTf in CH\textsubscript{2}Cl\textsubscript{2} (1.5 eq.) was added at -78°C. The reaction was stirred for 1 hour at this temperature and allowed to warm to 0°C for 20 minutes. The reaction was cooled down to -78°C, aldehyde (1.1 eq.) was added in one portion and the mixture allowed to stir for 30 minutes at -78°C. The reaction was allowed to warm to 0°C for 30 minutes. A 1M solution of NaOAc in 90% methanol/water (5 mL) was added and after 5 min, 30% aqueous H\textsubscript{2}O\textsubscript{2} (0.5 mL) was added dropwise (caution: initial reaction is exothermic). The reaction was extracted with CH\textsubscript{2}Cl\textsubscript{2} (x 3). The combined organic extracts were washed with NaHC\textsubscript{0}\textsubscript{3}aq and brine, dried (MgSO\textsubscript{4}) and concentrated \textit{in vacuo} to afford the syn-aldolate 627.

General protocol E

Trifluoromethanesulfonylic acid (1.2 eq.) was added to a 1.0M solution of Et\textsubscript{3}B in hexanes (1.2 eq.) at room temperature. Reaction mixture was heated up to 40°C, stirred for 10 minutes and cooled down to 0°C. A solution of N-acyloxazolidin-2-one 624 (1 eq.) in CH\textsubscript{2}Cl\textsubscript{2} was added and allowed to stir for 10 minutes. N,N-diisopropylethylamine (1.4 eq.) was added and the reaction was stirred for 20 minutes at 0°C and cooled down to -78°C. Aldehyde (1.1 eq.) was added, stirred during 30 min and the mixture warmed to 0°C over 1 hour. pH 7.0 phosphate buffer was added, allowed to stir for 5 min and a 2:1 solution of methanol/hydrogen peroxide added dropwise. Reaction was extracted with CH\textsubscript{2}Cl\textsubscript{2} (x 3), the combined organic extracts were washed with NaHCO\textsubscript{3}aq, brine, dried (MgSO\textsubscript{4}) and concentrated \textit{in vacuo} to afford the syn-aldolate 627.
General protocol F

\[
\begin{align*}
\text{CH}_2\text{Cl}_2, 0 \text{ to } -78^\circ\text{C} & \quad \text{R} \\
\begin{array}{c}
\text{1- Bu}_2\text{BOTf, } \text{Pr}_2\text{NEt} \\
\text{2- R}_2\text{CHO}
\end{array} & \quad \text{OH} \\
\begin{array}{c}
\text{A 1.0M solution of Bu}_2\text{BOTf in CH}_2\text{Cl}_2 \ (1.2 \text{ eq.}) \\
\text{was added via syringe to a stirred}
\end{array} & \quad \text{syn-627}
\end{align*}
\]

A 1.0M solution of Bu₂BOTf in CH₂Cl₂ (1.2 eq.) was added via syringe to a stirred solution of N-acyloxazolidin-2-one 624 (1 eq.) in CH₂Cl₂ at 0°C and allowed to stir at this temperature for 5 minutes. N,N-diisopropylethylamine (1.4 eq.) was added, the reaction stirred for 25 minutes at 0°C and cooled down to -78°C. Aldehyde (1.1 eq.) was added, and the reaction was stirred for 2 hours and allowed to warm to 0°C for 30 minutes. pH 7.0 phosphate buffer was added, allowed to stir for 5 min and a 2:1 solution of methanol/hydrogen peroxide added dropwise. The reaction was extracted with CH₂Cl₂ (x 3) and the combined organic extracts were washed with NaHCO₃, brine, dried (MgSO₄) and concentrated in vacuo to afford the syn-aldolate 627.

General protocol G

\[
\begin{align*}
\text{CH}_2\text{Cl}_2, 0 \text{ to -78}^\circ\text{C} & \quad \text{R}_1 \\
\begin{array}{c}
\text{1- 9-BBN.OTf, } \text{Pr}_2\text{NEt} \\
\text{2- R}_2\text{CHO}
\end{array} & \quad \text{OH} \\
\begin{array}{c}
\text{Same procedure as in General protocol F, a 0.5M solution of 9-BBN.OTf in hexanes}
\end{array} & \quad \text{syn-627}
\end{align*}
\]

Same procedure as in General protocol F, a 0.5M solution of 9-BBN.OTf in hexanes was used as the Lewis acid.

Procedures for the preparation of anti-aldolates:

General protocol H

\[
\begin{align*}
\text{EtOAc, rt} & \quad \text{R}_1 \\
\begin{array}{c}
\text{1- MgCl}_2, \text{Et}_3\text{N} \\
\text{2- R}_2\text{CHO} \\
\text{3- TMSCl}
\end{array} & \quad \text{OH} \\
\begin{array}{c}
\text{Magnesium chloride (0.1 eq.), triethylamine (2 eq.), aldehyde (1.2 eq.) and}
\end{array} & \quad \text{anti-628}
\end{align*}
\]

Magnesium chloride (0.1 eq.), triethylamine (2 eq.), aldehyde (1.2 eq.) and chlorotrimethylsilane (1.5 eq.) were added successively to a solution of N-acyloxazolidin-2-one 624 (1 eq.) in THF at room temperature. Reaction was stirred for 24 hours and pushed through a plug of silica (5 cm x 1 cm) with Et₂O (50 mL). The ether solution was concentrated in vacuo, methanol added along with 2 drops of trifluoroacetic acid and the reaction stirred at room temperature for 30 minutes. The solvent was removed under reduced pressure to afford anti-aldolate 628.
Chapter 8

Experimental

General protocol I

1- MgCl₂, Et₃N
2- RjCHO
3- TMSCl/NaSbF₆

EtOAc, rt

\[
\text{O} \quad \text{OH}
\]

\[
\text{R} \quad \text{R}_1
\]

Same procedure as in General protocol H, sodium hexafluoroantimonate (0.3 eq.) was used to accelerate the reaction.

General protocol J

\[
\text{O} \quad \text{OH}
\]

\[
\text{R} \quad \text{R}_1
\]

A 1.0M solution of Et₂Zn in toluene (0.1 eq.) was added dropwise to a stirred solution of syn-aldolate 629 (1 eq.) in CH₂Cl₂ at room temperature. The reaction was stirred for 2 hours. Saturated NH₄Cl aq was added and the reaction extracted with CH₂Cl₂ (x 3). The combined organic extracts were washed with brine, dried (MgSO₄), and concentrated in vacuo to afford anti-aldolate 630.

\[
\text{syn-3-[(Z)-3-Hydroxy-2,5-diphenyl-4-pentenoyl]-1,3-oxazolidin-2-one 461 }
\]

Reaction of 3-(2-phenylacetyl)-1,3-oxazolidin-2-one 459 (0.200 g, 0.98 mmol) with a 1.0M solution of Bu₂BOTf in CH₂Cl₂ (1.45 mL, 1.45 mmol), triethylamine (0.22 mL, 1.58 mmol) and \textit{trans}-cinnamaldehyde (0.47 mL, 6.44 mmol) in CH₂Cl₂ (5 mL), according to general protocol D, afforded after purification through silica gel chromatography (20% ethyl acetate/petrol) the title compound \textit{syn}-461 (0.125 g, 0.37 mmol) in 38% yield as a colourless oil, \( \nu_{\text{max}} \) (neat)/cm⁻¹ 3532 (br, OH), 1778 (C=O)ox, 1694 (C=O)am, 1599 (C=C)ar, 1494 (C=C)br; \( \delta_{\text{H}} \) (300MHz, CDCl₃, Me₄Si) 2.45 (1H, br s, OH), 3.89 (1H, ddd, J 11.0, 9.0, 7.0, CH₃H₃N), 3.99 (1H, ddd, J 11.0, 9.0, 7.0, CH₃H₂N), 4.24 (1H, app dt, J 9.0, 7.0, CH₃H₂O), 4.29 (1H, app dt, J 9.0, 7.0, CH₃H₂O), 4.95 (1H, app t, J 7.0, CHO). 5.24
(1H, d, $J$ 7.0 CHPh), 6.20 (1H, dd, $J$ 16.0, 7.0, CH=CHPh), 6.65 (1H, d, $J$ 16.0, CH=CHPh), 7.21-7.50 (10H, m, Ph-); $\delta_C$ (CDCl$_3$) 42.6, 54.9, 61.7, 74.0, 126.6, 127.8, 128.1, 128.4, 128.5, 128.7, 129.9, 132.5, 133.9, 136.5, 152.8, 172.7; m/z (CI $^+$, NH$_3$) 355 (41, MNH$_4^+$), 338 (12, M$^+$), 337 (50, M$^+$), 320 (100%, M$^+$-OH); (Found (ES$^+$) $\text{MH}^+$ 355.1653 C$_{20}$H$_{23}$N$_2$O$_4$ requires 355.1652).

**syn-3-[(E)-3-Hydroxy-2-isopropyl-4-hexenoyl]-1,3-oxazolidin-2-one 463**

![Image of syn-463](image)

**General protocol D.** Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one 458 (0.164 g, 0.96 mmol) with Bu$_2$BOTf (1.15 mL, 1.15 mmol), triethylamine (0.18 mL, 1.25 mmol) and trans-crotonaldehyde (0.09 mL, 1.06 mmol) in CH$_2$Cl$_2$ (5 mL) afforded after purification through silica gel chromatography (25% ethyl acetate/petrol) the title compound syn-463 (0.097 mg, 0.40 mmol) in 42% yield as a white solid.

**General protocol E.** Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one 458 (0.164 g, 0.96 mmol) with a 1.0M solution of Et$_3$B in hexanes (1.91 mL, 1.91 mmol), trifluoromethane sulfonic acid (0.17 mL, 1.91 mmol), N$_2$N-diisopropylethylamine (0.39 mL, 2.23 mmol) and trans-crotonaldehyde (0.15 mL, 1.75 mmol) in CH$_2$Cl$_2$ (5 mL) afforded after purification through silica gel chromatography (25% ethyl acetate/petrol) the title compound syn-463 (0.229 g, 0.95 mmol) in 60% yield as a white solid.

**General protocol G.** Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one 458 (0.965 g, 5.85 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (14.10 mL, 7.02 mmol), N$_2$N-diisopropylethylamine (1.32 mL, 7.60 mmol) and trans-crotonaldehyde (0.53 mL, 6.44 mmol) in CH$_2$Cl$_2$ (30 mL) afforded after purification through silica gel chromatography (25% ethyl acetate/petrol) the title compound syn-463 (1.090 g, 4.54 mmol) in 72% yield as a low-melting point white solid, $\nu_{max}$ (nujol)/cm$^{-1}$ 3454 (br, OH), 1770 (C=O)$_{ar}$, 1690 (C=O)$_{am}$; $\delta_H$ (300MHz, CDCl$_3$, Me$_4$Si) 0.92 (3H, d, $J$ 6.5, CH(CH$_3$)$_2$), 0.97 (3H, d, $J$ 6.5, CH(CH$_3$)$_2$), 1.72 (3H, d, $J$ 5.5, CH=CHCH$_3$), 1.99-2.11 (1H, m, CH(CH$_3$)$_2$), 2.23 (1H, br s, OH), 4.01-4.10 (3H, m, CH$_2$N, CH$_2$Pr), 4.34-4.48 (3H, m, CH$_2$O, CHO), 5.60-5.81 (2H, m, CH=CHCH$_3$); $\delta_C$ (CDCl$_3$) 18.2, 20.4, 21.1, 28.6, 43.2, 54.3, 62.0, 73.5, 130.0, 130.0, 154.7, 174.7; m/z (CI $^+$, iso-butane) 242 (6, M$^+$), 224.1 (75, M$^+$-OH), 171.0 (64, M$^+$-CHOHCHCHCH$_3$), 156.0 (100%); (Found (FAB$^+$) M$^+$ 242.1393 C$_{12}$H$_{20}$NO$_4$ requires 242.1392).
**Experimental**

**syn-3-(3-Hydroxy-2-methyl-3-phenylpropanoyl)-1,3-oxazolidin-2-one 467**

![Syn-467](image)

Reaction of 3-propionyl-1,3-oxazolidin-2-one 457 (0.545 g, 3.81 mmol) with a 0.5M solution of 9-BBN.O Tf in hexanes (9.14 mL, 4.57 mmol), N,N-diisopropylethylamine (0.86 mL, 4.95 mmol) and benzaldehyde (0.43 mL, 4.19 mmol) in CH$_2$Cl$_2$ (20 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 20-30% ethyl acetate/petrol) the title compound *syn*-467 (0.653 g, 2.62 mmol) in 69% yield as a white crystalline solid, mp 102-104°C (lit. 105-106°C); $\nu_{max}$ (KBr disc)/cm$^{-1}$: 3561 (s, OH), 1766 (C=O)$_{ox}$, 1682 (C=O)$_{am}$, 1603 (C=C)$_{ar}$, 1494 (C=C)$_{ar}$; $\delta_H$ (300MHz, CDCl$_3$, Me$_4$Si) 1.15 (3H, d, $J_{7.0}$, C\textsubscript{3}Hi), 3.07 (1H, d, $J_{3.0}$, OH), 3.95-4.07 (2H, m, C\textsubscript{2}N), 4.12 (1H, qd, $J_{7.0,3.5}$, C\textsubscript{2}CH$_3$), 4.31-4.45 (2H, m, CH$_2$O), 5.13 (1H, app t, $J_{3.0}$, CHOH), 7.24-7.43 (5H, m, Ph-H); $\delta_C$ (CDCl$_3$) 10.8, 43.0, 44.6, 62.4, 73.9, 126.4, 127.9, 128.6, 141.6, 153.5, 177.2; m/z (CI$,^+$, NH$_3$) 267 (41, M$+\cdot$NH$_4^+$), 250 (10, MH$^+$), 232 (38, M$^+$-OH), 206 (22, MH$^+$-CO$_2$), 161 (100%); (Found (ES$^+$) MH$^+$ 250.1081, C$_{13}$H$_{16}$NO$_4$ requires 250.1079).

**(<S>-Benzyl-S-[<S><S>-hydroxy]-dimethyl-4-pentenoyl)-1,3-oxazolidin-2-one 440**

![Syn-440](image)

Reaction of (<S)-4-benzyl-3-propionyl-1,3-oxazolidin-2-one 423 (0.998 g, 4.29 mmol) with a 0.5M solution of 9-BBN.O Tf in hexanes (11.1 mL, 5.58 mmol), N,N-diisopropylethylamine (1.05 mL, 6.01 mmol) and methacrolein (0.40 mL, 4.72 mmol) in CH$_2$Cl$_2$ (20 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 10-20% ethyl acetate/petrol) the title compound *syn*-440 (0.892 g, 2.94 mmol) in 69% yield as a colourless oil, $[\alpha]_D^{25} +59$ (c 1.00, CH$_2$Cl$_2$); $\nu_{max}$ (KBr disc)/cm$^{-1}$: 3452 (s, OH), 1787 (C=O)$_{ox}$, 1695 (C=O)$_{am}$, 1653 (C=C), 1602 (C=C)$_{ar}$, 1498 (C=C)$_{ar}$; $\delta_H$ (300MHz, CDCl$_3$, Me$_4$Si) 1.19 (3H, d, $J_{7.0}$, CHCH$_3$), 1.74 (3H,
s, CH$_2$=C(CH$_3$)), 2.80 (1H, dd, J 13.0, 9.5, CH$_3$H$_2$Ph), 2.94 (1H, d, J 3.0, OH), 3.28 (1H, dd, J 13.0, 3.5, CH$_3$H$_2$Ph), 3.97 (1H, qd, J 7.0, 3.0, CH$_2$CH$_3$), 4.18-4.27 (2H, m, CH$_2$O), 4.37-4.44 (1H, m, CH$_3$), 4.99 (1H, br s, CH$_3$H$_3$=C(CH$_3$)), 5.13 (1H, br s, CH$_3$H$_3$=C(CH$_3$)); $\delta_C$ (CDCl$_3$) 10.4, 19.8, 38.1, 40.5, 55.6, 66.6, 74.3, 112.2, 127.8, 129.4, 129.8, 135.4, 144.0, 153.4, 177.5; m/z (Cl$^+$, NH$_3$) 321 (28, M+NH$_4$), 304 (57, MH$^+$), 286 (13, MH$^+\cdot$H$_2$O), 251.1 (100), 234 (36%, MH$^+$-CHOHC(CH$_3$)=CH$_2$); (Found (ES$^+$) MH$^+$ 303.1549 C$_{17}$H$_{22}$NO$_4$ requires 303.1549).

(4S)-4-Benzyl-3-[(2S)-2-[(S)-hydroxy(phenyl)methyl]-3-methylbutanoyl]-1,3-oxazolidin-2-one 473

Reaction of (4R)-4-benzyl-3-propionyl-1,3-oxazolidin-2-one 423 (0.700 g, 3.00 mmol) with a 0.5M solution of 9-BBN.O Tf in hexanes (7.21 mL, 3.61 mmol), N,N-diisopropylethylamine (0.73 mL, 4.21 mmol) and benzaldehyde (0.34 mL, 3.30 mmol) in CH$_2$Cl$_2$ (15 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 10-20% ethyl acetate/petrol) the title compound syn-473 (0.837 g, 2.47 mmol) in 82% yield as a colourless oil, [$\alpha$]$_D^2$ +69.8 (c 1.01, CH$_2$Cl$_2$) (lit,$^{151}$ +75.7, CH$_2$Cl$_2$, c 1.00); $\nu_{max}$ (neat)/cm$^{-1}$ 3488 (br, OH), 1773 (C=O)$_{as}$, 1700 (C=O)$_{am}$; $\delta_H$ (300MHz, CDCl$_3$, Me$_4$Si) 1.15 (3H, d, J 7.0, CH$_3$), 2.70 (1H, dd, J 13.5, 9.5, CH$_3$H$_2$Ph), 3.05 (1H, d, J 2.0, OH), 3.17 (dd, 1H, J 13.5, 3.3, CH$_3$H$_2$Ph), 3.96-4.09 (3H, m, CH$_2$O, CH(CH$_3$)), 4.48-4.55 (1H, m, CH$_3$), 5.02 (1H, d, J 2.6, CHO), 7.11-7.34 (10H, m, Ph-H); $\delta_C$ (CDCl$_3$) 11.3, 38.2, 44.9, 55.6, 66.6, 74.2, 126.5, 127.8, 128.0, 128.7, 129.4, 129.8, 135.4, 141.7, 153.3, 177.1; m/z (EI$^+$) 339 (6, M$^+$), 233 (63, M$^+$-PhCHOH), 57 (100%); (Found (ES$^+$) MH$^+$ 340.1545 C$_{20}$H$_{22}$NO$_4$ requires 340.1543).
syn-3-{2-[Cyclohexyl(hydroxy)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one 476

Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one 458 (1.500 g, 8.77 mmol) with a 0.5M solution of 9-BBN.O Tf in hexanes (21.11 mL, 10.53 mmol), N,N-diisopropylethylamine (1.99 mL, 11.40 mmol) and cyclocarboxaldehyde (1.17 mL, 9.65 mmol) in CH₂Cl₂ (40 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 10-20% ethyl acetate/petrol) the title compound 476 (1.451 g, 5.11 mmol) in 58% yield as a white solid, mp 131-133°C; ν max (KBr disc)/cm⁻¹ 3510 (s, OH), 1773 (C=O)ox, 1676 (C=O)am; δH (300MHz, CDCl₃, Me₄Si) 1.02 (3H, d, J 7.0, CH(CH₃)₂), 1.03 (3H, d, J 7.0, CH(CH₃)₂), 1.12-1.27 (4H, m, Cy-H), 1.30-1.38 (1H, m, Cy-H), 1.61-1.67 (2H, m, Cy-H), 1.73-1.77 (2H, m, Cy-H), 1.83-1.91 (1H, m, Cy-H), 2.04-2.10 (1H, m, Cy-H), 2.31 (1H, septet of d, J 7.0, 5.0, CH(CH₃)₂), 3.72-3.78 (1H, m, CH₂O), 4.04 (2H, app t, J 8.0, CH₂N), 4.22 (1H, dd, J 7.0, 5.0, CH₂O), 4.41 (2H, app dt, J 8.0, 1.8, CH₂O); δC (CDCl₃) 19.6, 21.5, 26.6, 26.7, 26.8, 27.4, 28.2, 30.6, 41.7, 43.0, 49.3, 61.9, 76.0, 153.7, 175.6; m/z (FAB⁺) 284 (97, MH⁺), 266 (100%, M⁺-OH); (Found (FAB⁺) MH⁺ 284.1868 C₁₅H₂₆NO₄ requires 284.1862).

