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

By

Wade Frank Petersen

Thesis presented for the degree of

Doctor of Philosophy

In the Department of Chemistry

University of Cape Town

April 2015

Supervisor: Professor Roger Hunter

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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!

A special thank you to Dr. Nashia Zílbeyaz for her huge impact in my development as a scientist.

To the entire Hunter group for the pleasant atmosphere created in the laboratory. Especially Gregory and Athi as well as the rest of my coffee buddies, Cathyrn, Rudy and Ana for all the late work nights, academic discussions and friendship.

To Dr. Gerhard Venter for the computational modelling as well as Pete Roberts, Noel Hendricks and Piero Benincasa, Hong Su and the Stellenbosch University Mass Spectrometry Unit for their analytical services.

My best friends Preshen and Kyle - thank you for the all the adventures… Enough said!

To my mentor Raymond Hunt and his Wife, Jessica – Thank you for the friendship, motivation and for being my 'big brother'.

To my family - thank you for all your prayers, love, keeping my food warm at night and motivational talks.

To Elaine Martin for her support, encouragement and helping me through this journey.

To my love, Nakeeta Bailey – Thank you for your understanding, patience and support during this thesis - I love you!

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

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

List of abbreviations

α	alpha
AcOH	acetic acid
Ar	aromatic
Ar_q	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*-butylazodicarboxlate
DCM	dichloromethane
DMAP	4-dimethylaminopyrdine
DME	dimethyl ether
DMF	N,N-dimethylformamide
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 chromotraphy
hr(s)	hour(s)
Hz	Hertz
IR	infrared
J	coupling constant
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
$LiAlH_4$	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
NEt_3	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

TFAA	trifluoroacetic acid anhydride
TfOH	triflic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
tolyl	toluenesulfonate
Trisyl (Tris)	triisopropylbenzenesulfonyl
v/v	volume to volume
xs	excess

Table of Contents

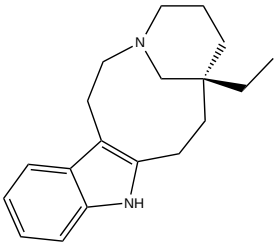
Chapter 1

Introduction

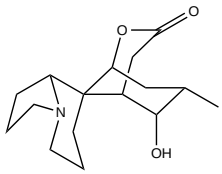
1.1Chiral Quaternary Centres

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 sp^3 carbon atom bearing no hydrogen atoms, examples of which are shown in **Figure 1**.

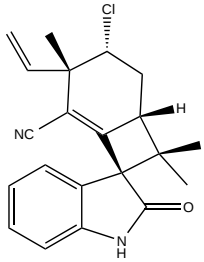
All-carbon quaternary



Quebrachamine

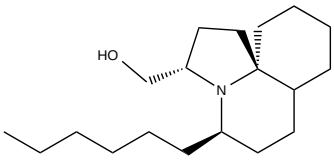


Serratezomine

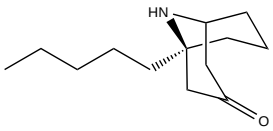


Welwitindolinone A isonitrile

aza-quaternary

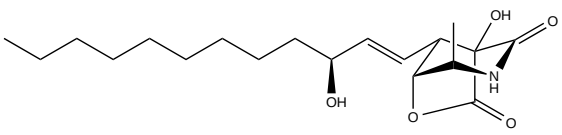


Lepadiformine



Adaline

oxa-quaternary



Awajanomycin

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**).[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.[6]

1.2 The Origin of Asymmetric Synthesis

The most widely used definition of asymmetric synthesis was that written by Marckwald[7] in 1904 where he states that:

> *''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.*

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. Similary, thirty years earlier Pasteur noted the following:

> *L'univers est dissymétrique*
>
> *The universe is dissymmetric*
>
> Louis Pasteur (1874)

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.[8] More importantly, in 1860 he pointed out that many natural products were optically active whereas compounds synthesised in a laboratory were not.[9] 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.[10] 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.[11] 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**.[12]

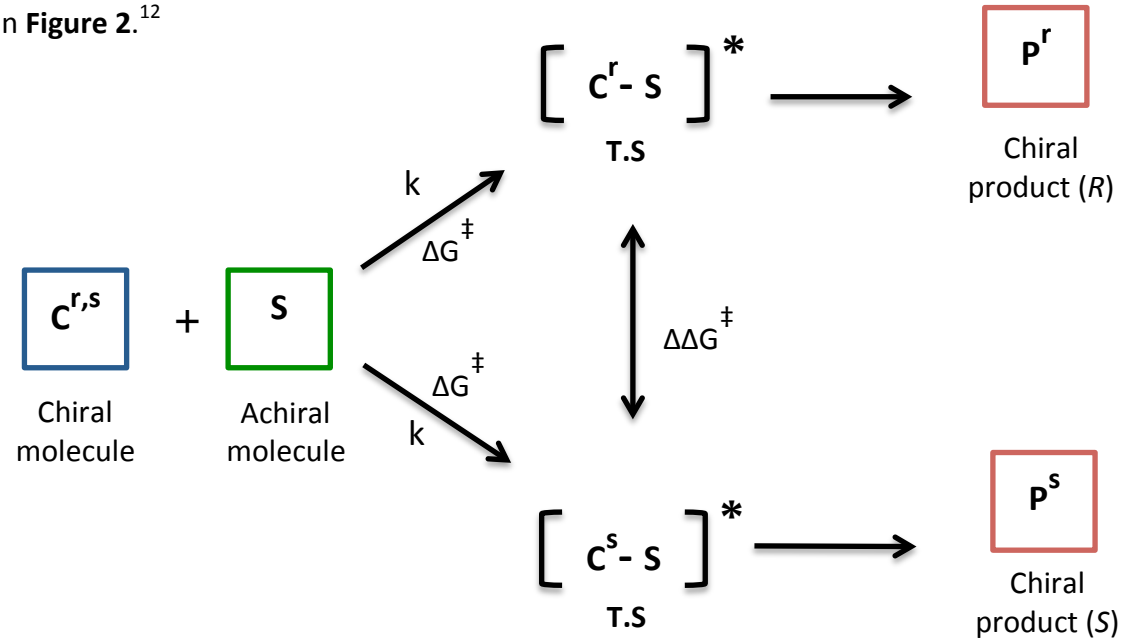


Figure 2. Transition state of an asymmetric reaction displaying the concept of asymmetric induction.

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 ^{o}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

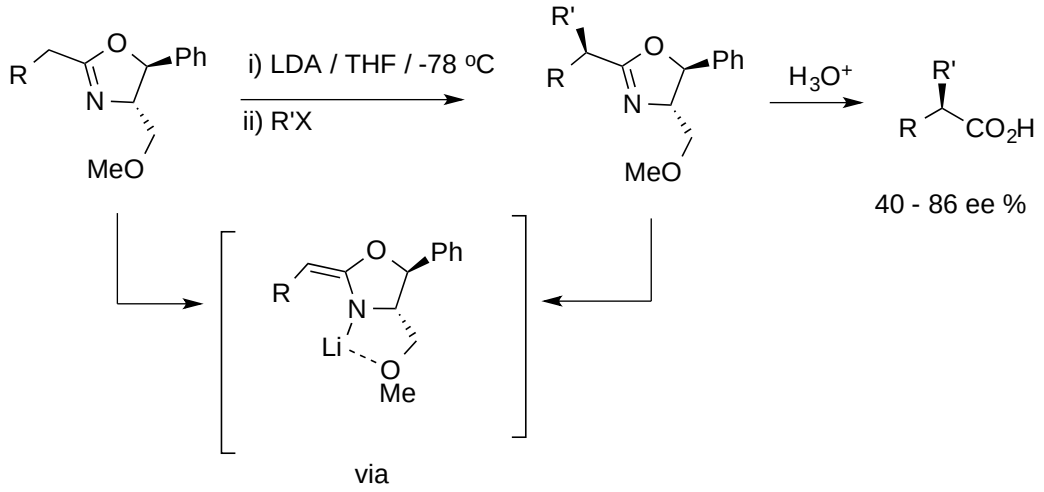
There are currently two major approaches to asymmetric induction. The first involves having a chiral directing group contained within the substrate prior to the key stereoselective reaction, which gives rise to a diastereoselective reaction in which asymmetric induction is referred to as being due to 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

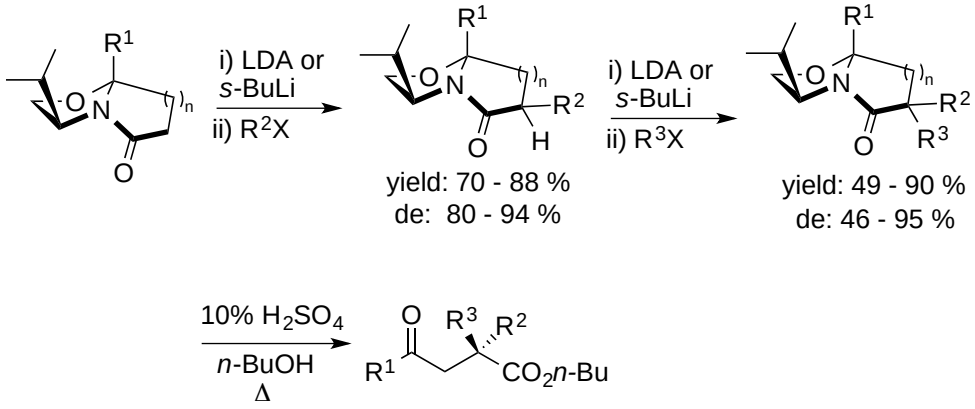
The true foundation of substrate-controlled chiral induction was laid by Meyers in 1976 who reported a highly successful diastereoselective methodology for the α-substitution of an achiral long-chain fatty acid into a chiral α-alkylalkanoic acids. The chiral directing group was provided by a chiral 2-oxazoline derivative (**Scheme 1**).[13] 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:



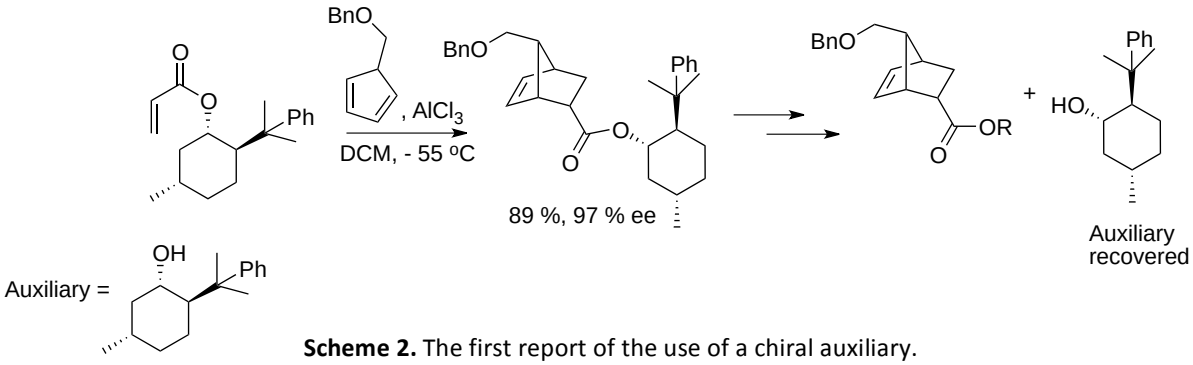
Bicyclic lactams:



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 1978[14] 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)**.



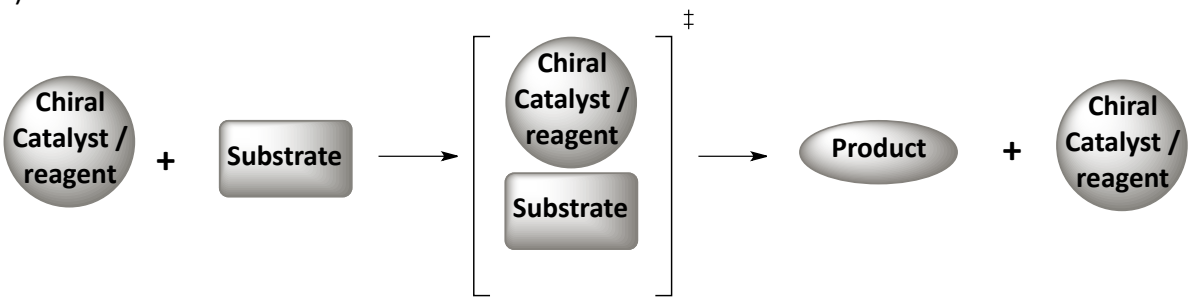
Scheme 2. The first report of the use of a chiral auxiliary.

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**).



Scheme 3. Reagent-controlled process

1.4.3. Criteria for an Efficient Asymmetric Method

A few criteria are essential for evaluating the efficiency of an asymmetric method[19]:

- 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.

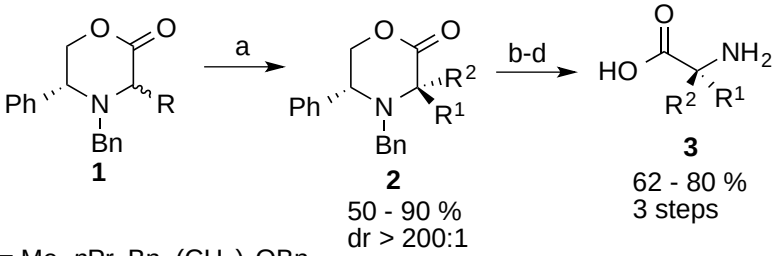
1.5 Substrate-Controlled Approach for Aza-Quaternary Centre Construction[16]

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

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**).[17]



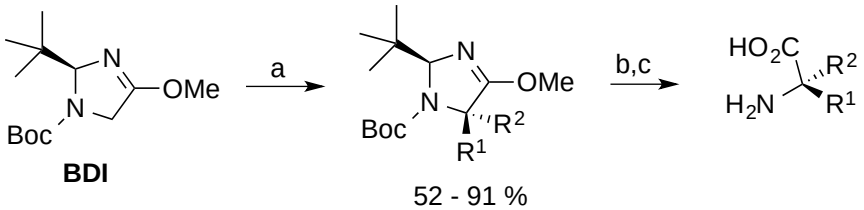
R^1 = Me, *n*Pr, Bn, $(CH_2)_2OBn$
R^2 = Et, Bn, allyl, CH_2CO_2Me, CH(OH)*n*Pr
X = Br, I

Reagents and conditions: (a) NaHMDS, DME, - 78 °C, ii) R^2X; (b) NaOH-MeOH; (c) H_2 (40 atm), Pd/C, EtOH, 40 °C; (d) Dowex-50W.

Scheme 4. Diastereoselective alkylation sequence of phenylglycine derived oxainones (**1**).

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 gave rise to α,α'-dialkylated amino acids

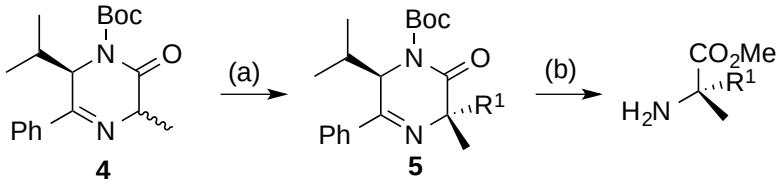
possessing no natural amino acid side chains in moderate to excellent yields and in very high selectivity (**Scheme 5**).



Reagents and conditions: (a) i) LDA, THF, - 78 ^{o}C ii) R^1X iii) *n*-BuLi iv) R^2X;
(b) i) TFA, DCM c) 4N TFA, H_2O, rt

Scheme 5. Double alkylation of a **BDI** to afford an unnatural α,α-disubstituted amino acid.

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*-acetylvaline in order to obtain one enantiomer.[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**).

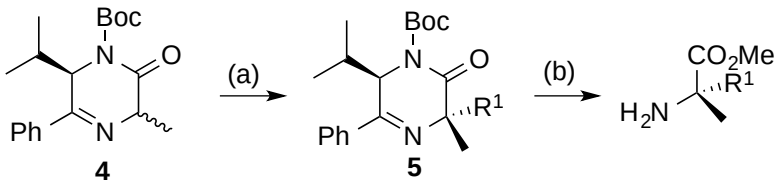


R^1 = allyl, propargyl, Bn, EtO_2CCH_2,
X = Br, I

Reagents and conditions: (a) K_2CO_3 (3 eq.), TBAI (10 mol %), CH_3CN, R^1X, rt; (b) i) 6N HCl, 150 ^{o}C ii) Propylene oxide, EtOH

Scheme 6. Diastereoselective alkylation of chiral pyrazinones under phase transfer catalysis.

In addition they described a palladium-catalyzed allylation 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.[19]



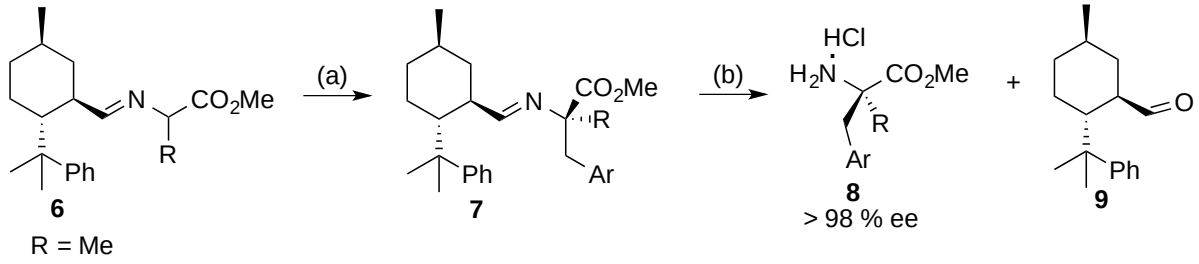
R1= allyl groups

47 - 85 %
de > 98 %

Reagents and conditions: (a) $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), THF, R^1OCO_2Et, rt; (b) i) 6N HCl, 150 ^oC ii) Propylene oxide, EtOH

Scheme 7. Diastereoselective Pd(0) catalyszed allylation of chiral pyrazinones .

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]



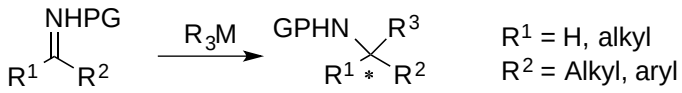
Reagents and conditions: (a) i) LDA, THF, - 78 ^oC ii) 3,4-dimethoxybenzyl bromide; (b) 1N HCl, Et_2O, rt

Scheme 8. Phenylmenthol chiral auxiliary use in the synthesis of quaternary amino acid **8**.

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.

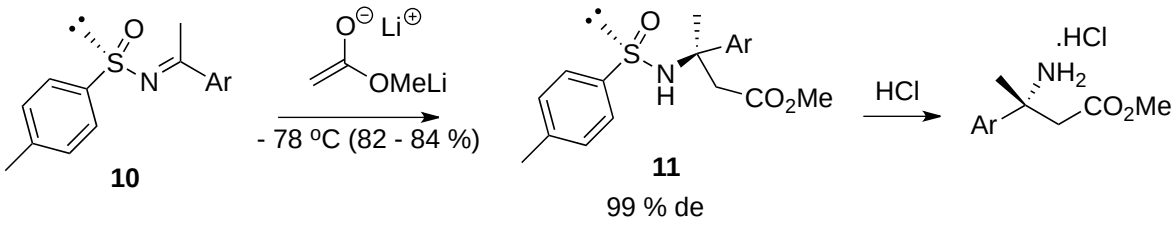
1.5.2 Addition to C=N Bonds

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**)[21] in which a ketimine is needed to achieve the desired product.



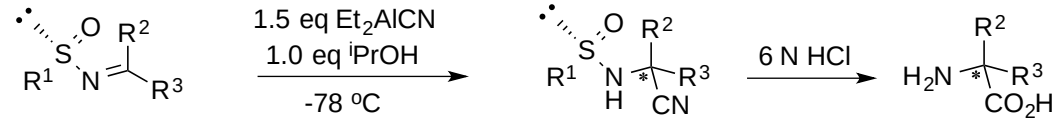
Scheme 9. Nucleophilic addition to imines.

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 approached was originally pioneered by Davis[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**).



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

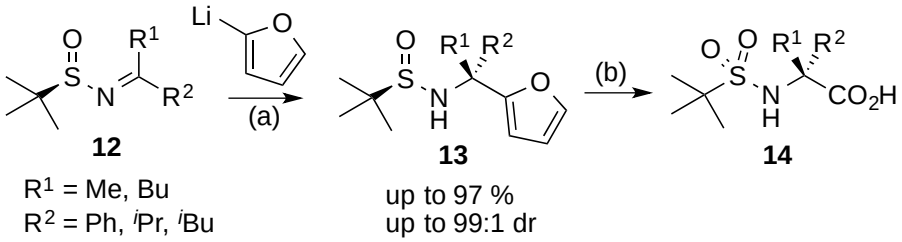
For application towards the stereoselective synthesis of α,α-disubstituted α-amino acids, chiral sulfinamides have been utilized as substrates in asymmetric Strecker reactions to afford a quaternary amino acid in moderate to excellent enantioselectivity upon acid hydrolysis (**Scheme 11**).[23]



R1 = *p*-toly, ^{t}Bu
R2 = Me, Et
R3 = Me_3C, Et, Ph, n-Bu, *p*-MeOPh, *p*-MePh, *p*-NO_2Ph

Scheme 11. Asymmetric Strecker reaction of chiral sulfinimines to afford α,α-disubstituted amino acids.

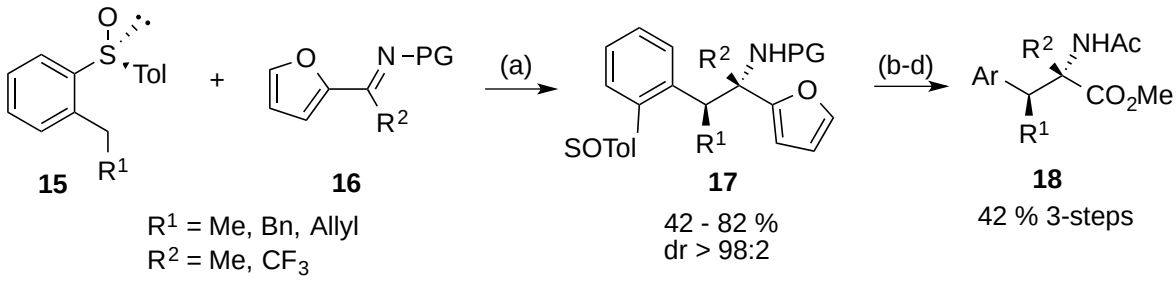
Ellman subsequently developed the *tert*-butyl sulfinamide grouping in order to overcome various limitations presented by the *p*-tolyl auxiliary when attempting Grignard additions to the imine bond.[24] In their application for the synthesis of α,α-disubstituted amino acids Ellman demonstrated that *tert*-butyl sulfinamines (**12**) were excellent substrates for diastereoselective Grignard addition of furan to afford sulfinamine **13** in moderate to excellent yields and dr (**Scheme 12**). These were subsequently converted to the quaternary amino acid derivative **14**.



Reagents and conditions: (a) $AlMe_3$, 0 °C, toluene; (b) $RuCl_3$, $NaIO_4$, DCM, CH_3CN, H_2O

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**).[25]

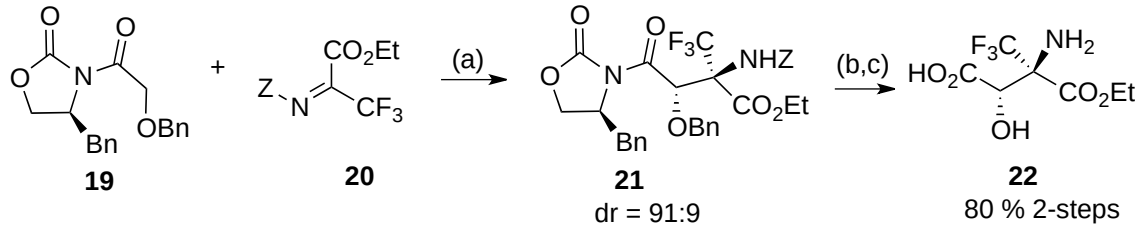


Reagents and conditions: (a) LDA, THF, - 78 °C; (b) TFA, MeOH (c) Ac_2O, Et_3N, DMAP; (c) $NaIO_4$, $RuCl_3$, $TMSCH_2N_2$

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 sulfinic acid obtained after hydrolysis needs to be isolated and recommitted to a synthetic sequence that would regenerate the sulfinamide for

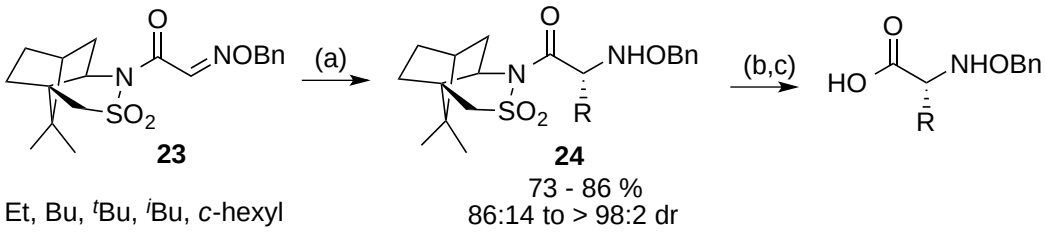
subsequent use. By contrast, Zanda made use of a chiral enolate derived from the Evans' oxazolidinone (**19**) for addition to achiral iminoester (**20**), which gave rise to aza-quaternary product **21** in dr = 91:9. Subsequent removal of the auxiliary and deprotection afforded **22** in 80 % yield over 2-steps (**Scheme 14**).[26]



Reagents and conditions: (a) $TiCl_4$, DIPEA (b) LiOH, H_2O_2 (c) H_2, $Pd(OH)_2$

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]



R = ^{i}Pr, Et, Bu, ^{t}Bu, ^{i}Bu, *c*-hexyl

Reagent and conditions: (a) RI, Bu_3SnH, Et_3B; (b) $Mo(CO)_6$; (c) LiOH

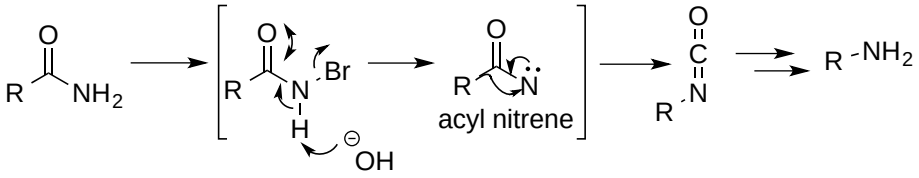
Scheme 15. Diastereoselective radical addition to chiral oximes.

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**).

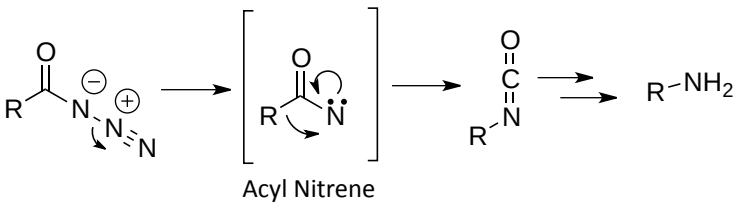


Scheme 16. The Hofmann rearrangement

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

The Curtius rearrangement[29]

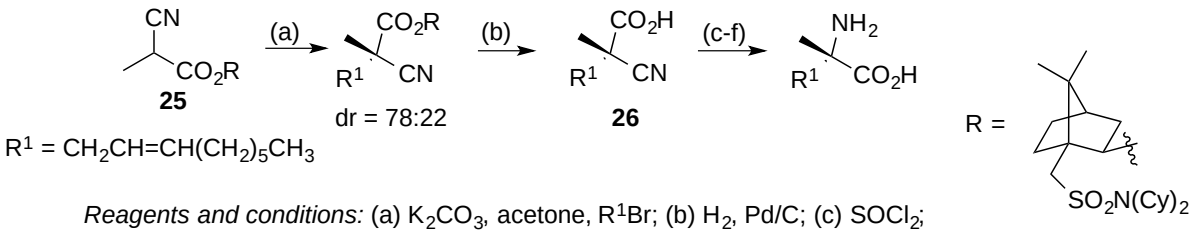
Similar to the Hofmann rearrangement, the Curtius rearrangement also proceeds to the amine via the isocyanate through an acylnitrene. The key difference between the two is that the Curtius involves the use of an acyl azide rather than an acetamide. Mechanistically, this poses interesting questions as 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**).



Scheme 17. Curtius rearrangement

Additional methodologies invoking the carboxylic azide and/or acyl nitrene 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

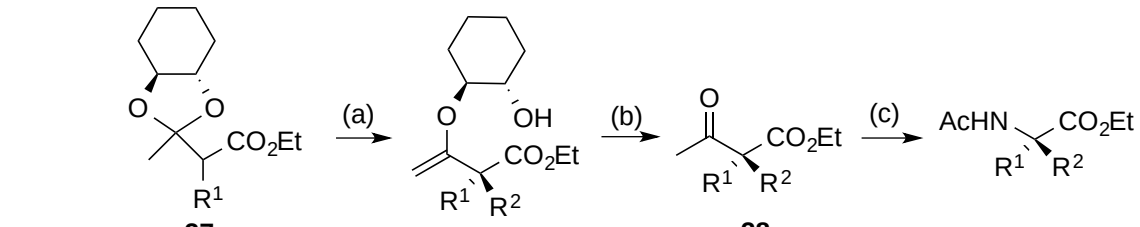
however proceed with retention of configuration of the migrating group. Thus, for aza-quaternary centre production a quaternized R group would already need to be in place. An example of this can been seen in the work by Cativiela who made use of a Curtius rearrangement for the transformation of α-cyano 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]



Reagents and conditions: (a) K_2CO_3, acetone, R^1Br; (b) H_2, Pd/C; (c) $SOCl_2$; (d) NaN_3; (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-disubtituted β-ketoester (**28**) as the key step (**Scheme 19**).



Reagent and condition: (a) LDA, R^2X, THF, HMPA, - 78 ^oC to - 40 ^oC; (b) BF_3.OEt, EtOH, H_2O, rt; (c) NaN_3, 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 $[NH_2]^+$. 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 π-acceptors are availible including oximes, azodicarboxylates, azides, nitro and nitroso compounds. **Figure 3** shows a few examples.

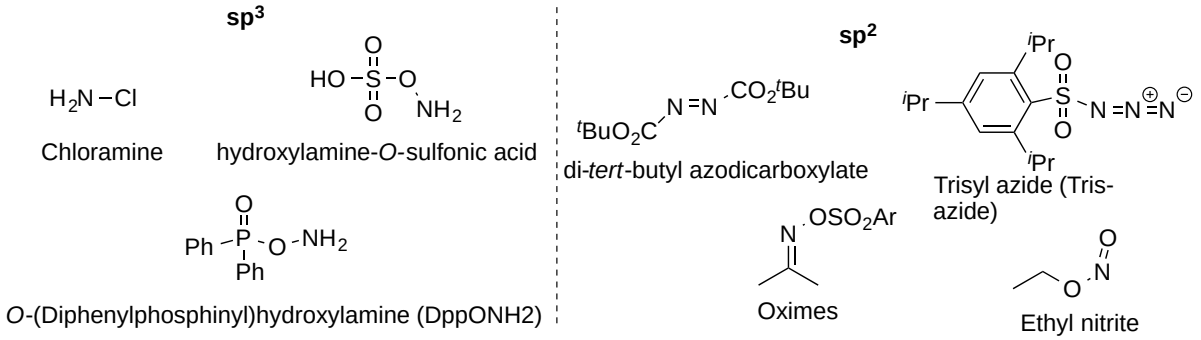
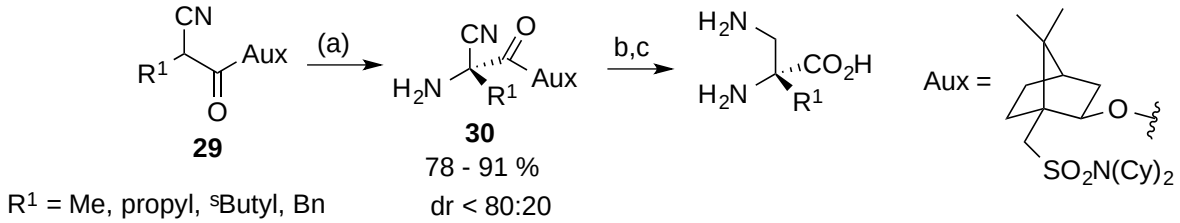


Figure 3. Various aminating reagents.

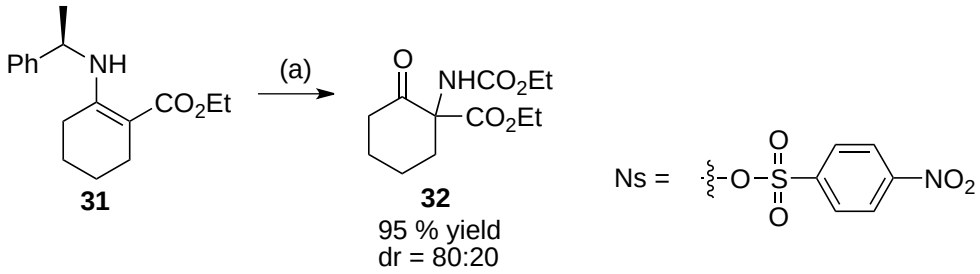
Cativiela carried out α-aminations on chiral camphorsulfonic acid-derived cyano esters **29** using *O*-(diphenylphosphinyl)hydroxylamine to afford amine **30** bearing an aza-quaternary centre in excellent yield, but moderate dr (> 80:20) (**Scheme 20**).[33]



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

Scheme 20. Diasteroselective a-amination using a camphor-derived auxiliary in a moderate dr.

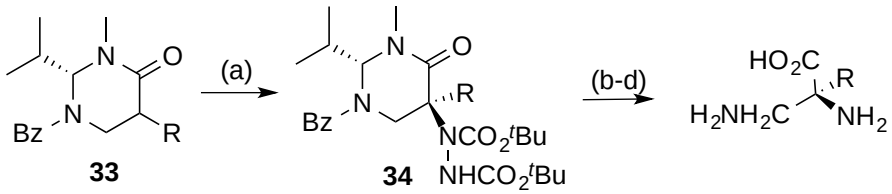
Felice *et al* reported the α-amination of a chiral phenylethylamine-derived enamine (**31**) with ethyl-*N*-((4-nitrobenzenesulfonyl)oxy)carbamate to afford the cyclic amino acid derivative **32** in excellent yield but similarly in only a moderate dr of 80:20 (**Scheme 21**). The absolute configuration was not determined.[34]



Reagents and conditions: (a) $NsONHCO_2Et$, DCM, 2 days

Scheme 21. Diastereoselective a-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]



Reagents and conditions: (a) i) LDA, THF, - 78 ºC ii) DTAD; (b) TFA, DCM, rt; (c) *Raney* Ni/H_2 (69 bar), MeOH, rt; (d) 6N HCl, 90 ºC.

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

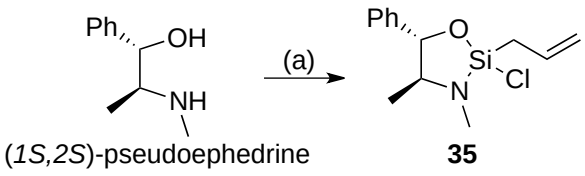
However, there are disadvantages to the method regarding the scope of R, and as mentioned before, it does not make use of a recyclable chiral directing group. These are three of few reports that make use of diastereoselective α-amination to access azaquaternary centres in chiral, non-racemic form, which 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 Et_3N in DCM (**Scheme 23**) and introduced in 2002.

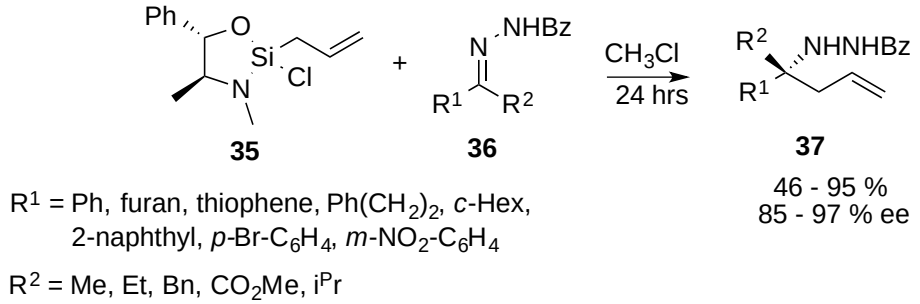


(*1S,2S*)-pseudoephedrine **35**

Reagents and conditions: (a) allyltrichlorosilane, Et_3N, DCM

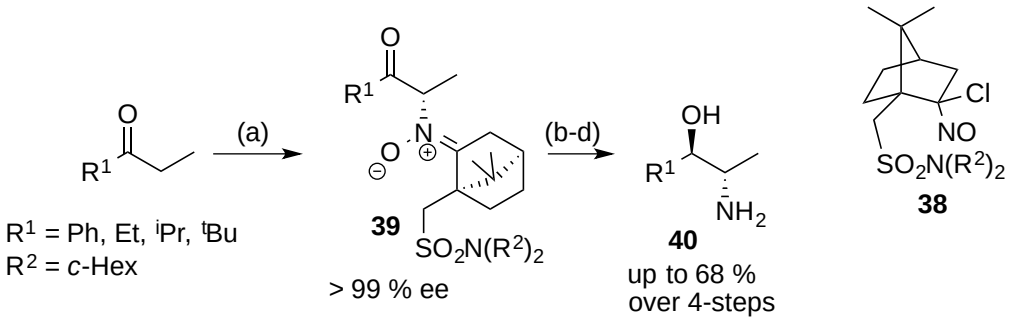
Scheme 23. Synthesis of the chiral allylating reagent **35**..

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]



Scheme 24. Enantioselective allylation of ketone-derived hydrazone **36** with **35**.

In order to produce the free amine, **37** was treated with SmI_2 and for the case of R_2 = CO_2Me gave rise to an α,α-disbstituted 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**).[37] 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.



Reagents and conditions: (a) i) LiHMDS, THF, $ZnCl_2$ ii) **38**; (b) 1N HCl; (c) $NaBH_4$, MeOH, (d) Zn (dust), 1N HCl / AcOH

Scheme 25. Enantioselective α-amination using a chiral aminating reagent.

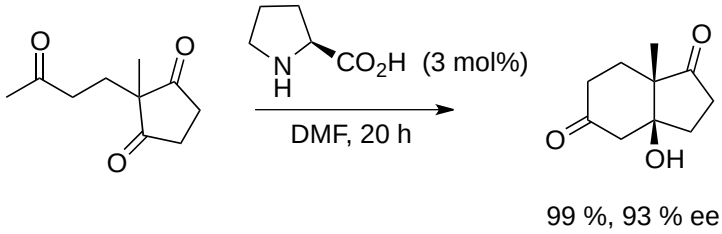
Interestingly, in spite of this work, there have been no subsequent reports of chiral aminating reagents. Overall, research in the development of chiral reagents has not received the amount of attention that might have been expected in terms of their potential impact in asymmetric synthesis.

1.6.2 Organocatalysis – Aminocatalysis[38]

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**).[39]



Scheme 26. Hajos – Parrish – Eder – Sauer – Wiechert reaction.

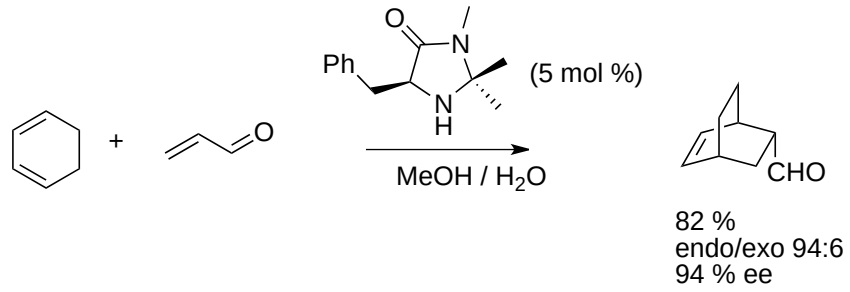
Hajos and Parish considered this work to qualify as a simple model of a biological system in which proline plays the role of the enzyme.[40]

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**).[41]

Scheme 27. Proline catalysed crossed aldol reaction of acetone and various aldehydes in excellent yield and enantioselectivity.

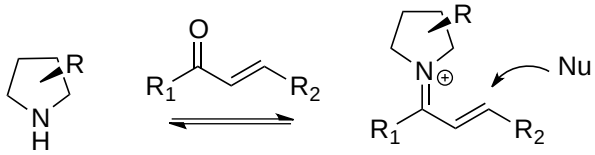
Shortly thereafter, MacMillan *et al* described the first asymmetric amine-catalysed Diels-Alder reaction (**Scheme 28**).[42] This reaction proceeded with excellent yield and an 94:6 endo/exo diasatereoselectivity as well as a 94 % ee. This work also introduced the 4-imidazolidinone catalyst (MacMillan's catalyst) to the scientific community.



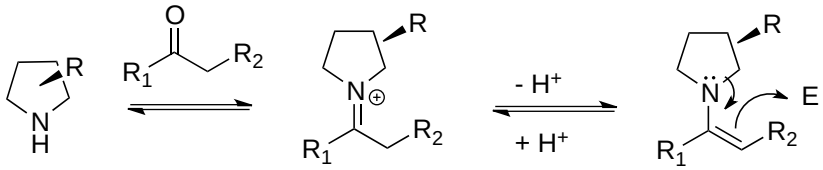
Scheme 28. The first amine catalysed asymmetric Diels-Alder reaction.

