New Methodology for the Synthesis of Chiral, Non-Racemic α-Tertiary Amine Centres: Application to the Synthesis of the Marine Alkaloid Lepadiformine

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Degree of Doctor of Philosophy

By

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Declaration

I declare that *"New Methodology for the Synthesis of Chiral, Non-Racemic α-Tertiary Amine Centres: Application to the Synthesis of the Marine Alkaloid Lepadiformine"* is my own work and that all sources that I have used or quoted have been indicted and acknowledged by means of complete references. I authorise the University to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Ana Andrijevic

Abstract

The development of new methodology for the synthesis of a chiral, non-racemic quaternary carbon bearing an α-nitrogen (an α-tertiary amine or ATA) continues to be an active area of modern research in current synthetic organic chemistry. As a privileged biological scaffold, ATAs are widespread amongst bioactive natural products, providing an inspiration in their complex architecture to synthetic chemists in drug discovery programmes.

Three experimental endeavours comprise this project, which are presented as separate sections of Chapter 2. The first part focuses on new methodology for all-carbon quaternization based on an auxiliary-based diastereoselective alkylation of an auxiliary-malonate, in which an imidazolidinone auxiliary provided excellent facial selectivities in the alkylation in conjunction with KHMDS as the base. Five derivatives were generated in high yields (>85 %) and selectivities (dr >95:5). Extension of the methodology to generate ATAs using the auxiliary-malonate system forms the basis of the second section. This was achieved via a modified Curtius rearrangement protocol performed on quaternary carboxylic acids, in turn obtained from a chemoselective cleavage of a PMB ester malonate-auxiliary system. The ATA products were obtained in high yields and with retention of stereoselectivity, and following the non-destructive removal of the auxiliary by methanolysis, produced enantioenriched α,α-disubstituted alanine and phenylalanine methyl esters. Additional steps on other suitable derivatives furnished α–quaternary proline and lysine derivatives, all in high *ee*s (96 – 98 %). The methodology offers a general approach to the production of enantioenriched ATAs, and in particular, access to both natural and unnatural α,α-disubstituted amino acids.

Application to an attempted synthesis of lepadiformine is described in the final section, whereby the ATA of the alkaloid is constructed in an acyclic form employing the newly developed methodology. Reductive (non-destructive) removal of the auxiliary provided an amino alcohol derivative that was further elaborated via a sequence involving ring-closing metathesis, hydrogenation, hydroxyl group oxidation and Grignard addition to afford a functionalised A-ring of lepadiformine A, with key functionality in place for elaboration to the target. However, dehydration of the tertiary alcohol from the Grignard step, although successful in a related model study, led to problems, bringing the total synthesis endeavour to a close. In spite of this setback, the divergent nature of the approach allows for new designs in the synthetic plan, particularly regarding the order of which the functionalised A ring from this work is elaborated into the A/B/C target.

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This thesis is dedicated to Elena and Mateja Nikolic, my precious star-children. You have moulded me, centred me enriched my life in unimaginable ways and I learn from you every day. I may have birthed you, but you have given me life and my love for you knows no bounds.

Abbreviations

Ac	Acetyl
ACN	Acetonitrile
AcOH	Acetic Acid
aq.	Aqueous
Ar	Aromatic
Ar_q	Aromatic quaternary
ATA	α-Tertiary amine
Bn	benzyl
BnBr	Benzyl Bromide
Boc	*tert*-butoxy carbonyl
Boc_2O	Di-*tert*-butyl dicarbonate
bs	Broad singlet
BtCl	1-Chlorobenzotriazole
BtH	1-*H*-benzotriazole
BtOH	1-Hydroxybenzotriazole
Bu	Butyl
Bz	Benzoyl
BzCl	Benzoyl chloride
CAN	Ceric ammonium nitrate
cat.	Catalytic
Cbz	Benzyloxycarbamate
CF_3COOH	Trifluoreoacetic acid
CH_2Cl_2	Dichloromethane / Methylene chloride
CH_3CN	Acetonitrile
c-Hex	Cyclohexyl
COSY	Correlation spectroscopy
C_q	Quaternary carbon
CSA	Camphorsulfonic acid
d	Doublet
DCC	1,3-Dicyclohexylcarbodiimide
DCM	Dichloromethane / Methylene chloride
dd	Doublet of doublets
DIAD	Diisopropylazodicarboxylate
DIBAL	Diisobutyl aluminium hydride
DIPEA	Diisopropylethylamine
DMAP	4-Dimethyamino pyridine / *N,N*-Dimethyamino pyridine
DME	Dimethyl ether
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DPPA	Diphenyl phosphoryl azide
dr	diastereomeric ratio
dt	Doublet of triplets
E^+	Electrophile
E1	Unimolecular elimination
E2	Bimolecular elimination
ee	Enantiomeric excess
eq.	Equivalent

Et	Ethyl
Et_2O	Diethyl ether
Et_3N	Triethylamine
EtOAc	Ethyl acetate
EtOH	Ethanol
g	Grams
H^+	Acidic conditions
HCl	Hydrochloric acid
Hex	Hexyl
HMPA	Hexamethylphosphoric triamide
HOBt	1-Hydroxybenzotriazole
HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
h	Hour
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
Hz	Hertz
i-Pr	Isopropyl
IR	Infrared spectrometry
J	Coupling constant
KHMDS	Potassium hexamethyldisilazide
LDA	Lithium diisopropylamide
$LiAlH_4$	Lithium aluminium hydride
lit.	Literature
LUMO	Lowest unoccupied molecular orbital
m	*Meta*
m	multiplet
M.p.	Melting point
m/z	Mass to charge ratio
M^+	Molecular ion
Me	Methyl
MeOH	Methanol
mg	Milligram(s)
MHz	Megahertz
ml	Millilitre(s)
mmol	Millimole(s)
Ms	Methanesulfonyl
NaHMDS	Sodium hexamethyl disilazide
NaOMe	Sodium methoxide
NMM	*N*-Methylmorpholine
Nu	Nucleophile
o	*Ortho*
p	*Para*
P.T.	Proton transfer

Pd/C	Palladium-on-carbon
PG	Protecting group
Ph	Phenyl
PMB	*p*-Methoxy benzyl
PPh_3	Triphenylphosphine
PTC	Phase transfer catalysis
Pyr.	Pyridine
q	Quartet
rt	room temperature
s	Singlet
SM	Starting material
S_N1	Unimolecular nucleophilic substitution
S_N2	Biomolecular nucleophilic substitution
t	Triplet
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
t-Bu	*t*-Butyl
td	Triplet of doublets
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
tlc	Thin layer chromatography
TPAP	tetrapropylammonium perruthenate
Ts	p-Toluenesulfonyl
UV	Ultraviolet
δ	Chemical shift in ppm

Table of Contents

Chapter 1: Introduction

Following an overview of general concepts in asymmetric synthesis this review will highlight approaches to the synthesis of α–tertiary amines in which the categorisation is disconnection-based, rather than methodology focused.

1.1 Chiral α-Tertiary Amines

The α-tertiary amine (ATA), *i.e* a tetrasubstituted carbon atom bonded to three carbon and one nitrogen substituents is a structural motif prevalent in numerous alkaloid natural products[1] and other biologically active molecules, and as such of great interest to the synthetic organic chemist. **Fig. 1** shows a selection of alkaloids and drugs featuring the ATA functionality.

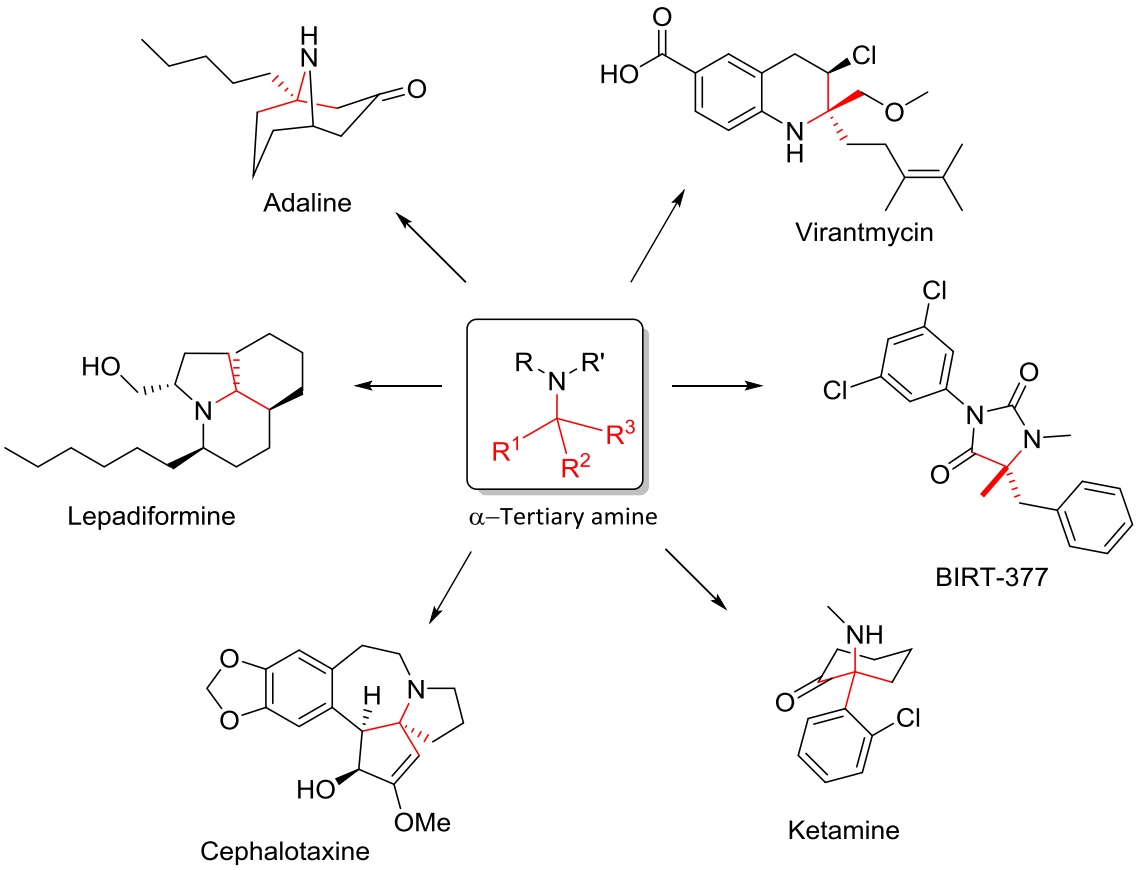


Figure 1 A selection of alkaloids and drugs bearing the ATA motif.

Similarly, small molecules such as α,α-disubstituted amino acids, both proteogenic and non-proteogenic, also presenting the motif, have found increasing applications in biochemical research and drug discovery,[2,3] spurring extensive exploration into the development of dependable and flexible methods for their construction. For the most part, structures bearing fully substituted

carbon centres need to be generated in enantiopure form as this is imperative to their function, creating an additional dimension of difficulty to the task of creating them. Although progress in this field over the last 10 years has been immense, the synthetic challenge is far from completely solved and new methodologies continue to emerge.

1.2 The Synthesis of Enantiopure Compounds

The generation of enantiopure compounds can be achieved by chiral resolution of a mixture of enantiomers, or by asymmetric synthesis via enantioselective catalytic processes or diastereoselective auxiliary-controlled approaches (see **Fig. 2**). This review will only discuss asymmetric synthesis approaches.

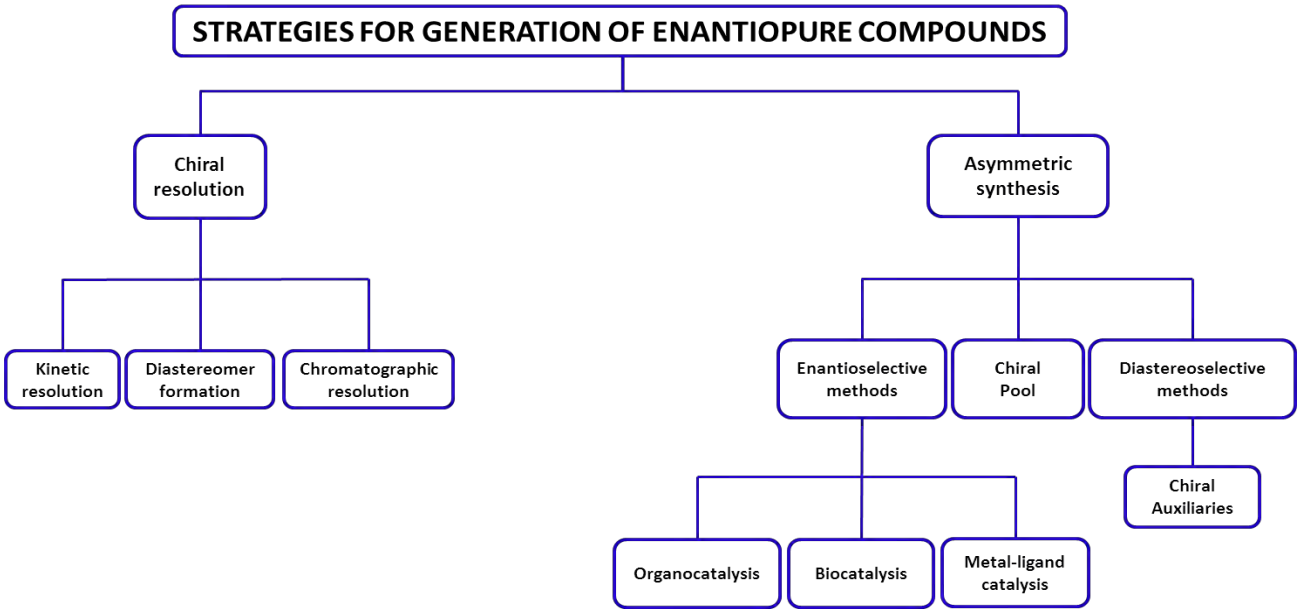


Figure 2 Available strategies for production of enantiopure compounds.

1.2.1 Catalytic Enantioselective Synthesis

Enantiocatalytic asymmetric synthesis is a field of organic chemistry that has experienced massive growth and maturity over the last 15 years,[4] and in which the drive has largely come from the ever-growing demand for chirally pure compounds in the pharmaceutical industry and others. It involves the use of a chiral catalyst in an enantioselective process, in which target molecules can be synthesized without the need for extra steps that are involved in auxiliary formation, attachment and removal. Although the catalysts often also require synthesis, catalyst molecules and complexes are used at much less than stoichiometric amounts, and are at times reusable for a number of cycles, making them cost-effective. The factors determining the efficiency of a chiral catalyst include:

- A high turn-over frequency (TOF), meaning that it should be capable of catalyzing high numbers of transformations quickly and with minimal loss of activity;

- Effectiveness at low catalyst loading;
- The ability to deliver products in high *ee*s.
- A degree of re-usability and ease of separation from the products

Metal catalysts with chiral organic ligands, chiral organic catalysts (organocatalysis) and biocatalysts are the main categories, and a general overview of each of these will be given in the following section.

Metal-ligand catalysis

The discovery of the very first metal-ligand catalytic asymmetric process for asymmetric hydrogenation in 1966 by Noyori and Nozaki[5] marked the birth of asymmetric catalysis from which all further advances and variations have stemmed. Following on from there, asymmetric hydrogenation was pursued by a number of research groups, which resulted in the rapid generation of various ligands and a steady improvement in *ee*s, as well as discoveries for broader application. Today, many of these processes display high enantioselectivities and catalyst efficiencies, making them suitable for industrial applications, asymmetric hydrogenation/reduction and epoxidation being predominant in industry.

Metal-ligand catalysts are generated by complexation of a chiral ligand to the metal, which creates a chiral environment for the reaction to take place and which generally proceeds by further complexation of the substrate/ reagent to the metal or ligands or both. The ligands, therefore, must encompass the correct functionality suited to the reaction in order to provide high reactivity, as well as suitable three-dimensional scaffolds to induce high stereoselectivities. Over the years metal-ligand catalysis has been successfully applied to virtually every reaction class, encompassing a larger variety of transformations than other forms of catalysis and employing numerous transition metals and thousands of chiral ligands. Among the myriad of ligands, there are several compound classes which have proven to have general applicability and versatility, and these are termed privileged ligands.[6] **Fig. 3** shows some of the most important of these classes. With a relatively small number of catalytically useful metals available, the advancement of the field is largely dependent on developing new ligand classes.

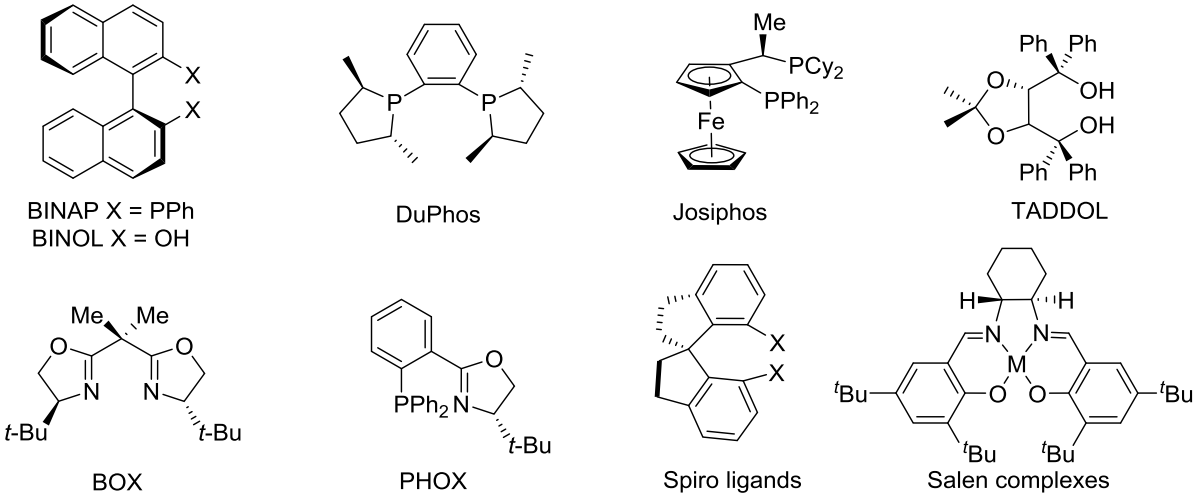


Figure 3 Privileged chiral ligands

Regarding ATA synthesis, examples of successful metal-ligand transformations include aziridinations, electrophilic aminations, electrophilic and nucleophilic alkylations of α-amino esters, additions to ketimines and Steglich rearrangements among others. Selected examples of these will be covered in the relevant section pertaining to each transformation. A downside to metal-ligand catalysis is the considerable cost, toxicity and scarcity of commonly used metal salts (eg Rh, Ru, Ir), which has prompted many researchers to investigate catalytic processes based on non-precious metals, such as Co, Fe and Cu.[7]

Organocatalysis

Notwithstanding the efficiency of metal-ligand catalysis, in recent years focus and effort has shifted to organocatalysis, particularly in the pharmaceutical context, as there is no contamination of final targets with traces of heavy metals. Organocatalysis involves the use of a small organic molecule like proline to promote the catalysis, and these are invariably stable to moisture and air. Although the green chemistry advantage of organocatalysis over metal-ligand type is undeniable, the field is not without its drawbacks. Organocatalysis reactions generally require much higher catalyst loadings and tend to be less general than that of metal-ligand catalysis. Furthermore, their activity and selectivity is often intrinsically connected to substrate structure, with small nuances leading to marked differences in results, in which there are limitations in terms of reaction classes due to specific mechanisms of action.

Although having its origins back in the twentieth century, particularly through the industrially-driven Hajos-Parrish-Eder-Sauer-Wiechert aldol reaction of the 1970s,[8–10] the birth of organocatalysis as we understand it today is usually taken to be only about fifteen years ago following seminal work by MacMillan, Barbas and List.[11–13] Since then, the field of organocatalysis has exploded and continues

to draw massive amounts of interest from researchers. The central idea is to create organic molecules capable of facilitating reactions in which selectivities are comparable to that of enzymatic processes, in effect bringing laboratory processes ever closer to mimicking nature. There are a number of different mechanisms by which this can be achieved: [14]

- Covalent reactive intermediates in which proline and its derivatives as well as imidazolidinone-type catalysts are the main examples (**Fig. 4**)
- Transition-state stabilization via weak interactions such as hydrogen bonding. A good example is Jacobsen's[15] thiourea scaffold as well as a chiral phosphoric acid (**Fig. 4**).[16] Much like how enzymes function, a prochiral molecule is affixed to the catalyst whose asymmetry creates a local chiral environment to the functional site thereby favouring a facial selectivity.
- Chiral phase-transfer catalysts (CPTCs). The CPTC forms an ion pair to facilitate the transfer of an ion or molecule from one reaction phase to another. Here, enantiomerically enriched quaternary ammonium salts are the most commonly used CPTC, particularly those derived from the cinchona alkaloids (**Fig. 4**).

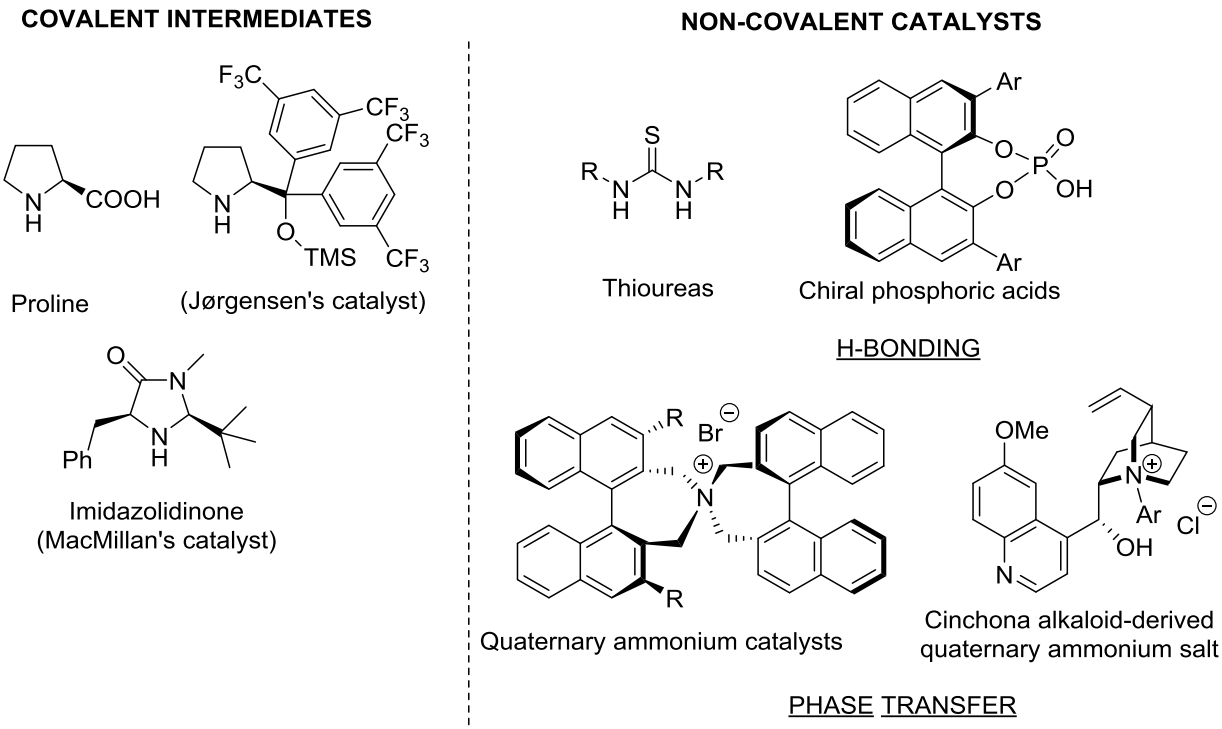
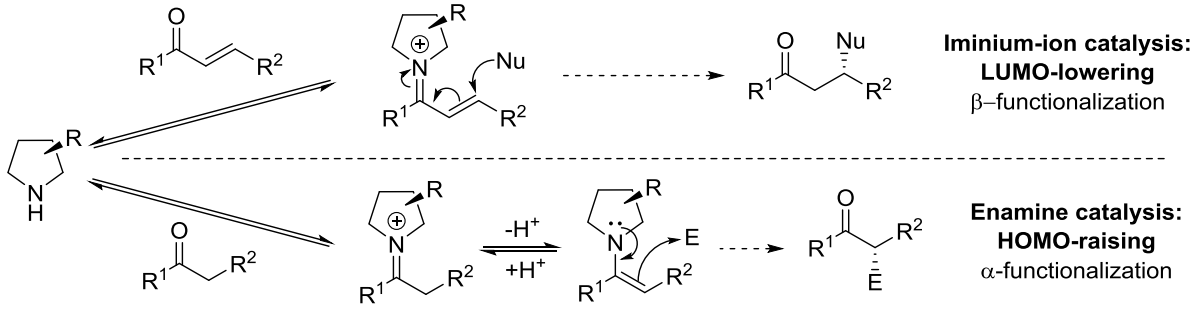


Figure 4 Examples of Organocatalysts and their mechanisms of operation

As is evident from **Fig. 4**, by far the most prevalent chemotype of organocatalysts are chiral amines; hence the field of organocatalysis is often simply termed aminocatalysis. Proline and its derivatives feature prominently as a sub-class, with numerous applications for asymmetric transformations

involving carbonyls. There are two distinct activation modes in aminocatalysis pertaining to carbonyl functionalizations: iminium-ion catalysis and enamine catalysis.[17] These two different pathways allow for both electrophilic and nucleophilic processes (**Scheme 1**).



Scheme 1 Two activation modes of aminocatalysis

Furthermore, opposite stereoselectivities can be achieved via enamine catalysis depending on the type of catalyst involved. In the H-bond directed mode, the approach of the electrophile is influenced by a H-bond donor atom on the catalyst, which effectively pulls the electrophile to add from the same face as the pendant chiral group in the preferred *E*, s-*trans* configuration. If no H-bond donor is present, the chiral group acts as a steric block, thereby promoting the electrophile approach from the opposite face- hence this is termed the steric model. These concepts are depicted in **Fig.5** with Proline and one of the Hayashi--Jørgensen diarylprolinol silyl ether catalysts as representative examples.

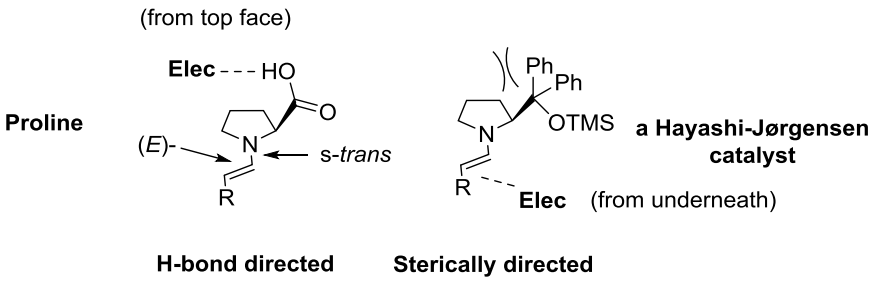


Figure 5 Enamine catalysis modes of chiral induction

The construction of ATAs by aminocatalysis via both covalent and non-covalent mechanisms has become hugely popular, with impressive results across the spectrum of available transformations, and these will be covered in the chemistry section on ATAs.

Biocatalysis[18]

Asymmetric biocatalysis refers to the use of an enzyme or whole cell to affect a stereoselective process. The specificity of an enzyme for only one of the two possible stereoisomers means that half of the starting material is lost in the process. Hence, their application in asymmetric syntheses of natural products is most prevalent in the early stages. The counterpoint of that is the lesser need for

protecting group manipulation, allowing for shorter syntheses. Reaction class applicability is limited to enzymatic processes but their high specificity, efficiency and need for mild (usually aqueous) reaction conditions make them amenable to industrial processes. Most often, enzymes applied to desymmetrizations and chiral resolutions in the context of amino acid synthesis, involve selective hydrolytic enzymes such as lipases, amidases, proteases and esterases. However, their successful application become increasingly difficult when quaternary centres are adjacent to the site of action.

1.2.2 Auxiliary-controlled diastereoselective synthesis[19]

This approach involves the coupling of suitable non-chiral synthetic precursors to a chiral auxiliary prior to a diastereoselective reaction, generating enantio-enriched or enantiopure products after removal of the auxiliary. The use of chiral auxiliaries in enantioselective syntheses is widespread and can be applied to numerous reactions. In general, the following three criteria determine the efficiency of an auxiliary:

- The ease of preparation and attachment.
- The auxiliary should induce a highly selective process and allow for a strong bias of diastereofacial selectivity in the bond being formed.
- A mild and non-destructive removal of the auxiliary must proceed without product racemization.

A plethora of auxiliaries exist today that fulfil the above criteria and some prominent ones are shown in **Fig 6.** Generally, these are derived from inexpensive, chiral natural sources and allow for a high degree of diastereoselectivity. The fact that these processes obviate the use of the auxiliary in stoichiometric quantities is a disadvantage, lessened however, if recovery in good yield is possible at the end of a process. Asymmetric alkylations, aldol and Diels-Alder reactions are examples where auxiliaries are most widely employed.

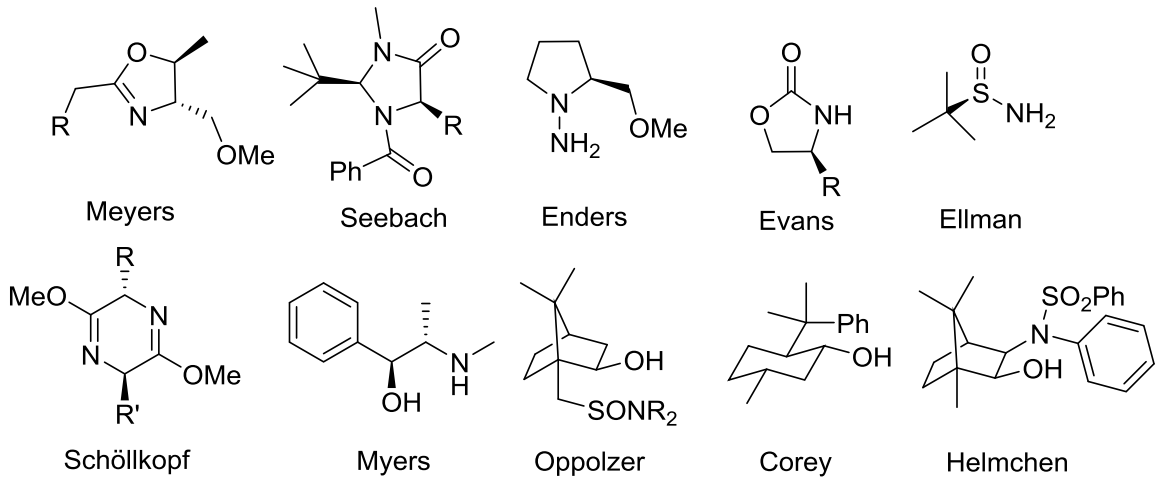
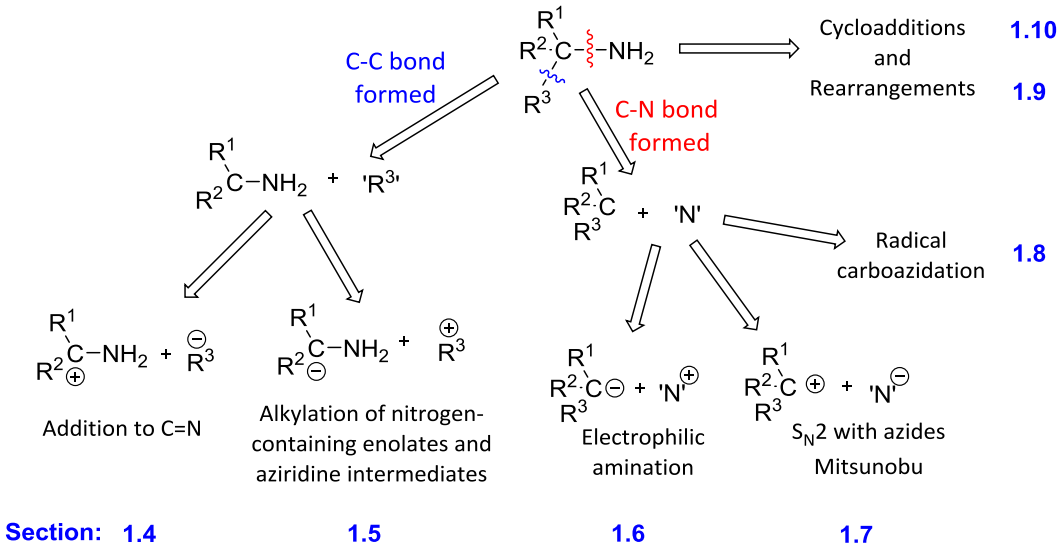


Figure 6 Examples of chiral auxiliaries successfully applied in asymmetric synthesis.

Application of these methodologies will now be discussed for the construction of ATAs, in which the emphasis is on the disconnection and functional group manipulation.

1.3 Categories of Asymmetric ATA Syntheses

As a preamble to the research carried out in the ATA methodology part of the thesis It was decided to illuminate the area by following a disconnection approach focusing on two major classifications for ATA synthesis: one where the quaternary centre comes about from a final C-C bond formation (blue in **Scheme 2**) with the amino group as part of the substrate, and the other where the amino group is installed in the final step (red in **Scheme 2**). These 2 categories can be further sub-divided into processes involving either electrophilic or nucleophilic nitrogen functionality. Cycloadditions and rearrangements have been classed separately. The chapter sub-headings (sections) in the thesis corresponding to these various sub-types are given in blue in **Scheme 2**. Selected lepadiformine syntheses will be reviewed according to the type of transformation employed to generate the ATA of the alkaloid, and as such will be incorporated into the respective category.



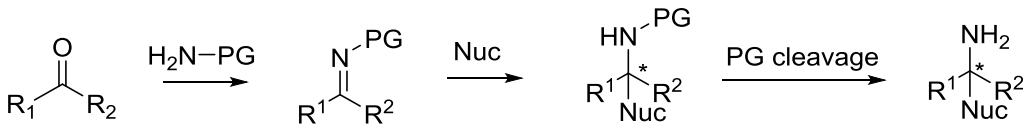
Scheme 2 Classification of ATA synthesis based on the type of bond formed to create the ATA.

1.4 C-C Bond Formation via an Electrophilic N-α-Carbon

The classification where a C-C bond is formed last via an iminium species covers some of the most commonly practiced methods for ATA construction, such as the Strecker and Mannich reactions, the aza-Prins reaction as well as *N*-acyliminium chemistry. Aziridine ring-opening reactions are another example, however these will not be covered.

1.4.1 Ketimine alkylation

Nucleophilic addition to a disubstituted imine (ketimine) derived from a ketone precursor is a direct way of generating an ATA. However, the electrophilicity of an *N*-alkyl-substituted imine is lower than that of its carbonyl counterpart owing to the electronegativity difference of nitrogen compared to oxygen, requiring the use of very reactive nucleophiles. For this reason, electron-withdrawing substituents on the N are called for to enhance the electrophilicity, in which case a wider range of nucleophiles can be used successfully. Popular examples of activating groups are: *N*-sulfinyl ketimines,[20] *N*-phosphenoyl ketimines,[21] *N*,*N*-dialkylated hydrazones[22] and *N*-acyl ketimines.[23] **Scheme 3** shows a typical sequence of imine formation, alkylation to generate the ATA and removal of the nitrogen-bonded group using Ellman's auxiliary



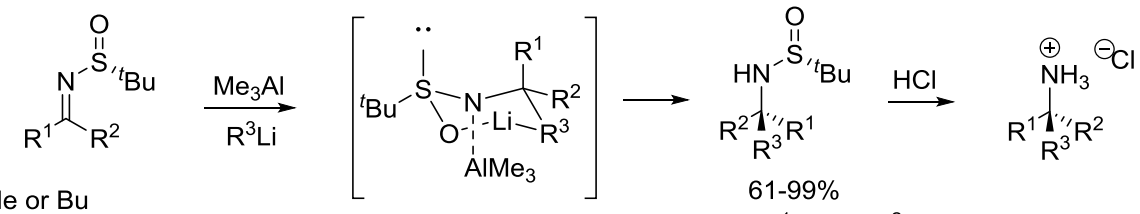
Scheme 3. The sequence of imine formation, nucleophilc addition and removal of the N-bonded group.

Asymmetric synthesis involving acyclic ketimines is further hampered by the equilibration of *E*- and *Z*- imines, a potential deciding factor in the stereo- outcome of the reaction.

Chiral, removable auxiliaries used for diastereoselective alkylations on imines can either be covalently bonded to the *N*-substituent, the carbonyl carbon of the imine, or even be bonded to the nucleophile (See Fig. 4). Alternatively, enantioselective catalytic reactions can be performed on an achiral imine.

Figure 7 Known locations for introduction of chiral auxiliaries for reactions on imines.

Auxiliary-based approaches for the most part utilize the first option in **Fig. 4** derived from the condensation of an enantiopure amine such as an amino acid or a derivative thereof, with a ketone. α-Methylbenzylamine, phenylglycinol, and ephedrine derivatives have all been used successfully as auxiliaries, although the *N*-*tert*-butanesulfinyl chiral sulfonamide auxiliary introduced by Ellman[20] in 1997 is probably the most widely utilized owing to its ease of preparation and removal (by acid) as well as high reaction *de*s. As mentioned, though, for acyclic ketimines a potential drawback is that the degree of selectivity, in keeping with a Zimmerman-Traxler chelated transition state, is largely dependent on the relative steric difference between the 2 substituents on the ketimine. In the example shown in **Scheme 4**,[24] the lowest level of stereoselectivity was seen with R^1 and R^2 as methyl and *i*-butyl even though the steric difference between the two groups is relatively large. In this regard, no reactions were done with groups more similar in size, such as R^1 = Me, R^2 = Et where one would have expected even lower selectivities.

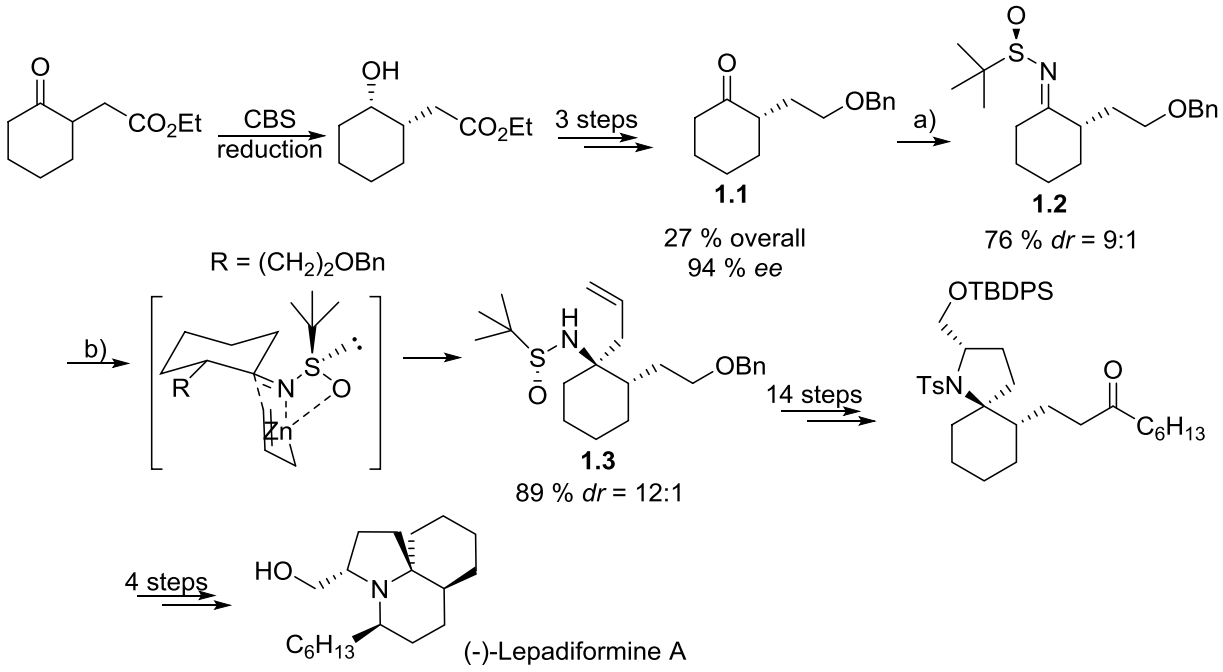


R^1 = Me or Bu
R^2 = ^{i}Pr, Ph, *i*Bu, Bu, ^{t}Bu, 2-Naphthyl
R^3 = Bu, Ph, Me, allylMgBr (no $AlMe_3$), *n*-PrCC, TMSCC

d.r. = 85:15 (R^1 = Me, R^2 = *i*Bu)
d.r = >99:1 (R^1 = Me; R^2 = Ph, *i*Pr, *t*Bu)

Scheme 4 Alkylation with *N*-*tert*-butanesulfinyl ketimines to generate ATAs.

Regarding application in total synthesis Zhao[25] made use of a chiral *N*-*tert*-butanesulfinamide as an asymmetric inductor for the Zn-mediated allylation of ketimine **1.2** to generate the requisite α-tertiary centre in the total synthesis of (-)-lepadiformine (**Scheme 5**).



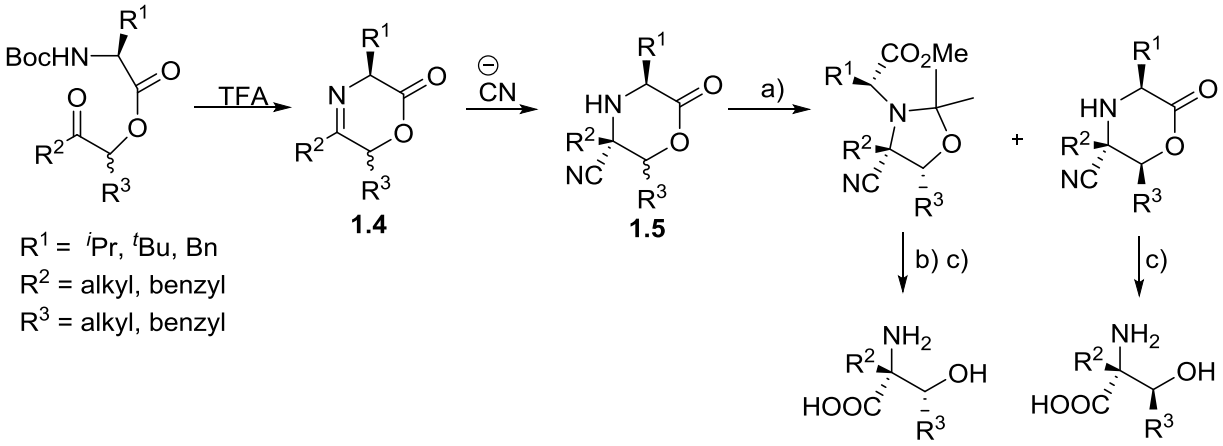
Scheme 5 *Reagents and conditions*: a) $Ti(OEt)_4$/THF, (*R*)-*tert*-butanesulfinamide; b) Zn, allyl bromide/THF.

The ketone **1.1** was generated in an overall yield of 27 % and 94 % *ee* from the corresponding γ-ester via a Corey-Bakshi-Shibata reduction using a dendrimer-supported prolinol catalyst[26] followed by a further 3 steps. Condensation with (*R*)-*tert*-butanesulfinamide provided the desired ketimine **1.2** as a 9:1 mixture of separable diastereomers. Direct allylation of **1.2** with organolithium and Grignard reagents gave very low yields; however, a Zn-mediated allylation proceeded smoothly, giving the ATA product **1.3** in excellent yield and diastereoselectivity. The stereoselectivity was rationalized using a chelate-controlled, chair-like Zimmerman-Traxler transition-state model where coordination of allyl-Zn to the sulfinyl oxygen directs the allylation via axial addition.

1.4.2 Strecker reaction

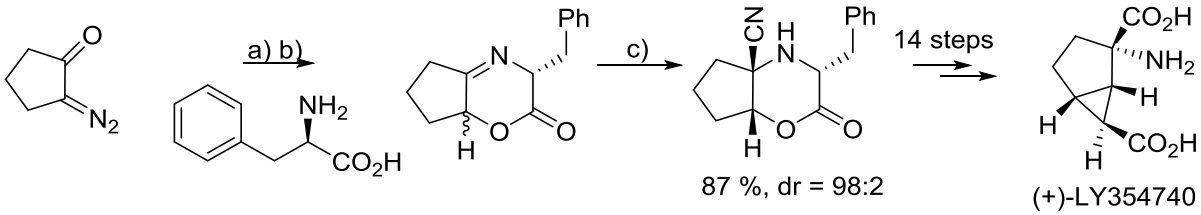
Similarly, the Strecker synthesis involves the addition of cyanide to the C=N bond of an imine to generate an α-aminonitrile, which are versatile intermediates for the synthesis of amino acids via hydrolysis. Chiral sulfinyl ketimines are commonly utilized but don't provide high drs when sterically similar R^1 / R^2 groups are present. Ohfune's[27] use of chiral cyclic ketimines in a diastereoselective Strecker reaction addresses this problem, providing access to a variety of α,α-disubstituted amino acids in high yield and selectivity (**Scheme 6**). Formation of an ester between an L-or D- amino acid and the hydroxyl group of a racemic α-acyloxy ketone followed by condensative cyclization with TFA generates a stereodefined ketimine **1.4** as a mixture of diastereomers relative to the α-acyloxy centre. This undergoes a highly diastereoselective *anti*-addition (relative to the amino acid α-substituent) generating two α-amino nitrile diastereomers **1.5** that can be cleverly resolved via

acetonide formation using 2,2-dimethoxypropane and camphorsulfonic acid. Oxidative cleavage of the auxiliary with ozone, followed by acidic hydrolysis, gave the quaternized amino acid.



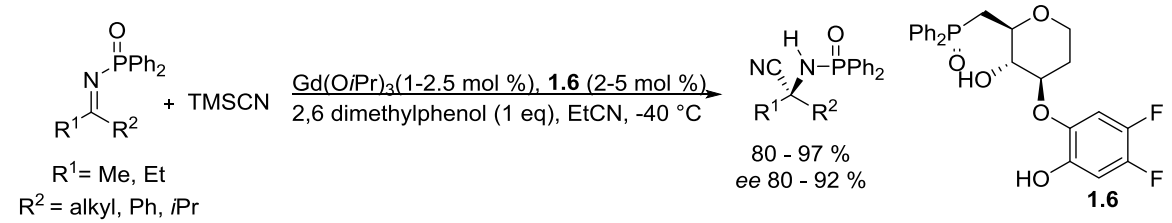
Scheme 6 *Reagents and conditions*: a) 2,2 dimethoxypropane, CSA (0.4 eq); b) H_3O^+; c) i) O_3, -78 °C, MeOH; ii) HCl (conc.) 100 °C, 16h.

This methodology can be extended to cases containing the ATA within a cycle, and a number of complex natural product syntheses have made use of this approach. An example is the synthesis of (+)-LY354740, a metabotropic glutamate receptor agonist as shown in **Scheme 7**.



Scheme 7 *Reagents and conditions*: a) $Cu(acac)_2$, toluene; b) TFA; c) TMSCN, ZnCl, *i*PrOH, rt, 18h

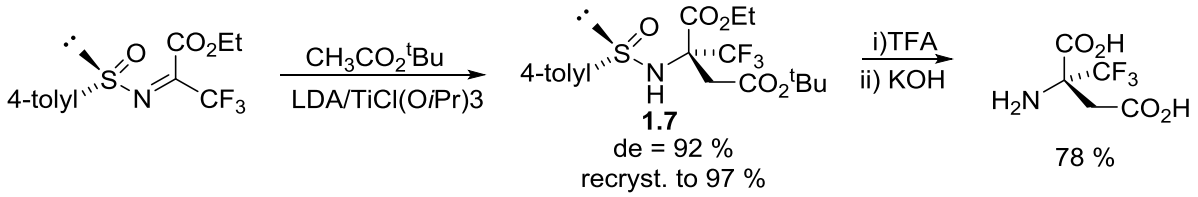
Development of an enantioselective version of the Strecker reaction has also been addressed in recent years ever since Jacobsen's first report in 2000,[15] in which a urea Schiff base catalyst was employed for the enantioselective cyanation of ketimines. Similarly, Shibasaki disclosed a protocol employing an efficient bi-functional gadolinium-based catalyst assembly with ligand **1.6** in 2007[28] for the obtainment of Strecker products in very high yield and enantioselectivity as shown in **Scheme 8**. Understandably, a high selectivity in both of the above-mentioned reports were achieved when R^1 was small and R^2 large. The amino acids were isolated as their HCl salts by refluxing the Strecker products in HCl (removal of phosphinoyl group with concomitant hydrolysis of the cyano group).



Scheme 8 Shibasaki's asymmetric Strecker reaction with ketimines

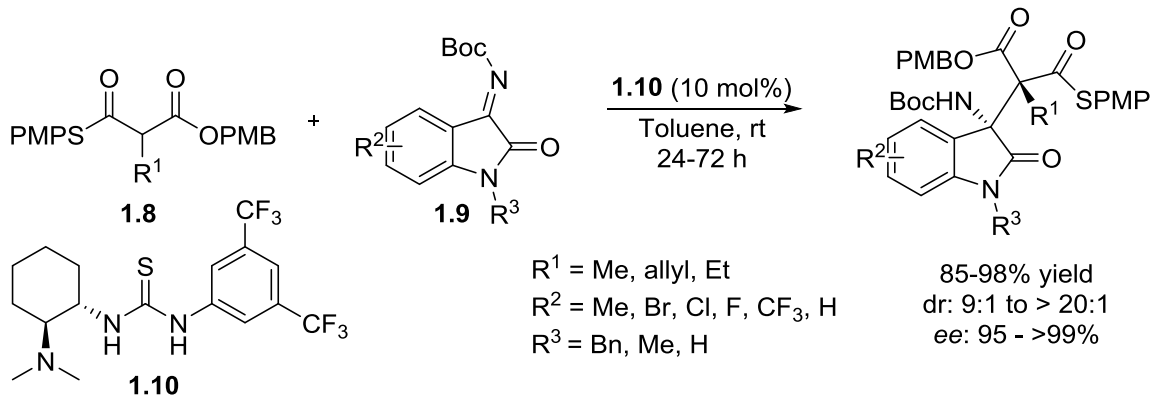
1.4.3 Mannich reactions

Nucleophilic addition of enols or enolates onto ketimines to give ATA structures qualifies as a Mannich reaction, in which efficient stereoselective examples are rare for acyclic variants and require strongly electron-withdrawing groups on the imine to facilitate the reaction. In the synthesis of α-trifluoromethylaspartic acid[29] (Tfm Asp) using an auxiliary approach, a titanium enolate derived from *t*-Bu acetate reacted with the enantiopure sulfimine to give the desired *N*-sulfinyl Tfm Asp ester **1.7** in a yield of 78 % and a de of 92 % (**Scheme 9**). The authors reported that only titanium enolates were reactive. Treating the esters with TFA to remove the sulfinyl and *t*-Bu groups, followed by saponification with KOH gave the Tfm Asp in a yield of 78 % and an *ee* of 97 %.



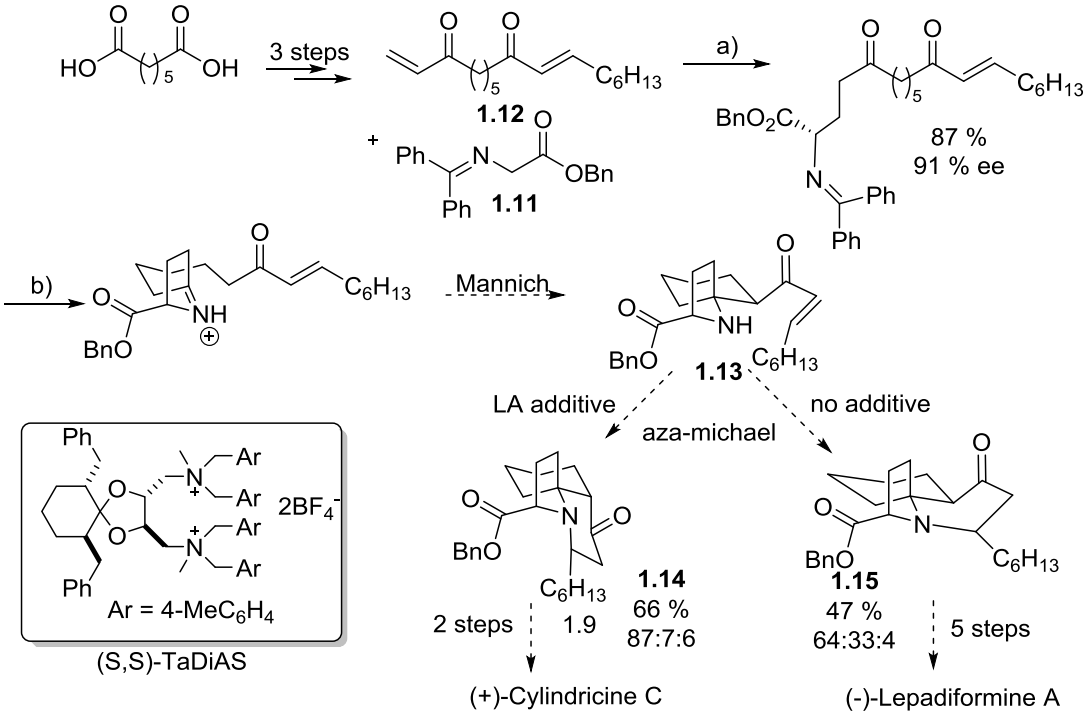
Scheme 9 Asymmetric Mannich reaction onto a chiral sulfimine.

2003 saw the first report on the catalytic enantioselective Mannich reaction of silyl-ketene acetals with ketimines by Jørgensen,[30] applicable to ATA synthesis. Carrying out Mannich reactions on isatin-derived ketimine frameworks has become an attractive protocol for generating 3,3 disubstituted 3-aminooxindoles, an important class of biologically active compounds. Very recently in 2015,[31] Liu and coworkers disclosed both a diastereo- and enantioselective method for the construction of vicinal tetrasubstituted centres via a catalytic asymmetric Mannich reaction of monothiomalonates **1.8** and isatin *N*-Boc ketimines, **1.9** using a thiourea catalyst **1.10** (**Scheme 10**). Only one derivative (with the bromo group in the 3 position on the ring) gave the lower dr of 9:1; all others were generally in the region of 20:1.



Scheme 10 Catalytic asymmetric Mannich reaction of linear α-substituted monothiomalonates with Isatin *N*-Boc ketimines.

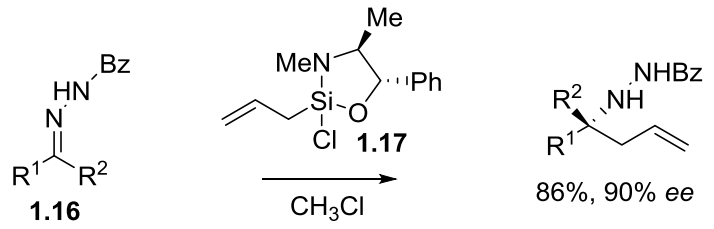
Shibasaki's[32] formal total synthesis of lepadiformine and total synthesis of cylindricine C features an impressive cascade of cyclizations, involving a Mannich addition to form the ATA (**Scheme 11**). The cyclization precursor was generated via an asymmetric organocatalyzed conjugate addition reaction between **1.11** and **1.12** (derived from pimelic acid), using a tartrate-derived diammonium salt ((S,S)-TaDiAS). The tandem Mannich/ aza-Michael sequence was initiated in acidic conditions in which the ratio of diastereomers obtained could be influenced by additives. Specifically, no additive resulted in a 1:2 ratio of **1.14** to **1.15** and trace amounts of a third diastereomer (64:33:4). Whereas the use of Lewis acidic additives produced a dr ratio of 87:7:6. Although only one stereocentre was set by the asymmetric conjugate addition, this had a drastic effect on the cyclization cascade. The pyrrolidine ring was generated by a transimination, which was followed by an intramolecular Mannich reaction to form the second ring and the aza-spirocycle **1.13**. The diastereoselectivity of the ensuing aza-Michael addition step was controlled by additives, which likely aided the enolization of **1.13**, allowing epimerization at the α-carbonyl carbon. Five additional steps from **1.15** furnished lepadiformine in an overall yield of 4 %.



Scheme 11 *Reagents and conditions*: a) (*S*,*S*)-TaDiAS, $CsCO_3$, -40 °C; b) CSA, $MgCl_2$, DCE, 50 °C.

1.4.4 Addition to Hydrazones

In the same way as with ketimines, nucleophilic addition to the the CN double bond of hydrazones gives rise to hydrazines, which can then undergo reductive cleavage to yield chiral amines. The example below, reported by Leighton *et al* in 2004,[33] shows the allylation of a ketone-derived hydrazone 1.16 with an ephedrine-derived chiral allylsilane 1.17, showcasing the rather rare use of reagent-based enantioselectivity (**Scheme 12**).

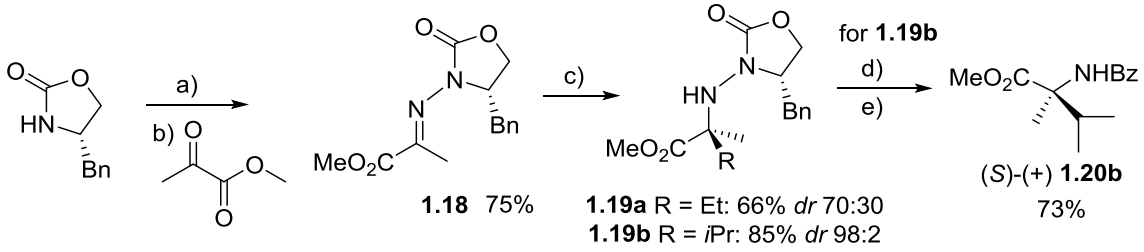


R^1 = Ph, furan, thiophene, $Ph(CH_2)_2$, *c*-Hex, 2-naphthyl, *p*-Br-C_6H_4, *m*-NO_2-C_6H_4
R^2 = Me, Et, Bn, CO_2Me, *i*Pr

Scheme 12 Addition of a chiral allylsilane to an acyclic hydrazine

Hydrazones and oxime ethers are known to be good radical acceptors because of the stabilization of the intermediate radical by the neighbouring heteroatoms. The advantage of radical methodologies over nucleophilic additions is the milder reaction conditions necessary, which translates to fewer side reactions. Although much progress has been made with aldimine acceptors, asymmetric ketimine radical additions are rare. In 2008 Gregory Friestad[34] reported the use of a manganese-

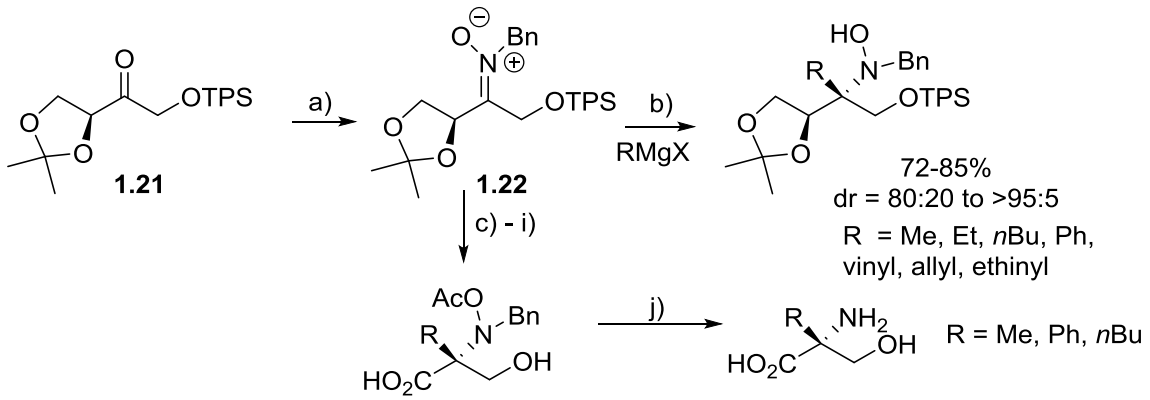
mediated coupling of an iodide with a hydrazone containing an Evans auxiliary at its terminus. The chiral hydrazone **1.18** was prepared by *N*-amination of an oxazolidinone, followed by condensation with methyl pyruvate to afford the hydrazine product in an *E*/*Z* ratio of 98:2, the geometrical isomers separable by column chromatography. Photolysis of manganese carbonyl [$Mn_2(CO)_{10}$] results in homolytic metal-metal bond cleavage, giving rise to two $Mn(CO)_5$ radicals, which abstract an iodide atom from the alkyl halide to form the reactive alkyl radical species. The radical addition reaction gave a superior dr with *i*-Pr **(1.19b**) compared to Et (**1.19a**) as shown in **Scheme 13**. Reductive N-N bond cleavage to afford the final quaternized product **1.20b** was achieved using a sequence involving *n*-BuLi, benzoic anhydride and SmI_2/MeOH.



Scheme 13 *Reagents and conditions*: a) KH; NH_2Cl, MTBE; b) *p*-TsOH, 4Å MS, Toluene, 80 °C; c) R-I, $Mn_2(CO)_{10}$, hv, $InCl_3$, CH_2Cl_2; d) *n*-BuLi, Bz_2O; e) SmI_2, MeOH

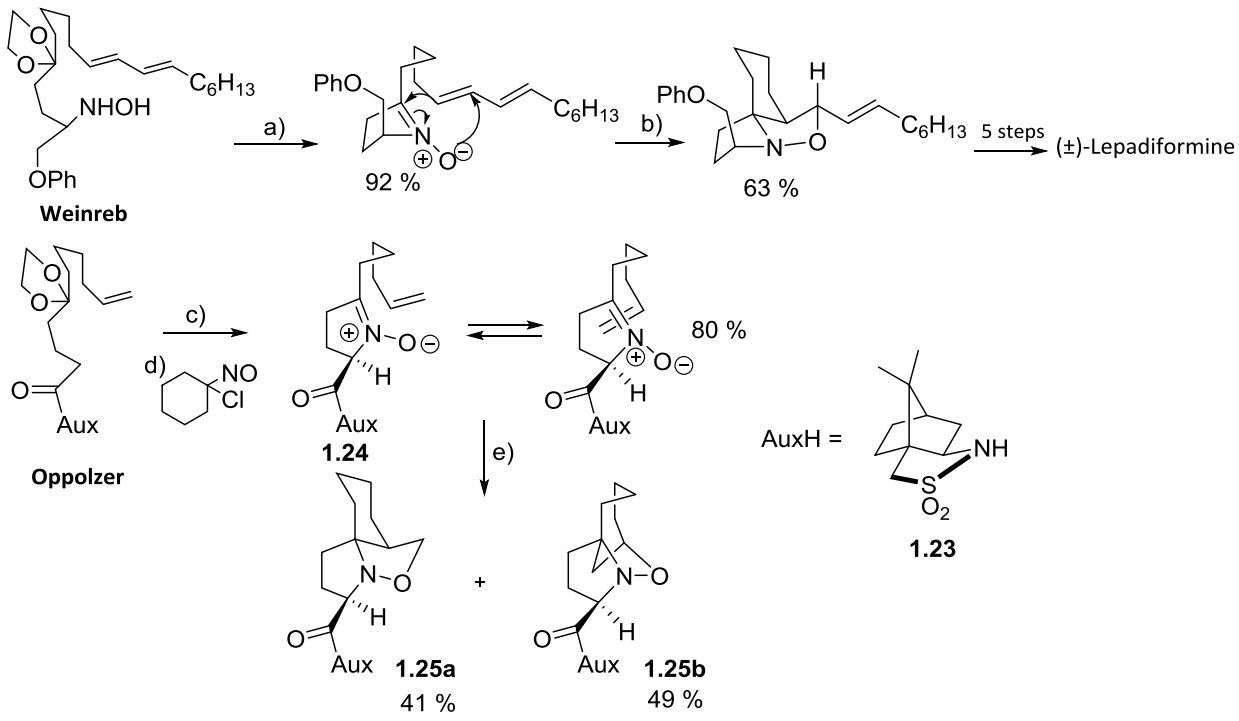
1.4.5 Addition to Nitrones

Addition of nucleophiles to nitrones is one way to overcome the low reactivity of imines, as the polarization of the nitrogen in the nitrone raises the electrophilicty of the α-carbon. However, not many examples exist for the generation of quaternary centres. Carda and Marco in 1998[35] reported some advances in this regard, when they disclosed on an acyclic nitrone **1.22** accessed from a silyl-protected erythrulose acetonide **1.21**, which could be alkylated by various Grignard reagents in good to excellent drs followed by hydrogenolysis to remove the auxiliary (**Scheme 14**). The steps to obtain the free amino acid were carried out for α-methyl-, phenyl- and *n*-Bu- serine and were somewhat lengthy.



Scheme 14 *Reagents and conditions*: a) BnNHOH; b) RMgX, THF, -78 °C, 5h; c) RMgX, THF, -78 °C, 5h, then Ac_2O, rt, 30 min; d) PPTS, aq. MeOH, reflux; e) $NaIO_4$; f) $NaClO_2$; g) CH_2N_2; h) TBAF, THF; i) NaOH, EtOH; j) H_2 (70 psi) $Pd(OH)_2$.

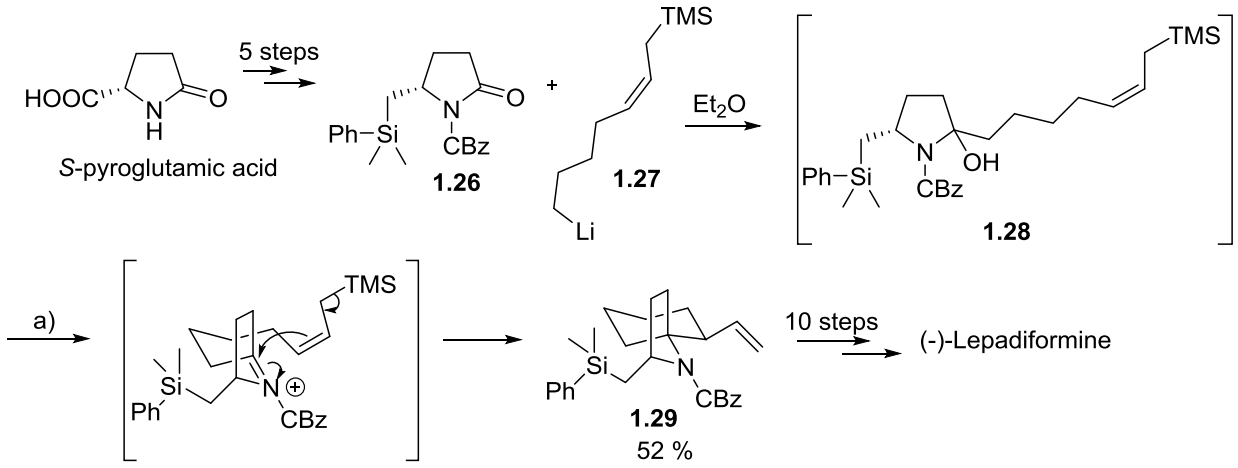
Nitrones are also good substrates for cycloaddition reactions and a number of alkaloid syntheses have made use of the [3 + 2] nitrone-alkene cycloaddition.[36] In their enantioselective approach to cylindricines, the Oppolzer group used a (2*R*)-bornane-10,2-sultam chiral auxiliary **1.23** to provide an enantiomerically pure nitrone **1.24** for the intramolecular nitrone/olefin dipolar cycloaddition (**Scheme 15**).[37] Prior to that Weinreb employed a very similar tactic in his racemic synthesis of lepadiformine, which consequently led to the elucidation of the correct structure thereof.[38] Although good stereoselectivity was achieved in Oppolzer's approach with the use of the chiral auxiliary, the regioselectivity of the cycloaddition was poor, producing two regioisomers arising from the conformations shown in Scheme #, with the desired isoxazolidine **1.25a** formed in a yield of 41 %.



Scheme 15 *Reagents and conditions*: a) 3N HCl; b) DMSO 195 °C; c) i) NaHMDS, THF -78 °C; d) i) 1-chloro-1-nitrosocyclohexane; ii) conc. HCl; e) PhMe, reflux.

The electron-withdrawing effect of a carbonyl group alpha to an imine greatly enhances the electrophilicity of the iminium carbon, allowing for a wider range of nucleophiles to be employed, in which alkenes, alkynes, as well as aromatic and heteroaromatic nucleophiles are all effective. Similarly, the cyclization of nucleophilic alkenes onto transiently formed *N*-acyliminium ions is a commonly practiced method for creating both C-N and C-C bonds in the same reaction. Weinreb

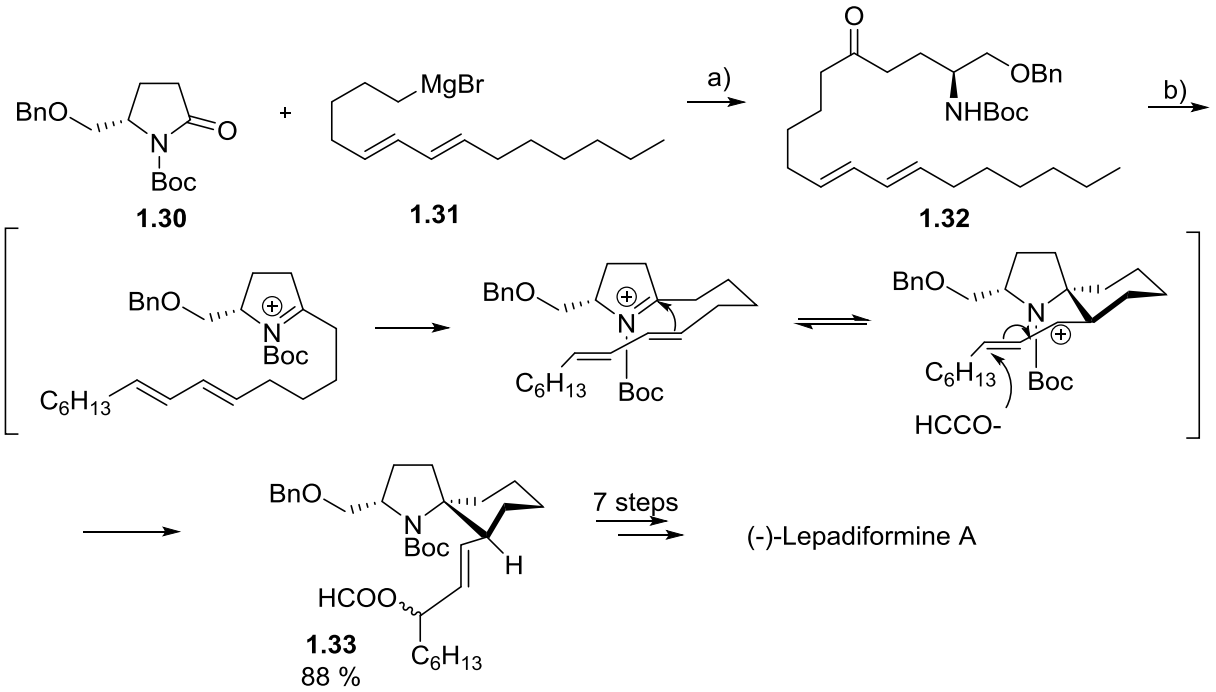
applied *N*-acyliminium ion/ allylsilane spirocyclization methodology to the racemic synthesis of lepadiformine, and in 2002 extended it to an enantioselective version.[39] Starting with (*S*)-pyroglutamic acid, Cbz-lactam **1.26** incorporating a bulky phenyldimethylsilyl group was synthesized in five steps (**Scheme 16**). Addition of lithio (*Z*)-allylsilane **1.27** to the lactam carbonyl of **1.26** gave adduct **1.28** as a hemiaminal, which was treated with boron trifluoride acetic acid to promote iminium ion formation and cyclization. Spirocycle **1.29** was isolated as a single stereoisomer in a yield of 52 % due to the pendant phenyldimethylsilyl group blocking one of the faces of the iminium ion, promoting addition of the allylsilane to the less hindered face as illustrated in the Scheme.



Scheme 16 *Reagents and conditions*: a) $BF_3 \cdot 2HOAc$, CH_2Cl_2

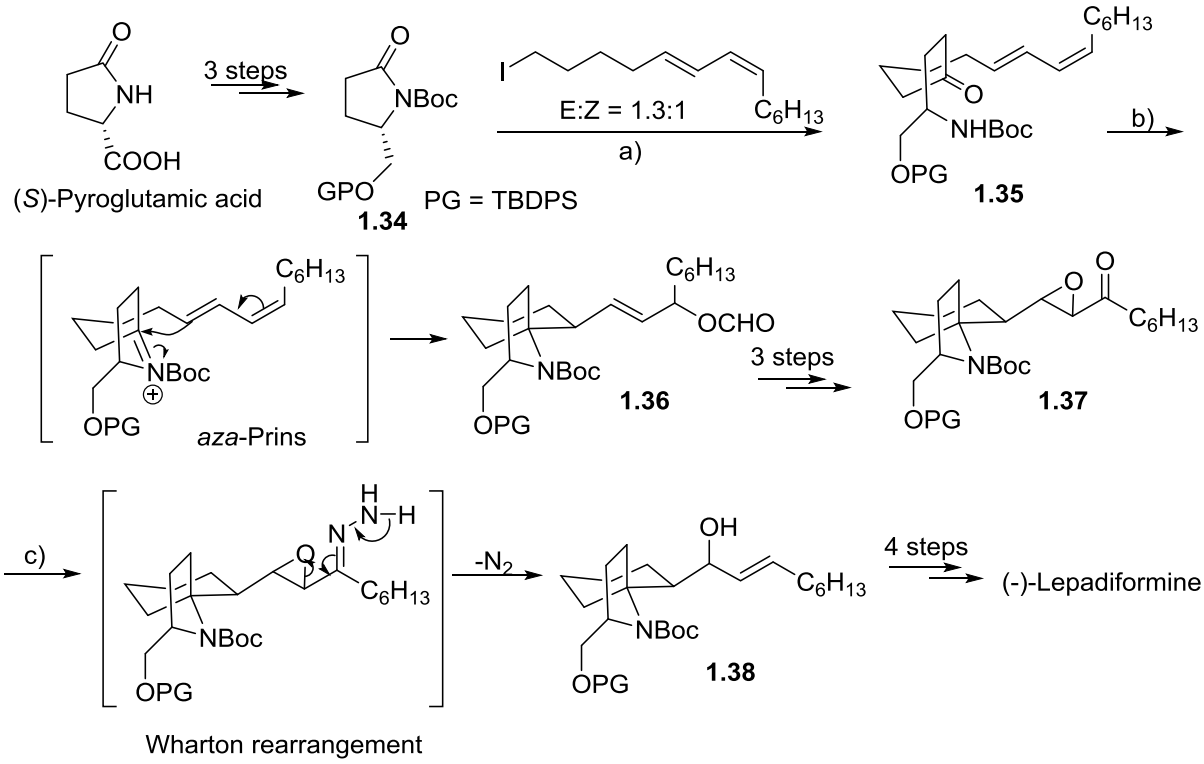
1.4.6 Aza-Prins

The aza-Prins reaction describes a nucleophilc attack by a diene onto an iminium carbon, usually carried out for the purposes of cyclization. Kibayashi *et al*. employed a similar strategy to Weinreb's by incorporating an aza-Prins cyclization (**Scheme 17**),[40] in their expedient synthesis of lepadiformine and the cylindricines. Known (*S*)-*N*-Boc-2-pyrrolidinone **1.30** was treated with Grignard **1.31** to generate ketone **1.32**. Treatment with formic acid promoted spirocyclization onto the in-situ generated *N*-acyliminium ion, along with formation of a formate ester at C-3, furnishing spirocycle **1.33** in a yield of 88 %. It was noted that conjugated dienes underwent spirocyclization smoothly, requiring shorter reaction times compared to non-conjugated olefins. **1.33** was generated with complete stereocontrol via 6-*exo*-trig cyclization onto the less sterically hindered face of the iminium ion (opposite the 5-benzyloxymethyl group). Other possible transition states leading to the opposite diastereomer were claimed to be disfavoured due to interactions between the *N*-Boc group and the axially positioned diene, as well as with the 1,3 diaxial hydrogen atoms of the emerging 6-membered ring.



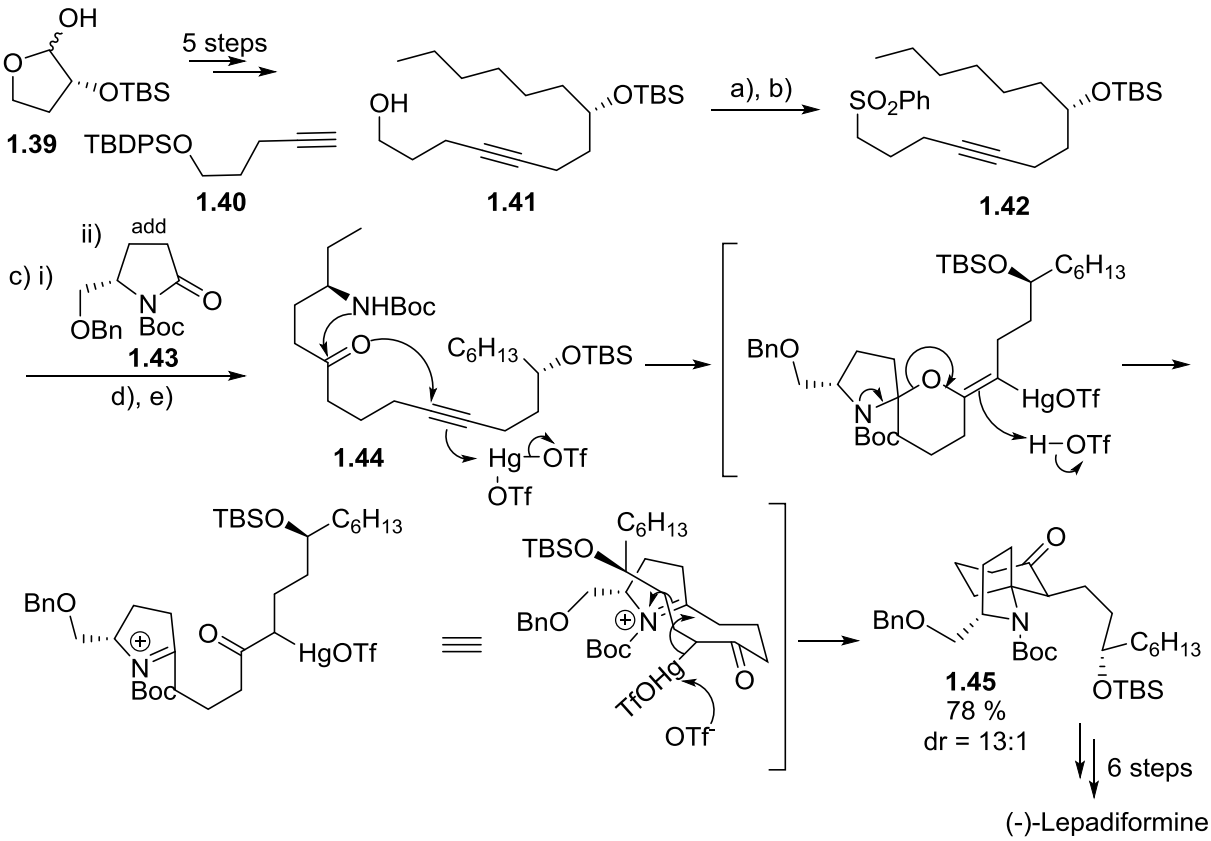
Scheme 17 *Reagents and conditions*: a) THF, 0 °C; b) HCO_2H, toluene/THF (95:5), 0 °C

In a somewhat similar approach to Kibayashi's, Hsung achieved a relatively short total synthesis of the (+)-cylindricines C-E as well as (-)-lepadiformine via a common intermediate accessed from an *aza*-Prins cyclization, followed by a Wharton rearrangement (**Scheme 18**).[41] Commencing with butyrolactam **1.34** (prepared in three steps from (*S*)-pyroglutamic acid), alkyl lithium addition/ ring opening afforded the Boc-protected amino ketone **1.35**. Treatment of **1.35** with formic acid led to the initial closing of the pyrrolidine ring, followed by *aza*-Prins cyclization onto the resultant iminium ion and trapping of the allylic cation by the formate anion, to give the azaspirocycle **1.36**. Removal of the formate group and further elaboration of the resultant allylic alcohol gave the epoxy ketone **1.37**, which underwent a Wharton rearrangement, without isolation of the hydrazone intermediate. Four steps, including an intramolecular aza-Michael addition furnished (-)-lepadiformine A in an overall yield of 7.1 %. The Cyclindricines were accessed via in-situ epimerization at C-5 of derivative **1.38**, which occurred upon exposure to basic conditions.



Scheme 18 *Reagents and conditions*: a) *t*-BuLi, THF; b) HCO_2H: THF: Toluene (50:3:47), -10 °C; c) NH_2NH_2, (5 eq), MeOH, AcOH, -10 °C

Recently, in 2015, Morimoto *et al* disclosed a facile total synthesis of (-)-lepadiformine A featuring a $Hg(OTf)_2$-catalyzed cycloisomerization reaction as a key step, which also involved cyclization onto an iminium ion but via a triple bond as the nucleophile source, (**Scheme 19**).



Scheme 19 *Reagents and conditions*: a) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C to rt; b) $NaSO_2Ph$, DMF, rt; c) i) *n*-BuLi, THF, -78 °C; d) SmI_2, THF/MeOH (2:1) -78 °C; e) $Hg(OTf)_2$ (0.2 eq), MeCN, -20 to 0 °C.

Starting with the hemi-acetal **1.39** and acetylide **1.40**, alcohol **1.41** was obtained in 5 steps and high overall yield, which was converted to sulfone **1.42** via an iodination/ sulfonylation sequence, and acylated with pyrrolidinone **1.43**. Thereafter, desulfonylation furnished the ynone **1.44,** the cyclization substrate containing all the carbons of the lepadiformine structure. Reaction of ynone **1.44** with mercuric triflate gave the desired spirocycle **1.45** in a 78 % yield with a dr of 13:1 via a cascade sequence. The postulated mechanism involves first a 6-*exo*-dig intramolecular oxymercuration with formation of the target pyrrolidine C ring followed by cleavage to an iminium ion and an α-mercurated ketone that cyclizes to generate the key A/C target spirocycle in a Ferrier-type reaction with correct absolute and relative stereochemistry. The authors present five possible transition states for the cyclization, in which the one leading to the desired product exhibits the least amount of steric repulsion between the bulky OBn, Boc and OTBS groups. The stereoselective cycloisomerization reaction is a fascinating example of a highly convergent process that can produce complex aza-spirocycles from a linear acyclic derivative in a single step. Conventional steps allowed B-ring closure to afford the target in 16 total steps and an impressive 28 % overall yield.

1.5 C-C Bond Formation via an N-α-Carbanion

The next sub-division as formulated in **Scheme 2**, focuses on alkylation of N-containing enolates in which the α-carbon has nucleophilic character. There are numerous variations on this theme and a selection of these will be covered. The Kazmaier-Claisen rearrangement, although strictly speaking is a pericyclic process, involves a nucleophilic α-carbon and as such will also be included here, as will the Steglich-Höfle rearrangement.

1.5.1 α-Carbanions with Memory of Chirality

The term in the organic literature "Memory of chirality" (MOC) refers to a process in which an intermediate 'remembers' the initial configuration of a stereogenic element destroyed in the formation of that intermediate and transfers the chiral information to the product, without external influence.

