Methodology Studies on the Synthesis of Chiral, Non-Racemic Aza-Quaternary Centres

By

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Abstract

The synthesis of chiral, non-racemic aza-quaternary centres is one of the biggest challenges in current organic synthesis. Many natural products contain them and as a privileged biological motif they are of interest to medicinal chemistry. The structural complexities of these functionalities invites the development of new methodologies for their synthesis.

The experimental part of the thesis appears in two Chapters. Chapter Two describes studies aimed at the enantioselective synthesis of chiral, non-racemic aza-quaternary centres via reagent-based approaches. In the first part studies are directed towards developing ephedrine-derived stoichiometric chiral aminating reagents in enantioselective nitrogen transfer, while in the second part of the Chapter the emphasis shifts to using an organocatalysis approach involving an ephedrine-hydrazide organocatalyst in conjunction with enantioselective amination methodology using an azodicarboxylate.

Chapter Three shifts to a substrate-controlled approach based on using chiral malonate-imidazolidinones as a template for amination. Using KHMDS as base it has been shown that the enolate of α-substituted chiral malonate-imidazolidinones can be azidated with trisyl azide in excellent diastereoselectivity in yields > 92 % and dr ≥ 97:3 by chiral HPLC. The products were subsequently transformed to α,α-disubstituted α-serine derivatives by a series of chemoselective steps: reduction of azide with Zn / AcOH, removal of the chiral auxiliary with LiSEt followed by reduction of the resultant thioester with lithium-tri-tert-butoxyaluminium hydride in up to 75 % yield over 4 steps. The methodology opens up the way towards establishing a general methodology for synthesizing quaternized amino acids with a broad range of R groups, both natural and unnatural in type.
Acknowledgements

I would like to dedicate this thesis to my supervisor, Prof. Roger Hunter - For his inspiring love for chemistry, unfailing support, teaching and belief in the creation of something beautiful – Thank you!

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To the NRF, SASOL and the UCT Chemistry department for financial assistance.

Finally, God, for giving me the strength to endure during this time.
List of abbreviations

α  alpha
AcOH  acetic acid
Ar  aromatic
Arq  aromatic quaternary
B  beta
bs  broad singlet
BDI  (S)-tert-Butyl-2-tert-butyl-4-methoxy-2,5-dihydroimidazole-1-carboxylate
Bn  benzyl
Boc  tert-butoxycarbonyl
BtH  1-H-benzotriazole
BtCl  1-chlorobenzotriazole
BtOH  1-hydroxybenzotriazole
Bu  butyl
C  Celsius
c-Hex  cyclohexyl
cm  centimeters
d  doublet
dd  double doublet
dq  double quartet
dr  diastereomeric ratio
DBAD  dibenzylazodicarboxylate
DCC  N,N-dicyclohexylcarbodiimide
DTAD  di-tert-butylazodicarboxylate
DCM  dichloromethane
DMAP  4-dimethylaminopyridine
DMF  dimethyl formamide
DMSO  dimethyl sulfoxide
E  electrophile
Ee  enantiomeric excess
Et  ethyl
eq  equivalence

g  gram(s)
H-bond  hydrogen-bond
Hex  hexyl
HCl  hydrochloric acid
HOMO  highest occupied molecular orbital
HPLC  high performance liquid chromatography
hr(s)  hour(s)
Hz  Hertz
IR  infrared
J  coupling constant

KHMDMS  potassium hexamethyldisilazide
LDA  lithium diisopropylamide
LiAlH₄  lithium aluminium hydride
LTBAH  lithium tri-tert-butoxyaluminium hydride
LUMO  lowest occupied molecular orbital

m  multiplet
M  molar
Me  methyl
MeOH  methanol
MeOD  dueterated methanol
min(s)  minute(s)
ml  millilitres
mM  millimolar
MS  mass spectroscopy

NaHMDS  sodium hexamethyldisilazide
NaOH  sodium hydroxide
NMM  N-methylmorpholine
NMR  nuclear Magnetic Resonance
NE₃  triethylamine
Nu  nucleophile

prop  propargyl
p  para-
P.T.  proton transfer
PTC  phase transfer catalysis

q  quartet
rt  room temperature
s  singlet
SM  starting material

t  triplet
TBAI  tetrabutylammonium iodide
TFA  trifluoroacetic acid
<table>
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<tr>
<td>TFAA</td>
<td>trifluoroacetic acid anhydride</td>
</tr>
<tr>
<td>TfOH</td>
<td>triflic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>toyl</td>
<td>toluenesulfonate</td>
</tr>
<tr>
<td>Trisyl (Tris)</td>
<td>triisopropylbenzenesulfonyl</td>
</tr>
<tr>
<td>v/v</td>
<td>volume to volume</td>
</tr>
<tr>
<td>xs</td>
<td>excess</td>
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Chapter 1

Introduction

1.1 Chiral Quaternary Centres

Nature is an inspirational source for synthetic organic chemistry in which the degree of complexity that many natural products exhibit demands the development of novel and creative methodologies in order to construct such frameworks. Not only do natural products encourage the development of new synthetic methodologies, but owing to their biological activities, they are of interest in medicinal chemistry as biologically privileged scaffolds. Many natural products contain chiral quaternary centres; a fully substituted \( \text{sp}^3 \) carbon atom bearing no hydrogen atoms, examples of which are shown in Figure 1.

**Figure 1.** Examples of chiral quaternary centres in natural products.
Quaternary centres may be of the all-carbon type or may contain three carbon bonds and a heteroatom. A nitrogen heteroatom gives rise to an aza-quaternary centre while similarly an oxygen atom gives an oxa-quaternary centre (Figure 1).\textsuperscript{1-5} One of the biggest challenges to the synthetic chemist is to be able to construct these fascinating, yet extremely sterically demanding frameworks in chiral, non-racemic form. Over the past 100 years the area of asymmetric synthesis has produced astonishing successes in the pursuit of developing highly stereoselective methodologies for synthesising chiral non-racemic molecules and this has granted practicing organic chemists access to many of nature’s synthetic mystiques.\textsuperscript{6}

1.2 The Origin of Asymmetric Synthesis

The most widely used definition of asymmetric synthesis was that written by Marckwald\textsuperscript{7} in 1904 where he states that:

\begin{quote}
"Asymmetric" syntheses are those that produce optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials, but with the avoidance of any separations.
\end{quote}

In simple terms, Marckwald’s defines asymmetric synthesis as the conversion of an achiral substance into a chiral but non-racemic product via a chiral intermediate or chiral reagent. Similarly, thirty years earlier Pasteur noted the following:

\begin{quote}
L’univers est dissymétrique
\end{quote}

\begin{quote}
The universe is dissymmetric
\end{quote}

\textit{Louis Pasteur (1874)}

\textbf{Pasteur, Le Bel and van’t Hoff}

Pasteur’s statement translates as ‘The Universe is disymmetric’, which in today’s terms can be taken as “The Universe is chiral”, and marked the beginning of a very exciting journey in the world of organic synthesis. In 1848 Pasteur made a discovery that opened the three-dimensional world that organic molecules exist in. In his work on stereochemistry he found that the ammonium salt of optically inactive tartaric acid could be physically split into two
optically active salts, one corresponding to the naturally occurring tartaric acid. More importantly, in 1860 he pointed out that many natural products were optically active whereas compounds synthesised in a laboratory were not. In 1874, Joseph Achille Le Bel and Jacobus Henricus van’t Hoff independently put forward that optically active organic molecules have a unique spacial arrangement around carbon atoms. Van’t Hoff subsequently coined the term *asymmetric carbon* and was the first recipient of the Nobel Prize in Chemistry. He did however bring it to the attention of the community that Le Bel had independently come to the same conclusions as him. The first mention of the word ‘asymmetric synthesis’ can be seen in the work of Nobel Laureate Hermann Emil Fischer. In his research on the stereochemistry of sugars, he found that when carrying out Kiliani-Fischer reactions he obtained various amounts of the two stereoisomeric sugars. These discoveries laid the foundation for the future of asymmetric synthesis.

### 1.3 Asymmetric Induction

A key component of asymmetric synthesis is the concept of asymmetric induction. This term describes the preferential formation of one stereoisomer over the other as a result of the influence of a chiral feature present in the substrate, reagent, catalyst or environment. According to Meyers, a fundamental aspect of successfully achieving a highly stereoselective reaction concerns maximizing the free-energy difference of two stereoisomeric transition-state intermediates. Graphical representation of his idea is shown in Figure 2.

![Figure 2. Transition state of an asymmetric reaction displaying the concept of asymmetric induction.](image-url)
The stereoisomeric ratio $P^r/P^s$ depends on the magnitude of the difference between the free energy of activation of the respective competing asymmetric transition states ($\Delta \Delta G^\ddagger$). It is approximated that a $\Delta \Delta G^\ddagger$ of ~2-3 kcal at 0 °C will provide a $P^s/P^r$ ratio of approximately 90:10. This corresponds to an 80 % stereoisomeric excess which is considered to be synthetically useful. For this reason, methodologies aimed at selectively producing one stereoisomer over the other must enforce a very specific environment under an optimal set of conditions in order to allow the formation of only one transition state over the other.

1.4 Current Strategies of Asymmetric Induction

There are currently two major approaches to asymmetric induction. The first involves having a chiral directing group contained within the substrate prior to the key stereoselective reaction, which gives rise to a diastereoselective reaction in which asymmetric induction is referred to as being due to substrate-control. The second involves application of a chiral catalyst or chiral reagent on a prochiral substrate (or site) and this applies to both enantioselective and diastereoselective processes. Since the chiral induction stems from the reagent rather than the substrate, these are known as reagent-controlled reactions.

1.4.1. Substrate-Controlled Synthesis

The true foundation of substrate-controlled chiral induction was laid by Meyers in 1976 who reported a highly successful diastereoselective methodology for the $\alpha$-substitution of an achiral long-chain fatty acid into a chiral $\alpha$-alkylalkanoic acids. The chiral directing group was provided by a chiral 2-oxazoline derivative (Scheme 1). The key feature controlling the stereoselectivity in this methodology was the geometrically fixed transition-state intermediate provided by chelation of the lithium cation. This brought to light that control of the facial selectivity and enolate/enamine geometry in any transition-state are the two essential components for achieving a highly diastereoselective reaction. Here, the facial selectivity was achieved through lithium chelation to the methoxy group which blocks the underneath face resulting in top-face attack in this case. The geometry of the aza-enolate was governed by steric interactions of the R group with the auxiliary in the deprotonation
step, which in this case presumably was not well controlled as evidenced by the large ee range (40 – 86 %). Later (1984) he improved these selectivities through the use of bicyclic lactams, which also had a notable application towards the synthesis of all-carbon quaternary centres (Scheme 1).13

**Pioneering work:**

\[
\begin{align*}
R &\quad \xrightarrow{i) \text{LDA / THF / -78 °C}} \quad R' \\
\text{O} &\quad \text{O} &\quad \text{Ph} \\
\text{MeO} &\quad \text{MeO} \\
\end{align*}
\]

\[
\begin{align*}
\text{\text{via}} &\quad \text{\text{via}} \\
\text{R} &\quad \text{R'} \\
\text{N} &\quad \text{N} \\
\text{Li} &\quad \text{Me} \\
\end{align*}
\]

40 - 86 ee %

**Bicyclic lactams:**

\[
\begin{align*}
\text{O} &\quad \text{O} &\quad \text{R}^1 \\
\text{N} &\quad \text{H} &\quad \text{R}^2 \\
\text{MeO} &\quad \text{Ph} &\quad \text{R'} \\
\end{align*}
\]

\[
\begin{align*}
yield: 70 - 88 \% &\quad \text{de: } 80 - 94 \% \\
\text{ii) } \text{R'} &\quad \text{ii) } \text{R'} \\
\text{X} &\quad \text{X} \\
\end{align*}
\]

\[
\begin{align*}
yield: 49 - 90 \% &\quad \text{de: } 46 - 95 \% \\
\text{ii) } \text{R}^3 &\quad \text{ii) } \text{R}^3 \\
\text{X} &\quad \text{X} \\
\end{align*}
\]

\[
\begin{align*}
10\% \text{H}_2\text{SO}_4 &\quad \Delta \\
n-\text{BuOH} &\quad \text{R}^1 \quad \text{R}^2 \quad \text{CO}_2\text{n-Bu} \\
\end{align*}
\]

**Scheme 1.** Meyers’ work on the synthesis of chiral alkylalkanoic acids

Shortly after the pioneering work numerous examples followed of successful diastereoselective approaches for the synthesis of chiral, non-racemic asymmetric centres, one of the most important contribution being the introduction of a removable and recyclable menthol-derived chiral directing group by E.J Corey in 197814 a terminology that was later redefined by Evans as “chiral auxiliary”, which has stood till today. In the article by Corey, he reported the use of a phenylmenthol chiral auxiliary that was applied to an
asymmetric Diels-Alder reaction as part of his prostaglandin synthesis F$_{2\alpha}$ and subsequently recovered post reaction (Scheme 2).

![Scheme 2. The first report of the use of a chiral auxiliary.](image)

This contribution by Corey opened the way for a rich area in the use of chiral auxiliaries in asymmetric synthesis, the most notable example being the work by David Evans at Harvard in the USA on the oxazolidinone chiral auxiliary, which will be discussed later. Since the chiral auxiliaries can be recovered and subsequently re-used, this became and is currently the premier approach in diastereoselective synthesis. It is also one of the themes of this thesis and so will constitute the majority of substrate-controlled methodologies reviewed herein. The other approach for diastereoselective synthesis, which won’t be focused on in this thesis, concerns using a chiral substrate from Nature’s chiral pool, eg carbohydrate, amino acid, terpene etc. Here, the same principle of intramolecular chirality transfer applies except the chiral inducing entity originates from the outset from within the substrate.

### 1.4.2. Reagent-Controlled Synthesis

The second and more appealing approach to asymmetric synthesis is the direct conversion of a prochiral substrate to a chiral, non-racemic product of which there are two main strategies, both of which present the chiral director via the reagent. Here, assuming the substrate to be achiral, the achievement of any asymmetric synthesis presents itself as an enantioselective process - undoubtedly one of the ultimate aims of organic synthesis emulating nature. Here, the sub-categorisation concerns catalysis or not as either involving the use of a stoichiometric amount of a chiral reagent or a sub-stoichiometric amount in a catalytic process. On this, in view of the content of this thesis only organocatalysis will feature in this review, i.e. biocatalysis and transition-metal catalytic enantiocatalysis will
not be reviewed. Although the concepts behind the transition-state intermediates of these processes are similar to those for substrate-controlled reactions, the main advantage of this approach is that a prochiral substrate can be used since the chiral induction stems from the reagent or catalyst. Furthermore, the catalyst / reagent is not incorporated into the substrate before the reaction occurs, but forms a chiral substrate / transition-state intermediate during the reaction that is subsequently eliminated from the product (Scheme 3).

1.4.3. Criteria for an Efficient Asymmetric Method

A few criteria are essential for evaluating the efficiency of an asymmetric method:

- The methodology must be highly stereoselective in terms of a dr (or de) or er (or ee).
- If a chiral auxiliary is utilised, it should be removable without affecting the newly formed stereocentre and should be recoverable without any racemization.
- If a chiral catalyst is employed, the catalyst loading should be low and the catalyst should be easily separated from the product.
- If a stoichiometric reagent is employed, the main template should be recoverable in order to resynthesize the reagent.
- Both the chiral auxiliary and the chiral catalyst should be readily available in both enantiomeric forms and be relatively inexpensive.

1.5 Substrate-Controlled Approach for Aza-Quaternary Centre Construction

Over the past few years there has been a marked increase in the development of methodologies geared towards the synthesis of chiral, non-racemic amines. These substrates are fundamental to organic synthesis as they provide access to the construction of natural and synthetic amino acids as well as many industrially important targets. The

**Scheme 3.** Reagent-controlled process
methodologies available for accessing C-N bonds may be classified into various categories, which include ring opening reactions (which won’t be reviewed herein), alkylation of chiral amino acid enolates / chiral enamines, additions to chiral imines bonds, rearrangements as well as α-aminations. One of the simplest and most general motifs found for aza-quaternary centres is the α,α-disubstituted amino acid, and methodologies geared towards the asymmetric synthesis of this class of molecule will be the main focus reviewed here.

1.5.1 Diastereoselective Alkylation of Chiral Enolates and Enaminates

In step with the pioneering work by Meyers mentioned earlier, the electrophilic α-alkylation of an α-substituted amino acid-derived enolates has been the most utilized approach for the asymmetric synthesis of an α,α-disubstituted amino acid. Ma and Ding showed that diastereoselective alkylation of a phenylglycine-derived oxazinone 1 obtained from a 3-step sequence involving a Strecker reaction afforded the corresponding dialkylated product 2 in excellent dr with a wide range of R groups (Scheme 4).

\[
\begin{align*}
\text{Reagents and conditions:} & \quad \text{NaHMS, DME, -78 °C, ii) R}_2\text{X;} \quad \text{NaOH-MeOH;} \\
& \quad \text{H}_2 (40 \text{ atm}), \text{Pd/C, EtOH, 40 °C; } \text{Dowex-50W.}
\end{align*}
\]

The enolate of 1 also reacted with various aldehydes to afford the corresponding products in lower drs ranging from 8:1 to 10:1. Similarly, in 1998 Seebach, in an extension of his well-known Self-Regeneration of Stereocentres (SRS) method, made use of a double alkylation of the lithium enaminate of glycine derivative (S)-tert-Butyl 2-tert-butyl-4-methoxy-2,5-dihydroimidazole-1-carboxylate (BDI). This approach relies on the formation of a temporary stereogenic centre that induces stereogenicity elsewhere and is then destroyed. In this case, ultimately, the Seebach methodology gave rise to α,α'-dialkylated amino acids
possessing no natural amino acid side chains in moderate to excellent yields and in very high selectivity (Scheme 5).

![Scheme 5. Double alkylation of a BDI to afford an unnatural α,α-disubstituted amino acid.](image)

Reagents and conditions: (a) i) LDA, THF, -78 °C ii) R¹X iii) n-BuLi iv) R²X; (b) i) TFA, DCM c) 4N TFA, H₂O, rt

Although this is highly efficient in preparing unnatural quaternary amino acids, the synthesis of BDI involves a 5-step procedure starting from pivalaldehyde and glycine and makes use of chiral resolution by fractional crystallization of diastereomeric salts obtained from camphorsulfonic acid and N-acetyvaline in order to obtain one enantiomer.\(^\text{16,18}\) Alkylations under phase transfer catalysis have also been developed. Nájera et al described the alkylation of Val-Ala-derived pyrazinone 4 with various electrophiles under phase transfer catalysis with TBAI (10 mol %) to afford pyrazinone 5 in excellent diastereoselectivity (Scheme 6).

![Scheme 6. Diastereoselective alkylation of chiral pyrazinones under phase transfer catalysis.](image)

Reagents and conditions: (a) K₂CO₃ (3 eq.), TBAI (10 mol %), CH₃CN, R¹X, rt; (b) i) 6N HCl, 150 °C ii) Propylene oxide, EtOH

In addition they described a palladium-catalyzed alkylation of the same Val-Ala-derived pyrazinone 4 with an allyl carbonate at room temperature to afford various allyl pyrazinones 5 in excellent diastereoselectivity (Scheme 7). The resulting pyrazinone 5 could be hydrolysed to afford various quaternary alanine amino acids.\(^\text{19}\)
As mentioned in section 1.5, Evans redefined the term chiral auxiliary to refer to only those chiral directing groups that can be non-destructively removed and recycled for future use. So far, in the diastereoselective approaches highlighted above the chiral directing groups are not non-destructively removed from the molecule and in terms of atom efficiency, which becomes much more important in industrial-scale applications. This is a big disadvantage despite the effectiveness in accessing these quaternary amino acids. This "destructibility" aspect is an inherent characteristic of most cyclic amino acid-derived enolate equivalents though. By contrast, acyclic variants are better suited for the non-destructive removal of the chiral auxiliary. An example of this can be seen in the work by Duhamel who benzylated the enaminate obtained from a phenylmenthol-derived iminoester (6) to afford 7, which was subsequently hydrolysed to the quaternary amino acid 8 in > 98 % ee with recovery of the phenylmenthol auxiliary 9 (Scheme 8).²⁰

Strangely, the authors do not describe any further variations on the alkylating agent or the R group beyond methyl, as their interest was only in the construction of proteinogenic amino acids (aza-tertiary). The synthesis of 8 was to demonstrate scope beyond simple amino acids.
1.5.2 Addition to C=N Bonds

Imines make for versatile substrates for the preparation of a variety of aza-quaternary centres via nucleophilic addition to the C=N bond (Scheme 9)\(^\text{21}\) in which a ketimine is needed to achieve the desired product.

\[
\begin{align*}
\text{NHPG} & \quad \text{R}^3\text{M} \\
\text{R}^1\text{R}^2 & \quad \text{GPHN} \\
\text{R}^3 & = \text{H, alkyl} \\
\text{R}^2 & = \text{Alkyl, aryl}
\end{align*}
\]

Scheme 9. Nucleophilic addition to imines.

Asymmetric variations that have been developed usually make use of a chiral directing group incorporated into the substrate. In these reactions the directing group blocks one face of the imine resulting in facial discrimination. Chiral sulfinamides have provided some of the best results. This approach was originally pioneered by Davis\(^\text{22}\) who made use of a p-tolyl sulfinimine (10) as an acceptor in a nucleophilic addition with the lithium enolate of methyl acetate to afford the β-amino acid derivative 11, bearing an aza-quaternary centre in 99 % de (Scheme 10).

\[
\begin{align*}
\text{S} & \quad \text{O} \\
\text{R}^1\text{N} & \quad \text{R}^2\text{H} \\
\text{R}^3 & = \text{p-tolyl, tBu} \\
\text{R}^2 & = \text{Me, Et} \\
\text{R}^3 & = \text{Me}_{3}\text{C, Et, Ph, n-Bu, p-MeOPh, p-MePh, p-NO}_2\text{Ph}
\end{align*}
\]

Scheme 10. Pioneering work by Davis demonstrating the diastereoselective addition to sulfinimines in excellent de to give rise to an aza-quaternary centre.

For application towards the stereoselective synthesis of α,α-disubstituted α-amino acids, chiral sulfinamides have been utilized as substrates in asymmetric Strecker reactions to afford a quaternary amino acid in moderate to excellent enantioselectivity upon acid hydrolysis (Scheme 11).\(^\text{23}\)

\[
\begin{align*}
\text{R}^1 & = \text{p-tolyl, tBu} \\
\text{R}^2 & = \text{Me, Et} \\
\text{R}^3 & = \text{Me}_{3}\text{C, Et, Ph, n-Bu, p-MeOPh, p-MePh, p-NO}_2\text{Ph}
\end{align*}
\]

Scheme 11. Asymmetric Strecker reaction of chiral sulfinimines to afford α,α-disubstituted amino acids.
Ellman subsequently developed the tert-butyl sulfinamide grouping in order to overcome various limitations presented by the p-tolyl auxiliary when attempting Grignard additions to the imine bond. In their application for the synthesis of α,α-disubstituted amino acids Ellman demonstrated that tert-butyl sulfinamines (12) were excellent substrates for diastereoselective Grignard addition of furan to afford sulfamine 13 in moderate to excellent yields and dr (Scheme 12). These were subsequently converted to the quaternary amino acid derivative 14.

![Diagram of Scheme 12]

Reagents and conditions: (a) AlMe3, 0 °C, toluene; (b) RuCl3, NaIO4, DCM, CH3CN, H2O

Scheme 12. Diastereoselective Grignard addition to a chiral tert-butyl sulfinamide.

Alternatively, the chiral auxiliary could be in the nucleophile. An example of this is found in the work by Fustero et al who recently described a highly diastereoselective nucleophilic addition of chiral p-tolylsulfinyl benzylcarbanion (15) to achiral 2-furyl ketimine (16) to afford the aza-quaternary centre in 17 in a dr > 98:2 in all cases. This was subsequently converted to the quaternary amino acid 18 in 3-steps (Scheme 13).

![Diagram of Scheme 13]

Reagents and conditions: (a) LDA, THF, - 78 °C; (b) TFA, MeOH; (c) Ac2O, Et3N, DMAP; (d) NaIO4, RuCl3, TMSCH2N2

Scheme 13. Diastereoselective addition of chiral p-tolylsulfinyl benzylcarbanions to imines.

The major drawback of these methodologies is that they requires destructive removal of the auxiliary. Thus the resulting sulfenic acid obtained after hydrolysis needs to be isolated and recommitted to a synthetic sequence that would regenerate the sulfinamide for
subsequent use. By contrast, Zanda made use of a chiral enolate derived from the Evans’ oxazolidinone (19) for addition to achiral iminoester (20), which gave rise to aza-quaternary product 21 in $\text{dr} = 91:9$. Subsequent removal of the auxiliary and deprotection afforded 22 in 80% yield over 2-steps (Scheme 14).²⁶

![Scheme 14. Diastereoselective addition of a chiral N-acyloxazolidinone to iminoesters.]

The only drawback with the addition to ketimines methods is, in most cases, the need for activation of the ketimine through the use of electron-withdrawing groups, which restricts the scope of R groups around the newly formed aza-quaternary centre. A solution to this is found in the work of Naito et al who employed a radical addition to a chiral camphor-derived glyoxylic oxime (23) for the synthesis of α-amino acid derivative 24 in moderate to excellent dr ranging from 86:14 - > 98:2. This was converted to the α-amino acid in 2-steps following auxiliary removal (Scheme 15).²⁷

![Scheme 15. Diastereoselective radical addition to chiral oximes.]

Although this was not developed for accessing quaternary amino acids, this was the first report of an asymmetric radical addition to C=N bonds and this laid the foundation for the development of enantioselective radical additions to ketimines for the synthesis of quaternary amino acids, which will be mentioned later in Section 1.6.2
1.5.3 Rearrangements

The Hofmann rearrangement$^{28}$

Falling under the class of rearrangements, The Hofmann rearrangement is the earliest methodology (1881) that gave organic chemists access to synthetic amino acids. This reaction proceeds via an isocyanate that is generated by the degradation of an $N$-haloamide through an acylnitrene intermediate generated under the reaction conditions. The isocyanate is then intercepted by water to form a carbamate which decarboxylates to give the amine (Scheme 16).

This work pioneered the development of various other useful rearrangement methodologies such as the Curtius and the Schmidt rearrangement.

The Curtius rearrangement$^{29}$

Similar to the Hofmann rearrangement, the Curtius rearrangement also proceeds to the amine via the isocyanate through an acylnitrene. The key difference between the two is that the Curtius involves the use of an acyl azide rather than an acetamide. Mechanistically, this poses interesting questions as to the mechanism of the Curtius rearrangement. Upon heating, the acyl azide decomposes to an acyl nitrene and subsequently rearranges to give the isocyanate which, following the same steps as the Hofmann, affords the amine (Scheme 17).

Additional methodologies invoking the carboxylic azide and/or acyl nitrène methodologies such as the Schmidt reaction$^{30}$ have also been developed. Although these rearrangements do not involve the use of an asymmetric reaction, an important thing to note is that they do
however proceed with retention of configuration of the migrating group. Thus, for aza-quaternary centre production a quaternized R group would already need to be in place. An example of this can been seen in the work by Cativiela who made use of a Curtius rearrangement for the transformation of α-cyano acid 26 - obtained from the alkylation of the camphor-derived cyano ester 25 in a moderate 80:20 dr - to its corresponding amino acid (Scheme 18).\(^{31}\)

\[
\begin{align*}
\text{CN} & \quad \text{CO}_2R \\
\text{(a)} & \quad \text{R}^1 & \quad \text{CN} & \quad \text{CO}_2R \\
\text{25} & \quad \text{(b)} & \quad \text{CO}_2H & \quad \text{CN} & \quad \text{R}^1 & \quad \text{CO}_2H \\
\text{R}^1 & = \text{CH}_2\text{CH=CH(CH}_2)_5\text{CH}_3 & \text{dr} & = 78:22
\end{align*}
\]

*Reagents and conditions:* (a) K₂CO₃, acetone, R¹Br; (b) H₂, Pd/C; (c) SOCl₂; (d) NaN₃; (e) toluene, reflux; (f) HCl, reflux

**Scheme 18.** Synthesis of quaternary amino acid employing a Curtius rearrangement.

In addition to the moderate dr, Cativiela reported that this methodology was limited to only using stabilized nucleophiles in the quaternization step. On the other hand, Tanka *et al* reported the synthesis of various quaternary α-amino acids through a sequence involving a Schmidt rearrangement of a chiral α,α-disubstituted β-ketoester (28) as the key step (Scheme 19).

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{CO}_2\text{Et} \\
\text{(a)} & \quad \text{R}^1 & \quad \text{OH} & \quad \text{CO}_2\text{Et} \\
\text{27} & \quad \text{(b)} & \quad \text{CO}_2\text{Et} & \quad \text{AcHN} & \quad \text{CO}_2\text{Et} \\
\text{31 -70 %} & \quad 92 \text{ to } >95 \text{ % de} & \quad \text{R}^1 & = \text{Me, Et} & \quad \text{R}^2 = \text{nPr, iPr, nBu, iBu, Bn, allyl} & \quad X = \text{Br, I}
\end{align*}
\]

*Reagent and condition:* (a) LDA, R²X, THF, HMPA, -78 °C to -40 °C; (b) BF₃.OEt, EtOH, H₂O, rt; (c) NaN₃, TfOH, reflux.