syn-3-(3-Hydroxy-2-methylpentanoyl)-1,3-oxazolidin-2-one 479

Reaction of the 3-propionyl-1,3-oxazolidin-2-one 457 (0.991 g, 6.93 mmol) with a 1.0M solution of Bu₂BOTf in CH₂Cl₂ (8.39 mL, 8.39 mmol), N,N-diisopropylethylamine (1.70 mL, 9.79 mmol) and propionaldehyde (0.56 mL, 7.69 mmol) in CH₂Cl₂ (35 mL), according to general protocol F, afforded after purification through silica gel chromatography (gradient, 25-40% ethyl acetate/petrol) the title compound syn-479 (0.427 g, 2.12 mmol) in 31% yield as a white solid, mp 60-62°C; ν max (KBr disc)/cm⁻¹ 3471 (br, OH), 1752 (C=O)ox, 1696 (C=O)am; δH (300MHz, CDCl₃, Me₄Si) 0.91 (3H, t, J 7.5, CH₂CH₃), 1.13 (3H, d, J 7.0, CHCH₃), 1.44 (2H, m, CH₂CH₃), 2.78 (1H, br s, OH), 3.79-3.89 (2H, m, CHOH, CHCH₃), 4.01-4.07 (2H, m, CH₂N), 4.37 (2H, app t, J 8.5, CH₂O); δC (CDCl₃) 8.3, 8.5, 24.8, 39.6, 40.8, 60.1, 71.2, 151.4, 175.6; m/z (Cl⁺, iso-butane) 202 (100,
syn-3-(3-Hydroxy-2-isopropylpentanoyl)-1,3-oxazolidin-2-one 480

Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one 458 (0.965 mg, 5.85 mmol) with a 1.0M solution of Bu₂BOTf in CH₂Cl₂ (7.02 mL, 7.02 mmol), N,N-diisopropylethylamine (1.43 mL, 8.19 mmol) and propionaldehyde (0.47 mL, 6.44 mmol) in CH₂Cl₂ (30 mL), according to general protocol F, afforded after purification through silica gel chromatography (gradient, 25-40% ethyl acetate/petrol) the title compound syn-480 (0.644 g, 2.81 mmol) in 48% yield as a white solid, mp 60-62°C; \( \nu_{\text{max}} \) (KBr disc)/cm⁻¹ 3463 (br, OH), 1752 (C=O)ox, 1696 (C=O)am; \( \delta_{\text{H}} \) (300MHz, CDCl₃, Me₄Si) 0.85 (3H, d, J 7.0, CH(CH₃)₂), 0.91 (3H, d, J 7.0, CH(CH₃)₂), 0.91 (3H, t, J 7.5, CH₂CH₃), 1.35 (1H, dqd, J 14.0, 10.0, 7.5, CH₄H₂CH₃), 1.51 (1H, dqd, J 14.0, 7.5, 2.3, CH₃H₂CH₃), 2.12 (1H, d of septets, J 8.0, 7.0, CH(CH₃)₂), 2.54 (1H, br s, OH), 3.83 (1H, app t, J 7.5, CH²Pr), 3.91-4.02 (3H, m, CH₂N, CHO); \( \delta_{\text{C}} \) (CDCl₃) 9.7, 19.2, 19.9, 24.4, 27.0, 41.8, 53.1, 60.8, 72.1, 153.3, 173.6; m/z (Cl⁺, iso-butane) 230 (5, MH⁺), 212 (8, M⁺OH), 171 (34%, M⁺-CH₂CH₃CHOH); (Found (FAB⁺) MH⁺ 230.1394 C₁₁H₂₀NO₄ requires 230.1392).

syn-3-(2-[Hydroxy(phenyl)methyl]-3-methylbutanoyl)-1,3-oxazolidin-2-one 481

Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one 458 (0.993 g, 5.81 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (11.7 mL, 5.85 mmol), N,N-diisopropylethylamine (1.40 mL, 8.19 mmol) and benzaldehyde (0.65 mL, 6.43 mmol) in CH₂Cl₂ (30 mL), according to general protocol G, afforded after purification through silica gel chromatography (25% ethyl acetate/petrol) the title compound syn-481 (0.811 g, 2.93 mmol) in 50% yield as a white solid, mp 93-95°C; \( \nu_{\text{max}} \) (KBr disc)/cm⁻¹ 3450 (s, OH), 1751
Experimental

\( (C=O)_{\text{ox}}, 1695 \ (C=O)_{\text{am}}, \delta_T (300\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})\) 1.01 (3H, d, J 7.0, CH(CH_3)_2), 1.08 (3H, d, J 7.0, CH(CH_3)_2), 2.36 (1H, septet of d, J 7.0, 5.5, CH(CH_3)_2), 2.41 (1H, d, J 3.0, OH), 3.62 (1H, ddd, J 11.0, 9.5, 7.0, CH_2NB), 3.84 (1H, ddd, J 11.0, 9.5, 7.0, CH_2NB), 4.07 (1H, app dt, J 9.0, 7.0, CH_2O), 4.24 (1H, app dt, J 9.0, 7.0, CH_2O), 4.88 (1H, dd, J 8.5, 5.5, C'H(Pr), 5.01 (1H, dd, J 8.0, 2.6, CHO), 7.25-7.40 (5H, m, Ph-H); \( \delta_C (\text{CDCl}_3)\) 15.5, 19.8, 27.1, 41.3, 53.0, 60.3, 72.9, 125.6, 126.7, 127.1, 140.9, 152.0, 172.7; m/z (CI\(^+\), NH\(_3\)) 295 (8, M\(^{+}\)N\(_4\)), 278 (5, M\(^{+}\)), 260 (28, M\(^{+}\)-OH), 234 (9, M\(^{+}\)-Pr), 105 (100%); (Found (ES\(^+\)) M\(^{+}\)N\(_4\)) 295.1653 C\(_{15}\)H\(_{23}\)N\(_2\)O\(_4\) requires 295.1652.

\( \text{syn-3-[2-[Hydroxy(4-methoxyphenyl)methyl]-3-methylbutanoyl]-1,3-oxazolidin-2-one} \)

\( \text{Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one 458 (1.500 g, 8.77 mmol) with a} \)
0.5M solution of 9-BBN.O\(_{\text{TF}}\) in hexanes (21.10 mL, 10.53 mmol), \( N,N\)-diisopropylethylamine (1.99 mL, 11.40 mmol) and \( p\)-anisaldehyde (1.17 mL, 9.65 mmol) \( \text{in CH}_2\text{Cl}_2 \) (40 mL), according to general protocol G, afforded after purification through \( \text{silica gel chromatography} \) (gradient, 10-20% ethyl acetate/petrol) the title compound \( \text{syn-482} \) (1.592 g, 5.18 mmol) in 60% yield as a white crystalline solid, \( mp 117-118^\circ C; \nu_{\text{max}} (KBr disc)/cm\(^{-1}\) 3449 (s, OH), 2838 (C-H)MeO, 1755 (C=O)\(_{\text{ox}}, 1691 (C=O)_{\text{am}}, 1610 (C=C)_{\text{ar}}, 1582 (C=C)_{\text{ar}}, 1510 (C=C)_{\text{ar}}; \delta_T (300\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})\) 1.02 (3H, d, J 7.0, CH(CH_3)_2), 1.08 (3H, d, J 7.0, CH(CH_3)_2), 2.24 (1H, d, J 3.5, OH), 2.35 (1H, septet of d, J 7.0, 5.5, CH(CH_3)_2), 3.65 (1H, ddd, J 11.0, 9.5, 7.0, CH_2NB), 3.79 (3H, s, ArOCH\(_3\)), 3.86 (1H, ddd, J 11.0, 9.5, 7.0, CH_2NB), 4.12 (1H, app dt, J 9.0, 7.0, CH_2NB), 4.26 (1H, app dt, J 9.0, 7.0, CH_2O), 4.48 (1H, d, J 8.5, 5.5, C'H(Pr), 4.97 (1H, dd, J 8.5, 3.5, CHOH), 6.84 (2H, d, J 8.5, Ar-H), 7.30 (2H, d, J 8.5, Ar-H); \( \delta_C (\text{CDCl}_3)\) 19.5, 21.3, 28.7, 42.9, 54.5, 55.6, 61.8, 74.0, 114.0, 128.5, 134.6, 153.6, 159.6, 174.2; m/z (EI\(^+\)) 307 (12, \( M^+\)), 171 (28, \( M^+\)-ArCHOH), 149 (100%); (Found (EI\(^+\)) \( M^+\)) 307.1426 C\(_{16}\)H\(_{21}\)NO\(_3\) requires 307.1420.

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**syn-3-(2-Benzyl-3-hydroxydecanoyl)-1,3-oxazolidin-2-one 483**

![struct483](image_url)

Reaction of 3-(3-phenylpropanoyl)-1,3-oxazolidin-2-one 460 (0.500 g, 2.28 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (5.48 mL, 2.74 mmol), N,N-diisopropylethylamine (0.56 mL, 3.20 mmol) and octanal (0.39 mL, 2.51 mmol) in CH$_2$Cl$_2$ (10 mL), according to general protocol G, afforded after purification through silica gel chromatography (20% ethyl acetate/petrol) the title compound **syn-483** (0.582 g, 1.68 mmol) in 74% yield as a colourless oil, $\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3474 (br, OH), 1775 (C=O) ox, 1695 (C=O) am, 1603 (C=C)$_{ar}$, 1495 (C=C)$_{ar}$; $\delta_{\text{H}}$ (300MHz, CDCl$_3$, Me$_4$Si) 0.81 (3H, t, J 7.0, CH$_3$), 1.16-1.28 (8H, m, Alk-H), 1.44-1.52 (4H, m, Alk-H), 2.65 (1H, br s, OH), 2.92 (1H, dd, J 13.0, 5.5, CH$_3$H$_2$Ph), 2.99 (1H, dd, J 13.0, 10.0, CH$_3$H$_2$Ph), 3.62 (1H, ddd, J 10.0, 9.0, 6.0, CH$_3$H$_3$N), 3.73-4.00 (3H, m, CH$_3$H$_2$N, CHO$_2$, CH$_2$H$_2$O), 4.18 (1H, app dt, J 9.0, 6.0, CH$_3$H$_2$O), 4.33-4.40 (1H, m, CH$_2$H$_2$N), 7.11-7.19 (5H, m, Ph-H); $\delta_{C}$ (CDCl$_3$) 14.5, 23.0, 26.4, 29.6, 29.9, 32.2, 33.5, 34.4, 42.9, 49.5, 62.1, 72.6, 126.8, 128.7, 129.4, 139.3, 153.7, 175.9; m/z (CI$^+$, NH$_3$) 365 (11, M$^+$H$_4$), 348 (13, M$^+$H$^+$), 237.2 (100%); (Found (ES$^-$) M$^-$ 348.2171 C$_{20}$H$_{29}$NO$_4$ requires 348.2169).

**syn-3-[((E)-3-Hydroxy-2-methyl-5-phenyl-4-pentenoyl]-1,3-oxazolidin-2-one 492**

![struct492](image_url)

Reaction of 3-propionyl-1,3-oxazolidin-2-one 460 (0.500 g, 3.50 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (8.40 mL, 4.20 mmol), N,N-diisopropylethylamine (0.79 mL, 4.55 mmol) and trans-cinnamaldehyde (0.49 mL, 3.85 mmol) in CH$_2$Cl$_2$ (15 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 20-40% EtOAc/petrol) the title compound **syn-492** (0.841 g, 3.06 mmol) in 88% yield as a white crystalline solid, mp 100-101°C; $\nu_{\text{max}}$ (KBr disc)/cm$^{-1}$: 3476 (s, OH), 1762 (C=O)$_{ar}$, 1683 (C=O)$_{am}$, 1575 (C=C)$_{ar}$, 1494 (C=C)$_{ar}$; $\delta_{\text{H}}$ (300MHz, CDCl$_3$, Me$_4$Si) 1.17 (3H, d, J 7.0, CH$_3$), 2.97 (1H, d, J 1.0, OH), 3.88-3.99 (3H, m, CH$_2$N, CHCH$_3$), 4.28-4.34 (2H, m, CH$_2$O), 4.58 (1H, ddd, J 6.0, 4.0, 1.3, CHO$_2$), 6.14 (1H, dd, J 16.0, 6.0, HC=CHPh), 6.59 (1H, d, J 16.0, HC=CHPh), 7.15-7.34 (5H, m, Ph-H); $\delta_{\text{C}}$...
Experimental

\((\text{CDCl}_3)\) 11.6, 43.1, 43.1, 62.4, 73.2, 126.9, 128.1, 129.0 (3C), 131.8, 136.9, 153.8, 176.8; 
m/z (EI\(^+\)) 275 (7, \(M^+\)), 143 (42, \(M^+\)-PhCHOCHCHOH), 104.1 (100%); (Found (ES\(^+\)) \(MNH_4^+\) 293.1495 \(\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_4\) requires 293.1496).

**anti-3-(3-Hydroxy-2-methyl-3-phenylpropanoyl)-1,3-oxazolidin-2-one 468\(^\text{153}\)**

![Anti-468](image)

Reaction of 3-propionyl-1,3-oxazolidin-2-one 457 (0.500 g, 3.50 mmol) with magnesium chloride (0.033 g, 0.35 mmol), triethylamine (0.97 mL, 6.99 mmol), benzaldehyde (0.43 mL, 4.19 mmol) and trimethylsilyl chloride (0.67 mL, 5.24 mmol) in ethyl acetate (7 mL), according to general protocol H, afforded after purification through silica gel chromatography (30\% ethyl acetate/petrol) the title compound **anti-468** (0.290 g, 1.16 mmol) in 33\% yield as a white crystalline solid, \(mp\) 102-104°C (lit.,\(^\text{153}\) 107-107.5°C); \(\nu_{\text{max}}\) (KBr disc)/cm\(^{-1}\) 3446 (s, OH), 1783 (C=O)\(_{\text{as}}\), 1665 (C=O)\(_{\text{v}}\); \(\delta_{\text{H}}\) (300MHz, CDCl\(_3\), Me\(_4\)Si) 1.05 (3H, d, \(J_7\ 7.0,\ CH_3\)), 2.87 (1H, d, \(J\ 5.0,\ OH\)), 4.00-4.06 (2H, m, CH\(_2\)N), 4.28 (1H, dq, \(J\ 8.5,\ 7.0,\ CHCH_3\)), 4.36-4.45 (2H, m, CH\(_2\)O), 4.78 (1H, dd, \(J\ 8.5,\ 5.0,\ CHOH\)), 7.26-7.43 (5H, m, Ph-H); \(\delta_{\text{C}}\) (CDCl\(_3\)) 15.2, 43.1, 44.8, 62.4, 77.5, 127.1, 128.5, 129.0, 142.1, 153.9, 176.9; m/z (Cl\(^+\), NH\(_3\)) 267 (94, \(MNH_4^+\)), 250 (48, \(MH^+\)), 105.1 (100\%); (Found (ES\(^+\)) \(MH^+\) 250.1079 \(\text{C}_{13}\text{H}_{16}\text{NO}_4\) requires 250.1079).

3-{(2R,3R)-3-Hydroxy-3-[(4R)-4-isopropenyl-1-cyclohexen-1-yl]-2-methylpropanoyl]-1,3-oxazolidin-2-one 545 and 3-{(2S,3S)-3-hydroxy-3-[(4R)-4-isopropenyl-1-cyclohexen-1-yl]-2-methylpropanoyl]-1,3-oxazolidin-2-one 546

![545-546](image)

Reaction of 3-propionyl-1,3-oxazolidin-2-one 457 (0.500 g, 3.50 mmol) with a 0.5M solution of 9-BBN.O Tf in hexanes (8.40 mL, 4.20 mmol), N,N-diisopropylethylamine (0.85 mL, 4.90 mmol) and L-(-)-perillaldehyde (0.60 mL, 3.85 mmol) in CH\(_2\)Cl\(_2\) (20 mL), according to general protocol G, afforded after purification through silica gel chromatography (20\% ethyl acetate/petrol) the title compound 545 + 546 (0.656 g, 2.24 mmol) in 64\% yield as a white solid, which was a mixture of diastereomers, \(mp\) 87-
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88°C; \( \nu_{\text{max}} \) (KBr disc)/cm\(^{-1} \) 3495 (s, OH), 1769 (C=O)\(_{\text{oxy}} \), 1691 (C=O)\(_{\text{am}} \); \( \delta_{\text{H}} \) (300MHz, CDCl\(_3 \), Me\(_4\)Si) 1.13 (3H, d, J 6.0, CH\(_3 \), 545), 1.15 (3H, d, J 6.0, CH\(_3 \), 546), 1.38-1.55 (1H, m, Cy-H), 1.74 (3H, s, CH\(_3\)C=CH\(_2 \)), 1.82-1.88 (1H, m, Cy-H), 1.92-2.06 (2H, m, Cy-H), 2.11-2.24 (2H, m, Cy-H), 2.76 (1H, s, OH, 545), 2.78 (1H, s, OH, 546), 3.75 (1H, m, Cy-H), 5.80-5.83 (1H, m, C=H=C); Sc(CDCl\(_3 \)) 10.2, 10.9, 21.2, 21.3, 25.7, 26.0, 26.5, 27.7, 27.8, 30.6, 30.9, 40.4, 40.8, 41.2, 41.7, 43.1, 62.4, 68.4, 74.3, 74.6, 109.0, 109.1, 122.4, 123.0, 136.2, 136.7, 149.9, 150.2, 153.6, 177.5, 177.6; m/z (EI\(^+ \)) 311 (9, M\(^+\)/), 294 (15, M\(^+\)\(-\text{NH}_3 \)), 276 (40, M\(^+\)-OH), 294 (15, M\(^+\)), 276 (40, M\(^+\)-OH), 161 (100), 144 (39%, M\(^+\)-COH\(_3\)); (Found (Cl, CH\(_4 \)) M\(^+\) 294.1695 C\(_{16}\)H\(_{24}\)N\(_4\) requires 294.1700).

3-(2R,3S,5S)-3-Hydroxy-2,5,9-trimethyl-8-decenoyl)-1,3-oxazolidin-2-one 549 and 3-(2S,3R,5S)-3-hydroxy-2,5,9-trimethyl-8-decenoyl)-1,3-oxazolidin-2-one 550

Reaction of 3-propionyl-1,3-oxazolidin-2-one 457 (0.300 g, 2.10 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (5.03 mL, 2.52 mmol), N,N-diisopropylethylamine (0.51 mL, 2.94 mmol) and (S)-citronellal (0.42 mL, 2.31 mmol) in CH\(_2\)Cl\(_2\) (10 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 20-30% ethyl acetate/petrol) the title compound 549 + 550 (0.576 g, 1.94 mmol) in 93% yield as a low viscosity colourless oil, which was a mixture of diastereoisomers, \( \nu_{\text{max}} \) (neat)/cm\(^{-1} \) 3502 (br, OH), 1771 (C=O)\(_{\text{oxy}} \), 1695 (C=O)\(_{\text{am}} \); \( \delta_{\text{H}} \) (300MHz, CDCl\(_3 \), Me\(_4\)Si) 0.92 (3H, app t, J 7.0, CH\(_3\), 549 + 550), 1.05-1.28 (2H, m, Alk-H), 1.20 (3H, d, J 7.0, O=CCH\(_2\)CH\(_3\), 549), 1.21 (3H, d, J 7.0, O=CCH\(_2\)CH\(_3\), 550), 1.30-1.48 (2H, m, Alk-H), 1.60 (3H, s, CH=CH\(_2\)), 1.68 (3H, s, CH=CH\(_2\)), 1.54-1.70 (1H, m, CH\(_2\)CH=CH\(_3\)), 1.92-2.08 (2H, m, CH\(_2\)CH=CH(CH\(_3\))\(_2\)), 2.73 (1H, d, J 2.3, OH, 549), 2.80 (1H, d, J 3.0, OH, 550), 3.73-3.83 (1H, m, O=CCH\(_2\)CH\(_3\)), 4.00-4.11 (3H, m, CHOH, CH\(_2\)N), 4.44 (2H, app t, J 8.0, CH\(_2\)O), 5.10 (1H, t, J 7.0, CH=CH(CH\(_3\))\(_2\)); \( \delta_{\text{C}} \) (CDCl\(_3 \)) 10.6, 11.0, 18.1, 19.3, 20.6, 25.7, 25.9, 26.0, 26.1 (2C), 29.3, 29.6, 36.9, 38.3, 41.4, 41.5, 42.2, 42.9, 43.0, 62.3, 68.4, 69.6, 69.8, 125.1, 131.6, 131.6, 153.6, 153.6, 177.9, 178.0; m/z (EI\(^+)\) 297.2 (11, M\(^+\)), 143 (100%, M\(^+\)-CH\(_3\)\(_2\)C=CHCH\(_2\)CH(CH\(_3\))CH\(_2\)CHOH); (Found (ES\(^+)\) M\(^+\) 298.2090 C\(_{16}\)H\(_{28}\)NO\(_4\) requires 298.2013).