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.

Iminium ion catalysis: LUMO-lowering



Enamine catalysis: HOMO-raising



Scheme 29. Two activation modes of aminocatalysis: Iminion ion catalysis and enamine catalysis.

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.

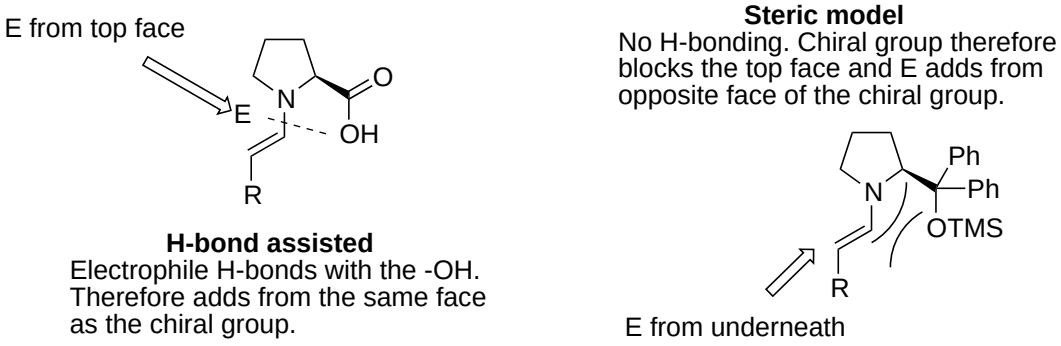
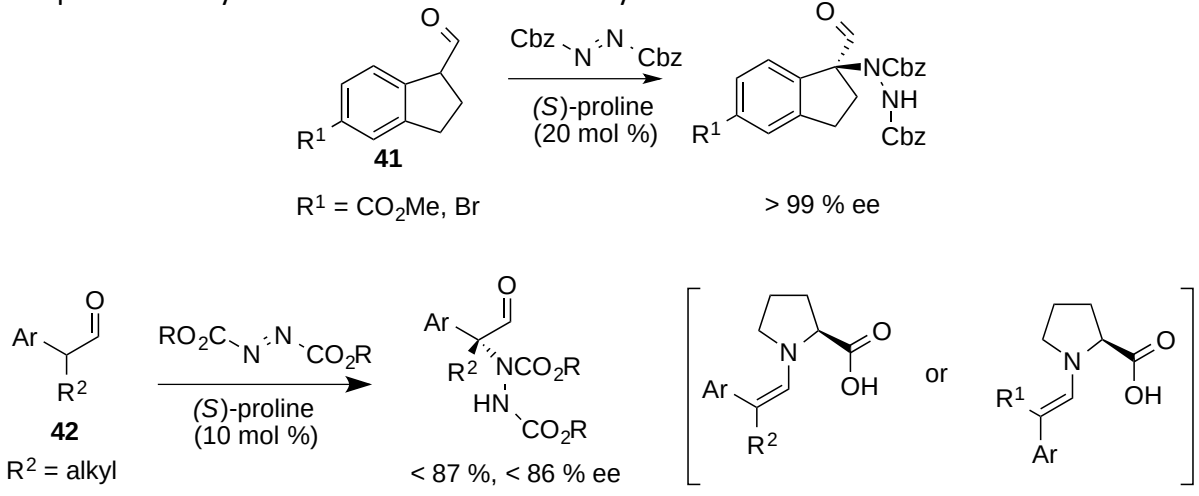


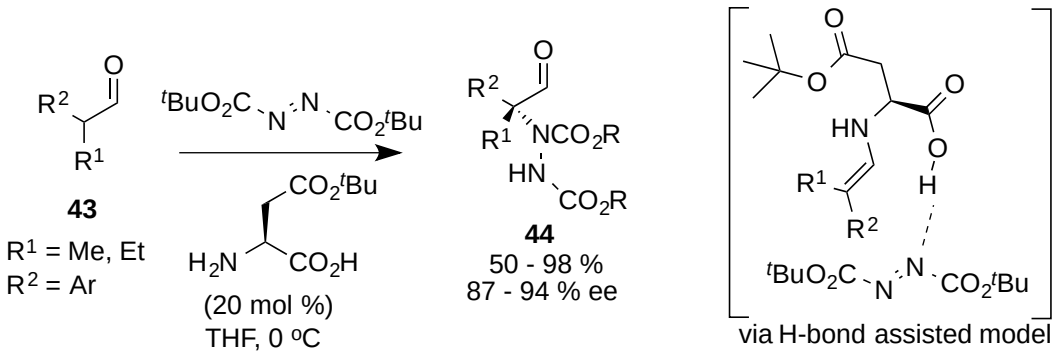
Figure 4. Modes of chiral induction.

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]



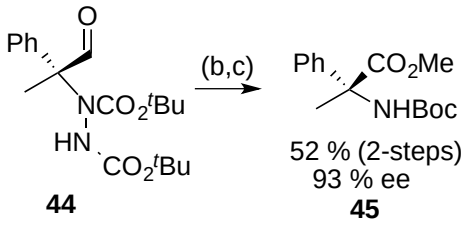
Scheme 30. Proine catalyzed α-amination of aldehydes vs ketones.

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 R_2 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 R_2 was replaced with an alkyl group, the ee dropped to ee < 65 %. Except for when R_2 = -CH_2OTBDMS, a bulking group, the ee = 89 %.



Scheme 31. Primary amine catalyzed α-amination of aldehydes.

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]



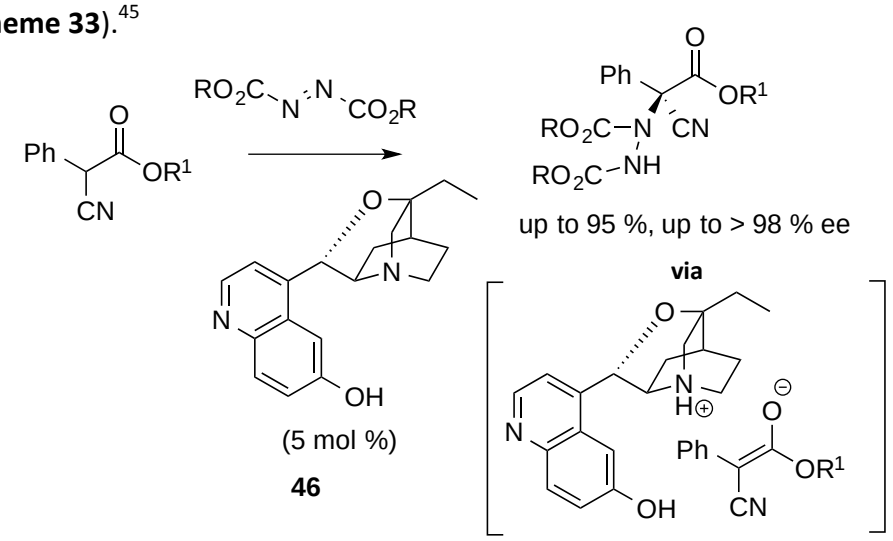
Reagents and conditions: (b) i) $NaClO_2$, H_2O_2, NaH_2PO_4 ii) $TMSCHN_2$, MeOH/EtOH, rt; (c) SmI_2, N_2, THF, MeOH, rt

Scheme 32. Conversion of **44** to the quaternary amino acid derivative **45**.

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.

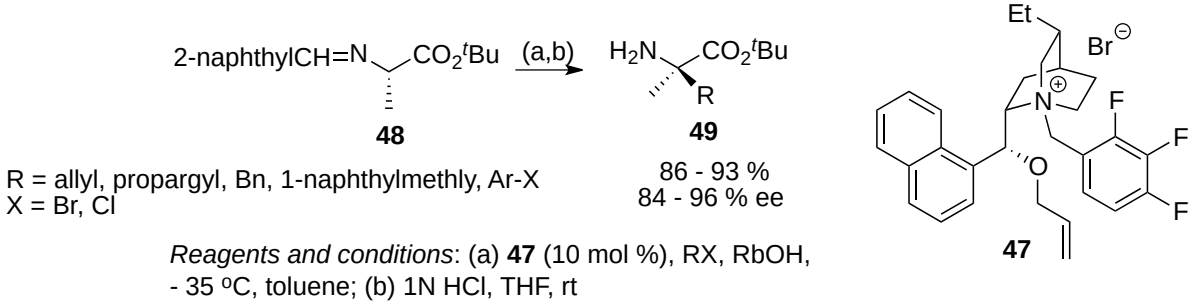
Non-covalent aminocatalysts for aza-quaternary centre construction

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]



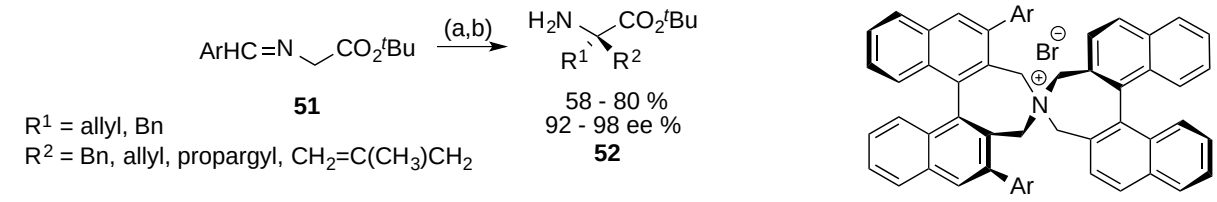
Scheme 33. Direct amination catalyzed by cinchona alkaloid derived catalysts.

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.

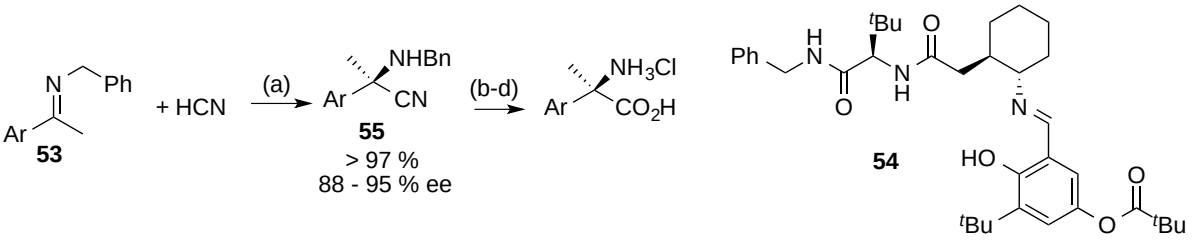
In a similar reaction, Maruoka *et al* designed a C_2-symmetric chiral quaternary ammonium bromide **50**, and applied it to the double alkylation of iminoglycinates **51** under phase-transfer catalysis to afford **52** in moderate yields and 92 – 98 % ee (**Scheme 35**).[47]



Reagents and conditions: (a) i) **50** (1 mol %), R^1Br, $CsOH.H_2O$ ii) R^2Br; (b) citric acid

Scheme 35. Enantioselective double alkylation of iminoglycinates via PTC.

The main draw-back 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 ^{t}Bu resulted in an ee % of 69 and 70 % respectively. Furthermore, if an *ortho*-substituted aromatic group was used the ee % decreased to 42 %.[48]

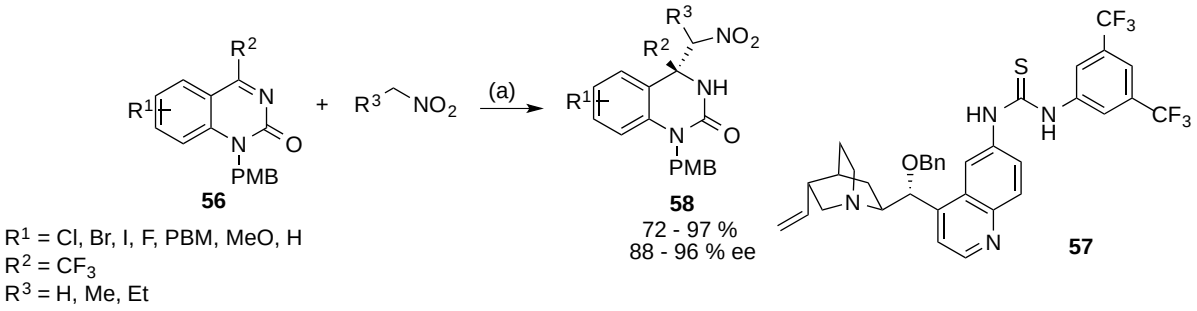


Reagents and conditions: (a) **54** (2 mol %), toluene, - 75 ^{o}C; (b) HCO_2H / Ac_2O; (c) *conc.* HCl, 105 ^{o}C; (d) H_2 / Pd-C, aq. MeOH / HCl

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

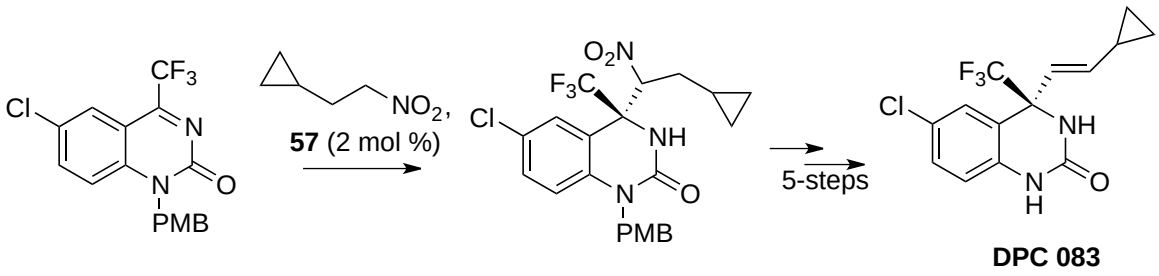
In another application of an H-bond catalyst for the synthesis of aza-quaternary motifs, Xie *et al* made use of an enantioselective aza-Henry reaction of 2(*1H*)-quinazoline (**56**) with

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**).



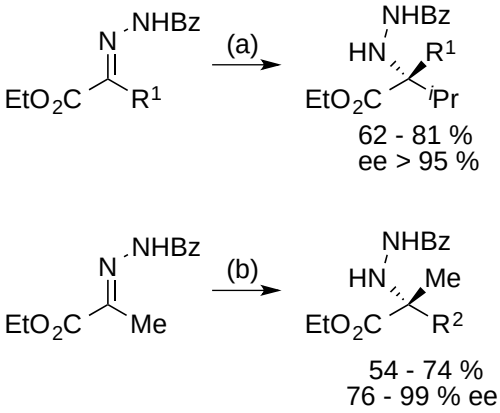
Scheme 37. Enantioselective aza-Henry reaction using bifunctional cinchona-derived cataylst **57**.

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 anit-HIV drug **DPC 083** via a key enantioselective aza-Henry reacion.

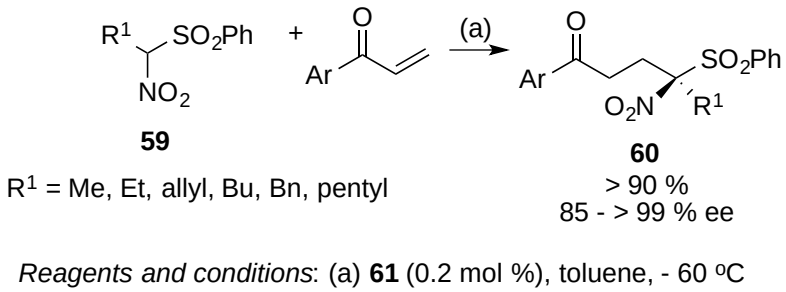
Kim *et al* have recently investigated the enantioselective radical addition to ketimines using bifunctional cinchona alkaloid catalysts for the synthesis of chiral, non-racemic quaternary amino acids (**Scheme 39**). Early reports indicate that enantioselectivities are very high for variations of the 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.



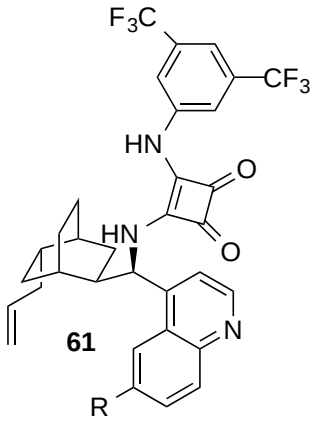
Reagents and conditions: (a) ^{i}PrI, **cat**, Ph_2SiH_2, Et_3B/O_2, $C_2H_4Cl_2$, -30 ^{o}C; (b) R^2I, **cat**, Ph_2SiH_2, Et_3B/O_2, $C_2H_4Cl_2$, - 30 ^{o}C

Scheme 39. Enantioselective radical addition to ketimines.

Another approach to aza-quarternary 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]



Reagents and conditions: (a) **61** (0.2 mol %), toluene, - 60 ^{o}C

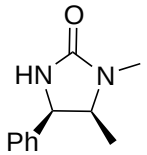


Scheme 40. Enantioselective alkylation of a stabilized carbanion via Michael-addition to vinyl ketones.

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 wont 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, (4*R*, 5*S*)-(-)-1,5-dimethyl-4-phenyl-2-imidazolidinone (**Aux**) (**Figure 5**) as the source of chiral induction.



Aux

Figure 5. Chiral 2-imidazolidinone **Aux.** The key scaffold of this thesis.

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**).

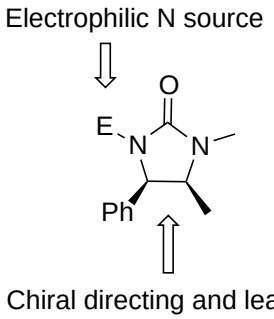


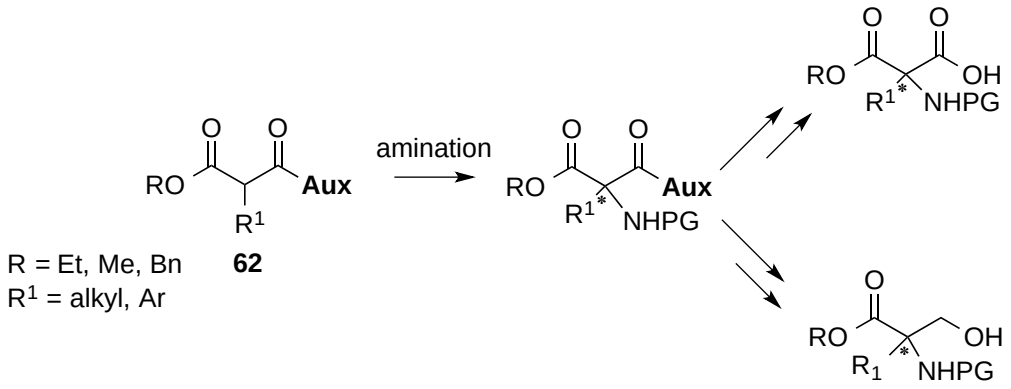
Figure 6. Envisaged chiral aminating reagent based on **Aux**.

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 susbtrate-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**).



Scheme 41. Diastereoselective amination of a chiral-malonate **62** for the synthesis of chiral, non-racemic aza-quaternary centres

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.

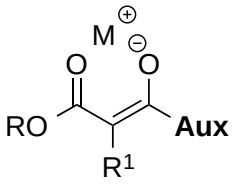


Figure 7. Envisaged metal chelation to fix the enolate geometry.

Furthermore, the auxiliary conformation around the C-N bond in the transition-state, involving either an s-*trans*$_{C\text{-}N}$ or an s-*cis*$_{C\text{-}N}$ conformation (**Figure 8**) was also considered to be of key importance. All these concepts will be addressed herein.

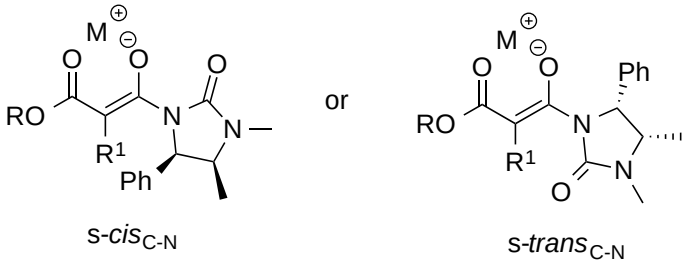


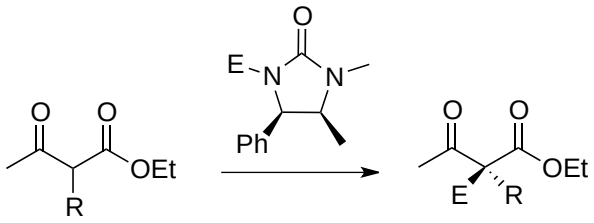
Figure 8. Auxiliary conformations in the transition-state.

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**).



63 E = nitrogen electrophile

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 know in organic synthesis via reagents of the type R_2N-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 'NH_2' 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 'NH_2' 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.

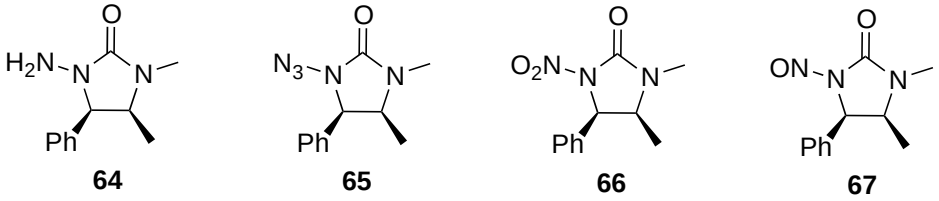
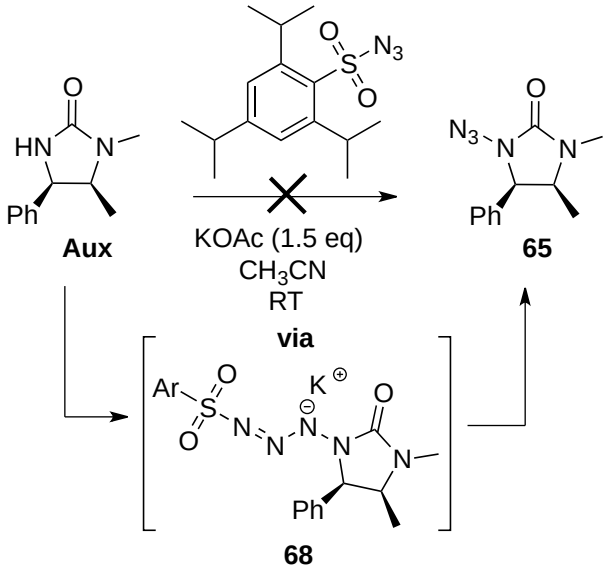


Figure 9. Imidazolidinone derivatives as possible electrophilic chiral aminating reagents**.**

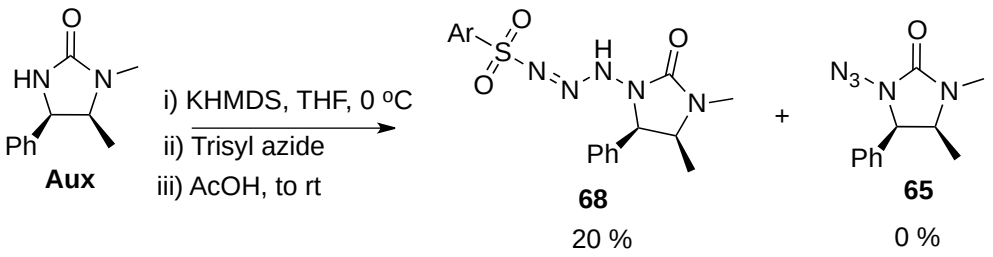
It was first decided to attempt the synthesis of **65** by reaction of **Aux** with trisyl azide. As degradation of the resulting triazene product to the desired azide is facilitated by potassium acetate, the reaction was first carried out using 1.2 eq of potassium acetate at room temperature (RT) on 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**.**

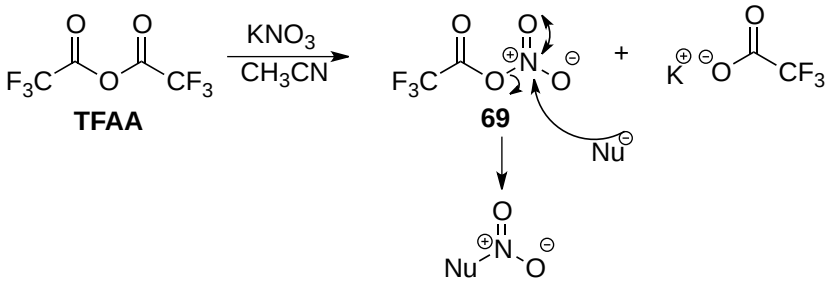
When carrying out the reaction with the much stronger base, KHMDS, in THF at 0 °C, warming to rt and quenching with acetic acid after 24 hrs in order to generate potassium acetate in situ, none of the desired azide **65** was obtained, although 20 % of **68** was isolated

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**.



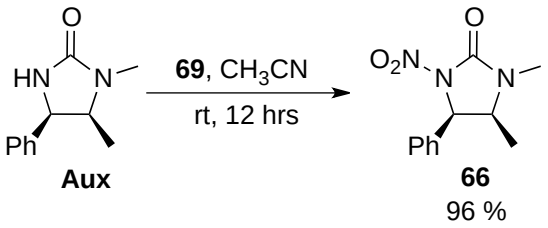
Scheme 44. Attempted azidation with the potassium anion of **Aux**.

For nitration of **Aux** using the customary H_2SO_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_2BF_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_NAc-type mechanism (**Scheme 45**).



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**).



Scheme 46. Synthesis of *N*-nitroimidazolidinone **66.**

TLC gave the first indication that a different compound was formed as **66** was much less polar that 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**).

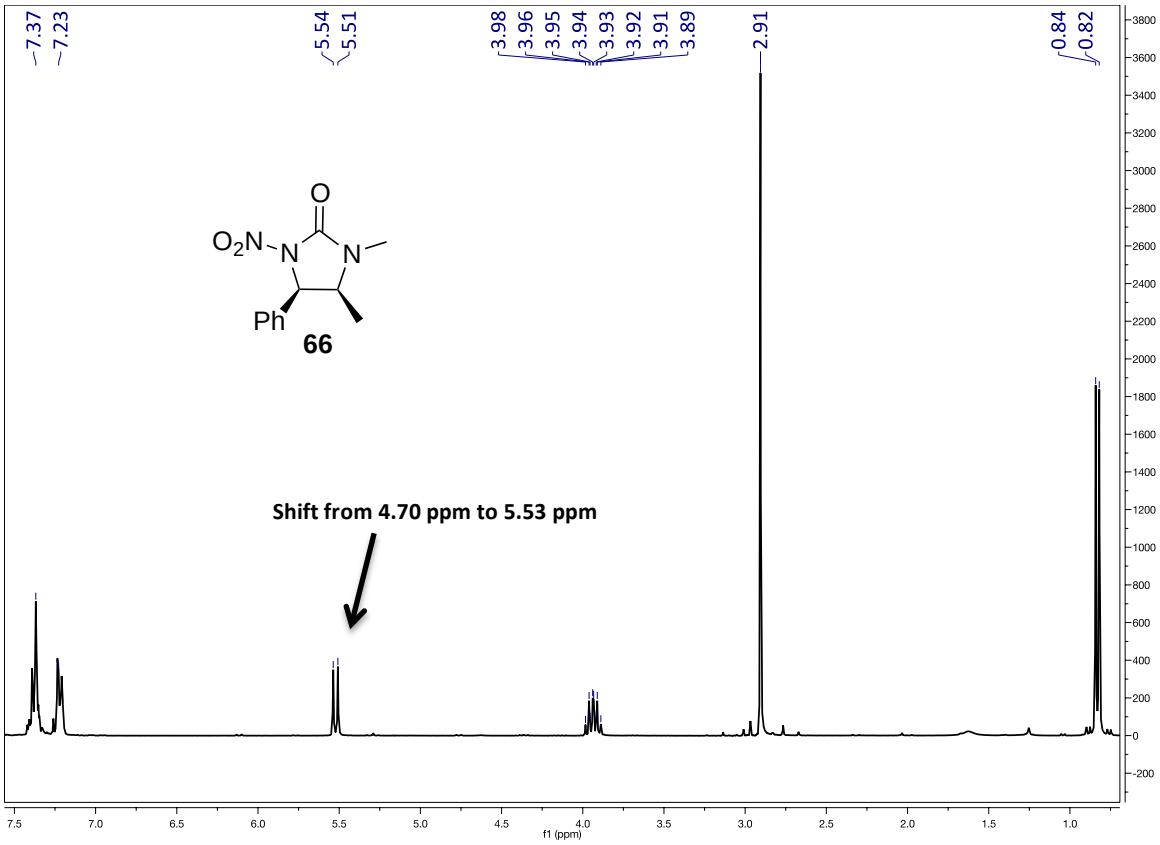


Figure 10. ^{1}H-NMR sprectum of N-Nitroimidazolidinone **66**.

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**).

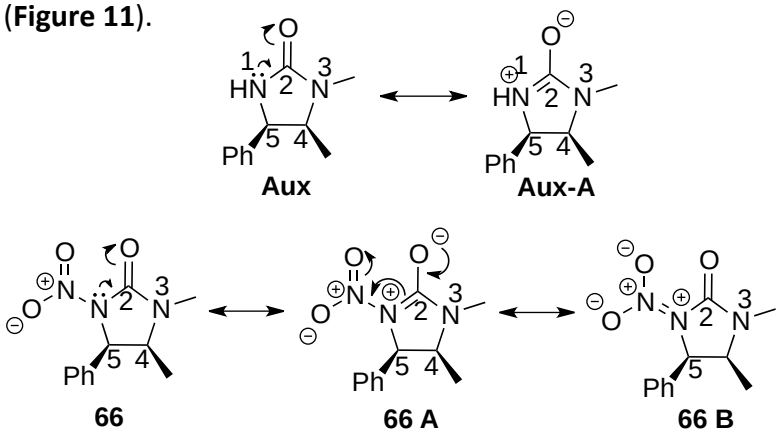


Figure 11. Main resonance contributors of **Aux** and **66**.

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.

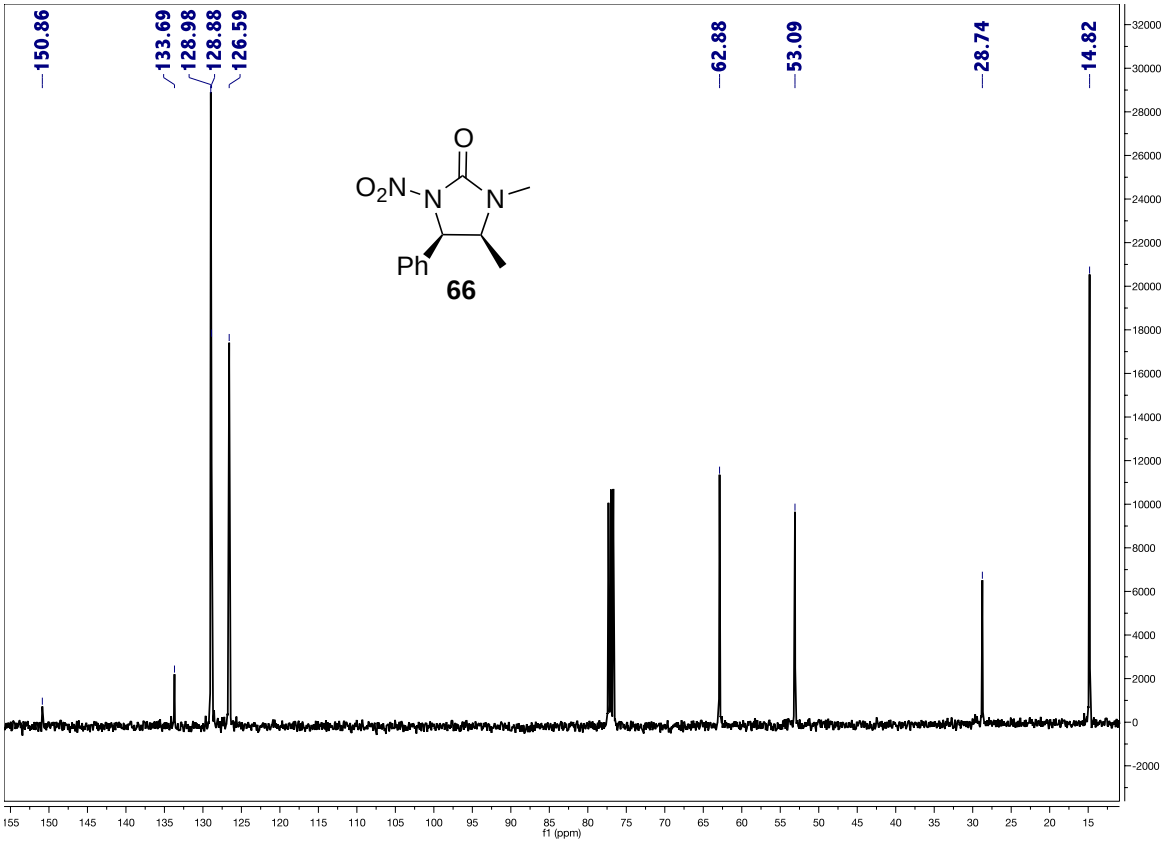
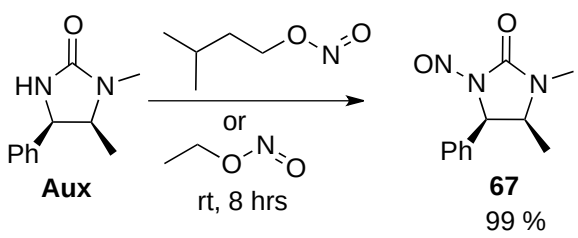


Figure 12. ^{13}C-NMR spectrum of **66**.

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**).



Scheme 47. Synthesis of **67** by reaction of **Aux** with amyl nitrite**.**

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**).

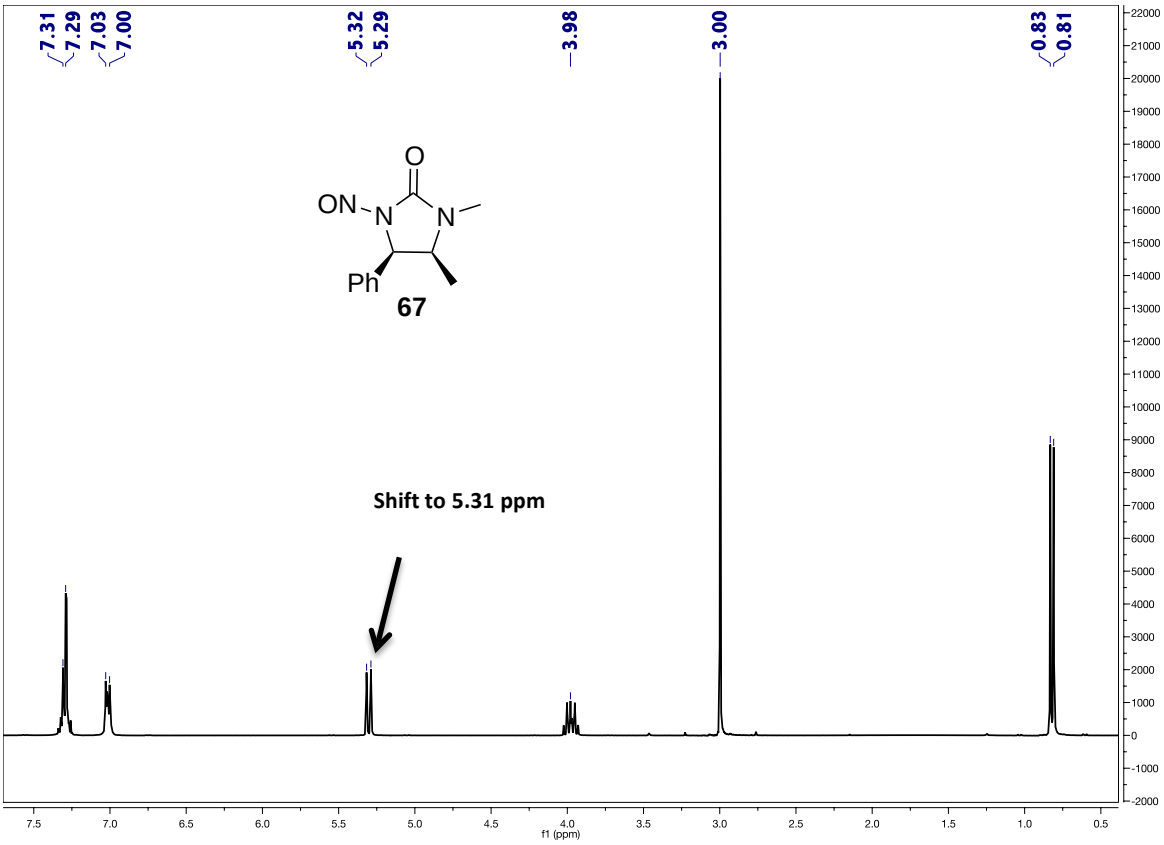
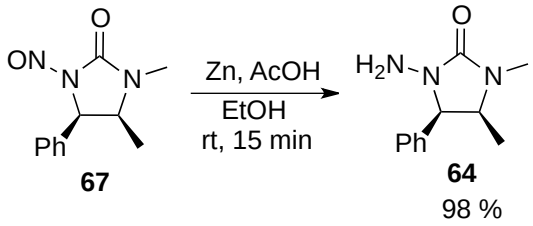


Figure 13. ^{1}H-NMR spectrum of **67.**

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**).



Scheme 48. Synthesis of hydrazide **64** via reduction of **67**.

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 H_2 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 NH_2 (**Figure 14**).

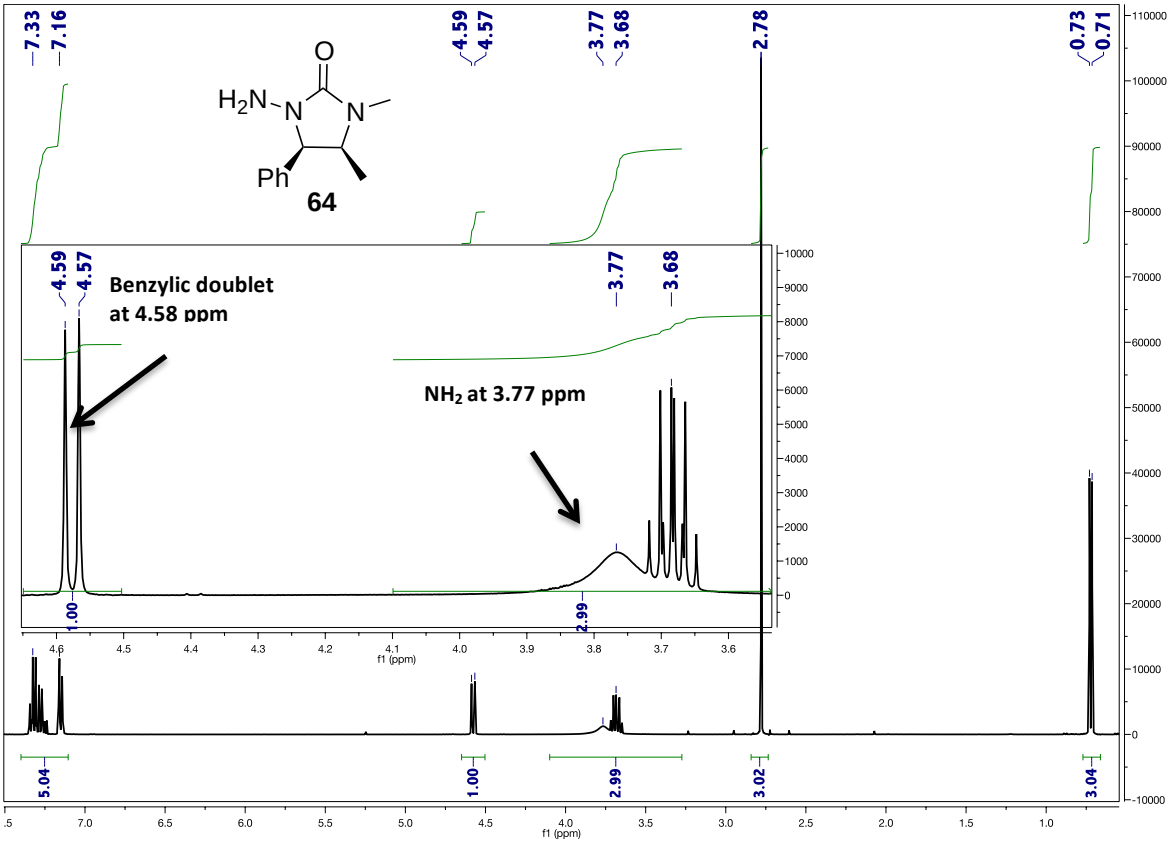


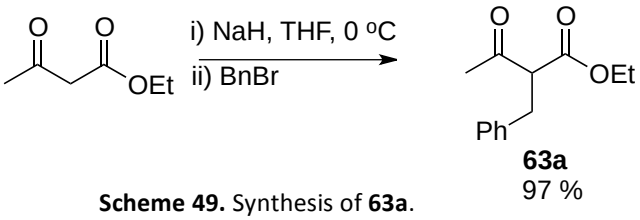
Figure 14. 1H-NMR spectrum of hydrazide **64** with an expansion of the 3.50 – 4.60 ppm range.

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 NH_2. A correct elemental analysis confirmed the correct molecular formula.