**Scheme 19.** Synthesis of quaternary amino acids via a key Schmidt reaction of 28.

The ketoester (28) was obtained in low to moderate yield but very high de (92 - >95 % de) through diastereoselective alkylation of chiral acetal (27) (derived from (1S, 2S)-cyclohexane-1,2-diol) with a variety of nucleophiles.\(^{32}\)
1.5.4 Diastereoselective α-Amination of Carbonyl Compounds

A more versatile approach towards the synthesis of aza-quaternary centres is through the direct introduction of nitrogen via a suitable nitrogen electrophile. This strategy is more attractive than the alkylation methodologies as it allows for greater variations in the R groups around the newly formed stereocentre, since the nitrogen atom is introduced last. As a synthon, electrophilic aminating reagents are essentially sources of \([\text{NH}_2]^+\). They present themselves either as an \(sp^3\) hybridized nitrogen bearing a leaving group of the form \(R_2N-LG\), of which \(N\)-haloamines and hydroxylamines bearing an O-leaving group are common. Alternatively, several \(sp^2\) \(\pi\)-acceptors are available including oximes, azodicarboxylates, azides, nitro and nitroso compounds. Figure 3 shows a few examples.

![Figure 3. Various aminating reagents.](image)

Cativiela carried out α-aminations on chiral camphorsulfonic acid-derived cyano esters 29 using \(O\)-(diphenylphosphinyl)hydroxylamine to afford amine 30 bearing an aza-quaternary centre in excellent yield, but moderate dr (> 80:20) (Scheme 20).³³

![Scheme 20. Diastereoselective α-amination using a camphor-derived auxiliary in a moderate dr.](image)

Reagents and conditions: (a) i) LiHMDS, THF, -78 °C ii) \(O\)-(diphenylphosphinyl)hydroxylamine; (b), \(H_2\)-Rh/\(Al_2O_3\), MeOH, \(NH_3\); (c) KOH, MeOH

\[ R^1 = \text{Me, propyl, } \text{tButyl, Bn} \]
Felice *et al.* reported the α-amination of a chiral phenylethylamine-derived enamine (31) with ethyl-N-((4-nitrobenzenesulfonyl)oxy)carbamate to afford the cyclic amino acid derivative 32 in excellent yield but similarly in only a moderate dr of 80:20 ([Scheme 21](#)). The absolute configuration was not determined.\(^34\)

![Diagram](#)

*Reagents and conditions:* (a) NsONHCO\(_2\)Et, DCM, 2 days

**Scheme 21.** Diastereoselective α-amination of phenylethylamine-derived enamine afforded 32 in a dr = 80:20.

The best example of a diastereoselective α-amination approach to the construction of α,α-disubstituted amino acids was reported by Castellanos in 2004 using the diastereoselective α-amination of chiral pyrimidinone 33 derived from valine and glycine, with di-tert-butyl azodicarboxylate to afford the hydrazide product 34 in excellent de, which was subsequently transformed to a quaternary amino acid in a 3-step sequence ([Scheme 22](#)).\(^35\)

![Diagram](#)

*Reagents and conditions:* (a) i) LDA, THF, -78 °C ii) DTAD; (b) TFA, DCM, rt; (c) Raney Ni/H\(_2\) (69 bar), MeOH, rt; (d) 6N HCl, 90 °C.

**Scheme 22.** Diastereoselective α-amination of a chiral pyrimidinone for the synthesis of quaternary amino acids.

However, there are disadvantages to the method regarding the scope of R, and as mentioned before, it does not make use of a recyclable chiral directing group. These are three of few reports that make use of diastereoselective α-amination to access azaquaternary centres in chiral, non-racemic form, which highlights the potential for methodology development in this area.
1.6 Reagent-Controlled Approach for Aza-Quaternary Centre Construction

As mentioned before, stereoselective reagent-controlled synthesis involves the transformation of a prochiral site, invariably contained in an achiral substrate into a chiral, non-racemic entity (site) through the use of a chiral catalyst or reagent. In the case of an achiral substrate the transformation is unambiguously defined as enantioselective if the product ee is above 0%. Such a designation is by degree and defined in terms of a % ee. Conversely, if the substrate contains one or more stereogenic centres in addition to the prochiral site, the transformation should be taken as diastereoselective. Here, complexities arise in that there may be a matched or mismatched double asymmetric induction process operating if the existing chirality in the substrate exerts an influence on the asymmetric induction process. Conversely, if the chirality does not play a role, as reflected in a 50:50 diastereomeric mixture produced with an achiral version of the chiral reagent, then the same reaction with the chiral reagent has connotations of being enantioselective with respect to the prochiral functionalization process.

1.6.1 Stoichiometric Chiral Reagents

An obvious approach to developing a reagent-based methodology is to incorporate chirality in an auxiliary fashion into the reagent on the understanding that it is lost on work-up. Such an approach demands the reagent to be in stoichiometric amount. An example applied to quaternary amino acid synthesis is Leighton’s ephedrine-derived chiral allylating reagent (35), synthesized by the reaction of (1S, 2S)-pseudoephedrine with allyltrichlorosilane and Et₃N in DCM (Scheme 23) and introduced in 2002.

![Scheme 23. Synthesis of the chiral allylating reagent 35.](image)

Reagents and conditions: (a) allyltrichlorosilane, Et₃N, DCM

Reagent 35 was successfully applied to the enantioselective allylation of ketone-derived hydrazone (36) to afford the aza-quaternary derivative (37) in good yield and very high ee % and with 98 % recovery of the pseudoephedrine (Scheme 24).³⁶
In order to produce the free amine, 37 was treated with SmI₂ and for the case of R₂ = CO₂Me gave rise to an α,α-disubstituted amino acid. To the best of our knowledge this is the only application of the use of a chiral reagent for the nucleophilic addition to ketimines. At the other end of the reactivity spectrum, the first report of a chiral aminating reagent occurred in 1992 by Oppolzer et al who made use of an α-chloro-α-nitroso-camphor derivative (38) as a source of an aza-electrophile towards a lithium enolate, producing, as a representative example, nitrone 39 in > 96 % ee, which was subsequently reduced to amine 40 in 3-steps (Scheme 25). Although this was not applied to the synthesis of aza-quaternary centres, it is an invaluable proof-of-principle for the concept of a chiral aminating reagent, a theme explored in this thesis.

Interestingly, in spite of this work, there have been no subsequent reports of chiral aminating reagents. Overall, research in the development of chiral reagents has not received the amount of attention that might have been expected in terms of their potential impact in asymmetric synthesis.
1.6.2 Organocatalysis – Aminocatalysis

The area of organocatalysis refers to the use of chiral organic catalysts to bring about stereoselective reactions, and falls under the umbrella of ‘green technology’. The major advantage they have over the classical organometallic catalysts is that they are typically non-toxic and are stable to water and air; qualities considered to qualify them to fall sufficiently within the description of ‘green’ chemistry. The substantially large majority of these are chiral amines, and therefore organocatalysis is often also referred to as aminocatalysis. The true beauty of aminocatalysis is that it allows chemists to construct complex molecules following directives given by nature.

Proline catalysis

The earliest example of aminocatalysis can be found in the 1970s in the work of Hajos, Parrish, Eder, Sauer and Wiechert who carried out a proline catalyzed intramolecular aldol cyclization in excellent yield and selectivity (Scheme 26).


Hajos and Parish considered this work to qualify as a simple model of a biological system in which proline plays the role of the enzyme.

Activation modes

Although this pioneering work was carried out in the 1970s, it wasn’t until the beginning of the 21st century that the true potential of this discovery was realised. In 2000, List, Lerner and Barbas reported that a catalytic amount of L-proline could be used to promote the direct aldol reaction between acetone and various aldehydes in excellent yields and enantioselectivities (Scheme 27).

![Scheme 27. Proline catalysed crossed aldol reaction of acetone and various aldehydes in excellent yield and enantioselectivity.](image)
Shortly thereafter, MacMillan et al described the first asymmetric amine-catalysed Diels-Alder reaction (Scheme 28). This reaction proceeded with excellent yield and an 94:6 endo/exo diastereoselectivity as well as a 94 % ee. This work also introduced the 4-imidazolidinone catalyst (MacMillan’s catalyst) to the scientific community.

\[
\text{Scheme 28. The first amine catalysed asymmetric Diels-Alder reaction.}
\]

From these key reports two activation modes of aminocatalysis emerged (Scheme 29) as iminium ion and enamine catalysis, and this laid the foundation for a rich era in asymmetric synthesis and catalysis. The latter is relevant to work described in this thesis.

**Enamine catalysis – Transition-state models**

As mentioned earlier in section 1.4.1 the key to obtaining a highly stereoselective reaction lies with being able to fix the enolate geometry in conjunction with diastereofacial selectivity. This is similarly true with enamine catalysis. Depending on the catalyst employed, there are two different models of chiral induction for setting the facial selectivity. The first involves a hydrogen bond-assisted model if the catalyst possesses a H-
bond donor atom. This draws the electrophile in and addition occurs from the same face as the chiral group. In the absence of an H-bond donor, the chiral directing group serves instead as a blocking group and therefore the electrophile (E) adds from the opposite face. This is known as a steric model. Known examples are illustrated in Figure 4 involving proline and the Jørgensen catalyst respectively.

![Figure 4](image)

**Figure 4.** Modes of chiral induction.

With respect to the geometry of the enamine, it can be seen in Figure 4 above, that the sterically less-demanding E-enamine is favoured and this feature has a telling influence on the varied success observed in aza-quaternary centre construction via proline catalysed α-amination. The enamine geometry also favours an s-trans conformation with respect to the C-N sigma bond. An example of the importance of enamine configuration can be seen in the proline catalyzed α-amination of two aldehydes shown in Scheme 30.43

![Scheme 30](image)

**Scheme 30.** Proline catalyzed α-amination of aldehydes vs ketones.
The aldehyde 41, produced the corresponding amination product in > 99 % ee via an E-enamine while the enantioselectivity of the reaction of 42 was largely dependent on R₂ due to obtaining a mixture of enamine geometrical isomers, and ees up to only 86 % were obtained for that reaction. In this regard, primary amines have an advantage over secondary amine catalysts due to steric hindrance. In 2013, Kokotos et al reported a highly enantioselective β-tert-butyl aspartate catalyzed α-amination of acyclic aldehydes 43 with di-tert-butyl azodicarboxylate to afford 44 in moderate to very high yields and high enantioselectivity (Scheme 31). When R₂ was replaced with an alkyl group, the ee dropped to ee < 65 %. Except for when R₂ = -CH₂OTBDMS, a bulking group, the ee = 89 %.

![Scheme 31. Primary amine catalyzed α-amination of aldehydes.](image)

The adduct 44 bearing a phenyl and methyl group was subsequently transformed to the quaternary amino acid methyl ester derivative 45 in 2-steps in 52 % overall yield and 93 % ee (Scheme 32).⁴⁴

![Scheme 32. Conversion of 44 to the quaternary amino acid derivative 45.](image)

Reagents and conditions: (b) i) NaClO₂, H₂O₂, NaH₂PO₄ ii) TMSCHN₂, MeOH/EtOH, rt; (c) SmI₂, N₂, THF, MeOH, rt

Usually, primary amines are inferior asymmetric enamine catalysts to secondary amines due to σ-bond rotation around the nitrogen. This will be discussed later in the thesis.
Non-covalent aminocatalysts for aza-quaternary centre construction

The limitations of secondary amine enamine catalysis begins to emerge when using ketones as the substrate. This is primarily due to the unfavourable steric aspects involved with enamine formation since ketones are more sterically demanding than aldehydes. A solution to this is found through the use of Cinchona alkaloids. Cinchona alkaloids provide chiral enolates as an acid-base pair upon deprotonation of a substrate and are able to successfully catalyze enantioselective α-aminations with yields and selectivity comparable to those of transition-metal catalysts. Jørgensen showed that the direct α-amination of various aryl cyanoacetates could be effected using tertiary amine cinchona alkaloids (46) in excellent yield. (Scheme 33).45

![Scheme 33. Direct amination catalyzed by cinchona alkaloid derived catalysts.](image)

Cinchona alkaloids have also been used under phase-transfer conditions for the synthesis of quaternary amino acids. Jew and Park et al made use of a hydrocinchonidinium bromide derivative 47 as a phase-transfer catalyst (PTC) for the enantioselective alkylation of iminoalaninates 48 in good to very high ee % and these were subsequently hydrolysed to the corresponding quaternary alanine amino acid 49 (Scheme 34).46

![Scheme 34. Enantioselective alkylation of iminoalaninates via cinchona-derived phase-transfer catalysis.](image)
In a similar reaction, Maruoka et al designed a $C_2$-symmetric chiral quaternary ammonium bromide 50, and applied it to the double alkylation of iminoglycinates 51 under phase-transfer catalysis to afford 52 in moderate yields and 92 – 98 % ee (Scheme 35).47

![Reaction Diagram](attachment:reaction_diagram.png)

*Reagents and conditions: (a) i) 50 (1 mol %), R$^1$Br, CsOH.H$_2$O ii) R$^2$Br; (b) citric acid*

Scheme 35. Enantioselective double alkylation of iminoglycinates via PTC.

The main drawback of these catalysts is the cost required either to purchase or synthesize them. Another class of non-covalent catalyst is the hydrogen-bonding type. Jacobson reported the first asymmetric Strecker reaction of various ketimines (53) using hydrogen-bonding catalyst 54 for the synthesis of quaternary products 55 in high yields and enantioselectivity, which were subsequently transformed to quaternary amino acids in 3-steps (Scheme 36). The ee % of 55 could be increased to > 99 % by recrystallization. Limitations to this methodology were the substituents of ketimine 53. The best results were obtained when one aromatic group and a methyl R group were employed. Replacing the methyl with an ethyl or 1Bu resulted in an ee % of 69 and 70 % respectively. Furthermore, if an ortho-substituted aromatic group was used the ee % decreased to 42 %.48

![Reaction Diagram](attachment:reaction_diagram1.png)

*Reagents and conditions: (a) 54 (2 mol %), toluene, - 75 °C; (b) HCO$_2$H / Ac$_2$O; (c) conc. HCl, 105 °C; (d) H$_2$ / Pd-C, aq. MeOH / HCl*

Scheme 36. Enantioselective Strecker reaction using hydrogen-bonding catalyst 54.

In another application of an H-bond catalyst for the synthesis of aza-quaternary motifs, Xie et al made use of an enantioselective aza-Henry reaction of 2(1H)-quinazoline (56) with
nitromethane using a bifunctional chiral cinchona-derived thiourea H-bond catalyst 57 to afford the aza-Henry adducts 58 in excellent yield and ee % (Scheme 37).

Scheme 37. Enantioselective aza-Henry reaction using bifunctional cinchona-derived catalyst 57.

As mentioned before, the limitation of ketimine addition methodologies is the need for electron-withdrawing groups in order to activate the ketimine and this is evident with 56, where a CF$_3$ group was used for the transformation. Nevertheless this was a key step in the synthesis of the anti-HIV drug, DPC 083 (Scheme 38).$^{49}$

Scheme 38. Synthesis of anti-HIV drug DPC 083 via a key enantioselective aza-Henry reaction.

Kim et al have recently investigated the enantioselective radical addition to ketimines using bifunctional cinchona alkaloid catalysts for the synthesis of chiral, non-racemic quaternary amino acids (Scheme 39). Early reports indicate that enantioselectivities are very high for variations of the R group in the ketimine as well as the alkyl halides. The nature of the stereo-induction process however is not known and further investigations are currently being carried out to determine this, although it is known to be a cinchona-derived catalyst.
Another approach to aza-quaternary construction is via alkylation of α-nitro enolates. Recently, Bera and Namboothiri reported the enantioselective Michael addition of α-nitrosulfone (59) to various vinyl ketones to afford the α-nitro-δ-ketosulfone (60) in excellent yield and very high enantioselectivity, via the use of cinchona-derived catalyst 61 (Scheme 40).^50_

\[ \text{Scheme 39. Enantioselective radical addition to ketimines.} \]

![Diagram of enantioselective radical addition to ketimines.](image)

\[ \text{Reagents and conditions: (a) } \text{PrI, cat, Ph}_2\text{SiH}_2, \text{Et}_3\text{B/O}_2, \text{C}_2\text{H}_4\text{Cl}_2, -30 \, ^\circ\text{C}; (b) } \text{R}_2\text{I, cat, Ph}_2\text{SiH}_2, \text{Et}_3\text{B/O}_2, \text{C}_2\text{H}_4\text{Cl}_2, -30 \, ^\circ\text{C} \]

The methodologies above highlight applications to the stereoselective synthesis of quaternary aza-centres as this is the primary focus of this thesis. There are, however, other methods available for the asymmetric introduction of nitrogen that are worth mentioning, although they won't be reviewed owing to their application primarily to the synthesis of aza-tertiary centres. These include stereoselective aza-Michael additions (both amine and azide nucleophiles) as well as nitrogen and carbon-centred radical methodologies.^51
1.7 Concepts in this Thesis Regarding the Development of New α-Amination Methodologies for Aza-Quaternization

As mentioned earlier, the introduction of the nitrogen atom last in the synthesis of an aza-quaternary centre is a more versatile approach as this allows for more variation of the R groups around the aza-centre. It requires α-amination as a direct method for installing the nitrogen atom, and is the central focus of endeavours in this thesis towards the development of new asymmetric α-amination methodologies for the synthesis of chiral, non-racemic aza-quaternary centres via both reagent-controlled as well as substrate-controlled strategies. Based on the current interest as well as previous success within the group, all of the methodologies investigated herein, centre around the use of an ephedrine-derived imidazolidinone, (4R, 5S)-(-)-1,5-dimethyl-4-phenyl-2-imidazolidinone (Aux) (Figure 5) as the source of chiral induction.

![Figure 5. Chiral 2-imidazolidinone Aux. The key scaffold of this thesis.](image)

1.7.1 Reagent-Controlled Approach – Concepts and Objectives

Stoichiometric chiral aminating reagents
As mentioned in section 1.6.1, there are not many reports in the chemistry literature involving the use of chiral reagents, and to the best of our knowledge, there is only one report of a chiral aminating reagent, namely the camphor-derived nitroso compound 38 (Scheme 25). The first investigation herein involved the design, synthesis and reactions of a chiral aminating reagent based on the chiral imidazolidinone Aux of the form E-Aux, where ‘E’ is seen to be a potential source of electrophilic nitrogen, and the Aux as the leaving group as well as the chiral directing group (Figure 6).
Organocatalysis
The second reagent-based approach described in the thesis involved studies into transforming Aux and its derivatives into suitable organocatalysts.

1.7.2 Substrate-Controlled Approach – Concepts and Objectives
Finally, this thesis also investigated a substrate-based approach involving the diastereoselective α-aminations of malonate-auxiliary systems (62) as a key step for the stereoselective synthesis of chiral, non-racemic α-amino acid derivatives following removal of the auxiliary (Scheme 41).

Malonates were chosen for this study owing to their well-known C-2 alkylation reactivity as well as the potential for further transformation and functionalization at C-1. However the most attractive feature was the possibility to fix the enolate geometry by metal chelation between the dicarbonyl system (Figure 7) which, in theory, could realize the preferential formation of a single enolate.
Furthermore, the auxiliary conformation around the C-N bond in the transition-state, involving either an $s$-trans$_{C-N}$ or an $s$-cis$_{C-N}$ conformation (Figure 8) was also considered to be of key importance. All these concepts will be addressed herein.

**Figure 7.** Envisaged metal chelation to fix the enolate geometry.

**Figure 8.** Auxiliary conformations in the transition-state.
Chapter 2

Studies Towards the Enantioselective Construction of Aza-Quaternary Centres

2.1 Stoichiometric Reagent-Controlled Approach

In contrast to a diastereoselective substrate-controlled approach that requires prior instillation of a chiral director, a reagent-controlled process has the advantage of using an achiral substrate directly, and introducing the chirality through the use of a chiral reagent. This is beneficial as it avoids the extra steps involved to insert and remove a chiral auxiliary. For this, it was decided to transform the chiral imidazolidinone Aux in a single step into a possible enantioselective electrophilic aminating agent of an α-substituted β-keto ester (Scheme 42).

![Scheme 42](image)

Scheme 42. Envisaged enantioselective amination of β-keto esters using a chiral aminating reagent.

It was decided to use a β-keto ester as nucleophile rather than a malonate as it contains different functional groups that can be discriminated, whereas malonates suffer from issues of ester group differentiation post functionalization. Electrophilic amination is well known in organic synthesis via reagents of the type R₂N-Lg where Lg is a good leaving group in which chloramine and sulfonic or phosphoric acid-derived hydroxylamines are typical reagents for this purpose. These are achiral however and do not transfer the ‘NH₂’ in a stereoselective manner. Similarly, alkyl nitrites and acetyl nitrates are typical achiral nitrosating and nitrating reagents respectively. Therefore, in addition to using an amino group as the transferring group it was also considered possible to extend the range to azido, nitro and nitroso as the respective transfer reagents or as synthetically useful masked ‘NH₂’ synthons, and this led to the identification of four potential chiral imidazolidinones for the asymmetric introduction of azide, nitro, nitroso or amino functional groups (Figure 9).
The synthesis of hydrazide 64 could be envisaged via reduction of 65, 66 or 67 and therefore its synthesis was kept for last.

![Figure 9. Imidazolidinone derivatives as possible electrophilic chiral aminating reagents.](image)

It was first decided to attempt the synthesis of 65 by reaction of Aux with trisyl azide. As degradation of the resulting triazene product to the desired azide is facilitated by potassium acetate, the reaction was first carried out using 1.2 eq of potassium acetate at room temperature (RT) on the understanding that the KOAc would also serve as a base (Scheme 43). This reaction however did not occur and all of the starting material was recovered. Owing to the potential explosive hazard of the product, temperatures above room temperature were avoided, and it was thought that at this temperature KOAc was not basic enough to remove the proton of Aux in order to effect the reaction.

![Scheme 43. Attempted synthesis of 65 by reaction of Aux with trisyl azide in the presence of KOAc.](image)

When carrying out the reaction with the much stronger base, KHMDS, in THF at 0 °C, warming to rt and quenching with acetic acid after 24 hrs in order to generate potassium acetate in situ, none of the desired azide 65 was obtained, although 20 % of 68 was isolated.
in its protonated form (Scheme 44), and so the azidation was abandoned and attention turned to the nitration of Aux for the synthesis of 66.

\[
\text{Aux} \xrightarrow{\text{i) KHMD, THF, 0 °C}} \text{Ar-NO}_2 + \text{N}_3-\text{Aux}
\]

\[
\begin{array}{c}
\text{68} \\
\text{20 %}
\end{array} + \begin{array}{c}
\text{65} \\
\text{0 %}
\end{array}
\]

Scheme 44. Attempted azidation with the potassium anion of Aux.

For nitration of Aux using the customary H$_2$SO$_4$ / HNO$_3$, in the first instance, there was a chemoselectivity concern between N-nitration and nitration of the auxiliary phenyl group due to the highly electrophilic nature of the nitronium ion. In the event, TLC of the reaction revealed several spots. Similarly, carrying out the reaction with NO$_2$BF$_4$ also gave a variety of spots. Thus, a milder nitrating agent was chosen in the form of trifluoroacetyl nitrate (69), which is well known in the literature and can be generated in situ by the reaction between trifluoroacetic acid anhydride (TFAA) and potassium nitrate (KNO$_3$) via a $S_N$Ac-type mechanism (Scheme 45).

\[
\text{TFAA} \xrightarrow{\text{KNO}_3, \text{CH}_3\text{CN}} \text{69}
\]

Scheme 45. Generation and reactivity of trifluoroacetyl nitrate.

This was applied to the nitration of Aux at RT, which gave $N$-nitroimidazolidinone 66 as a crystalline yellow solid in 96 % yield after chromatographic purification (Scheme 46).

\[
\text{Aux} \xrightarrow{69, \text{CH}_3\text{CN, rt, 12 hrs}} \text{66}
\]

96 %

Scheme 46. Synthesis of $N$-nitroimidazolidinone 66.
TLC gave the first indication that a different compound was formed as 66 was much less polar than the starting material. Analysis of the $^1$H NMR spectrum showed a downfield shift of all the protons when compared to those of Aux, in accordance with the presence of the electron-withdrawing nitro group (Figure 10).

![Figure 10](image.png)

*Figure 10. $^1$H-NMR spectrum of N-Nitroimidazolidinone 66.*

The largest shift was seen for the benzylic proton doublet from 4.70 ppm in Aux to 5.53 ppm due to the further delocalization of the N lone pair into the nitro group which leaves a greater degree of positive charge on N-1, which is transmitted to the adjacent benzylic H via inductive effects (Figure 11).

![Figure 11](image.png)

*Figure 11. Main resonance contributors of Aux and 66.*
Key confirmation that a successful nitration had taken place was obtained from the IR spectrum which revealed two sharp bands at 1537 cm\(^{-1}\) and 1370 cm\(^{-1}\) typical of a nitro group. It was a concern that since TFAA (2 eq.) was used to generate the nitrating agent, a trifluoroacetylation might have occurred instead of the desired nitration. A trifluoroacetylated imidazolidinone would display similar \(^1\)H shifts as it is also very electron-withdrawing and can produce resonance effects similar to that of 66. However, the \(^{13}\)C-NMR of 66 displayed only 9 carbon resonances which confirmed that no acylation took place (Figure 12). In addition, an \(^{19}\)F-NMR spectrum did not show a fluorine resonance.

The synthesis of 66 was then subsequently confirmed by elemental analysis. Similarly, the synthesis of nitrosoimidazolidinone 67 was achieved in high yield via acyl substitution of Aux with amyl nitrite in DCM or ethyl nitrite in EtOH (Scheme 47).

![Figure 12. \(^{13}\)C-NMR spectrum of 66.](image)

![Scheme 47. Synthesis of 67 by reaction of Aux with amyl nitrite.](image)
Similarly, the IR spectrum of the product indicated the presence of a N-nitroso group by the presence of the characteristic N=O absorption bands at 1426 cm\(^{-1}\) and 1398 cm\(^{-1}\). As before, the diagnostic signal in the \(^1\)H-NMR of 67 was the downfield shift of the benzylic proton to 5.31 ppm when compared to Aux (Figure 13).

The \(^1\)H-NMR spectra of 66 and 67 very nicely correlate with NMR spectroscopy theory as nitro groups are more electron-withdrawing than nitroso groups and this can be seen distinctly in the relative degree of deshielding in the benzylic resonances, namely 5.53 ppm for the nitro and 5.31 ppm for the nitroso compound. As mentioned before, access to hydrazide 64 was envisaged to be viable by reduction of 66 or 67. A nitroso functionality is a known intermediate in the reduction pathway of a nitro group to the corresponding amine and it therefore seemed sensible to start with 67 for the synthesis of the hydrazide 64. The reduction was carried out using Zn and acetic AcOH, which afforded the desired amino-imidazolidinone 64 in 98 % yield after chromatographic purification (Scheme 48).
The reduction could also be performed via catalytic hydrogen using Pd/C. For the purposes of safety and cost, however, the Zn/AcOH methodology was selected as the preferred option. Interestingly though, any attempts with Zn/AcOH or H₂ to reduce the N-nitroimidazolidinone 66 to the hydrazide resulted in the cleavage of the N-N bond, in which imidazolidinone Aux was recovered in quantitative yield. The H-NMR of spectrum of hydrazide 64 showed a broad singlet at 3.77 ppm integrating for two protons for the NH₂ (Figure 14).

In addition, the benzylic doublet shifted upfield to 4.58 ppm when compared to 5.31 ppm in the starting material and this was consistent with the loss of the electron-withdrawing nitroso group.
Furthermore the IR spectrum revealed the absence of the nitroso signals as well as a broad band at 3685 cm⁻¹ for the NH₂. A correct elemental analysis confirmed the correct molecular formula.

**Application to the amination of β-ketoesters**

Ethyl 2-benzylacetooacetate (63a) was chosen as a model for a possible amination with 64, and synthesized via C-2 benzylation of ethyl acetoacetate in 96 % yield using NaH as the base (Scheme 49).

![Scheme 49. Synthesis of 63a.](image)

The ¹H-NMR and ¹³C-NMR spectra of 63a were identical to the literature data. Hydrazide 64 was first investigated for the amination of 63a to afford 70 using base catalysis (Table 1).