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(2R,3R)-3-{3-[(4R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-2-methylpropanoyl}-1,3-oxazolidin-2-one 553 and (2S,3S)-3-{3-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-2-methylpropanoyl}-1,3-oxazolidin-2-one 554

Reaction of 3-propionyl-1,3-oxazolidin-2-one 457 (0.200 g, 1.40 mmol) with a 0.5M solution of 9-BBN.OTf in CH$_2$Cl$_2$ (3.36 mL, 1.68 mmol), N,N-diisopropylethylamine (0.34 mL, 1.96 mmol) and (R)-(−)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (0.19 mL, 1.54 mmol) in hexanes (7 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 40-50% ethyl acetate/petrol) the title compound 553 + 554 (0.222 g, 0.81 mmol) in 58% as a thick colourless oil, which was a 2:1 mixture of diastereoisomers, $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3447 (br, OH), 1771 (C=O)$_{\text{ox}}$, 1699 (C=O)$_{\text{am}}$; $\delta_H$ (300MHz, CDCl$_3$, Me$_4$Si) 1.28 (3H, d, J 6.5, CH=CC$_H$3, 553), 1.34 (3H, s, CH$_3$), 1.38 (3H, d, J 6.5, CH=CC$_H$3, 554), 1.43 (3H, s, CH$_3$), 2.55 (1H, d, J 6.5, OH, 553), 3.11 (1H, d, J 3.0, OH, 554), 3.72-4.18 (5H, m, CH$_2$OH, CH$_2$C$_H$3, CH$_2$, CH(O)), 4.05 (2H, app t, J 7.5, CH$_2$N), 4.44 (2H, app t, J 7.5, CH$_2$O); $\delta_C$ (CDCl$_3$) 11.2, 12.1, 25.6, 25.8, 26.8, 27.1, 39.5, 41.3, 43.1, 62.3, 62.4, 66.6, 67.8, 68.4, 72.0, 73.1, 75.6, 77.2, 109.8, 110.1, 153.2, 153.6, 175.6, 178.0; $m/z$ (Cl$^+$, NH$_3$) 291 (30%, M+NH$_4^+$), 274 (46, M+H$^+$), 256 (5, M$^+$-OH), 230 (20, M+H$^+$-CO$_2$), 144 (13, M+H$^+$-CHOHR), 105.0 (100%); (Found (ES$^+$) MH$^+$ 274.1282 C$_{12}$H$_{20}$NO$_6$ requires 274.1285).

syn-3-[[2-2-Furyl(hydroxy)methyl]-3-methylbutanoyl]-1,3-oxazolidin-2-one 557

Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one 458 (0.500 g, 2.92 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (7.02 mL, 3.51 mmol), N,N-diisopropylethylamine (0.66 mL, 3.80 mmol) and 2-furaldehyde (0.27 mL, 3.22 mmol) in CH$_2$Cl$_2$ (15 mL), according to general protocol G, afforded after purification through silica gel chromatography (20% ethyl acetate/petrol) the title compound syn-557 (0.292 g, 1.09 mmol) in 38% yield, mp 96-98°C; $\nu_{\text{max}}$ (KBr disc)/cm$^{-1}$ 3446 (s, OH), 1769 (C=O)$_{\text{ox}}$, 1676 (C=O)$_{\text{am}}$; $\delta_H$ (300MHz, CDCl$_3$, Me$_4$Si) 0.97 (3H, d, J 7.0, CH(CH$_3$)$_2$), 0.99 (3H, d, J 7.0,
Chapter 8 Experimental

\[
\text{CH(CH_3)_2, 2.25 (1H, app octet, } J 7.0, \text{ CH(CH}_3)_2, 2.35 (1H, br s, } O_H), 3.81 (1H, ddd, } J 11.0, 9.0, 7.5, \text{ CH}_4H_8N), 3.89 (1H, ddd, } J 11.0, 9.0, 6.5, \text{ CH}_4H_8N), 4.24 (1H, app dt, } J 9.0, 6.5, \text{ CH}_4H_8O), 4.29 (1H, app dt, } J 9.0, 7.5, \text{ CH}_4H_8O), 4.44 (1H, dd, } J 8.5, 6.5, \text{ CH}^HPr), 5.03 (1H, d, } J 8.5, \text{ CHOH), 6.24 (2H, d, } J 1.3, \text{ fur-H), 7.29 (1H, app t, } J 1.3, \text{ fur-H); } \delta_c (\text{CDCl}_3) 19.7, 20.7, 28.6, 43.0, 52.5, 62.1, 68.0, 107.3, 110.8, 142.4, 154.0, 155.1, 173.7; m/z (CI^+, NH_3) 285 (44, A/NH_4^+), 267 (42, A/f), 189 (100%, A/-fur); (Found (ES^+) M NH_4^+ 285.1447 C_{13}H_{21}N_2O_5 requires 285.1445).
\]

\[
\text{syn-3-[3-(2-Furyl)-3-hydroxy-2-methylpropanoyl]-1,3-oxazolidin-2-one 560 and anti-3-[3-(2-furyl)-3-hydroxy-2-methylpropanoyl]-1,3-oxazolidin-2-one 561}
\]

\[
\text{Reaction of 3-propionyl-1,3-oxazolidin-2-one 457 (0.500 g, 3.50 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (8.40 mL, 4.20 mmol), N,N-diisopropylethylamine (0.85 mL, 4.90 mmol) and 2-furaldehyde (0.32 mL, 3.85 mmol) in CH}_2Cl_2 (15 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 20-30% ethyl acetate/petrol) the title compound \text{syn-560 (0.162 g, 0.68 mmol) in 19% yield as a pale yellow solid, mp 77-79°C; } \nu_{\text{max}} (KBr disc)/cm^{-1} 3399 (br, OH), 1773 (C=O)_{ox}, 1681 (C=O)_{am}, 1506 (C=C)_{ar}; \delta_t (300MHz, CDCl_3, Me_4Si) 1.12 (3H, d, } J 7.0, \text{ CH}_3), 2.96 (1H, d, } J 3.5, \text{ OH), 3.82-3.90 (2H, m, CH}_2N), 4.07 (1H, qd, } J 7.0, 4.5, \text{ CHCH}_3), 4.23-4.30 (2H, m, CH}_2O), 4.95 (1H, app t, } J 4.0, \text{ CHOH), 6.15-6.20 (2H, m, fur-H), 7.21 (1H, dd, } J 1.7, 0.8, \text{ fur-H); } \delta_c (\text{CDCl}_3) 12.2, 42.6, 43.0, 62.4, 69.1, 107.1, 110.6, 142.3, 154.4, 176.6; m/z (EI^+) 239 (44, M^+), 143 (42, M^+-CHOHfur), 84 (100%); (Found (ES^+) MH^+ 240.0867 C_{11}H_{14}NO_5 requires 240.0866) and the \text{anti-aldolate 561 (0.032 g, 0.13 mmol) in 4% yield as a colourless oil, } \nu_{\text{max}} (\text{neat})/cm^{-1} 3459 (br, OH), 1776 (C=O)_{ox}, 1693 (C=O)_{am}, 1526 (C=C)_{ar}; \delta_t (300MHz, CDCl_3, Me_4Si) 1.03 (3H, d, } J 7.0, \text{ CH}_3), 3.11 (1H, br s, } O_H), 3.98 (2H, m, CH}_2N), 4.30 (1H, dq, } J 8.5, 7.0, \text{ CHCH}_3), 4.36 (2H, app t, } J 8.0, \text{ CH}_2O), 4.76 (1H, d, } J 8.5, \text{ CHOH), 6.25-6.28 (2H, m, fur-H), 7.32-7.33 (1H, m, fur-H); \delta_c (\text{CDCl}_3) 14.9, 42.8, 43.1, 62.5, 70.6, 108.1, 110.6, 142.8, 153.9, 154.5, 176.5; m/z (EI^+) 239 (17, M^+), 143 (100, M^+-CHOHfur); (Found (ES^+) MH^+ 240.0867 C_{11}H_{14}NO_5 requires 240.0866).
\]

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anti-3-[3-(2-Furyl)-3-hydroxy-2-methylpropanoyl]-1,3-oxazolidin-2-one 561

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{H} & \quad \text{O} \\
\text{anti-561} & \quad \text{O} & \quad \text{O} & \quad \text{N} \\
\text{anti} & \quad \text{561} & \quad \text{O} & \quad \text{OH} \\
\text{f} & \quad \text{3} & \quad \text{3} & \quad \text{Hydroxy-2-methylpropanoyl} \\
\text{anti} & \quad \text{561} & \quad \text{O} & \quad \text{OH}
\end{align*}
\]

Reaction of 3-propionyl-1,3-oxazolidin-2-one 457 (0.500 g, 3.50 mmol) with magnesium chloride (0.033 g, 0.35 mmol), triethylamine (0.97 mL, 6.99 mmol), sodium hexafluoroantimonate (0.271 g, 1.05 mmol), 2-furaldehyde (0.35 mL, 4.19 mmol) and trimethylsilyl chloride (0.67 mL, 5.24 mmol) in ethyl acetate (7 mL), according to general protocol I, afforded after purification through silica gel chromatography (20% ethyl acetate/petrol) the title compound anti-561 (0.639 g, 2.67 mmol) in 77% yield as a colourless oil. Spectroscopic data were consistent with the spectroscopic data reported in the previous paragraph.

syn-3-[3-Hydroxy-2-methyl-3-(2-pyridinyl)propanoyl]-1,3-oxazolidin-2-one 564

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{OH} & \quad \text{O} \\
\text{syn-564} & \quad \text{syn} & \quad \text{564} & \quad \text{O} & \quad \text{OH} \\
\text{syn} & \quad \text{564} & \quad \text{O} & \quad \text{OH}
\end{align*}
\]

Reaction of 3-propionyl-1,3-oxazolidin-2-one 457 (0.480 g, 3.36 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (8.06 mL, 4.02 mmol), \(N,N\)-diisopropylethylamine (0.82 mL, 4.70 mmol) and 2-pyridinecarboxaldehyde (0.35 mL, 3.70 mmol) in CH\(_2\)Cl\(_2\) (15 mL), according to general protocol G, afforded after purification through alumina gel chromatography (gradient, 40-100% ethyl acetate/petrol) the title compound syn-564 (0.225 g, 0.90 mmol) in 27% yield as a yellow oil, \(\nu_{\text{max}} \text{ (neat)/cm}^{-1}\) 3544 (OH), 1772 (C=O)\(_{\text{ox}}\), 1700 (C=O)\(_{\text{am}}\), 1593 (C=C)\(_{\text{ar}}\); \(\delta_H \text{ (300MHz, CDCl}_3, \text{Me}_2\text{Si)}\) 0.87 (3H, d, J 7.0, CH\(_3\)), 4.04 (2H, app t, J 8.0, CH\(_2\)N), 4.06 (1H, qd, J 7.0, 2.5, CHCH\(_2\)), 4.35-4.43 (2H, m, CH\(_2\)O), 5.19 (1H, d, J 2.5, CHO), 7.14-7.20 (1H, m, Pyr-H), 7.49 (1H, d, J 8.0, Pyr-H), 7.66 (1H, app dt, J 8.0, 1.6, Pyr-H), 8.47 (1H, d, J 5.0, Pyr-H); \(\delta_C \text{ (CDCl}_3\) 9.1, 43.3, 44.9, 62.6, 72.5, 121.3, 123.0, 137.4, 148.2, 154.0, 159.3, 175.3; \(m/z \) (Cl\(^+\), iso-butane) 251 (32, MH\(^+\)), 108 (100%); (Found (ES\(^+\)) MH\(^+\) 251.1029 C\(_{12}\)H\(_{15}\)N\(_2\)O\(_4\) requires 251.1026).
**Experimental**

*.syn-3-[3-Hydroxy-3-(1H-indol-3-yl)-2-methylpropanoyl]-1,3-oxazolidin-2-one 568*

![syn-568](image)

Reaction of 3-propionyl-1,3-oxazolidin-2-one 457 (0.485 g, 3.39 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (8.39 mL, 4.19 mmol), N,N-diisopropylethylamine (0.85 mL, 4.90 mmol) and 3-indolecarboxaldehyde (0.558 g, 3.84 mmol) pre-dissolved in 10 mL of THF, according to general protocol G, afforded after recrystallisation from ethyl acetate the title compound syn-568 (0.450 g, 1.56 mmol) in 46% yield as a white solid, *mp 147-149°C; νmax (KBr disc)/cm⁻¹ 3454 (s, indole N-H), 3307 (s, OH), 1778 (C=O)ox, 1078 (C=O)am; δH (300MHz, CD3COCD3, Me4Si) 1.21 (3H, d, J 7.7, C/H3), 3.76 (1H, d, J 4.5, OH), 4.21 (1H, app dt, J 9.0, 7.5, CH3H3O), 4.35-4.45 (2H, m, CHCH3, CH3H3O), 5.36 (1H, app t, J 5.0, CHO), 6.99 (1H, ddd, J 8.0, 7.0, 1.1, Ph-H), 7.08 (1H, ddd, J 8.0, 7.0, 1.1, Ph-H), 7.27 (1H, d, J 1.8, CHNH), 7.37 (1H, d, J 8.0, Ph-H), 7.78 (1H, d, J 8.0, Ph-H), 10.06 (1H, br s, NHind); δC (CDCl3) 13.1, 44.1, 45.0, 63.4, 9.8, 112.4, 119.0, 119.9, 120.8, 122.5, 123.7, 127.3, 138.1, 154.8, 176.8; m/z (EI⁺) 288 (41, M⁺), 270 (39, M⁺-H2O), 227 (100%); (Found (ES⁺) M+NH4⁺ 306.1453 C15H20N3O4 requires 306.1448).

*syn-3-[2-(Benzyloxy)-3-hydroxypentanoyl]-1,3-oxazolidin-2-one 572 and anti-3-[2-(benzyloxy)-3-hydroxypentanoyl]-1,3-oxazolidin-2-one 575*

![syn-572](image)

![anti-575](image)

Reaction of 3-[2-(benzyloxy)acetyl]-1,3-oxazolidin-2-one 571 (0.300 g, 1.28 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (3.06 mL, 1.53 mmol), N,N-diisopropylethylamine (0.31 mL, 1.79 mmol) and propionaldehyde (0.10 mL, 1.41 mmol) in CH2Cl2 (6 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 20-40% ethyl acetate/petrol) the title compound syn-572 (0.187 g, 0.66 mmol) in 52% yield as a white solid, mp 93-95°C; νmax (KBr disc)/cm⁻¹ 3509 (s, OH), 1773 (C=O)ox, 1703 (C=O)am, 1499 (C=C)ar; δH (300MHz, CDCl3, Me4Si)
0.87 (3H, t, J 7.5, CH₂CH₃), 1.53-1.66 (2H, m, CH₂CH₃), 2.15 (1H, br s, OH), 3.77 (1H, td, J 7.0, 2.5, CH₃OH), 3.95 (2H, app t, J 8.0, CH₂N), 4.36 (2H, app t, J 8.0, CH₂O), 4.38 (1H, d, J 11.0, OCH₃H₃Ph), 4.64 (1H, d, J 11.0, OCH₃H₃Ph), 5.06 (1H, d, J 2.5, CHOCH₂Ph), 7.22-7.31 (m, 5H, Ph-H); δC (CDCl₃) 10.4, 27.5, 42.9, 63.2, 73.3, 74.3, 79.3, 128.5, 128.8 (4C), 137.5, 153.9, 171.6; m/z (CI⁺, NH₃) 311 (11, MSfH₄ + ), 294 (10, MH⁺), 105 (100%); (Found (ES⁺) MH⁺ 294.1339 C₅H₂₀N₅ requires 294.1336), and the title compound anti-585 (0.032 g, 0.13 mmol) in 4% yield as a white solid, mp 96-97°C; v_max (KBr disc)/cm⁻¹ 3440 (s, OH), 1785 (C=O) ox, 1719 (C=O) am; δH (300MHz, CDCl₃, Me₄Si) 0.92 (3H, t, J 7.5, CH₂CH₃), 1.45 (1H, dqd, J 14.0, 8.5, 7.5, CH₃H₃Ph), 1.73 (1H, dqd, J 14.0, 7.5, 3.0, CH₃H₃Ph), 2.08 (1H, d, J 9.0, OMe), 3.66-3.74 (1H, m, CHOH), 3.90 (1H, ddd, J 11.0, 9.0, 7.0, CH₃H₃N), 3.78 (1H, ddd, J 11.0, 9.0, 7.0, CH₃H₃N), 4.26 (1H, app dt, J 9.0, 7.0, CH₃H₃O), 4.33 (1H, app dt, J 9.0, 7.0, CH₃H₃O), 4.49 (2H, s, CH₂Ph), 5.12 (1H, d, J 7.0, CHOCH₂Ph), 7.22-7.30 (5H, m, Ph-H); δC (CDCl₃) 9.9, 27.0, 42.9, 63.0, 73.6, 74.6, 79.5, 128.5, 128.7, 129.0, 137.5, 154.4, 172.7; m/z (EI⁺) 294 (2, MH⁺), 217 (32, MH⁺-Ph), 187 (100%, MH⁺-PhCHO₂); (Found (ES⁺) MH⁺ 294.1340 C₅H₂₀N₅ requires 294.1336).

**syn-3-(2-Bromo-3-hydroxypentanoyl)-1,3-oxazolidin-2-one 581**

![syn-581](image)

Reaction of 3-(2-bromoacetyl)-1,3-oxazolidin-2-one 580 (1.000 g, 4.81 mmol) with a 0.5M solution of 9-BBN·OTf in hexanes (11.54 mL, 5.77 mmol), N,N-diisopropylethylamine (1.17 mL, 6.73 mmol) and propionaldehyde (0.38 mL, 5.29 mmol) in Et₂O (25 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 20-30% ethyl acetate/petrol) the title compound syn-581 (0.468 g, 1.76 mmol) in 37% yield as a colourless oil, v_max (neat)/cm⁻¹ 3485 (br, OH), 1778 (C=O) ox, 1703 (C=O) am, 702 (s, C-Br); δH (300MHz, CDCl₃, Me₄Si) 0.94 (3H, t, J 7.5, CH₂CH₃), 1.44-1.71 (2H, m, CH₂CH₃), 3.12 (1H, br s, OMe), 3.73-3.78 (1H, m, CHOH), 4.00-4.05 (2H, m, CH₂N), 4.40-4.45 (2H, m, CH₂O), 5.63 (1H, d, J 3.0, CHBr); δC (CDCl₃) 10.2, 27.9, 43.1, 49.7, 62.7, 72.2, 152.9, 169.9; m/z (Cl⁺, iso-butane) 266-268 (58, M⁺), 248-250 (100, M⁺-OH), 207-209 (17, M⁺-CHOHCH₂CH₃), 186 (47%, M⁺-Br); (Found (ES⁺) MH⁺ 266.0025 C₅H₁₃NO₄ requires 266.0022).
**anti-3-(2-Azido-3-hydroxypentanoyl)-1,3-oxazolidin-2-one 587**

![Structure](image)

Sodium azide (0.070 g, 1.10 mmol) was added to a stirred solution of syn-aldolate 581 (0.058 mg, 0.22 mmol) in acetone (2 ml). Reaction mixture was refluxed for 3 hours and filtered to remove salts. The solvent was removed in vacuo to afford the title compound anti-587 (0.039 g, 0.17 mmol) in 78% yield as a mixture of diastereoisomers (anti:syn, 83:17), $v_{\text{max}}$ (neat)/cm$^{-1}$ 3475 (br, OH), 2108 (N=N=N), 1778 (C=O)$_{\text{ox}}$, 1703 (C=O)$_{\text{am}}$, 1668 (C=N); $\delta_H$ (300MHz, CDCl$_3$, Me$_4$Si) 0.99 (3H, t, $J$ 7.5, CH$_2$CH$_3$), 1.43-1.85 (2H, m, CH$_2$CH$_3$), 2.40 (1H, d, $J$ 7.0, OH), 3.78-3.88 (1H, m, CHOH), 4.04 (2H, app t, $J$ 8.0, CH$_2$N$_3$), 4.43 (2H, app t, $J$ 8.0, CH$_2$O), 4.94 (1H, d, $J$ 8.0, CHN$_3$, anti-isomer), 5.00 (1H, d, $J$ 2.3, CHN$_3$, syn-isomer); $\delta_C$ (CDCl$_3$) 8.3, 25.8, 41.7, 61.5, 61.6, 72.4, 152.7, 169.1; $m/z$ (CI$^+$, NH$_3$) 246 (100, MNH$_4$$^+$), 229 (3, NH$_3$), 187 (59%, MH$^+$.N$_3$); (Found (ES$^+$) MNH$_4$$^+$ 246.1195 C$_8$H$_{16}$N$_3$O$_4$O$_2$ requires 246.1197).

