New Approaches for the Synthesis of Unusual Amino Acids

A thesis presented in part fulfilment of the requirements for the degree of Doctor of Philosophy

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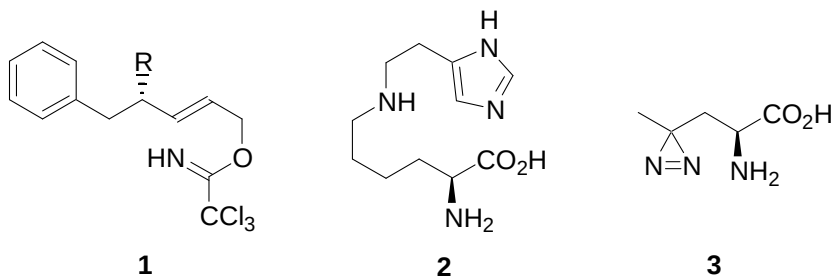
Abstract

The thermal and metal-catalysed aza-Claisen rearrangement of allylic trichlororacetimidates has found widespread application in the synthesis of nitrogen-containing molecules including alkaloids, antibiotics and unnatural amino acids.[1] We have recently investigated the use of this reaction for the rearrangement of chiral molecules.[2] This has led to the development of a highly diastereoselective, ether-directed palladium(II)-catalysed process which has been used for the synthesis of β-hydroxy-α-amino acids. To expand the scope and understanding of the rearrangement, a number of analogues of **1** have been synthesised and subjected to a palladium(II)-catalysed rearrangement (**Figure 1**).

Gizzerosine **2** ((*S*)-2-amino-9-(4-imidazolyl)-7-azanonanoic acid) is a potent agonist for the H_2-receptor (**Figure 1**). It brings about gizzard erosion and ulceration in broiler chickens. This disease is colloquially known as 'Black Vomit' due to bleeding of lesions and subsequent regurgitation.[3] Its biological profile suggests it could be a promising drug candidate for gastric achlorhydria and osteoporosis, although only small amounts can be isolated from fish meal for biological studies. A short and highly efficient synthesis has been developed in ten steps and 31% overall yield.

Protein-protein inteactions are the key to organising cellular processes in space and time. Protein-protein interactions are involved in viral fusion and so are promising targets for anti-viral drugs. Photoactivatable amino acids have been used to identify these interactions.[4] Activation by ultraviolet light induces covalent cross-linking (known as photo cross-linking) of the interacting proteins which can be detected with high specificity by simple western blotting. Significant progress has been made towards the development of a stereoselective synthesis of photoactivatable amino acids incorporating a diazirine ring, such as photo-leucine **3**, which generate a reactive carbene after the light induced loss of nitrogen (**Figure 1**).



1 **2** **3**

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Preface

This thesis represents the original work of Katherine Nora Fanning unless stated otherwise in the text. The research described herein was carried out in the Loudon and Henderson Laboratories of the University of Glasgow, between October 2004 and September 2007, under the supervision of Dr. Andrew Sutherland. Part of this thesis has been published previously.

K. N. Fanning, A. G. Jamieson and A. Sutherland, *Org. Biomol. Chem*., 2005, **3**, 3749.

K. N. Fanning, A. G. Jamieson and A. Sutherland, *Curr. Org. Chem*., 2006, **10**, 1007.

K. N. Fanning and A. Sutherland, *Tetrahedron Lett.*, 2007, **48**, 8479.

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I would like to thank all my 'chemistry girls', with whom I've had many glasses of wine and in-depth life discussions! Gemma, Jenny, Nicola and Katrina, you've made my years in Glasgow very memorable and special.

To Stoff, champion tea-maker and provider of bear hugs! Thank you for all your patience, strength and love.

This thesis is dedicated to my loving family.

Níl aon tintéan mar do thintéan féin.

Abbreviations

Å	ångstrom
Ac	acetyl
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxy carbonyl
Bu	butyl
Cbz	benzyloxycarbonyl
CI	chemical ionisation
cod	cyclooctadiene
COSY	correlated spectroscopy
d	doublet (NMR)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
d.e.	diastereomeric excess
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine (Hünig's Base)
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DTT	dithiothreitol
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
e.e.	enantiomeric excess
EI	electron impact
Et	ethyl
FAB	fast atom bombardment
h	hour(s)
HMPA	hexamethylphosphoramide
i	*iso*
IR	infrared
LDA	lithium diisopropylamine
M	molar (mol L^{-1})
m	multiplet (NMR)
m	*meta*

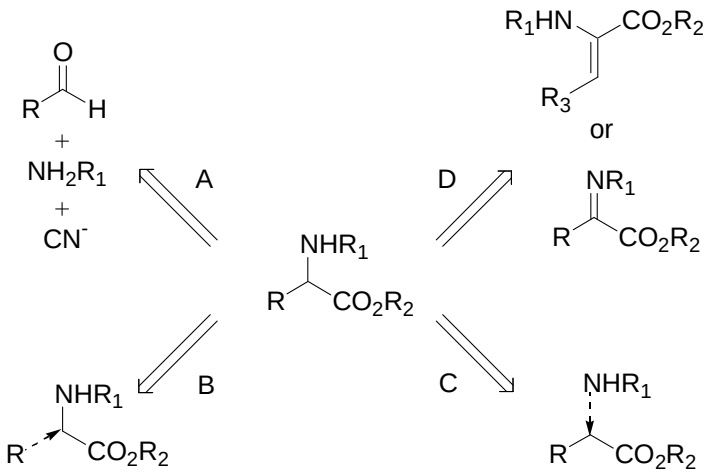
MCPBA	*m*-chloroperbenzoic acid
Me	methyl
MEM	2-methoxyethoxymethyl
min	minutes(s)
mol	mole
MOM	methoxymethyl
Ms	methanesulfonyl (mesyl)
n	*normal*
MS	molecular sieves
NBS	*N*-bromosuccinimide
NMI	*N*-methylimidazole
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*
PCC	pyridinium chlorochromate
Ph	phenyl
PPM	parts per million
q	quartet (NMR)
r.t.	room temperature
s	singlet (NMR)
t	*tertiary*
t	triplet (NMR)
TBAF	*tetra*-*n*-butylammonium fluoride
TEA	triethylamine
TBDPS	*tert*-butyldiphenylsilyl
TBDMS	*tert*-butyldimethylsilyl
TMG	tetramethylguanidine
TMS	trimethylsilyl
Troc	trichloroethoxy carbonyl
Ts	*p*-toluenesulfonyl (tosyl)

1 Introduction

1.1 The Synthesis of α-Amino Acids

Optically active α- and β-amino acids are fundamental building blocks for the preparation of many pharmaceutical agents as well as natural products. Amino acids are also extensively used as chiral starting materials, auxiliaries and catalysts in modern organic chemistry. Amino acids can exist in both natural (L) and unnatural forms (D). The twenty proteinogenic amino acids are L and all except cysteine have the (*S*) absolute configuration at the α-carbon. In the field of protein chemistry, unnatural amino acids can be incorporated into proteins to study protein function and structure. Over 700 naturally occurring amino acids are known.[5]

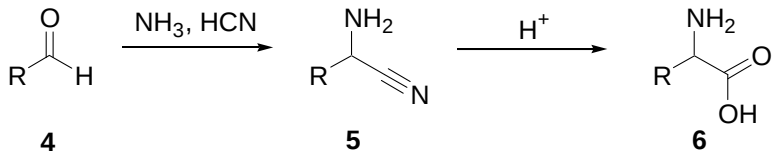
Most molecules in nature exist in either of two chiral enantiomers, forms that mirror each other in structure. In chemistry, chiral molecules are important because one enantiomer of a given compound may be biologically active, whereas its mirror-image enantiomer is inactive. For example, the common amino acid alanine has two chiral forms, (*S*)-alanine and (*R*)-alanine, but only (*S*)-alanine is prevalent in proteins. Enriching only the bioactive chiral form of a compound has been a major focus among chemists for decades. Presented here is an overview of four areas of the field of amino acid synthesis, exemplifying some traditional and more recent approaches. Catalytic asymmetric synthesis is an enzyme-like process that can rapidly produce an excess of one chiral compound form, a process with numerous practical applications. Several different catalytic asymmetric approaches to α-amino acids involving carbon-carbon, carbon-nitrogen and carbon-hydrogen bond forming reactions have been developed (**Scheme 1**).[6] Recent publications have highlighted the advances made in the asymmetric Strecker reaction (path A), catalytic asymmetric synthesis of α-amino acids (path B), asymmetric carbon-nitrogen bond forming reactions (path C) and catalytic asymmetric hydrogenation of dehydroamino acids (path D). This introduction will mainly focus on the recent developments in the fields mentioned above.



Scheme 1

1.2 Asymmetric Strecker Synthesis

The Strecker amino acid synthesis generates amino acids from corresponding aldehydes and a general scheme is shown below (**Scheme 2**). It represents one of the simplest and most economical methods for the preparation of α-amino acids on a laboratory scale as well as on a technical scale.[7] This reaction was first reported by Strecker in 1850.[8] In the traditional Strecker synthesis, the aldehyde **4** is condensed with an amine e.g. ammonia to give a Schiff base which reacts with a nucleophile e.g. hydrogen cyanide to give a racemic mixture of α-aminonitriles **5**. These precursors can then be hydrolysed to the corresponding α-amino acids **6**.



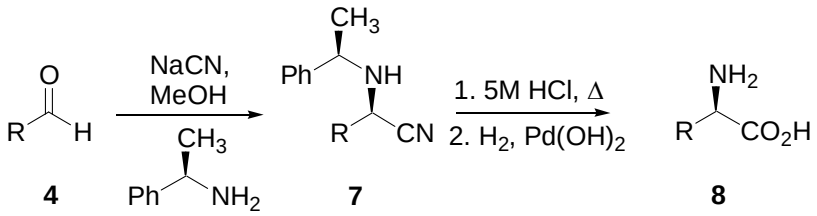
4 **5** **6**

Scheme 2

Stereocontrol can be incorporated into this reaction through chirality in the aldehyde, the amine, the nucleophile or by using a chiral catalyst. The catalytic asymmetric Strecker-type reaction offers one of the most direct and viable methods for the asymmetric synthesis of α-amino acids. Although unknown until the mid-1990s, current challenges still focus on the development of enantioselective catalysts with high activity and broad substrate generality, which leads to a practical, efficient, and environmentally friendly chemical synthesis.

1.2.1 The Strecker Reaction Using Organocatalysts

There are usually fewer toxicity issues associated with organocatalysis, although little is known about the toxicity of many organic catalysts. Of particular importance is that most reactions are tolerant of water and air and are often easy to perform. These factors often affect metal-catalysed reactions and that provides a significant advantage in terms of operational simplicity. Several versions of the Strecker reaction have been developed using completely different types of organic molecules which were found to possess catalytic hydrocyanation properties. The first asymmetric Strecker reaction was reported by Harada in 1963, over one hundred years after the introduction of the racemic version (**Scheme 3**).[9] Chiral α-methylbenzylamine was condensed with an aldehyde **4** to form a chiral imine **7**. The stereogenic center was able to direct the addition of the imine with enantiomeric excess ranging from 9 - 58%. Hydrolysis and hydrogenation gave the free amino acid **8**.



Scheme 3

The first catalysed asymmetric Strecker reaction was reported by Lipton and co-workers using the cyclic chiral dipeptide **9** as an organocatalyst (**Figure 2**).[10] This approach avoids some problems encountered when using a chiral reagent e.g. cost and non-recoverability. Diketopiperazines were chosen due to the success of these molecules as efficient organocatalysts in the previously developed hydrocyanation of aldehydes.[11] The catalyst was prepared from (*S*)-phenylalanine and (*S*)-α-amino-δ-guanidinobutyric acid. The basic guanidine side chain is a pre-requisite for asymmetric induction and the acceleration of proton transfer with hydrogen cyanide and the aldimine intermediate.

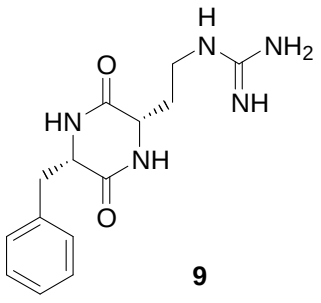
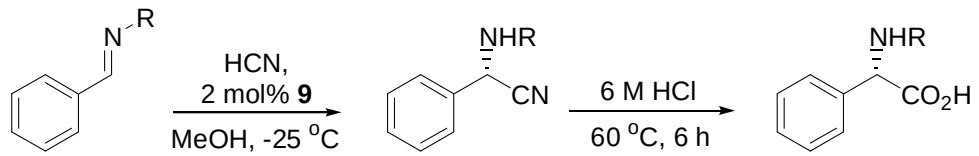


Figure 2

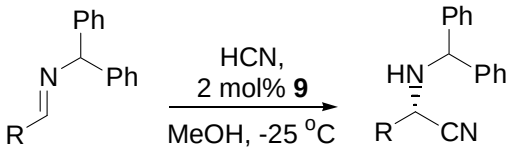
Studies were attempted initially using benzaldehyde, ammonia and hydrogen cyanide, but due to the instability of the intermediate, 2-aminophenylacetonitrile, these were unsuccessful. Thus, the reactions were attempted again using *N*-substituted imines **10** (**Scheme 4**). It was noted that the presence of alkyl groups on the imine nitrogen resulted in the formation of the corresponding (*S*)-α-amino nitriles **11** in high yields and exceptionally high enantiomeric excesses. The nitriles were hydrolysed using 6M hydrochloric acid to give the (*S*)-α-amino acids **12**, however, only the benzhydryl-protected α-amino nitrile gave satisfactory results without loss of enantiomeric excess. Benzaldyhyde can therefore be transformed to (*S*)-phenylglycine in three steps and in 92% yield with >99% e.e.[11]



10 **11** **12**

Scheme 4

Therefore, a number of *N*-benzhydryl imines **13** were subjected to reaction with the catalyst **9** (**Scheme 5**). In all cases, the (*S*)-isomer **14** was the major product. It was found that the products derived from aromatic aldehydes generally were produced in high enantiomeric excess. In contrast to the aromatic substrates, the organocatalyst does not appear to be suitable for the hydrocyanation of imines derived from alkyl-substituted or heteroaromatic aldehydes. The catalytic abilities of the dipeptide were also very sensitive to various parameters such as solvent viscosity.

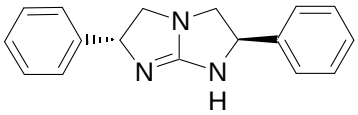


13 **14**

R	Yield	e.e.
Ph	97%	>99%
4-Cl-Ph	94%	>99%
3-NO_2	71%	<10%
3-Pyr	86%	<10%
^{t}Bu	80%	17%

Scheme 5

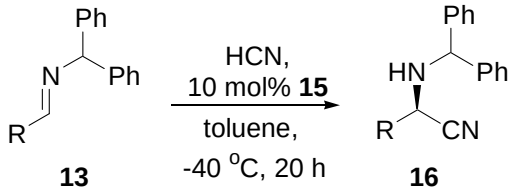
Corey and Grogan also used a guanidine-derived chiral bifunctional organocatalyst **15** in a novel enantioselective Strecker reaction (**Figure 3**).[12] The catalyst is readily available in a multistep synthesis from D-phenylglycine.



15

Figure 3

The reaction was carried out with achiral *N*-benzhydryl imines **13** as before to give (*R*)-α-amino nitriles **16** (**Scheme 6**). The guanidine catalyst was easily recovered in 80-90% yield by extraction from the crude reaction mixture. The (*R*)-α-amino nitriles were cleanly converted to the (*R*)-aryl glycines using 6M hydrochloric acid. Again, the *N*-benzhydryl group is a pre-requisite for good enantioselectivity. *N*-Benzyl and *N*-(9'-fluorenyl) groups resulted in poor enantioselectivity (0-25%). Compared to Lipton's organocatalyst, aromatic substrates gave slightly lower enantioselectivities.[10] In contrast to Lipton's catalyst, aliphatic aldimines led to high yields and good enantioselectivies (63-84%).