Application to the amination of β-ketoesters

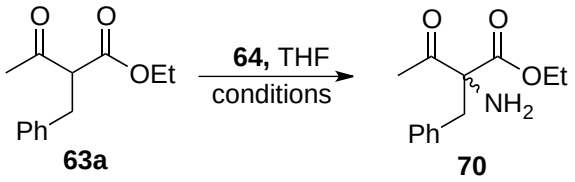
Ethyl 2-benzylacetoacetate (**63a**) was chosen as a model for a possible amination with **64**, and synthesized via C-2 benzylation of ethyl acetoacetate in 96 % yield using NaH as the base (**Scheme 49**).



Scheme 49. Synthesis of **63a**.

The ^{1}H-NMR and ^{13}C-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 1. Reactions attempted for the synthesis of **70**



Conditions	Base (1.2 eq)	Lewis acid	Temperature (°C)	Yield of 70 (%)	Recovered 64 (%)
1	NaOEt	-	reflux	0	quant.
2	NaH	-	reflux	0	quant.
3	NaH	BF_3.OEt (1 eq)	reflux	0	quant.
4	LDA	-	reflux	0	quant.
5	LDA	BF_3.OEt (1 eq)	reflux	0	quant.
6	KHMDS	-	reflux	0	quant.
7	KHMDS	BF_3.OEt (1 eq)	reflux	0	quant.

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).

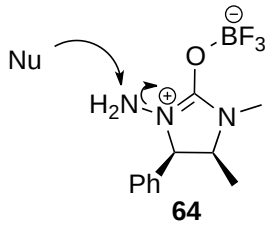
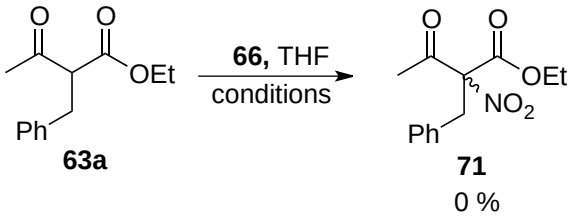


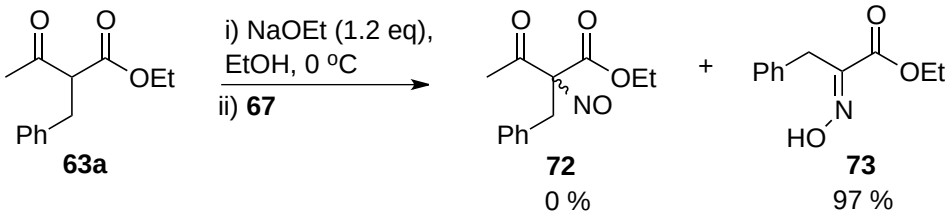
Figure 15. Envisaged lewis acid assisted transfer of **64** to an incoming nucleophile.

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. Envsiaged enantioselective nitration of **63a** to afford **71.**

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**).



Scheme 51. NaOEt mediated reaction of **63a** with **67**.

It was postulated that **72** does indeed form, but is quickly converted to **73** via a base-mediated deacetylation (**Figure 16**).

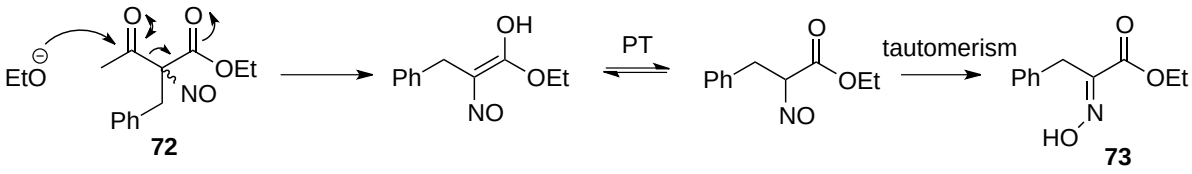
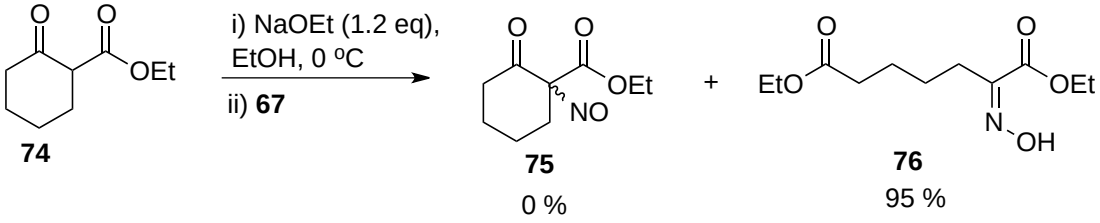


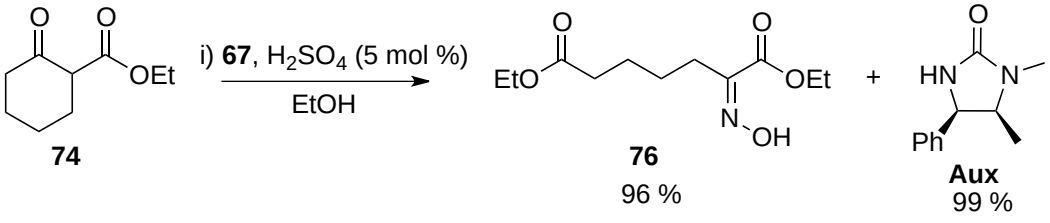
Figure 16. Suggested deacylation of **72** to form oxime **73**.

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**).



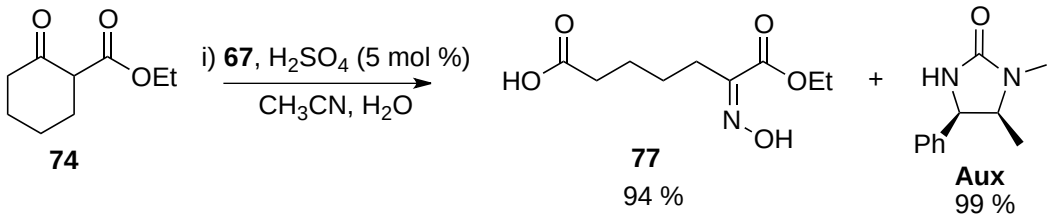
Scheme 52. Reaction of **74** and **67** with NaOEt.

The reaction could also be brought about by an acid-catalyzed process. Hence, reaction of **74** with **67** and 5 mol % H_2SO_4 in EtOH also gave **76** within 10 min, which was isolated in 96 % yield (**Scheme 53**).



Scheme 53. Acid catalyzed reaction of **74** with **67** also afford the undesired oxime **76.**

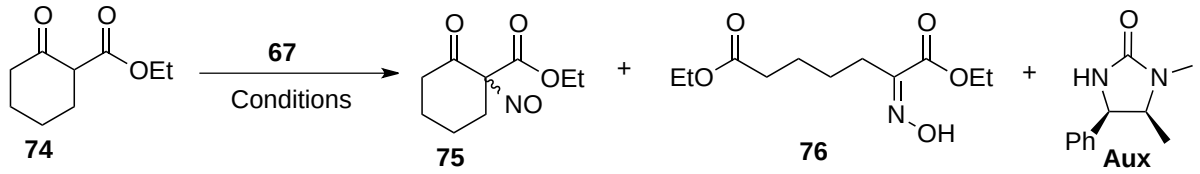
This indicated that fragmentation could also be promoted by acid-catalyzed activation of the carbonyl group followed by attack by the poorly nucleophilic EtOH (**Scheme 53**). Presumably, the ketone carbonyl group electrophilicty is also enhanced by the electron-withdrawing nitroso group. To provide 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).

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.

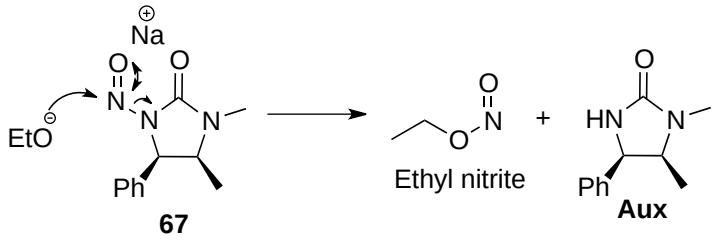
Table 2. Reaction of **74** with **67** under various conditions



§	Base / Acid	Solvent	Eq	Yield 75 (%)	Yield 76 (%)	Aux recovered (%)
1	NaOEt	EtOH	1.2	0	91	98
2	H_2SO_4	EtOH	0.05	0	94	97
3	NaH	THF	1.2	0	0	0[a]

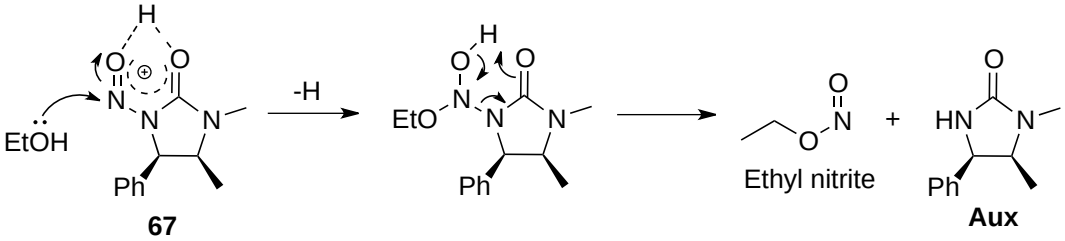
[a] **67** completely recovered

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**.



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**).



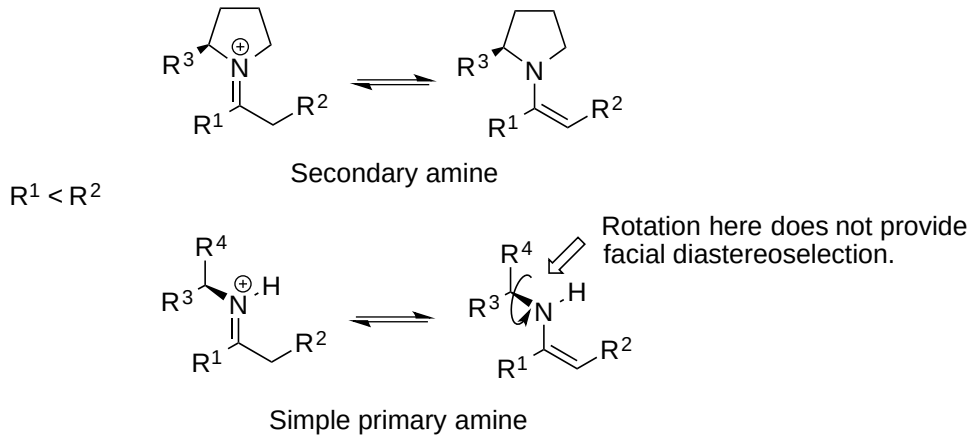
Scheme 56. Denitrosation of **67** to afford ethyl nitrite under acid catalysis.

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.

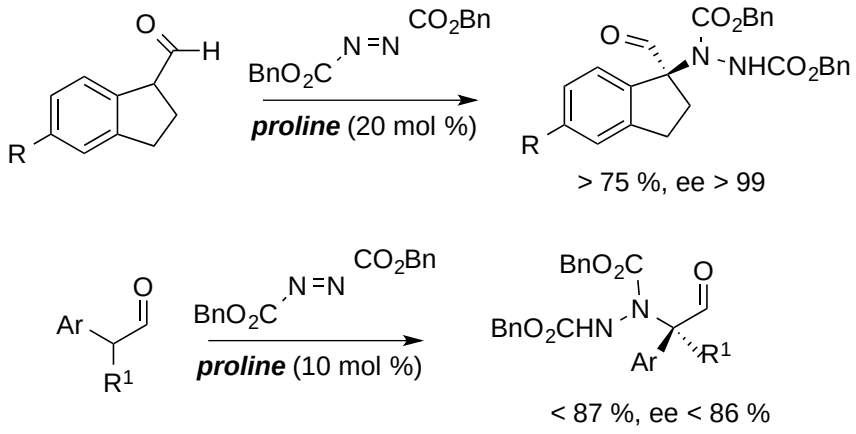
2.2 Aminocatalysis Approach

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**).



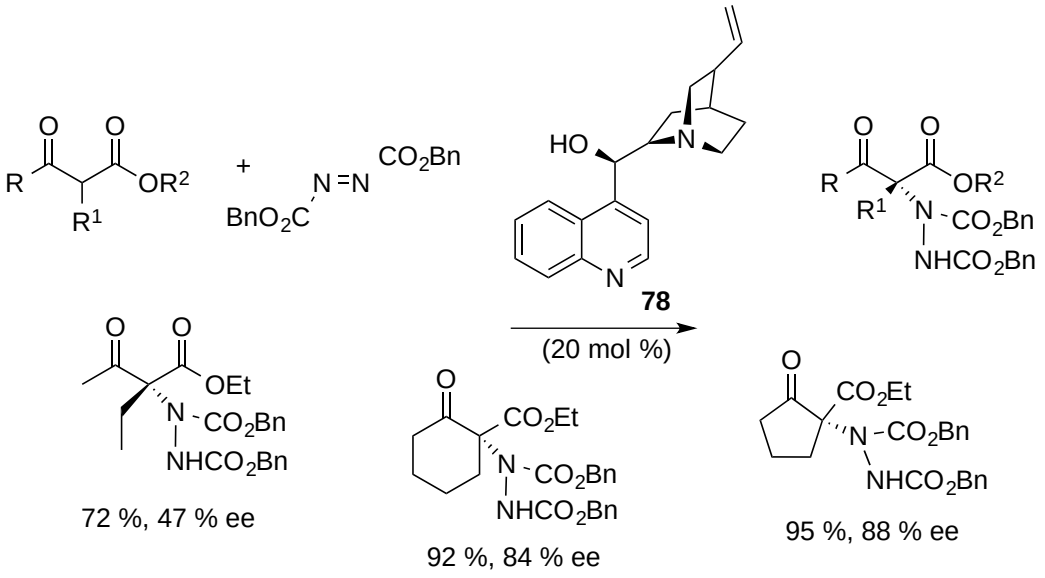
Scheme 57. Rotational freedom of simple primary amines restricts efficient facial selectivity.

Secondary amines have shown some success in the enantoselective 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.



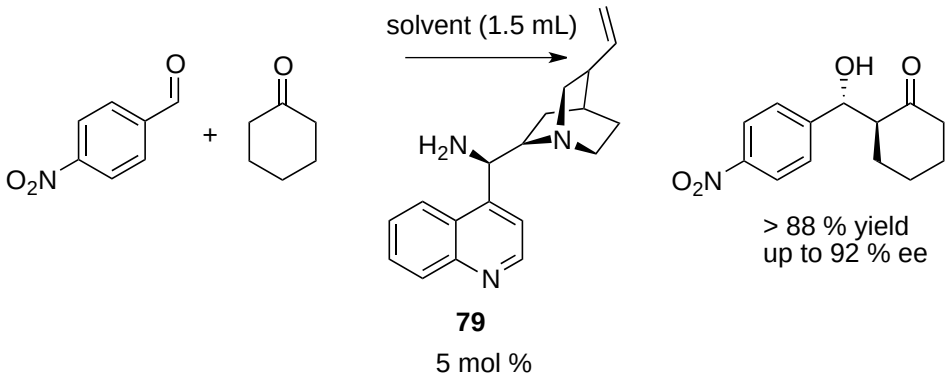
Scheme 58. Varied success of secondary amines in the α-amination of carbonyl compounds.

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.



Scheme 59. α-Amination of β-keto esters by cinchona alkaloids.

Cinchona alkaloid-derived primary amines have also been developed and were shown to effectively catalyze enantioselective aldol reactions (**Scheme 60**).



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

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**).

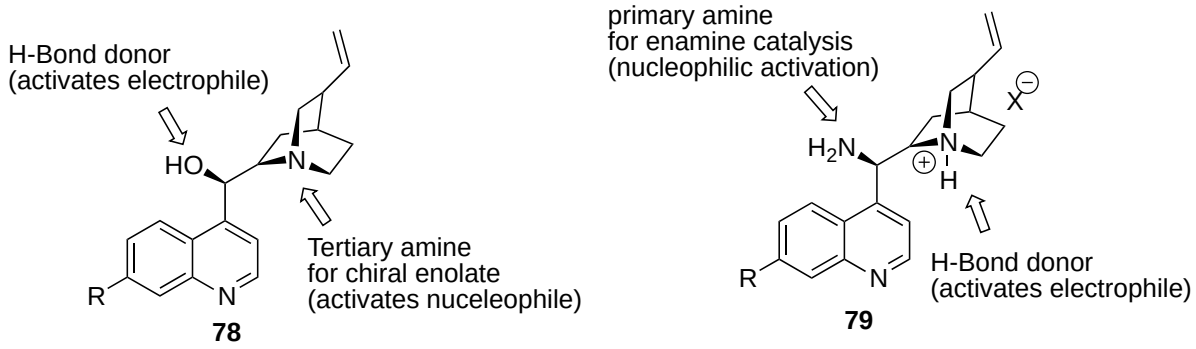


Figure 17. Bifunctional characteristics of cinchona alkaloid derivatised aminocatalysts.

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**).

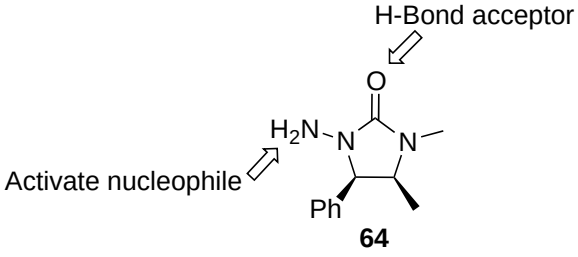
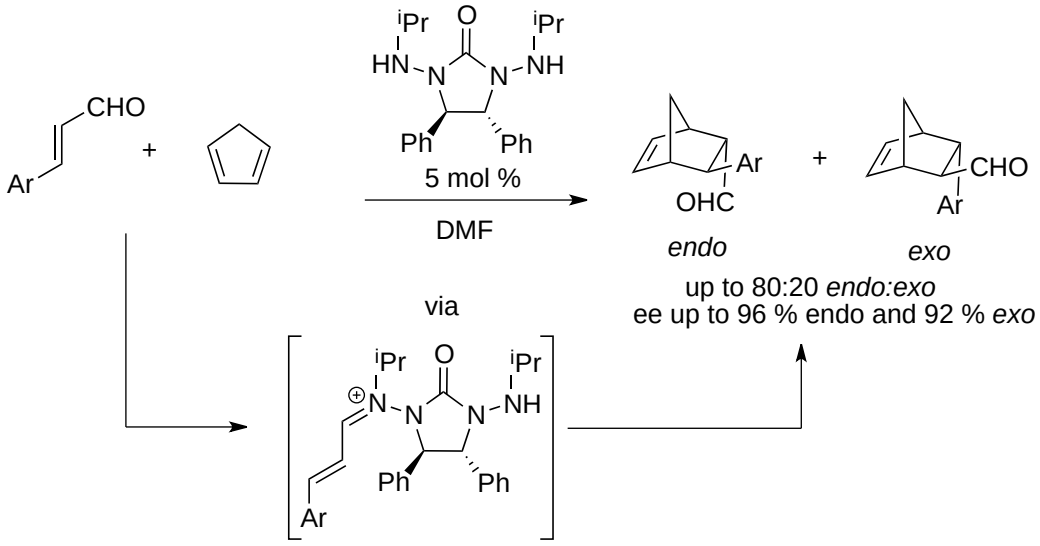


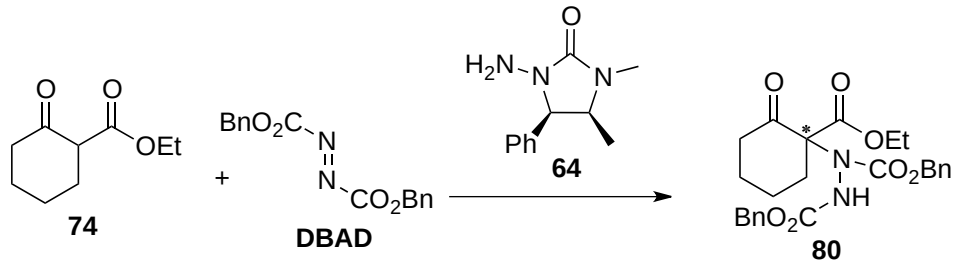
Figure 18. Envisgaed bifunctional characteristics of **64** to restrict rotational degrees of freedom.

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.

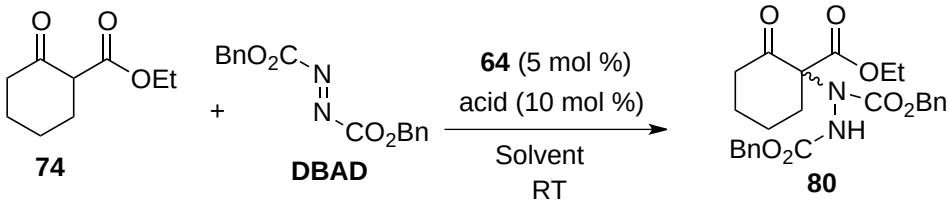
As this was the first usage of a chiral hydrazide as an enamine catalyst it was decided to use a known organocatalytic α-amination transformation as a basis for development. The azodicarboxylates have been successfully applied to the enantioselective α-amination of various carbonyl compounds, including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



Scheme 62. Envisaged α-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** summaries the results.

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



Entry	Catalyst (5 mol %)	Acid (10 mol %)	Solvent	Time	Conversion of 22 % (TLC)	Yield % (isolated)	ee % (HPLC)
1	none	TFA	IPA	120h	0[a]	0	-
2		*p*- TsOH	IPA	120h	0[a]	0	-
3		TfOH	IPA	18 h	100	85	0
4		TFA	DCM	120h	0[a]	0	-
5		*p*- TsOH	DCM	120h	0[a]	0	-
6	**64**	TFA	IPA	96h	70 %	65	67
7		**TFA**	**DCM**	**60 hrs**	**100 %**	**92**	**68**
8		TFA	THF	120h	60 %	50	67
9		none	DCM	144h	0[a]	0	-
10		*p*- TsOH	DCM	72 h	100 %	90	64
11	**Proline**	TFA	DCM	144h	0[a]	0	-
12	**Leu**	TFA	DCM	5 d	0[a]	0	-

[a]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 ^{1}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.

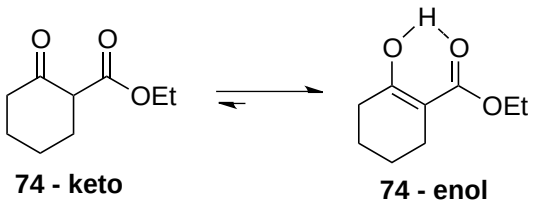


Figure 19. Keto-ester **74** exists predominantly in the enol form.

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).

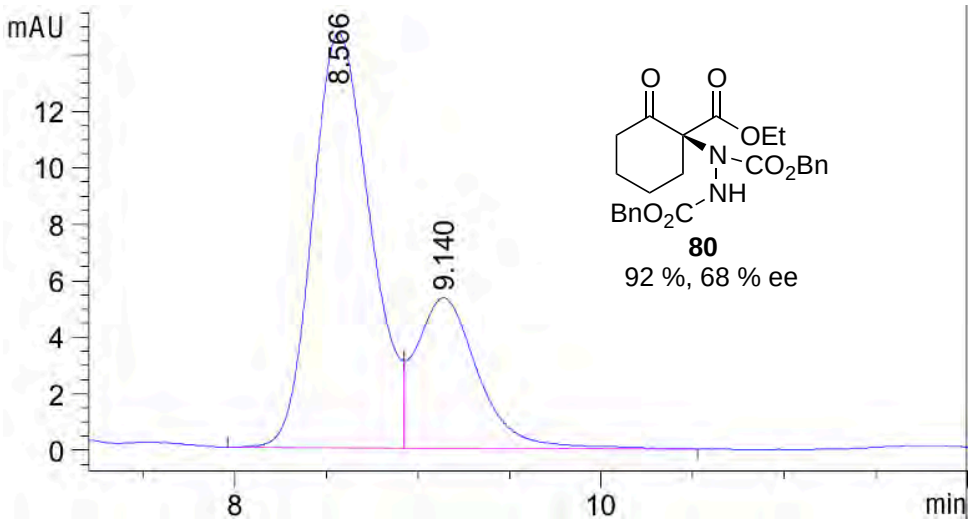


Figure 20A. HPLC trace **80** obtained in 68 % ee.

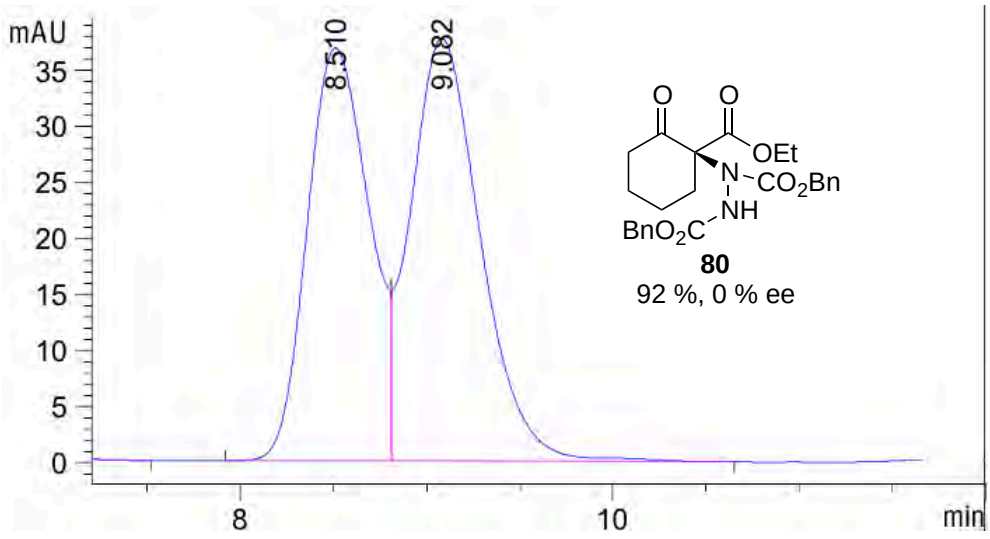
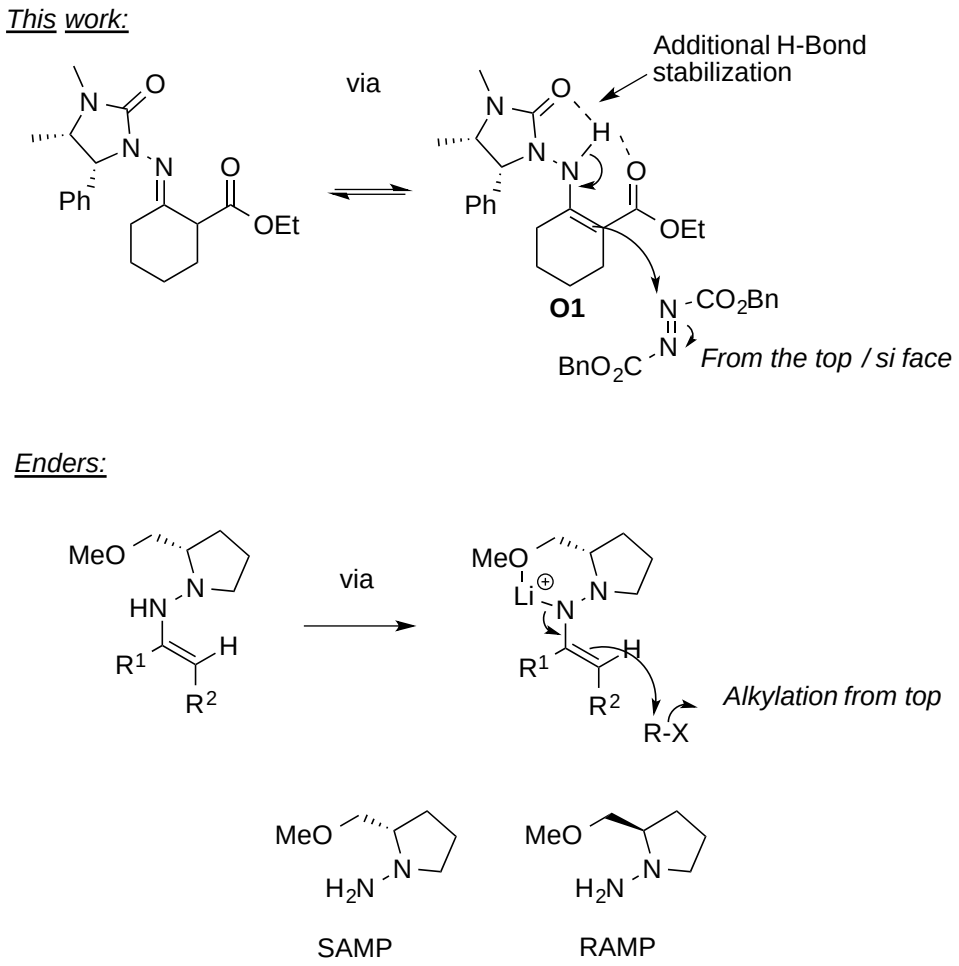


Figure 20B. HPLC trace of the **80** obtained as a racemate.

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 $[\alpha]_D$ obtained for **80** was compared to that of the literature[54], 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 method[21e] (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**).

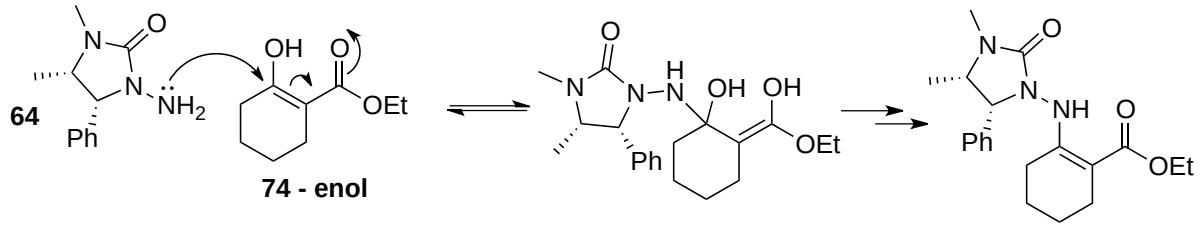


Figure 21. Postulated imine formation via a Michael addition to enol **74**.

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.[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 interepreted as the HOMO being raised relative to that in a molecule not possessing an α-hetereoatom, 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-NH_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.[56]

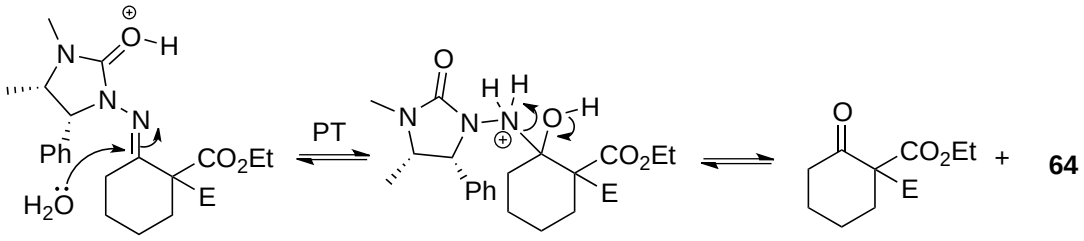
Next, optimizations to determine the ideal catalyst and TFA loading was carried out as shown in **Table 4**. Reaction times were based on complete conversion of the starting material (by TLC) followed by quenching immediately.

Table 4: Optimization of catalyst and TFA loading.

Entry	Mol % 14	Mol % TFA	Time	Ee % (HPLC)
1	5	5	72 hrs[b]	67
2	5	10	60 hrs[b]	67
3	5	20	50 hrs[b]	68
4	10	10	60 hrs[b]	68
5	20	10	60 hrs[b]	68
6	**5**	**10**	**10 hrs**[c]	**68**
7	5	20	10 hrs[c]	67
8	5	100	9 hrs[c]	66

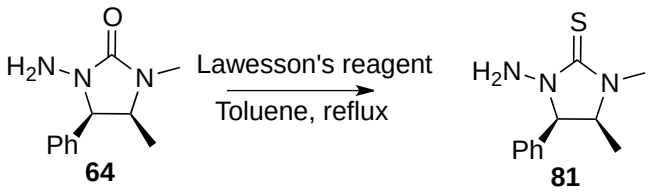
[a]Monitored by TLC. [B]Concentration of the reaction mixture = 0.33 M. [c]Concentration of the reaction mixture = 0.67 M

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.

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**.

The ^{1}H-NMR spectrum of **81** was expected to be more or less identical to **64** and therefore ^{13}C-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**).

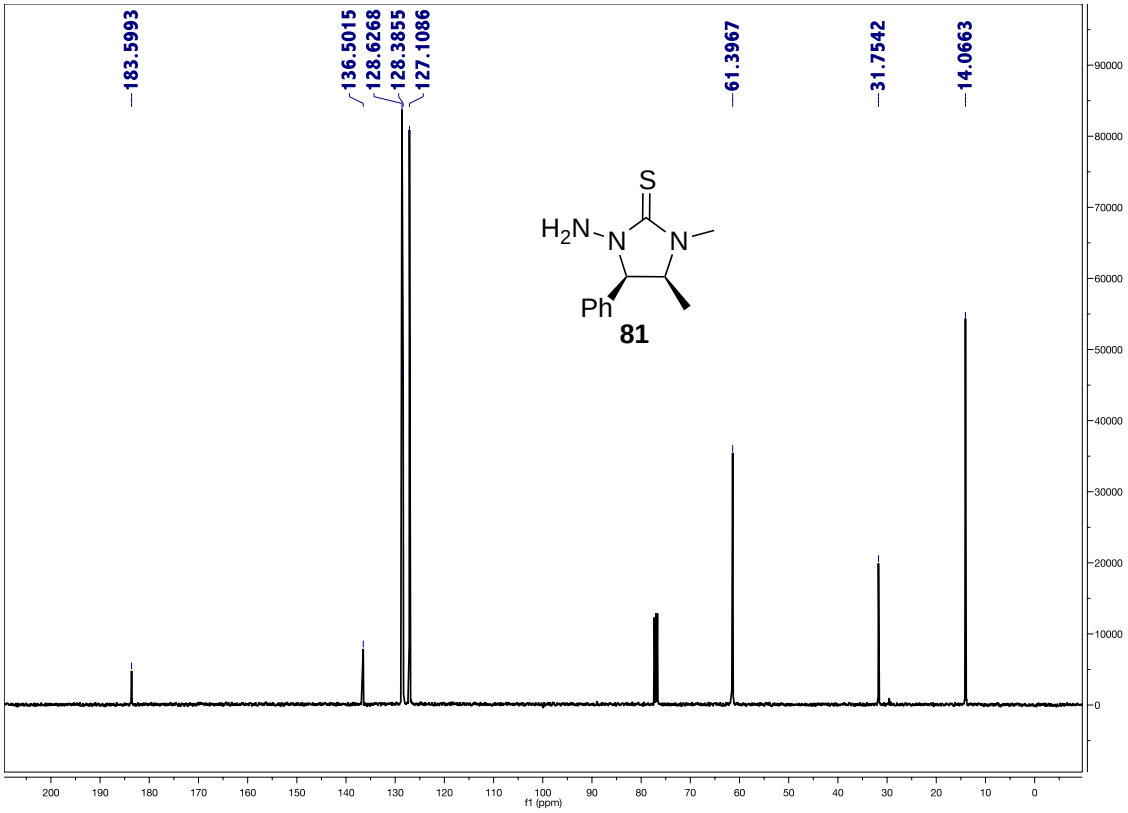


Figure 22. ^{13}C-NMR spectrum of **81**.

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**).

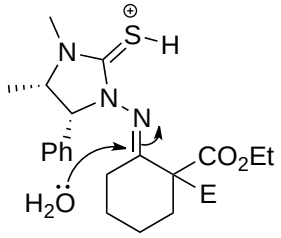


Figure 23. Activation of **81** by protonation

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:

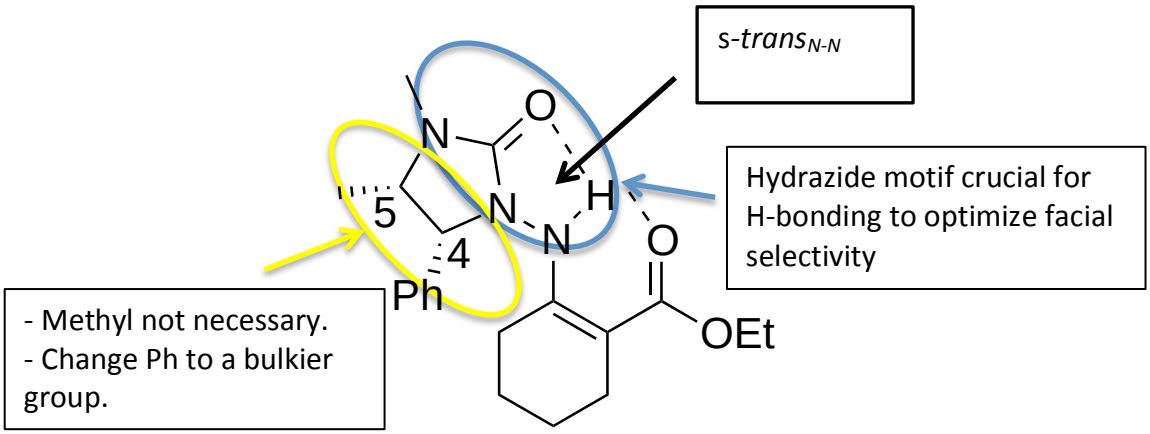
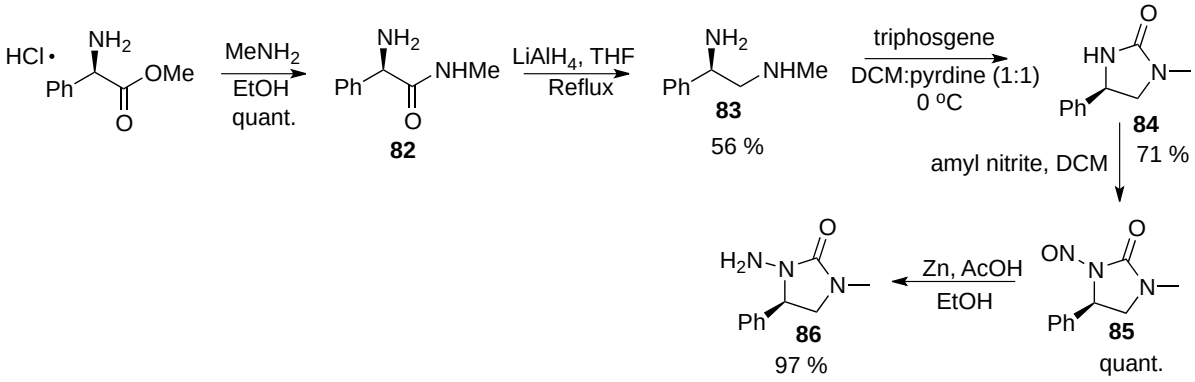


Figure 24. SAR results of **64**.

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**).



Scheme 66. Synthesis of hydrazide **84** from (*R*)-(-)-2-Phenyl glycine methyl ester hydrochloride.

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 $LiAlH_4$ followed by cyclization of the diamine product with triphosgene to afford imidazolidinone **84** (approx. 60 % over 2-steps). The ^{1}H-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 ^{1}H-NMR

spectrum (**Figure 25**) was assigned accordingly and elemental analysis of a recrystallized sample confirmed its molecular formula.