Tertiary aromatic amides with appropriate *ortho g*roups in the aromatic ring possess axial chirality (atropisomerism) due to a slow σ-bond rotation (shown by an arrow in **Figure 8**), in which the relationship between the two conformers about the Ar-CO bond σ-bond is enantiomeric if R^1 and R^2 are achiral, and diastereomeric if R^1 or R^2 are chiral.

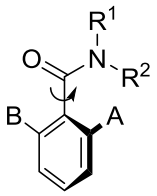
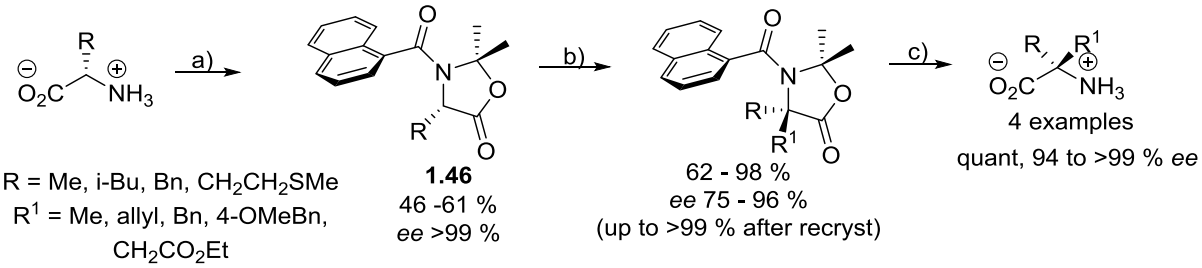


Figure 8 Axial chirality of tertiary aromatic amides

Kouklovski and Alezra made use of this stereogenicity in the asymmetric synthesis of quaternary α-alkyl amino acids via a MOC process (**Scheme 20**).[42] An oxazolidinone, **1.46,** generated from an amino acid, acetone and the appropriate aryl acid chloride, was isolated as a single diastereomer due to the axial chirality induced by the amino acid central chirality. Base-mediated enolization, though destroying the chiral centre, retained the atropisomer axis resulting ultimately in a highly stereoselective alkylation reaction. Very specific reaction conditions and enolization times were necessary in order to attain high yields and selectivities, and fine-tuning was necessary for some derivatives. Leucine, alanine, phenylalanine and methionine were alkylated via this methodology in yields of up 96 % and *ee*s up to 96 %. Recrystallization improved *ee*s to >99 % and these products were then refluxed in HBr to liberate the almost enantiopure quaternary amino acids in quantitative yield.



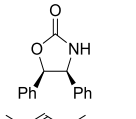
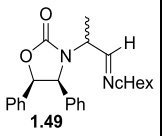
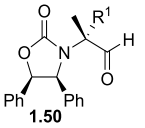
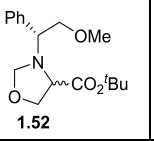
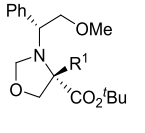
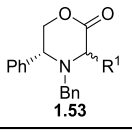
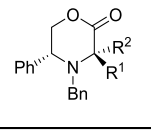
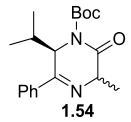
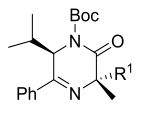
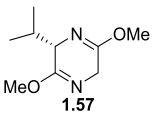
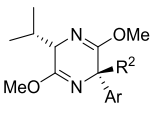
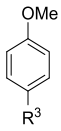
Scheme 20 *Reagents and conditions*: a) i) dry acetone, Lewis acid M.S 4 Å, rt; ii) 1-naphthoyl chloride, rt; b)i) KHMDS-2DME (1.5 eq), THF or Et_2O/tol or THF/tol, -78 °C; ii) R^1X (5 eq).

In 2014, the protocol was extended to include aldehyde electrophiles for producing enantiopure β-hydroxy quaternary α-amino acids.[43]

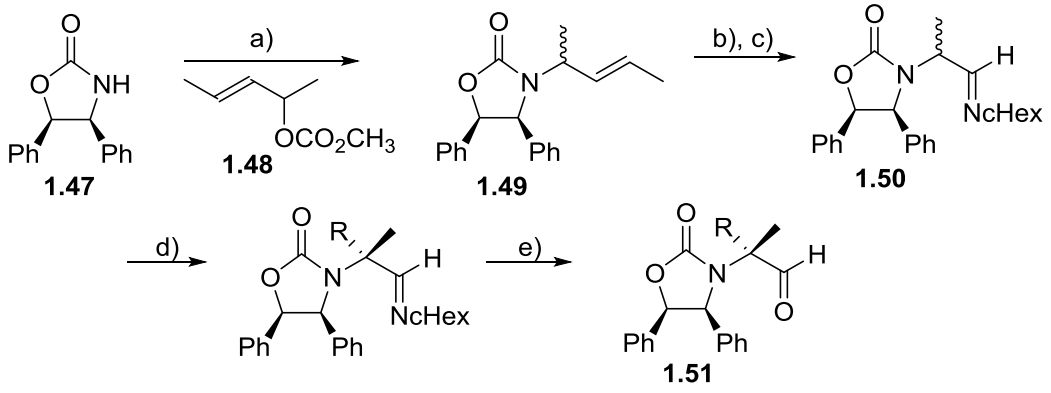
1.5.2 Chiral Amino Acid Enolate Equivalents

However, undoubtedly one of the most prevalent and versatile approaches for the generation of α-tertiary amine centres involves the diasteroselective alkylation of chiral amino acid enolate equivalents. The templates are often glycine-derived Schiff bases, and mostly cyclic. Various derivatives of chiral imidazolidinones, oxazinones, bis-lactim ethers and tetrahydropyrazinones have been successfully employed. **Table 1** below summarizes a selection of reports pertaining to enolate alkylation of a range of chiral templates, derived from amino acids or other members of the chiral pool, used for the production of quaternary amino acids. Although the template designs are structurally different, they all rely on the same basic principle for chiral induction: a high degree of facial selectivity achieved by the generation of a rigid enolate with a set geometry, (whether through chelation effects or by virtue of being endocyclic) followed by electrophile approach onto the least hindered face of the enolate to ultimately give products in high drs.

Table 1 Examples of Diastereoselective Enolate Alkylations Using Chiral Templates

Entry	Starting materials	Alkylation template	Yields, selectivities 1st alkylation	Yields, selectivities 2nd alkylation	R^1	R^2	steps to amino acid
1	 O_3, *c*$HexNH_2$	 **1.49**		 **1.50**	Bn, allyl, *i*Pr, *n* Bu, *i*Bu, 3,4-(OMe)$C_6H_3CH_2$		oxidation, hydrogenation 82 - 94 %
		3 steps		47-75 % (4 steps); d.r.>90:10			
2	(*R*)-Phenylglycinol methyl ether, $BrCH_2CO_2t$Bu, $(CH_2O)_n$	 **1.52**			Me, allyl, Bn, PhCO, CH_2CO_2Me		H^+ cleavage hydrogenolysis (71 % for R^1 = Me, 75 % for R^1 = Bn)
		3 steps: 79 %		73-97 %; de 81 to >95 %			
3	R^1CHO, NaCN (*R*)-phenylglycinol	 **1.53**			Me, *n* Pr, Bn, $(CH_2)_2OBn$	Et, Bn, allyl, CH_2CO_2Me, $CH(OH)CH_3$, $CH(OH)n$ Pr	hydrolysis, hydrogenation, Dowex 62 - 80% over 3 steps
		33 - 48 % 3 steps		50 -90 % d.r > 200:1			
4	Val-Ala	 **1.54**			Allyl, Bn, propargyl, Et_2OCCH_2		H^+ cleavage; 72 - 91 %
		3 steps		60 - 75 % d.r 92:8 to >98:2			
5	Val-Gly	 **1.57**			Ar:  R^3= H or OMe	Me, Bn, allyl, propargyl, MOM, EtO_2CCH_2, *n* Bu	H^+ cleavage 56 - 75 % (2 examples)
		2 steps		50 - 92 % dr 89:11 to >98:2			

The five entries will now be briefly discussed. Entry 1 in **Table 1** depicts an interesting approach by Wenglowski and Hegedus[44] who utilized an Evans-type oxazolidinone **1.47** as the chirality inducer. The synthesis of the template **1.50** involved an intermolecular Pd(0)-catalyzed allylic amination between the oxazolidinone **1.47** and an allylic carbamate **1.48**, followed by ozonolysis and condensation with cyclohexylamine (**Scheme 21**).

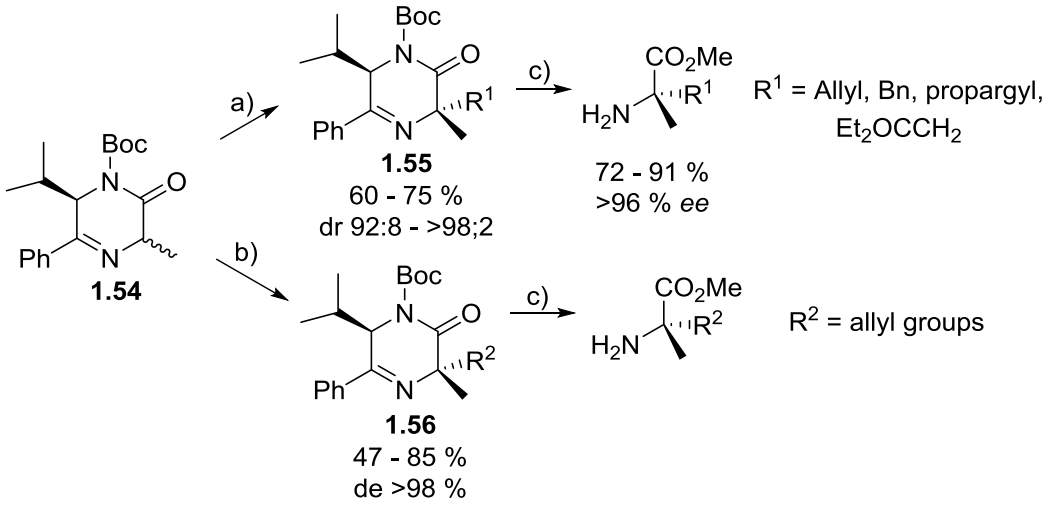


Scheme 21 *Regents and conditions*: a) $Pd(PPh_3)_4$-dppe, DMF, rt; b) O_3, Me_2S, DCM -78 °C to rt; c) cyclohexylamine, $MgSO_4$, DCM; d) RX-KHMDS, THF, -78 °C to – 45 °C; e) HCl-THF

After some difficulties, the authors reported that best results were achieved when the entire four-step sequence from **1.49** to the dialkylated aldehyde **1.51** was carried out without purification of the intermediates. Alkylation took place via the *Z*-aza-enolate of **1.50**, in which the imine nitrogen and carbonyl oxygen were not chelated and the authors put forth the reasoning that such a conformation was preferred in order to minimize the dipole interaction between the N^- and C=O, achieving high drs of >90:10.

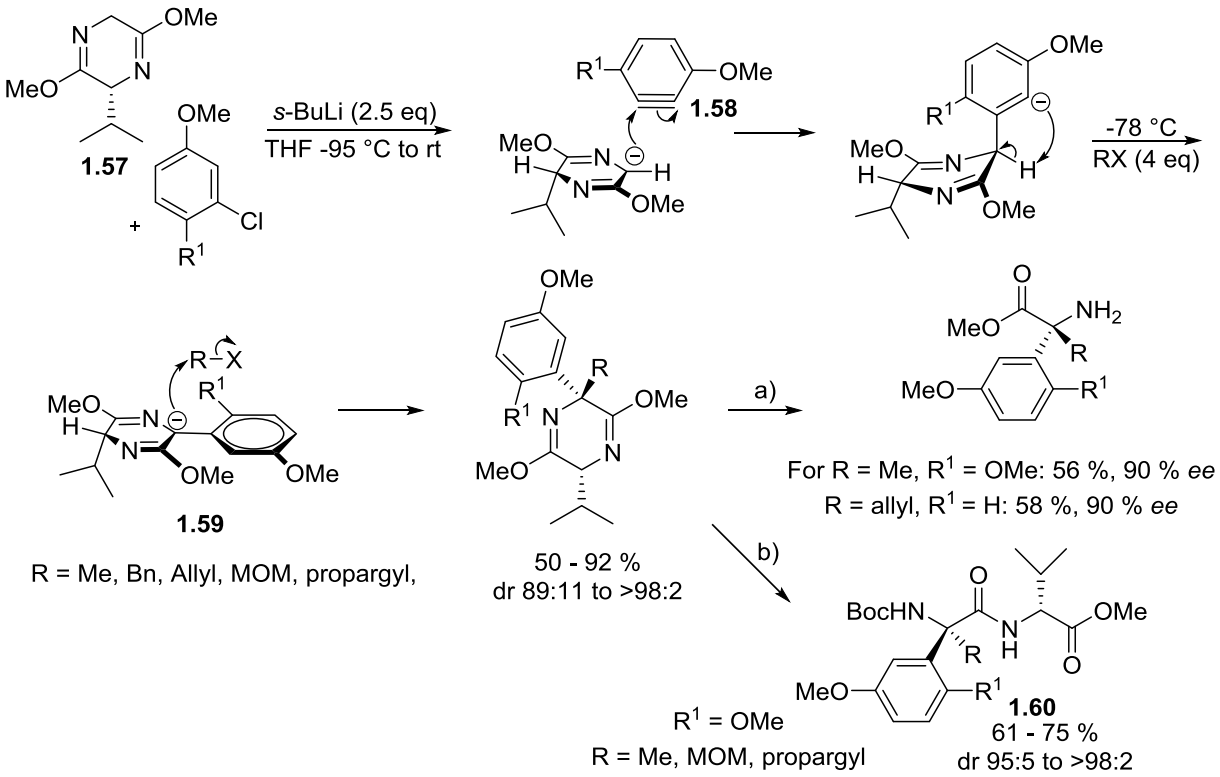
The example in **Table 1**, entry 2 is Husson's[45] protocol for generating quaternary serine derivatives, featuring an expedient synthesis of an oxazolidine alkylation template **1.52** that was achieved via an S_N2 reaction between (*R*)-phenylglycinol methyl ether and $BrCH_2CO$*t*Bu, followed by a [3 +2] dipolar cycloaddition involving paraformaldehyde. Quaternized products were accessed in good yields and selectivities via the electrophile approaching *anti*- to the phenyl group during the alkylation. Acidic cleavage of the auxiliary was problematic owing to the presence of the acid sensitive *t*-Bu ester, and the ethyl acetate derivative spontaneously lactonizing under the acidic conditions.

Ma and Ding used an oxazinone **1.53** obtained from a Strecker product (NaCN addition to an imine derived from (*R*)-phenylglycinol and R^1CHO) as a highly efficient alkylation template (**Table 1, Entry 3**).[46] Electrophile approach resulted in a *cis* relationship with the phenyl substituent derived from the auxiliary (except in the case of methyl bromoacetate), due to alkylation proceeding *anti* to the *N*-Bn group. Entry 4 in **Table 1** is an example of a versatile template developed by Nájera in 2000,[47] in which highly diastereoselective alkylations of a Val-Ala-derived pyrazinone **1.54** furnished quaternized pyraziniones **1.55**, which upon acidic cleavage yielded a range of quaternary alanine amino acids (**Scheme 22**). The same template underwent Pd-catalyzed allylation with an allyl carbamate, furnishing a variety of allyl-substituted pyrazinones **1.56**, likewise hydrolyzed to quaternary alanine derivatives.



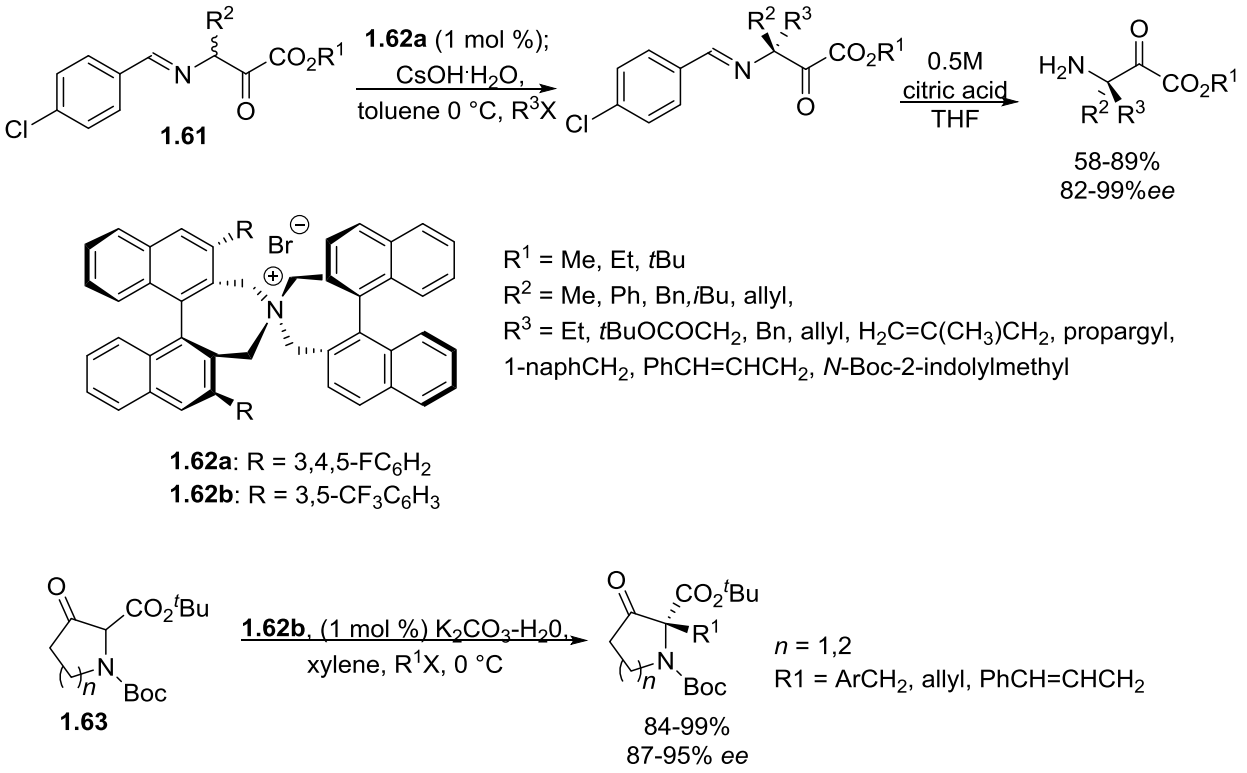
Scheme 22 *Reagents and conditions*: a) K_2CO_3 (3 eq.), TBAI (10 mol %), CH_3CN, R^1X, rt; b) $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), THF, R_2OCO_2Et, rt; c) i) 6N HCl, 150 °C; ii) propylene oxide, EtOH.

The final example (**Table 1,** entry 5) showcases a recent application by Barrett and coworkers[48] of the Schöllkopf auxiliary for generating aryl-substituted quaternary amino acids. This ingenious methodology achieved an arylation and subsequent alkylation in a one-pot operation (**Scheme 23**). 1,4-Dimethoxy-2-benzyne **1.58** was generated via an *ortho*-metallation and elimination sequence using *sec*-BuLi, whilst in the same pot the bis-lactim template **1.57** was deprotonated, resulting in nucleophilic attack of the resultant enolate onto the benzyne. The resultant aryl carbanion then underwent proton exchange to afford the more stable template carbanion **1.59**, allowing for a second alkylation with a range of S_N2-reactive electrophiles in good overall yield and selectivity (80-92 % and drs of 96:4 and > 98:2). Less reactive electrophiles such as *n*-Bu in the second alkylation gave lower yields (50 -71%) but still high drs (95:5 to >98:2). One attractive feature of this methodology is that it can access α-arylated quaternary amino acids - these are a difficult target class – even if the choice of substituents on the aryl ring is limited. Hydrolysis to the amino acid products was problematic, especially for derivatives with two methoxy groups on the ring. Using 0.5M HCl, the imidate α to the quaternary centre was only partially hydrolysed, giving methyl ester dipeptides **1.60**. Eventually, acidic hydrolysis with 6M H_2SO_4 hydrolysed the dipeptide bond but only for the less bulky and less substituted derivatives, whilst the others were isolated as valine dipeptides.



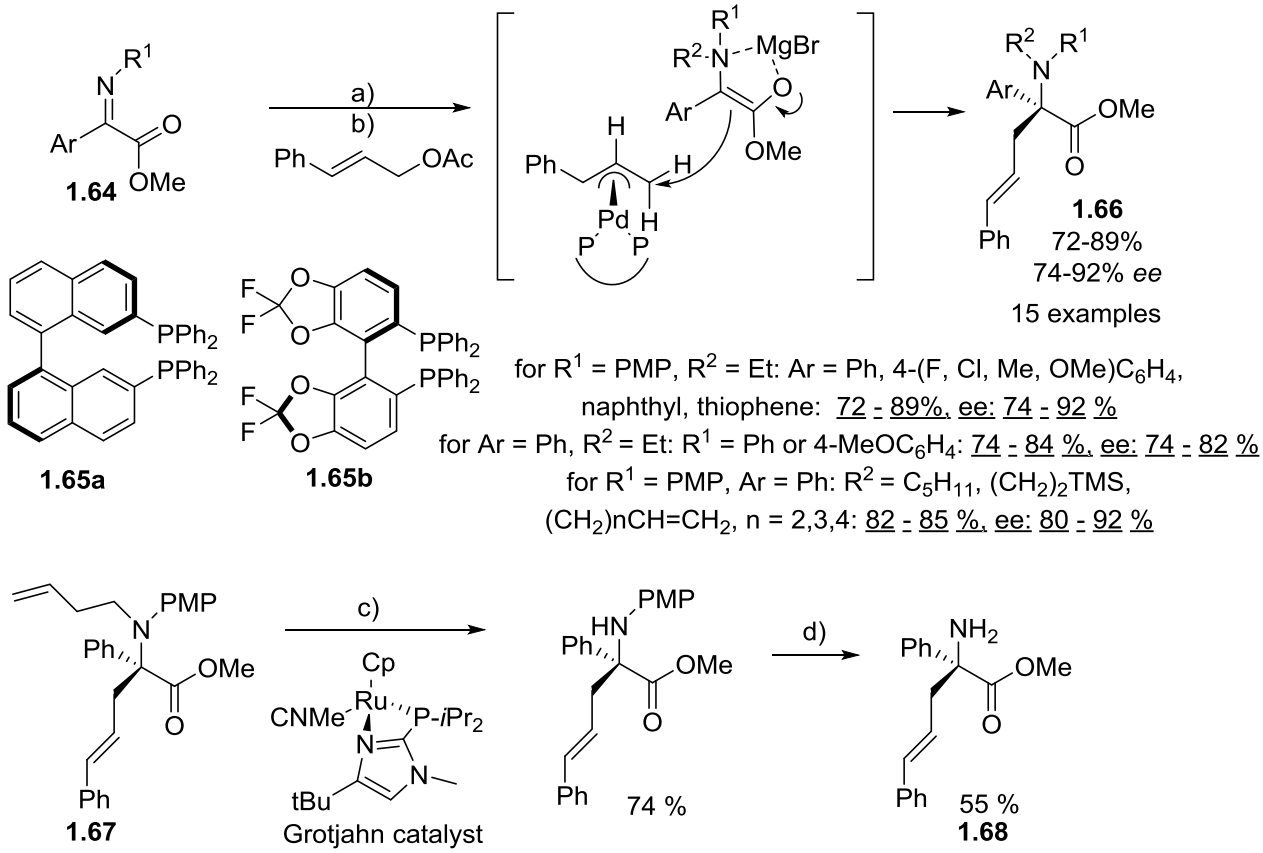
Scheme 23 *Reagents and conditions*: a) 6M H_2SO_4, 20 °C, 72h; b) i) 0.5M HCl, THF, 20 °C, 36h; ii) Boc_2O, *i*-Pr_2NEt, CH_2Cl_2, 20 °C, 48h.

The obvious drawback of the methodologies depicted in **Table 1** is the low atom efficiency, since all the templates are destructively removed at the end of the process, and in some cases the synthesis of the alkylation template is lengthy (methodologies recycling the auxiliary do exist, but are less prolific). For this reason, enantioselective approaches using chiral catalysts have seen increased development in recent years, particularly phase-transfer catalysis.[3,49] The early quaternary ammonium salts such as TADDOL, although efficient, often lacked generality. Maruoka's C_2-symmetric chiral quaternary ammonium bromide catalyst **1.62**, introduced in 2000, proved superior, with successful application to a much wider variety of substituents in the stereoselective sequential double alkylation of glycine-derived Schiff bases **1.61**, as well as alanine-, isobutyl- and phenylglycine derivatives and cyclic amino acids (**Scheme 24**).[50,51] Alkylations were carried out using five equivalents of cesium hydroxide and 1.2 equivalents of the electrophile, while hydrolysis to the quaternary amino acid esters was achieved with 0.5 M citric acid in yields of 58-89 % and *ee*s of 82 to 99 %. In 2005, the same catalyst was successfully applied to the enantioselective alkylation of cyclic α-amino β-ketoesters **1.63**.[50] Cinchona alkaloid derivatives and copper-salen complexes are other examples of salts that have found successful application in the PTC-catalyzed asymmetric alkylation of amino-acid derived Schiff bases.



Scheme 24 Alkylation of amino-acid derived Schiff bases according to Maruoka *et al*. 2000 and 2005

Although PTC catalysis is successful in many instances of *N*-containing enolate alkylations, the best results for asymmetric allylations are generally achieved using chiral palladium complexes. Kozlowski *et al.*[52] have reported an ingenious way of creating α-aryl-α-allyl amino acids via a three-component coupling of α-iminoesters, Grignard reagents and cinnamyl acetate (**Scheme 25**). The methodology offers an elegant solution to the difficult problem of creating aryl-containing ATAs, particularly for targets where the second substituent is bigger than a methyl.

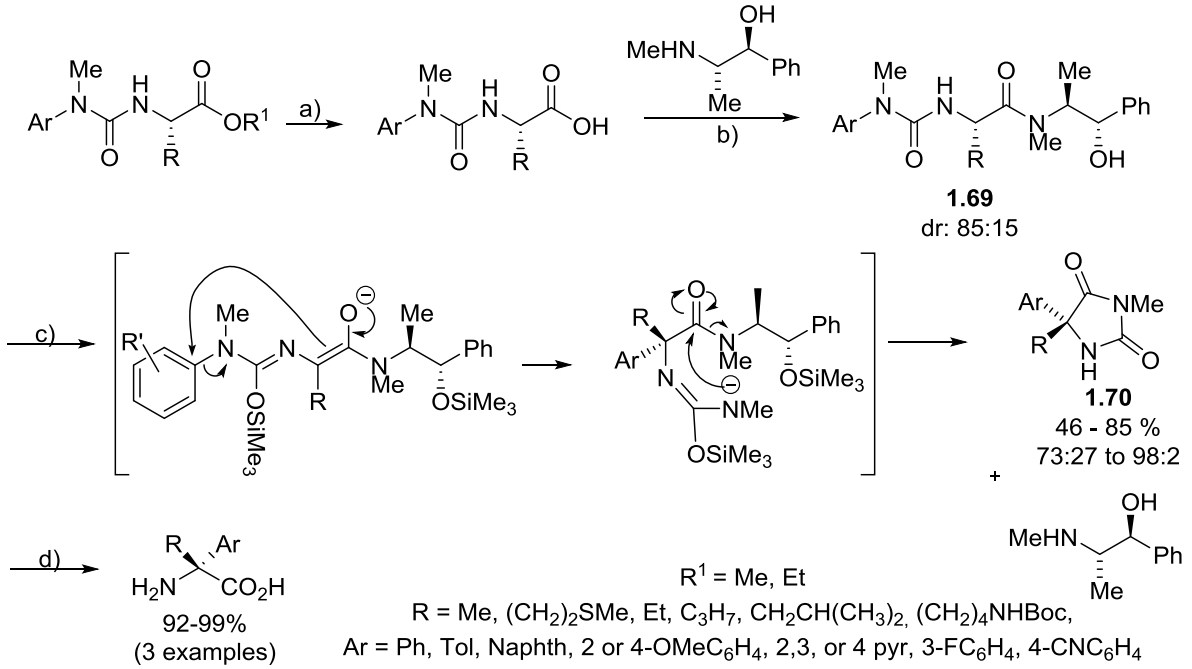


Scheme 25 *Reagents and conditions*: a) R^2MgBr, -78 °C, THF to rt; b) **1.65a** or **1.65b** (4.9 mol %), $[\eta^3\text{-}C_3H_5PdCl]_2$ (7.5 mol %), -78 °C to rt.; c) Grotjahn catalyst (5 mol %), H_2O, CF_3COOH, acetone, 75 °C; d) CAN (3 eq), MeCN/ H_2O, -10 °C to rt.

The enolate generated by the umpolung addition of the alkyl Grignard onto the iminoester **1.64** was reported as being far more reactive than if it were created by direct deprotonation, likely due to nuances in the degrees of solvation/ aggregation. The use of chiral bisphosphine ligands **1.65a** and **1.65b** on palladium (II), rendered the tandem *N*-alkylation/π-allylation of **1.64** enantioselective, and a variety of α-aryl-α-allyl amino acid ester derivatives **1.66** were obtained in good yields (72 – 89 %) and enantioselectivities (74 – 92 % *ee*). Both electron-donating and electron-withdrawing aryl substituents reacted effectively, although yields were reduced with *ortho*-substituted aryls. The Grignard reagents could also be successfully varied to provide novel and useful *N*-alkyl, α-aryl-α-allyl amino acid variants, although deprotection of the *N*-alkyl groups lengthened the sequence somewhat. Thus *N*-alkyl amino acid esters were accessed by CAN deprotection of the PMP group. Access to the free amine from derivative **1.67** was possible via olefin isomerization using the Grotjahn catalyst, which under thermal, acidic conditions isomerized the terminal alkene by two carbons to the enamine. The resultant enamine was then hydrolysed *in situ* under the acidic conditions, following which, CAN deprotection furnished the free amine **1.68**. The presence of allylic

groups allowed for ring closing metathesis methodology, enabling the synthesis of higher ring homologues of α-proline.

Another impressive arylation quaternization methodology developed was reported by the Clayden group in 2013.[53] A variety of arylated amino acids were generated via an intramolecular process, involving an amino acid enolate and an aryl electrophile, bridged by a urea linker. The new C-C bond was installed α to the amino acid via the migration of the *N*-phenyl substituent of the urea onto the enolate through an S_NAr process. Subsequent cyclization gave rise to hydantoins, which upon hydrolysis generated quaternary aryl amino acids. In 2015,[54] an asymmetric protocol for this transformation using pseudoephedrine as a chiral auxiliary tethered to a range of amino acid derivatives (**Scheme 26**) was disclosed.



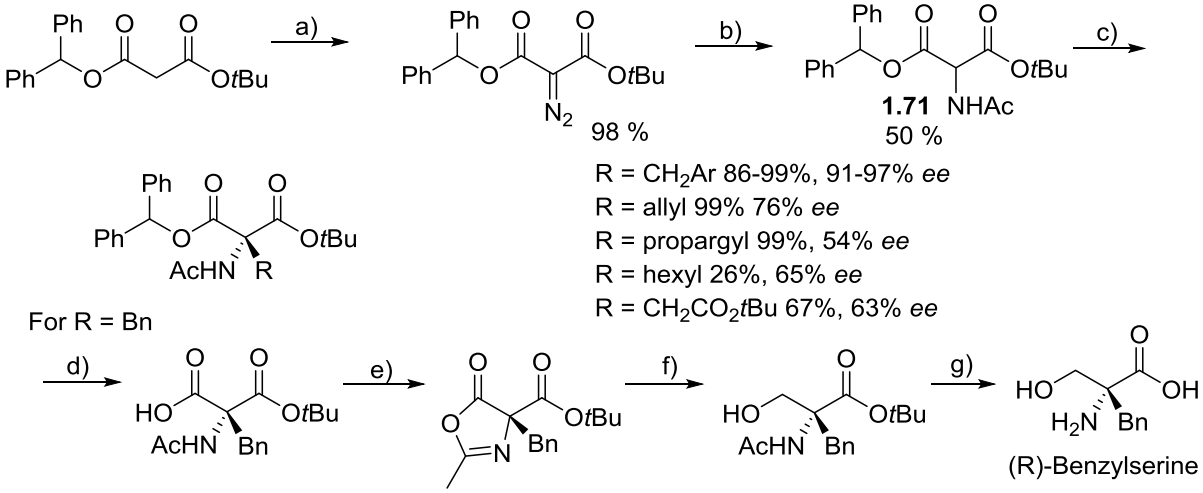
Scheme 26 *Reagents and conditions*: a) LiOH, H_2O, THF b) EDC.HCl, HOBt, *i*-Pr_2Net, CH_2Cl_2, rt; c) i) LDA (2 eq), THF, -78 °C; ii) Me_3SiCl (2.1 eq) iii) LDA (2 eq) -78 to 20 °C; iv) K_2CO_3, MeOH; d) NaOH (4M), reflux.

Ethyl or methyl esters of various amino acids were acylated with appropriate carbamoyl chlorides and then coupled to pseudoephedrine after hydrolysis of the ester. The resultant ureas **1.69** were treated with LDA and Me_3SiCl, to furnish hydantoins **1.70** with regeneration of pseudoephedrine. The yields and selectivities of the rearrangement were found to depend on the number of equivalents of Me_3SiCl, in which 2.1 equivalents was optimal. This stoichiometry suggested the initial silylation of the pseudoephedrine hydroxyl, followed by trapping of the urea anion, allowing for an intermediate that could undergo deprotonation with further LDA to the reactive enolate species. Alanine, methionine, butyrine, *n*-propylglycine, leucine, lysine, and proline were all arylated with a

phenyl and other electron-rich rings. Yields were moderate to good, with high levels of stereoselectivity. Results worsened with increasing steric bulk of the amino acid and valine and phenylglycine ureas did not react. Electron-deficient rings gave lower yields and much lower selectivities, while substrates bearing allyl, benzyl and indolyl- groups on the amino acids did not rearrange successfully.

1.5.3 α-Amidomalonate Carbanions

The enantioselective alkylation of prochiral α-amino malonates is an uncommon but further intriguing approach for accessing ATAs. Of crucial importance is the chemodifferentiation of the malonate esters in the end game. Park *et al*. [55] achieved overall transformation in 2015 with the use of Maruoka's chiral phase-transfer catalyst **1.62a**, (**Scheme 27**). The amido-malonates were accessed via the diazotization of malonates followed by conversion to a carbenoid that inserted into the NH bond of acetamide. Various amido-malonates were tested, arriving at **1.71** as the best substrate for α-alkylation, which was then subjected to PTC alkylation using **1.62a** with KOH as base. Activated benzylic electrophiles gave much better enantioselectivities than activated aliphatic ones, while alkylation with unactivated electrophiles was disappointing. A typical endgame post alkylation is illustrated for (*R*)-α-benzylserine in **Scheme 27** involving hydrogenolysis to achieve chemoselective ester differentiation, azalactone formation, reduction and finally acidic hydrolysis to afford the ATA.

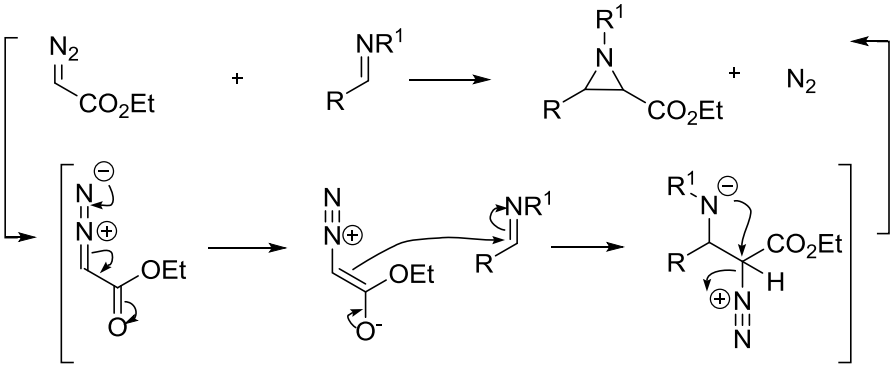


Scheme 27 *Regents and conditions*: a) *p*-ABSA, Et_3N, CH_3CN, 0 °C; b) $AcNH_2$, $Rh_2(OAc)_4$, $ClCH_2CH_2Cl$, reflux; c) **1.62a** (5 mol %), RX, 50 % KOH, (5 eq), toluene; d) Pd/C, H_2, MeOH, rt; e) EtOC(O)Cl, NMM, THF, -10 °C; f) $NaBH_4$, THF, H_2O, rt; g) 6N HCl, MeOH, reflux.

1.5.4 α-Aziridinyl Carbanions

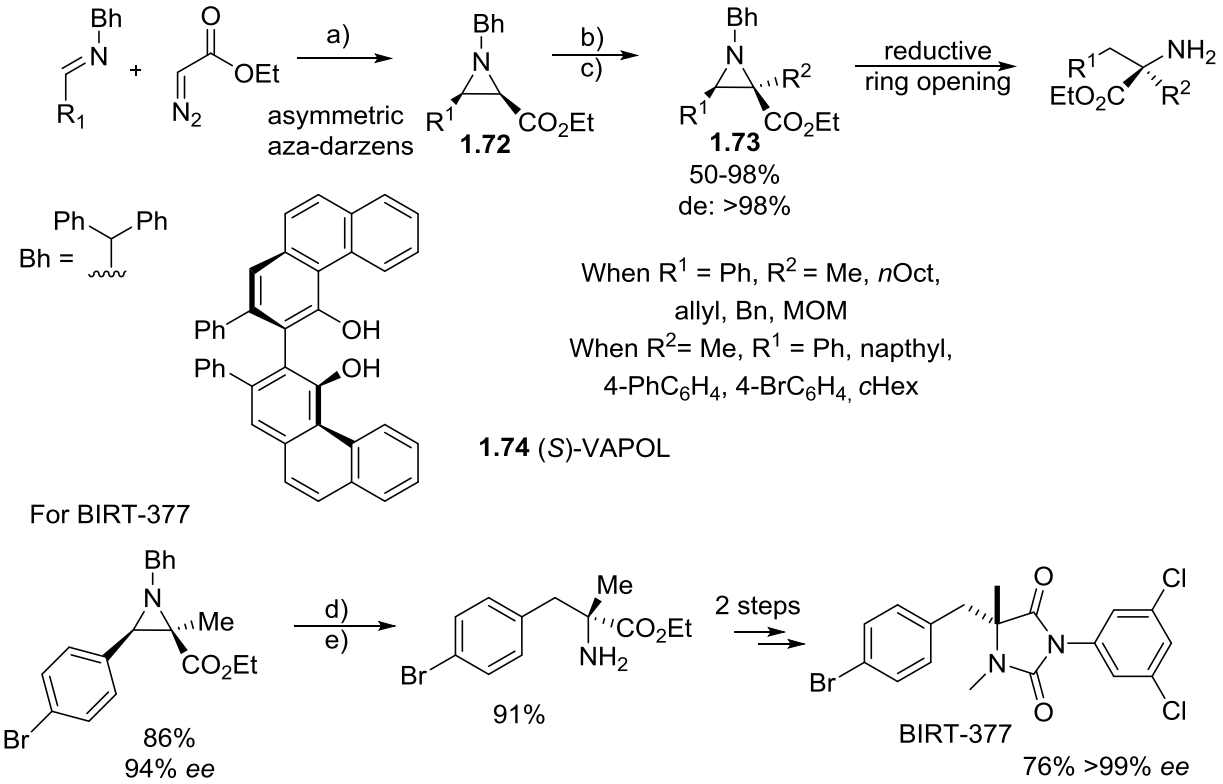
Enantiomerically pure aziridines are useful and versatile building blocks in the synthesis of ATAs in which aziridine 2-carboxylates are particularly desirable as intermediates of α,α-disubstituted amino

acids. A typical route to aziridine 2-carboxylates is via the aza-Darzens reaction involving the reaction of ethyl diazoacetate with an aldimine (**Scheme 28**).



Scheme 28 Mechanism of the aza-Darzens reaction

Access to ATAs is, however, not possible via this route as the reaction only works well with unsubstituted diazo esters, but not when a group is present α to the ester. This is where electrophilic substitution via a carbanion at the α-position of the aziridine can provide a solution, which although challenging, is possible owing to the acidity of the C-2 proton. The difficulty in alkylation of chirally pure aziridine-2-carboxylates stems from their propensity to undergo ring opening and self-condensation reactions upon enolate formation.[56] Normally, only thioesters of aziridin-2-carboxylates are useful, or a chelating substituent on *N* is needed in order to stabilize the enolate.[57] Nevertheless, Wulff and co-workers were able to employ a benzhydrol group on nitrogen very successfully in the alkylation, and extended the methodology in their synthesis of the LFA antagonist BIRT-377 (**Scheme 29**).[58] The generation of the required aziridine 2-carboxylate **1.72** in an enantioselective fashion was achieved by employing (*S*)-VAPOL-B as a catalyst for the asymmetric aza-Darzens reaction, which gave the aziridine **1.72** in 87 % yield and 94 % *ee*. Thereafter, alkylation with LDA and a range of electrophiles proceeded with retention of configuration at C-2 to give quaternary aziridines **1.73**. Primary alkyl iodides gave moderate yields while aldehydes gave excellent yields but with no selectivity at the alcohol chiral centre. The benzhydrol group was found to be crucial to the reaction and the aziridine also had to be substituted at C-3. Following alkylation, quaternary amino acids could be accessed via removal of the benzhydrol group and hydrolytic ring opening, and this was done for the derivative from which BIRT-377 was accessed.



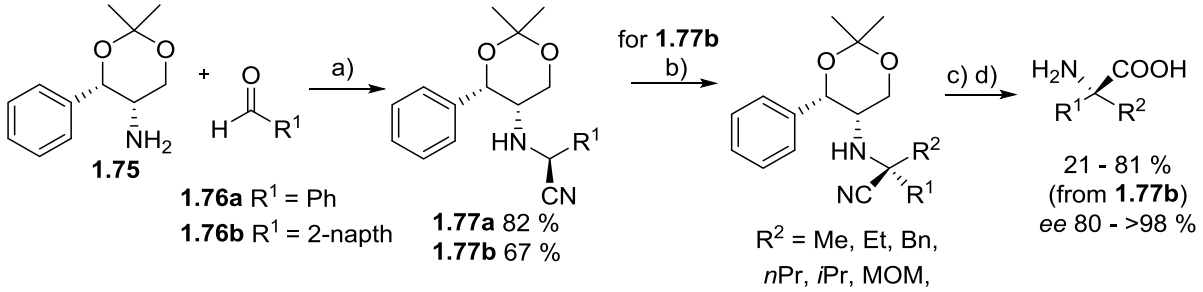
Scheme 29 *Reagents and conditions* a) 1 mol % (*S*)-VAPOL-B catalyst (prepared by heating **1.74** with triphenyl borate in CCl_4 at 85 °C), CCl_4, rt; b) LDA, -78 °C DME/Et_2O (5:1); c) R^2X, warm to 25 °C; d) BH_3Me_3N (12 eq), TFA (9 eq) CH_2Cl_2 0 °C to rt; e) Et_3SiH (3 eq) TFA, reflux.

In the past, the generation of chirally pure substituted aziridines was mainly achieved by elaboration of acyclic members of the chiral pool, but as the example above shows, asymmetric catalytic methods are becoming a popular and more direct strategy.

1.5.5 α-Amino Nitrile Carbanions

The use of α-amino nitriles as synthetic equivalents of α-amino carbanions has been practiced for decades. They owe their utility to the strong anion stabilizing ability of the nitrile group and provide useful precursors and building blocks for many nitrogen containing compounds.

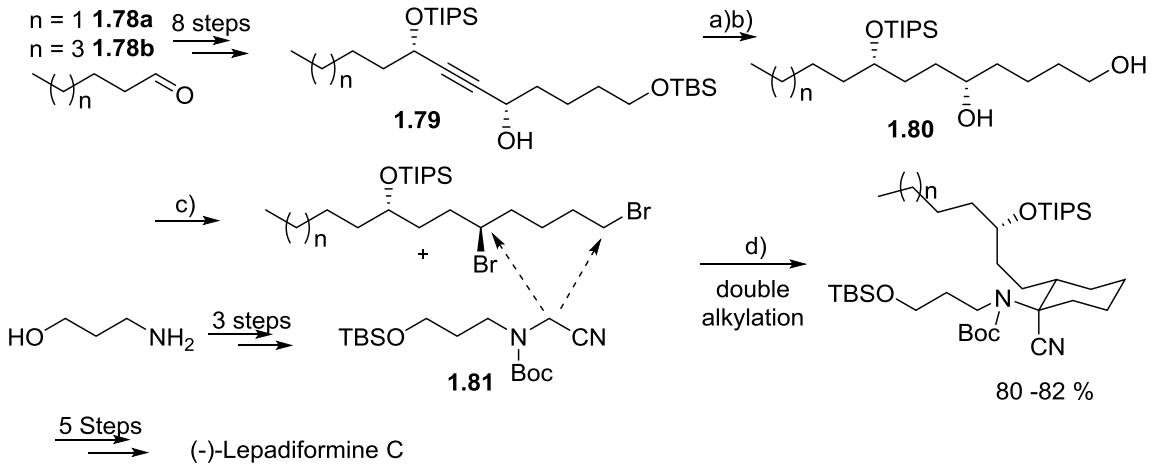
The enantioselective synthesis of a series of α-aryl, α-alkyl amino acids was recently achieved by alkylation of a chiral α-aminonitrile **1.77**, derived from the Strecker product of an aromatic aldehyde **1.76** and the Weinges auxiliary **1.75** as illustrated in **Scheme 30**.[59] The phenyl group of the auxiliary is postulated as blocking the rear face of the keteneiminate β-carbon, resulting in frontside attack by the electrophile.



Scheme 30 *Reagents and conditions*: a) KCN (1.3 eq), pH 5, H_20/MeOH 1:1, rt; b) KHMDS (1.3 eq), R^2X (1.3 eq), THF, -78 °C; c) 12 N HCl -10 to 55 °C; d) Raney-Ni, air, 2M NaOH, 120 °C.

The Strecker reaction of 2-naphthaldehyde **1.76b** and benzaldehyde with KCN gave aminonitrile **1.77b** as a single diastereomer after crystallization. Anion formation with KHMDS and subsequent alkylation with a range of electrophiles proceeded smoothly, although the products had to be immediately subjected to nitrile hydrolysis and oxidative auxiliary removal. The final quaternary amino acids were isolated in yields of 21 – 81 % and in high enantiomeric purities (80 to > 98 %).

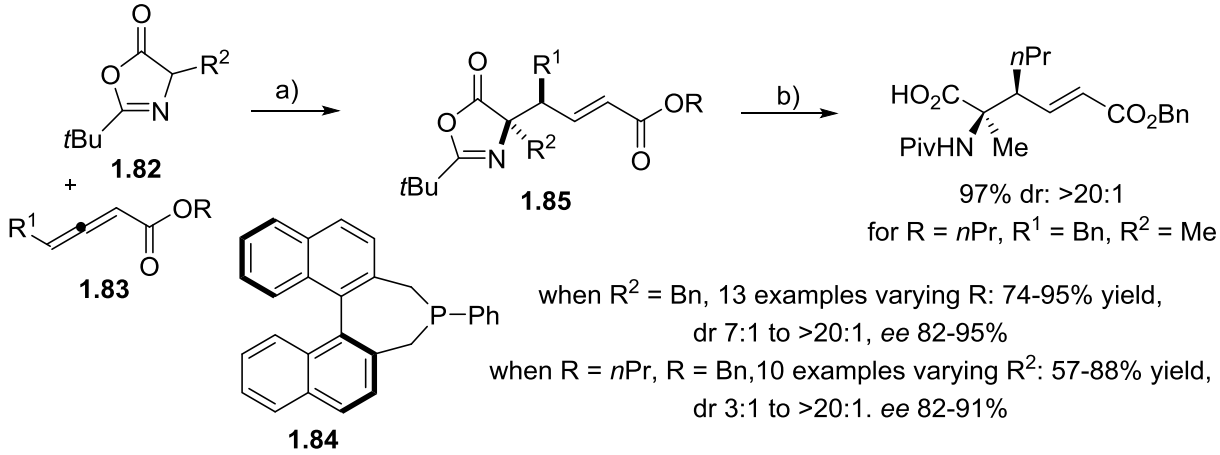
Nitrile-stabilized carbanions (ketene iminates) can also be useful in the construction of complex scaffolds through intermolecular alkylation followed by cyclization, and indeed have proven valuable in a recent total synthesis of lepadiformine. Rychnovsky devised a method for diastereoselective spirocyclization by generating an α-amino alkyllithium reagent from an α-amino nitrile (**Scheme 31**).[60] The highlight of this convergent synthesis is the expedient and stereoselective construction of all three rings from acyclic precursors. The enantiomerically pure dibromide was prepared from aldehyde **1.78** using an enantioselective ketone reduction employing a chiral hydrogen-transfer catalyst; Elaboration of the side chain involved an oxidation and a second Nyori-Ikariya reduction, followed by alkyne reduction of **1.79** with platinum oxide and removal of the TBS group. S_N2 bromination of the two hydroxyl groups of **1.80** using bromine, PPh_3 and triethylamine, generated the dibromide in good overall yield. The initial nitrile anion of **1.81** displaces the primary bromide and the additional equivalent of base generates a second nitrile anion which then closes the ring in a 6-*exo*-tet fashion. Attempts to include the hydroxymethyl side-chain for lepadiformine A on the amino nitrile were unsuccessful.



Scheme 31 *Reagents and conditions*: a) PtO_2, H_2, (200 psi); b) PPTS, MeOH; c) PPh_3, Br_2, Et_3N; d) LDA (3.5 eq), DMPU/THF (1:1)-78 °C to 0 °C.

1.5.6 Addition of N α–carbanion to Allenoates

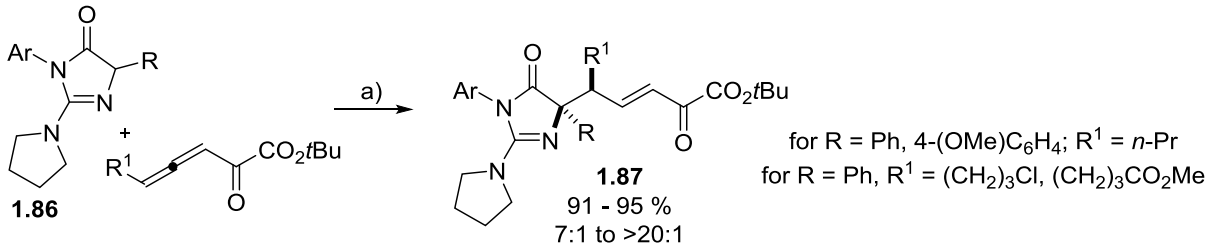
In 2015, Fu and co-workers[61] disclosed a stereoselective protocol for the ϒ-addition of a racemic heterocycle **1.82** to a racemic allenoate **1.83** using a chiral phosphine catalyst **1.84** for creating enantioselectivity ultimately. The sequence involved a cascade of steps that was initiated by addition of the chiral catalyst **1.84** to the allene central carbon in a Michael addition. Thereafter, proton exchange with the heterocycle (oxazolone **1.82** in **Scheme 32**) followed by a second and stereoselective Michael addition of the oxazolone carbanion to the vinylphosphonium salt, proton transfer and phosphine elimination (regeneration) furnished the γ-addition product **1.85**. Acid hydrolysis allowed access to a range of α,α-disubstituted amino acids in good yields, diastereoselectivity and enantioselectivity (**Scheme 32**).



Scheme 32 *Reagents and conditions*: a) 5-10 mol % **1.84**, 10 % 2-chloro-6-methylphenol, *i*-Pr_2O, 0°C; b) 1 M HCl, 80 °C.

It is impressive, starting with relatively simple racemic substrates, that two stereocenters could be generated with good relative and absolute selectivities, one being a quaternary centre. Furthermore,

the protocol proved to be rather general, tolerating various functionalities in both the allenoate and the oxazolone. The one drawback, though, was that the reaction failed with R^2 = aryl. This problem was overcome by employing an imidazolone template **1.86** instead of an oxazolone. Aryl groups stabilize the conjugate base of the nucleophile through resonance, thereby decreasing its nucleophilic potential and reactivity. However, substitution of the electron-withdrawing oxygen with nitrogen provided, through its resonance releasing effect, a desired increase in nucleophilicity. Indeed, good yields and selectivities were obtained with various aryl- substituted nucleophiles, providing 2-amino-3,5-dihydro-4H-imidazol-4-one adducts **1.87**, which are valuable targets in their own right aside from being precursors of α,α-disubstituted amino acids (**Scheme 33**).



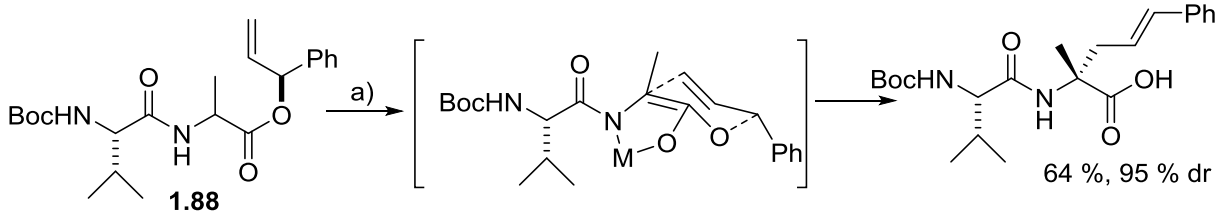
Scheme 33 *Reagents and conditions*: a) 10 mol % **1.87**, 10 % 2-fluoro-6-methoxyphenol, toluene, 10°C.

The methodology provides a class of compounds which could undergo a range of transformations to yield interesting and complex molecules by manipulating different functionalities.

1.5.7 Rearrangements involving an N-α carbanion

Kazmaier-Claisen Rearrangement

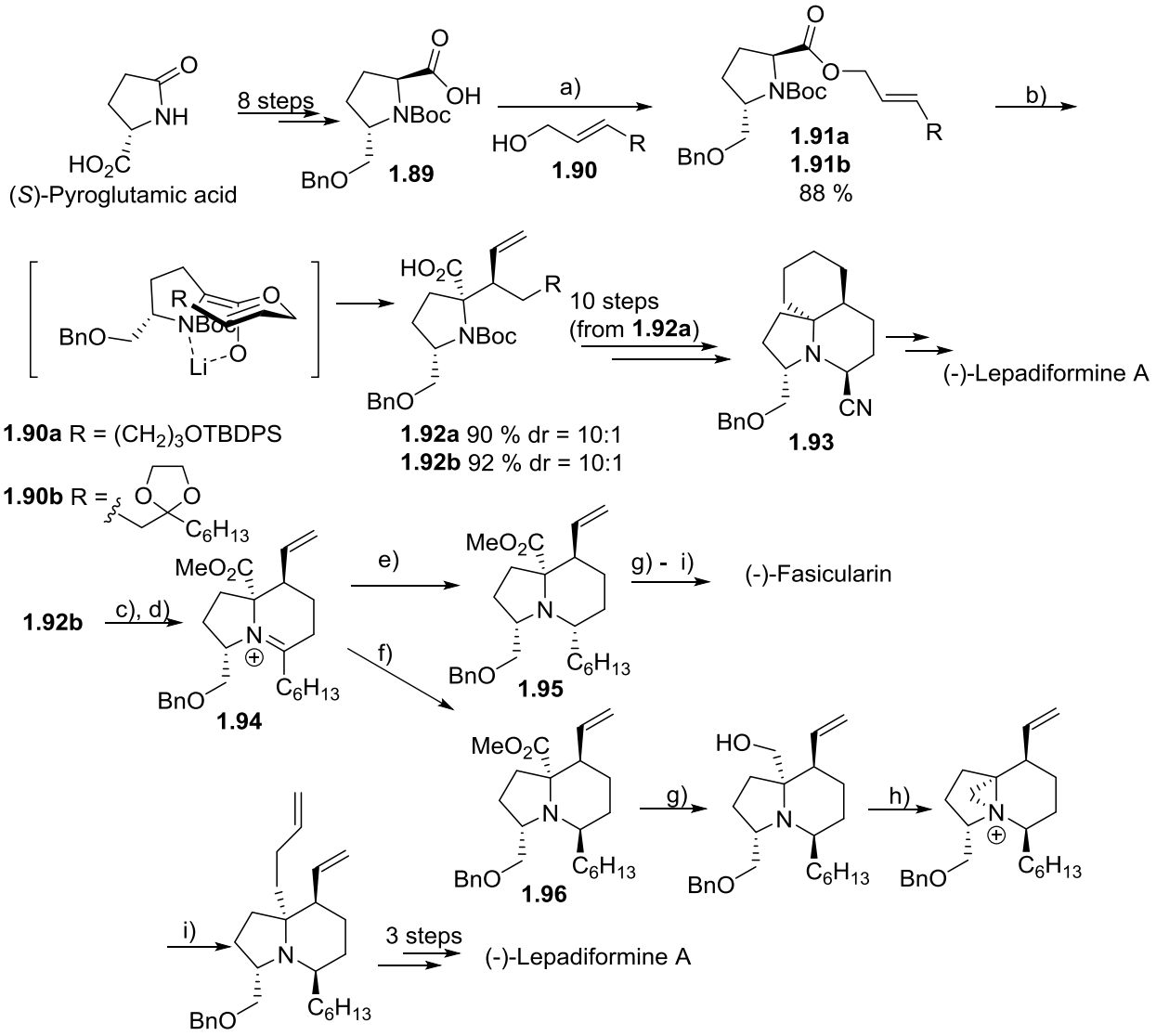
In this variant of the ester-enolate Claisen Rearrangement, a chelated metal enolate of *N*-protected amino acid allyl esters **1.88** undergoes a Claisen rearrangement at room temperature (**Scheme 34**). Metal salts such as $MnCl_2$ are added in order to chelate the enolate, setting the enolate geometry to ensure high diastereoselectivity in the rearrangement.



Scheme 34 *Reagents and conditions*: a) i) LDA (4 eq), $MnCl_2$ (1.2 eq) THF -78 °C to rt.

Kim *et al*[62] incorporated a cyclic amino acid α to the allylic ester to bring about a combination of the Kazmaier and Ireland-Claisen rearrangements stereoselectively, generating the ATA required for their Formal total synthesis of lepadiformine (**Scheme 35**). In the Ireland-Claisen version, the allyl ester of a carboxylic acid is converted to its silyl-stabilized enolate (silyl ketene acetal), which

rearranges at temperatures below 100 °C to ultimately give chain-extended carboxylic acids. Their synthesis began with (*S*)-pyroglutamic acid, which was converted to acid **1.89** in 8 known steps, followed by production of the allylic ester **1.91** via a DCC coupling procedure with allylic alcohol **1.90a** and in their revised synthesis **1.90b**. The rearrangement proceeded upon the treatment of **1.91a** and **b** with LHMDS and TBSCl via a chair-like transition state in which selective formation of the (*Z*)-silyl ketene acetal was crucial to the stereoselectivity of the reaction, ultimately furnishing the desired products **1.92a** and **b** both in a ratio of 10:1. Presumably, chelation of the lithium by the nitrogen and the oxygen of the enolate ensured selectivity for the (*Z*)-configuration. Further in the synthesis, ring-closing metathesis brought about ring closure at the spirocyclic junction, and simple functional group manipulation generated the Weinreb intermediate **1.93**, a common intermediate in the total enantioselective synthesis of (-)-lepadiformine.

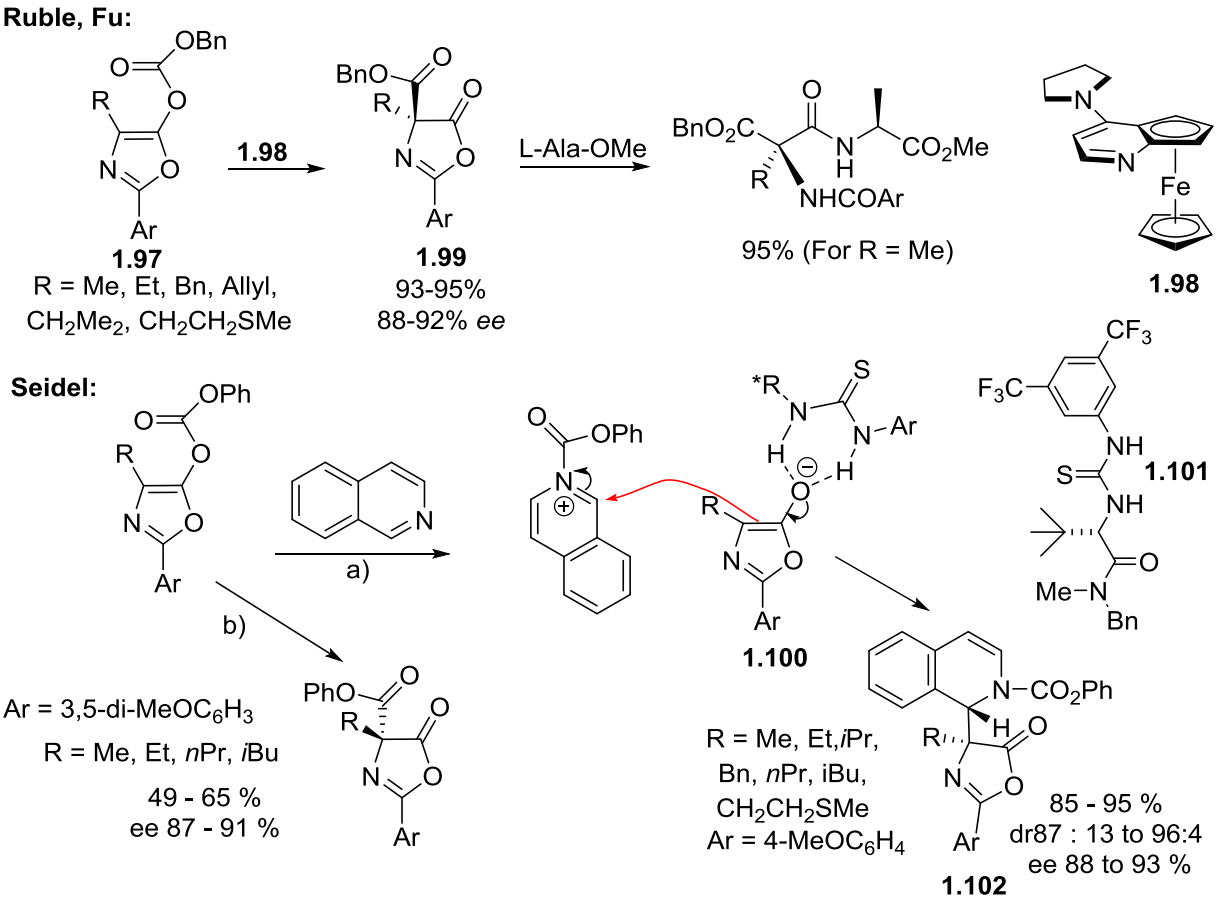


Scheme 35 *Reagents and conditions*: a) DCC, DMAP, CH_2Cl_2, rt; b) LiHMDS, TBSCl, THF, -78 °C to rt; c) $TMSCHN_2$, MeOH, rt; d) TFA/ CH_2Cl_2 (3:5), 0 °C to rt; e) L-Selectride, THF, -78 °C; f) $NaCNBH_3$, MeOH, -78 °C; g) $LiAlH_4$, THF, -78 to 0 °C; h) MsCl, Et_3N, Et_2O, 0 °C; i) allylMgBr, CuI, THF, - 78 °C to rt.

In their revised and more concise synthesis of lepadiformine and Fasicularin published in 2014, the key step was a stereoselective reductive amination of a common intermediate, giving rise to indolizidines **1.95** and **1.96** (**Scheme 35**), precursors of lepadiformine and Fasicularin respectively.[63] A more complex rearrangement product **1.92b** was devised and synthesized from a known ketone and arrived at as before, via the Claisen rearrangement protocol. An iminium salt **1.94** was generated by treatment of **1.92b** with TFA, removing both the Boc and ketal groups. Based on their in-depth model studies for the reductive amination, they were able to generate either stereoisomer of the indolizidine product in high selectivities depending on the reagent employed in the reductive amination step. The alkaloids were accessed via an aziridine-mediated carbon homologation from a hydroxymethyl to a homoallyl group and an additional three steps in the case of (-)-lepadiformine.

Steglich-Höfle rearrangement

The rearrangement of an O-acylated azalactone **1.97** into the corresponding C-acylated oxazinone **1.99** offers a practical entry into quaternary oxazolones as precursors of α-alkylated α-amino malonic acids. Since the mechanism involves an acyl transfer, the reaction is typically catalyzed by DMAP, whose chiral derivatives have been developed for asymmetric transformations. The first example of an asymmetric catalytic Steglich-Höfle rearrangement was reported in 1998 by Ruble and Fu[64] who utilized a planar chiral, ferrocene-derived 4-(pyrrolidino)pyridine catalyst **1.98** to access products in yields of 93-95 % and *ee*s of 88-92 % (**Scheme 36**). More recently, Seidel[65] disclosed a dual-catalysis approach for the asymmetric Steglich rearrangement, which was incidentally also applicable to azalactone addition to isoquinolines. The use of an isoquinoline instead of DMAP as a nuceophilic activator generated the intermediate **1.100** which made it possible for the incorporation of the isoquinoline into the product (mechanism shown in red), providing entry into highly functionalized α,β-diamino acid derivatives **1.102**. No further transformations of the derivatives were reported in the account however.

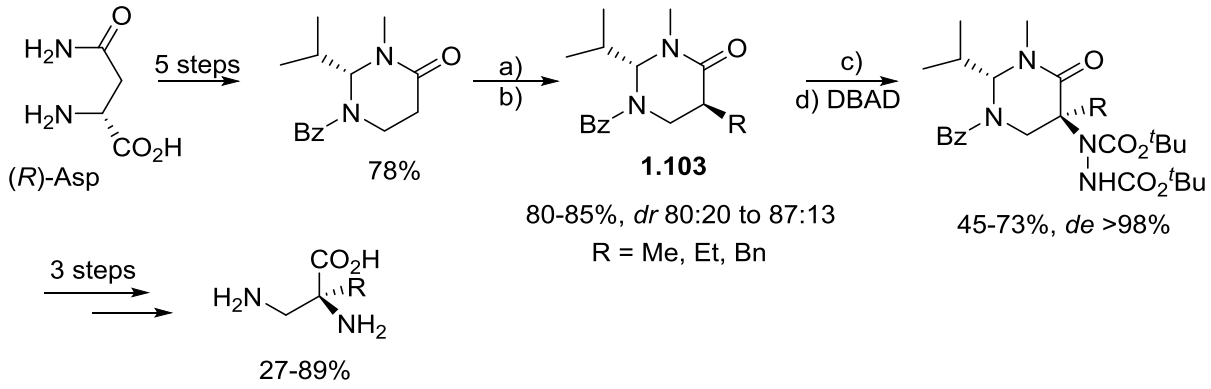


Scheme 36 *Reagents and conditions*: a) **1.101** (10 mol %), mesityline/ pentane (1:2), 4 Å MS, -15 to -35 °C; b) **1.101** (20 mol %), DMAP (20 mol %), PhMe, 4 Å MS, -78 °C.

1.6 C-N Bond Formation via an Electrophilic Nitrogen

1.6.1 Electrophilic amination with an azodicarboxylate

Aminating enolates with a suitable electrophilic nitrogen source is one of the simplest and quickest ways to generate ATAs in which azodicarboxylates, *N*-hydroxycarbamate, nitrosobenzene, NH_2-LG (LG = leaving group) and azidoiodane reagents have been used. Although diastereoselective auxiliary-based approaches using electrophilic amination for synthesizing α-secondary amines is common, their use in ATA generation is rare, the work of Castellanos *et al* in 2002 being noteworthy.[66] In their route, lithium enolates of D- or L- asparagine-derived tetrahydropyrimidinones **1.103** were aminated with di-*tert*-butyl azodicarboxylate (DBAD) in yields of 80 to 85 % and drs of up to 87:13. A further three steps including destructive removal of the auxiliary, (a disadvantage) gave enantiopure α,α-dialkyl amino acids (**Scheme 37**). In the amination reaction, the bulky amino acid side chain blocks one of the faces of the enolate, ensuring electrophile approach from the opposite face.



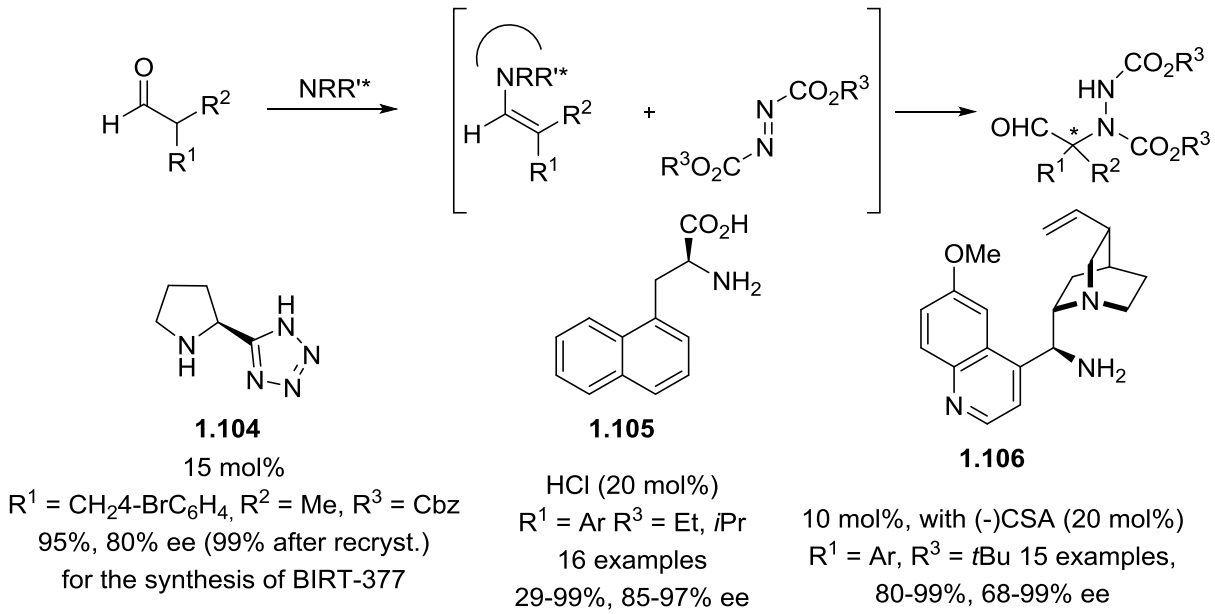
Scheme 37 *Reagents and condition*: a) LDA, THF, -78 °C b) RX, -30 °C; c) LDA, THF, -78 °C, 2h.

By contrast, catalytic approaches are far more prolific.[67] The first catalytic asymmetric electrophilic amination was reported by Evans[68] back in 1997 who utilized a chiral magnesium bis (sulfonamide) complex to activate aryl carboximides toward reaction with DBAD to generate α-secondary amines. Azodicarboxylates are the most widely used aminating reagent due to their high electrophilicity and ease of steric bulk manipulation which has a bearing on enantioselectivity. Di-*tert*-butyl or dibenzyl azodicarboxylates are favoured, because the products they yield can easily be transformed into amines via removal of the Boc or Cbz group and cleavage of the N-N bond. Unfortunately, their electrophilicity is much lower than that of azodicarboxylates with smaller ester groups, creating the need for further activation of the nucleophile. Different activation models for reactions with azodicarboxylates will be covered in the following section where the sub-sections focus on the nucleophilic partner.

1.6.1.1 Aldehyde Enamines

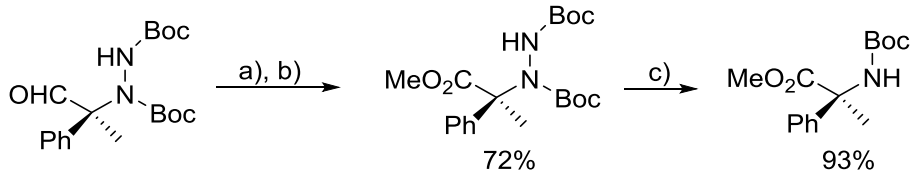
The use of chiral amine catalysts to generate chiral enamines from α-substituted prochiral aldehydes has been successful in many instances. The scope of enamine strategies can be limited, particularly for acyclic variants where selectivity depends on controlling *E* or *Z*-enamine selectivity.

Proline and its derivatives have been used extensively for enamine-based approaches, as well as primary amines derived from a range of sources such as amino acids. Similarly, the Cinchona alkaloid framework, where additional H-bonding interactions can come into play, has also been intensely investigated. **Scheme 39** illustrates a few relevant examples.



Scheme 38 Chiral amines used for enamine activation towards electrophilic amination with azodicarboxylates.

Barbas *et al*[69] employed the proline derived tetrazole **1.104** in their enantioselective total synthesis of BIRT-377, which delivered the product in 95 % yield and 80 % *ee*, effectively raised to 99 % by recrystallization. A further seven steps delivered BIRT-377 in an impressive overall yield of 76 %. In 2011, Wang and co-workers[70] discovered that the simple primary amino acid **1.105** was a potent catalyst for amination of branched benzaldehydes with diethyl azodicarboxylate (DEAD) or isopropyl azodicarboxylate.[70] The use of 20 mol % of the HCl salt of **1.105**, furnished the desired products in up to 99 % yield and 97 % ee. Lu *et al*[71] employed the cinchona alkaloid variant **1.106**, also possessing a primary amine for the same transformation, in conjunction with 20 mol % of (-)-camphorsulfonic acid [(-)-CSA] and DBAD as the aminating reagent. The efficiency of the reaction was highly dependent on the chirality match between the amine and the CSA, with lower selectivities and yields observed when (+)-CSA was used. A further three operations gave the protected amino acids in good yields (**Scheme 39**).

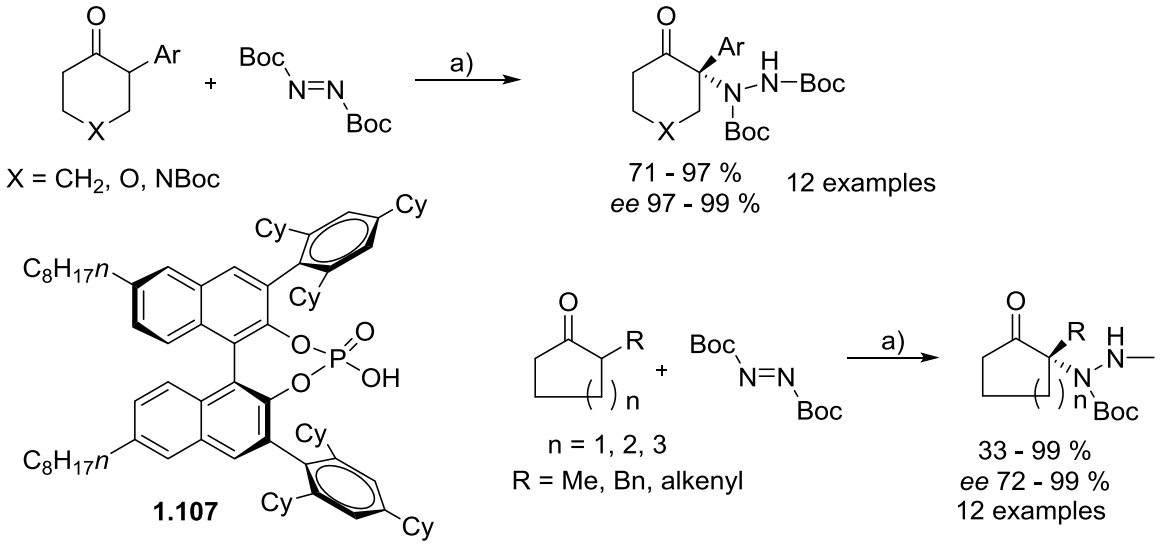


Scheme 39 *Reagents and conditions*: a) $NaClO_2$, H_2O_2; b) $TMSCNH_2$; c) SmI_2

Although the enamine activation strategy is successful for the amination of simple α-branched aldehydes with azodicarboxylates leading to ATAs ultimately, ketone counterparts cannot be activated in this way due to a decreased reactivity and increased steric bulk. Employing a chiral Brønsted base or organosuperbase to abstract the α-proton in this case is a good way of overcoming the low acidity of the α-proton and prime α-branched ketones toward reaction with azodicarboxylates.[72]

1.6.1.2 Ketone activation

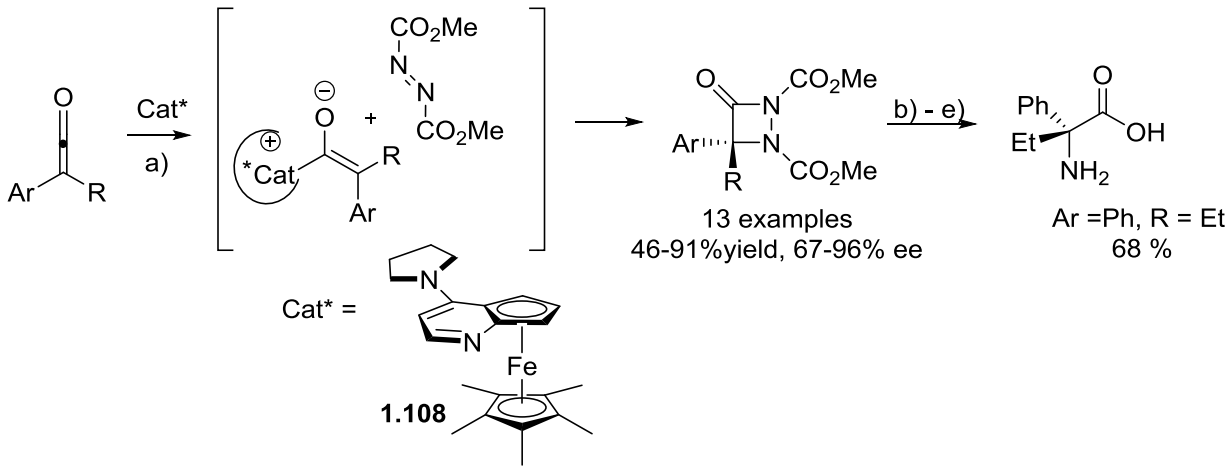
In a different approach for ketone activation, Toste and Yang[73] disclosed an asymmetric amination protocol of branched cyclic ketones involving catalysis by a chiral phosphoric acid **1.107** (**Scheme 40**). Both alkenyl and aryl 2-substituted cyclic ketones could be directly aminated using DBAD and 10 mol % of the catalyst. Various substituted aryls at the α-position of the cyclohexanone were tolerated, including electron neutral, electron-donating and electron-withdrawing groups attached to the aromatic ring. A broad scope was also achieved with respect to alkenyl substituents on the cyclohexanone.



Scheme 40 *Reagents and conditions*: a) **1.107** (10 mol %), 5 Å MS, 45 °C, 'neat'

1.6.1.3 Ketenes and Lewis Base Catalysis

Ketenes are excellent substrates for ionic [2+2] cycloaddition reactions with diazo compounds once nucleophilically activated, providing entry into highly substituted cyclic compounds, such as the versatile aza-β-lactams in particular. Berlin and Fu[74] were the first to report on this type of enantioselective reaction by employing a chiral, planar DMAP type catalyst **1.108**. The resulting lactams could be converted to hydantoins, or α,α-disubstituted amino acids (**Scheme 41**). For this type of transformation, so far only aryl ketenes have been reported.



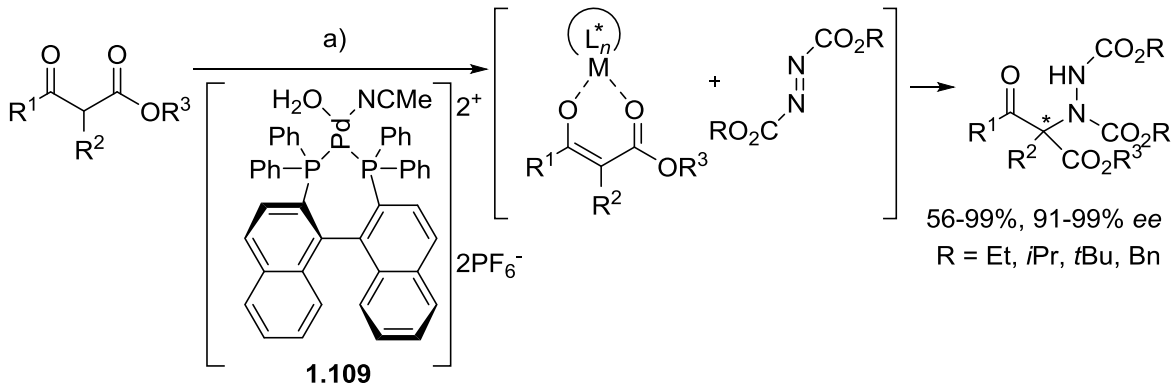
Scheme 41 *Reagents and conditions*: a) **1.108** (5 mol %), CH_2Cl_2, -20 °C; b) K_2CO_3, MeOH; c) pyridine then TFA; d) SmI_2, MeOH; e) conc. HCl.

1.6.1.4 Stabilised enolates

Apart from favourable reactivity, this type of substrate is 'popular' as it provides an easily functionalizable handle on the aminated adduct. Furthermore, a better chelation control in chiral metal complex-catalysed reactions can be achieved as in the case of using two carbonyl groups.. Since Jørgensen's first account of α-amination of β-keto esters in 2003,[75] an impressive body of work has been published using dicarbonyls with differing activation models, two of which will be discussed below.

Chiral Lewis acid activation

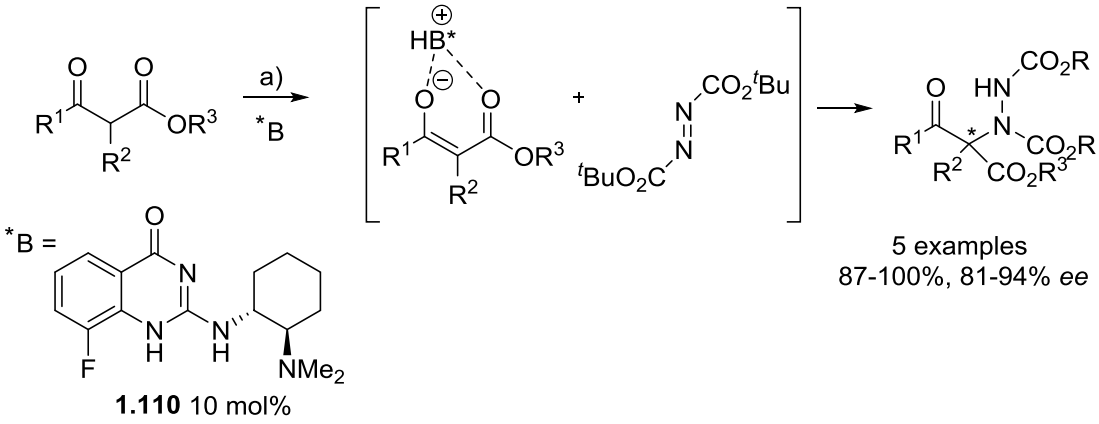
Chiral ligands complexed to a Lewis acid effectively catalyse amination of carbonyls and many examples are found in the literature. A notable example Is that of Kim *et al,*[76] who developed a BINAP derived chiral palladium(II) complex **1.109**, stable to air and moisture which was capable of catalysing a wide range of β-keto esters in excellent yields and enantioselectivities (**Scheme 42**). Apart from a low catalyst loading (5 mol %), the catalyst could also be bound to an ionic liquid and recycled 5 times without loss of activity. The same catalyst was found to be efficient in the α-amination of α-cyano ketones.