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Base (1.2 eq)</th>
<th>Lewis acid</th>
<th>Temperature (°C)</th>
<th>Yield of 70 (%)</th>
<th>Recovered 64 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOEt</td>
<td>-</td>
<td>reflux</td>
<td>0</td>
<td>quant.</td>
</tr>
<tr>
<td>2</td>
<td>NaH</td>
<td>-</td>
<td>reflux</td>
<td>0</td>
<td>quant.</td>
</tr>
<tr>
<td>3</td>
<td>NaH</td>
<td>BF₃.OEt (1 eq)</td>
<td>reflux</td>
<td>0</td>
<td>quant.</td>
</tr>
<tr>
<td>4</td>
<td>LDA</td>
<td>-</td>
<td>reflux</td>
<td>0</td>
<td>quant.</td>
</tr>
<tr>
<td>5</td>
<td>LDA</td>
<td>BF₃.OEt (1 eq)</td>
<td>reflux</td>
<td>0</td>
<td>quant.</td>
</tr>
<tr>
<td>6</td>
<td>KHMDS</td>
<td>-</td>
<td>reflux</td>
<td>0</td>
<td>quant.</td>
</tr>
<tr>
<td>7</td>
<td>KHMDS</td>
<td>BF₃.OEt (1 eq)</td>
<td>reflux</td>
<td>0</td>
<td>quant.</td>
</tr>
</tbody>
</table>

A variety of bases were screened, however all failed to produce any reaction and both 64 and starting material 63a were recovered quantitatively. Increasing the temperature also
did not provide the desired amination product. In order to enhance the leaving ability of the imidazolidinone the relatively hard Lewis acid BF$_3$.OEt was introduced in the hope that O-complexation would improve the electrophilicity of the amino nitrogen as shown in (Figure 15), but this also failed to promote reaction (entries 3, 5 and 7).

![Figure 15. Envisaged lewis acid assisted transfer of 64 to an incoming nucleophile.](image)

At this stage it was concluded that 64 was not electrophilic enough despite attempts to enhance electrophilicity. It was presumed that an sp$^2$ hybridized nitrogen would be more effective for this transformation because of the opportunity for p$_{π}$-p$_{π}$ overlap, and so the investigation was therefore turned to the chiral transfer of a nitro group using N-nitroimidazolidinone 66 to afford nitro derivative 71 (Scheme 50).

![Scheme 50. Envisaged enantioselective nitration of 63a to afford 71.](image)

This reaction was subjected to the same base-catalyzed conditions as per Table 1, but once again, no reaction occurred and there was a complete recovery of 66. As before, it was suspected that 66 was not electrophilic enough for this reaction and this was reasoned to be due to delocalization of electrons between all three nitrogen atoms. Lastly, the asymmetric nitrosation of 63a was attempted using chiral N-nitrosoimidazolidinone 67. The first experiment was carried out using NaOEt as a base at 0°C. After 5 min there was a complete conversion of 67 and this was accompanied by the formation of imidazolidinone Aux (by TLC), suggesting that the nitroso group was successfully transferred. A product was isolated in 97 % after column chromatography and its $^1$H-NMR spectrum revealed this to be oxime 73 rather than the expected nitroso derivative 72 (Scheme 51).
It was postulated that 72 does indeed form, but is quickly converted to 73 via a base-mediated deacetylation (Figure 16).

To probe this reaction mechanism, it was decided to utilize a cyclic β-ketoester on the basis that deacylation would retain the acyl group. Significantly, reaction of cyclohexanone carboxylic ester 74 produced oxime 76, which was produced after 10 min in a 90 % isolated yield and with complete recovery of Aux, strongly supporting the proposed mechanism (Scheme 52).

The reaction could also be brought about by an acid-catalyzed process. Hence, reaction of 74 with 67 and 5 mol % H₂SO₄ in EtOH also gave 76 within 10 min, which was isolated in 96 % yield (Scheme 53).
This indicated that fragmentation could also be promoted by acid-catalyzed activation of the carbonyl group followed by attack by the poorly nucleophilic EtOH (Scheme 53). Presumably, the ketone carbonyl group electrophilicity is also enhanced by the electron-withdrawing nitroso group. To provide further evidence for this deacylation pathway, the acid mediated process was carried out in acetonitrile (Ar grade), and acid 77 was obtained in 94 % yield (Scheme 54), vindicating the mechanism.

![Scheme 54. Acid catalyzed reaction of 74 with 67 in acetonitrile (not dry).](image)

At this point it was wondered whether the fragmentation could be suppressed by nitrosating under aprotic conditions. However, when the reaction was conducted in THF using NaH as a base, no reaction was obtained and 67 was completely recovered. Table 2 summarizes these results.

**Table 2. Reaction of 74 with 67 under various conditions**

<table>
<thead>
<tr>
<th>§</th>
<th>Base / Acid</th>
<th>Solvent</th>
<th>Eq</th>
<th>Yield 75 (%)</th>
<th>Yield 76 (%)</th>
<th>Aux recovered (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOEt</td>
<td>EtOH</td>
<td>1.2</td>
<td>0</td>
<td>91</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>H2SO4</td>
<td>EtOH</td>
<td>0.05</td>
<td>0</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>NaH</td>
<td>THF</td>
<td>1.2</td>
<td>0</td>
<td>0</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>67 completely recovered
The crucial result shown in entry 3 in Table 2 suggests that under protic conditions (entries 1 and 2) 67 is in fact not responsible for nitrosation and that the actual NO\(^+\) transfer agent is generated under the reaction conditions. Ethyl nitrite is a well-known; nitrosating agent and as mentioned previously was used for the synthesis of 67. It seems likely, therefore, that under the reaction conditions as per entry 1, the enolate formed by the reaction with NaOEt and the substrate does not react directly with 67 (based on the result obtained with entry 3), but rather that a reaction between NaOEt and 67 takes place to generate ethyl nitrite and Aux instead (Scheme 55). The enolate of 74 then reacts with the ethyl nitrite to form 75 that subsequently undergoes fragmentation to afford oxime 76.

\[\text{Scheme 55. Suggested reaction of NaOEt and 67 to generate ethyl nitrite which serves as the actual nitrosating agent.}\]

For the case of entry 2, a literature search revealed that under acidic conditions N-nitrosoacetamides denitrosate to afford a nitrosonium ion following protonation.\(^{52}\) This precedent was extended regarding how 67 might undergo an identical denitrosation in EtOH to also afford ethyl nitrite, which appears to be the actual nitrosating agent (Scheme 56).

\[\text{Scheme 56. Denitrosation of 67 to afford ethyl nitrite under acid catalysis.}\]

To confirm this, the condition shown in entries 1 and 2 were repeated using ethyl nitrite rather than 67, which gave identical results to that shown in Table 2. For this reason the enantioselective nitrosation approach was brought to a close as the results indicated that the achiral reagent ethyl nitrite was in fact responsible for the NO transfer, precluding the possibility of any asymmetric induction. All investigation toward the development of a
chiral amination was stopped at this point and attention turned to the area of organocatalysis.

2.2 Aminocatalysis Approach

As stated in Chapter 1, aminocatalysis is defined as the use of small organic amines to catalyze organic transformations. As a logical extension of application of the chiral imidazolidinone template Aux, it was thought that hydrazide 64 could be used as an aminocatalyst due to the presence of a primary amino group, and in continuing with the interest in aza-quaternary centre formation, would thus be of interest to the possibility of achieving an enantioselective α-amination of carbonyl compounds. Comparing with conventional secondary amine catalysts like proline, a crucial advantage for a quaternization promoted by 64 was the likelihood of a less-congested environment in the catalytic intermediate transition-state (primary amine), while retaining a degree of conformational rigidity (imidazolidinone ring). The latter is probably the main reason simple primary amines have demonstrated very limited success when compared to simple secondary amines such as proline due to the lack of a defined facial selectivity (Scheme 57).

Secondary amines have shown some success in the enantioselective α-amination of aldehydes for the synthesis of aza-quaternary centres (Scheme 58) but are ineffective when applied to more sterically demanding substrates such as ketones, and this is where primary amine catalysis has a chance to shine.
Cinchona alkaloid-derived aminocatalysts have been shown to be as effective in the α-amination of aldehydes as many secondary amine catalysts. However, unlike secondary amines, they are also able to effectively catalyze the α-amination of ketones and esters (Scheme 59) via chiral ammonium enolates rather than a covalent enamine, which is sterically less demanding.

Cinchona alkaloid-derived primary amines have also been developed and were shown to effectively catalyze enantioselective aldol reactions (Scheme 60).
The success of primary amine-derived cinchona alkaloid catalysts to be able to carrying out these sterically demanding reactions is due to its bifunctional characteristics that restrict the rotational freedom through non-covalent interactions that enable a fixed chiral environment (Figure 17).

As mentioned earlier, the only drawback of the cinchona alkaloids however is the cost of these catalysts. For this reason 64 was investigated as a cheaper alternative for α-amination to form aza-quaternary centres in which inspiration was provided by the bifunctional activation modes of the cinchona catalysts since it was thought that the carbonyl group of 64 might be able to play a similar directing role in the transition state of the reaction (Figure 18).

**Scheme 60.** Cinchona-derived primary amine for applied to asymmetric Aldol reaction.

**Figure 17.** Bifunctional characteristics of cinchona alkaloid derivatised aminocatalysts.

**Figure 18.** Envisaged bifunctional characteristics of 64 to restrict rotational degrees of freedom.
A thorough search of the literature did not reveal any examples of the use of chiral hydrazides as enamine organocatalysts, although one report did demonstrate the use of them as iminium-ion catalysts in enantioselective Diels-Alder reactions. (Scheme 61).\(^{53}\)

Scheme 61. The first report of a chiral hydrazide for use as an organocatalyst.

As this was the first usage of a chiral hydrazide as an enamine catalyst it was decided to use a known organocatalytic \(\alpha\)-amination transformation as a basis for development. The azodicarboxylates have been successfully applied to the enantioselective \(\alpha\)-amination of various carbonyl compounds, including in the generation of azaquaternary centres. Hence, it was decided to study the \(\alpha\)-amination of cyclic \(\beta\)-ketoester 74, which is used as a standard model compound for the development of new catalysts in electrophilic \(\alpha\)-substitutions (Scheme 62). Substrate 74 was also chosen because of an unambiguous \(Z\)-geometry in the enamine, while dibenzyl azodicarboxylate (DBAD) was chosen in order to have a UV-active chromophore in the product for TLC monitoring and chiral HPLC ee evaluations.

Scheme 62. Envisaged \(\alpha\)-amination of 74 via enamine catalysis using 64.
The reaction was first attempted using 5 mol % of 64. Thereafter, various parameters were changed in order to optimize the reaction. Table 3 summarizes the results.

**Table 3: Optimization of the reaction conditions for the α-amination of 74.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (5 mol %)</th>
<th>Acid (10 mol %)</th>
<th>Solvent</th>
<th>Time</th>
<th>Conversion of 22 % (TLC)</th>
<th>Yield % (isolated)</th>
<th>ee % (HPLC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>TFA</td>
<td>IPA</td>
<td>120h</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>p- TsOH</td>
<td>IPA</td>
<td>IPA</td>
<td>120h</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>TfOH</td>
<td>IPA</td>
<td>IPA</td>
<td>18 h</td>
<td>100</td>
<td>85</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>TFA</td>
<td>DCM</td>
<td>DCM</td>
<td>120h</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>p- TsOH</td>
<td>DCM</td>
<td>DCM</td>
<td>120h</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
<td>TFA</td>
<td>IPA</td>
<td>96h</td>
<td>70 %</td>
<td>65</td>
<td>67</td>
</tr>
<tr>
<td>7</td>
<td>TFA</td>
<td>DCM</td>
<td>DCM</td>
<td>60 hrs</td>
<td>100 %</td>
<td>92</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>TFA</td>
<td>DCM</td>
<td>THF</td>
<td>120h</td>
<td>60 %</td>
<td>50</td>
<td>67</td>
</tr>
<tr>
<td>9</td>
<td>no</td>
<td>none</td>
<td>DCM</td>
<td>144h</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>p- TsOH</td>
<td>DCM</td>
<td>DCM</td>
<td>72 h</td>
<td>100 %</td>
<td>90</td>
<td>64</td>
</tr>
<tr>
<td>11</td>
<td>Proline</td>
<td>TFA</td>
<td>DCM</td>
<td>144h</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>Leu</td>
<td>TFA</td>
<td>DCM</td>
<td>5 d</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Full recovery of 74.

As expected, no reaction was observed in the absence of any acid, as this is necessary for imine formation (Entry 9). A range of acids were subsequently screened in order to determine which one would be suitable for use as a co-catalyst. Here it was important to establish the level, if any, of any blank reaction (ie without an amine) proceeding via an enol. Entries 1, 2, 4 and 5 pertaining to the blank reactions revealed that both TFA and p-TsOH were suitable co-catalyst candidates as no product was formed after 5 days based on a quantitative recovery of starting material. By comparison, entry 3 with TfOH as a strong acid and no amine catalyst showed complete conversion of the β-keto ester under the same reaction conditions within 18 hrs to produce an 85 % yield of aminated product. Presumably, acid catalysis on the diazo compound works here enhancing electrophilicity via nitrogen protonation. The <sup>1</sup>H-NMR of 74 revealed it to exist solely as the enol tautomer due
to hydrogen bonding in the 6-membered chelate (Figure 19) and acid catalysis on the diazo starting material is thus required for reaction with this relatively stable enol.

![Figure 19](image)

**Figure 19.** Keto-ester 74 exists predominantly in the enol form.

Thereafter, (entries 6, 7, 8, 10) various changes of solvent and acid (TFA or p-TsOH based on the blank study) were scrutinized, which revealed that the best combination was TFA in DCM, which returned a near-quantitative yield (92%) and an ee of 68% ee (Figure 20A and 20B) in 60hrs (entry 7).

![Figure 20A](image)

**Figure 20A.** HPLC trace 80 obtained in 68 % ee.

![Figure 20B](image)

**Figure 20B.** HPLC trace of the 80 obtained as a racemate.
Although there was a fair amount of overlap in the HPLC traces (presumably due to the presence of non-interconverting s-cis and s-trans diastereomers around the tertiary hydrazide within each enantiomer), it was presumed OK to split the peak areas as displayed above for the calculation of the ee. The major peak eluted at 8.5 min and the minor peak at 9.1 min. The racemic reference was obtained by the reaction using TfOH catalysis which showed an equal area percentage at the respective retention times. The sign of the [α]D obtained for 80 was compared to that of the literature54, which confirmed an (S)-configuration suggesting the possibility of an H-bond assisted transition-state model shown in Scheme 63. A parallel can be drawn with Enders’ SAMP/RAMP hydrazone method21e (although this methodology was never applied to the synthesis of aza-quaternary centres), which proceeds via a metal-chelated aza-enolate rather than an H-bond assisted enamine (Scheme 63).

Scheme 63. Envisaged H-bond assisted transition state compared to Enders’ hydrazone method.
This provided encouragement that this catalyst system was worthwhile developing further, as it could, in principle, offer two key advantages over Enders’ hydrazone method. First, Enders’ method is not catalytic, and second, it requires destructive removal of the chiral directing group post-reaction. Based on the ee obtained for 80, it was decided to carry out a thorough Structure-Activity (SAR) investigation of the reaction in the hope of improving the ee as well as to shed light on the mechanism of the reaction. In the first instance it was important to confirm that the reaction was in fact occurring via the enamine and not the chiral enolate formed by the deprotonation of the methyl proton as this was considered to be of paramount importance for understanding the origin of the enantioselectivity and the possibility of improving on it. As already pointed out, no reaction was observed in the absence of acid (Entry 9) and this already suggested that the reaction did proceed via the enamine rather than the chiral enolate, since it was likely that an enolate mechanism could proceed without the need for acid catalysis and simply proceed by virtue of the basicity of the amino group. However, evidence of a condensation product between 74 and 64 prior to product formation could be seen by TLC, and so this product was isolated. The $^1$H-NMR spectrum of this product appeared to be a 1:3 mixture of imine and its enamine tautomer O1 (Scheme 63). This was then used as the catalyst, which when subjected to the conditions of entry 7 in Table 3, also gave 80 in an identical yield and reaction time, thus strongly suggesting that the reaction was indeed proceeding via the enamine. As mentioned earlier, 74 is mostly enolized and this raises the important question concerning the mechanism of formation of the imine and, thereafter, the enamine. Two mechanisms can be postulated. The first, occurring via the standard imine/enamine formation on the keto tautomer once (or if) formed, while the second, in light of the $^1$H-NMR data proceeding via a Michael addition to the β-hydroxyenoate ester (enol) to form the enamine directly on elimination (or via the imine followed by tautomerism) (Figure 21).

![Figure 21. Postulated imine formation via a Michael addition to enol 74.](attachment:image.png)
Nevertheless, both mechanisms give rise to the same enamine and although extremely intriguing, it had no influence on the overall transformation and therefore no further investigations were conducted. No reaction was observed with proline and it was thought that this was due to the formation of the imine being more sterically demanding with the secondary amine (Entry 11). Conversely though, the primary amino acid leucine also failed to produce a reaction (Entry 12) and this was presumed to be due to a lack of nucleophilicity in light of 64 being more nucleophilic due to a phenomenon known as ‘the α-effect’. In 1962 Edwards and Pearson coined the term the α-effect, which referred to the enhanced nucleophilicity of an atom due to the presence of an adjacent atom with a lone pair of electrons.\textsuperscript{55} Many theories have been postulated to explain this phenomenon although no general consensus has been achieved. One explanation is that the ground state of the nucleophile is destabilized by lone pair – lone pair repulsions. In FMO terms this may be interpreted as the HOMO being raised relative to that in a molecule not possessing an α-heteroatom, making the N more reactive (nucleophilic). Another view, though, is that the lone pair(s) of the adjacent atom is able to stabilize the electron-deficient transition state in a way similar to that in $S_N2$ reactions. It was concluded then that the hydrazine (-$N$\textsubscript{2}N\textsubscript{2}H\textsubscript{2}) moiety was crucial for catalytic activity and that this structural motif possessed a unique blend of steric and electronic effects that manifested somewhere between a primary and secondary amine in terms of nucleophilicity.\textsuperscript{56}

Next, optimizations to determine the ideal catalyst and TFA loading was carried out as shown in \textbf{Table 4}. Reaction times were based on complete conversion of the starting material (by TLC) followed by quenching immediately.

\textbf{Table 4: Optimization of catalyst and TFA loading.}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mol % 14</th>
<th>Mol % TFA</th>
<th>Time (^b)</th>
<th>Ee % (HPLC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>5</td>
<td>72 hrs\textsuperscript{b}</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>10</td>
<td>60 hrs\textsuperscript{b}</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>20</td>
<td>50 hrs\textsuperscript{b}</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>10</td>
<td>60 hrs\textsuperscript{b}</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>10</td>
<td>60 hrs\textsuperscript{b}</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>10</td>
<td>10 hrs\textsuperscript{c}</td>
<td>68</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>20</td>
<td>10 hrs\textsuperscript{c}</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>100</td>
<td>9 hrs\textsuperscript{c}</td>
<td>66</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Monitored by TLC. \textsuperscript{b}Concentration of the reaction mixture = 0.33 M. \textsuperscript{c}Concentration of the reaction mixture = 0.67 M
Unfortunately despite all efforts in this regard, the ee could not be improved. Surprisingly, though, doubling the concentration of the reaction mixture to 0.67 M (from ~ 0.33 M) saw an approximate 6-fold increase in the rate of reaction (entries 6 and 7) without affecting the enantioselectivity. Although the conditions displayed in entry 8 gave the quickest overall reaction time, it was decided to use 10 mol % TFA (entry 6) as the standard conditions in order to minimize reagent usage. From this study it can be seen that the rate increased with increasing acid concentration, whereas the rate remained constant with increasing 64, supporting the idea that the acid played a role in the activation of the DBAD starting material. There is a rate-determining step in any catalytic cycle and in this case it referred to the hydrolysis of the imine. It was thought then that since increasing the concentration of 64 had no effect on the rate of reaction, the acid might also serve in facilitating the hydrolysis of the imine by protonating the carboxyl group of 64 and thereby enhancing the electrophilicity of the imine through induction (Scheme 64).

![Scheme 64. Acid assisted hydrolysis of the imine for catalyst turnover.](image)

In order to test this hypothesis the thiourea derivative 81 was synthesized by the reaction of 64 with Lawesson’s reagent (Scheme 65).

![Scheme 65. Synthesis of thiourea derivative 81.](image)

The 1H-NMR spectrum of 81 was expected to be more or less identical to 64 and therefore 13C-NMR spectroscopy was used. This revealed all eight expected resonance with the diagnostic peak being the downfield thiocarbonyl resonance at 183.6 ppm (Figure 22).
Reaction with 81 as the catalyst only gave a 35 % yield after 10 hrs with an ee of 52 %, confirming the importance of having a urea moiety. Sulfur is a much softer Lewis base compared to oxygen, and therefore protonation of the thiourea sulphur is much slower than that of oxygen in the urea case. This reduces catalyst turnover and explains the lower yield observed (Figure 23).

In addition, the drop in ee with 81, implied that hydrogen bonding to the urea carbonyl oxygen played an important role in the enantioselectivity. Based on the envisaged transition-state model it was surmised that the methyl group at C-5 was not necessary for
chiral induction being far from the enamine, and that increasing the steric bulk at C-4 might increase the ee. Figure 24 summarizes these perceptions:

![Figure 24. SAR results of 64.](image)

- Methyl not necessary.
- Change Ph to a bulkier group.

First it was decided to confirm that the methyl group was not necessary for enantioselectivity by synthesizing hydrazide 86 in a linear sequence starting from (R)-(−)-2-phenylglycine methyl ester hydrochloride (Scheme 66).

```
HCl Ph NH2 OMe MeNH2 MeNH2 Ph NH2 OEt
EtOH quant. MeNH2 NHMe LiAlH4, THF reflux
Ph NHMe Ph NHMe Ph NHMe triphosgene DCM:pyridine (1:1)
0 °C amyl nitrite, DCM
Ph NHMe Ph NHMe
82 83 84 85
56 % 71 % 97 % quant.
H2N N N O
Ph Ph Ph
86 87
97 %
```

![Scheme 66. Synthesis of hydrazide 84 from (R)-(−)-2-Phenyl glycine methyl ester hydrochloride.](image)

The first step involved aminolysis of the amino acid ester group with ethanolic methylamine to afford methylamide 82 in quantitative yield. The amide was then reduced to the diamine 83 in refluxing LiAlH₄ followed by cyclization of the diamine product with triphosgene to afford imidazolidinone 84 (approx. 60 % over 2-steps). The ¹H-NMR data of 84 was in agreement with that of the literature. 84 was then reacted with amyl nitrite in DCM to afford N-nitroso derivative 85. As before, the presence of absorption bands at 1427 and 1407 cm⁻¹ in the IR spectrum confirmed the presence of the nitroso group. The ¹H-NMR
spectrum (Figure 25) was assigned accordingly and elemental analysis of a recrystallized sample confirmed its molecular formula.

![Figure 25. 1H-NMR spectrum of 85.](image)

The nitroso compound 85 was then reduced to hydrazide 86 with Zn/AcOH as before to reveal a spot-to-spot conversion by TLC. Thereafter its catalytic activity was evaluated without further purification as shown in Scheme 67. Unsurprisingly, the rate of reaction was identical to that of 64 producing 80 in 90 % yield. This confirmed that the hydrazide motif was in fact responsible for the rate of the reaction.

![Scheme 67. Evaluation of hydrazide 86 in α-amination resulted in 92 % yield and 21 % ee.](image)
Surprisingly, carrying out the reaction with 86 using the same conditions as with 64 resulted in a dramatic drop in the enantioselectivity to 21 % revealing that the C-5 methyl, probably in combination with the C-4 phenyl group, was also required for enantioselectivity. The methyl group is far from the site of amination and so it was concluded that its influence was more of a conformational nature, possibly something to do with maintaining the N-N s-trans conformation shown in Figure 24. Armed with this new information it was therefore decided to synthesize a hydrazide derivative possessing a larger C-4 substituent while still retaining the C-5 methyl group. This identified the naphthyl derivative 90 (Figure 26), whose synthesis was envisaged as possible via the nitrosation/reduction protocol on imidazolidinone 89, which could be obtained by a urea fusion reaction on ephedrine derivative 88. This in turn was disconnected back to the chiral-pool starting material L-alanine (Figure 26).

![Figure 26. Retrosynthetic analysis for the synthesis of hydrazide 90.](image)

For the synthesis of imidazolidinone 89 (Scheme 68), the first step involved the reduction of L-alanine with LiAlH₄ followed by Boc protection to afford N-Boc-alaninol 87 in 93 % yield over the 2 steps according to a literature procedure. Its analytical and spectroscopic data was in agreement with that of the literature. Compound 87 was then converted to the aldehyde using a Swern oxidation, which was followed by addition with naphthyllithium, formed from reaction of 1-bromonaphthalene and ¹BuLi at −78 °C to afford the protected amino alcohol 88 in 75 % yield as a 3:1 mixture of diastereomers based on the integration in the ¹H-NMR spectrum.

![Scheme 68. Synthesis of imidazolidinone 89.](image)
Target imidazolidinone 89 was then obtained as a single diastereomer in 39 % yield (over 2-steps) by LiAlH₄ reduction of 88 and after work-up, the resulting ephedrine derivative reacted with urea with 1 eq. HCl at 200 °C. The ¹H-NMR of 89 in CDCl₃ (Figure 27) confirmed its synthesis.

The region between 7.40 ppm and 8.00 ppm revealed seven aromatic protons corresponding to the naphthalene ring, the doublet at 5.66 ppm corresponded to H-4, the NH proton occurred at 5.17 ppm, the double quartet at 4.18 ppm corresponding to H-5, while the two methyl groups for -NMe and H-6 resonated at 2.80 ppm and 0.60 ppm respectively. More importantly, however, was whether the C-5 methyl substituent efficiently directed the fusion reaction in order to produce the desired syn relationship between the C-4 and C-5 substituents as for imidazolidinone Aux. Mechanistic considerations, since the precursor 88 was a mixture of diastereomers, implied that diastereoselectivity was due to an Sₐ₁ mechanism (HCl as catalyst). Examination of the coupling constant between the C-4 and C-5 protons revealed it to be 8.5 Hz, which supported that the substitutents were indeed syn as this corresponded to an approximate 0° dihedral angle according to the Karplus equation as required by a cis-relationship.
Furthmore, had the cyclisation not been stereoselective, diastereomers would have been produced, which would have shown up in the $^1$H-NMR spectrum by virtue of a doubling of some of the signals – this was not observed (Figure 27). Imidazolidinone 89 was then subjected to the standard nitrosation and reduction conditions to afford catalyst 90, which was evaluated, and as expected, produced the same rate of reaction, affording 80 in 93% yield. However, disappointingly, the ee dropped dramatically to 17%. Table 5 summaries the results of the three catalysts.

**Table 5: Summary of the catalytic activity of the synthesized hydrazides.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield 25 (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>92</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>86</td>
<td>90</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>93</td>
<td>17</td>
</tr>
</tbody>
</table>

$^a$Isolated yield. $^b$Determined by HPLC. $^c$From sign of the [$\alpha$]$_D$.

At this point the variation in the ee between the different substrates was extremely puzzling and due to time constraints, investigations including the use of computational modeling were not conducted. This will be a topic for future work.
Chapter 3

Aza-Quaternary Centres via Diastereoselective α-Azidation

3.1 Chiral Auxiliaries

The use of chiral auxiliaries is one of the best and most synthetically economic way of accessing aza-quaternary centres, many of them based on amino acid motifs, which extends options based on the chiral pool. From the pioneering work by D. A. Evans on chiral auxiliaries a new definition of a chiral auxiliary evolved. According to Evans, a synthetically useful auxiliary needs to satisfy three conditions\textsuperscript{57}: (1) A facile incorporation into the substrate; (2) It must promote a high level of diastereofacial selectivity and (3) The auxiliary must be removable non-destructively without racemisation and be re-usable. This became the primary focus of the Evans’ research group when he began the work at the beginning of the 1980s. Despite the diverse and highly efficient advances in diastereoselective synthesis at the time, all of the methodologies failed to meet all three of these requirements in which shortcomings were experienced particularly with points 1) and 3). These two points become more important when considering the large-scale applications of auxiliary methodology to stereoselective synthesis in terms of cost and time. This led to the development of the now well-known amino acid-derived Evans’ oxazolidinone auxiliary methodology as depicted in Scheme 69.\textsuperscript{15,57}

\begin{equation}
\text{Evans oxazolidinone}
\end{equation}

\begin{align*}
\text{HN} & \text{O} \\
\text{N} & \text{O} \\
\text{C} & \text{O} \\
\text{N} & \text{O}
\end{align*}

\text{i) } n-\text{BuLi}
\text{ii) } \text{O} \text{Cl} \\
\text{88 - 99 %}

\text{i) } \text{LDA / THF}
\text{ii) } \text{RX} \\
\text{R = Bn, Et, Allyl}
\text{de 92 - 99.99 %}

Scheme 69. Synthesis and diastereoselective alkylation of a propionic acid-oxazolidinone derivative in excellent de.
The oxazolidinone auxiliary shown in the scheme above was derived from reduction of (S)-valine followed by carbamate formation and was first used in the diastereoselective alkylation of chiral propionic acid–oxazolidinone derivatives. The chiral propionamides were synthesized by acylation of the lithium anion of the oxazolidinone with the respective acid chloride in excellent yield. This was subsequently alkylated with various electrophiles in excellent diastereoselectivity. To complete the methodology, the auxiliary could be removed non-destructively and without racemization by hydrolysis, reduction as well as transesterification (Scheme 70).