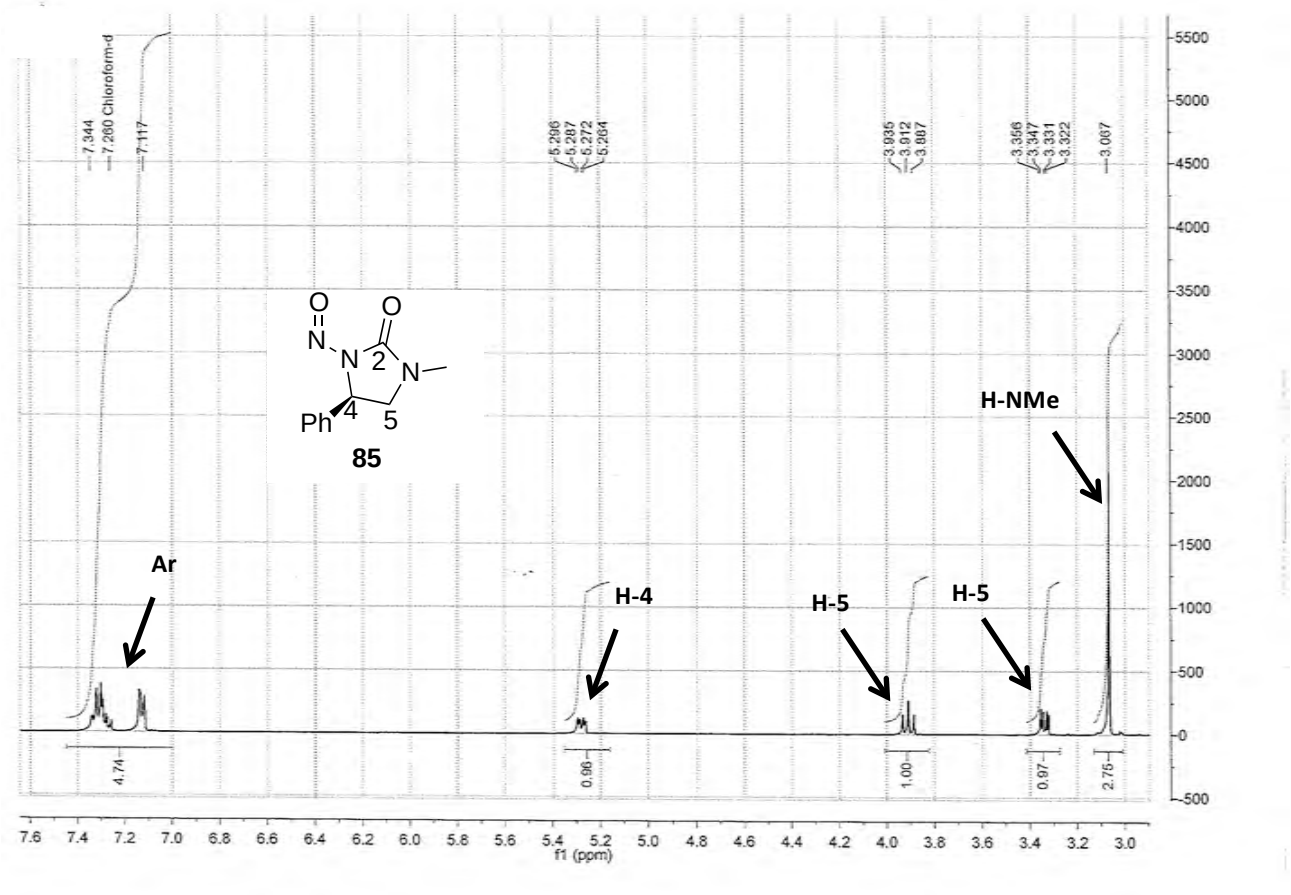
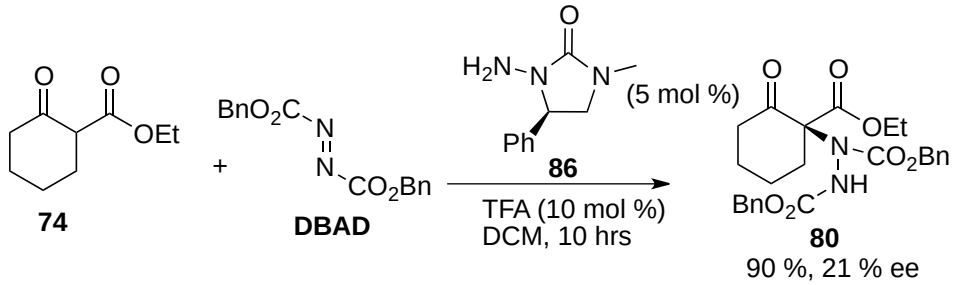


Figure 25. ^{1}H-NMR spectrum of **85**.

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.

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**).

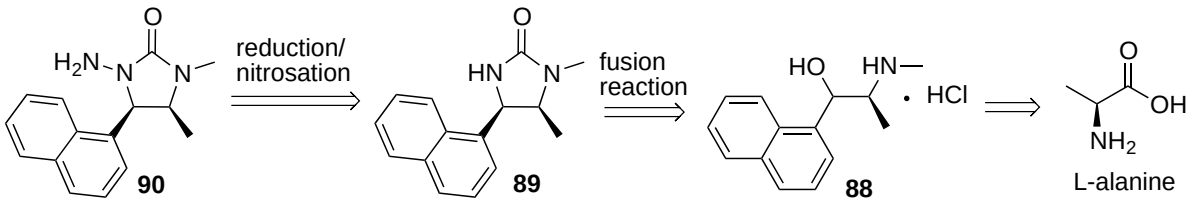
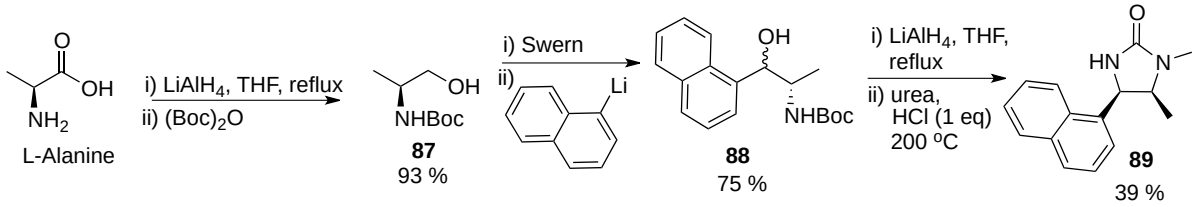


Figure 26. Retrosynthetic analysis for the synthesis of hydrazide **90**.

For the synthesis of imidazolidinone **89** (**Scheme 68**), the first step involved the reduction of L-alanine with $LiAlH_4$ 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 ^{t}BuLi 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 ^{1}H-NMR spectrum.



Scheme 68. Synthesis of imidazolidinone **89**.

Target imidazolidinone **89** was then obtained as a single diastereomer in 39 % yield (over 2-steps) by $LiAlH_4$ reduction of **88** and after work-up, the resulting ephedrine derivative reacted with urea with 1 eq. HCl at 200 °C. The ^{1}H-NMR of **89** in $CDCl_3$ (**Figure 27**) confirmed its synthesis.

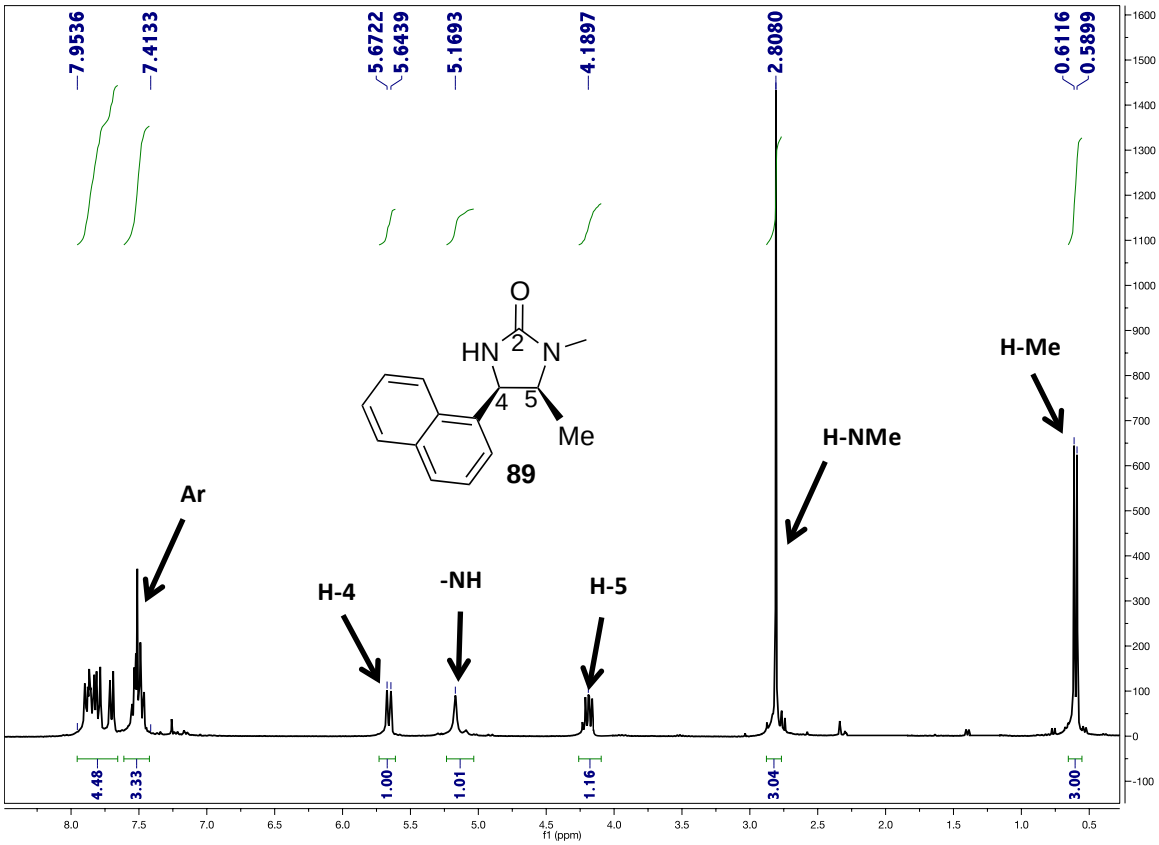
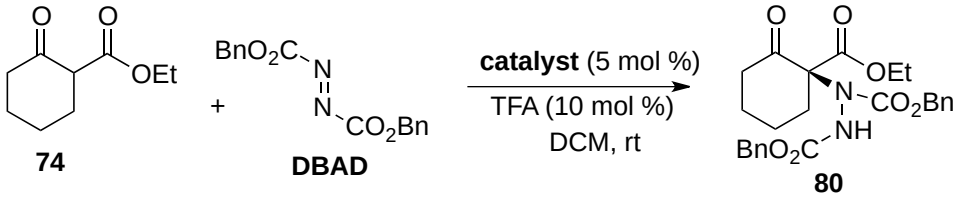


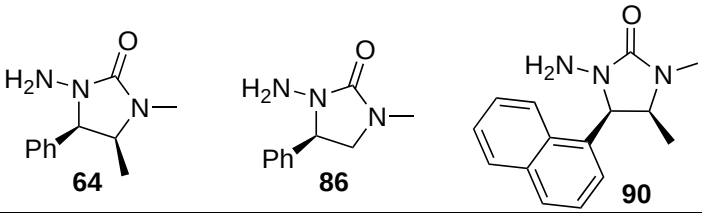
Figure 27. ^{1}H-NMR spectrum of imidazolidinone **89**.

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 S_N1 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.





Entry	Catalyst	Yield 25 (%)[a]	Ee (%)[b]
1	**64**	92	68
2	**86**	90	21
3	**90**	93	17

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

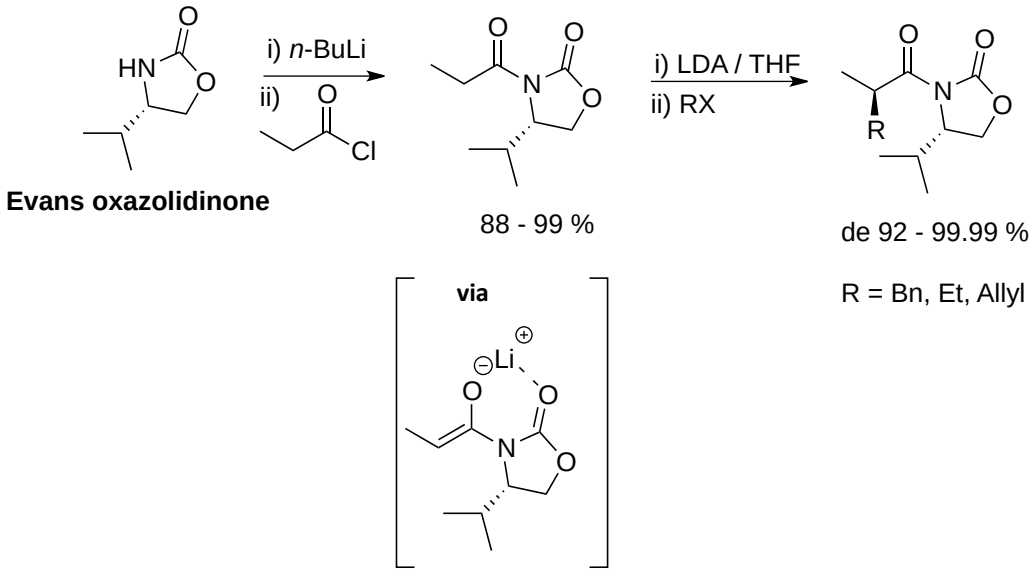
At this point the variation in the ee between the different substrates was extremely puzzling and due to time constraints, investigations including the use of computational modeling were not conducted. This will be a topic for future work.

Chapter 3

Aza-Quaternary Centres via Diastereoselective α-Azidation

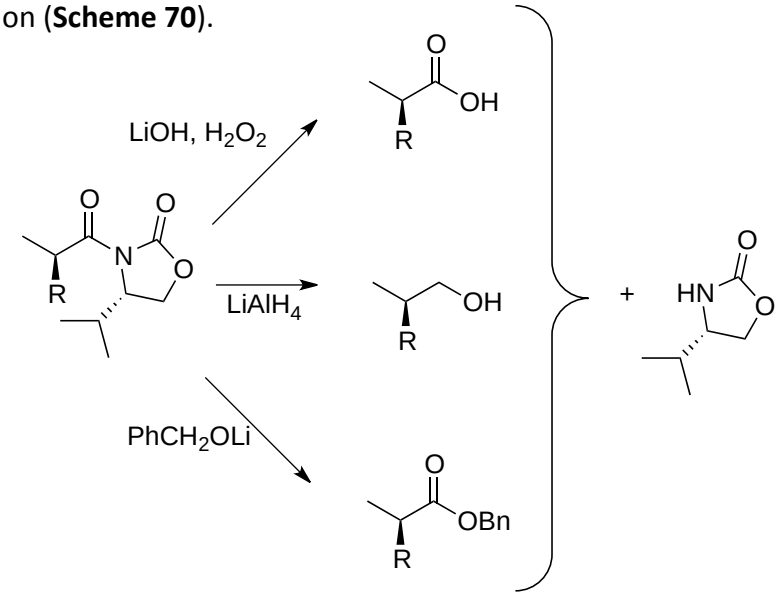
3.1 Chiral Auxiliaries

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[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**.[15,57]



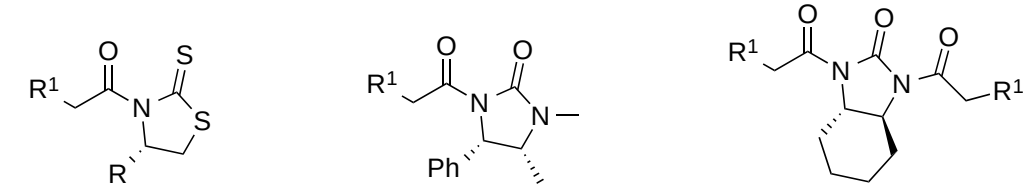
Scheme 69. Synthesis and diastereoselective alkylation of a propionic acid-oxazolidinone derivative in excellent de.

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.

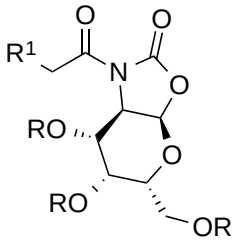
This work marked the start of a rich era of asymmetric synthesis, as many other chiral auxiliaries were subsequently developed based on the same motif (**Figure 28**).[58]



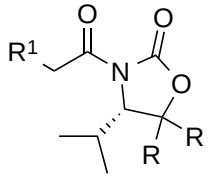
Fujita / Nagao (1985)

Cardillo (1988)

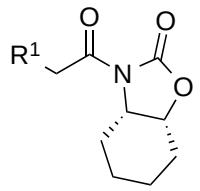
Davies (1991)



Kunz (1992)



Seebach (1998)



Parrodi (2001)

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**.

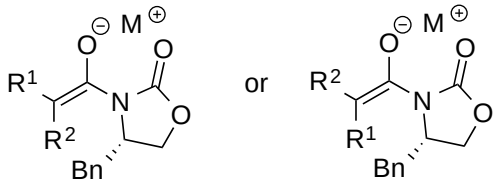
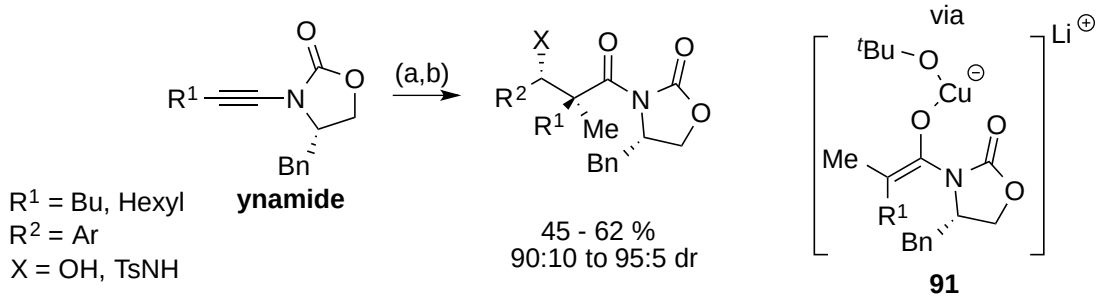


Figure 29. Enolate geometry problem of disubstituted acyloxazolidinones.

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-disubstitued chiral enolate starting from a simple acyclic chiral **ynamide** involving a copper catalyszed 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).



R^1 = Bu, Hexyl
R^2 = Ar
X = OH, TsNH

ynamide

45 - 62 %
90:10 to 95:5 dr

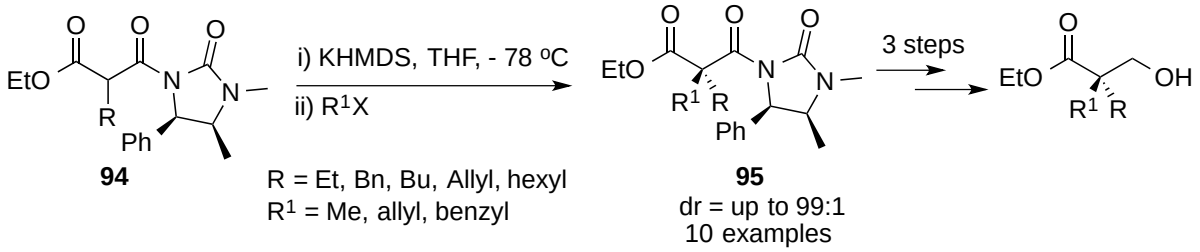
91

Reagents and conditions: (a) i) $Me_2CuLi.LiBr.SMe_2$, Et_2O, - 40 ^oC
ii) *t*-BuOOH, - 80 ^oC; (b) i) R^2CHO or TsN=CHR, - 80 ^oC, ii) H_3O^+

Scheme 71 Disubstituted enolate geometry control obtained through carbometalation-oxidation sequence.

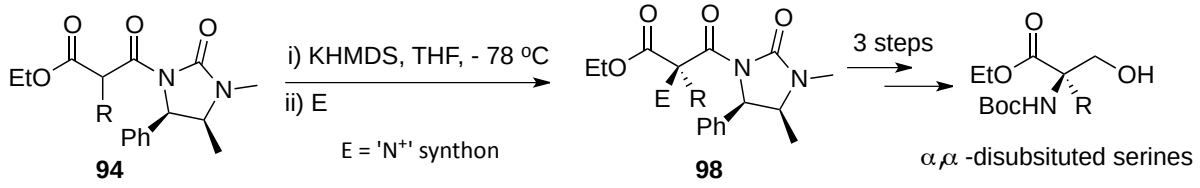
3.3 Rationale for Research Conducted

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-disubustituted β-hydroxy ester in three steps, (**Scheme 72**).[61] Transition-state models for this methodology will be discussed later.



Scheme 72. Stereoselective formation of chiral quaternary centres by diastereoselctive alkylation of chiral malonate-imidazolidinones **94**.[61]

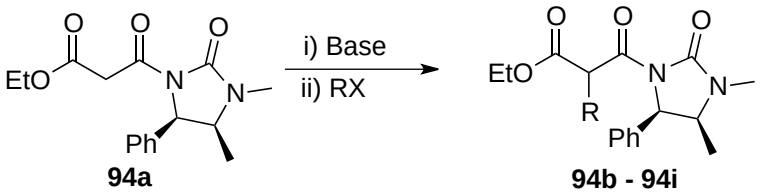
It was envisaged that this methodology could be extended to the stereoselective construction of chiral aza-quaternary centres by replacing the alkylating agent with a nitrogen electrophile (E) in an amination process to produce a product bearing an aza-quaternary centre (**98**), which would then be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

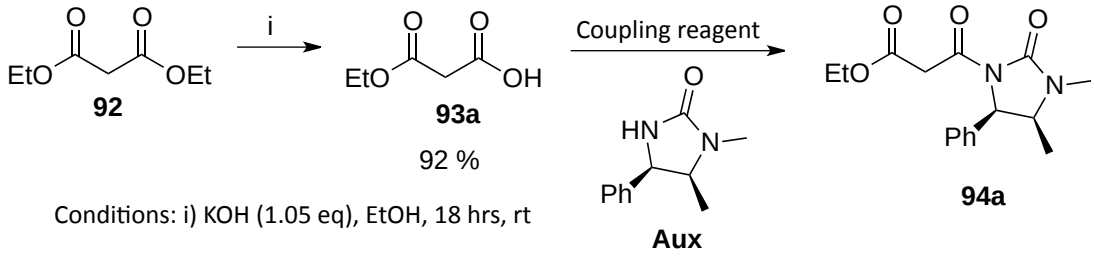
3.4 Synthesis of Chiral Malonate-Imidazolidinones 94.

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.



Scheme 74. Divergent approach for the construction of substituted malonate - imidazolidinones **94b - 94i**.

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.



Scheme 74. Synthesis of chiral malonate – imidazolidinone **94**.

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.

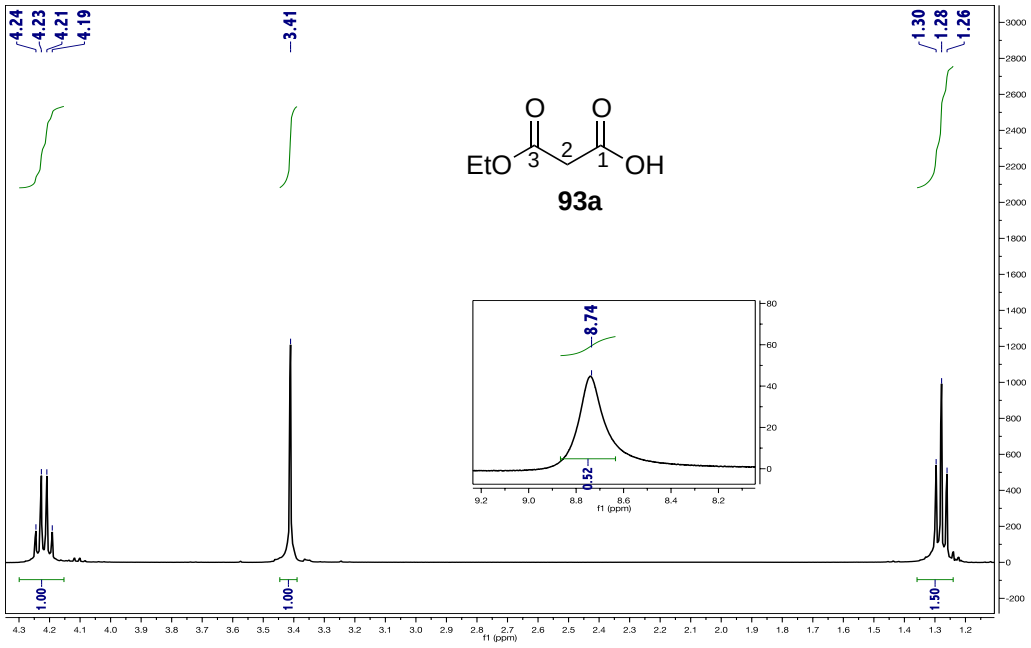


Figure 30. ^{1}H-NMR spectrum of half acid **93a**.

The quartet at 4.22 ppm and the triplet at 1.28 ppm corresponded to the CH_2 and the CH_3 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.

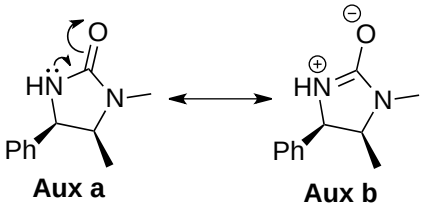
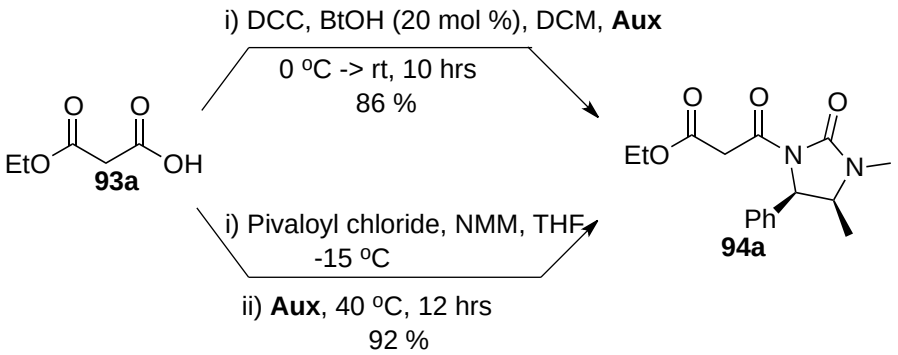


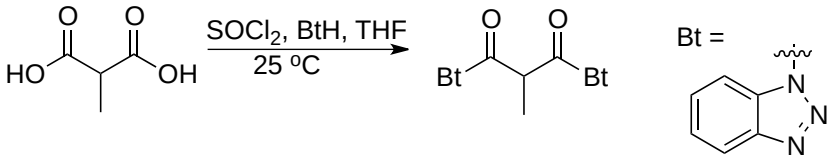
Figure 31. Resonance contributors of imidazolidinone **Aux** provides an explanation for the weakly nucelophilic N-H.

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.



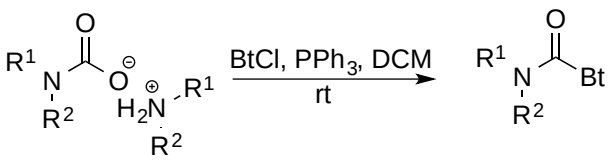
Scheme 75. Synthesis of **94a** via peptide coupling of **93a** with **Aux** using DCC or pivaloyl chloride.

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]



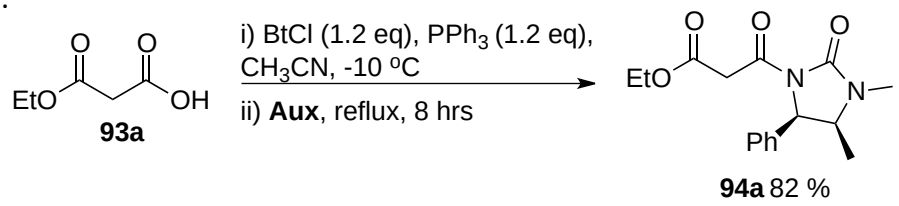
Scheme 76. Katritzky *et al* made use of an *N*-acylbenzotriazole as an activated carboxylic acid derivative.

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 PPh_3 and 1-chlorobenzotriazole, (BtCl, **Scheme 77**), thereby avoiding the use of $SOCl_2$ 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 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, PPh_3 methodology applied to the synthesis of **94a**.

The first step in the reaction is between PPh_3 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_NAc reaction with **Aux** to form **94a**.

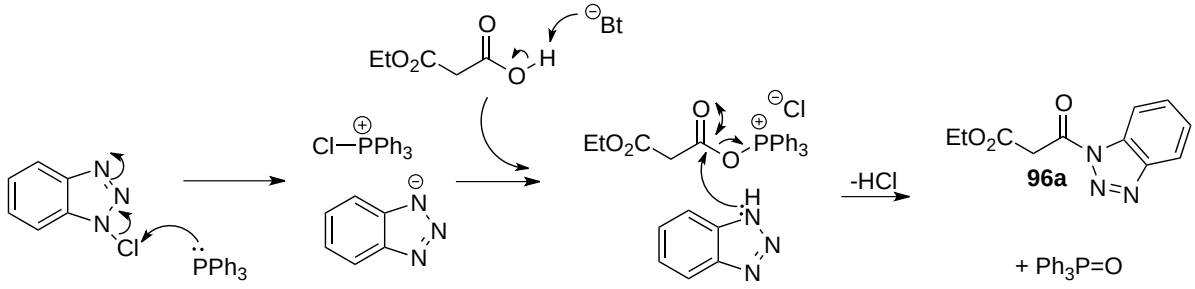
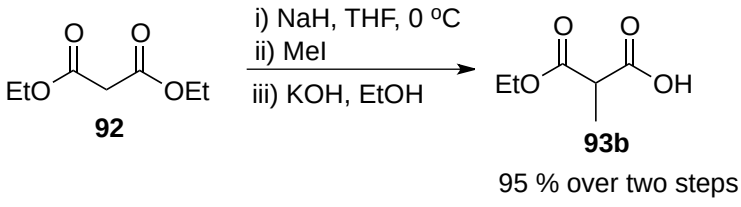


Figure 32. Proposed mechanism for the formation of the benzotriazole derivative **96a**.

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 ^{1}H-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**.

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**).

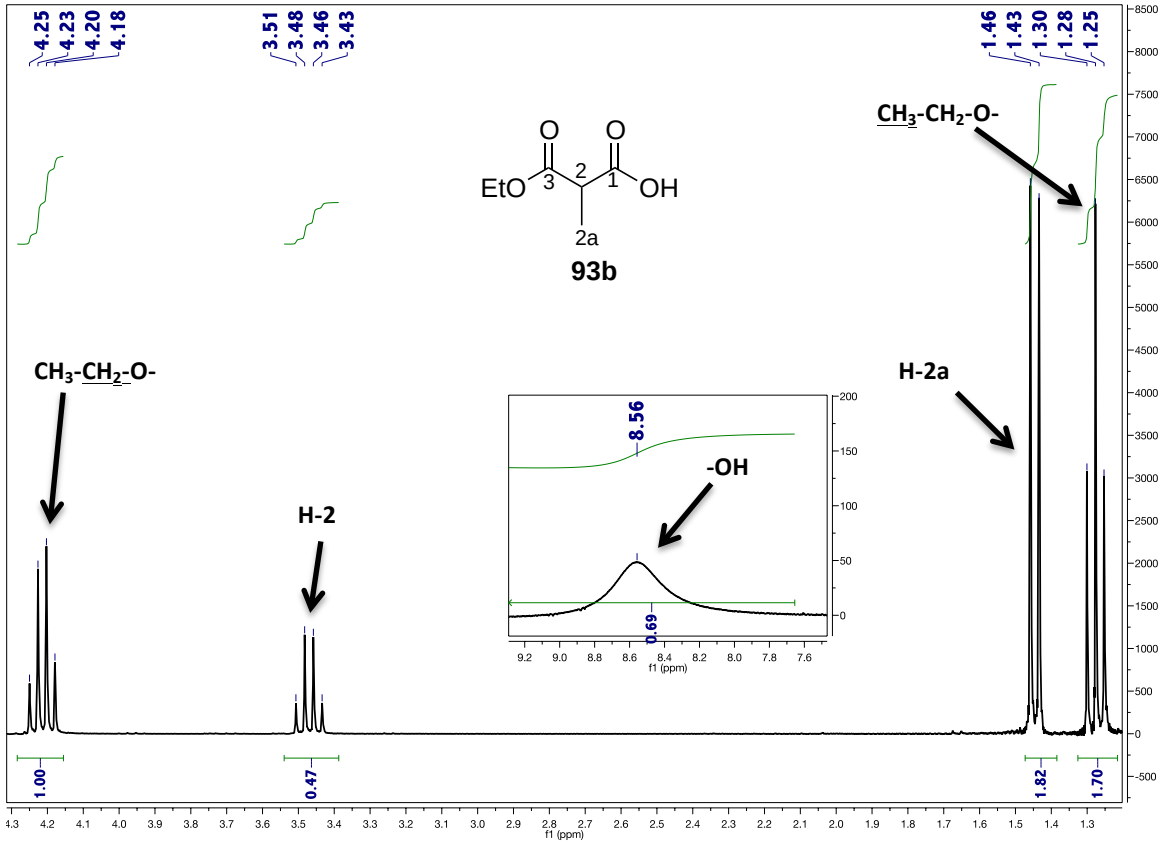
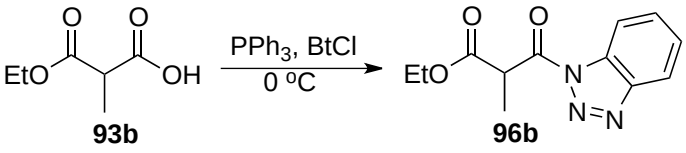


Figure 33. ^{1}H-NMR spectrum of **93b**.

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**).

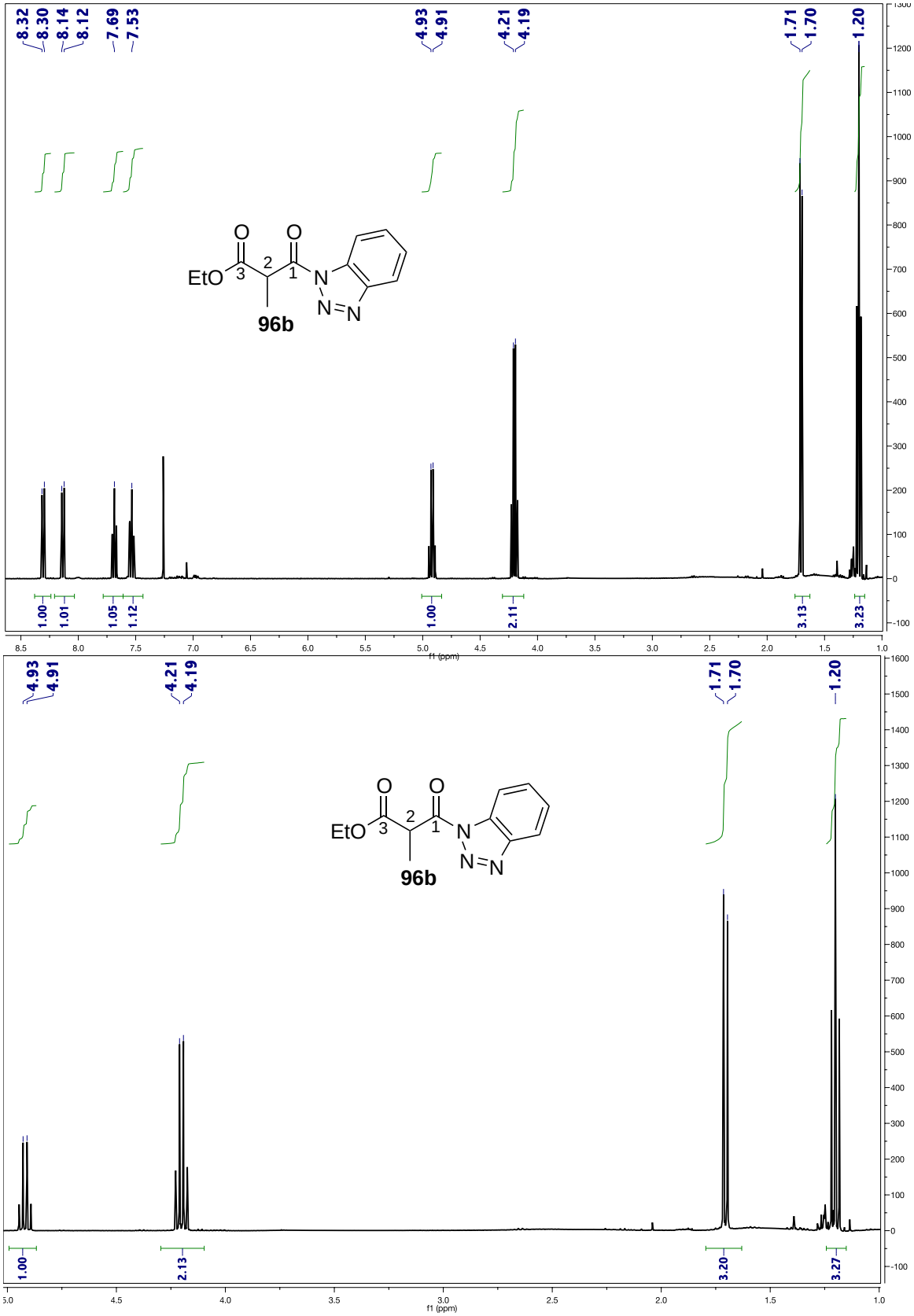


Figure 34a. ^{1}H-NMR spectrum of **96b** with expansion expansion of 1.00 ppm – 5.00 ppm range.

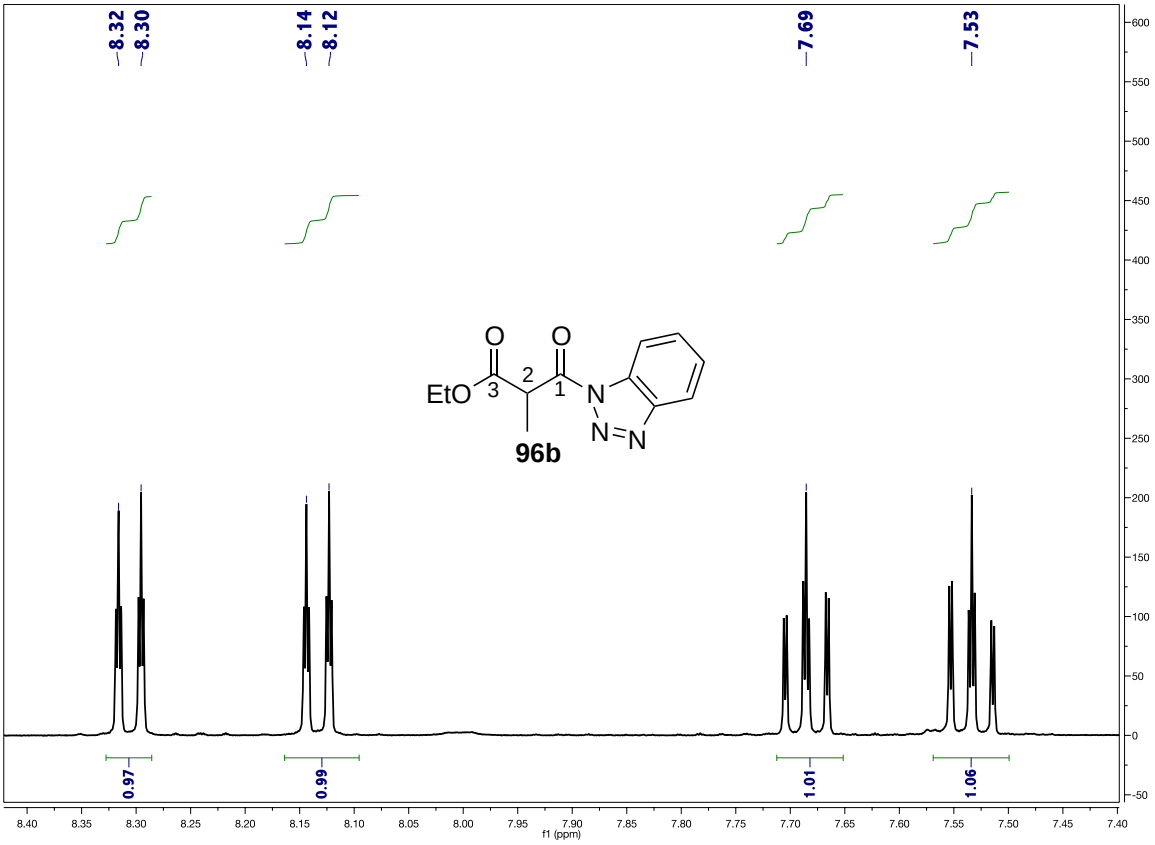


Figure 34b. Expansion of the 7.40 ppm - 8.40 ppm range of 1H-NMR spectrum of **96b**.

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.

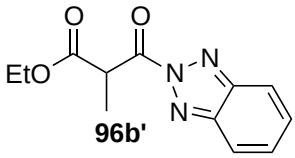
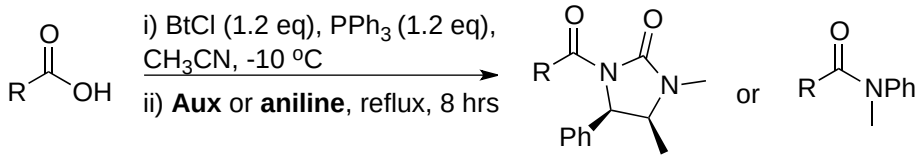
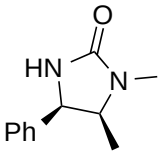
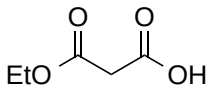
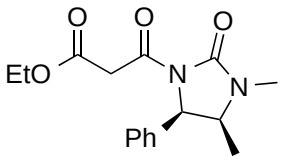
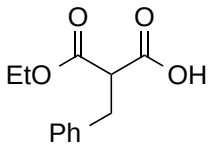
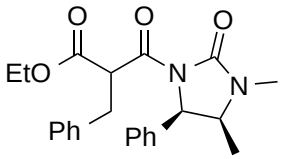
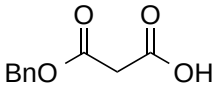
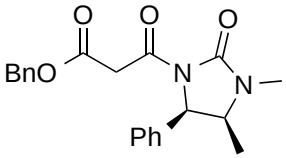
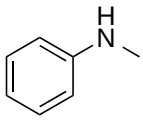
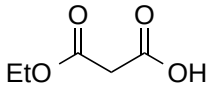
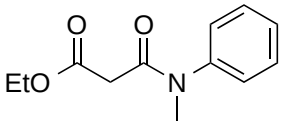
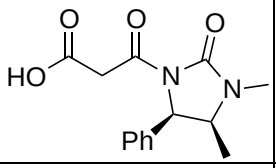
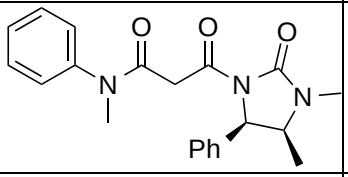
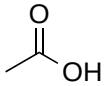
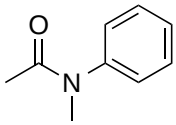
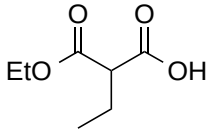
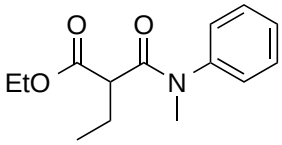
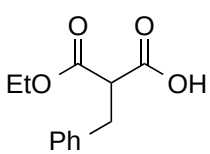
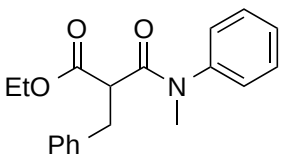
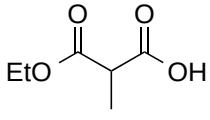
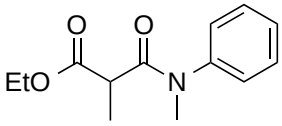


Figure 35. Regiosisomer of **96b'** was not detected.