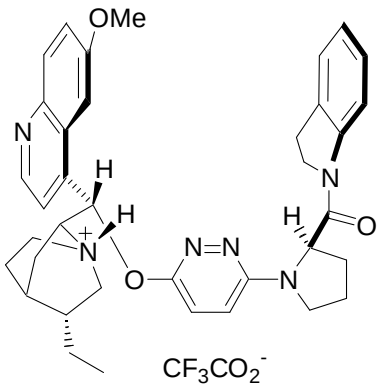


13 **16**

R	Yield	e.e.
Ph	96%	86%
4-TBSO-Ph	98%	88%
4-MeO-Ph	99%	84%
4-F-Ph	97%	86%
^{t}Bu	95%	84%

Scheme 6

Recently, Corey and co-workers have developed a new chiral catalyst for the enantioselective Strecker reaction, a chiral ammonium salt **17** that has both an activating and a binding site for *N*-allyl aldimines (**Figure 4**).[13] The organocatalyst was developed from a previous catalyst **18**, which had been used for the enantioselective dihydroxylation of olefins to form 1,2-diols (**Figure 4**).[14] It was thought that the U-shaped binding pocket in **17** could hold the aldehyde-derived part of the aldimine through hydrogen-bonding. Attack of the cyanide ion on the carbon of the hydrogen-bonded imine would give an α-amino nitrile.



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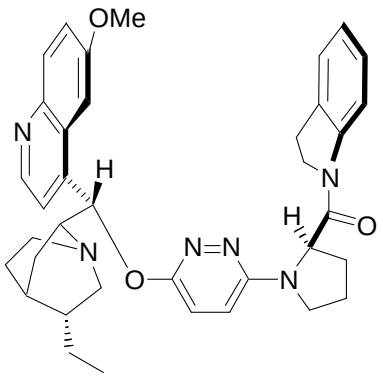

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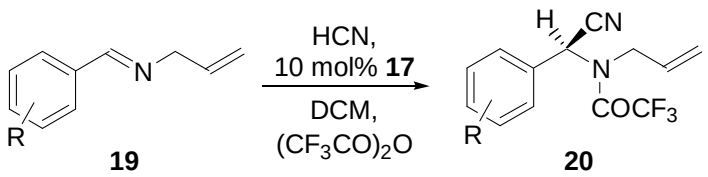
Figure 4

The catalyst was employed in the reaction of a series of *N*-allylbenzaldimines **19** to give the corresponding (*S*)-α-amino nitrile **20** (**Scheme 7**). Allyl was preferred to benzyl as the *N*-protecting group. The catalyst was also recovered through silica column chromatography.



R	Yield	e.e
Ph	95%	92%
p-F-Ph	96%	89%
m-MeO-Ph	96%	>99%
Naphthyl	95%	79%

Scheme 7

The asymmetric Strecker reaction can be catalysed by a urea-derived Schiff base organocatalyst, as demonstrated by Sigman, Jacobsen and Vachal.[15] Following the synthesis of a Schiff base library, **21** was identified as an effective and soluble catalyst for the asymmetric hydrocyanation of aromatic imines (**Figure 5**). The elements of the catalyst that are responsible for the high enantioselectivity are the bulky substituents at the amino position and at the 3-position of the salicylimine moiety.

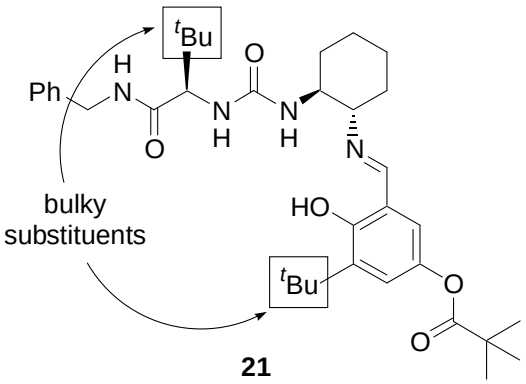
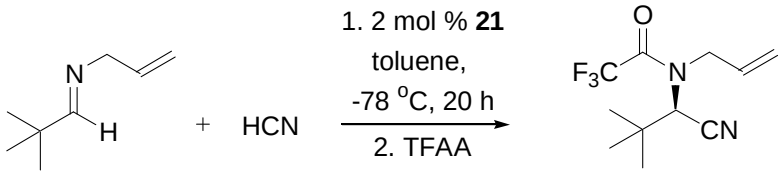


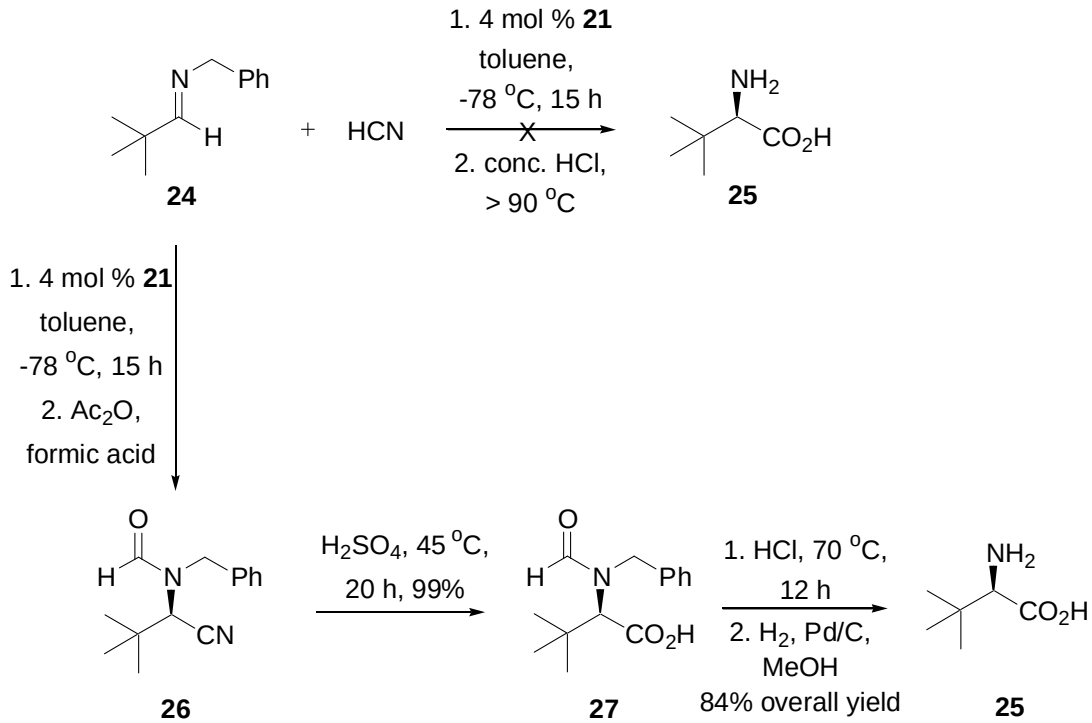
Figure 5

This catalyst was used in the formation of the Strecker adduct **23** in 75% yield and 95% e.e. (**Scheme 8**). This catalyst not only displays high enantioselectivity but also displays broad substrate scope, giving good enantioselectivities with aromatic imines bearing *N*-allyl substituents, acyclic aliphatic *N*-allyl imines **22**, cycloalkyl imines and cyclic imines. *Z*-imines can also be employed efficiently.



Scheme 8

With this highly selective reaction, it is also possible to synthesise enantiomerically enriched α-amino acids. The catalyst **21** was employed in the Strecker reaction of the imine **24** to give the α-amino nitrile intermediate (**Scheme 9**). Hydrolysis to yield the α-amino acid, D-*tert*-leucine **25** was attempted. Unfortunately, the harsh conditions resulted in significant decomposition of **25**. Therefore, the amino nitrile was protected as the formamide **26** (85% overall yield). Hydrolysis and deformylation was carried out in a one-pot procedure using concentrated hydrochloric acid at 70 °C but some racemisation was observed. Hydrolysis of **26** was therefore carried out to the corresponding acid **27** using concentrated sulfuric acid at 45 °C (99% yield). Deformylation was carried out using concentrated hydrochloric acid and the benzyl group was removed by hydrogenation to yield the α-amino acid **25** in >99% e.e. and 84% overall yield.



Scheme 9

Following these successful results, Jacobsen and co-workers developed an superior urea-derived organocatalyst **28** (**Figure 6**).[16] When using aliphatic as well as aromatic

aldimines, excellent enantioselectivities (96-99%) were achieved (**Scheme 10**). All results obtained when using the previous urea-derived organocatalyst were improved upon. The Jacobsen-type α-amino acid synthesis is used in industry by Rhodia ChiRex for the synthesis of optically active α-amino acids.

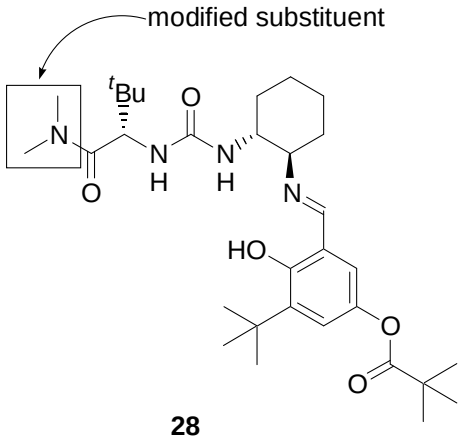


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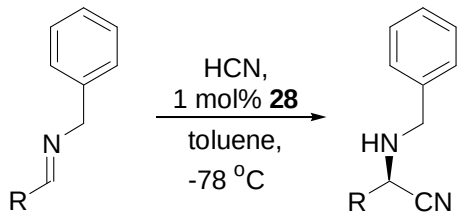
Figure **6**



29 **30**

R	e.e
Ph	99%
*i*Pr	97%
*t*Bu	99%
*n*Pent	96%

Scheme **10**

Recently, List and Pan employed a thiourea-derived Jacobsen catalyst **31** in the first organocatalytic asymmetric three-component Strecker reaction (**Figure 7**).[17] There has only been one previously reported direct asymmetric catalytic three-component Strecker reaction.[18] A series of α-amido nitriles were formed in excellent yields and enantioselectivies from aldehydes, amines and acyl cyanides.

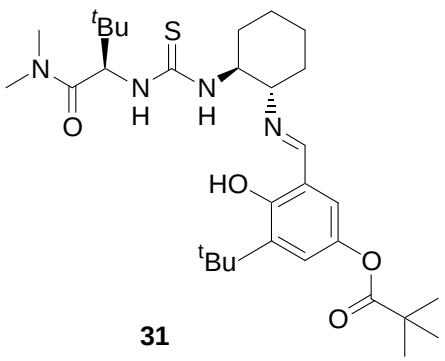


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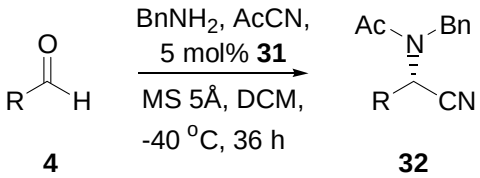
Figure 7

Optimal reaction conditions were established and a number of reactions of aldehydes **4** with benzyl amine and acetyl cyanide were carried out (**Scheme 11**). Particularly high enantioselectivities were observed with aromatic aldehydes, α,β-unsaturated aldehydes, aliphatic branched and unbranched aldehydes. Similar results were achieved using benzaldehyde with different amines and acyl cyanides. This newly developed variant of the Strecker reaction avoids the use of highly toxic hydrogen cyanide and does not require pre-formation of the intermediate.

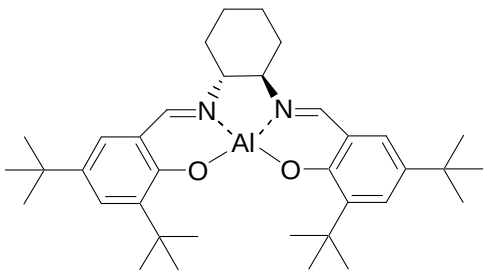


R	Yield	e.e.
Ph	94%	97%
2-naphthyl	92%	97%
^{t}Bu	46%	97%
^{t}BuCH$_2$	97%	96%

Scheme 11

1.2.2 The Strecker Reaction using Metal Catalysts

Despite the ability of chiral metal complexes to act as versatile catalysts being widely known, it was 1998 before the first asymmetric metal-catalysed Strecker reaction was reported by Sigman and Jacobsen.[19] It was already known that salen complexes act as efficient catalysts for asymmetric epoxidation and kinetic resolution (salen = *N*,*N*'-bis(salicylidene)-ethylenediamine dianion).[20,21] After a screening process using various metal complexes of the readily available salen ligand, it was found that the best results were achieved with aluminium(III) **33** (**Figure 8**). The product was isolated in 45% e.e.

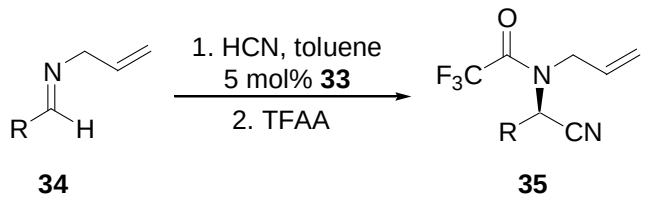


33

Figure 8

A variety of *N*-allyl imines **34** were subjected to a reaction with the catalyst **33** and substituted aryl imines appear to be the best substrates (**Scheme 12**). In contrast, alkyl-substituted imines underwent the addition of HCN with considerably lower enantioselectivity. Despite varying both the steric and electronic properties of the ligand

and changing the *N*-substituent, no significant improvement in enantioselectivity was observed for alkyl-substituted imines.

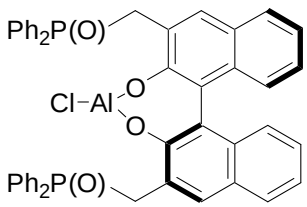


34 **35**

R	Yield	e.e.
Ph	91%	95%
p-$CH_3C_6H_4$	99%	94%
1-naphthyl	95%	93%
^{t}Bu	69%	37%

Scheme 12

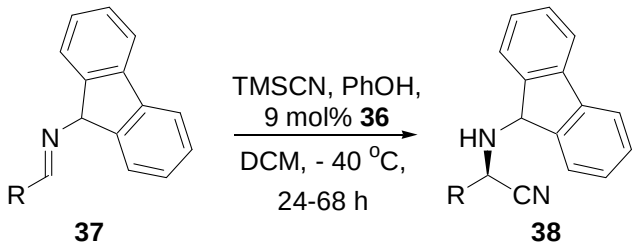
A range of BINOL-derived phosphoric acids also catalyse a number of interesting processes involving imines. Mannich reactions seem to be ideally suited to this class of organocatalysts. Aluminium has also been employed in a binaphthol-based phosphinoyl-containing catalyst **36**, as reported by the Shibasaki group (**Figure 9**).[22] For a number of asymmetric catalytic reactions, it has been found that bifunctional complexes are promising catalysts due to the attachment of both electrophilic and nucleophilic substrates to the chiral catalyst in the transition state complex.[23]



36

Figure 9

It had been a particular focus of the Shibasaki group to use α,β-unsaturated imines as they had not been used before and aliphatic *N*-aldimines which had thus far given unsatisfactory results. Through a series of reactions, it was found that the *N*-substituent had a significant effect on the outcome of the reaction and that *N*-fluorenyl gave the best results. The reaction had been further optimised when a significant solvent effect was found. In the presence of achiral protic additives a beneficial effect was observed in relation to the rate of reaction. Thus, a number of *N*-fluorenyl aldimines **37** were subjected to hydrocyanation with the catalyst **36** and TMSCN in phenol and DCM (**Scheme 13**). Of note is the broad range of substrates tolerated by this catalyst. The reaction proceeds well for both aliphatic *N*-aldimines and α,β-unsaturated imines and is the first example of catalytic asymmetric hydrocyanation of α,β-unsaturated imines.