Scheme 70. Non-destructive auxiliary removal.

This work marked the start of a rich era of asymmetric synthesis, as many other chiral auxiliaries were subsequently developed based on the same motif (Figure 28).58

Figure 28. Chiral auxiliaries for diastereoselective alkylation reactions developed after the pioneering work by Evans in 1981.
3.2 α,α-Disubstituted Enolate Geometry Problem

Today, more than 30 years later, the chiral auxiliary approach is still the most reliable way of stereoselective α-functionalization. However, the Achilles’ heel of this methodology is revealed in applications towards the synthesis of quaternary carbon centres due to the challenge in controlling the enolate geometry in the transition-state of terminal disubstituted enolates. A representative example using Evans’ acyl oxazolidinone is shown in Figure 29.

![Figure 29. Enolate geometry problem of disubstituted acyloxazolidinones.](image)

Each enolate would give rise to a particular diastereomer. Evans, or any other group, did not subsequently report the synthesis of quaternized products using this methodology and this confirmed that controlling the enolate geometry of these systems was in fact not possible. In recent times, there has been excellent progress made in this area, specifically in the work by Gleason, through the use of chiral bicyclic thioglycolate lactams in 2006, although this involved destruction removal of the chiral directing group.\(^{59}\) Similarly, in 2012 Marek et al reported an elegant approach for obtaining a stereodefined α,α-disubstituted chiral enolate starting from a simple acyclic chiral ynamide involving a copper catalysed carbometalation-oxidation sequence of a chiral ynamide to afford the all-C quaternary product in high dr ranging from 90:10 to 95:5, with recovery of the chiral oxazolidinone, via a Cu enolate 91 (Scheme 71).\(^{60}\) The method however is reported as being limited to aryl aldehydes and methyl cooperates (for the addition to the ynamide).

![Scheme 71 Disubstituted enolate geometry control obtained through carbometalation-oxidation sequence.](image)

Reagents and conditions: (a) i) \(\text{Me}_2\text{CuLi.LiBr.SMe}_2\), Et\(_2\)O, -40 °C
ii) \(t\)-BuOOH, -80 °C; (b) i) \(R^2\text{CHO}\) or \(\text{TsN}=\text{CHR}\), -80 °C, ii) \(\text{H}_3\text{O}^+\)
3.3 Rationale for Research Conducted

Recently we reported a highly diastereoselective auxiliary-controlled methodology for the construction of all-carbon quaternary centres in chiral, non-racemic form. This was developed involving stereoselective alkylation of a chiral malonate–imidazolidinone (94) in excellent dr to afford 95, followed by transformation with auxiliary removal to an enantioenriched quaternary α,α-disubstituted β-hydroxy ester in three steps, (Scheme 72). Transition-state models for this methodology will be discussed later.

![Scheme 72. Stereoselective formation of chiral quaternary centres by diastereoselective alkylation of chiral malonate-imidazolidinones 94.](image)

It was envisaged that this methodology could be extended to the stereoselective construction of chiral aza-quaternary centres by replacing the alkylating agent with a nitrogen electrophile (E) in an amination process to produce a product bearing an aza-quaternary centre (98), which would then be subsequently transformed into an α,α-disubstituted serine derivative (Scheme 73).

![Scheme 73. Envisaged construction of α,α-disubstituted serine derivatives via a diastereoselective amination of 94.](image)

3.4 Synthesis of Chiral Malonate-Imidazolidinones 94.

To this end, first a divergent approach for accessing a range of derivatives of 94 with varying ‘R’ groups was decided on involving synthesis of the unsubstituted intermediate 94a (where R = H), followed by alkylations with various alkyl halides (Scheme 74). This was more convenient and less time-consuming than synthesizing each substituted malonate independently.
Intermediate 94a could be easily prepared via a peptide-style coupling between the half acid (93a) obtained by monohydrolysis of diethyl malonate (92) and ephedrine-derived chiral imidazolidinone Aux (Scheme 74). The choice of coupling reagent will be discussed in detail a bit later.

Diethyl malonate (92) was chosen as starting material as it is cheap and readily available, and its monohydrolysis was carried out using KOH (1.05 eq) in EtOH for 18 hrs at rt. Half acid 93a was obtained in 92 % yield following an acid-base extraction. The $^1$H-NMR spectrum (Figure 30) was in agreement with that of the literature and showed the presence of a broad singlet at 8.74 ppm corresponding to the carboxylic acid –OH.

Figure 30. $^1$H-NMR spectrum of half acid 93a.
The quartet at 4.22 ppm and the triplet at 1.28 ppm corresponded to the CH₂ and the CH₃ respectively of the ethyl ester, while the singlet at 3.41 ppm was assigned to the C-2 methylene group. The next step involved coupling the chiral auxiliary (Aux) with the half acid. Chiral imidazolidinone Aux is supposedly only weakly nucleophilic at nitrogen due to resonance stabilization into the carbonyl group (Figure 31) and it was suspected that standard coupling protocols such as acid chloride methodologies or carbodiimide coupling reagents such as DCC and EDC might not be very effective. However, at least the imidazolidinone was expected to be more nucleophilic than the oxazolidinone, which is known to require deprotonation to its anion for acylation to be effective.

![Figure 31. Resonance contributors of imidazolidinone Aux provides an explanation for the weakly nucleophilic N-H.](image)

In spite of this, however, the standard methods were nevertheless attempted as the β-carbonyl (at C-3) of 93a would inductively increase the electrophilicity of the activated acid carbon at C-1 serving to make up the ‘reactivity deficit’ of Aux. Acid chloride methodology was first investigated by reacting 93a with oxalyl or thionyl chloride for formation of the acid chloride. The resulting acid chloride was volatile though, which made isolation difficult. In addition, a fair amount of decarboxylation occurred when carrying out these reactions, so this approach was abandoned. The next coupling reactions tried used DCC as well as the mixed anhydride method using pivaloyl chloride, which successfully yielded 94a in 86 % and 92 % yield respectively after column chromatography (Scheme 75). Although both methodologies afforded the desired chiral malonate–imidazolidinone 94a in excellent yields, they both were not without their disadvantages.

![Scheme 75. Synthesis of 94a via peptide coupling of 93a with Aux using DCC or pivaloyl chloride.](image)
The typical urea side product obtained from the DCC reaction was difficult to remove. Only after multiple filtrations with cold DCM and subsequent column chromatography was the pure product afforded in 86% yield. The filtration process became more cumbersome when the reaction was carried out on a multi-gram scale. Although the work-up of the mixed anhydride methodology required only an aqueous extraction to remove the excess base and acyl chloride, this approach afforded a maximum yield of 92% only when using a sacrificial amount of the acid as well as freshly distilled pivaloyl chloride (5 eq. each). Excess substrate was used to account for decarboxylation and to ensure a complete conversion of Aux. For these reasons, it was decided to investigate another type of carboxylic acid activator, hopefully as one with a more convenient post-reaction processing procedure and one that would minimize the use of toxic chemicals. Katritzky and co-workers have amply demonstrated the use of N-acylbenzotriazoles as activated carboxylic acid derivatives by reacting the acid chloride with benzotriazole, and such derivatives are reported as air- and water-stable alternatives to acid chlorides (Scheme 76).62

However, as mentioned earlier, a method that avoids the use of toxic chemicals was preferred so it was desirable to circumvent the intermediacy of the acid chloride. In 2011, Hunter and Msutu et al showed that benzotriazole N-acylation could be achieved from carbamate salts via reaction with PPh3 and 1-chlorobenzotriazole, (BtCl, Scheme 77), thereby avoiding the use of SOCl2 as reported by Katritzky. Furthermore, BtCl is readily obtained via oxidation of benzotriazole (BtH) with bleach.63 Thus, it was surmised whether this methodology could be applied to carboxylic acid 93a.

![Scheme 76](image)

**Scheme 76.** Katritzky et al made use of an N-acylbenzotriazole as an activated carboxylic acid derivative.

![Scheme 77](image)

**Scheme 77.** Direct conversion of a carbamate salt to an N-acylbenzotriazole.63
This reagent combination was thus reacted with 93a in acetonitrile, followed by refluxing with the auxiliary, which gratifyingly gave 94a in 82% yield after column chromatography (Scheme 78).

![Scheme 78. BtCl, PPh3 methodology applied to the synthesis of 94a.](image)

The first step in the reaction is between PPh3 and BtCl to generate a chlorophosphonium salt which is stabilized by the liberated Bt anion. The Bt anion then deprotonates the carboxylic acid to afford BtH and subsequent attack of the carboxylate ion on the chlorophosphonium ion and substitution by the BtH gives rise to the malonate-Bt derivative 96a (Figure 32), which then undergoes a S_N2 reaction with Aux to form 94a.

![Figure 32. Proposed mechanism for the formation of the benzotriazole derivative 96a.](image)

Derivative 96a was found to be stable towards water and air but sensitive to chromatographic purification. A di-benzotriazole derivative prepared from α-methyl malonic acid was isolated by Katritzky as shown in Scheme 76 and it was thought that the mono-benzotriazole derivative of diethyl methylmalonate might be more stable towards column chromatography and allow confirmation by 1H-NMR spectroscopy that the reaction does indeed proceed via the benzotriazole derivative. To this end the half acid of diethyl methylmalonate (93b) was synthesized by alkylation of diethyl malonate with MeI using NaH as a based followed by a monohydrolysis with KOH to afford 93b in 95% yield over the two steps (Scheme 79).

![Scheme 79. Synthesis of diethyl methylmalonate half acid 93b.](image)
The $^1$H-NMR spectrum of 93b was also in agreement with that from the literature data and similar to that of 93a, also revealing a downfield broad singlet at 8.56 ppm corresponding to the carboxylic acid –OH group. Otherwise everything else was in place (Figure 33).

Figure 33. $^1$H-NMR spectrum of 93b.

Compound 93b was then treated with the PPh$_3$ / BtCl reagent combination in DCM at 0 °C and after 2 min the reaction was complete by TLC. The reaction mixture was then washed with sat. NaHCO$_3$ and subjected to column chromatography to afford benzotriazole derivative 96b (Scheme 80).

Scheme 80. Synthesis of benzotriazole derivative 96b.

An accurate percentage yield could not be obtained as 96b was also fairly sensitive to chromatographic purification, but enough material was obtained to confirm its structure by $^1$H-NMR spectroscopy (Figures 34a and 34b).
Figure 34a. $^1$H-NMR spectrum of 96b with expansion of 1.00 ppm – 5.00 ppm range.
The diagnostic peaks in the $^1$H-NMR spectrum of 96b were the four distinct aromatic resonances each integrating for a single proton and corresponding to the four protons on the benzotriazole ring. The four resonances confirmed that the regioselectivity of the Bt was as shown in 96b, as the regioisomer 96b’ (Figure 35) would have displayed two aromatic signals only due to symmetry.

![Figure 35](image)

**Figure 35.** Regiosomer of 96b’ was not detected.

The ethyl ester group was assigned as before to the quartet at 4.20 ppm and the triplet at 1.20 ppm, for the CH$_2$ and CH$_3$ protons respectively. The methyl doublet resonated at 1.71 ppm, while the C-2 methine quartet shifted downfield to 4.92 ppm in comparison to 3.47 ppm in 93b, highlighting the electron-withdrawing and hence deshielding effect of the benzotriazole group. This also implies an increase in electrophilicity at C-1, a feature reflected in the ease by which even relatively deactivated amines like N-methylaniline coupled in high yield. A summary of the results from acylation experiments varying the nucleophile as auxiliary Aux or aniline and the acid partner in terms of the α-R group is shown in Table 6.
Table 6. Scope of the coupling with two different nucleophiles

\[
\begin{align*}
& \text{i) BtCl (1.2 eq), PPh}_3 \text{ (1.2 eq), } \\
& \text{CH}_3\text{CN, } -10 \, ^\circ\text{C} \\
& \text{ii) Aux or aniline, reflux, 8 hrs} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aux or aniline</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>EtO_2_CO_2_OH</td>
<td>EtO_2_CO_2_NO_Ph</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>\text{HN} &amp; \text{N}</td>
<td>EtO_2_CO_2_OH</td>
<td>EtO_2_CO_2_NO_Ph</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>\text{HN} &amp; \text{N} &amp; \text{Ph}</td>
<td>BnO_2_CO_2_OH</td>
<td>BnO_2_CO_2_NO_Ph</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>EtO_2_CO_2_OH</td>
<td>EtO_2_CO_2_N_Ph</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>HO_2_CO_2_N_Ph</td>
<td>BenO_2_CO_2_N_Ph</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>\text{Ph} &amp; \text{N}</td>
<td>\text{CO}_2\text{H}</td>
<td>\text{N} _\text{Ph}</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>EtO_2_CO_2_OH</td>
<td>EtO_2_CO_2_N_Ph</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>EtO_2_CO_2_OH</td>
<td>EtO_2_CO_2_N_Ph</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>EtO_2_CO_2_OH</td>
<td>EtO_2_CO_2_N_Ph</td>
<td>90</td>
</tr>
</tbody>
</table>

^aIsolated after column chromatography.
The yields were excellent ranging between 81 – 97 % in all but one of the cases (entry 6). The methodology was also effective for the acetylation of N-methylaniline (entry 7) which serves as an excellent alternative to acetyl chloride or acetic anhydride. As with all peptide coupling methodologies there are advantages and drawbacks. The BtH by-product formed during the reactions can be removed and recovered by an acid / base extraction and used to re-synthesize the BtCl reagent, but the triphenylphosphine oxide by-product must be removed by column chromatography, which carries all of the usual problems in separation depending on the Rf of the product. This was unfortunately the case for the chiral malonate-imidazolidinone 94a in which multiple columns needed to be performed in order to realise a pure product, as attempts to purify by recrystallization post-column were unsuccessful in removing trace amounts of Ph3P=O. For this reason it was decided to stay with the pivaloyl chloride coupling methodology for the synthesis of 94a. Nevertheless the PPh3 / BtCl system serves as a good addition to the peptide coupling repertoire as it uses cheap reagents and is semi-recyclable. All three approaches investigated for the synthesis of 94a produced identical 1H-NMR and 13C-NMR spectroscopic data. A fully assigned 1H-NMR spectrum of 94a is shown in (Figure 36).

![Figure 36. 1H-NMR spectrum of 94a.](image-url)
Typical ethyl ester resonances were assigned to the quartet at 4.18 ppm and the triplet at 1.24 ppm. The two methyl groups, H-Me and –NMe were assigned to the doublet at 0.79 ppm and the singlet at 2.81 ppm respectively. Protons H-4’ and H-5’ were identified as the double quartet at 3.93 ppm and the doublet at 5.33 ppm in that order and the diastereotopic protons at C-2 corresponded to the AB doublet at 3.98 ppm. Integration of the aromatic region 7.10 ppm – 7.34 accordingly confirmed the presence of 5 aromatic protons for the phenyl ring. The $^{13}$C-NMR spectrum (Figure 37) revealed 14 resonances which was in agreement with the expected number of resonances for 94a in which there were key signals at 167.6 ppm, 165.0 ppm and 155.4 ppm corresponding to the C-1, C-3 and C-2’ C=O stretches.

The next objective was the alkylation of 94a with various electrophiles for the synthesis of various α-substituted malonate-imidazolidinones (94b – 94h) heading for the diastereoselective amination studies, and these were prepared according to our previous work involving alkylation of the malonate potassium enolate (from KHMDS) with a primary alkyl, allyl, propargyl or benzyl halide at a temperature from -78 °C to rt.61 Yields following
chromatographic purification were greater that 94 % in each case and products were obtained as a 50:50 mixture of diastereomers due to a mixture of CO-auxiliary rotamers (resulting in opposite diastereofacial selectivities). This was fine, however, as the crucial step came next in the form of diastereoselective introduction of the nitrogen electrophile via the planar metal enolate. Table 7 summarizes the results for synthesis of 94b-94h.

Table 7. Synthesis of α-substituted malonate-imidazolidinones

<table>
<thead>
<tr>
<th>Entry</th>
<th>RX</th>
<th>Cpd</th>
<th>R</th>
<th>Yield (%)&lt;sup&gt;a,d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeI</td>
<td>94b</td>
<td>Me</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>EtI&lt;sup&gt;b&lt;/sup&gt;</td>
<td>94c</td>
<td>Et</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>n-Butyl bromide&lt;sup&gt;c&lt;/sup&gt;</td>
<td>94d</td>
<td>n-Butyl</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>n-Hexyl Bromide&lt;sup&gt;c&lt;/sup&gt;</td>
<td>94e</td>
<td>n-Hexyl</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>BnBr</td>
<td>94f</td>
<td>Bn</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>Allyl bromide</td>
<td>94g</td>
<td>Allyl</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>Propargyl bromide</td>
<td>94h</td>
<td>Propargyl</td>
<td>96</td>
</tr>
</tbody>
</table>

<sup>a</sup>isolated yield. <sup>b</sup>Reflex. <sup>c</sup>10 mol % TBAI and reflux. <sup>d</sup> Obtained as 50:50 mixtures of diastereomers.

Benzylation and allylated compounds 94f and 94h were new and only their NMR data will be shown. It was possible to separate the diastereomers of 94f by column chromatography and for simplicity the <sup>1</sup>H and <sup>13</sup>C NMR spectra for one of them are represented in Figure 38 and Figure 39. In the <sup>1</sup>H-NMR (Figure 38), benzylation was confirmed by virtue of diagnostic signals in the form of an AB doublet pair at 3.19 ppm and 3.28 ppm for the diastereotopic
H-2a protons as well as the five extra aromatic protons in the aromatic region at around 7.10 – 7.40 ppm. The H-2 proton had a very large downfield shift and was assigned to the double doublet at 5.17 ppm (from 3.98 ppm in 94a). Overall, all signals were assigned confirming that 94f was successfully synthesized.

Figure 38. $^1$H-NMR spectrum of 94f.
Similarly, the $^{13}$C-NMR spectrum of 94f revealed the expected 19 resonances (Figure 39). Key signals were the presence of eight aromatic resonances for the two phenyl rings including two aromatic quaternary carbons at 135.9 ppm and 138.9 ppm, the latter corresponding to that of the benzyl group, as well as the C-2a peak at 34.4 ppm. C-2 shifted to 52.6 ppm (43.3 ppm in 94a) also supporting that alkylation had taken place.

Figure 39. $^{13}$C-NMR spectrum of 94f.
By comparison, the diastereomers of 94h could not be separated and therefore doubling of most of the NMR (Figure 40 and 41) peaks were observed; however HRMS confirmed its synthesis.
3.5 α-Azidation of Mono-Substituted Malonate-Imidazolidinones

For the amination a suitable source of nitrogen electrophile had to be selected. As mentioned earlier the diazodicarboxylates have been used as efficient aminating reagents; however, chemoselective reduction of the resulting hydrazide to the amine can be challenging. For this reason it was decided to choose an electrophile that would be easier to convert into an amino group. This identified two potential strategies for investigation as α-azidation or nitration. A scan of the literature revealed that nitromalonates tend to form dimers, making isolation difficult. By comparison, azidation methodology as previously reported by Evans et al appeared to be the more attractive option. Here, the azidation of oxazolidinone-based carboximide enolates with trisyl azide to form aza-tertiary centres (97) was reported (Scheme 81). In this case, crucial to the diastereoselectivity was the intermediacy of a chelated (Z)-enolate with the potassium cation in the auxiliary hole followed by addition of the azide electrophile anti- to the more hindered face of the auxiliary in accordance with the anti- steric principle and keeping with earlier work on diastereoselective alkylations. Based on the Evans protocol, three key issues needed to be considered before attempting the azidation on the malonate-auxiliary substrates 94b – h, as: (i) the choice of the azidating agent and the reaction time before quenching; (ii) the quench reagent, and (iii) the diastereoselection.

![Scheme 81](image)

Scheme 81. Evans’ formation of aza-tertiary centres (97) by direct α-azidation with trisyl azide.

Firstly, Evans found that the use of the trisyl azide electrophile, rather than tosyl azide or p-nitrobenzenesulfonyl azide resulted in significantly less formation of the diazo product and it was therefore decided to adopt it as the electrophile. Secondly, the optimum reaction time for azide transfer found by Evans was between 1-2 min before quenching with AcOH. However, if this was extended to 30 min the yield of 97 dropped from 92 % to 78 %. If the acid quench was omitted, none of the desired product was obtained at all. Evans does not provide a specific explanation for this or mention if any other products formed, although,
there are indications that this was due to the elimination of the oxazolidinone auxiliary. Based on our previous work, the malonate-imidazolidinone enolates were found to be significantly more robust so elimination of the imidazolidinone moiety during the reaction was not considered to be a cause for concern. The quench reagent in point (ii) was interpreted by Evans as being largely responsible for the transformation of the tautomeric sulfonyle triazene intermediates generated during the reaction (Scheme 82) in which one tautomer (T1) led to the desired azide (97) while the other (T2) gave the diazo product. Upon isolation, Evans found that the equilibrium of T1 : T2 = 3:1 and these interconverted at a rate of approximately 0.1 – 1 s⁻¹ at 25 °C. This was then subjected to a variety of conditions in which it was found that only Me₄N⁻OAc or KOAc (solid or generated in situ by the reaction of the K⁺ with AcOH) resulted in almost exclusive formation of azide 97, while basic reagents such as pyridine and KHCO₃ resulted in the diazo compound as the major product.

Scheme 82. Degradation pathways of sulfonyle triazene intermediates T1 and T2.

Degradation of the quaternary sulfonyle triazene intermediate (94b – h; Q1 and Q2) to afford a diazo product was excluded as an α-hydrogen, which is necessary for the required elimination, was absent (Figure 42). In the end KOAc was chosen, which was generated in situ by the addition of AcOH.

Figure 42. Envisaged sulfonyle triazene intermediates following quaternization of 94b - 4h (Q1 and Q2).
Finally, as the third of the designated points, and most importantly, was consideration of the origin of the diastereoselectivity for the envisaged azidation of 94b – h. In the azidation work by Evans shown above, the reaction proceeded via the sterically less demanding and kinetic (Z)-enolate, with the auxiliary in the s-cis$_{C-N}$ conformation due to chelation of the potassium cation in the auxiliary hole (Scheme 83).

Scheme 83. Azidation of carboximide enolates proceeds via s-cis$_{C-N}$ with metal chelation in the auxiliary hole.

It is pertinent to point out, however, that the Evans’ case is a system with only one choice of where to accommodate the cation – in the enolate / auxiliary hole – which promotes an s-cis auxiliary conformation. By comparison, the substituted malonate-imidazolidinone enolate has two choices for positioning the cation referred to here as the malonate hole or the auxiliary hole. While the former necessitates a (Z)-enolate with an auxiliary conformation unknown, the latter was sure to fix the auxiliary conformation as s-cis but with the enolate geometry unknown (Figure 43).

Figure 43. Configurational and conformational analysis of the malonate-imidazolidinone enolates.
Based on our previous work, crystal structure analyses of quaternized products (Figure 44) obtained via alkylation of various substituted malonate-imidazolidinones (where R > Me), revealed that the transition state must have proceeded via the s-trans (Z)-enolate in order to explain the observed diastereoselectivity.\textsuperscript{61}

Subsequent calculations revealed that, prior to deprotonation, the s-trans conformation was lower in energy than the s-cis and this provided additional support that under kinetic control, complexation of the potassium ion into the malonate hole was preferred leading to formation of the (Z)-enolate. From this model it was expected that the quaternary azides 98b – h would have an R configuration around the newly formed aza-quaternary centre following azidation of 94b – h using the (-)-(4R, 5S) auxiliary. In the event azidation of 94b – h afforded quaternized azides 98b - h in > 90\% yield and > 97:3 dr as evidenced by chiral HPLC analysis, Table 8. The reaction was initially carried out in similar fashion to that described by Evans involving enolate generation at low temperature (-85 °C) followed by introduction of the trisyl azide at this temperature and quenching with AcOH after 2 min. TLC studies revealed, however, that 2 min was not a long enough reaction time for complete conversion of the starting material and it was found by careful TLC quenching that a slow warming to –10 °C and quenching at this temperature gave the best yields.
IR spectroscopy provided the diagnostic tool to confirm that azidation had successfully taken place by virtue of a sharp band at approximately 2120 cm^{-1} corresponding to the azide stretch in each of the products. As only nitrogen atoms were added, the NMR data of the compounds 98b – h were extremely similar to that of the respective starting materials. The characteristic change in each case, however, was the absence of H-2 in the ^1H-NMR as well as the downfield shift of C-2 in the ^13C-NMR due to the electron-drawing azido group. A few compounds will be selected in order to highlight these observations. In the ^1H-NMR spectrum of 98b, the H-2 proton that occurred at 4.65 ppm in starting material 94b is absent (Figure 45). The ^13C-NMR spectrum of 98b reveals all 15 carbon resonances with the aforementioned C-2 proton occurring at 69.5 ppm, shifted from 45.9 ppm in 94b (Figure 46). All other peaks in the NMR data were appropriately assigned and this together with the IR spectrum and elemental analysis confirmed the structure of 98b.

Table 8. Diastereoselective Azidation of 94

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R</th>
<th>Yield (%)^a</th>
<th>dr^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>98b</td>
<td>Me</td>
<td>97</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>2</td>
<td>98c</td>
<td>Et</td>
<td>96</td>
<td>98:2</td>
</tr>
<tr>
<td>3</td>
<td>98d</td>
<td>n-Butyl</td>
<td>95</td>
<td>99:1</td>
</tr>
<tr>
<td>4</td>
<td>98e</td>
<td>n-Hexyl</td>
<td>97</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>5</td>
<td>98f</td>
<td>Bn</td>
<td>91</td>
<td>97:3</td>
</tr>
<tr>
<td>6</td>
<td>98f</td>
<td>Bn</td>
<td>89</td>
<td>78:22^c</td>
</tr>
<tr>
<td>7</td>
<td>98g</td>
<td>Allyl</td>
<td>97</td>
<td>99:1</td>
</tr>
<tr>
<td>8</td>
<td>98h</td>
<td>Propargyl</td>
<td>95</td>
<td>99:1</td>
</tr>
</tbody>
</table>

^aIsolated yields. ^bDetermined by chiral HPLC. ^cEnolate generated at 0 °C and trisyl azide introduced at 0 °C.
Figure 45. $^1$H-NMR spectrum of 98b.

Figure 46. $^{13}$C-NMR spectrum of 98b.
The NMR data strongly suggests that a single diastereomer was formed, however HPLC analysis showed a major peak at 4.21 min confirming a dr > 99:1 for the diastereoselectivity.

![Figure 47. HPLC chromatograph of 98b confirming >99:1 dr.](image)

The $^1$H-NMR (Figure 48) and $^{13}$C-NMR spectrum (Figure 49) of 98c similarly shows the characteristic changes. The dr of the reaction was also corroborated by HPLC as 98:2.

![Figure 48. $^1$H-NMR spectrum of 98c.](image)
Moving on to a much larger chain, the $^1$H-NMR spectra of 98e, showed a clear doubling of peaks for H-5’ and the CH$_3$ of the ester (Figure 50).
Doubling was also observable in the $^{13}$C-NMR spectrum (Figure 51 - expansions).

Initially this was worrying, as it seemed to imply that the azidation was not very diastereoselective. The HPLC of 98e, though, showed only one peak at 12.44 min (Figure 52). Gratifyingly however, subsequent transformation of 98e to 99e (which will be mentioned later) confirmed a single peak that corresponded to a $\text{dr}>99:1$. It was speculated that the doubling of signals could involve cis/trans rotamers around the C-N$_{\text{Aux}}$ $\sigma$-bond of 98e due to the very large hexyl group, in which case VT NMR studies would be able to confirm this and will be a topic of future study.

![Figure 51. $^1$H-NMR and $^{13}$C-NMR spectrum of 98e.](image)

![Figure 52. HPLC chromatograph of 98e showing only one diastereomer.](image)
In addition, 98e was the only azide that existed as an oil suggesting the presence of isomers, which prevented crystal packing necessary for producing a solid. Looking at the NMR data of an azide with a functionalized R group, namely 98h containing a propargyl as the R group (Figure 53), also as expected produced the same diagnostic NMR signals as 94h.
This, together with the characteristic changes described for 98b, 98b and 98e which together with its IR data and elemental analysis confirmed its synthesis while HPLC indicated the diastereomeric ratio to be 99:1. Returning to the key question of the diastereoselectivity of the azidation reaction, when examining the crystal structures of quaternized azides 98f and 98g shown in Figure 54, it can been seen that the absolute configuration around the newly formed aza-quaternary centre was S with the azido group anti- to the bulky face of the auxiliary when the whole molecule is written in the all cis conformation.