Scheme 42 *Reagents and conditions*: a) **1.109** (5 mol %), MeOH, rt.

Chiral Lewis base catalysis

Carrying out the amination via a chiral enolate derived from a chiral Brønsted bases was first reported by Jørgensen. Multifunctional catalysts with one or multiple H-bond donor sites which serve to anchor the enolate, gave very good results when in co-operation with tertiary amines bases present on the same molecule. Hydroxyl and thiourea moieties are common H-bond donor sites, and catalysts based on the cinchona alkaloids are also an obvious example. Other motifs have also proven effective such as Takemoto's bifunctional tertiary amine catalyst **1.110**, which incorporated 2-aminoquinazoline as the H-bond donor, and owing to its conformational rigidity was capable of inducing highly asymmetric aminations (81-94 % *ee*)(**Scheme 43**). [77]

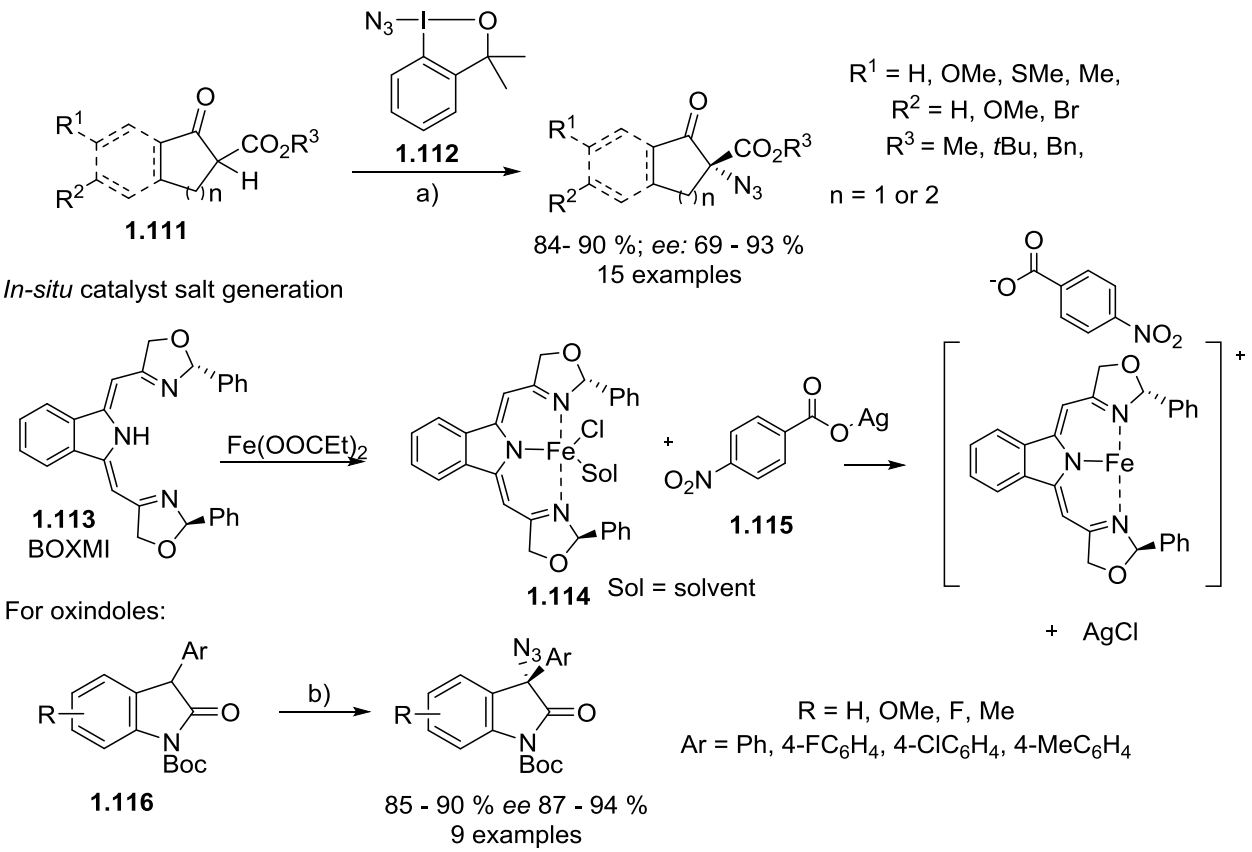


Scheme 43 Chiral Lewis base catalysis for asymmetric amination of β-keto esters

1.6.2 Electrophilic Azidations

Organoazides are highly desirable targets in organic synthesis as they can engage in many types of transformations such as simple reduction to the amino group, generation of nitrenes, cascade reactions and can play the role of triggering rearrangement and cycloaddition reactions. Developing stereoselective azidation reactions is therefore an important endeavour in synthetic chemistry. While nucleophilic azidation reagents such as sodium azide are well known for azide introduction, electrophilic azidations have only come to the fore relatively recently as the traditional reagents are toxic and explosive. Sulfonyl azides are widely used, but generally give best results with strongly nucleophilic lithium enolates.[78] Furthermore, dicarbonyls often suffer from competing diazo transfer and rearrangement reactions.[79] The creation of an umpolung azide *in-situ* is a way of overcoming this hurdle and can be done by using strong oxidizing agents, exemplified by the sodium azide and IBX protocol.[80] However, in these pathways the active azidation reagent is still a mystery or highly unstable and as such cannot be isolated, making progress on asymmetric induction mechanistic thinking difficult. In contrast, the superior stability of the benziodoxol-based hypervalent iodine reagents introduced by Zhdankin in 1994,[81] allow for the development of catalytic asymmetric methodology with greater ease.

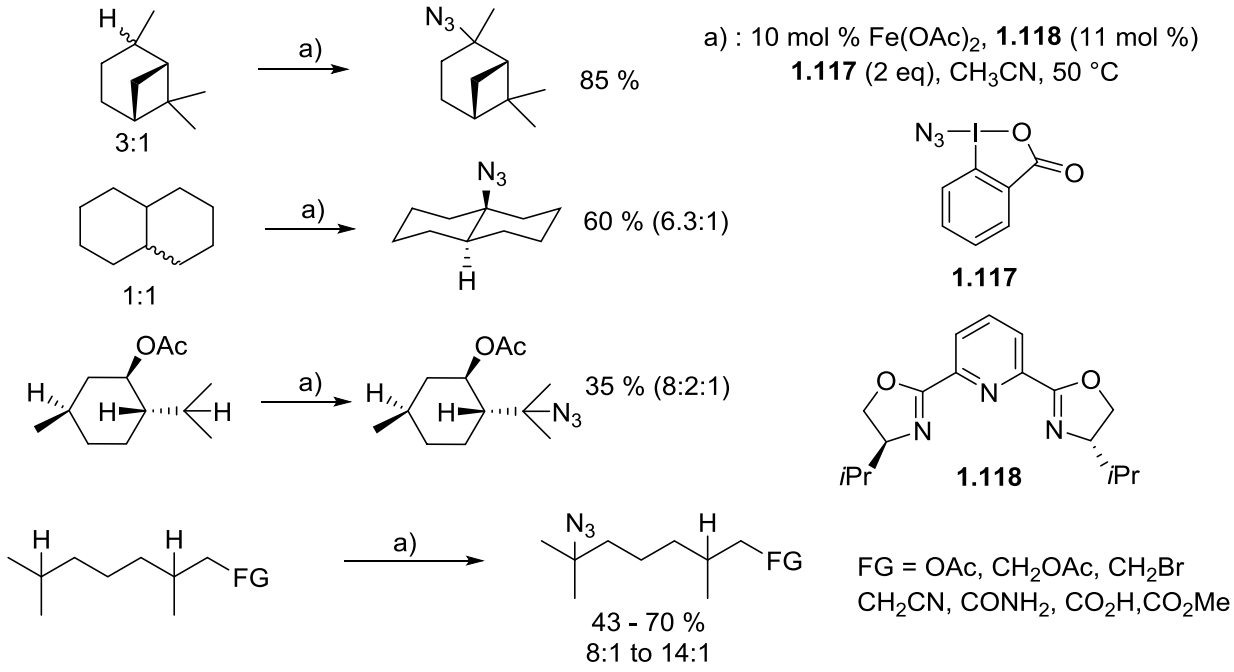
Gade *et al*[82] reported on the first enantioselective azidation of cyclic β-keto esters **1.111** and oxindoles **1.116** catalysed by Iron salts combined with chiral pincer ligands **1.113** ('boxmi") **(Scheme 44**) in 2013. For the enantioselective azidation of β-keto esters, the best results were obtained with *in-situ* formation of the catalyst (generated by mixing the iron (II) chloride complex **1.114** and silver benzoate **1.115**), without the need for removal of silver chloride. Bulky ester substituents were necessary for good enantioselectivities and cyclic six-membered rings could only be obtained with moderate selectivities; the protocol was unfortunately not effective for acyclic ketoesters. 3-aryloxindoles were also successfully azidated in high yields and selectivities, regardless of the nature and position of oxindole substituents.



Scheme 44 *Reagents and conditions*: a) **1.114** (10 mol %), **1.115** (10 mol %), **1.112** (1.5 eq), Et_2O, rt; b) $Fe(OOCEt)_2$ (10 mol %), **1.113** (10 mol %), **1.112** (1.5 eq), Et_2O, rt.

Hartwig and Sharma[83] utilized a very similar azidation reagent **1.117** in a metal-catalysed azidation of tertiary C-H bonds, using tridentate nitrogen ligands of the pybox family **1.118** (**Scheme 45**). Because the methodology is mild and selective for the tertiary C-H site, it allowed for late-stage azidation of complex structures without the use of excess amounts of valuable material. Furthermore, it tolerated aqueous conditions and a variety of functional groups such as esters, carboxylic acids,

amides and protected alcohols. In cases with multiple tertiary C-H sites, the regioselectivity of the reaction was such that azidation took place at the more electron- rich site, and this held true for cyclic substrates as well. When applied to more complex systems with several functional groups and strained rings, which could react or influence azidation preference, selectivity was still excellent (5:1 to 11:1:1) and yields were moderate to good (24 -80 %). In terms of stereoselectivity in ring systems, axial azide attack was favoured, thus even when a mixture of diastereomers was reacted, the result was one major azide product.



Scheme 45 Selected examples of tertiary C-H bond azidations

1.7 C-N Bond Formation via a Nucleophilic Nitrogen

Forming the C-N bond in the last step of ATA generation by action of a nucleophilic nitrogenous reagent is fairly uncommon, the aza-Michael and S_N2 reactions at a quaternary carbon being representative examples.

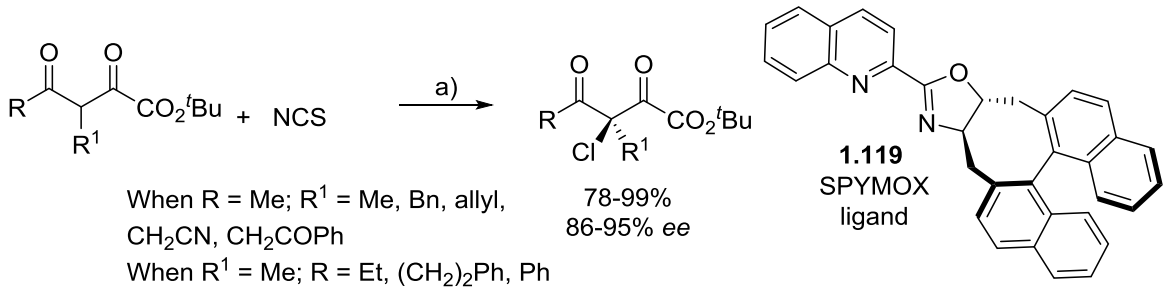
1.7.1 Aza-Michael Addition

The aza-Michael addition is one of the most versatile and direct ways to create the C-N bond and access useful β-amino carbonyl compounds and heterocycles, owing to the broad variety of nucleophiles, acceptors and catalysts that can be employed. Enals, enones, conjugated esters, nitro olefins and vinyl sulfones are all appropriate Michael acceptors, whilst moderate nitrogen nucleophiles such as sulphonamides, carbamates, oximes, hydrazines, azides or nitrogen-containing heterocycles can participate as Michael donors. Furthermore, both basic (aminocatalysis) and acidic catalysis can be employed.[84] As such, it features prominently in organic synthetic chemistry and in

numerous total syntheses of natural products. The intramolecular version in particular, provides a reliable way to construct heterocycles, often with a high degree of diastereoselectivity. Shibasaki took advantage of it in his total synthesis of lepadiformine *(vide supra*), as did a number of cylindricine syntheses,[85–87] a recent one of which will be covered in section 1.10. Asymmetric aza-Michael-initiated domino reactions can be highly effective, offering an expedient construction of complex heterocycles.[88] Access to enantioenrinched aziridines bearing a quaternary carbon has been achieved via an organocatalyzed aza-Michael initiated ring closing reaction (leaving group present on the nitrogen), hence the ATA is not directly set by the aza-Michael. These derivatives were further proliferated to α,α-disubstituted amino acids via regioselective ring-opening reactions.[89] However, as prolific as it is for the construction of asymmetric α-secondary amines, applicability rarely extends to ATAs. The limitation in the context of stereoselectivity for ATAs, lies in the difficulty in controlling the *cis*/*trans* geometry at the double bond terminus of the disubstituted enone or enal. Hence, it is yet to be developed as a general approach for asymmetric ATA construction.

1.7.2 S_N2 with NaN_3

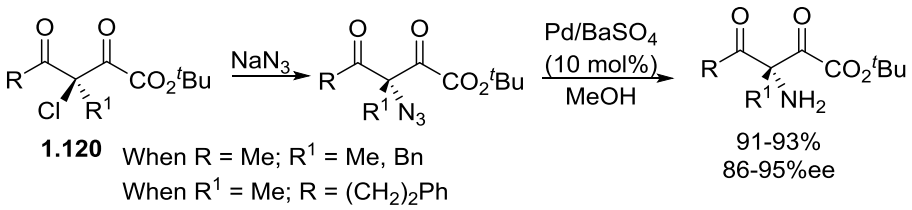
The generally accepted dogma of S_N2 reactions being unable to accesss quaternary centres from tertiary halides as taught in most undergraduate courses is apparently not entirely true. In 2012 Shibatomi *et al*[90] demonstrated that chlorinated β-keto esters could then be displaced in an S_N2 reaction with a variety of nucleophiles, including sodium azide, providing access to the ATA in enantioenriched form. To achieve enantioselective chlorination, a number of chiral ligands were tested for chelation to copper (II), coupled with NCS as a chlorinating reagent. Spirooxazoline ligand containing a quinolone backbone **1.119** gave the best selectivities and yields, with a reaction scope that extended to both cyclic and acyclic variants as well as aliphatic and aromatic esters (**Scheme 46**). One requirement for high selectivity was the presence of a bulky ester group in the substrate. α-Alkyl malonates could also be chlorinated in good to high selectivities.



Scheme 46 *Reagents and conditions*: a) **1.119** (12 mol %), $Cu(OTf)_2$, benzene, rt.

Simple S_N2 substitution of quaternary chlorinated derivatives **1.120** proceeded smoothly with sodium azide, the product of which could in turn be reduced to a free amine, thereby delivering

ATAs without any alteration in enantiopurity of the derivatives (**Scheme 47**). The S_N2 mechanism was supported by X-ray crystallographic data which revealed an inversion of configuration at the quaternary carbon.

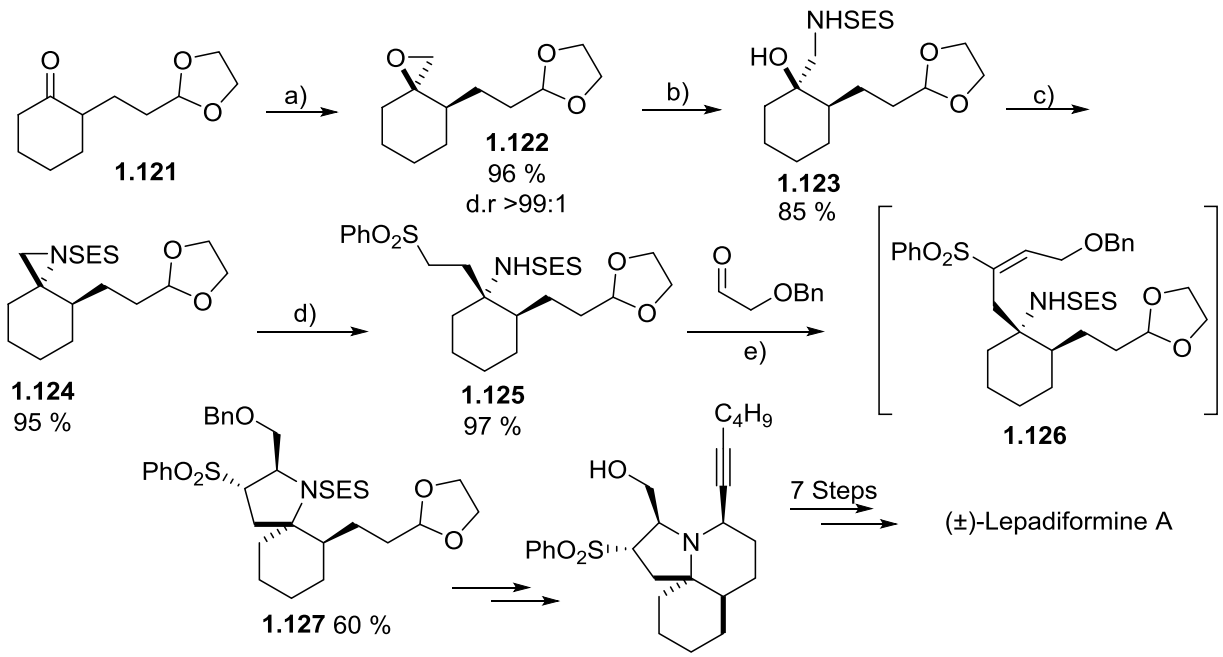


1.120 When R = Me; R^1 = Me, Bn
When R^1 = Me; R = $(CH_2)_2Ph$

Scheme 47 S_N2 displacement of chlorinated β-keto esters with NaN3 to generate quaternary azides

1.7.3 S_N2 via Mitsunobu

The Mitsunobu approach to ATAs from the corresponding tertiary α-hydroxy esters has been achieved with HN_3 as the nucleophile, following which azide reduction and ester hydrolysis furnishes quaternary amino acids.[91] Craig and Caldwell were able to apply this principle using a SES-protected primary amine intermediate (SES = 2-(trimethylsilyl)ethylsulfonyl) for an early construction of the ATA of lepadiformine via an epoxidation-aziridination sequence (**Scheme 48**).[92] Starting from the substituted cyclohexanone **1.121**, a substrate-controlled stereoselective epoxidation delivered the epoxide **1.122** in a yield of 96 % and almost perfect diastereoselectivity. The high levels of selectivity observed were a result of the bulky acetal side chain positioned equatorially, and the approach of the Corey sulfoxonium ylide equatorial onto the ketone carbonyl. The epoxide was then opened with the anion of $SESNH_2$ to afford amino alcohol **1.123**, which underwent a modified Mitsunobu reaction to give the ATA as the spiroaziridine **1.124** with complete inversion of configuration. The aziridine was opened by the α-sulfonyl carbanion of methyl phenyl sulfone (step d)) to give the precursor **1.125** for the crucial cyclization tandem reaction. Conversion to the dilithio dianion (α- to sulfonyl and on N) and reaction of it with 2-benzyloxyethanal led to addition of the carbanion, and the ensuing alkoxide was activated *in-situ* with benzoyl chloride, resulting in the elimination to the vinyl sulfone intermediate **1.126**. This then underwent formation of the N-SES protected pyrrolidine **1.127** via a 5-*endo*-trig cyclization. From here one could proceed to the target alkaloid. Interestingly, 5-*endo*-trig cyclizations are disfavoured according to Baldwin's rules,[93] and the clever use of the sulfone functionality in order to induce a disfavoured ring-closure is one of the highlights of the synthesis.

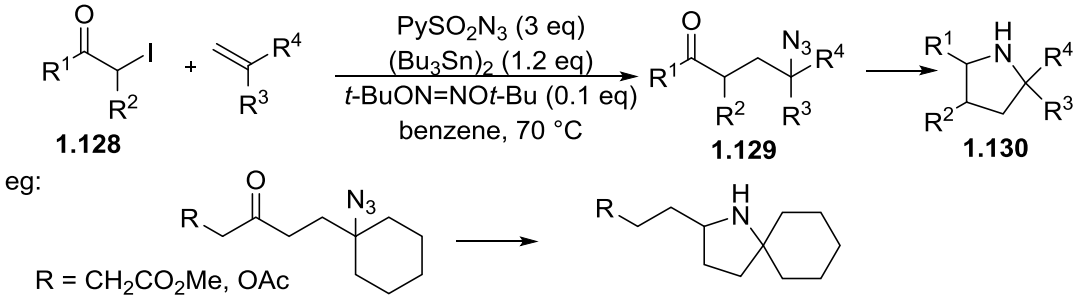


Scheme 48 *Reagents and conditions*: a) $Me_3S(O)I$, NaH, DMSO; b) $SESNH_2$, K_2CO_3, DMF; c) 1,1'-(azodicarbonyl)dipiperidine (ADDP), PMe_3, THF; d) $PhSO_2Me$, *n*-BuLi, THF; e) i) *n*-BuLi; ii) PhCOCl.

1.8 Radical Azidation[94]

Radically mediated processes provide an efficient, mild and often general method for azide introduction. This next section will briefly present the advances in the generation of ATAs via radical protocols.

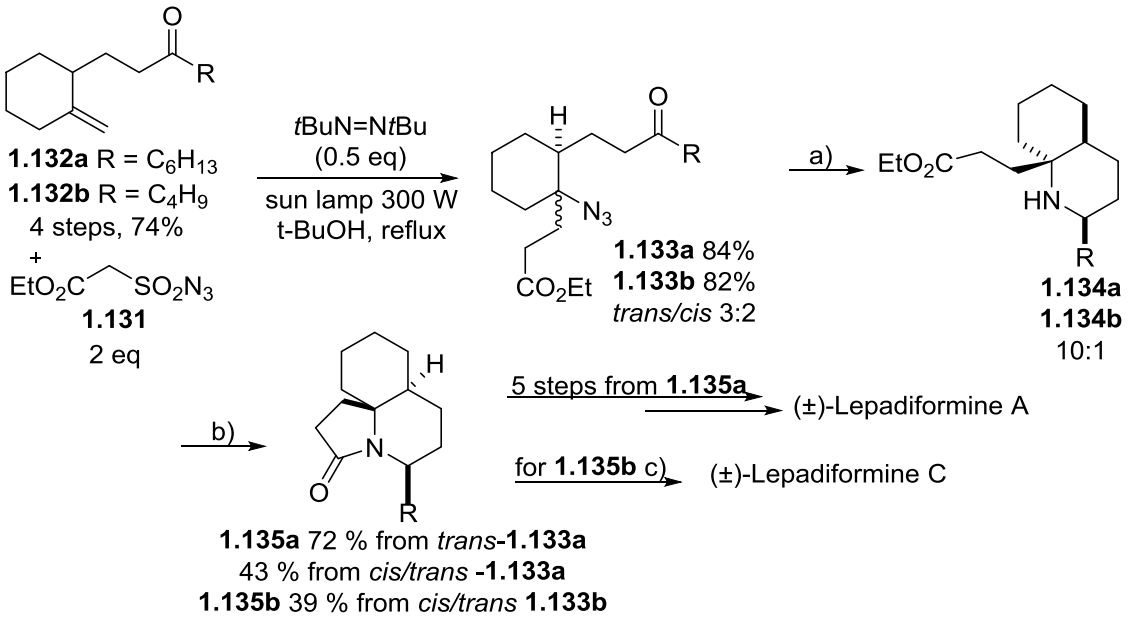
Improving on the carboazidation of alkenes, Renaud utilized α-iodoketones **1.128** for radical carboazidation to generate α-tertiary azide **1.129**, with functionalized substituents such as esters and protected hydroxyls for providing a facile entry into substituted pyrrolidines **1.130** (**Scheme 49**).



Scheme 49 Radical carboazidation of α-iodoketones

This provided a solution to ATA generation in natural products such as monomorine I, cylindricine C and lepadiformine. However, the methodology is not without drawbacks, with the main one being the use of organotin reagents and the need to use a three-fold excess of arylsulfonyl azide.

Refining his α-iodoketone methodology, Renaud developed a single reagent for both alkene addition as well as the azide source in the form of ethoxycarbonylmethylsulfonyl azide **1.131** in which SO_2 is expelled during the addition. A sun lamp provided the energy necessary for the radical initiation with di-*tert*-butyldiazine. Thus far the methodology is applicable to monosubstituted alkenes giving rise to tertiary azides, whilst quaternary azides are generated for cyclic structures only; azidation on disubstituted alkene groups leading to open chain quaternary azides has not been reported (except when both groups on the alkene are methyl groups). To illustrate its utility, Renaud employed desulfitative carboazidation to construct an azaspirocentre, and applied this to the total synthesis of (±)-lepadiformines A and C (**Scheme 50**).[95,96]



Scheme 50 *Reagents and conditions*: a) H_2 (50 bar), $Pd/CaCO_3$ (cat.), EtOH, 100 °C; b) Me_2AlCl (2 eq), DCE, reflux; c)

Methylenecyclohexanes **1.132a** and **b** were subjected to the carboazidation reaction with the sulfonyl azide **1.131** to afford the azido esters **1.133a** and **b** as a 3:2 mixture of separable *trans/cis* isomers. Azide reduction, followed by stereoselective reductive amination, gave a 10:1 mixture of azadecalin diastereomers **1.134a** and **b**. Lactamazation gave the tricyclic lactams **1.135a** and **b**, a common intermediate for both (±)-lepadiformine A and C. The ingenuity of the methodology lies in the fact that both the alkyl radical and the azido group are present in the same reagent making the process efficient and atom-economical.

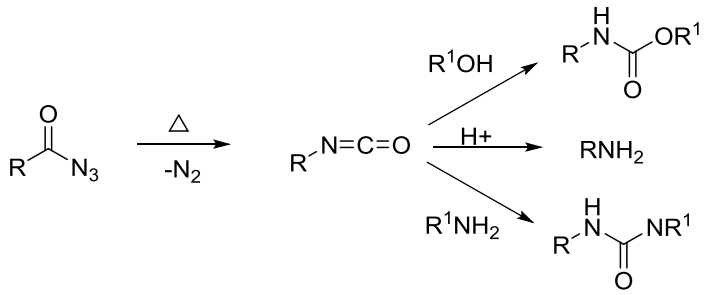
1.9 Molecular Rearrangements

A practical alternative to direct ATA synthesis is to make use of molecular rearrangements, in which the quaternization takes place with a surrogate group. The amino moiety can be generated after

rearrangement to a quaternary carbon, or the rearrangement itself generates the ATA. A crucial feature of many rearrangements is a well-defined transition sate that leads to high levels of stereospecificity and/or selectivity.[97] Furthermore, the fact that these are atom-economic processes by nature, adds to their efficacy as successful synthetic methodologies. Steglich, Curtius and Schmidt rearrangements can be classified as [1,2] sigmatropic, whilst the Overman and cyanate to isocyanate rearrangements are [3,3] sigmatropic processes. [2,3] Sigmatropic rearrangements are generally less common for the construction of ATAs, particularly stereoselectively, successful examples being the aza-Wittig rearrangement[98] and sulfide rearrangement.[99]

1.9.1 Curtius rearrangement

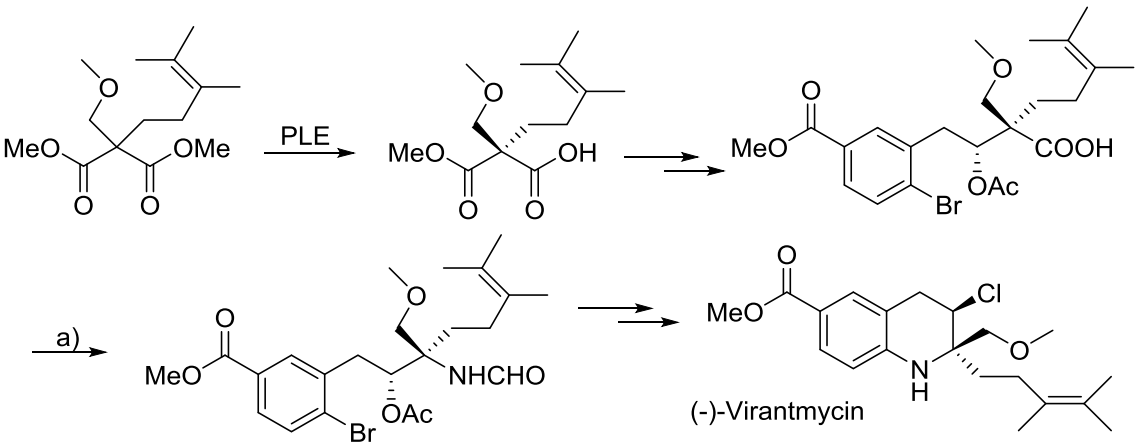
This rearrangement reaction dates back to 1890,[100] when Theodor Curtius noted the decomposition of an acyl azide with loss of nitrogen gas, giving rise to aniline following the hydrolysis of the intermediate isocyanate. The azides were generated from the reaction of acid chlorides or mixed anhydrides with sodium azide. Since then it has become a valuable and much used tool in the synthetic chemist's arsenal for the generation of amines from appropriate carboxylic acids. Trapping of the isocyanate with a variety of nucleophiles is a widely used method for the synthesis of amine derivatives (**Scheme 51**).



Scheme 51 Curtius rearrangement

Reaction of the intermediate isocyanate with an alcohol gives rise to carbamates, whilst amine interception yields ureas. Achieving the transformation from carboxylic acid to carbamate without the need to isolate acyl azides has become possible in recent years with the introduction of diphenylphosphoryl azide (DPPA) as the azidating reagent. The rearrangement is known to proceed with retention of configuration when a chiral centre is present α to the carboxylic acid and as such is highly applicable for the asymmetric generation of ATAs, provided the stereocentre is set in the precursor. A report by the Back group in 2009,[101] implemented biocatalysis in conjunction with the Curtius rearrangement in order to access a range of quaternary acids in generally high yields and selectivities. Pig liver esterase was used to desymmetrize a series of quaternary malonates and the resultant quaternary carboxylic acids were subjected to a Curtius rearrangement. As with most biocatalysed processes, the degree of selectivity was related to the steric differences between the

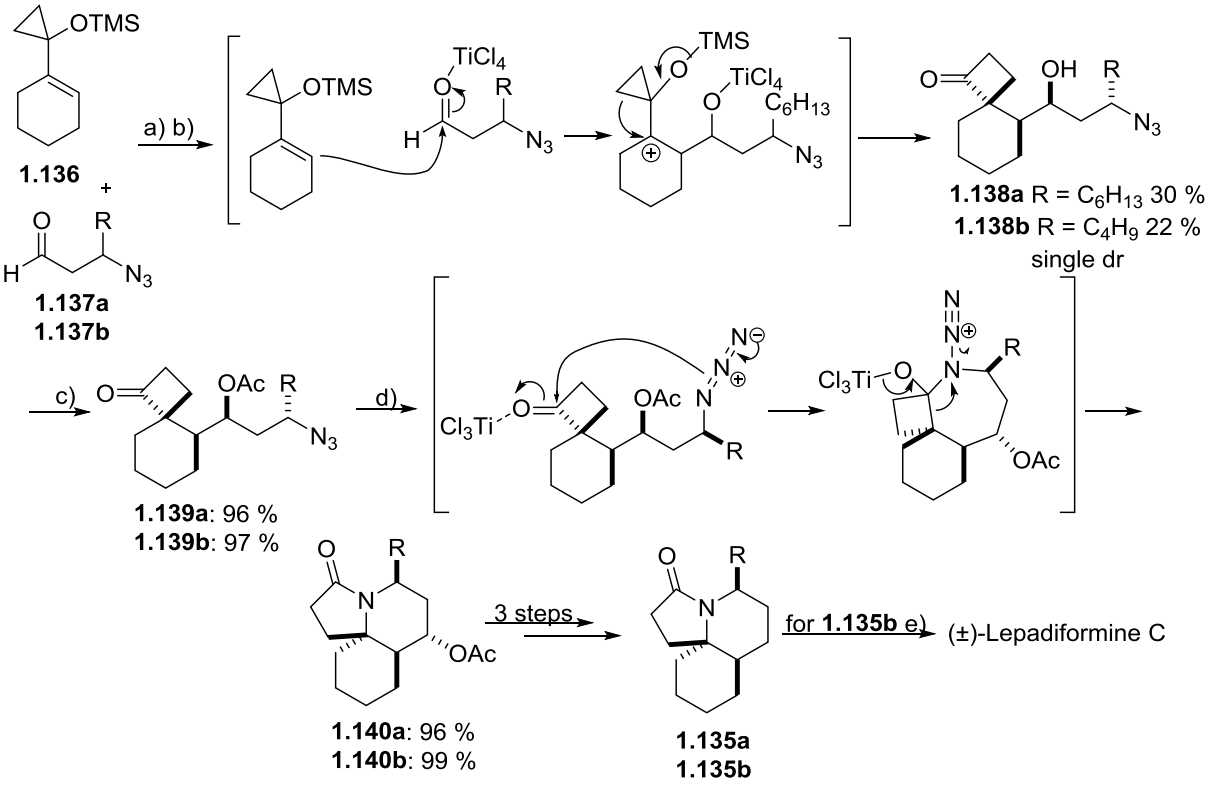
two substituents on the malonate. The protocol was successfully applied to the enantioselective total synthesis of (-)-Virantmycin (**Scheme 52**).



Scheme 52 *Reagents and conditions*: a) i) DPPA, DMAP, Et_3N, toluene, reflux; ii) $NaBH_4$, THF, rt.

1.9.2 Schmidt rearrangement

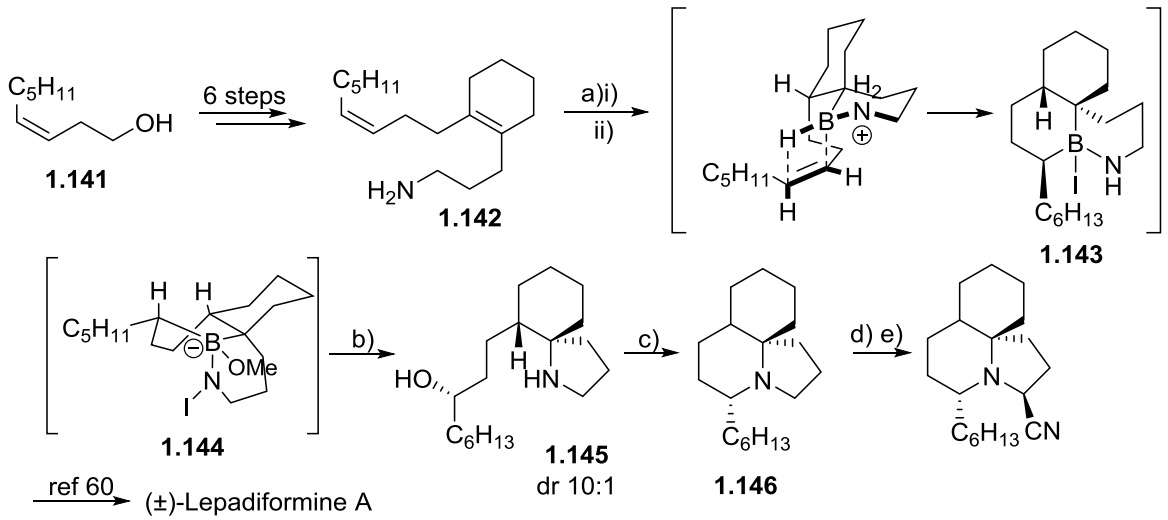
The Schmidt rearrangement is similar to the Curtius rearrangement except originally involved formation of the azide from a carboxylic acid and hydrazoic acid (HN_3) and involves acid catalysis in the rearrangement, rather than direct thermal treatment. Intramolecular Schmidt reactions are particularly useful in alkaloid syntheses in which the principle can be extended to an alkyl azide decomposing with nucleophilic interception by a carbonyl function to give amides and lactams with ring expansion ultimately. Fused lactams can be accessed via 3-azidopropylketones, but stereocontrol is often awkward for this type of conversion. Aube overcame this difficulty to effect good stereoselectivity by careful consideration of transition states and reaction rates when he described a facile method for applying this to the racemic synthesis of lepadiformines A and C respectively, **Scheme 53**.[102]



Scheme 53 *Reagents and conditions*: a) $TiCl_4$, CH_2Cl_2, 0 °C; b) $TiCl_4$, CH_2Cl_2, 40 °C; c) Ac_2O, pyr, DMAP, CH_2Cl_2, rt; d) $TiCl_4$, CH_2Cl_2, rt; e) $LiAlH_4$.

In his approach, he made use of the Prins reaction in order to deliver the [5,3] spirocyclic keto azide necessary for a Schmidt ring expansion reaction. For the lepadiformine syntheses, a variation on the Prins reaction was carried out on substrate **1.137a** and **b** that incorporated an azide into the appropriate chain, as well as an aldehyde instead of an acetal, reacting with cyclopropane **1.136**. This gave rise to cyclobutanones **1.138a** and **b** as single diastereomers. Optimal results for the Schmidt rearrangement were achieved by protecting the hydroxyl group as an acetate and then treating with $TiCl_4$ to deliver the lactams **1.140a** and **b** in excellent yields. Deacetylation, xanthate formation and Barton-McCombie deoxygenation furnished lactams **1.135a** and **b**, common intermediates of Renaud's synthesis of the lepadiformines.

In 2015, Shenvi and Tabor[103] accomplished a short, racemic synthesis of the lepadiformine core via a stereoselective hydroamination process, also based on a rearrangement, but here of C-B to C-N. Starting with a simple achiral amino diene **1.142**, sequential amine-directed hydroboration followed by oxidative shift of the alkyl onto nitrogen, generated the lepadiformine skeleton **1.146**, rendering 3 chiral centres, obtained with high diastereoselectivity (**Scheme 54**).



Scheme 54 *Reagents and conditions*: a) i) BH_3·DMS, CH_2Cl_2, -78 °C to 0 °C; ii) I_2, 22 °C; b) I_2, NaOMe then NaOH, H_2O_2; c) CBr_4, Et_3N, PPh_3, CH_2Cl_2; d) MCPBA, CH_2Cl_2; e) TFA, KCN.

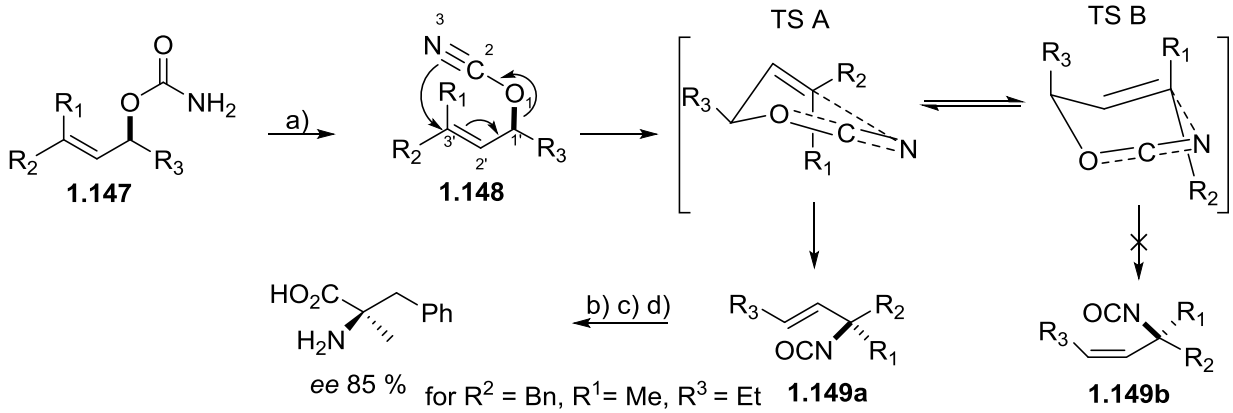
The amino diene **1.142** was generated in six steps starting with commercially available alcohol **1.141**. Subjecting **1.142** to optimized hydroboration conditions furnished the borinic imide **1.143**, which upon treatment with iodine and NaOMe underwent a 1,2 alkyl shift to deliver **1.145** after an oxidative work-up in a 10:1 dr. The hydroboration proceeds via a strained transition state, which is nonetheless favoured because of the high potential energy of the ammonium borane. The 1,2 alkyl shift predominates over competing reactions such as oxidation to an imine, via the strained intermediate **1.144**, to give rise to the amino alcohol **1.145**. For the synthesis of lepadiformine, only the installation of the hydroxymethyl chain remained, but this proved to be problematic, prompting the authors to investigate their hydroamination sequence with the hydroxymethyl chain incorporated in the substrate. Unfortunately, hydroboration was unsuccessful for these types of substrates (amino esters, alcohols and ethers were tested, under numerous conditions), likely as a result of the formation of borane chelates. Despite this deficiency, hydroamination is certainly a powerful methodology on paper for drastically streamlining the syntheses of complex alkaloids.

1.9.3 [3,3] sigmatropic rearrangements

[3,3] Sigmatropic rearrangement are commonplace in organic chemistry as one can access regio- and stereoselective carbon-carbon or carbon-heteroatom bonds with relative ease. Examples that give rise to ATAs include the Kazmeier- Claisen rearrangement described earlier, the rearrangement of a cyanate to an isocyanate and the Overman rearrangement.

Cyanate to an isocyanate rearrangement

Improving on Holm's original report, Ichikawa *et al*[104] developed a convenient method for accessing the cyanate from the corresponding carbamate, **Scheme 55**.

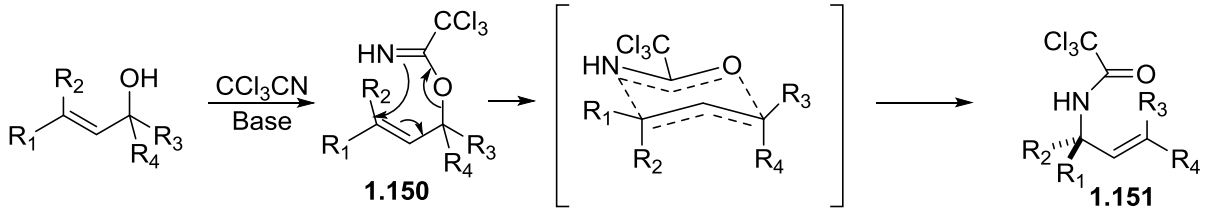


Scheme 55 *Reagents and conditions*: a) PPh_3, Et_3N, CBr_4, CH_2Cl_2, 0 °C; b) O_3, DCM, -78 °C; c) $NaClO_2$, 2-methylbut-2-ene, NaH_2PO_4, *t*-BuOH, H_2O; d) 6N HCl, reflux.

Dehydration of the carbamate **1.147** affords a transient allyl cyanate intermediate **1.148**, which in turn spontaneously rearranges with complete 1,3- transfer of chirality to the isocyanate **1.149a**. The six- membered transition state allows for 2 possibilities; The 1,3-diaxial strain in transition state B (TS B) raises its energy thus the resultant *Z*- isomer **1.149b** is never observed. As the reaction is stereospecific and proceeds under mild conditions, it has served as a key step in generating ATA motifs in several total syntheses such as adaline and euphococcinine reported by Spino *et al*,[105] and (*S*)-ketamine by Kiyooka.[106]

The Overman rearrangement

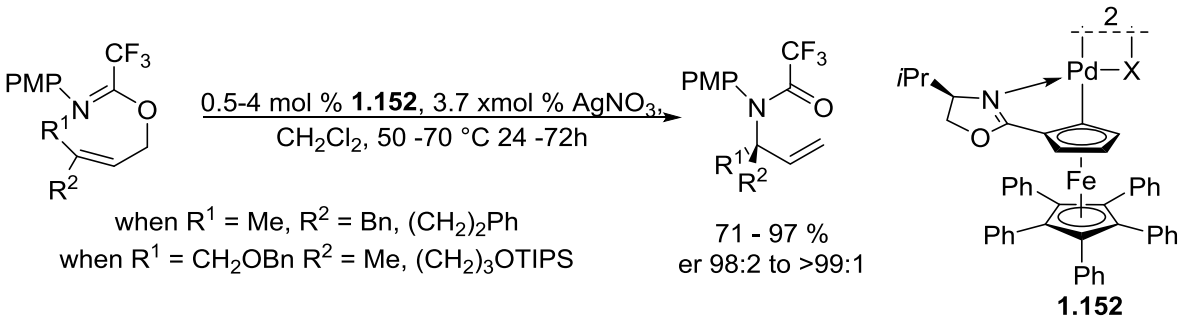
Also termed the aza-Claisen rearrangement, this [3,3] sigmatropic rearrangement involves an iminium C=N bond as the π component, providing access to allylic amines from the counterpart allylic alcohols (**Scheme 56**). An allylic trichloroacetimidate **1.150** gives rise to an allylic trichloroacetamide **1.151** with clean 1,3-transposition of the alkenyl moiety, proceeding via a chair-like transition state.



Scheme 56 Mechanism of the aza-Claisen rearrangement

Although originally thermally promoted, transition metals have also been shown to be effective. (eg Pd and Hg). This is advantageous as it allows for lower temperatures and the use of chiral catalysts for stereoselective conversions. The Peters[107] group developed several palladacycle catalysts for the enantioselective aza-Claisen rearrangement, the optimal being **1.152** (**Scheme 57**). Excellent *ee*s were achieved (96 to 98 %), albeit only for conversions where one of the substituents was bulky,

whereas when both were larger than methyl, higher catalyst loadings were necessary and a decrease in yields was observed. However, one must control the geometry of the disubstituted alkene terminus.

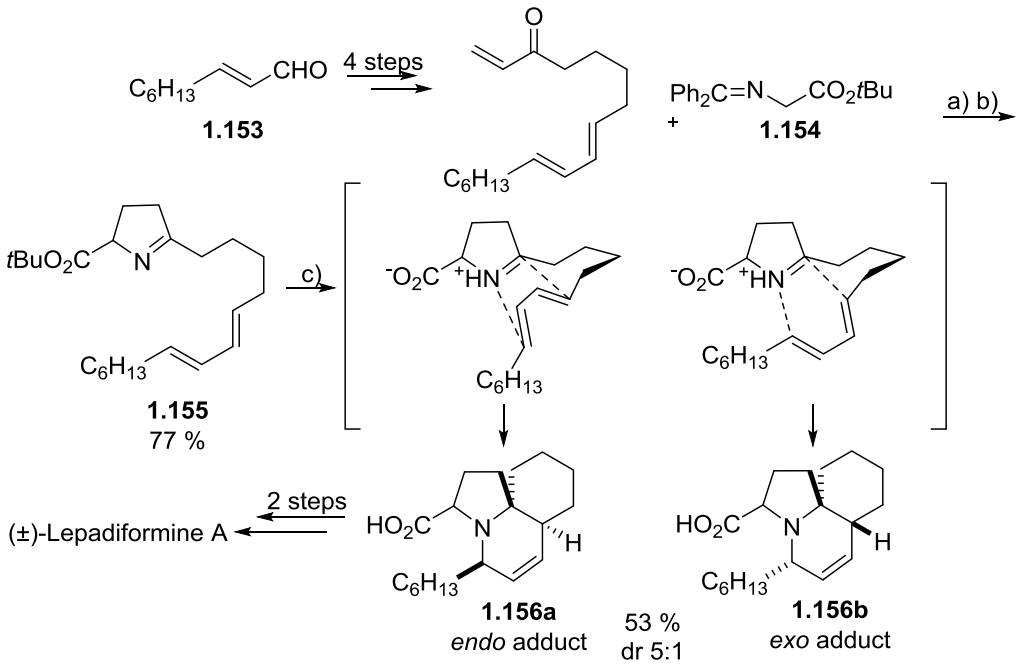


Scheme 57 Asymmetric aza-Claizen earrangement according to Peters *et al*.

1.10 Cycloaddition strategies

1.10.1 Diels-Alder

This well-known and much practiced cycloaddition reaction is a very useful and efficient way to generate cyclic structures. When adequately substituted dienes and dienophiles are used, molecules with a high degree of complexity can be generated in a single step. For the construction of ATAs, aza-Diels-Alder [4 + 2], 1,3 dipolar cycloadditions of azomethine ylids [3 +2] and formal [2 + 2] can all be applied. Unconjugated imines are generally poor dienophiles, but their reactivity towards Diels-Alder reactions can be greatly enhanced by protonation. Lygo and co-workers[108] used the aza-intramolecular Diels Alder (aza-IMDA) reaction in a short, protecting group-free synthesis of (±)-lepadiformine A (**Scheme 58**).

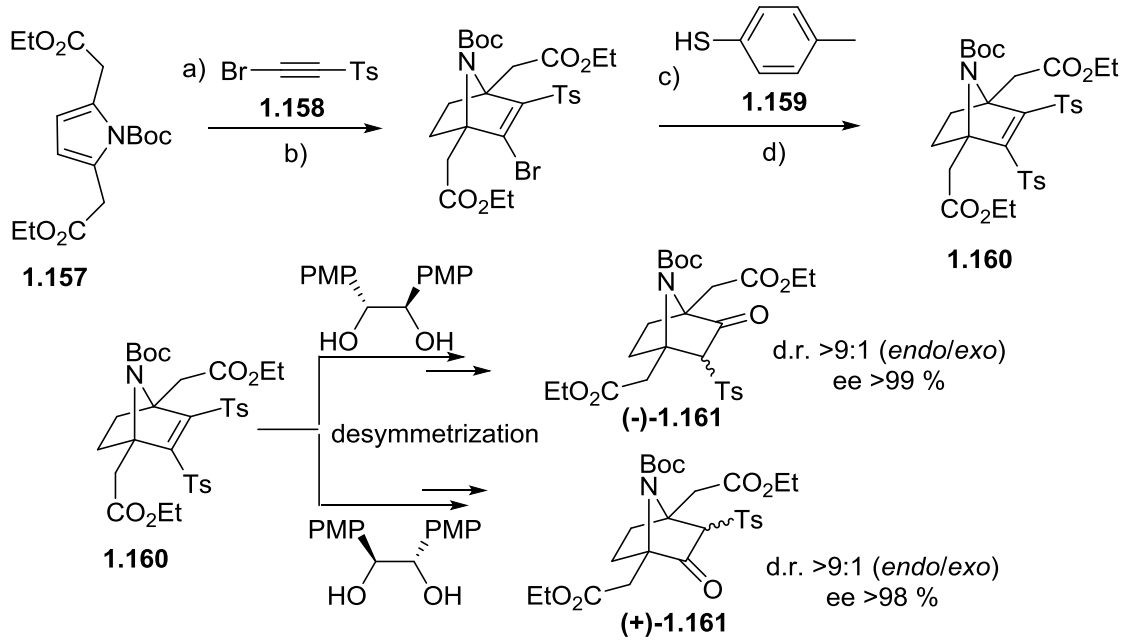


Scheme 58 *Reagents and conditions*: a) $CsCO_3$, *i*Pr_2O, $PhCH_2$-NMe_3Br; b) 15 % aq. Citric acid, THF, K_2CO_3; c) CF_3CHOH, 60 °C.

Starting with the commercially available *trans*-2-nonenal **1.153** and glycine imine **1.154**, they accessed the cyclic imine ester **1.155** in 6 steps. A wide range of Diels-Alder reaction conditions were then performed on this substrate, finally arriving at the optimal set shown in Scheme #. Of the four possible diastereomers that could have arisen from the cycloaddition, preferential addition of the diene *anti* to the carboxyl group gave rise to only two products **1.156a** and **b**, resulting from *exo* and *endo* addition, with a dr of 5:1 in favour of the desired *endo*-cycloadduct. The major cycloadduct possessed the correct relative stereochemistry for three out of four stereocenters of lepadiformine A, accessed as a racemate by a further two steps. The generation of two rings and three stereocenters, one of which is an azaspirocenter from a linear, achiral precursor in a single step, serves as an elegant demonstration of the power of the aza-IMDA reaction.

The design of an intermediate that can be proliferated to more than one complex natural product target is an advantageous feature of any approach. In 2015 Pandey and Janakiram[109] formulated the synthesis of a bridge-head substituted 7-azabicyclo heptane **1.161** from which a range of ATA scaffolds could potentially be accessed by selective bond cleavage on different loci on the molecule, and were able to apply it in the total syntheses of both (+)-cylindricines C-E and (-)-lepadiformine A (**Schemes 59** and **60**). The first part of their synthetic endeavour involved the generation of the bicyclic ATA intermediate **1.161** in non-racemic form, by the desymmetrisation of compound meso-**1.160**. Meso-**1.160** was prepared in four steps, starting with a cycloaddition of **1.157** and **1.158**

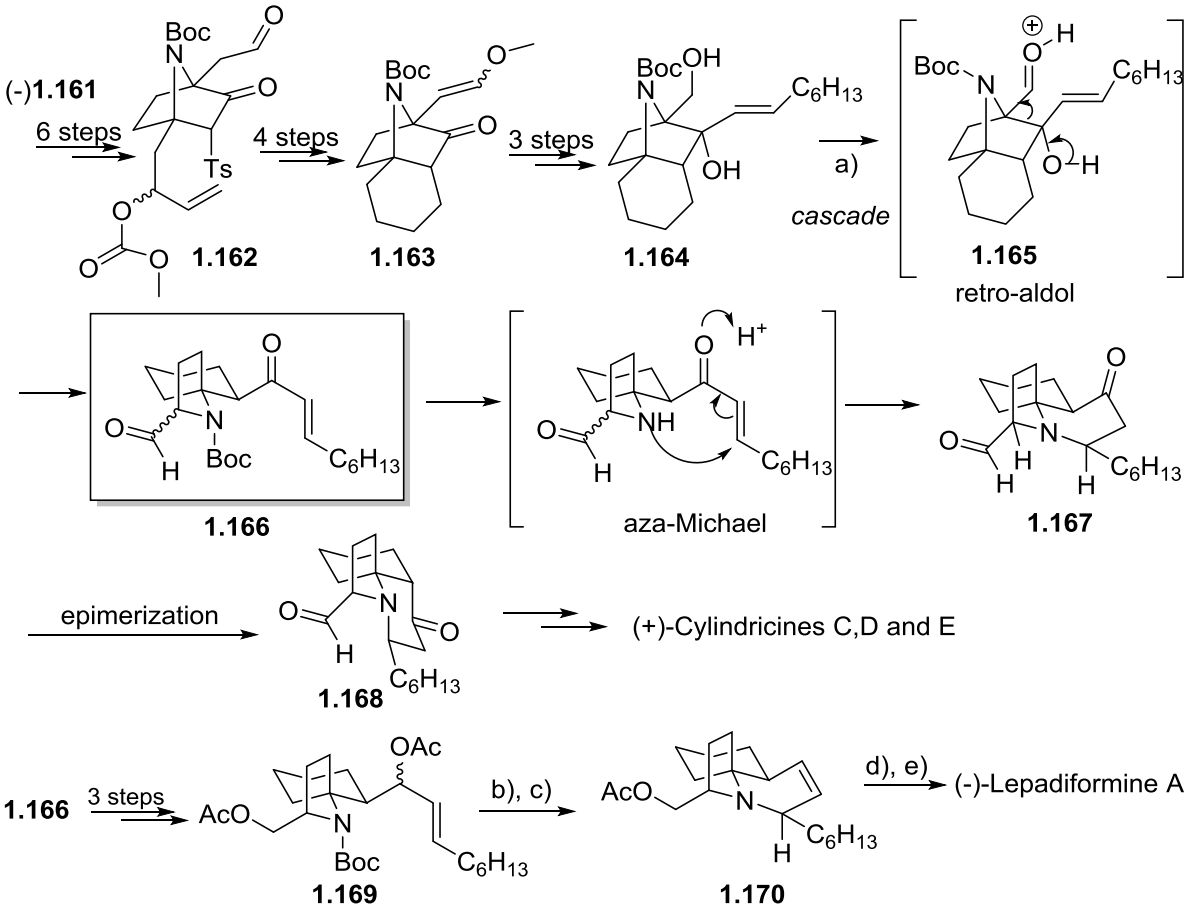
followed by selective reduction, nucleophilic substitution with the sodium salt of **1.159** and finally an oxidation. The desymmetrisation reaction (via an oxa-Michael addition, substitution of Ts and ketal hydrolysis) using (*R*),(*R*)-hydroanisoin was carried out on the boc-deprotected analogue of **1.160**, to give (-)-**1.161** in a dr of 9:1 (*endo*:*exo*) and as a pure enantiomer. (*S*),(*S*)-hydroanisoin afforded the opposite enantiomer.



Scheme 59 *Reagents and conditions*: a) toluene, 55 °C; b) H_2-Pd/C; c) NaH; d) *m*-CPBA.

Next, the aza-bicycle (-)-**1.161** was elaborated to **1.164**, the precursor necessary for the cascade reaction which would lead to lepadiformine A (**Scheme 60**). The fused ring of **1.163** was generated by a biphasic Tsuji-Trost cyclization of **1.162**, the diastereselectivity of which resulted from allylation of the *exo*-face of the bicyclic framework, preferred due to minimization of steric repulsion with protons on the endo-face. To obtain the cylindricines, compound **1.164** was subjected to Dess-Martin oxidation, which triggered the cascade rearrangement leading to tricycle **1.168**. The cascade was postulated to proceed via the unstable intermediate **1.165**, which underwent a retro-aldol fragmentation to **1.166** and due to the acidic medium of the reaction, resulted in boc- deprotection , which allowed for the aza-Michael addition to furnish **1.167**. The stereoselectivity of the addition was likely a result of the *trans* geometry of the enone, coupled with the influence of the spirocentre, directing the addition from underneath. The authors' synthetic plan was to terminate the sequence at that point so as to access lepadiformine from here and cylindricines via C-5 epimerization of **1.167**; however, epimerization to the energetically more favoured ring junction stereoisomer took place spontaneously at the end of the cascade, thus furnishing the requisite intermediate for the cylindricines **1.168**. For lepadiformine synthesis, the cascade had to be interrupted at the Boc

deprotection stage so as to avoid the aza-Michael addition and subsequent epimerization. This was accomplished by using AcOH instead of TFA in the oxidation step leading to the retro-aldol, which was followed by reduction and subsequent acetylation of the hydroxyl groups to deliver **1.169**. Boc-deprotection, followed by Tsuji-Trost cyclization gave **1.170**, from which lepadiformine was accessed in two simple steps.



Scheme 60 *Reagents and conditions*: a) DMP, CH_2Cl_2/TFA (3:1), 0 °C; b) DMP, CH_2Cl_2, AcOH, 0 °C; c) TFA; d) $[Pd(PPh_3)_4]$, K_2CO_3.

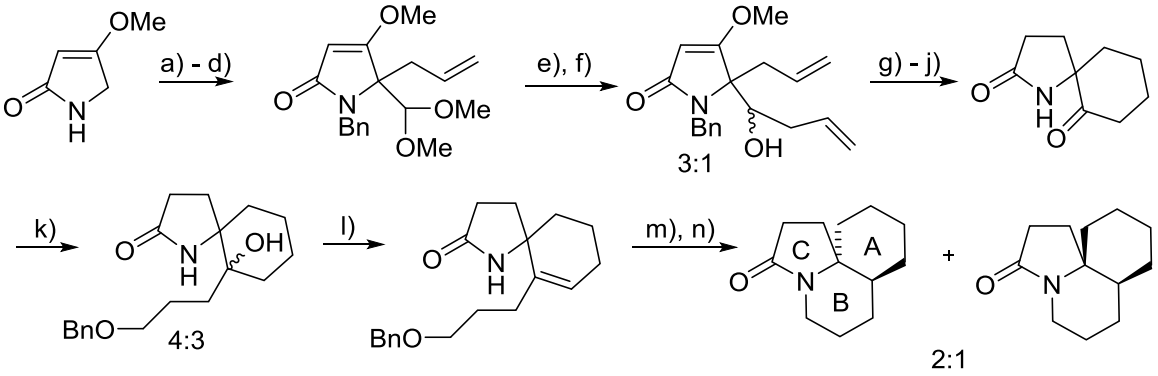
Another example of a cycloaddition strategy for the synthesis of (±)-lepadiformine is that of Funk and Greshock who employed an amidoacrolein cycloaddition.[110]

This survey of current strategic approaches for ATA creation highlights the vast amount of progress that has been made in this area in recent years, whilst being inclusive of some of the more classical methods still applicable today. The examples of lepadiformine syntheses have included a number of elegant, efficient and ingenious strategies that utilize a wide range of transformations to achieve synthesis of the ATA en route to the target alkaloid.

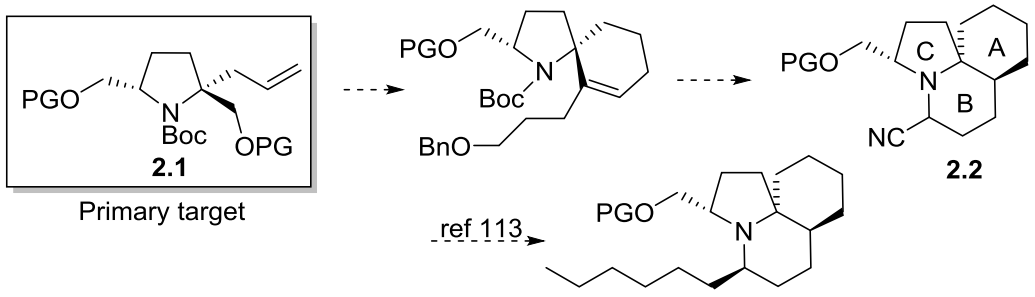
Chapter 2: Studies in Diastereoselective Construction of ATAs and Application to Lepadiformine Synthesis

2.1 Direct Approach to the C-ring of Lepadiformine

The primary objective of the project was the enantioselective total synthesis of lepadiformine and within that context, the development of a methodology for the asymmetric construction of the ATA motif present in the spiro- ring junction thereof. Because the ATA of lepadiformine and related compounds is embedded in the spirocyclic framework, the majority of synthesis strategies[32,111] rely on inherent constraints of the existing or emerging ring to control the diasteroselectivity of ATA formation. Convergent syntheses for its construction involving cycloadditions or spirocyclization strategies are thus not straightforward and in this project a divergent approach was adopted based on prior construction of the ATA. The strategy was based on a previously reported synthetic route developed in this research group by Hunter and Richards in 2003,[112] entailing a diastereoselective construction of the tricyclic core of the lepadiformines in racemic form (**Scheme 61**). Key steps in the sequence involved 5,5 dialkylation of a tetramate, ring-closing metathesis to produce the A/C azaspirocycle, and a stereoselective hydrogenation (2:1) for the *trans* A/B 1-azadecalin system. Although somewhat lengthy, as well as not enantioselective, the advantage of the route was that it was amenable to modification into an enantioselective synthesis, the pursuit of which formed the basis of this project.

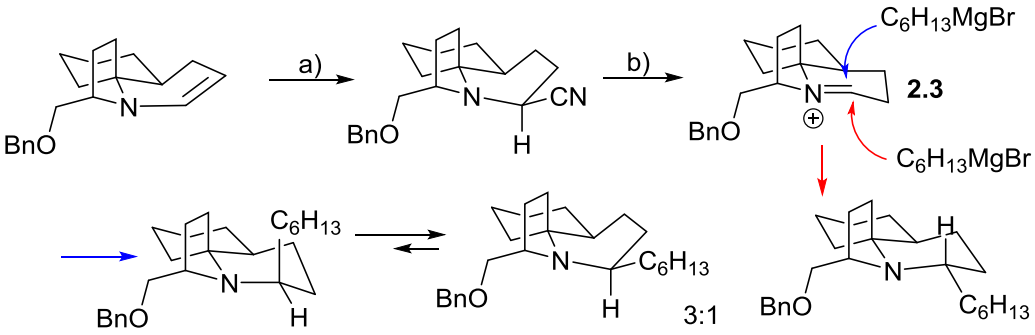


Scheme 61 *Reagents and conditions*: a) *n*-BuLi (2 eq), THF, -78 °C, allylBr (1 eq); b) KOH, Bu_4NHSO_4, BnBr, THF; c) *n*-BuLi (1.2 eq), THF, -78 °C, TMSCl (1.5 eq); d) $HC(OMe)_3$, $BF_3 \cdot OEt_2$; e) CF_3CO_2H (1% H_2O), 35 °C; f) allylMgCl, THF -78 °C to 0 °C; g) $RuCl_2(PCy_3)_2$=CHPh, CH_2Cl_2, 40 °C; h) Na, NH_3 (liq), -33 °C; i) H_2 Pd-C; j) TPAP (5 mol %), NMO, CH_3CN, powdered MS; k) $BrMg(CH_2)_3OBn$ (3 eq), THF, 0 °C; l) $CuSO_4$, *p*-xylene, reflux; m) H_2, Pd-C; n) i) MsCl, Et_3N, THF, ii) NaH, DMF.



Scheme 62 Refinement to an enantioselective synthesis

In order to achieve such a refinement, an asymmetric construction of the pyrrolidine intermediate **2.1** containing two of the four stereocentres present in (-)-lepadiformine A (including the ATA) was targeted. The overall idea is shown in **Scheme 62.** From the pyrrolidine **2.1**, much of the chemistry previously developed could be applied in order to arrive at the tricycle **2.2** Improving the stereoselectivity of hydrogenation step was certainly crucial, as well as specifically evaluating the influence of the protecting groups. The incorporation of the hexyl side-chain was intended according to Weinreb's method,[113] involving Grignard addition onto the iminium salt of **2.3**, generated form an α-amino nitrile intermediate (**Scheme 63**). Weinreb reported a 3:1 selectivity for the desired epimer, arising from the preferential axial attack of the Grignard onto the top face of the imine carbon.



Scheme 63 *Reagents and conditions*: a) HCl, MeOH, KCN, H_2O, Me_2CO; b) $C_6H_{13}MgBr$, $BF_3{\cdot}Et_2O$, THF.

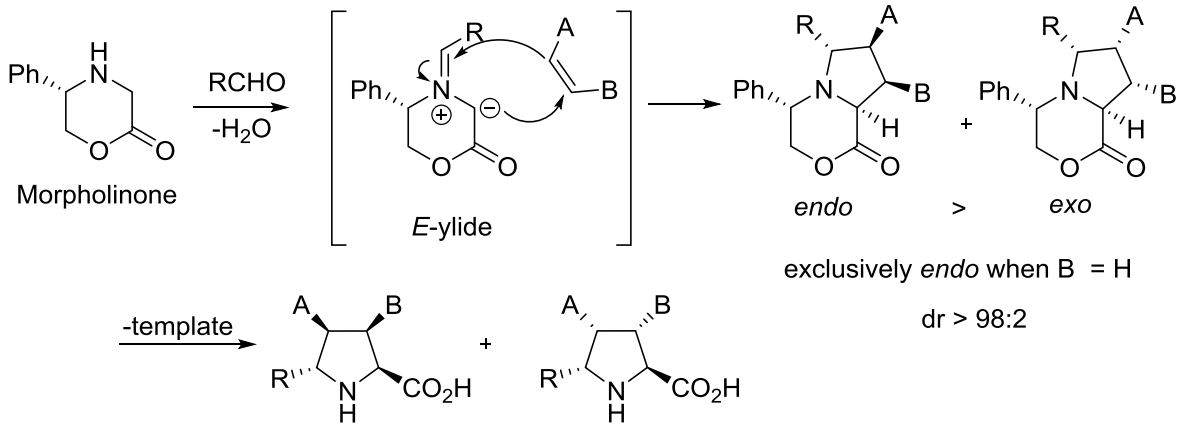
Before embarking on new methodology for enantioselective ATA construction, first an attempted strategy for the direct synthesis of **2.1** based on a protocol developed by Harwood was explored. This methodology involved a diastereoselective 1,3 dipolar cycloaddition of a chiral, stabilized azomethine ylid with an aldehyde.

2.1.1 Azomethine Ylid Cycloaddition Strategy

Precedent

In the early 1990s, Harwood *et al*[114–118] reported that an azomethine ylid derived from an enantiomerically pure morpholinone and paraformaldehyde underwent a highly diastereoselective

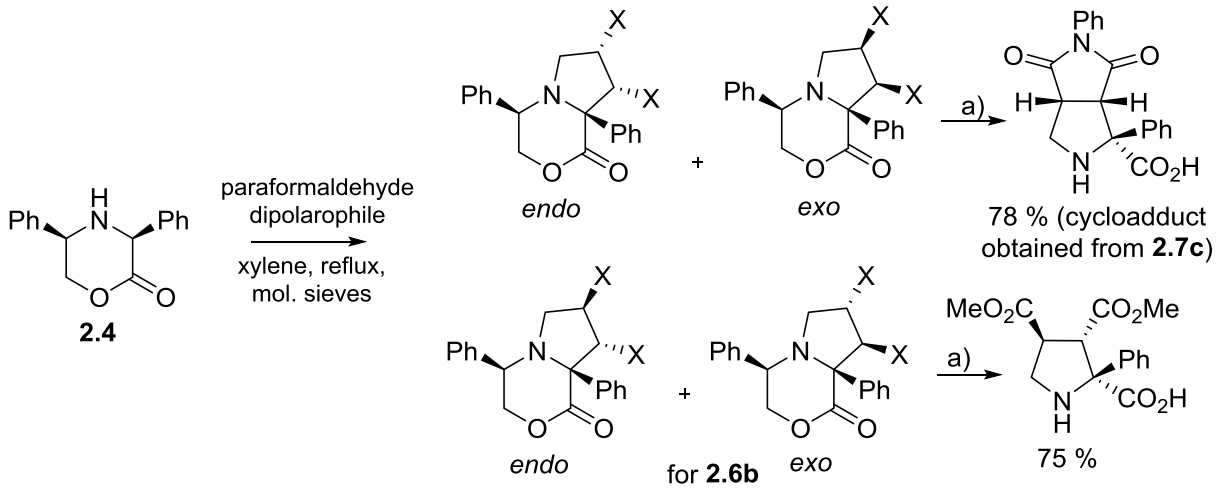
1,3-dipolar cycloaddition with a range of alkene and alkyne dipolarophiles, under both thermal and catalysed conditions in which for aldehydes other than formaldehyde, the iminium geometry was predominantly *E*- based on the configuration of the iminium ion (**Scheme 64**).



Scheme 64 Harwood's 1,3 dipolar cycloaddition protocol for generation of substituted prolines.

The preferred stereomode for the cycloaddition wrt disubstituted dipolarophiles (with **A** and **B**) was variable, but for mono-substituted dipolarophiles, *endo* adducts were produced exclusively, albeit in lower yields. Furthermore, the cycloaddition facial selectivity on the dipole proceeded *anti* to the morpholine phenyl group blocking the underneath face. Following reductive cleavage of the chiral auxiliary a tetra (or tri-) substituted pyrrolidine could be obtained stereoselectively, **Scheme 64.**

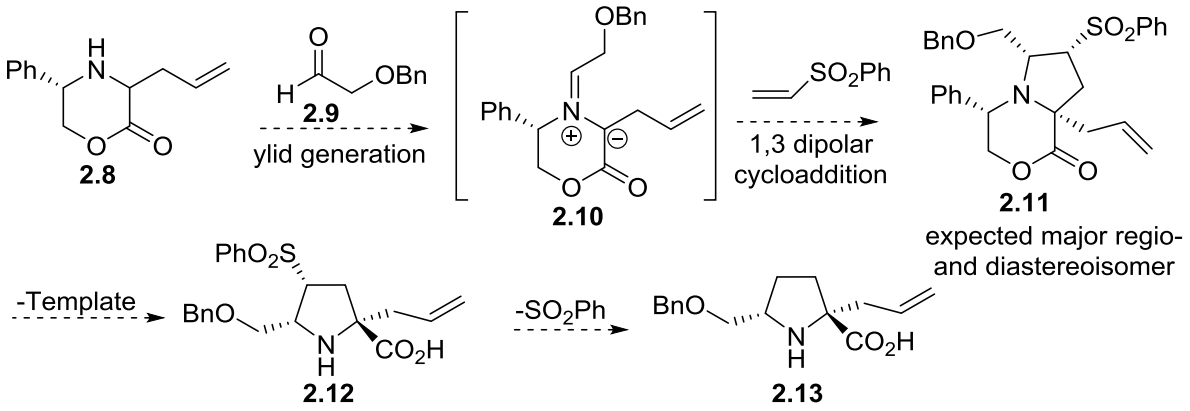
This methodology was extended to 3-phenyl substituted morpholinone **2.4**, from which phenyl-substituted proline derivatives could be accessed containing an enantioenriched ATA (**Scheme 65**). In these cases, only *endo* products were isolated for acyclic dipolarophiles, whilst cyclic ones showed a low level of selectivity for the endo adducts.



Dipolarophile		Isolated yield (%) *endo*	Isolated yield (%) *exo*
MeO_2C CO_2Me **2.5**	a	89	0
MeO_2C **2.6** CO_2Me	b	95	0
O Z O **2.7**	Z = NPh c Z = NMe d	44 53	28 29

Scheme 65 *Reagents and conditions*: a) $Pd(OH)_2/C$, H_2, 5 bar, MeOH, TFA

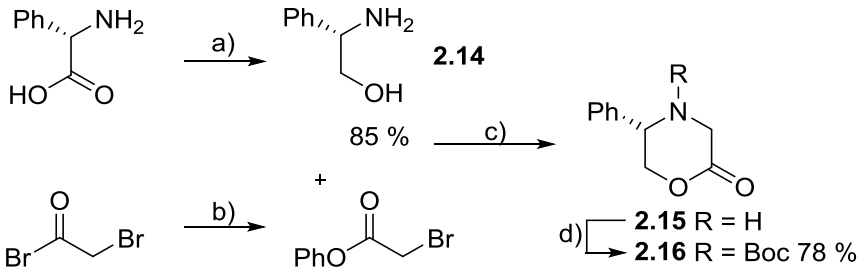
Based on the latter it was thought that an allylated equivalent might meet our needs in respect of lepadiformine. Furthermore, the use of a suitably substituted aldehyde in the ylide generation step would give rise to the requisite C-5 substituent on the target pyrrolidine. To this end, the projected sequence envisaged is shown in **Scheme 66**.



Scheme 66 Desired sequence leading to **2.13**, entailing a diastereoselctive 1,3 dipolar cycloaddition

The strategy entailed generation of allylated morpholinone **2.8,** from which the ylide **2.10** would arise by condensation with aldehyde **2.9**, followed by cycloaddition with phenyl vinyl sulfone. A sulfone group was an attractive functionality for dipolarophile activation in this case, due to its electron-withdrawing nature, coupled with the fact that it would likely be removeable at the end of the process reductively. For the purposes of lepadformine synthesis, *endo*/ *exo* selectivity and the regioselectivity for the cycloaddition were inconsequential, as the sulfonyl group would be removed, and in the Scheme it is represented as being derived from an *exo* mode (often sulfonyl goes *exo* in view of steric strain in the transition state); however, of crucial importance would be the level of diastereoselectivity of the cycloaddition controlling the configurations at the quaternary and C-5 centres in the final product. These would be governed by the degree of facial selectivity for the approaching dipolarophile, and the configuration of the iminium salt. Based on Harwood's observations, the dipolarophile was anticipated to approach from the face opposite the phenyl on the morpholinone, which would deliver the adduct **2.11** as the major product. If successful, the methodology would provide rapid access to the desired substituted proline derivative **2.13** in appropriate diastero- and enantio form for lepadiformine, following template degradation and removal of the sulfone moiety.

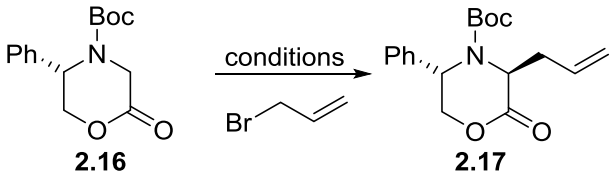
To this end, the synthesis of the morpholinone **2.8** began with reduction of (*S*)-phenylglycine with $LiAlH_4$ to afford (*S*)-phenylglycinol **2.14** in good yield and without racemization, as judged by the agreement of the $[\alpha]_D$ value to that of literature reported value. $[\alpha]_D^{20}$ = -49.0 ($CHCl_3$, *c* = 1.0); lit[119] $[\alpha]_D^{20}$ = -49.3° ($CHCl_3$, *c* = 1); (**Scheme 67**). Glycinol **2.14** was then condensed with phenyl 2-bromoacetate to give the morpholinone product **2.15** in modest yields of 30 – 40 % after column chromatography. This was established as being due to dimerization, which necessitated immediate protection of the condensation adduct **2.15** with Boc anhydride, avoiding aqueous work-up and chromatography, to effectively increase the yield to 70 %. [120]



Scheme 67 *Reagents and conditions:* a) $LiAlH_4$ (1 eq), THF, reflux; b) Phenol, 80 °C, neat; c) DIPEA (2.5 eq), CH_3CN, rt; d) Et_3N, Boc_2O, EtOAc, rt.

Next, the allyl moiety was installed in the 3-position using conventional alkylation methodology for which the results are shown in **Table 2**.

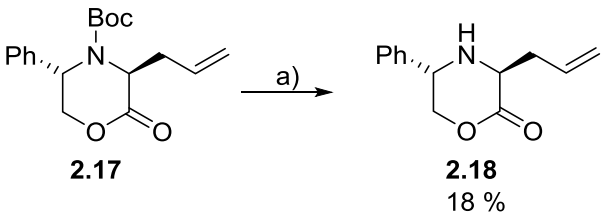
Table 2 Optimization of allylation reaction conditions



Solvent	Base	Temp (°C)	Yield (%)
THF	LiHMDS	-78 to 25	< 10
THF	NaHMDS	-78 to 0	< 30
THF/DME (50/50)	NaHMDS	-78 to 0	40
THF	KHMDS	-78 to 0	52
THF/DME (50/50)	KHMDS	-78 to 0	63

Of the solvents tested, the best results were obtained using a 50/50 mixture of THF and DME, in which KHMDS proved superior over LiHMDS. As expected, the allylation was stereoselective by virtue of the product **2.17** appearing as a single spot on tlc, and with no doubling of any peaks in the ^{1}H NMR spectrum once isolated. The relative stereochemistry was not known with any certainty but was likely to be *anti-* to the Ph group on both stereoelectronic and steric grounds as indicated by the product structure in **Table 2**. Although noteworthy, this was inconsequential, as the stereocentre would be destroyed in the ylide generation step. The desired aldehyde partner **2.10** in the condensation was generated in three steps from ethane 1,2-diol by monoprotection and oxidation procedures. In order to generate the ylid for the cycloaddition, **2.17** had to be Boc-deprotected with TFA prior to condensation with the aldehyde. This proved problematic due to *in-situ* dimerization to

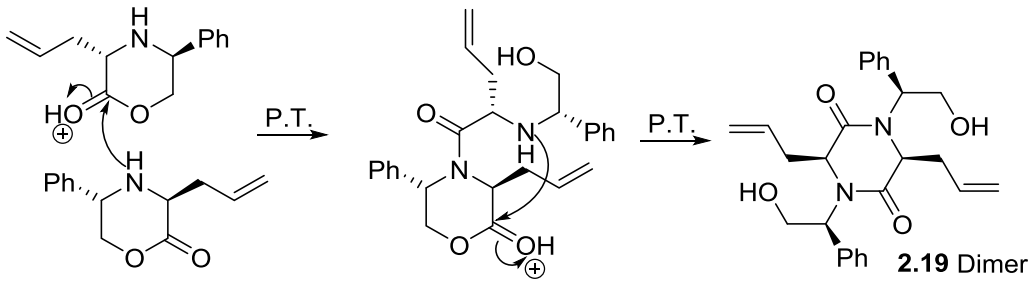
2.19, as mentioned before for compound **2.15** and yields of the desired deprotected morpholinone **2.18** could not be raised above 18 % (**Scheme 68**).



2.17 **2.18** 18 %

Scheme 68 *Reagents and conditions*: a) TFA (1.2 eq), anisole (1.2 eq), DCM, 0 °C to rt.

Following the reaction by tlc indicated the transient formation of the product spot which was quickly consumed to give another slightly less polar spot just above it, presumably corresponding to the dimer. Chromatographic isolation and subsequent ^{1}H NMR and IR spectral analysis confirmed that the minor product was the desired de-protected morpholinone **2.18**, the data correlating closely to that reported in the literature for the same compound.[121] **Scheme 69** shows the mechanism of the dimerization, which is catalysed by TFA.



Scheme 69 Mechanism of dimerization of **2.18** leading to **2.19**

Several protocols for Boc removal were tested which did not involve acidic conditions, but all failed to deliver the desired deprotected morpholinone, resulting either in degradation of the substrate, or no reaction. Other research groups who experienced the same stumbling block, simply replaced the Boc for a Bn or Cbz group, thus avoiding the use of TFA. However, deprotection in those cases requires hydrogenolysis which would likely result in concomitant reduction of the allyl. Nevertheless, a Cbz derivative was prepared and allylated hoping for a chemoselective deprotection. Unfortunately, and probably unsurprisingly, the allyl moiety was reduced at a faster rate than CbZ removal. The disappearance of the diagnostic allylic protons in the 5.80 and 5.20 ppm region of the ^{1}H NMR spectrum was confirmation of this.

Another option was to access the morpholinone **2.18** via an addition reaction of an allylic nucleophile onto an oxazinone.[122,123] However, these types of reactions give variable results and are

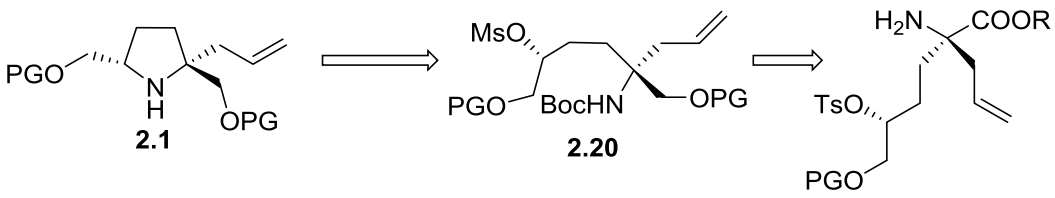
often low-yielding due to the chemoselectivity issue between the imine and the lactone.[122,124] Although reasonable improvement for obtaining **2.18** via this route has been made in recent years,[121] before embarking on such a synthetic endeavour, other possible hindrances that could be expected further in the synthesis had to be evaluated:

- Aldehydes other than formaldehyde have only been reported in azomethine ylide generation with morpholinones *without* substituents at C-3, in which only moderate selectivity for the *E*-iminium was achieved.[114] Having an allyl group in place at C-3 would likely lead to a distribution of imine *E/Z-isomers*, since the steric differentiation between phenyl and allyl is small. This would translate to a reduction in the diastereoselectivity of the reaction with respect to the configuration at C-5 of the pyrrolidine product.
- Monoactivated diapolarophiles were reported to react very poorly in the cycloaddition involving substritution at C-3 and in some instances not at all;[116,125] a bis-sulfonyl derivative would likely be problematic in terms of SO_2Ph excision at the end of the process. Furthermore, although a boost in reactivity would be achieved by a doubly activated dipolarophile, the generated product would be a densely substituted proline derivative, the formation of which may be hampered by the high level of steric crowding.
- The usual hydrogenolysis procedure for dismantling of the template using Pearlman's catalyst would not be viable in this case due to the presence of the allyl group, thus other methods would need to be sought.

In light of these potential difficulties, it was deemed prudent to consider a different approach.