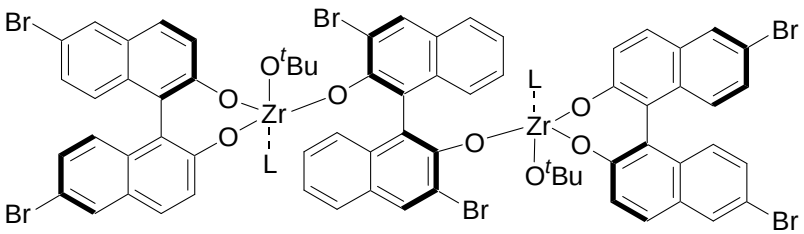


37 **38**

R	Yield	e.e.
Ph	92%	95%
2-furan	92%	90%
CH=CHPh	80%	96%
^{t}Bu	97%	78%

Scheme 13

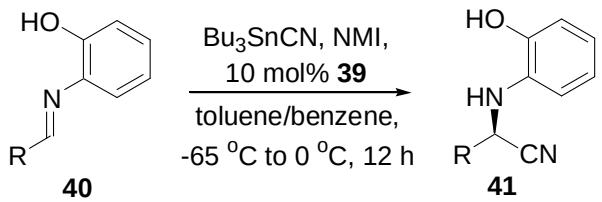
The group of Kobayashi have reported the use of a chiral zirconium(IV) complex as a catalyst for the enantioselective Strecker reaction (**Figure 10**).[24] The catalyst **39** includes a 1:1 mixture of 2 binaphthols, (*R*)-3,3'-dibromo-1,1'-binaphthol and (*R*)-6,6'-dibromo-1,1'-binaphthol.



39

Figure 10

The substrate **40** is derived from benzaldehyde to give *N*-*o*-hydroxyphenol (**Scheme 14**). This *N*-substituent was found to be beneficial in previous reactions with Kobayashi's zirconium catalysts.[25] The imine is able to coordinate to the zirconium through the hydroxy group and the imino group. Due to the more rigid conformation that is produced, the enantioselectivites are higher. Tributyltin cyanide was used as the cyanide donor. The substrate range for this catalyst is quite high, including aromatic, heteroaromatic and aliphatic imines. In comparison to the aromatic imines, the aliphatic imines were converted to the corresponding α-amino nitriles with lower enantioselectivities in the range of 74-83%.



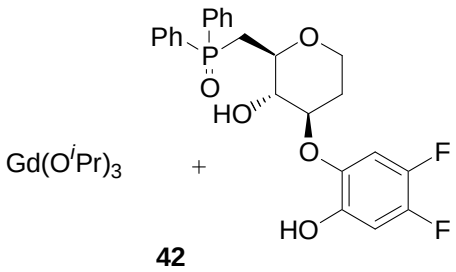
40 **41**

R	Yield	e.e.
Ph	92%	91%
1-naphthyl	98%	91%
1-thiophene	89%	92%
$CH_2CH(CH_3)_2$	79%	83%

Scheme 14

The tin oxide formed as a by-product during this reaction is recovered quantitatively and re-converted into the cyanide source. Unfortunately, the price of this cyanide source is considerably higher than HCN or TMSCN and the atom economy is lower.

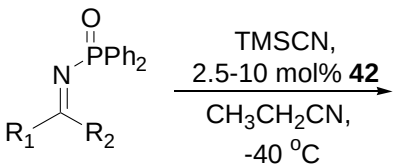
The Shibasaki group has also developed a lanthanide(III) complex **42** for use in the asymmetric Strecker reaction of ketoimines.[26] Prior to this, there were two examples of the catalytic enantioselective Strecker reaction using ketoimines as substrates.[16,27,28] The catalyst was developed with a view to increasing the substrate generality e.g. disubstituted α-amino acids which are of considerable biological importance.[29] The active catalyst is based on $Gd(O^iPr)_3$ and D-glucose-derived ligand in a 2:3 ratio (**Figure 11**). Studies show that one of the lanthanide species acts as a Lewis acid and the other acts as a nucleophile.



42

Figure 11

The *N*-substituent again had a bearing on the enantioselectivity of the reaction and it was found that diphenylphosphinoyl **43** gave the best result. High enantioselectivities were achieved using aryl methyl ketoimines and primary alkyl-substituted ketoimines, although secondary alkyl-substituted ketoimines gave moderate enantioselectivity (**Scheme 15**). Most of the products **44** could be directly subjected to acid hydrolysis to produce the corresponding α,α-disubstituted α-amino acids.



43 **44**

R_1	R_2	Yield	e.e
Ph	Me	94%	95%
p-Me-Ph	Me	93%	98%
1-naphthyl	Me	67%	94%
$(CH_2)_4CH_3$	Me	73%	72%

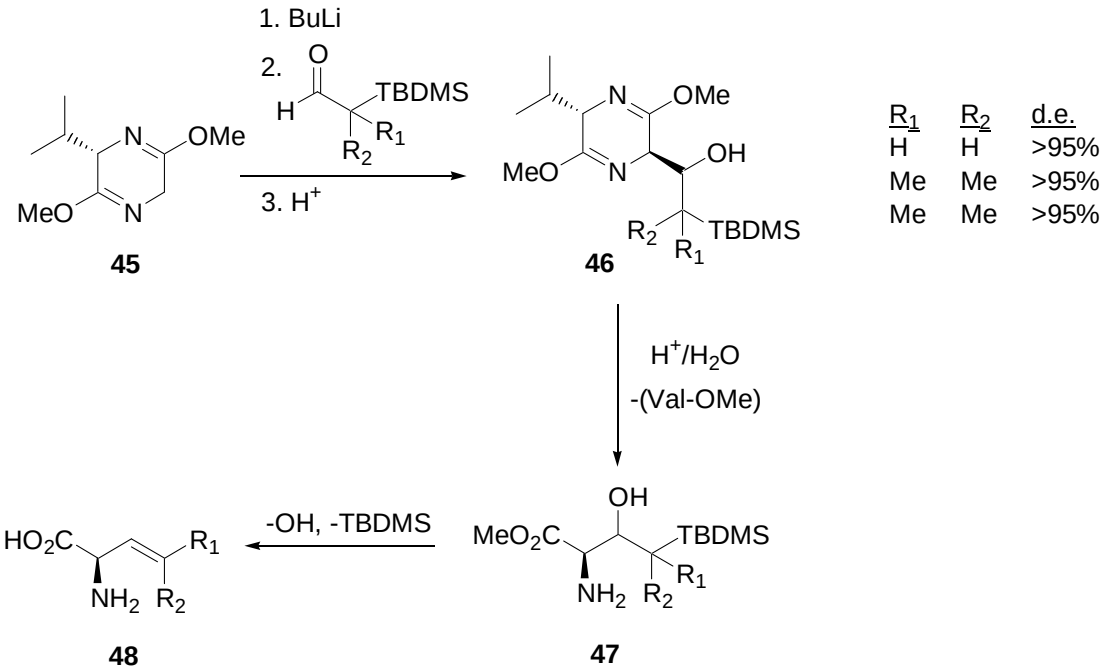
Scheme 15

Following on from this successful result, the catalyst was found to be just as effective in a 1:2 $Gd(O^iPr)_3$: D-glucose-derived ligand ratio when using 1 equivalent of 2,6-dimethylphenol (DMP) as an additive.[30] New, more economical reaction conditions were also subsequently reported which allowed the catalyst loading to be reduced to as low as 0.1 mol%.

A multitude of catalysts and chiral ligands have been developed for the asymmetric Strecker synthesis of α-amino acids and those discussed above are only a short selection.

1.3 The Use of Glycine Equivalents

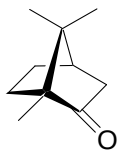
Glycine templates have a dominant role in the synthesis of α-amino acids and chirality can be introduced through two major strategies. Either glycine is coupled to a chiral auxiliary that can direct the formation of the new stereogenic centre or a chiral catalyst can be used. The number of chiral auxiliaries that can be attached to glycine to induce chirality is constantly growing. The templates can act as nucleophiles, electrophiles or through radical mechanisms. Some of the first efficient examples of a nucleophilic derivatisation were by Schöllkopf and co-workers using a bis-lactim ether glycine enolate.[31] They developed this heterocycle to act as a chiral auxiliary and induce the desired structure and conformation in the target molecule. The heterocyclic intermediate is necessarily more rigid that its open chain analogue and as such, should lead to greater asymmetric induction. A number of silylated aldehydes were added to the lithiated bis-lactam ether **45** to give aldol-type products **46** in >95% d.e. (**Scheme 16**). On acid hydrolysis, the ester **47** is liberated and is converted to the corresponding α-amino acid **48** by treating with 5M HCl under reflux. Bis-lactam ethers can also be used to synthesise α,α-disubstituted α-amino acids by cyclising the chiral auxiliary with racemic alanine instead of glycine. The disubstituted amino acids are produced in good yields and enantiomeric excess in most cases.[32]



Scheme 16

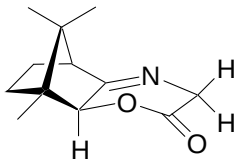
Following the work of Schöllkopf, in 1988 Williams and co-workers developed a similar system in which a cyclic optically active lactone consisting of a glycine equivalent and a chiral auxiliary was used as a glycine template.[33] This was deprotonated to form the enolate which underwent condensation with electrophiles.

Lu and co-workers have published another example of a chiral glycine enolate in which a tricyclic iminolactone **50** derived from (1*R*)-(+)-camphor **49** was coupled with glycine to give the chiral template (**Figure 12**).[34] Camphor is a versatile and inexpensive starting material and the Lu group have investigated its use previously in asymmetric synthesis.[35] Again, due to the cyclic nature of the template the transition state will be more rigid and thus, should enhance the steric effect of the auxiliary. Lactones only give rise to the *Z*-enolates which will therefore provide a single alkylated product if the electrophile approaches specifically from one of the reaction faces.



(1*R*)-(+)-Camphor

49

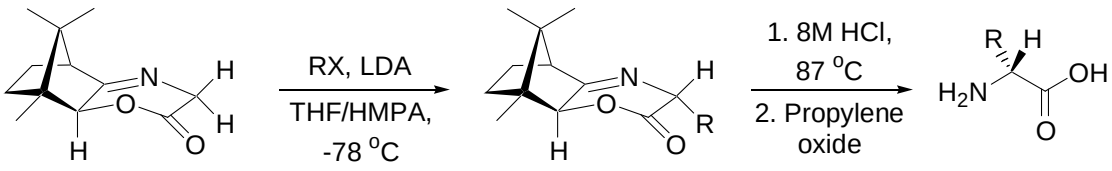


Tricyclic iminolactone

50

Figure 12

The template **50** could then be deprotonated at the α-carbon to form the enolate (**Scheme 17**). Alkylation of the iminolactone gave the α-substituted products **51** in good yields (74-96%) and excellent diastereoselectivities (>98%). The combination of LDA as base and HMPA/THF as a solvent system gave the best yields. This chiral auxiliary directs the formation of the *endo*-product in high diastereomeric excess, serving as a strong indication that the alkylation occurs exclusively from the bottom face. Hydrolysis of the alkylated products was performed in 8M HCl to give the corresponding D-amino acids **52** in good yields. The chiral auxiliary was also recovered in excellent yield.

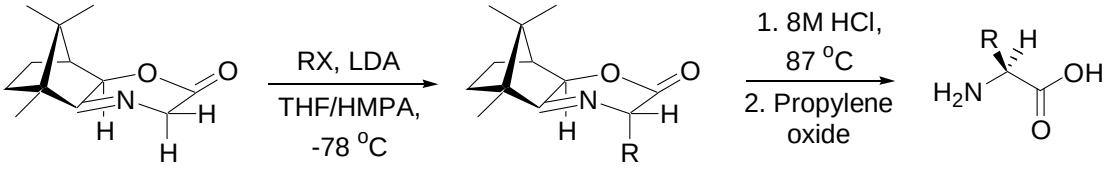


50 **51** **52**

RX	Yield	d.e.
MeI	81%	>98%
$PhCH_2Br$	93%	>98%
$CH_2=CHCH_2Br$	83%	>98%

Scheme 17

In theory, L-amino acids can be similarly synthesised using the chiral template derived from the opposite enantiomer of camphor, (1*S*)-(-)-camphor. Unfortunately, the unnatural camphor is significantly more expensive. Lu and co-workers have gone on to synthesise the L-amino acids simply by exchanging the position of the lactone on the chiral template **50** derived from the natural (1*R*)-(+)-camphor **49**.[36] This new chiral template **53** was subjected to a number of alkylations with alkyl halides as before (**Scheme 18**). LDA as base gave the best yields and diastereomeric excesses of >98%. Again, the chiral template directs the formation of the *endo*-product. Upon hydrolysis of the alkylated iminolactones **54** in 8M HCl, the corresponding α-amino acids **55** were produced.