**syn-3-(3-Hydroxy-2-phenylpentanoyl)-1,3-oxazolidin-2-one 591**

![Structure](image)

Reaction of 3-(2-phenylacetyl)-1,3-oxazolidin-2-one 459 (0.994 g, 4.85 mmol) with a 1.0M solution of Bu$_2$BOTf in CH$_2$Cl$_2$ (5.86 mL, 5.86 mmol), N,N-diisopropylethylamine (1.20 mL, 6.83 mmol) and propionaldehyde (0.39 mL, 5.37 mmol) in CH$_2$Cl$_2$ (20 mL), according to general protocol F, afforded after purification through silica gel chromatography (25% ethyl acetate/petrol) the title compound syn-591 (0.464 g, 1.76 mmol) in 37% yield as a colourless oil, $v_{\text{max}}$ (neat)/cm$^{-1}$ 3519 (br, OH), 2171 (C=O)$_{\text{ox}}$, 1694 (C=O)$_{\text{am}}$, 1601 (C=C)$_{\text{ar}}$, 1583 (C=C)$_{\text{ar}}$; $\delta_H$ (300MHz, CDCl$_3$, Me$_4$Si) 0.99 (3H, t, $J$ 7.5, CH$_2$CH$_3$), 1.35-1.48 (2H, m, CH$_2$CH$_3$), 2.70 (1H, d, $J$ 2.7, OH), 3.92 (1H, ddd, $J$ 11.0, 9.5, 6.5, CH$_3$H$_2$N), 4.06 (1H, ddd, $J$ 11.0, 9.5, 7.0, CH$_3$H$_2$N), 4.11-4.17 (1H, m, CH$_2$OH), 4.29 (1H, app dt, $J$ 9.5, 7.0, CH$_3$H$_2$O), 4.38 (1H, app dt, $J$ 9.5, 6.5, CH$_3$H$_2$O), 5.04 (1H, d, $J$ 5.5, CHPh), 7.26-7.44 (5H, m, Ph-H); $\delta_C$ (CDCl$_3$) 10.5, 27.6, 42.9, 53.5, 62.0, 74.0,
128.1, 128.7, 130.3, 134.2, 153.0, 174.2; m/z (Cl\(^{+}\), NH\(_{3}\)) 281 (20, MNH\(_{4}\)^{+}), 264 (19, MH\(^{+}\)), 223 (100%); (Found (ES\(^{+}\)) MH\(^{+}\) 264.1227 C\(_{14}\)H\(_{18}\)NO\(_{4}\) requires 264.1230).

**syn-3-[3-Hydroxy-2-(4-methoxyphenyl)pentanoyl]-1,3-oxazolidin-2-one 594**

![Syn-594](image)

Reaction of 3-[2-(4-methoxyphenyl)acetyl]-1,3-oxazolidin-2-one 593 (0.300 g, 1.28 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (3.06 mL, 1.53 mmol), N,N-diisopropylethylamine (0.31 mL, 1.79 mmol) and propionaldehyde (0.10 mL, 1.41 mmol) in CH\(_{2}\)Cl\(_{2}\) (5 mL), according to general protocol G, afforded after purification through silica gel chromatography (gradient, 20-40% ethyl acetate/petrol) the title compound syn-594 (0.288 g, 0.98 mmol) in 77% yield as a colourless oil, \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 3504 (br, NH, OH), 2837 (C-H)\(_{\text{MeO}}\), 1773 (C=O)\(_{\text{ox}}\), 1683 (C=O)\(_{\text{ar}}\), 1609 (C=C)\(_{\text{ar}}\), 1507 (C=C)\(_{\text{ar}}\); \(\delta_{H}\) (300MHz, CDCl\(_{3}\), Me\(_{4}\)Si) 0.91 (3H, t, J 7.5, CH\(_{2}\)CH\(_{3}\)), 1.23-1.37 (1H, m, CH\(_{3}\)H\(_{5}\)CH\(_{3}\)), 1.39 (1H, dqq, J 14.0, 7.5, 4.5, CH\(_{3}\)H\(_{5}\)CH\(_{3}\)), 2.52 (1H, br s, OH), 3.71 (3H, s, ArOCH\(_{3}\)), 3.83 (1H, ddd, J 11.0, 9.0, 6.5, CH\(_{3}\)H\(_{5}\)N), 3.96 (1H, ddd, J 11.0, 9.0, 7.0, CH\(_{3}\)H\(_{5}\)N), 4.05 (1H, ddd, J 8.0, 5.5, 4.5, CHO\(_{3}\)), 4.20 (1H, app dt, J 9.0, 7.0, CH\(_{3}\)H\(_{5}\)O), 4.29 (1H, app dt, J 9.0, 6.5, CH\(_{3}\)H\(_{5}\)O), 4.89 (1H, d, J 5.5, CHAr), 6.78 (2H, d, J 9.0, Ar-H), 7.26 (2H, d, J 9.0, Ar-H); \(\delta_{C}\) (CDCl\(_{3}\)) 10.6, 27.7, 43.0, 52.8, 55.6, 62.1, 74.0, 114.3, 126.3, 131.5, 153.1, 159.6, 174.6; m/z (Cl\(^{+}\), NH\(_{3}\)) 311 (13, M\(_{2}\)NH\(_{4}\)^{+}), 294 (15, MH\(^{+}\)), 105.1 (100%); (Found (ES\(^{+}\)) MH\(^{+}\) 294.1334 C\(_{15}\)H\(_{20}\)NO\(_{5}\) requires 294.1336).
Experimental

(4S)-4-Benzyl-3-[(2S,3S)-3-hydroxy-2-methyl-3-phenylpropanoyl]-1,3-oxazolidin-2-one

Reaction of (4S)-4-benzyl-3-(3-methylbutanoyl)-1,3-oxazolidin-2-one 472 (0.700 g, 2.68 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (7.00 mL, 3.50 mmol), N,N-diisopropylethylamine (0.64 mL, 3.66 mmol) and benzaldehyde (0.3 mL, 2.95 mmol) in CH$_2$Cl$_2$ (15 mL), according to general protocol G, afforded after purification through silica gel chromatography (10% ethyl acetate/petrol) the title compound syn-600 (0.634 g, 1.73 mmol) in 65% yield as a colourless oil, $\alpha_R^{25'}$ +67.2 (c 2.84, CH$_2$Cl$_2$); $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3471 (br s, OH), 1779 (C=O)$_{\text{am}}$, 1693 (C=O)$_{\text{ar}}$, 1493 (C=C)$_{\text{ar}}$; $\delta_H$ (300MHz, CDCl$_3$, Me$_4$Si) 1.09 (3H, d, J 7.0, CH(CH$_3$)$_2$), 1.16 (3H, d, J 7.0, CH(CH$_3$)$_2$), 2.30 (1H, d, J 3.5, OH), 2.42 (1H, septet of d, J 7.0, 5.5, CH(CH$_3$)$_2$), 2.56 (1H, dd, J 13.0, 10.5, CH$_2$($\rho$Ph)), 3.24 (1H, dd, J 13.0, 3.5, CH$_3$H$_2$Ph), 3.59 (1H, app t, J 8.5, CH$_3$H$_2$O), 3.92 (1H, dd, J 9.0, 2.3, CH$_3$H$_2$O), 4.19-4.27 (1H, m, CH$_2$N), 4.46 (1H, dd, J 8.5, 5.5, CH$_3$Pr), 5.00 (1H, dd, J 8.5, 3.5, CHO$_2$H), 7.16-7.40 (10H, m, Ph-$\eta$); $\delta_C$ (CDCl$_3$) 19.6, 21.3, 28.9, 38.5, 54.8, 55.9, 66.0, 74.8, 127.1, 127.7, 128.4, 128.7, 129.3, 129.7, 135.7, 142.6, 153.5, 174.0; $m/z$ (CI$^+$, NH$_3$) 385 (17, MNH$_4^+$), 368 (8, MH$^+$), 279.2 (100%); (Found (ES$^+$) MH$^+$ 368.1858 C$_{22}$H$_{26}$NO$_4$ requires 368.1862).
Experimental

\textit{anti-(4S)-4-Benzyl-3-\{(2S)-2-\[(R)-hydroxy(phenyl)methyl\]-3-methylbutanoyl\}-1,3-oxazolidin-2-one 604}

Reaction of \((4S)-4\text{-benzyl-3-\{(2S,3S)-3-hydroxy-2-methyl-3-phenylpropanoyl\}-1,3-oxazolidin-2-one \textit{syn-600} (0.100 g, 0.27 mmol) with a 1.0M solution of \(\text{Et}_2\text{Zn}\) in toluene (0.03 mL, 0.03 mmol) in \(\text{CH}_2\text{Cl}_2\) (2mL), according to general protocol J, gave a mixture of \(N\)-acyl oxazolidin-2-one \textit{472} (20%), \textit{syn-aldolate 600} (< 10%) and the title compound \textit{604} (70%). The crude mixture was purified by silica gel chromatography (gradient, 10-40% ethyl acetate/petrol) to afford the title compound \textit{anti-604} (0.040 g, 0.11 mmol) in 40% yield and > 95% d.e. as a colourless oil, \([\alpha]_D^{22}+104\) (c 1.61 in \(\text{CH}_2\text{Cl}_2\)); \(\nu_{\max} \text{(neat)/cm}^{-1}\) 3501 (br, OH), 1779 (C=O), 1699 (C=O), 1604 (C=C), 1495 (C=C), \(\delta_{s}\) (300MHz, \(\text{CDCl}_3, \text{Me}_4\text{Si}\)) 1.03 (3H, d, \(J \text{ 7.0, CH}_3\)), 1.20 (3H, d, \(J \text{ 7.0, CH}_3\)), 2.33 (1H, d of septets, \(J \text{ 9.5, 7.0, CH(CH}_3)_2\)), 2.58 (1H, dd, \(J \text{ 13.5, 10.2, CH}_4\text{H}_3\text{Ph}\)), 3.22 (1H, dd, \(J \text{ 13.5, 3.5, CH}_4\text{H}_3\text{Ph}\)), 3.45 (1H, app t, \(J \text{ 8.1, CH}_4\text{H}_3\text{OH}\)), 3.53 (1H, d, \(J \text{ 9.5, OH}\)), 3.88 (1H, app dd, \(J \text{ 9.0, 2.0, CH}_4\text{H}_3\text{OH}\)), 4.17-4.25 (1H, m, \(\text{CH}_2\text{N}\)), 4.22 (1H, dd, \(J \text{ 9.5, 4.5, CH}^\text{Pr}\)), 5.08 (1H, dd, \(J \text{ 9.5, 4.5, CHPh}\)), 7.16-7.31 (10H, m, Ph-H); \(\delta_c\) (\(\text{CDCl}_3\)) 20.5, 21.1, 28.8, 38.3, 55.6, 55.9, 66.1, 72.8, 125.6, 127.7, 127.7, 128.6, 129.3, 129.7, 135.6, 143.0, 153.2, 176.6; \(m/z\) (CI+\(\text{NH}_3\)) 385 (7, \(\text{M+NH}_3^+\)), 368 (11, \(\text{M}^+\)), 324 (5, \(\text{M}^+-\text{CO}_2\)), 195.1 (100%); (Found (ES+) \(\text{M}^+\) 368.1857 \(\text{C}_{22}\text{H}_{26}\text{NO}_4\) requires 368.1862).

\textit{syn-3-\{2-\[Hydroxy(4-nitrophenyl)methyl\]-3-methylbutanoyl\}-1,3-oxazolidin-2-one 609}

Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one \textit{458} (0.297 g, 1.74 mmol) with a 0.5M solution of 9-BBN.OTf in hexanes (4.21 mL, 2.11 mmol), \(N,N\)-diisopropylethylamine (0.40 mL, 2.28 mmol) and \(p\)-nitrobenzaldehyde (292 mg, 1.93 mmol) in \(\text{CH}_2\text{Cl}_2\) (10 mL), according to general protocol G, afforded after purification...
through silica gel chromatography (20% ethyl acetate/petrol) the title compound syn-613 (0.393 g, 1.22 mmol) in 70% yield as a pale yellow solid, mp 108-110°C; \( \nu_{\text{max}} \) (KBr disc)/cm\(^{-1}\) 3408 (s, OH), 1744 (C=O)\(_{\text{ox}}\), 1691 (C=O)\(_{\text{am}}\), 1523 (N=O)\(_{\text{con}}\), 1352 (N=O)\(_{\text{con}}\); \( \delta \) (300MHz, CDCl\(_3\), Me\(_4\)Si) 0.93 (3H, d, J 7.0, CH(CH\(_3\))\(_2\)), 1.02 (3H, d, J 7.0, CH(CH\(_3\))\(_2\)), 2.27 (1H, app octet, J 7.0, CH(CH\(_3\))\(_2\)), 2.93 (1H, d, J 2.6, OH), 3.81 (1H, ddd, J 11.0, 9.0, 8.0, CH\(_4\)H\(_8\)N), 3.97 (1H, ddd, J 11.0, 9.0, 6.0, CH\(_4\)H\(_8\)N), 4.32 (1H, app dt, J 9.0, 6.0, CH\(_4\)H\(_8\)O), 4.37 (1H, app dt, J 9.0, 8.0, CH\(_4\)H\(_8\)O), 4.46 (1H, app t, J 6.0, CH\(_3\)Pr), 5.18 (1H, dd, J 6.0, 2.6, CHOH), 7.60 (2H, d, J 9.0, Ar-H), 8.19 (2H, d, J 9.0, Ar-H); \( \delta \) (CDCl\(_3\)) 20.1, 21.4, 28.3, 42.9, 54.4, 62.1, 73.0, 123.8, 127.9, 147.7, 149.7, 153.8, 174.4; m/z (CI\(^+\), NH\(_3\)) 340 (100, MNH\(_4^+\)), 323 (10%, MH\(^+\)); (Found (ES\(^+\)) MNH\(_4^+\) 340.1503 C\(_{15}\)H\(_{22}\)N\(_3\)O\(_6\) requires 340.1503); (Found: C, 55.5; H, 5.50; N, 8.47. C\(_{15}\)H\(_{18}\)N\(_2\)O\(_6\) requires C, 55.9; H, 5.63; N, 8.47%).
8.4 Preparation of α,β-unsaturated amides

Procedure for the elimination reaction with KHMDS:

General protocol K

\[
\text{KHMDS} \quad \text{THF, -78°C} \rightarrow \text{HO-} \quad \text{amide (E)-631}
\]

A 0.5M solution of KHMDS in toluene (1.5 eq.) was added dropwise to a stirred solution of syn-aldolate 627 (1 eq.) in THF at -78°C under nitrogen. The reaction was stirred at -78°C for two hours. Saturated NH₄Cl was added and the reaction extracted with CH₂Cl₂ (x 3). The combined organic extracts were washed with brine, dried (MgSO₄), and concentrated in vacuo to afford α,β-unsaturated amide (E)-631.

\((E)-3\text{-Cyclohexyl-}N\text{-}(2\text{-hydroxyethyl})\text{-}2\text{-isopropyl-2-propenamide 478}\)

\[
\text{HO-} \quad \text{amide (E)-478}
\]

Reaction of syn-3-{2-[cyclohexyl(hydroxy)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one 476 (0.100 g, 0.35 mmol) with a 0.5M solution of KHMDS in toluene (1.06 mL, 0.53 mmol) in THF (2 mL), according to general protocol K, gave the title compound (E)-478 (0.075 g, 0.31 mmol) in 93% d.e. The crude product was purified for analysis by silica gel chromatography (gradient, 20-30% ethyl acetate/petrol), to afford the title compound (E)-478 (0.064 g, 0.27 mmol) in 77% yield and > 95% d.e. as a white solid, mp 84-86°C; νmax (KBr disc/cm⁻¹) 3291 (br, OH, NH), 1652 (C=O)am, 1619 (C=C), 1541 (C=O)am; δH (300MHz, CDCl₃, Me₄Si) 1.01-1.37 (6H, m, Cy-H), 1.18 (6H, d, J 7.0, CH(CH₃)₂), 1.60-1.78 (4H, m, Cy-H), 2.25-2.39 (1H, m, Cy-H), 2.83 (1H, septet, J 7.0, CH(CH₃)₂), 2.95 (1H, t, J 4.5, OH), 3.44 (2H, app q, J 5.5, 5.0, NH₂), 3.74 (2H, app q, J 5.5, 5.0, CH₂OH), 5.59 (1H, d, J 10.0, CH=CH), 6.08 (1H, br s, NH); δC (CDCl₃) 22.1 (2 C), 26.1 (2 C), 26.2, 28.6, 33.3 (2 C), 37.0, 42.9, 63.3, 137.9, 142.0, 173.1; m/z (EI⁺) 239 (65, M⁺), 224 (85, M⁺-CH₃), 179 (68%, M⁺-HOCH₂CH₂NH⁺); (Found (EI⁺) M⁺ 239.1886 C₁₄H₂₅NO₂ requires 239.1885)
(E)-N-(2-Hydroxyethyl)-2-methyl-2-pentenamide 484

Reaction of syn-3-(3-hydroxy-2-methylpentanoyl)-1,3-oxazolidin-2-one 479 (0.050 g, 0.25 mmol) with a 0.5M solution of KHMDS in toluene (0.75 mL, 0.37 mmol) in THF (3 mL), according to general protocol K, afforded the title compound (E)-484 (0.026 g, 0.17 mmol) in 67% yield and > 95% d.e. as a white solid of low melting point, \( \nu_{\text{max}} (\text{KBr disc})/\text{cm}^{-1} \)

\[
\begin{align*}
\text{3405 (br, OH, NH), 1701 (C=O)_{\text{am}}, 1615 (C=C), 1538 (C=O)_{\text{am}}; } & \delta_{\text{H}} (300\text{MHz, CDCl}_3, Me_4 Si) \ 1.04 (3\text{H, t, } J 7.5, \text{ CH}_2\text{CH}_3), 1.85 (3\text{H, s, } CH_3), 2.17 (2\text{H, app pentet, } J 7.5, \text{ CH}_2\text{CH}_3), 2.86 (1\text{H, br s, } OH), 3.50 (2\text{H, app q, } J 6.0, 5.0, \text{ CH}_2\text{NH}), 3.77 (2\text{H, app t, } J 5.0, \text{ CH}_2\text{OH}), 6.19 (1\text{H, s, } NH), 6.38 (1\text{H, t, } J 7.5, \text{ HC=C}); & \delta_{\text{C}} (\text{CDCl}_3) 11.5, 12.2, 20.6, 41.7, 61.4, 128.7, 137.5, 169.7; m/z (Cl\text{+}, NH_3) 158 (100%, MH\text{+}); (\text{Found (ES) } MH\text{+} 158.1179) C_8H_{16}NO_2 \text{ requires 158.1176).}
\end{align*}
\]