![Figure 54](image1.png)

**Figure 54.** Crystal structure of azides 98f and 98g showing an S configuration around the aza-quaternary centre.

Since enolate generation must have given the same Z-enolate as with the all-C quaternizations the observed diastereoselectivity implied that the azidation had in fact taken place via the auxiliary in an s-cis\textsubscript{C-N} conformation and not via the anticipated s-trans\textsubscript{C-N} conformation as with the all-C case. These results pointed strongly towards the potassium ion having being ejected from the malonate hole by the charged trisyl azide reagent into the auxiliary hole, forcing an s-cis conformation as with the Evans system (Figure 55).

![Figure 55](image2.png)

**Figure 55.** Proposed trisyl azide assisted conformational switch from s-trans to s-cis enolate.
The whole sequence of events is depicted in Figure 55 and is summarized by the following steps:

1) The Z-enolate is formed as usual at -85 °C as the kinetic enolate with the potassium preferring the malonate hole.

2) Here, the auxiliary adopts a preferred s-trans conformation to reduce steric strain with the R group.

3) Approach of the azide into a stereoelectronically aligned positioning with respect to the enolate π-system results in ejection of the potassium ion into the auxiliary hole. This switches the auxiliary conformation to s-cis resulting in a reversal of diastereofacial bias of addition. The latter assumes that the Z-enolate configuration holds throughout which is reasonable.

Empirical support for this is provided by the surprising result obtained in the azidation of 94b (R = Me) bearing an α-methyl substituent to for 98b which showed a dr > 99:1 (Table 8, entry 1). In previous work from the group on the generation of all-C quaternary centres it was found that allylation of 94b resulted in virtually no diastereoselectively (dr of 60:40 was obtained). The result obtained in the allylation of 94b was therefore reasoned (and reported in the paper61) as being due to the small methyl group not being large enough to restrict formation of the s-cis conformer because of reduced steric strain between the methyl group and the bulky substituents on the auxiliary. Additional calculations on substituted malonates (prior to deprotonation) revealed that the energy barrier to convert from the s-trans C-N to the s-cis C-N enolate was lower for R = Me than for any other R > Me and this was in line with the 60:40 dr obtained in the allylation of 94b. By comparison, the locked s-cis conformation now invoked to explain the diastereoselectivity of azidation in which the bulky substituents are now close to the R group, has the least tendency to undergo any conformational flip with the small methyl case, which is what is observed in terms of a high diastereoselectivity. In any event, the high azidation diastereoselectivities for all R groups is testimony to a chelated and hence locked s-cis auxiliary conformation even with bulky R groups. Regarding uncovering the important experimental parameters controlling the diastereoselectivity as well as the rate of the displacement of the potassium, enolate generation at different temperatures was an obvious place to start. When the enolate was generated at 0°C and the azide electrophile introduced at the same
temperature, the reaction yield remained unchanged, but the dr dropped to 78:22 (Table 8, entry 6). This was confirmed by HPLC with the major diastereomer at 9.7 min and the minor at 11 min (Figure 56). The peak at 9.1 min was confirmed to be the starting material by injection of 94f in an independent HPLC analysis.

When the enolate was generated at –85 °C, warmed to 0 °C and trisyl azide introduced at this temperature, the dr obtained was found to be the same as that generated under the normal reaction conditions (i.e. dr = 97:3). Assuming the need of the electrophile to still demand cation expulsion at 0 °C on stereoelectronic (alignment) grounds, once again resulting in a chelated s-cis auxiliary conformation, these results indicate that enolate generation at 0 °C involves the formation of some of the E-enolate (approximately 80:20 Z:E).
3.6 Transformation of 98 to α,α′-Disubstituted Serine Derivatives.

To complete the asymmetric azidation methodology a non-destructive removal of the chiral auxiliary was required. The challenge with this step was chemodifferentiating reductively between the carbonyl groups of the ester and the chiral auxiliary, as well as the azide functional group. From previous work on the all-C quaternization it was known that standard methods for removing the auxiliary such as hydride reduction, metal hydroperoxide or hydroxide-mediated hydrolysis were either ineffective or did not produced the desired chemoselectivity. To overcome this a sequence that made use of Fukuyama reduction was developed involving the exchange of the chiral auxiliary using LiSEt to form a thioester that was subsequently subjected to a Fukuyama reduction to produce an aldehyde. This was rapidly exposed to reduction to the primary alcohol with NaBH₄ (Scheme 84).

![Chemoselective removal of the auxiliary by LiSEt followed by conversion to the β-hydroxy ester via a Fukutama reduction sequence.](image)

It was envisaged that this sequence could be applied to the transformation of 98 to afford α,α-disubstituted serine derivatives. It is known that thiols are able to reduce azides to the corresponding amines and it was thought that it might be possible to achieve both the reduction of the azide to the amine as well as the removal of the chiral auxiliary to afford thioester 100 in one step using LiSEt in the presence of excess EtSH (Scheme 85).

![Envisaged one pot conversion of 98 to the corresponding thioamine 100 using LiSEt in the presence of excess of EtSH.](image)
TLC of this reaction however showed a complex mixture of products and this made it difficult to isolate the desired product. For this reason it was decided to first convert the azide to the amine 99 before the reaction with LiSEt (Scheme 86).

Hydrogenation over Pd-C offers the most convenient method for this transformation as filtration is the only post-reaction processing required, particularly in the case of producing an amine where an aqueous work-up generally needs to be avoided. Hydrogenation of saturated R groups successfully produced amine 99 and this will be shown later. In the case of 98g and 98h containing allyl and propargyl groups respectively, however, this approach would be ineffective owing to the incompatibility of double bonds with hydrogenation. For now, attention will be placed on azide reduction methodologies that are compatible with unsaturated functional groups. Hence, these were subjected to Staudinger conditions for this transformation instead. Specifically, monitoring the reaction of 98g with PPh₃ and H₂O (Scheme 87) by TLC showed an immediate (1 – 2 min) formation of triphenylphosphine oxide, auxiliary Aux and a more polar product that was assumed to be the amino acid 101g from azide reduction and hydrolysis of the auxiliary.

As the reaction proceeded, however (to allow for complete conversion), there was a decrease in the concentration of the polar spot together with the formation of a less polar product (relative to 98g). The reaction was allowed to proceed to this more polar product.
which was isolated in 70 % following chromatographic purification. At first glance its $^1$H NMR spectrum run in CDCl$_3$ strongly suggested that 101g was indeed the desired amino acid (Figure 57).

An ethyl ester quartet and triplet occurred at the expected shifts of 4.25 ppm and 1.26 ppm respectively. The two multiplets at around 2.89 ppm and 3.16 ppm were assigned to the two diastereotopic protons H-2a, while a vinyl region typical of an allyl group could be discerned downfield in the usual region of around 5 ppm. Finally, a broad singlet at 11.29 for the –OH could also be seen, although there was no sign of a broad 2H resonance for an amino group. As mentioned before, compound 101g was less polar than the starting material 98g and this was the first indication that the structure of 101g was incorrect as it was expected that the presence of both the free amine and the carboxylic acid group would render it much more polar. However, a $^{13}$C-NMR produced the required eight resonances for 101g (Figure 58) and this further supported the assumed structure 101g.
The carboxylic acid C=O was assigned to the downfield signal at 174.2 ppm and the ester to the resonance at 162.2 ppm. The alkene signals appeared at 128.1 ppm and 121.7 ppm and the quaternary C-2 at 84.0 ppm. An HRMS would have provided ultimate confirmation for the structure of 101g but the compound was found to be fairly unstable at room temperature as a TLC the day following its synthesis showed a variety of spots effectively ruling out HRMS, which required sending the sample away. It was then decided to subject 101g to a LiBH₄ reduction on the basis that if 101g was indeed the structure the reduction would result in the chemoselective reduction of the ester to afford the quaternary serine amino acid 102g (Scheme 88).

Scheme 88. Envisaged reduction of 101g with LiBH₄ to afford quaternary serine 102g.
In the event, however, a single product could not be isolated. Similarly, the reaction of 101g with LiAlH₄ at –78 °C did not reveal any evidence of 102g either. The major clue to solving this structure resided in the assigned carboxylic acid resonance in the ¹³C-NMR of 101g at 174.2 ppm. Carboxylic acids usually resonate between 180 ppm – 200 ppm and the observed 174.2 ppm corresponded more to an ester or amide. The second piece of evidence was the presence of only one broad singlet corresponding to the –OH and no evidence of another broad singlet to account for the NH₂. It is common knowledge that NH or OH groups do not always produce reliable signal integrations, however in this case the absence of a discernible amino resonance provided the final piece of the puzzle that the actual structure obtained from the reaction of 98g with PPh₃ and H₂O was in fact the triazolone 103g shown in Scheme 89, which explained the lower polarity compared to 98g as well as the observed instability.

![Scheme 89. Reaction of 98g under Staudinger conditions afforded triazole 103g.](image)

The ¹³C-NMR resonance at 174.2 ppm was now more appropriate as C-3 is effectively an N-functionalised amide. Although more downfield than usual, the chemical shift could be rationalized as being due to the electron-withdrawing triazole moiety deshielding C-3 (Figure 59, 103g-B).

![Figure 59. Resonance structures of 103g.](image)

Following the mechanism of a typical Staudinger reduction of an azide to an amine, triazolone 103g is thought to have formed via the phosphazide formed from addition of the triphenylphosphine to the azide as normal, undergoing a SₕAc reaction with expulsion of auxiliary, rather than proceeding to the iminophosphorane (Figure 60).
Thus, a different method for the reduction of the azide to an amine in the presence of olefins was required. A scan of the literature revealed that Zn in the presence of NH₄Cl is able to efficiently reduce azides to amines and this was found to achieve a high-yielding chemoselective reduction of 98 to the corresponding amine as well as being compatible with double and triple bonds. Table 9 summarizes the results of the conversion of a range of derivatives of 98 to 99.

Table 9. Reduction of azide 98 to the corresponding amine 99

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>99b</td>
<td>Me</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>99e</td>
<td>n-Hexyl</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>99f</td>
<td>Bn</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>99g</td>
<td>Allyl^b</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>99h</td>
<td>Propargyl^b</td>
<td>92</td>
</tr>
</tbody>
</table>

^a Isolated yield. ^b Reduction with Zn, NH₄Cl

The NMR spectrum of 99e run in CDCl₃ as representative is shown Figure 61. The upfield shift of carbon C-2 to 66.4 ppm from 73.3 ppm as well as the IR spectrum revealing the absence of the 2117 cm⁻¹ azide stretch confirmed its synthesis. Also of note was a 2H broad singlet for the amino group at around 2.5 ppm.
Figure 61. $\textsuperscript{1}H$-NMR and $\textsuperscript{13}C$-NMR spectrum of 99e.
In addition a single set of resonances in both spectra provided confirmation that the azidation to afford 98e produced a single diastereomer and that the doubling of NMR signals in 98e was due to rotomers. Following reduction to the amine, the auxiliary was chemoselectively removed via a $S_N$Ac reaction with LiSEt to form thioester 100, with complete recovery of the chiral auxiliary Aux and with no evidence of dithioester formation. Surprisingly this reaction occurred at −78 °C using only 1.2 eq. LiSEt in contrast to the 10 eq. LiSEt at 40 °C that was necessary for the all-carbon quaternary case. It is presumed that the chemoselectivity in conjunction with this rate enhancement is due to a neighbouring-group assistance by the free amino group which involves co-ordination to the lithium cation bringing the SEt anion closer to the acyl centre and thereby increasing the rate (Figure 62). The results for the general applicability with respect to the R groups are summarized in Table 10. Surprisingly all the thioesters, including those where R = alkyl, were UV active and the ee % could be determined by HPLC (UV-detector).

![Figure 62. NH$_2$ assisted removal of the auxiliary with LiSEt.](image)

### Table 10. Removal of the chiral auxiliary to form thioester 100

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cpd</th>
<th>R</th>
<th>Yield of 100 (%)$^a$</th>
<th>ee (%)$^b$</th>
<th>% of Aux recovered$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>99b</td>
<td>Me</td>
<td>93</td>
<td>&gt; 99</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>99e</td>
<td>n-Hexyl</td>
<td>94</td>
<td>&gt; 99</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>99f</td>
<td>Bn</td>
<td>92</td>
<td>96</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>99g</td>
<td>Allyl$^b$</td>
<td>94</td>
<td>&gt; 99</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>99h</td>
<td>Propargyl$^b$</td>
<td>94</td>
<td>&gt; 99</td>
<td>97</td>
</tr>
</tbody>
</table>

$^a$Isolated yield.$^b$By chiral HPLC.
The $^1$H-NMR of 100f (Figure 63) as representative of the series revealed the typical ethyl ester signals at 4.25 ppm and 1.30 ppm. The ethyl thioester signals, by comparison, appeared upfield at 2.85 ppm (quartet) and at 1.23 ppm (triplet) assigned to H-3a and H-3b respectively. The NH$_2$ occurred upfield at 1.90 ppm while the anticipated diastereotopic AB doublet pair for H-2a could be observed at 3.34 ppm. The aromatic region integrated for the expected five protons.

![Figure 63. $^1$H-NMR spectrum of 100f with expansions.](image-url)
In addition, the 11 resonances of the $^{13}$C-NMR of 100f could all be appropriately assigned for the structure (Figure 64), the diagnostic signal being the thioester carbonyl C-3 at 201.4 ppm. C-1 occurred at 170.1 ppm and the aza-quaternary centre at 72.1 ppm. All this data strongly supported the structure proposed.

![Figure 64. $^{13}$C-NMR spectrum of 100f.](image)

The original work by Fukuyama reported that terminally substituted olefins were reduced to the corresponding alkane under the Fukuyama conditions and for this reason Evans et al developed a modification of this procedure involving the use of an excess of a sacrificial olefin (1-hexene) together with a poisoned Pd catalyst (Lindlar), which suppressed the unwanted olefin reduction (Scheme 90).

Scheme 90. Evans modification of the Fukuyama reduction reported to suppress the reduction of terminal olefins.
Amines are known to poison heterogeneous Pd catalysts, so inspired by the
demonstrated work by Evans together with the observed rate enhancement of acyl
substitution due to the assistance of the amine it was thought that for 100g and 100h
containing unsaturation, the amine might be able to assist the chemoselective reduction of
the thioester in the presence of the double bond to afford the corresponding aldehyde 101,
which would be rapidly reduced by NaBH₄ and then amino-protected to afford the serine
derivative 102 (Scheme 91). As a back-up plan it was thought that the Evans modification
would provide a potential solution, and therefore pursuing a Fukuyama reduction protocol
for 100g and 100h containing useful unsaturated functionality in the R group was not a
primary concern at this point.

![Scheme 91: Envisaged Fukuyama protocol for the conversion of 100 to quaternary serine derivative 102.](image)

The potential issue of self-condensation of amino aldehyde, 101, however was a major
concern, although the amino group of 100 could be protected beforehand with probable
loss of assistance in the Fukuyama, whose importance in any chemoselectivity wasn’t
known. It was thought, though, that the nucleophilic addition step of the amine to the
aldehyde would be very slow based on steric considerations so to get a handle on this,
compound 100g was subjected to a Boc protection in THF (Scheme 92).

![Scheme 92: Investigation of the rate of Boc protection of 100g.](image)
Pleasingly in context, when 1.05 eq. (Boc)_2O was used, no conversion to a product was observed (by TLC) after 18 hrs. Increasing the amount to 3 eq. and warming to 40 °C for a further 18 hrs also did not provide a synthetically useful conversion to the product even after the addition of 1 eq. LiClO_4, a known activator for Boc protection. These results indicated that the self-condensation of amino aldehyde 101 would similarly occur very slowly, if at all. Propargylic derivative 100h was then subjected to a Fukuyama reduction. 100h was chosen as a model as it was assumed that if chemoselectivity could be realized for the triple bond, the reaction would also be chemoselective for 100g containing a double bond. In the event, using the standard Fukuyama conditions of 3 eq. Et_3SiH and Pd-C (10 mol %) in THF no product was obtained after 12 hrs at rt, and 100h was recovered. A scan of the literature showed that Fukuyama reductions usually take 30 min - 2 hrs for complete conversion of the SM and this suggested that the presence of the free amine was indeed poisoning the Pd-C. Increasing to 6 eq. Et_3SiH and continuing stirring for a further 12 hrs saw approximately 70 % conversion of 100h by TLC. Addition of another 3 eq. Et_3SiH (9 eq. in total) achieved complete conversion within 30 min, and importantly, 100g was isolated in 96 % yield (Scheme 93) in which one of the π-bonds of the triple bond had been reduced.

![Scheme 93](image)

**Scheme 93.** Fukuyama reduction of 100h after 2 hrs using 9 eq. Et_3SiH formed 100g in 96 % yield.

In view of both the large number of equivalents of Et_3SiH required and the imperfect chemoselectivity, it was thought that the Evans’ modification would unlikely be effective. Up to this point, the most telling observation regarding finding a solution to the chemoselectivity was that of the rate enhancement seen in the removal of the auxiliary with LiSEt. As mentioned before, standard hydride reductions on the all-carbon quaternary centre were ineffective. However, it was thought that the free amine would be able to amplify the reactivity difference between the ester and the thioester via assistance between the amino group of the substrate and the reagent, in which a low temperature of reaction was probably important. In the event, though, reduction of 100f (as a
representative model due to its UV activity) with NaBH₄ (2 eq) at 0 °C in EtOH and quenching immediately after all the starting material was consumed (TLC), gave mostly the over-reduced diol product 104f in high yield after Boc protection (Scheme 94).

Scheme 94. NaBH₄ reduction of 100f resulted in reduction of both the ester and thioester and diol 104f was obtained in 89 % yield over two steps.

The structure of 104f was confirmed by its ¹H-NMR spectrum (Figure 65), which showed four hydrogens for the reduced hydroxymethylene groups as diastereotopic AB doublet pairs at 3.75 ppm and 3.57 ppm. The rest of the signals appeared as expected.

Figure 65. ¹H-NMR spectrum of 104f.

It was thought that since NaBH₄ has 4 hydrides per molecule, the over reduction was due to using 2 eq. of NaBH₄, but when this was reduced down to 0.5 eq. it took very long to obtain
full conversion and the diol was still the major product observed. Following another thorough perusal of literature a report was uncovered describing the mono-reduction of disubstituted malonate (105) to the β-hydroxy ester (107) using lithium tri-tert-butoxyaluminium hydride (LTBAH) as shown Scheme 95.

![Scheme 95. Mono-reduction of di-substituted malonates with LTBAH.](image)

Here it was proposed that the steric bulk of aluminate intermediate 106 prevents over reduction to the diol. In conjunction with electronic effects this provides an explanation for the over-reduction of 100f even when 0.5 eq NaBH₄ was used. In the case of the LTBAH reduction, the aluminate species 106 blocks another LTBAH molecule from reducing the second ester group. However, if the tert-butoxy groups were replaced with hydrogens as would be the case with NaBH₄ this would in fact have an activating effect as the hydride would be brought closer to the second ester group to act as a transfer agent rather than as a blocking group (Figure 66).

![Figure 66. Reduction of both ester and thioester of 100f due to the activation by the borohydride intermediate.](image)

Although the NaBH₄ reduction gave 89% of the diol, the 7% obtained for the desired product indicated that chemoselectivity was being achieved to some extent. It was concluded, hence, that the free amine was indeed delivering the hydride to the thioester in
the first instance, but thereafter over-reduction was being promoted as shown in Figure 66 resulting in diol formation. Thioester 100h was reacted with LTBAH (2 eq) at 0 °C in THF for complete conversion of the SM (by TLC), and the reaction worked up followed by amino group protection with 1.2 eq. (Boc)$_2$O with 5 mol % DMAP. After column chromatography, the desired α,α-disubstituted serine derivative 102h retaining both triple bond and ester functionalities was obtained in 65 % yield over the two steps (Scheme 96).

\[ 100h \xrightarrow{i) \text{LTBAH (2 eq), THF, 0 °C}} 102h \]

\[ \text{NH}_2 \quad \text{EtO} \quad \text{O} \]

\[ \text{O} \quad \text{EtO} \quad \text{i) LTBAH (2 eq), THF, 0 °C} \quad \text{O} \quad \text{EtO} \quad \text{ii) (Boc)$_2$O} \]

\[ \text{OH} \quad \text{NH}_2 \quad \text{Boc} \]

Scheme 96. Chemoselective reduction of 100h with LTBAH to afford the target serine derivative 102h.

Compound 102h is not UV active and the ee could not be determined without derivatization. Owing to time constraints the derivatization was not carried out but will be a principal focus of future work. Thioester 100h, however, was UV active and its HPLC trace revealed the ee to be > 99%. Since the chemistry involved in the conversion from 100 to 102 would not affect the aza-quaternary centre, for convenience the ee value was extrapolated from 100 and it was therefore concluded that the 102h would also possess > 99 % ee. The NMR data is presented in Figure 67 and Figure 68. The $^1$H-NMR spectrum revealed the typical ethyl ester quartet and triplet at 4.20 ppm and 1.27 ppm respectively together with the nine CH$_3$ protons for the Boc protecting group as a singlet at 1.44ppm. Extremely gratifying, and for the first time post any reduction was the appearance of the alkynyl hydrogen (2c) as a triplet at 2.31 ppm, and an ABX double doublet pair at 2.93 ppm and 2.82 ppm for the propargylic hydrogens (H-2a). A collapsed AB doublet at 3.85 ppm was assigned to the diastereotopic hydroxymethylene protons at H-3. The $^{13}$C-NMR spectrum further supported the structure of 102h as it revealed the expected 11 resonances (Figure 68). The carbonyls were revealed at 173.1 ppm for C-1 and 156.6 ppm for the Boc group. The quaternary carbons occurred at 80.7 ppm, 79.9 ppm and 72.2 ppm for C-2b, C-5 and C-2 respectively. The quaternary carbons occurred at 80.7 ppm, 79.9 ppm and 72.2 ppm for C-2b, C-5 and C-2 respectively. The terminal alkyne C-2c was assigned to the 64.2 ppm resonance. The resonances at 63.9 ppm, 62.6 ppm, 23.1 ppm and 14.4 ppm
corresponded to C-3, C-1a, C-2a and C-1b respectively. The CH$_3$ for the Boc group could be seen at 28.7 ppm (C-6). This together with HRMS confirmed the successful synthesis of 102h.
To show general applicability, the procedure was also applied to 100f, possessing a saturated and larger alkyl group (Scheme 97) and this similarly afforded 102f in 70 % yield over 2 steps in 97 % ee by HPLC (Figure 69), this time ascertained for the final derivative in view of UV-activity due to the benzyl group. The major enantiomer eluted at 10.14 min while the minor eluted at 11.18 min.

![Image: Scheme 97. Conversion of 100f to 102f.]

The 1H-NMR data shown in Figure 70 revealed the usual ester triplet and quartet at 1.23 ppm and 4.16 ppm for H-1b and H-1a. The diastereotopic AB doublet pairs were nicely resolved resonating at 2.83 ppm and 3.09 ppm for H-2 as well as at 4.08 ppm and 4.47 ppm for H-3. The nine protons for the Boc protecting group H-6 was assigned to the singlet at 1.47 ppm, while the aromatic region showed the expected 5 protons.
Similarly the $^{13}$C-NMR produced the desired 13 resonances and assigned as per Figure 71.

The synthesis of 102f was further confirmed by HRMS.
3.7 Conclusions and Future work

3.7.1 Conclusions
The successful synthesis of serine derivatives 102 marked the development of a general approach towards the stereoselective construction of aza-quaternary centres. This was achieved through a diastereoselective azidation step of various malonate–imidazolidinones 98b – h as the key step, which proceeded in excellent yield (>90%) and diastereoselectivity (> 97:3 dr). Analysis of the crystal structure obtained for 98f and 98g in conjunction with previous work led to the conclusion that reaction had occurred via a transition-state involving a (Z)-enolate with the K⁺ cation chelated into the auxiliary hole together with the auxiliary in a s-cisCN conformation. This surprising result was contrary to the s-transCN transition state observed when carrying out alkylation reactions rather than azidation. With the assistance of computational modeling it was proposed that the reversal of the auxiliary conformation is due to the charged trisyl azide electrophile displacing the potassium cation out of the malonate hole into the auxiliary hole. This also made it possible to account for the 99:1 diastereoselectively obtained when R = Me (94b), compared to the alkylation case when a dr = 60:40 was obtained for this substrate. Following reduction to the amine, the auxiliary was removed using 1.2 eq. LiSEt at –78 °C, once again in contrast to the 10 eq. LiSEt and 40 °C required in the alkylation work, suggesting that the LiSEt substitution was proceeding via an amine-assisted process. The amino thioesters were transformed to (N)-Boc-Serine derivatives 102 via chemoselective reduction with LTBAH followed by Boc protection. The overall sequence is presented in Scheme 98.

![Scheme 98](image)

Scheme 98. Overall sequence for the general synthesis of α,α-disubstituted serine derivatives.

3.7.2 Future work
Up until now, 102 has only been considered as a serine derivative. However, by varying the R group, which this methodology appears to offer, equally one could view the targets as
quaternized hydroxymethyl amino acids. Furthermore, since a primary hydroxyl group may be easily transformed further, the target synthon opens up several possibilities for producing quaternized amino acids containing two distinct R groups. Some examples are shown in Figure 71, and this will be carried out in the future. The possibility of extending this methodology to enantioselective α-aminations of prochiral substituted malonates using chiral enolates or PTC will also be investigated.

Figure 71. Quaternary amino acids that could be accessed using the developed methodology.
Chapter 4
Experimental

General information

All reagents were available by commercial sources (Sigma-Aldrich, Merck) and were used without further purification. All solvents were freshly distilled. Dichloromethane was distilled from phosphorus pentoxide under nitrogen. Acetonitrile was distilled from calcium hydride under nitrogen. THF was distilled over sodium wire with benzophenone under nitrogen. Reactions were monitored by TLC using aluminium-backed Merck silica-gel 60 F_{254} plates and were observed using both ultraviolet and fluorescent light or spraying with a 2.5% solution of anisaldehyde in a mixture of sulfuric acid and ethanol (1:10 v/v). Column chromatography was carried out using Kieselgel 60 silica-gel (Merck). Nuclear Magnetic Resonance spectra were recorded on a Varian Mercury 300 MHz (75.5 MHz for $^{13}$C) or a Bruker 400 MHz (101 MHz for $^{13}$C) instrument. The chemical shifts ($\delta$, ppm) of the deuterated solvents used were, CDCl$_3$ (7.26 in $^1$H NMR and 77.0 in $^{13}$C), CD$_3$OD (4.87 in $^1$H NMR and 49.2 in $^{13}$C NMR). Chemical shifts ($\delta$) were reported in ppm and $J$ values are quoted in Hz. Mass spectra were recorded on a JEOL GCmatell and were recorded in Electron ionisation mode. Melting points / decomposition temperatures were determined using a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. Infrared spectra were recorded on Perkin-Elmer Paragon 1000 FT-IR spectrophotometer on NaCl plates. Elemental analyses were performed using a Fisons EA 1108 CHNS elemental analyser. The enantiomeric excess (ee) of the products were determined by HPLC on an Agilent 1220 Series using a Diacel Chiracel OD (250 × 4.6 mm) or Chiralpak AD (250 × 4.6 mm) column. Optical rotations were obtained using a Perkin Elmer 343 polarimeter at $\lambda = 589$ nm and 20 °C. The concentration $c$ refers to g/100ml.
(4R,5S)-1,5-dimethyl-3-nitro-4-phenylimidazolidin-2-one (66)

![Structure of 66]

To a stirred solution of KNO₃ (0.848 g, 8.34 mmol) in CH₃CN (30 mL) at 0 °C was added trifluoroacetic anhydride (0.810 mL, 5.77 mmol) dropwise and the reaction mixture stirred at this temperature for 2 hrs. Aux (0.500 g, 4.12 mmol) was then added in one portion and the reaction mixture stirred for 18 hrs. The solvent was removed under reduced pressure and sat. NaHCO₃ (30 mL) was added slowly. The mixture was extracted with DCM (3 x 20 mL), the organic layer dried with MgSO₄ and the solvent removed under reduced pressure to yield the title compound as a yellow solid. The compound was purified by recrystallisation with DCM/hexane to afford 66 as yellow needles (0.594 g, 96 %); IR νₘₐₓ (NaCl) / cm⁻¹ 1764 (C=O), 1537 (N-O), 1370 (N-O); ¹H NMR δ (300 MHz, CDCl₃, ppm) 0.83 (d, J = 6.9 Hz, 3H, Me), 2.91 (s, 3H, NMe), 3.93 (dq, J = 8.7 Hz, 6.9 Hz, 1H, H-5), 5.52 (d, J = 8.7 Hz, 1H, H-4), 7.19 – 7.45 (m, 5H, Ar); ¹³C NMR δ (101 MHz, CDCl₃, ppm). 14.8 (Me), 28.7 (NMe), 53.1 (C-5), 62.9 (C-4), 126.6 (Ar), 128.9 (Ar), 129.0 (Ar), 133.7 (Ar₂), 150.9 (C-2); Anal. Calc. for C₁₁H₁₃N₃O₃ (%): C, 56.16; H, 5.57; N, 17.86. Found (%): C, 56.35, H, 5.42, 17.67

(4S,5R)-1-amino-3,4-dimethyl-5-phenylimidazolidine-2-thione (81)

![Structure of 81]

To a stirred solution of 64 (0.100 g, 0.49 mmol) in toluene, was added Lawesson’s reagent (0.236 g, 1.2 eq) and the reaction refluxed for 2hrs. The solvent was then removed and the crude solid subjected to column chromatography to afford 81 as a white solid (0.106 g, 98 %). An analytical sample was prepared by recrystallisation from DCM/hexane. IR νₘₐₓ (NaCl) / cm⁻¹ 3654 (NH₂), 1650, 1480; ¹H NMR δ (400 MHz, CDCl₃, ppm) 0.83 (d, J = 6.4 Hz, 3H, Me), 3.14 (s, 3H, NMe), 3.96 (dq, J = 9.2 Hz, 6.8 Hz, 1H, H-4), 4.17 (bs, 2H, NH₂), 4.90 (d, J = 9.2 Hz, 1H, H-5), 7.10 (m, 2H, Ar), 7.34 (m, 3H, Ar); ¹³C NMR δ (101 MHz, CDCl₃, ppm) 13.9 (Me), 33.0 (NMe), 58.5 (C-4), 69.5 (C-5), 127.6 (Ar), 128.4 (Ar), 128.7 (Ar), 134.4 (Ar₂), 185.8 (C-2);
Anal. Calc. for C_{11}H_{15}N_{3}S (%): C, 59.69; H, 6.83; N, 18.99; S, 14.49. Found (%): C, 59.84; H, 6.74; N, 18.90; S, 14.39.