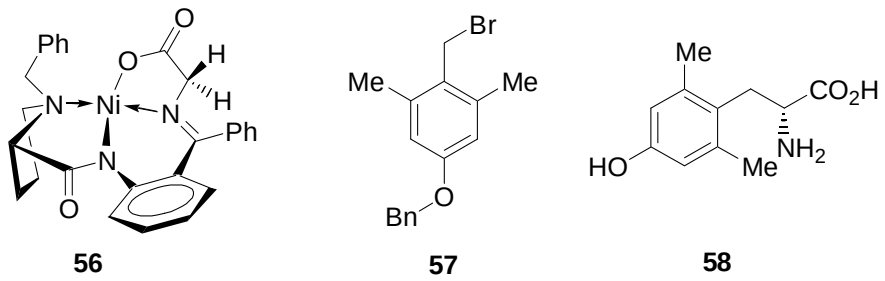


53 **54** **55**

RX	Yield	d.e.
MeI	78%	>98%
$PhCH_2Br$	88%	>98%
$CH_2=CHCH_2Br$	90%	>98%

Scheme 18

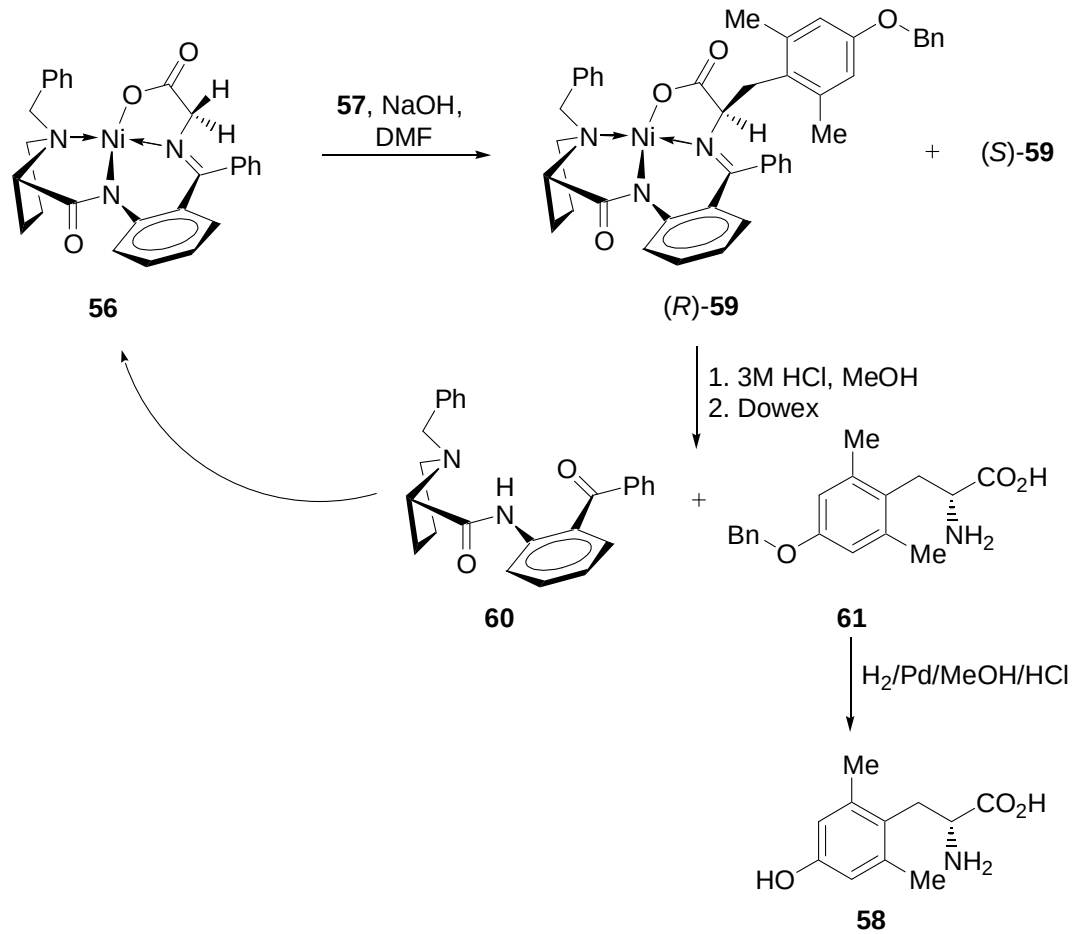
A nickel(II) complex of the chiral non-racemic Schiff base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone ((*S*)-BPB) **56** was introduced by Belokon and co-workers and has significant advantages over other chiral equivalents of nucleophilic glycine in terms of cost and availability (**Figure 13**).[37] It is also distinguished from other commercially available chiral equivalents of glycine by the fact that its alkylation is usually conducted under thermodynamically controlled conditions at room temperature in the presence of potassium hydroxide or sodium hydroxide. Soloshonok and co-workers have developed an alkylation of this Schiff base complex to synthesise (*S*)-2',6'-dimethyltyrosine (DMT) **58** (**Figure 13**) which is a component of the ultraselective δ-opioid dipeptide antagonist.[38,39] The alkylating agent **57** was chosen due to the *O*-benzyl-protecting group which is stable towards moderate nucleophilic and electrophilic reactions but can be easily removed by hydrogenation.



56 **57** **58**

Figure 13

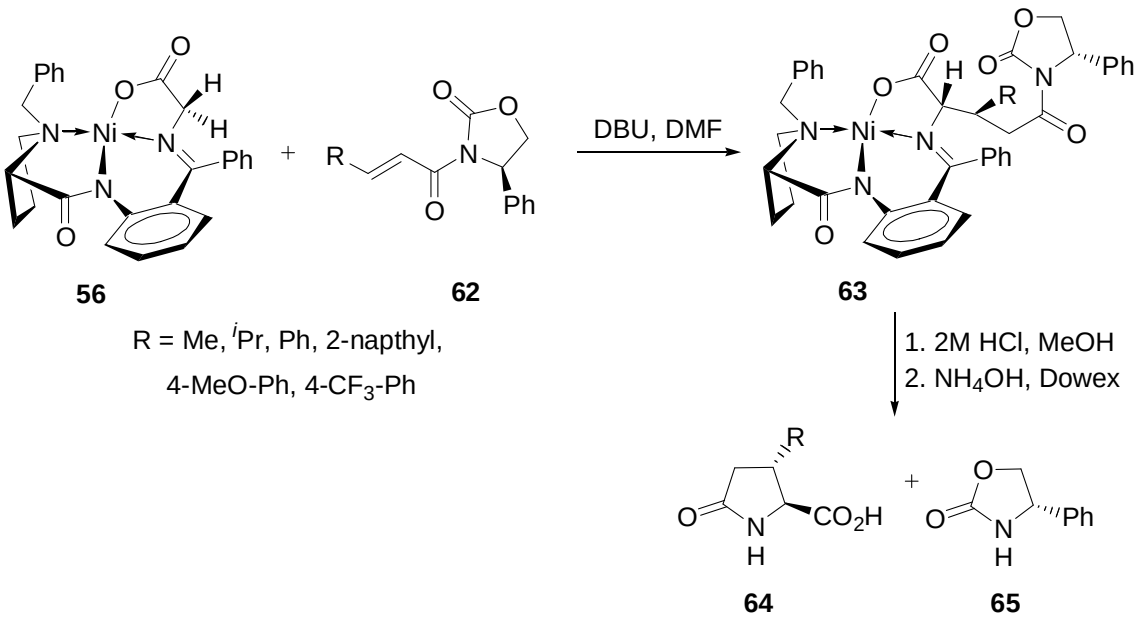
Benzylation of **56** by **57** gave the (*R*)- diastereomer (*R*)-**59** and (*S*)-diastereomer (*S*)-**59** in an 8:1 ratio and 95% yield (**Scheme 19**). The desired (*R*)-diastereomer was decomposed in 3M HCl and the benzyl group was removed under hydrogenation conditions. This yielded the free amino acid **58** along with quantitative recovery of the chiral auxiliary **60** which can be recycled to **56**.



Scheme 19

The same group have gone on to synthesise pyroglutamic acids using the nickel(II) complex **56**.[40] These acids can be readily transformed into glutamic acids, glutamines and prolines.[41] Michael addition reactions were carried out between the Schiff base complex **56** and 4-substituted *N*-(*E*-enoyl)oxazolidinon-2-ones **62** at room temperature in the presence

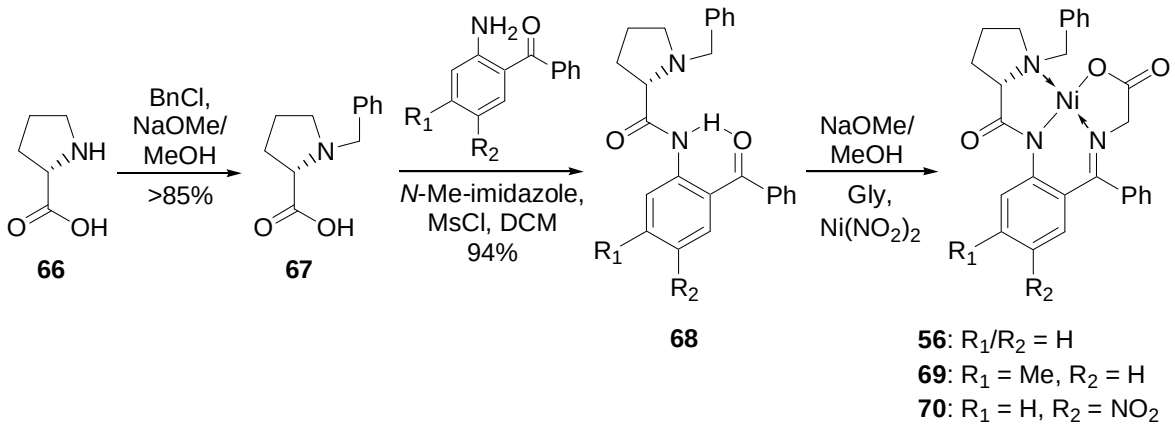
of DBU (**Scheme 20**). The 4-phenyl-oxazolidin-2-ones have been used previously and are superior in controlling the stereochemistry of the addition compared to 4-benzyl and 4-isopropyl analogues.[42,43] In virtually all cases, yields for the addition were ≥97% and diastereomeric excesses was >98%. Considering these results, the steric and/or electronic nature of the substituents does not influence the stereochemical outcome, only the reaction rate. The addition products **63** were decomposed with 2M HCl and concentrated ammonia to give the chiral auxiliary in 87-95% yield and the corresponding pyroglutamic acids **64** in 93-95% yield.



56 **62** **63** **64** **65**

Scheme 20

Soloshonok also developed an improved synthesis of the nickel(II) complex **56** used previously including two new analogues **69** and **70**.[44] The method involves application of inexpensive reagents and operationally convenient conditions (**Scheme 21**). The previous synthesis reported by Belokon and co-workers began from enantiomerically pure proline and while it does generate the desired complex, it is not amenable to large scale preparation due to, for example, the problems associated with the control of pH, the use of excess thionyl chloride and the use of almost 50% excess **67** during the amidation step. Thus, starting from (*S*)-proline **66**, commercially available and cheap NaOMe was employed as base. For the amidation, cheaper methanesulfonyl chloride was used in place of *p*-toluenesulfonyl chloride which is harder to handle. The complexes were prepared using previously reported conditions.[37]



Scheme 21

This group has also gone on to evaluate a new generation of nucleophilic glycine equivalents, still maintaining the nickel(II) complex of the Schiff base of glycine.[45] The complex **71** proved to be the most synthetically useful (**Figure 14**). Recently, Soloshonok and co-workers have employed this nickel(II) complex in the synthesis of new thalidomide derivatives, **73** and **74** (**Figure 14**).[46] Thalidomide **72** was marketed as a sedative in 1956, though the racemic mixture has teratogenic activity.[47] It has been widely thought that the (*S*)-enantiomer exhibits this activity, though this has remained uncertain as optically active thalidomide undergoes rapid racemisation, via the formation of the corresponding enolate.[48,49] Therefore the design and synthesis of stable analogues of thalidomide has recently become an important area of development, as thalidomide has selective inhibitory activity of tumour necrosis factor-α which is a clinically important activity against serious diseases such as rheumatoid arthritis, Crohn's disease, leprosy, AIDS, etc.[50,51]

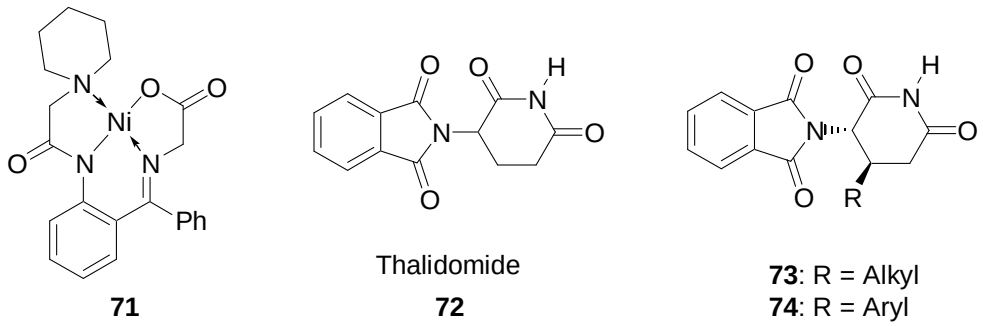
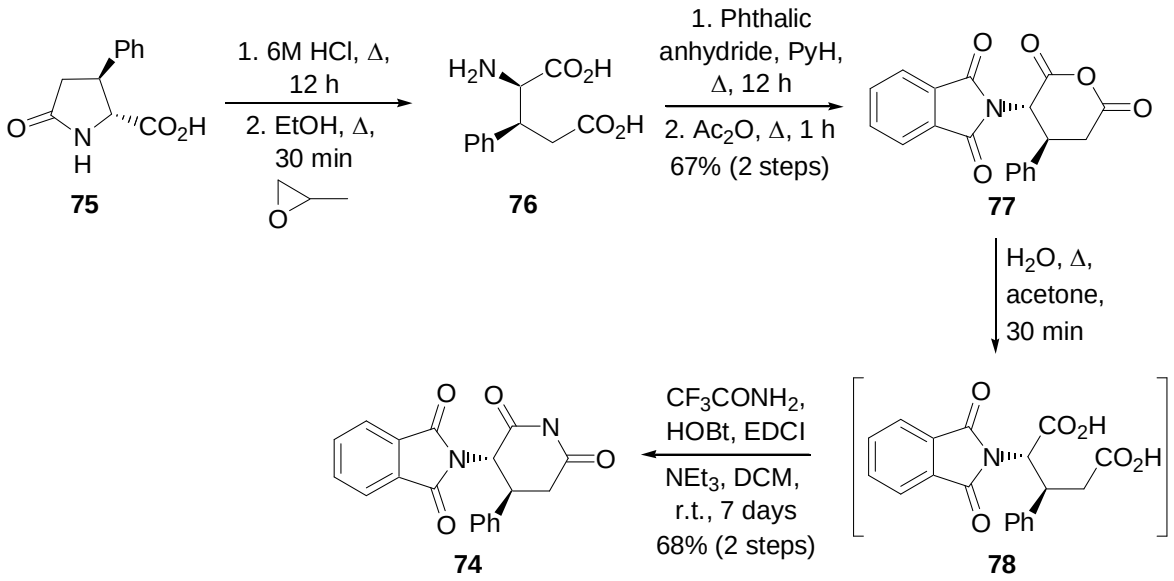


Figure 14

It was thought that β-substituted pyroglutamic acids **64**, synthesised previously, would be appropriate precursors for the preparation of the corresponding derivatives of 4-substituted thalidomide. Unfortunately, the methodology developed previously would yield *trans*-pyroglutamic acids which would not be suitable precursors.[45] The *cis*-pyroglutamic acids are very difficult to prepare in optically active form. However, considering that *cis*-4-

substituted thalidomides might be conformationally unstable, together with the suggestion that the C3 proton acidity would be as high as in thalidomide, it was assumed that upon glutarimide formation, the phthalimide group at C3 would undergo eperimisation giving rise to the target *trans*-products **73** and **74**.

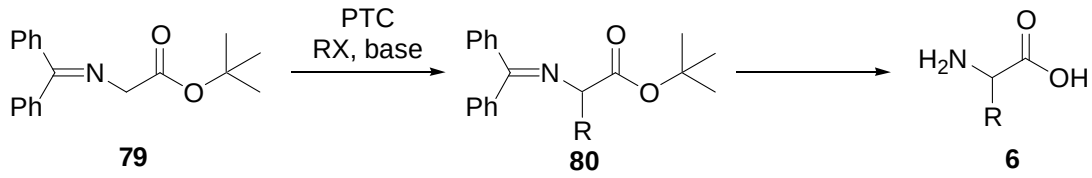
Therefore, (2*R*,3*S*)-β-phenyl pyroglutamic acid **75** was synthesised. Hydrolysis with 6M HCl yielded the corresponding 3-phenylglutamic acid **76** (**Scheme 22**).[52] Using a literature procedure, **76** was transformed into *N*-phthaloyl anhydride **77** which was isolated as a single diastereomer in 67% yield over two steps.[53] Determination of the relative stereochemistry revealed a 3,4-*trans* relationship and there was no trace of the *cis*-diastereomer. A condensation reaction of the intermediate dicarboxylate **78** was employed to yield the target molecule **74**, which was isolated in 68% yield over two steps as a single diastereomer with >98% enantiomeric excess. The alkyl derivative, (3*S*,4*R*)-4-methyl thalidomide was synthesised following the same route in 51% overall yield.