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



Entry	**Aux** or aniline	Substrate	Product	Yield (%)[a]
1				82
2				81
3				90
5				81
6				51
7				96
8				97
9				91
10				90

[a]Isolated 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 $Ph_3P=O$. For this reason it was decided to stay with the pivaloyl chloride coupling methodology for the synthesis of **94a**. Nevertheless the PPh_3 / 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 ^{1}H-NMR and ^{13}C-NMR spectroscopic data. A fully assigned ^{1}H-NMR spectrum of **94a** is shown in (**Figure 36**).

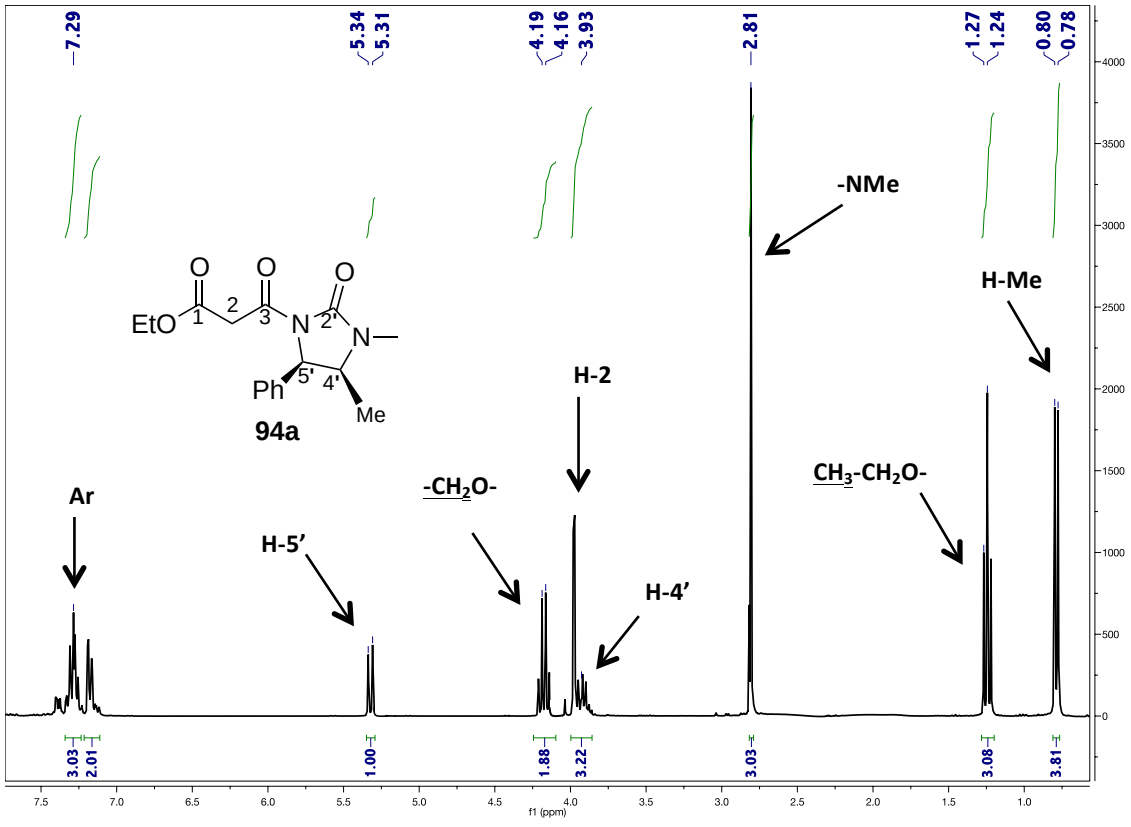


Figure 36. 1H-NMR spectrum of **94a**.

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.

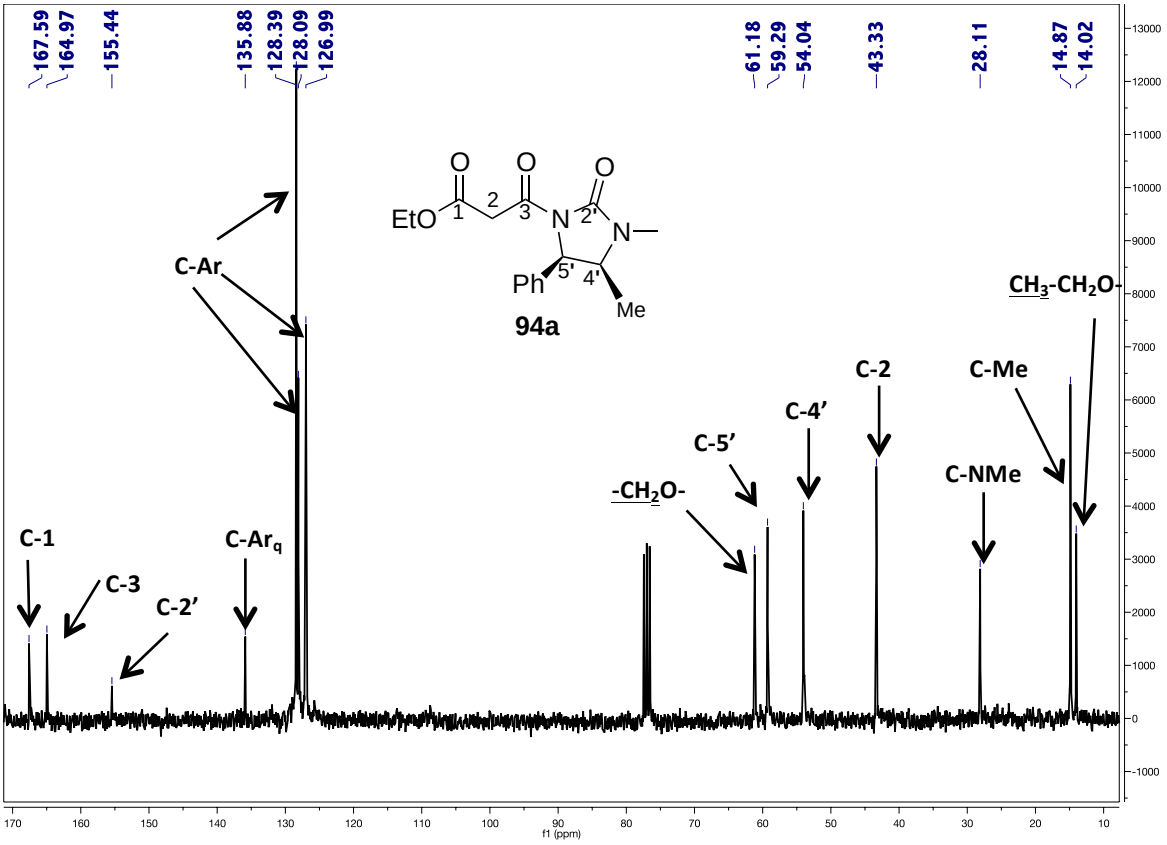
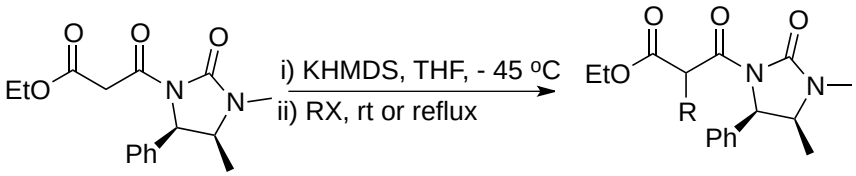


Figure 37. ^{13}C-NMR spectrum of **94a**.

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 diastereselective 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



94a **94b - h**

Entry	RX	Cpd	R	Yield (%)[a,d]
1	MeI	**94b**	Me	96
2	EtI[b]	**94c**	Et	97
3	*n*-Butyl bromide[c]	**94d**	*n*-Butyl	96
4	*n*-Hexyl Bromide[c]	**94e**	*n*-Hexyl	95
5	BnBr	**94f**	Bn	94
6	Allyl bromide	**94g**	Allyl	97
7	Propargyl bromide	**94h**	Propargyl	96

[a]isolated yield. [b]Reflux. [c]10 mol % TBAI and reflux.[d]Obtained as 50:50 mixtures of diastereomers.

Benzylated and allylated compounds **94f** and **94h** were new and only their NMR data will be shown. It was possible to separate the diasteromers of **94f** by column chromatography and for simplicity the ^{1}H and ^{13}C NMR spectra for one of them are represented in **Figure 38** and **Figure 39**. In the ^{1}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.

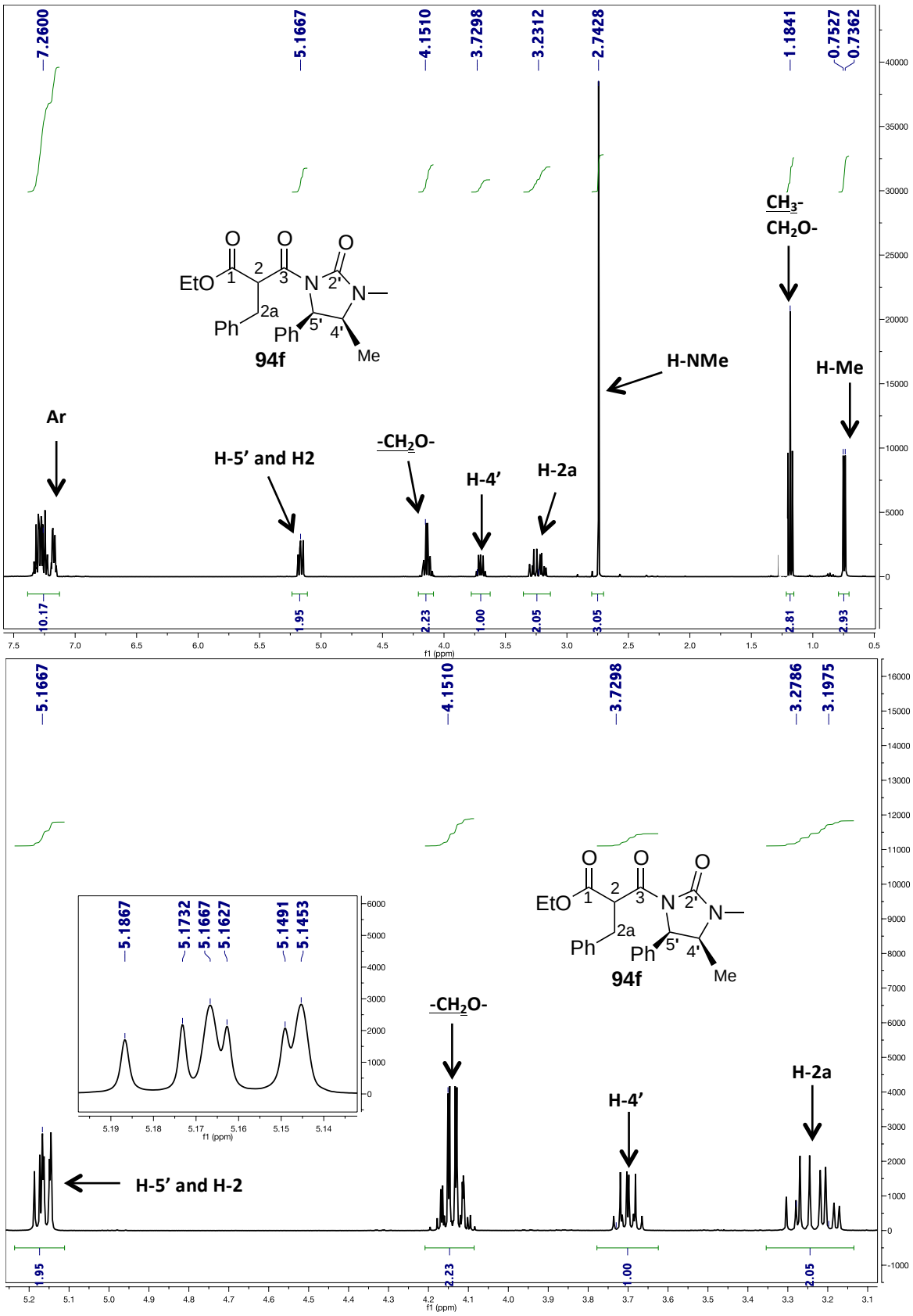


Figure 38. ^{1}H-NMR spectrum of **94f**.

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.

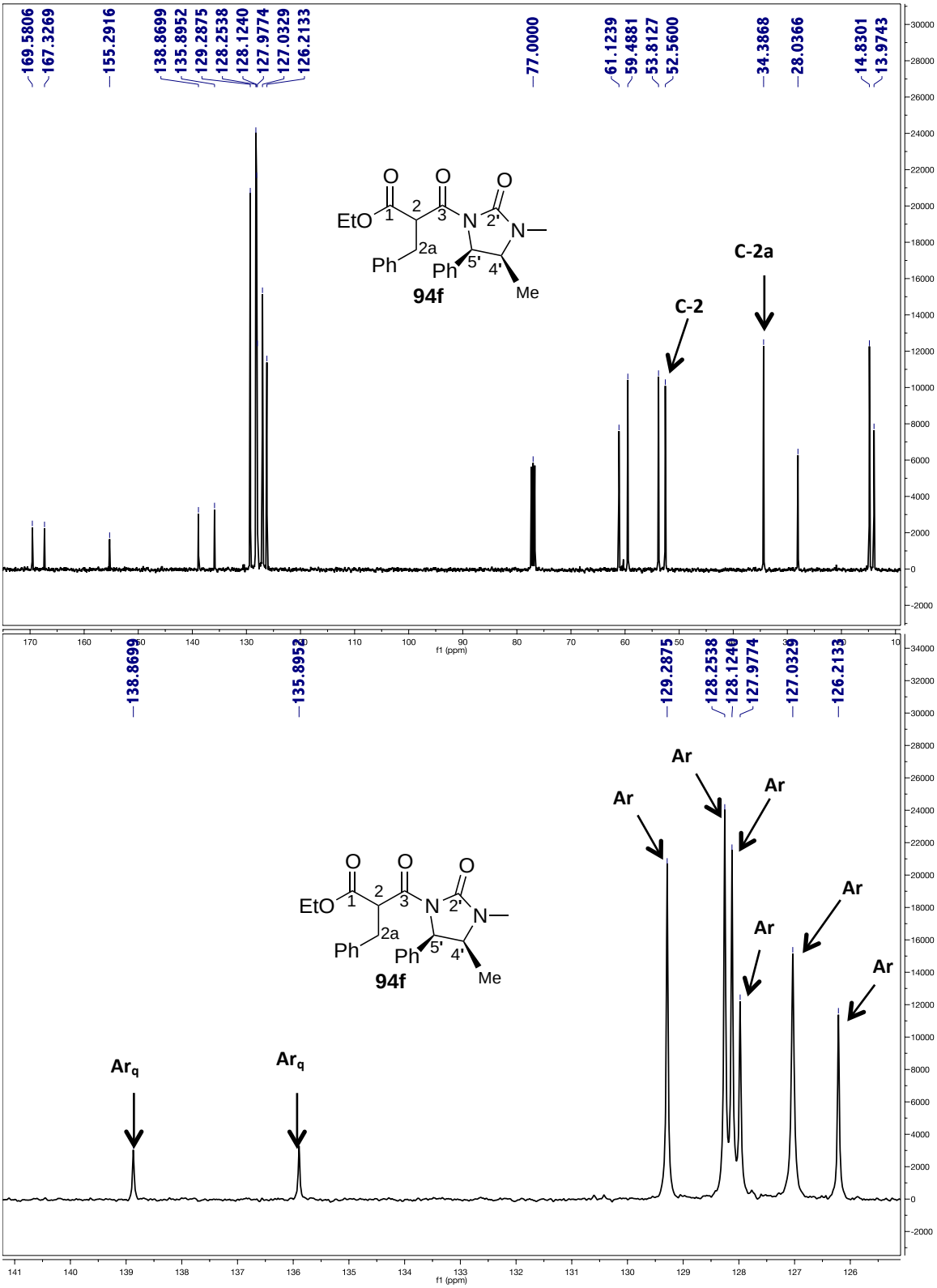


Figure 39. ^{13}C-NMR spectrum of **94f**.

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.

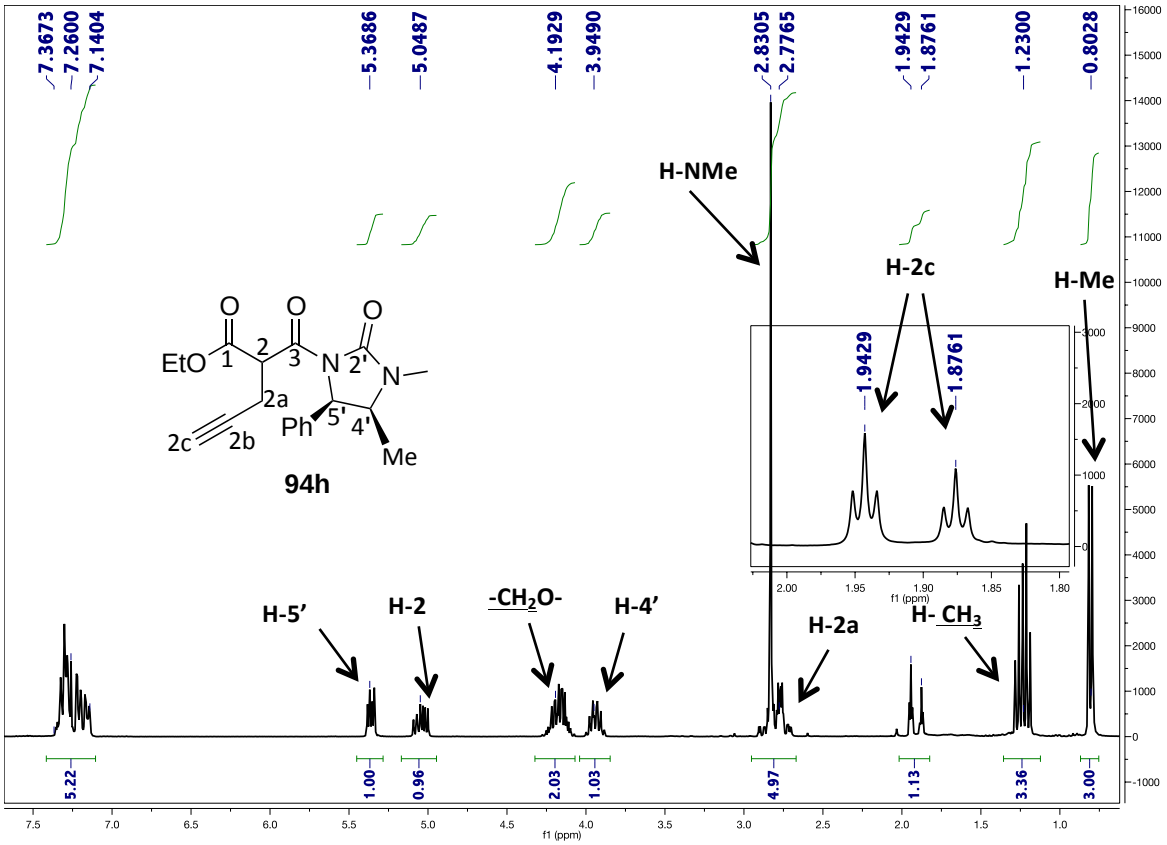


Figure 40. ^{1}H-NMR spectrum of **94h**.

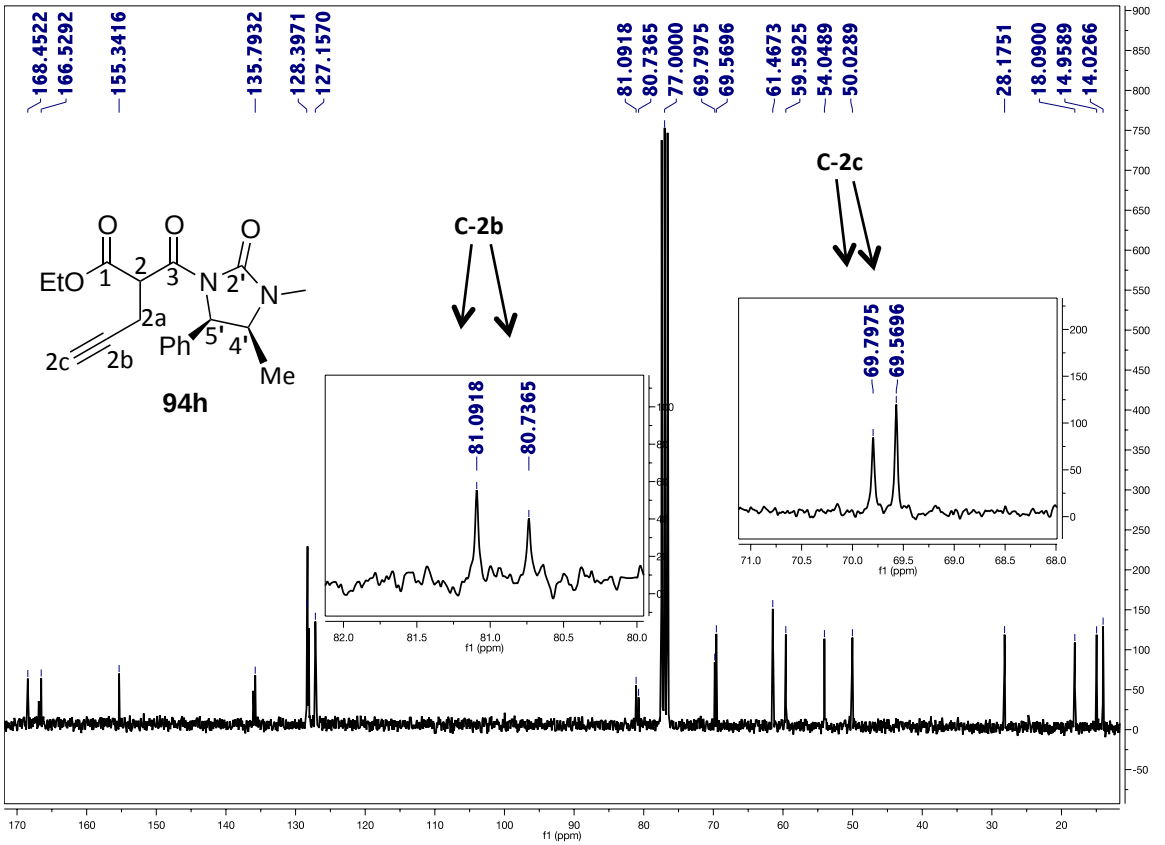
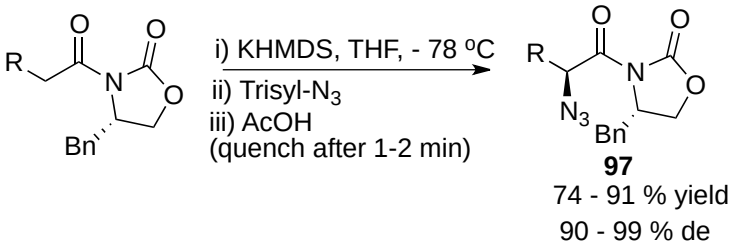


Figure 41. ^{13}C-NMR spectrum of **94h**.

3.5 α-Azidation of Mono-Substituted Malonate-Imidazolidinones

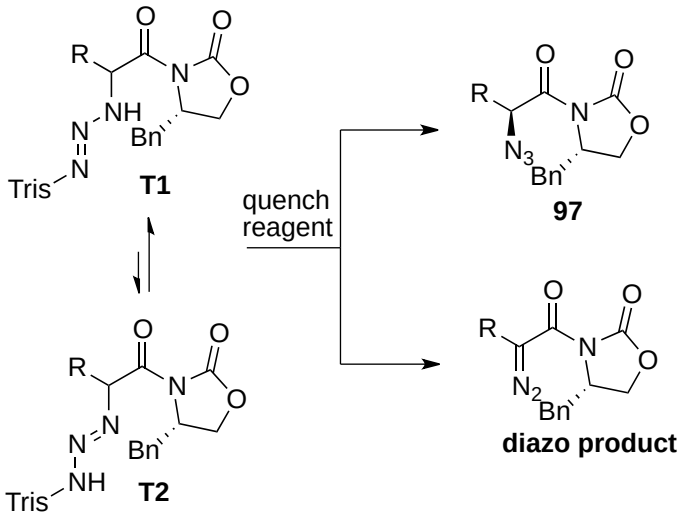
For the amination a suitable source of nitrogen electrophile had to be selected. As mentioned earlier the diazodicarboxylates have been used as efficient aminating reagents; however, chemoselective reduction of the resulting hydrazide to the amine can be challenging. For this reason it was decided to 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.[64] By comparison, azidation methodology as previously reported by Evans *et al* appeared to be the more attractive option.[65] 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. 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 sulfonyl 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 $Me_4N^{+-}OAc$ 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 $KHCO_3$ resulted in the diazo compound as the major product.



Scheme 82. Degradation pathways of sulfonyl triazene intermediates **T1** and **T2**.

Degradation of the quaternary sulfonly 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.

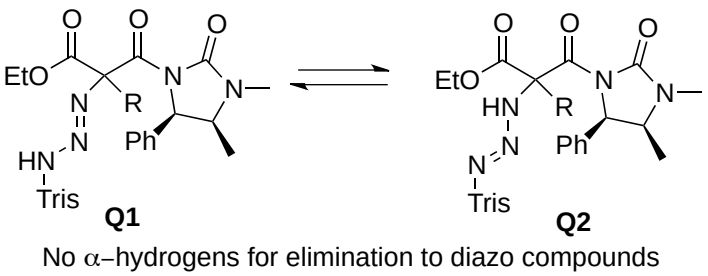
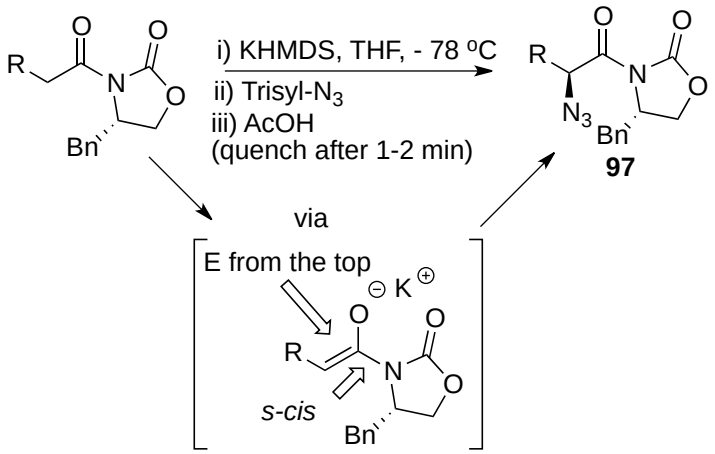


Figure 42. Envisaged sulfonyl triazene intermediates following quaternization of **94b - 4h** (**Q1** and **Q2)**.

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*$_{C\text{-}N}$ conformation due to chelation of the potassium cation in the auxiliary hole (**Scheme 83**).



Scheme 83. Azidation of carboximide enolates proceeds via s-*cis*$_{C\text{-}N}$ 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**).

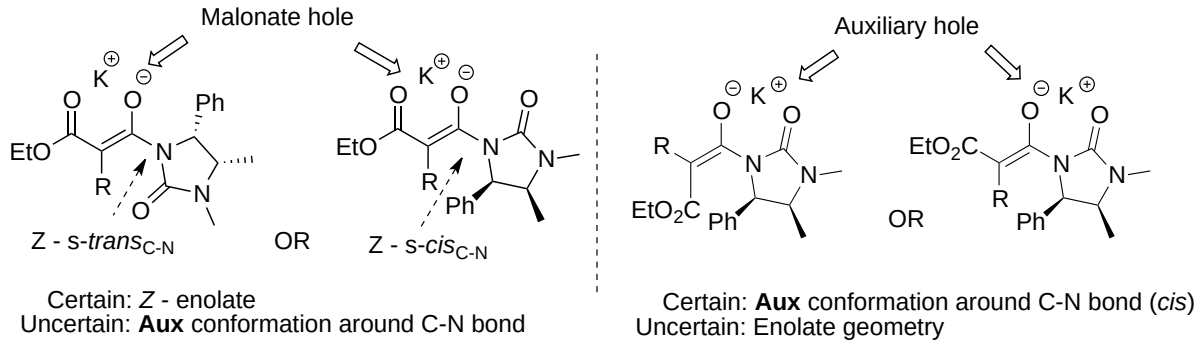


Figure 43. Configurational and conformational analysis of the malonate-imidazolidinone enolates.

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.[61]

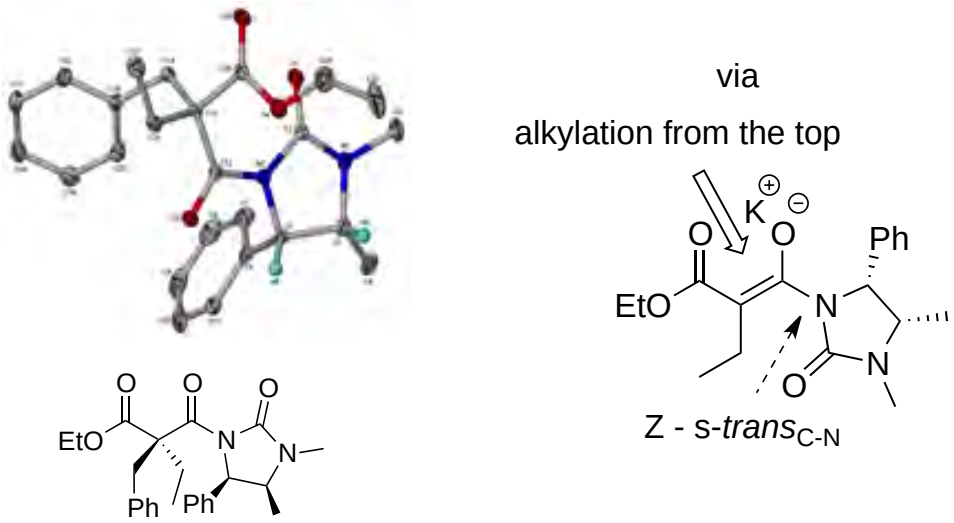
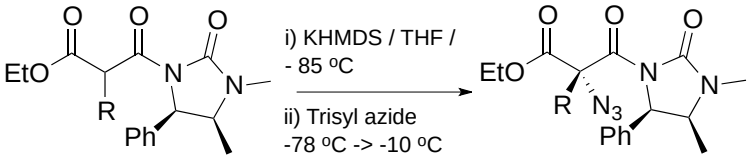


Figure 44. Crystal structure of quaternization product obtained via benzylation of **94c**.

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 (-)-(4*R*, 5*S*) 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.

Table 8. Diastereoselective Azidation of **94**



94b - h **98b - h**

Entry	Product	R	Yield (%)[a]	dr[b]
1	**98b**	Me	97	>99:1
2	**98c**	Et	96	98:2
3	**98d**	*n*-Butyl	95	99:1
4	**98e**	*n*-Hexyl	97	>99:1
5	**98f**	Bn	91	97:3
6	**98f**	Bn	89	78:22[c]
7	**98g**	Allyl	97	99:1
8	**98h**	Propargyl	95	99:1

[a]Isolated yields. [b]Determined by chiral HPLC. [c]Enolate generated at 0 °C and trisyl azide introduced at 0 °C.

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 ^{1}H-NMR as well as the downfield shift of C-2 in the ^{13}C-NMR due to the electron-drawing azido group. A few compounds will be selected in order to highlight these observations. In the ^{1}H-NMR spectrum of **98b**, the H-2 proton that occurred at 4.65 ppm in starting material **94b** is absent (**Figure 45**). The ^{13}C-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**.

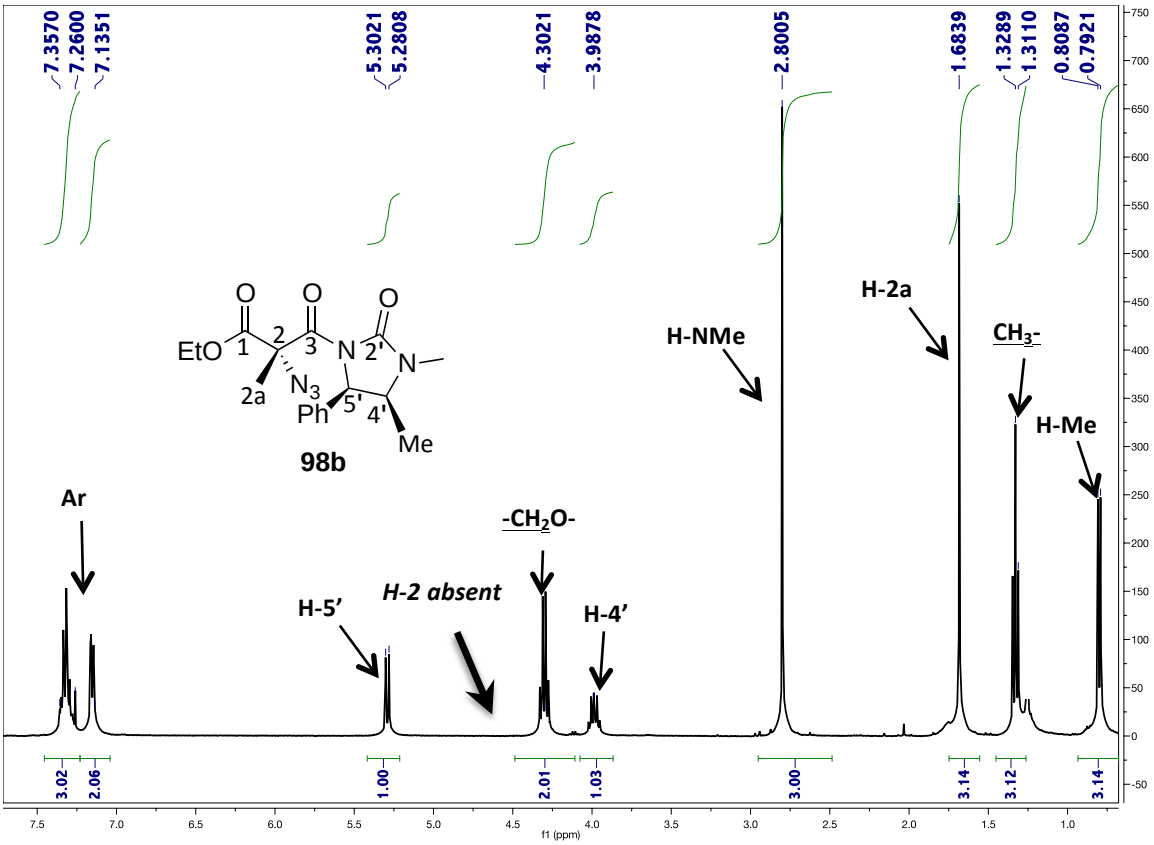


Figure 45. ^{1}H-NMR spectrum of **98b**.

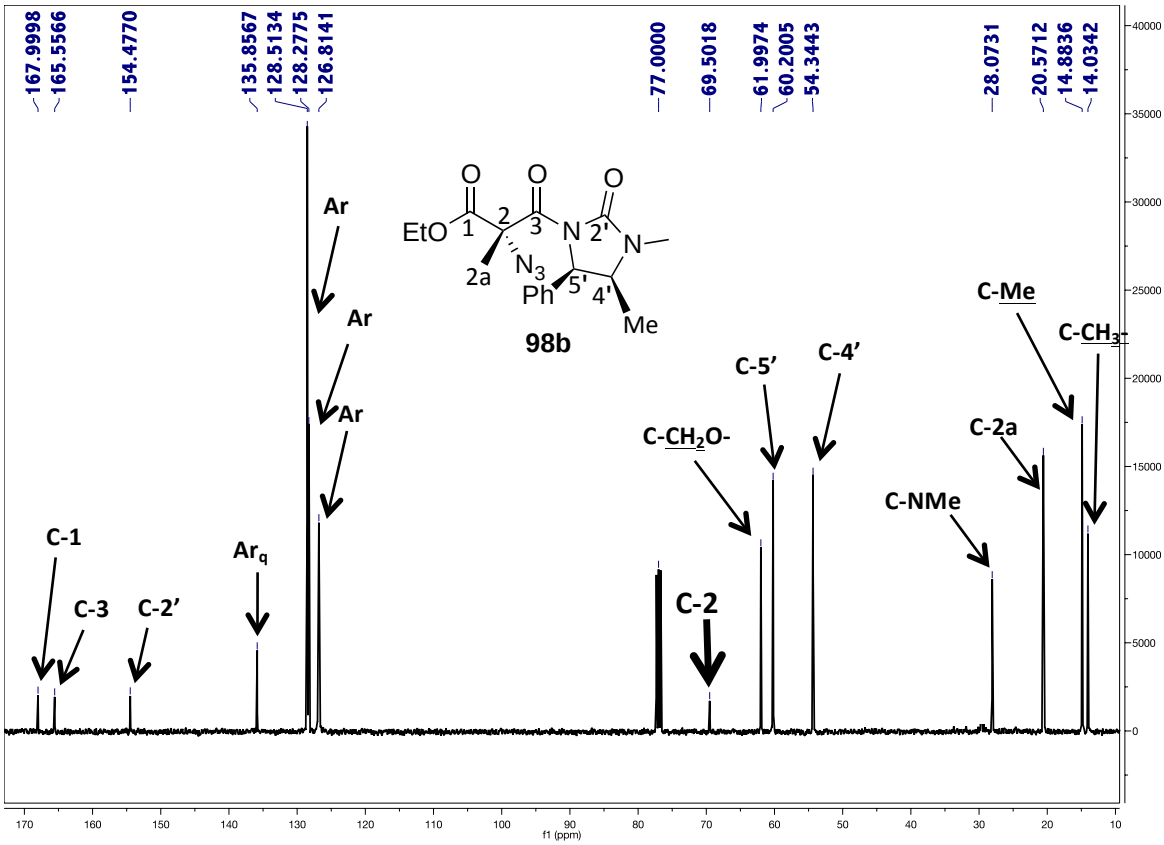


Figure 46. ^{13}C-NMR spectrum of **98b**.

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.

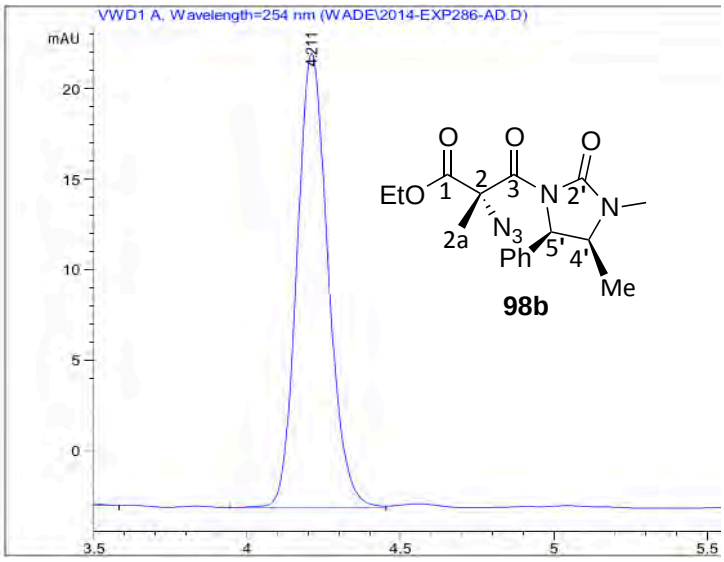


Figure 47. HPLC chromatograph of **98b** confirming >99:1 dr.

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.