_Tert-butyl (R)-(2-(methylamino)-2-oxo-1-phenylethyl)carbamate\textsuperscript{67}_

\begin{center}
\includegraphics[width=0.3\textwidth]{tert-butyl-carbamate.png}
\end{center}

To a stirred solution of \((R)-N\text{-}Boc\text{-}phenylglycine (6.00 g, 23.9 mmol)\) and \(N\text{-}methylmorpholine (2.63 mL, 23.9 mmol)\) in THF (70 mL) at -15 °C was added dropwise a solution of freshly distilled pivaloyl chloride (3.23 mL, 0.1 M, 26.3 mmol) and the reaction stirred at this temperature for 15 min. Ethanolic methylamine (3.42 mL, 33 wt %, 28.6 mmol) was then added and the reaction mixture warmed to rt and stirred for 1 hr. A dilute solution of citric acid (1M, 80 mL) was added and the mixture extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with sat. NaHCO₃ (100 mL) followed by washing with brine (100 mL). After drying over MgSO₄, filtering and removing the solvent, the mixture was subjected to flash chromatography and further purified by recrystallisation with DCM:hexane to afford the title compound as fine-white needles (6.10 g, 97 %). \(^1\)H NMR \(\delta\) (400 MHz, CDCl₃, ppm) 1.40 (s, 9H, -(CH₃)₃), 2.74 (s, 3H, -NCH₃), 5.18 (s, 1H, -NHMe), 5.89 (s, 1H, -CH-), 6.24 (-NHBoc) 7.12 – 7.38 (m, 5H, Ar).

_(R)-2-amino-N-methyl-2-phenylacetamide (82)\textsuperscript{68}_

\begin{center}
\includegraphics[width=0.2\textwidth]{amino-acetamide.png}
\end{center}

**Method A (via aminolysis):** To commercially available \((R)-(\text{-})-\text{phenylglycine hydrochloride methyl ester (5.00 g, 24.8 mmol)\) was added ethanolic methylamine (12.2 ml, 33 wt %, 129.6 mmol). The reaction was sealed and stirred at rt for 12 hrs. The solvent was then rotary evaporated and the crude slurry taken up in methanol (100 ml). Solid K₂CO₃ (7.00 g) was then added and the mixture stirred for 1 hr before being filtered through celite to afford the title compound as a yellow oil (4.01 g, 99 %).
**Method B (via Boc deprotection):** To a stirring solution of TFA in DCM (100 mL) at 0 °C was added N-Boc-phenylglycine-N-methylamide (6.00 g, 22.7 mmol) slowly and the reaction allowed to warm to rt. After 6 hrs the solvents were removed under reduced pressure and sat. NaHCO₃ (70 mL) was added. The solution was extracted with chloroform:methanol (1:1, 3 x 50 mL) and dried with Na₂SO₄. The mixture was then filtered and the solvent removed under reduced pressure to afford the title compound as a yellow oil (3.35 g, 90%).

³H NMR δ (300 MHz, CDCl₃, ppm) 2.16 (s, 2H, NH₂), 2.76 (d, J = 4.8 Hz, 3H, -NCH₃), 4.49 (s, 1H, H-2), 7.09 (bs, 1H, NHMe), 7.31 (m, 5H, Ar); ¹³C NMR δ (101 MHz, CDCl₃, ppm) 26.0 (-NCH₃), 59.8 (C-2), 126.9 (Ar), 127.9 (Ar), 128. 8 (Ar), 141.1 (Ar₂), 173.6 (C-1).

(R)-N³-methyl-2-phenylethane-1,2-diamine (83)⁶⁹

To a stirred slurry of LiAlH₄ (2.31 g, 60.1 mmol) in THF (40 ml) at 0 °C under an Argon atmosphere was added (R)-phenylglycine-methylamide (4.00 g, 24.4 mmol) dropwise in THF (20 ml) and the solution kept at this temperature for 1 hr. The reaction mixture was then refluxed for 6 hrs and then cooled to 0 °C. A solution of NaOH (8.0 mL, 3.75 M, 30.0 mmol) was added slowly and the mixedtured stirred for 1 hr. The salts were filtered off and the organic layer dried with MgSO₄. The solution was then filtered and the solvent removed under reduced pressure to afford the diamine as a yellow oil (2.00 g, 56 %) which was sufficiently pure by ¹H-NMR to be used directly in the next step. ¹H NMR δ (300 MHz, CDCl₃, ppm) 1.71 (bs, 2H, -NH₂), 2.40 (d, J = 1.5 Hz, 3H, -NCH₃), 2.71 (m, 2H, H-1), 4.00 (m, 1H, H-2), 7.27 (m, 5H, Ar); ¹³C NMR δ (101 MHz, CDCl₃, ppm) 36.3 (-NCH₃), 55.3 (C-1), 59.9 (C-2), 126.3 (Ar), 127.1 (Ar), 128.4 (Ar), 144.6 (Ar₂).
(R)-1-methyl-4-phenylimidazolidin-2-one (84)\textsuperscript{70}

To a stirred solution of (R)-N\textsuperscript{2}-methyl-2-phenylethane-1,2-diamine (3.72 g, 24.8 mmol) in DCM:pyridine (1:1, 30 ml) at -10°C was added triphosgene (2.45 g, 8.26 mmol dropwise in dry DCM (10 mL) and the solution allowed to reach rt and stirred for 4 hrs. DCM (30 ml) was then added and the reaction mixture was then washed with 1M HCl (3 x 30 ml) followed by sat. NaCl (30 ml). The organic layer was then dried with MgSO\textsubscript{4}, filtered and the product purified by column chromatography after solvent evaporate ion to yield 84 as a colourless solid (3.11 g, 71 %). \textsuperscript{1}H NMR δ (400 MHz, CDCl\textsubscript{3}, ppm) 2.79 (s, 3H, -NCH\textsubscript{3}), 3.19 (dd, J = 8.8 Hz, 7.3 Hz, 1H, H-5), 3.76 (t, J = 8.8 Hz, 1H, H-5), 4.73 (dd, J = 8.8 Hz, 7.3 Hz, 1H, H-4) 7.24 (m, 2H, Ar), 7.39 (m, 3H, Ar); \textsuperscript{13}C NMR δ (101 MHz, CDCl\textsubscript{3}, ppm) 30.5 (-NCH\textsubscript{3}), 53.6 (C-5), 56.0 (C-4), 126.0 (Ar), 128.0 (Ar), 128.8 (Ar), 141.6 (Ar\textsubscript{q}), 162.3 (C-2).

General procedure for the synthesis of N-nitroso-2-imidazolidinones (67 and 85)

To a stirred solution of the 2-imidazolidinone Aux or 85 (2.50 mmol) in DCM 25 (mL) under Argon pressure was added isopentyl nitrite (0.47 ml, 3.50 mmol, 1.4 eq) and the reaction mixture stirred at rt for 18 hrs. The solvent was then removed under reduced pressure to yield a yellow solid which was recrystallised from DCM/methanol.

(4R,5S)-1,5-Dimethyl-3-nitroso-4-phenylimidazolidin-2-one (67):

With Aux (0.475 g, 2.50 mmol) to afford 67 as yellow needles (0.537 g, 98 %): m.p.: 212-213 °C; IR ν\textsubscript{max} (NaCl)/ cm\textsuperscript{-1} 1761 (C=O), 1604, 1426, 1398, 1165; \textsuperscript{1}H NMR δ (300 MHz, CDCl\textsubscript{3}, ppm) 0.82 (d, J = 6.7 Hz, 3H, Me), 2.99 (s, 3H, NMe), 3.98 (dq, J = 8.5 Hz, 6.7 Hz, 1H, H-5), 5.30 (d, J = 8.5 Hz, 1H, H-4), 7.02 (m, 2H, Ar), 7.28 (m, 3H, Ar); \textsuperscript{13}C NMR δ (101 MHz, CDCl\textsubscript{3}, ppm) 13.9 (Me), 28.8 (NMe), 54.4 (C-5), 66.8 (C-4), 127.6 (Ar), 128.0 (Ar), 128.6 (Ar), 135.6
(Arq), 162.6 (C-2); Anal. Calc. for C_{11}H_{13}N_{3}O_{2} (%): C, 60.26; H, 5.98; N, 19.17. Found (%): C, 60.24 H, 5.86; N, 18.99

(R)-1-Methyl-3-nitroso-4-phenylimidazolidin-2-one (87):

With 84 (0.441 g, 2.50 mmol) to afford 85 as yellow needles (0.503 g, 98 %). m.p. : 117-119 °C; IR ν max (NaCl) / cm⁻¹ 1744, 1457, 1427, 1407, 1304; ¹H NMR δ (400 MHz, CDCl₃, ppm) 3.07 (s, 3H, NMe), 3.33 (dd, J = 9.6 Hz, 3.6 Hz, H-5), 3.91 (t, J = 9.6Hz, 1H, H-5), 5.28 (dd, J = 9.6 Hz, 3.6 Hz, 1H, H-4) 7.12 (m, 2H, Ar), 7.34 (m, 3H, Ar); ¹³C NMR δ (101 MHz, CDCl₃, ppm) 30.5 (NMe), 52.6 (C-5), 53.7 (C-4), 125.4 (Ar), 128.5 (Ar), 129.1 (Ar), 137.5 (Arq), 152.9 (C-2); Anal. Calc. for C_{10}H_{11}N_{3}O_{2} (%): C, 58.53; H, 5.40; N, 20.48. Found (%): C, 58.53; H, 5.26; N, 20.32.

General procedure for the reduction of N-nitroso-2-imidazolidinones to the corresponding hydrazide (64 and 86)

To a stirred solution of N-nitroso-2-imidazolidinone 67 or 85 (2.00 mmol) in ethanol at –10 °C was added glacial acetic acid (1.14 ml, 20.0 mmol, 10 eq) followed by zinc dust (0.78 g, 11.9 mmol, 6 eq). The reaction was monitored by TLC to completion (10 – 30 min ) The reaction mixture was then filtered through a pad of celite and the solvent removed under reduced pressure to yield a white solid. The solid was dissolved in distilled water (25 ml) and the product extracted with DCM (3 x 20 ml). The combined organic extracts was dried with MgSO₄, filtered and the solvent removed under reduced pressure to give a white solid which was purified by recrystallised from DCM/hexane to give the desired compound.
(4S,5R)-1-amino-3,4-dimethyl-5-phenylimidazolidin-2-one (64):

With 67 (0.438 g, 2.0 mmol) afforded 64 as colourless needles (0.411 g, 98 %): m.p: 135-137 °C; IR νmax (NaCl) / cm⁻¹ 3685 (NH₂), 1706 (C=O), 1H NMR δ (400 MHz, CDCl₃, ppm) 0.72 (d, J = 6.6 Hz, 3H, Me), 2.78 (s, 3H, NMe), 3.68 (dq, J = 8.3 Hz, 6.6 Hz, 1H, H-4), 3.76 (bs, 2H, NH₂), 4.60 (d, J = 8.3 Hz, 1H, H-5), 7.16 (m, 2H, Ar), 7.30 (m, 3H, Ar); ¹³C NMR δ (101 MHz, CDCl₃, ppm) 14.9 (Me), 28.2 (NMe), 54.4 (C-4), 58.3 (C-5), 126.8 (Ar), 128.5 (Ar), 128.7 (Ar), 133.0 (Arq), 153.5 (C-2); Anal. Calc. for C₁₁H₁₅N₃O (%): C, 64.37; H, 7.37; N, 20.47. Found (%): C, 64.77 H, 7.54; N, 19.92

N-Boc-(L)-alaninol (87)⁷¹

To a stirred suspension of LiAlH₄ (6.00 g, 158 mmol) in THF (80 ml) at 0 °C under Argon was added L-alanine (6.00 g, 67.3 mmol) in portions and the solution kept at this temperature for 1 hr. The reaction mixture was then refluxed for 18 hrs and allowed to cool to rt. The reaction flask was then placed into an ice-bath and the mixture quenched with a solution of NaOH (20 mL, 3.75 M, 75.0 mmol). After filtering the salts, the solution was reduced to half its volume and NaHCO₃ (40 ml, 3.75 M) was added. The reaction flask was then cooled to 0 °C and (Boc)₂O (14.7 g, 67.3 mmol) was added in portions. Stirring continued at this temperature for 1 hr followed by stirring at rt for 5 hrs. The organic layer was then separated and the aqueous layer extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were dried with MgSO₄, filtered and the solvent removed under reduced pressure to give a colourless solid. This was then purified by column chromatography to afford the title compound 87 as a colourless solid (9.91 g, 84 %). ¹H NMR δ (300 MHz, CDCl₃, ppm) 1.12 (d, J = 6.6 Hz, 3H, H-1), 1.42 (s, 9H, H-6), 2.95 (bs, 1H, O-H), 3.49 (m, 1H, H-3), 3.58 (m, 1H, H-3), 3.73 (m, 1H, H-2), 4.75 (bs, 1H, N-H); ¹³C NMR δ (101 MHz, CDCl₃, ppm) 17.3 (C-1), 28.3(C-6), 48.6 (C-2), 67.1 (C-3), 79.6 (C-5), 156.3 (C-4).
**N-Boc-(L)-alaninal**

To a solution of oxalyl chloride (1.30 ml 15.4 mmol) in DCM (40 ml) cooled to -78 °C under an Argon atmosphere was added DMSO (1.62 ml, 22.8 mmol) dropwise and the reaction mixture was stirred for 15 min. To this was added a solution of N-Boc-alaninol (2.00 g, 11.4 mmol) in DCM (16 ml) and stirring was continued for 30 min at this temperature. NEt₃ (8.0 ml, 57.1 mmol) was then introduced slowly and the reaction mixture was allowed to warm to 0 °C and stirred for 30 min. Water (20 ml) was then added and the organic layer separated. The aqueous phase was then extracted with DCM (3 x 40 ml). The combined organic extracts were washed with HCl (2 x 30 ml, 2 M, 120.0 mmol) followed by sat. NaHCO₃ (30 ml) and subsequently dried with MgSO₄ and filtered. The solvents were removed under reduced pressure and the residue filtered through a pad of silica to yield a colourless solid (d, J = 7.5 Hz, 3H, H-1), 1.43 (s, 9H, C-6), 4.19 (m, 1H, H-2), 5.12 (bs, 1H, N-H), 9.54 (s, 1H, H-3); ^{13}C NMR δ (101 MHz, CDCl₃, ppm) 14.6 (C-1), 28.2 (C-6), 55.5 (C-2), 80.0 (C-5), 155.3 (C-4), 199.7 (C-3),

**Tert-butyl-((2S)-1-hydroxy-1-(naphthalen-1-yl)propan-2-yl)carbamate (88)**

To a solution of 1-bromonaphthalene (0.97 ml, 6.93 mmol) in THF (15 ml) at – 78 °C was added t-BuLi in pentane (4.07 ml, 1.7 M, 6.93 mmol) and the solution stirred at this temperature for 1 hr. A solution of N-Boc-(L)-alaninal (1.00 g, 5.77 mmol) in THF (15 ml) was then added slowly and the reaction mixture allowed to warm to rt before being quenched with sat. NH₄Cl (20 ml). The organic layer was separated and the aqueous layer extracted with diethyl ether (2 x 20 ml). The combined organic extracts were dried with MgSO₄, filtered and the solvents removed under reduced pressure to give a clear oil. The product
was purified by flash chromatography to afford the title compound as a 3:1 mixture of diastereomers (1.46 g, 84 %) by $^1$H NMR evaluation. For characterization purposes, one of the diastereomers was isolated. IR $\nu_{\text{max}}$ (NaCl) / cm$^{-1}$ 3439 (O-H), 1215 (C=O); $^1$H NMR $\delta$ (300 MHz, CDCl$_3$, ppm) 0.93 (d, $J = 6.6$ Hz, 3H, H-3), 1.51 (s, 9H, H-6), 2.89 (bs, 1H, -OH), 4.15 (m, 1H, H-2), 5.05 (d, $J = 8.1$ Hz, 1H, H-1), 5.74 (s, 1H, -NH), 7.43 – 8.29 (m, 7H, Ar), $^{13}$C NMR $\delta$ (101 MHz, CDCl$_3$, ppm) 13.4 (C-3), 28.5 (C-6), 50.8 (C-2), 72.3 (C-1), 79.5 (C-5), 123.2 (Ar), 123.5 (Ar), 125.1 (Ar), 125.5 (Ar), 126.3 (Ar), 127.9 (Ar), 128.7 (Ar), 130.3 (Ar$_q$), 133.5 (Ar$_q$), 137.1 (Ar$_q$), 155.8 (C-4); HRMS (ES): calc. 302.1756 for C$_{18}$H$_{24}$NO$_3$ [M + H]$^+$; requires 302.1753.

(4$S$, 5$R$)-1,5-dimethyl-4-(naphthalen-1-yl)imidazolidin-2-one (89)

![Diagram of the compound](image)

To a slurry of LiAlH$_4$ (0.630 g, 16.5 mmol) in THF (15 mL) at 0 °C was added slowly a solution of 88 as two diastereomers (1.00 g, 3.32 mmol) in THF (10 mL) and the mixture refluxed for 12 hrs. The reaction mixture was then quenched slowly with a solution of NaOH (3.75 M, 7.50 mmol, 2.0 mL) solution at 0 °C. The salts were then filtered through celite and the solvent removed under reduced pressure to afford a yellow oil. To this, was added urea (0.598 g, 9.95 mmol and HCl (0.33 mL, 10M, 3.32 mmol). The mixture was then heated to 200 °C in a melt under Argon for 8 hrs and then cooled to rt. A solution of HCl (20 ml, 1M, 20 mmol) was then added and the solution extracted with DCM (3 x 30 mL). The organic extracts were dried with MgSO$_4$, filtered and the solvent removed under reduced pressure to give a solid which was subjected to column chromatography to afford the product 89 as a white solid (0.150 g, 33 %). $^1$H NMR $\delta$ (300 MHz, CDCl$_3$, ppm). 0.60 (s, $J = 6.6$ Hz, 2H, Me), 2.81 (s, 3H, NMe), 4.19 (dq, $J = 8.4$ Hz, 6.6 Hz, 1H, H-5), 5.17 (s, 1H, -NH), 5.16 (d, $J = 8.4$ Hz, 1H, H-4), 7.46 – 7.93 (m, 7H, Ar).
Mono-ethyl malonate (93a)

To a stirred solution of diethyl malonate (5.00 g, 31.2 mmol) in EtOH (100 mL) at 0°C was added dropwise ethanolic KOH (1.87 M, 20 mL, 1.1 eq) and the reaction stirred for 12 hrs. A solution of HCl (2 M, 20 mL) was then added and the ethanol removed under reduced pressure. The resulting aqueous solution was extracted with EtOAc (3 x 30 mL) and the organic layer dried with MgSO₄. The solvent was removed under reduced pressure and the residue purified by column chromatography to afford the title compound as a colourless oil (3.78 g, 92 %). ¹H NMR δ (400 MHz, CDCl₃, ppm) 1.28 (t, J = 7.2 Hz, 3H, H-1b), 3.41 (s, 2H, H-2), 4.22 (q, J = 7.2 Hz, 2H, H-1a), 8.75 (bs, 1H, -OH); ¹³C NMR δ (101 MHz, CDCl₃, ppm) 14.0 (C-1b), 40.9 (C-2), 61.9 (C-1a), 166.7 (C-1), 171.1 (C-3).

2-Ethoxycarbonylproanoic acid (93b)

To a stirred solution of diethyl α-methylmalonate (1.00 g, 5.74 mmol) in EtOH (20 mL) at 0°C was added ethanolic KOH (0.63 M, 10 mL, 1.1 eq) dropwise and the reaction stirred for 12 hrs. A solution of HCl (2 M, 20 mL) was then added and the ethanol removed under reduced pressure. The resulting aqueous solution was extracted with EtOAc (3 x 30 mL) and the organic layer dried with MgSO₄. The solvent was removed under reduced pressure and the residue purified by column chromatography to afford the title compound as a colourless oil (0.789 g, 94 %). ¹H NMR δ (400 MHz, CDCl₃, ppm) 1.28 (t, J = 7.1 Hz, 3H, H-2b), 1.45 (d, J = 7.3 Hz, 3H, H-3) 3.47 (q, J = 7.3 Hz, 1H, H-2), 4.21 (q, J = 7.1 Hz, 2H, H-1a); ¹³C NMR δ (101 MHz, CDCl₃, ppm) 13.5 (C-2b), 14.0 (C-3), 45.9 (C-2), 61.7 (C-2a), 169.9 (C=O), 175.5 (C-1).
Ethyl-3-((4S, 5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-3-oxopropanoate (94a)

Method A (DCC):
To a stirred solution of 93a (1.00 g, 7.57 mmol), was added BtOH (0.142 g, 1.05 mmol) and Aux (1.00 g, 5.26 mmol) in dry DCM (30 ml) at 0 °C over a period of 30 min together with a solution of DCC (0.32 M, 20 ml, 1.2 eq) in dry DCM and the reaction allowed to warm to rt. After 10 hrs, the reaction mixture was filtered through celite and the filtrate washed with sat. NaHCO₃ (3 x 30 ml). The organic layer was dried with MgSO₄ and subjected to flash chromatography to afford the title compound (1.47 g, 92 % yield).

Method B (BtCl / PPh₃):
To a stirred solution of PPh₃ (2.38 g, 9.08 mmol) in dry CH₃CN (35 ml) at −10 °C was added in one portion BtCl (1.39 g, 9.08 mmol) and after 1 min, 93a (1.00 g, 7.57 mmol) was added dropwise in dry CH₃CN (15 ml). After 15 min Aux (1.00 g, 5.26 mmol) was added and the reaction mixture refluxed for 8 hrs. The reaction mixture was allowed to cool to rt and the CH₃CN removed under reduced pressure. The residue was dissolved in DCM (40 ml), washed with sat. Na₂CO₃ (3 x 30 ml) and dried with MgSO₄. Following filtration and evaporation the residue was purified by flash chromatography to afford the title compound (1.31g, 82 %).

Method C (Pivaloyl chloride):
To a solution of 93a (5.61 g, 42.5 mmol, 1.62 eq) and N-methylmorpholine (4.25 g, 42.0 mmol, 1.60 eq) in dry THF at −15 °C under an Argon atmosphere was added dropwise a solution of freshly distilled pivaloyl chloride in dry THF (36.8 mmol, 1.4 eq, 0.5 M) and the reaction allowed to stir at this temperature for 30 min. Thereafter, Aux (5.00 g, 26.3 mmol) was added over a period of 5 min and the contents slowly warmed to rt and left to stir overnight at 30 °C. After 12 hrs, the organic solvent was removed in vacuo, and EtOAc (150 ml) was added to the crude residue to dissolve the organic product, which was subsequently washed with 1M HCl (3 x 75 mL) followed by sat. NaHCO₃ (3 x 75 mL). The
organic extract was then dried with MgSO₄ and the product purified by column chromatography after removal of the organic solvent to afford 94a (7.36 g, 92 %).

94a was obtained as a colourless solid that was recrystallized from EtOAc / hexane. M.p.: 84-85 ºC; ; [α]²⁰₂⁰ = −6.2, (c = 1.0, DCM); IR νmax (cm⁻¹) 3008, 2860, 1736, 1687; ¹H NMR (400 MHz, CDCl₃) δ 0.80 (d, J = 6.6 Hz, 3H, Me), 1.26 (t, J = 7.2 Hz, 3H, H-1b), 2.81 (s, 3H, NMe), 3.93 (dq, J = 8.7, 6.6 Hz, 1H, H-4'), 3.94 (d, J = 16.0 Hz, 1H, H-2), 4.01 (d, J = 16.0 Hz, 1H, H-2), 4.18 (q, J = 7.2 Hz, 2H, H-1a), 5.32 (d, J = 8.7 Hz, 1H, H-5'), 7.10 - 7.34 (m, 5H, Ar); ¹³C NMR (75.5 MHz, CDCl₃) δ 14.2 (C-1b), 15.1 (Me), 28.3 (NMe), 43.5 (C-2), 54.2 (C-2), 59.5 (C-4'), 61.3 (C-5'), 127.2 (Ar), 128.3 (Ar), 128.6 (Ar), 136.1 (Arq), 155.6 (C2'), 165.1 (C-3), 167.7 (C-1); Anal. Calc. for C₁₆H₂₀N₂O₄ (%): C, 63.14; H, 6.61; N, 9.20. Found (%): C, 63.16; H, 6.59; N, 9.18.

**General procedure for the synthesis of α-substituted malonate-imidazolidinone substrates (94b – 94h):**

To a stirred solution of 94a (0.500 g, 1.64 mmol) in dry THF (30 mL) at −45 ºC under an Argon atmosphere was added a solution of KHMDS in toluene (0.5 M, 3.94 mL, 1.97 mmol) dropwise and the reaction mixture allowed to stir at this temperature for 30 min. The appropriate alkylation agent (1.97 mmol, 1.2 eq) was then added dropwise and the reaction mixed was allowed to stir at the specified temperature. After 6 hrs the reaction was quenched with sat. NH₄Cl (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried with MgSO₄, filtered and the solvent removed under reduced pressure. The residue was subjected to flash chromatography to afford 94b – 94h as a mixture of diastereomers.
Ethyl-3-((4S, 5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-methyl-3-oxopropanoate (94b)

With MeI (0.13 ml, 1.97 mmol, 1.2 eq.) at rt to obtain title compound as an off-white solid (0.501 g, 96 %). Recrystallization from EtOAc/ hexane afforded one diastereomer: mp 152-153 °C; [α]_D^20 = -31.9, (c = 1.0, DCM); IR ν_max (cm⁻¹) 3010, 2863, 1732, 1689; ¹H NMR (300 MHz, CDCl₃) δ 0.80 (d, J = 6.6 Hz, 3H, Me), 1.21 (t, J = 7.6 Hz, H-1b), 1.39 (d, J = 7.5 Hz, H-2a), 2.81 (s, NMe), 3.90 (dq, J = 8.7, 6.6 Hz, H-4'), 4.25-4.05 (m, H-1a), 4.65 (q, J = 7.5 Hz, H-2), 5.30 (d, J = 8.7 Hz, H-5'), 7.20 – 7.35 (m, 5H, Ar); ¹³C NMR (75.5 MHz, CDCl₃) δ 13.5 (C-2a), 14.2 (C-1b), 15.2 (Me), 28.4 (NMe), 45.9 (C-2) 54.3 (C-4'), 59.8 (C-5'), 61.2 (C-1a), 127.3 (Ar), 128.2 (Ar), 138.5 (Ar), 155.7 (C-2'), 169.0 (C-3), 171.1 (C-1); Anal. Calcd. for C₁₇H₂₂N₂O₄ (%): C, 64.13; H, 6.97; N, 8.80. Found (%): C, 64.02; H, 7.04; N, 8.89.