Disconnection to an acyclic precursor

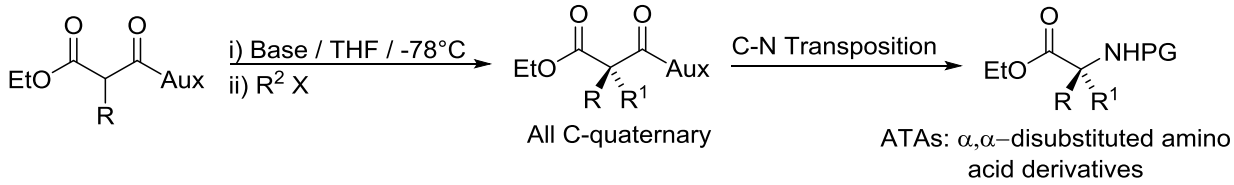
The level of complexity in the target pyrrolidine **2.1** made its asymmetric synthesis via direct methods a challenge. A disconnection was therefore made to the acyclic precursor **2.20**, revealing the necessity for the construct of an ATA bearing a bulky, functionalized substituent from which the C ring would be generated (**Scheme 70**).



Scheme 70 Disconnection of pyrrolidine **2.1** to an acyclic quaternary amino acid derivative

From the outset, the aim was to achieve a chiral non-racemic synthesis via some form of diastereoselective process. Of the available methods for ATA construction, alkylation of an *N*-

containing enolate was one option, specifically via the Schöllkopf method using a chiral template. Although proven to be efficacious in many instances, this type of approach is not without drawbacks; low atom efficiency is one, but more pertinent was the often-encountered frustration with template degradation when congested quaternary systems are involved. Furthermore, installation of the requisite groups would likely call for a highly reactive enolate species, feared to be difficult to attain using template-based approaches. These factors prompted the vision of formulating and developing a new methodology for ATA construction from which lepadiformine could be accessed, as well as providing a general and widely applicable quaternization protocol. In the event, the methodology chosen centred on the use of malonate via an auxiliary-directed process. The amino functionality of the ATA was envisaged as arising from a carboxylic acid precursor using the well-established Curtius methodology, as reviewed in Chapter 1. The creation of a successful protocol for producing all-carbon quaternary compounds in an asymmetric fashion is a challenging task in itself and to achieve this, we hoped to exploit the high reactivity of the C-2 in malonates, coupled with the possible induction of facial selectivities by cyclic chiral auxiliaries, which had the advantage of being recyclable. The challenges, however, in such an approach were not trivial and our expectations regarding these are projected in the next Chapter. The general strategy is depicted in **Scheme 71.**



Scheme 71 Proposed sequence of all-C quaternary generation and transposition to ATAs.

The following sections will cover three related endeavours: 1) diastereoselective alkylation of auxiliary-malonate systems to furnish all-carbon quaternary centres; 2) transposition of the quaternary malonates to ATAs; 3) application of the methodology to an attempted synthesis of lepadiformine.

2.2 Malonates as Substrates for Asymmetric Synthesis

Malonate derivatives are versatile substrates in organic synthesis owing to the high reactivity at C-2 and the ease of further manipulations at the carboxyl function. For the creation of chiral, non-racemic malonates essentially three strategies can be adopted for prochiral discrimination as: 1) desymmetrization of the ester groups using a chiral catalyst; 2) facial enantioselectivity on a prochiral malonate (enolate) face using a chiral catalyst; 3) diastereoselective alkylation using auxiliary-controlled methodology. These strategies will be illustrated in turn with recent literature examples.

2.2.1 Enzymatic Desymmetrisation

Desymmetrisation, as the name implies, is the loss of one or more symmetry elements in a molecule, which in context involves transformation of one of the enantiotopic arms of a prochiral substrate into a chiral, non-racemic product. Relevant to this thesis is the case of enzymatic desymmetrization of malonates using an esterase enzyme, in which selective hydrolysis of one of the two enantiotopic ester groups occurs on a racemic substrate, **Fig. 9**.

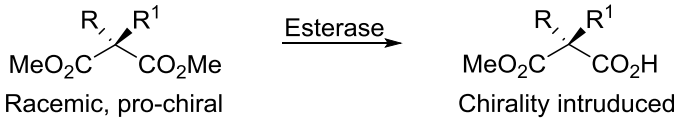
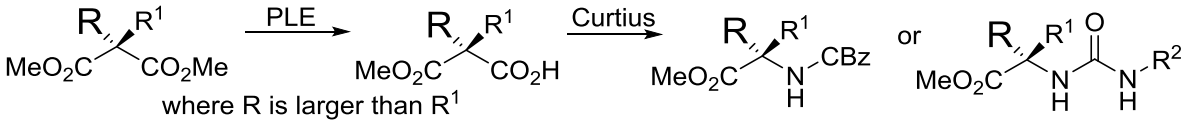


Figure 9 Esterase desymmetrisation of malonates.

Many examples of enzymatic desymmetrization can be found in the literature, but these are usually target-specific due to the way the molecule docks into the active site of the enzyme. Recently, porcine liver esterase (PLE) has gained popularity for the enantioselective hydrolysis of a range of dialkylated methyl malonates to afford chiral, non-racemic half esters that can be subjected to a Curtius rearrangement to generate α, α'-quaternary amino acid derivatives ultimately.[101] Yields of the half-esters are high, and reported stereoelectivities range from 42 to > 98 % *ee*, in which the enantioselectivity depends on the relative steric demand of the two groups at the emerging chiral centre, **Scheme 72**.



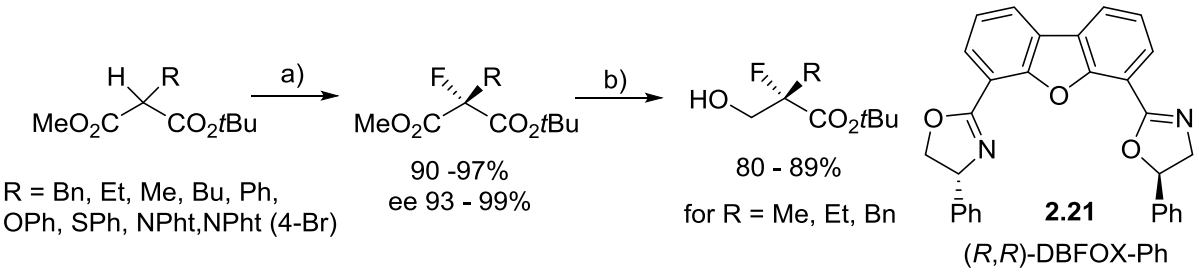
Scheme 72 Generation of ATAs from racemic malonates desymmetrized by PLE

Although a relatively wide scope of α-groups has been demonstrated, the substrate-specific nature of the process is limiting. Furthermore, the stereospecificity of PLE hydrolysis also means that one cannot access the opposite enantiomer of these adducts via this route unless enzyme antipodes are available, which is more often not the case. Enzymatic reactions require specific conditions such as aqueous or polar medium and the use of phosphate buffers to maintain a constant pH of 7 -8.

2.2.2 Catalytic Enantioselective Methods

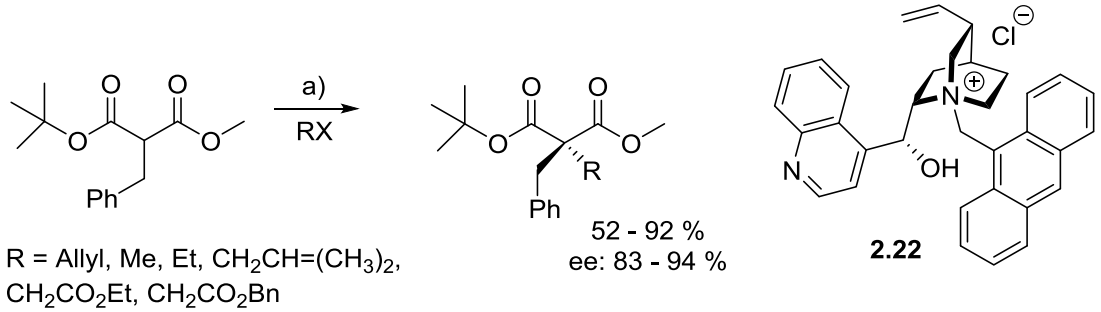
An alternative to enzymatic desymmetrization is to transform a prochiral substrate using a chiral catalyst in an enantioselective reaction. In context, this has been achieved using catalytic enantioselective fluorination of a range of C-2 substituted *t*-butyl methyl malonates with a π-box-type catalyst **2.21**, which affords the products in high yield and selectivity. The esters can then be

chemoselectively differentiated via $LiAl(OtBu)_3H$ reduction of only the methyl ester. These aren't candidates for ATA production pertinent to this thesis, however, but serve as an illustration of the use of malonate esters to generate quaternary carbons asymmetrically and of the subsequent chemodifferentiation achievement. **Scheme 73** illustrates.



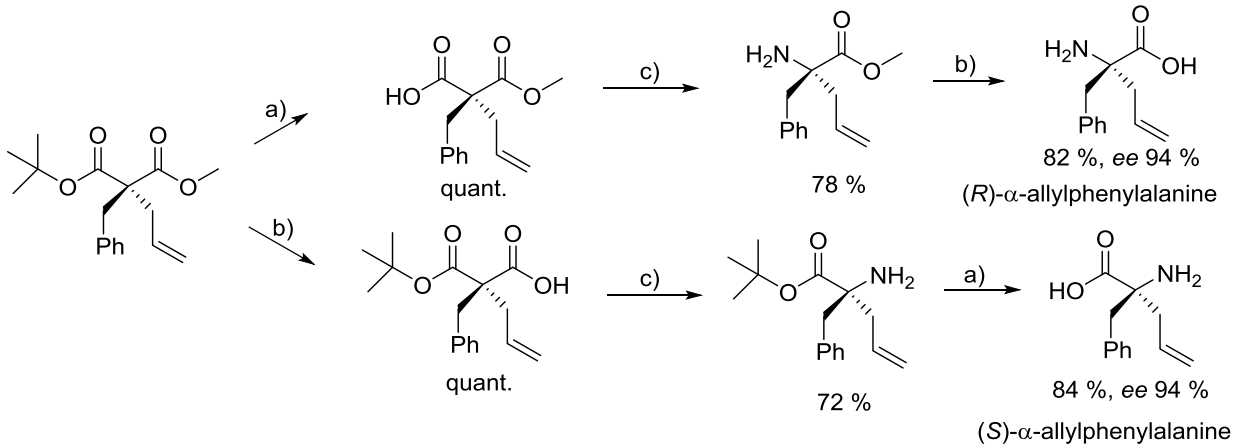
Scheme 73 *Reagents and conditions*: a) $(PhSO_2)_2N$-F (1.2 eq), $Zn(OAc)_2$, 10 mol%, (*R,R*)-DBFOX-Ph, 11 mol%, MS 4 Å, CH_2Cl_2, reflux; b) $LiAl(OtBu)_3H$ (5 eq), THF, -78 °C to rt.

Similarly, catalytic asymmetric alkylation reactions onto α-benzyl-substituted malonic diesters have also been reported employing phase transfer conditions.[126] A chinchona-derived catalyst **2.22** was shown to facilitate the enantioselective alkylation of α-benzyl *tert*-butyl methyl malonate with a range of electrophiles, affording quaternary malonates in yields of 52 to 92 % and *ee*s of 84 to 94 % (**Scheme 74**).



Scheme 74 *Reagents and conditions*: a) **2.22** (10 mol %), toluene, 50 % KOH, -20 °C, 48 – 96h.

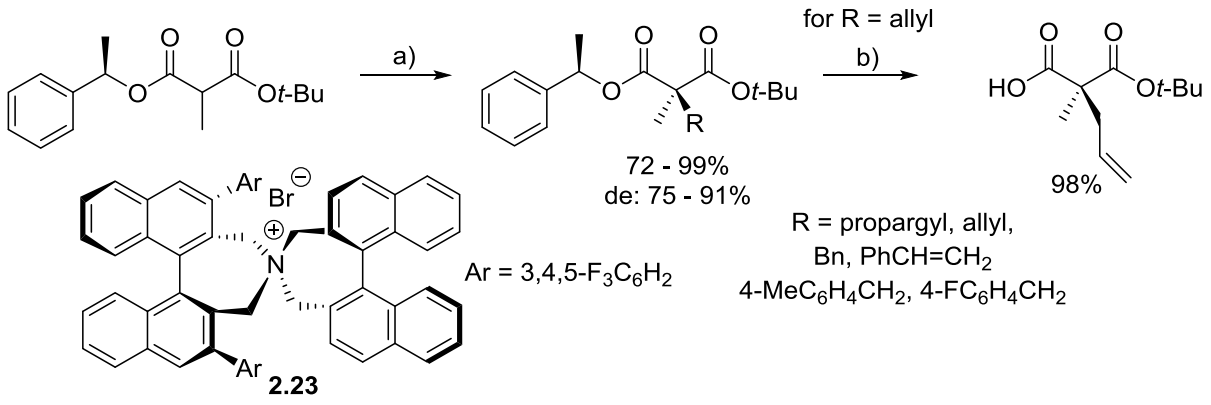
Extension to the ATAs was demonstrated for the allylated derivative, in which either of the ester groups could be chemoselectively hydrolysed depending on conditions applied, and the resultant acid subsequently committed to a Curtius rearrangement step. Hydrolysis of the remaining ester furnished either enantiomer of α-allylphenylalanine as shown in **Scheme 75**.



Scheme 75 *Reagents and conditions*: a) TFA, CH_2Cl_2, rt; b) LiOH, MeOH, H_2O, reflux; c) DPPA, Et_3N, toluene, reflux then $NaHCO_3$, THF, H_2O, reflux.

2.2.3 Diastereoselective Methods

In the abovementioned examples, the chiral catalyst distinguishes between the two faces of a prochiral malonate based on size differences. In the following example of a catalytic diastereoslective process, a binaphthyl type quaternary ammonium salt **2.23** catalyzes α-alkylation of 2-methybenzyl *tert*-butyl malonates under phase-transfer conditions.[127] A range of benzyl ester moieties were tested, methylbenzyl giving the best selectivities, where the (*R*)-isomer gave slightly better selectivities compared to the (*S*)-isomer, likely as a result of the match/mismatch between the substrate and catalyst. In total, six derivatives were generated in yields of 72 – 99 % and des of 75 – 91 %, **Scheme 76**.

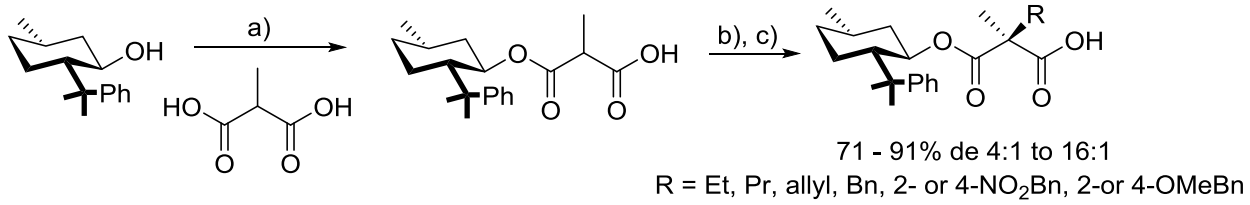


Scheme 76 *Reagents and conditions*: a) **2.23** (5 mol%), RBr (5 eq), 50% KOH (5eq), toluene, -40 °C; b) 50% KOH, MeOH, rt.

The authors report that unactivated alkyl halides gave very low yields and were thus not included in the account. This, however, is standard for quaternization via S_N2 alkylation. Alkylations to the quaternary malonates were only carried out on methyl-substituted variants, another limitation of the methodology. A chemoselective hydrolysis of the benzyl ester was achieved on the allyl and

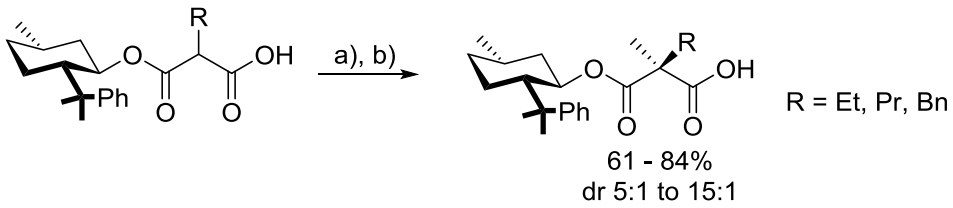
benzyl derivatives using 50 % KOH. Different benzyl esters were screened in order to achieve the correct balance between chemoselective deprotection with retention of the *t*-butyl ester and stereoselectivity.

Prior to the present work only one example of asymmetric generation of a quaternary malonate via a diastereoselective auxiliary-directed process could be found in the literature. Fukumoto *et.al*[128] in 1989 reported on the functionalization of one of the termini of α-methyl malonic acid with 8-phenyl menthol as auxiliary to generate a chiral malonic half ester. Subjecting the half-ester to 2 equivalents of LDA produced a dianion, which was alkylated with a range of electrophiles to arrive at the quaternized products in good yields. Selectivities varied from 4:1 to 16:1, increasing for bulkier alky halides as expected, alkylating onto the face opposite the phenyl group with the auxiliary in the conformation depicted in **Scheme 77**.



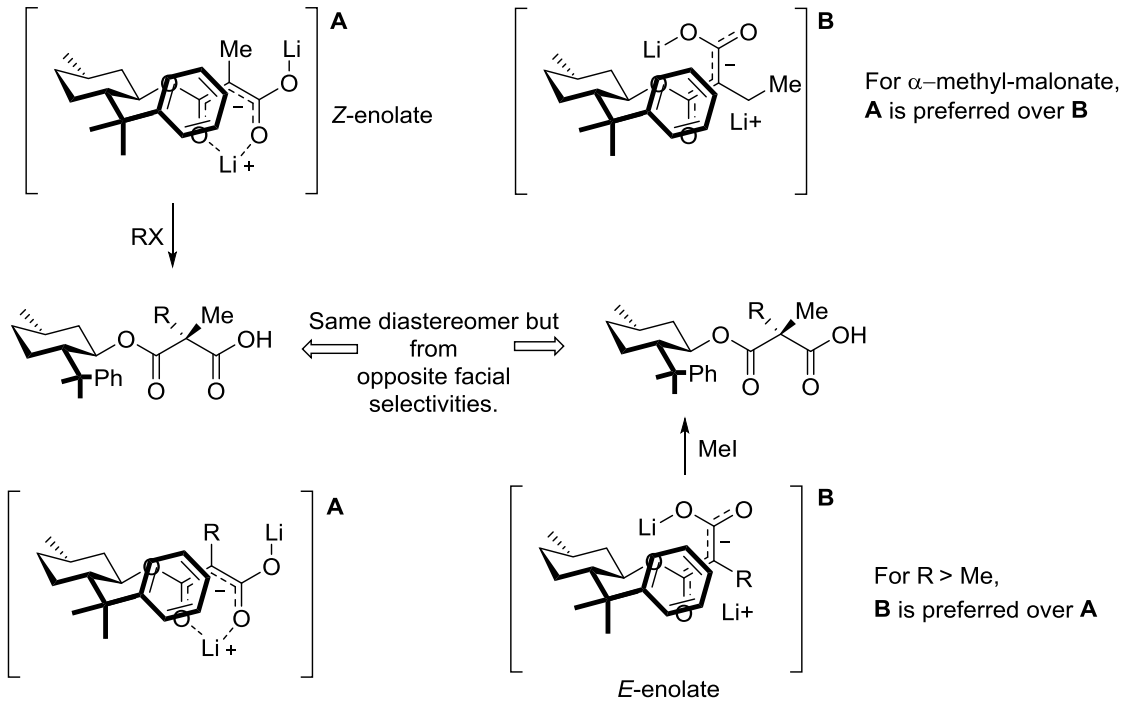
Scheme 77 *Reagents and conditions*: a) DCC, DMAP; b) LDA (2 eq), THF, -78 °C; c) RX

Unexpectedly, when malonates substituted with various groups were methylated, the same diastereoselectivity was observed, indicating methylation took place from the opposite face to the alkylations with other groups as is depicted in **Scheme 78**.



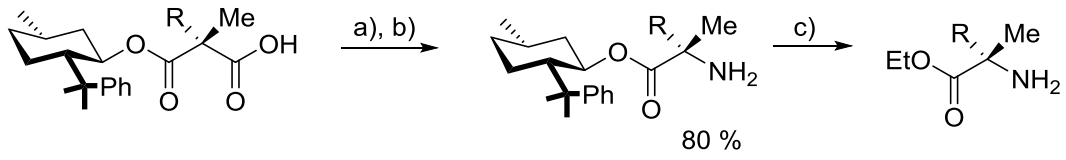
Scheme 78 *Reagents and conditions*: a) LDA (2 eq), THF, -78 °C; b) MeI

The authors offered an explanation for facial selectivity reversal by postulating transition state models **A** and **B** shown in **Scheme 79**, which differ in the enolate configuration. Thus, with methyl as the α-group a *Z*-enolate is preferred, while with an α-group larger than methyl (depicted as R) an *E*-enolate is preferred in order to minimize steric strain with the auxiliary. The net result is opposite configurations, which due to opposite order of group introduction result in the same diastereoselectivity overall.



Scheme 79 Transition state models for explaining the retention of diastereoselectivity

Conversion of the alkylated product to a quaternary amino acid was achieved via the Curtius rearrangement with subsequent hydrogenolysis of the carbamate, followed by hydrolysis of the phenylmenthyl ester with KOH, **Scheme 80** (final yields were not given).



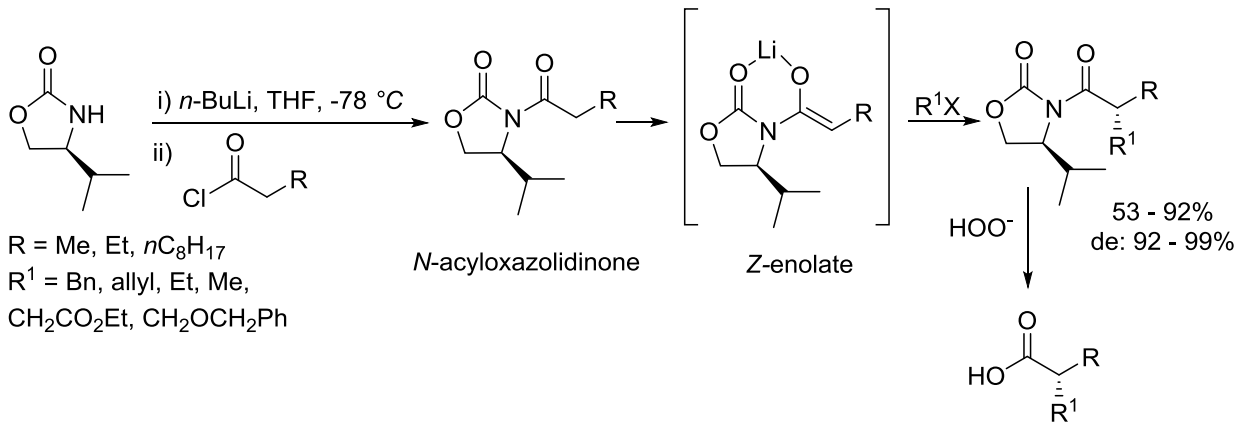
Scheme 80 *Reagents and conditions*: a) DPPA, Et_3N, $PhCH_2OH$; b) Pd-C, cyclohexene; c) i) KOH 18-Crown-6, ii) HCl-EtOH.

Given the relatively narrow scope and modest levels of selectivity in the abovementioned accounts, it was evident that there was ample incentive for developing an auxiliary-controlled asymmetric methodology for the synthesis of quaternized malonates.

2.3 Choosing the Right Auxiliary

In Chapter One the three criteria for a successful auxiliary were discussed as: 1) ease of preparation and attachment, 2) induction of a high degree of facial selectivity, 3) non-destructive removal without racemization of products. One of the most prevalent cyclic auxiliary types is the oxazolidinone class of chiral auxiliary, developed and introduced into the chemistry literature by the

Evans group in 1981.[129] The auxiliary was easily prepared from (*S*)-valinol in which its first application by Evans was in the diastereoselective α-alkylation of an acid as depicted in **Scheme 81**.[130]



Scheme 81 Diastereoselective alkylation of an *N*-acyloxazolidinone

The mechanistic principles in this classic piece of chemistry have become textbook material. Thus, acylation of the lithium anion of the auxiliary with the appropriate acid chloride furnishes an *N*-acyl-oxazolidinone substrate in high yield. Its selective enolization using *n*-BuLi kinetically gives rise to a chelated *Z*-enolate, and subsequent alkylation proceeds with high diastereoselectivity via *anti*-addition to the bulky isopropyl group on the chelated auxiliary. The auxiliary could then be easily removed by hydroperoxide ion, reductively or by transesterification, and then recovered, adding to the utility of this methodology by satisfying all three criteria for high methodology efficiency. Owing to the wide scope and high efficacy of Evans' and Evans-type auxiliaries, this approach is still practised today and the literature abounds with examples of successful asymmetric α-functionalization for the synthesis of chiral building blocks, medicinally valuable compounds and in natural product syntheses. Over the years, structurally related auxiliaries of the Evans' type have emerged and been fine-tuned for specific synthetic challenges, some examples of which are shown in **Fig. 10**.

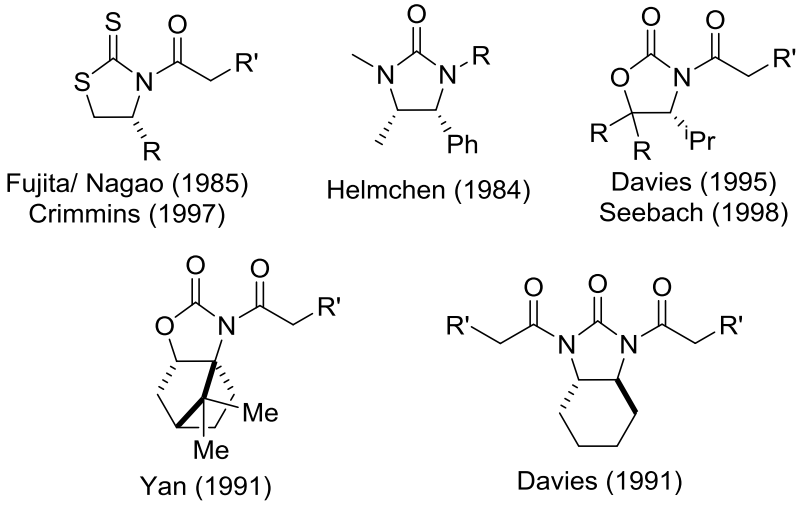


Figure 10 Structural variants based on the Evans' auxiliary motif.

2.4 The Enolate Geometry Problem of α,α-Disubstituted Enolates

Despite the broad utility of the Evans' auxiliary, transposition to quaternary centres via disubstituted enolates is not easily accomplished due to the difficulty in controlling enolate geometry in such systems as illustrated in **Figure 11**.

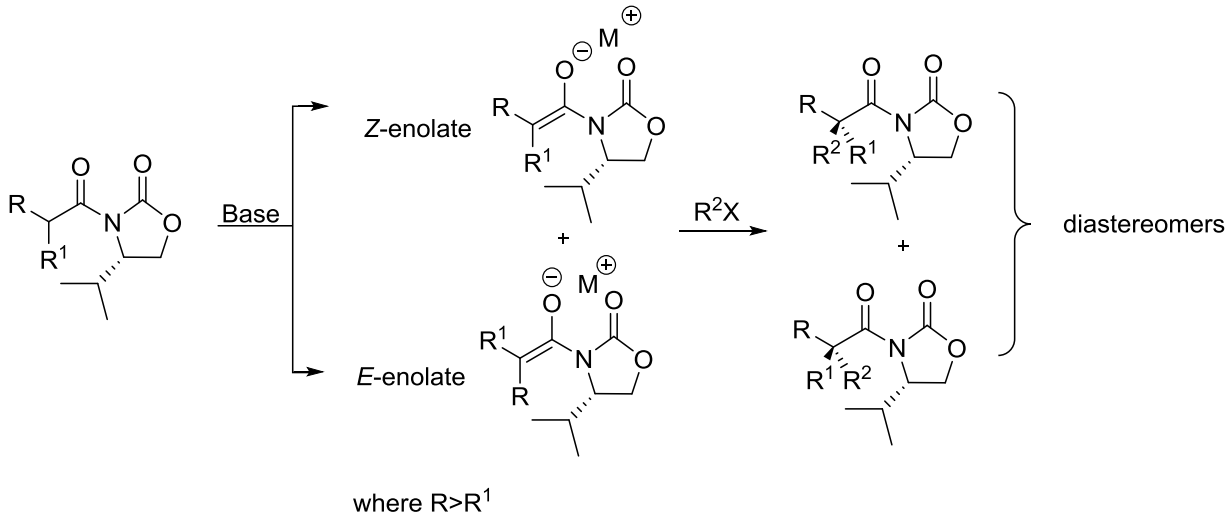
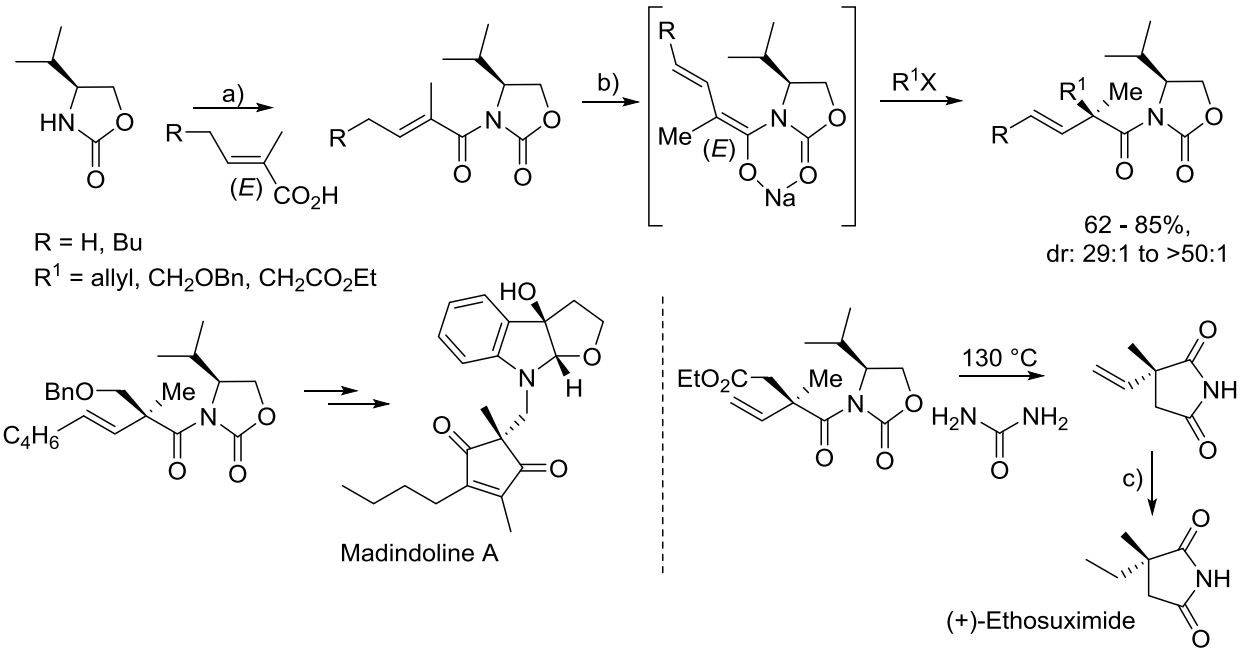


Figure 11 The disubstituted enolate geometry problem of *N*-acyloxazolidinones

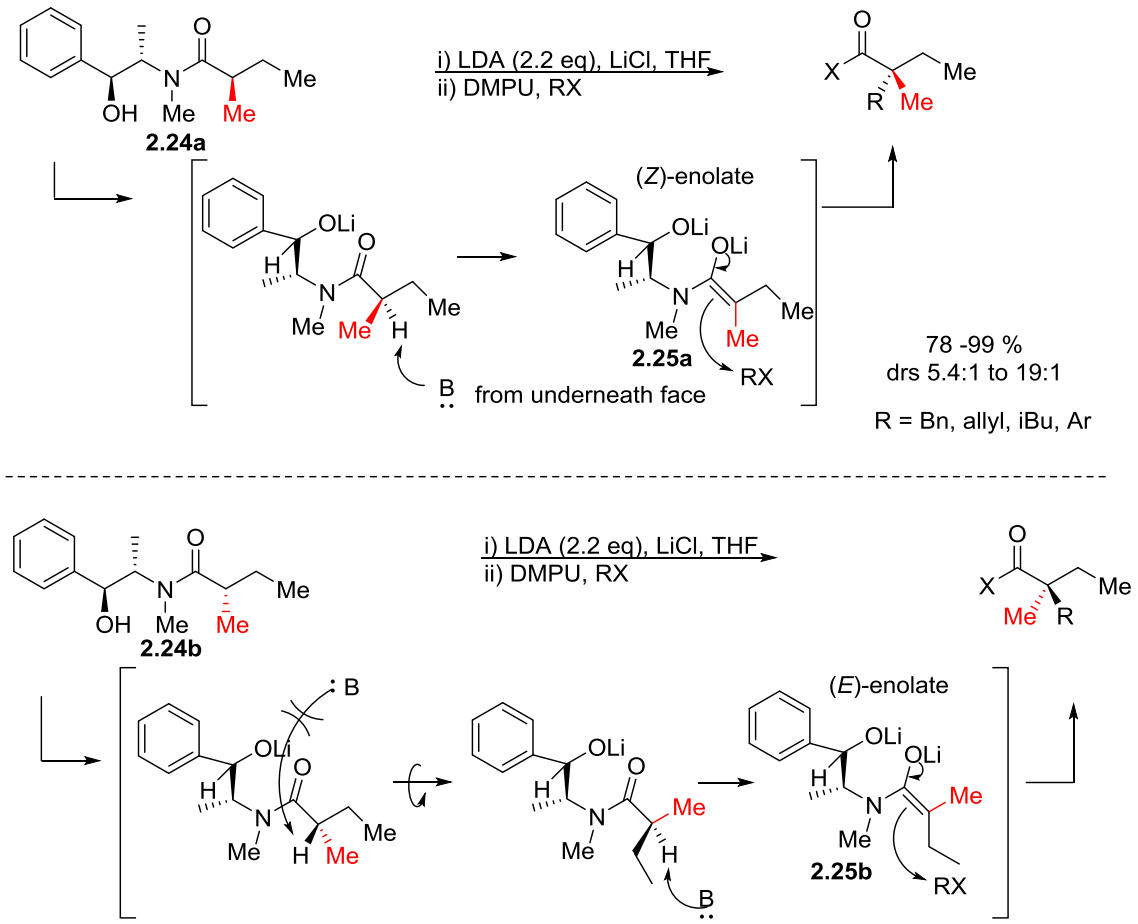
Of the few examples that do exist, the scope is often limited. In 2003, Kobayashi reported on a regio- and diastereoselective alkylation of α,β-unsaturated imides to generate quaternary centres, and applied it to a total synthesis of madindoline A and (+)-ethosuximide (**Scheme 82**).[131] The geometry of the double bond in the substrate dictated the geometry of the enolate; thus, γ-proton abstraction with NaHMDS gave the *E*-enolate which reacted with electrophiles at the α-position. Only

quaternary centres bearing an α-methyl group were generated in the report and only three of the eight electrophiles (R^1X) tested gave satisfactory results.



Scheme 82 *Reagents and conditions*: a) $SOCl_2$, *n*-BuLi, THF (96 %); b) NaHMDS, -78 °C; c) H_2, PtO_2, EtOH.

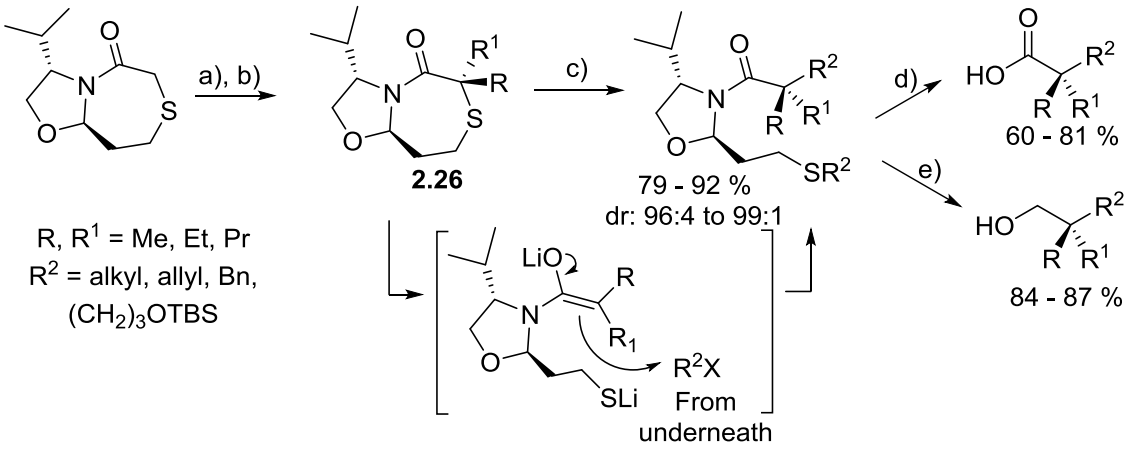
Similarly, a strategy reported by Myers and co-workers in 2008[132] reported the use of pseudoephedrine as a chiral auxiliary to generate enantiomerically pure α-methylbutyramides **2.24a** and **2.24b**, differing only in α-stereogenicity. The control of enolate geometry was realized through a stereospecific enolization with 2 equivalents of LDA, delivering *Z*-enolate **2.25a** and *E*-enolate **2.25b** respectively based on the stereogenicity at the α-carbonyl centre in the substrate as depicted in **Scheme 83**.



Scheme 83 Myers' use of pseudeoephedrine as an auxiliary to effect stereospecific enolization.

Alkylation occurred onto the face opposite the pendant benzylic alkoxide to generate alkyl, allyl, and benzyl quaternised products in high yields with average to good stereoselectivity. Hydrolysis to the acid or reductive cleavage of the pseudoephedrine auxiliary to the primary alcohol completed the sequence.

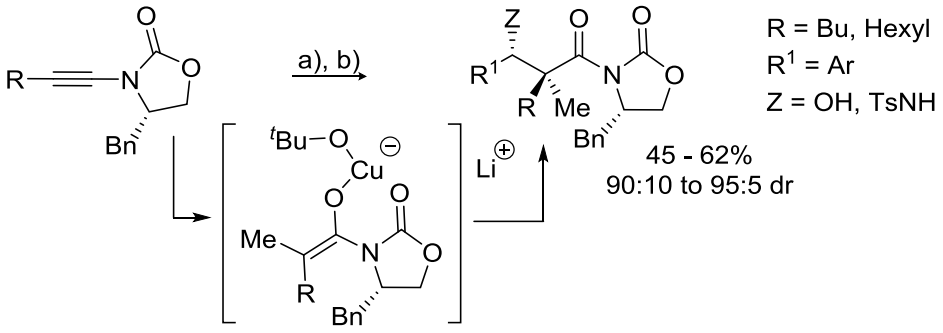
In the approach by Gleason, the chirality of the starting bicyclic thioglycolate lactam **2.26**, which was shown not to be dependent on the size of R and R^1, but rather on the order of their introduction, dictated enolate geometry via reductive cleavage (C-S), **Scheme 84**.[133]



Scheme 84 *Reagents and conditions*: i) LDA, LiCl, THF, 0 °C; ii) R-X; b) LDA, LiCl, THF, 0 °C, R^1X; c) i)Li, NH_3, THF, -78 °c; ii) R^2X; d) 6M H_2SO_4, dioxane, reflux; e) LiH_2NBH_3, THF, -78 to -66 °C.

Stereospecific reductive enolization took place and the subsequent reaction with various electrophiles on the face opposite the alkyl-SLi tether afforded the quaternized derivatives with excellent drs, the only drawback being the destructive removal of the auxiliary. This intriguing approach of effectively controlling the disubstituted enolate geometry differs from conventional methods.

More recently in 2012, the Marek group disclosed a method for generating a stereodefined disubstituted chiral enolate from an acyclic ynamide coupled to an oxazolidinone auxiliary (**Scheme 85**).[134] The process entailed a highly diastereoselective copper-catalysed carbometalation-oxidation sequence, furnishing quaternary aldol products in good yields. Only aryl aldehydes and methyl cuprates were reactive, however.



Scheme 85 *Reagents and conditions*: a) i) $Me_2CuLi.LiBr.SMe_2$, Et_2O, -40 °C ii) *t*-BuOOH, - 80 °C; b) i) R^1CHO or $TsN{=}CHR_2$; ii) H_3O^+

2.5 Key Concepts and Objectives for Research Conducted

The key question in developing a malonate-based diastereoselective protocol for all-C quaternization was that of enolate geometry control. It was perceived that this might be accomplished by the presence of the additional (malonate) carbonyl promoting coordination to the metal cation and in so doing locking the enolate into a chelated *Z*-conformation. Should this be the case, however, it would allow free rotation around the imide C-N bond, which provided a cause of concern regarding facial selectivity on the enolate, (Options A (i) and A (ii) in **Fig. 12**). Conversely, if chelation were to occur to place the metal cation into the auxiliary hole, the imide bond conformation would be locked (s-*cis*$_{C\text{-}N}$), whilst enolate geometry would be variable, (Options B (i) and B (ii)). The counter-ion being a determining factor for chelation would obviously demand a thorough investigation of available bases for enolization. Ultimately, either scenario A (i) or A (ii) would lead to high levels of facial selectivity so long as propensity for ONE of the two possible imide bond conformations occurred.

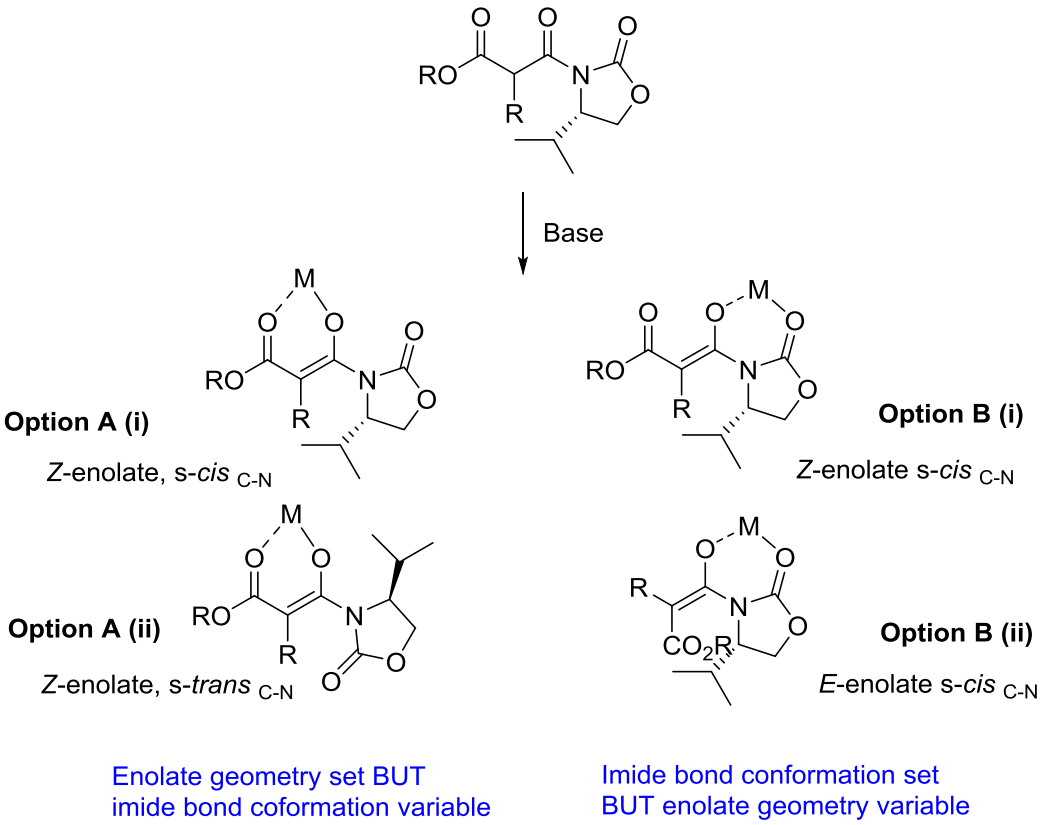


Figure 12 Possible scenarios arising from enolization of an auxiliary-malonate system

2.6 Generation of all-carbon quaternary malonates

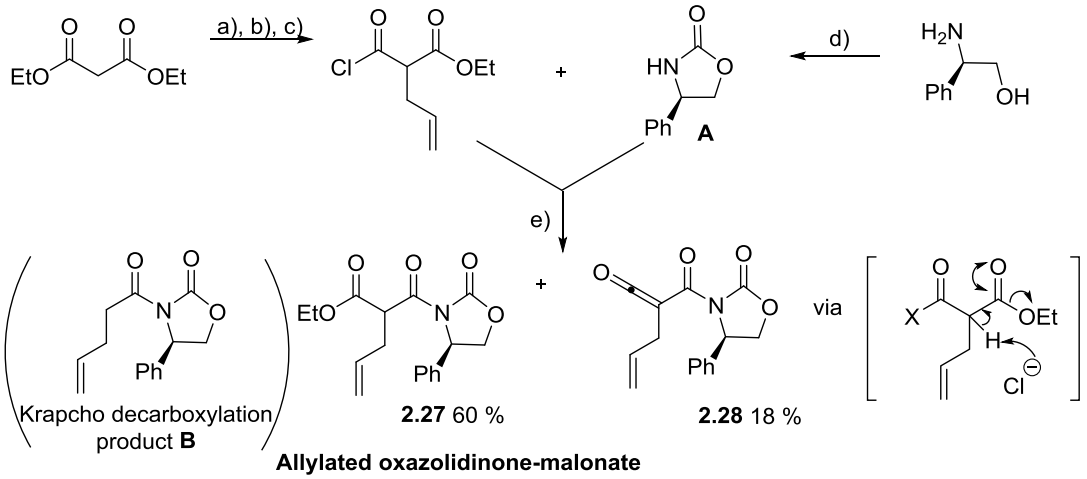
2.6.1 Malonate- Oxazolidinone system

The broad utility and efficacy of the Evans' auxiliary made it the obvious starting point for exploring malonate quaternization reactions. The oxazolidinone derived from (*R*)-phenylglycinol was chosen as

the chiral auxiliary over the (*S*)-valinol-derived variant primarily because UV activity allowed for easier reaction profiling.

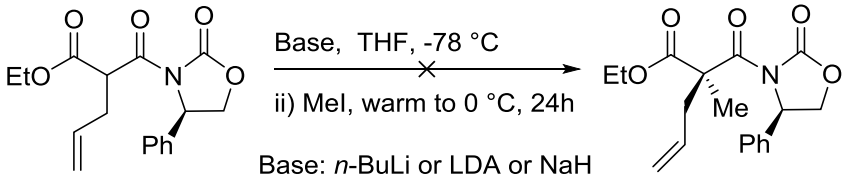
The first issue addressed was the question of the stability and reactivity of any α-alkylated malonate oxazolidinone, in which allyl was chosen as the α-substituent. To this end diethyl malonate was readily alkylated using sodium hydride and allyl bromide in refluxing THF to give the mono α-allylated diester in a yield of 92 % after chromatography. This product was then mono-hydrolysed with ethanolic KOH (1.05 eq) and the half acid-ester isolated using acid-base extraction. Diagnostic peaks in the ^{1}H NMR spectrum of the product were that of the carboxylic OH, which appeared at 8.13 ppm as a broad singlet, as well as the allylic protons resonating at 5.79, 5.13 and 2.68 ppm. The multiplet at 3.51 ppm was assigned to H-2 of the malonate. Evans' auxiliary was synthesized by treating (*R*)-phenylglycinol with Et_3N and triphosgene (0.5 eq) in DCM at 0 °C. The optical rotation was measured, which correlated with the literature value. $[\alpha]_D^{20}$ = -53° ($CHCl_3$, *c* = 1.0), [lit.[135] $[\alpha]_D^{20}$ = -54° ($CHCl_3$, *c* = 1.0)].

The mono-acid was converted to an acid chloride using oxalyl chloride and catalytic pyridine in DCM. Once thoroughly dried, a THF solution of the acid chloride was introduced into a solution of the lithium anion of the auxiliary (generated form the reaction of Evan's auxiliary **A,** with *n*-BuLi in THF at -78 °C). The yields for the coupling reaction were variable, as malonate acid chlorides are susceptible to decarboxylation. Some by-product formation was also evident, since both the desired allylated oxazolidinone-malonate **2.27**, and the ketene elimination product **2.28** were isolated from the reaction in a ratio of about 3:1 and a combined yield of 78 %. These two products were easily discernible on tlc, and the identity of **2.28** was confirmed by virtue of its ^{1}H NMR spectrum in which a clear absence of ethoxy signals (triplet at 1.2 ppm and multiplet at 4.2 ppm region) supported the notion of elimination. The proton count of 13 (for **2.28**) and the fact that no α-Hs were visible in the 2 ppm region of the spectrum eliminated the Krapcho decarboxylation product **B** as the identity of product **2.28**. However, its formation could not be excluded, as several other minor spots were seen on the tlc but were not isolated; the ketene arising from auxiliary expulsion being another possible product (the yield of auxiliary recovery from the reaction was < 10 %). **Scheme 86** summarises these findings.



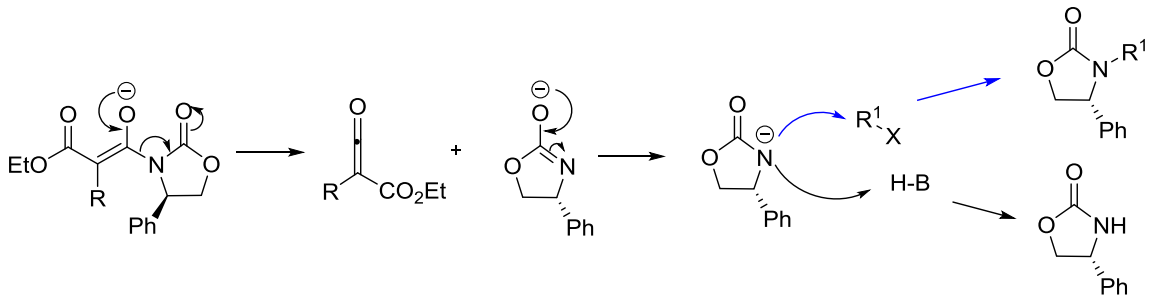
Scheme 86 *Reagents and conditions*: a) i) NaH (1.2 eq), THF, 0 °C to rt, 30 min; ii) AllylBr, reflux, 8h (92 %); b) KOH (1.05 eq), EtOH, rt, 24h; (95 %); c) pyridine (5 mol %), $COCl_2$, DCM, reflux, 2h; d) Et_3N (1.2 eq), triphosgene (0.5 eq), DCM, 0 °C; e) *n*-BuLi (1.1 eq), THF, -78 °C to rt.

Quaternization under various conditions was then attempted but to no avail (**Scheme 87**).



Scheme 87 Attempted quaternization with lithium and sodium bases

As the reaction warmed from -78 °C to around 0 °C, tlc indicated the slow formation of a slightly less polar spot on tlc, presumed to be the methylated product. However, the oxazolidinone auxiliary was also observed, building in intensity on the plate over time. Chromatographic isolation revealed a less than 10 % yield of the methylated product, 50 % auxiliary recovery, with only 25 % recovery of the starting material. A plausible mechanism for auxiliary production is via elimination of the enolate to afford a ketene derivative of the malonate as shown in **Scheme 88**. Partial alkylation of the auxiliary (blue arrow in mechanism) also took place, as a small amount of alkylated auxiliary was isolated (less than 10 %). The ketene was not isolated but the presence of a non-polar spot high up on the tlc plate was a good indication of its formation.



Scheme 88 Mechanism of auxiliary expulsion

Hence, a more chemically robust auxiliary malonate system was required that could withstand the reaction conditions. Upon literature inspection, it was decided to study the analogous ephedrine-derived imidazolidinone auxiliary designed by Helmchen[136] to see if elimination was suppressed. The two auxiliaries are depicted in **Fig 13**.

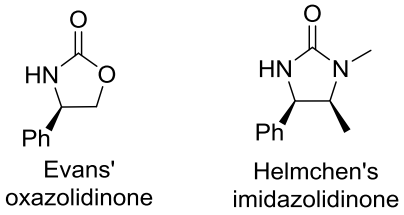
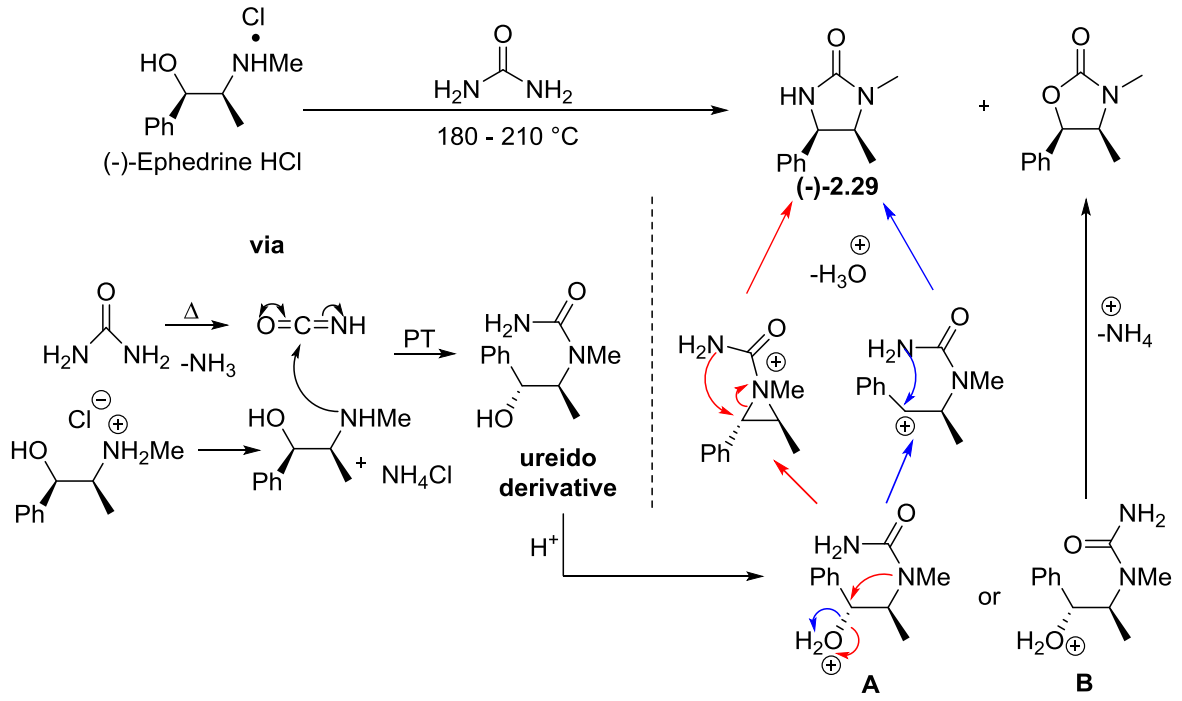


Figure 13 Evans' oxazolidinone and Helmchen's imidazolidinone auxiliaries.

2.6.2 Malonate-Imidazolidinone system

The corresponding imidazolidinone was easily prepared on a multigram scale via Close's[137] fusion reaction of urea and ephedrine in a yield of 52 %. This was in agreement to the reported yields for its production, the low values being attributed to the competing formation of the oxazolidinone. The first step in the proposed mechanism is the breakdown of urea into cyanic acid (shown as the more stable tautomer isocyanic acid) and ammonia driven by the high temperature of the reaction. The nitrogen of the ephedrine (shown as the 1*S*, 2*R* enantiomer in Scheme 89) then reacts with the acid to form the ureido intermediate. At this point, cyclization can occur via either the N or the O of the urea, leading to imidazolidinone or oxazolidinone respectively. The origin of the stereoselectivity as retention of configuration in the ring closure is unclear. Such a diastereoselectivity precludes a single S_N2 inversion, so the mechanism appears to either be a stereocontrolled S_N1 (blue arrows in mechanism shown in **Scheme 89**), or two S_N2 inversions (red arrows), the latter presumably involving first the *N*-Me nitrogen to form an aziridinium intermediate followed by a second substitution (rearrangement) to form the less-strained five-membered ring. **Scheme 89** summarises these ideas. The absolute configuration of the auxiliary used here links to the one needed for (-)-lepadiformine. This will be explained later.



Scheme 89 Fusion reaction and mechanistic thoughts on the preparation of imidazolidinone **2.29**

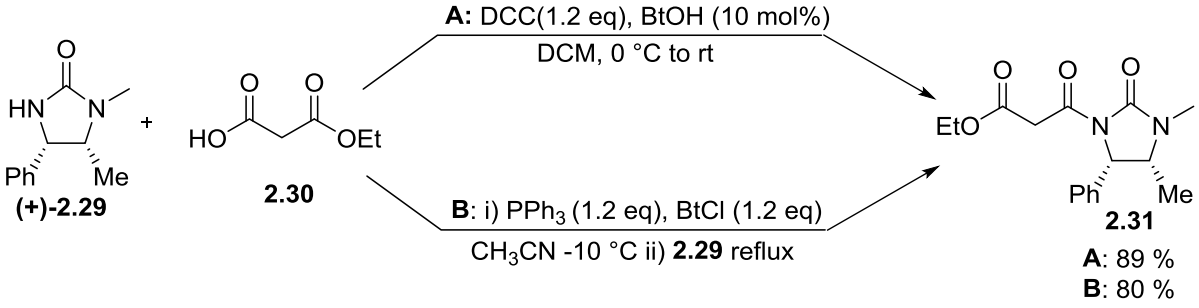
The opposite antipode of the auxiliary could similarly be prepared by the use of the other enantiomer of ephedrine.

Following the fusion reaction the residue could be recrystallized with DCM/ EtOAc or ethanol. The accumulated mother liquors over a number of runs could then be purified by column chromatography. The signals obtained in the ^{1}H NMR spectrum of (-)-**2.29** were identical for those reported in the literature,[138] and the optical rotation measured for the auxiliary matched the reported value. $[\alpha]_D^{20}$ = -43° (MeOH, *c* = 1.0), [lit.[138] $[\alpha]_D^{20}$ = -41° (MeOH, *c* = 0.9)]. Auxiliary **2.29** is also available commercially.

An efficient way of coupling the unsubstitued malonate half acid with the auxiliary had to be found, and several methods were investigated. Acid chloride methodology was investigated first by refluxing the half acid with either thionyl chloride or oxalyl chloride, removing excess reagent and then refluxing the residual acid chloride with the imidazolidinone auxiliary in acetonitrile,[139] rather than via its lithium anion (extra step). Reasonably high yields (~70 %) could be obtained but only when a large excess of acid was used in order to account for decarboxylation. In addition, the volatility of the unalkylated malonoyl chloride made isolation from the reaction mixture difficult, also obviating higher equivalents of acid to be committed. Mechanistically, reaction probably proceeds via acylation of the imidazolidinone urea carbonyl oxygen followed by O to N transposition, as the corresponding oxazolidinone can't be acylated this way.

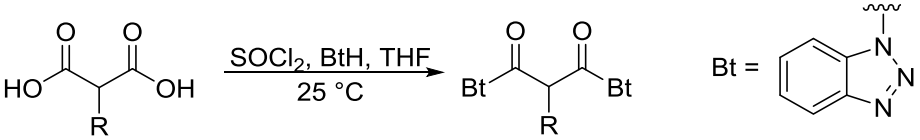
The mixed anhydride method using pivaloyl chloride gave lower yields (~60 %) as well as producing a number of side-products and was therefore also not the protocol of choice.

It was thus decided to investigate the peptide-like coupling of auxiliary (+)-**2.29** with ethyl malonate half- acid **2.30** with DCC. This was not appropriate for coupling the oxazolidinone because of poor nucleophilicity but it was felt as described above that the superior nucleophilicity of the imidazolidinone might be sufficient to promote the reaction. Indeed that turned out to be the case. A typical procedure involved the gradual introduction of a solution of DCC (1.2 eq) in DCM into a stirring mixture of the half acid-ester of malonate, the auxiliary and a catalytic amount of HOBt in DCM at 0 °C. After complete addition the mixture was allowed to warm up to rt (**Scheme 90**). Pleasingly, the desired imidazolidinone derivative was obtained in 89 % yield after chromatography. Proof of successful coupling was provided by ^{1}H NMR spectroscopy in which signals diagnostic for the auxiliary and the ester functionality of the malonate were present. Signals arising from the auxiliary included the multiplets in the aromatic region (correctly integrating for 5 protons) followed by a doublet at 5.32 ppm assigned to the benzylic hydrogen on the ring; an *N*-Me singlet at 2.81 ppm, and an upfield doublet integrating for 3 protons at 0.80 ppm for the methyl at C-4 of the auxiliary. Similarly, the ethoxy multiplets appeared with the normal chemical shifts. The only drawback with the procedure, as is often the case with DCC-promoted coupling reactions was that the dicyclohexyl urea by-product was very close in polarity to the product, hampering isolation, although most of it was removed by several precipitations from cold ethyl acetate. This was by no means ideal, especially when multi-gram reaction scales were needed.



Scheme 90 DCC and BtCl coupling techniques

An alternative approach using *N*-acylbenzotriazoles as activated carboxylic acid analogues was examined next. The protocol was based on the work done by Katritzky[140] who demonstrated the utility of *N*-acylbenzotriazoles as air- and water-stable alternatives to acid chlorides. In his reports however, an acid chloride intermediary was required for reaction with benzotriazole (BtH).



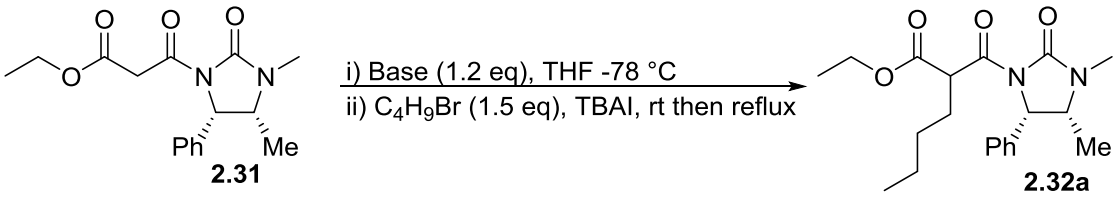
Scheme 91 Katritzky's activation of carboxylic acids using Bt.

A protocol that avoids the use of acid chlorides was devised by Hunter and Msutu[141] who showed that *N*-acylbenzotriazoles could be obtained from the reaction of carbamate salts, triphenylphosphine PPh_3 and 1-chlorobenzotriazole (BtCl). The BtCl reagent was in turn easily prepared in multi-gram scales by oxidation of BtH with bleach. Successful extension of the methodology to carboxylic acids meant that it could be applied to our system. The procedure entailed the initial reaction of BtCl and PPh_3 in ACN for 10 minutes at – 10 °C to generate the chlorophosphonium salt. Subsequent addition of the carboxylic acid with continued stirring, furnished the Bt-derivative after 1 hour. Auxiliary **(+)-2.29** was then introduced and the mixture refluxed for 8 hours. The protocol provided a good yield of 80 %, but isolation and purification was again problematic owing to the arduous removal of BtH and triphenylphosphine oxide. Nevertheless, either option offered an alternative method superior to the acid chloride methodology. Ultimately going forward the DCC method was preferred as it required no reagent synthesis and gave slightly better yields.

2.6.3 Optimization of alkylation reaction conditions

Before attempting quternization, reaction conditions for the alkylation of **2.31** to form a tertiary centre needed to be developed, with the reasonable expectation that they could be successfully implemented in the second alkylation. A range of kinetic bases were tested, with 1-bromobutane as the electrophile. Although not the most reactive, if successful, it would be a good indication that the reaction would work with the more reactive electrophiles like methyl and allyl halides. Furthermore, butyl presented a model system relevant to early steps in lepadiformine construction. The results of the study are shown in **Table 3**. The enolate was generated by the slow addition of the appropriate base at -78 °C in THF. After stirring for an hour, 1-bromobutane was syringed in and the reaction allowed to warm up to rt. The reaction was aided by the addition of a catalytic amount of TBAI for the *in-situ* halogen exchange between Br and I to generate a more reactive electrophile. After 12 hours at rt, based on the results of tlc monitoring, reflux conditions were applied.

Table 3 Optimization of Reaction Conditions for the Alkylation of **2.31**



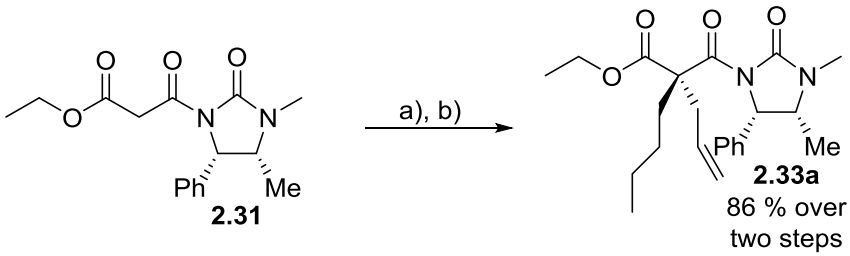
Entry	Base	Reaction Conversion (%)
1	LDA	< 10[a,b]
2	LiHMDS	< 10[a,b]
3	NaHMDS	50[a]
4	KHMDS	98[c]

[a] Estimated by TLC after 72 hrs. [b]Addition of LiCl and HMPA also tested. [c] After column chromatography

In contrast to the reported literature on alkylations of acylated imidazolidinone systems,[138,142,143] no reaction took place when lithium bases were tested under a number of conditions. Similarly, the reaction stalled at roughly 50 % conversion when NaHMDS was used, but gratifyingly, the enolate generated with KHMDS provided a 100 % conversion of substrate (tlc) in a 98 % yield of desired product after chromatography. The butyl derivative **2.32a** was clearly visible on the tlc as two spots of equal intensity for the two diastereomers. The ^{1}H NMR spectrum indeed revealed a 50:50 ratio of diastereomers, as determined by the relative integrations of various duplicated diagnostic signals. Most notably, two discernible doublets for the auxiliary benzylic hydrogen were visible at 5.37 and 5.29 ppm, and an even more obvious duplication was evident in terms of two α-methine malonate multiplets appearing at 4.80 and 4.62 ppm for individual diastereomers. Two methyl triplets of the ethoxy group were also seen (at 1.25 and 1.19 ppm) as well as two highfield doublets for the auxiliary methyl group.

2.6.4 Quaternization reaction

Having arrived at optimal alkylation conditions for the mono-alkylation, it was anticipated that success would follow in the crucial quaternization step using these conditions and allyl bromide as the electrophile. Thus, **2.32a** was enolized at -78 °C with 1.2 equivalents of KHMDS, and allyl bromide was added after an hour, followed by warming to rt, **Scheme 92**. The reaction progressed smoothly, giving the quaternized derivative **2.33a** in a high yield of 87 % after chromatographic purification.



Scheme 92 *Reagents and conditions*: a) i) KHMDS, THF -78 °C, ii) C_4H_6Br rt; b) i) KHMDS, THF -78 °C, ii) allylBr, rt.

The ^{1}H NMR spectrum of product **2.33a** is shown in **Fig 14**, with diagnostic signals being the allylic protons resonating at 5.35 and 4.22 ppm, integrating for 1 and 2 hydrogens respectively. Further upfield, the signals at 2.92 and 2.73 ppm were assigned to each diastereotopic proton of the allyl group. The absence of a signal in the region expected for the malonate α-methine hydrogen (H-2) was also a strong indication that alkylation had taken place. Pleasingly, though, there was no visible doubling of any of the resonances in the ^{1}H NMR spectrum, suggesting a high level of diastereoselectivity for the quaternization, which was later corroborated by HPLC analysis to be 98:2.

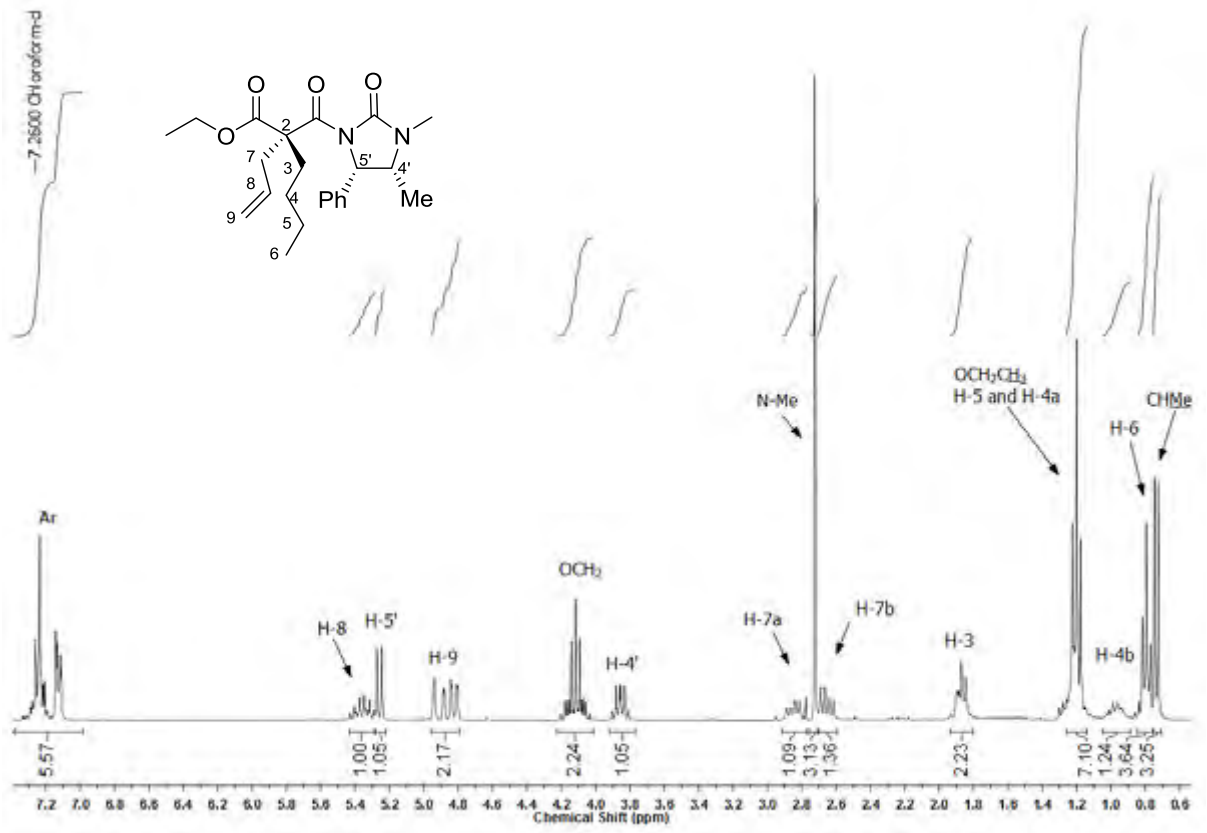
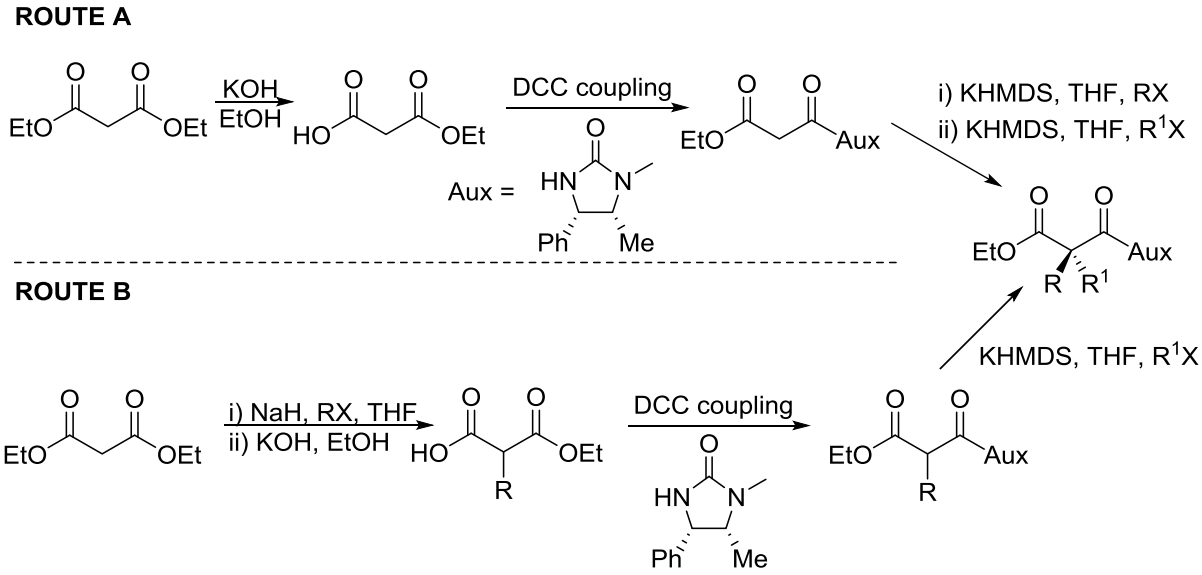


Figure 14 Assigned ^{1}H NMR spectrum of **2.33a**

The reactivity dependence on counter-ion is noteworthy. An obvious possibility is that chelation of the lithium (and to a lesser extent sodium) occurs into the auxiliary hole. This takes it away from the site of alkylation where it is needed to assist with departure of the leaving group. This can't be the only reason otherwise Evans' oxazolidinones wouldn't alkylate, so enolate stability with Li or Na counter-ions must also play a role. By comparison, potassium is too large for the auxiliary hole and the enolate is more ionic anyway and hence more reactive. Aggregation probably also plays a role in that lithium enolates are known to aggregate more than potassium ones, which have more open accessible structures. Addition of LiCl and HMPA, which are known to dissociate enolates, didn't switch on reactivity in the lithium enolate case. However, It is well-known that the diastereoselectivity in Evans' oxazolidinone alkylation to afford chiral tertiary carbons at the alkylation site depends on: i) control of enolate geometry; and ii) a preferred (chelated) conformation of the enolate. In the present case, the potassium result suggested that the first criterion might be satisfied by virtue of the counter-ion placement in the malonate hole to afford a *Z*-enolate.

2.6.5 Reaction Scope

To investigate the scope of the methodology, a choice had to be made as to which route towards the targets would be adopted. **Scheme 93** shows the two possible sequences in which option A involved two sequential alkylations on a common precursor (malonate-imidazolidinone) in order to furnish the quaternized target, while option B proceeded via an α-substituted malonate as starting point.



Scheme 93 Possible routes towards quaternized targets

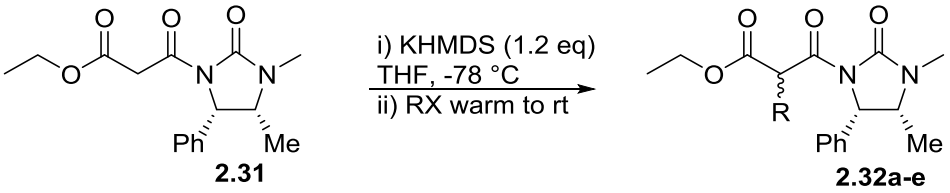
Several derivatives were prepared via both routes for comparison and each option had its own advantages and drawbacks. **Table 4** compares the two methodologies in terms of efficiency in which the green colouration depicts an advantage, while orange shading a drawback.

Table 4 Comparison of routes A and B for the generation of α-substituted auxiliary-malonate derivatives

Process/route	ROUTE A	ROUTE B
DCC Coupling	• Consistent high yields. • Predictable isolation after coupling. • DCC reaction can be done once on a large scale.	• Yields were lower for all alkylated derivatives tested. • Isolation more difficult as products closer to urea side-product; not possible in some cases. • DCC reaction to be done for each individual derivative.
Alkylation	• First alkylation conditions require the use of expensive KHMDS and a precious SM (auxiliary-malonate). • Difficulties in installing bulky electrophiles as R.	• First alkylation uses cheap reagents of NaH and diethyl malonate. • Bulky electrophiles can be incorporated as R.

After weighing up the advantages and drawbacks of each, it was decided that route A was the better option. Thus, **2.31** was prepared on a multi-gram scale , then enolized at -78 °C using 1.2 eq of KHMDS and after the electrophile was syringed in the reaction was allowed to warm to rt overnight. All of the alkylated products **2.32 a** to **e** were visible on tlc slightly above the starting material as two distinct spots for the two diastereomers. The first alkylation to furnish mono-substituted auxiliary-malonate derivatives proceeded in high yields but without selectivity (**See Table 5**). This was mechanistically significant and will be discussed later.

Table 5 Reaction Scope of the Mono-alkylation of **2.31**



2.31 **2.32a-e**

Compound	R	Yield (%)	dr[b]
2.32a	Bu	98[a]	51:49
2.32b	Et	94[a]	51:49
2.32c	Allyl	92	52:48
2.32d	$(CH_2)_3OBn$	87[a]	52:48
2.32e	Me	90	50:50

[a]Warmed to 65 °C; [b] determined by NMR

The diastereomers of some of the compounds were separable by column chromatography whilst others were analysed as diastereomeric mixtures. ^{1}H NMR spectra of diastereomeric mixtures displayed distinct signal duplication, which were most evident for hydrogens pertaining to the auxiliary, as well as for H-2, which had shifted downfield compared to the unalkylated analogue to 4.83 and 4.79 ppm. All derivatives showed expected signals associated with the auxiliary-malonate backbone as well as those corresponding to the alkyl chain in question.

The installation of unactivated electrophiles and longer alkyl chains was successful, but required heat in order to achieve high yields. The fact that the reactions could be refluxed in THF clearly indicated a greater stability of the malonate-imidazolidinone enolates compared to their oxazolidinone counterparts. This could be understood by considering the electron-releasing resonance effect (outweighing its inductive effect) of the *N*-Me nitrogen in **2.29,** which reduces the stability of the imidazolidinone anion as a leaving group. By comparison, in the oxazolidinone case, the more electronegative oxygen helps to stabilise the anion leaving group by a strong inductive effect (outweighing its resonance effect). This comparison is depicted in **Fig 15.**

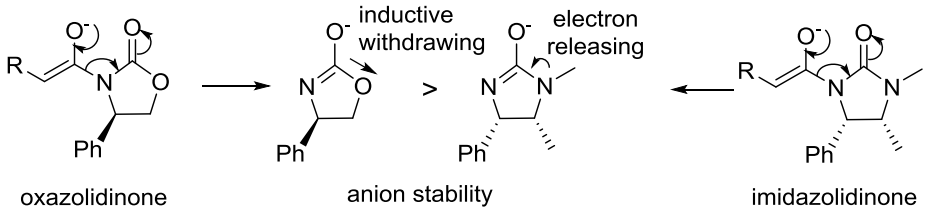
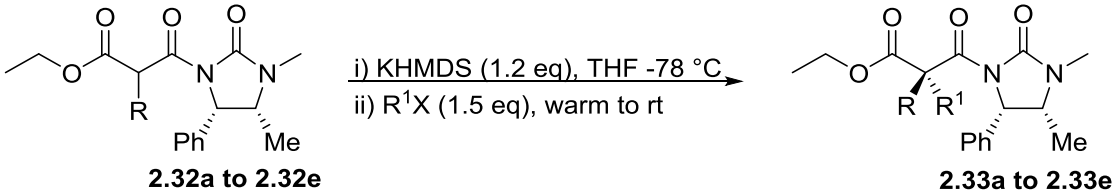


Figure 15 Electronic effects on stability of imidazolidinones vs oxazolidinones

With a range of mono-substituted auxiliary malonates successfully generated, the scope of the crucial quaternization reaction was examined by employing the optimal reaction conditions and various S_N2-reactive electrophiles. The results are shown in **Table 6**.

Table 6 Scope of Quaternization of Monoalkylated Auxiliary malonates **2.32a** to **2.33e**



Entry	Compound	R	R^1	Yield (%)[a]	d.r [b]
1	**2.33a**	Bu	Allyl	85	98:2
2	**2.33b**	Et	Bn	89	96:4
3	**2.33c**	Allyl	Me	92	95:5
4	**2.33d**	$(CH_2)_3OBn$	Allyl	93	98:2
5	**2.33e**	Me	Allyl	93	60:40

[a]After chromatography; [b]measured by HPLC

The reaction proceeded smoothly to furnish quaternized products **2.33a** to **2.33e** in excellent yields and selectivities (apart from entry 5). Unsurprisingly, due to the increased steric crowding and decreased reactivity of the enolate, only S_N2 reactive electrophiles were effective. Evidence for the successful installation of the second alkyl group was provided by ^1H and ^{13}C NMR spectroscopy. The hydrogen at C-2 was no longer present in any of the spectra, and all contained signals arising from the auxiliary, the ethoxy signals and all the resonances associated with the two substituents on the malonate. For compound **2.33b**, an additional five hydrogens were present in the aromatic region, and the benzylic singlet appeared at 3.37 ppm. The methyl singlet of **2.33c** appeared at 1.45 ppm. The new allylic multiplets for **2.33d** were visible at 5.50 and 4.90 ppm. With the exception of compound **2.33e**, no doubling of signals was evident. In the ^{13}C NMR spectra, C-2 resonated in the 55 ppm region for all analogues.

The diastereoselectivity in the quaternized products **2.33a** to **2.33e** was measured by chiral HPLC which gave a good separation of the 2 diastereomers. Immediately evident from the results in **Table 6** is that with R as Me, there was essentially no diastereoselectivity for the allylation (entry 5), whereas all other combinations where R was a two-carbon unit or larger and R^1 was any chain length

including methyl, drs of 95:5 and above were achieved, with virtually complete diastereoselectivity observed for bulkier R groups. Yields were good to excellent for all derivatives. A single crystal X-Ray structure was determined for compound **2.33b.** Importantly, the diastereoselectivity translated to placing the R^1 group *syn* to the bulky groups on the auxiliary *when the molecule was drawn in the all-cis conformation* as shown in **Figure 16**. This relationship was corroborated in subsequent X-Ray analyses.