Scheme 22

1.3.1 Phase-Transfer Catalysis

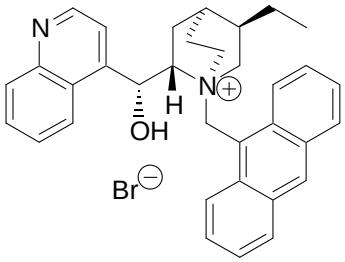
The use of chiral phase transfer catalysts has had a major impact on synthesis over the years, especially for the synthesis of unnatural amino acid derivatives via asymmetric alkylation reactions. A number of groups have worked on developing new catalysts for enantioselective alkylation since the first report of alkylation of ^{t}butyl glycinate benzophenone Schiff base **79** with a *cinchona* alkaloid-type phase transfer catalyst by O'Donnell and co-workers (**Scheme 23**).[54]



79 **80** **6**

Scheme 23

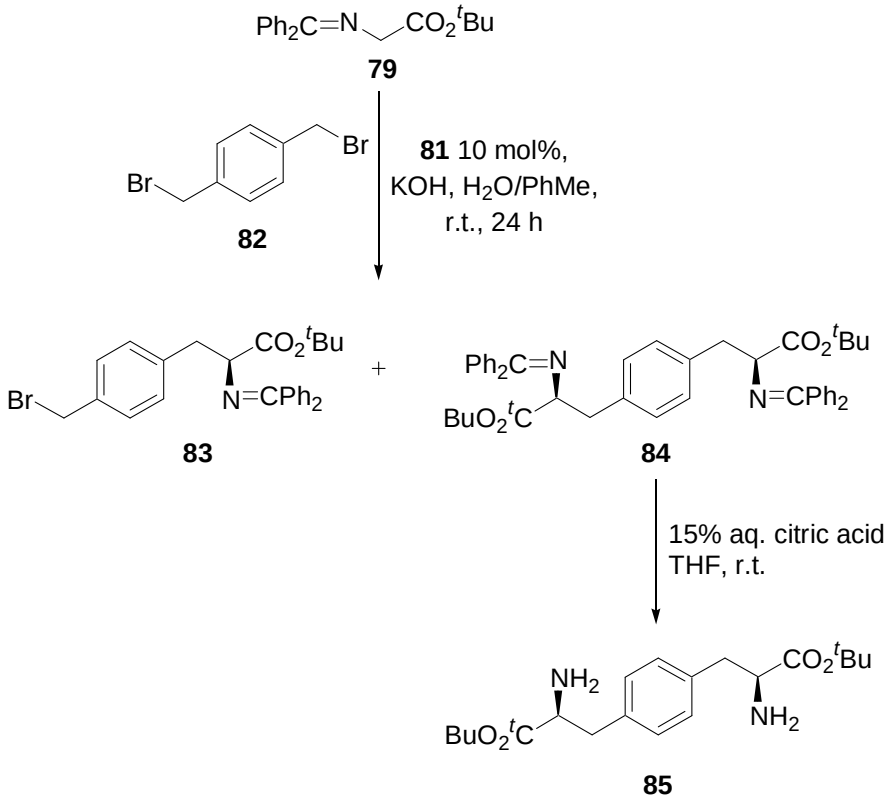
Following this, Lygo and co-workers reported a phase transfer catalyst which was a *cinchona* alkaloid derivative **81** (**Figure 15**).[55] The introduction of the bulky *N*-anthracenylmethyl group led to an enhancement of the stereoselectivity. The catalyst was subsequently used in the enantioselective synthesis of α-amino acids via the alkylation of glycine imines under liquid-liquid phase transfer conditions.[56] The catalyst was also employed in the enantioselective synthesis of bis-α-amino acids which can act as cross-linking agents in plants and bacteria. Unnatural bis-α-amino acids have also been applied in the synthesis of novel analogues of biologically active peptides.[57]



81

Figure 15

Initial investigations involving the alkylation of the glycine equivalent **79** with the dibromide **82** demonstrated that either the mono- or di-alkylated product could be produced depending on the reaction conditions (**Scheme 24**). With excess dihalide, the mono-alkylated product **83** was obtained in a 10:1 ratio over the di-alkylated product **84**. Using stoichiometric quantities of the dihalide reversed this selectivity. Hydrolysis of **84** led to the α-amino ester **85** being produced in 72% diastereomeric excess and >95% e.e. A variety of other dihalides were used and all produced the corresponding bis-α-amino acids in >95% e.e.



Scheme 24

The Maruoka group continued to develop a chiral phase transfer catalyst for the double alkylation of a Schiff base of glycine.[58] Their optimised catalyst is a chiral ammonium bromide salt **86** (**Figure 16**).

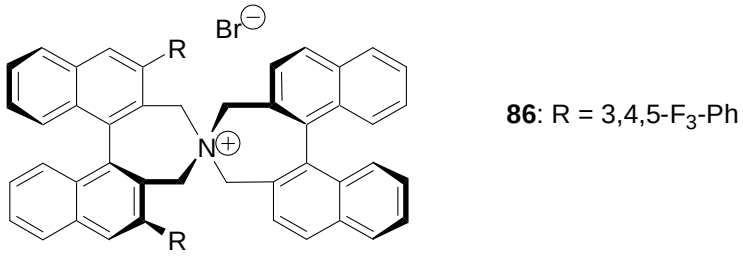
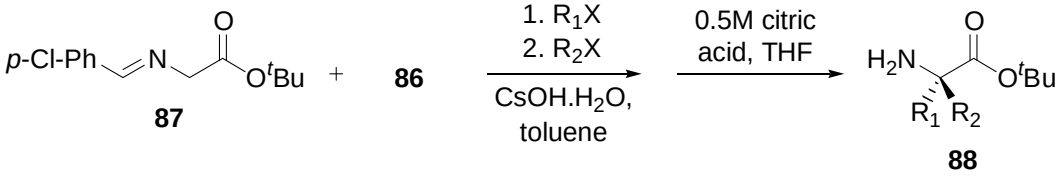
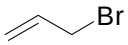
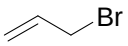


Figure 16

Alkylation reactions were carried out using 1-3 mol% of the above catalyst with various alkyl halides (**Scheme 25**). It was found that the reactions proceeded with high enantioselectivity and yields. Of note is the fact that if the halides are added in reverse order, the absolute configuration of the alkylated product was confirmed to be opposite, indicating the intervention of the expected chiral ammonium enolate in the second alkylation.



R$_1$X	R$_2$X	Yield	e.e.
	PhCH$_2$Br	80%	98% (*R*)
PhCH$_2$Br		74%	92% (*S*)

Scheme 25

The group then extended the scope of their chiral phase transfer catalyst to the aldol reaction of glycine Schiff base **79** with aldehydes **4** under organic/aqueous biphasic conditions.[59] The structural motif of the modified (*R,R*)-catalyst **89** remained the same but the substituent was changed to 3,5-bis(3,5-bis(trifluoromethyl)phenyl)phenyl (**Figure 17**). In this system, the modifications enhanced both the diastereo- and enantioselectivities.

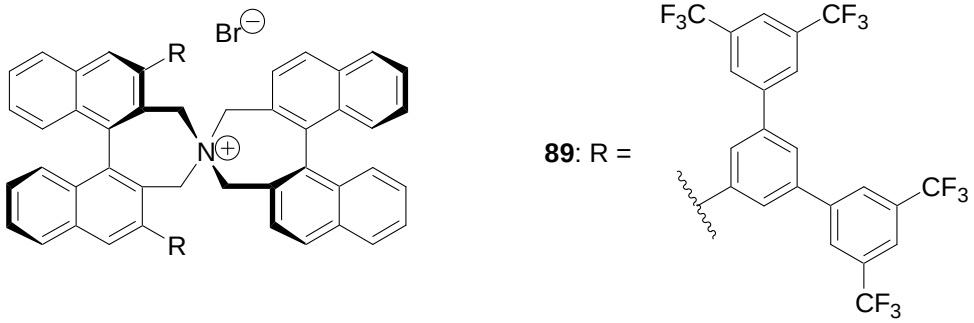
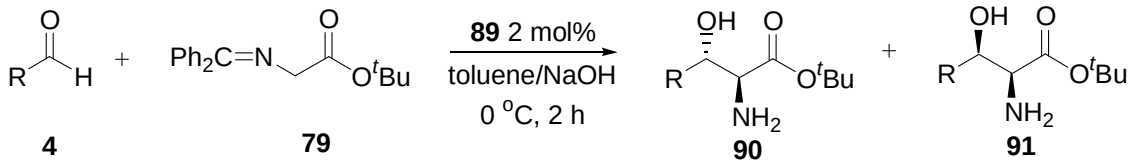


Figure 17

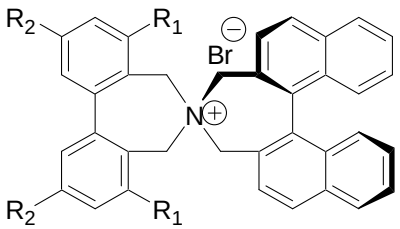
Generally, the aldol reaction of a variety of aldehydes **4** with the above catalyst and the glycine Schiff base **79** proceeded well giving predominantly the *anti*-isomer **90** with excellent enantioselectivity for the α-stereocentre (**Scheme 26**).



R	Yield	*anti*:*syn*	e.e.(*anti*)
PhCH$_2$CH$_2$	71%	3.3:1	96%
^{i}Pr$_3$SiOCH$_2$	72%	20:1	98%
CH$_3$(CH$_2$)$_4$CH$_2$	65%	10:1	91%

Scheme 26

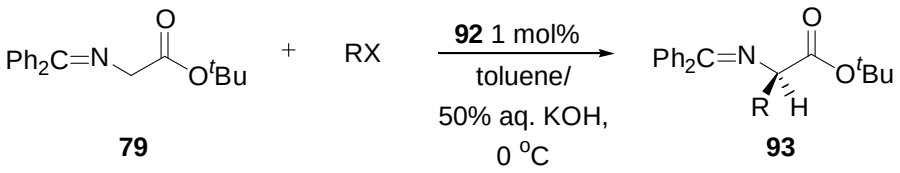
Following these positive results, it became clear that although the conformationally rigid binaphthyl structure was a characteristic feature of the catalyst and seemed essential for attaining high enantioselectivity, modifications to the structure proved to be difficult. A new chiral ammonium bromide salt catalyst **92** was reported by Maruoka and co-workers (**Figure 18**).[60] The new design features an achiral biphenyl moiety which has scope for substituents. The most effective catalyst was found to have 3,5-diphenylphenyl substituents as R_1 and phenyl groups as R_2.



92: R_1 = 3,5-diphenylphenyl, R_2 = Ph

Figure 18

The catalyst was evaluated in a phase transfer alkylation with various alkyl halides and the previously employed glycine Schiff base **79** (**Scheme 27**). Good to high yields (61-95%) and excellent enantioselectivites (92-95%) were obtained. The (*R*)-diastereomer **93** predominated.

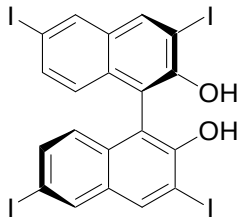


RX	Yield	e.e.
$PhCH_2Br$	81%	95%
$CH_2=CHCH_2Br$	85%	93%
EtI	61%	93%

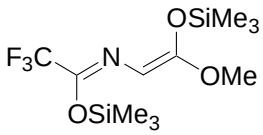
Scheme 27

The catalytic enantioselective aldol reaction of glycine derivatives with aldehydes has also been investigated by Kobayashi and co-workers.[61] A chiral zirconium catalyst was employed, as this group had previously demonstrated that chiral zirconium complexes activate both azomethine compounds and aldehydes effectively and various catalytic reactions have been carried out.[62] The catalyst is prepared from the BINOL-derived ligand **94** and $Zr(O^tBu)_4$ (**Figure 19**). Initial investigations were carried out with benzaldehyde and a glycine-derived silicon enolate **95**, which in this case was easily prepared on a large scale from glycine methyl ester and can be stored over a long period (**Figure 19**). The most

successful result obtained with benzaldehyde was 92% yield and 95% e.e. for the *anti*-diastereomer.



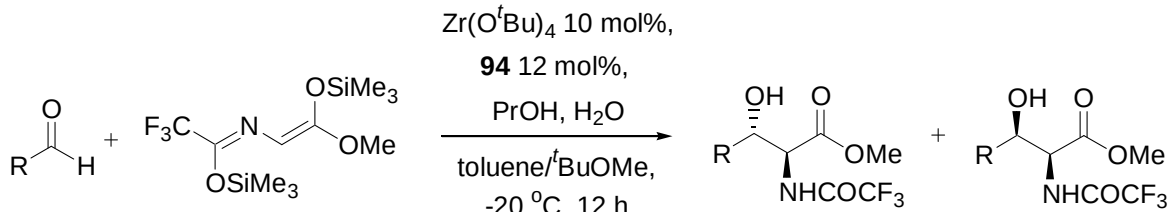
94



95

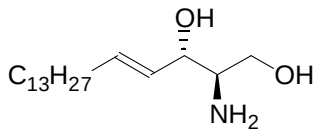
Figure 19

Following this, the group investigated the aldol reaction of other benzaldehyde derivatives using the same silicon enolate **95** (**Scheme 28**). Both electron-withdrawing and donating groups at the *para* or *meta* positions were found to be good substrates. An efficient asymmetric synthesis of L-*erythro*-sphingosine **97** was carried out to demonstrate the application of this methodology. Sphingosine is part of an essential cell membrane component, sphingolipid.[63] The initial aldol condensation gave the desired *anti*-diastereomer in 95% yield and 97% e.e. for the α-stereocenter.



4 **95** **96a** **96b**

R	Yield	*anti*:*syn*	e.e.(*anti*)
Ph	92%	90:10	95%
4-Cl-C$_6$H$_4$	91%	84:16	94%
2-naphthyl	93%	94:6	95%
TBDPSOCH$_2$C≡C	85%	80:20	95%

97 = 

Scheme 28

Recently, Shibasaki and co-workers have developed novel two-centre organocatalysts **98**, **99** and **100** which are tartrate-derived diammonium salts named TaDiAS (**Figure 20**).[64] The catalysts all contain a 2,6-disubstitued cyclohexane spiroacetal, to affect the chiral environment more strongly around the quaternary ammonium salts. Previously, this type of

catalyst was found to catalyse the asymmetric Michael reaction of a glycine-derived Schiff base with an α,β-unsaturated ketone with modest selectivity (60% e.e.).[65]

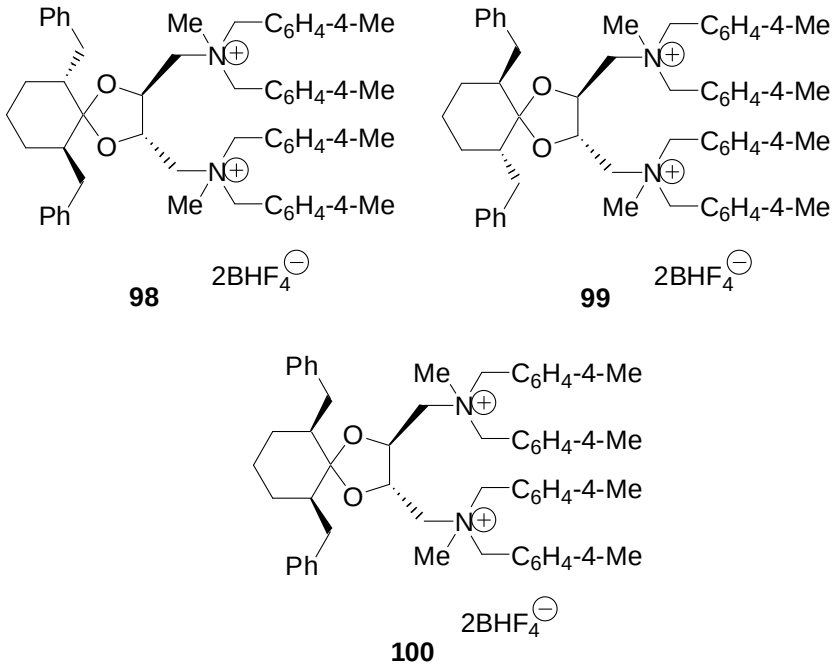
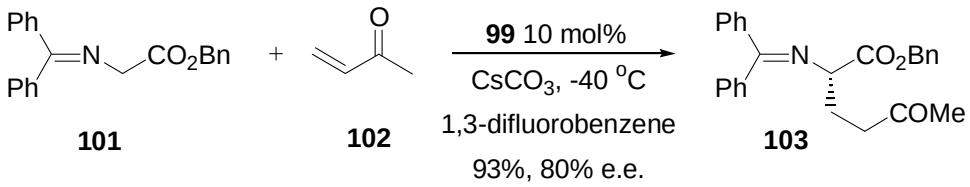


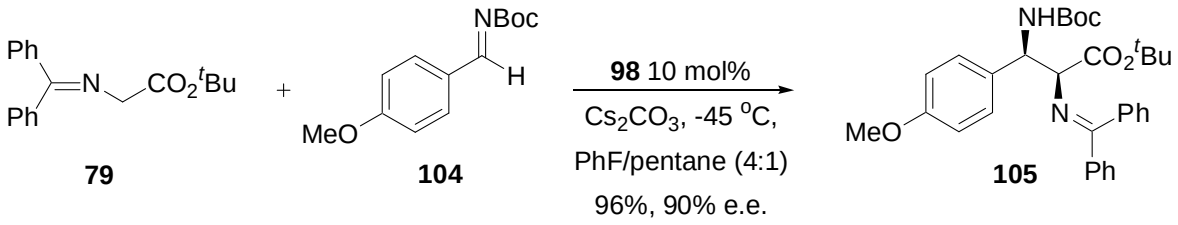
Figure 20

Asymmetric Michael reactions were carried out with the second catalyst **99** and α,β-unsaturated ketones **102** (**Scheme 29**). It was found that the highest selectivity was achieved with the benzyl ester of the glycine-derived Schiff base **101** in 1,3-difluorobenzene (93% yield, 80% e.e.). This catalyst is also suitable for acrylates though the reactions generally proceeded in good yield and higher enantioselectivies with the first catalyst **98**.