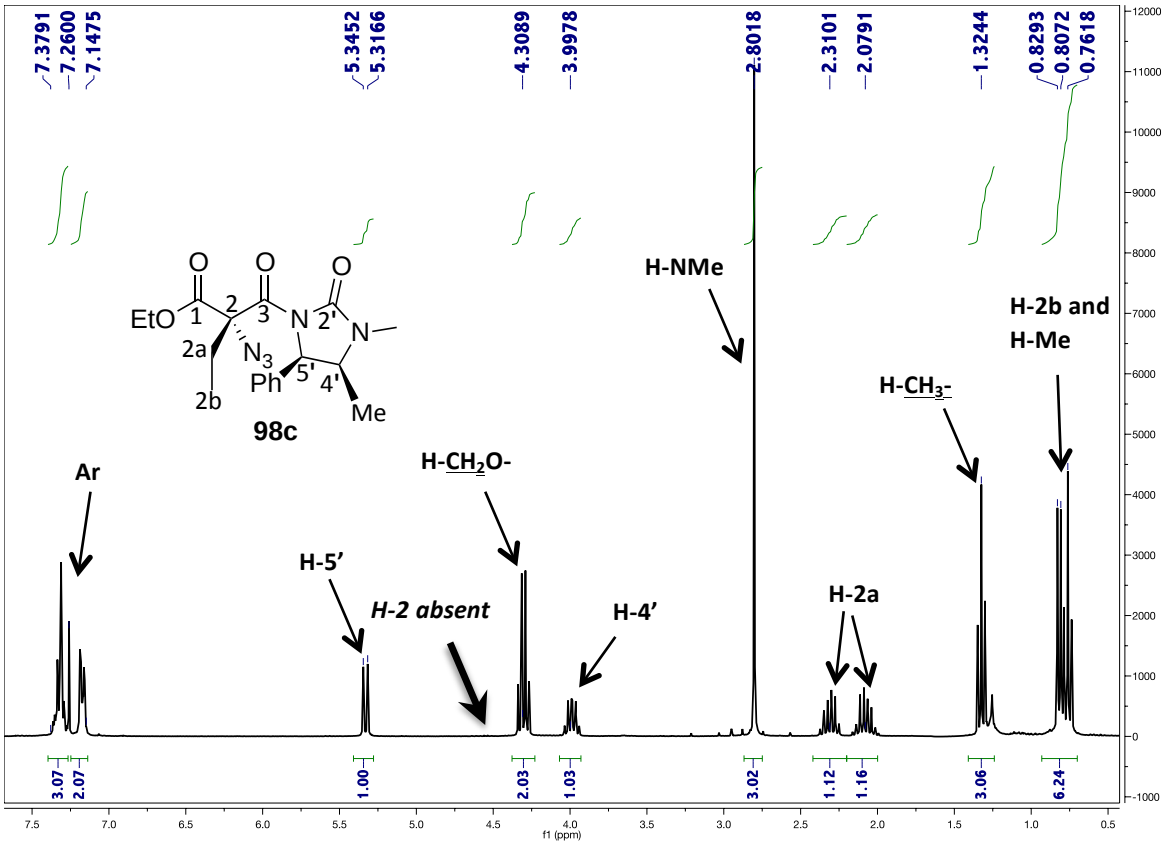


Figure 48. ^{1}H-NMR spectrum of **98c**.

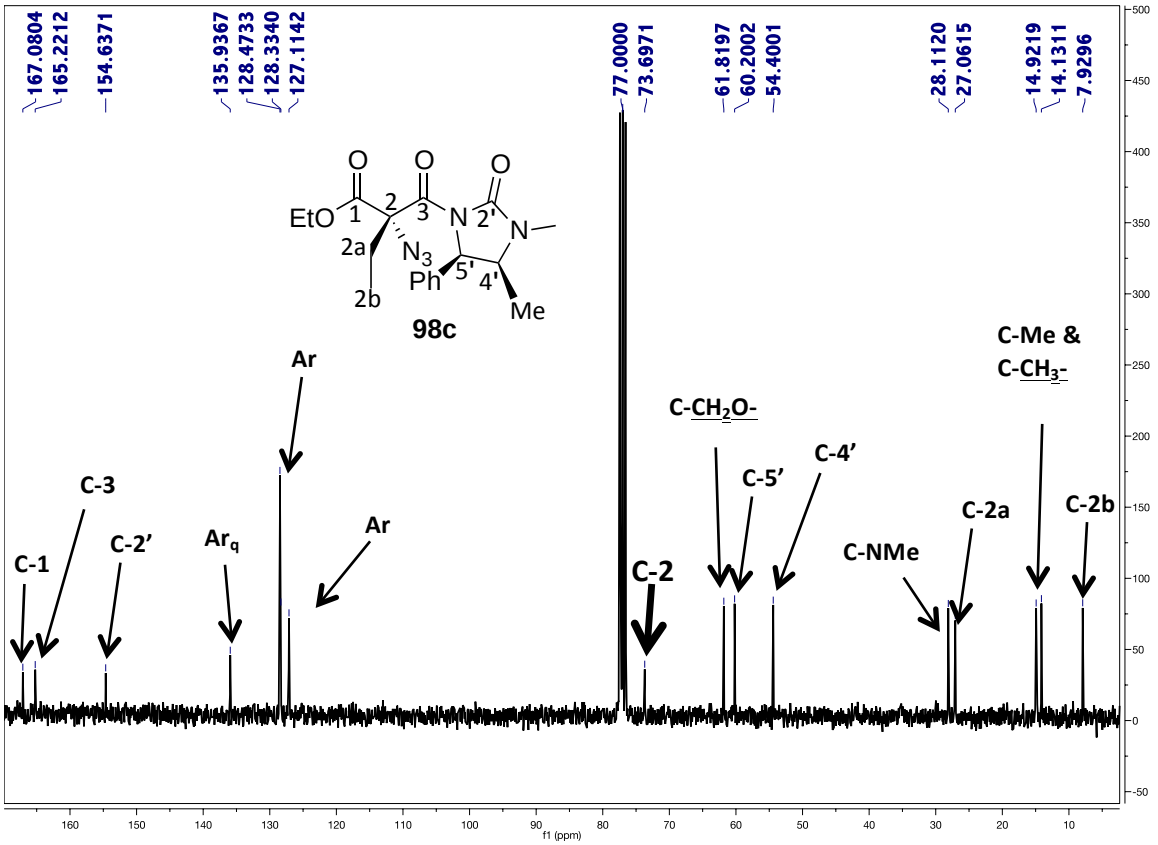


Figure 49. ^{13}C-NMR spectrum of **98c**.

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**).

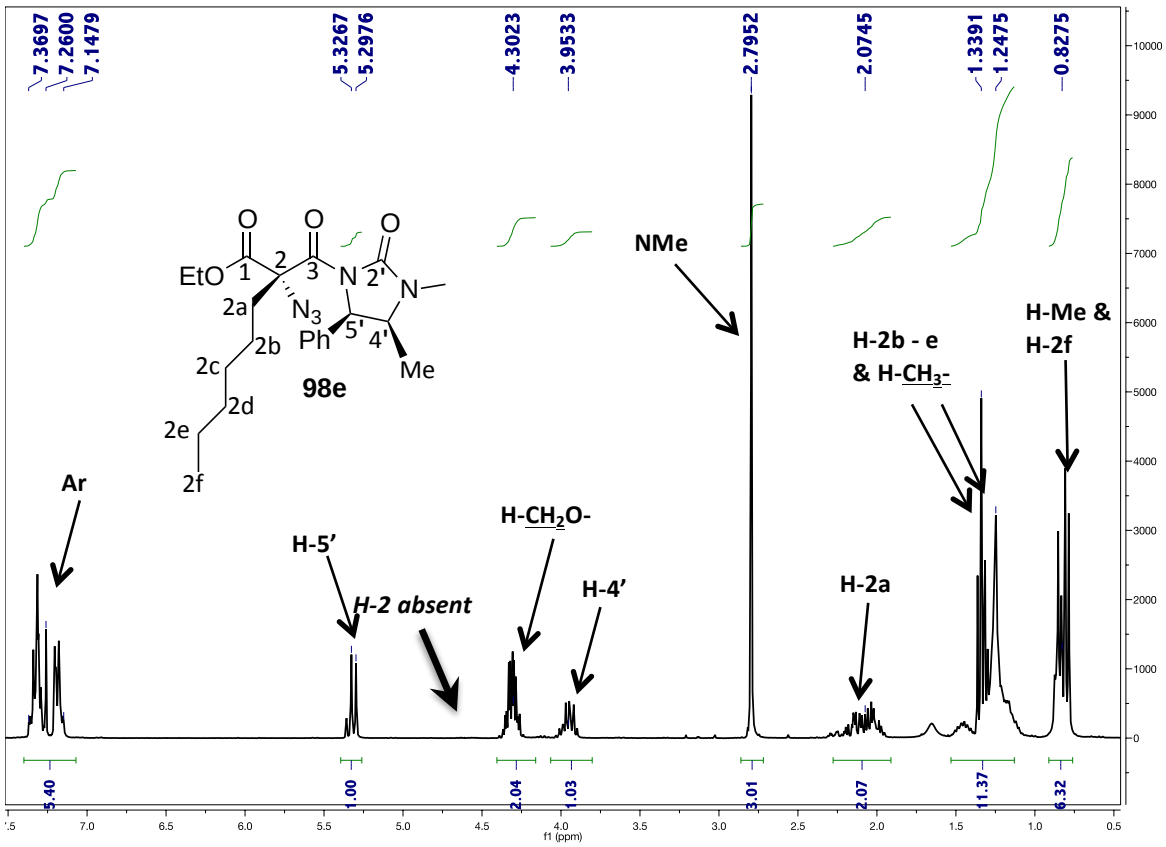


Figure 50. ^{1}H-NMR spectrum of **98e**.

Doubling was also observable in the ^{13}C-NMR spectrum (**Figure 51** - expansions).

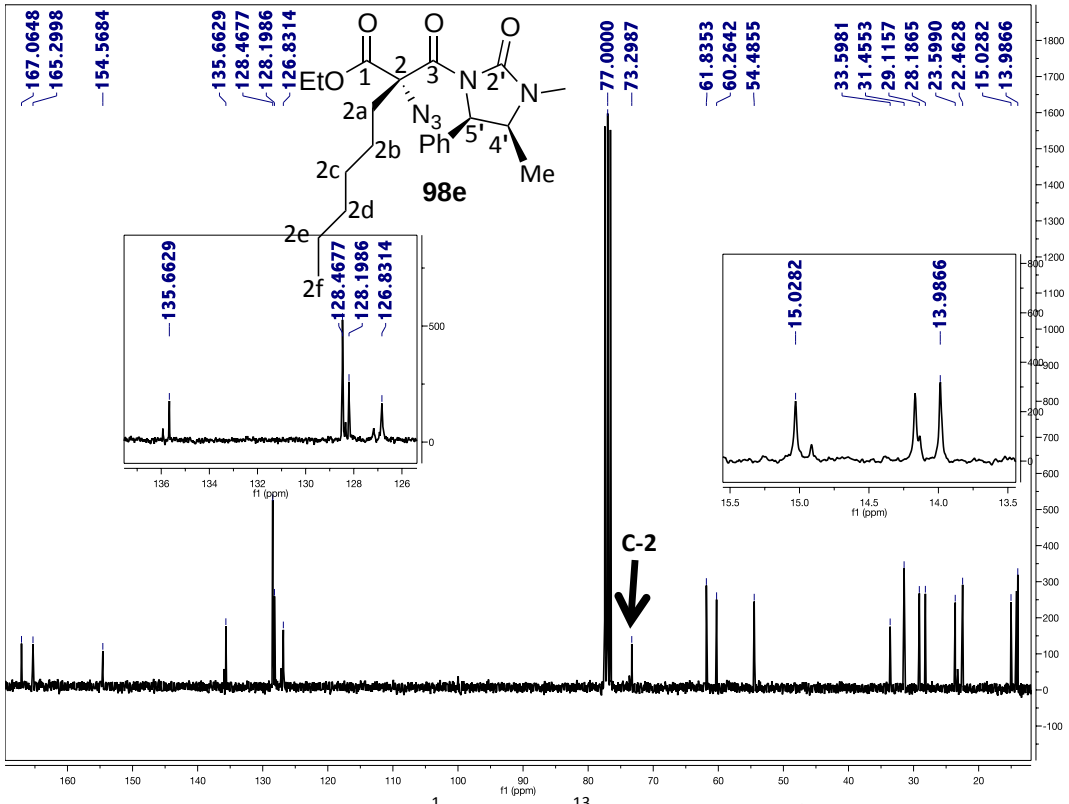


Figure 51. ^{1}H-NMR and ^{13}C-NMR spectrum of 9**8e**.

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 dr >99:1. It was speculated that the doubling of signals could involve *cis*/*trans* rotamers around the C-N_{Aux} σ-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.

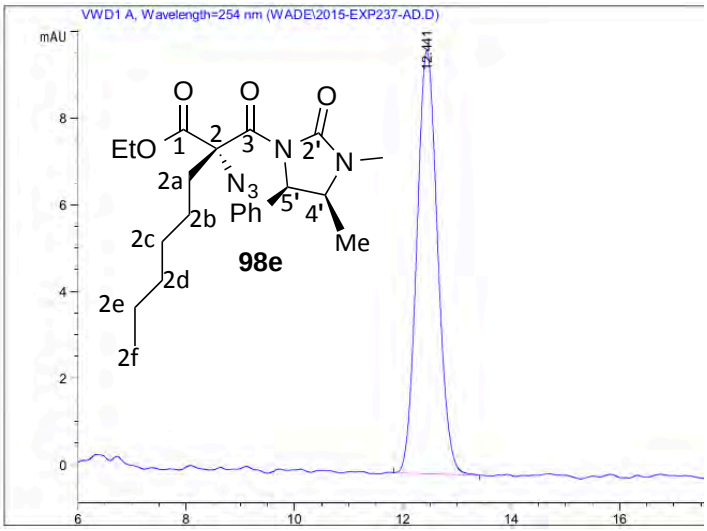


Figure 52. HPLC chromatograph of **98e** showing only one diastereomer.

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.**

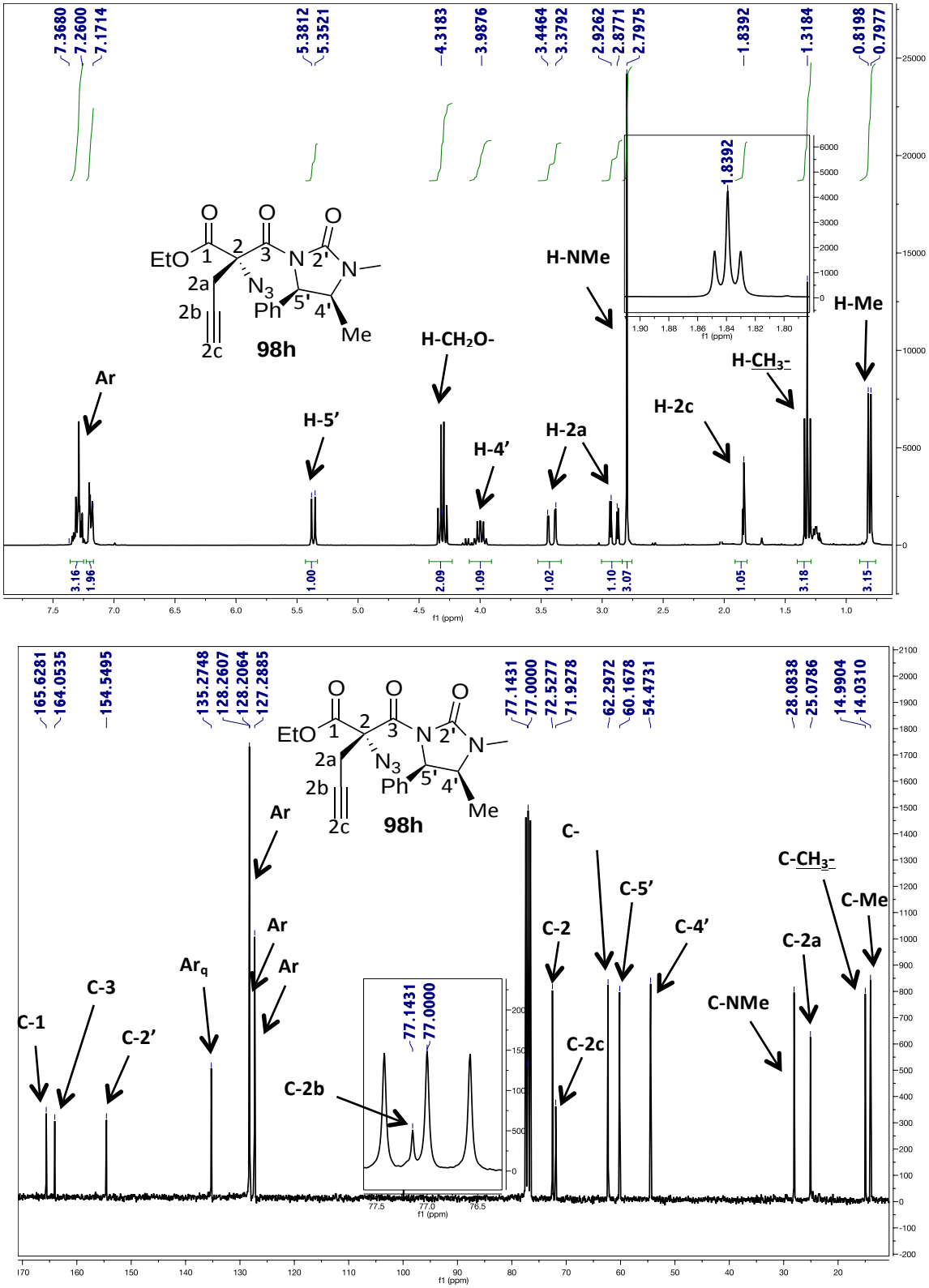


Figure 53. ^{1}H-NMR and ^{13}C-NMR spectrum of **98h.**

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.

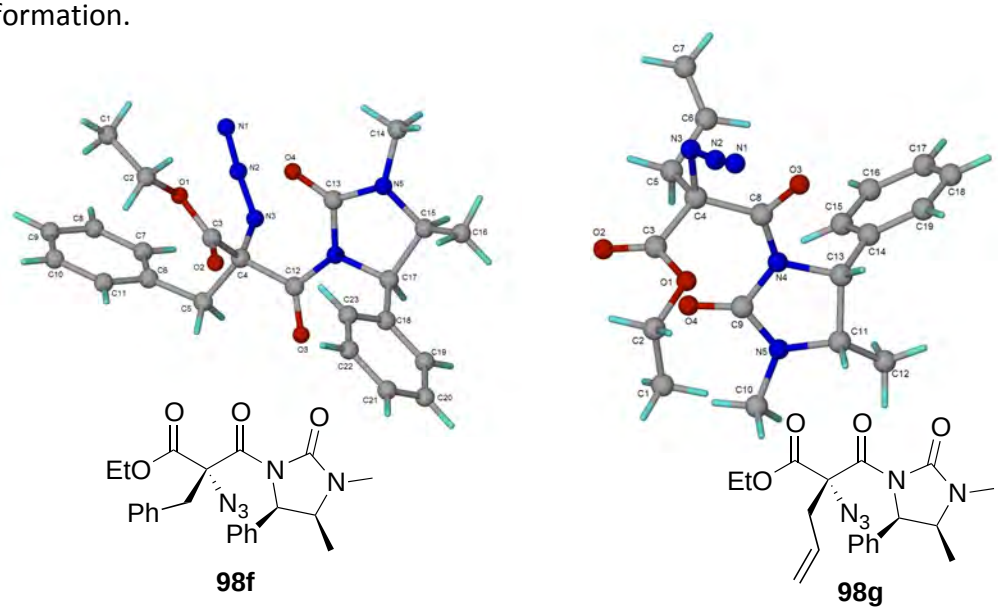


Figure 54. Crystal structure of azides **98f** and **98g** showing an *S* configuration around the aza-quaternary centre.

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*$_{C\text{-}N}$ conformation and not via the anticipated s-*trans*$_{C\text{-}N}$ 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**).

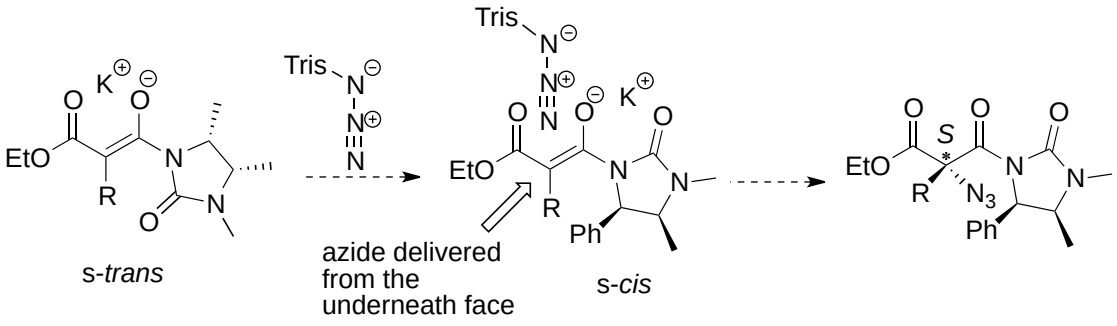


Figure 55. Proposed trisyl azide assisted conformational switch from s-*trans* to s-*cis* enolate.

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 paper[61]) 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-$trans_{C\text{-}N}$ to the s-$cis_{C\text{-}N}$ 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.

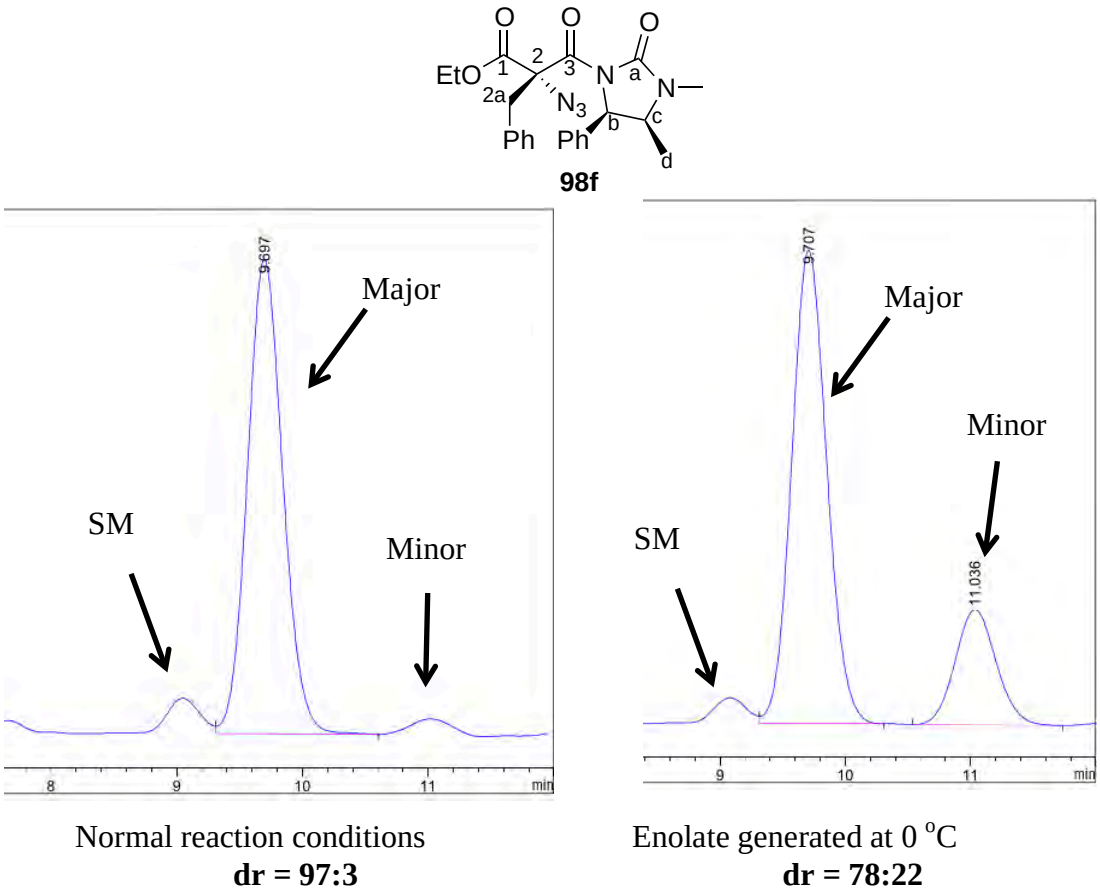
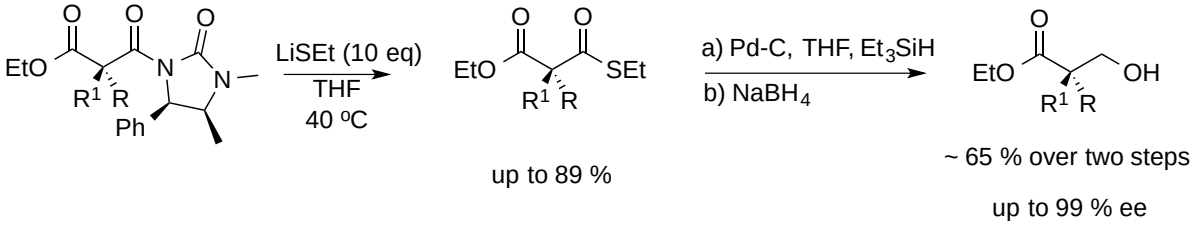


Figure 56. HPLC traces of **98f** obtained under enolate generation at different temperatures.

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*).

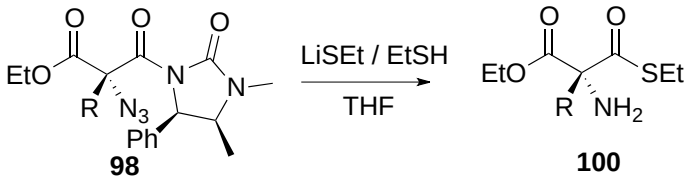
3.6 Transformation of 98 to α,α'-Disubstituted Serine Derivatives.

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 $NaBH_4$ (**Scheme 84**).[61]



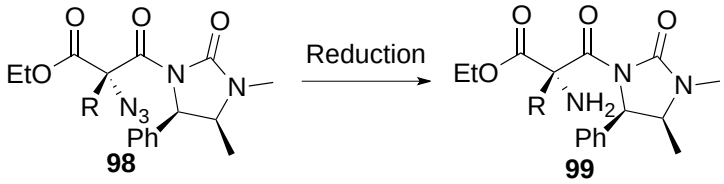
Scheme 84. Chemoselective removal of the auxiliary by LiSEt followed by conversion to the β-hydroxy ester via a Fukutama reduction sequence.

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**).



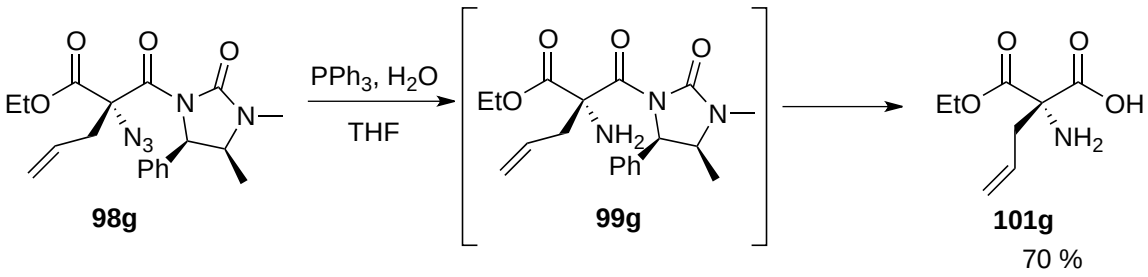
Scheme 85. Envisaged one pot conversion of **98** to the corresponding thioamine **100** using LiSEt in the presence of excess of EtSH.

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**).



Scheme 86. Azide reduction to form corresponding amine **99**.

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 PPh_3 and H_2O (**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.



Scheme 87. Perceived Reaction of **98g** under Staudinger conditions.

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**).

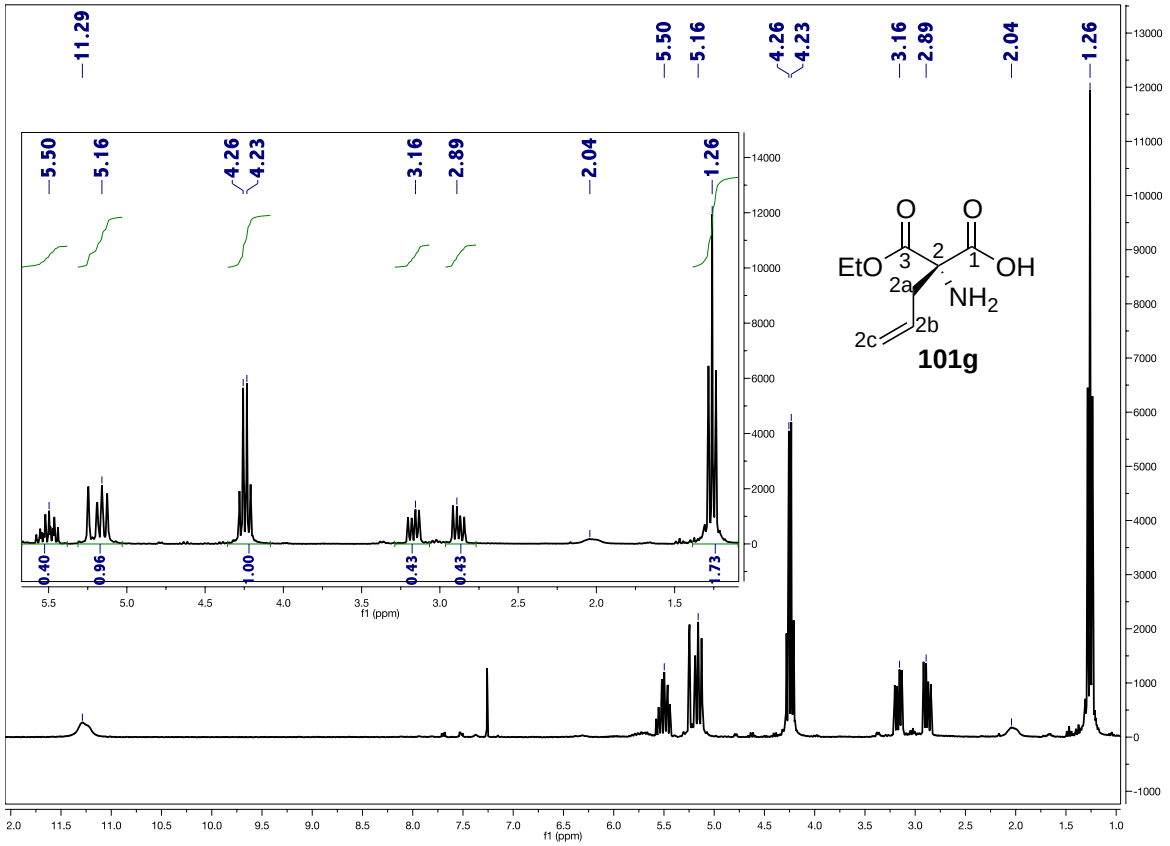


Figure 57. ^{1}H-NMR spectrum of the compound speculated to be **101g**.

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**.

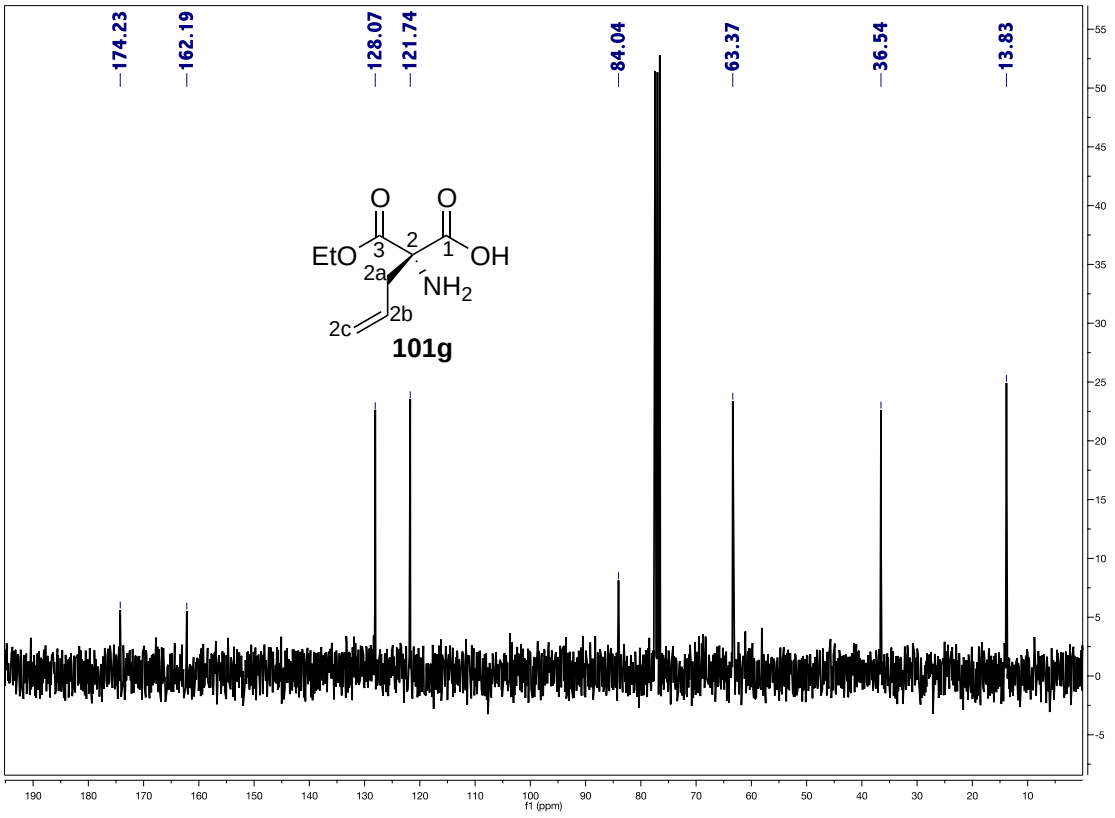
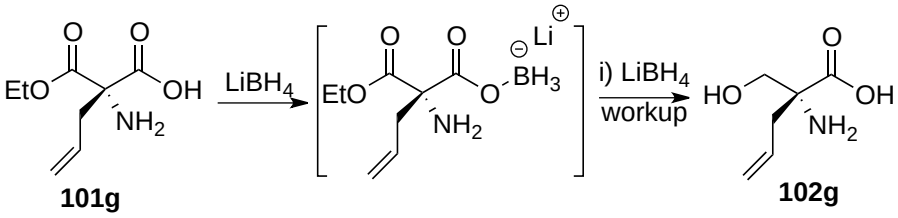


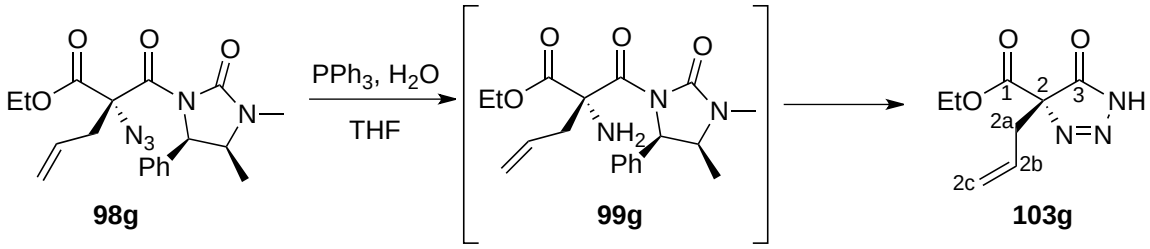
Figure 58. ^{13}C-NMR spectrum of the compound speculated to be **101g**.

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 $LiBH_4$ 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 $LiBH_4$ to afford quaternary serine **102g**.

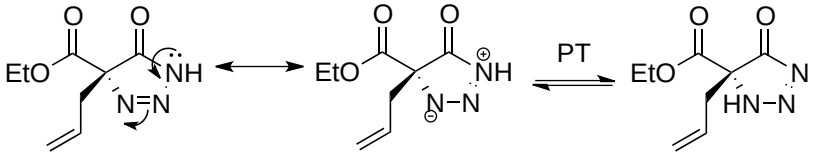
In the event, however, a single product could not be isolated. Similarly, the reaction of **101g** with $LiAlH_4$ at – 78 °C did not reveal any evidence of **102g** either. The major clue to solving this structure resided in the assigned carboxylic acid resonance in the ^{13}C-NMR of **101g** at 174.2 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 correspondeding to the –OH and no evidence of another broad singlet to account for the NH_2. 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 PPh_3 and H_2O was in fact the triazolone **103g** shown in **Scheme 89**, which explained the lower polarity compared to **98g** as well as the observed instability.



98g **99g** **103g**

Scheme 89. Reaction of **98g** under Staudinger conditions afforded triazole **103g**.

The ^{13}C-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**).



103g - A **103g - B** **103g - C**

Figure 59. Resonance structures of **103g**.

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 S_NAc reaction with expulsion of auxiliary, rather than proceeding to the iminophosphorane (**Figure 60**).

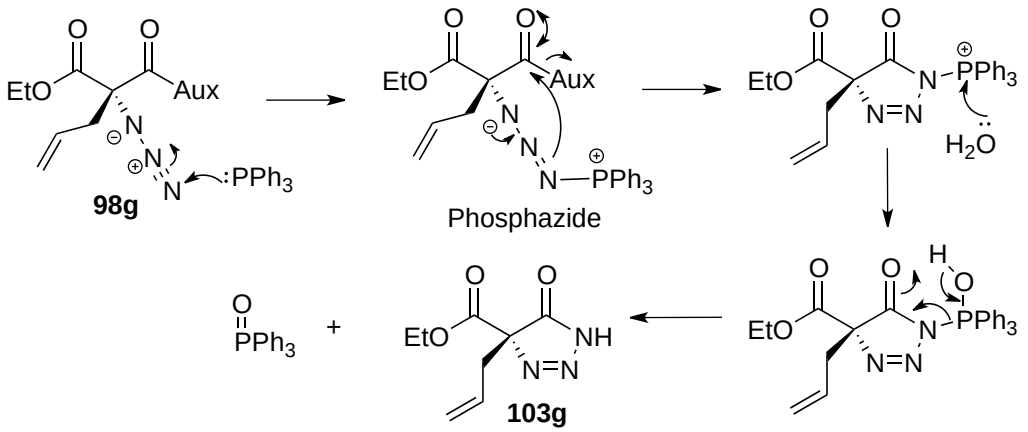
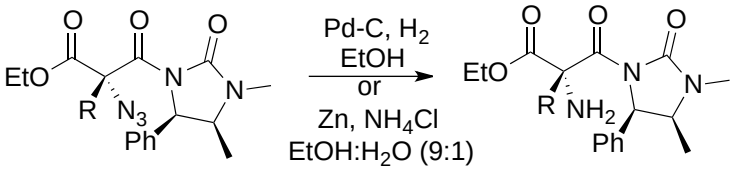


Figure 60. Proposed mechanism for the formation of **103g**.

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 than Zn in the presence of NH_4Cl is able to efficiently reduce azides to amines[66] 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**



98b - 98h **99b - 99h**

Entry	Product	R	Yield (%)[a]
1	**99b**	Me	90
2	**99e**	*n*-Hexyl	95
3	**99f**	Bn	94
4	**99g**	Allyl[b]	91
5	**99h**	Propargyl[b]	92

[a]Isolated yield. [b]Reduction with Zn, NH_4Cl

The NMR spectrum of **99e** run in $CDCl_3$ 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.

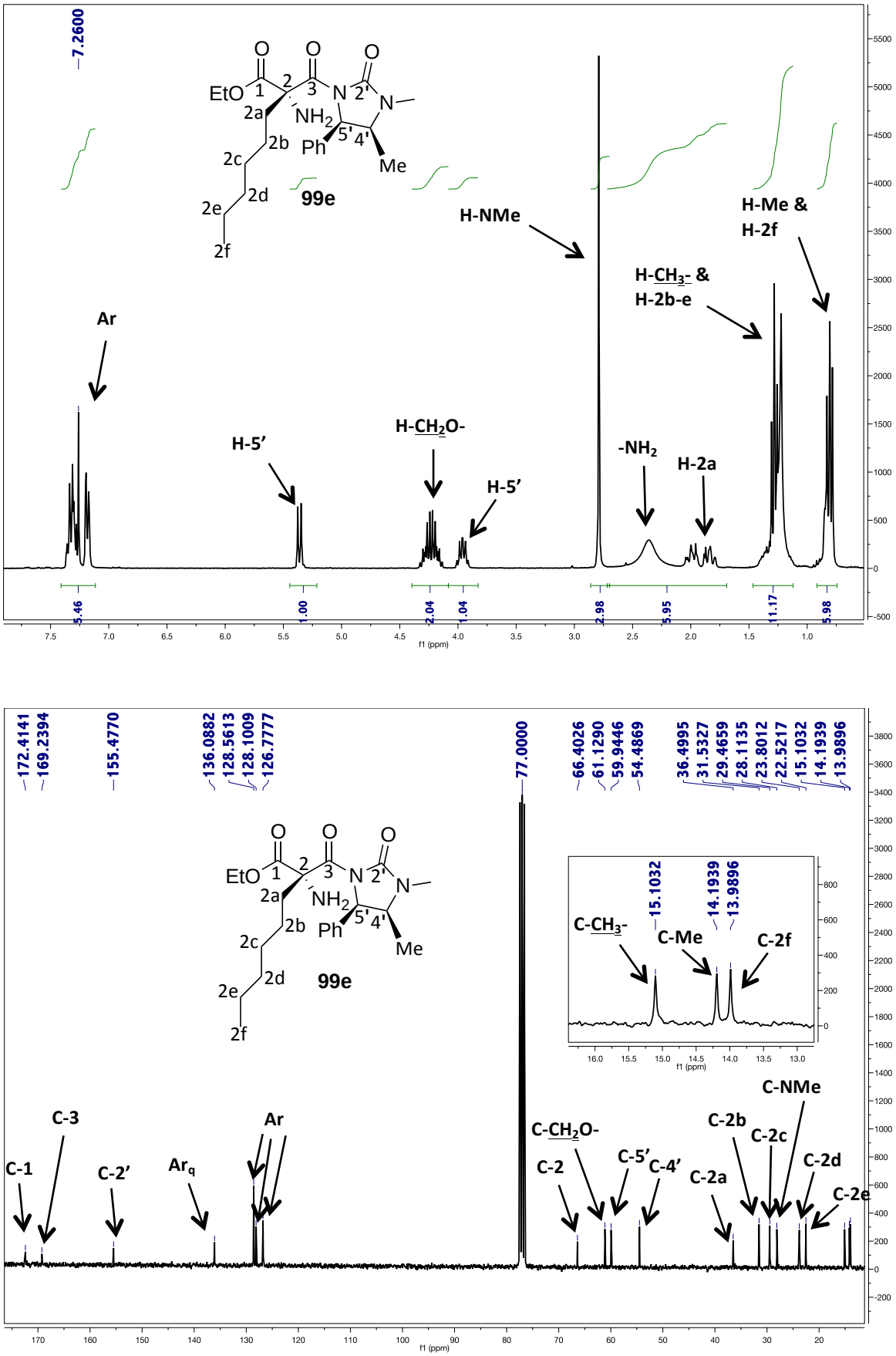


Figure 61. ^{1}H-NMR and ^{13}C-NMR spectrum of **99e**.