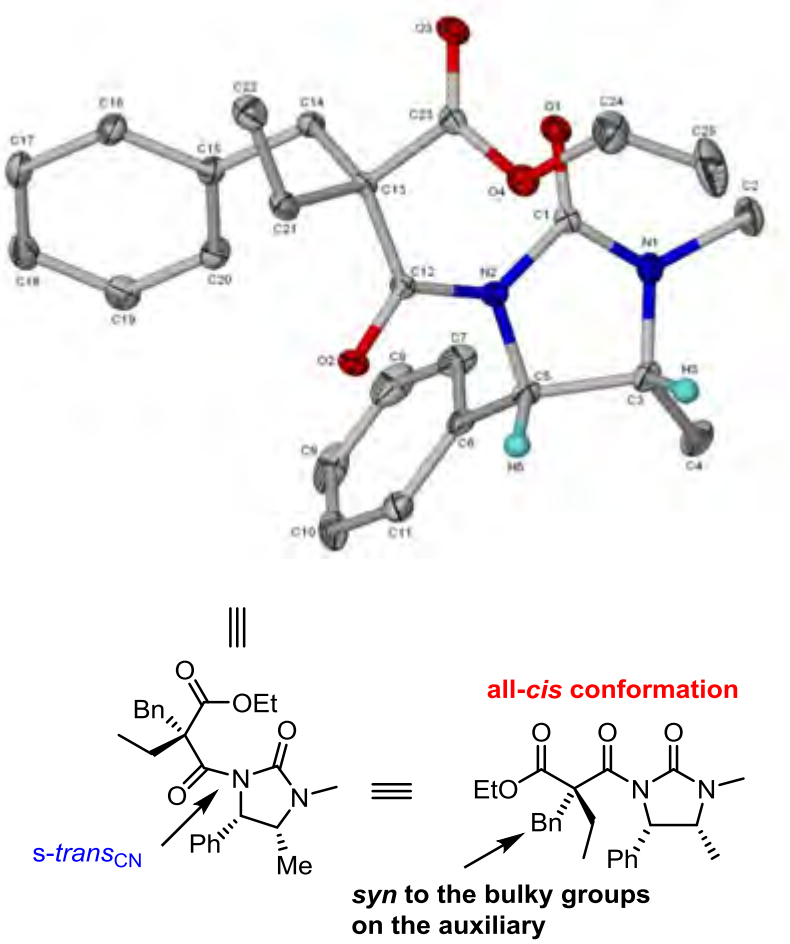


Figure 16 X-ray structure of **2.33b**

2.6.6 Transition state postulation

Information on the origin of the diastereoselectivity can be gleaned from the X-ray structures where the auxiliary is seen to adopt an s-*trans*$_{C\text{-}N}$ conformation, as shown in **Figure 16** for **2.33b.** If one extends this to the transition state and couples it to an electrophile trajectory that is expected to be *anti*- to the bulky phenyl and methyl groups on the auxiliary, one reaches the conclusion that the reaction proceeds via a *Z*-enolate from the *si*-face. This type of enolate configuration could only be possible by potassium chelation into the six-membered malonate hole, which in turn would leave the auxiliary unchelated. However, there is a converse option that could still account for the

observed diastereoselectivity and this would involve an *E*-enolate and the auxiliary in an s-*cis*$_{C\text{-}N}$ conformation, probably with potassium chelated. The two transition state options, **X** and **Y**, are illustrated in **Figure 17**.

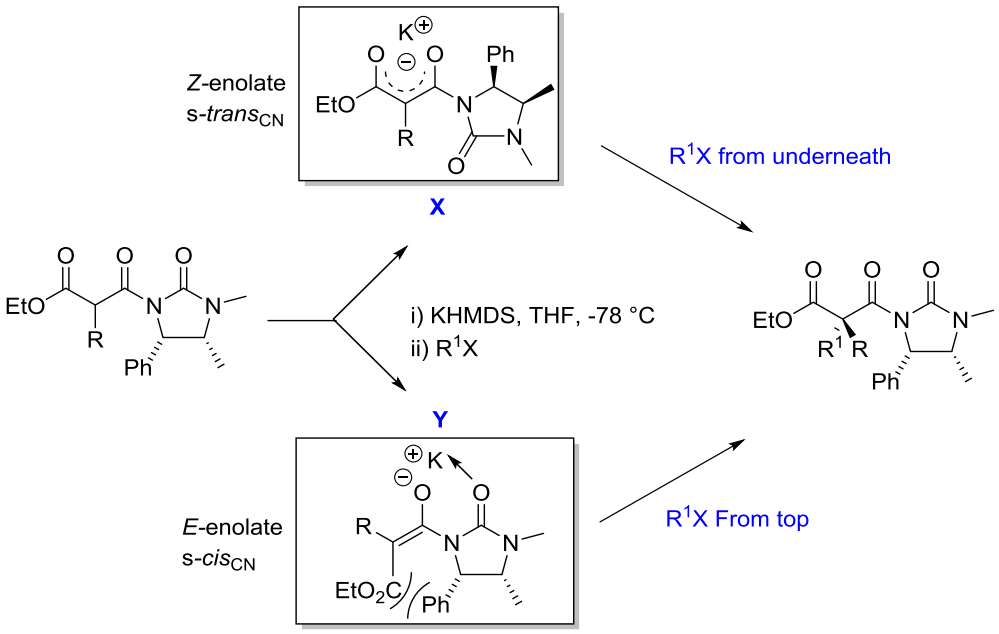


Figure 17 Proposed transition state of quaternization.

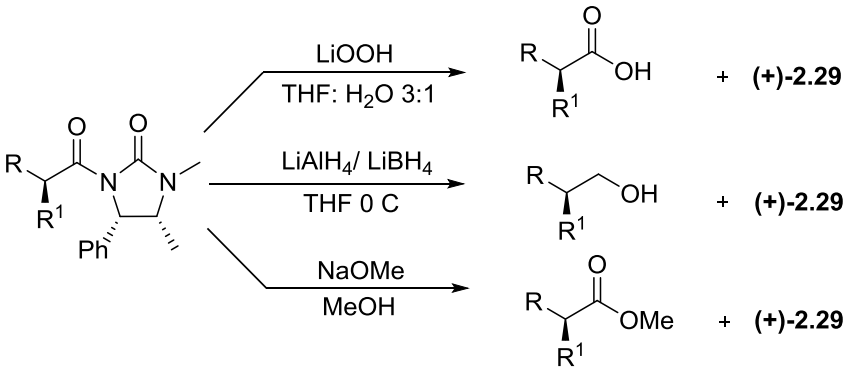
A key piece of information in the appraisal of the relative merits of the two transition state intermediates **X** and **Y** was that with R as Me, no diastereoselectivity was observed but with R as two carbons in size or more a very high diastereoselectivity was observed. This crucial empirical observation was not consistent with the intermediacy of **Y**, since the R group consistently would point away from any point of steric non-bonded interaction with the auxiliary. Conversely, the intermediacy of **X** would allow explanation of the diastereoselectivity by virtue of R = Me allowing rotation of the unchelated auxiliary, so that the 40:60 mixture would be as a result of both s-*cis* and s-*trans* conformers reacting with opposite facial selectivity. Moving to a bulkier R group would then restrict auxiliary C-N rotational movement, locking it into the sterically least demanding s-*trans* conformation (R/CO preferred).

Furthermore, as indicated previously, the fact that only the potassium cation was effective in the reaction also suggests the counter-ion being close to the site of electrophile attack in the form of a *Z*-enolate, since lithium (and to a lesser extent sodium) would be expected to go into the auxiliary hole. The potassium chelation model, with the cation in the malonate hole (via **X**), offers an effective solution to the problem of controlling geometry at the terminus of a disubstituted enolate, except

with one of the groups as an ester. Details of this work can be found in our publication in 2015 in the Journal of Organic Chemistry.[144]

2.7 Transposition of quaternary all-Cs to ATAs

With the successful realization of a stereoselective methodology for construction of all-C quaternary centres, extension to ATAs required a quaternary carboxylic acid as the substrate for the Curtius transposition. Chemoselective auxiliary detachment was targeted for this purpose, and of the methods developed by Evans[130] for the oxazolidinone cleavage and successfully applied by workers to the imidazolidione variant,[47,138,143] only the first one involving saponification with LiOOH was directly applicable in our case, as shown in **Scheme 94**.



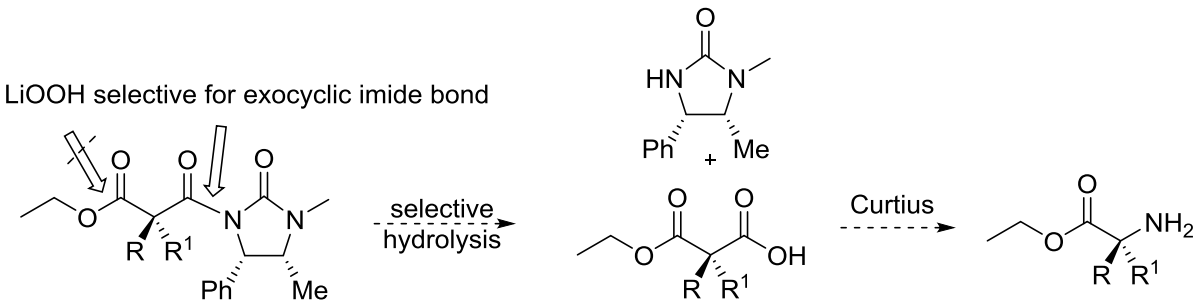
Scheme 94 Known methods for imidazolidinone cleavage

In the all-C quaternization study published in *JOC*,[144] successful chemoselective auxiliary removal was achieved using ten equivalents of lithium ethanethiolate in THF at 40 °C to afford the quaternized ester / thioester. The thioester could then be selectively reduced to the aldehyde using a Fukuyama reduction with Et_3SiH / Pd-C. Hence, with this backdrop, in the present context it appeared that studies initially needed to focus on selective auxiliary removal either via hydrolysis to an ester/acid or to form the ester/thioester product, which would then need to be further selectively hydrolysed. Reductive options were ruled out in view of the need for subsequent re-oxidation. Studies on hydrolytic removal are described next.

2.7.1 Hydrolysis studies on the imide bond

The malonate-imidazolidinone bond was initially targeted for selective hydrolysis based on the premise that the lithium ion of LiOOH would chelate into the imidazolidinone hole, promoting attack by the hydroperoxide anion at the exocyclic carbonyl. This was presumably the basis of the deprotection with the ethanethiolate. In his comparative studies on HOO^- and OH^- reactivity, Wiberg reported that hydroperoxide ion does not react with ethyl acetate, in contrast to its rapid reaction with activated esters such as phenyl benzoate, in which reactivity far exceeds that of hydroxide.[145]

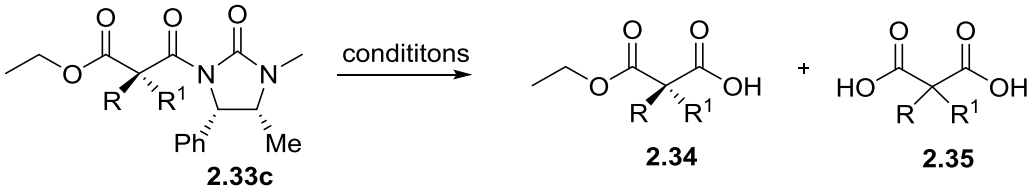
This difference can be rationalized by the more nucleophilic (softer) and less basic nature of the HOO^- ion based on the hyperconjugative α-effect. Later, Evans showed a remarkable chemoselectivity of LiOOH for carboximide hydrolysis in the presence of unactivated esters (benzyl and methyl), albeit in the context of selective oxazolidinone auxiliary cleavage.[146] Although to the best our knowledge no examples existed for chemoselective imidazolidinone cleavage in the presence of esters, it was surmised that similar selectivity effects might manifest as in the unactivated ester-oxazolidinone cases based on the imidazolidinone carbonyl being the softer site. **Scheme 95** shows the strategy formulated for obtaining ATAs and amino acid ester derivatives specifically via a chemoselective hydrolysis of the malonate-imidazolidinone bond.



Scheme 95 Proposed sequence to ATAs entailing a chemoselective hydrolysis with LiOOH

To this end, imidazolidinone cleavage with LiOOH was studied using LiOOH generated by the addition of LiOH (1.6 eq) to a solution of H_2O_2 (4 eq) in a THF/ H_2O mixture (3/1) at 0 °C, followed by subsequent addition of the substrate and warming to rt (**Table 7**, entry 1). Here, no reaction was observed after 24 hours according to tlc, prompting a broader study of temperature, equivalents and solvent. The results are shown in **Table 7**. Under mild conditions and low LiOOH equivalents, no auxiliary cleavage was observed (entries 1 and 2). When equivalents were increased or harsher conditions applied, auxiliary cleavage occurred selectively but in competition with cleavage of both groups to afford the di-acid **2.35**, although still at low conversion (entries 4 to 9). The addition of 2 equivalents of LiCl has been reported to aid the imide bond cleavage but unfortunately this did not have any marked effect on conversion either (entries 4, 5 and 9). Surmising that the congested and relatively hydrophobic environment might be retarding the hydrolysis, the unalkylated auxiliary malonate **2.31** was then committed to a few of the same hydrolysis conditions (a in the Table), and although yields and selectivities were better in these cases, the reaction was still not completely selective nor went to full conversion (entries 12 and 13).

Table 7 Results for the Cleavage of **2.33c** and **2.31** with LiOOH



Entry	R	R^1	Solvent	LiOH (eq)	H_2O_2 (eq)	Temp	Time	Yield 2.34 (%)	Yield 2.35 (%)
1	Bu	allyl	THF/H_2O (3/1)	1.6	4	rt	24h	0	0
2	Bu	allyl	THF/H_20 (3/1)	1.6	4	50	48h	0	0
3	Bu	allyl	THF/H_20 (3/1)	1.6	4	100[a]	24h	18	10
4	Bu	allyl	THF /H_2O (4/1)	1.6	4	50[b]	24h	10	0
5	Bu	allyl	THF /H_2O (4/1)	1.6	4	100[a,b]	24h	15	0
6	Bu	allyl	THF /H_2O (4/1)	3	4	100[a]	24h	12	8
7	Bu	allyl	THF/ H_2O (4/1)	5	10	50	48h	20	22
8	Bu	allyl	THF/ H_2O (4/1)	5	10	50[b]	24h	26	20
9	Bu	allyl	THF/ H_2O (4/1)	1.6	4	150[b,c]	30 min	13	10
10	Bu	allyl	THF/DMF/H_2O (3/3/1)	1.6	4	50	24h	21	0
11	Bu	allyl	THF/DMF/H_2O (3/3/1)	1.6	4	100[a]	24h	32	17
12	H	H	THF/ H_2O (4/1)	1.6	4	50	24h	42	11
13	H	H	THF/ H_2O (4/1)	1.6	4	100[a]	24h	48	23

[a] Reaction carried out in a sealed tube [b] 2 equivalents of LiCl added [c]MW assisted

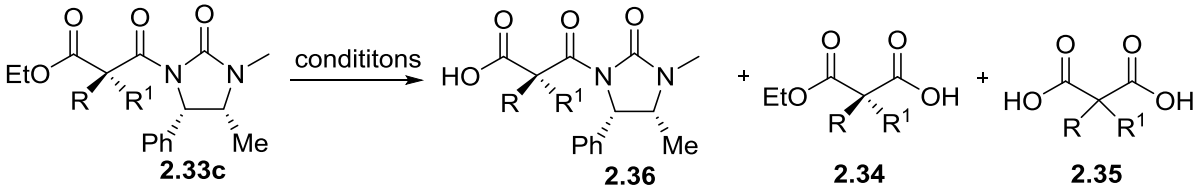
For identification purposes, the products from entry 3 were extractively isolated from the reaction mixture, then chromatographed on a short column and their identity confirmed by ^{1}H NMR spectroscopy. For subsequent reactions, however, only the mono-acid **2.34** was isolated from the column (after extractive work-up) due to the difficulty in recovering the highly polar di-acid from the column. The yield of the di-acid was therefore determined by the weight difference between the acid product mixture and the isolated mono-acid, being reasonably confident of its identity by comparison of the tlc standard obtained previously.

Evidently, apart from hydrophobicity aspects, the electron-releasing nature of the *N*-Me moiety on the auxiliary was reducing the lability of the imide bond and hampering its hydrolysis. Given the lower-than-expected reactivity of the imide bond, it was decided to target the ethyl ester, in the hope that conditions for its chemoselective hydrolysis could be found.

2.7.2 Hydrolysis studies on the ethyl ester

Although less likely to succeed by base mediated hydrolysis, chemoselective cleavage of the ethyl ester was nonetheless attempted in the hope that the less sterically congested environment around the ethyl ester (compared to the malonate-auxiliary region) would lead to preferential reaction at that site. In contrast to the reactivity of the HOO^- ion, shown to be largely unaffected by steric effects,[146] the reactivity of the much larger solvated HO^- ion does follow expected steric-governed trends, and is harder too, which we hoped would be responsive to the ester over the imide. A range of bases were tested under different conditions, starting with the weakly basic LiOH through to KOH, and the results are summarized in **Table 8**.

Table 8 Results of Base Hydrolysis of **2.33c**

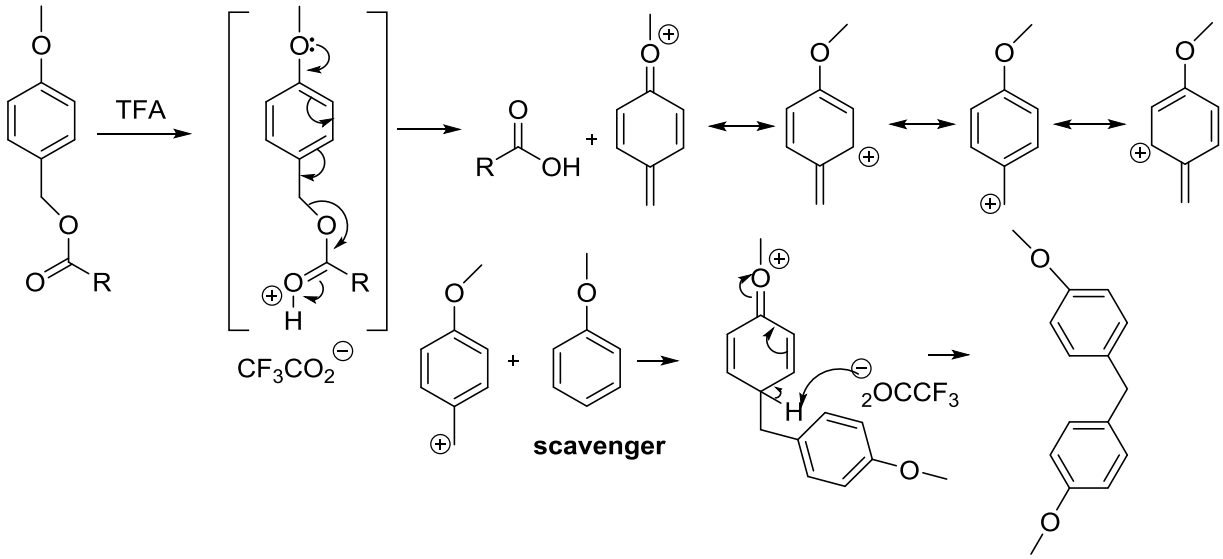


Entry	Base (eq)	Solvent	Temp.	Time	Yield 2.36 (%)	Yield 2.34 (%)	Yield 2.35 (%)
1	LiOH (1.1)	EtOH	rt	48h	0	0	0
2	LiOH (1.1)	EtOH	reflux	24h	0	0	0
3	LiOH (1.1)	EtOH/H_20 (5/1)	reflux	24h	0	0	0
4	NaOH (1.1)	EtOH/H_20 (5/1)	rt	24h	16	0	0
5	NaOH (1.5)	EtOH/H_20 (5/1)	rt	24h	13	0	6
6	NaOH (1.5)	EtOH/H_20 (5/1)	50 °C	24h	24	9	17
7	KOH (1.1)	EtOH/H_20 (5/1)	0 °C	48h	0	0	0
8	KOH (1.1)	EtOH/H_20 (5/1)	rt	48h	11	0	34

Employing LiOH resulted in no cleavage (entries 1, 2 and 3) and although NaOH displayed some selectivity for the ester, yields for the conversion were low (entries 4, 5 and 6). Reactions with KOH were not chemoselective at all and also gave low yields (entries 7 and 8). In these cases, all products obtained from reactions were extractively isolated, chromatographed and identified by ^{1}H NMR spectroscopy.

The low reactivity of the ester bond was again ascribed to the highly congested and hydrophobic environment. Acid hydrolysis was tested briefly, but wasn't pursued further due to the evidence of several side-reactions as well as low conversions. Ultimately, it was concluded that selective

hydrolysis for this particular system was not possible. Re-design of the system was necessary in which the chemoselectivity between the ester and imide was inherent by virtue of an ester cleavage specificity. Of the possible ester candidates, those involving hydrogenolysis such as benzyl esters were not considered as that would preclude the use of unsaturated groups derived from the alkylation. The PMB and *t*-Bu esters were identified as possible candidates as their deprotection is achieved with TFA (no auxiliary cleavage was evident in the preliminary acid hydrolysis reactions.) and follows a different mechanism to hydrolysis. The PMB variant was chosen over the *t*-Bu due to concerns that the bulky *t*-Bu substituent might negatively impact alkylation reactions of the malonate. The TFA-mediated deprotection mechanism of a PMB ester is shown in **Scheme 96.**

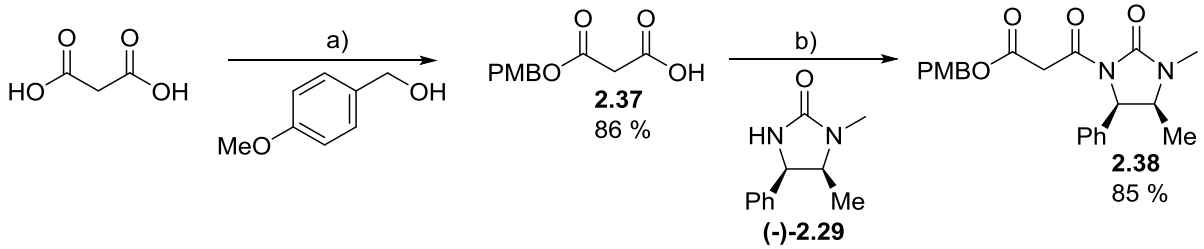


Scheme 96 Mechanism of PMB ester cleavage by TFA.

Unlike acid or base hydrolysis, which requires approach of the OH^- at the congested carbonyl carbon, the fragmentation of a PMB ester is driven by protonation of the ester carbonyl group followed by heterolytic cleavage to afford a resonance-stabilised carbocation. Although the imidazolidinone was deemed to be more Lewis basic it was expected that no further cleavage could ensue. These mechanistic considerations bore fruit in practice. As with the Boc deprotection with TFA, anisole was added as a carbocation scavenger.

2.7.3 PMB ester studies

In order to probe the chemoselectivity of PMB deprotection in a malonate-imidazolidinone system, allyl- methyl-PMB malonate was chosen as a model system. Its synthesis is outlined in **Schemes 97** and **98** using a double DCC condensation strategy.

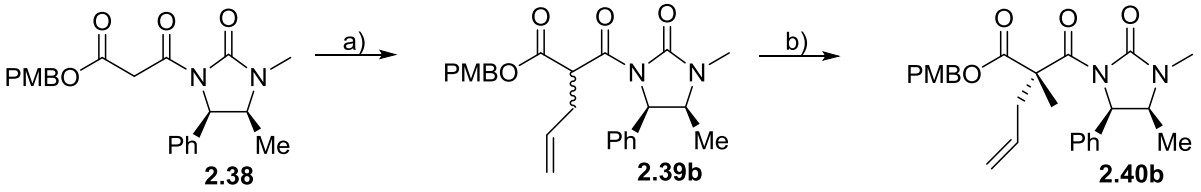


Scheme 97 *Reagents and conditions*: a) DCC, DCM, rt, 2h; b) DCC, BtOH **2.29**, DCM, rt, 12h

The starting point of the sequence was in this case malonic acid, a cheap and readily available reagent. A known procedure was followed for the mono-esterification of malonic acid,[147] adjusted here using DCC and PMBOH with an excess of malonic acid (1.4 eq) to supress diesterification (**Scheme 97**). Pleasingly, the mono-PMB malonic acid could be isolated extractively and its ^{1}H NMR spectrum revealed no further need for purification. A second DCC coupling of auxiliary **(-)-2.29** with mono-PMB malonic acid **2.37** was performed employing the same conditions as in the ethyl ester series, furnishing the auxiliary malonate substrate **2.38** in a yield of 85 % from the mono-acid after chromatography. Owing to the reversal in the order of cleavage (ester vs. auxiliary), in the PMB series the opposite antipode of the auxiliary was employed so as to maintain the correct stereochemistry required for (-)-lepadiformine since the ATA would be generated on the opposite terminus of the malonate.

Formation of the auxiliary-PMB malonate was confirmed by ^{1}H NMR analysis, which showed all the diagnostic signals for the auxiliary: the downfield doublet at 5.28 ppm corresponding to the benzylic auxiliary hydrogen; the singlet integrating for 3 hydrogens at 2.78 ppm arising from the *N*-methyl and the distinctive doublet at 0.76 ppm accounting for three hydrogens assigned to the methyl group of the auxiliary. In addition, 2 new multiplets integrating for 4 hydrogens were now visible in the aromatic region; the downfield singlet at 3.78 ppm was assigned to the methoxy group, while the singlet at 5.09 ppm was assigned to the benzylic hydrogens on the PMB. Although diastereotopic, presumably they were too far away from the chiral imidazolidinone to resolve. Similarly, the diastereotopic malonate methylene hydrogens appeared as a singlet at 3.99 ppm. The ^{13}C NMR spectrum had all the expected resonances, most notably 3 carbonyl resonances (at 167.6, 164.9 and 155.6 ppm).

Alkylation of the auxiliary-PMB malonate system was achieved analogously to the ethyl ester series, using KHMDS to form the anion at -78 °C followed by addition of allyl bromide and warming to rt (**Scheme 98**).



Scheme 98 *Reagents and conditions*: a) i) KHMDS (1.2 eq), THF, -78 °C; ii) allylBr (1.5 eq), warm to rt, 12h; b) KHMDS (1.2 eq), THF, -78 °C ii) MeI (2 eq) warm to rt, 24h.

The monoallylated derivative **2.39b** was isolated in a yield of 97 % after column chromatography and as a 50/50 ratio of diastereomers as expected, **Figure 17** shows the assigned ^{1}H NMR spectrum of **2.39b**. In the ^{1}H NMR spectrum, distinct signal duplication was seen for the hydrogens present on the auxiliary (H-4', H-5', H-6' and N-Me), as well as for the diastereotopic PMB methylene hydrogens (H-6), which appeared as two sets of AB doublets (5.15 and 5.05 ppm); the PMB methoxy singlets were also duplicated (3.83 and 3.82 ppm). In addition, the H-2 singlet of **2.38** which had resonated at 3.99 ppm, now shifted downfield and appeared as two dd sets (only one discernible at 4.85 ppm) corresponding to 1H in total by integration.

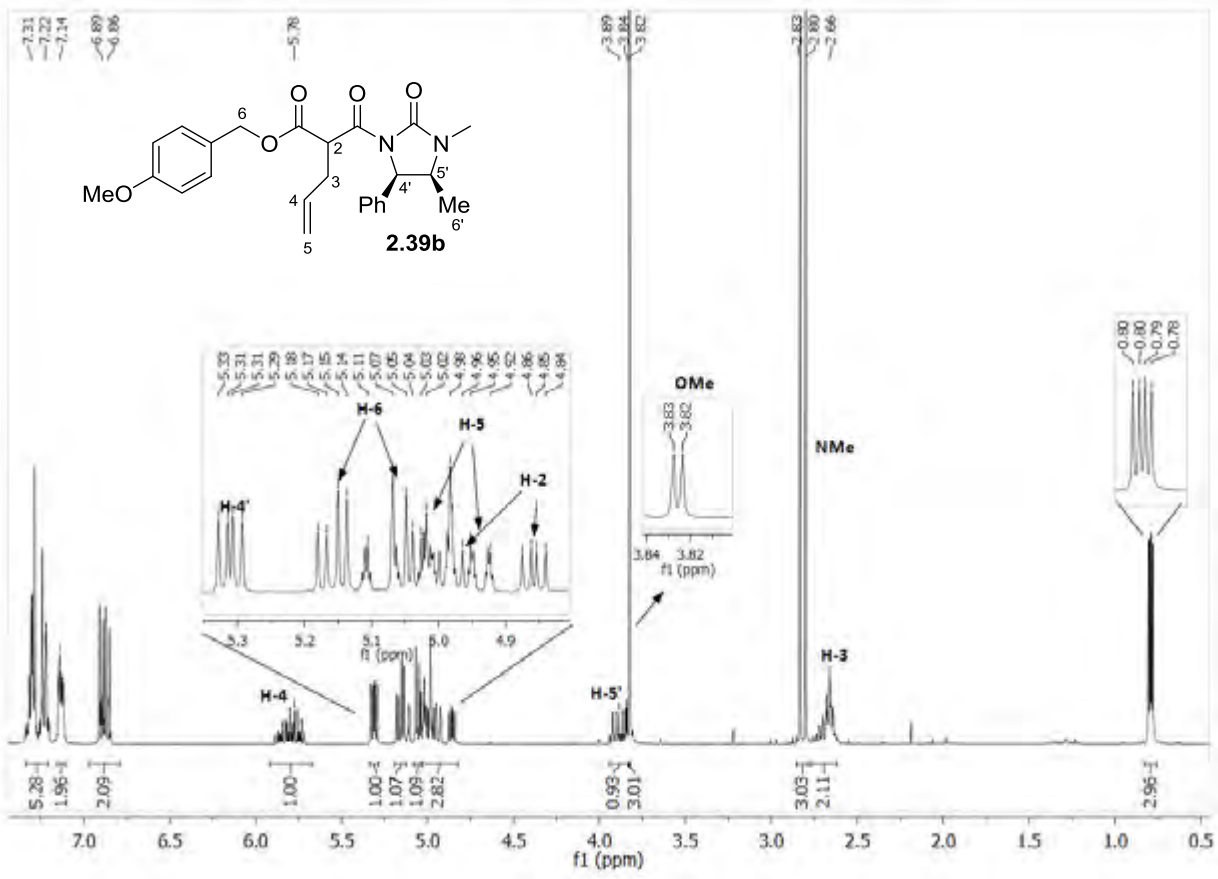


Figure 17 Assigned ^{1}H NMR spectrum of **2.39b**

The reactivity of the system towards quaternization was unchanged when compared to the ethyl ester series and proceeded smoothly with methyl iodide as the alkylating agent to furnish the quaternized derivative **2.40b** in a yield of 90 % after purification (**Scheme 98**). While the signals for the PMB methoxy, the NMe, H-4', H-6, H-5 and H-6' were all clearly duplicated in the ^{1}H NMR spectrum (shown in **Figure 17**) of the mono-allylated derivative, no discernible duplication for these signals was observed for the quaternized product. The new methyl singlet resonated at 1.47 ppm, and the notable absence of H-2 was a definite indicator of the second group installation. The assigned ^{1}H NMR spectrum of **2.40b** is shown in **Figure 18**. HPLC analysis indicated a dr ratio of 98:2, see **Figure 19**.

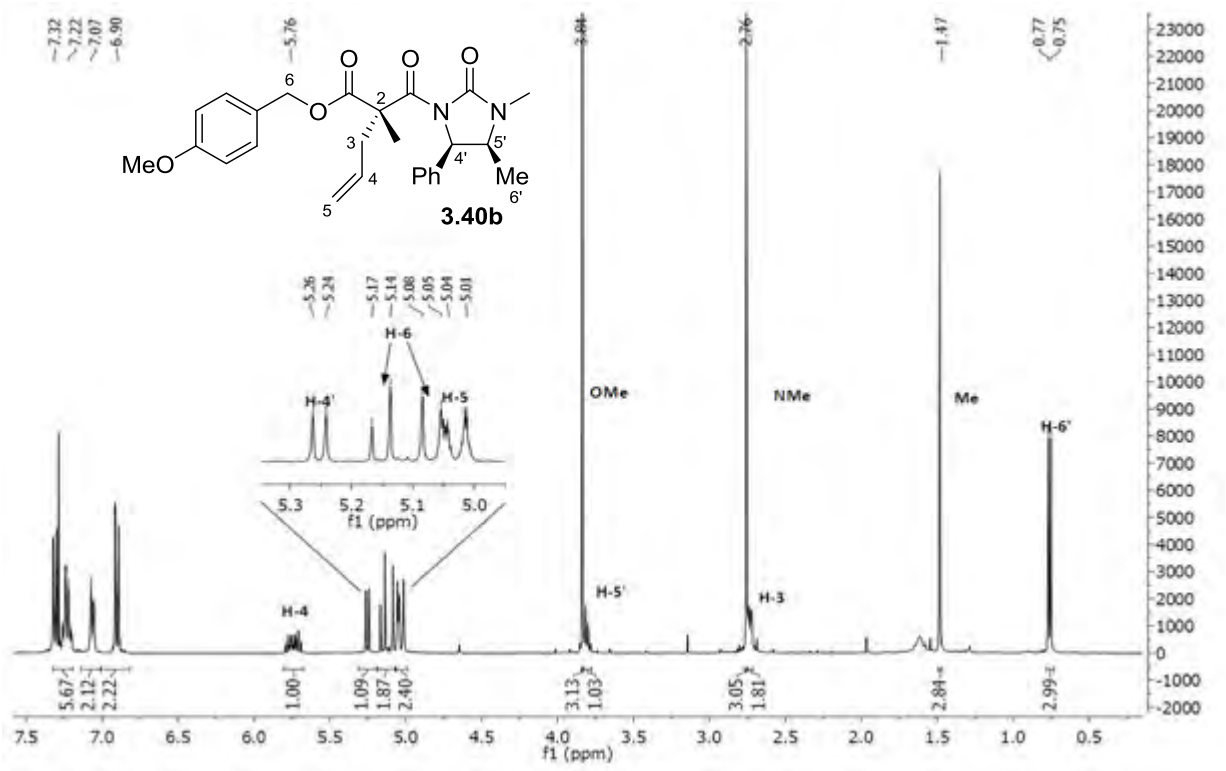


Figure 18 Assigned ^{1}H NMR spectrum of **3.40b**

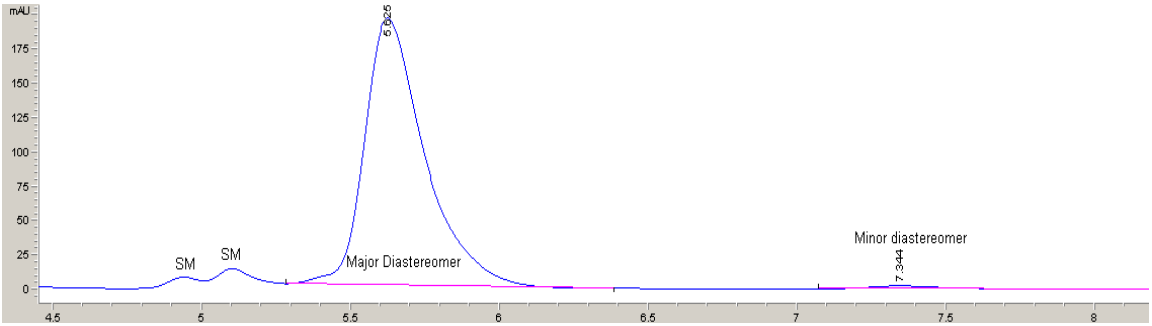


Figure 19 HPLC trace for compound 3.40b

2.7.4 Chemoselective PMB ester cleavage

A reported procedure for PMB ester removal with TFA[148] was applied to **2.40b** involving anisole (1.1 eq) as carbocation scavenger at rt (**Scheme 99**). The reaction was followed by tlc, which required neutralization of the TFA in the tlc aliquot with aqueous $NaHCO_3$ for easy visualization, noting complete consumption of starting material after 3 hours.

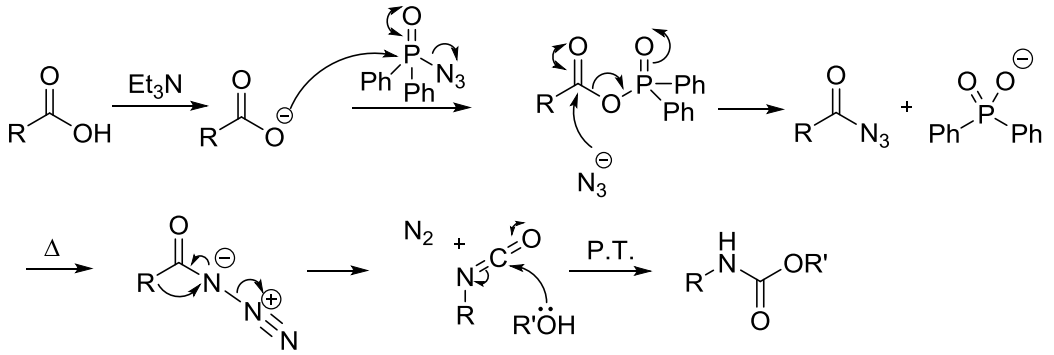
2.40b **2.41b** 98 %

Scheme 99 TFA catalysed PMB ester cleavage

Following the removal of solvent and excess TFA, the product was isolated by acid-base extraction, which produced acid **2.41b** of sufficient purity for characterization. No auxiliary cleavage was observed under these conditions and the yield of the acid was virtually quantitative (98 %). The IR absorption spectrum showed a distinctive broad OH absorbance at 3431 cm^{-1}. The aromatic region of the ^1H NMR spectrum integrated for only 5 hydrogens for the auxiliary phenyl; in addition, the benzylic AB doublets of the PMB group were absent as well as the methoxy singlet, all of which confirmed the loss of the PMB. A new, very broad singlet appeared at 5.45 ppm, corresponding to the carboxylic acid hydroxyl. This is surprisingly highfield for this type of signal and probably reflects intermolecular hydrogen bonding in $CDCl_3$. All other peaks were essentially unchanged when compared to the PMB ester precursor.

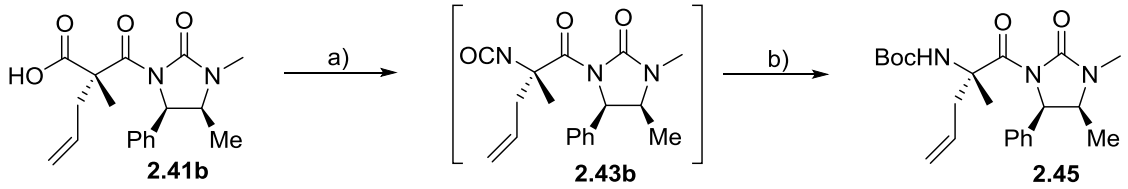
2.7.5 Curtius Rearrangement Optimization

With a dependable methodology for generating non-racemic quaternary malonate half-esters, the stage was set for transformation to the ATAs via Curtius rearrangement. Following the literature on this well-established reaction, a one-pot procedure was investigated, involving conversion to the acyl azide with diphenyl phosphoryl azide (DPPA) followed by *insitu* thermal Curtius rearrangement and trapping out of the isocyanate with *t*-BuOH to furnish the Boc-protected amine. The mechanism of the reaction is shown in **Scheme 100**. Deprotonation of the acid by Et_3N generates a carboxylate which substitutes the phosphoryl azide with expulsion of N_3^-. The azide ion then carries out a S_NAc reaction onto the carbonyl of the phosphorylated acid which results in the formation of the acyl azide and diphenylphosphate ion. The concerted rearrangement from the acyl azide to the isocyanate is heat driven, releasing N_2 gas in the process. Finally, nucleophilic addition to the isocyanate with *t*-butyl alcohol gives the *N*-Boc carbamate. Ureas can similarly be prepared by intercepting the isocyanate with amines.



Scheme 100 The Curtius rearrangement mechanism with alcohol interception of the isocyanate

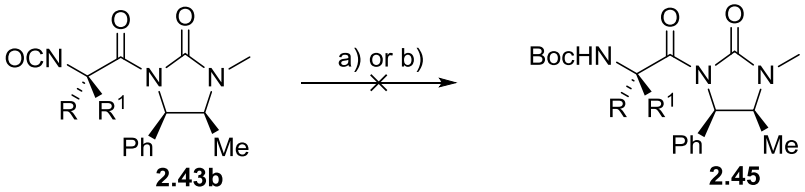
A typical procedure entailed the addition of Et_3N to a solution of **2.41b** in toluene, followed by DPPA and refluxing for several hours until complete consumption of the acid was observed. *t*-BuOH was then added and the reflux continued (**Scheme 101**).



Scheme 101 *Reagents and conditions*: a) Et_3N (2.5 eq), DPPA (1.2 eq), toluene, reflux; b) *t*-BuOH (5 eq), reflux

Several attempts under various conditions were made in this direction but the carbamate product **2.45** could not be detected, the isocyanate **2.43b** being the only product isolated in yields of 40 – 50 %. As expected, the ^{1}H NMR spectrum of **2.43** looked very similar to that of **2.41b**, apart from the disappearance of the broad carboxylic OH peak at 5.45 ppm. The absence of a *t*-Bu singlet in the 1 -2 ppm region, excluded formation of the Boc- protected derivative. The carbonyl peak in the ^{13}C NMR spectrum of **2.43b** also displayed the expected shift from 171.1 ppm (acid) to 125.3 ppm (isocyanate). Confirmation of rearrangement was provided by the IR spectrum in which a medium, sharp absorption band at 2253 cm^{-1} for the N=C=O stretch was taken as indicative of isocyanate formation (azides typically give rise to absorptions closer to 2140 cm^{-1}). In an attempt to improve yields and scrutinise the reaction, the intermediate acyl azide was allowed to form first at room temperature in which the formation of a product spot with an increased rf on the tlc, indicated acyl azide formation from the acid; once all of the acid had been consumed, reflux conditions were applied. As the reaction progressed, consumption of the acyl azide spot was seen, reciprocated by steady formation of isocyanate **2.43b** as judged by tlc. Addition of *t*-BuOH to this reaction mixture, once again resulted in no carbamte formation and the yield of the isocyanate did not improve (43 % after column chromatography). **2.43b** was a stable crystalline solid, easily withstanding aqueous work-up and column chromatography, which indicated a low reactivity, mirroring the setbacks

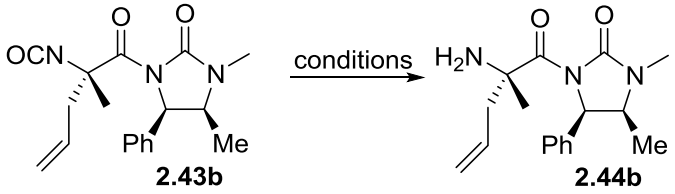
experienced with hydrolysis/ auxiliary cleavage. Again, this was not surprising, as Curtius rearrangements in sterically crowded environments of quaternary systems are often problematic, sometimes requiring the use of stronger nucleophiles to intercept the isocyanate. To examine whether such an approach might bear fruit, a 1M solution of lithium *tert*-butoxide was prepared by treating dry *t*-BuOH with *n*-BuLi at 0 °C. Addition of 1.1 equivalent of *t*-BuOLi to a solution of isocyanate **2.43b** in THF did not result in carbamate formation but rather led to a few side reactions. Another way to increase reactivity in these systems is with Lewis acid activation, in which titanium tetra-*t*-butoxide (Ti(O*t*-Bu)$_4$) has been reported as an efficient catalyst for the reaction of hindered isocyanates and alcohols. This method was tested, whereby the isocyanate **2.43b** was refluxed with 1.5 equivalents of *t*-BuOH and Ti(O*t*-Bu)$_4$ (0.1 eq). However, no change in the starting material was seen after 24 hours. Over the following 24 hours, another 3 equivalents of *t*-BuOH were added in half-equivalent increments, but still no significant amount of isocyanate conversion was observed (**Scheme 102**). Several runs with increased equivalents of the Lewis acid were also performed but conversion to **2.45** could not be accomplished.



Scheme 102 *Reagents and conditions*: a) *t*-BuOLi, THF, 0 °C to rt; b) *t*-BuOH (1.5 to 4.5 eq), Ti(O*t*-Bu)$_4$ (0.1 to 0.5 eq), toluene, reflux.

The protocol developed by Lebel and co-workers in 2005,[149] whereby a combination of tetrabutylammonium bromide (Bu_4NBr) and $Zn(OTf)_2$ was used to catalyse the carbamate formation, was also considered on paper, but despite the method having the advantage of being a mild one-pot procedure (starting from the acid), the mediocre yields reported for quaternary malonates (60-75 %) were deemed unsatisfactory and thus the protocol was not tested. Instead a step-wise sequence involving hydrolysis of the isocyanate to the corresponding amine under various hydrolysis conditions was adopted, from which a standard Boc protection could presumably be performed. The findings are summarized in **Table 9**.

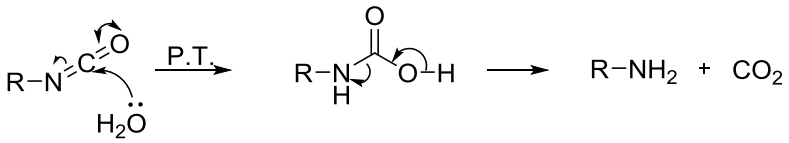
Table 9 Optimization of Isocyanate to Amine Hydrolysis Conditions



2.43b **2.44b**

Entry	Solvent	Temperature	Yield 2.44b (%)
1	H_2O	Rt to reflux	0
2	H_2O/ THF	Rt to reflux	0
3	H_2O/ Toluene	Rt to reflux	0
4	H_2O/ ACN	Rt to reflux	0
5	ACN/ aq. NaOH	Rt to 40 °C	10 and decomp.
6	ACN/ 1 M HCl	Rt	20
7	ACN/ 5 M HCl	60 °C	90

Generally, isocyanates are known to decompose in aqueous systems via the carbamic acid intermediate, which gives rise to the free amine following a spontaneous decarboxylation (**Scheme 103**).



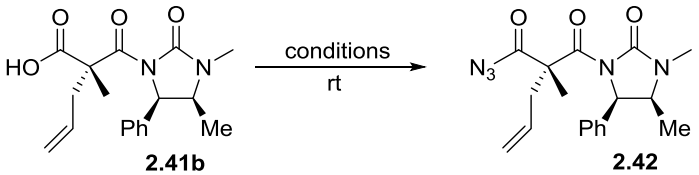
Scheme 103 Decomposition of isocyanates upon reaction with water.

Surprisingly, refluxing **2.43b** in water returned no free amine even when water-miscible solvents were added to achieve homogeneity (entries 1 to 4). This gave definitive proof of the extreme hydrophobic environment around the grouping. Base hydrolysis was also tested but resulted mostly in unwanted side-reactions (entry 5). Fortunately, heating **2.43b** in a mixture of acetonitrile and 5M aqueous HCl gave a clean conversion to the amine **2.44b** which could be extractively isolated in a yield of 90 %. Evidently, such harsh conditions were required in order to overcome the steric congestion and hydrophobicity around the isocyanate. Importantly, the imide bond remained intact. Evidence for the formation of the amine was given by ^{1}H NMR spectroscopy, with the appearance of an exchangeable broad singlet at 2.25 ppm arising from the NH_2. The diagnostic NH_2 stretch at 3392 cm^{-1} corroborated the assignment. All auxiliary, allyl and methyl signals in the ^{1}H and ^{13}C NMR spectra were essentially unchanged compared to the isocyanate precursor.

Next, the consistently low yields for the rearrangement were addressed. Suspecting that the presence of several by-products from acyl azide formation as well as some unreacted DPPA may

have resulted in side-reactions at the high temperatures needed for the rearrangement, it was deemed prudent to carry out a stepwise procedure and isolate the acyl azide prior to the thermal rearrangement. There was some concern over whether the acyl azide could withstand column chromatography, however, but the high stability of the isocyanate led us to believe that the acyl azide might behave similarly. The results of the study are shown in **Table 10**.

Table 10 Optimization of Reaction Conditions for Acyl Azide Formation

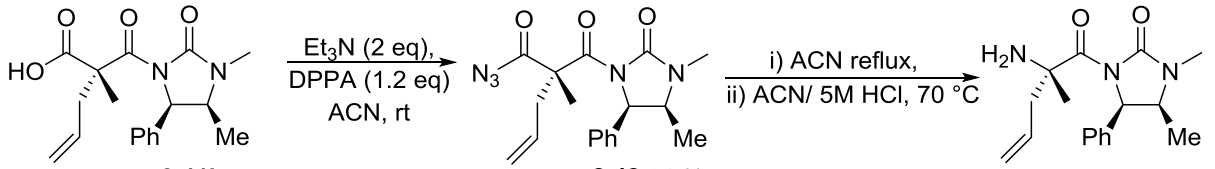


2.41b **2.42**

Entry	Solvent	Eq Et_3N	Eq DPPA	Isolated Yield 2.42 (%)
1	Toluene	1.2	1.2	42
2	Toluene	1.8	1.2	48
3	THF	1.8	1.2	50
4	CH_3CN	1.2	1.2	66
5	CH_3CN	1.2	1.5	50
6	CH_3CN	2.0	1.2	91

All reactions done at rt.

At first, yields of **2.42** (from column chromatography) were low but eventually optimal conditions were established; CH_3CN was the best solvent and highest yields were obtained with 2 equivalents of Et_3N. Because treatment of the acid with Et_3N converts it to the triethylammonium salt, direct tlc analysis was not possible to determine if all of the acid had been converted to the acyl azide due to the presence of excess Et_3N and the diphenylphosphate ion by-product, all of which appeared close to the tlc baseline. Thus, an acidic mini-work up with ethyl acetate was performed on aliquots of the reaction mixture in order to visualize the acid and follow the reaction. For isolation purposes, no work up was carried out and the acyl azide was purified directly by flash chromatography in a yield of 91 %. Thermal rearrangement of the purified acyl azide in refluxing ACN resulted in complete conversion to the isocyanate **2.43b** (evidenced by tlc). At that point, hydrolysis to the amine was performed without isolation of the isocyanate using the optimized conditions established earlier. Acid-base extraction was a favourable way to isolate the amine, which was achieved in an overall yield of 88 % from the acid **2.41b**, vindicating the purification step (**Scheme 104**).



2.41b **2.42** 91 % **2.44b** 85 %

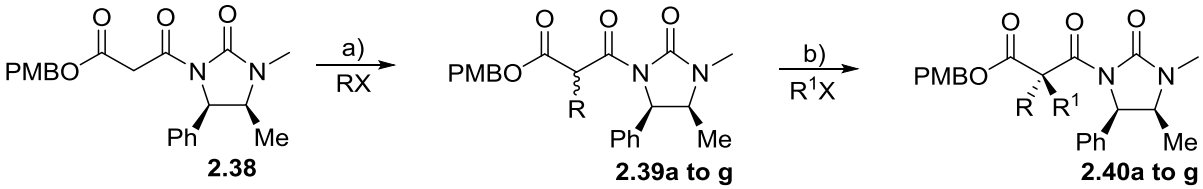
Scheme 104 Modified Curtius rearrangement/ hydrolysis protocol

2.7.6 Reaction scope of the PMB malonate-auxiliary system

Encouraged by this result, a further six quaternized analogues were synthesized according to the sequential alkylation procedure, and the results are shown in **Table 11**. The nature of the R group introduced was determined by the choice of the α,α-disubstituted amino acid target ultimately (after auxiliary removal), in which the emphasis was on the production of quaternized naturally occurring ones. Here, one of the R groups had to be either the amino acid side chain itself (entries 1 and 2), or be able to generate the side chain in question by virtue of manipulation post rearrangement (entries 3 and 4). Where applicable, the target amino acid for respective derivatives is included in the Table for clarity. Compound **2.40f**, entry 6 was designed as a precursor for the lepadiformine sequence. The alkyl halides for compounds **2.40c** and **d** required synthesis, which will be covered in the section relevant to their application.

Excellent yields and selectivities (determined by HPLC) were obtained for all 6 derivatives following column chromatography. All ^{1}H NMR spectra of the quaternized products contained the familiar auxiliary resonances, as well as the characteristic AB doublets of the diastereotopic benzylic hydrogens on the PMB (5.15 and 5.05 ppm regions, with a *J* value of 13 Hz) and the signals associated with the tether in question.

Table 11 Scope of sequential di-alkylation of PMB malonate-auxiliary **2.38**



Entry	Compound	R	R^1	Isolated Yield (%)[a]	dr[b]	Target
1	**2.40a**	Bn	Me	95	98:2	Methyl-phenylalanine
2	**2.40b**	Allyl	Me	94	98:2	Allyl-alanine
3	**2.40c**	$(CH_2)_4N_3$	Allyl	90	98:2	Allyl-lysine
4	**2.40d**	$(CH_2)_3OBn$	Bn	94	97:3	Benzyl-Proline
5	**2.40e**	Et	Allyl	92	94:6	N/A
6	**2.40f**	$(CH_2)_3OBn$	Allyl	96	98:2	Lepadiformine precursor
7	**2.40g**	Bn	Allyl	94	96:4	Allyl-phenylalanine

[a] Over two steps; [b] determined by HPLC

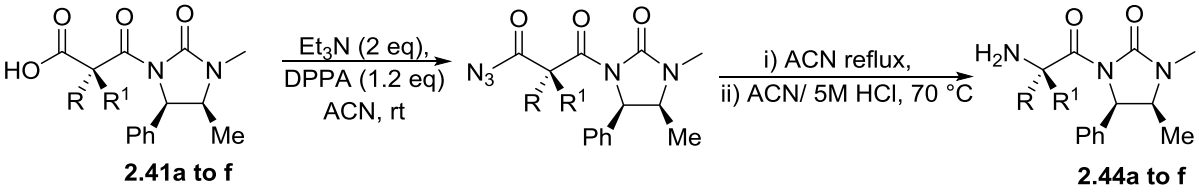
Applying the TFA-catalysed PMB deprotection conditions to analogues **2.40a** to **f** reproduced high yields in every case (**Table 12**). The ^{1}H NMR spectra of all the acids showed the expected loss of signals associated with the PMB group, and featured a broad singlet in the region between 5 and 6 ppm for the carboxyl hydrogen.

Table 12 PMB Deprotection Results for Derivatives **2.40a** to **g**

Entry	Compound	R	R^1	Yield (%)
1	**2.41a**	Bn	Me	95
2	**2.41b**	Allyl	Me	94
3	**2.41c**	$(CH_2)_4N_3$	Allyl	86
4	**2.41d**	$(CH_2)_3OBn$	Bn	91
5	**2.41e**	Et	Allyl	95
6	**2.41f**	$(CH_2)_3OBn$	Allyl	98

Next, the modified Curtius rearrangement/ hydrolysis protocol was applied to acids **2.41a** to **f** via a purified acyl azide as described previously, which gratifyingly furnished ATAs **2.44a** to **f** in high yields following extractive work-up procedures (**Table 13**). Yields for the three-step sequence were consistently high overall, with approximate yields (in order) of 85 %

Table 13 Results of the Modified Curtius Procedure to Generate ATAs **2.44a** to **f**



2.41a to f **2.44a to f**

Entry	Compound	R	R^1	Yield (%)[a,b]
1	**2.44a**	Bn	Me	79
2	**2.44b**	Allyl	Me	88
3	**2.44c**	$(CH_2)_4N_3$	Allyl	86
4	**2.44d**	$(CH_2)_3OBn$	Bn	87
5	**2.44e**	Et	Allyl	86
6	**2.44f**	$(CH_2)_3OBn$	Allyl	90

[a]Final yield over two steps from the acid; [b]Extractive isolation

The ^{1}H NMR spectra of the amine products showed a characteristic NH_2 broad singlet peak in the 2.20 ppm region, which was corroborated by the presence of broad absorbance stretches in the 3400 cm^{-1}region in the IR spectra. Similarly, the distinctive isocyanate absorption stretch at 2253 cm^{-1} had disappeared. There was no discernible duplication of signals in the spectrum, suggesting that the rearrangement and hydrolysis had proceeded without epimerization of the products. This preliminary assumption was satisfactory at that point as *ee*s would be assessed by chiral HPLC on the final products after removal of the auxiliary. Although this modified Curtius route to amines from carboxylic acids was a three-step sequence, the need for only one flash column and the high yields obtained compensated for the additional operations.

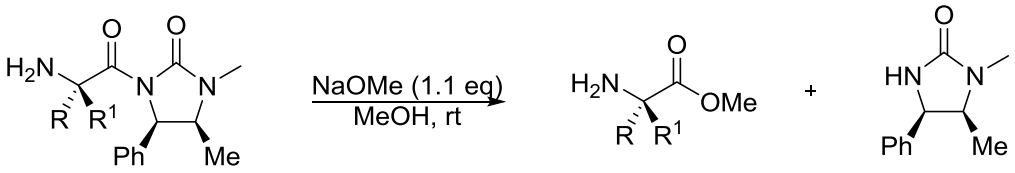
2.8 Generation of α,α-disubstituted amino acids

2.8.1 Quaternary alanines

The successful diastereoselctive assembly of a targeted range of ATAs provided entry into enantioselective production of α,α-disubstituted amino acid esters via a transesterification auxiliary cleavage reaction. The known transesterification using 1.1 equivalent of 1M MeONa in MeOH at 0 °C was applied to compounds **2.44a** and **b** bearing methyl as the R^1 group (**2.40g** was not elaborated further). Since no reaction progress was evident at this temperature, the reaction was allowed to warm up to rt. Reaction times varied form half an hour to 3 hours, and following aqueous work-up

and a flash column generated α,α-disubstituted amino acid esters **2.46a** and **2.46b** in good yield, as well as recovered auxiliary (80 – 89 % yield). The results are summarized in **Table 14**.

Table 14 Methanolysis of ATAs **2.44a** and **b** to Generate Quaternary Alanines

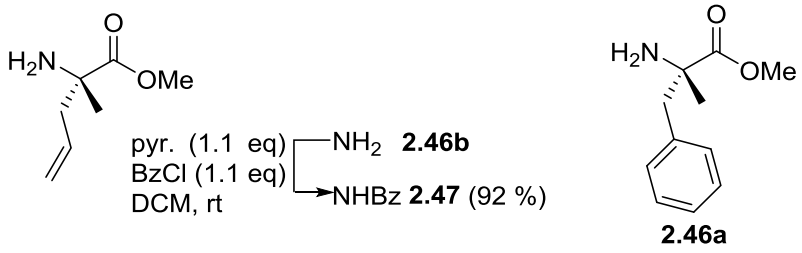


2.44a and b **2.46a and b** **(-)-2.29**

Entry	Compound	R	R^1	Isolated Yield (%)	ee[a] (%)
1	**2.46a**	Bn	Me	79	94
2	**2.46b**	Allyl	Me	76	96[b]

[a]Determined by chiral HPLC; [b]*ee* of the NH-Bz derivative **2.47**

(*S*)-α-Allyl-alanine methyl ester and (*S*)-α-methyl-phenylalanine methyl ester were obtained in 79 and 76 % yield respectively. The absolute configuration was assigned as S based on previously observed selectivities in the quaternization. (*S*)-α-Allyl-alanine methyl ester **2.46b** was benzoylated for the purposes of HPLC detection by reaction with pyridine and BzCl in DCM (**Fig. 20**). Both quaternary alanines were fully characterized, and their data correlated with reported values, confirming the assignment of absolute stereochemistry as (S). For **2.47**: $[\alpha]_D^{20}$= +9.80°, ($CHCl_3$, *c* = 1), [lit.[150] $[\alpha]_D^{20}$ = +9.74° ($CHCl_3$, *c* = 1.0)]. For **2.46a**: $[\alpha]_D^{20}$= -8.9°, ($CHCl_3$, *c* = 0.67), [lit.[151] $[\alpha]_D^{20}$= -14.1° ($CHCl_3$, *c* = 1.6)]

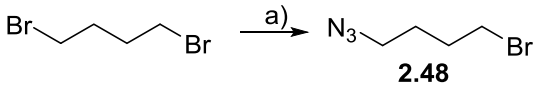


(S)-α–allylalanine methyl ester **2.46a** (*S*)-α-methylphenylalanine methyl ester

Figure 20 Quaternary alanines

2.8.2 α,α-Disubstituted lysine

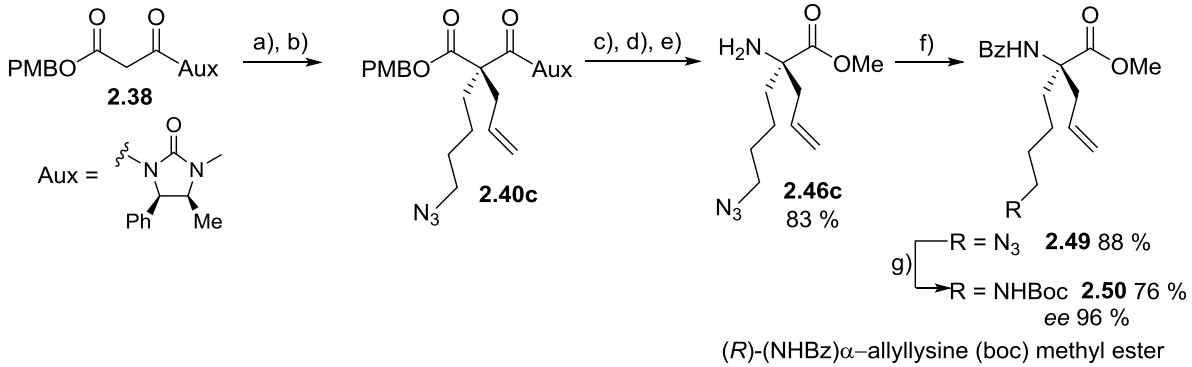
The lysine side-chain comprises a 4-carbon unit with a primary amine terminus. As a precursor to the side chain, a four-carbon unit terminating with an azide was chosen as the substituent on the malonate, the amine expected to be accessible via reduction of the azide. This was preferred to other *N*-protected moieties such as a phthalimide (this would require strong nucleophilic conditions for deprotection).The requisite electrophile, 1-azido-4-bromobutane, was generated from the azidation of 1,4-dibromobutane, according to a known procedure outlined in **Scheme 107**.



Scheme 107 *Reagents and conditions*: a) NaN_3 (3 eq), DMF, 50 °C

Yields for the conversion were low within the 20 % range but did at least correlate with those quoted in the literature of 22 %.[152] The yield was improved to 30 % by increasing the number of equivalents of NaN_3 from 1.5 to 3 and using freshly distilled 1,4-dibromobutane, although raising the number of equivalents of NaN_3 above 3, as well as increasing the temperature did not result in higher yields. Separation of the unreacted 1,4-dibromobutane from the product was problematic, primarily because of the similarity in rf and difficulty in visualization of the spots on tlc, and it was imperative that **2.48** not be contaminated with 1,4-dibromobutane as this would lead to unwanted side-products in the alkylation step and a loss of valuable material. However, careful chromatography using a low polarity MeOH/ DCM (2/98) solvent system and employing CAN spray for visualization made product isolation possible.

With the desired four-carbon tether featuring an azide terminus in hand, sequential dialkylation, deprotection and Curtius rearrangement/ hydrolysis was performed as discussed in the previous sections, furnishing the ATA methyl ester **2.46c**. (**Scheme 108** shows the complete sequence from the auxiliary malonate to the α-allyl lysine derivative as an *N*-benzoate).



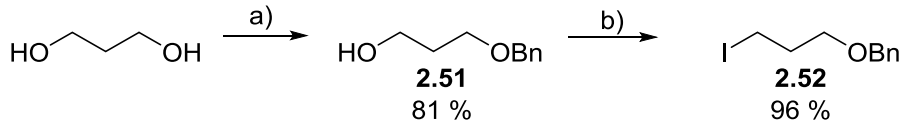
Scheme 108 *Regents and conditions*: a) i) KHMDS (1.2 eq), THF, -78 °C; ii) **2.48** (1.5 eq), warm to rt, 12h; b) KHMDS (1.2 eq), THF, -78 °C ii) AllylBr (2 eq) warm to rt, 24h; c) TFA (6 eq), anisole (1.1 eq), DCM, rt, 3 h; d) i) Et_3N (2 eq), DPPA (1.2 eq), ACN, rt; ii) ACN reflux 4h, then 5M HCl, 70 °C; e) NaOMe (1.1 eq), MeOH, rt, 2h; f) BzCl (1.1 eq), pyr (1.2 eq), DCM, rt; g) $P(Ph)_3$ (2 eq), THF/H_2O (6:1), rt, 9h, then Boc_2O (2 eq) rt, 15 min.

The amine of ATA **2.46c** was protected with a benzoyl group using benzoyl chloride and pyridine in DCM to give the Bz protected amino acid methyl ester **2.49** in a yield of 88 % after chromatography. The Bz group was again chosen due to its ability to impart UV activity to the molecule for analytical purposes (HPLC). No broad singlet at 2.79 ppm in the product corresponding to the NH_2 was visible in the ^1H NMR spectrum, the NH giving rise to a new amide downfield singlet at 7.15 ppm. Resonances in the aromatic region both in the ^1H and ^{13}C NMR spectra were a definitive indicator of

the presence of the benzoyl group. Reduction of the azide to the amine needed to be performed next and a number of methods exist for this transformation. In analogous work done by colleagues in the research group, quaternary azides were cleanly reduced to ATAs using a Zn/NH_4Cl protocol. Naturally, this was attempted first but did not give clean conversions, persistently forming several side-products. The Staudinger reaction with *in situ* Boc-protection of the resultant amine was then considered as an attractive alternative. In the Staudinger reaction, the PPh_3 reacts with the azide to form a phosphazide, which upon loss of N_2 gas generates an iminophosphorane. Aqueous work up furnishes the amine and phosphine oxide. When a mixture of THF and water are used as solvent, the amine is generated without work-up and Boc anhydride can be added for *In situ* protection. Reaction of **2.49** with two equivalents of PPh_3 in THF/H_2O (6:1) at rt for 9 hours pleasingly revealed a very polar product on the tlc plate, and once the azide had been fully consumed, 2 equivalents of Boc_2O were added, which resulted in full conversion to a much less polar spot within 15 minutes. Following chromatography the diprotected α-allyl-lysine methyl ester **2.50** was isolated in a yield of 76 % after chromatography. The *t*-Bu singlet of the Boc integrating for 9 hydrogens was visible at 1.33 ppm and the broad singlet at 4.49 ppm was assigned to the Boc-protected NH. In addition, a new carbonyl resonance arising from the Boc C=O appeared at 156.1 ppm in the ^{13}C NMR spectrum. The er of the final product was determined by chiral HPLC as 98:2.

2.8.3 α,α-Disubstituted proline

The tether chosen as a precursor for quaternary proline was a three-carbon chain unit with a protected hydroxyl terminus. A benzyl group was selected for this purpose but of course this would be incompatible with any unsaturated R group at the quaternary centre. Obtaining proline via this substituent would entail a ring closing reaction between the amino group of the amino acid. The requisite alkyl halide was synthesised in simple, high yielding steps as shown in **Scheme 105**. Monoprotection of the hydroxyl group was carried out using sodium hydride and benzyl bromide. In order to achieve high yields, an excess (2 equivalents) of 1,3- propane diol was used together with an inverse addition of NaH, i.e. the NaH was added in small portions to the solution of the diol in THF at 0 °C over a period of 30 minutes in order to minimize dianion formation. After another 30 minutes at rt, benzyl bromide was syringed into the reaction, which was refluxed overnight. Isolation by chromatography furnished **2.51** in a yield of 81 %. ^1H NMR spectral data was the same as that reported in the literature.[153]

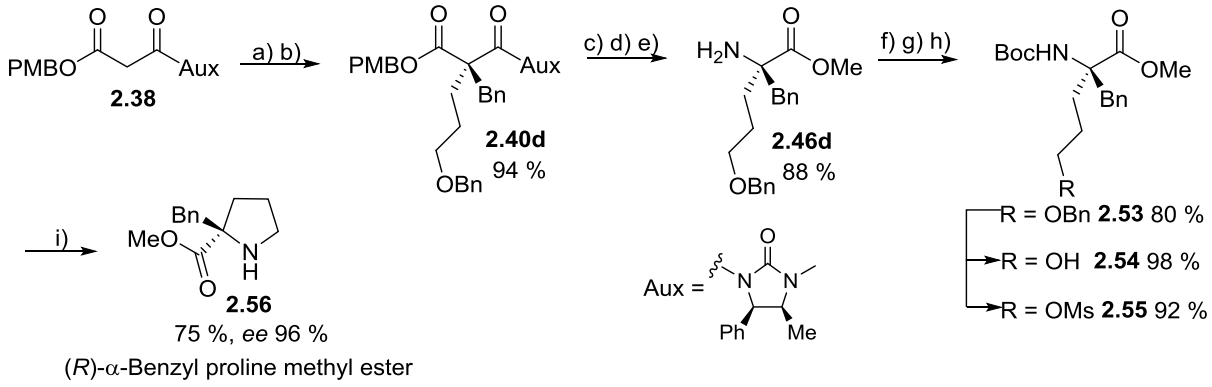


Scheme 105 *Reagents and conditions*: a) NaH (0.5 eq), THF 0 °C, then BnBr (0.5 eq), reflux; b) PPh_3(1.3 eq), imidazole (1.3 eq), I_2(1.3 eq), toluene, rt, 12h.

An Appel reaction was then employed for converting the remaining hydroxyl group into its iodide. This well-known reaction is a mild and convenient way of generating an alkyl halide from the corresponding alcohol and is carried out using an excess of PPh_3 and CX_4 (where X = Cl or Br). A variation for obtaining the iodide involves the addition of iodine and imidazole in place of the carbon tetrahalide. Thus, a solution of **2.51** in toluene was cooled to 0 °C and imidazole (1.3 eq), PPh_3 (1.3 eq) and I_2 (1.3 eq) were added successively. The equivalents of PPh_3 had to be kept to a minimum as it had a very similar rf to the product, but anything below 1.3 equivalents gave lower yields. Complete conversion to the iodide **2.52** took place within 8 hours as evidenced by tlc, which was obtained following a work up with sodium thiosulfate by flash chromatography in a 96 % yield.

The resultant iodide was susceptible to hydrolysis by moisture and would slowly degrade, even when stored at -20 °C. It was therefore better to stockpile the mono-protected alcohol **2.51** and prepare the iodide freshly as needed. This tether was also used for the sequence pursued in the lepadiformine work, which will be discussed later.

The iodide **2.52** was used in the alkylation of auxiliary malonate and the ensuing synthetic steps (already covered in depth) outlined in **Scheme 106**, furnished the amino acid methyl ester **2.46d**. Further elaboration to the α-benzyl proline derivative involved four additional operations. The first step was the Boc protection of the amine where it was discovered that a good yield (80 %) could only be achieved if base (Et_3N) was excluded from the reaction. The ^1H NMR spectrum of the product **2.53** clearly revealed the new carbamate hydrogen singlet at 5.30 ppm. A *t*-Bu singlet integrating for 9 hydrogens was also visible at 1.39 ppm.



Scheme 106 *Reagents and conditions*: a) i) KHMDS (1.2 eq), THF, -78 °C; ii) **2.52** (1.5 eq), warm to reflux, 12h; b) KHMDS (1.2 eq), THF, -78 °C ii) BnBr (2 eq) warm to rt, 24h; c) TFA (6 eq), anisole (1.1 eq), DCM, rt, 3 h; d) i) Et_3N (2 eq), DPPA (1.2 eq), ACN, rt; ii) ACN reflux 4h, then 5M HCl, 70 °C; e) NaOMe (1.1 eq), MeOH, rt, 2h; f) Boc_2O (1.5 eq), *t*-BuOH, rt, 24h; g) H_2, Pd/C (10 mol%), MeOH, rt, 2h; h) pyridine (2 eq), MsCl (2 eq), DMAP (0.5 eq), DCM, rt, 12h; i) TFA (1.5 eq), DCM, 0 °C, 2h; then Et_3N (3 eq), THF, rt, 1h.

The benzyl protecting group on the hydroxyl was removed under standard hydrogenolysis conditions using 10 mol % Pd/C in MeOH under a hydrogen atmosphere. The reaction was complete within 2 hours furnishing the alcohol **2.54** in a yield of 98 % after column chromatography. Debenzylation was corroborated by loss of five hydrogens in the aromatic region of the ^{1}H NMR spectrum, as well as the appearance of a new broad singlet at 1.59 ppm for the OH. To cyclize to the proline derivative, the two-step sequence of hydroxyl group mesylation followed by intramolecular nucleophilic substitution was chosen over the one-pot Mitsunobu procedure, primarily because literature yields for a similar system utilizing the Mitsunobu protocol were reported as only moderate (60 %).[154] Mesylation of the hydroxyl group proceeded smoothly in DCM using 2 equivalents of pyridine, 0.5 equivalents of DMAP and 2 equivalents of mesyl chloride. The product and the SM had very similar rfs on the tlc plate and also had the same appearance after spray visualization. Several low polarity tlc runs were required to achieve their separation and thus follow the reaction which was complete within 5 hours. Chromatographic isolation gave the mesylated product **2.55** in a yield of 92 %. In the ^{1}H NMR spectrum of the product, a new singlet at 3.70 ppm integrating for 3 protons was assigned to the mesyl methyl group. Most other signals were unchanged when compared to the alcohol, except for the multiplet of the methylene alpha to the OMs which had now shifted downfield from 3.81 ppm to 4.13 ppm. The broad singlet for the hydroxyl at 1.59 ppm was also absent.

The Boc removal and cyclization steps were carried out sequentially, without isolation of the deprotected amine. Deprotection was carried out in DCM at 0 °C using 1.5 equivalents of TFA. When all of the starting material had been consumed (ca. 2hours), the solvent and excess TFA were removed under vacuum, and the residue re-dissolved in THF. Addition of 3 equivalents of Et_3N and

stirring at rt for a further hour resulted in cyclization, which furnished the desired (*R*)-α-benzyl proline methyl ester **2.56** following a conventional isolation in a 75 % yield for the two steps. The mesyl and *t*-Bu singlets were now absent from the ^{1}H NMR spectrum and the broad singlet of the amino hydrogen had shifted upfield from 5.31 ppm in the Boc-protected analogue to 2.06 ppm. Chiral HPLC revealed an *ee* of 96 % for the final product.

2.9 Application of the quaternization methodology to the construction of (-)-Lepadiformine

2.9.1 Towards (-)-Lepadiformine A via Malic Acid-based Tethers

From the outset of planning the synthesis of the target it was clear that the choice of R groups on the malonate α-position was a crucial design aspect. Incorporating an allyl group was necessary for the construction of the A ring via ring-closing metathesis, and this fitted nicely with it being the R^1 group in the form of a reactive S_N2 electrophile (allyl iodide) in the alkylation. Conversely, the second group needed to be functionalized at its terminus so as to provide an opportunity for heterocyclisation to form the C-ring. While lepadiformine C lacks a chiral centre in the C ring, making for a simple achiral tether, lepadiformines A and B both contain a C-ring chiral centre at C-5 bearing a hydroxymethyl group, which meant that a more complex tether needed to be considered. **Figure 21** shows the substituents on the ATA needed for lepadiformine A.

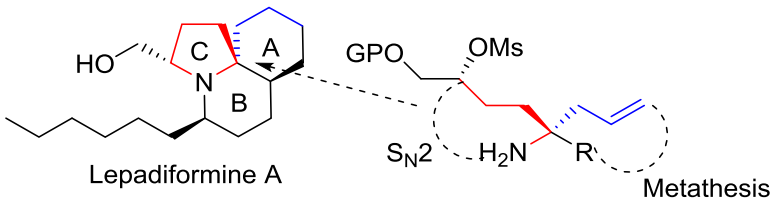
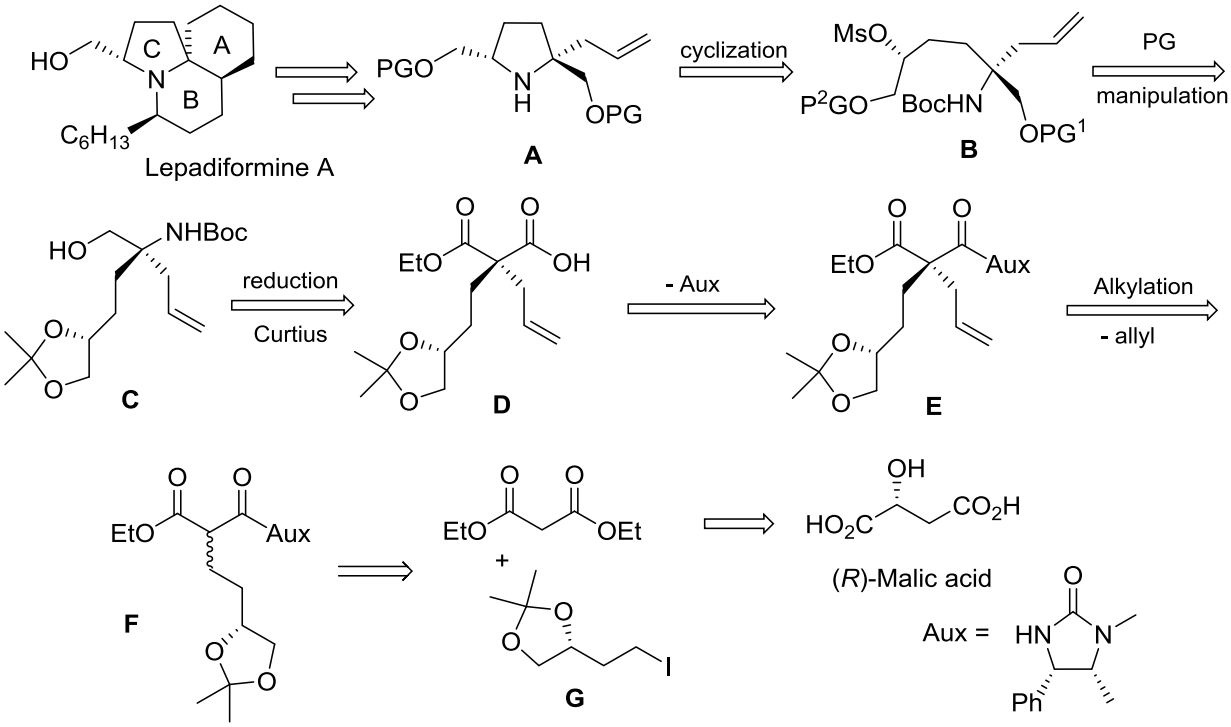


Figure 21 The ATA of lepadiformine A translated to an acyclic derivative

The Curtius methodology just described in section 2.7 was developed after initial attempts to make inroads on the targeted synthesis. The strategy of lepadiformine construction remained the same throughout, and initially it was assumed in the first-generation synthesis that chemoselective auxiliary removal would be possible to provide a carboxyl group (as an ester / acid) for the Curtius rearrangement. In this next section two synthesis approaches are thus described: (i) the first one attempted based on generation of the carboxyl function via auxiliary removal, and (ii) a second-generation approach that made uses of the successful methodology for Curtius rearrangement involving a PMB ester.

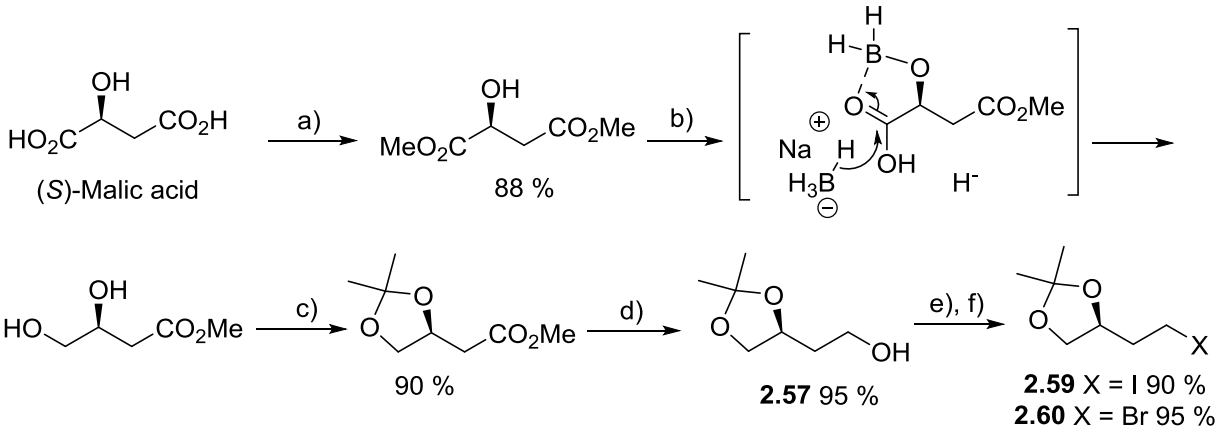
The disconnection envisaged for lepadiformine A using the first strategy described above is shown in **Scheme 109**.



Scheme 109 Retrosynthesis of lepadiformine A

The disconnection shown in **Scheme 109** assumes C-ring construction early in the synthesis in keeping with the earlier work from the group described in section 2.1. Hence, disconnection of the A and B rings from the target generated key chiral synthon **A** as a disubstituted pyrrolidine, which by way of a C-ring cyclisation strategy and a Curtius transposition could be disconnected back to the key α,α'-disubstituted malonate **D** derived by selective hydrolysis of the auxiliary in **E**. In turn, for synthesis of mono-substituted malonate **F**, a ketal-protected iodide **G** needed to be synthesised, which could be derived from (*R*)-Malic acid**.** At this stage we were aware that the alternative of leaving the C-ring construction till late in the synthesis had the advantage that epoxidation of the required terminal alkene had been shown to be diastereoselective (the epoxide would then be opened in a 5-*exo*-tet fashion to afford the target), which would make for a shorter synthesis overall. However, at this stage it was decided to stay with the route published in 2002 centred on building up from the C-ring.

Synthesis of iodide **G** was relatively straightforward starting with malic acid. Although in the context of the naturally occurring isomer of lepadiformine, the tether required the use of (*R*)-malic acid, the substantially cheaper and more abundant (*S*)-malic acid was chosen for investigating the sequence with the intent of switching to the (*R*) isomer later on or by using Mitsunobu chemistry. Being a readily available chiral pool reagent with numerous examples of application in synthesis, a literature procedure for obtaining the ketal-protected iodide from (*S*)-malic acid was available and is shown in **Scheme 110**.

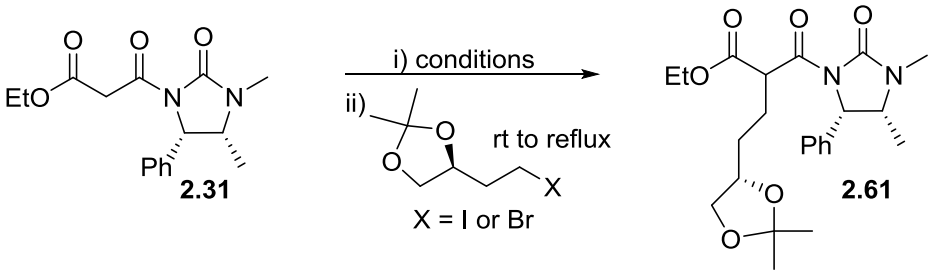


Scheme 110 *Reagents and conditions*: a) H^+, MeOH; b) BH_3SMe_2, 5 mol % $NaBH_4$; c) $(CH_3O)_2C(CH_3)_2$, *p*-TsOH, C_3H_6O; d) $LiAlH_4$ (1 eq), THF, -20 °C; e) Et_3N (1.2 eq), MsCl (1.2 eq), DMAP (10 mol %), DCM, 0 °C; f) NaX, acetone reflux.