(E)-N-(2-Hydroxyethyl)-2-isopropyl-2-pentenamide 485

Reaction of syn-3-(3-hydroxy-2-methylpentanoyl)-1,3-oxazolidin-2-one 480 (0.100 g, 0.44 mmol) with a 0.5M solution of KHMDS in toluene (1.30 mL, 0.65 mmol) in THF (3 mL), according to general protocol K, afforded the title compound (E)-485 (0.080 g, 0.43 mmol) in 99% yield and > 95% d.e. as a colourless oil, \( \nu_{\text{max}} (\text{neat})/\text{cm}^{-1} \)

\[
\begin{align*}
\text{3338 (br, OH, NH), 1653 (C=O)_{\text{am}}, 1538 (C=O)_{\text{am}}; } & \delta_{\text{H}} (300\text{MHz, CDCl}_3, Me_4 Si) 1.03 (3\text{H, t, } J 7.5, \text{ CH}_2\text{CH}_3), 1.16 (6\text{H, d, } J 7.0, \text{ CH(CH}_3)_2), 2.14 (2\text{H, app pentet, } J 7.5, \text{ CH}_2\text{CH}_3), 2.81 (1\text{H, septet, } J 7.0, \text{ CH(CH}_3)_2), 3.43 (2\text{H, app q, } J 5.5, 4.5, \text{ CH}_2\text{NH}), 3.50 (1\text{H, br s, } OH), 3.73 (2\text{H, app t, } J 5.0, \text{ CH}_2\text{OH}), 5.77 (1\text{H, t, } J 7.5, \text{ HC=C}); & \delta_{\text{C}} (\text{CDCl}_3) 13.2, 20.1, 20.7 (2\text{C}), 27.2, 41.7, 61.8, 133.0, 142.2, 171.9; m/z (Cl\text{+}, iso-butane) 186 (88, MH\text{+}), 185 (32, MH\text{+}), 125 (100%, MH\text{+}-HOCH_2CH_2NH); (\text{Found (FAB\text{+}) } MH\text{+} 186.1495) C_{10}H_{20}NO_2 \text{ requires 186.1494).}
\end{align*}
\]
Experimental

(E)-N-(2-Hydroxyethyl)-2-methyl-3-phenyl-2-propenamide 486

Reaction of syn-3-(3-hydroxy-2-methyl-3-phenylpropanoyl)-1,3-oxazolidin-2-one 467 (0.200 g, 0.80 mmol) with a 0.5M solution of KHMDS in toluene (2.41 mL, 1.20 mmol) in THF (4 mL), according to general protocol K, afforded the title compound (E)-486 (0.143 g, 0.70 mmol) in 91% yield and > 95% d.e. as a white solid, mp 101-103°C; \( \nu_{\text{max}} \) (KBr disc)/cm\(^{-1}\) 3284 (br, OH, NH), 1644 (C=O)\(_{\text{am}}\), 1620 (C=C), 1575 (C=O)\(_{\text{am}}\); \( \delta_{\text{H}} \) (300MHz, CDCl\(_3\), Me\(_4\)Si) 2.04 (3H, d, \( J \) 1.4, CHC(CH\(_3\))), 3.08 (1H, br s, OH), 3.46-3.51 (2H, m, CH\(_2\)N), 3.74 (2H, app t, \( J \)5.0, CH\(_2\)O), 6.48 (1H, br s, NH), 7.19 (1H, s, HC=C), 7.20-7.33 (5H, m, Ar-H); \( \delta_{\text{C}} \) (CDCl\(_3\)) 14.6, 43.3, 62.8, 128.3, 128.7, 129.7, 131.7, 135.0, 136.3, 171.2; m/z (Cl\(^+\), NH\(_3\)) 206 (100%, MH\(^+\)); (Found (ES\(^+\)) MH\(^+\) 206.1177 C\(_{12}\)H\(_{16}\)NO\(_2\) requires 206.1176).

(E)-N-(2-Hydroxyethyl)-2-isopropyl-3-phenyl-2-propenamide 487

Reaction of syn-3-{2-[hydroxy(phenyl)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one 481 (0.085 g, 0.31 mmol) with a 0.5M solution of KHMDS in toluene (1.08 mL, 0.54 mmol) in THF (3 mL), according to general protocol K, afforded title compound (E)-487 (0.068 g, 0.29 mmol) in 92% d.e. The crude product was purified for analysis by silica gel chromatography (40% ethyl acetate/petrol) to afford the title compound (E)-487 (0.046 g, 0.20 mmol) in 69% yield and > 95% d.e. as a white solid, mp 101-103°C; \( \nu_{\text{max}} \) (KBr disc)/cm\(^{-1}\) 3317 (s, OH, NH), 1641 (C=O)\(_{\text{am}}\), 1612 (C=C), 1538 (C=O)\(_{\text{am}}\); \( \delta_{\text{H}} \) (300MHz, CDCl\(_3\), Me\(_4\)Si) 1.24 (6H, d, \( J \) 7.0, CH(CH\(_3\))\(_2\)), 2.95 (1H, br s, OH), 3.07 (1H, septet, \( J \) 7.0, CH(CH\(_3\))\(_2\)), 3.52 (2H, app q, \( J \) 5.5, 5.0, CH\(_2\)NH), 3.79 (2H, app t, \( J \) 5.0, CH\(_2\)OH), 6.33 (1H, br s, NH), 6.79 (1H, br s, HC=C), 7.25-7.39 (5H, m, Ph-H); \( \delta_{\text{C}} \) (CDCl\(_3\)) 21.9 (2C), 28.5, 42.8, 63.0, 128.0, 128.8, 129.1, 130.1, 136.1, 145.7, 172.4; m/z (El\(^+\)) 233 (19, M\(^+\)), 173 (48, M\(^+\)- HOCH\(_2\)CH\(_2\)NH), 145(57, M\(^+\)- HOCH\(_2\)CH\(_2\)NHC\(_2\)HCO), 91 (100%, PhCH\(_2\))\(^+\); (Found (ES\(^+\)) MH\(^+\) 234.1489 C\(_{14}\)H\(_{20}\)NO\(_2\) requires 234.1489).
(E)-N-(2-Hydroxyethyl)-2-isopropyl-3-(4-methoxyphenyl)-2-propenamide 488

Reaction of \textit{syn}-3-{2-[hydroxy(4-methoxyphenyl)methyl]-3-methylbutanoyl}]-1,3-oxazolidin-2-one 482 (0.200 g, 0.65 mmol) with a 1.0M solution of KHMDS in toluene (1.95 mL, 0.98 mmol) in THF (4 mL), according to general protocol K, gave the title compound \textit{(E)}-488 (0.155 g, 0.59 mmol) in 90% d.e. The crude product was purified for analysis by silica gel chromatography (40% ethyl acetate/petrol) to afford the title compound \textit{(E)}-488 (0.110 g, 0.42 mmol) in 64% yield and > 95% d.e. as a white solid, mp 91-93°C; $\nu_{\text{max}}$ (KBr disc)/cm$^{-1}$ 3279 (s, OH), 3064 (C=\(\equiv\)N), 2834 (C-H) MeO, 1645 (C=O)$_{\text{am}}$, 1620 (C=C), 1606 (C=C)$_{\text{am}}$, 1542 (C=O)$_{\text{am}}$, 1510 (C=C)$_{\text{ar}}$; $\delta_{\text{H}}$ (300MHz, CDCl$_3$, Me$_4$Si) 1.24 (6H, d, J 7.0, CH(CH$_3$)$_2$), 3.09 (1H, septet, J 7.0, CH(CH$_3$)$_2$), 3.18 (1H, br s, OH), 3.50 (2H, app dt, J 5.5, 5.0, CH$_2$NH), 3.75-3.85 (2H, m, CH$_2$OH), 3.82 (3H, s, ArOCH$_3$), 6.38 (1H, br s, NH), 6.73 (1H, s, CH=C), 6.89 (2H, d, J 9.0, Ar-H), 7.21 (2H, d, J 8.5, Ar-H); $\delta_{\text{C}}$ (CDCl$_3$) 21.9 (2C), 28.4, 42.8, 55.7, 62.9, 114.2, 128.5, 129.7, 130.5, 144.1, 159.4, 172.6; m/z (EI$^+$) 263 (35, M$^+$), 203 (26, M$^+$-HOCH$_2$CH$_2$NH), 84 (100%); (Found (EI$^+$) M$^+$ 263.1518 C$_{15}$H$_{21}$NO$_3$ requires 263.1521).

(\textit{E})-2-Benzyl-N-(2-hydroxyethyl)-2-decenamide 489

Reaction of \textit{syn}-3-{2-benzyl-3-hydroxydecanoyl}-1,3-oxazolidin-2-one 483 (0.135 g, 0.39 mmol) with a 0.5M solution of KHMDS in toluene (1.17 mL, 0.58 mmol) in THF (3 mL), according to general protocol K, gave the title compound \textit{(E)}-489 (0.110 g, 0.36 mmol) in 92% d.e. The crude product was purified for analysis by silica gel chromatography (60% ethyl acetate/petrol) to afford the title compound \textit{(E)}-489 (0.086 g, 0.28 mmol) in 73% yield and > 95% d.e. as a colourless oil, $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3342 (br, OH, NH), 1656 (C=O)$_{\text{am}}$, 1620 (C=C), 1537 (C=O)$_{\text{am}}$; $\delta_{\text{H}}$ (300MHz, CDCl$_3$, Me$_4$Si) 0.88 (3H, t, J 7.0, CH$_3$), 1.23-1.28 (8H, m, Alk-H), 1.39-1.46 (2H, m, CH$_2$CH$_2$CH=C), 2.21 (2H, app q, J 7.5, CH$_2$CH=C), 2.97 (1H, br s, OH), 3.33 (2H, app q, J 5.5, 5.0, CH$_2$NH), 3.57 (2H, m, CH$_2$OH), 3.69 (2H, s, CH$_2$Ph), 6.17 (1H, br t, J 5.0, NH), 6.54 (1H, t, J 7.5, HC=CCH$_3$),
7.16-7.30 (5H, m, Ph-H); δ(\text{CDCl}_3) 14.5, 23.0, 28.9, 29.3, 29.5, 32.1, 33.1, 43.1, 62.9, 126.8, 128.5, 129.1, 134.0, 139.0, 139.3, 170.5; m/z (EI⁺) 303 (10, M⁺), 243 (13, M⁺-HOCH₂CH₂NH), 91 (100%, PhCH₂⁺); (Found (ES⁺) M⁺ 304.2275 Ci₉H₉O₂ requires 304.2271).

**(2E,4E)-N-(2-Hydroxyethyl)-2-isopropyl-2,4-hexadienamide 490 and (2Z,4E)-N-(2-hydroxyethyl)-2-isopropyl-2,4-hexadienamide 491**

Reaction of syn-3-\{(E)-3-hydroxy-2-isopropyl-4-hexenoyl\}-1,3-oxazolidin-2-one 463 (0.200 g, 0.83 mmol) with a 0.5M solution of KHMDS in toluene (2.50 mL, 1.25 mmol) in THF (5 mL), according to general protocol K, gave the title compound (E,E)-490 (0.153 g, 0.78 mmol) in 40% d.e. which was purified through silica (pre-coated with silver nitrate) gel chromatography to afford the title compound (E,E)-490 (0.016 g, 0.08 mmol) in 10% yield as a pale oil, δ(300MHz, CDCl₃, Me₄Si) 1.20 (6H, d, J 7.0, CH(CH₃)₂), 1.83 (3H, dd, J 7.0, 1.5, CH=CHCH₃), 2.95 (1H, septet, J 7.0, CH(CH₃)₂), 3.20 (1H, br s, OH), 3.45 (2H, app dt, J 5.5, 4.0, CH₂NH), 3.74 (2H, app t, J 5.0, CH₂OH), 5.89 (1H, dqd, J 13.0, 7.0, 1.5, CHCH=CHCH₃), 6.21 (1H, br s, NH), 6.33 (1H, br d, J 10.5, CHCH=CHCH₃), 6.39 (1H, ddq, J 13.0, 10.5, 1.5, CHCH=CHCH₃), δ(\text{CDCl}_3) 19.0, 21.8 (2C), 28.6, 42.8, 63.0, 126.6, 130.6, 135.2, 141.0, 172.5; m/z (EI⁺) 197 (23, M⁺), 182 (33, M⁺-CH₃), 169 (38, M⁺-CH₃CH), 154 (100, M⁺-CH₃CH₂), 137 (28, M⁺-HO(CH₂)₂NH), 109 (43, M⁺-HO(CH₂)₂NHC), and the geometric isomer (Z,E)-491 (0.015 g, 0.08 mmol) in 9% yield, δ(300MHz, CDCl₃, Me₄Si) 1.08 (6H, d, J 7.0, CH(CH₃)₂), 1.77 (3H, dd, J 7.0, 1.5, CH=CHCH₃), 2.64 (1H, septet, J 7.0, CH(CH₃)₂), 3.00 (1H, br s, OH), 3.53 (2H, app dt, J 5.6, 4.6, CH₂NH), 3.78 (2H, app t, J 5.0, CH₂OH), 5.79 (1H, dq, J 15.0, 7.0, CHCH=CHCH₃), 5.99 (1H, d, J 11.0, CHCH=CHCH₃), 6.13 (1H, br s, NH), 6.28 (1H, ddq, J 15.0, 11.0, 1.5, CHCHCH₃).
(2E,4E)-N-(2-hydroxyethyl)-2-methyl-5-phenyl-2,4-pentadienamide 493

Reaction of syn-3-[(E)-3-hydroxy-2-methyl-5-phenyl-4-pentenoyl]-1,3-oxazolidin-2-one 492 (0.275 g, 1.00 mmol) with a 0.5M solution of KHMDS (3.00 mL, 1.50 mmol) in THF (5 mL), according to general protocol K, gave the title compound (E)-493 (0.223 g, 0.97 mmol) in 60% d.e. The crude product was purified for analysis by recrystallisation from hot ethyl acetate, to afford the title compound (E)-493 (0.147 g, 0.64 mmol) in 64% yield and >95% d.e. as a white solid, mp 141-142°C; \( \nu_{\text{max}}(\text{KBr disc})/\text{cm}^{-1} \) 3293 (br, OH), 3250 (br, NH), 1642 (C=O), 1585 (C=C), 1542 (C=O); \( \delta_{\text{H}} \) (300MHz, CDCl\(_3\), Me\(_4\)Si) 2.08 (3H, s, \( \gamma \)/3), 2.87 (1H, t, \( J \) 5.0, OH), 3.55 (2H, app q, \( J \) 5.5, 5.0, CH\(_2\)NH), 3.80 (2H, app q, \( J \) 5.0, 5.0, CH\(_2\)OH), 6.32 (1H, br s, NH), 6.83 (1H, d, \( J \) 15.0, CHCH=CHPh), 7.01 (1H, d, \( J \) 11.5, CHCH=CHPh), 7.10 (1H, dd, \( J \) 15.0, 11.0, CHCH=CHPh), 7.28-7.48 (5H, m, Ph-H); \( \delta_{\text{C}} \) (CDCl\(_3\)) 13.6, 43.3, 63.1, 124.0, 127.3, 128.9, 129.1, 129.9, 134.9, 137.0, 138.6, 170.5; \( m/z \) (EI\(^+\)) 231 (33, \( M^+ \)), 171 (80, MH\(^+\)-HOCH\(_2\)CH\(_2\)NH), 154 (78, \( M^+ \)- Ph), 141 (47, \( M^+ \)- PhCH), 128 (100, \( M^+ \)- PhCHCH), 115 (38%, \( M^+ \)- PhCHCHCH); (Found (ES\(^+\)) MH\(^+\) 232.1330 C\(_{14}\)H\(_{18}\)NO\(_2\) requires 232.1332).

(E)-N-(2-Hydroxyethyl)-3-[(4R)-4-isopropenyl-1-cyclohexen-1-yl]-2-methyl-2-propenamide 547

Reaction of aldolates 545 + 546 (0.100 g, 0.34 mmol) with a 0.5M solution of KHMDS in toluene (2.05 mL, 1.02 mmol) in THF (4 mL), according to general protocol K, gave the title compound (R,E)-547 in 50% d.e. The crude mixture was purified by silica gel chromatography (60% ethyl acetate/petrol) to afford the title compound (R,E)-547 (0.043 mg, 0.17 mmol) in 51% isolated yield and > 95% d.e. as a white solid, [\( \alpha \]\(_{D}\)\(^{25} \)] -72.2 (c 0.90, CH\(_2\)Cl\(_2\)); mp 67-69°C; \( \nu_{\text{max}}(\text{KBr disc})/\text{cm}^{-1} \) 3300 (br, NH), 3292 (s, OH), 1634 (C=O); 1603 (C=C), 1538 (C=O); \( \delta_{\text{H}} \) (300MHz, CDCl\(_3\), Me\(_4\)Si) 1.35-1.48 (1H, m, Cy-H), 1.68 (3H, s, H\(_2\)CC=CH\(_2\)), 1.75-1.84 (1H, m, Cy-H), 1.95 (3H, s, CH\(_3\)C=CH), 2.00-2.11 (2H, m, Cy-H), 2.16-2.24 (3H, m, Cy-H), 3.28 (1H, s, OH), 3.42 (2H, app q, \( J \) 5.5, 5.0, CH\(_2\)NH), 187
3.68 (2H, app t, J 5.0, CH₂OH), 4.67 (2H, d, J 7.0, C=CH₂), 5.76 (1H, m, C=CHCH₂), 6.33 (1H, br s, NH), 6.66 (1H, s, CH₃C=CH); δC (CDCl₃) 14.7, 21.2, 28.0, 29.4, 31.6, 40.8, 43.3, 62.9, 109.3, 128.5, 131.5, 134.6, 149.7, 171.8; m/z (EI⁺) 249 (16, M⁺), 208 (11, M⁺-CH₂CH(CH₂)), 189 (10%, M⁺-OHCH₂CH₂NH), 121 (55%, Cy⁺), 91 (100%); (Found (ES⁺) MH⁺ 250.1802 C₁₅H₂₄N₂O₂ requires 250.1802).

(2E,5S)-N-(2-hydroxyethyl)-2,5,9-trimethyl-2,8-decadienamide 551

Reaction of aldolates 549 + 550 (0.150 mg, 0.51 mmol) with a 0.5M solution of KHMDS in toluene (1.52 mL, 0.76 mmol) in THF (3 mL), according to general protocol K, gave the title compound (S,E)-551 (0.121 mg, 0.48 mmol) in 60% d.e. The crude product was purified by silica gel chromatography (60% ethyl acetate/petrol) to afford the title compound (S,E)-551 (0.071 g, 0.28 mmol) in 55% yield and > 95% d.e. as a colourless oil, [α]D²⁰ +2.7 (c 2.61, CH₂Cl₂), νmax (neat)/cm⁻¹: 3402 (br, OH, NH), 1657 (C=O) am, 1615 (C=C), 1538 (C=O) am; δH (300MHz, CDCl₃, Me₄Si) 0.90 (3H, d, J 6.5, CHCH₃), 1.12-1.27 (1H, m, CH₃H₂CH₂CH=C(CH₃)₂), 1.30-1.42 (1H, m, CH₃H₂CH₂CH₂CH=C(CH₃)₂), 1.55-1.65 (1H, m, CHCH₃), 1.60 (3H, s, CH=C(CH₃)₂), 1.68 (3H, s, CH-C(CH₃)₂), 1.85 (3H, s, CH=CCH₃), 1.90-2.05 (2H, m, CH₂CH₂CH=C(CH₃)₂), 2.10-2.19 (2H, m, CH₂CH=CHCH₃), 3.48 (2H, app q, J 5.5, 5.0, CH₂NH), 3.61 (1H, br s, OCH₂), 3.72-3.76 (2H, m, CH(CH₂)₉), 5.07 (1H, t, J 7.0, CH=C(CH₃)₂), 6.41 (1H, br s, NH), 6.44 (1H, t, J 6.5, CH=C); δC (CDCl₃) 13.2, 18.1, 20.0, 26.0, 26.1, 33.1, 36.1, 37.2, 43.1, 62.8, 124.9, 131.1, 131.8, 136.6, 171.0; m/z (EI⁺) 253 (46, M⁺), 238 (18, M⁺-CH₃), 193 (5, M⁺-HOCH₂CH₂NH), 170 (41, M⁺-CH₂CH₂C=CHCH₂CH₂), 109 (100%); (Found (ES⁺) MH⁺ 254.2112 C₁₅H₂₈N₂O₂ requires 254.2115).