Scheme 29

The catalytic asymmetric Mannich-type reaction was also investigated using these phase-transfer catalysts. The catalytic asymmetric reaction in general is less common in the literature. An *N*-Boc protected imine **104** was employed and it was found that the first catalyst **98** gave the best reactivity as well as enantioselectivity. The *syn*-product **105** was isolated in 96% yield (*anti*:*syn* 1:99) and 90% e.e. for the α-stereocenter (**Scheme 30**). Enolisable alkyl imines were also suitable.

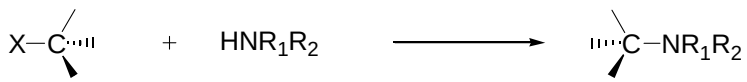


Scheme 30

1.4 Asymmetric Carbon-Nitrogen bond forming reactions

1.4.1 Nucleophilic Amination

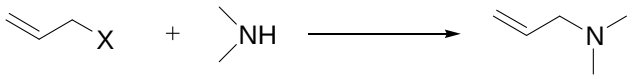
The amine functionality is one of the most ubiquitous in organic chemistry. Its importance is exemplified by the diverse nature of molecules that contain this functional group, which includes natural products, pharmacological agents and fine chemicals. For this reason carbon-nitrogen bond formation is of great interest. Naturally, this field is constantly growing and only a small selection of recent results will be presented here. The generation of α-amino acids by introducing the amino group through the use of nucleophilic aminating reagents is generally based on S_N2 substitutions. Carbon-nitrogen bonds are often formed by the attack of a nucleophilic nitrogen atom **107** on an electrophilic carbon centre **106** bearing a leaving group (**Scheme 31**). Chirality is introduced prior to the nucleophilic amination. Generally, the process involves reacting a compound having a primary or secondary amino or amido group with an arylating compound, in the presence of a weak base and a transition metal catalyst, under reaction conditions effective to form an *N*-aryl amine or *N*-aryl amide compound.



106 **107** **108**

Scheme 31

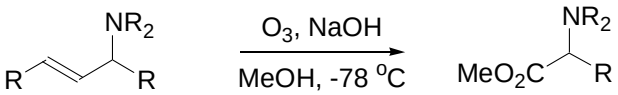
Allylic amines are fundamental building blocks in organic chemistry and the allyl fragment can be encountered in many natural products. Allylic amines can be transformed into many different products such as α- and β-amino acids, alkaloids and carbohydrate derivatives.[66] The amination of alkenes **109** bearing a carbon-heteroatom or carbon-halide bond is one if the simplest ways of synthesising these allylic amines **111** (**Scheme 32**).



109 **110** **111**

Scheme 32

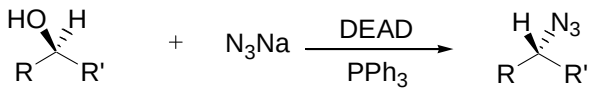
The allylic amines can then be converted into the corresponding *N*-protected α-amino esters **113** by oxidative cleavage (**Scheme 33**). The conversion has been previously achieved though ozonolysis in the presence of methanolic sodium hydroxide (2.5M) at -78 ^{o}C without loss of stereochemical purity.[67]



112 **113**

Scheme 33

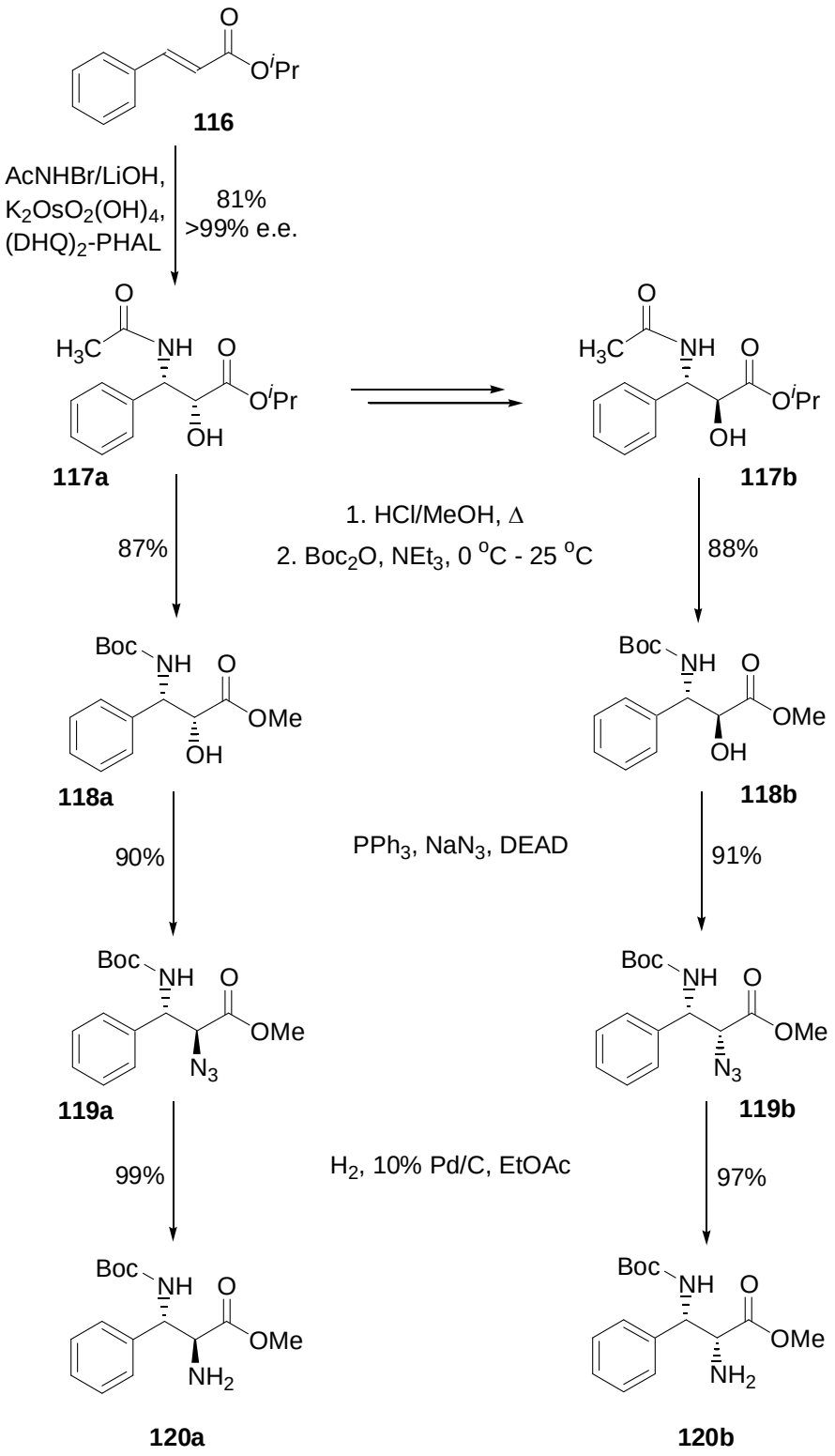
The Mitsunobu reaction offers one of the most attractive ways to transform allylic alcohols in allylic amines with inversion of stereochemistry as the reaction can be performed under mild conditions with a wide range of amine nucleophiles (**Scheme 34**).[68] Suitable nucleophiles include phthalimide and sodium azide. Hydrolysis (Gabriel reaction) or selective reduction (Staudinger reaction) makes the amines accessible.



114 **115**

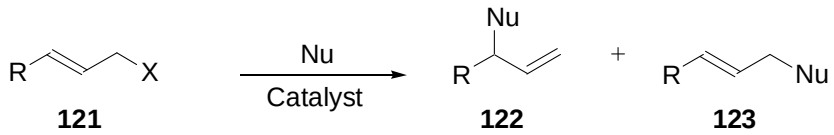
Scheme 34

Lee and co-workers have reported the synthesis of both *syn* and *anti*-2,3-diamino-phenylpropionic acids **120a** and **120b** using a Mitsunobu reaction to install the 2-amino group (**Scheme 35**).[69] Isopropyl cinnamate **116** was converted into the *syn*-acetylamino alcohol **117a** using Sharpless' asymmetric amino-hydroxylation procedure (81% yield, >99% e.e.). This was further transformed to give the corresponding *anti*-acetylamino alcohol **117b**. A Mitsunobu reaction was attempted on these amino alcohols, however an oxazoline product was obtained. Therefore the acetyl group was exchanged for a Boc-group and concomitant transesterification of the isopropyl ester to the methyl ester also occurred. The new substrates **118a** and **118b** for the Mitsunobu reaction gave the corresponding α-azide products **119a** and **119b** with clean inversion of stereochemistry. Finally, selective hydrogenation furnished the desired diamino acids.



Scheme 35

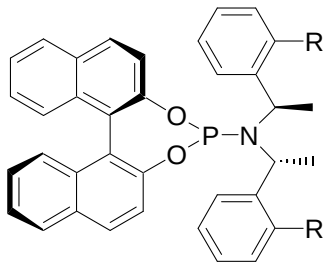
Asymmetric allylic substitution has been shown to be a powerful technique for the preparation of a wide range of chiral molecules (**Scheme 36**). The metal-catalysed reaction uses palladium most often and the regiochemistry normally favours the linear product **123**.[70]



121 **122** **123**

Scheme 36

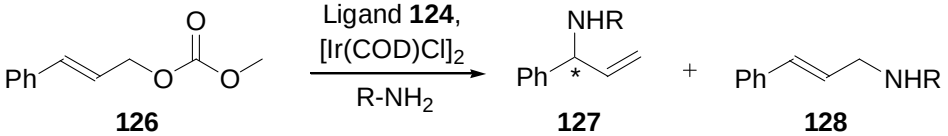
More recently, increasing interest has been shown in iridium-catalysed allylic substitutions which normally favour the branched products **122**.[71,72] Alexakis and co-workers have reported the phosphoramidite ligand **124** (R = OMe) which was applied in iridium-catalysed allylic aminations (**Figure 21**).[73] It had been previously shown that monodentate, strong π-accepting ligands such as **125** (R = H) were very efficient in iridium-catalysed allylic substitutions (**Figure 21**).[74]



124: R = OMe
125: R = H

Figure 21

As was expected, the branched product **127** was favoured over the linear product **128** (**Scheme 37**). Yields and enantioselectivities were excellent.

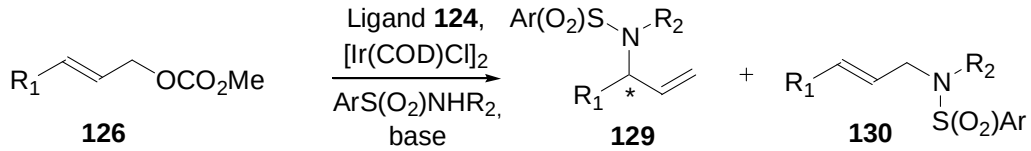


126 **127** **128**

Amine	Conv.	Ratio	e.e
Benzyl	98%	98:2	97% (*R*)
Allyl	>99%	99:1	97% (-)
^{n}Hexyl	>99%	98:2	98% (*R*)

Scheme 37

Simultaneously, Helmchen and co-workers also reported the above ligand and the results that they achieved in the iridium-catalysed allylic amination with sulfonamides as nucleophiles (**Scheme 38**).[75] The reactions were performed using LiN(CH_2Ph)*p*-Ts as the nucleophile and good to excellent results were obtained. Again, the branched product **129** was preferred over the linear product **130**. *p*-Nosylamides were investigated in an attempt to reduce steric effects.



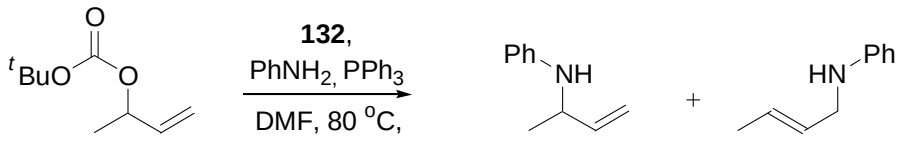
126 **129** **130**

R_1	$ArSO_2$	R_2	Base	Yield	Ratio	e.e.
Ph	*p*-Ts	CH_2Ph	LiHDMS	92%	49:1	98% (*S*)
CH_2CH_2Ph	*p*-Ts	CH_2Ph	LiHDMS	60%	4:1	95% (*R*)
Ph	*p*-Ns	CH_2Ph	-	91%	13:1	96% (*R*)
CH_2CH_2Ph	*o*-Ns	CH_2Ph	NEt_3	79%	3:1	97% (*R*)
Ph	*p*-Ns	$(CH_2)_2CH=CH_2$	NEt_3	80%	19:1	97% (*R*)

Scheme 38

Since then, Alexakis and co-workers have generated a new ligand where R = Me and with this a spectacular increase in the rate of reaction was observed in the asymmetric allylic amination with benzylamine.[76] The enantioselectivity was improved also to 98.3% e.e. Very recently, Carreira and co-workers have introduced the use of sulfamic acid H_2NSO_3H as an ammonia equivalent in allylic substitutions.[77] In general, primary amines can only be prepared through protected forms of ammonia. The iridium-catalysed reactions proceeded with complete regioselectivity in yields of up to 82%.

Recently, Plietker introduced the first iron-catalysed regioselective allylic amination.[78] The catalyst was $[Bu_4N][Fe(CO)_3NO]$ **132** and the amination in the presence of primary amines proceeded with high regioselectivity in favour of the *ipso*-substitution product **133** (**Scheme 39**). Unfortunately, catalyst decomposition in the reaction of less substituted allyl carbonates led to low yields but this was improved upon addition of piperidinium chloride. In the case shown below the yield was increased from 36% to 84%.