The synthesis began with the Fischer esterification of malic acid, achieved by bubbling dry HCl gas through a solution of (*S*)-malic acid in methanol for fifteen minutes and allowing the reaction to stir overnight (**Scheme 110**). This procedure was chosen as it was perceived to be the most suitable for large-scale preparation of dimethyl malate. Purification by vacuum distillation after removal of solvent, conveniently delivered the product in a yield of 88 %. Owing to the slow decomposition of dimethyl malate, the next step was performed immediately. In order to obtain the desired 1,2-acetonide, the method developed by Saito *et al*[155] was followed as it allowed for a chemoselective reduction that minimized formation of the triol, which would have resulted in mixed acetonide (1,2 vs 2,4 hydroxyl groups) formation subsequently. The procedure entailed the use of BH_3SMe_2 and catalytic sodium borohydride in THF at rt and the origin of the chemoselectivity due to chelation involving a borinate formed by exchange is shown. The common view of the reaction mechanistically is that it goes via an initial exchange of the proton of the hydroxyl group with BH_3SMe_2, realising H_2 gas in the process. This is followed by chelation of the resultant borinate borane to the closer of the two ester carbonyls, directing the reduction at that position, whilst the other ester is left unchanged. It was imperative that the reaction be closely monitored, though, as over-reduction to the triol took place if not immediately quenched by the addition of ethanol after consumption of starting material. The resultant triethyl borate ($B(OEt)_3$) side product was removed by repeatedly azeotroping with toluene, and the pure diol was obtained by column chromatography of the residue in a yield of 72 %. The ^1H NMR spectroscopic data of the product agreed with that in the literature.[155] The ketalization step was performed according to a known procedure using catalytic *p*-toluenesulfonic acid (*p*-TsOH) and dimethoxypropane in acetone, and the reaction was complete within an hour, after which the *p*-TsOH was neutralised by the addition of triethylamine. The resultant salt was removed by filtration through a silica pad, followed by a thorough washing with ether. Vacuum distillation proved the

most efficient way to purify large quantities of the acetonide in reproducible yields of around 90 %. Similarly, the ^{1}H NMR spectral data was identical to that published in the literature.[155] Reduction of the ester was carried out using 1 equivalent of $LiAlH_4$ in THF at -20 °C and was complete within 2 hours (**Scheme 110**). Quenching with the slow addition of THF/$H_2$0 (50/50) until all precipitated lithium salts were white was followed by the filtration of the mixture through Celite. The product was purified by distillation in a yield of 95 %, and once again the ^{1}H NMR spectrum matched that of the reported data.[155] The primary alcohol of **2.57** was then transformed to its iodide using a two-step mesylation/S_N2 substitution protocol. The mesylation was carried out using Et_3N and MsCl in DCM, giving the mesylate in a yield of 98 % following flash chromatography. Conversion to the alkyl halide was achieved virtually quantitatively by heating the mesylate product with three equivalents of NaI (or NaBr) in acetone. With the production of the requisite electrophile concluded, its implementation in the alkylation of auxiliary-malonate system **2.31** was probed. Initially, the iodo-derivative **2.59** was chosen owing to its superior reactivity compared to its bromo- counterpart. Application of optimal alkylation conditions developed for the auxiliary malonate system furnished the desired α-substituted auxiliary-malonate in only a 23 % yield (**Table 15**). Furthermore, the iodide electrophile was unstable in solution and underwent considerable decomposition during the course of the reaction and could not be recovered after work-up. Various alkylations were carried out varying the base and the leaving group as shown in **Table 15** but no improvement in yield could be achieved. However, the bromo- derivative **2.60** displayed very little decomposition compared to the iodo- counterpart, and unreacted electrophile was recovered virtually quantitatively based on the yield of product, after work-up and column chromatography.

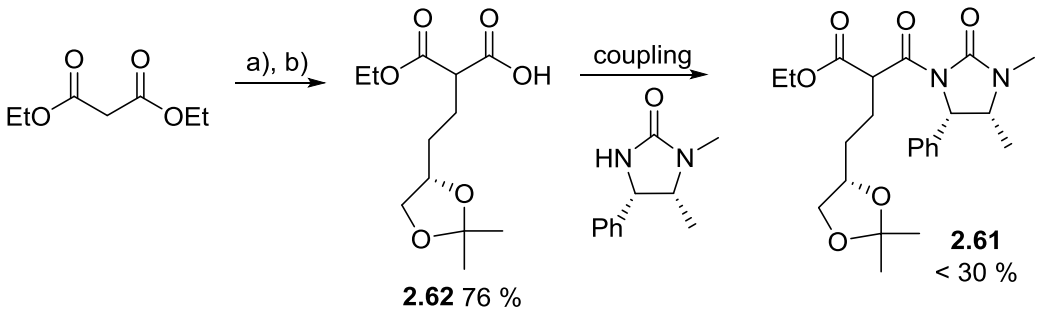
Table 15 Alkylation of auxiliary-ethyl malonate with acetonide-containing electrophiles



Entry	Base (eq)		X	E^+ equivalents	Isolated Yield 2.61 (%)
1	KHMDS (1.1)	THF	I	1.5	20[b]
2	KHMDS (1.1)	THF	I	2.5	23[b]
3	NaH	THF	I	1.5	0[b]
4	KHMDS (1.1)	THF	Br[a]	2.0	27[c]

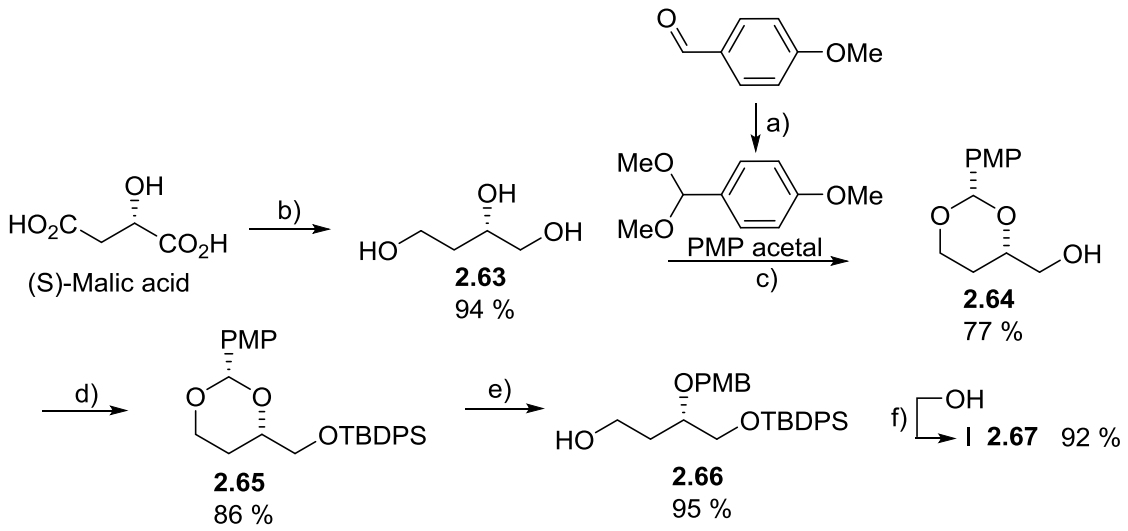
[a]10 mol % TBAI added; [b]no E^+ recovered [c] unreacted E^+ recovered after reaction

An alternative route for accessing the alkylated auxiliary malonate system was thus investigated, involving the alkylation of diethyl malonate first, followed by mono-hydrolysis and auxiliary coupling (referred to as route B, as set out in **Scheme 93**, *vide supra*). The alkylation step was carried as before by inverse addition of NaH to diethyl malonate, followed by introduction of **2.60** (chosen over the iodo-derivative owing to its greater stability) and warming to reflux, furnishing the product in a yield of 76 % after chromatography (**Scheme 111**). Mono-hydrolysis to the half acid-ester was performed as before using KOH in EtOH, furnishing the desired alkylated mono-acid **2.62** in a yield of 77 %. However, several attempts to couple the alkylated mono-acid to the auxiliary using the range of methodologies available, all gave disappointingly low yields and several side-products. Coupling reactions using the Bt and DCC activation methods would stall at roughly 30 % conversion, even at elevated temperatures. Solvent and additive variation (DMAP and BtOH for DCC) did not improve results. Mixed anhydride activation with pivalic anhydride resulted in a complex tlc profile due to the decomposition of the acid. This was attributed to acetonide hydrolysis since the reaction medium was slightly acidic due to the triethylammonium ion present.



Scheme 111 *Reagents and conditions*: a) i) NaH (1.2 eq), THF, 0 °C; b) **2.60** (1.5 eq), reflux; b) KOH (1.2 eq), EtOH, rt.

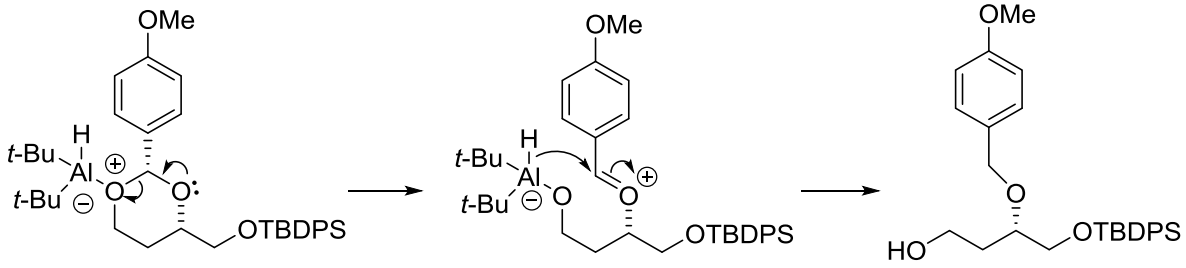
Owing to the unstable nature of **2.59** and **2.60**, which was thought to be due to the acid lability of the acetonide, an analogous tether was sought bearing O-protecting groups that were less labile. Upon investigation of the literature, it was decided to replace the acetonide with PMB and TBDPS ether groups, since these could be selectively manipulated later on in the sequence. **Scheme 112** shows its synthesis according to a known protocol.[156]



Scheme 112 *Reagents and conditions*: a) $CH(OMe)_3$ (10 eq), *p*-TsOH (5 mol %), MeOH, reflux; b) $BH_3{\cdot}SMe_2$ (4 eq), $B(OMe)_3$ (2 eq), THF, 0 °C to rt.; c) PMP acetal (2 eq), CSA (5 mol %), DCM, rt; d) imidazole (1.1 eq), TBDPSCl (1.1 eq), CH_3CN, rt. e) DIBAL-H (4 eq), toluene, -78 °C; f) PPh_3 (1.3 eq), imidazole (1.2 eq), I_2 (1.3 eq).

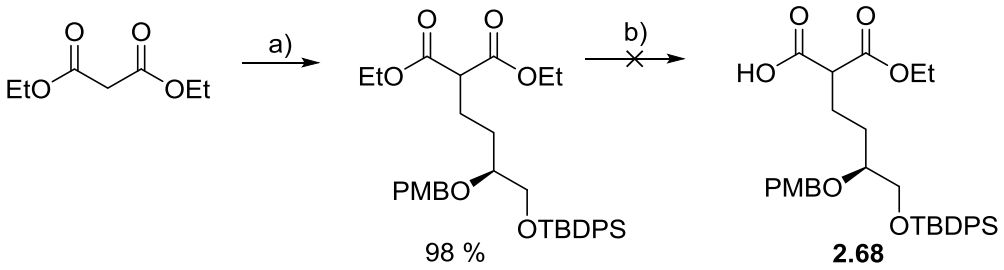
Thus, starting with (*S*)-malic acid again, reduction using BH_3SMe_2 in the presence of $B(OMe)_3$ was performed, allowing full reduction to the triol **2.63**. The PMP acetal needed for the protection of the diol was generated from anisaldehyde and trimethyl orthoformate in dry MeOH, using a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH). Acetal formation of anisaldehyde was first attempted using *p*-TsOH under Dean-Stark conditions, but this gave low yields and a number of side-products. Next the triol **2.63**, PMP acetal and a catalytic amount of camphorsulfonic acid (CSA) were reacted at rt in DCM to furnish the PMP acetal **2.64** in a yield of 77 % after column chromatography. The reaction was followed by tlc which showed the expected marked increase in rf as well as UV activity for the newly formed product. The formation of the less stable five-membered 1,2-acetal was minimal and the two regioisomeric products were separated by chromatography. ^{1}H NMR spectroscopy confirmed the identity of the product, with diagnostic signals evident in the aromatic region, as well as the downfield singlet at 5.50 ppm for the PMP hydrogen. The diastereotopic

hydrogens at C-4 each gave rise to a doublet of doublets at 4.29 ppm and a multiplet at 4.01 ppm. Next, TBDPS protection of the primary hydroxyl was achieved using TBDPSCl and imidazole in CH_3CN, to furnish compound **2.65** in an isolated yield of 86 %. Disappearance of the hydroxyl resonance from 2.02 ppm and a new *t*-Bu singlet at 1.11 ppm as well as extra resonances in the aromatic region indicated the successful installation of the TBDPS group. Finally, alcohol **2.66** was generated in a yield of 95 % following column chromatography by the regioselective reduction of **2.65** using 4 equivalents of DIBAL in toluene at – 78 °C. The sequence of PMP formation followed by regioselective reduction is an effective way of installing a bulky protecting group such as PMB onto a relatively sterically hindered hydroxyl group, avoiding unnecessary protecting group manipulations. The aluminium of the bulky reducing agent coordinates to the more accessible oxygen, which results in an oxocarbenium ion involving the C-2 and not the C-1 oxygen. Finally, reduction of it results in a C-2 PMB-protected product, with the protecting group on the sterically more hindered oxygen (**Scheme 113**).



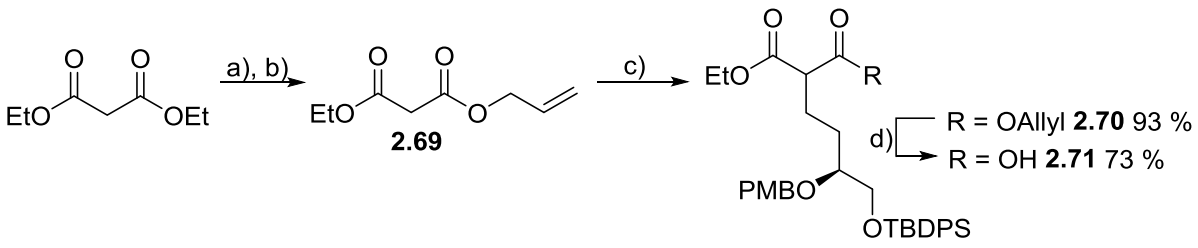
Scheme 113 Mechanism of the regioselective reduction of the PMP acetal

The ^{1}H NMR spectrum of the alcohol contained two distinctive AB doublets for the diastereotopic benzylic hydrogens; the new broad OH signal appeared at 2.09 ppm. The regio-outcome of the reaction was not scrutinized, however, relying on the close correlation of NMR spectral data to that in the literature,[157] where the regioselectivity of the reaction had been confirmed by virtue of COSY experiments on the acetate derivative of **2.66**. To convert the alcohol to the iodide, a one-pot Appel reaction was performed using PPh_3, imidazole and iodine in toluene, furnishing the desired iodide **2.67** in an isolated yield of 92 %. At this point it was decided to follow route 'B' for generation of the alkylated auxiliary-malonate. To this end, diethyl malonate was alkylated with **2.67** according to the general procedure using NaH in an excellent yield of 98 % (**Scheme 114**); however, monohydrolysis with KOH under several varied conditions was sluggish possibly due to the presence of hydrophobic groups on the tether.



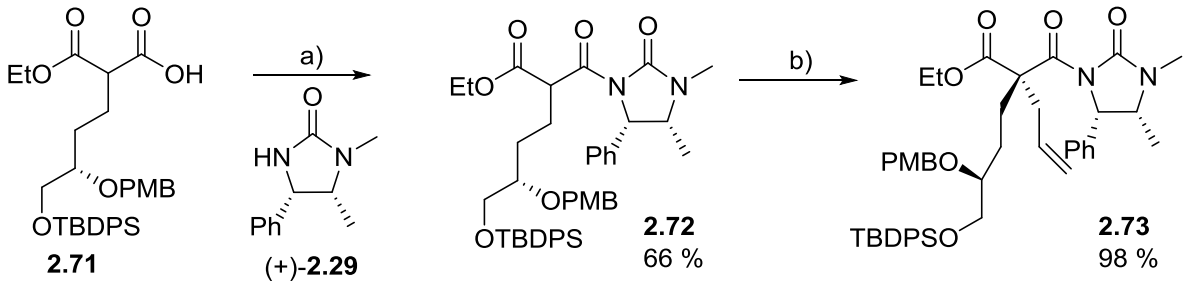
Scheme 114 *Reagents and conditions*: a) i) NaH, (1.2 eq), THF, 0 °C; ii) **2.67** (1.2 eq), reflux; b) EtOH/ H_20 (80/20), KOH (1.2 to 3.0 eq), rt to 50 °C.

One way to circumvent this problem was by variation of the ester groups for easier cleavage. Allyl ethyl malonate was chosen to replace diethyl malonate as the alkylation substrate, in the hope of cleaving the allylic ester using a palladium catalyst. To this end, diethyl malonate was mono-hydrolysed using 1.2 equivalent of KOH in EtOH as before and the allyl/ethyl ester **2.69** was generated via DCC coupling of allyl alcohol and ethyl malonic half-acid in a yield of 75 % after chromatography (**Scheme 115**). The ^{1}H NMR spectrum of the product revealed the allyl double bond signals at 5.91 ppm for the C-H and 5.21 ppm for the terminal CH_2, while the methylene hydrogens of the allyloxy group resonated at 4.65 ppm. The ethyl ester methyl triplet and methylene quartet were also evident and the malonic methylene multiplet appeared at 2.39 ppm. Alkylation of **2.69** was successfully carried out using NaH in refluxing THF furnishing **2.70** in a yield of 93 % following column chromatography. Although the product was a 50/50 mixture of diastereomers due to the two stereogenic centres present, the doubling of signals in the ^{1}H NMR spectrum was noticeable only for the ester methyl triplet and the allylic C-H, with the remaining signals essentially overlapping. All the allylic ester and ethyl ester peaks were present as for the unalkylated version, their chemical shifts essentially unchanged. The absence of the malonic methylene at 2.39 ppm confirmed that alkylation had been successful, the malonic methine triplet now appearing at 3.36 ppm. All signals expected for the tether were accounted for.



Scheme 115 *Reagents and conditions*: a) EtOH/ H_20 (80/20), KOH (1.2 eq), rt; b) allylOH (3.0) eq, DCC (1.2 eq), DCM rt. c) i) NaH (1.2 eq), THF, 0 °C; ii) **2.67** (1.2 eq), reflux; d) EtOH, KOH (2.5 eq), reflux.

Applying reported conditions for allylic cleavage using $Pd(PPh_3)_4$ and morpholine resulted in no reaction whatsoever. Surmising that the allylic ester would be more susceptible to hydrolysis than the ethyl ester group due to allylalkoxide being a better leaving group, compound **2.70** was subjected to hydrolysis using KOH in ethanol. The reaction was monitored by tlc, and only one acid product could be seen. As 1.5 equivalents of KOH could not achieve complete conversion, another equivalent was added after 24 h and this was sufficient to drive the reaction further. Half-acid **2.71** was isolated in a yield of 73 %, with the remaining 27 % of starting material also recovered. There was no evidence of ethyl ester hydrolysis. The ^{1}H NMR spectrum of **2.71** resembled that of **2.70**, but was devoid of allylic signals and instead contained a very broad singlet for the carboxylic OH at 8.90 ppm. Several of the methodologies used in developing the malonate alkylation methodology were used in attempting to couple the mono-acid **2.71** to the auxiliary (+)-**2.29** (acid chloride, DCC and Bt activation), in which the Bt protocol gave the best results, furnishing auxiliary malonate **2.72** in a yield of 66 % yield for the coupled product as a 50/50 mixture of diastereomers that were separable by column chromatography (**Scheme 116**). Key signals in the ^{1}H NMR spectrum were those pertaining to the auxiliary - namely a doublet at 5.34 ppm for the benzylic hydrogen and a double quartet at 3.91 ppm for the hydrogen α to the methyl as well as a singlet at 2.79 ppm for the *N*-methyl and a doublet for the methyl at 0.78 ppm (for one of the diastereomers). The remaining resonances largely resembled the ^{1}H NMR spectrum of the acid **2.71**, with the expected disappearance of the carboxylic OH resonance at 8.90 ppm. The ^{13}C NMR spectrum displayed an additional carbonyl resonance at 155.2 ppm as well as additional aromatic singlets for the phenyl group of the auxiliary. The quaternization of derivative **2.72** was accomplished with 1.2 equivalents of KHMDS and 1.5 equivalents of allyl bromide to give the quaternary derivative **2.73** in an excellent yield of 98 % following chromatographic purification.



Scheme 116 *Reagents and conditions*: a) i) BtCl (1.2 eq), PPh_3 (1.3 eq), CH_3CN 0 °C; ii) (+)-**2.29** (1.2 eq), reflux; b) i) KHMDS (1.2eq), THF, -78 °C; ii) allylBr, (1.5 eq), rt.

The ratio of diastereomers was determined to be 32:1 from the ^{1}H NMR spectrum, which now also displayed the distinctive allylic peaks: a multiplet at 5.42 ppm for the CH, a multiplet at 4.92 ppm for

the terminal CH_2 and the diastereotopic CH_2 multiplets were detected at 2.81 and 2.69 ppm. Similarly, the ^{13}C NMR spectrum contained the diagnostic allylic resonances at 133.3 ppm and 118.1 ppm. The assigned ^{1}H NMR spectrum of the quaternary auxiliary-malonate product **2.73** is shown in **Fig. 22** in which the relative stereochemistry was assigned based on the outcome of the quaternization model study.

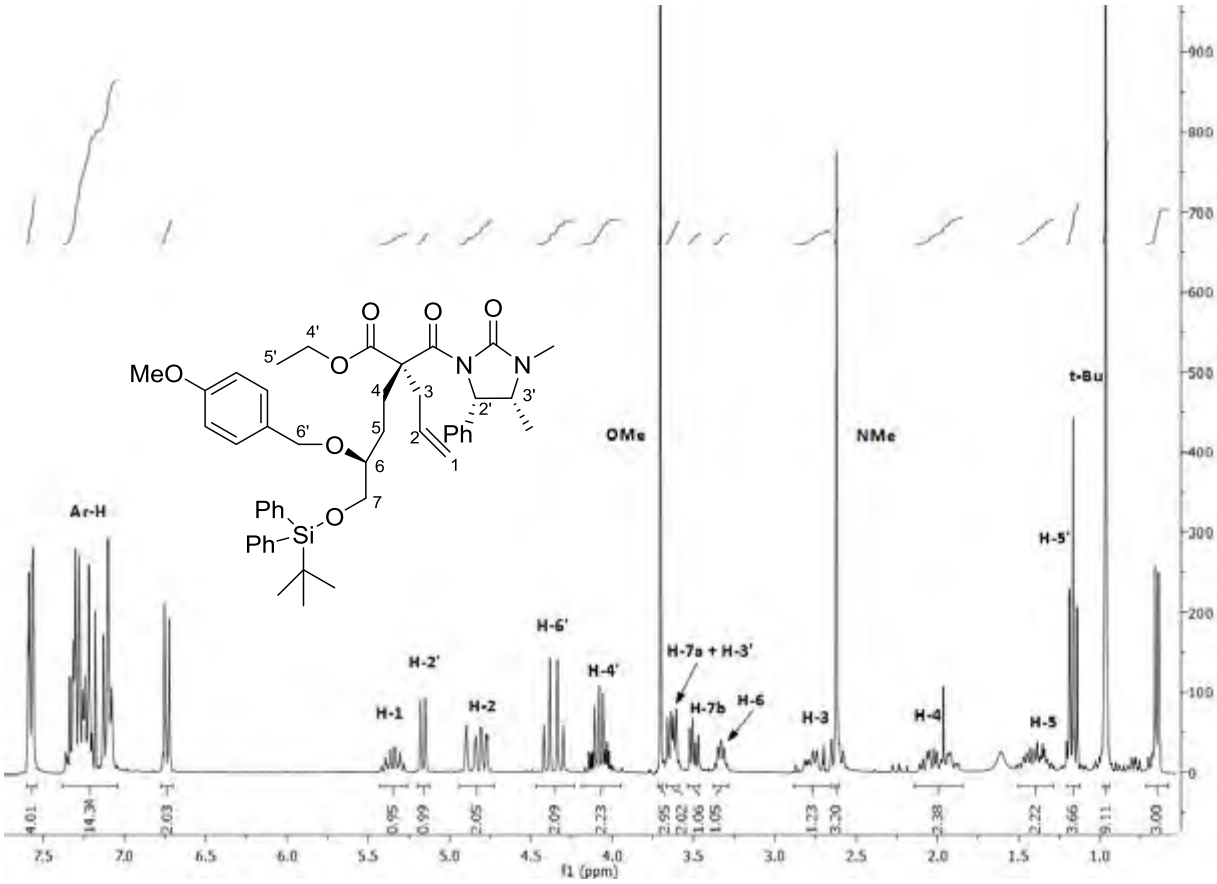


Figure 22 Assigned ^{1}H NMR spectrum of quaternary auxiliary-malonate **2.73**

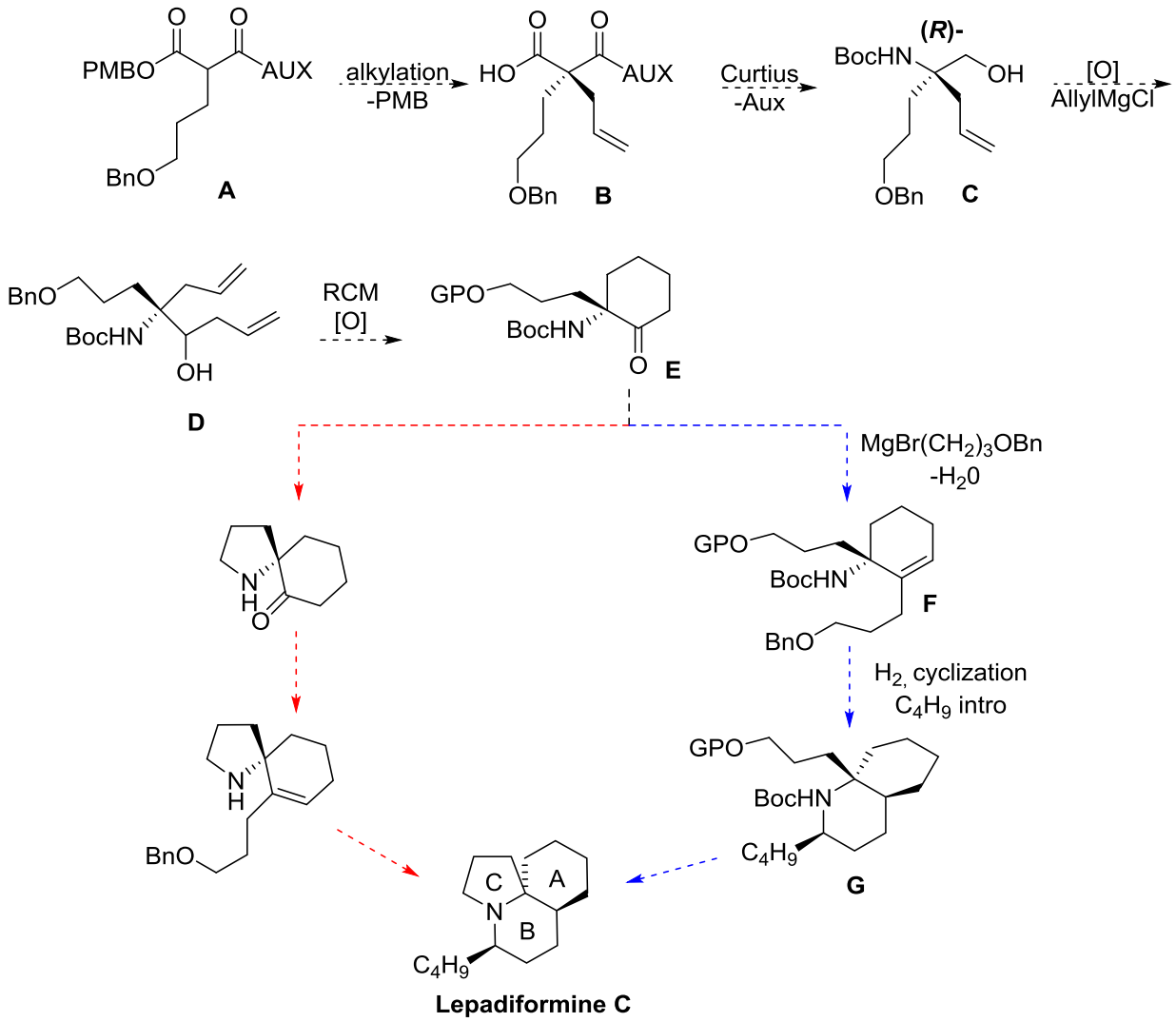
Next came the selective removal of the auxiliary so as to be able to carry out the Curtius transposition step. Subjecting **2.73** to an attempted selective hydrolysis of the auxiliary based on the idea that metal ions like lithium would selectively chelate into the auxiliary hole consumed an enormous amount of effort but was to no avail.

These hydrolysis studies were ongoing with development of the end-game of the quaternization methodology, in which once it became clear that the best approach for the Curtius rearrangement involved using PMB esters, it also emerged that this tether would be incompatible, or at the very least necessitate a re-protection step (OPMB ether susceptible to TFA). Given the earlier success in the monohydrolysis reaction with the allyl ester, going forward with diallyl malonate was another option. However, given the relatively lengthy synthesis of the tether, a decision was made to move

onto a simpler variant. Nonetheless, its successful implementation in the quaternization step showed that even bulky, functionalized side chains could be incorporated via this methodology.

2.9.2 Towards (-)-Lepadiformine C

It was at this stage that lepadiformine C, which lacks the chiral centre in the C ring looked to be a more realistic target. Here one could use a less complex electrophile, $I(CH_2)_3OBn$ (**2.52**) and a full plan towards a lepadiformine C synthesis using this tether as well as implementing the revised Curtius methodology based on the PMB ester emerged as depicted in **Scheme 117**.



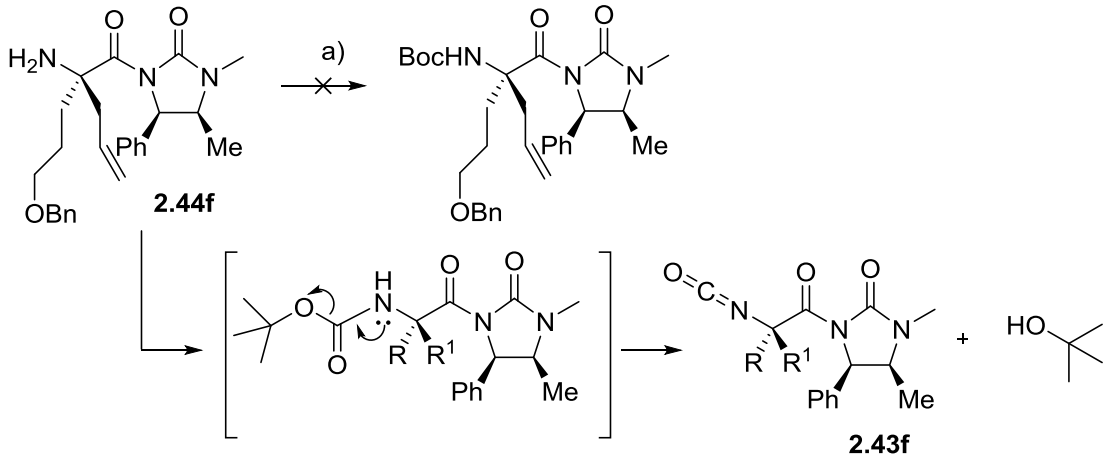
Scheme 117 Synthetic plan for lepadiformine C

Applying the quaternization methodology on the alkylated malonate derivative **A**, followed by PMB cleavage would set up the requisite acid **B** for the Curtius transposition. Reductive removal of the auxiliary on the resultant ATA would give rise to the amino alcohol **C**, from which the diallyl alcohol

D could be accessed following oxidation and Grignard addition. A ring-closing metathesis reaction would furnish the A ring, at which point closure of the C ring could be pursued to the aza-spirocycle (route shown in red), or alternatively, further elaboration to cyclohexene **F** could be undertaken (route shown in blue). Because of the modest level of selectivity (2:1) achieved in the hydrogenation of the aza-spiro analogue in Richards' approach, it was decided to leave the C ring closure for later, in the hope that there would be a stereoselective reduction from the underneath face of cyclohexene **F** based on the notion that the tether would have the larger A-value compared to the *N*-Boc. Alternatively, deprotection to the amine via an assisted hydrogenation (the question of catalyst interference was a possibility though) or amine reprotection with a smaller protecting group provided further options. Use of a chiral catalyst with a diastereoselective bias was yet another possibility. Though not a trivial problem, the feeling was that a solution could probably be found. Hence, aza-decalin **G** was envisaged to arise from cyclohexene **F,** via a stereoselective hydrogenation, B-ring closure and side-chain introduction. Finally, C-ring closure would furnish lepadiformine C.

Results pertaining to this approach towards lepadiformine C will be covered in the next section, commencing with elaboration from auxiliary-tethered ATA **2.44f**, the synthesis of which has been addressed in section 2.7.

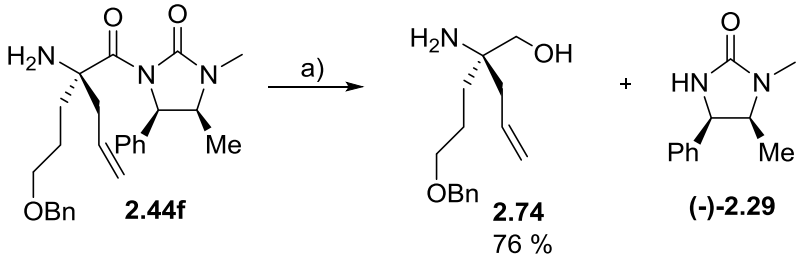
Protecting the amino group of **2.44f** before decoupling of the auxiliary was decided on, primarily because of the ease of handling of products as well as avoiding possible side-reactions.



Scheme 118 *Reagents and conditions*: a) Et_3N (1.2 eq), Boc_2O (1.2 eq), THF, rt.

To this end, a standard Boc protection protocol was performed on **2.44f** using Et_3N (1.2 eq) and Boc_2O in THF (**Scheme 118**). Tlc analysis showed an expected change in the Rf, from the starting amine streak-like spot at rf 0.3 to 0.7 for the product. However the ^1H NMR spectrum revealed the absence of *t*-Bu hydrogens in the 1.20-1.50 ppm region giving a clear indication that the product of

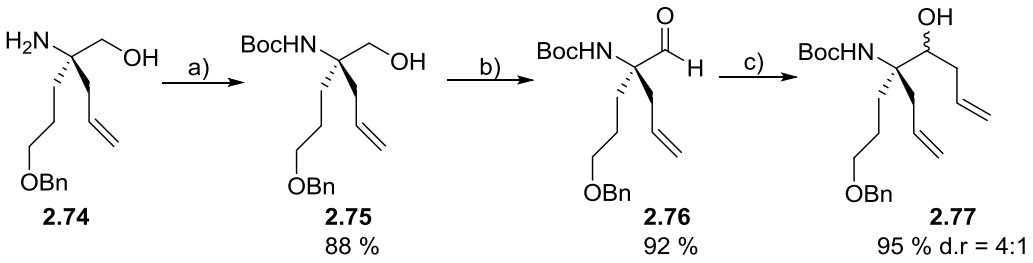
the reaction was not the Boc-protected amine. Upon closer inspection of the ^{1}H NMR spectrum, the identity of the isolated product was concluded to be the isocyanate **2.43f**, arising via expulsion of the *t*-butoxide anion as shown in **Scheme 118** due to steric hindrance between the Boc group and the auxiliary around the crowded auxiliary centre. The linear isocyanate is far less energetically demanding, and BuO^{-} expulsion is entropically favoured. Tlc comparison with the intermediate isocyanate product from the Curtius rearrangement did indeed indicate that these were the same compound, and this was corroborated by ^{1}H and ^{13}C NMR spectra which were identical in appearance for the two compounds. The diagnostic N=C=O stretch at 2253 in the IR spectrum of the product further supported the assignment. Rather than investing time in optimizing conditions for Boc-protection at that stage, removing the auxiliary first was deemed as a possible solution, with the aim of decongesting the molecule enough for subsequent Boc-protection to be successful. Hence, **2.44f** was subjected to reductive cleavage conditions using three equivalents of $LiBH_4$ and here the choice of solvent was important for good yields; in THF the reaction was sluggish and did not go to completion, whilst reduction in Et_2O proceeded much faster, giving the amino alcohol **2.74** in an isolated yield of 76 % (Scheme). The auxiliary was also recovered in a yield of 80 %.



Scheme 119 *Reagents and conditions*: a) $LiBH_4$ (3 eq), Et_2O, -20 ° to 0 °C.

All of the signals characteristic of the auxiliary were absent from the ^{1}H and ^{13}C NMR spectra of **2.74**, and the appearance of a new singlet at a shift of 3.98 ppm integrating for 2 hydrogens corresponding to the methylene α to the hydroxyl as well as a broad hydroxyl singlet at 2.00 ppm supported the product assignment. The IR spectrum also revealed the characteristic sharp stretch at 3693 cm^{-1} for the hydroxyl, as well as a broad stretch at 3444 cm^{-1} for the primary amine.

Subjecting **2.74** to standard Boc-protection conditions with Et_3N (1.1 equivalents) and Boc anhydride (1.1 equivalents) now furnished the desired Boc-protected amino alcohol **2.75** in a yield of 88 % in which the ^{1}H NMR spectrum unmistakably displayed the *t*-Bu singlet at a shift of 1.42 ppm. Similarly, the ^{13}C NMR spectrum showed a tall peak at a shift of 28.5 ppm corresponding to the *t*-butyl methyl groups, as well as an expected carbonyl shift at 156.5 ppm. Next, oxidation to the aldehyde **2.76** was performed using Dess-Martin periodinane as the oxidising reagent, which proceeded smoothly to deliver **2.76** in a yield of 92 % following flash chromatography (**Scheme 120**).



2.74 **2.75** 88 % **2.76** 92 % **2.77** 95 % d.r = 4:1

Scheme 120 *Reagents and conditions*: a) Et_3N (1.1 eq), Boc_2O (1.1 eq), DCM, rt; b) DMP (1.1 eq), CH_2Cl_2, 0 °C, 1h, then aq. $NaHCO_3$; c) AllylMgCl (1.2 eq), THF, - 78 to -20 °C, 2 h.

The presence of the aldehyde was verified by ^{1}H NMR spectroscopy which showed the distinctive aldehyde singlet at 9.45 ppm, as well as the absence of both the hydroxyl signal at 2.00 ppm, and the α-hydroxy methylene signal. A shift at 200.6 ppm in the ^{13}C NMR spectrum for the newly formed carbonyl could also be seen, that was not present in the spectrum of **2.75**. Although stable to flash chromatography, the aldehyde was committed to the Grignard addition step quickly to avoid decomposition. A Grignard addition using allylMgCl (bought commercially) was carried out at -78 °C but the reaction required warming to -20 °C for a clean, high yielding conversion, ultimately furnishing the diallyl adduct **2.77** in a yield of 95 % after column chromatography.

The first obvious indication from the ^{1}H NMR spectrum that the addition had taken place was the absence of the aldehyde signal in the region of 9.50 ppm. More importantly, two distinct sets of signals were visible for both allyl groups. The new hydroxyl resonance appeared at 4.56 ppm, corroborated by the broad absorbance stretch at 3415 cm^{-1} in the IR absorption spectrum. The multiplet at 3.59 ppm was assigned to the α-hydroxyl hydrogen. 2D NMR analysis in the form of COSY was carried out in order to unambiguously assign individual allylic signals. The addition was stereoselective with a dr of 4:1 as determined by ^{1}H NMR spectroscopy; the origin of the stereoselectivity can be rationalized by considering one of two possible Felkin-Anh transition states for addition to carbonyls (**Fig. 23**). The first one, depicted as transition state **A**, involves chelation control; here, chelation of Mg to the carbonyl of the Boc is not likely as it would entail a 7-membered ring intermediate, although involving the *N* of the NBoc group isn't out of the question and addition from the least hindered trajectory in this transition state would result in diastereomer **2.77a**. The other possibility is depicted as conformation **B**, in which the nitrogen aligns itself perpendicular to the C=O, to allow for orbital overlap between the π* of the C=O and σ* of the C-N, lowering the energy of the LUMO. Nucleophile attack from the least hindered pathway on this conformation would lead to the opposite diastereomer **2.77b**. Grignard reactions tend to involve chelation control, hence it is postulated that the major product in this case was a result of addition via transition state **A**, the chelation control model. The relative stereochemistry between the

quaternary centre (known to be R) and the α-centre of **2.77** was not determined (eg by X-Ray of a suitable derivative), however, as this chiral centre would be removed at a later stage in the synthesis.

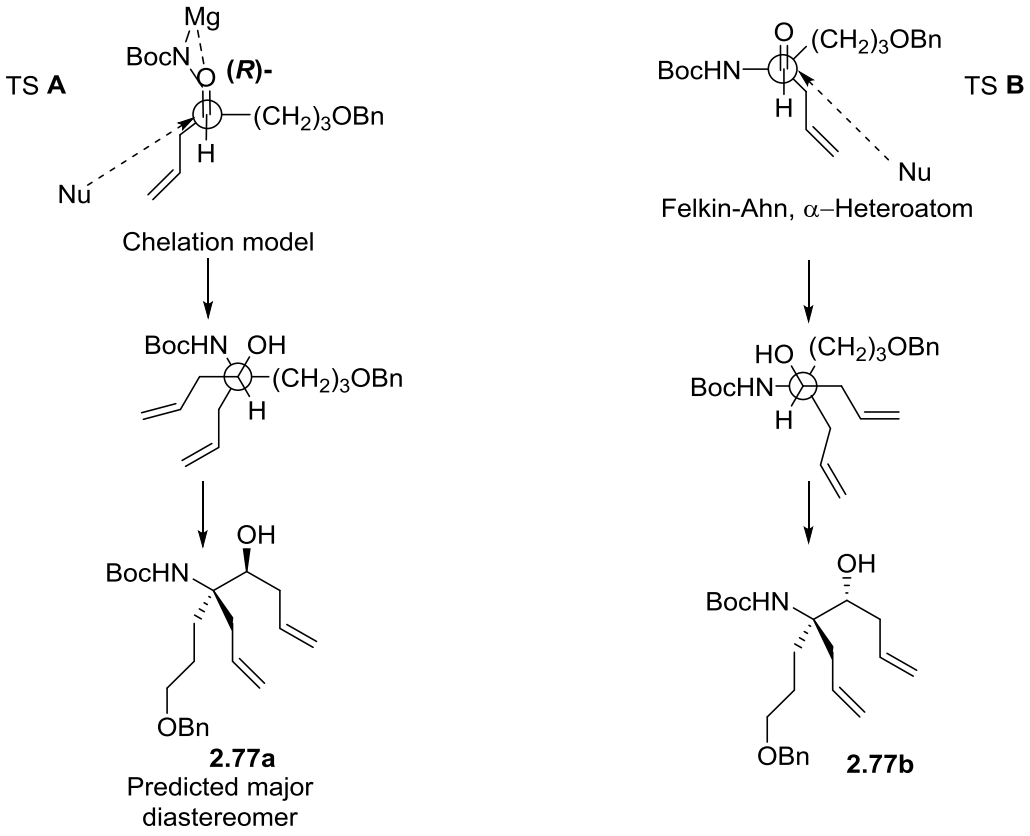
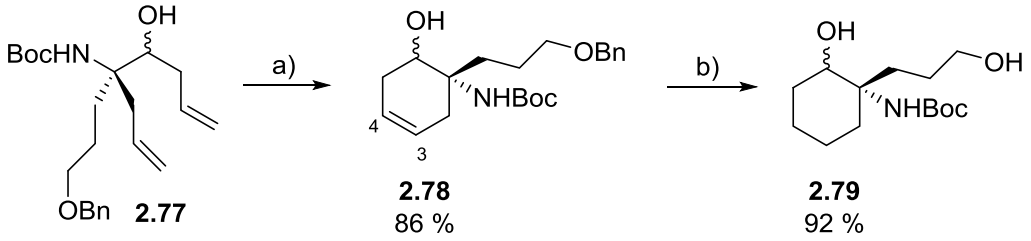


Figure 23 Proposed transition states to predict the stereoselectivity in the Grignard addition

Having successfully installed the second allyl group, the stage was set for a ring-closing metathesis reaction using Grubb's first-generation catalyst. This ruthenium-based alkylidene complex has high functional group tolerance for alcohols, amides, aldehydes and carboxylic acids. When applied to **2.77** with a catalyst loading of 5 mol %, cyclization was effected smoothly in refluxing DCM (**Scheme 121**). The reaction changed colour from purple to black and the was complete within three hours as evidenced by tlc. Metathesis reactions are reportedly often plagued by contamination by Ruthenium side-products and a number of purification methods have been reported for their removal. In this case, careful column chromatography was enough to ensure pure cyclohexene product **2.78** in a yield of 86 %, which was further purified by recrystallization to give colourless needle-like crystals. The two diastereomers were separable by chromatography in this case. The ^{1}H NMR spectrum (pure diastereomer) displayed the expected changes in the olefinic region, containing only two multiplets at 5.35 and 5.75 ppm arising from H-3 and H-4. The hydroxyl and NH signals were unchanged, as well

as the benzyl ether peaks. Similarly, the ^{13}C NMR spectrum was devoid of allylic resonances, the olefinic signals now present at 127.0 and 122.6 ppm.



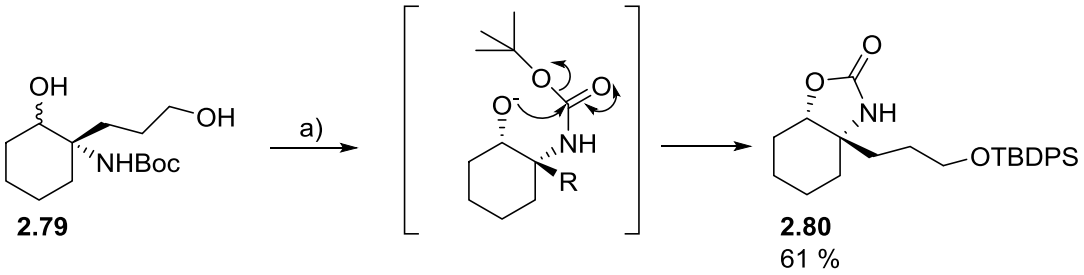
Scheme 121 *Reagents and conditions*: a) $RhCl_2(PCy_3)_2$=CHPh, CH_2Cl_2, 40 °C; b) Pd/C, H_2, EtOH, rt.

Next, the benzyl protecting group was removed using hydrolytic conditions, with concomitant reduction of the olefinic bond in the ring, achieved by using 10 % Pd/C under a hydrogen atmosphere. Tlc showed the expected decrease in the Rf of the newly formed product, and the reaction was complete within six hours to afford the cyclohexanol product **2.79** in a yield of 92 % following column chromatography. Both debenzylation and reduction were corroborated by the ^1H and ^{13}C NMR spectra, which were free of signals in the aromatic and olefinic regions, as well as the signal for a benzylic methylene. Two unambiguous broad singlets were visible for the two hydroxyls, at 2.26 ppm for the primary and 4.90 ppm for the secondary. The protection of the primary hydroxyl had to be carried out and a TBDPS group was chosen for this purpose. This group seemed appropriate for the remaining reactions. Apart from requiring a protecting group other than benzyl (the Grignard addition further on in the sequence would involve the same three carbon benzyl ether), a bulky substituent on the pendant chain would hopefully induce higher selectivities in the reduction step further in the sequence, as mentioned in the synthetic plan outline.

The regioselecivity of the protection was not expected to be a problem as it was anticipated to take place first at the primary hydroxyl. However, attempting the protection under standard conditions using imidazole and TBDPSCl was proving to be sluggish, with less than 50 % conversion evident after 24 hours at rt, as determined by tlc analysis. Hence, it was decided to resort to using a stronger base, but to keep the temperature low. Dissolving **2.79** in THF and treating it with NaH (1.1 eq) and TBDPSCl (1.1) at 0 °C gave the expected tlc profile of an increase in Rf (**Scheme 122**). Tlc analysis also indicated that there was still a considerable amount of starting material present and that the reaction wasn't progressing, thus it was allowed to warm up to 10 °C, which resulted in further consumption of the starting material and formation of one major product spot higher up on the tlc plate. However, the isolated product, obtained in 61 % yield after chromatography, revealed only one *t*-Bu signal (at 1.06 ppm) in the ^1H NMR spectrum, which based on the chemical shift appeared likely to be that of a TBDPS group. This was confirmed by the presence of appropriate resonances in the aromatic region of the spectrum as well as the absence of the primary hydroxyl resonance. Thus,

it was concluded that the TBDPS had indeed been installed, but that the Boc group was no longer present. In conjunction with the tlc profile, together with the absence of a primary amino resonance in the ^{1}H NMR spectrum led to the conclusion that the oxazolidinone **2.80** had been generated by nucleophilic attack of the alkoxide of the secondary alcohol onto the carbonyl of the carbamate (**Scheme 122**). The product observed was likely the *cis* isomer, which would have arisen from the cyclization of the predicted major diastereomer from the Grignard reaction (4:1). The yield of 61 % of the oxazolidinone supported this view. The tlc profile of the reaction also supported this, as there were three other minor spots present, the most polar one of which corresponded to the starting material and was therefore likely to be the remaining *trans*-isomer which did not cyclize, and a second, slightly higher spot was likely from the TBDPS-protected *trans* isomer.

All of the resonances in the ^{1}H and ^{13}C NMR spectra correlated with the proposed structure.

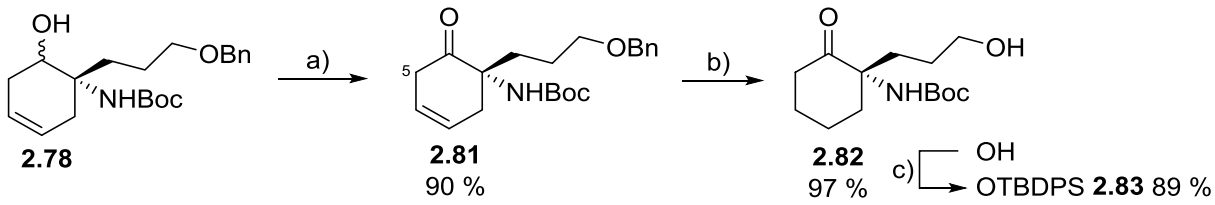


2.79 **2.80** 61 %

Scheme 122 *Reagents and conditions*: a) NaH (1.1 eq), TBDPSCl (1.1 eq), THF, 0 °C to 10 °C.

Although this setback was not insurmountable and a set of conditions where the cyclization does not take place could possibly be found, the easiest approach was to oxidise the secondary alcohol earlier. Thus the sequence was altered to oxidize prior to hydrogenation / hydrogenolysis, which was achieved using standard Swern conditions on **2.78** to deliver the cyclohexenone **2.81** in a yield of 90 % after chromatographic purification (**Scheme 123**). Oxidation using the TPAP/ NMO protocol was also tested, but gave lower yields. The signals for the secondary hydroxyl and the associated α-hydroxyl hydrogen were no longer present in the ^{1}H NMR spectrum and the diastereotopic hydrogens at C-5 had shifted downfield from a region of 2.20 – 2.40 ppm in the substrate, to 2.90 – 3.08 ppm in the product being now a- to a carbonyl group. The ^{13}C NMR spectrum displayed the anticipated ketone resonance at 207.5 ppm. Removal of the benzyl group and reduction of the olefinic bond was carried out as before using palladium on carbon under a hydrogen atmosphere, furnishing the product **2.82** in a yield of 97 % after column chromatography. Again, the disappearance of aromatic signals in both ^{1}H and ^{13}C NMR spectra, as well as the absence of the olefinic signals were confirmation that the benzyl group was removed and that the double bond had been reduced. TBDPS protection was again carried out using NaH and TBDPSCl in THF and the reaction was complete after 6 hours to give the desired product **2.83** in an isolated yield of 89 %. The

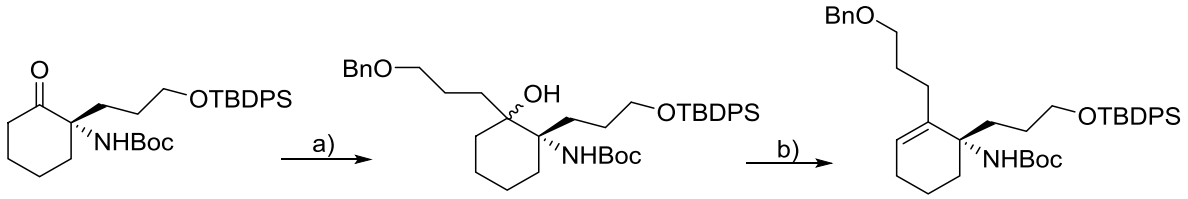
^{1}H NMR spectrum now clearly displayed two signals integrating for 9 protons each at 1.04 ppm and 1.41 ppm, confirming the presence of two *t*-Bu groups, one from the Boc and the other from the TBDPS. The other obvious indicator was the appearance of signals in the aromatic region integrating correctly for ten hydrogens. Similarly, the ^{13}C NMR spectrum showed new aromatic peaks as well two distinct *t*-Bu carbons and methyl signals.



2.78 **2.81** 90 % **2.82** 97 % **2.83** 89 %

Scheme 123 *Reagents and conditions*: a) i) $COCl_2$ (1.2 eq), DMSO (2.4 eq), DCM, -78 °C; ii) Et_3N (4 eq), 0 °C; b) Pd/C (10 mol %), H_2, EtOH, rt; c) NaH (1.2 eq), TBDPSCl, (1.2 eq), THF, rt.

With the O-protected ketone in hand, Grignard addition of the 3-carbon tether bearing the benzyl ether terminus was investigated. The Grignard reagent was generated by addition of $Br(CH_2)_3OBn$ to freshly activated Mg turnings in THF and stirring for 10 to 20 minutes. At first, conversion to the Grignard was low even with the addition of a crystal of iodine. After a few attempts it was discovered that the THF solution of the alkyl bromide had to be very concentrated in order to achieve full conversion. Once the Grignard reagent was fully formed and cooled, a solution of the cyclohexanone **2.83** in THF was introduced at 0 °C but the reaction required warming to rt for good conversion, ultimately furnishing the Grignard adduct **2.84** in a yield of 79 % after chromatographic purification (**Scheme 124**).

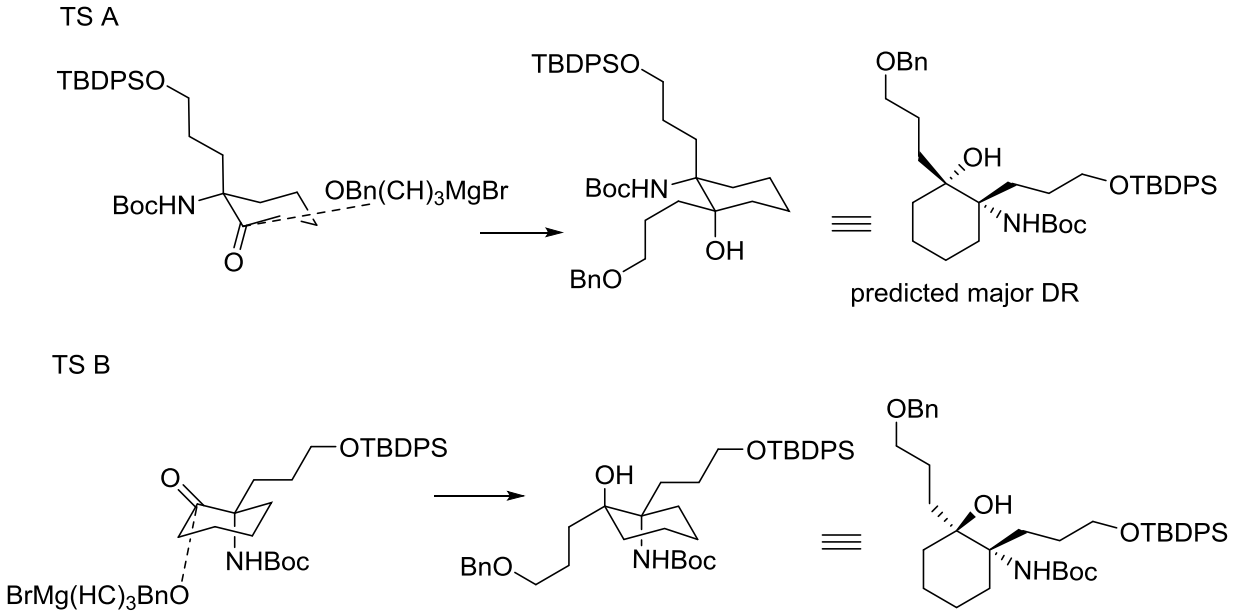


2.83 **2.84** 79 % **2.85** 22 %

Scheme 124 *Reagents and conditions*: a) $BnO(CH_2)_3MgBr$ (2 eq), THF, 0 °C; b) $CuSO_4$ (5 eq), *p*-xylene, reflux.

The ^{1}H NMR spectrum confirmed the identity of the product **2.84**, as all the signals expected for the tether were present, as well as a broad singlet at 5.42 ppm coming from the hydroxyl. This was true for the ^{13}C NMR spectrum too, in which the carbonyl resonance at 207.5 ppm had also disappeared, and all twenty six resonances could be accounted for. A single carbonyl stretch at 1708 cm^{-1} was present in the IR absorbance spectrum for the carbamate, as well as a diagnostic broad absorbance stretch at 3408 cm^{-1} assigned to the hydroxyl. The parent ion was found to be 660.4076 $[M+H]^+$ correlating to the correct molecular formula of $C_{40}H_{58}NO_5Si$. ^{1}H NMR and ^{13}C spectra indicated the

presence of two diastereomers in a ratio of 14:1, the major presumably arising from equatorial attack by the bulky Grignard reagent on a cyclohexanone chair conformation with one of the substituents equatorial (this was postulated as being the NBoc group earlier but this might be incorrect). The two possible chair conformations are labelled as transition state A, where the NBoc is equitorail (TS A), and transition state B with the alkyl chain in equatorial position (TS B), **Scheme 125**. In any event this was of no consequence because of the intention to dehydrate subsequently, with loss of that particular stereogenic centre.



Scheme 125 Proposed transition states of the Grignard addition and predicted major diastereomer arising from TS A.

Thereafter, the dehydration step needed to be carried out and the protocol of using dry $CuSO_4$ in refluxing xylene was employed. Richards' accounts pertaining to the analogous racemic synthesis (**Scheme 61**) screened several dehydration methodologies and concluded that the $CuSO_4$/ xylene system gave the highest yields and cleanest conversions. In this case, however, successful dehydration with the $CuSO_4$ was only accomplished after numerous attempts under various conditions, in a modest yield of 22 % after chromatography. Conversions were not clean either, with several by-products forming during the reaction, as evidenced by tlc. The dehydration was also performed on the deprotected amine derivative; however, this did not have a positive effect on the outcome either. The product **2.85** was not characterized fully so although its formation could not be categorically proven, indication of successful conversion mainly came from the ^{1}H NMR spectrum, which no longer contained the broad hydroxyl signal at 5.49 ppm and featured a new doublet of doublets at 5.00 ppm for either an *exo* or *endo* cyclic alkene. Unfortunately, the trials exhausted all

of the available material and the sequence could not be continued at that point. Although the synthesis broke down at that stage, the fact that some product was obtained from the dehydration step was a sign that conditions for the dehydration could possibly be optimized to increase yields. Alternatively, other dehydration methods could be applied, such as using phosphorous oxychloride. The marked difference in the results of the dehydration in this system to that of the aza-spirocycle, implied that the more rigid bicyclic system was better-suited substrate for the dehydration. Any future work would therefore entail earlier closure of the C ring (i.e. route shown in red in **Scheme 117**) for comparison.

2.10 Conclusions and Future work

2.10.1 Conclusion

A novel methodology for the stereoselective construction of quaternary carbons was accomplished via high-yielding sequential alkylations on auxiliary-malonate systems **2.31a** to **d**, in which the second alkylation proceeded with high diastereoselectivity (>95:5) to deliver quaternary malonates **2.33a** to **d.** With the aid of a crystal structure for derivative **2.33b**, it was concluded that the reaction proceeds via a *Z*-enolate with the K^+ cation chelated into the malonate hole, and the imide bond in a s-*trans*$_{C\text{-}N}$ conformation. Adaptation of the sequence to incorporate a PMB malonate ester, allowed for chemoselective ester cleavage under acidic conditions, furnishing quaternary carboxylic acids **2.41 a** to **f** which were successfully transformed to a range of ATAs **2.44a** to **f** via a modified Curtius procedure. Subsequent methanolysis reactions delivered various α,α-disubstituted amino acid methyl esters in high yields (75 – 82 %) and *ee*s (>95 %), with concomitant recovery of the auxiliary. As a demonstration of utility, enantioenriched α-allyl-alanine, α-methyl-phenylalanine, α-allyl-lysine and α-benzyl-proline derivatives were generated via this protocol.

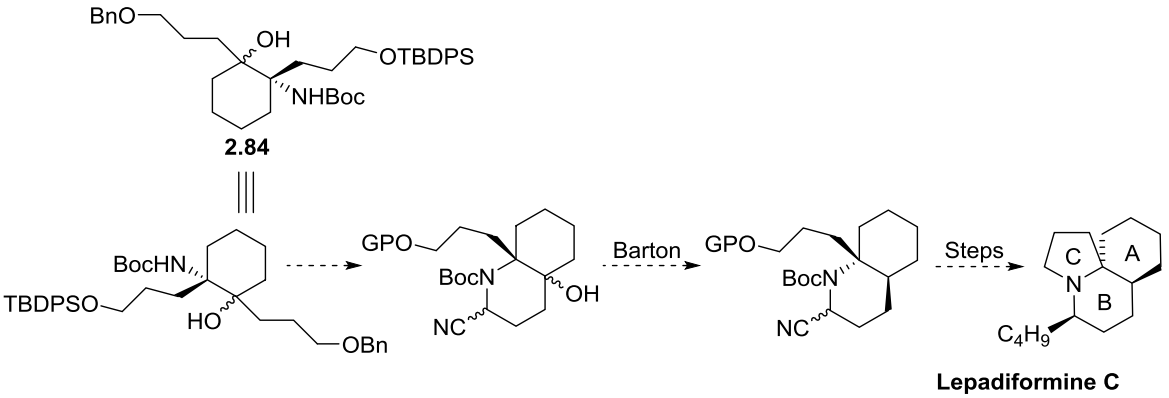
The methodology was applied to the enantioselective construction of the requisite ATA contained within the lepadiformines in the form of amino alcohol **2.74**, which was further proliferated towards cyclohexane derivative **2.84** in seven steps, at which point a problematic dehydration step terminated the sequence prematurely.

2.10.2 Future Work

Extension of this methodology to generate additional α-substituted natural amino acids is currently underway with quaternary leucine, tryptophan, methionine and serine in different stages of completion, all following the same trend with regards to selectivity thusfar; findings will be published in due course. With regards to the synthetic sequence towards (-)-lepadiformine C, two options could be investigated in order to accomplish a successful total synthesis:

- Earlier closure of the C-ring and construction of the B-ring last using the Richards protocol.

- Removal of the hydroxyl group of compound **2.84** following the Grignard step using radical deoxygenation methodology (Barton-McCombie).[158] In order to generate the required *trans* A/B azadecalin ring junction stereochemistry one would presumably need to carry out the deoxygenation on a fused A/B azadecalin. Radicals equilibrate, and conversion to the favoured *trans* [6.6] azadecalin stereochemistry would be favoured and independent of the diastereoselectivity in the Grignard step. However, one would need to deoxygenate at a quaternary centre (tertiary radical) in which formation of an appropriate precursor from the tertiary alcohol might be challenging. **Scheme 126** below summarises these ideas.



Scheme 126 Possible route for completion of lepadiformine C synthesis from **2.84.**

Chapter 3: Experimental Section

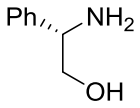
3.1 General Methods

All reactions were carried out in oven-dried glassware, and performed under a nitrogen atmosphere unless otherwise stated. Reagents were obtained from commercial sources (Sigma–Aldrich, Fluka, Merck, Kimix) and used as obtained unless stated. The following reaction solvents were distilled under nitrogen, from the drying agents indicated: THF (Na wire, benzophenone), DCM (P_2O_5), Et_2O (CaH_2), CH_3CN (CaH_2), toluene (CaH_2).
Reaction temperatures were achieved with heat/silicone oil (for > 25 ^oC), ice/NH_4Cl salt (for 0 ^oC), and acetone/liquid nitrogen (< -20 ^oC). Aqueous solutions were prepared using deionized water.

All reactions were monitored by tlc using aluminium-backed Merck silica-gel 60 F_{254} plates, and column chromatography was carried out using Kieselgel 60 silica-gel (Merck). Active compounds were observed under UV-lamp (ultraviolet), while non-UV active compounds were sprayed with a 2.5 % solution of *p*-anisaldehyde in a mixture of sulphuric acid and ethanol (1:10 v/v), iodine vapour, or ceric ammonium sulphate solution and then heated for visualization.

Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker 400 MHz spectrometer (^1H at 399.95 MHz and ^{13}C at 100.6 MHz), or a Varian Mercury 300 MHz spectrometer (^1H at 300.08 MHz and ^{13}C at 75.46 MHz). Chemical shifts (δ) and *J*-coupling values were reported in units of ppm and Hz respectively. Chemical shifts for ^1H and ^{13}C were recorded relative to residual chloroform, 7.26 and 77.16 ppm respectively. High resolution mass spectra (HRMS) were recorded on Waters Synapt G2 in electrospray positive mode. Elemental analyses were performed using a Fisons EA 1108 CHNS elemental analyzer. Infra-Red (IR) spectroscopy was performed on a Perkin-Elmer Paragon 1000 FT-IR Spectrometer on NaCl plates, with vibrations measured in units of cm^{-1}. Optical rotations were obtained using a Perkin Elmer 343 polarimeter at 20 °C and are reported as: $[\alpha]_D^{20}$ (*c* g/ml, solvent). Determination of melting points was done using a Reichert-Jung Thermovar hot stage microscope (HSM) and are uncorrected. The enantiomeric excess (ee) of products was determined by HPLC on an Agilent 1220 Series using a Diacel OD (250 x 4.6 mm) or Chiralpak AD (250 x 4.6 mm)

(*S*)-Phenylglycinol (2.14)

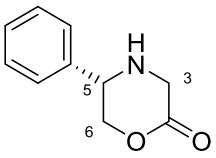


$LiAlH_4$ (2.51 g, 6.62 mmol, 2 eq) was placed in THF (200 ml) and cooled to 0 °C in an ice bath. (S)-Phenylglycine (5.0 g, 3.31 mmol) was added in 10 increments over 30 minutes. The mixture was stirred at 0 °C for an hour, following which it was refluxed overnight. After this time, it was cooled to 0 °C and quenched by a slow addition of water (5.0 ml), followed by NaOH (2.5 mL, 2M, 5.0 mmol). Stirring was continued for 20 min at room temperature, until all the $LiAlH_4$ was consumed and the white lithium salts remained. Filtering through Celite, washing with DCM (150 ml) and drying with $MgSO_4$ gave a bright-yellow solution which when concentrated to yield a dark-orange solid. This material was recrystallized to yield the product as an off-white powder (3.86 g, 2.81 mmol, 85 %).

M.p. (DCM/EtOAc) = 73-76 °C, lit = 74 – 76 °C;[159] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H, aromatic), 5.62 (s, 1H, OH), 4.11 (m, 1H, CH), 3.59 (dd, 1H, CH_2a), 3.56 (dd, 1H, CH_2b), 2.28 (broad s, 2H, NH_2).

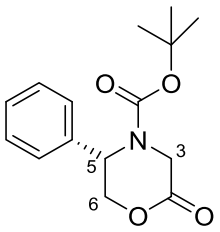
The data obtained corresponds to the published data for this compound.

(*S*)-5-Phenylmorpholin-2-one (2.15)[120]



(*S*)-Phenylglycinol **2.14** (1.500 g, 10.933 mmol) and Hünig's base (4.712 ml, 27.332 mmol, 2.5 eq) in acetonitrile (30 ml) were placed in a dropping funnel and added to a stirring solution of phenyl 2-bromoacetate (3.531 g, 16.400 mmol, 1.5 eq) in acetonitrile (10 ml) over 30 minutes. After overnight stirring, the reaction mixture was concentrated and the residue subjected to flash chromatography using EtOAc/ Hexanes (50/50) which included filtration through a plug (1 cm) of anhydrous sodium carbonate placed on top of the silica gel. Morpholinone **2.15** was isolated (1.368 g, 7.761 mmol, 70 % yield), which was immediately taken through to the Boc protection step.

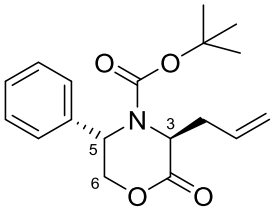
***tert*-Butyl (*S*)-2-oxo-5-phenylmorpholine-4-carboxylate (2.16)**[120]



Morpholinone, **2.15** (1.00 g, 5.640 mmol) and triethylamine (0.745 ml, 5.640 mmol, 1 eq) were stirred in ethyl acetate (40 ml), and di-*tert*-butyl dicarbonate (1.426 g, 6.204 mmol, 1.1. eq) was added . The reaction solution was then stirred at room temperature for 6 hours, following which it was diluted with diethyl ether (40 ml), washed with HCl (1M, 50 ml), then saturated aqueous sodium carbonate (50 ml). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated to a yellowish oil. Recrystallization gave **2.16** as a white crystalline solid (1.218 g, 4.394 mmol, 78 %).

M.p. (diethyl ether/ hexanes) = 86 – 89 °C, lit.[120] 87 – 88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H, aromatic), 5.18 – 5.14 (m, 1H, H-5), 4.70 – 4.48 (m, 3H, H-6 + H-3a), 4.19 (d, *J* = 11.9 Hz, H-3b) 1.33 (s, 9H, *t*-Bu).The data obtained corresponds to the published data for this compound.

***tert*-Butyl (3*S*,5*S*)-3-allyl-2-oxo-5-phenylmorpholine-4-carboxylate (2.17)**

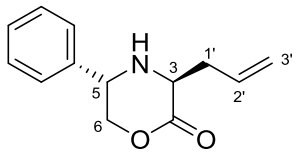


A solution of **2.16** (2.671 g, 9.630 mmol) in THF/DME (50/50, 100 ml) was cooled to -78 °C, followed by the dropwise addition of KHMDS (0.5 M, 19.3 ml, 9.63 mmol, 1 eq) and further stirring at -78 °C for one hour. Alyll bromide (1.24 ml, 14.45 mmol, 1.5 eq) was then syringed in slowly and the reaction left at -78 °C for 3 hours after which it was quenched by the addition of saturated ammonium chloride (15 ml) and diluted with diethyl ether (30 ml). The organic phase was then successively washed with HCl (1M, 20 ml), saturated aqueous sodium bicarbonate (20 ml) and brine (30 ml), then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude allylated product **2.17**. Purification by chromatography yielded **2.17** as a colourless crystalline solid (1.926 g, 6.067 mmol, 63 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 6.57 (m, 5H, aromatic), 5.92 – 5.99 (m, 1H, CH_2=C*H*), 5.28 – 5.20 (m, 2H, CH=CH_2), 5.13 – 4.95 (m, 2H, H-5 + H-6a), 4.85 (dd, *J* = 11.8, 3.1 Hz, 1H, H-3), 4.51 – 4.36 (m,

1H, H-6b), 2.92 – 2.62 (m, 2H, CHCH_2), 1.38 (s, 9H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8 (C=O lactam), 153.7 (C=O Boc), 132.4 (*C*H=CH_2), 129.1 (Ar), 128.0 (Ar), 125.6 (Ar), 119.7 (CH=*C*H_2), 81.6 (*C*$(CH_3)_3$), 69.9 (C-6), 56.9 (C-3), 54.9 (C-5), 38.5 (*C*H_2CH=CH_2), 28.2 (C(*C*$H_3)_3$).

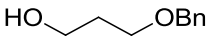
(3*S*,5*S*)-3-allyl-5-phenylmorpholin-2-one (2.18)[120]



The allylated Boc-morpholinone **2.17** (0.300 g, 0.945 mmol) was dissolved in DCM (50 ml) and cooled to 0 °C. To this stirring solution was added anisole (0.130 ml, 1.134 mmol, 1.2 eq) and TFA (0.092 ml, 1.134 mmol, 1.2 eq) and the mixture allowed to warm up to rt over the course of an hour. Following the addition of saturated $NaCO_3$ at 0 °C, the organic layer was immediately isolated and the aqueous phase extracted with DCM (3 x 20 ml). Pooled organic fractions were dried over anhydrous MgSO4, filtered and concentrated, and the residue was subjected to flash chromatography using EtOAc/hexanes (30/70) to yield the title allylated morpholinone **2.18** (0.037 g, 0.170 mmol, 18 %) as a yellow oil. ^{1}H NMR spectral data IR data corresponded closely to that published in literature.[121]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 5H, aromatic), 5.91 – 5.80 (m, 1H, H-2'), 5.22 – 5.11 (m, 1H, H-3'a), 5.18 – 5.17 (m, 1H, H-3b), 4.41 – 4.37 (m, 3H, H-5 and H-6), 3.95 – 3.90 (m, 1H, H-3), 3.60 (broad s, 1H, NH), 2.67 – 2.60 (m, 2H, H-1').

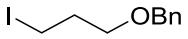
3-(Benzyloxy)propan-1-ol (2.51)



1,3-propanediol (20.0 ml, 0.277 mol, 1.9 eq) was placed in dry THF (300 ml) and cooled to 0 °C. NaH (60 % 5.881 g, 0.147 mol, 1 eq) was added in 15 portions over a period of 30 min and the reaction was left to stir at room temperature for 30 minutes, following which benzyl bromide (17.5 ml, 0.147 mol, 1 eq) was syringed into the mixture. The reaction was left at room temperature for one hour, and then refluxed overnight. Once cooled, a mixture of THF and water (50/50, 100 ml) was added slowly, the solvent evaporated, water was added (100 ml) and the mixture extracted with Et_2O (3 x 200 ml) and EtOAc (200 ml). The organic extracts were washed with saturated aqueous sodium bicarbonate (100 ml) and brine (100 ml), dried over anhydrous $MgSO_4$ and concentrated. Flash chromatography using EtOAc/ hexane (15/85) yielded the title compound **2.51** (21.0 g, 0.126 mol, 86 %) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H, aromatic), 4.52 (s, 2H, OCH_2Ph), 3.72 (m, 2H, CH_2OBn), 3.59 (t, *J* = 6.8 Hz, 2H, CH_2OH), 2.50 (broad s, 1H, OH), 2.00 – 1.89 (m, 2H, CH_2CH_2); ^{13}C

NMR (101 MHz, $CDCl_3$) 138.1 (Ar_q), 128.3 (Ar), 127.9 (Ar) 127.7 (Ar), 73.0 (O*C*H_2Ph), 69.3 (*C*H_2OBn), 60.9 (*C*H_2OH), 32.3 (CH_2*C*H_2).

((3-Iodopropoxy)methyl)benzene (2.52)

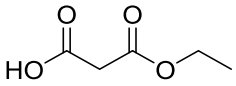


The alcohol, **2.51** (2.00 g, 12.03 mmol) was placed in dry toluene (100 ml). Imidazole (1.31 g, 19.25 mmol, 1.6 eq), triphenylphosphine (5.05 g, 19.25 mmol, 1.6 eq) and iodine (3.97 g, 15.64 mmol, 1.3 eq) were added successively to the stirring mixture. The reaction was left to stir at room temperature for 4 hours and then saturated aqueous sodium thiosulphate solution (100 ml) was added and stirring continued for 15 minutes. The aqueous layer was extracted with diethyl ether (3 x 100 ml) and the combined organic fractions were washed with saturated aqueous sodium bicarbonate (100 ml) and brine (80 ml). Once dried over anhydrous $MgSO_4$ and concentrated, the residue was subjected to flash chromatography using EtOAc/ hexane (5/95) to afford iodide **2.52** (3.19 g, 11.55 mmol, 96 %) as a clear liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H, aromatic), 4.53 (s, 2H, OC*H*$_2$Ph), 3.55 (t, *J* = 5.8 Hz, 2H, C*H*$_2$OBn), 3.31 (t, *J* = 6.8 Hz, 2H, IC*H*$_2$), 2.12 – 2.07 (m, 2H, CH_2C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) 138.4 (Ar_q), 128.6 (Ar), 128.7 (Ar) 127.8 (Ar), 73.3 (O*C*H_2Ph), 69.8 (*C*H_2OBn), 33.7 (CH_2*C*H_2), 3.4 (*C*H_2I).

Ethyl malonate-auxiliary series

3-Ethoxy-3-oxopropanoic acid (2.30)[144]

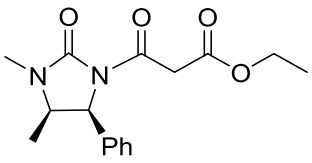


To a solution of diethyl malonate (20.0 ml, 0.131 mol) in EtOH (150 mL) at 0 °C was added dropwise a solution of aq. KOH (2.5 M, 57.70 ml, 0.144 mol, 1.1 eq) and the contents allowed to slowly warm up to rt. After 3 hours the EtOH was removed under reduced pressure, the concentrate diluted with water (50 mL) and extracted with DCM (3 x 50 ml) to remove unreacted diethyl malonate. The aqueous layer was then acidified with conc. HCl to pH = 2 and then re-extracted with DCM (3 × 50 ml), the organic extracts combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to obtain the half-acid (15.6 g, 0.118 mol, 90 %) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (broad s, 1H, COOH), 4.38 – 4.10 (m, 2H, C*H*$_2$$CH_3$), 3.48 – 3.17 (m, 2H, H-2), 1.40 – 1.17 (m, 3H, CH_2C*H*$_3$).

Synthesis of auxiliary malonate

Ethyl 3-((4*R*,5*S*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-3-oxopropanoate (2.31)

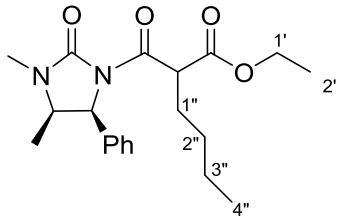


Malonate half ester **2.30** (5.00 g, 37.85 mmol), (4*R*, 5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one **(+)-2.29** (7.23 g, 37.85 mmol, 1 eq) and HOBt (1.16 g, 7.57 mmol, 20 mol %) were dissolved in DCM and stirred at 0 °C. A solution of DCC (9.83 g, 45.42 mmol, 1.2 eq) and in DCM was gradually added to the mixture via a pressure-equalizing dropping funnel and once addition was complete, the cooling bath was removed. The reaction was complete within 3 hours at room temperature after which time it was filtered through Celite, the solvent evaporated and the resultant residue purified by column chromatography with ethyl acetate/hexane (20/80) to furnish auxiliary malonate **2.31** (10.25 g, 33.69 mmol, 89 %) as a colourless solid. Mp 84 °C (EtOAc/ hexane); [α]D20 = –6.2, (*c* = 1.0, DCM); IR ν_{max} (cm^{-1}) 3008 (C-H aromatic), 2860 (C-H alkanes), 1736 (C=O ester), 1687 (C=O imide); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 3H, aromatic), 7.18 (m, 2H, aromatic), 5.32 (d, *J* = 8.7 Hz, 1H, C*H*Ph), 4.18 (q, *J* = 7.2 Hz, 2H, CH_2CH$_3$), 4.02 (s, 1H H-2a), 3.97 (s, 1H, H-2b), 3.93 (dq, *J* = 8.7, 6.6 Hz, 1H, C*H*CH$_3$), 2.81 (s, 3H, NCH_3), 1.26 (t, *J* = 7.2 Hz, 3H, CH$_2$CH_3), 0.80 (d, *J* = 6.6 Hz, 3H, CHCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.7 (C=O), 165.1 (C=O), 155.6 (C=O), 136.1 (Ar$_q$), 128.6 (Ar), 128.3 (Ar), 127.2 (Ar), 61.3 (C-1'), 59.5 (*C*HPh), 54.2 (*C*HCH$_3$), 43.5 (C-2), 28.3 (N*C*H$_3$), 15.1 (C-2'), 14.2 CH*C*H$_3$); Anal. Calc. for $C_{16}H_{20}N_2O_4$ (%): C, 63.14; H, 6.61; N, 9.20. Found (%): C, 63.19; H, 6.57; N, 9.24.

General procedure for mono-alkylation of auxiliary malonate **2.31** to prepare α-substituted auxiliary malonates **2.32a – 2.32e**

A solution of **2.31** (1 eq) in tetrahydrofuran was cooled to -78 °C followed by the dropwise addition of KHMDS in toluene (0.5 M, 1.2 eq) and stirring at this temperature was continued for a further 30 minutes after which time the electrophile (1.5 - 3 eq) was added in one portion to the anion solution. The reaction was slowly warmed to room temperature and stirred for a further 8 hours. It was then quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated to give the crude product which was chromatographed using ethyl acetate/ hexanes (30/70).

Ethyl 2-((4*R*,5*S*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)hexanoate (2.32a)

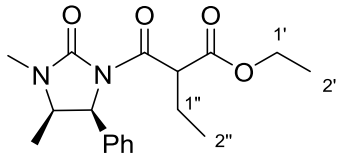


Title butyl-substituted auxiliary malonate **2.32a** was obtained (0.462 g, 1.284 mmol, 98 %) via the general alkylating procedure from **2.31** (0.400 g, 1.131 mmol) using KHMDS (3.15 ml, 1.575 mmol) 1-bromobutane (0.42 ml, 3.932 mmol, 3.0 eq) and TBAI (0.241 g, 0.655 mmol, 0.5 eq). In this case, the reaction was refluxed overnight and column chromatography with EtOAc/ hexane (15/85) yielded **2.32a** as a colourless oil in a 51:49 mixture of diastereomers as determined by NMR spectroscopy. IR: ν_{max} (cm^{-1}) 3010 (C-H aromatic), 2861 (C-H aliphatic), 1732 (2x C=O, ester and amide), 1689 (C=O, urea); HRMS (ES): calc. 361. 2127; $C_{20}H_{29}N_2O_4$ $[M + H]^+$ requires 361.2125.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 3H, aromatic), 7.23 (m, 1H, aromatic), 7.12 (m, 1H, aromatic), 5.31 (d, *J* = 8.6 Hz, 1H, C*H*Ph), 4.63 (dd, *J* = 5.3, 3.4 Hz, 1H, H-2), 4.24-4.08 (m, 2H, H-1'), 3.91 (m, 1H, C*H*CH_3), 2.82 (s, 3H, NCH_3), 2.00-1.75 (m, 2H, H-1"), 1.35-1.28 (m, 2H, H-3"), 1.25-1.18 (m, 2H, H-2"), 1.20 (t, *J* = 7.2 Hz, 3H, H-2'), 0.82 (t, *J* = 7.2 Hz, 3H, H-4"), 0.80 (d, *J* = 6.4 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.4 (C=O, ester), 168.4 (C=O, amide), 155.7 (C=O, urea), 136.2 (Ar), 128.4 (Ar), 128.2 (Ar), 127.2 (Ar), 61.1 (C-1'), 59.7 (*C*HPh), 54.0 (*C*HCH_3), 51.1 (C-2), 29.2 (C-1"), 28.3 (N*C*H_3), 27.6 (C-3"), 22.6 (C-2"), 15.1 (CH*C*H_3), 14.3 (C-2') 14.2 (C-4").

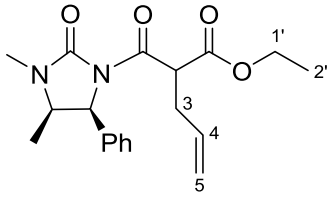
Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 3H, aromatic), 7.23 (m, 1H, aromatic), 7.12 (m, 1H, aromatic), 5.36 (d, *J* = 8.6 Hz, 1H, C*H*Ph), 4.61 (dd, *J* = 6.4, 1.2 Hz, 1H, H-2), 4.24-4.08 (m, 2H, H-1'), 3.91 (m, 1H, C*H*CH_3), 2.81 (s, 3H, NC*H*$_3$), 2.00-1.75 (m, 2H, H-1"), 1.35-1.28 (m, 2H, H-3"), 1.25-1.18 (m, 2H, H-2"), 1.26 (t, *J* = 7.2 Hz, 3H, H-2'), 0.87 (t, *J* = 7.2 Hz, 3H, H-4"), 0.79 (d, *J* = 6.4 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.5 (C=O, ester), 168.8 (C=O, amide), 155.7 (C=O, urea), 136.7 (Ar), 128.6 (Ar), 128.3 (Ar), 127.3 (Ar), 61.1 (C-1), 59.8 (*C*HPh), 54.2 (*C*HCH_3), 51.3 (C-2), 29.3 (C-1"), 28.7 (N*C*H_3), 27.9 (C-2"), 22.7 (C-3"), 15.1 (CH*C*H_3), 14.3 (C-2') 14.2 (C-4").