(ZS)-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-N-(2-hydroxyethyl)-2-methyl-2-propenamide (S,E)-555

Reaction of aldolates 553 + 554 (0.100 g, 0.37 mmol) with a 0.5M solution of KHMDS (1.10 mL, 0.55 mmol) in THF (2 mL), according to general protocol K, gave the title
compound \((S,E)-555\) in 80% d.e. The crude mixture was purified by silica gel chromatography (70% ethyl acetate/petrol) to afford the title compound \((S,E)-555\) (0.035 g, 0.15 mmol) in 42% yield and >95% d.e. as a colourless oil, \([\alpha_d^{+4.5} (c 1.54, \text{CH}_2\text{Cl}_2)\]; 

\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 3305 (br, OH, NH), 1668 (C=O)\(\text{am}\), 1622 (C=C), 1538 (C=O)\(\text{am}\); \(\delta_H\) (300MHz, CDCl\(_3\), Me\(_4\text{Si}\)) 1.41 (3H, s, CH\(_3\)), 1.44 (3H, s, CH\(_3\)), 1.93 (3H, d, J 1.2, CH(CH\(_3\))), 3.27 (1H, s, OH), 3.47 (2H, app q, J 5.5, 5.0, CH\(_2\)NH), 3.61 (1H, app t, J 8.0, CH\(_2\)H\(_2\)OCHOCH=), 3.74 (2H, app t, J 5.0, CH\(_2\)OH), 4.15 (1H, dd, J 8.0, 6.0, CH\(_2\)H\(_2\)OCHOCH=), 4.84 (1H, app q, J 8.0, 6.5, CH\(_2\)OCHOCH=), 6.25 (1H, dq, J 8.0, 1.2, CH=C), 6.52 (1H, br s, NH); \(\delta_C\) (CDCl\(_3\)) 13.8, 26.2, 27.0, 43.0, 62.3, 69.2, 72.9, 110.1, 132.8, 135.1, 170.1; \(m/z\) (Cl\(^+\), iso-butane) 230 (98, MH\(^+\)), 214 (20, M\(^+\) - CH\(_3\)), 172 (68, M\(^+\) - (CH\(_3\))\(_2\)CO), 141 (63, M\(^+\) - HOCH\(_2\)CH\(_2\)NHCO), 88 (100%); (Found (ES\(^+\)) MH\(^+\) 230.1389 C\(_{11}\)H\(_{20}\)NO\(_4\) requires 230.1387).

Reaction of \((S,E)\)-amide 555 (0.020 g, 0.09 mmol) with a 0.5M solution of KHMDS (0.22 mL, 0.11 mmol) in THF (1 mL), according to general protocol K, afforded back the title compound \((S,E)-555\) (0.014 g, 0.06 mmol) in >95% d.e., [\(\alpha_d^{+4.5}\) (c 0.62, \text{CH}_2\text{Cl}_2)].

\((E)-3-(2-furyl)-N-(2-hydroxyethyl)-2-isopropyl-2-propenamide 558\) and \((Z)-3-(2-furyl)-N-(2-hydroxyethyl)-2-isopropyl-2-propenamide 559\)

\((E)-3-(2-furyl)-N-(2-hydroxyethyl)-2-isopropyl-2-propenamide 558\) and \((Z)-3-(2-furyl)-N-(2-hydroxyethyl)-2-isopropyl-2-propenamide 559\)

Reaction of \(\text{syn-3-\{2-[2-furyl(hydroxy)methyl]-3-methylbutanoyl\}-1,3-oxazolidin-2-one 557}\) (0.100 g, 0.37 mmol) with a 0.5M solution of KHMDS in toluene (1.12 mL, 0.56 mmol) in THF (2mL), according to general protocol K, gave the title compound \((E)-558\) with 40% d.e. The crude product was partially purified by silica gel chromatography (60% ethyl acetate/petrol) to afford the title compound \((E)-558\) (0.035 g, 0.16 mmol) in 42% yield and 60% d.e. as a yellow oil, \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 3319 (br, OH, NH), 1644 (C=C), 1538 (C=O)\(\text{am}\); \(\delta_H\) (300MHz, CDCl\(_3\), Me\(_4\text{Si}\)) 1.08 (6H, d, J 7.0, CH\(_3\)), \((Z)-559\)) 1.18 (6H, d, J 7.0, CH\(_3\)), \((E)-558\), 2.74 (1H, br s, OH)), 3.33 (1H, septet, J 7.0, CH(CH\(_3\))), 3.40 (2H, app q, J 5.5, 4.5, CH\(_2\)NH), 3.68 (2H, app t, J 5.0, CH\(_2\)OH), 6.30 (2H, d, J 1.3, fur-H), 6.38 (1H, s, NH, \((Z)-559\)), 6.52 (1H, s, NH, \((E)-558\)), 6.45 (1H, s, HC=), 7.37 (1H, app t, J 1.3, fur-H); \(\delta_C\) (CDCl\(_3\)) 21.3 (2C), 29.1, 42.7, 62.7, 112.0, 112.5, 118.2, 142.4, 143.3, 151.4, 172.0;
m/z (El+) 223 (100, M+), 163.0 (60%, M+-HOCH₂CH₂NH); (Found (ES+) MH⁺ 224.1281 C₁₂H₁₈N₃O₃ requires 224.1281).

(E)-N-(2-hydroxyethyl)-2-methyl-3-(2-furyl)-2-propenamide 562

Reaction of anti-3-[3-(2-furyl)-3-hydroxy-2-methylpropanoyl]-1,3-oxazolidin-2-one 561 (0.200 g, 0.84 mmol) with a 0.5M solution of KHMDS in toluene (2.51 mL, 1.26 mmol) in THF (5 mL), according to general protocol K, afforded after silica gel chromatography (60% ethyl acetate/petrol) the title compound (E)-562 (0.100 g, 0.51 mmol) in 61% yield and >95% d.e. as an orange oil, ν_{max} (neat)/cm⁻¹ 3376 (br, OH), 1646 (C=O) am, 1609 (C=C), 1538 (C=O) am; δ_H (300MHz, CDCl₃, Me₄Si) 2.17 (3H, d, J 1.1, CH₃), 3.05 (1H, br s, OH), 3.47 (2H, app t, J 5.0, CH₂NH), 3.71 (2H, app t, J 5.0, CH₂OH), 6.39 (1H, dd, J 3.5, 1.8, fur-CH), 6.40 (1H, br s, NH), 6.45 (1H, d, J 3.5, fur-CH), 7.12 (1H, d, J 0.9, CH=C(CH₃)), 7.41 (1H, d, J 1.6, fur-CH); δ_C (CDCl₃) 14.7, 43.3, 62.8, 112.2, 114.4, 122.7, 127.8, 143.8, 152.3, 170.7; m/z (El⁺) 195 (43, M⁺), 135 (100%, M⁺-HOCH₂CH₂NH); (Found (ES⁺) MH⁺ 196.0966 C₁₆H₁₄N₃O₃ requires 196.0968).

(E)-N-(2-hydroxyethyl)-2-methyl-3-(2-pyridinyl)-2-propenamide 565

Reaction of syn-3-[3-hydroxy-2-methyl-3-(2-pyridinyl)propanoyl]-1,3-oxazolidin-2-one 564 (0.150 g, 0.60 mmol) with a 0.5M solution of KHMDS in toluene (1.80 mL, 0.90 mmol) in THF (3 mL), according to general protocol K, gave 0.109 g of an unpurified mixture of the title compound (E)-565 (67%) in >95% d.e. and oxazolidinone 456 (33%) via retro-aldol pathway, as a brown oil, ν_{max} (neat)/cm⁻¹ 3318 (br, NH, OH), 3059 (C-H)ar, 1732, 1651 (C=O) am, 1621 (C=C), 1538 (C=O) am; δ_H (300MHz, CDCl₃, Me₄Si) 2.28 (3H, s, CH₃), 3.10 (1H, br s, OH), 3.52 (2H, app q, J 5.0, 5.0, CH₂N), 3.78 (2H, app t, J 5.0, CH₂OH), 7.02 (1H, br s, NH), 7.15-7.20 (1H, m, Pyr-H), 7.29 (1H, s, H(C=)), 7.32 (1H, d, J 7.5, Pyr-H), 7.67 (1H, app dt, J 7.5, 1.4, Pyr-H); δ_C (CDCl₃) 14.7, 43.2, 62.1, 122.7, 125.8, 132.4, 136.2, 136.8, 149.6, 155.5, 171.0; m/z (Cl⁺, iso-
butane) 207 (44, \(M^+\)), 189 (6, \(M^+-\text{OH}\)), 146 (45, \(M^+-\text{HO(CH}_2\text{)_2NH}\)), 118 (20, \(M^+-\text{CONH(CH}_2\text{)_2OH}\)), 88.0 (100%, oxazolidin-2-one+\(H^+\)).

\((Z)-2\text{-}(\text{benzyloxy})\text{-}\text{N}(2\text{-hydroxyethyl})\text{-2-pentenamide} \ 576\)

\[
\text{HO-} \quad \text{NH} \quad \text{O} \quad \text{H} \quad \text{O}
\]

\((Z)-576\)

Reaction of syn-3-[2-(benzyloxy)-3-hydroxypentanoyl]-1,3-oxazolidin-2-one 572 (0.200 g, 0.68 mmol) with a 0.5M solution of KHMDS in toluene (2.05 mL, 1.02 mmol) in THF (3 mL), according to general protocol K, gave a complex mixture of products which was purified by silica gel chromatography (gradient 60-100% ethyl acetate/petrol) to afford the title compound \((Z)-576\) (0.030 g, 0.12 mmol) in 18% yield and \(> 95\%\) d.e. as a pale-coloured oil, \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 3419 (OH), 1649 (C=O am), 1634 (C=C), 1520 (C=O am), 1071 (C-O); \(\delta\)\text{H} (300MHz, CDCl\(_3\), Me\(_4\)Si) 0.96 (3H, t, \(J 7.5, \text{CH}_2\text{CH}_3\)), 2.16 (2H, pentet, \(J 7.5, \text{CH}_2\text{CH}_3\)), 2.92 (1H, br s, OH), 3.32 (2H, app q, \(J 5.5, 5.0, \text{CH}_2\text{OH}\)), 3.57 (2H, app t, \(J 5.0, \text{CH}_2\text{N}\)), 4.70 (2H, s, CH\(_2\)Ph), 6.24 (1H, t, 7.5, \(\text{HC}=\text{C}\)), 6.76 (1H, br s, NH), 7.26-7.34 (5H, m, Ph-H); \(\delta\)\text{C} (CDCl\(_3\)) 13.8, 19.7, 42.7, 62.8, 76.1, 127.3, 128.8, 129.0, 129.2, 136.9, 147.3, 165.5; \(m/z\) (CI\(^+\), NH\(_3\)) 250 (100, \(M^+\)), 160 (23%, \(M^+-\text{CH}_2\text{Ph}\)); (Found (ES\(^+\) \(M^+\) \(250.1436\) C\(_4\)H\(_20\)NO\(_3\) requires 250.1438).

\((2R)-2\text{-hydroxy-2-propyl-3-morpholinone} \ 577\) and \((2S)-2\text{-hydroxy-2-propyl-3-morpholinone} \ 578\)

\[
\begin{align*}
\text{NH} & \quad \text{O} \\
\text{O} & \quad \text{OH} \\
\text{C} & \quad \text{O} \\
\end{align*}
\]

\((R)-577\)

\[
\begin{align*}
\text{NH} & \quad \text{O} \\
\text{O} & \quad \text{OH} \\
\text{C} & \quad \text{O} \\
\end{align*}
\]

\((S)-578\)

Reaction of \((Z)-2\text{-}(\text{benzyloxy})\text{-}\text{N}(2\text{-hydroxyethyl})\text{-2-pentenamide} \ 576\) (0.020 g, 0.08 mmol) with Pd/C (0.005 g) under hydrogen for 12 hours in CH\(_2\)Cl\(_2\) (1 mL) afforded after filtration over celite 0.010 g of an unpurified mixture of the title compound as a 1:1 mixture of isomers \((R)-577\) and \((S)-578\) (90%) and oxazolidin-2-one (10%), \(\delta\)\text{H} (300MHz, CDCl\(_3\), Me\(_4\)Si) 0.89 (3H, t, \(J 7.5, \text{CH}_2\text{CH}_2\text{CH}_3\)), 0.88 (3H, t, \(J 7.5, \text{CH}_2\text{CH}_2\text{CH}_3\)), 1.58 (2H, sextet, \(J 7.5, \text{CH}_2\text{CH}_2\text{CH}_3\)), 1.39 (2H, sextet, \(J 7.5, \text{CH}_2\text{CH}_2\text{CH}_3\)), 2.84 (2H, app t, \(J 7.5, \text{CH}_2\text{CH}_2\text{CH}_3\)), 3.40 (2H, app dt, \(J 5.5, 5.0, \text{CH}_2\text{NH}\)), 3.70 (2H, app t, \(J 5.0, \text{CH}_2\text{O}\)), 6.97
(1H, br s, NH), 7.31 (1H, br s, NH); δC (CDCl3) 14.0, 14.2, 17.1, 18.7, 37.2, 39.0, 40.9, 62.0, 62.7, 65.4; m/z (EI) 159.1 (12, M+), 88.0 (100%, oxazolidin-2-one + H+).

(Z)-2-azido-N-(2-hydroxyethyl)-2-pentenamide 588

Reaction of anti-3-(2-azido-3-hydroxypentanoyl)-1,3-oxazolidin-2-one 587 (0.058 g, 0.26 mmol) with a 0.5M solution of KHMDS in toluene (0.77 mL, 0.38 mmol) in THF (1.5 mL), according to general protocol K, afforded 0.042 g of a mixture of the title compound (80%) in > 95% d.e. and oxazolidin-2-one (20%). The crude product was purified by silica gel chromatography (60% ethyl acetate/petrol) to afford the title compound (Z)-588 (0.017 g, 0.09 mmol) in 36% yield and >95% d.e. as a colourless oil, νmax (neat)/cm⁻¹ 3324 (br, OH, NH), 2117 (N=N=N), 1652 (CO) am, 1627 (CO conj, 1538 (CO) am; δH (300MHz, CDCl3, Me4Si) 1.09 (3H, t, J 7.5, CH2CH3), 2.31 (2H, app quintet, J 7.5, CH2CH3), 2.85 (1H, br s, OH), 3.48 (2H, app dt, J 5.5, 4.5, CH2NH), 3.77 (2H, app t, J 5.0, CH2OH), 6.18 (1H, t, J 7.5, CH=CH), 6.76 (1H, br s, NH); δC (CDCl3) 13.7, 20.4, 42.9, 62.3, 129.9, 130.5, 164.0; m/z (CI+, NH) 185 (30, MH+), 159 (100), 157 (84%, M+–OH); (Found (ES⁺) MH⁺ 185.1031 C7H13N4O2 requires 185.1033).

(E)-N-(2-hydroxyethyl)-2-phenyl-2-pentenamide 592

Reaction of syn-3-(3-hydroxy-2-phenylpentanoyl)-1,3-oxazolidin-2-one 591 (0.200 g, 0.76 mmol) with a 0.5M solution of KHMDS in toluene (2.24 mL, 1.12 mmol) in THF (2 mL), according to general protocol K, gave a mixture (0.161 g) of the title compound (E)-592 (70%) in > 95% d.e., the parent N-acyl oxazolidin-2-one 459 (15%) and an unknown product (15%). The crude product was purified by silica gel chromatography (40% ethyl acetate/petrol) to afford the title compound (E)-592 (0.056 g, 0.26 mmol) in 34% yield and > 95% d.e. as a colourless oil, νmax (neat)/cm⁻¹ 3418 (br, OH, NH), 1657 (C=O) am, 1617 (C=C), 1522 (C=O) am; δH (300MHz, CDCl3, Me4Si) 0.99 (3H, t, J 7.5, CH2CH3), 1.98 (2H, app pentet, J 7.5, CH2CH3), 3.16 (1H, br s, OH), 3.39 (2H, app q, J 5.5, 5.0, CH2NH), 3.66
(E)-N-(2-hydroxyethyl)-2-(4-methoxyphenyl)-2-pentenamide 595

Reaction of syn-3-[3-hydroxy-2-(4-methoxyphenyl)pentanoyl]-1,3-oxazolidin-2-one 594 (0.100 g, 0.34 mmol) with a 0.5M solution of KHMDS in toluene (1.02 mL, 0.51 mmol) in THF (2 mL), according to general protocol K, gave a mixture of the title compound (E)-595 (80%) in 75% d.e. and the parent N-acyl oxazolidin-2-one 593 (20%). The crude product was purified by silica gel chromatography (60% ethyl acetate/petrol) to afford the title compound (E)-595 (0.033 g, 0.13 mmol) in 39% yield and >95% d.e. as a colourless oil, \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 3420 (br, OH, NH), 1653 (\( \delta_\text{C} \) = O in \( \text{C} = \text{O} \)), 1617 (C=C), 1512 (C=O) am; \( \delta_\text{H} \) (300MHz, CDCl\(_3\), Me\(_4\)Si) 0.91 (3H, t, \( J = 7.5 \), CH\(_2\)C\(_3\)), 1.92 (2H, app pentet, \( J = 7.5 \), CH\(_2\)CH\(_3\)), 2.80 (1H, s, OH), 3.33 (2H, app q, \( J = 5.5 \), 4.5, CH\(_2\)N), 3.59 (2H, app t, \( J = 5.0 \), CH\(_2\)O), 3.77 (3H, s, ArOCH\(_3\)), 5.80 (1H, s, NH), 6.87 (2H, d, \( J = 9.0 \), Ar-H), 6.93 (1H, t, \( J = 7.5 \), HC=CAr), 7.04 (2H, d, \( J = 9.0 \), Ar-H); \( \delta_\text{C} \) (CDCl\(_3\)) 13.8, 23.1, 43.5, 55.7, 63.0, 114.7, 127.7, 131.4, 134.6, 143.7, 159.7, 169.2; m/z (El\(^+\)) 249 (28, \( M^+ \)), 161 (100%, \( M^+\)-HO(CH\(_2\))\(_2\)NHCO); (Found (ES\(^+\)) \( MH^+ \) 250.1437 C\(_{14}\)H\(_{20}\)NO\(_3\) requires 250.1438).
8-5 Preparation of carboxylic acids and oxazolines

General protocol L

\[
\begin{align*}
\text{(E)}-\alpha,\beta-\text{Unsaturated amide } & \text{631 was refluxed for five hours in 6.0M HCl. Reaction} \\
\text{mixture was allowed to cool to room temperature, saturated with sodium} \\
\text{chloride, and extracted with ethyl acetate (5 x 10 ml). The combined} \\
\text{organic layers were dried over magnesium sulphate and the solvent} \\
\text{removed } \textit{in vacuo} \text{ to afford } \alpha,\beta-\text{unsaturated carboxylic acid (E)-501.}
\end{align*}
\]

\[
\text{(E)-2-methylpenten-2-oic acid 495}
\]

\[
\begin{align*}
\text{The hydrolysis of (E)-N-(2-hydroxyethyl)-2-methyl-2-pentenamide } & \text{484 (0.300 g, 1.91} \\
\text{mmol) in 6.0M HCl (5 mL), according to general protocol L, afforded the title} \\
\text{compound (E)-495 (0.230 g, 2.02 mmol) in 91% yield and > 95% d.e. as a low-melting} \\
\text{white solid, } \nu_{\text{max}} \textit{(neat)/cm}^{-1} \text{ 3429 (br, OH), 1700 (C=O), 1646 (C=C); } \delta_{\text{H}} \textit{(300MHz, CDCl}_3) \text{ 0.99 (3H,} \\
t, J 7.5, \text{CH}_2\text{CH}_3), \text{ 1.76 (3H, d, } J \text{ 0.9, CH=CCH}_3), \text{ 2.14 (2H, app pentet, J 7.5, CH}_2\text{CH}_3),} \\
\text{ 6.83 (1H, tq, 7.5, 1.4, CH=CCH}_3), \text{ 10.5-11.8 (1H, br s, COOH); } \delta_{\text{C}} \textit{(CDCl}_3) \text{ 12.2, 13.2,} \\
\text{ 22.6, 126.8, 147.2, 174.3.}
\end{align*}
\]

\[
\text{(E)-3-cyclohexyl-2-isopropyl-2-propenoic acid 496}\]

\[
\begin{align*}
\text{The hydrolysis of (E)-3-cyclohexyl-N-(2-hydroxyethyl)-2-isopropyl-2-propenamide } & \text{478 (0.053 g, 0.22} \\
\text{mmol) in 6.0M HCl (2 mL), according to general protocol L, afforded the title} \\
\text{compound (E)-496 (0.043 g, 0.22 mmol) in 99% yield and > 95% d.e. as a colourless} \\
\text{oil, } \nu_{\text{max}} \textit{(neat)/cm}^{-1} \text{ 1677 (C=O), 1621 (C=C)}_\textit{conj}; \delta_{\text{H}} \textit{(300MHz, CDCl}_3, \text{ Me}_4\text{Si}) \text{ 0.90-1.30} \\
\text{(6H, m, Cy-H), 1.13 (6H, d, J 7.0, CH=CCH}_3), \text{ 1.52-1.72 (4H, m, Cy-H), 2.33 (1H, dtt, J} \\
\text{10.5, 10.0, 3.5, CH), 2.84 (1H, septet, J 7.0, CH(CH}_3)_2), 6.54 (1H, d, J 10.0, CH=CCH}_3),}
\end{align*}
\]
Chapter 8

Experimental

10.26 (1H, br s, COOH); δC (CDCl₃) 20.2, 24.5, 24.8, 26.4, 31.3, 31.9, 36.4, 134.1, 148.2, 172.7; m/z (El⁺) 197.3 (15%, MH⁺), 196.3 (15%, M⁺); (Found (El⁺) M⁺ 196.1454 C₁₂H₂₀O₂ requires 196.1458).