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_NAc 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).

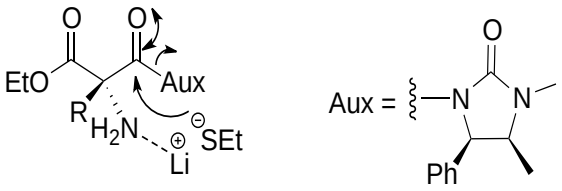
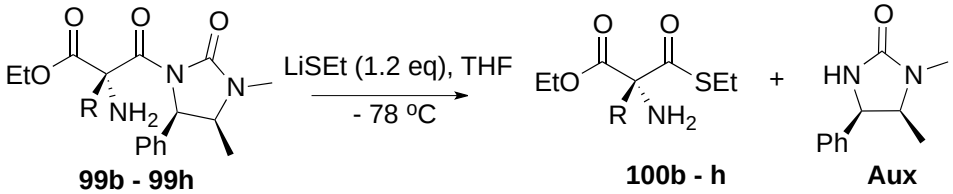


Figure 62. NH_2 assisted removal of the auxiliary with LiSEt.

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



99b - 99h **100b - h** **Aux**

Entry	Cpd	R	Yield of 100 (%)[a]	ee (%)[b]	% of Aux recovered[a]
1	**99b**	Me	93	> 99	98
2	**99e**	*n*-Hexyl	94	> 99	97
3	**99f**	Bn	92	96	98
4	**99g**	Allyl[b]	94	> 99	99
5	**99h**	Propargyl[b]	94	> 99	97

[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.

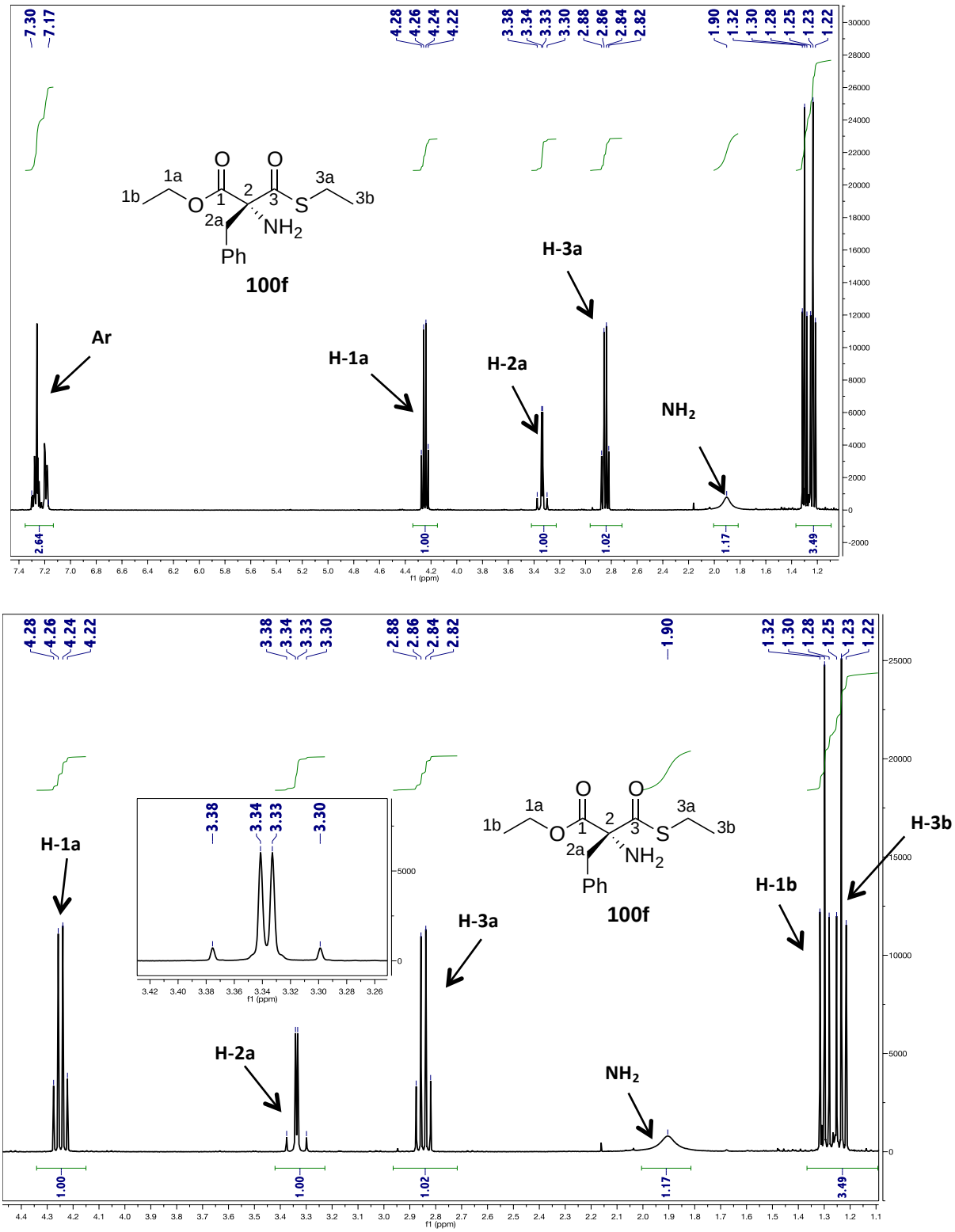


Figure 63. ^{1}H-NMR spectrum of **100f** with expansions.

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.

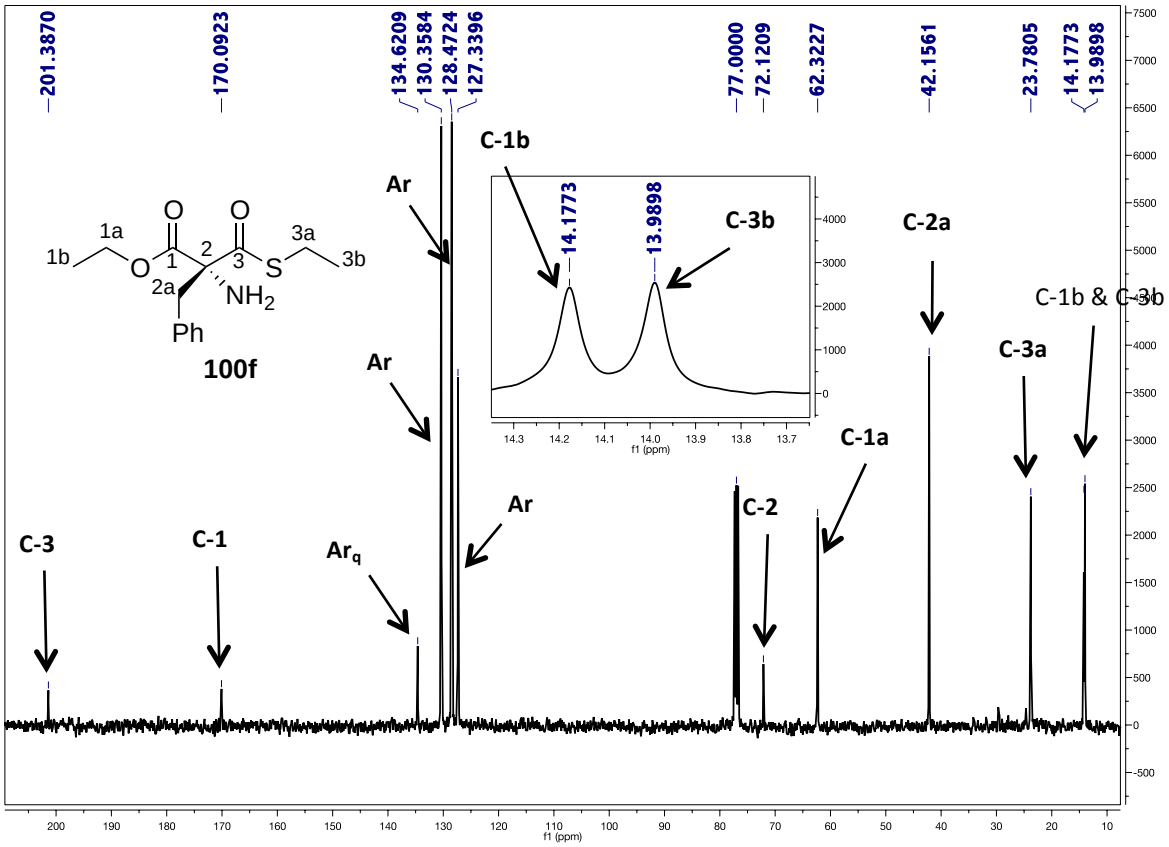
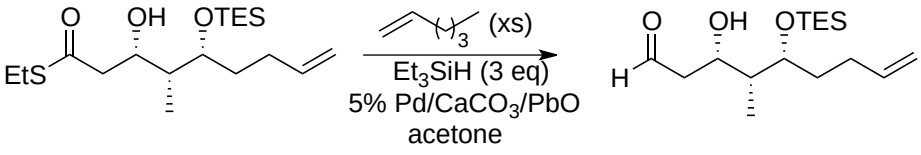


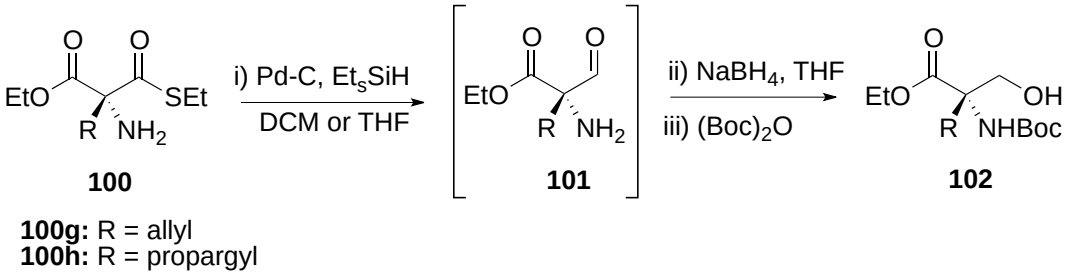
Figure 64. ^{13}C-NMR spectrum of **100f**.

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**).[67]



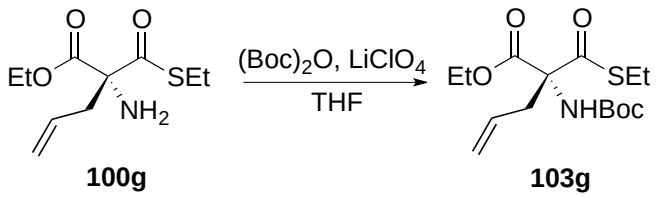
Scheme 90. Evans modifcation of the Fukuyama reduction reported to suppress the reduction of terminal olefins.

Amines are known to poison heterogeneous Pd catalysts, so inspired by the aforementioned 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 $NaBH_4$ 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.



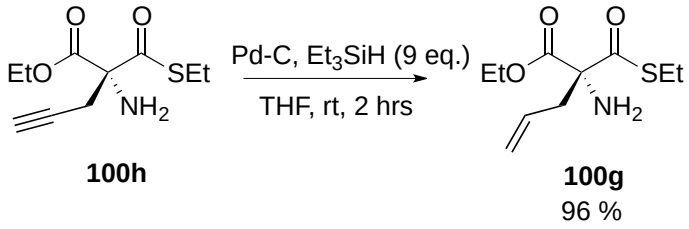
Scheme 91. Envisaged Fukuyama protocol for the conversion of **100** to quaternary serine derivative **102**.

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.**

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.

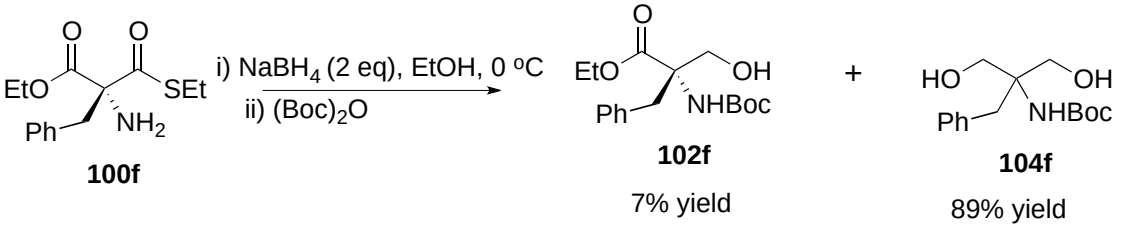


100h **100g** 96 %

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 $NaBH_4$ (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. $NaBH_4$ 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 ^{1}H-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.

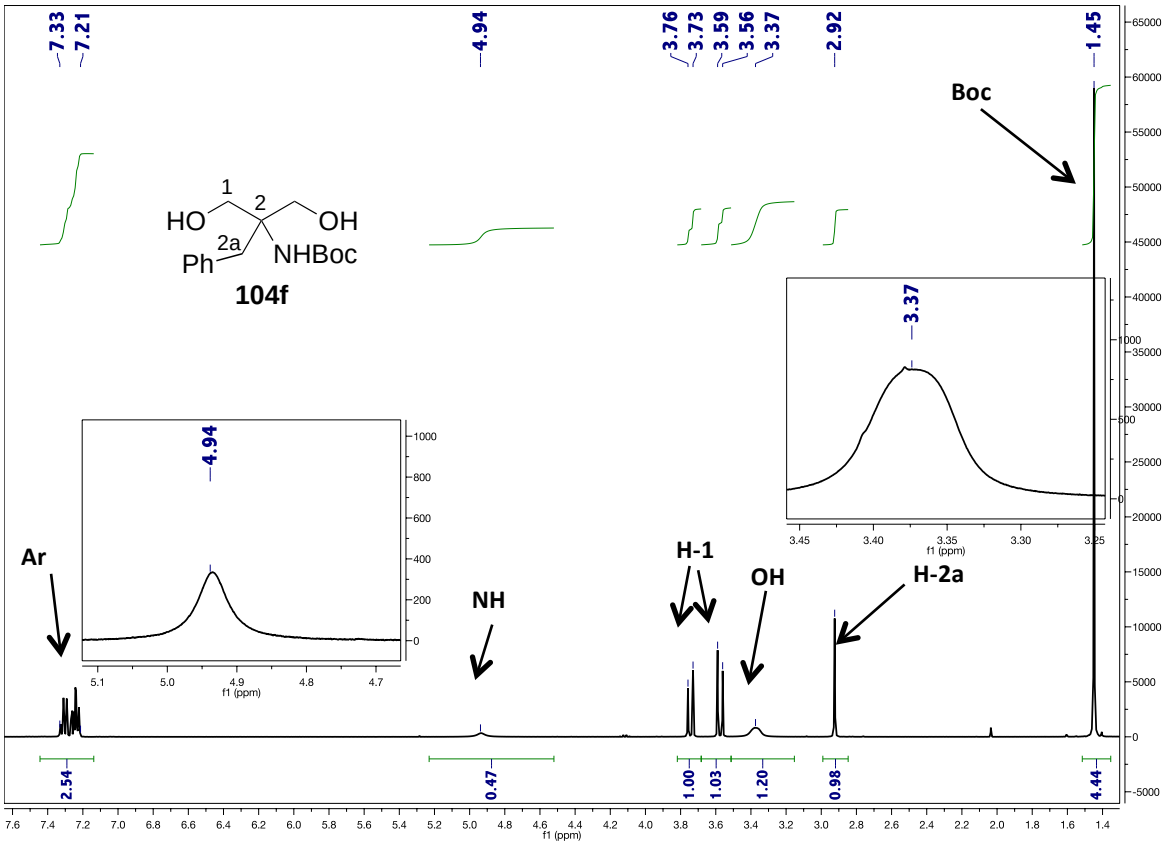
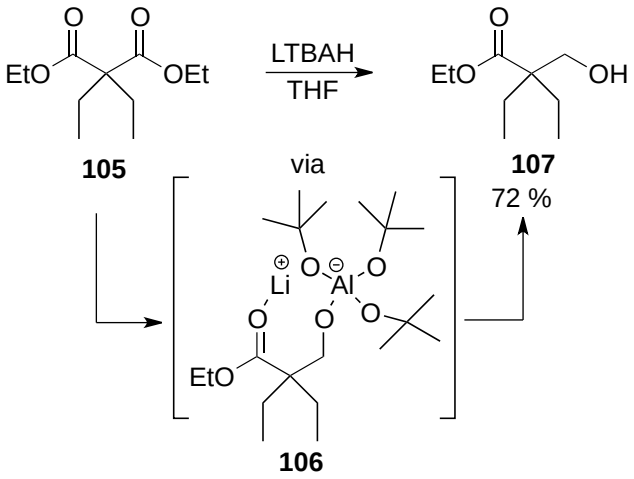


Figure 65. ^{1}H-NMR spectrum of **104f**.

It was thought that since $NaBH_4$ has 4 hydrides per molecule, the over reduction was due to using 2 eq. of $NaBH_4$, 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 di-substituted 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.

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 $NaBH_4$ 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 $NaBH_4$ 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**).

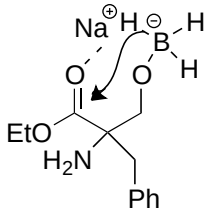
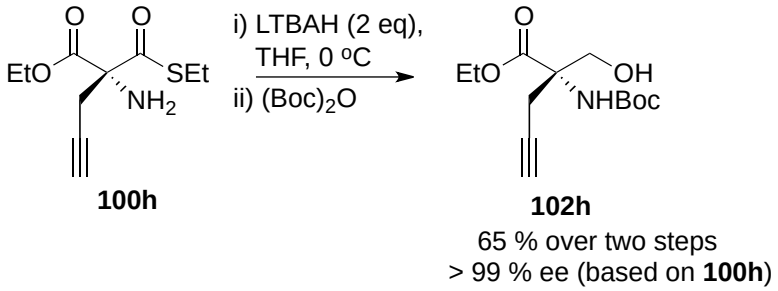


Figure 66. Reduction of both ester and thioester of **100f** due to the activation by the borohydride intermediate.

Although the $NaBH_4$ 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. $(Boc)_2O$ 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)**.



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**.

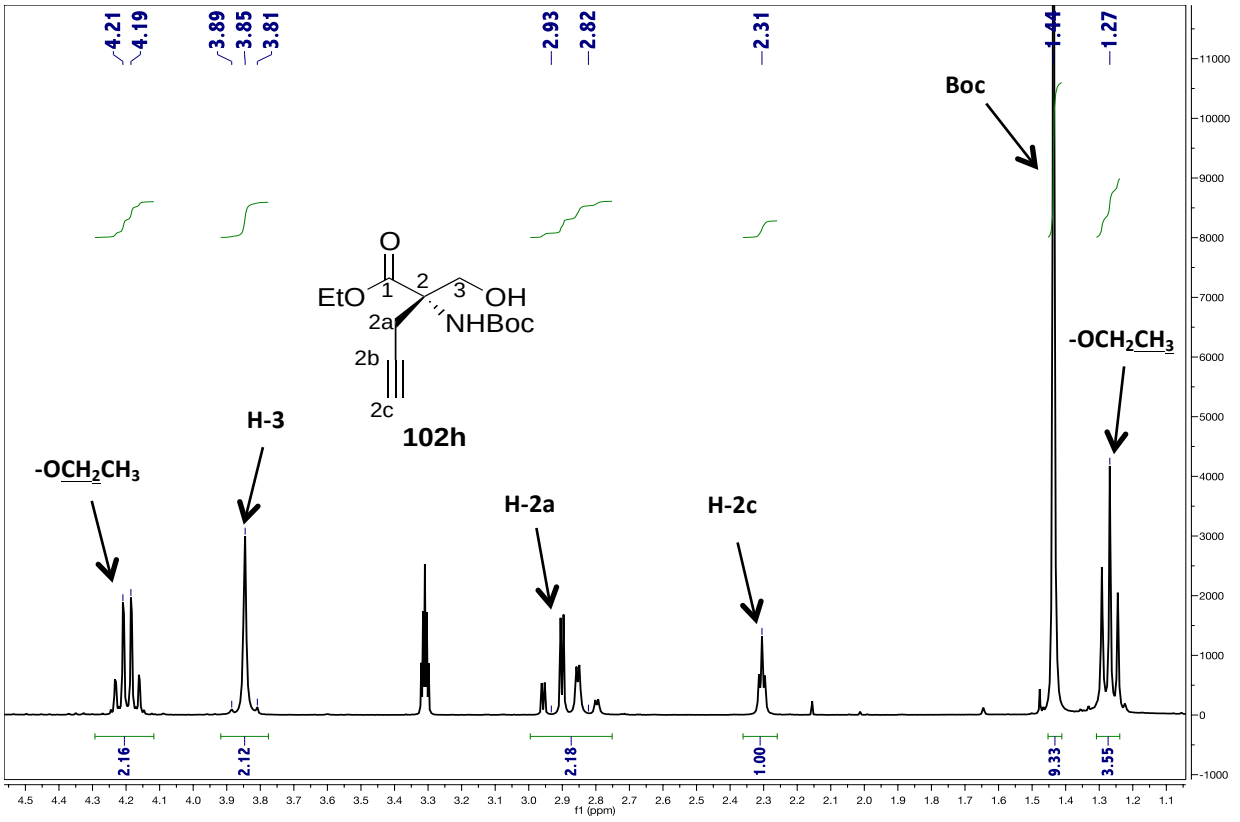


Figure 67. ^{1}H-NMR spectrum of **102h** in CD_3OD

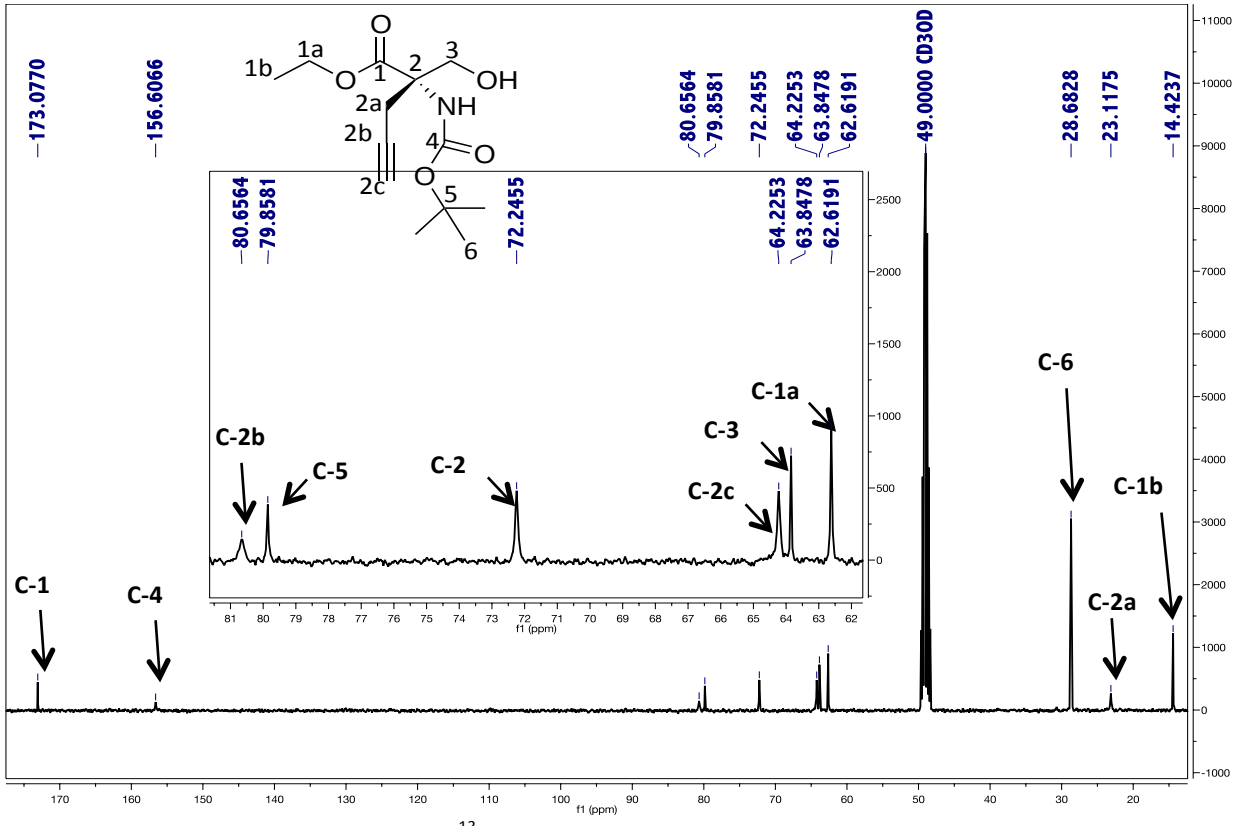
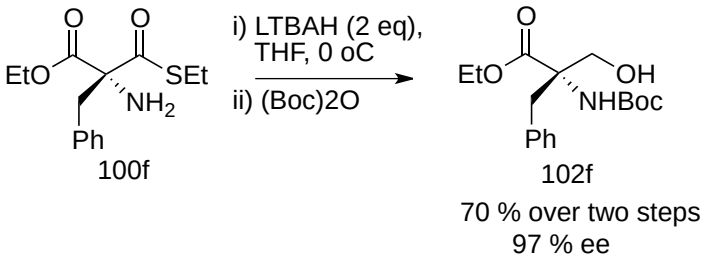


Figure 68. ^{13}C-NMR spectrum of **102h** in CD_3OD.

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 acertained 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.



Scheme 97. Conversion of **100f** to **102f**.

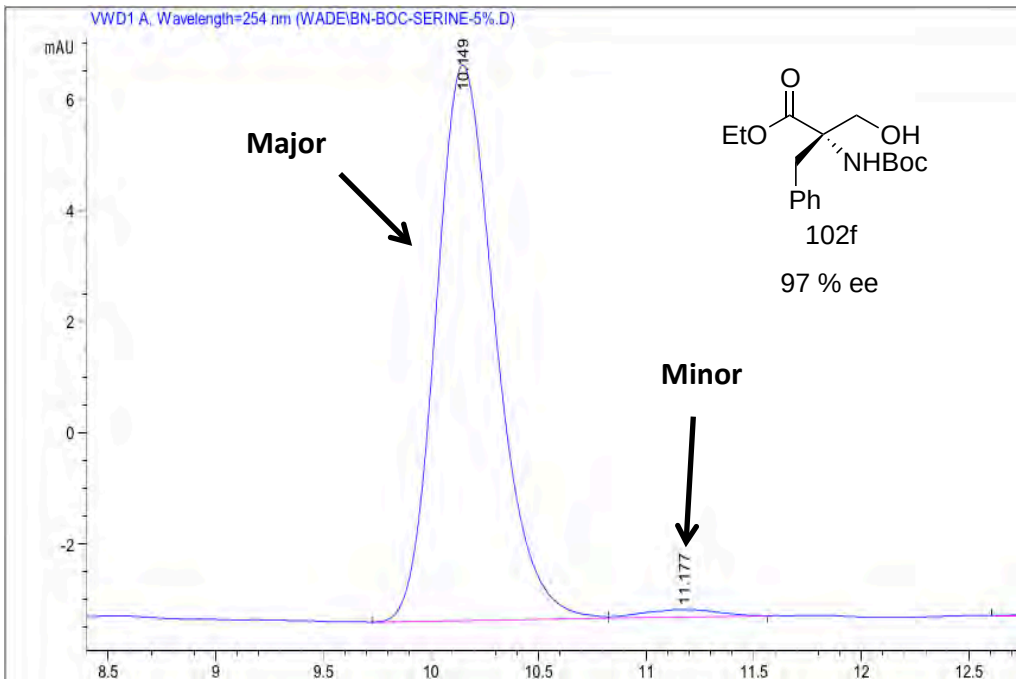


Figure 29. HPLC of **102f**.

The ^{1}H-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.

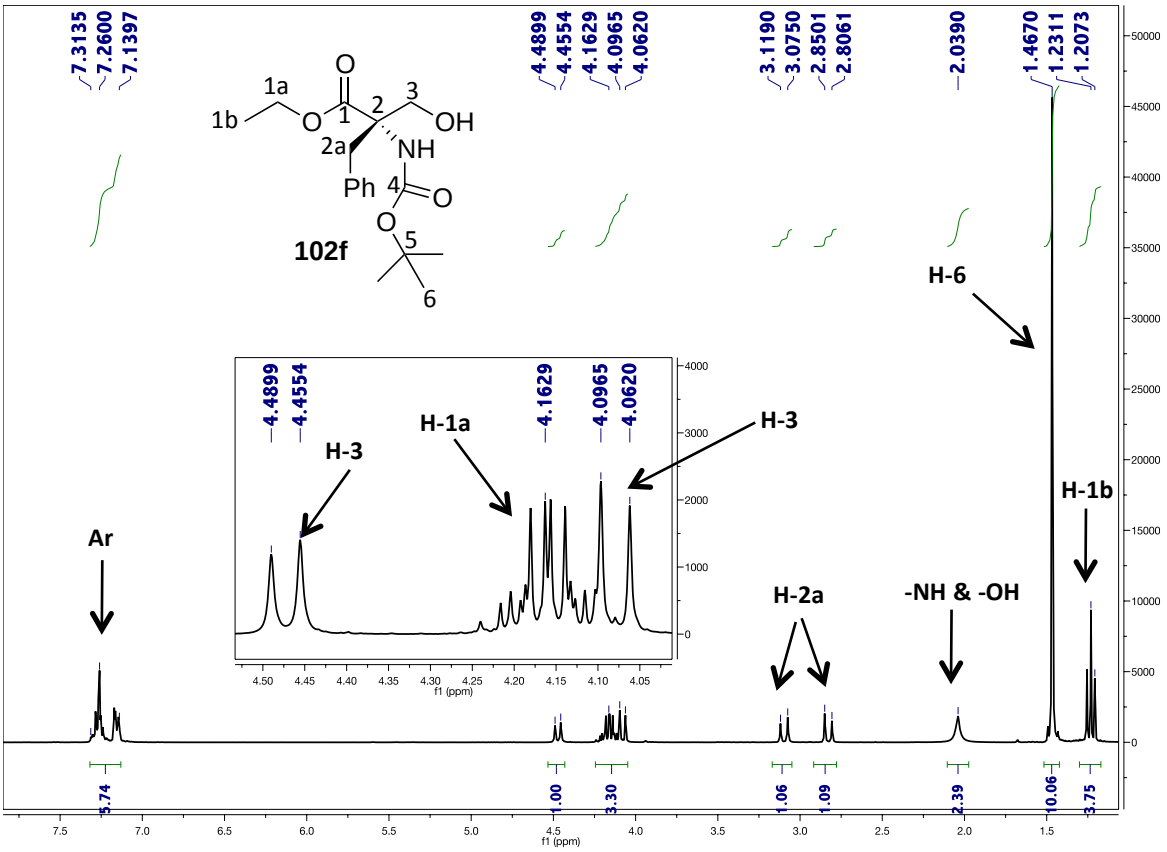


Figure 70. ^{1}H-NMR spectrum of **102f**.

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.

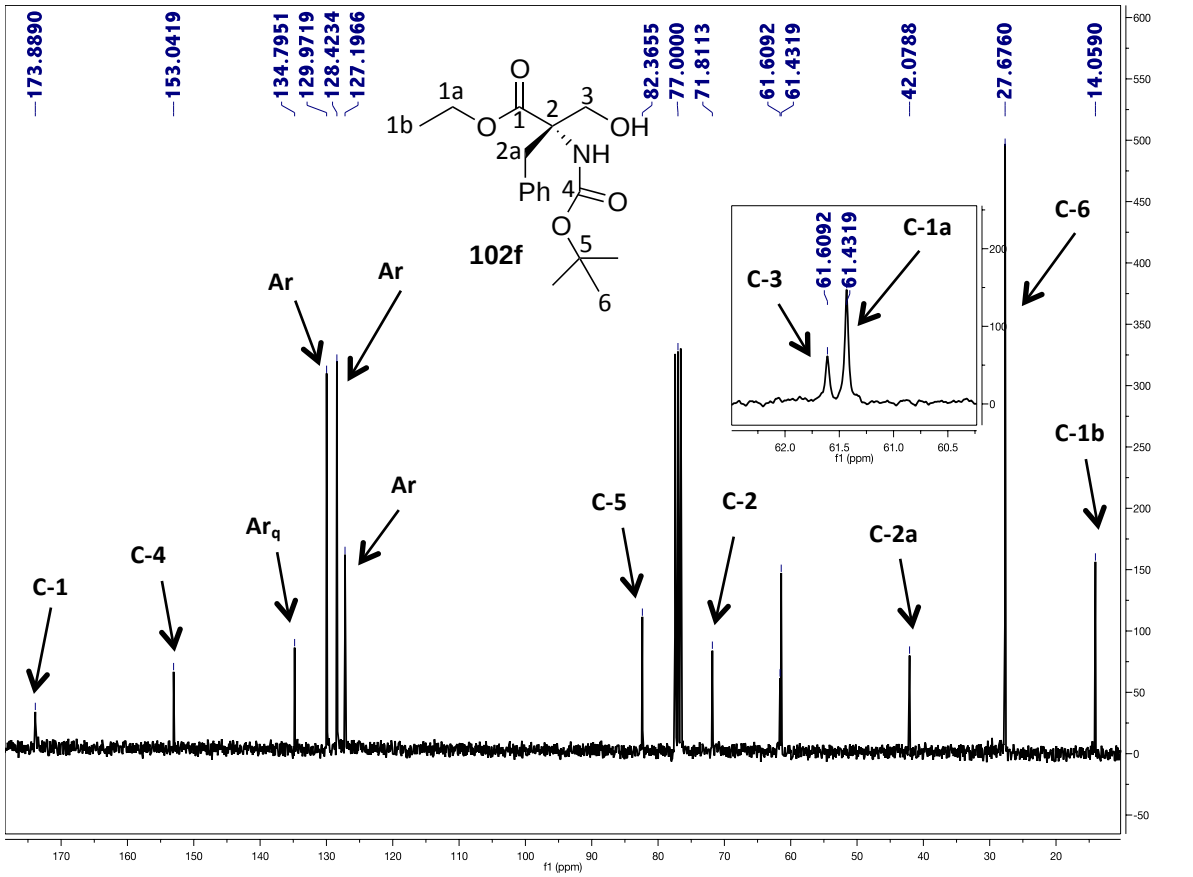
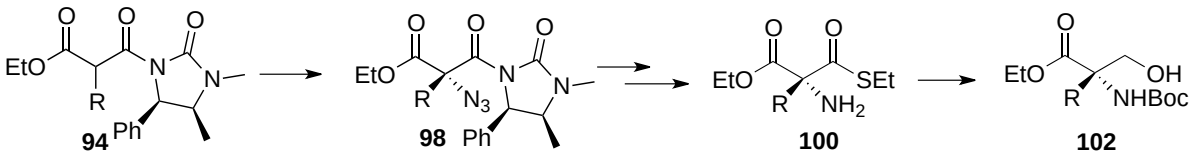


Figure 71. ^{13}C-NMR spectrum of **102f**.

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-*cis*$_{CN}$ conformation. This surprising result was contrary to the s-*trans*$_{C\text{-}N}$ 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. Overall sequence for the general synthesis of α,α-disubstitued 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.

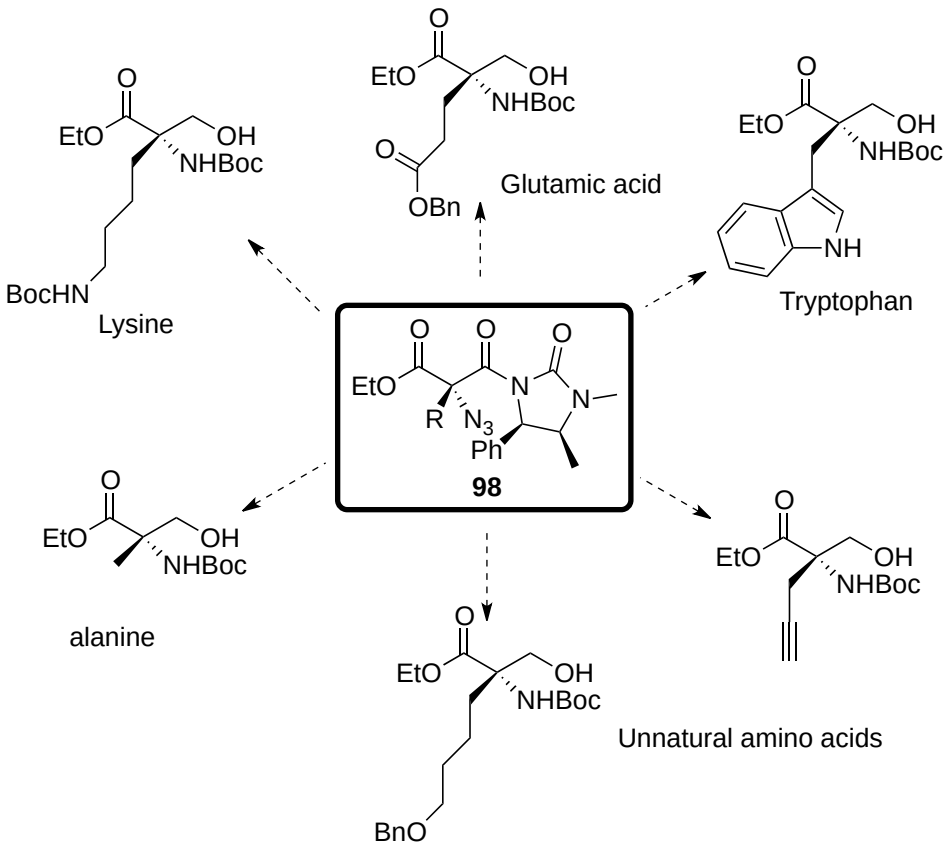


Figure 71. Quaternary amino acids that could be accessed using the developed methodology.

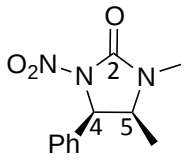
Chapter 4

Experimental

General information

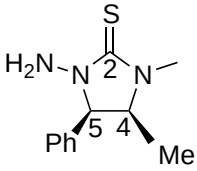
All reagents were available by commercial sources (Sigma-Aldrich, Merck) and were used without further purification. All solvents were freshly distilled. Dichloromethane was distilled from phosphorus pentoxide under nitrogen. Acetonitrile was distilled from calcium hydride under nitrogen. THF was distilled 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 (δ, ppm) of the deuterated solvents used were, $CDCl_3$ (7.26 in ^{1}H NMR and 77.0 in ^{13}C), CD_3OD (4.87 in ^{1}H NMR and 49.2 in ^{13}C NMR). Chemical shifts (δ) 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 λ = 589 nm and 20 °C. The concentration *c* refers to g/100ml.

(4*R*,5*S*)-1,5-dimethyl-3-nitro-4-phenylimidazolidin-2-one (66)



To a stirred solution of KNO_3 (0.848 g, 8.34 mmol) in CH_3CN (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. $NaHCO_3$ (30 mL) was added slowly. The mixture was extracted with DCM (3 x 20 mL), the organic layer dried with $MgSO_4$ 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 ν_{max} (NaCl) / cm^{-1} 1764 (C=O), 1537 (N-O), 1370 (N-O); ^{1}H NMR δ (300 MHz, $CDCl_3$, 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); ^{13}C NMR δ (101 MHz, $CDCl_3$, 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 (Ar_q), 150.9 (C-2); Anal. Calc. for $C_{11}H_{13}N_3O_3$ (%): C, 56.16; H, 5.57; N, 17.86. Found (%) C, 56.35, H, 5.42, 17.67

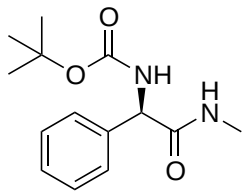
(4*S*,5*R*)-1-amino-3,4-dimethyl-5-phenylimidazolidine-2-thione (81)



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 recrsytallization from DCM/hexane. IR ν_{max} (NaCl) / cm^{-1} 3654 (NH_2), 1650, 1480; ^{1}H NMR δ (400 MHz, $CDCl_3$, 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, NH_2), 4.90 (d, *J* = 9.2 Hz, 1H, H-5), 7.10 (m, 2H, Ar), 7.34 (m, 3H, Ar); ^{13}C NMR δ (101 MHz, $CDCl_3$, 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 (Ar_q), 185.8 (C-2);

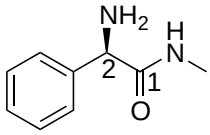
Anal. Calc. for $C_{11}H_{15}N_3S$ (%): C, 59.69; H, 6.83; N, 18.99; S, 14.49. Found (%) C, 59.84; H, 6.74; N, 18.90; S, 14.39.