Ethyl 2-((4*R*,5*S*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)butanoate (2.32b)



Title ethyl-substituted auxiliary malonate **2.32b** was obtained (0.388 g, 1.23 mmol, 94 %) via the general alkylating procedure from **2.31** (0.400 g, 1.31 mmol) using KHMDS (3.15 ml, 1.58 mmol) and iodoethane (0.31 ml, 3.93 mmol, 3.0 eq). In this case, the reaction was refluxed overnight and column chromatography with EtOAc/ hexane (25/75) yielded **2.32b** as a colourless solid and in a 51:49 mixture of diastereomers as determined by NMR spectroscopy. Mp 126-129 °C; $[\alpha]_D^{20}$ = -4.5, (*c* = 1.0, DCM); IR: ν_{max} (cm^{-1}) 3010 (C-H aromatic), 2886 (C-H aliphatic), 1732 (2x C=O, ester and amide), 1689 (C=O, urea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 3H, aromatic), 7.21 (m, 2H, aromatic), 5.31 (d, *J* = 8.8 Hz, 1H, C*H*Ph), 4.59 (dd, *J* = 5.6, 2.8 Hz 1H, H-2), 4.25-4.08 (m, 2H, H-1'), 3.91 (dq, *J* = 8.8, 6.8 Hz, 1H, C*H*CH_3), 2.82 (s, 3H, NCH_3), 2.04-1.86 (m, 2H, H-1"), 1.20 (t, *J* = 7.2 Hz, 3H, H-2'), 0.97 (t, *J* = 8.0 Hz, 3H, H-2"), 0.80 (d, *J* = 6.8 Hz, 3H, CHCH_3); ^{13}C (100.6 MHz, $CDCl_3$) δ 170.3 (C=O, ester), 168.1 (C=O, amide), 155.7 (C=O, urea), 136.2 (Ar_q), 128.5 (Ar), 128.2 (Ar), 127.3 (Ar), 61.0 (C-1'), 59.8 (C-*C*HPh), 54.2 (*C*HCH_3), 52.7 (C-2), 28.3 (N*C*H_3), 22.1 (C-1"), 15.2 (CH*C*H_3), 14.2 (C-2'), 12.2 (C-2"); Anal. Cal. for $C_{18}H_{24}N_2O_4$ (%): C, 65.04; H, 7.28; N, 8.43. Found (%): C, 64.85; H, 7.06; N, 8.36.

Ethyl 2-((4*R*,5*S*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)pent-4-enoate (2.32c)



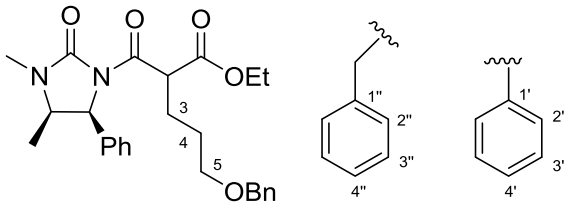
Title allyl-substituted auxiliary malonate **2.32c** was obtained (0.415 g, 1.21 mmol, 92 % yield) via the general alkylating procedure from **2.31** (0.400 g, 1.31 mmol) using KHMDS (3.15 ml, 1.58 mmol) and allyl bromide (mmol, 1.8 eq) at rt. Column chromatography with EtOAc/ hexane (20/80) yielded **2.32c** as a colourless oil in a 52:48 mixture of diastereomers as determined by NMR spectroscopy. IR: ν_{max} (cm^{-1}) 3010 (C-H aromatic), 2959 (C-H aliphatic), 1732 (2x C=O, ester and amide), 1689 (C=O, urea); HRMS (ES): Calc. 345.1814; $C_{19}H_{25}N_2O_4$, $[M + H]^+$ requires 345.1813.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H, aromatic), 7.20 (m, 1H, aromatic), 7.17 (m, 1H, aromatic), 5.81-5.45 (m, 1H, H-4), 5.35 (d, *J* = 8.8 Hz, 1H, C*H*Ph), 5.09 (m, 1H, H-5a), 4.97 (m,

1H, H-5b), 4.91 (m, 1H, H-2), 4.25-4.11 (m, 2H, H-1'), 3.98 – 3.85 (m, 1H, C*H*CH_3), 2.83 (s, 3H, NCH_3), 2.50-2.21 (m, 2H, H-3), 1.25 (t, *J* = 7.2 Hz, 3H, H-2'), 0.80 (d, *J* = 6.4 Hz, 3H, CHCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6 (C=O, ester), 169.7 (C=O, amide), 155.1 (C=O, urea), 136.1 (Ar), 135.0 (C-4), 128.5 (Ar), 128.2 (Ar), 127.2 (Ar), 117.1 (C-5), 61.3 (C-1'), 58.8 (*C*HPh), 54.1 (*C*HCH_3), 50.9 (C-2), 32.8 (C-3), 28.3 (N*C*H_3), 15.2 (CH*C*H_3), 14.3 (C-2').

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H, aromatic), 7.20 (m, 1H, aromatic), 7.17 (m, 1H, aromatic), 5.81-5.45 (m, 1H, H-4), 5.30 (d, *J* = 8.8 Hz, 1H, CHPh), 5.09 (m, 1H, H5a), 4.80 (dd, *J* = 5.4, 3.6 Hz, 1H, H-5b), 4.91 (m, 1H, H-2), 4.25-4.11 (m, 2H, H-1'), 2.82 (s, 3H, NCH_3), 2.50-2.21 (m, 2H, H-3), 1.21 (t, *J* = 7.2 Hz, 3H, H-2'), 0.80 (d, *J* = 6.4 Hz, 3H, CHCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6 (C=O, ester), 170.7 (C=O, amide), 155.1 (C=O, urea), 136.7 (Ar), 135.4 (C-4), 128.6 (Ar), 128.3 (Ar), 127.3 (Ar), 117.1 (C-5), 61.3 (C-1'), 58.8 (*C*HPh), 54.2 (*C*HCH_3), 51.1 (C-2), 32.8 (C-3), 28.3 (N*C*H_3), 15.2 (CH*C*H_3), 14.3 (C-2').

Ethyl 5-(benzyloxy)-2-((4*R*,5*S*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)pentanoate (2.32d)



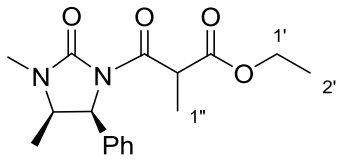
Title α-substituted auxiliary malonate **2.32d** was obtained (0.515 g, 1.140 mmol, 87 %) via the general alkylating procedure from **2.31** (0.400 g, 1.312 mmol) using KHMDS (3.15 ml, 1.575 mmol) and alkyl halide **2.52** (0.435 g, 1.574 mmol, 1.2 eq) under reflux conditions. Column chromatography with EtOAc/ hexane (20/80) yielded **2.32d** as a gummy solid in a 52:48 mixture of diastereomers as determined by NMR spectroscopy.

Major diastereomer: HRMS (ES): *m/z* found 453.2352, $C_{26}H_{33}N_2O_5$ $[M+H]^+$ requires 453.2350; $[\alpha]_D^{20}$= -26.2, (DCM, *c* = 1); IR: ν_{max} (cm^{-1}) 3053 (C-H aromatic), 2937 (C-H aliphatic), 1732 (C=O ester), 1687 (C=O imide); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 6.99 (m, 10H, aromatic), 5.28 (d, *J* = 8.7 Hz, 1H, C*H*Ph), 4.74 (dd, *J* = 8.6, 5.4 Hz, 1H, H-2), 4.47 (s, 2H OCH_2Ph), 4.14 – 4.07 (m, 2H, CH_2CH_3), 3.81 (dt, *J* = 8.7, 3.6 Hz, 1H, C*H*CH_3), 3.49 (t, *J* = 6.4 Hz, 2H, H-5), 2.78 (s, 3H, NCH_3), 2.03 – 1.87 (m, 2H, H-3), 1.78 – 1.74 (m, 2H, H-4), 1.26 (t, *J* = 6.6 Hz, 3H, CH_2CH_3), 0.79 (d, *J* = 6.6 Hz, 3H, CHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3 (C=O), 168.6 (C=O), 155.5 (C=O), 138.5 (C1'), 135.9 (C1''), 128.5 (C3'), 128.3 (C3''), 128.0 (C2'), 127.4 (C2''), 126.9 (C4''), 125.9 (C4'), 72.7 (O*C*H_2Ph), 70.1 (C-5), 61.1 (*C*H_2CH_3), 59.6 (*C*HPh), 53.9 (C-2), 50.8 (*C*HCH_3), 28.1 (N*C*H_3), 27.5 (C-4), 25.5 (C-3), 14.9 (CH*C*H_3), 14.1 (CH_2CH_3).

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 6.99 (m, 10H, aromatic), 5.36 (d, *J* = 8.7 Hz, 1H, C*H*Ph), 4.83 (t, *J* = 7.0 Hz, 1H, H-2), 4.44 (s, 2H, OC*H*$_2$Ph), 4.14 – 4.07 (m, 2H, C*H*$_2$CH$_3$), 3.91 (dt, *J* = 8.7, 3.6, 1H, C*H*CH$_3$), 3.44 (t, *J* = 6.4 Hz, 2H, H-5), 2.81 (s, 3H, NC*H*$_3$), 2.03 – 1.87 (m, 2H, H-3), 1.74 – 1.64 (m, 2H, H-4), 1.19 (t, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$), 0.77 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$).

Ethyl 3-((4*R*, 5*S*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-methyl-3-oxopropanoate (2.32e)



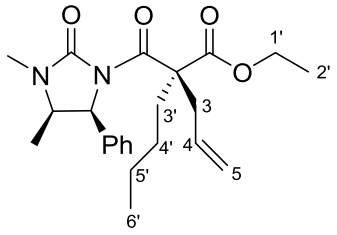
Title methyl-substituted auxiliary malonate **2.32e** was obtained (0.375 g, 1.118 mmol, 90 %) via the general alkylating procedure from **2.31** (0.400 g, 1.312 mmol) using KHMDS (3.15 ml, 1.575 mmol), MeI (0.25 ml, 3.936 mmol, 3 eq) at room temperature as an off-white solid and as a mixture of diastereomers. Saturated aq. $Na_2S_2O_3$ was also used in the work-up. Recrystallization from EtOAc/ hexane to a constant Mp afforded one single diastereomer. Mp 152-153 °C; $[\alpha]_D^{20}$ = -31.9° (DCM, *c* = 1.0); IR: ν_{max} 3010 (C-H aromatic), 2863 (C-H aliphatic), 1732 (2 × C=O, ester and imide), 1689 (C=O, urea); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 3H, aromatic), 7.22 (m, 2H, aromatic), 5.30 (d, *J* = 8.7 Hz, 1H, C*H*Ph), 4.65 (q, *J* = 7.5 Hz, 1H, H-2), 4.14 (m, 2H, H-1'), 3.90 (dq, *J* = 8.7, 6.6 Hz, 1H, C*H*CH$_3$), 2.81 (s, 3H, NC*H*$_3$), 1.39 (d, *J* = 7.5 Hz, 3H, H-1"), 1.21 (t, *J* = 7.6 Hz, 3H, H-2'), 0.8 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.1 (C=O, ester), 169.0 (C=O, amide), 155.7 (C=O, urea), 136.2 (Ar$_q$), 128.5 (Ar), 128.2 (Ar), 127.3 (Ar), 61.2 (C-1'), 59.8 (*C*HPh), 54.3 (*C*HCH$_3$), 45.9 (C-2), 28.4 (NCH$_3$), 15.2 (CH*C*H$_3$), 14.2 (C-2'), 13.5 (C-2"); 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.

General procedure for alkylation of α-substituted auxiliary-malonates **2.32a – 2.32e** to prepare α,α-disubstituted auxiliary-malonates **2.33a – 2.33e**

To a solution of the appropriate derivative of **2.32** (1 eq) in THF at -78 °C was added a solution of KHMDS (1.2 eq, 0.5 M) and the reaction contents allowed to stir at this temperature for 30 min. Thereafter, the appropriate alkylating agent (1.5 – 3 eq.) was slowly added, the reaction contents allowed to slowly warm up to rt and left to stir overnight for 20 hrs. The reaction was quenched with sat. aqueous NH_4Cl, extracted with EtOAc, the organic extracts dried over $MgSO_4$, filtered under vacuum and the organic solvent removed *in vacuo*. The crude residue was chromatographed using

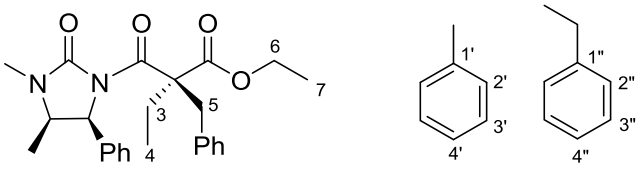
EtOAc / hexane mixtures to afford the derivative **2.33**, which was analysed by chiral HPLC and NMR spectroscopy for diastereoselectivity.

Ethyl (*S*)-2-((4*R*,5*S*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)-2-methylpent-4-enoate (2.33a)



The title disubstituted auxiliary malonate **2.33a** was prepared (0.189 g, 0.472 mmol, 85 %) via the general alkylating procedure from **2.32a** (0.200 g, 0.555 mmol), KHMDS (1.44 ml, 0.721 mmol, 1.3 eq, 0.5 M) and allyl iodide (0.15 ml, 1.66 mmol, 3.0 eq). Chromatography with EtOAc/ hexane (20/ 80) afforded **2.33a** as a colourless solid in 98:2 ratio of diastereomers. Mp = 88-90 °C (EtOAc/ hexane); $[\alpha]_D^{20}$ = -30.2, (DCM, *c* = 0.8); IR: ν_{max} 3009 (C-H aromatic), 2989 (C-H aliphatic), 1738 (2 x C=O, ester and amide), 1674 (C=O, urea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H, aromatic), 7.20 (m, 2H, aromatic), 5.41 (m, 1H, H-4), 5.31 (d, *J* = 8.4 Hz, 1H, C*H*Ph), 4.97 (m, 1H, H-5a), 4.89 (m, 1H, H-5b), 4.17 (m, 2H, H-1'), 3.91 (dq, *J* = 8.4, 6.4 Hz, 1H, C*H*CH_3), 2.92 (m, 1H, H-3a), 2.79 (s, 3H, NC*H*$_3$), 2.73 (m, 1H, H-3b), 1.93 (m, 2H, H-3'), 1.35-1.19 (m, 3H, H-5' + H-4'a), 1.26 (t, *J* = 7.2 Hz, 3H, H-2'), 1.02 (m, 1H, H-4'b), 0.86 (t, *J* = 7.2 Hz, 3H, H-6'), 0.79 (d, *J* = 6.4 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6 (C=O, ester), 170.0 (C=O, amide), 155.3 (C=O, urea), 136.7 (Ar), 133.4 (C-4), 128.5 (Ar), 128.2 (Ar), 127.3 (Ar), 118.0 (C-5), 60.6 (C-1'), 60.5 (*C*HPh), 58.4 (C-2), 54.4 (*C*HCH_3), 38.1 (C-3), 32.8 (C-3'), 28.3 (N*C*H$_3$), 26.3 (C-4'), 23.1 (C-5'), 15.1 (CH*C*H$_3$), 14.4 (C-2'), 14.1 (C-6'); Anal. Calc. $C_{23}H_{32}N_2O_4$ (%): C, 68.53; H, 8.05; N, 6.99. Found (%): C, 68.53; H, 7.89; N, 7.00.

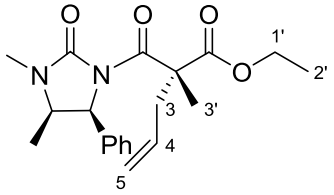
Ethyl (*S*)-2-benzyl-2-((4*R*,5*S*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)butanoate (2.33b)



The title disubstituted auxiliary malonate **2.33b** was prepared (0.219 g, 0.536 mmol, 89 %) via the general alkylating procedure from **2.32b** (0.200 g, 0.602 mmol), KHMDS (1.57 ml, 0.783 mmol, 1.3 eq, 0.5 M) and benzyl bromide (0.21 ml, 1.806 mmol, 3.0 eq). Chromatography with EtOAc/ hexane

(25/ 75) afforded **2.33b** as a colourless solid in a 96:4 mixture of diastereomers. Mp = 107-110 °C (EtOAc/ hexane); $[\alpha]_D^{20}$ = -42.0 (DCM, *c* = 0.8); IR: ν_{max} 3008 (C-H aromatic), 2863 (C-H aliphatic), 1739 (2 x C=O, ester and amide), 1635 (C=O, urea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 3H, aromatic), 7.25 (m, 2H, aromatic), 7.07 (m, 1H, aromatic), 6.98 – 6.84 (m, 4H, aromatic), 5.37 (d, *J* = 7.2 Hz, 1H, C*H*Ph), 4.04 (q, *J* = 9.6 Hz, 2H, H-6), 3.95 (dq, *J* = 8.5, 6.6 Hz, 1H, C*H*CH_3), 3.37 (s, 2H, H-5), 2.81 (s, 3H, NC*H*$_3$), 1.91 (m, 2H, H-3), 1.12 (t, *J* = 9.6 Hz, 3H, H-7), 0.87 (t, *J* = 7.5 Hz, 3H, H-4), 0.86 (d, *J* = 7.5 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.5 (C=O, ester), 169.9 (C=O, amide), 155.6 (C=O, urea), 137.12 (C-1'), 136.7 (C-1"), 130.7 (C-2"), 128.6 (C-3'), 128.2 (C-4'), 128.0 (C-2'), 127.8 (C-3"), 126.41 (C-4"), 61.0 (C-6), 60.5 (*C*HPh), 55.4 (C-2), 54.7 (*C*HCH_3), 39.5 (C-5), 28.36 (N*C*H_3), 26.65 (C-3), 15.1 (CH*C*H_3), 14.1 (C-7), 9.1 (C-4); Anal. Calc. $C_{25}H_{30}N_2O_4$ (%): C, 71.07; H, 7.16; N, 6.63. Found (%): C, 70.81; H, 6.99; N, 6.67.

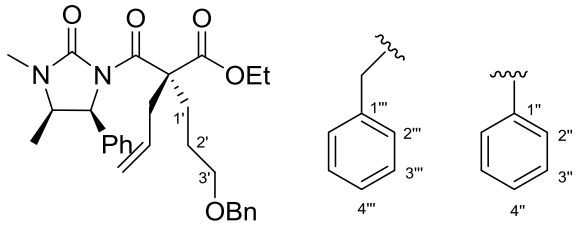
Ethyl (*R*)-2-((4*R*,5*S*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)-2-methylpent-4-enoate (2.33c)



The title disubstituted auxiliary-malonate **2.33c** was obtained (0.191 g, 0.535 mmol, 92 %) via the general alkylating procedure from **2.32c** (0.200 g, 0.581 mmol) with MeI (0.109 ml, 1.743 mmol, 3 eq) as a colourless oil in a 95:5 mixture of diastereomers. $[\alpha]_D^{20}$ = -33.3 (DCM, *c* = 1.0); IR: ν_{max} 3010 (C-H aromatic), 2991 (C-H aliphatic), 1735 (2 x C=O, ester and amide), 1675 (C=O, urea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 3H, aromatic), 7.17 (m, 2H, aromatic), 5.73 (m, 1H, H-4), 5.29 (d, *J* = 8.4 Hz, 1H, C*H*Ph), 5.04 (m, 1H, H-5a), 5.01 (m, 1H, H-5b), 4.19 (m, 2H, H-1'), 3.90 (dq, *J* = 8.4, 6.4 Hz, 1H, C*H*CH_3), 2.79 (s, 3H, NC*H*$_3$), 2.70 (m, 2H, H-3), 1.45 (s, 3H, H-3'), 1.27 (t, *J* = 7.2 Hz, 3H, H-2'), 0.79 (d, *J* = 6.4 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.1 (C=O, ester), 170.2 (C=O, amide), 155.9 (C=O, urea), 136.7 (Ar), 133.8 (C-4), 128.6 (Ar), 128.2 (Ar), 127.0 (Ar), 118.2 (C-5), 60.8 (C-1'), 60.5 (*C*HPh), 54.5 (C-2), 54.5 (*C*HCH_3), 40.5 (C-3), 28.3 (N*C*H_3), 21.4 (C-3'), 15.1 (CH*C*H_3), 14.3 (C-2'); HRMS (ES): *m/z* calc. 359.1971; $C_{20}H_{27}N_2O_4$, $[M + H]^+$ requires 358.1971.

Analogous reaction with **2.32e** and allyl bromide gave **2.33e** in a 60:40 ratio of diastereomers.

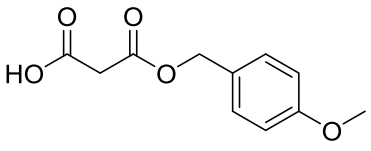
(*S*)-Ethyl2-(3-(benzyloxy)propyl)-2-((4*R*,5*S*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)pent-4-enoate (2.33d)



The title disubstituted auxiliary-malonate **2.33d** was obtained (0.201 g, 0.41 mmol, 93 %) via the general alkylating procedure from **2.32d** (0.200 g, 0.442 mmol) with allyl bromide (0.057 ml, 0.663 mmol, 1.5 eq) as a gummy solid in a 98:2 mixture of diastereomers. HRMS (ES): *m/z* found 493.2667, $C_{29}H_{37}N_2O_5$ $[M+H]^+$ requires 493.2658; $[\alpha]_D^{20}$= -36.9, (DCM, c = 1); IR: ν_{max} (cm^{-1}) 3034 (C-H alkenes), 2978 (C-H aromatic), 2862 (C-H alkanes), 1736 (C=O ester), 1674 (C=O imide); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.23 (m, 8H, aromatic), 7.19 (m, 2H, aromatic), 5.50 – 5.36 (m, 1H, C*H*=CH_2), 5.28 (d, *J* = 8.5 Hz, 1H, C*H*Ph), 4.98 (m, 1H, CH=CH_2a), 4.89 (m, 1H, CH=CH_2b), 4.47 (m, 2H, OCH_2Ph), 4.27 – 4.18 (m, 2H, C$H_2$$CH_3$), 3.86 – 3.66 (dq, *J* = 8.5, 6.6 Hz, 1H, C*H*CH_3), 3.49 – 3.40 (m, 2H, H-3'), 2.93 (m, 1H, CH_2=CHCH_{2a}), 2.75 (s, 3H, NCH_3), 2.74 (m, 1H, CH=CH_2CH_{2b}), 2.10 – 2.05 (m, 2H, H-1'), 1.69 – 1.58 (m, 1H, H-2'), 1.46 – 1.33 (m, 1H, H-2'), 1.26 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 0.77 (d, *J* = 6.6 Hz, 3H, CHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 (C=O), 169.7 (C=O), 155.3 (C=O), 138.8 (C-1''), 136.7 (C1'''), 133.3 (CH_2=*C*H), 128.5 (C-3''), 128.4 (C-3'''), 128.2 (C-2''), 127.7 (C-2'''), 127.6 (C-4'''), 127.3 (C-4''), 118.2 (CH=*C*H_2), 72.9 (O*C*H_2Ph), 70.5 (C-3'), 64.9 (q C), 60.6 (O*C*$H_2$$CH_3$), 58.2 (*C*HPh), 54.3 (*C*HCH_3), 38.2 (*C*H_2CH=CH_2), 29.7 (C-1'), 28.2 (N*C*H_3), 24.6, (C-2'), 15.1 (CH*C*H_3), 14.3 (CH_2*C*H_3).

PMB Ester-malonate-auxiliary series

3-((4-Methoxybenzyl)oxy)-3-oxopropanoic acid (2.37)[147]

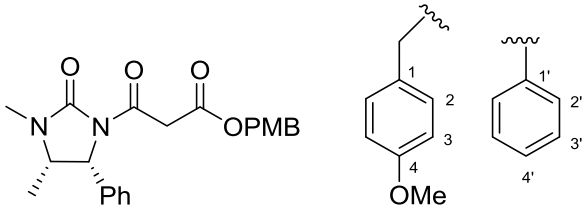


To a cooled solution of malonic acid (15.00 g, 0.144 mol, 1 eq) and *p*-methoxybenzyl alcohol (19.9 ml, 0.144 mol, 1 eq) in DCM (350 ml) was added a solution of DCC (29.71 g, 0.144 mol, 1 eq) in DCM (150 ml) via a dropping funnel over a period of 30 min, whilst stirring vigorously. The cooling bath was then removed and the reaction left to stir for 1 hour at room temperature after which time the solid urea precipitate was removed by filtration through a pad of Celite, and the filtrate evaporated. The residue was taken up in ethyl acetate (250 ml) and the organic layer extracted with saturated

aqueous sodium bicarbonate solution (2 x 200 ml). The combined aqueous extracts were washed once with ethyl acetate (100 ml), acidified to pH 3 with 3M HCl and then extracted with ethyl acetate (1 x 300 and 2 x 150 ml). The organic extracts were dried over anhydrous $MgSO_4$, filtered and evaporated to yield title product **2.37** (27.77 g, 0.124 mol, 86 %) as a light yellow liquid. This product was pure enough as judged by ^{1}H NMR spectroscopy to proceed to the next step.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (broad s, 1H, COO*H*), 7.31 - 7.29 (m, 2H, aromatic), 6.81 – 6.77 (m, 2H, aromatic), 5.15 (s, 2H, CH_2Ph), 3.81 (s, 3H, OCH_3), 3.45 (s, 2H, CH_2).

4-Methoxybenzyl 3-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-3-oxopropanoate (2.38)

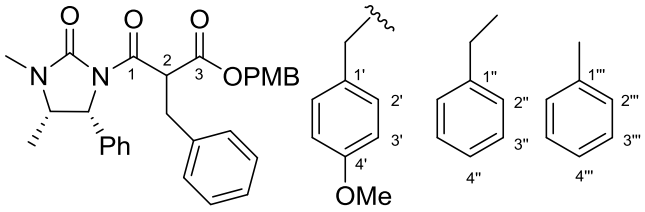


Mono-*p*-methoxybenzyl malonate **2.37** (1.00 g, 4.46 mmol, 1 eq) and **(-)-2.29** (0.85 g, 4.47 mmol, 1 eq) were dissolved in dichloromethane (100 ml) and stirred at 0 °C. A solution of DCC (1.09 g, 5.28 mmol, 1.2 eq) and HOBt (0.12 g, 20 mol %) in dichloromethane (60 ml) was gradually added to the mixture via a pressure-equalizing dropping funnel. Once addition was complete, the cooling bath was removed. The reaction was followed by tlc, which indicated completion within 3 hours at room temperature after which time it was filtered through Celite, the solvent evaporated and the resultant residue purified by column chromatography with ethyl acetate/hexane (30/70). The product **2.38** was obtained as a thick, clear gum (1.50 g, 3.78 mmol, 85 %). HRMS (ES): *m/z* found 397.1725, $C_{22}H_{25}N_2O_5$ $[M+H]^+$ requires 397.1719; $[\alpha]_D^{20}$= -30.3, (DCM, *c* = 1); IR: ν_{max} (cm^{-1}) 3067 (C-H aromatic), 2961 (C-H aliphatic), 1732 (C=O ester), 1687 (C=O imide); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.19 (m, 5H, aromatic), 7.17 – 7.08 (m, 2H, aromatic), 6.86 (d, *J* = 8.7 Hz, 2H, aromatic), 5.28 (d, *J* = 8.7 Hz, 1H, C*H*Ph), 5.09 (s, 2H, OCH_2), 3.99 (m 2H, CH_2), 3.87 (dq, *J* = 8.7, 6.6 Hz, 1H, C*H*CH_3), 3.78 (s, 3H, PhOCH_3), 2.78 (s, 3H, NCH_3), 0.76 (d, *J* = 6.6 Hz, 3H, CHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6 (C=O), 164.9 (C=O), 159.8 (C-4), 155.6 (C=O), 136.1 (C-1'), 130.2 (C-2), 128.6 (C-3'), 128.2 (C-1), 127.9 (C-2'), 127.2 (C-4'), 114.1 (C-3), 66.9 (O*C*H_2Ph), 59.5 (*C*HPh), 55.4 (*C*HCH_3), 54.2 (O*C*H_3), 43.5 (CO*C*H_2CO), 28.3 (N*C*H_3), 15.1 (CH*C*H_3).

Mono-alkylation of auxiliary malonate **2.38** with alkyl halides to generate α-substituted auxiliary malonates **2.39a** to **2.39e**

A solution of **2.38** (1 eq) in THF (0.01M) was cooled to -78 °C followed by the dropwise addition of KHMDS in toluene (0.5 M, 1.2 eq) and stirring at this temperature was continued for a further 30 minutes after which time the electrophile (1.5 eq) was added in one portion to the anion solution. The reaction was slowly warmed to room temperature and stirred for a further 8 hours. It was then quenched with saturated aqueous ammonium chloride solution (*ca*. ½ reaction vol.) and extracted three times with EtOAc (1 x reaction vol. and 2 x ½ reaction vol.). The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated to give the crude product which was chromatographed using EtOAc/ hexanes (20/80).

4-Methoxybenzyl 2-benzyl-3-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-3-oxopropanoate (2.39a)



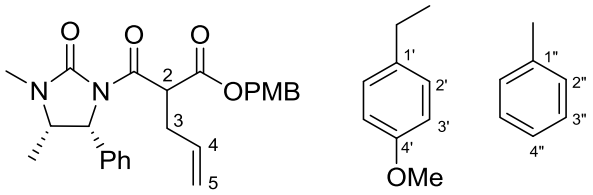
The title compound **2.39a** was obtained (1.05 g, 2.16 mmol, 95 %) as a thick oil using general alkylating procedure from **2.38** (0.900 g, 2.27 mmol), KHMDS (0.5 M, 5.45 ml, 2.73 mmol) and benzyl bromide (0.41 ml, 3.41 mmol) in a 54:46 ratio of diastereomers as determined by ^{1}H NMR spectroscopy. HRMS (ES): *m/z* found 487.2245, $C_{29}H_{31}N_2O_5$ $[M+H]^+$ requires 487.2233; IR: ν_{max} (cm^{-1}) 3027 (C-H aromatic), 2933 (C-H aliphatic), 1724 (C=O ester, amide), 1680 (C=O imide).

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.15 (m, 11H, aromatic), 7.09 – 6.82 (m, 3H, aromatic), 5.51 (d, *J* = 8.2 Hz, 1H, C*H*Ph), 5.36 (dd, *J* = 9.4, 5.6 Hz, 1H, H-2), 5.21 (d, *J* = 12.1 Hz, 1H, OC*H*$_2$*a*Ph), 5.13 (d, *J* = 12.1, Hz, 1H, OC*H*$_2$*b*Ph), 3.90 (s, 3H, OC*H*$_3$), 3.80 – 3.74 (m, 1H, CH_3C*H*), 3.46 – 3.16 (m, 2H, C*H*$_2$Ph), 2.83 (s, 3H, NC*H*$_3$), 0.82 (d, *J* = 6.4 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7 (C=O), 167.4 (C=O), 159.6 (C-4'), 155.4 (C=O), 138.9 (C-1''), 136.0 (C-1'''), 129.9 (C-2'), 129.5 (C-3'''), 128.5 (C-3''), 128.4 (C-1'), 128.3 (C-2'''), 128.0 (C-2''), 127.1 (C-4'''), 126.4 (C-4''), 114.0 (C-3'), 66.7 (O*C*H_2Ph), 59.7 (O*C*H_3), 55.4 (*C*HPh), 53.9 (*C*HCH$_3$), 52.7 (C-2), 34.5 (*C*H_2Ph), 28.2 (N*C*H_3), 15.0 (CH*C*H_3).

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.15 (m, 11H, aromatic), 7.09 – 6.82 (m, 3H, aromatic), 5.50 (d, *J* = 8.7 Hz, 1H, C*H*Ph), 5.34 (dd, *J* = 9.4, 5.5 Hz, 1H, H-2), 5.19 (d, *J* = 11.8, 1H, OC*H2a*Ph), 5.12 (d, *J* = 11.8, 1H, OC*H2b*Ph), 3.93 – 3.86 (m, 4H, OC*H*$_3$ + CH_3C*H*), 3.46 – 3.16 (m, 2H,

CH_2Ph), 2.87 (s, 3H, NCH_3), 0.83 (d, *J* = 6.0 Hz, 3H, CH_3CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5 (C=O), 167.9 (C=O), 159.7 (C-4'), 155.4 (C=O), 138.6 (C-1''), 136.2 (C-1'''), 129.9 (C-2'), 129.3 (C-3'''), 128.7 (C-3''), 128.5 (C-1'), 128.4 (C-2'''), 128.0 (C-2''), 126.9 (C-4'''), 126.3 (C-4''), 114.0 (C-3'), 66.9 (O*C*H_2Ph), 59.6 (O*C*H_3), 55.4 (*C*HPh), 53.8 (*C*HCH_3), 52.4 (C-2), 34.4 (*C*H_2Ph), 28.3 (N*C*H_3), 15.0 (CH*C*H_3).

4-Methoxybenzyl 2-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)pent-4-enoate (2.39b)

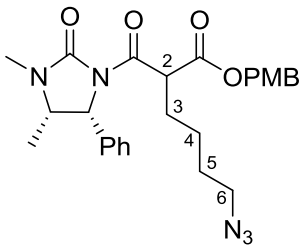


Title compound **2.39b** was obtained (0.961 g, 2.20 mmol, 97 %) as a colourless gum using general alkylating procedure from **2.38** (0.900 g, 2.27 mmol), KHMDS (0.5 M, 5.45 ml, 2.73 mmol) and allyl bromide (0.30 ml, 3.41 mmol) in a 51:49 ratio of diastereomers as determined by NMR spectroscopy. HRMS (ES): *m/z* found 437.2042, $C_{25}H_{29}N_2O_5$ $[M+H]^+$ requires 437.2031; IR: ν_{max} (cm^{-1}) 3071 (C-H aromatic), 2922 (C-H aliphatic), 1729 (C=O ester), 1679 (C=O imide).

Major diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.09 (m, 8H, aromatic), 6.88 – 6.82 (m, 2H, aromatic), 5.88 – 5.71 (m, 1H, H-4), 5.30 (d, *J* = 8.7 Hz, 1H, C*H*Ph), 5.15 (d, *J* = 12.1 Hz, 1H, OCH_2aPMP), 5.03 (d, *J* = 12.1 Hz, 1H, OCH_2bPMP), 5.03 – 4.92 (m, 2H, H-5), 4.91 – 4.83 (m, 1H, H-2), 3.87 – 3.83 (m, 1H, C*H*CH_3), 3.82 (s, 3H, OCH_3), 2.80 (s, 3H, NCH_3), 2.74 – 2.62 (m, 2H, H-3), 0.79 (d, *J* = 6.6 Hz, 3H, CHCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7 (C=O), 167.9 (C=O), 159.7 (C-4'), 155.6 (C=O), 136.4 (C-1''), 135.3 (C-4), 130.1 (C-2'), 128.6 (C-3''), 128.2 (C-1'), 128.1 (C-2''), 127.2 (C-4''), 117.2 (C-5), 114.0 (C-3'), 66.8 (O*C*H_2Ph), 59.7 (OCH_3), 55.4 (*C*HPh), 54.1 (*C*HCH_3), 51.2 (C-2), 32.7 (C-3), 28.3 (N*C*H_3), 15.1 (CH*C*H_3).

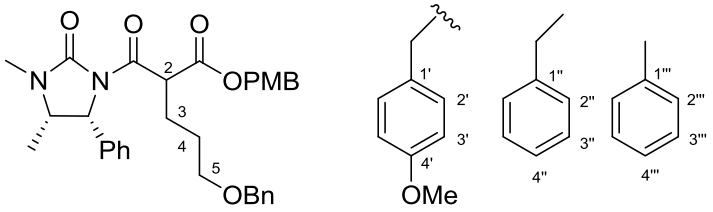
Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.05 (m, 8H, aromatic), 6.98 – 6.66 (m, 2H, aromatic), 5.95 – 5.61 (m, 1H, H-4), 5.32 (d, *J* = 8.6 Hz, 1H, C*H*Ph), 5.17 (d, *J* = 12.0 Hz, 1H, OCH_2aPMP), 5.05 (d, *J* = 12.0 Hz, 1H, OCH_2bPMP), 4.97 – 4.91 (m, 2H, H-5), 4.88 - 4.85 (m, 1H, H-2), 3.94 – 3.87 (m, 1H, C*H*CH_3), 3.83 (s, 3H, OCH_3), 2.83 (s, 3H, NCH_3), 2.76 – 2.67 (m, 2H, H-3), 0.80 (d, *J* = 6.6 Hz, 1H, CHCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7 (C=O), 167.5 (C=O), 159.7 (C-4'), 155.6 (C=O), 136.0 (C-1''), 134.9 (C-4), 130.0 (C-2'), 128.4 (C-3''), 128.2 (C-1'), 128.1 (C-2'') 127.2 (C-4''), 117.2 (C-5), 114.0 (C-3'), 66.7 (O*C*H_2Ph), 59.7 (OCH_3), 55.4 (*C*HPh), 54.0 (*C*HCH_3), 50.9 (C-2), 32.6 (C-3), 28.2 (N*C*H_3), 15.0 (CH*C*H_3).

4-Methoxybenzyl 6-azido-2-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)hexanoate (2.39c)



Title compound **2.39c** was obtained (0.847 g, 1.72 mmol, 85 %) as a viscous oil using general alkylating procedure from **2.38** (0.800 g, 2.02 mmol), KHMDS (0.5M, 4.85 ml, 2.42 mmol), bromo azide **2.54** (0.427 g, 2.42 mmol) and TBAI (0.369 g, 1.14 mmol). In this case, the reaction had to be warmed to 60 °C to achieve full conversion. Title product **2.39c** was obtained as a 50:50 mixture of diastereomers, as determined by NMR spectroscopy, separable by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 6.87 (m, 7H, aromatic), 6.87 – 6.71 (m, 2H, aromatic), 5.24 (d, *J* = 3.5 Hz, 1H, C*H*Ph), 5.05 (d, *J* = 7.1 Hz, 1H, OCH_2*a*Ph), 4.96 (d, *J* = 7.1 Hz, 1H, OCH_2*b*Ph), 4.81 – 4.68 (m, 1H, H-2), 3.86 – 3.75 (m, 1H, C*H*CH_3), 3.74 (s, 3H, OCH_3), 3.20 – 3.01 (m, 2H, H-6), 2.71 (s, 3H, NCH_3), 1.93 – 1.75 (m, 2H, H-3), 1.54 – 1.36 (m, 2H, H-5), 1.39 – 1.22 (m, 2H, H-4), 0.69 (d, *J* = 3.5 Hz, 3H, CHCH_3).

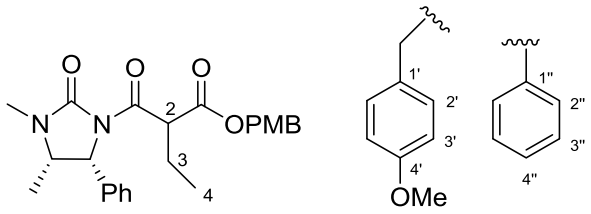
4-Methoxybenzyl 5-(benzyloxy)-2-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)pentanoate (2.39d)



Title compound **2.39d** was obtained (0.317 g, 0.582 mmol, 97 %) as a colourless gum, using general alkylating procedure from **2.38** (0.200 g, 0.50 mmol), KHMDS (0.5M, 1.20 ml, 0.60 mmol) and iodide **2.52** (0.166 g, 0.60 mmol). In this case, the reaction had to be warmed to 60 °C to achieve full conversion. Title product **2.39d** was obtained as a 51:49 mixture of diastereomers, as determined by NMR spectroscopy, separable by column chromatography. HRMS (ES): *m/z* found 545.2609, $C_{32}H_{38}N_2O_6$ $[M+H]^+$ requires 545.2601; Major diastereomer: $[\alpha]_D^{20}$= -20.3, (DCM, *c* = 0.58); IR: ν_{max} (cm^{-1}) 3063 (C-H aromatics), 2866 (C-H aliphatic), 1732 (C=O ester), 1687(C=O imide); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 10H, aromatic), 7.12 (m, 2H, aromatic), 6.88 (m, 2H, aromatic), 5.31 (d, *J* = 8.7 Hz, 1H, C*H*Ph), 5.16 (d, *J* = 12.0 Hz, 1H, CH_2aPhOMe), 5.04 (d, *J* = 12.0 Hz, 1H, CH_2bPhOMe), 4.87 (t, *J* = 7.0 Hz, 1H, H-2), 4.43 (s, 2H, OCH_2Ph), 3.85 – 3.81 (m, 1H, C*H*CH_3), 3.82 (s, 3H, OCH_3), 3.43 (t, *J* = 6.4

Hz, 2H, H-5), 2.78 (s, 3H, NCH_3), 2.00 (m, 2H, H-3), 1.60 (m, 2H, H-4), 0.78 (d, *J* = 6.6 Hz, 3H, CH_3CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1 (C=O), 168.3 (C=O), 159.7(C-4'), 155.5 (C=O) , 138.8 (C-1'''), 136.56 (C-1''), 130.0 (C-2'), 128.6 (C-3'''), 128.3 (C-3''), 128.2 (C-1'), 128.1 (C-2'''), 127.7 (C-4''), 127.4 (C-2''), 127.0 (C-4'''), 114.0 (C-3') 72.7 (O*C*H_2Ph), 69.9 (C-5), 66.7 (O*C*H_2PhOMe), 59.6 (*C*HPh), 55.4 (*C*HCH$_3$), 53.9 (O*C*H$_3$), 50.9 (C-2), 28.2 (N*C*H$_3$), 27.6 (C-4), 25.5 (C-3), 15.0 (CH*C*H$_3$).

4-Methoxybenzyl 2-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)butanoate (2.39e)



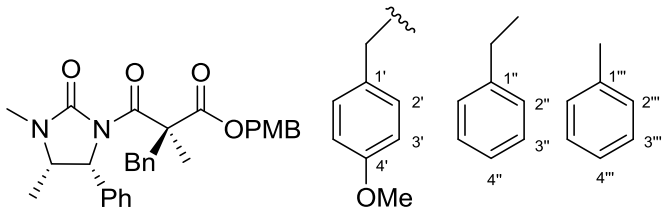
Title compound **2.39e** was obtained (0.896 g, 2.11 mmol, 93 %) using general alkylating procedure from **2.38** (0.900 g, 2.27 mmol), KHMDS (0.5 M, 5.45 ml, 2.73 mmol) and iodoethane (0.27 ml, 3.41 mmol) in a 51:49 ratio of diastereomers as determined by NMR spectroscopy. Crystallization of the diastereomeric mixture which was a colourless gum, yielded a single diastereomer as glass-like crystals. M.p. 91 -94 °C ($CHCl_3$/ hexane)HRMS (ES): *m/z* found 425.2079, $C_{24}H_{29}N_2O_5$ $[M+H]^+$ requires 425.2076; IR: ν_{max} (cm^{-1}) 3063 (C-H aromatic), 2968 (C-H aliphatic), 1723 (C=O ester, amide), 1680 (C=O urea); Major diastereomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.11 (m, 5H, aromatic), 7.10 – 7.03 (m, 2H, aromatic), 6.82 – 6.75 (m, 2H, aromatic), 5.24 (d, *J* = 8.7 Hz, 1H, C*H*Ph), 5.08 (d, *J* = 12.1 Hz, 1H, O*C*H_2*a*PMB), 4.95 (d, *J* = 12.1 Hz, 1H, O*C*H_2*b*PMB), 4.56 (dd, *J* = 8.1, 5.7 Hz, 1H, H-2), 3.89 – 3.79 (m, 1H, C*H*CH$_3$), 3.75 (s, 3H, OCH$_3$), 2.76 (s, 3H, NCH$_3$), 1.97 – 1.80 (m, 2H, H-3), 0.89 (t, *J* = 7.4 Hz, 3H, H-4), 0.72 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2 (C=O), 168.1 (C=O), 159.6 (C-4'), 155.6 (C=O), 136.1 (C-1"), 130.0 (C-2'), 128.4 (C-3"), 128.2 (C-1'), 128.1 (C-2"), 127.2 (C-4"), 114.0 (C-3'), 66.5 (O*C*H_2Ph), 59.8 (OCH$_3$), 55.4 (*C*HPh), 54.1 (*C*HCH$_3$), 52.8 (C-2), 28.3 (N*C*H$_3$), 22.05 (C-3), 15.1 (CH*C*H$_3$), 12.4 (C-4).

<u>Alkylation of α-substituted auxiliary malonates **2.39a** to **2.39e** with alkyl halides to generate α,α-disubstituted auxiliary malonates **2.40a – 2.40g**</u>

To a solution of the appropriate derivative of **2.39** (1 eq) in THF at -78 °C was added a solution of KHMDS (1.2 eq, 0.5 M) and the reaction contents allowed to stir at this temperature for 30 min. Thereafter, the appropriate alkylating agent (1.5 – 3 eq) was slowly added, the reaction contents allowed to slowly warm up to rt and left to stir overnight for 20 hrs. The reaction was quenched with sat. aqueous NH_4Cl, extracted with EtOAc, the organic extracts dried over $MgSO_4$, filtered under

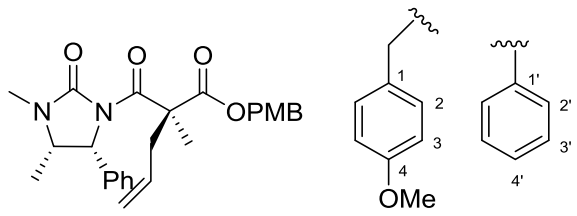
vacuum and the organic solvent removed *in vacuo*. The crude residue was chromatographed using EtOAc / hexane mixtures to afford the derivative **2.40**, which was analysed by chiral HPLC and NMR spectroscopy for diastereoselectivity.

4-Methoxybenzyl (*S*)-2-benzyl-3-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-methyl-3-oxopropanoate (2.40a)



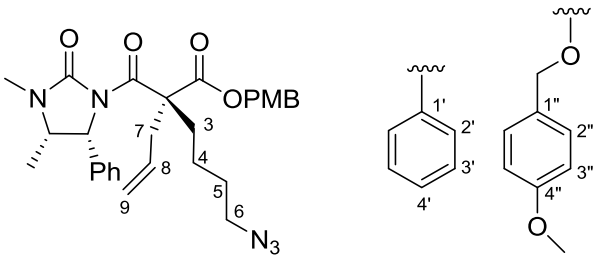
The title compound **2.40a** was obtained (0.889 g, 1.78 mmol, 96 %) as a colourless solid via the general alkylation method using **2.39a** (0.900 g, 1.85 mmol), KHMDS (0.5 M, 4.44 ml, 2.22 mmol) and methyl iodide (0.180 ml, 2.78 mmol, 1.5 eq). M.p. 98 - 101 °C (Chloroform/ hexane). Chiral HPLC on a C18 column eluting with ACN: H_20 (60:40) revealed a 98:2 diastereomer ratio. Minor diastereomer retention time = 10.4 min; that of the major diastereomer = 11.2 min. HRMS (ES): *m/z* found 501.2390, $C_{30}H_{33}N_2O_5$ $[M+H]^+$ requires 501.2369. $[\alpha]_D^{20}$= -45.8, (DCM, *c* = 1); IR: ν_{max} (cm^{-1}) 3008 (C-H aromatics), 2955 (C-H alkanes), 1722 (C=O ester, amide), 1669 (C=O urea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.14 (m, 8H, aromatic), 7.13 – 6.95 (m, 4H, aromatic), 6.89 – 6.79 (m, 2H, aromatic), 5.13 (d, *J* = 8.5 Hz, 1H, C*H*Ph), 5.05 (d, *J* = 11.9 Hz, 1H, OCH_{2a}PMP), 4.93 (d, *J* = 11.9 Hz, 1H, OCH_{2b}PMP), 3.81 (s, 3H, OCH_3), 3.80 – 3.73 (m, 1H, CH_3C*H*), 3.39 (d, *J* = 13.7 Hz, 1H, CH_2aPh), 3.35 (d, *J* = 13.7 Hz, 1H, CH_2bPh) 2.75 (s, 3H, NCH_3), 1.46 (s, 3H, CCH_3), 0.73 (d, *J* = 6.6 Hz, 3H, CH_3CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4 (C=O), 169.8 (C=O), 159.7 (C-4'), 155.3 (C=O), 137.2 (C-1''), 136.5 (C-1'''), 130.6 (C-2'), 130.5 (C-3'''), 128.5 (C-3''), 128.2 (C-1'), 128.1 (C-2'''), 128.0 (C-2''), 126.9 (C-4'''), 126.8 (C-4''), 113.9 (C-3'), 66.6 (O*C*H_2Ph), 60.6 (O*C*H_3), 56.5 (*C*HPh), 55.5 (C-2), 54.4 (*C*HCH_3), 41.7 (*C*H_2Ph), 28.2 (N*C*H_3), 22.1 (C*C*H_3), 15.1 (CH*C*H_3).

4-Methoxybenzyl (*S*)-2-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)-2-methylpent-4-enoate (2.40b)



The title compound **2.40b** was obtained (0.762 g, 1.69 mmol, 90 %) as a viscous oil via the general alkylation method using **2.39b** (0.820 g, 1.88 mmol), KHMDS (0.5 M, 4.51 ml, 2.26 mmol) and methyl iodide (0.18 ml, 2.82 mmol, 1.5 eq). Chiral HPLC on a C18 column eluting with ACN: H_20 (50:50) revealed a 98:2 diastereomer ratio. Minor diastereomer retention time = 22.9 min; that of the major diastereomer = 18.8 min. $[\alpha]_D^{20}$= -46.2, (DCM, *c* = 1); HRMS (ES): *m/z* found 451.2233, $C_{26}H_{31}N_2O_5$ $[M+H]^+$ requires 451.2233; IR ν_{max} (cm^{-1}): 3063 (C-H aromatics), 2937 (C-H alkanes), 1723 (C=O ester, amide), 1676 (C=O urea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.13 (m, 6H, aromatic), 7.07 – 7.00 (m, 2H, aromatic), 6.91 – 6.84 (m, 2H, aromatic), 5.76 – 5.62 (m, 1H, CH_2=C*H*), 5.23 (d, *J* = 8.6 Hz, 1H, C*H*Ph), 5.13 (d, *J* = 12.0 Hz, 1H, OCH_{2a}Ph), 5. 05 (d *J* = 12.0 Hz, 1H, OCH_{2b}Ph), 5.02 – 4.97 (m, 2H, CH=CH_2), 3.81 (s, 3H, OCH_3), 3.80 – 3.75 (m, 1H, CH_3C*H*), 2.73 (s, 3H, NCH_3), 2.72 – 2.66 (m, 2H, CH_2=CHCH_2), 1.46 (s, 3H, CCH_3), 0.73 (d, *J* = 6.6 Hz, 3H, CHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 (C=O), 170.2 (C=O), 159.7 (C-4), 155.2 (C=O), 136.6 (C-1'), 133.8 (CH_2=*C*H), 130.5 (C-2), 128.6 (C-3'), 128.4 (C-1'), 128.1 (C-2'), 126.9 (C-4'), 118.2 (*C*H_2=CH), 114.0 (C-3), 66.5 (O*C*H_2Ph), 60.4 (O*C*H_3), 55.5 (*C*HPh), 55.2 (qC), 54.3 (*C*HCH_3), 40.7 (*C*H_2CH=CH_2), 28.2 (N*C*H_3), 21.4 (*C*H_3),15.1 (CH*C*H_3).

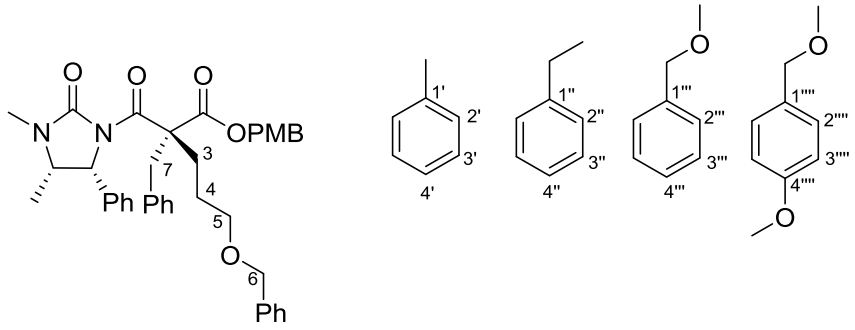
4-Methoxybenzyl (*R*)-2-allyl-6-azido-2-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)hexanoate (2.40c)



The title compound **2.40c** was obtained (0.32 g, 0.60 mmol, 95 %) as a viscous oil via the general alkylation method using **2.39c** (0.31 g, 0.63 mmol), KHMDS (0.5 M, 1.50 ml, 0.75 mmol) and allyl bromide (0.06 ml, 0.75 mmol, 1.2 eq). Chiral HPLC on a C18 column eluting with ACN: H_20 (70:30) revealed a 98:2 diastereomer ratio. Minor diastereomer retention time = 9.7 min; that of the major diastereomer = 6.9 min. $[\alpha]_D^{20}$= -31.2°, ($CHCl_3$, *c* = 1); HRMS (ES): *m/z* found 534.2721, $C_{29}H_{36}N_5O_5$

$[M+H]^+$ requires 534.2716; IR ν_{max} (cm^{-1}): 3055 (C-H aromatics), 2911 (C-H alkanes), 2135 (N_3), 1719 (C=O ester, amide), 1668 (C=O urea); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 – 7.06 (m, 5H, aromatic), 6.99 (m, 2H, aromatic), 6.81 (m, 2H, aromatic), 5.36 – 5.22 (m, 1H, H-8), 5.18 (d, *J* = 8.7 Hz, 1H, C*H*Ph), 5.04 (d, *J* = 11.9 Hz, 1H, OCH_2*a*Ph), 4.97 (d, *J* = 11.9 Hz, 1H, OCH_2*b*Ph), 4.93 – 4.78 (m, 2H, H-9), 3.78 – 3.68 (m, 4H, OCH_3 and C*H*CH_3), 3.12 (td, *J* = 6.8, 2.5 Hz, 2H, H-6), 2.95 – 2.84 (m, 1H, H-7a), 2.71 – 2.61 (m, 4H, NCH_3 and H-7b), 1.97 – 1.77 (m, 2H, H-5), 1.52 – 1.38 (m, 2H, H-4), 1.36 – 1.21 (m, 1H, H-3a), 1.14 – 0.97 (m, 1H, H-3b), 0.67 (d, *J* = 6.6 Hz, 3H, CHCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3 (C=O), 169.5 (C=O), 159.8 (C-4”), 155.2 (C=O), 136.5 (C-1’), 133.0 (C-8), 130.6 (C-2”), 128.5 (C-2’), 128.2 (C-1”), 128.1 (C-3’), 127.2 (C-4’), 118.4 (C-9), 114.0 (C-3”), 66.5 (O*C*H_2Ph), 60.5 (*C*HPh), 58.2 (C-2), 55.5 (*C*HCH_3), 54.2 (O*C*H_3), 51.2 (C-6), 38.1 (C-7), 32.9 (C-3), 29.2 (C-4), 28.2 (N*C*H_3), 21.4 (C-5), 15.1 (CH*C*H_3).

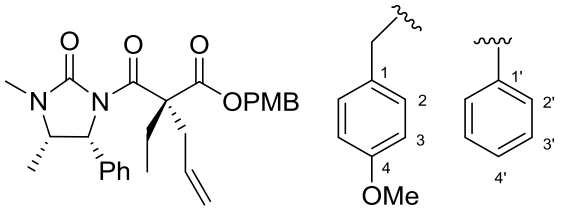
4-Methoxybenzyl (*R*)-2-benzyl-5-(benzyloxy)-2-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)pentanoate (2.40d)



The title compound **2.40d** was obtained (1.25 g, 1.97 mmol, 90 %) as a gummy solid via the general alkylation method using **2.39d** (1.20 g, 2.20 mmol), KHMDS (0.5 M, 5.29 ml, 2.64 mmol) and benzyl bromide (0.32 ml, 2.64 mmol, 1.2 eq). Chiral HPLC on a C18 column eluting with ACN: H_2O (70:30) revealed a 97:3 diastereomer ratio. Minor diastereomer retention time = 11.2 min; that of the major diastereomer = 13.1 min. $[\alpha]_D^{20}$= -4.2°, ($CHCl_3$, *c* = 1); HRMS (ES): *m/z* found 635.3124, $C_{39}H_{43}N_2O_6$ $[M+H]^+$ requires 635.3121; IR ν_{max} (cm^{-1}): 3033 (C-H aromatics), 2891 (C-H alkanes), 1717 (C=O ester, amide), 1671 (C=O urea); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 – 6.92 (m, 15H, aromatic), 6.94 – 6.69 (m, 4H, aromatic), 5.17 (d, *J* = 8.7 Hz, 1H, C*H*Ph), 4.88 (d, *J* = 11.7 Hz, 1H, OCH_2*a*Ph), 4.77 (d, *J* = 11.7 Hz, 1H, OCH_2*b*Ph), 4.42 – 4.26 (m, 2H, H-6), 3.71 (s, 3H, OCH_3), 3.64 (dd, *J* = 8.7, 6.6 Hz, 1H, C*H*CH_3), 3.42 – 3.22 (m, 4H, H-7 and H-5), 2.62 (s, 3H, NCH_3), 2.02 – 1.82 (m, 2H, H-3), 1.73 – 1.58 (m, 1H, H-4a), 1.46 – 1.31 (m, 1H, H-4b), 0.65 (d, *J* = 6.6 Hz, 3H, CHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3 (C=O), 169.8 (C=O), 159.9 (C-4’’’’), 155.4 (C=O), 139.1 (C-1’), 137.0 (C-1’’), 136.6 (C-1’’’), 130.8 (C-2’’’’), 130.6 (C-3’), 128.4 (C-3’’’ and C-1’’’’), 128.0 (C-3’’), 127.9 (C-4’’’), 127.8 (C-2’’), 127.7 (C-2’), 127.5 (C-2’’’),

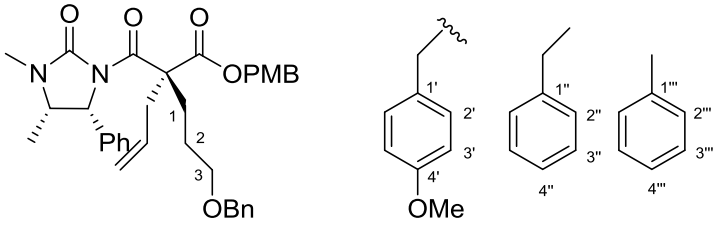
126.5 (C-4'' and C-4'), 114.1 (C-3''''), 73.0 (C-6), 70.6 (C-5), 66.5 (O*C*H_2Ph), 61.0 (*C*HPh), 60.0 (C-2), 55.5 (*C*HCH_3), 54.4 (O*C*H_3), 40.1 (C-7), 30.6 (C-3), 28.2 (N*C*H_3), 25.1 (C-4), 15.1 (CH*C*H_3).

4-Methoxybenzyl (*R*)-2-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)-2-ethylpent-4-enoate (2.40e)



The title compound **2.40e** was obtained (0.997 g, 2.15 mmol, 91 %) as a viscous oil via the general alkylation method using **2.39e** (1.00 g, 2.36 mmol), KHMDS (0.5 M, 5.66 ml, 2.83 mmol) and allyl bromide (0.31 ml, 3.54 mmol, 1.5 eq). Chiral HPLC on a C18 column eluting with ACN: $H_2$0 (50:50) revealed a 94:6 diastereomer ratio. Minor diastereomer retention time = 19.5 min; that of the major diastereomer = 18.0 min. HRMS (ES): *m/z* found 465.2350, $C_{27}H_{33}N_2O_5$ $[M+H]^+$ requires 465.2344; $[\alpha]_D^{20}$= -53.42°, ($CHCl_3$, *c* = 0.8); IR: ν_{max} (cm^{-1}) 3027 (C-H aromatic), 2917 (C-H alkanes), 1727 (C=O ester, amide), 1680 (C=O urea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.13 (m, 5H, aromatic), 7.05 (d, *J* = 6.4 Hz, 2H, aromatic), 6.92 – 6.82 (m, 2H, aromatic), 5.47 – 5.31 (m, 1H, CH_2=*CH)*, 5.25 (d, *J* = 8.6 Hz, 1H, C*H*Ph), 5.11 (d, *J* = 11.9 Hz, 1H, OCH_{2a}Ph), 5.03 (d, *J* = 11.9, 1H, OCH_{2b}Ph) 5.00 – 4.84 (m, 2H, CH=CH_2), 3.81 (s, 3H, OCH_3), 3.79 – 3.70 (m, 1H, CH_3C*H*), 2.99 – 2.74 (m, 2H, CH_2=CHCH_2), 2.72 (s, 3H, NCH_3), 2.05 – 1.93 (m, 2H, CH_3CH_2), 0.80 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 0.73 (d, *J* = 6.6 Hz, 3H, CHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (C=O), 169.7 (C=O), 159.7 (C-4), 155.2 (C=O), 136.6 (C-1'), 133.3 (*C*H=CH_2), 130.5 (C-2), 128.5 (C-3'), 128.4 (C-1), 128.1 (C-2'), 127.2 (C-4'), 118.1 (*C*H_2=CH), 114.0 (C-3), 66.3 (O*C*H_2Ph), 60.5 (O*C*H_3), 58.8 (qC), 55.5 (*C*HPh), 54.3 (*C*HCH_3), 37.6 (*C*H_2CH=CH_2), 28.2 (N*C*H_3), 26.3 (*C*$H_2$$CH_3$), 15.1 (CH*C*$H_3$), 8.7 ($CH_2$*C*$H_3$).

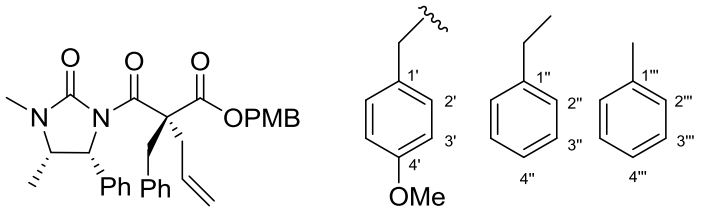
(*R*)-4-Methoxybenzyl 2-(3-(benzyloxy)propyl)-2-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)pent-4-enoate (2.40f)



The title compound **2.40f** was prepared (1.771 g, 3.03 mmol, 97 %) as a thick gum via the general alkylation procedure using **2.39d** (1.700 g, 3.12 mmol), KHMDS in toluene (0.5 M, 7.50 ml, 3.74

mmol) and allyl bromide (0.43 ml, 4.99 mmol). Chiral HPLC on a C18 column eluting with ACN: H_20 (50:50) revealed a 98:2 diastereomer ratio. Major diastereomer retention time = 10.3 min; that of the minor diastereomer = 11.4 min. HRMS (ES): *m/z* found 585.2971, $C_{35}H_{41}N_2O_6$ $[M+H]^+$ requires 585.2965; $[\alpha]_D^{20}$= -36.9° (DCM, c = 1); IR: ν_{max} (cm^{-1}) 3033 (C-H Aromatics), 2866 (C-H alkanes), 1734 (C=O ester), 1674 (C=O imide); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.11 (m, 10H, aromatic), 7.04 (d, *J* = 6.5 Hz, 2H, aromatic), 6.87 (d, *J* = 8.7 Hz, 2H, aromatic), 5.47 – 5.32 (m, 1H, C*H*=CH_2), 5.22 (d, *J* = 8.6 Hz, 1H, C*H*Ph), 5.07 (d, *J* = 11.9 Hz, 1H, OC*H*$_2$aPhOMe), 5.05 (d, *J* = 11.9 Hz, 1H, OC*H*$_2$bPhOMe), 4.97 (dd, *J* = 17.0, 2.1 Hz, 1H, CH=C*H*$_2$a), 4.88 (dd, *J* = 10.1, 2.1 Hz, 1H, CH=C*H*$_2$b), 4.43 (s, 2H, OC*H*$_2$Ph), 3.79 (s, 3H, OC*H*$_3$), 3.75 – 3.64 (m, 1H, C*H*CH_3), 3.49 – 3.31 (m, 2H, H-3), 2.98 – 2.85 (m, 1H, CH_2=CHC*H*$_2$), 2.80 – 2.70 (m, 1H, CH_2=CHC*H*$_2$), 2.67 (s, 3H, NC*H*$_3$), 2.13 – 1.94 (m, 2H, H-2), 1.72 – 1.51 (m, 1H, H-1), 1.47 – 1.29 (m, 1H, H-1), 0.70 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.16 (C=O), 169.42 (C=O), 159.6 (C-4'), 155.1 (C=O), 138.8 (C-1'''), 136.52 (C-1''), 133.1 (CH=*C*H_2), 130.5 (C-2'), 128.4 (C-3'''), 128.4 (C-3''), 128.3 (C-1'), 128.0 (C-2'''), 127.7 (C-4''), 127.5 (C-2''), 127.1 (C-4'''), 118.2 (*C*H=CH_2), 113.9 (C-3'), 72.7 (O*C*H_2Ph), 70.3 (C-3), 66.3 (O*C*H_2PMB), 60.4 (*C*HPh), 58.1 (C_q), 55.3 (*C*HCH_3), 54.0 (O*C*H_3), 38.0 (CH_2=CH*C*H_2), 29.8 (N*C*H_3), 28.01 (C-1), 24.5 (C-2), 14.9 (CH*C*H_3).

4-Methoxybenzyl (*S*)-2-benzyl-2-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)pent-4-enoate (2.40g)



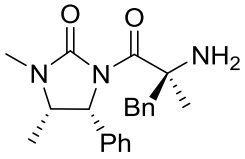
The title compound **2.40g** was obtained (0.896 g, 1.70 mmol, 92 %) as a clear oil via the general alkylation method using **2.39a** (0.900 g, 1.85 mmol), KHMDS (0.5 M, 4.44 ml, 2.22 mmol) and allyl bromide (0.24 ml, 2.78 mmol, 1.5 eq). Chiral HPLC on a C18 column eluting with ACN: H_20 (75:25) revealed a 96:4 diastereomer ratio. Minor diastereomer retention time = 4.2 min; that of the major diastereomer = 5.0 min. $[\alpha]_D^{20}$= -25.4, (DCM, *c* = 1); HRMS (ES): *m/z* found 527.2522, $C_{32}H_{35}N_2O_5$ $[M+H]^+$ requires 527.2501; IR: ν_{max} (cm^{-1}) 3067 (C-H aromatic), 2925 (C-H aliphatic), 1727 (C=O ester, amide), 1572 (C=O urea); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.14 (m, 10H, aromatic), 7.08 (m, 2H, aromatic), 6.93 – 6.87 (m, 2H, aromatic), 5.68 – 5.54 (m, 1H, C*H*=CH_2), 5.17 (d, *J* = 8.6 Hz, 1H, C*H*Ph), 5.12 (d, *J* = 2.0 Hz, 1H, C*H*$_2$*a*=CH), 5.05 (d, *J* = 11.9 Hz, 1H, OC*H*$_2$*a*Ph), 5.03 – 4.98 (m, 1H, C*H*$_2$*b*=CH), 4.93 – 4.84 (m, 1H, OC*H*$_2$*b*Ph), 3.85 (s, 3H, OC*H*$_3$), 3.80 – 3.71 (m, 1H, CH_3C*H*), 3.46 (d, *J* = 13.7 Hz, 1H, C*H*$_2$*a*Ph), 3.43 – 3.28 (m, 1H, C*H*$_2$*a*CH=CH_2), 2.97 (m, 1H, C*H*$_2$*b*CH=CH_2), 2.86 (d, *J* = 15.8 Hz, 1H, C*H*$_2$*b*Ph), 2.77 (s, 3H,NC*H*$_3$), 0.77 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9 (C=O),

168.8 (C=O), 159.7 (C-4'), 155.2 (C=O), 137.2(C-1''), 136.4 (C-1'''), 133.5 (CH_2=*C*H), 130.5 (C-2' andC-3'''), 128.4 (C-3''), 128.1 (C-2'' and C-2'''), 128.0(C-1'), 127.1 (C-4'''), 126.8 (C-4''), 118.4 (*C*H_2=CH), 113.9 (C-3'), 66.4 (O*C*H_2Ph), 60.5 (O*C*H_3), 60.2 (C-2), 55.4 (*C*HPh), 54.3 (*C*HCH_3), 39.5 (CH_2=CH*C*H_2), 39.2 (*C*H_2Ph), 28.2 (N*C*H_3), 15.0 (CH*C*H_3).

General PMB removal procedure and modified Curtius rearrangement procedure to obtain ATAs **2.44a to 2.44f** from disubstituted auxiliary PMB malonates **240a – 2.40f**:

The appropriate disubstituted auxiliary malonate PMB ester (1 eq) was dissolved in DCM and anisole (1.2 eq) was added. Trifluoroacetic acid (6 eq) was introduced slowly via syringe, and the reaction stirred at room temperature for 2 hours. Solvent and excess TFA were removed on the rotary evaporator and the crude mixture chromatographed using ethyl acetate/hexane (70/30) to afford the corresponding disubstituted auxiliary acid. The quaternary acid derivative (1 eq) was dissolved in acetonitrile (0.01M), and Et_3N (2 eq) and diphenyphosphoryl azide (1.2 eq) were successively added. The mixture was allowed to stir at room temperature for 3 hours after which time the solvent was removed *in vacuo* and the residue flash chromatographed with ethyl acetate/ hexane (10/90) to give the acyl azide as a clear gum. This was immediately committed to the next step, whereby it was dissolved in acetonitrile (0.01M) and refluxed at 85 °C. The rearrangement to isocyanate was complete within 6 hours as evidenced by TLC. The reaction was cooled to 60 °C and HCl (6M) was added to effect the hydrolysis (30 minutes). The reaction mixture was then cooled to RT and the amine isolated by extractive work up. Thus, after removal of acetonitrile, water was added and the mixture extracted once with diethyl ether to remove non-amine material. The aqueous layer was then treated with sodium hydroxide solution (5 %) until pH 10 -12 to liberate the amine from its hydrochloride salt and extracted with three times with ethyl acetate and once with chloroform/ethanol (75/25). The organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to give the α-tertiary amine.

(4*S*,5*R*)-1-((*S*)-2-Amino-2-methyl-3-phenylpropanoyl)-3,4-dimethyl-5-phenylimidazolidin-2-one (2.44a)

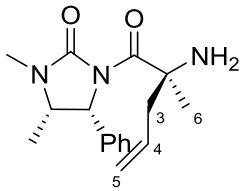


The disubstituted auxiliary malonate PMB ester **2.40a** (0.620 g, 1.51 mmol) was subjected to the general procedure for PMB removal using anisole (0.20 ml, 1.82 mmol, 1.2 eq) and TFA (0.69 ml, 9.06 mmol, 6 eq) to give benzyl, methyl- substituted auxiliary acid **2.41a** (0.492 g, 1.43 mmol, 95 %)

as a clear oil. This was then committed to the general modified procedure for Curtius rearrangement with Et_3N (0.40 ml, 2.86 mmol, 2 eq), DPPA (0.37 ml, 1.72 mmol, 1.2 eq) and HCl (5M, 2 ml) for the hydrolysis, yielding α-tertiary amine **2.44a** (0.397 g, 1.13 mmol, 79 % from the acid) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.11 (m, 8H, aromatic), 7.05 – 6.95 (m, 2H, aromatic), 5.11 (d, *J* = 8.5 Hz, 1H, C*H*Ph), 1), 3.75 – 3.69 (m, 1H, CH_3C*H*), 3.28 (d, *J* = 13.7 Hz, 1H, CH_2aPh), 3.22 (d, *J* = 13.7 Hz, 1H, CH_2bPh), 2.73 (s, 3H, NCH_3), 2.36 (broad s, 2H, NH_2), 1.22 (s, 3H, CCH_3), 0.72 (d, *J* = 6.6 Hz, 3H, CH_3CH).

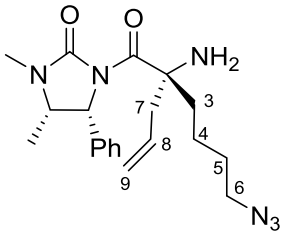
(4*S*,5*R*)-1-((*S*)-2-Amino-2-methylpent-4-enoyl)-3,4-dimethyl-5-phenylimidazolidin-2-one (2.44b)



The disubstituted auxiliary malonate PMB ester **2.40b** (0.760 g, 1.69 mmol) was subjected to the general procedure for PMB removal using anisole (0.22 ml, 2.03 mmol, 1.2 eq) and TFA (0.77 ml, 10.14 mmol, 6 eq) to give allyl, methyl-substituted auxiliary acid **2.41b** (0.525 g, 1.59 mmol, 94 %) as a clear oil. All of the acid was then committed to the general modified procedure for Curtius rearrangement with Et_3N (0.45 ml, 3.18 mmol, 2 eq), DPPA (0.40 ml, 1.87 mmol, 1.2 eq) and HCl (5M, 3 ml) for the hydrolysis, yielding allyl, methyl-substituted auxiliary α-tertiary amine **2.44b** (0.422 g, 1.40 mmol, 88 % from the acid) as a colourless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.19 (m, 3H, aromatic), 7.13 – 7.01 (m, 2H, aromatic), 5.80 – 5.62 (m, 1H, H-4), 5.22 (d, *J* = 8.4 Hz, 1H, C*H*Ph), 5.09 – 4.95 (m, 2H, H-5), 3.94 – 3.78 (m, 1H, C*H*CH_3), 2.77 (s, 3H, NCH_3), 2.58 (dd, *J* = 13.7, 8.1 Hz, 1H, H-3a), 2.43 (dd, *J* = 13.7, 8.1 Hz, 1H, H-3b), 2.25 (broad s, 2H, NH_2), 1.32 (s, 3H, H-6), 0.73 (d, *J* = 6.6 Hz, 3H, CHCH_3).

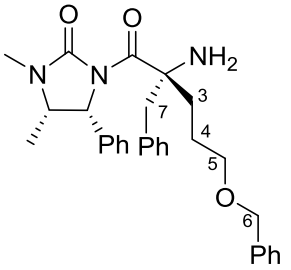
(4*S*,5*R*)-1-((*R*)-2-Allyl-2-amino-6-azidohexanoyl)-3,4-dimethyl-5-phenylimidazolidin-2-one (2.44c)



The disubstituted auxiliary malonate PMB ester **2.40c** (0.850 g, 1.59 mmol) was subjected to the general procedure for PMB removal using anisole (0.20 ml, 1.91 mmol, 1.2 eq) and TFA (0.72 ml, 9.54 mmol, 6 eq) to give the disubstituted auxiliary acid **2.41c** (0.566 g, 1.37 mmol, 86 %) as a clear oil. All of the acid was then committed to the general modified procedure for Curtius rearrangement with Et_3N (0.39 ml, 2.72 mmol, 2 eq), DPPA (0.41 ml, 1.90 mmol, 1.2 eq) and HCl (5 M, 4 ml) for the hydrolysis, yielding α-tertiary amine **2.44c** (0.447 g, 1.16 mmol, 85 %) as a colourless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.15 (m, 3H, aromatic), 7.08 (m, 2H, aromatic), 5.54 – 5.33 (m, 1H, H-8), 5.25 (d, *J* = 8.5 Hz, 1H, C*H*Ph), 5.08 – 4.85 (m, 2H, H-9), 3.87 (dt, *J* = 8.5, 6.6 Hz, 1H, C*H*CH_3), 3.20 – 3.09 (m, 2H, H-6), 2.79 (s, 2H, NH_2), 2.76 (s, 3H, NC*H*$_3$), 2.74 – 2.65 (m, 1H, H-7a), 2.40 (dd, *J* = 13.7, 8.0 Hz, 1H, H-7b), 1.98 – 1.82 (m, 1H, H-3a), 1.79 – 1.66 (m, 1H, H-3b), 1.56 – 1.41 (m, 2H, H-5), 1.35 – 1.15 (m, 2H, H-4), 0.73 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$).

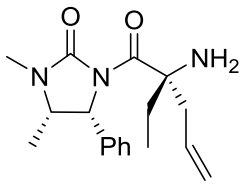
(4*S*,5*R*)-1-((*R*)-2-Amino-2-benzyl-5-(benzyloxy)pentanoyl)-3,4-dimethyl-5-phenylimidazolidin-2-one (2.44d)



The disubstituted auxiliary malonate PMB ester **2.40d** (1.200 g, 1.89 mmol) was subjected to the general procedure for PMB removal using anisole (0.24 ml, 2.27 mmol, 1.2 eq) and TFA (0.87 ml, 11.34 mmol, 6 eq) to give the disubstituted auxiliary acid **2.41d** (0.885 g, 1.72 mmol, 91 %) as a clear oil. All of the acid was then committed to the general modified procedure for Curtius rearrangement with Et_3N (0.49 ml, 3.44 mmol, 2 eq), DPPA (0.44 ml, 2.06 mmol, 1.2 eq) and HCl (5M, 5 ml) for the hydrolysis, yielding auxiliary α-tertiary amine **2.44d** (0.728 g, 1.50 mmol, 87 % from the acid) as a colourless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.16 (m, 10H, aromatic), 7.12 – 6.98 (m, 5H, aromatic), 5.20 (d, *J* = 8.4 Hz, 1H, C*H*Ph), 4.37 (s, 2H,H-6), 3.93 – 3.78 (m, 1H, C*H*CH_3), 3.45 (d, *J* = 13.3 Hz, 1H, H-7a), 3.40 – 3.26 (m, 2H, H-5), 2.79 (d, *J* = 13.3 Hz, 1H, H-7b), 2.76 (s, 3H, NC*H*$_3$), 2.40 (broad s, 2H, NH_2), 2.05 – 1.90 (m, 1H, H-3a), 1.75 – 1.44 (m, 3H, H-3b and H-4), 0.72 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$).

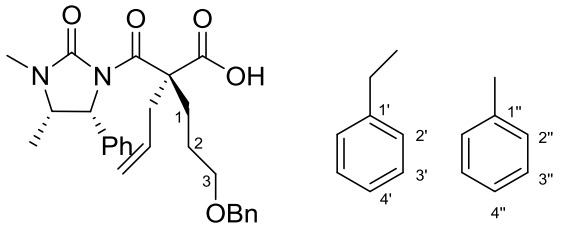
(4*S*,5*R*)-1-((*R*)-2-Amino-2-ethylpent-4-enoyl)-3,4-dimethyl-5-phenylimidazolidin-2-one (2.44e)



The disubstituted auxiliary malonate PMB ester **2.40e** (0.700 g, 1.51 mmol) was subjected to the general procedure for PMB removal using anisole (0.20 ml, 1.82 mmol, 1.2 eq) and TFA (0.69 ml, 9.06 mmol, 6 eq) to give ethyl, allyl- substituted auxiliary acid **2.41e** (0.492 g, 1.43 mmol, 95 %) as a clear oil. This was then committed to the general modified procedure for Curtius rearrangement with Et_3N (0.40 ml, 2.86 mmol, 2 eq), DPPA (0.37 ml, 1.72 mmol, 1.2 eq) and HCl (5M, 2 ml) for the hydrolysis, yielding α-tertiary amine **2.44e** (0.366 g, 1.16 mmol, 81 % from the acid) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.50 (m, 2H, aromatic), 7.36 – 7.26 (m, 3H, aromatic), 5.53 – 5.39 (m, 1H, CH_2=C*H*), 5.14 – 4.91 (m, 2H, CH=C*H*$_2$), 4.87 (d, *J* = 8.9 Hz, 1H, C*H*Ph), 4.11 – 3.98 (dq, *J* = 10.6, 6.3 Hz, 1H, CH_3C*H*), 2.35 – 2.29 (m, 2H, CH_3C*H*$_2$), 2.34 (s, 3H, NC*H*$_3$), 1.80 (m, 1H, CH_2=CHC*H*$_2$*a*), 1.58 (m, 1H, CH_2=CHC*H*$_2$*b*), 1.26 (broad s, 2H, NH_2), 1.18 (d, *J* = 6.3 Hz, 3H, CHC*H*$_3$), 0.64 (t, *J* = 7.4 Hz, 3H, CH_2C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8 (C=O), 156.9 (C=O), 137.5 (Ar_q), 130.4 (*C*H=CH_2), 129.1 (Ar), 128.9 (Ar), 128.6 (Ar), 120.9 (CH=*C*H_2), 65.1 (C_q), 60.7 (*C*HPh), 53.1 (*C*HCH_3), 41.5 (*C*H_2CH=CH_2), 33.0 (*C*$H_2$$CH_3$), 29.8 (N*C*$H_3$), 16.7 (CH*C*$H_3$), 7.5 ($CH_2$*C*$H_3$).

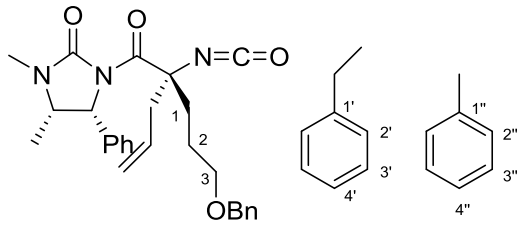
(*R*)-2-(3-(Benzyloxy)propyl)-2-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)pent-4-enoic acid (2.41f)



The title acid **2.41f** was prepared (0.389 g, 0.838 mmol, 98 %) as a colourless oil via the general procedure for PMB removal from the disubstituted auxiliary malonate derivative **2.40f** (0.500 g, 0.86 mmol), with anisole (0.11 ml, 1.03 mmol, 1.2 eq) and TFA (0.40 ml, 5.13 mmol, 6 equivalents).

HRMS (ES): *m/z* found 465.2332, $C_{27}H_{33}N_2O_5$ $[M+H]^+$ requires 465.2345; $[\alpha]_D^{20}$= -45.7° (DCM, c= 1); IR: ν_{max} (cm^{-1}) 3431 (OH), 3056 (C-H aromatics), 2978 (C-H alkanes), 1732 (C=O carboxylic acid), 1677 (C=O imide); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.21 (m, 10H, aromatic), 5.44 – 5.35 (m, 1H, C*H*=CH_2), 5.31 (d, *J* = 8.7 Hz, 1H, C*H*Ph), 5.05 – 4.86 (m, 2H, CH=CH_2), 4.44 (s, 2H, OCH_2Ph), 3.99 – 3.82 (m, 1H, C*H*CH_3), 3.51 – 3.30 (m, 2H, H-3), 3.11 – 2.96 (m, 1H, CH_2=CHCH_{2a}), 2.73 (s, 3H, NCH_3), 2.82 – 2.60 (m, 1H, H-1a), 2.04 – 1.94 (m, 2H, H-1b + CH_2=CHCH_{2b}), 1.74 – 1.59 (m, 1H, H-2a), 1.56 – 1.42 (m, 1H, H-2b), 0.75 (d, *J* = 6.5 Hz, 3H, CHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2 (C=O), 166.8 (C=O), 137.5 (C-1''), 136.3 (C-1'), 133.1 (*C*H=CH_2), 128.5 (C-3''), 127.9 (C-3') 127.7 (C-2''), 127.4 (C-2'), 127.2 (C-4'), 127.0 (C-4''), 119.6 (*C*H_2=CH), 73.5 (O*C*H_2Ph), 72.9 (C-3), 60.6 (*C*HPh), 58.7 (C_q), 54.2 (*C*HCH_3), 41.7 (*C*H_2=$CHCH_2$), 30.6 (C-1), 28.3 (N*C*H_3), 24.4 (C-2), 14.9 (CH*C*H_3).