Ethyl-3-((4S, 5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-ethyl-3-oxopropanoate (94c)

With ethyl iodide (0.16 ml, 1.97 mmol, 1.2 eq.) at 65 °C to afford 94c as a colourless solid (0.528 g, 97 %). Recrystallization from EtOAc / hexane to a constant mp afforded one single diastereomer: mp 128-129 °C; [α]_D^20 = -4.5, (c = 1.0, DCM); IR ν_max (cm⁻¹) 3010, 2863, 1732, 1689; ¹H NMR (400 MHz, CDCl₃) δ 0.80 (d, J = 6.8 Hz, 3H, Me), 0.97 (t, J = 8.0 Hz, 3H, H-2b), 1.20 (t, J = 7.2 Hz, 3H, H-1b), 2.04-1.86 (m, 2H, H-2a), 2.82 (s, 3H, NMe), 3.91 (dq, J = 8.8, 6.8 Hz, 1H, H-4’), 4.25-4.08 (m, 2H, H-1a), 4.59 (dd, J = 5.6, 2.8 Hz 1H, H-2), 5.31 (d, J = 8.8 Hz, 1H, H-5’), 7.15 – 7.35 (m, 5H, Ar); ¹³C (100.6 MHz, CDCl₃) δ 12.2 (C-2b), 14.2 (C-1b), 15.2 (Me), 22.1 (C-2a), 28.3 (NMe), 52.7 (C-2), 54.2 (C-4’), 59.8 (C-5’), 61.0 (C-1a), 127.3 (Ar), 128.2 (Ar), 128.5 (Ar), 156.2 (Arq), 155.7 (C-2’), 169.1 (C-3), 170.3 (C-1); Anal. Calcd. for C₁₃H₂₄N₂O₄ (%): C, 65.04; H, 7.28; N, 8.43. Found (%): C, 64.11; H, 7.31; N, 8.51.

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Ethyl-3-((4S, 5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-n-butyl-3-oxopropanoate (94d)

With 1-bromobutane (0.22 ml, 1.97 mmol, 1.2 eq.) and TBAI (0.121 g, 0.328 mmol, 20 mol %) at 65 °C to afford the title compound as a clear oil (0.566 g, 96 %). IR ν\text{max} (cm\textsuperscript{-1}) 3010 (Ar), 1732 (C=O, ester and amide), 1689 (C=O, urea); HRMS (ES): calc. 361.2127 for C\textsubscript{20}H\textsubscript{29}N\textsubscript{2}O\textsubscript{4} [M + H]\textsuperscript{+}; requires 361.2129.

Major diastereomer: \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 0.80 (d, J = 6.4 Hz, 3H, Me), 0.82 (t, J = 7.2 Hz, 3H, H-2d), 1.20 (t, J = 7.2 Hz, 3H, H-1b), 1.25-1.18 (m, 2H, H-2c), 1.35-1.28 (m, 2H, H-2b), 2.00-1.75 (m, 2H, H-2a), 2.82 (s, 3H, NMe), 3.91 (dq, J = 8.6 Hz, 6.4 Hz, 1H, H-4'), 4.24-4.08 (m, 2H, H-1a); \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}) δ 14.2 (C-2d), 14.3 (C-1b), 15.1 (Me), 22.6 (C-2c), 27.6 (C-2b), 28.3 (NMe), 29.2 (C-2a), 51.1 (C-2), 54.0 (C-4'), 59.7 (C-5'), 61.1 (C-1a), 127.2 (Ar), 128.2 (Ar), 128.4 (Ar), 136.2 (Ar\textsubscript{q}), 155.7 (C-2'), 168.4 (C-3), 170.4 (C-1).

Minor diastereomer: \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 0.79 (d, J = 6.4 Hz, 3H, Me), 0.87 (t, J = 7.2 Hz, 3H, H-2d), 1.25-1.18 (m, 2H, H-2b), 1.26 (t, J = 7.2 Hz, 3H, H-1b), 1.35-1.28 (m, 2H, H-2c), 2.00-1.75 (m, 2H, H-2a), 2.81 (s, 3H, NMe), 3.91 (dq, J = 8.6 Hz, 6.4 Hz, 1H, H-4'), 4.24-4.08 (m, 2H, H-1a), 4.61 (dd, J = 6.4, 1.2 Hz, 1H, H-2), 5.36 (d, J = 8.6 Hz, 1H, H-5'), 7.10 - 7.29 (m, 5H, Ar); \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}) δ 14.2 (C-2d), 14.3 (C-1b), 15.1 (C-Me), 22.7 (C-2c), 27.9 (C-2b), 28.7 (C-NMe), 29.3 (C-2a), 51.3 (C-2), 54.2 (C-4'), 59.8 (C-5'), 61.1 (C-1a), 127.3 (Ar), 128.3 (Ar), 128.6 (Ar), 136.7 (Ar\textsubscript{q}), 155.7 (C-2'), 168.8 (C-3), 170.4 (C-1).
Ethyl-3-((4S, 5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-n-hexyl-3-oxopropanoate (94e)

With 1-bromohexane (0.28 ml, 1.97 mmol, 1.2 eq.) and TBAI (0.121 g, 0.328 mmol, 20 mol %) at 65 °C to afford title compound as a clear oil (0.604 g, 95 %). Chromatographic purification afforded a single diastereomer. IR ν max (cm⁻¹) 3010 (Ar), 1732 (C=O, ester and amide), 1689 (C=O, urea); HRMS (ES): calc. 389.2440 for C₂₂H₃₃N₂O₄ [M + H]⁺; requires 389.2443.

Major diastereomer: ¹H NMR (400 MHz, CDCl₃) δ 0.80 (d, J = 6.8 Hz, 3H, Me), 0.84 (t, J = 7.2 Hz, 3H, H-2f), 1.20 (t, J = 7.2 Hz, 3H, H-1b), 1.35 - 1.17 (m, 8H, H-2e - b), 1.88 (m, 2H, H-2a), 2.82 (s, 3H, NMe), 3.92 (dq, J = 8.8 Hz, 6.8 Hz, 1H, H-4’), 4.24-4.08 (m, 2H, H-1a), 4.63 (dd, J = 4.6, 3.6 Hz, 1H, H-2), 5.31 (d, J = 8.8 Hz, 1H, H-5’), 7.15 – 7.30 (m, 5H, Ar); ¹³C NMR (100.6 MHz, CDCl₃) δ 14.2 (C-2f), 14.2 (C-1b), 15.1 (C-Me), 22.6 (C-2e), 27.6 (C-2d), 28.3 (C-NMe), 28.9 (C-2a), 29.2 (C-2c), 29.3 (C-2b), 51.3 (C-2), 54.2 (C-4’), 59.7 (C-5’), 61.1 (C-1a), 127.2 (Ar), 128.2 (Ar), 128.4 (Ar), 136.2 (Ar), 155.7 (C-2’), 164.8 (C-3), 170.4 (C-1).

Minor diastereomer: ¹H NMR (400 MHz, CDCl₃) δ 0.79 (d, J = 6.8 Hz, 3H, Me), 0.85 (t, J = 7.2 Hz, 3H, H-2f), 1.25 (t, J = 7.2 Hz, 3H, H-1b), 1.35-1.17 (m, 8H, H-2e - b), 1.87 (m, 2H, H-2a), 2.82 (s, 3H, NMe), 3.92 (dq, J = 8.4 Hz, 6.8 Hz, 1H, H-4’), 4.24-4.08 (m, 2H, H-1a), 4.79 (dd, J = 6.0, 2.4 Hz, 1H, H-2), 5.36 (d, J = 8.4 Hz, 1H, H-5’), 7.16 – 7.30 (m, 5H, Ar); ¹³C NMR (100.6 MHz, CDCl₃) δ 14.2 (C-2f), 14.2 (C-1b), 15.2 (C-Me), 22.7 (C-2e), 27.9 (C-2d), 28.3 (C-NMe), 28.9 (C-2a), 29.2 (C-2c), 29.3 (C-2b), 51.3 (C-2), 54.2 (C-4’), 59.8 (C-5’), 61.1 (C-1a), 127.3 (Ar), 128.3 (Ar), 128.6 (C-3), 136.7 (Ar), 155.6 (C-2’), 168.8 (C-3), 170.5 (C-1).
Ethyl-3-((4S, 5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-benzyl-3-oxopropanoate (94f)

With BnBr (0.24 ml, 1.97 mmol, 1.2 eq.) at rt to obtain 94f as a clear oil (0.606 g, 94%). Chromatographic purification afforded a single diastereomer. IR ν_{max} (cm⁻¹) 3021 (Ar), 1729 (C=O ester and amide), 1688 (C=O, urea); HRMS (ES): calc. 394.1814 for C_{23}H_{26}N_{2}O_{4} [M + H]^+; requires 395.1887;

Major diastereomer: $^1$H NMR (400 MHz, CDCl₃, ppm) δ 0.75 (d, J = 6.6 Hz, 3H, Me), 1.21 (t, J = 7.1 Hz, 3H, H-1b), 2.81 (s, 3H, NMe), 3.17 (dd, J = 13.8 Hz, 8.2 Hz, 1H, H-2a), 3.23 (dd, J = 13.8 Hz, 8.2 Hz, 1H, H-2a), 3.89 (dq, J = 8.7 Hz, 6.6 Hz, H-4'), 4.14 (q, J = 7.1 Hz, 2H, H-1a), 5.33 (d, J = 8.7 Hz, 1H, H-5'), 5.33 (dd, J = 8.2 Hz, 6.6 Hz, H-2), 6.8 – 7.25 (m, 10H, Ar); $^{13}$C NMR (101 MHz, CDCl₃, ppm) δ 14.0 (C-1b), 14.9 (Me), 28.1 (NMe), 34.4 (C-2a), 52.3 (C-2), 53.7 (C-4'), 59.4 (C-5'), 61.1 (C-1a), 126.2 (Ar), 126.7 (Ar), 127.8 (Ar), 128.2 (Ar), 128.4 (Ar), 129.1 (Ar), 136.0 (Ar), 136.0 (Ar), 138.5 (Ar), 155.3 (C-2'), 167.9 (C-3), 169.5 (C-1);

Minor diastereomer: $^1$H NMR (400 MHz, CDCl₃, ppm) δ 0.74 (d, J = 6.6 Hz, 3H, Me), 1.18 (t, J = 7.12 Hz, 3H, H-1b), 2.74 (s, 3H, NMe), 3.19 (dd, J = 13.8 Hz, 8.2 Hz, 1H, H-2a), 3.27 (dd, J = 13.8 Hz, 8.2 Hz, 1H, H-2a), 3.70 (dq, 8.6 Hz, 6.6 Hz, 1H, H-4'), 4.14 (m, 2H, H-1a), 5.16 (d, J = 8.6 Hz, 1H, H-5'), 5.16 (dd, J = 9.6 Hz, 5.4 Hz), 7.15 – 7.35 (m, 5H, Ar); $^{13}$C NMR (101 MHz, CDCl₃, ppm) δ 14.0 (C-1b), 14.8 (C-Me), 28.0 (C-NMe), 34.4 (C-2a), 52.6 (C-2), 53.8 (C-4'), 59.5 (C-5'), 61.1 (C-1a), 126.2 (Ar), 127.0 (Ar), 128.0 (Ar), 128.1 (Ar), 128.3 (Ar), 129.3 (Ar), 135.9 (Ar), 138.9 (Ar), 155.3 (C-2'), 167.3 (C-3), 169.6 (C-1).
Ethyl-3-((4S,5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-allyl-3-oxopropanoate (94g)

With allyl bromide (0.17 ml, 1.97 mmol, 1.2 eq.) at rt to afford the title compound as a clear oil (0.549 g, 97 %). IR ν_{max} (cm⁻¹) 3010 (Ar), 1732 (C=O, ester and amide), 1689 (C=O, urea);
HRMS (ES): calc. 345.1814 for C_{19}H_{25}N_{2}O_{4} [M + H]^+; requires 345.1813.
Major diastereomer: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(δ\) 0.80 (d, \(J = 6.4\) Hz, 3H, Me), 1.25 (t, \(J = 7.2\) Hz, 3H, H-1b), 2.50-2.21 (m, 2H, H-2a), 2.83 (s, 3H, NMe), 3.89 (dq, \(J = 8.8\) Hz, 6.4 Hz, 1H, H-4'), 4.25-4.11 (m, 2H, H-1a), 4.91 - 5.09 (m, 2H, H-2c), 5.35 (d, \(J = 8.8\) Hz, 1H, H-5'), 5.89 - 5.78 (m, 1H, H-2b), 7.15 - 7.30 (m, 5H, Ar);
\(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(δ\) 14.3 (C-1b), 15.2 (Me), 28.3 (NMe), 32.6 (C-2a), 50.9 (C-2), 54.1 (C-4'), 58.8 (C-5'), 61.3 (C-1a), 116.1 (C-2b), 127.2 (Ar), 128.2 (Ar), 128.5 (Ar), 135.0 (C-2c), 136.1 (Ar\(_a\)), 155.1 (C-2'), 169.7 (C-3), 171.6 (C-1).
Minor diastereomer: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(δ\) 0.80 (d, \(J = 6.4\) Hz, 3H, Me), 1.21 (t, \(J = 7.2\) Hz, 3H, H-1b), 2.50-2.21 (m, 2H, H-2a), 2.82 (s, 3H, H-NMe), 4.25-4.11 (m, 2H, H-1a), 4.91 (m, 1H, H-2), 4.80 (dd, \(J = 5.4, 3.6\) Hz, 1H, H-2c), 5.09 (m, 1H, H-2c), 5.30 (d, \(J = 8.8\) Hz, 1H, H-5'), 5.81-5.45 (m, 1H, H-2b), 7.16 - 7.31 (m, 5H, Ar).
\(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(δ\) 14.3 (C-1b), 15.2 (C-Me), 28.3 (C-NMe), 32.8 (C-2a), 51.1 (C-2), 54.2 (C-4'), 58.8 (C-5'), 61.3 (C-1a), 117.1 (C-2b), 127.3 (Ar), 128.3 (Ar), 128.6 (C-3), 135.4 (C-2c), 136.1 (Ar\(_a\)), 155.1 (C-2'), 170.7 (C-3), 171.6 (C-1).

Ethyl-3-((4S, 5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-propargyl-3-oxopropanoate (94h)

With propargyl bromide (80 % in toluene, 0.22 ml, 1.97 mmol, 1.2 eq.) at rt to obtain 94h as a clear oil (0.537 g, 96 %). HRMS (ES): calc. 343.1658 for C_{19}H_{23}N_{2}O_{4} [M + H]^+; requires 345.1663.
Major diastereomer: $^1$H NMR (300 MHz, CDCl$_3$) δ 0.81 (d, $J = 6.6$ Hz, 3H, Me), 1.21 (t, $J = 7.1$ Hz, 3H, H-1b), 1.94 (t, $J = 2.6$ Hz, 1H, H-2c), 2.79 (m, 2H, H-2a), 2.83 (s, 3H, NMe), 3.94 (dq, $J = 8.6$ Hz, 6.6 Hz, 1H, H-4'), 4.17 (m, 2H, H-1a), 5.04 (m, 1H, H-2), 5.35 (d, $J = 8.6$ Hz, 1H, H-5'), 7.13 – 7.36 (m, 5H, Ar). $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 14.0 (C-1b), 15.0 (C-Me), 18.1 (C-2a), 28.2 (C-NMe), 50.0 (C-2), 54.0 (C-4'), 59.6 (C-5'), 61.5 (C-1a), 69.6 (C-2c), 81.1 (C-2b), 127.2 (Ar), 128.1 (Ar), 128.3 (Ar), 135.8 (Ar$_q$), 155.3 (C-2'), 166.5 (C-1), 168.5 (C-3).

Minor diastereomer: $^1$H NMR (300 MHz, CDCl$_3$) δ 0.81 (d, $J = 6.6$ Hz, 3H, Me), 1.21 (t, $J = 7.1$ Hz, 3H, H-1b), 1.88 (t, $J = 2.6$ Hz, 1H, H-2c), 2.79 (m, 2H, H-2a), 2.83 (s, 3H, NMe), 3.94 (dq, $J = 8.4$ Hz, 6.6 Hz, 1H, H-4'), 4.17 (m, 2H, H-1a), 5.04 (m, 1H, H-2), 5.37 (d, $J = 8.6$ Hz, 1H, H-5'), 7.13 – 7.36 (m, 5H, Ar). $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 14.0 (C-1b), 14.9 (C-Me), 18.2 (C-2a), 28.1 (C-NMe), 50.1 (C-2), 53.9 (C-4'), 59.6 (C-4'), 61.5 (C-1a), 68.8 (C-2c), 80.7 (C-2b), 127.0 (Ar), 128.1 (Ar), 128.4 (Ar), 136.1 (Ar$_q$), 155.3 (C-2'), 166.9 (C-1), 168.6 (C-3).

2,4,6-Triisopropylbenzenesulfonyl azide (Trisyl azide)$^{73}$

![2,4,6-Triisopropylbenzenesulfonyl azide](image)

To a stirring solution of 2,4,6-triisopropylbenzenesulfonyl chloride (2.00 g, 6.60 mol) in H$_2$O:acetone (1:1, 50 ml) at 0 °C was added NaN$_3$ (0.52 g, 7.92 mmol) slowly and the reaction mixture stirred for 2 hrs. The solution was then reduced to half its volume under reduced pressure over a 30 °C water bath. The residual aqueous layer was extracted with diethyl ether (3 x 30 ml) and the combined organic extracts dried with MgSO$_4$ and filtered. The solvents were once again removed under reduced pressure over a 30 °C water bath to afford a white solid (1.88 g, 92 %): m.p. : 39 – 41 °C (Lit 39 – 43 °C); $^1$H NMR δ (300 MHz, CDCl$_3$, ppm) 1.27 (d, $J = 6.9$ Hz, 6H, H-4a), 1.29 (d, $J = 6.9$ Hz, 12H, H-2a), 2.94 (sept, $J = 6.9$ Hz, 1H, H-4b), 4.07 (sept, $J = 6.9$ Hz, 2H, H-2b), 7.23 (s, 2H, H-3); $^{13}$C NMR δ (101 MHz, CDCl$_3$, ppm) 23.4 (C-4a), 24.7 (C-2a), 29.9 (C-4b), 34.3 (C-2b), 124.1 (C-3), 132.1 (C-1), 150.9 (C-4), 154.8 (C-2).
General procedure for the diastereoselective azidation (98b – 98h):

To a stirred solution of 94b – 94h (0.500 g) in dry THF (40 mL) at –85 °C under Ar gas was added KHMSD dropwise in toluene (0.5 M, 1.2 eq) over 15 min and the reaction mixture stirred at this temperature for 45 min. A solution of 2,4,6-triisopropylbenzenesulfonyl azide (1.2 eq) in dry THF (5 mL) was added dropwise and the reaction mixture stirred at this temperature for 45 min. The cold bath was then allowed to reach 0 °C before glacial acetic acid (4.6 eq) was added, the bath removed and the mixture stirred for 12 hrs at room temperature. To this was added sat. NaHCO₃ (40 mL) and the organic material extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried with MgSO₄, filtered and the solvent removed under reduced pressure. A sample of this residue was analyzed by chiral HPLC in order to determine the diastereoselectivity of the azidation, and the rest subjected to chromatographic purification to afford 98b – 98h. Analytical samples were prepared by recrystallization from diethyl ether.

(2S)-Ethyl-2-azido-3-((4S, 5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-methyl-3-oxopropanoate (98b)

With 94b (0.500g, 1.57 mmol), KHMSD (3.77 ml, 1.88 mmol, 1.2 eq) and trisyl azide (0.583 g, 1.88 mmol, 1.2 eq) to obtain 98b as a white solid (0.551, 98 %). m.p.: 127 – 128; [α]_D^20 = -43.7 (c = 0.60, CH₂Cl); IR νmax (NaCl) / cm⁻¹ 2120 (azide), 1737 (C=O ester and amide), 1686 (C=O urea). The diastereomer ratio was determined to be > 99:1 by HPLC using a Daicel Chiralpack AD column (hexane/i-PrOH (70/30): flow rate 1.0 mL/min: τ_major = 4.2 min; τ_minor = 4.6 min, > 99:1 dr; ¹H NMR δ (400 MHz, CDCl₃, ppm) 0.80 (d, J = 6.6 Hz, 3H, Me), 1.33 (t, J = 7.2 Hz, 3H, H-1b), 1.68 (s, 3H, H-2a), 2.80 (s, 3H, NMe), 3.98 (dq, J = 8.4 Hz, 6.6 Hz, 1H, H-4'), 4.30 (q, J = 7.2 Hz, 2H, H-1a), 5.29 (d, J = 8.4 Hz, 1H, H-5'), 7.12 – 7.38 (m, 5H, Ar); ¹³C NMR δ (101 MHz, CDCl₃, ppm) 14.0 (Me), 14.9 (C-1b), 20.6 (2a), 28.0 (C-NMe), 54.3 (C-4'), 60.2 (C-5'), 62.0 (C-1a), 69.5 (C-2), 126.8 (Ar), 128.3 (Ar), 128.5 (Ar), 135.9 (Ar₈), 154.5 (C-2'), 165.6 (C-3), 168.0 (C-1); Anal. Calc. for C₁₇H₂₂N₅O₄ (%): C, 56.82; H, 5.89; N, 19.49.
Found (%): C, 56.69; H, 5.99; N, 19.44.

(2S)-Ethyl-2-azido-3-((4S, 5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-ethyl-3-oxopropanoate (98c)

With 94c (0.500 g, 1.50 mmol), KHMDS (3.60 ml, 1.80 mmol, 1.2 eq) and trisyl azide (0.557 g, 1.80 mmol, 1.2 eq) to obtain 98b as a white solid (0.541 g, 96%). IR νmax (NaCl) / cm⁻¹: 2125 (azide), 1733 (C=O ester and amide), 1688 (C=O urea). The diastereomer ratio was determined to be 99:1, by HPLC using a Daicel Chiralpack AD column (hexane/i-PrOH (70/30)); ¹H NMR (400 MHz, CDCl₃, ppm) δ 0.76 (t, J = 7.5 Hz, 3H, H-2b), 0.81 (d, J = 6.6 Hz, 3H, Me), 1.32 (t, J = 7.1 Hz, 3H, H-1b), 2.09 (m, 1H, H-2a), 2.31 (m, 1H, H-2a), 2.80 (s, 3H, NMe), 3.99 (dq, J = 8.6 Hz, 6.6 Hz, 1H, H-4'), 4.30 (q, J = 7.1 Hz, 2H, H-1a), 5.33 (d, J = 8.6 Hz, 1H, H-5'), 7.15 – 7.38 (m, 5H, Ar); ¹³C NMR (101 MHz, CDCl₃, ppm) δ 7.9 (C-2b), 14.1 (Me), 14.9 (C-1b), 27.1 (C-2a), 28.1 (NMe), 54.4 (C-4'), 60.2 (C-5'), 61.8 (C-1a), 73.7 (C-2), 127.1 (Ar), 128.3 (Ar), 135.9 (Arq), 154.6 (C-2'), 165.2 (C-3), 167.1 (C-1). Anal. Calc. for C₁₈H₂₃N₅O₄ (%): C, 57.90; H, 6.21; N, 18.76. Found (%): C, 57.95; H, 6.23; N, 18.88.

(2S)-Ethyl-2-azido-3-((4S, 5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-hexyl-3-oxopropanoate (98e)

With 94e (0.500 g, 1.24 mmol), KHMDS (2.97 ml, 1.49 mmol, 1.2 eq) and trisyl azide (0.460 g, 1.49 mmol, 1.2 eq) afforded 98e as a colourless oil (0.541 g, 98%); [α]D²⁰ = -59.4 (c = 0.65, CH₃Cl); IR νmax (NaCl) / cm⁻¹: 2126 (azide), 1733 (C=O ester and amide), 1688 (C=O urea). The diastereomer ratio was determined to be > 99:1, by HPLC using a Daicel Chiralpack AD
column (hexane/i-PrOH (70/30): flow rate 1.0 mL/min: \( \tau_{\text{maior}} = 12.4 \text{ min} \); \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm) \( \delta \) 0.80 (d, \( J = 6.7 \) Hz, 3H, H-Me), 0.85 (t, \( J = 6.5 \) Hz, 3H, H-2f), 1.08 – 1.52 (m, 8H, H-2e-b), 1.32 (t, \( J = 7.1 \) Hz, 3H, H-1b), 1.95 – 2.29 (m, 2H, H-2a), 2.80 (s, 3H, -NMe), 3.94 (dq, \( J = 8.7 \) Hz, 6.7 Hz, 1H, H-4'), 4.31 (m, 2H, H-1a), 5.31 (d, \( J = 8.7 \) Hz, 1H, H-5'), 7.15 – 7.39 (m, 5H, Ar); \( \beta \). \(^{13}\)C NMR (101 MHz, CDCl\(_3\), ppm) \( \delta \) 14.0 (C-2f), 14.2 (C-Me), 22.5 (C-2e), 23.6 (C-2d), 28.2 (C-NMe), 29.1 (C-2c), 31.5 (C-2b), 33.6 (C-4'), 54.5 (C-4'), 60.3 (C-5'), 61.8 (C-1a), 73.3 (C-2), 126.8 (Ar), 128.2 (Ar), 128.5 (Ar), 135.7 (Arq), 154.6 (C-2'), 165.3 (C-3), 167.1 (C-1); HRMS (ES) : calc. 430.2454 for C\(_{22}\)H\(_{32}\)N\(_5\)O\(_4\) [M + H]+; requires 430.2459.

\((25)-\)Ethyl-2-azido-3-\(((4S, 5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-benzyl-3-oxopropanoate (98f)

With 94f (0.500g, 1.27 mmol), KHMDS (3.04 ml, 1.52 mmol, 1.2 eq) and trisyl azide (0.471 g, 1.52 mmol, 1.2 eq) to obtain 98f as a colourless solid (0.499 g, 90 %); [\( \alpha \)]\(_D\)^20 = -73.3 (c = 0.80, CH\(_2\)Cl\(_2\)); m.p.: 122 – 124 °C; IR \( \nu_{\text{max}} \) (NaCl) / cm\(^{-1}\) 2125 (azide), 1733 (C=O ester and amide), 1688 (C=O urea). The diastereomer ratio was determined to be 97:3, by HPLC using a Daicel Chiralpack AD column (hexane/i-PrOH (70/30): flow rate 1.0 mL/min: \( \tau_{\text{maior}} = 9.7 \) min; \( \tau \) \( \text{minor} = 11.0 \) min. \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm) \( \delta \) 0.82 (d, \( J = 6.6 \) Hz, 3H, Me), 1.23 (t, \( J = 7.2 \) Hz, 3H, H-1b), 2.83 (s, 3H, NMe), 3.38 (d, \( J = 14.4 \) Hz, 1H, H-2a), 3.58 (d, \( J = 14.4 \) Hz, 1H, H-2a), 3.90 (d, \( J = 6.6 \) Hz, 1H, H-4'), 4.22 (q, \( J = 7.2 \) Hz, 2H, H-1a), 5.31 (d, \( J = 6.6 \) Hz, 1H, H-5'), 7.03 – 7.37 (m, 10H, Ar); \(^{13}\)C NMR \( \delta \) (101 MHz, CDCl\(_3\), ppm) 13.9 (Me), 14.9 (C-1b), 28.1 (C-NMe), 40.2 (C-2a), 54.5 (C-4'), 60.5 (C-5'), 61.9 (C-1a), 73.5 (C-2), 127.0 (Ar), 127.3 (Ar), 127.9 (Ar), 128.2 (Ar), 128.4 (Ar), 130.6 (Ar), 134.5 (Arq), 135.5 (Arq), 154.8 (C-2'), 165.0 (C-3), 166.6 (C-1); Anal. Calc. for C\(_{23}\)H\(_{25}\)N\(_5\)O\(_4\) (%): C, 63.44; H, 5.79; N, 16.08. Found (%): C, 63.65; H, 5.81; N, 16.21.
(2S)-Ethyl-2-azido-3-((4S, 5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-allyl-3-oxopropanoate (98g)

With 94g (0.500g, 1.45 mmol), KHMDS (3.48 ml, 1.74 mmol, 1.2 eq) and trisyl azide (0.539 g, 1.74 mmol, 1.2 eq) afforded 98g as a white solid (0.548, 98%). m.p.: 101 – 102 °C; IR \( \nu_{\text{max}} \) (NaCl) / cm\(^{-1}\) 2125, 1735, 1686, 1215. The diastereomer ratio was determined to be 99:1 by HPLC using a Daicel Chiralpack AD column (hexane/i-PrOH (70/30): flow rate 1.0 mL/min: \( \tau \) m\( \text{aior} = 3.6 \) min. \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm) \( \delta \) 0.81 (d, \( J = 6.6 \) Hz, 3H, Me), 1.32 (t, \( J = 7.2 \) Hz, 3H, H-1b), 2.80 (s, 3H, NMe), 2.82 (ddt, \( J = 14.7 \) Hz, 6.8 Hz, 1.4 Hz, 1H, H-2a), 3.00 (ddt, \( J = 14.7 \) Hz, 7.4 Hz, 1.2 Hz, 1H, H-2a), 3.98 (dq, \( J = 8.4 \) Hz, 6.6 Hz, 1H, H-4'), 4.29 (q, \( J = 7.2 \) Hz, 2H, H-1a), 4.99 (m, 1H, H-2c), 5.10 (m, 1H, H-2c), 5.30 (d, \( J = 8.4 \) Hz, 1H, H-5'), 5.62 (m, 1H, H-2b), 7.14 – 7.35 (m, 5H, Ar). \(^{13}\)C NMR (101 MHz, CDCl\(_3\), ppm) \( \delta \) 14.1 (Me), 14.9 (C-1b), 28.1 (C-NMe), 38.8 (C-2a), 54.4 (C-4'), 60.3 (C-5'), 61.9 (C-1a), 72.4 (C-2), 119.4 (C-2c), 127.1 (Ar), 128.3 (Ar), 128.4 (Ar), 131.2 (C-2b) 135.7 (Ar\(_a\)), 154.5 (C-2'), 165.6 (C-3), 168.0 (C-1). Anal. Calc. for C\(_{19}\)H\(_{23}\)N\(_5\)O\(_4\) (%): C, 59.21; H, 6.01; N, 18.17. Found (%): C, 59.43; H, 5.90; N, 18.28.