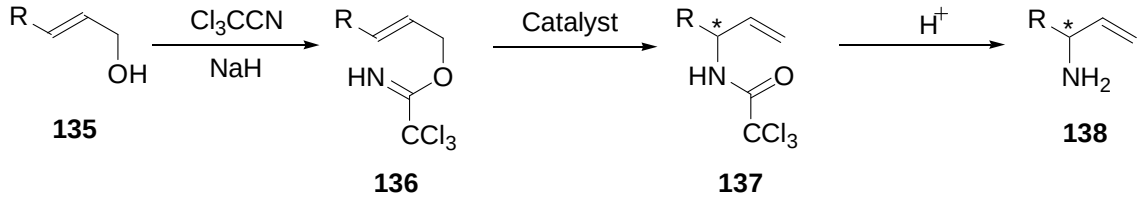


131 **133** 98:2 **134**

Scheme 39

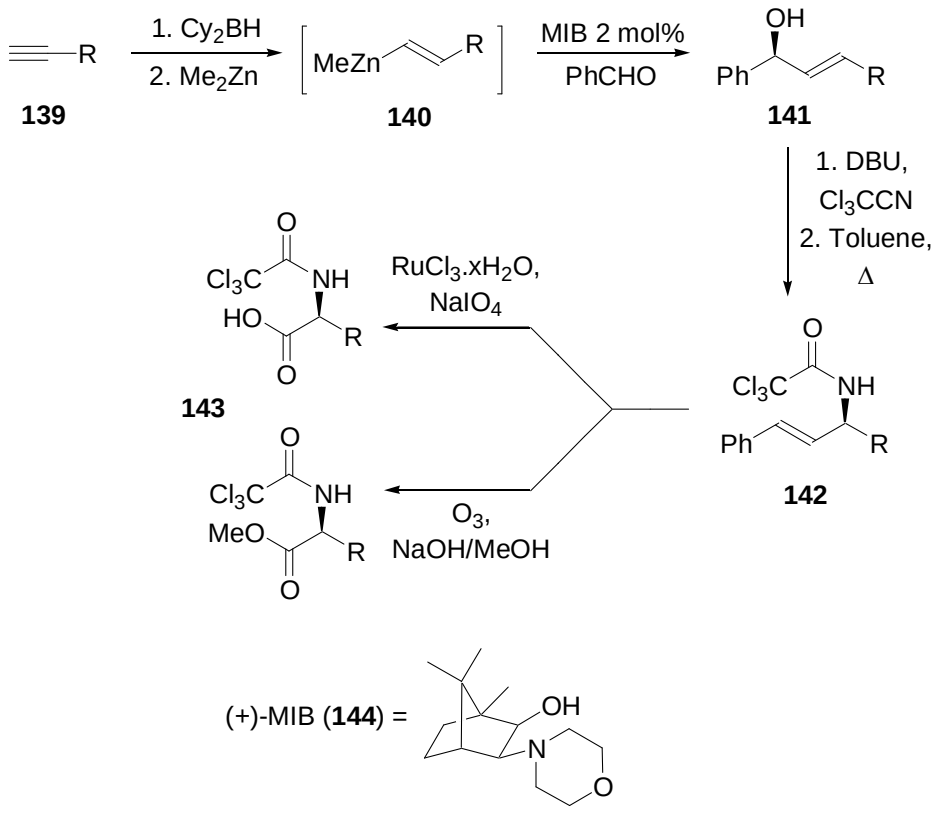
Another efficient method for the synthesis of allylic amines is Overman's 3,3-sigmatropic rearrangement (**Scheme 40**). This was first introduced by Overman in 1974 and transforms allylic alcohols **135** into allylic amines **138**.[79] The reaction can be catalysed by heat, mercury(II) and palladium(II) and Overman himself has developed a number of complex

catalysts for this purpose.[80] Very recently, Gonda and co-workers have reported their results from microwave accelerated rearrangements.[81]



Scheme 40

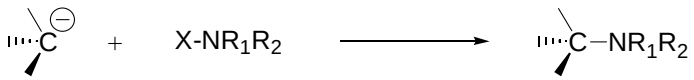
Walsh and co-workers introduced an efficient and highly diastereoselective route to D or L α-amino acids from terminal alkynes **139** using the (3,3)-sigmatropic thermal rearrangement.[82] An attractive feature of this methodology is that it provides access to sterically hindered allylic amines that may be difficult to synthesise otherwise. Reaction of benzaldehyde with terminal alkynes catalysed by the ligand MIB (3-exo-morpholinoisoborneol) **144** gave allylic alcohols **141** with excellent enantioselectivity of 88-97% and yields of 65-94%. The alcohols **141** were converted into the protected allylic amines **142** by thermal rearrangement (**Scheme 41**). The stereochemistry that was set from the vinylation reaction is transferred to the allylic amines. The enantioselectivity was maintained and yields for this step were 64-96%. Oxidative cleavage of the allylic amines gave amino acids **143** in 57-92% yield for the ruthenium pathway and 75-94% for the ozonolysis pathway.



Scheme 41

1.4.2 Electrophilic Amination

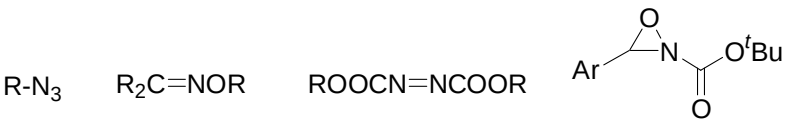
The electrophilic amination of carbonyl compounds is a conceptually attractive method for the synthesis of nitrogenous compounds. However, the small number of suitable *N*-electrophiles also limits its popularity. Electrophilic amination provides a great improvement with respect to the classical methods such as those based on the attack of the nucleophilic nitrogen atom to an electrophilic carbon, which are hampered by the difficulty in accessing electrophilic precursors and the frequent difficult reaction conditions.[83] Electrophilic amination essentially is the reverse of nucleophilic amination in that the carbon nucleophile **145** replaces a good leaving group on the electrophilic nitrogen **146** (**Scheme 42**).



145 **146** **108**

Scheme 42

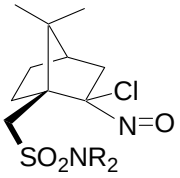
Electrophilic reagents of the type X-NR_1R_2 **146** usually contain halogens or oxygen functions as leaving groups. Other reagents can act as amino cation equivalents and some examples are given in **Figure 22**. Azides **147** and oximes **148** can react with Grignard or organolithium species to yield the triazene salts and imines respectively which can be converted to the corresponding amines. Reaction of enolates with dialkyl azodicarboxylates **149** yields the α-hydrazido compounds which can be hydrogenated to the α-amino compounds. *N*-protected oxaziridines **150** can transfer the *N*-protected fragment under mild conditions to *N*-nucleophiles, but give moderate yields with *C*-nucleophiles.[84]



147 **148** **149** **150**

Figure 22

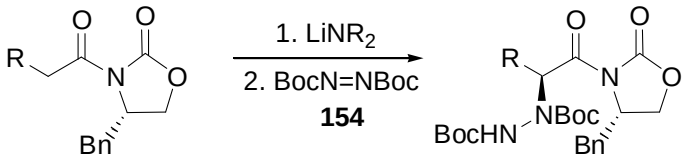
The first example of an asymmetric electrophilic amination using a chiral reagent was reported in 1992 by Oppolzer and co-workers.[85] They developed chiral α-chloro-α-nitroso reagents **151** and **152** which aminated prochiral ketone enolates with high enantioselectivity (**Figure 23**). Zinc enolates of ketones also reacted with these α-chloro-α-nitroso reagents to give nitrones with high diastereomeric excess.



151: R = cyclohexyl
152: R = isopropyl

Figure 23

Evans and Vederas both published enantioselective synthetic routes to α-amino acids using chiral *N*-acyloxazolidinone enolates **153** and commercially available di-^{t}butyl azodicarboxylate **154**.[86] In the case of Evans and co-workers, the lithium enolates derived from the *N*-acyloxazolidinones reacts readily with di-^{t}butyl azodicarboxylate to give the hydrazide products **155** in excellent kinetic ratios and yields (**Scheme 43**). These are practical precursors for α-amino acids.

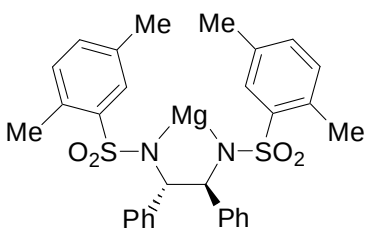


153 **155**

R	Kinetic Ratio (2*S*:2*R*)	Yield
Me	98:2	92%
$CH_2CH=CH_2$	98:2	94%
Ph	97:3	96%
CMe_3	>99:1	96%

Scheme 43

The first enantioselective amination of *N*-acyloxazolidinones in the presence of a chiral catalyst was described by Evans and co-workers.[87] The catalyst that was developed was a magnesium bis(sulphonamide) complex **156** (**Figure 25**). Aryl-substituted carboximides were used as they were expected to be moderately active towards enolisation and would give structurally well-defined enolate complexes.

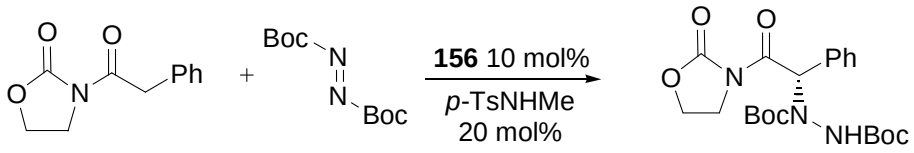


156

Figure 25

Using 10 mol% of this catalyst, which had been developed through a screening library, *N*-acyloxazolidinone **157** was aminated in the presence of di-*tert*-butyl azodicarboxylate **154**.

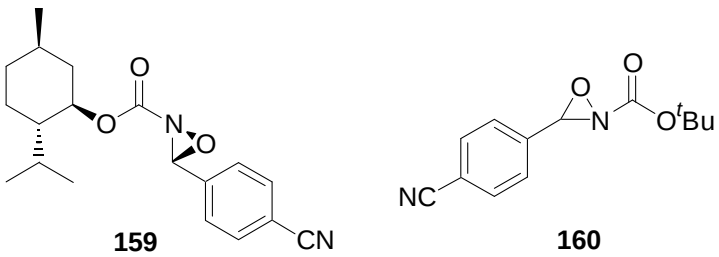
This gave the hydrazide **158** with an enantiomeric ratio of 2*S*:2*R* 93:7 in 93% yield (**Scheme 44**). Recyrstallisation leads to enantiomeric enrichment (99% e.e.). A number of aryl-substituted imides can be used including those with electron-withdrawing or donating substituents and disubstituted aryl substituents.



157 **154** **158**

Scheme 44

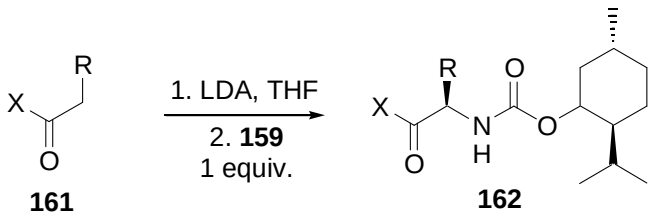
A new chiral 3-aryl-*N*-alkyloxycarbonyloxaziridine **159** derived from (-)-menthol was reported in 2001 by Armstrong and co-workers (**Figure 25**).[88] The chemistry of oxaziridines has been widely studied and it has been shown that the attack of a nucleophile occurs at either the oxygen or nitrogen of the ring depending on the nucleophile and the substituents on the ring. This reagent was synthesised based on the work of Vidal and Collet who showed previously that *N*-alkoxycarbonyloxaziridines such as **160** transfer nitrogen rather than oxygen to a number of nucleophiles.[84a,84b]



159 **160**

Figure 25

Compound **159** was tested as a reagent for the electrophilic amination of lithium enolates and while yields were good, the maximum diastereoselectivity achieved was only 21% (**Scheme 45**). The low selectivity is possibly due to the low facial selectivity in the approach of the oxaziridine to the enolate.

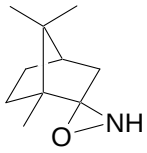


161 **162**

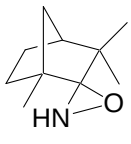
R	X	Yield	d.e.
H	O^{t}Bu	60%	-
H	Ph	59%	-
Me	OMe	57%	5%
Me	OEt	52%	8%
^{i}Pr	OEt	49%	17%

Scheme 45

The first stable enantiomerically pure chiral *N*-H oxaziridines **163** and **164**, derived from (1*R*)-(+)-camphor and (1*R*)-(-)-fenchone respectively, was described by Page and co-workers in 2002 (**Figure 26**).[89] They were investigated as asymmetric sources of electrophilic nitrogen for the amination of various carbon nucleophiles such as esters and nitriles. Yields were moderate to good but in general, enantioselectivity was moderate



163

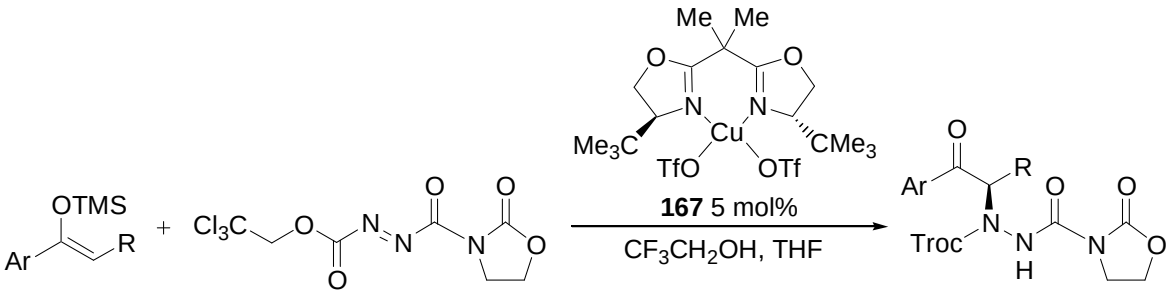


164

Figure 26

Azodicarboxylates have been used extensively as aminating reagents that give hydrazine derivatives, which are direct precursors of amines. Some of the aminations discussed previously included azodicarboxylates as the nitrogen source. Apart from sulfonyl azides, azodicarboxylates have proven to be the most successful aminating reagents. They are widely available, relatively cheap and highly reactive and have been used in the α-amination of a number of substrates.

Evans described the use of copper(II) complexes as chiral Lewis acids.[90] The chiral copper(II) complex [Cu-(*S*,*S*)-^{t}Bu-box](OTf)$_2$ **167** catalysed the electrophilic amination of the isomerically pure enolsilanes of aryl ketones **165** with azodicarboxylate derivatives **166** (**Scheme 46**). Trifluoroethanol was needed as an additive to promote catalyst turnover. As the R group increased in size, reaction times also increased. The methodology was extended to cyclic enolsilanes and acylpyrrole enolsilanes with similar success.