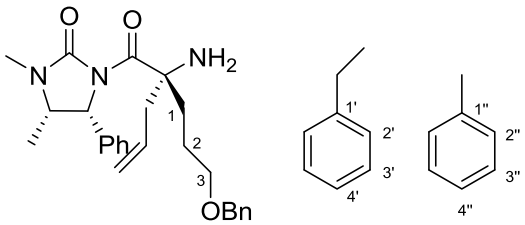
(4*S*,5*R*)-1-((*R*)-2-(3-(Benzyloxy)propyl)-2-isocyanatopent-4-enoyl)-3,4-dimethyl-5-phenylimidazolidin-2-one (2.43f)



The disubstituted auxiliary acid **2.41f** (0.100 g, 0.215 mmol) was dissolved in acetonitrile (50 ml) and triethylamine (0.06 ml, 0.43 mmol, 2 eq) and DPPA (0.056 ml, 0.258 mmol, 1.2 eq) were added successively. The mixture was allowed to stir at room temperature for 3 hours, following which the solvent was evaporated and the residue chromatographed using EtOAc/ hexanes (10/90), yielding the acyl azide product **2.42f** (0.097g, 0.198 mmol, 92 %). Acyl azide **2.42f** was re-dissolved in CH_3CN

and refluxed for 4 hours. Once concentrated, the residue was chromatographed with EtOAc/hexane (15/85) giving the isocyanate **2.43f** (0.082 g, 0.178 mmol, 90 %) as a colourless crystalline solid. M. p. 84 – 86 °C (DCM/hexane); HRMS (ES): *m/z* found 462.2396 $[M+H]^+$ for $C_{27}H_{31}N_3O_4$ requires 462.2393; $[\alpha]_D^{20}$ = -38.5° (DCM, c = 1); IR: ν_{max} (cm^{-1}) 3033 (C-H aromatic), 2909 (C-H aliphatic), 2253 (NCO), 1731 (C=O), 1692 (C=O imide); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.10 (m, 10H, aromatic), 5.81 – 5.53 (m, 1H, C*H*=CH_2), 5.25 (d, *J* = 8.3 Hz, 1H, C*H*Ph), 5.15 – 4.92 (m, 2H, CH=C*H*$_2$), 4.39 (s, 2H, OC*H*$_2$Ph), 3.86 (dq, *J* = 8.3, 6.6 Hz, 1H, C*H*CH_3), 3.41 – 3.32 (m, 2H, H-3), 3.31 – 3.23 (m, 1H, CH_2=CHC*H*$_{2a}$), 2.75 (s, 3H, NC*H*$_3$), 2.75 – 2.70 (m, 1H, H-1a), 2.55 -2.46 (m, 1H, CH_2=CHC*H*$_{2b}$), 1.96 (m, 1H, H-1b), 1.70 – 1.58 (m, 1H, H-2a), 1.40 – 1.21 (m, 1H, H-2b), 0.79 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1 (C=O), 154.1 (C=O), 138.5 (C-1''), 136.1 (C-1'), 132.5 (*C*H=CH_2), 128.3 (C-3''), 128.1 (C-3' and C-2''), 127.3 (C-2'), 127.2 (C-4'), 126.9 (C-4''), 125.3 (NC=O), 119.0 (*C*H_2=CH), 72.5 (O*C*H_2Ph), 72.4 (C-3), 69.6 (*C*NCO), 62.0 (*C*HPh), 53.8 (*C*HCH_3), 40.9 (*C*H_2=$CHCH_2$), 33.1 (C-1), 28.1 (N*C*H_3), 24.4 (C-2), 14.6 (CH*C*H_3).

(4*S*,5*R*)-1-((*R*)-2-Amino-2-(3-(benzyloxy)propyl)pent-4-enoyl)-3,4-dimethyl-5-phenylimidazolidin-2-one (2.44f)



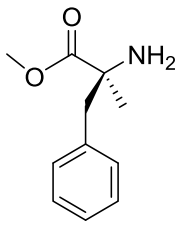
The disubstituted auxiliary malonate derivative **2.40f** (0.500 g, 0.86 mmol), was subjected to the general procedure for PMB removal using anisole (0.11 ml, 1.03 mmol, 1.2 eq) and TFA (0.40 ml, 5.13 mmol, 6 equivalents) to deliver the quaternary acid **2.41f** (0.389 g, 0.84 mmol, 98 %) as a colourless oil. This was then committed to the general modified Curtius rearrangement procedure using Et_3N (0.22 ml, 1.68 mmol, 2 eq), DPPA (0.20 ml, 1.68 mmol, 1.2 eq) and HCl (6 M, 5.00 ml) in the hydrolysis step to give the α-tertiary amine **2.44f** (0.300 g, 0.69 mmol, 82 %) as a light yellow oil. HRMS (ES): *m/z* found 436.2612 $[M+H]^+$ for $C_{26}H_{34}N_3O_3$ requires 436.2600; $[\alpha]_D^{20}$= -23.2° (DCM, c = 1); IR: ν_{max} (cm^{-1}) 3392 (NH), 3054 (C-H aromatic), 2987 (C-H alkanes), 1716 (C=O), 1671 (C=O imide); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.16 (m, 8H, aromatic), 7.09 – 7.06 (m, 2H, aromatic), 5.54 – 5.39 (m, 1H, CH_2=C*H*), 5.24 (d, *J* = 8.5 Hz, 1H, C*H*Ph), 5.03 – 4.96 (m, 2H, C*H*$_2$=CH), 4.41 (s, 2H, OC*H*$_2$Ph), 3.83 (dq, *J* = 8.5, 6.6 Hz, 1H, C*H*CH_3), 3.46 – 3.33 (m, 2H, H-3), 2.74 (s, 3H, NC*H*$_3$), 2.70 (dd, *J* = 14.0, 7.9 Hz, 1H, CH_2=CHC*H*$_{2a}$), 2.46 (dd, *J* = 14.0, 7.9, 1H, CH_2=CHC*H*$_{2b}$), 2.17 (broad s, 2H, NH_2), 1.94 – 1.76 (m, 2H, H-1), 1.63 – 1.45 (m, 2H, H-2), 0.74 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9

(C=O), 155.8 (C=O), 138.9 (C-1''), 137.1 (C-1'), 133.8 (*C*H=CH_2), 128.6 (C-3''), 128.42 (C-3'), 128.1 (C-2''), 127.7 (C-2'), 127.5 (C-4'), 127.0 (C-4''), 118.7 (*C*H_2=CH), 72.9 (O*C*H_2Ph), 70.8 (C-3) , 62.6 (*C*HPh), 61.5 (*C*NH_2), 54.2 (*C*HCH_3), 42.4 (CH_2=CH*C*H_2), 34.0 (C-1), 28.5 (N*C*H_3), 24.5 (C-2), 15.2 (CH*C*H_3).

Methanolysis procedure for conversion of derivatives **2.44a – 2.44d** to give methyl ester amino acid derivatives **2.46a** to **2.46d**

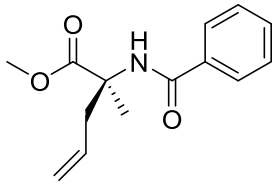
The appropriate ATA was placed in anhydrous MeOH (50 ml), and NaOMe (1M, 1.1 eq) was introduced via dropwise addition. The reaction was stirred for 1 hour after which time water (10 ml) was added and the methanol removed on a rotary evaporator. The aqueous mixture was extracted with ethyl acetate (2 x 20 ml) and once with chloroform/ ethanol (75/25, 20 ml) and the pooled organic fractions were dried with anhydrous $MgSO_4$, filtered and concentrated. Chromatographic purification of products was carried out using MeOH/ DCM (5/95 to 10/90).

Methyl (*S*)-2-amino-2-methyl-3-phenylpropanoate (2.46a)



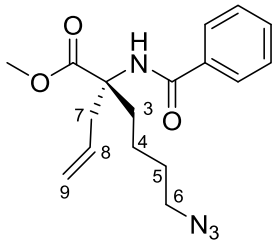
Amino acid methyl ester **2.46a** was obtained (0.195 g, 1.01 mmol, 79 %) as a viscous oil via the general methanolysis procedure from ATA **2.44a** (0.450 g, 1.28 mmol) and NaOMe (1.40 ml) as a clear gum. Auxiliary **(-)-2.29** was also recovered (0.249 g, 1.31 mmol, 95 %) as tan needle-like crystals. Chiral HPLC on an AD column eluting with IPA: Hex (10:90) revealed a 97:3 enantiomeric ratio. Minor enantiomer retention time = 10.1 min; that of the major enantiomer = 11.3 min. HRMS (ES): *m/z* found 194.1175, $C_{11}H_{16}NO_2$ $[M+H]^+$ requires 194.1172; $[\alpha]_D^{20}$= -8.2°, ($CHCl_3$, *c* = 0.67), [lit. $[\alpha]_D^{20}$= -14.1° ($CHCl_3$, *c* = 1.6)][151]; IR: ν_{max} (cm^{-1}) 3374 (NH_2), 3027 (C-H aromatics), 2956 (C-H alkanes), 1731 (C=O), 1601 (NH bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.12 (m, 3H, aromatic), 7.08 – 7.03 (m, 2H, aromatic), 3.61 (s, 3H, OC*H*$_3$), 3.04 (d, *J* = 13.2 Hz, 1H, C*H*$_2$*a*Ph), 2.72 (d, *J* = 13.2 Hz, 1H, C*H*$_2$*b*Ph), 1.63 (broad s, 2H, N*H*$_2$), 1.30 (s, 3H, CC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6 (C=O), 136.7 (Ar_q), 130.1 (Ar), 128.4 (Ar), 127.1 (Ar), 59.0 (C_q), 52.2 (O*C*H_3), 47.1 (*C*H_2Ph), 26.7 (*C*H_3).

Methyl (*S*)-2-benzamido-2-methylpent-4-enoate (2.47)



The general methanolysis procedure using ATA **2.44b** (0.400 g, 1.33 mmol) and NaOMe (1M, 1.46 ml) furnished the α-allyl alanine methyl ester **2.46b** (0.144, 1.01 mmol, 76 %) as a light yellow gum which was then taken up in DCM (20 ml) and anhydrous pyridine (0.12 ml, 1.46 mmol, 1.2 eq) was added followed by benzoyl chloride (0.17 ml, 1.46 mmol, 1.2 eq) and the reaction was left to stir for 6 hours. No work-up was performed; after removal of DCM on the rotary evaporator the residue was chromatographed with ethyl acetate/ hexane (40/60) giving *N*-benzoyl α-allyl alanine methyl ester **2.47** (0.230 g, 0.929 mmol, 92 %) as a light-yellow gum. Auxiliary **(-)-2.29** was recovered (0.240 g, 1.26 mmol, 90 %) as yellowish needle-like crystals from the methanolysis reaction. Chiral HPLC on an AD column eluting with IPA: Hex (10:90) revealed a 98:2 enantiomeric ratio. Minor enantiomer retention time 6.3 min; that of the major enantiomer 7.1 min HRMS (ES): *m/z* found 248.1291, $C_{14}H_{18}NO_3$ $[M+H]^+$ requires 248.1287;$[\alpha]_D^{20}$= +9.80°, ($CHCl_3$, *c* = 1), [lit.$[\alpha]_D^{20}$ = +9.74° ($CHCl_3$, *c* = 1.0)];[150] IR: ν_{max} (cm^{-1}) 3346 (NH), 3067 (C-H aromatics), 2929 (C-H alkanes), 1731 (C=O), 1640 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.68 (m, 2H, aromatic), 7.51 – 7.34 (m, 3H, aromatic), 6.92 (s, 1H, NH), 5.81 – 5.59 (m, 1H, CH_2=C*H*), 5.23 – 5.06 (m, 2H, CH=CH_2), 3.80 (s, 3H, OCH_3), 3.20 – 2.99 (m, 1H, CH_2=CHCH_2a), 2.68 (m, 1H, CH_2=CHCH_2b), 1.73 (s, 3H, CCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8 (C=O), 166.6 (C=O), 135.0 (Ar_q), 132.6 (*C*H=CH_2), 131.7 (Ar), 128.7 (Ar), 127.0 (Ar), 119.7 (CH=*C*H_2), 60.4 (C_q), 52.9 (O*C*H_3), 40.9 (*C*H_2CH=CH_2), 23.1 (*C*H_3).

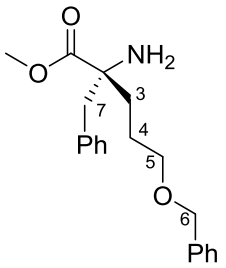
Methyl (*R*)-2-allyl-6-azido-2-benzamidohexanoate (2.49)



The general methanolysis procedure using ATA **2.44c** (0.400 g, 1.04 mmol) and NaOMe (1M, 1.25 ml) furnished the quaternary amino acid methyl ester **2.46c** (0.185 g, 0.822 mmol, 78 %) as a gummy solid which was then taken up in DCM (20 ml) and anhydrous pyridine (0.16 ml, 2.06 mmol, 2.5 eq) was added followed by benzoyl chloride (0.110 ml, 0.986 mmol, 1.2 eq) and the reaction was left to

stir for 6 hours. No work-up was performed; after removal of DCM on the rotary evaporator the residue was chromatographed with ethyl acetate/ hexane (40/60) giving *N*-benzoyl ester **2.49** (0.239 g, 0.723 mmol, 88 %) as a light-yellow gum. Auxiliary (-)-**2.29** was recovered (0.180 g, 0.946 mmol, 91 %) as yellowish needle-like crystals from the methanolysis reaction. Chiral HPLC on an AD column eluting with IPA: Hex (10:90) revealed a 98:2 enantiomeric ratio. Minor enantiomer retention time = 9.1 min; that of the major enantiomer = 8.1 min HRMS (ES): *m/z* found 331.1771, $C_{17}H_{23}N_4O_3$ $[M+H]^+$ requires 331.1770 ;$[\alpha]_D^{20}$= -15.75°, ($CHCl_3$, *c* = 1); IR: ν_{max} (cm^{-1}) 3329 (NH), 3071 (C-H aromatics), 2945 (C-H alkanes), 2090 (N_3) 1728 (C=O), 1654 (C=O) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.71 (m, 2H, aromatic), 7.61 – 7.36 (m, 3H, aromatic), 7.15 (broad s, 1H, NH), 5.70 – 5.51 (m, 1H, H-8), 5.13 – 5.01 (m, 2H, H-9), 3.83 (s, 3H, OCH_3), 3.39 (dd, *J* = 13.9, 7.3 Hz, 1H, H-7a), 3.30 – 3.14 (m, 2H, H-6), 2.70 (ddd, *J* = 13.6, 12.0, 4.6 Hz, 1H, H-3a), 2.57 (dd, *J* = 13.9, 7.3 Hz, 1H, H-7b), 1.90 (ddd, *J* = 13.6, 12.0, 4.6 Hz, 1H, H-3b), 1.64 – 1.50 (m, 2H, H-5), 1.48 – 1.29 (m, 1H, H-4a), 1.23 – 1.04 (m, 1H, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4 (C=O), 166.4 (C=O), 135.1 (Ar_q), 132.3 (C-8), 131.7 (Ar), 128.8 (Ar), 127.0 (Ar), 119.3 (C-9), 65.3 (C-2), 53.1 (C-6), 51.2 (OCH_3), 39.7 (C-7), 34.5 (C-3), 28.7 (C-5), 21.7 (C-4).

Methyl (*R*)-2-amino-2-benzyl-5-(benzyloxy)pentanoate (2.46d)

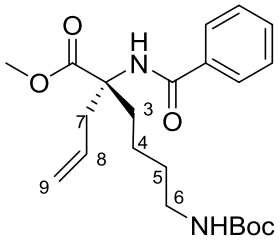


Title quaternary amino acid methyl ester **2.46d** was obtained (0.140 g, 0.43 mmol, 73 %) as a clear oil via the general methanolysis procedure from ATA **2.44d** (0.300 g, 0.59 mmol) and NaOMe (1M, 0.71 ml). Auxiliary **(-)-2.29** was also recovered (0.098 g, 0.52 mmol, 88 %) as tan needle-like crystals.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.14 (m, 8H, aromatic), 7.12 – 6.98 (m, 2H, aromatic), 4.42 (s, 2H, H-6), 3.62 (s, 3H, OCH_3), 3.41 (t, *J* = 6.3 Hz, 2H, H-5), 3.11 (d, *J* = 13.2 Hz, 1H, H-7a), 2.73 (d, *J* = 13.2 Hz, 1H, H-7b), 2.00 – 1.88 (m, 1H, H-3a), 1.85 (broad s, 2H, NH_2), 1.65 (m, 1H, H-3b), 1.54 – 1.39 (m, 1H, H-4a), 1.23 – 1.12 (m, 1H, H-4b).

Synthesis of quaternary lysine derivative

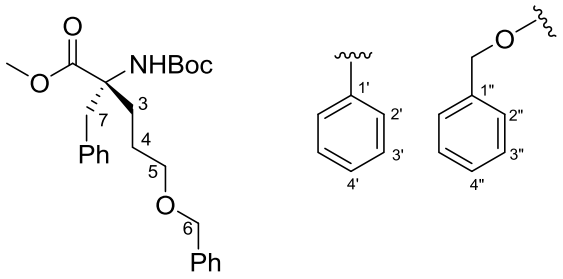
Methyl (*R*)-2-allyl-2-benzamido-6-((*tert*-butoxycarbonyl)amino)hexanoate (2.50)



Quaternary amino acid methyl ester **2.49** (0.065 g, 0.196 mmol) and PPh_3 (0.103 g, 0.393 mmol, 2 equivalents) were dissolved in THF/H_20 (6/1, 30 ml) and stirred at rt for 9 hours, followed by the addition of Boc_2O (0.085 g, 0.393 mmol, 2 equivalents) in THF (5 ml). The protection step was complete within 15 minutes as indicated by tlc, following which the THF was removed on the rotary evaporator and water (5 ml) and EtOAc (15 ml) were added. The aqueous layer was extracted with EtOAc (3 x 10 ml) and the combined organic fractions dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resultant residue was chromatographed using EtOAc/ hexanes (15/85) delivering the title quaternary lysine amino acid methyl ester derivative **2.50** (0.046 g, 0.149 mmol, 76 %) as a light-yellow thick oil. Chiral HPLC on an AD column eluting with IPA: Hex (10:90) revealed a 98:2 enantiomeric ratio. Minor enantiomer retention time = 12.8 min; that of the major enantiomer = 9.9 min HRMS (ES): *m/z* found 405.2389, $C_{22}H_{33}N_2O_5$ $[M+H]^+$ requires 405.2380; $[\alpha]_D^{20}$= -12.8°, ($CHCl_3$, *c* = 1); IR: ν_{max} (cm^{-1}): 3407 (NH), 3339 (NH) 3071 (C-H aromatics), 2929 (C-H alkanes), 1733 (C=O ester), 1686 (C=O) 1654 (C=O);^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.66 (m, 2H, aromatic), 7.57 – 7.27 (m, 3H, aromatic), 7.08 (s, 1H, N*H*Bz), 5.69 – 5.36 (m, 1H, H-8), 5.06 – 4.78 (m, 2H, H-9), 4.49 (broad s, 1H, N*H*Boc), 3.74 (s, 3H, OCH_3), 3.28 (dd, *J* = 13.9, 7.3 Hz, 1H, H-7a), 3.01 – 2.86 (m, 2H, H-6), 2.68 – 2.54 (m, 1H, H-3a), 2.51 (dd, *J* = 13.9, 7.3 Hz, 1H, H-7b), 1.88 – 1.72 (m, 1H, H-3b), 1.47 – 1.36 (m, 2H, H-5), 1.33 (s, 9H, *t*Bu), 1.29 – 1.22 (m, 1H, H-4a), 1.10 – 0.87 (m, 1H, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4 (C=O), 166.4 (C=O), 156.1 (C=O), 135.1 (Ar_q), 132.4 (C-8), 131.6 (Ar), 128.7 (Ar), 127.0 (Ar), 119.2 (Ar), 79.2 (C_q *t*-Bu), 65.2 (C-2), 53.0 (OCH_3), 40.2 (C-6), 39.7 (C-7), 34.6 (C-3), 29.8 (C-5), 28.5 (*t*-Bu), 21.5 (C-4).

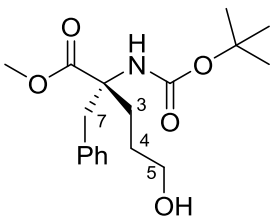
Synthesis of quaternary proline derivative

Methyl (*R*)-2-benzyl-5-(benzyloxy)-2-((*tert*-butoxycarbonyl)amino)pentanoate (2.53)



Quaternary amino acid methyl ester **2.46d** (0.170 g, 0.519 mmol) was dissolved in *t*-BuOH (60 ml) and to this was added Boc_2O (0.170 g, 0.779 mmol, 1.5 equivalents) and the mixture allowed to stir overnight at rt. No work-up was performed and following removal of *t*-BuOH on the rotary evaporator, the residue was chromatographed using EtOAc/ hexanes (10/90) furnishing the Boc-protected amino acid methyl ester **2.53** (0.169 g, 0.395 mmol, 76 %) as a gummy liquid. Chiral HPLC on an AD column eluting with IPA: Hex (10:90) revealed a 96:4 enantiomeric ratio. Minor enantiomer retention time = 12.1 min; that of the major enantiomer = 10.7 min HRMS (ES): *m/z* found 428.2440, $C_{25}H_{34}NO_5$ $[M+H]^+$ requires 428.2437 ;$[\alpha]_D^{20}$= -42.5°, ($CHCl_3$, *c* = 1); IR: ν_{max} (cm^{-1}) 3332 (NH), 2955 (C-H aromatics), 2919 (C-H alkanes), 1733 (C=O), 1670 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 – 7.10 (m, 8H, aromatic), 7.03 – 6.91 (m, 2H, aromatic), 5.30 (broad s, 1H, NH), 4.40 (s, 2H, H-6), 3.66 (s, 3H, OCH_3), 3.52 (d, *J* = 13.3 Hz, 1H, H-7a), 3.45 – 3.31 (m, 2H, H-5), 3.03 (d, *J* = 13.3 Hz, 1H, H-7b), 2.47 – 2.29 (m, 1H, H-3a), 1.95 – 1.83 (m, 1H, H-3b), 1.65 – 1.50 (m, 1H, H-4a), 1.39 (s, 9H, *t*-Bu), 1.36 – 1.26 (m, 1H, H-4b). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C=O), 154.2 (C=O), 138.7 (C-1'), 136.7 (C-1"), 130.0 (C-3'), 128.6 (C-3"), 128.3 (C-2'), 127.7 (C-2"), 127.6 (C-4"), 126.9 (C-4'), 79.3 (C_q *t*-Bu), 72.9 (C-6), 70.0 (C-5), 65.0 (C-2), 52.6 (OCH_3), 41.2 (C-7), 32.5 (C-3), 28.6 (*t*-Bu), 24.8 (C-4).

Methyl (*R*)-2-benzyl-2-((tert-butoxycarbonyl)amino)-5-hydroxypentanoate (2.54)

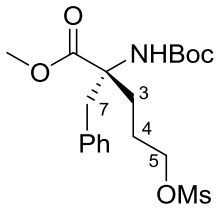


Boc-protected amino acid ester **2.53** (0.150 g, 0.351 mmol) was dissolved in deoxygenated methanol (50 ml) and to this was carefully added Pd/C (0.037 g, 10 wt %, 10 mol %) under a nitrogen atmosphere. The reaction was placed under a hydrogen atmosphere and stirred vigorously for 2 hours. Filtration through Celite, followed by concentration on the rotary evaporator yielded a

colourless gum, which was purified by column chromatography using EtOAc/hexane (30/70) to furnish alcohol **2.54** (0.116 g, 0.344 mmol, 98 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.08 (m, 3H, aromatic), 6.72 – 6.98 (m, 2H, aromatic), 5.32 (broad s, 1H, NH), 3.68 (s, 3H, OCH_3), 3.59 – 3.44 (m, 3H, H-7a, H-5), 3.01 (d, *J* = 13.5 Hz, 1H, H-7b), 2.49 – 2.41 (m, 1H, H-3a), 1.95 – 1.88 (m, 1H, H-3b), 1.65 – 1.45 (m, 2H, OH, H-4a), 1.40 (s, 9H, *t*-Bu), 1.36 – 1.20 (m, 1H, H-4b).

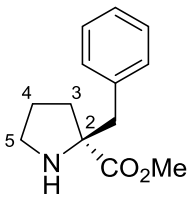
Methyl (*R*)-2-benzyl-2-((*tert*-butoxycarbonyl)amino)-5-((methylsulfonyl)oxy)pentanoate (2.55)



The alcohol **2.54** (0.060 g, 0.177 mmol) was dissolved in DCM (20 ml) and to this was added pyridine (0.30 ml, 0.354 mmol, 2 equivalents), DMAP (0.011 g, 0.09 mmol, 0.5 equivalents) and mesyl chloride (0.030 ml, 0.354 mmol, 2 equivalents) and the reaction stirred at rt for 4 hours. The mixture was transferred to a separating funnel and washed with aqueous saturated sodium bicarbonate (15 ml) and the aqueous layer was extracted with DCM (3 x 20 ml). Pooled organic fractions were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* and the residue was committed to flash chromatography using EtOAc/ hexanes (10/90) to yield the title quaternary amino acid methyl ester **2.55** (0.068 g, 0.163 mmol, 92 %) as a colourless gum.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.10 (m, 3H, aromatic), 7.09 – 6.82 (m, 2H, aromatic), 5.31 (broad s, 1H, NH), 4.25 – 4.04 (m, 2H, H-5), 3.70 (s, 3H, OCH_3), 3.53 (d, *J* = 13.5 Hz, 1H, H-7a), 2.99 (d, *J* = 13.5 Hz, 1H, H-7b), 2.94 (s, 3H, SCH_3), 2.59 – 2.45 (m, 1H, H-3a), 2.03 – 1.89 (m, 1H, H-3b), 1.81 – 1.62 (m, 1H, H-4a), 1.55 – 1.45 (m, 1H, H-4b), 1.41 (s, 9H, *t*-Bu).

Methyl (*S*)-2-benzylpyrrolidine-2-carboxylate (2.56)

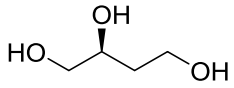


Boc-protected quaternary amino acid methyl ester **2.55** (0.080 g, 0.193 mmol) was dissolved in DCM (40 ml) and cooled to 0 °C followed by the addition of TFA (0.08 ml, 1.01 mmol, 5.5 equivalents).

Stirring was continued at this temperature for 2 hours, after which time tlc analysis indicated complete deprotection of the starting material. The intermediate free amine was not isolated and the reaction mixture was concentrated *in vacuo* to remove solvent and TFA. The yellowish liquid was re-taken up in THF (30 ml) followed by the addition of triethylamine (0.25 ml, 1.93 mmol, 10 equivalents) and the solution was stirred at rt for an hour. Following THF removal on the rotary evaporator, water (15 ml) and EtOAc (40 ml) were added and the aqueous layer extracted with EtOAc (3 x 30 ml). Combined organic fractions were dried over anhydrous $MgSO_4$, filtered, concentrated and the resultant residue was chromatographed using EtOAc/ hexanes (20/80) to furnish the α-benzyl quaternary proline derivative **2.56** (0.032 g, 0.145 mmol, 75 %) as a clear viscous liquid. Chiral HPLC on an AD column eluting with IPA: Hex (10:90) revealed a 98:2 enantiomeric ratio. Minor enantiomer retention time = 6.2 min; that of the major enantiomer 4.4 min HRMS (ES): *m/z* found 220.1338, $C_{13}H_{18}NO_2$ $[M+H]^+$ requires 220.1338; $[\alpha]_D^{20}$= -10.0°, ($CHCl_3$, *c* = 1); IR: ν_{max} (cm^{-1}) 3349 (NH), 3029 (C-H aromatics), 2950 (C-H alkanes), 1733 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.01 (m, 5H, aromatic), 3.58 (s, 3H, OCH_3), 3.10 (d, *J* = 13.1 Hz, 1H, CH_2aPh), 3.00 – 2.83 (m, 2H, H-5), 2.80 (d, *J* = 13.1 Hz, 1H, CH_2bPh), 2.06 (broad s, 1H, NH), 1.85 – 1.70 (m, 1H, H-3a), 1.72 – 1.56 (m, 1H, H-3b) 1.44 – 1.40 (m, 2H, H-4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0 (C=O), 137.6 (Ar_q), 129.8 (Ar), 128.3 (Ar), 126.8 (Ar), 70.7 (C-2), 52.1 (O*C*H_3), 46.1 (C-5), 45.5 (*C*H_2Ph), 35.8 (C-3), 24.5 (C-4).

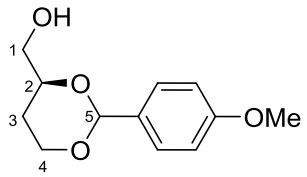
Synthesis of OPMB, OTBDPS tether[156]

(*S*)-(–)-1,2,4-Butanetriol (2.63)



Borane-dimethylsulfide complex (22.8 ml, 0.232l, 3.2 eq) and trimethyl borate (25.0 mL, 0.22 mol, 3 eq) were stirred for 15 minutes in THF (300 ml) at 0 °C. (*S*)-malic acid (10.00 g, 0.0746 mol) was then added and the reaction was left to stir at room temperature overnight. Methanol (60 ml) was carefully introduced at 0 °C, followed by removal of the solvent *in vacuo* and filtration of the resultant residue through a short pad of silica, eluting with methanol/dichloromethane (20/80). Evaporation of the solvent afforded the triol **2.63** (7.44 g, 70.1 mmol, 94 %) as a colourless oil, which was of sufficient purity to be used in the next step as judged by tlc.

(2*S*)-2,4-[(*S*)-*p*-Methoxybenzylidenedioxy]butanol (2.64)



To a stirred mixture of the triol **2.63** (6.50 g, 61.25 mmol) and *p*-methoxybenzaldehyde dimethylacetal (20.7 ml, 121.6 mmol) in dichloromethane (250 ml), was added CSA (1.43 g, 6.14 mmol, 10 mol %) and the reaction left to stir overnight. Triethylamine (*ca* 2ml) was then added and the solvent evaporated. The residue was subjected to column chromatography using EtOAc/ hexane (50/50) to furnish the title PMP acetal alcohol **2.64** (10.58 g, 47.16 mmol, 77 %) as a colourless oil.

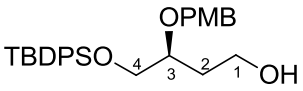
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.1 Hz, 2H, aromatic), 6.89 (d, *J* = 8.1 Hz, 2H, aromatic), 5.50 (s, 1H, H-5), 4.29 (dd, *J* = 11.5, 5.1 Hz, 1H, H-4a), 4.01 – 3.94 (m, 2H, H-4b + H-2), 3.89 (s, 3H, OCH_3), 3.71 – 3.62 (m, 2H, H-1), 2.02 (broad s, 1H, OH), 1.96 – 1.88 (m, 1H, H-3a), 1.45 (d, *J* = 13.3 Hz, 1H, H-3b).

(2*S*)-1-(*t*-Butyldiphenylsiloxy)-2,4-[(*S*)-*p*-methoxybenzylidenedioxy]butane (2.65)

A solution of imidazole (1.46 g, 21.41 mmol, 1.2 eq) and *t*-butylchlorodiphenylsilane (5.90 mL, 21.41 mmol, 1.2 eq) in acetonitrile (200 mL) was cooled to 0 °C and to this was added PMP acetal-alcohol **2.64** (4.00 g, 17.84 mmol) dissolved in acetonitrile (30 mL). The reaction mixture was left to stir at room temperature for 5 h, after which time it was cooled to 0 °C and quenched with water (20 ml). It was then extracted with ethyl acetate (3 x 100 ml), and the combined organic fractions were washed with water (50 ml) then brine (50 ml), dried over anhydrous $MgSO_4$ and filtered. Upon removal of the solvent, column chromatography with EtOAc/hexane (10/90) was performed on the residue, yielding the TBDPS ether **2.65** (7.08 g, 15.30 mmol, 86 %) as a colourless gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.70 (m, 4H, aromatic), 7.55 – 7.35 (m, 8H, aromatic), 6.90 – 6.83 (m, 2H, aromatic), 5.48 (s, 1H, H-5), 4.38 (dd, *J* = 11.5, 5.1 Hz, 1H, H-4a), 4.09 – 3.95 (m, 2H, H2 + H1a), 3.90 – 3.86 (m, 1H, H-1b), 3.81 (s, 3H, OCH_3), 3.71 – 3.61 (m, 1H, H-4b), 1.98 – 1.83 (m, 1H, H-3a), 1.68 – 1.59 (m, 1H, H-3b), 1.11 (s, 9H, *t*-Bu).

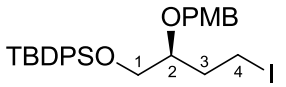
(3*S*)-4-(*t*-Butyldiphenylsiloxy)-3-(*p*-methoxybenzyloxy)butanol (2.66)



A solution of acetal **2.65** (2.80 g, 6.05 mmol) in toluene (150 ml) was cooled to -78 °C and to this was added DIBAL (1.5 M in toluene, 16.14 ml, 24.21 mmol, 4 eq). Stirring was continued at -78 °C for a further 3 h, following which, methanol (17 ml) was added slowly. Once the mixture reached room temperature, saturated aqueous potassium sodium tartrate (80 ml) was added and stirring was continued for a further 15 minutes. The layers were separated and the aqueous layer was extracted with DCM (3 x 100 ml). Pooled organic fractions were washed with brine (100 ml), dried over anhydrous $MgSO_4$ and concentrated to a thick oil. Purification by column chromatography eluting with EtOAc/hexane (30/70) afforded the alcohol **2.66** as a clear oil (2.67 g, 5.75 mmol, 95 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 – 7.62 (m, 4H, aromatic), 7.50 – 7.34 (m, 6H, aromatic), 7.21 (d, *J* = 8.7 Hz, 2H, aromatic), 6.86 (d, *J* = 8.7 Hz, 2H, aromatic), 4.60 (d, *J* = 11.3 Hz, 1H, OC*H*$_2$aPh), 4.42 (d, *J* = 11.3 Hz, 1H, OC*H*$_2$bPh), 3.80 (s, 3H, OC*H*$_3$), 3.77 (m, 1H, H-3), 3.76 – 3.65 (m, 4H, H-4 and H-1), 2.09 (broad s, 1H, OH), 1.87 – 1.75 (m, 2H, H-2), 1.08 (s, 9H, *t*-Bu).

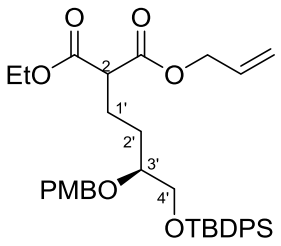
(2*S*)-1-(*t*-Butyldiphenylsiloxy)-4-iodo-2-(*p*-methoxybenzyloxy)butane (2.67)



Alcohol **2.66** (2.00 g, 4.30 mmol) was placed in dry toluene (200 ml). Imidazole (0.47 g, 6.88 mmol, 1.6 equivalents), PPh_3 (1.81g, 6.88 mmol, 1.6 equivalents) and iodine (1.42 g, 5.59 mmol, 1.3 equivalents) were added successively to the stirring mixture. The reaction was left to stir at room temperature for 4 hours and then saturated sodium thiosulphate solution (100 ml) was added. The aqueous layer was extracted with diethyl ether (3 x 10 ml) and washed with saturated sodium bicarbonate (100 ml) followed by brine (100 ml). It was then concentrated and subjected to flash chromatography using EtOAc/ hexanes (5/95) to afford the iodide **2.67** (2.27 g, 3.95 mmol, 92 %) as a clear liquid.

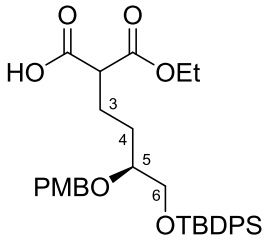
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.65 (m, 4H, aromatic), 7.49 – 7.28 (m, 6H, aromatic), 7.25 – 7.23 (m, 2H, aromatic), 6.88 – 6.85 (m, 2H, aromatic), 4.55 (d, *J* = 10.5 Hz, 1H, OC*H*$_2$aPh), 4.41 (d, *J* = 10.5 Hz, 1H, OC*H*$_2$bPh), 3.95 – 3.83 (m, 1H, H-1a), 3.81 (s, 3H, OC*H*$_3$), 3.77 – 3.61 (m, 1H, H-2), 3.72 – 3.60 (m, 1H, H-1b), 3.21 – 3.02 (m, 2H, H-4), 1.97 – 1.77 (m, 2H, H-3), 1.07 (s, 9H, *t*-Bu).

1-Allyl 3-ethyl 2-((*S*)-4-((tert-butyldiphenylsilyl)oxy)-3-((4-methoxybenzyl)oxy)butyl)malonate (2.70)



Ethyl allyl malonate **2.69** (2.00 ml, 13.20 mmol) was slowly added to a stirred suspension of NaH (60 % dispersion in oil, 0.53 g, 13.20 mmol) in tetrahydrofuran (100 ml) at 0 °C. The anion was allowed to form by vigorous stirring at room temperature for a further 45 minutes. A solution of the iodide **2.67** (7.61 g, 13.20 mmol) in THF (50 ml) was added in one portion to the clear anion solution. The reaction was stirred at room temperature for an hour then slowly brought up to 60 °C. After 8 hours, it was cooled and quenched with saturated ammonium chloride solution (50 ml) and extracted with ethyl acetate (3 x 100 ml). The organic extracts were washed with brine (50 ml), dried over anhydrous $MgSO_4$, filtered and evaporated to give the crude product. Column chromatography using EtOAc/hexane (20/80) gave the alkylated malonate product **2.70** (7.59 g, 12.28 mmol, 93 %) as a thick oil in a 50:50 ratio of diastereomers as determined by ^{1}H NMR spectroscopy. HRMS (ES): *m/z* found 619.3055, $C_{36}H_{47}O_7Si$ $[M+H]^+$ requires 619.3048; IR: ν_{max} (cm^{-1}) 3068 (C-H aromatics), 2933 (C-H aliphatic), 1748 (C=O), 1729 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.65 (m, 4H, aromatic), 7.49 – 7.38 (m, 6H, aromatic), 7.25 (d, *J* = 6.6 Hz, 2H, aromatic), 6.88 (d, *J* = 8.7 Hz, 2H, aromatic), 6.05 – 5.82 (m, 1H, CH_2=C*H*), 5.39 – 5.22 (m, 2H, CH=CH_2), 4.68 – 4.63 (m, 2H, CH_2=CHCH_2), 4.59 (d, *J* = 11.3 Hz, 1H, OCH_2*a*Ph), 4.45 (d, *J* = 11.3 Hz, 1H, OCH_2*b*Ph), 4.25 – 4.17 (m, 2H, C$H_2$$CH_3$), 3.83 (s, 3H, OC$H_3$), 3.77 (dd, *J* = 10.6, 5.2 Hz, 1H, H-4'a), 3.66 (dd, *J* = 10.6, 5.5 Hz, 1H, H-4'b), 3.56 – 3.49 (m, 1H, H-3'), 3.36 (t, *J* = 7.6 Hz, 1H, H-2), 2.13 – 1.90 (m, 2H, H-1'), 1.73 – 1.56 (m, 2H, H-2'), 1.28 (t, *J* = 7.1, 3H, CH_2CH_3), 1.10 (s, 9H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4 (C=O) 169.2 (C=O,), 159.3 (Ar_{PMB}), 135.8 (2 x Ar_{Si}), 133.7 (Ar_{qSi}), 133.6 (Ar_{qSi}), 131.9 (Ar_{qPMB}), 131.0 (Ar_{Si}), 129.8 (Ar_{Si}), 129.4 (Ar_{PMB}), 127.9 (Ar_{Si}), 127.8 (Ar_{si}), 118.6 (CH=*C*H_2), 113.9 (Ar_{PMB}), 78.9 (C-3'), 71.9 (O*C*H_2Ph), 66.1 (C-4'), 65.9 (CH_2=CH*C*H_2), 61.5 (*C*$H_2$$CH_3$), 55.4 (O*C*$H_3$), 52.1 (C-2), 29.5 (*C*(CH_3)$_3$), 27.0 (C(*C*H_3)$_3$, 24.9 (C-2'), 19.4 (C-1'), 14.2 (CH_2*C*H_3).

(5*S*)-6-((*tert*-Butyldiphenylsilyl)oxy)-2-(ethoxycarbonyl)-5-((4-methoxybenzyl)oxy)hexanoic acid (2.71)



To a solution of mono-alkylated allyl ethyl malonate **2.70** (6.00 g 9.70 mmol) in EtOH (200 mL) at 0 °C was added dropwise a solution of KOH (2.5 M in EtOH, 5.80 ml, 14.5 mmol, 1.5 eq) and the ice-bath removed. Since tlc analysis indicated incomplete hydrolysis after stirring at rt overnight, a further equivalent of KOH was added and stirring continued for a further 3 hours, after which time the EtOH was removed under reduced pressure and the concentrate diluted with water (100 mL) and extracted with DCM (3 x 100 ml) to remove unreacted starting material. The aqueous layer was then acidified with conc. HCl to pH = 3 and then re-extracted with DCM (1 x 300 and 2 × 150 ml), the organic extracts combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to obtain the half-acid **2.71** (4.10 g, 7.08 mmol, 73 %) as a colourless oil in a diastereomeric ratio of 50:50 as determined by ^{1}H NMR spectroscopy. HRMS (ES): *m/z* found 579.2733, $C_{33}H_{43}O_7Si$ $[M+H]^+$ requires 579.2731; IR: ν_{max} (cm^{-1}) 3457 (OH), 3073 (C-H aromatic), 2957 (C-H alkenes), 1734 (C=O).

Diastereomer 1:

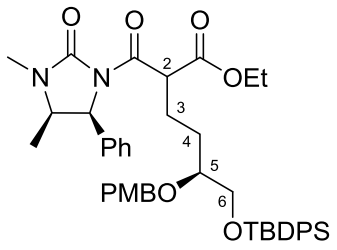
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (broad s, COO*H*), 7.69 – 7.62 (m, 4H, aromatic), 7.45 – 7.30 (m, 6H, aromatic), 7.19 (d, *J* = 8.5 Hz, 2H, aromatic), 6.82 (d, *J* = 8.5 Hz, 2H, aromatic), 4.54 (d, *J* = 11.3 Hz, 1H, OCH_{2a}Ph), 4.40 (d, *J* = 11.3 Hz, 1H, OCH_{2b}Ph), 4.23 – 4.09 (m, 2H, CH_2CH$_3$), 3.76 (s, 3H, OCH_3), 3.73 (dd, J = 10.6, 5.4 Hz, 1H, H-6), 3.64 – 3.56 (m 1H, H-6), 3.52 – 3.43 (m, 1H, H-5), 3.31 (t, J = 7.5, 1H, H-2), 2.07 – 1.85 (m, 2H, H-3), 1.72 – 1.49 (m, 2H, H-4), 1.24 (t, J = 7.2, 3H, CH$_2$CH_3), 1.05 (s, 9H, *t*Bu Hs); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4 (C=O), 169.8 (C=O), 159.3 (Ar_{PMB}), 135.7 (Ar_{Si}), 135.6 (Ar_{Si}), 133.5 (Ar_{qSi}), 133.4 (Ar_{qSi}), 131.9 (Ar_{qPMB}), 131.0 (Ar_{Si}), 129.8 (Ar_{Si}), 129.5 (Ar_{PMB}), 127.9 (Ar_{Si}), 127.6 (Ar_{Si}), 113.6 (Ar_{PMB}), 78.8 (C-5), 71.9 (O*C*H$_2$Ph), 65.9 (C-6), 61.8 (*C*H$_2$CH$_3$), 55.4 (O*C*H$_3$), 51.5 (C-2), 29.3 (Si*C*), 27.0 (C(*C*H$_3$)$_3$), 25.1 (C-4), 19.3 (C-3), 14.2 (CH$_2$*C*H$_3$).

Diastereomer 2:

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (broad s, COO*H*), 7.69 – 7.62 (m, 4H, aromatic), 7.45 – 7.30 (m, 6H, aromatic), 7.19 (d, *J* = 8.5 Hz, 2H, aromatic), 6.82 (d, *J* = 8.5 Hz, 2H, aromatic), 4.54 (d, *J* = 11.3 Hz, 1H, OCH_{2a}Ph), 4.40 (d, *J* = 11.3 Hz, 1H, OCH_{2b}Ph), 4.23 – 4.09 (m, 2H, CH_2CH$_3$), 3.76 (s, 3H, OCH_3), 3.73 (dd, *J* = 10.6, 5.4 Hz, 1H, H-6), 3.64 – 3.56 (m 1H, H-6), 3.52 – 3.43 (m, 1H, H-5), 3.34 (t, *J* = 7.5, 1H, H-2), 2.07 – 1.85 (m, 2H, H-3), 1.72 – 1.49 (m, 2H, H-4), 1.27 (t, *J* = 7.2, 3H, CH$_2$CH_3), 1.05 (s, 9H, *t*Bu Hs);

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5 (C=O), 169.7 (C=O), 159.3 (Ar_{PMB}), 135.6 (Ar_{Si}), 135.5 (Ar_{Si}), 133.5 (Ar_{qSi}), 133.4 (Ar_{qSi}), 131.7 (Ar_{qPMB}), 131.0 (Ar_{Si}), 129.7 (Ar_{Si}), 129.4 (Ar_{PMB}), 127.7 (Ar_{Si}), 127.6 (Ar_{Si}), 113.8 (Ar_{PMB}), 78.8 (C-5), 71.9 (O*C*H_2Ph), 65.0 (C-6), 61.9 (*C*H_2CH$_3$), 55.6 (OCH$_3$), 51.5 (C-2), 29.9 (Si*C*), 26.9 (C(*C*H$_3$)$_3$), 25.2 (C-4), 19.4 (C-3), 14.2 (CH$_2$*C*H$_3$).

(5*S*)-Ethyl 6-((*tert*-butyldiphenylsilyl)oxy)-2-((4*R*,5*S*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)-5-((4-methoxybenzyl)oxy)hexanoate (2.72)



To a solution of 1-chlorobenzotriazole (0.689 g, 4.50 mmol, 1.3 eq) in acetonitrile (200 ml) was added PPh_3 (1.26 g, 4.50 mmol, 1.3 eq) at 0 °C and the mixture stirred for 10 minutes. The alkylated mono-acid **2.71** (2.00 g, 3.46 mmol, 1 eq) in acetonitrile (50 ml) was then syringed in and the reaction left to warm up to room temperature. Over the next 20 minutes, the reaction colour changed from mauve to bright yellow, at which point auxiliary **(+)-2.29** (0.861 g, 4.50 mmol, 1.3 eq) was introduced and the reaction refluxed overnight. Once cooled, saturated aqueous sodium bicarbonate solution (80 ml) was added and the mixture vigorously stirred at 50 °C for 2 hours. Next, the organic layer was isolated and extracted with saturated aqueous sodium bicarbonate (50 ml), washed with brine and dried over anhydrous $MgSO_4$, then filtered and concentrated under reduced pressure. The crude product was chromatographed using EtOAc/ hexanes (20/80) to give the auxiliary-alkylated malonate **2.72** (1.71 g, 2.28 mmol, 66 %) as a thick, colourless gum in a 50:50 ratio of diastereomers as determined by ^{1}H NMR spectroscopy. HRMS (ES): *m/z* found 751.3740, $C_{44}H_{55}N_2O_7Si$ $[M+H]^+$ requires 751.3735; $[\alpha]_D^{20}$= -44.4°, (DCM, c = 1); IR: ν_{max} (cm^{-1}) 3033 (C-H aromatic), 2901 (C-H alkanes), 1730 (C=O ester, amide), 1685 (C=O urea).

Diastereomer 1:

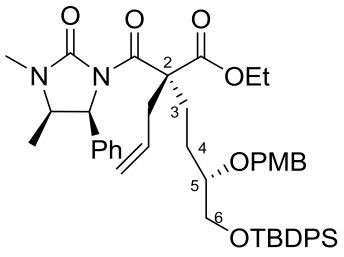
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 – 7.55 (m, 4H, aromatic), 7.50 – 7.15 (m, 11H, aromatic), 7.13 – 7.06 (m, 2H, aromatic), 6.89 – 6.84 (m, 2H, aromatic), 5.34 (d, *J* = 8.6 Hz, 1H, C*H*Ph), 4.76 (dd, *J* = 8.7, 5.2 Hz, 1H, H-2), 4.53 (d, *J* = 11.2 Hz, 1H, OC*H*$_{2a}$Ph), 4.43 (d, *J* = 11.2 Hz, 1H, OC*H*$_{2b}$Ph), 4.26 – 4.11 (m, 2H, CH$_3$C*H*$_2$), 3.91 (dq, *J* = 8.6, 6.6 Hz, 1H, C*H*CH$_3$), 3.78 (s, 3H, OC*H*$_3$), 3.67 – 3.51 (m, 2H, H-6), 3.50 – 3.41 (m, 1H, H-5), 2.79 (s, 3H,NC*H*$_3$), 2.02 – 1.83 (m, 2H, H-3), 1.51 – 1.39 (m, 1H, H-4), 1.28 – 1.18 (m, 3H, CH$_2$C*H*$_3$), 1.03 (s, 9H, *t*-Bu), 0.78 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3 (C=O), 168.1 (C=O), 159.1 (Ar_{qPMB}), 155.6 (C=O), 136.0 (Ar_q), 135.6 (Ar_{Si}), 135.5 (Ar_{Si}), 133.7 (Ar_{qSi}), 133.6

(Ar_{qSi}), 131.2 (Ar_{qPMB}), 129.7 (Ar), 129.6 (Ar_{PMB}), 129.2 (2 x Ar_{Si}), 128.0 (Ar), 127.8 (Ar_{Si}), 127.6 (Ar_{Si}), 127.1 (Ar), 113.7 (Ar_{PMB}), 79.5 (C-5), 71.9 (O*C*H_2Ph), 66.3 (C-6), 61.1 (*C*H_2CH_3), 59.8 (*C*HPh), 55.4 (O*C*H_3), 54.1 (*C*HCH_3), 51.1 (C-2), 29.9 (N*C*H_3), 28.3 (*C*$(CH_3)_3$), 27.0 (C(*C*$H_3)_3$), 24.7 (C-4), 19.4 (C-3), 15.2 (CH*C*H_3), 14.3 (*C*H_3CH_2).

Diastereomer 2:

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 4H, aromatic), 7.45 – 7.10 (m, 13H, aromatic), 6.88 – 6.76 (m, 2H, aromatic), 5.25 (d, *J* = 8.6 Hz, 1H, C*H*Ph), 4.68 (dd, *J* = 8.7, 5.2 Hz, 1H, H-2), 4.55 (d, *J* = 11.2 Hz, 1H, OCH_2*a*Ph), 4.43 (d, *J* = 11.1 Hz, 1H, OCH_2*b*Ph), 4.20 – 4.05 (m, 2H, CH_3CH_2), 3.79 (s, 3H, OCH_3), 3.77 – 3.72 (m, 1H, C*H*CH_3), 3.75 – 3.66 (m, 1H, H-6a), 3.66 – 3.58 (m, 1H, H-6b), 3.55 – 3.43 (m, 1H, H-5), 2.80 (s, 3H, NCH_3), 2.17 – 2.06 (m, 1H, H-3a), 1.99 – 1.81 (m, 1H, H-3b), 1.77 – 1.63 (m, 2H, H-4), 1.20 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.04 (s, 9H, *t*-Bu), 0.77 (d, *J* = 6.6 Hz, 3H, CHCH_3).

Ethyl (2*S*,5*S*)-2-allyl-6-((*tert*-butyldiphenylsilyl)oxy)-2-((4*R*,5*S*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)-5-((4-methoxybenzyl)oxy)hexanoate (2.73)

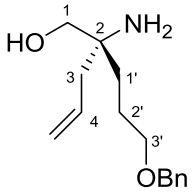


A solution of **2.72** (1.50 g, 2.00 mmol, 1 eq) in THF (200 ml) was cooled to -78 °C followed by the dropwise addition of KHMDS in toluene (0.5 M, 4.8 ml, 2.40 mmol, 1.2 eq) and stirring at this temperature was continued for a further 30 minutes after which time allyl bromide (0.26 ml, 3.00 mmol, 1.5 eq) was added in one portion to the anion solution. The reaction was slowly warmed to room temperature and allowed to stir overnight. It was then quenched with saturated aqueous ammonium chloride solution (100 ml), the THF removed on the rotary evaporator and the mixture and extracted with EtOAc (1 x 200 and 2 x 100 ml). The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated to give the crude product which was chromatographed using EtOAc/ hexanes (15/85) to give the title quaternary auxiliary malonate **2.73** (1.55 g, 1.96 mmol, 98 %) as a thick colourless gum, in a diastereomeric ratio of 97:3 as determined by ^{1}H NMR spectroscopy.

HRMS (ES): *m/z* found 791.4046, $C_{47}H_{59}N_2O_7Si$ $[M+H]^+$ requires 791.4040; IR: ν_{max} (cm^{-1}) 3029 (C-H aromatic), 2921 (C-H alkanes), 1727 (C=O ester, amide), 1679 (C=O urea); ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.69 – 7.60 (m, 4H, aromatic), 7.45 – 7.14 (m, 13H, aromatic), 6.82 (m, 2H, aromatic), 5.51 – 5.33 (m,

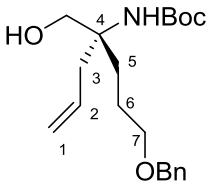
1H, C*H*=CH_2), 5.24 (d, *J* = 8.5 Hz, 1H, C*H*Ph), 4.99 – 4.84 (m, 2H, CH_2=CH), 4.48 (d, *J* = 11.2 Hz, 1H, OCH_{2a}Ph), 4.40 (d, *J* = 11.2 Hz, 1H, OCH_{2b}Ph), 4.24 – 4.07 (m, 2H, C$H_2$$CH_3$), 3.79 (s, 3H, OC$H_3$), 3.76 – 3.65 (m, 2H, H-6a and C*H*CH3), 3.62 – 3.50 (m, 1H, H-6b), 3.46 – 3.32 (m, 1H, H-5), 2.90 – 2.76 (m, 2H, CH_2=CHCH_2), 2.70 (s, 3H, NCH_3), 2.19 – 1.95 (m, 2H, H-3), 1.57 – 1.38 (m, 2H, H-4), 1.25 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.05 (s, 9H, *t*-Bu), 0.73 (d, *J* = 6.6 Hz, 3H CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4 (C=O), 169.7 (C=O), 159.1 (Ar_{qPMB}), 155.2 (C=O), 136.7 (Ar_q), 135.8 (Ar_{Si}), 135.7 (Ar_{Si}), 133.8 (Ar_{qSi}), 133.7 (Ar_{qSi}), 133.3 (*C*H=CH_2), 131.3 (Ar_{qPMB}), 129.8 (Ar), 129.3 (Ar_{PMB}), 129.2 (Ar_{Si}), 128.5 (Ar_{Si}), 128.1 (Ar), 127.8 (Ar_{Si}), 127.2 (Ar_{Si}), 127.0 (Ar), 118.1 (CH=*C*H_2), 113.8 (Ar_{PMB}), 79.9 (C-5), 71.9 (O*C*H_2Ph), 66.1 (C-6), 60.6 (*C*$H_2$$CH_3$), 58.3 (*C*HPh), 55.4 (O*C*H_3), 54.3 (*C*HCH_3), 53.1 (C-2), 37.9 (CH_2=CH*C*H_2), 28.7 (NMe), 28.2 (*C*(CH_3)$_3$), 27.0 (C(*C*H_3)$_3$), 26.1 (C-4), 19.4 (C-3), 15.1 (CH*C*H_3), 14.4 (CH_2*C*H_3).

(*R*)-2-Amino-2-(3-(benzyloxy)propyl)pent-4-en-1-ol (2.74)



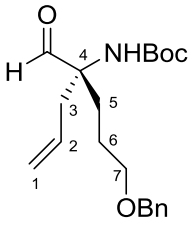
To a cooled suspension of lithium borohydride (0.030 g, 1.38 mmol, 2.5 eq) in diethyl ether (5 ml) at 0 °C was added a solution of α-tertiary amine **2.44f** (0.240 g, 0.55 mmol) in diethyl ether (60 ml) and the reaction allowed to warm up to 10 °C over the next 3 hours. Next, the reaction was diluted with diethyl ether (5 ml) and water (0.1 ml) and NaOH (15 %, 0.2 ml) were slowly added. Stirring was continued for a further 15 minutes at room temperature followed by the addition of anhydrous $MgSO_4$. Thereafter, the mixture was filtered, the solvent removed under reduced pressure, and the residue chromatographed with methanol/dichloromethane (10/90) to give the pure amino alcohol **2.74** (0.104 g, 0.42 mmol, 76 %) as a clear liquid. Auxiliary # was also recovered (0.068 g, 0.36 mmol 65 %) as colourless needle-like crystals. HRMS (ES): *m/z* found 250.1814, $C_{15}H_{24}NO_2$ $[M+H]^+$ requires 250.1807; $[\alpha]_D^{20}$-1.2° (DCM, *c* = 1); IR: ν_{max} (cm^{-1}) 3693 (OH), 3444 (NH_2), 3054 (C-H aromatic), 2927 (C-H alkanes), 1552 (NH bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.08 (m, 5H, aromatic), 5.88 – 5.55 (m, 1H, H-4), 5.13 – 4.96 (m, 2H, H-5), 4.43 (s, 2H, OCH_2Ph), 3.40 (t, *J* = 6.3 Hz, 2H, H-3'), 3.28 (s, 2H, H-1), 2.14 – 1.91 (m, 2H, H-3), 2.04 - 1.99 (broad s, 3H, NH_2 and OH), 1.64 – 1.50 (m, 2H, H-1'), 1.47 – 1.33 (m, 2H, H-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3 (Ar_q), 133.1 (C-4), 128.4 (Ar), 127.7 (Ar), 127.6 (Ar), 119.1 (C-5), 73.0 (C-1), 70.6 (O*C*H_2Ph), 67.5 (C-3'), 55.0 (C_q), 41.0 (C-3), 31.9 (C-1'), 23.7 (C-2').

(*R*)-*tert*-Butyl (7-(benzyloxy)-4-(hydroxymethyl)hept-1-en-4-yl)carbamate (2.75)



To a solution of amino alcohol **2.74** (0.080 g, 0.321 mmol) in dichloromethane (20 ml) was added Boc_2O (0.084 g, 0.385 mmol, 1.2 eq). The reaction was refluxed for 8 hours after which time it was cooled, washed with water (20 ml) and the organic layer concentrated. The residue was purified by flash chromatography using EtOAc/hexane (40/60) to give the Boc-protected amino alcohol **2.75** (0.098 g, 0.282 mmol, 88 %) as a slightly yellow oil. HRMS (ES): *m/z* found 350.2291, $C_{20}H_{32}NO_4$ $[M+H]^+$ requires 350.2284; $[\alpha]_D^{20}$-2.2° (DCM, *c* = 1); IR: ν_{max} (cm^{-1}) 3426 (NH), 3086 (C-H aromatic), 2933 (C-H alkanes), 1689 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.25 (m, 5H, aromatic), 5.81 – 5.75 (m, 1H, H-2), 5.19 – 5.13 (m, 2H, H-1), 4.82 (broad s, 1H, N*H*), 4.52 (s, 2H, OCH_2Ph), 4.20 (broad s 1H, OH), 3.75 – 3.66 (m, 2H, H-7), 3.50 (t, *J* = 5.1 Hz, 2H,CH_2OH), 2.38 (m, 2H, H-3), 1.65 (m, 4H, H-5, H-6), 1.42 (s, 9H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5 (C=O), 138.5 (Ar_q), 133.2 (C-2), 129.7 (Ar), 128.5 (Ar), 127.8 (Ar), 119.3 (C-1), 80.0 (*C*$(CH_3)_3$), 73.2 (O*C*H_2Ph), 70.5 (C-7), 68.1 (*C*H_2OH), 58.8 (C-4), 39.3 (C-3) 31.5 (C-5), 28.5 (C(*C*$H_3)_3$), 23.8 (C-6).

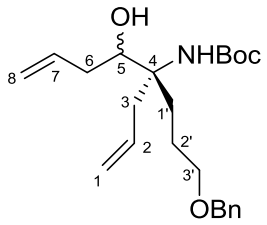
(*R*)-*tert*-Butyl (7-(benzyloxy)-4-formylhept-1-en-4-yl)carbamate (2.76)



Dess-Martin periodinane (0.175 g, 0.412 mmol, 1.2 eq) was placed in dichloromethane (20 ml) and cooled to 0 °C. The boc-protected amino alcohol **2.75** (0.120 g, 0.343 mmol) was then introduced and the reaction left to warm up to room temperature and stirred for 2 hours. Upon completion, sodium hydroxide solution (1 M, 3.00 ml) was slowly added and the mixture left to stir a further 10 minutes. Extraction with dichloromethane (3 x 40 ml) followed and the combined organic layers were washed with brine (30 ml), dried over anhydrous $MgSO_4$ and concentrated. The residue was flash chromatographed with EtOAc/hexane (10/90) to give aldehyde **2.76** (0.110 g, 0.316 mmol, 92 %) HRMS (ES): *m/z* found 348.2133, $C_{20}H_{22}NO_4$ $[M+H]^+$ requires 348.2131; $[\alpha]_D^{20}$-2.5° (DCM, *c* = 1); IR: ν_{max} (cm^{-1}) 3423 (NH), 3055 (C-H aromatics), 2987 (C-H alkanes), 1736 (C=O aldehyde), 1712 (C=O Boc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H, *H*CO), 7.53 – 6.84 (m, 5H, aromatic), 5.71 – 5.49 (m, 1H,

H-2), 5.30 (broad s, 1H, N*H*), 5.11 (m, 2H, H-1), 4.47 (s, 2H, OCH_2Ph), 3.43 (t, *J* = 6.0 Hz, 2H, H-7), 2.82 (m, 1H,H-3a), 2.50 (m, 1H,H-3b), 2.05 – 1.99 (m, 1H, H-5a), 1.80 -1.75 (m, 1H, H-5b), 1.72 – 1.51 (m, 2H, H-6), 1.44 (s, 9H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.6 (HC=O), 154.6 (C=O), 138.5 (Ar_q), 131.7 (C-2), 128.5 (Ar), 127.8 (Ar), 127.8 (Ar) 119.7 (C-1), 73.0 (O*C*H_2Ph), 69.8 (C-7), 65.2 (*C*$(CH_3)_3$), 53.4 (C-4), 37.4 (C-3), 29.8 (C-5), 28.5 (*t*-Bu), 23.9 (C-6).

tert-Butyl ((4*R*)-4-(3-(benzyloxy)propyl)-5-hydroxyocta-1,7-dien-4-yl)carbamate (2.77)



To a solution of aldehyde **2.76** (0.100 g, 0.288 mmol) in THF (50 ml) was added allylmagnesium chloride (1 M solution in THF, 0.35 ml, 0.35 mmol, 1.2 eq) via a syringe at -78 °C. Stirring was continued at this temperature for 2 hours then warmed up to -20 °C and stirred for a further 4 hours after which time the reaction was quenched by the addition of water (5 ml) followed by HCl (1 M, 1 ml) and warmed up to room temperature. It was then diluted and extracted with ethyl acetate (3 x 30 ml) and the organic extracts washed with saturated sodium bicarbonate solution (10 ml) and brine (20 ml), then dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography using EtOAc/ hexane (30/70) to give the allylated product **2.77** (0.107 g, 0.274 mmol, 95 %) as a colourless oil, as a 4:1 ratio of diastereomers as determined by ^{1}H NMR spectroscopy. HRMS (ES): *m/z* found 390.2631, $C_{23}H_{36}NO_4$ $[M+H]^+$ requires 390.2644; $[\alpha]_D^{20}$-2.1° (DCM, *c* = 1); IR: ν_{max} (cm^{-1}) 3415 (OH), 3073 (C-H aromatic), 2978 (C-H alkane), 1712 (C=O Boc).

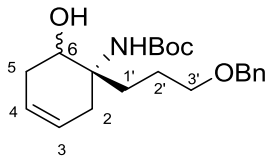
Major diastereomer

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.16 (m, 5H, aromatic), 6.07 – 5.92 (m, 1H, H-7), 5.88 – 5.75 (m, 1H, H-2), 5.21 – 5.16 (m, 1H, H-8), 5.15 – 5.11 (m, 1H, H-8), 5.10 – 5.05 (m, 2H, H-1), 4.75 (broad s, 1H, NH), 4.56 (broad s, 1H, OH), 4.50 (s, 2H, OCH_2Ph), 3.68 – 3.53 (m, 1H, H-5), 3.54 – 3.40 (m, 2H, H-3'), 2.39 – 2.33 (m, 1H, H-6a), 2.32 – 2.28 (m, 2H, H-1'), 2.17 – 2.06 (m, 1H, H-6b), 2.00 – 1.90 (m, 1H, H-3a), 1.85 – 1.71 (m, 1H, H-3b), 1.69 – 1.54 (m, 2H, H-2'), 1.45 - 1.40 (m, 9H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (C=O), 138.7 (Ar_q), 136.6 (C-2), 132.9 (C-7), 128.3 (Ar) 127.6 (Ar), 127.5 (Ar), 119.7 (C-1), 116.4 (C-8), 80.0 (*C*$(CH_3)_3$), 75.3 (O*C*H_2Ph), 72.9 (C-5), 70.6 (C-3'), 60.8 (C-4), 39.1 (C-3), 37.0 (C-6), 29.6 (C-1'), 28.3 (*t*-Bu), 23.8 (C-2').

Minor diastereomer:

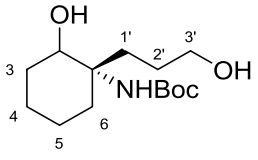
^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (C=O), 138.7 (C-1”), 133.5 (C-2), 129.8 (C-7), 128.3 (C-3”), 127.6 (C-4”), 127.5 (C-2”), 118.2 (C-1), 116.4 (C-8), 83.1 (*C*$(CH_3)_3$), 75.6 (O*C*H_2Ph), 73.0 (C-5), 69.3 (C-3’), 60.8 (C-4), 39.1 (C-3), 37.0 (C-6), 31.5 (C-1’), 28.3 (*t*-Bu), 23.8 (C-2’).

tert-Butyl ((1*R*)-1-(3-(benzyloxy)propyl)-6-hydroxycyclohex-3-en-1-yl)carbamate (2.78)



The diallyl compound **2.77** (0.130 g, 0.334 mmol) was dissolved in deoxygenated dichloromethane (10 ml) and Grubbs first-generation catalyst (0.027 g, 0.033 mmol, 10 mol %) was added. The reaction was refluxed for 3 hours during which the colour changed from purple to black. The solvent was removed via rotary evaporation and the residue columned with EtOAc/ hexane (30/70) to yield the title compound **2.78** (0.104 g, 0.287 mmol, 86 %) as a colourless solid. Recrystallization from chloroform/ hexane afforded the major diastereomer as fine needle-like crystals. Major diastereomer: Melting point: 91 – 94 °C (chloroform/ hexane). HRMS (ES): *m/z* found362.2329, $C_{21}H_{32}NO_4$ $[M+H]^+$ requires 362.2331; $[\alpha]_D^{20}$= +28.8, (DCM, *c* = 1); IR: ν_{max} (cm^{-1}) 3428 (OH), 3055 (C-H aromatic), 2978 (C-H aliphatic), 1685 (C=O Boc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.18 (m, 5H, aromatic), 5.71 – 5.01 (m, 1H, H-4), 5.51 – 5.39 (m, 1H, H-3), 5.22 (broad s, 1H, OH), 4.63 (s, 1H, NH), 4.50 (s, 2H, O*C*H_2Ph), 3.79 – 3.68 (m, 1H, H-6), 3.60 – 3.44 (m, 2H, H-3’), 2.43 – 2.32 (m, 1H, H-5a), 2.27 – 2.19 (m, 2H, H-5b and H-2a), 2.16 – 2.01 (m, 1H, H-2b), 2.06 (m, 1H, H-2’a), 1.83 – 1.68 (m, 2H, H-2’b and H-1’a), 1.66 – 1.54 (m, 1H, H-1’b), 1.42 (s, 9H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) 157.6 (C=O), 138.7 (C-1’’), 128.5 (C-3’’), 127.8 (C-2’’), 127.6 (C-4’’), 127.0 (C-4), 122.6 (C-3), 80.3 (*C*$(CH_3)_3$), 73.1 (O*C*H_2Ph), 72.8 (C-1), 70.8 (C-3’), 58.3 (C-6), 37.5 (C-2), 32.8 (C-5), 30.7 (C-1’), 28.4 ((*C*$H_3)_3$), 23.9 (C-2’).

tert-Butyl ((1*S*)-2-hydroxy-1-(3-hydroxypropyl)cyclohexyl)carbamate (2.79)

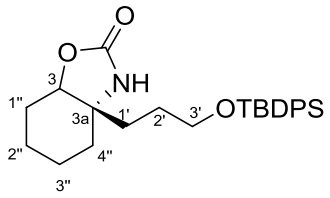


Cyclohexene **2.78** (0. 65 g, 1.80 mmol) was dissolved in deoxygenated ethanol (10 ml) and to this was carefully added Pd/C (10 % wt, 0.192 g, 10 mol%) under a nitrogen atmosphere. The mixture was placed under a hydrogen atmosphere and stirred vigorously for 5 hours. Filtration through

Celite, followed by concentration yielded a yellow gum which was purified by column chromatography using EtOAc/ hexane (30/70) to furnish the cyclohexanol product **2.79** (0.453 g, 1.66 mmol, 92 %) as a clear gum.

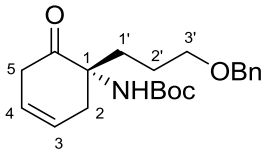
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (broad s, 1H, CHO*H*), 4.65 (s, 1H, NH), 3.76 – 3.57 (m, 2H, H-3'), 3.55 – 3.46 (m, 1H, H-2), 2.28 (broad s, 1H, CH_2O*H*), 2.14 – 1.99 (m, 1H, H-3a), 2.00 – 1.86 (m, 1H, H-6a), 1.85 – 1.64 (m, 3H, H-4a, H-5a, H-6b), 1.66 – 1.50 (m, 3H, H-3b, H-2'), 1.50 – 1.44 (m, 1H, H-5b), 1.42 (s, 9H, *t*-Bu), 1.37 – 1.23 (m, 3H, H-3, H-4b). WHERE ARE THE H-1 'protons??

(3a*S*)-3a-(3-((*tert*-Butyldiphenylsilyl)oxy)propyl)hexahydrobenzo[*d*]oxazol-2(3H)-one (2.80)



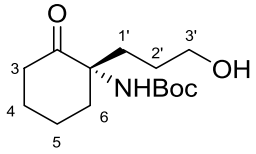
The diol **2.79** (0.100 g, 0.37 mmol, 1 eq) was dissolved in THF (60 ml) and cooled to 0 °C. To this was added NaH (60 % dispersion in oil, 0.015 g, 0.37 mmol, 1 eq) and stirring was continued for 15 minutes after which time TBDPSCl 0.11 ml, (0.41 mmol, 1.1 eq) was syringed in. The reaction was left at 10 °C for a further hour, following which water (20 ml) was added and the THF was removed on the rotary evaporator, followed by extraction with DCM (3 x 50 ml). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography using EtOAc/ hexanes (15/85) furnished the oxazolidinone **2.80** (0.099 g, 0.23 mmol, 61 %) as a viscous oil. HRMS (ES): *m/z* found 438.2455, $C_{26}H_{36}NO_3Si$ $[M+H]^+$ requires 438.2464; $[\alpha]_D^{20}$= -11.3°, (DCM, *c* = 1); IR: ν_{max} (cm^{-1}) 3422 (NH), 3071 (C-H aromatics), 2940 (C-H alkanes), 1748 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 – 7.60 (m, 4H, aromatic), 7.52 – 7.33 (m, 6H, aromatic), 5.11 (broad s, 1H, NH), 4.24 (t, *J* = 4.0 Hz, 1H, H-3), 3.69 (t, *J* = 5.5 Hz, 2H, H-3'), 2.06 – 1.89 (m, 1H, H-1'a), 1.73 – 1.26 (m, 11H, 5xCH_2, H-1'b), 1.06 (s, 9H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (C=O), 135.7 (Ar_q x 2), 133.8 (Ar x 2), 129.8 (Ar x 2), 127.9 (Ar x2), 80.6 (C-3), 63.8 (C-3a), 59.1 (C-3'), 34.3 (C-4''), 32.8 ($C(CH_3)_3$), 27.1 ($C(CH_3)_3$), 26.9 (C-1'), 25.7 (C-1''), 19.5 (C-2'), 19.3 (C-2"), 18.7 (C-3'').

***tert*-Butyl (*R*)-(1-(3-(benzyloxy)propyl)-6-oxocyclohex-3-en-1-yl)carbamate (2.81)**



DMSO (0.47 ml, 6.65 mmol, 2.4 eq) was added to a solution of oxalyl chloride (0.28 ml, 3.32 mmol, 1.2 eq) in dichloromethane (20 ml) at -78 °C and the mixture was left to stir for 20 minutes. Cyclohexenol **2.78** (1.00 g, 2.77 mmol) in DCM (50 ml) was then syringed in and stirring of this mixture was continued for a further 30 minutes at -78 °C. Triethylamine (1.42 ml, 11.08 mmol, 4 eq) was then added and the reaction allowed to warm up to room temperature. Once the components were concentrated *in vacuo*, flash chromatography was carried out using EtOAc/ hexane (10/90) to furnish the cyclohexenone product **2.81** (0.896 g, 2.49 mmol, 90 %)as a thick, colorless gum. HRMS (ES): *m/z* found 360.1985, $C_{21}H_{30}NO_4$ $[M+H]^+$ requires 360.1980; $[\alpha]_D^{20}$= +2.1, (DCM, *c* = 1); IR: ν_{max} (cm^{-1}) 3407 (NH), 3054 (C-H aromatic), 2982 (C-H alkanes), 1708 (C=O ketone) 1701 (C=O Boc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H, aromatic), 5.97 (broad s, 1H, N*H*), 5.75 – 5.66 (m, 1H, H-4), 5.67 – 5.58 (m, 1H, H-3), 4.47 (s, 2H, OCH_2Ph), 3.51 – 3.36 (m, 2H, H-3'), 3.28 (d, *J* = 16.2 Hz, 1H, H-2a), 3.08 (ddd, *J* = 21.1, 5.5, 2.8 Hz, 1H, H-5a), 2.93 (d, *J* = 21.1 Hz, 1H, H-5b), 2.55-2.48 (m, 1H, H-1'a), 2.41 – 2.28 (m, 1H, H-2b), 2.19 – 2.06 (m, 1H, H-1'b), 1.66 – 1.50 (m, 2H, H-2'), 1.43 (s, 9H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.6 (C=O), 154.4 (C=O), 138.6 (Ar_q), 128.5 (Ar), 127.7 (Ar), 125.3 (Ar), 124.6 (C-4), 123.3 (C-3), 81.6 (*C*$(CH_3)_3$), 73.0 (C-1), 69.9 (O*C*H_2Ph), 63.6 (C-3'), 39.6 (C-5), 38.3 (C-2), 30.3 (C-1'), 28.5 (C(*C*$H_3)_3$), 24.4 (C-2').

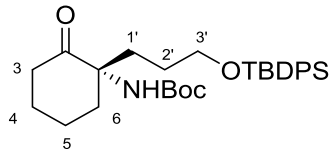
***tert*-Butyl (*S*)-(1-(3-hydroxypropyl)-2-oxocyclohexyl)carbamate (2.82)**



Cyclohexenone **2.81** (0.650 g, 1.81 mmol) was dissolved in deoxygenated ethanol (100 ml) and to this was carefully added Pd/C (0.192 g, 10 wt %, 10 mol %) under a nitrogen atmosphere. The reaction was placed under a hydrogen atmosphere and stirred vigorously for 4 hours. Filtration through Celite, followed by concentration on the rotary evaporator yielded a yellow gum, which was purified by column chromatography using EtOAc/hexane (30/70) to furnish the cyclohexanone product **2.82** (0.476 g, 1.75 mmol, 97 %) as a colourless solid, which recrystallized to delicate crystals. M.p (chloroform/ hexane) 113 – 115 °C; HRMS (ES): *m/z* found 272.1818, $C_{14}H_{26}NO_4$ $[M+H]^+$

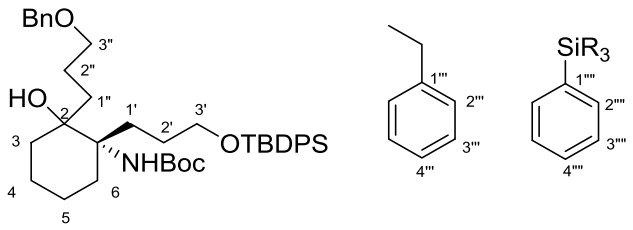
requires 272.1815; $[\alpha]_D^{20}$= -1.4, (DCM, *c* = 1); IR: ν_{max} (cm^{-1}) 3581 (OH), 3424 (NH), 3054 (C-H aromatic), 2947 (C-H alkane), 1712 (C=O ketone), 1681 (C=O Boc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (broad s, 1H, NH), 4.14 – 3.95 (m, 1H, H-3'a), 3.65 – 3.51 (m, 1H, H-3'b), 2.56 – 2.25 (m, 2H, H-3), 2.14 – 1.96 (m, 2H, H-6), 1.95 – 1.69 (m, 5H, H-4, H-1' and OH), 1.64 – 1.47 (m, 4H, H-5 and H-2'), 1.45 (s, 9H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.1 (C=O), 156.0 (C=O), 79.7 ($C(CH_3)_3$), 62.4 (C_q), 60.8 (C-3'), 38.0 (C-3), 35.9 (C-6), 33.9 (C-4), 28.6 ($CCH_3)_3$), 22.9 (C-2'), 22.5 (C-1'), 20.9 (C-5).

tert-Butyl (*S*)-(1-(3-((_tert_-butyldiphenylsilyl)oxy)propyl)-2-oxocyclohexyl)carbamate (2.83)



Alcohol **2.82** (0.350 g, 1.29 mmol) was dissolved in dichloromethane (100 ml) and cooled to 0 °C. To this solution was added NaH (0.057 g, 1.42 mmol, 1.1 eq), followed by TBDPSCl (0.40 ml, 1.55 mmol, 1.2 eq). The reaction was warmed to room temperature and left to stir for 3 hours, after which time water (30 ml) was slowly added and the mixture extracted with dichloromethane (3 x 60 ml). Combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was subjected to column chromatography using EtOAc/ hexanes (10/90) to deliver the title cyclohexanone **2.83** (0.585 g, 1.15 mmol, 89 %) as an opaque gum. HRMS (ES): *m/z* found 510.3046, $C_{30}H_{44}NO_4Si$ $[M+H]^+$ requires 510.3040; $[\alpha]_D^{20}$= +25.6, (DCM, *c* = 1); IR: ν_{max} (cm^{-1}) 3400 (NH), 3073 (C-H aromatic) 2933 (C-H alkane), 1703 (C=O ketone), 1701 (C=O Boc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.57 (m, 4H, aromatic), 7.47 – 7.32 (m, 6H, aromatic), 5.90 (broad s, 1H, NH), 3.78 – 3.44 (m, 2H, H-3'), 2.84 – 2.65 (m, 1H, H-3a), 2.57 – 2.22 (m, 3H, H-6 and H-1'a), 2.23 – 2.07 (m, 1H, H-1'b), 2.05 – 1.96 (m, 1H, H-3b), 1.74 – 1.62 (m, 4H, H-4 and H-5), 1.56 – 1.43 (m, 1H, H-2'a), 1.41 (s, 9H, *t*-Bu Boc), 1.19 – 1.09 (m, 1H, H-2'b), 1.04 (s, 9H, *t*-BuSi); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.9 (C=O), 154.9 (C=O), 135.7 (Ar_q), 135.0 (2 x Ar), 129.8 (2 x Ar), 127.8 (2 x Ar), 79.1 ($OC(CH_3)_3$), 65.0 (C_q), 63.6 (C-3'), 39.1 (C-3), 38.0 (C-6), 29.7 ($SiC(CH_3)_3$), 28.6 ($OC(CH_3)_3$), 28.1 (C-4), 27.0 ($SiC(CH_3)_3$), 26.7 (C-1'), 21.8 (C-2'), 19.4 (C-5).

***tert*-Butyl ((1*S*)-2-(3-(benzyloxy)propyl)-1-(3-((tert-butyldiphenylsilyl)oxy)propyl)-2-hydroxycyclohexyl)carbamate (2.84)**



To a freshly prepared solution of $MgBr(CH_2)_3OBn$ (1 M in THF, 0.34 ml, 0.392 mmol, 2 eq) at 0 °C was added a solution of the cyclohexanone **2.83** (0.100 g, 0.196 mmol) in THF (20 ml) and the reaction was allowed to warm up to rt and stirred for a further hour. Upon completion, the mixture was cooled to 0 °C and water (10 ml), followed by HCl (1 M, 10 ml) were added and stirring was continued for another 15 minutes. The mixture was then extracted with EtOAc (1 x 80 ml and 2 x 60 ml) and the combined organic fractions were washed with saturated sodium bicarbonate (100 ml), dried over anhydrous $MgSO_4$, filtered and concentrated on the rotary evaporator. Purification by column chromatography using EtOAc/hexanes (10/90) furnished the Grignard adduct **2.84** (0.102 g, 0.155 mmol, 79 %) as a gummy liquid in a 14:1 ratio of diastereomers as determined by NMR spectroscopy. HRMS (ES): *m/z* found 660.4076, $C_{40}H_{58}NO_5Si$ $[M+H]^+$ requires 660.4084; $[\alpha]_D^{20}$= +16.7, (DCM, *c* = 1); IR: ν_{max} (cm^{-1}) 3407 (broad, OH), 3056 (C-H aromatics), 2930 (C-H alkanes), 1708 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.56 (m, 4H, aromatic), 7.43 – 7.27 (m, 11H, aromatic), 5.42 (broad s, 1H, NH), 4.52 (s, 2H, C*H*$_2$Ph), 4.26 (broad s, 1H, OH), 3.79 – 3.61 (m, 2H, H-3”), 3.61 – 3.39 (m, 2H, H-3’), 2.46 – 2.32 (m 1H, H-3a), 1.94 – 1.79 (m, 1H, H-3b), 1.73-1.50 (m, 8H, H-1’, H-1”, H6, H-4), 1.49 – 1.42 (m, 2H, H-2”), 1.40 (s, 9H, Boc *t*-Bu), 1.21 (m, 4H, H-2’ and H-5), 1.06 (s, 9H, Si-*t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7 (C=O), 139.0 (C-1”’), 135.8 (C-2””), 134.3 (C-1””), 129.7 (C-4””), 128.5 (C-3”’), 127.8 (C-3””), 127.5 (C-2”’), 126.0 (C-4”’), 80.2 (O*C*$(CH_3)_3$), 76.1 (C-2), 72.8 (O*C*H_2Ph), 71.6 (C-3’), 64.5 (C-3”), 62.9 (C-1), 32.9 (C-3), 31.8 (Si*C*$(CH_3)_3$), 30.9 (C-6), 28.5 (OC(*C*$H_3)_3$), 27.1, (SiC(*C*$H_3)_3$), 27.0 (C-1”), 23.6 (C-1’ and C-4), 22.2 (C-2”), 21.5 (C-2’), 19.4 (C-5).

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