(2S)-Ethyl-2-azido-3-((4S, 5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-propargyl-3-oxopropanoate (98h)

With 94h (0.500g, 1.47 mmol), KHMDS (3.50 ml, 1.75 mmol, 1.2 eq) and trisyl azide (0.542 g, 1.75 mmol, 1.2 eq) the title compound was obtained as a colourless solid (0.549 g, 98%). m.p.: 140 – 142 °C; IR \( \nu_{\text{max}} \) (NaCl) / cm\(^{-1}\) 2124, 1735, 1686, 1217; The diastereomer ratio was determined to be 99:1 by HPLC using a Daicel Chiralpack AD column (hexane/i-PrOH (70/30): flow rate 1.0 mL/min: \( \tau \) m\( \text{aior} = 8.9 \) min. \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm) \( \delta \) 0.80 (d, \( J = 6.6 \) Hz, 3H, Me), 1.32 (t, \( J = 7.1 \) Hz, 3H, H-1b), 1.84 (t, \( J = 2.7 \) Hz, 1H, H-2c), 2.80 (s, 3H, NMe), 2.90 (dd, \( J = 14.5 \) Hz, 2.7 Hz, 1H, H-2a), 3.41 (dd, \( J = 14.5 \) Hz, 2.7 Hz, 1H, H-2a), 4.00
(dq, J = 8.7 Hz, 6.6 Hz, 1H, H-4’), 4.31 (q, J = 7.1 Hz, 2H, H-1a), 5.37 (d, J = 8.7 Hz, 1H, H-5’), 7.13 – 7.36 (m, 5H, Ar); $^{13}$C NMR (101 MHz, CDCl$_3$, ppm) δ 14.0 (Me), 15.0 (C-1b), 25.1 (C-2a), 28.1 (NMe), 54.5 (C-4’), 60.2 (C-5’), 62.3 (C-1a), 71.9 (C-2c), 72.5 (C-2), 77.1 (C-2b), 127.3 (Ar), 128.2 (Ar), 128.3 (Ar), 135.3 (Ar$_q$), 154.5 (C-2’), 164.1 (C-3), 165.6 (C-1); Anal. Calc. for C$_{19}$H$_{21}$N$_5$O$_4$ (%): C, 59.52; H, 5.52; N, 18.27. Found (%): C, 59.37; H, 5.54; N, 18.19.

General procedure for the azide reduction of 98 (9b – 9h):

**Method A:** To a suspension of Pd-C (10 mol %) in 1:1 THF:EtOH under Argon was added slowly a solution of 98 in THF. The flask was then purged with H$_2$, fitted with a balloon filled with H$_2$, and the reaction mixture stirred at rt for 6 hrs. The mixture solution was then filtered through celite and washed with EtOH (3 x 20 mL). The solvent was then removed under reduced pressure and the residue purified by flash chromatography. Compounds were recrystallized with DCM/hexane.

**Method B:** To a stirred solution of 98 in EtOH:H$_2$O (9:1) was added ammonium chloride (3 eq) and Zn dust (1.4 eq), and the reaction mixture stirred at rt until complete conversion of the SM (approximately 2 hrs). Occasionally it was necessary to add small amounts of Zn in order to obtain complete conversion. The reaction mixture was then filtered through celite and the EtOH removed under reduced pressure. Sat. NaHCO$_3$ (20 ml) was added to the resulting residue and the organic material extracted with EtOAc (3 x 30 ml). The combined organic extracts were dried with MgSO$_4$, filtered, evaporated under reduced pressure and the crude residue subjected to purification by flash chromatography. Compounds were recrystallized with DCM/hexane.
**(S)-Ethyl-2-amino-3-((4S,5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-methyl-3-oxopropanoate (99b)**

![Chemical Structure](image)

Via method A: **98b** (0.400 g, 1.11 mmol) in 1:1 THF:EtOH (15 mL) and Pd-C (0.118 g, 10 mol %) to afford **99b** as a white solid. m.p.: 115 – 117 °C; [α]_D^{20} = -124.2 (c = 0.50, CH₂Cl₂); IR ν_{max} (NaCl) / cm⁻¹ 3418, 1729, 1681, 1645, 1423; ¹H NMR (400 MHz, CDCl₃, ppm) δ 0.79 (d, J = 6.6 Hz, 3H, Me), 1.27 (t, J = 7.1 Hz, 3H, H-1b), 1.50 (s, 3H, H-2a), 2.47 (s, 2H, NH₂), 2.79 (2, 3H, NMe), 3.96 (dq, J = 8.8 Hz, 6.6 Hz, 1H, H-4'), 4.22 (m, 2H, H-1a), 5.36 (d, J = 8.8 Hz, 1H, H-5'), 7.15 – 7.36 (m, 5H, Ar); ¹³C NMR (101 MHz, CDCl₃, ppm) δ 14.1 (Me), 15.1 (C-1b), 23.8 (C-2a), 28.1 (NMe), 54.5 (C-4'), 59.7 (C-5'), 61.2 (C-1a), 63.5 (C-2), 126.8 (Ar), 128.1 (Ar), 128.5 (Ar), 136.1 (Arq), 155.5 (C-2'), 169.7 (C-3), 173.6 (C-1); Anal. Calc. for C₁₇H₂₃N₃O₄ (%): C, 61.25; H, 6.95; N, 12.60. Found (%): C, 61.00; H, 6.82; N, 12.62.

**(2S)-Ethyl-2-amino-2-((4S,5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)octanoate (99e)**

![Chemical Structure](image)

Via method B: **98e** (0.500 g, 1.16 mmol) in 9:1 EtOH:H₂O (15 ml), NH₄Cl(0.187g, 3.49 mmol) and Zn dust (0.106 g, 1.62 mmol) to afford a white solid (0.448, 96 %). Recrystallization with diethyl ether and hexane afforded colourless needles. m.p.: 97-99; [α]_D^{20} = -100.7 (c = 0.55, CH₃Cl); IR ν_{max} (NaCl) / cm⁻¹ 3418, 1729, 1681, 1643, 1426; ¹H NMR (400 MHz, CDCl₃, ppm) δ 0.79 (d, J = 6.7 Hz, 3H, Me), 0.81 (t, J = 6.5 Hz, 3H, H-2f), 1.14 – 1.44 (m, 8H, H-2e-b), 1.28 (t, J = 7.1 Hz, 3H, H-1b), 1.77 – 2.07 (m, 2H, H2-a), 2.36 (bs, 2H, -NH₂), 2.79 (s, 3H, -NMe), 3.96 (dq, J = 8.8 Hz, 6.7 Hz, 1H, H-4'), 4.22 (m, 2H, H-1a), 5.36 (d, J = 8.8 Hz, 1H, H-5'), 7.12 – 7.39 (m, 5H, Ar); ¹³C NMR (101 MHz, CDCl₃, ppm) δ 14.0 (C-2f), 14.2 (Me), 15.1 (C-1b), 22.5 (C-2e), 23.8 (C-2d), 28.1 (NMe), 29.5 (C-2c), 31.5 (C-2b), 36.5 (C-2a), 54.5 (C-4'), 59.9 (C-5').
61.1 (C-1a), 66.4 (C-2), 126.8 (Ar), 128.1 (Ar), 128.6 (Ar), 136.1 (Ar), 155.5 (C-2'), 169.2 (C-3), 172.4 (C-1); Anal. Calc. for C_{22}H_{33}N_{3}O_{4} (%): C, 65.48; H, 8.24; N, 10.41. Found (%): C, 65.37; H, 8.29; N, 10.51.

(2S)-Ethyl-2-amino-2-benzyl-3-[(4S, 5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl]-3-oxopropanoate (99f)

Via method A: 98f (0.800 g, 1.84 mmol) and Pd-C (0.194 g) to afford 99f as a white solid (0.737 g, 98%). M.p.: 141-143; [α]_{D}^{20} = -11.5 (c = 0.61, CH₂Cl₂); IR ν_{max} (NaCl) / cm⁻¹ 3418, 1729, 1681, 1422; ¹H NMR δ (400 MHz, CDCl₃, ppm) 0.81 (d, J = 6.6 Hz, 3H, Me), 1.23 (t, J = 7.2 Hz, 3H, H-1b), 2.34 (s, 2H, NH₂), 2.83 (s, 3H, NMe), 3.26 (d, J = 14.2 Hz, 1H, H-2a), 3.35 (d, J = 14.2 Hz, 1H, H-2a), 3.97 (dq, J = 8.4 Hz, 6.6 Hz, 1H, H-4'), 4.21 (q, J = 7.2 Hz, 2H, H-1a), 5.31 (d, J = 8.4 Hz, 1H, H-5'), 7.16 – 7.35 (m, 10H, Ar). ¹³C NMR δ (101 MHz, CDCl₃, ppm) 13.9 (Me), 15.1 (C-1b), 28.1 (NMe), 41.9 (C-2a), 54.5 (C-4'), 60.1 (C-5'), 61.0 (C-1a), 67.4 (C-2), 126.8 (Ar), 126.9 (Ar), 128.1 (Ar), 128.1 (Ar), 128.6 (Ar), 130.6 (Ar), 135.7 (Arₐ), 136.2 (Arₐ), 154.6 (C-2'), 167.9 (C-3), 172.3 (C-1); Anal. Calc. for C_{23}H_{27}N_{3}O_{4} (%): C, 67.46; H, 6.65; N, 10.26. Found (%): C, 67.73; H, 6.57; N, 10.49.

General procedure for the removal of the chiral auxiliary with LiSEt (100b – 100 h):

To a stirred solution of ethanethiol (1.2 eq) in dry THF at – 78 °C under Argon was added dropwise a solution of n-BuLi in hexanes (1.6 M, 1.2 eq). A solution of 99 in dry THF was then added dropwise. After 2 hrs the reaction was quenched with H₂O (10 mL) and extracted with EtOAc (3 x 15 mL), and the combined organic extracts dried with MgSO₄. After filtering, the solvent was removed under reduced pressure and the residue subjected to chromatographic purification.
(2R)-Ethyl-2-amino-2-((ethylthio)carbonyl)octanoate (100e)

With 99e (0.450 g, 1.12 mmol), ethanethiol (0.10 ml, 1.34 mmol) and n-BuLi (0.84 ml, 1.34 mmol) afforded 100e as a colourless oil (0.289 g, 94 %). IR ν_{max} (NaCl) / cm \(^{-1}\) 3420 (NH\(_2\)), 1740 (C=O, C-1), 1688 (C=O, C-3); \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm) δ 0.85 (t, J = 6.6 Hz, 3H, H-2f), 1.18 – 1.36 (m, 14H, H-1b, H-3b and H-2b-e), 1.98 (m, 2H, H-2a), 2.11 (bs, 2H, -NH\(_2\)), 2.83 (t, J = 7.4 Hz, 2H, H-3a), 4.21 (t, J = 7.1 Hz, 2H, H-1a); \(^13\)C NMR (101 MHz, CDCl\(_3\), ppm) δ 13.9 (C-2f), 13.9 (C-3b), 14.2 (C-1b), 22.4 (H-2e), 23.4 (C-2d), 23.6 (C-3a), 29.3 (C-2c), 31.4 (C-2b), 36.7 (C-2a), 62.1 (C-1a), 71.9 (C-2), 170.6 (C-1), 201.5 (C-3).

(2R)-Ethyl-2-amino-2-benzyl-3-(ethylthio)-3-oxopropanoate (100f)

With 99f (0.450 g, 1.10 mmol) in THF (5 ml), ethanethiol (0.10 ml, 1.32 mmol, 1.2 eq) in THF (10 ml) and n-BuLi (0.82 ml, 1.32 mmol, 1.2 eq) afforded 100f as a colourless oil (0.294 g, 95 %). IR ν_{max} (NaCl) / cm \(^{-1}\) 3418 (NH\(_2\)), 1741 (C=O, C-1), 1687 (C=O, C-3); \(^1\)H NMR δ (400 MHz, CDCl\(_3\), ppm) 1.23 (t, J = 7.4 Hz, 3H, H-3b), 1.30 (t, J = 7.2 Hz, 3H, H-1b), 1.90 (bs, 2H, NH\(_2\)), 2.84 (q, J = 7.4 Hz, 2H, H-3a), 3.31 (d, J = 13.6 Hz, 1H, H-2a), 3.36 (d, J = 13.6 Hz, 1H, H-2a), 4.24 (q, J = 7.2 Hz, 2H, H-1a), 7.13 – 7.33 (m, 5H, Ar); \(^13\)C NMR δ (101 MHz, CDCl\(_3\), ppm) 14.0 (C-3b), 14.2 (C-1b), 23.8 (C-3a), 42.2 (C-2a), 62.32 (C-1a), 72.1 (C-2), 127.4 (Ar), 128.5 (Ar), 130.4 (Ar), 134.6 (Ar\(_q\), 170.1 (C-1), 201.4 (C-3).
(2R)-Ethyl-2-amino-2-allyl-3-(ethylthio)-3-oxopropanoate (100g)

With 99g (0.500 g, 1.39 mmol), ethanethiol (0.12 ml) and n-BuLi (1.04 ml) afforded 100g as a colourless oil (0.301 g, 94 %). IR $\nu_{\text{max}}$ (NaCl) / cm$^{-1}$ 3420 (NH$_2$), 1741 (C=O, C-1), 1688 (C=O, C-3); $^1$H NMR (400 MHz, CDCl$_3$, ppm) $\delta$ 1.24 (t, $J$ = 7.3 Hz, 3H, H-3b), 1.29 (t, $J$ = 7.1 Hz, 3H, H-1b), 2.38 (bs, 2H, NH$_2$), 2.68 – 2.92 (m, 4H, H-2a and H-3a), 4.25 (m, 2H, 1a), 5.23 (m, 2H, H-2c), 5.72 (m, 1H, H-2b); $^{13}$C NMR (101 MHz, CDCl$_3$, ppm) $\delta$ 14.0 (C-3b), 14.2 (C-1b), 23.8 (C-3a), 40.9 (C-2a), 62.5 (C-1a), 70.9 (C-2), 121.2 (H-2c), 131.0 (H-2b), 169.8 (C-1), 200.4 (C-3).

(2R)-Ethyl-2-amino-2-propargyl-3-(ethylthio)-3-oxopropanoate (100h)

With 99h (0.500 g, 1.40 mmol), ethanethiol (0.13 ml) and n-BuLi (1.05 ml) afforded 100h as a colourless oil (0.303 g, 94 %). IR $\nu_{\text{max}}$ (NaCl) / cm$^{-1}$ 3420 (NH$_2$), 1742 (C=O, C-1), 1689 (C=O, C-3); The enantiomeric excess was determined to be > 99 % by HPLC using a Daicel Chiralpack AD column (hexane/i-PrOH (90/10): flow rate 1.0 mL/min: $\tau$ major = 5.7 min. $^1$H NMR (400 MHz, CDCl$_3$, ppm) $\delta$ 1.22 (t, $J$ = 7.4 Hz, 3H, H-3b), 1.26 (t, $J$ = 7.1 Hz, 3H, H-1b), 2.06 (t, $J$ = 2.6 Hz, 1H, H-2c), 2.40 (bs, 2H, NH$_2$), 2.78 – 3.00 (m, 4H, H-3a and H-2a), 4.22 (m, 2H, H-1a); $^{13}$C NMR (101 MHz, CDCl$_3$, ppm) $\delta$ 13.9 (C-3b), 14.1 (C-1b), 23.8 (C-3a), 27.3 (C-2a), 62.6 (C-1a), 70.3 (C-2c), 72.2 (C-2), 77.9 (C-2b), 169.1 (C-1), 199.8 (C-3);
General procedure for the one-pot transformation of thioester 100 to the $\alpha$, $\alpha$ - disubstituted serine derivative 102:

To a stirred solution of 100 in dry THF at 0 °C under an Argon atmosphere was added a solution of LiAl(O-tBu)$_3$H (2.2 eq) in THF dropwise over a period of 15 min which upon complete conversion of the starting material (approx. 6 hrs) was quenched with HCl (2.0 M, 2 mL). The reaction mixture was then basified with NaOH (2.0 M, 5 mL), and (Boc)$_2$O (1.4 eq) and DMAP (20 mol %) added. After 8 hrs, H$_2$O (5 mL) was added and the reaction mixture extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried with MgSO$_4$, filtered, the organic solvent evaporated and the residue subjected to flash chromatography to afford 102.

(S)-Ethyl-2- benzyl-2-((tert-butoxycarbonyl)amino)-3-hydroxypropanoate (102f)

With 100f (0.120 g, 0.43 mmol) in THF (10 mL) and LiAl(O-tBu)$_3$H (0.240 g, 0.94 mmol, 2.2 eq) in THF (5 mL), (Boc)$_2$O (0.131 g, 0.60 mmol) and DMAP (0.011 g, 0.086 mmol) afforded 102f as a yellow oil (0.095 g, 70 %). $[\alpha]_D^{20} = +2.9$ (c = 1.0, CH$_2$Cl$_2$); The enantiomeric excess was determined to be 96 % by HPLC using a Daicel Chiralpack AD column (hexane/i-PrOH (95/5): flow rate 1.0 mL/min; $\tau$ major = 10.14 min; $\tau$ minor = 11.18 min. $^1$H NMR (300 MHz, CDCl$_3$, ppm) $\delta$ 1.23 (t, J = 7.1 Hz, 3H, H-1b), 1.47 (s, 9H, H-6), 2.03 (s, 2H, -OH + -NH), 2.83 (d, J = 13.2 Hz, 1H, H-2a), 3.10 (d, J = 13.2 Hz, 1H, H-2a), 4.08 (d, J = 10.4 Hz, 1H, H-3), 4.16 (m, 2H, H-1a), 4.47 (d, J = 10.4 Hz, 1H, H-3), 7.12 – 7.32 (m, 5H, Ar). $^{13}$C NMR (101 MHz, CD$_2$OD, ppm) $\delta$ 14.1 (C-1b), 27.7 (C-6), 42.1 (C-2a), 61.4 (C-1a), 61.6 (C-3), 71.8 (C-2), 82.4 (C-5), 127.2 (Ar), 128.4 (Ar), 130.0 (Ar), 134.8 (Ar$_q$), 153.0 (C-4), 173.9 (C-1); HRMS (ES): calc. 324.1811 for C$_{17}$H$_{26}$NO$_5$ [M + H]$^+$; requires 324.1817.
(S)-Ethyl-2-propargyl-2-((tert-butoxycarbonyl)amino)-3-hydroxypropanoate (102h)

With 100h (0.100 g, 0.44 mmol) in THF (10 mL) and LiAl(O-tBu)₃H (0.245 g, 0.96 mmol, 2.2 eq) in THF (5 mL), (Boc)₂O (0.134 g, 0.60 mmol) and DMAP (0.011 g, 0.088 mmol) afforded 102h as a yellow oil (0.078 g, 65 %). The enantiomeric excess was extrapolated from 100h which was determined to be > 99 % by HPLC using a Daicel Chiralpack AD column (hexane/i-PrOH (90/10): flow rate 1.0 mL/min: \( \tau_{\text{major}} = 5.7 \) min; \([\alpha]^{20}_D = + 49.8 \) (c = 0.4, MeOH); \(^1\)H NMR (400 MHz, CD₃OD, ppm) \( \delta \) 1.27 (t, \( J = 7.1 \) Hz, 3H, H-1b), 1.44 (s, 9H, H-6), 2.31 (t, \( J = 2.6 \) Hz, 1H, H-2c), 2.82 (dd, \( J = 16.9 \) Hz, 2.6 Hz, 1H, H-2a), 2.93 (dd, \( J = 16.9 \) Hz, 2.6 Hz, 1H, H-2a), 3.83 (d, \( J = 11.0 \) Hz, 1H, H-3), 3.87 (d, \( J = 11.0 \) Hz, 1H, H-3), 4.20 (m, 2H, H-1a); \(^{13}\)C NMR (101 MHz, CD₃OD, ppm) \( \delta \) 14.4 (C-1b), 23.1 (C-2a), 28.7 (C-6), 62.6 (C-1a), 63.8 (C-3), 64.2 (C-2c), 72.2 (C-2), 79.9 (C-2b), 80.7 (C-5), 156.6 (C-4), 173.1 (C-1). HRMS (ES): calc. 272.1498 for C₁₃H₂₂NO₅ [M + H]\(^{+}\); requires 272.1496.

3-(Benzyloxy)-3-oxopropanoic acid

To a stirred solution of malonic acid (2.00 g, 19.2 mmol) and benzyl alcohol (2.00 mL, 19.2 mmol) in dry CH₃CN (50 mL) at 0 °C, was added over a period of 45 min a solution of DCC (19.5 mmol, 0.39 M) in CH₃CN. After 8 hrs the mixture was filtered through celite and the solvent removed under reduced pressure. A solution of sat. NaHCO₃ (100 mL) was then added and extracted with diethyl ether (3 x 40 mL). The aqueous layer was then acidified to pH 3 with 1M HCl and extracted with ethyl acetate (3 x 60 mL). The organic layer was dried over MgSO₄ and filtered, and the solvent removed under reduced pressure to afford the title compound as a white solid (3.35 g, 90 %). \(^1\)H NMR \( \delta \) (300 MHz, CDCl₃, ppm) 3.42 (s, 2H, H-2), 5.15 (s, 2H, H-3a), 7.26 – 7.40 (m, 5H, Ar), 8.54 (bs, 1H, -OH); \(^{13}\)C NMR \( \delta \) (101 MHz,
CDCl$_3$, ppm) 40.8 (C-2), 67.6 (C-3a), 128.3 (Ar), 128.5 (Ar), 128.6 (Ar), 135.0 (Ar$_q$), 166.5 (C-3), 171.2 (C-1).

**General procedure for the acylation of N-Methylaniline or Aux via the BtCl/PPh$_3$ method:**

To a stirred solution of PPh$_3$ in dry CH$_3$CN at –10 °C was added in one portion BtCl and after 1 min, the appropriate acid was added dropwise in dry CH$_3$CN. After 15 min Aux or N-methylaniline was added and the reaction mixture refluxed for 8 hrs. The reaction mixture was allowed to cool to rt and the CH$_3$CN removed under reduced pressure. The residue was dissolved in DCM (40 ml), washed with sat. Na$_2$CO$_3$ (3 x 30 ml) and dried with MgSO$_4$. Following filtration and evaporation the residue was purified by flash chromatography.

**Benzyl-3-((4S,5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-3-oxopropanoate**

With PPh$_3$ (0.165 g, 0.63 mmol) in dry CH$_3$CN (15 ml), BtCl (0.097 g, 0.63 mmol), 3-(Benzylxy)-3-oxopropanoic acid (0.122 g, 0.63 mmol) in dry CH$_3$CN (4 ml), and Aux (0.100 g, 0.53 mmol) to afford the title compound as a clear oil (0.174 g, 90 %). $^1$H NMR (400 MHz, CDCl$_3$, ppm) $\delta$ 0.78 (d, $J = 6.6$ Hz, 3H, Me), 2.80 (s, 3H, -NMe), 3.89 (dq, $J = 8.6$ Hz, 6.6 Hz, 1H, H-4'), 4.01 (d, $J = 16.4$ Hz, 1H, H-2), 4.07 (d, $J = 16.4$ Hz, 1H, H-2), 5.15 (d, $J = 12.6$, 1H, H-1a), 5.19 (d, $J = 12.6$, 1H, H-1a), 5.30 (d, $J = 8.6$, 1H, H-5'), 7.11 – 7.39 (m, 10H, Ar); $^{13}$C NMR (101 MHz, CD$_3$OD, ppm) $\delta$ 14.9 (Me), 28.1 (NMe), 43.4 (C-2), 54.0 (C-4'), 59.3 (C-5'), 66.9 (C-1a), 127.0 (Ar), 128.1 (Ar), 128.2 (Ar), 128.3 (Ar), 128.4 (Ar), 128.5 (Ar), 135.6 (Ar$_q$), 135.9 (Ar$_q$), 155.4 (C-2'), 164.7 (C-3), 167.3 (C-1); HRMS (ES): calc. 367.1658 for C$_{21}$H$_{23}$N$_2$O$_4$ [M + H]$^+$; requires 367.1659.
Ethyl-2-methyl-3-(methyl(phenyl)amino)-3-oxopropanoate\textsuperscript{74}

![Structure](image)

With PPh\textsubscript{3} (0.294 g, 1.12 mmol) in dry CH\textsubscript{3}CN (15 ml), BtCl (0.172 g, 1.12 mmol), \textit{93b} (0.164 g, 1.12 mmol) in dry CH\textsubscript{3}CN (4 ml) and \textit{N-methylaniline} (0.100 g, 0.93 mmol) to afford the title compound as a clear oil (0.219 g, 90%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, ppm) δ 1.20 (t, \textit{J} = 7.1 Hz, 3H, H-1\textit{b}), 1.27 (d, \textit{J} = 7.0 Hz, 3H, H-2\textit{a}), 3.28 (s, 3H, -NMe), 3.37 (q, \textit{J} = 7.0 Hz, H-2), 4.08 (m, 2H, H-1\textit{a}), 7.18 – 7.44 (m, 5H, Ar).

\textit{N-methyl-N-phenylacetamide}\textsuperscript{75}

![Structure](image)

With PPh\textsubscript{3} (0.294 g, 1.12 mmol) in dry CH\textsubscript{3}CN (15 ml), BtCl (0.172 g, 1.12 mmol), \textit{acetic acid} (0.067 g, 1.12 mmol) in dry CH\textsubscript{3}CN (4 ml) and \textit{N-methylaniline} (0.100 g, 0.93 mmol) to afford the title compound as a clear oil (0.135 g, 96%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, ppm) δ 1.86 (s, 3H, CH\textsubscript{3}), 3.25 (s, 3H, -NMe), 7.07 – 7.53 (m, 5H, Ar); \textsuperscript{13}C NMR (101 MHz, CD\textsubscript{3}OD, ppm) δ 22.3 (CH\textsubscript{3}), 37.1 (NMe), 127.0 (Ar), 127.6 (Ar), 129.6 (Ar), 144.5 (Ar\textsubscript{a}), 170.5 (C=O).

Ethyl-2-benzyl-3-(methyl(phenyl)amino)-3-oxopropanoate

![Structure](image)

With PPh\textsubscript{3} (0.294 g, 1.12 mmol) in dry CH\textsubscript{3}CN (15 ml), BtCl (0.172 g, 1.12 mmol), \textit{2-benzyl-3-ethoxy-3-oxopropanoic acid} (0.249 g, 1.12 mmol) in dry CH\textsubscript{3}CN (4 ml) and \textit{N-methylaniline} (0.100 g, 0.93 mmol) to afford the title compound as a clear oil (0.260 g, 91%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, ppm) δ 1.22 (t, \textit{J} = 7.2 Hz, 3H, H-1\textit{b}), 3.02 – 3.24 (m, 2H, H-2\textit{a}), 3.15 (s, 3H, -NMe), 3.52 (m, 1H, H-2), 4.13 (m, 2H, H-1\textit{a}), 6.44 – 7.30 (m, 10H, Ar); \textsuperscript{13}C NMR (101 MHz, CD\textsubscript{3}OD, ppm) δ 14.0 (C-1\textit{b}), 35.2 (C-2\textit{a}), 37.3 (NMe), 50.9 (C-2), 61.2 (C-1\textit{a}), 126.5 (Ar).
127.5 (Ar), 127.9 (Ar), 128.2 (Ar), 129.1 (Ar), 129.4 (Ar), 138.3 (Ar), 143.1 (Ar), 168.4 (C-1),
169.3 (C-3); HRMS (ES): calc. 312.1600 for C_{19}H_{22}NO_3 [M + H]^+; requires 312.1598.


11) IUPAC, 1996


15) Evans, D. A. \textit{Aldrichimica Acta.} \textbf{1982}, 15, 23


17) (a) D. Ma and K. Ding, Org. Lett., 2000, 2, 2515; (b) K. Ding and D. Ma, Tetrahedron, 2001, 57, 6361


50) Bera, K.; Namboothiri, I. N. N. *Chem. Comm.* 2013, 49, 10632


69) Shih, N.; Reichard, G.; Stengone, C.; Org. Lett. 2003, 5, 4249


74) Zeng, H.; Shao, H. Green Chem. Lett. Rev. 2013, 6, 222


77) Kozlowski, M. C.; Metz, A. E. J. Org. Chem., 2015, 80, 1


95) Aoyagi, Y.; Williams, R. M. *Synlett* **1998**, 1099