Tert-butyl (_R_)-(2-(methylamino)-2-oxo-1-phenylethyl)carbamate[67]



To a stirred solution of (*R*)-*N*-Boc-phenylglycine (6.00 g, 23.9 mmol) and *N*-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. $NaHCO_3$ (100 mL) followed by washing with brine (100 mL). After drying over $MgSO_4$, 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 δ (400 MHz, $CDCl_3$, ppm) 1.40 (s, 9H, -$(CH_3)_3$), 2.74 (s, 3H, -NCH_3), 5.18 (s, 1H, -N**H**Me), 5.89 (s, 1H, -CH-), 6.24 (-N**H**Boc) 7.12 – 7.38 (m, 5H, Ar).

(_R_)-2-amino-_N_-methyl-2-phenylacetamide (82)[68]

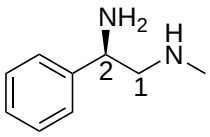


Method A (via aminolysis): To commercially available (*R*)-(-)-phenylglycine hydrochloride methyl ester (5.00 g, 24.8 mmol) was added ethanolic methylamine (12.2 ml, 33 wt %, 129.6 mmol). The reaction was sealed and stirred at rt for 12 hrs. The solvent was then rotary evaporated and the crude slurry taken up in methanol (100 ml). Solid K_2CO_3 (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. $NaHCO_3$ (70 mL) was added. The solution was extracted with chloroform:methanol (1:1, 3 x 50 mL) and dried with Na_2SO_4. 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 %).

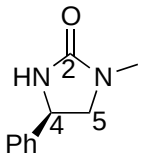
^{1}H NMR δ (300 MHz, $CDCl_3$, ppm) 2.16 (s, 2H, NH_2), 2.76 (d, *J* = 4.8 Hz, 3H, -NCH_3), 4.49 (s, 1H, H-2), 7.09 (bs, 1H, N**H**Me), 7.31 (m, 5H, Ar); ^{13}C NMR δ (101 MHz, $CDCl_3$, ppm) 26.0 (-NCH_3), 59.8 (C-2), 126.9 (Ar), 127.9 (Ar), 128. 8 (Ar), 141.1 (Ar_q), 173.6 (C-1).

(*R*)-*N*^{1}-methyl-2-phenylethane-1,2-diamine (83)[69]



To a stirred slurry of $LiAlH_4$ (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 mixtured stirred for 1 hr. The salts were filtered off and the organic layer dried with $MgSO_4$. 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 ^{1}H-NMR to be used directly in the next step. ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm) 1.71 (bs, 2H, -NH_2), 2.40 (d, *J* = 1.5 Hz, 3H, -NCH_3), 2.71 (m, 2H, H-1), 4.00 (m, 1H, H-2), 7.27 (m, 5H, Ar); ^{13}C NMR δ (101 MHz, $CDCl_3$, ppm) 36.3 (-NCH_3), 55.3 (C-1), 59.9 (C-2), 126.3 (Ar), 127.1 (Ar), 128.4 (Ar), 144.6 (Ar_q).

(*R*)-1-methyl-4-phenylimidazolidin-2-one (84)[70]

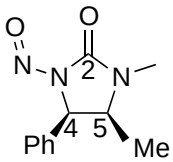


To a stirred solution of (*R*)-N^1-methyl-2-phenylethane-1,2-diamine (3.72 g, 24.8 mmol) in DCM:pyridine (1:1, 30 ml) at -10°C was added triphosgene (2.45 g, 8.26 mmol dropwise in dry DCM (10 mL) and the solution allowed to reach rt and stirred for 4 hrs. DCM (30 ml) was then added and the reaction mixture was then washed with 1M HCl (3 x 30 ml) followed by sat. NaCl (30 ml). The organic layer was then dried with $MgSO_4$, filtered and the product purified by column chromatography after solvent evaporate ion to yield **84** as a colourless solid (3.11 g, 71 %). ^{1}H NMR δ (400 MHz, $CDCl_3$, ppm) 2.79 (s, 3H, -NCH_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); ^{13}C NMR δ (101 MHz, $CDCl_3$, ppm) 30.5 (-NCH_3), 53.6 (C-5), 56.0 (C-4), 126.0 (Ar), 128.0 (Ar), 128.8 (Ar), 141.6 (Ar_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.

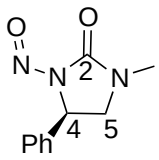
(4*R*,5*S*)-1,5-Dimethyl-3-nitroso-4-phenylimidazolidin-2-one (67):



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_{max} (NaCl) / cm^{-1} 1761 (C=O), 1604, 1426, 1398, 1165; ^{1}H NMR δ (300 MHz, $CDCl_3$, 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); ^{13}C NMR δ (101 MHz, $CDCl_3$, 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

(Ar_q), 162.6 (C-2); Anal. Calc. for $C_{11}H_{13}N_3O_2$ (%): 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):

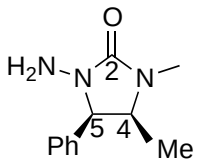


With **84** (0.441 g, 2.50 mmol) to afford **85** as yellow needles (0.503 g, 98 %). m.p. : 117-119 °C; IR ν_{max} (NaCl) / cm^{-1} 1744, 1457, 1427, 1407, 1304; ^{1}H NMR δ (400 MHz, $CDCl_3$, ppm) 3.07 (s, 3H, NMe), 3.33 (dd, *J* = 9.6 Hz, 3.6 Hz, H-5), 3.91 (t, *J* = 9.6Hz, 1H, H-5), 5.28 (dd, *J* = 9.6 Hz, 3.6 Hz, 1H, H-4) 7.12 (m, 2H, Ar), 7.34 (m, 3H, Ar); ^{13}C NMR δ (101 MHz, $CDCl_3$, ppm) 30.5 (NMe), 52.6 (C-5), 53.7 (C-4), 125.4 (Ar), 128.5 (Ar), 129.1 (Ar), 137.5 (Ar_q), 152.9 (C-2); Anal. Calc. for $C_{10}H_{11}N_3O_2$ (%): 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)**

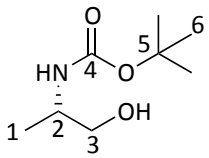
To a stirred solution of *N*-nitroso-2-**imidazolidinone 67** or **85** (2.00 mmol) in ethanol at –10°C was added glacial acetic acid (1.14 ml, 20.0 mmol, 10 eq) followed by zinc dust (0.78 g, 11.9 mmol, 6 eq). The reaction was monitored by TLC to completion (10 – 30 min) The reaction mixture was then 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 $MgSO_4$, 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.

(4*S*,5*R*)-1-amino-3,4-dimethyl-5-phenylimidazolidin-2-one (64):



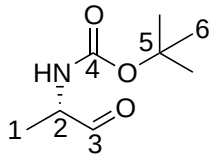
With **67** (0.438 g, 2.0 mmol) afforded **64** as colourless needles (0.411 g, 98 %): m.p: 135-137 °C; IR ν_{max} (NaCl) / cm^{-1} 3685 (NH_2), 1706 (C=O), ^{1}H NMR δ (400 MHz, $CDCl_3$, ppm) 0.72 (d, *J* = 6.6 Hz, 3H, Me), 2.78 (s, 3H, NMe), 3.68 (dq, *J* = 8.3 Hz, 6.6 Hz, 1H, H-4), 3.76 (bs, 2H, NH_2), 4.60 (d, *J* = 8.3 Hz, 1H, H-5), 7.16 (m, 2H, Ar), 7.30 (m, 3H, Ar); ^{13}C NMR δ (101 MHz, $CDCl_3$, 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 (Ar_q), 153.5 (C-2); Anal. Calc. for $C_{11}H_{15}N_3O$ (%): 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]**



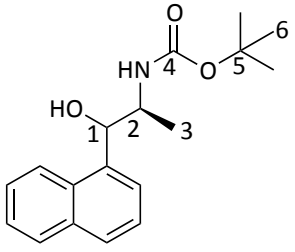
To a stirred suspension of $LiAlH_4$ (6.00 g, 158 mmol) in THF (80 ml) at 0 °C under Argon was added L-alanine (6.00 g, 67.3 mmol) in portions and the solution kept at this temperature for 1 hr. The reaction mixture was then refluxed for 18 hrs and allowed to cool to rt. The reaction flask was then placed 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 $NaHCO_3$ (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 $MgSO_4$, 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 %). ^{1}H NMR δ (300 MHz, $CDCl_3$, 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); ^{13}C NMR δ (101 MHz, $CDCl_3$, 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**[72]



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. NEt_3 (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. $NaHCO_3$ (30 ml) and subsequently dried with $MgSO_4$ 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, $CDCl_3$, 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),

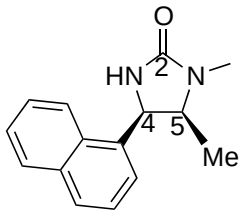
***Tert*-butyl-((2*S*)-1-hydroxy-1-(naphthalen-1-yl)propan-2-yl)carbamate (88)**



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. NH_4Cl (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 $MgSO_4$, filtered and the solvents removed under reduced pressure to give a clear oil. The product

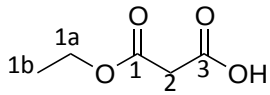
was purified by flash chromatography to afford the title compound as a 3:1 mixture of diastereomers (1.46 g, 84 %) by ^{1}H NMR evaluation. For characterization purposes, one of the diastereomers was isolated. IR ν_{max} (NaCl) / cm^{-1} 3439 (O-H), 1215 (C=O); ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm) 0.93 (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 δ (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)



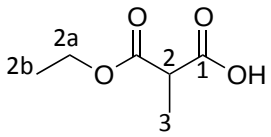
To a slurry of LiAlH4 (0.630 g, 16.5 mmol) in THF (15 mL) at 0 °C was added slowly a solution of **88** as two diastereomers (1.00 g, 3.32 mmol) in THF (10 mL) and the mixture refluxed for 12 hrs. The reaction mixture was then quenched slowly with a solution of NaOH (3.75 M, 7.50 mmol, 2.0 mL) solution 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 δ (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)



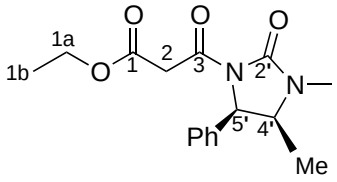
To a stirred solution of diethyl malonate (5.00 g, 31.2 mmol) in EtOH (100 mL) at 0°C was added dropwise ethanolic KOH (1.87 M, 20 mL, 1.1 eq) and the reaction stirred for 12 hrs. A solution of HCl (2 M, 20 mL) was then added and the ethanol removed under reduced pressure. The resulting aqueous solution was extracted with EtOAc (3 x 30 mL) and the organic layer dried with $MgSO_4$. 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 %). ^{1}H NMR δ (400 MHz, $CDCl_3$, 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); ^{13}C NMR δ (101 MHz, $CDCl_3$, ppm) 14.0 (C-1b), 40.9 (C-2), 61.9 (C-1a), 166.7 (C-1), 171.1 (C-3).

2-Ethoxycarbonylpropanoic 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 $MgSO_4$. 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 %). ^{1}H NMR δ (400 MHz, $CDCl_3$, 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); ^{13}C NMR δ (101 MHz, $CDCl_3$, 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-((4*S*, 5*R*)-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. $NaHCO_3$ (3 x 30 ml). The organic layer was dried with $MgSO_4$ and subjected to flash chromatography to afford the title compound (1.47 g, 92 % yield).

Method B (BtCl / PPh_3):

To a stirred solution of PPh_3 (2.38 g, 9.08 mmol) in dry CH_3CN (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 CH_3CN (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 CH_3CN removed under reduced pressure. The residue was dissolved in DCM (40 ml), washed with sat. Na_2CO_3 (3 x 30 ml) and dried with $MgSO_4$. 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. $NaHCO_3$ (3 x 75 mL). The

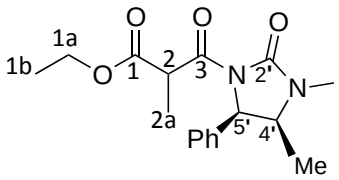
organic extract was then dried with $MgSO_4$ and the product purified by column chromatography after removal of the organic solvent to afford **94a** (7.36 g, 92 %).

94a was obtained as a colourless solid that was recrystallized from EtOAc / hexane. M.p.: 84-85 °C; ; $[\alpha]_D^{20}$ = – 6.2, (*c* = 1.0, DCM); IR ν_{max} (cm^{-1}) 3008, 2860, 1736, 1687; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75.5 MHz, $CDCl_3$) 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 (Ar_q), 155.6 (C2'), 165.1 (C-3), 167.7 (C-1); Anal. Calc. for $C_{16}H_{20}N_2O_4$ (%): 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):

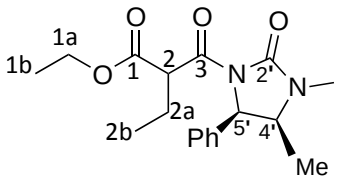
To a stirred solution of **94a** (0.500 g, 1.64 mmol) in dry THF (30 mL) at – 45 °C under an Argon atmosphere was added a solution of KHMDS in toluene (0.5 M, 3.94 mL, 1.97 mmol) dropwise and the reaction mixture allowed to stir at this temperature for 30 min. The appropriate alkylating agent (1.97 mmol, 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. NH_4Cl (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried with $MgSO_4$, 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-((4*S*, 5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-methyl-3-oxopropanoate (94b)



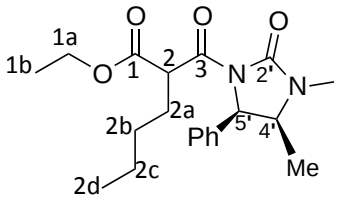
With MeI (0.13 ml, 1.97 mmol, 1.2 eq.) at rt to obtain title compound as an off-white solid (0.501 g, 96 %). Recrystallization from EtOAc/ hexane afforded one diastereomer: mp 152-153 °C; $[\alpha]_D^{20}$ = -31.9, (*c* = 1.0, DCM); IR ν_{max} (cm^{-1}) 3010, 2863, 1732, 1689; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75.5 MHz, $CDCl_3$) 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), 128.5 (Ar), 136.2 (Ar_q), 155.7 (C-2'), 169.0 (C-3), 171.1 (C-1); Anal. Cal. for $C_{17}H_{22}N_2O_4$ (%): C, 64.13; H, 6.97; N, 8.80. Found (%): C, 64.02; H, 7.04; N, 8.89.

Ethyl-3-((4*S*, 5*R*)-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; $[\alpha]_D^{20}$ = - 4.5, (*c* = 1.0, DCM); IR ν_{max} (cm^{-1}) 3010, 2863, 1732, 1689; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C (100.6 MHz, $CDCl_3$) 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), 136.2 (Ar_q), 155.7 (C-2'), 168.1 (C-3), 170.3 (C-1); Anal. Calcd. for $C_{18}H_{24}N_2O_4$ (%): C, 65.04; H, 7.28; N, 8.43. Found (%): C, 64.11; H, 7.31; N, 8.51.

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

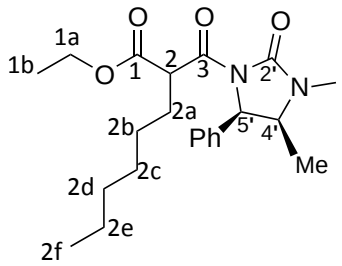


With 1-bromobutane (0.22 ml, 1.97 mmol, 1.2 eq.) and TBAI (0.121 g, 0.328 mmol, 20 mol %) at 65 °C to afford the title compound as a clear oil (0.566 g, 96 %). IR ν_{max} (cm^{-1}) 3010 (Ar), 1732 (C=O, ester and amide), 1689 (C=O, urea); HRMS (ES): calc. 361.2127 for $C_{20}H_{29}N_2O_4$ $[M + H]^+$; requires 361.2129.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) 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); 4.63 (dd, *J* = 5.3, 3.4 Hz, 1H, H-2), 5.31 (d, *J* = 8.6 Hz, 1H, H-5’), 7.10 – 7.30 (m, 5H, Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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_q), 155.7 (C-2’), 168.4 (C-3), 170.4 (C-1).

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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_q), 155.7 (C-2’), 168.8 (C-3), 170.4 (C-1).

Ethyl-3-((4*S*, 5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-*n*-hexyl-3-oxopropanoate (94e)

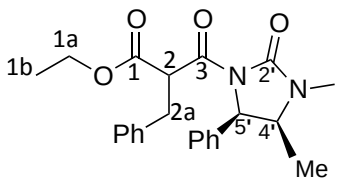


With 1-bromohexane (0.28 ml, 1.97 mmol, 1.2 eq.) and TBAI (0.121 g, 0.328 mmol, 20 mol %) at 65 °C to afford title compound as a clear oil (0.604 g, 95 %). Chromatographic purification afforded a single diastereomer. IR ν_{max} (cm^{-1}) 3010 (Ar), 1732 (C=O, ester and amide), 1689 (C=O, urea); HRMS (ES): calc. 389.2440 for $C_{22}H_{33}N_2O_4$ $[M + H]^+$; requires 389.2443.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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_q), 155.7 (C-2'), 164.8 (C-3), 170.4 (C-1).

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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_q), 155.6 (C-2'), 168.8 (C-3), 170.5 (C-1).

Ethyl-3-((4*S*, 5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-benzyl-3-oxopropanoate (94f)

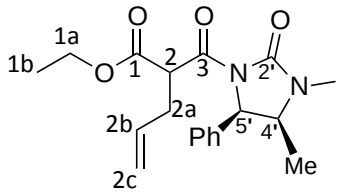


With BnBr (0.24 ml, 1.97 mmol, 1.2 eq.) at rt to obtain 9**4f** as a clear oil (0.606 g, 94 %). Chromatographic purification afforded a single diastereomer. IR ν_{max} (cm^{-1}) 3021 (Ar), 1729 (C=O ester and amide), 1688 (C=O, urea); HRMS (ES): calc. 394.1814 for $C_{23}H_{26}N_2O_4$ $[M + H]^+$; requires 395.1887;

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$, 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, $CDCl_3$, 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_q), 138.5 (Ar_q), 155.3 (C-2'), 167.9 (C-3), 169.5 (C-1);

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$, 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, $CDCl_3$, 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_q), 138.9 (Ar_q), 155.3 (C-2'), 167.3 (C-3), 169.6 (C-1).

Ethyl-3-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-allyl-3-oxopropanoate (94g)

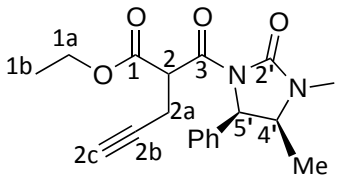


With allyl bromide (0.17 ml, 1.97 mmol, 1.2 eq.) at rt to afford the title compound as a clear oil (0.549 g, 97 %). IR ν_{max} (cm^{-1}) 3010 (Ar), 1732 (C=O, ester and amide), 1689 (C=O, urea); HRMS (ES): calc. 345.1814 for $C_{19}H_{25}N_2O_4$ $[M + H]^+$; requires 345.1813.

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_q), 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_q), 155.1 (C-2'), 170.7 (C-3), 171.6 (C-1).

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

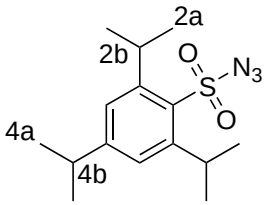


With propargyl bromide (80 % in toluene, 0.22 ml, 1.97 mmol, 1.2 eq.) at rt to obtain 9**4h** as a clear oil (0.537 g, 96 %). HRMS (ES): calc. 343.1658 for $C_{19}H_{23}N_2O_4$ $[M + H]^+$; requires 345.1663.

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]

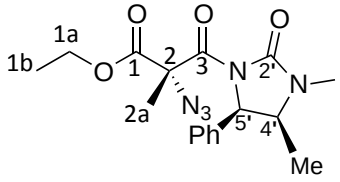


To a stirring solution of 2,4,6-triisopropylbenzenesulfonyl chloride (2.00 g, 6.60 mol) in H_2O:acetone (1:1, 50 ml) at 0 °C was added NaN_3 (0.52 g, 7.92 mmol) slowly and the reaction mixture stirred for 2 hrs. The solution was then reduced to half its volume under reduced pressure over a 30 °C water 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 KHMDS 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. $NaHCO_3$ (40 mL) and the organic material extracted with EtOAc (3 x 30 ml). The combined organic extracts were dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. A sample of this residue was analyzed by chiral HPLC in order to determine the diastereoselectivety of the azidation, and the rest subjected to chromatographic purification to afford **98b – 98h.** Analytical samples were prepared by recrystallization from diethyl ether.

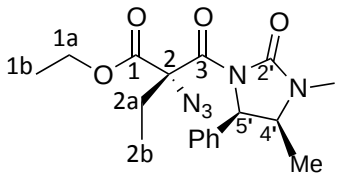
(2*S*)-Ethyl-2-azido-3-((4*S*, 5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-methyl-3-oxopropanoate (98b)



With **94b** (0.500g, 1.57 mmol), KHMDS (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; $[\alpha]_D^{20}$ = -43.7 (c = 0.60, CH_3Cl); IR ν_{max} (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_{maior} = 4.2 min; τ_{minor} = 4.6 min, > 99:1 dr; ^{1}H NMR δ (400 MHz, $CDCl_3$, 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); ^{13}C NMR δ (101 MHz, $CDCl_3$, 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 (Ar_q), 154.5 (C-2'), 165.6 (C-3), 168.0 (C-1); Anal. Calc. for $C_{17}H_{21}N_5O_4$ (%): C, 56.82; H, 5.89; N, 19.49.

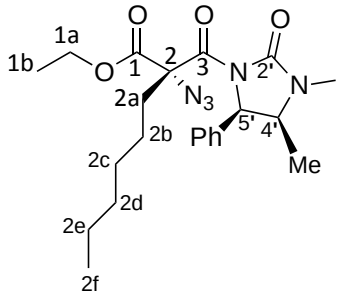
Found (%): C, 56.69; H, 5.99; N, 19.44.

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



With **94c** (0.500g, 1.50 mmol), KHMDS (3.60 ml, 1.80 mmol, 1.2 eq) and trisyl azide (0.557 g, 1.80 mmol, 1.2eq) to obtain **98b** as a white solid (0.541, 96 %). IR ν_{max} (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); ^{1}H NMR (400 MHz, $CDCl_3$, 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); ^{13}C NMR (101 MHz, $CDCl_3$, 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), 128.5 (Ar), 135.9 (Ar_q), 154.6 (C-2'), 165.2 (C-3), 167.1 (C-1). Anal. Calc. for $C_{18}H_{23}N_5O_4$ (%): C, 57.90; H, 6.21; N, 18.76. Found (%): C, 57.95; H, 6.23; N, 18.88.

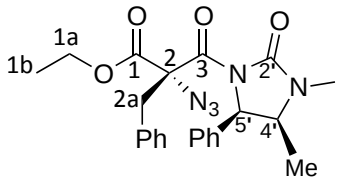
(2*S*)-Ethyl-2-azido-3-((4*S*, 5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-hexyl-3-oxopropanoate (98e)



With **94e** (0.500g, 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 (0.541g, 98 %); $[\alpha]_D^{20}$ = -59.4 (c = 0.65, CH_3Cl); IR ν_{max} (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

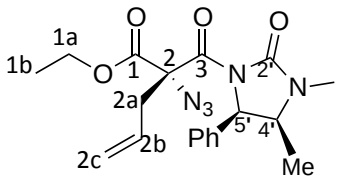
column (hexane/*i*-PrOH (70/30): flow rate 1.0 mL/min: τ maior = 12.4 min; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.80 (d, *J* = 6.7 Hz, 3H, H-Me), 0.85 (t, *J* = 6.5 Hz, 3H, H-2f), 1.08 – 1.52 (m, 8H, H-2e-b), 1.32 (t, *J* = 7.1 Hz, 3H, H-1b), 1.95 – 2.29 (m, 2H, H-2a), 2.80 (s, 3H, -NMe), 3.94 (dq, *J* = 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);). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 14.0 (C-2f), 14.2 (C-Me), 15.0 (C-1b), 22.5 (C-2e), 23.6 (C-2d), 28.2 (C-NMe), 29.1 (C-2c), 31.5 (C-2b), 33.6 (C-2a), 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 (Ar_q), 154.6 (C-2'), 165.3 (C-3), 167.1 (C-1); HRMS (ES): calc. 430.2454 for $C_{22}H_{32}N_5O_4$ $[M + H]^+$; requires 430.2459.

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



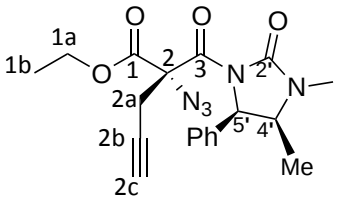
With **94f** (0.500g, 1.27 mmol), KHMDS (3.04 ml, 1.52 mmol, 1.2 eq) and trisyl azide (0.471 g, 1.52 mmol, 1.2 eq) to obtain **98f** as a colourless solid (0.499 g, 90 %); $[\alpha]_D^{20}$ = -73.3 (c = 0.80, CH_2Cl_2); m.p.: 122 – 124 °C; IR ν_{max} (NaCl) / cm^{-1} 2125 (azide), 1733 (C=O ester and 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: τ maior = 9.7 min; τ minor = 11.0 min. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 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), 3.98 (dq, *J* = 8.5 Hz, 6.6 Hz, 1H, H-4'), 4.22 (q, *J* = 7.2 Hz, 2H, H-1a), 5.31 (d, *J* = 8.5 Hz, 1H, H-5'), 7.03 – 7.37 (m, 10H, Ar); ^{13}C NMR δ (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 (Ar_q), 135.5 (Ar_q), 154.8 (C-2'), 165.0 (C-3), 166.6 (C-1) ; Anal. Calc. for $C_{23}H_{25}N_5O_4$ (%): C, 63.44; H, 5.79; N, 16.08. Found (%): C, 63.65; H, 5.81; N, 16.21.

(2*S*)-Ethyl-2-azido-3-((4*S*, 5*R*)-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 ν_{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: τ_{maior} = 3.6 min. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 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) δ 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_q), 154.5 (C-2'), 165.6 (C-3), 168.0 (C-1). Anal. Calc. for $C_{19}H_{23}N_5O_4$ (%): C, 59.21; H, 6.01; N, 18.17. Found (%): C, 59.43; H, 5.90; N, 18.28.

(2*S*)-Ethyl-2-azido-3-((4*S*, 5*R*)-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 ν_{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: τ_{maior} = 8.9 min. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 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

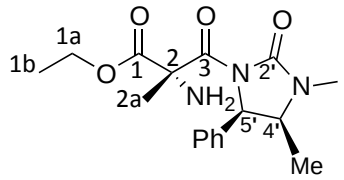
(dq, *J* = 8.7 Hz, 6.6 Hz, 1H, H-4'), 4.31 (q, *J* = 7.1 Hz, 2H, H-1a), 5.37 (d, *J* = 8.7 Hz, 1H, H-5'), 7.13 – 7.36 (m, 5H, Ar); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 14.0 (Me), 15.0 (C-1b), 25.1 (C-2a), 28.1 (NMe), 54.5 (C-4'), 60.2 (C-5'), 62.3 (C-1a), 71.9 (C-2c), 72.5 (C-2), 77.1 (C-2b), 127.3 (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 $C_{19}H_{21}N_5O_4$ (%): 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.

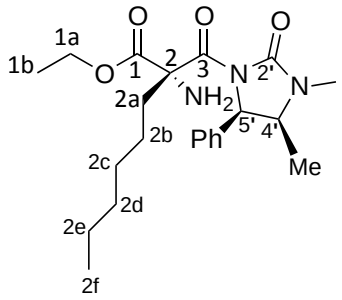
Method B: To a stirred solution of **98** in EtOH:H_2O (9:1) was added ammonium chloride (3 eq) and Zn dust (1.4 eq), and the reaction mixture stirred at rt until complete conversion of the SM (approximately 2 hrs). Occasionally it was necessary to add small amounts of Zn in order to obtain complete 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 reside 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-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-methyl-3-oxopropanoate (99b)



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 sold. m.p.: 115 – 117 °C; $[\alpha]_D^{20}$ = -124.2 (c = 0.50, CH_2Cl_2); IR ν_{max} (NaCl) / cm^{-1} 3418, 1729, 1681, 1645, 1423; ^{1}H NMR (400 MHz, $CDCl_3$, 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, NH_2), 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); ^{13}C NMR (101 MHz, $CDCl_3$, 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 (Ar_q), 155.5 (C-2'), 169.7 (C-3), 173.6 (C-1); Anal. Calc. for $C_{17}H_{23}N_3O_4$ (%): C, 61.25; H, 6.95; N, 12.60. Found (%): C, 61.00; H, 6.82; N, 12.62.

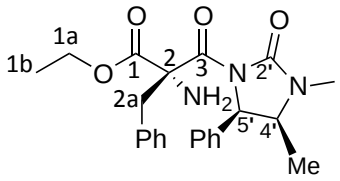
(2*S*)-Ethyl-2-amino-2-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)octanoate (99e)



Via method B: **98e** (0.500 g, 1.16 mmol) in 9:1 EtOH:H_2O (15 ml), NH_4Cl(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; $[\alpha]_D^{20}$ = -100.7 (c = 0.55, CH_3Cl); IR ν_{max} (NaCl) / cm^{-1} 3418, 1729, 1681, 1643, 1426; ^{1}H NMR (400 MHz, $CDCl_3$, 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, -NH_2), 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); ^{13}C NMR (101 MHz, $CDCl_3$, 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_q), 155.5 (C-2'), 169.2 (C-3), 172.4 (C-1); Anal. Calc. for $C_{22}H_{33}N_3O_4$ (%): C, 65.48; H, 8.24; N, 10.41. Found (%): C, 65.37; H, 8.29; N, 10.51.

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

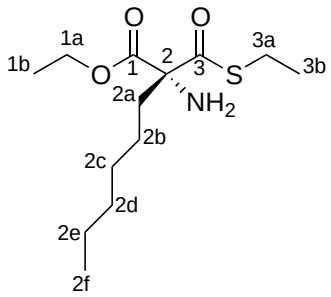


Via method A: **98f** (0.800 g, 1.84 mmol) and Pd-C (0.194 g) to afford **99f** as a white solid (0.737 g, 98 %). M.p.: 141-143; $[\alpha]_D^{20}$ = -11.5 (c = 0.61, CH_2Cl_2); IR ν_{max} (NaCl) / cm^{-1} 3418, 1729, 1681, 1640, 1422; ^{1}H NMR δ (400 MHz, $CDCl_3$, ppm) 0.81 (d, *J* = 6.6 Hz, 3H, Me), 1.23 (t, *J* = 7.2 Hz, 3H, H-1b), 2.34 (s, 2H, NH_2), 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). ^{13}C NMR δ (101 MHz, $CDCl_3$, 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 (Ar_q), 136.2 (Ar_q), 154.6 (C-2'), 167.9 (C-3), 172.3 (C-1); Anal. Calc. for $C_{23}H_{27}N_3O_4$ (%): 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):

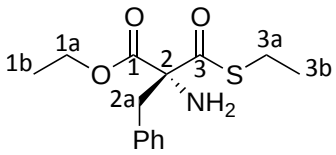
To a stirred solution of ethanethiol (1.2 eq) in dry THF at – 78 °C under Argon was added dropwise a solution of *n*-BuLi in hexanes (1.6 M, 1.2 eq). A solution of **99** in dry THF was then added dropwise. After 2 hrs the reaction was quenched with H_2O (10 mL and extracted with EtOAc (3 x 15 mL), and the combined organic extracts dried with $MgSO_4$. After filtering, the solvent was removed under reduced pressure and the residue subjected to chromatographic purification.

(2*R*)-Ethyl-2-amino-2-((ethylthio)carbonyl)octanoate (100e)



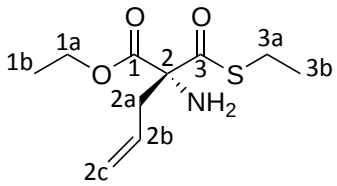
With **99e** (0.450 g, 1.12 mmol), ethanethiol (0.10 ml, 1.34 mmol) and *n*-BuLi (0.84 ml, 1.34 mmol) afforded **100e** as a colourless oil (0.289 g, 94 %). IR ν_{max} (NaCl) / cm^{-1} 3420 (NH_2), 1740 (C=O, C-1), 1688 (C=O, C-3); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.85 (t, *J* = 6.6 Hz, 3H, H-2f), 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).

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



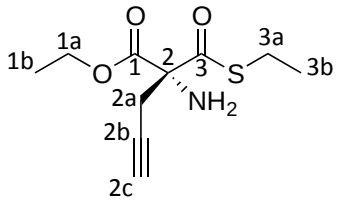
With **99f** (0.450 g, 1.10 mmol) in THF (5 mL), ethanethiol (0.10 ml, 1.32 mmol, 1.2 eq) in THF (10 mL) and *n*-BuLi (0.82 ml, 1.32 mmol, 1.2 eq) afforded **100f** as a colourless oil (0.294 g, 95 %). IR ν_{max} (NaCl) / cm^{-1} 3418 (NH_2), 1741 (C=O, C-1), 1687 (C=O, C-3); ^{1}H NMR δ (400 MHz, $CDCl_3$, 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).

(2*R*)-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 ν_{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) δ 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) δ 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).

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

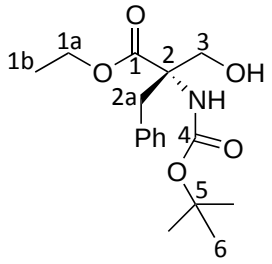


With **99h** (0.500 g, 1.40 mmol), ethanethiol (0.13 ml) and *n*-BuLi (1.05 ml) afforded **100h** as a colourless oil (0.303 g, 94 %). IR ν_{max} (NaCl) / cm^{-1} 3420 (NH_2), 1742 (C=O, C-1), 1689 (C=O, C-3); The enantiomeric excess was determined to be > 99 % by HPLC using a Daicel Chiralpack AD column (hexane/*i*-PrOH (90/10): flow rate 1.0 mL/min: τ_{maior} = 5.7 min. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 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) δ 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 α , α -disubstituted serine derivative 102:

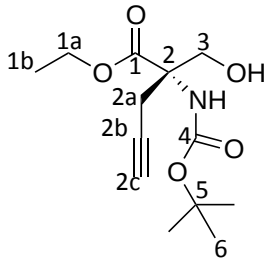
To a stirred solution of **100** in dry THF at 0 °C under an Argon atmosphere was added a solution of LiAl(O-^{t}Bu)$_3$H (2.2 eq) in THF dropwise over a period of 15 min which upon complete conversion of the starting material (approx. 6 hrs) was quenched with HCl (2.0 M, 2 mL). The reaction mixture was then basified with NaOH (2.0 M, 5 mL), and $(Boc)_2O$ (1.4 eq) and DMAP (20 mol %) added. After 8 hrs, H_2O (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)



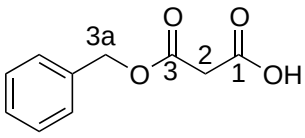
With **100f** (0.120 g, 0.43 mmol) in THF (10 mL) and LiAl(O-^{t}Bu)$_3$H (0.240 g, 0.94 mmol, 2.2 eq) in THF (5 mL), $(Boc)_2O$ (0.131 g, 0.60 mmol) and DMAP (0.011 g, 0.086 mmol) afforded **102f** as a yellow oil (0.095 g, 70 %). $[\alpha]_D^{20}$ = + 2.9 (*c* = 1.0, CH_2Cl_2); The enantiomeric excess was determined to be 96 % by HPLC using a Daicel Chiralpack AD column (hexane/*i*-PrOH (95/5): flow rate 1.0 mL/min: τ_{maior} = 10.14 min; τ_{minor} = 11.18 min. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 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_3OD, ppm) δ 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-^{t}Bu)$_3$H (0.245 g, 0.96 mmol, 2.2 eq) in THF (5 mL), (Boc)$_2$O (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: τ maior = 5.7 min; $[\alpha]_D^{20}$ = + 49.8 (*c* = 0.4, MeOH); ^{1}H NMR (400 MHz, CD_3OD, ppm) δ 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, CD_3OD, ppm) δ 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 $C_{13}H_{22}NO_5$ $[M + H]^+$; requires 272.1496.

3-(Benzyloxy)-3-oxopropanoic acid



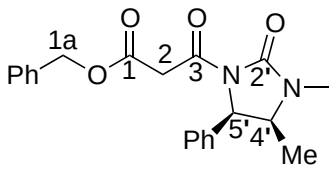
To a stirred solution of malonic acid (2.00 g, 19.2 mmol) and benzyl alcohol (2.00 mL, 19.2 mmol) in dry CH_3CN (50 mL) at 0 °C, was added over a period of 45 min a solution of DCC (19.5 mmol, 0.39 M) in CH_3CN. After 8 hrs the mixture was filtered through celite and the solvent removed under reduced pressure. A solution of sat. $NaHCO_3$ (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 $MgSO_4$ 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 δ (300 MHz, $CDCl_3$, 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 δ (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:

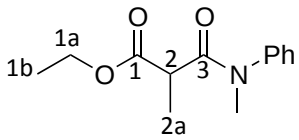
To a stirred solution of PPh_3 in dry CH_3CN at – 10 °C was added in one portion BtCl and after 1 min, the appropriate acid was added dropwise in dry CH_3CN. After 15 min **Aux** or ***N*-methylaniline** was added and the reaction mixture refluxed for 8 hrs. The reaction mixture was allowed to cool to rt and the CH_3CN removed under reduced pressure. The residue was dissolved in DCM (40 ml), washed with sat. Na_2CO_3 (3 x 30 ml) and dried with $MgSO_4$. Following filtration and evaporation the residue was purified by flash chromatography.

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



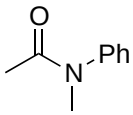
With PPh_3 (0.165 g, 0.63 mmol) in dry CH_3CN (15 ml), BtCl (0.097 g, 0.63 mmol), 3-(Benzyloxy)-3-oxopropanoic acid (0.122 g, 0.63 mmol) in dry CH_3CN (4 ml), and **Aux** (0.100 g, 0.53 mmol to afford the title compound as a clear oil (0.174 g, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.78 (d, *J* = 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_3OD, ppm) δ 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 $C_{21}H_{23}N_2O_4$ $[M + H]^+$; requires 367.1659.

Ethyl-2-methyl-3-(methyl(phenyl)amino)-3-oxopropanoate[74]



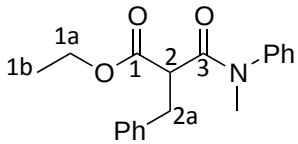
With PPh_3 (0.294 g, 1.12 mmol) in dry CH_3CN (15 ml), BtCl (0.172 g, 1.12 mmol), **93b** (0.164 g, 1.12 mmol) in dry CH_3CN (4 ml) and ***N*-methylaniline** (0.100 g, 0.93 mmol) to afford the title compound as a clear oil (0.219 g, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.20 (t, *J* = 7.1 Hz, 3H, H-1b), 1.27 (d, *J* = 7.0 Hz, 3H, H-2a), 3.28 (s, 3H, -NMe), 3.37 (q, *J* = 7.0 Hz, H-2), 4.08 (m, 2H, H-1a), 7.18 – 7.44 (m, 5H, Ar).

***N*-methyl-*N*-phenylacetamide**[75]



With PPh_3 (0.294 g, 1.12 mmol) in dry CH_3CN (15 ml), BtCl (0.172 g, 1.12 mmol), **acetic acid** (0.067 g, 1.12 mmol) in dry CH_3CN (4 ml) and ***N*-methylaniline** (0.100 g, 0.93 mmol) to afford the title compound as a clear oil (0.135 g, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.86 (s, 3H, CH_3), 3.25 (s, 3H, -NMe), 7.07 – 7.53 (m, 5H, Ar); ^{13}C NMR (101 MHz, CD_3OD, ppm) δ 22.3 (CH_3), 37.1 (NMe), 127.0 (Ar), 127.6 (Ar), 129.6 (Ar), 144.5 (Ar_q), 170.5 (C=O).

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



With PPh_3 (0.294 g, 1.12 mmol) in dry CH_3CN (15 ml), BtCl (0.172 g, 1.12 mmol), 2-**benzyl-3-ethoxy-3-oxopropanoic acid** (0.249 g, 1.12 mmol) in dry CH_3CN (4 ml) and ***N*-methylaniline** (0.100 g, 0.93 mmol) to afford the title compound as a clear oil (0.260 g, 91 %). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.22 (t, *J* = 7.2 Hz, 3H, H-1b), 3.02 – 3.24 (m, 2H, H-2a), 3.15 (s, 3H, -NMe), 3.52 (m, 1H, H-2), 4.13 (m, 2H, H-1a), 6.44 – 7.30 (m, 10H, Ar); ^{13}C NMR (101 MHz, CD_3OD, ppm) δ 14.0 (C-1b), 35.2 (C-2a), 37.3 (NMe), 50.9 (C-2), 61.2 (C-1a), 126.5 (Ar),

127.5 (Ar), 127.9 (Ar), 128.2 (Ar), 129.1 (Ar), 129.4 (Ar), 138.3 (Ar_q), 143.1 (Ar_q), 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.

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