(E)-2-methyl-3-phenyl-2-propenoic acid 497

\[
\text{HO} \quad \text{(E)-497}
\]

The hydrolysis of (E)-N-(2-hydroxyethyl)-2-methyl-3-phenyl-2-propenamide 486 (0.048 g, 0.23 mmol) in 6.0M HCl (3 mL), according to general protocol L, afforded the title compound (E)-497 (0.036 g, 0.22 mmol) in 95% yield and > 95% d.e. as a colourless oil, vmax (neat)/cm⁻¹ 3445 (br, OH), 1668 (C=O), 1616 (C=C)conjugated, 1492 (C=C)aromatic; δH (300MHz, CDCl₃, Me₄Si) 2.08 (s, 3H, CH₃CC=Ph), 7.26-7.36 (5H, m, Ph-H), 7.77 (1H, s, CH=CHPh), 11.36 (1H, br s, COOH); δC (CDCl₃) 12.7, 126.5, 127.4, 127.7, 128.8, 134.5, 140.1, 173.4; m/z (El⁺) 162.1 (68%, M⁺), 161.0 (36%, M⁺-H), 117.2 (58%, M⁺-COOH); (Found (El⁺) M⁺ 162.0672 C₁₀H₁₀O₂ requires 162.0675).

(2E,4E)-2-methyl-5-phenyl-2,4-pentadienoic acid 498

\[
\text{HO} \quad \text{(E)-498}
\]

The hydrolysis of (E,E)-N-(2-hydroxyethyl)-2-methyl-5-phenyl-2,4-pentadienamide 493 (0.200 g, 0.58 mmol) in 6.0M HCl (5 mL), according to general protocol L, afforded the title compound (E,E)-498 (0.135 g, 0.45 mmol) in 77% yield and > 95% d.e. as a pale brown solid, mp 158-160°C (lit., 157 160.0-162.5°C); vmax (KBr disc)/cm⁻¹ 3445 (br, OH), 1683 (C=O), 1622 (C=C)conjugated, 1495 (C=C)aromatic; δH (300MHz, CDCl₃, Me₄Si) 1.98 (3H, d, J 1.1, CH₃), 6.83 (1H, d, J 15.5, CHCH=CHPh), 7.00 (1H, dd, J 15.5, 11.5, CHCH=CHPh), 7.17-7.45 (6H, m, CHCH=CHPh, Ph-H), 10.00-12.00 (1H, br s, COOH); δC (CDCl₃) 11.5, 122.7, 125.4, 126.2, 127.8, 127.9, 135.4, 139.2, 139.6, 173.0; m/z (El⁺) 188 (33, M⁺), 143 (62, M⁺-COOH), 128 (80, M⁺-COOH-CH₃), 115 (100%, M⁺-C(CH₃)COOH-H⁺); (Found (ES⁺) MNH₄⁺ 206.1175 C₁₂H₁₆NO₂ requires 206.1176).
Chapter 8 Experimental

(E)-2-benzyl-2-decenoic acid 499

The hydrolysis of (E)-2-benzyl-N-(2-hydroxyethyl)-2-decenamide 489 (0.200 g, 0.58 mmol) in 6.0M HCl (5 mL), according to general protocol L, afforded the title compound (E)-499 (0.135 mg, 0.45 mmol) in 77% yield and > 95% d.e., δH (300MHz, CDCl3, Me4Si) 0.80 (3H, t, J 7.0, CH3), 1.12-1.25 (8H, m, Alk-H), 1.29-1.38 (2H, m, CH2CH2CH=C), 2.19 (2H, app q, J 7.5, CH2CH2CH=C), 3.58 (2H, s, C=C(CH3)2), 6.97-7.17 (5H, m, Ph-H); δC (CDCl3) 13.0, 21.6, 27.5, 28.0, 28.2, 28.3, 30.7, 31.2, 125.0, 127.2, 127.3, 129.2, 138.5, 146.1, 171.9; m/z (EI+) 260.3 (66, M+), 242 (9, M+ - CH3), 161 (14, M+ - H2O), 91 (100%); (Found (EI+) M+ 278.2118, requires 278.2120).

Preparation of oxazolines

General protocol M

Thionyl chloride (5 eq.) was added dropwise to a stirred solution of α,β-unsaturated amide (E)-631 (1 eq.) in CH2Cl2 in an ice bath. Reaction mixture was stirred for 2 hours at this temperature. A 5.0M solution of NaOH (3 mL) was added dropwise and the reaction extracted with CH2Cl2 (x 3). The combined organic extracts were washed with brine, dried (MgSO4), and concentrated in vacuo to afford oxazoline (E)-500

2-[(E)-1-methyl-1-butenyl]-4,5-dihydro-1,3-oxazole 505

Reaction of (E)-N-(2-hydroxyethyl)-2-methyl-2-pentenamide 484 (0.112 g, 0.71 mmol) with thionyl chloride (0.26 mL, 3.57 mmol) in CH2Cl2 (4 mL), according to general protocol M, gave the title compound (E)-505 (0.087 g, 0.63 mmol) in 88% yield and > 95% d.e. as a colourless oil, νmax (neat)/cm⁻¹ 1700 (C=N), 1653 (C=C); δH (300MHz, CDCl3) 0.97 (3H, t, J 7.6, CH2CH3), 1.85 (3H, s, CH=CH2), 2.12 (2H, app pentet, J 7.5,
2-[(E)-1-methyl-2-phenyl-1-ethenyl]-4,5-dihydro-1,3-oxazole 507

Reaction of (E)-N-(2-hydroxyethyl)-2-methyl-3-phenyl-2-propenamide 486 (0.570 g, 2.78 mmol) with thionyl chloride (0.89 mL, 12.20 mmol) in CH₂Cl₂ (15 mL), according to general protocol M, gave the title compound (E)-507 (0.503 g, 2.69 mmol) in 97% yield and > 95% d.e. as a pale yellow oil, νmax (neat)/cm⁻¹ 1707 (C=N), 1640 (C=C), 1614 (C=C)ar, 1491 (C=C)ar; δH (300MHz, CDCl₃, Me₄Si) 2.21 (3H, d, J 1.5, CH=CC₃), 4.01 (2H, app t, J 9.5, CH₂N), 4.36 (2H, app t, J 9.5, CH₂O), 7.35-7.40 (5H, m, Ph-H); δC (CDCl₃) 15.4, 55.4, 67.9, 125.7, 128.2, 128.7, 129.9, 135.6, 136.7, 167.3; m/z (EI⁺) 187 (27, M⁺), 186 (100, M⁺-H), 129 (7, M⁺-OCH₂CH₃N), 115 (25%, CH₃CCPh⁺); (Found (EI⁺) M⁺ 187.0998 C₁₂H₁₃NO requires 187.0997).
8.6 Preparation of oxazinanediones

Procedure for the rearrangement reaction with diethylzinc

General protocol N

\[ \text{R} \quad \text{OH} \quad \text{Et}_2\text{Zn} \quad \text{CH}_2\text{Cl}_2, \text{rt} \]

\[ \text{HO} \quad \text{N} \quad \text{O} \quad \text{R} \quad \text{R}_1 \]

A 1.0M solution of \( \text{Et}_2\text{Zn} \) in toluene (0.1 eq.) was added dropwise to a stirred solution of \textit{syn}-aldolate \textbf{627} (1 eq.) in \( \text{CH}_2\text{Cl}_2 \) at room temperature. The reaction was stirred for 2 hours. Saturated \( \text{NH}_4\text{Cl}_{aq} \) was added and the reaction extracted with \( \text{CH}_2\text{Cl}_2 \) (x 3). The combined organic extracts were washed with brine, dried (\( \text{MgSO}_4 \)), and concentrated \textit{in vacuo} to afford \textit{syn}-oxazinanedione \textbf{632}.

\textit{syn}-6-Ethyl-3-(2-hydroxyethyl)-5-methyl-1,3-oxazinane-2,4-dione \textbf{522}

\[ \text{HO} \quad \text{N} \quad \text{O} \quad \text{O} \quad \text{R} \]

Reaction of \textit{syn}-3-(3-hydroxy-2-methylpentanoyl)-1,3-oxazolidin-2-one \textbf{479} (0.050 g, 0.25 mmol) with a 1.0M solution of \( \text{Et}_2\text{Zn} \) in toluene (0.03 mL, 0.03 mmol) in \( \text{CH}_2\text{Cl}_2 \) (2 mL), according to general protocol N, afforded the title compound \textbf{522} (0.029 g, 0.14 mmol) in 58% yield and > 95% d.e. as a colourless oil, \( \nu_{\text{max}}\text{ (neat)/cm}^{-1} \)

\(3433\) (br, OH), 1750 (C=O)\textsubscript{\textit{ax}}, 1695 (C=O)\textsubscript{\textit{ani}}, \(\delta_{\text{HF}}(300\text{MHz, CDCl}_3, \text{Me}_4\text{Si}) \) 0.98 (3H, t, \( J 7.5, \text{CH}_2\text{CH}_3 \)), 1.17 (3H, d, \( J 7.0, \text{CHCH}_3 \)), 1.55 (1H, dqq, \( J 14.0, 7.5, 5.0, \text{CH}_3\text{H}_8\text{CH}_3 \)), 1.71 (1H, dqd, \( J 14.0, 9.0, 7.5, \text{CH}_3\text{H}_8\text{CH}_3 \)), 1.92 (1H, br s, \( \text{OH} \)), 2.79 (1H, qd, \( J 7.0, 3.5, \text{CHCH}_3 \)), 3.74 (2H, app t, \( J 5.0, \text{CH}_2\text{OH} \)), 3.91 (1H, ddd, \( J 14.0, 5.5, 5.0, \text{CH}_3\text{H}_8\text{N} \)), 3.99 (1H, app dt, \( J 14.0, 5.5, \text{CH}_3\text{H}_8\text{N} \)), 4.34 (1H, ddd, \( J 9.0, 5.0, 3.5, \text{CHCH}_2\text{CH}_3 \)); \( \delta_{\text{C}}(\text{CDCl}_3) \) 8.6, 8.6, 22.0, 38.0, 48.1, 60.0, 77.7, 151.2, 171.9; \( m/z \text{ (Cl}^+, \text{iso-butane) 202 (87, \text{MH}^+) \text{, 158 (60\%, \text{MH}^+-\text{CO}_2)} \); (Found (FAB\textsuperscript{+}) \text{MH}^{+} 202.1080 \text{C}_9\text{H}_{16}\text{NO}_4\text{ requires 202.1079).} \)

198
syn-6-Ethyl-3-(2-hydroxyethyl)-5-isopropyl-1,3-oxazinane-2,4-dione 524

Reaction of syn-3-(3-hydroxy-2-isopropylpentanoyl)-1,3-oxazolidin-2-one 480 (0.250 g, 1.09 mmol) with a 1.0M solution of Et$_2$Zn in toluene (0.11 mL, 0.11 mmol) in CH$_2$Cl$_2$ (5 mL), according to general protocol N, afforded the title compound syn-524 (0.220 g, 0.96 mmol) in 88% yield and > 95% d.e. as a colourless oil, $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3436 (br, OH), 1749 (C=O)$_{\text{ox}}$, 1691 (C=O)$_{\text{am}}$; $\delta_{t}$ (300MHz, CDCl$_3$, Me$_4$Si) 0.97 (3H, d, J 7.0, CH(CH$_3$)$_2$), 1.00 (3H, t, J 7.5, CH$_2$CH$_3$), 1.02 (3H, d, J 7.0, CH(CH$_3$)$_2$), 1.60 (1H, dqd, J 14.0, 7.5, 5.0, CH$_{\text{A}}$H$_{\text{B}}$CH$_3$), 1.80 (1H, dqd, J 14.0, 9.0, 7.5, CH$_{\text{A}}$H$_{\text{B}}$CH$_3$), 2.08-2.21 (1H, septet of d, J 7.0, 5.0, CH(CH$_3$)$_2$), 2.25 (1H, br s, OH), 2.52 (1H, dd, J 5.0, 4.0, CH$^3$Pr), 3.74 (2H, app t, J 5.5, CH$_2$OH), 3.89 (1H, app dt, J 14.0, 5.5, CH$_{\text{A}}$H$_{\text{B}}$N), 4.01 (1H, app dt, J 14.0, 5.5, CH$_{\text{A}}$H$_{\text{B}}$N), 4.39 (1H, ddd, J 9.0, 5.0, 4.0, CHEt); $\delta_{C}$ (CDCl$_3$) 9.0, 18.8, 21.2, 22.3, 14.5, 43.1, 48.4, 59.8, 78.0, 151.6, 170.0; m/z (CI$^+$, NH$_3$) 247 (94, M$^+$), 230 (100, M$^+$), 186 (31%, M$^+$-CO$_2$); (Found (ES$^+$) M$^+$ 230.1387 C$_{11}$H$_{20}$NO$_4$ requires 230.1387).

syn-6-Cyclohexyl-3-(2-hydroxyethyl)-5-isopropyl-1,3-oxazinane-2,4-dione 525

Reaction of syn-3-{2-[cyclohexyl(hydroxy)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one 476 (0.070 g, 0.25 mmol) with a 1.0M solution of Et$_2$Zn in toluene (0.03 mL, 0.03 mmol) in CH$_2$Cl$_2$ (2 mL), according to general protocol N, afforded the title compound syn-525 (0.064 g, 0.22 mmol) in 90% yield and > 95% d.e. as a white solid, mp 100-102$^\circ$C; $\nu_{\text{max}}$ (KBr disc)/cm$^{-1}$ 3408 (br, OH), 1757 (C=O)$_{\text{ox}}$, 1696 (C=O)$_{\text{am}}$; $\delta_{t}$ (300MHz, CDCl$_3$, Me$_4$Si) 0.93 (3H, d, J 7.0, CH(CH$_3$)$_2$), 1.06 (3H, d, J 7.0, CH(CH$_3$)$_2$), 0.82-1.30 (6H, m, Cy-H), 1.48-1.78 (4H, m, Cy-H), 2.07 (1H, t, J, OH), 2.14-2.24 (2H, m, CH(CH$_3$)$_2$, Cy-H), 2.59 (1H, app t, J 3.0, CH$^3$Pr), 3.73-3.79 (2H, m, CH$_2$OH), 3.82-3.90 (1H, m, CHCy), 4.02-4.10 (2H, m, CH$_2$N); $\delta_{C}$ (CDCl$_3$) 17.8, 22.0, 24.1, 24.4, 24.6, 25.0,
Experimental

26.8, 28.5, 36.4, 43.2, 46.4, 60.1, 80.7, 151.9, 170.0; m/z (Cl⁺, iso-butane) 284 (65, MH⁺), 240 (100%, MH⁺-CO₂); (Found (FAB⁺) MH⁺ 284.1855 C₁₃H₂₆NO₄ requires 284.1862).

**syn-3-(2-Hydroxyethyl)-5-isopropyl-6-phenyl-1,3-oxazinane-2,4-dione 517**

![syn-517](image)

Reaction of *syn-*3-(3-hydroxy-2-methyl-3-phenylpropanoyl)-1,3-oxazolidin-2-one 467 (0.150 g, 0.60 mmol) with a 1.0M solution of Et₂Zn in toluene (0.06 mL, 0.06 mmol) in CH₂Cl₂ (3 mL), according to general protocol N, afforded the title compound *syn-*517 (0.147 g, 0.58 mmol) in 97% yield and 90% d.e. as a colourless oil, vₘₐₓ (neat)/cm⁻¹ 3447 (br, OH), 1755 (C=O)ox, 1703 (C=O)am, 1500 (C=C)ar; δH (300MHz, CDCl₃, Me₄Si) 1.01 (3H, d, J 7.5, CH₃), 2.17 (1H, s, OH), 2.99 (1H, qd, J 7.5, 3.5, CH₂CH₃), 3.75-3.82 (2H, m, CH₂OH), 3.97 (1H, app dt, J 14.0, 5.5, CH₄H₂BN), 4.05 (1H, app dt, J 14.0, 5.5, CH₄H₂BN), 5.62 (1H, d, J 3.5, CHPh), 7.24-7.38 (5H, m, Ph-H); δC (CDCl₃) 10.4, 41.5, 44.6, 61.2, 78.1, 126.0, 129.2, 129.4, 134.4, 152.4, 173.2; m/z (Cl⁺, NH₃) 267 (15, MNH₄⁺), 206 (47, MH⁺-CO₂), 105 (100%); (Found (ES⁺) MH⁺ 250.1081 C₁₃H₁₈NO₄ requires 250.1079).

**anti-3-(2-Hydroxyethyl)-5-isopropyl-6-phenyl-1,3-oxazinane-2,4-dione 518**

![anti-518](image)

Reaction of *anti-*3-(3-hydroxy-2-methyl-3-phenylpropanoyl)-1,3-oxazolidin-2-one 468 (0.050 g, 0.20 mmol) with a 1.0M solution of Et₂Zn in toluene (0.02 mL, 0.02 mmol) in CH₂Cl₂ (1 mL), according to general protocol N, afforded the title compound *anti-*518 (0.047 g, 0.19 mmol) in 96% yield and > 95% d.e. as a white solid, vₘₐₓ (neat)/cm⁻¹ 3435 (br, OH), 1755 (C=O)ox, 1694 (C=O)am, 1501 (C=C)ar; δH (300MHz, CDCl₃, Me₄Si) 1.02 (3H, d, J 7.0, CH₃), 2.21 (1H, br s, OH), 2.89 (1H, qd, J 11.5, 7.0, CH(CH₃)), 3.77-3.80 (2H, app t, J 5.5, CH₂OH), 3.94 (1H, ddd, J 14.0, 6.0, 4.5, CH₄H₂BN), 4.06 (1H, app dt, J 14.0, 5.5, CH₄H₂BN), 5.04 (1H, d, J 11.5, CHPh), 7.24-7.38 (5H, m, Ph-H); δC (CDCl₃) 10.1, 40.4, 43.5, 59.6, 80.5, 126.1, 127.9, 128.7, 134.2, 151.1, 170.5; m/z (Cl⁺, NH₃) 267
(\text{MNH}^+, 100\%), 250 (46, \text{MH}^+), 208 (55), 206 (87\%, \text{MH}^+-\text{CO}_2); (\text{Found} (\text{ES}^+)) \text{MH}^+ 250.1077 \text{C}_{13}\text{H}_{16}\text{NO}_4 \text{requires} 250.1079).

**syn-3-(2-Hydroxyethyl)-5-isopropyl-6-[(E)-1-propenyl]-1,3-oxazinane-2,4-dione 541**

![Syn-541](image)

Reaction of **syn-3-[(E)-3-hydroxy-2-isopropyl-4-hexenoyl]-1,3-oxazolidin-2-one 463** (0.200 g, 0.83 mmol) with a 1.0M solution of Et$_2$Zn in toluene (0.08 mL, 0.08 mmol) in CH$_2$Cl$_2$ (5 mL), according to general protocol O, afforded the title compound **syn-541** (0.129 g, 0.54 mmol) in 65% yield and > 95% d.e as a colourless oil, $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3430 (br, OH), 1755 (C=O)$_{\text{ox}}$, 1699 (C=O)$_{\text{am}}$; $\delta_{\text{H}}$ (300MHz, CDCl$_3$, Me$_4$Si) 0.97 (3H, d, $J$ 7.0, CH(CH$_3$)$_2$), 1.03 (3H, d, $J$ 7.0, CH(CH$_3$)$_2$), 1.71 (3H, d, $J$ 7.0, CH$_3$CH=CH), 1.97 (1H, t, $J$ 5.5, CH$_2$), 2.10 (1H, app octet, $J$ 7.0, CH(CH$_3$)$_2$), 2.55 (1H, dd, $J$ 6.5, 4.5, CH$_3$Pr), 3.74 (2H, app dt, $J$ 5.5, 5.5, CH$_2$OH), 3.94-3.98 (2H, m, CH$_2$N), 4.92 (1H, app t, $J$ 6.5, CHCH=CHCH$_3$), 5.47 (1H, ddd, $J$ 15.0, 7.0, 1.5, CH$_3$CH=CH), 5.91 (1H, dq, $J$ 15.0, 7.0, CH$_3$CH=CH) ; $\delta_{\text{C}}$ (CDCl$_3$) 17.0, 19.7, 20.3, 24.8, 43.2, 49.5, 60.1, 76.6, 122.1, 132.7, 151.3, 169.7; m/z (EI$^+$) 241 (41, M$^+$), 198 (100\%, M$^+$-CO$_2$); (Found (EI$^+$) M$^+$ 241.1313 \text{C}_{12}\text{H}_{19}\text{NO}_4 \text{requires} 241.1314).

**syn-3-(2-Hydroxyethyl)-5-isopropyl-6-phenyl-1,3-oxazinane-2,4-dione 608**

![Syn-608](image)

Reaction of **syn-3-2-[hydroxy(phenyl)methyl]-3-methylbutanoyl]-1,3-oxazolidin-2-one 481** (0.300 g, 1.08 mmol) with a 1.0M solution of Et$_2$Zn in toluene (0.11 mL, 0.11 mmol) in CH$_2$Cl$_2$ (5 mL), according to general protocol O, gave the title compound **syn-608** in 80\% d.e. The crude product was purified by silica gel chromatography (40\% ethyl acetate/petrol) to afford the title compound **syn-608** (0.155 g, 0.56 mmol) in 52\% yield and > 95\% d.e. as a white solid, $mp$ 92-94$^\circ$C; $\nu_{\text{max}}$ (KBr disc)/cm$^{-1}$ 3447 (br, OH), 1734 (C=O)$_{\text{ox}}$, 1684 (C=O)$_{\text{am}}$; $\delta_{\text{H}}$ (300MHz, CDCl$_3$, Me$_4$Si) 0.85 (3H, d, $J$ 7.0, CH(CH$_3$)$_2$), 0.94
(3H, d, J 7.0, CH(CH₃)₂), 1.88-1.90 (1H, septet of d, J 7.0, 4.0, CH(CH₃)₂), 2.76 (1H, br s, OH), 2.85 (1H, app t, J 4.0, CH₃Pr), 3.85 (2H, app t, J 5.0, CH₂OH), 4.01 (1H, app dt, J 14.0, 5.0, CH₄H₂N), 4.12 (1H, app dt, J 14.0, 5.0, CH₄H₂N), 5.79 (1H, d, J 4.0, CHPh), 7.33-7.43 (5H, m, Ph-H); δC (CDCl₃) 21.0, 24.6, 27.4, 46.0, 53.3, 62.3, 79.8, 127.0, 130.3, 130.7, 136.4, 154.1, 172.6; m/z (CI⁺, NH₃) 295 (85, M⁺H⁺), 278 (52, M⁺H⁺), 234 (44, M⁺H⁺-CO₂), 189.2 (100%); (Found (ES⁺) M⁺ 278.1385 C₁₅H₂₀NO₄ requires 278.1387).

**syn-3-(2-Hydroxyethyl)-5-isopropyl-6-(4-methoxyphenyl)-1,3-oxazinane-2,4-dione 610**

![Chemical structure of syn-610](image)

Reaction of **syn-3-{2-[hydroxy(4-methoxyphenyl)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one 482** (0.100 g, 0.33 mmol) with a 1.0M solution of Et₂Zn in toluene (0.03 mL, 0.03 mmol) in CH₂Cl₂ (3 mL), according to general protocol O, gave the title compound **syn-610** in 80% d.e. The crude product was purified by silica gel chromatography (20% ethyl acetate/petrol) to afford the title compound **syn-610** (0.061 g, 0.20 mmol) in 61% yield and > 95% d.e. as a white solid, mp 79-81°C; νmax (KBr disc)/cm⁻¹ 3353 (br, OH), 1740 (C=O)ₗₚ, 1691 (C=O)ₜₚ; δH (300MHz, CDCl₃, Me₄Si) 0.87 (3H, d, J 7.0, CH(CH₃)₂), 0.98 (3H, d, J 7.0, CH(CH₃)₂), 1.96 (1H, septet of d, J 7.0, 4.0, CH(CH₃)₂), 2.16-2.26 (1H, m, CH₃Pr), 2.79 (1H, t, J 4.0, OH)), 3.83 (3H, s, ArOCH₃), 3.81-3.87 (2H, m, CH₂OH), 4.02 (1H, app dt, J 14.0, 5.5, CH₄H₂N), 4.16 (1H, app dt, J 14.0, 5.5, CH₄H₂N), 5.71 (1H, d, J 4.0, CHAr), 6.94 (2H, d, J 8.5, Ar-H), 7.29 (2H, d, J 8.5, Ar-H); δC (CDCl₃) 19.8, 23.1, 26.0, 44.7, 52.0, 55.7, 61.3, 78.4, 114.6, 126.7, 127.1, 152.9, 160.1, 171.4; m/z (EI⁺) 307 (29, M⁺), 263 (4, M⁺-CO₂), 84 (100%); (Found (EI⁺) M⁺ 307.1419 C₁₅H₂₀NO₄ requires 307.1420).
Experimental

\[ \text{syn-3-(2-Hydroxyethyl)-5-isopropyl-6-(4-nitrophenyl)-1,3-oxazinane-2,4-dione 613} \]

\[
\text{HO-} \quad \text{N} \quad \text{O}
\]

\[ \text{syn-613} \]

Reaction of \( \text{syn-3-\{2-[hydroxy(4-nitrophenyl)methyl]-3-methylbutanoyl\}-1,3-oxazolidin-2-one 613} \) (0.250 g, 0.78 mmol) with a 1.0M solution of \( \text{Et}_2\text{Zn} \) in toluene (0.08 mL, 0.08 mmol) in \( \text{CH}_2\text{Cl}_2 \) (4 mL), according to general protocol O, gave the title compound \( \text{syn-614} \) in 70% d.e. The crude product was purified by silica gel chromatography (40% ethyl acetate/petrol) to afford the title compound \( \text{syn-614} \) (0.126 g, 0.39 mmol) in 51% yield in >95% d.e. as a yellow solid, \( \text{mp } 149-151^\circ\text{C} \), \( \nu_{\text{max}} \) (neat)/\( \text{cm}^{-1} \) 3513 (br, OH), 1762 (C-O)\text{ox}, 1700 (C=O)\text{am}, 1600 (C=C)\text{ar}, 1522 (N=O)\text{am}, 1347 (N=O)\text{am}; \( \delta_{\text{H}} \) (300MHz, CDCl\text{3}, Me\text{4Si}) 0.89 (3H, d, \( J = 7.0 \), CH(CH\text{3})\text{2}), 0.96 (3H, d, \( J = 7.0 \), CH(CH\text{3})\text{2}), 1.81 (1H, \text{septet of d}, \( J = 7.0 \), 3.5, CH(CH\text{3})\text{2}), 2.16 (1H, br s, OH), 2.94 (1H, \text{app t}, \( J = 3.5 \), CH\text{2Pr}), 3.88 (2H, \text{app t}, \( J = 5.0 \), CH\text{2OH}), 4.04 (1H, \text{ddd}, \( J = 14.0 \), 6.5, 4.5, CH\text{4H\text{3N}}), 4.18 (1H, \text{app dt}, \( J = 14.0 \), 5.0, CH\text{4H\text{3N}}), 5.89 (1H, d, \( J = 3.5 \), CH\text{Ar}), 7.62 (2H, d, \( J = 8.5 \), Ar-H), 8.30-8.35 (2H, m, J = 8.5, Ar-H); \( \delta_{\text{C}} \) (CDCl\text{3}) 19.4, 23.3, 26.3, 44.7, 51.6, 60.9, 77.5, 124.6, 126.6, 142.1, 148.3, 152.0, 170.2; \( m/z \) (CI\text{+}, iso-butane) 323 (80, M\text{H\text{+}}), 279 (87, M\text{H\text{+}}-\text{CO}_2), 88 (100%); (Found (FAB\text{+}) M\text{H\text{+}} 323.1244 C_{15}H_{19}N_{2}O_{6} requires 323.1243).
Reference List


Reference List


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Reference List


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Reference List


A research was made on sciFinder using evans and aldol reaction as keywords.


Appendix 1. X-Ray crystallographic Data for (E)-3-cyclohexyl-N-(2-hydroxyethyl)-2-isopropyl-2-propenamide 478
Appendix 1

Table 1. Crystal data and structure refinement for (E)-478.

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<tr>
<td>R indices (all data)</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.232 and -0.215 eÅ(^{-3})</td>
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Notes: Disorder modelled for cyclohexyl ring based on C1A. Atoms C2A–C6A disordered in 55:45 ratio with C2C–C6C respectively. Extensive H–bonding is present lattice based on the following contacts.

Hydrogen bonds with \(H..A < r(A) + 2.000\) Å and \(<\text{DHA}> 110\) deg.

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<th>&lt;DHA&gt;</th>
<th>d(D..A)</th>
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Table 2. Atomic coordinates ($10^4$) and equivalent isotropic displacement parameters ($\AA^2 \times 10^3$) for \textit{(E)}-478. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

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### Table 3. Bond lengths [Å] and angles [°] for (E)-478.

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Symmetry transformations used to generate equivalent atoms.
Table 4. Anisotropic displacement parameters ($\AA^2 \times 10^3$) for (E)-478. The anisotropic displacement factor exponent takes the form: $-2\ gpi^2 \ h^2 \ a^*^2 \ U_{11} + ... + 2\ h \ k \ a^* \ b^* \ U$

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Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for (E)-478.

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*Appendix 1*
Appendix 2. X-Ray crystallographic Data for syn-3-[2-(Benzyloxy)-3-hydroxypentanoyl]-1,3-oxazolidin-2-one 572
Table 1. Crystal data and structure refinement for syn-572.

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Hydrogen bonds [Å and °].

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**Table 2.** Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for *syn-572*. $U(eq)$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

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Symmetry transformations used to generate equivalent atoms.
Table 4. Anisotropic displacement parameters (Å² x 10³) for syn-Sll. The anisotropic displacement factor exponent takes the form: 

\[ -2\Delta^2 \left[ h^2a^2u_{11} + \ldots + 2hkab^12 \right] \]

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COMMUNICATION

An (E)-selective synthesis of trisubstituted (E)-α,β-unsaturated acid derivatives†

Fred J. P. Feuillet, Diane E. J. E. Robinson and Steven D. Bull*

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Potassium alkoxides of N-acyloxazolidin-2-one derived syn-aldolates undergo a novel tandem intramolecular cyclisation elimination reaction to afford trisubstituted (E)-α,β-unsaturated amides in high d.e., which may be converted into their corresponding acids or oxazolines in good yield.

There are currently few general methods available for the diastereoselective synthesis of (E)-α,β-unsaturated acids/esters/amides that are substituted at both their α- and β-positions.1 These types of trisubstituted α,β-unsaturated acid derivatives are important targets because they serve as versatile substrates for a wide range of synthetic methodology,2 and for the construction of a wide range of natural products.3,4 Previously, (E)-acid derivatives of this type have been prepared using Wittig,5 or Horner–Emmons6 methodology, however alternative diastereoselective protocols employing excess Sml2 or CrCl27 to effect the reductive elimination of a-halo-α-hydroxy-esters or amides have recently been described. We now report an alternative approach towards this class of acid fragment, that employs syn-α-hydroxy-N-acyloxazolidin-2-ones as substrates for a novel intramolecular cyclisation/elimination reaction to afford trisubstituted (E)-α,β-unsaturated amides in high d.e. In the course of our synthetic studies we prepared nine racemic syn-aldolates 2a–i in high d.e. via reaction of the boron enolates of N-acyloxazolidin-2-ones 1a–d (1a R = Me; 1b R = Ph; 1c R = α-Pr; 1d R = PhCH=CH-) with a series of aldehydes according to well established literature precedent.7 It was found that treatment of these syn-aldolates 2a–h with 1.5 equivalents of KHMDS in THF at −78 °C resulted in a clean elimination reaction to afford the corresponding α,β-unsaturated amides (E)-3a–h in 67–99% isolated yield, and in >90% d.e. in all cases.8 It is noteworthy that this simple elimination methodology is general in scope, with linear and branched R-substituents being tolerated at the α-position of the syn-aldolates 2a–h, and with aliphatic, unsaturated, and aromatic (neutral and electron rich) R-substituents being tolerated at the β-position (Scheme 1, Table 1). The only limitation of this methodology occurred during elimination of 2i (R = Ph, R1 = Et) which gave 3i in a lower 47% isolated yield as a result of a competing retro-aldol reaction which gave (N-phenylacetyl)oxazolidin-2-one 1e (R = Ph) and propionaldehyde (not isolated) as competing side-products in 32% yield.

It is well known that sterically unhindered N-acyloxazolidin-2-ones can undergo endocyclic ring cleavage via either inter- or intramolecular attack of nucleophiles at their oxazolidin-2-one carbonyl groups.10 Consequently, it was proposed that the high diastereoselectivities observed for the formation of (E)-α,β-unsaturated amides 3a–h in this reaction could be explained by invoking an intramolecular endocyclic cleavage mechanism. Thus, potassium alkoxide 4 initially undergoes intramolecular attack at the oxazolidin-2-one carbonyl resulting in O–O carbonyl migration, to afford 1,3-oxazinane-2,4-dione alkoxide 5. Subsequent anion equilibration of alkoxide 5 to enolate 6 would then enable stereoselective elimination of carbon dioxide to occur to afford the trisubstituted secondary amide (E)-3 in high d.e. (Fig. 1).

It has been reported previously that reaction of the Zn enolate of α-bromo-N-acyloxazolidin-2-ones 7 with benzaldehyde did not afford the expected aldolate product, but instead gave a mixture of rearranged 1,3-oxazinane-2,4-diones diastereoisomers 8 and 9 in good yield (Scheme 2).11 Since this implied that Zn alkoxides of α-hydroxy-N-acyloxazolidin-2-ones underwent rearrangement to their corresponding 1,3-oxazinane-2,4-diones, we treated syn-aldolate 2f with 10 mol% of Et2Zn in CH2Cl2 at room temperature to cleanly afford its corresponding 1,3-oxazinane-2,4-dione 10 in 88% yield.12 Subsequent treatment of 10 with KHMDS in THF at −78 °C gave (E)-3f in >90% d.e., thus providing good evidence that the potassium alkoxide of

Table 1 Synthesis of (E)-α,β-unsaturated amides 3a–h

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldolate</th>
<th>R1</th>
<th>Product</th>
<th>d.e.%</th>
<th>% Yield*</th>
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<tr>
<td>1</td>
<td>2a</td>
<td>Me</td>
<td>Ph</td>
<td>3a</td>
<td>&gt;95</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>Me</td>
<td>Et</td>
<td>3b</td>
<td>&gt;95</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>PhCH2-</td>
<td>Me(CH3)2-</td>
<td>3c</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>α-Pr</td>
<td>cyclobex</td>
<td>3d</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>(E)-Ph(CH=CH-)</td>
<td>3e</td>
<td>&gt;95</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>α-Pr</td>
<td>Et</td>
<td>3f</td>
<td>&gt;95</td>
</tr>
<tr>
<td>7</td>
<td>2g</td>
<td>α-Pr</td>
<td>Ph</td>
<td>3g</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td>2h</td>
<td>α-Pr</td>
<td>p-MeOPh-</td>
<td>3h</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>2i</td>
<td>Ph</td>
<td>Et</td>
<td>3i</td>
<td>&gt;95</td>
</tr>
</tbody>
</table>

* All diastereoselectivities were determined via 1H NMR spectroscopic analysis (300 MHz) of the crude reaction product.† Yields are for pure (E)-diastereoisomers isolated after chromatographic purification.

Fig. 1 Intramolecular cyclisation/elimination mechanism for the formation of (E)-α,β-unsaturated amides 3.
1,3-oxazinane-2,4-dione 5 is a key intermediate in controlling diastereoselectivity during stereoselective elimination of the potassium enolates of syn-aldolates 2a-h (Scheme 3).

We next explored elimination of the corresponding anti-aldol 11 which was prepared via treatment of 1a with MgCl₂, TMSCl, Et₃N and benzaldehyde in EtOAc according to Evans’ recently published procedure.¹³ Treatment of anti-aldol 11 with KHMDS in THF at -78 °C afforded amide (E)-3a in >95% d.e. identical to that observed previously for elimination of syn-2a under the same conditions (Scheme 4). This is consistent with the key elimination step of both syn-2a and anti-11 occurring via an E1cB-type mechanism, to afford a common enolate intermediate 6 that decomposes to afford α,β-unsaturated amides (E)-3a in high d.e.

In order to demonstrate the synthetic utility of this methodology, a range of diastereomerically pure trisubstituted secondary amides (E)-3a-e were hydrolysed to their parent acids 12a-e by refluxing in 6 M HCl for two hours in 91-99% yield.¹⁴ The potential synthetic versatility of this methodology arising from the presence of the N-hydroxyalkyl substituent of α,β-unsaturated amides 3a-e was also demonstrated via conversion of 3b to its corresponding trisubstituted-α,β-unsaturated oxazoline (E)-13 on treatment with thionyl chloride in 88% yield (Scheme 5, Table 2, entry 6).¹⁵

In conclusion, we have demonstrated that treatment of easily prepared N-acyloxazolidone-syn-aldolates with KHMDS affords an alkoxide intermediate which undergoes a stereoselective base mediated elimination reaction to afford trisubstituted (E)-α,β-unsaturated amides in high d.e.

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### Notes and references


8. Treatment of (E)-2a in THF with KHMDS at 0 °C afforded amide (E)-3a in an inferior 80% d.e.

9. The (E)-stereochemistry of amide 3d was confirmed via X-ray crystallographic analysis.


### Table 2 Yields of (E)-α,β-unsaturated acids 12a-e and (E)-oxazoline 13

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amide</th>
<th>R</th>
<th>R₁</th>
<th>Product % Yield</th>
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</thead>
<tbody>
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<td>3a</td>
<td>Me</td>
<td>Ph</td>
<td>12a</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>Me</td>
<td>Et</td>
<td>12b</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>PhCH=</td>
<td>Me(CH₃)=</td>
<td>12c</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>iPr</td>
<td>cyclohexyl</td>
<td>12d</td>
</tr>
<tr>
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<td>3e</td>
<td>iPr</td>
<td>(E)-Ph(CH=CH)-</td>
<td>12e</td>
</tr>
<tr>
<td>6</td>
<td>3b</td>
<td>Me</td>
<td>Et</td>
<td>13</td>
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