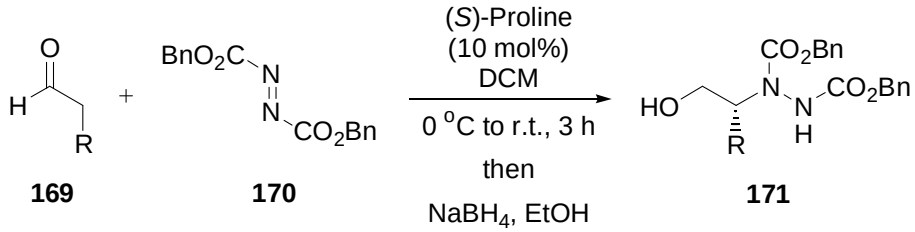


165 **166** **168**

Ar	R	Yield	e.e.
Ph	Me	95%	99%
Ph	Et	93%	98%
4'-MeOPh	Me	96%	99%
4'-MeOPh	Ph	94%	97%

Scheme 46

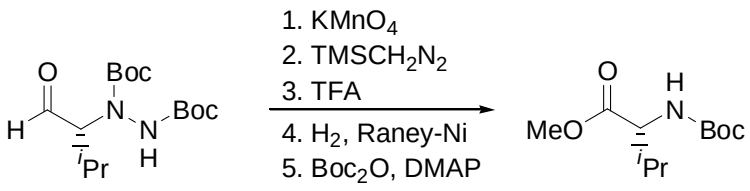
Proline has also been to found to catalyse the direct asymmetric α-amination of carbonyl compounds with azodicarboxylates.[91] Particular advantages of the use of proline as a catalyst include non-toxicity and the ready availability of both enantiomeric forms. List described the direct α-amination of aldehydes and found this to be highly efficient and enantioselective process.[91a] The methodology could give access to a wide range of optically active molecules including α-amino aldehydes, α-amino alcohols and α-amino acids. In the reaction of isobutyraldehyde **169** with dibenzyl azodicarboxylate **170** using (*S*)-proline as catalyst, the expected 2-hydrazino alcohol **171** was obtained in 99% yield and 96% e.e. after *in situ* $NaBH_4$ reduction (**Scheme 47**). The reactions that were carried out were found to be time-dependent and extended reaction times led to partial racemisation.



R	Yield	e.e.
^{i}Pr	99%	96%
^{n}Bu	94%	97%
Me	97%	>95%
Bn	95%	>95%

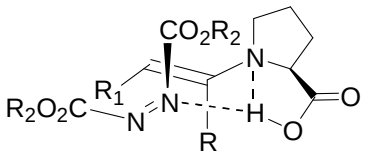
Scheme 47

Simultaneously, Jørgensen and co-workers also reported the direct proline-catalysed α-amination of aldehydes to yield the corresponding α-aminated aldehydes.[91b] These were also reduced *in situ* with $NaBH_4$ as this prevents the decrease in e.e. due to the acidity of the α-position next to the carbonyl group. The conversion of the aminated aldehydes **172** to *N*-Boc-protected α-amino esters **173** was also demonstrated (**Scheme 48**). The aldehyde **172** was oxidised with $KMnO_4$ to the acid which was esterified. Hydrolysis of the Boc-groups, reduction and Boc-protection produces the *N*-Boc-protected valine methyl ester **173**. Shortly after, Jørgensen and co-workers extended the substrate range to include ketones, again using azodicarboxylates as the nitrogen source.[92]

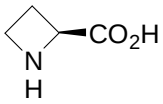


Scheme 48

While proline is a very efficient catalyst, it has recently been shown that other amino acids can catalyse the asymmetric α-amination of aldehydes and ketones. The enantioselectivity observed with the proline-catalysed reaction was explained with a proline-enamine transition state **174** and it was thought that by modifing the nature and size of the catalytic heterocycle, the outcome of the reaction would be affected (**Figure 27**).[91c] Greck and co-workers have investigated the corresponding 4-membered heterocycle, L-azetidine carboxylic acid **175**, as a catalyst (**Figure 27**).[93] Yields and enantioselectivity were comparable to those obtained with proline.



174



175

Figure 27

1.5 Catalytic Asymmetric Hydrogenation

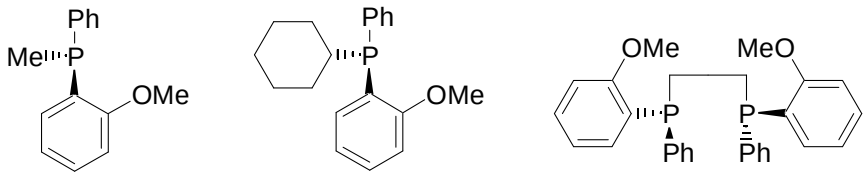
Catalytic enantioselective hydrogenation employs dihydrogen and small amounts of chiral transition-metal complexes and is one of the most efficient methods for producing a wide range of enantiomerically pure compounds.[94] Hydrogenation is economical and environmentally friendly and provides an ideal route to amines. Typically, rhodium(I) and ruthenium(II) complexes are most often used and these will be the main focus of this section. The scope of this reaction has been gradually extended in terms of reactant structure and catalyst efficiency over many years. The ideal catalyst combines high enantioselectivity with high catalytic activity and wide substrate scope.

The development of asymmetric hydrogenation was first introduced by Knowles and Horner in the 1960s after the discovery of Wilkinson's homogenous hydrogenation catalyst [$RhCl(PPh_3)_3$].[95,96] Knowles reported that the monophosphine CAMP ligand **177**, which replaced the triphenylphosphine in Wilkinson's catalyst provided enantiomeric excesses of up to 88% in the hydrogenation of dehydroamino acids (**Figure 28**).[97] Knowles also reported the chelating bisphosphine ligand DiPAMP **178** (**Figure 28**).[98] DiPAMP has been employed in the industrial synthesis of L-DOPA (Knowles-Monsanto synthesis) due to its high catalytic efficiency in rhodium-catalysed asymmetric hydrogenation of dehydroamino acids.[99] This work led to Knowles being awarded the Nobel Prize in 2001, along with Noyori and Sharpless. Work in the 1980s focussed on chiral rhodium catalysts and the substrate scope was limited to α-dehydroamino acids. Since then, many chiral phosphorus

ligands have been developed and many other transition metals have been used for catalytic asymmetric hydrogenation, for example ruthenium, iridium, platinum, titanium, zirconium and palladium.

1.5.1 Rhodium

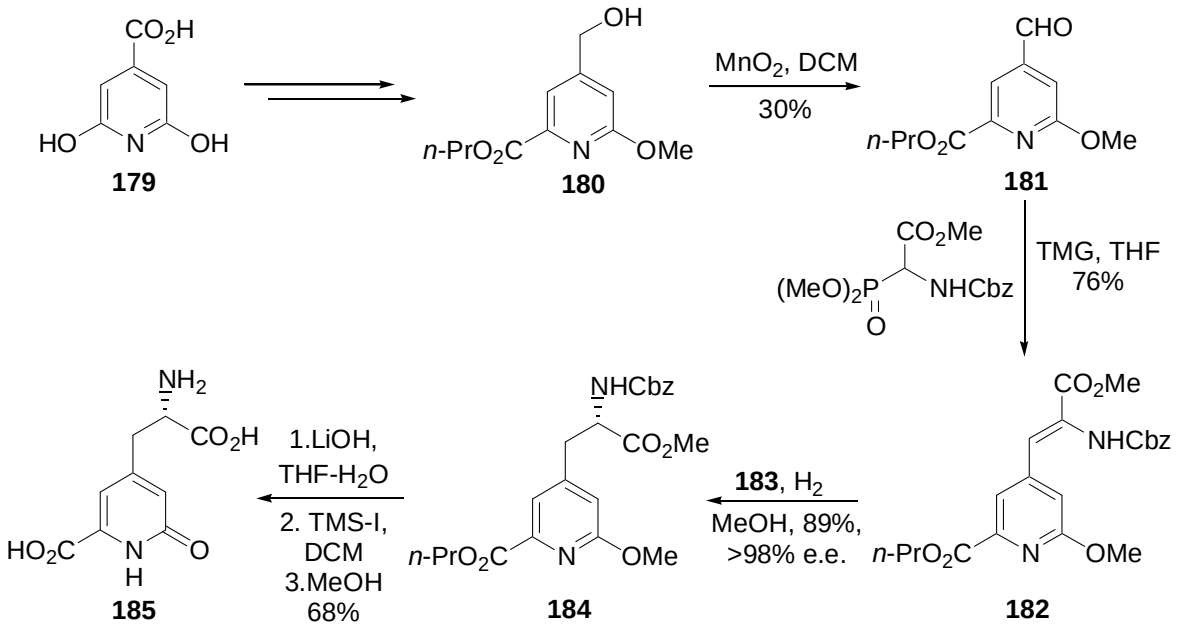
Rhodium-catalysed asymmetric hydrogenation has famously been used in the commercial production of the amino acid, L-3,4-dihydroxyphenylalanine (L-DOPA), which is used to treat Parkinson's disease. In 1968, Knowles and his group replaced the triphenylphosphine in Wilkinson's rhodium catalyst with a chiral phosphine and hydrogenated a prochiral olefin.[96a] Their first hydrogenations gave only 15% e.e. but continued modifications resulted in the creation of methylphenyl-*o*-anisylphosphine (PAMP) **176**, which gave 58% e.e. (**Figure 28**). Finally, when the phenyl group in PAMP was modified to a more hindered cyclohexyl to give methylcyclohexyl-*o*-anisylphosphine (CAMP) **177**, the e.e. increased to 88%. Later, the e.e. was further improved to 95% using DiPAMP **178**, a dimeric form of PAMP (**Figure 28**).



PAMP **176** CAMP **177** DiPAMP **178**

Figure 28

These ligands are still being used widely today, for example, in the asymmetric synthesis of the isomeric nonproteinogenic (*S*)-(-)-acromelobic acid **185** by Adamczyk and co-workers.[100] The synthesis begins from commercially available citrazinic acid and 2,5-lutidine respectively. Citrazinic acid **179** was converted to **180** in four steps and 23% overall yield (**Scheme 49**). The alcohol was oxidised to the corresponding aldehyde **181** in 30% yield and this was then treated with *N*-(benzyloxycarbonyl)phosphonoglycine trimethyl ester to yield the dehydroamino acid derivative **182**. This was then subjected to the asymmetric hydrogenation with a catalytic amount of Knowles' catalyst, (*R*,*R*)-[Rh(DiPAMP)(COD)]BF_4 **183**, to give (*S*)-(+)-**184** in 89% yield and >98% e.e. (**Figure 29**). The protecting groups were then removed in one step to yield **185**.



Scheme 49

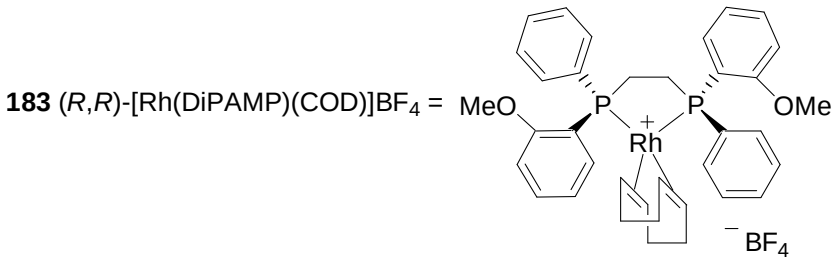
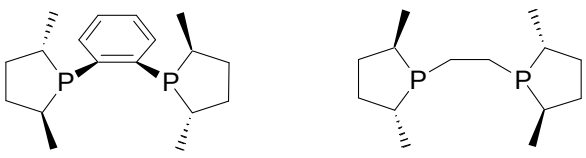


Figure 29

Burk later introduced a range of chiral hydrogenation catalysts based on the highly successful 1,2-bis(phospholano)benzene (DuPHOS) and 1,2-bis(phospholano)ethane (BPE) ligands.[101] These were (*S*,*S*)-Me-DuPHOS **186** and (*R*,*R*)-Me-BPE **187** (**Figure 30**). These were used in the rhodium-catalysed hydrogenation of a series of β,β-disubstituted enamides and enantioselectivities of 85-99% were achieved.

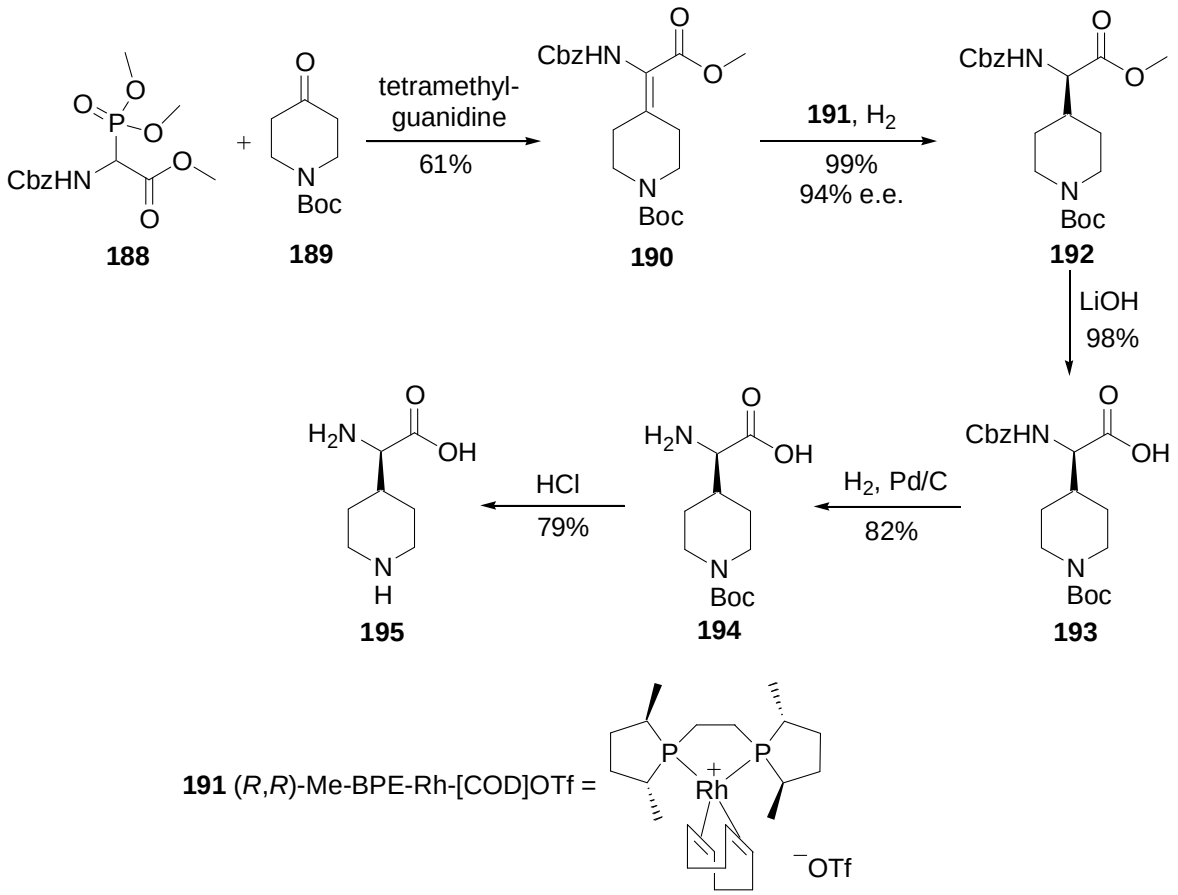


186 **187**

Figure 30

The group of Shieh have further demonstrated the synthetic usefulness of the BPE ligand in rhodium-catalysed hydrogenation by preparing the unnatural α-amino acid (*R*)-4-piperidinylglycine **195.**[102] This amino acid is an important building block in novel

pharmaceuticals such as thrombin inhibitors.[103] Excellent enantioselectivity had been reported previously in the synthesis of *N*-Cbz-protected enamides which are precursors for the asymmetric hydrogenation.[100a,104] Thus the required *N*-Cbz–protected enamide **190** was prepared from commercially available *N*-Cbz-phosphonoglycine trimethyl ester **188** and *N*-Boc-4-piperidinone **189** in 61% yield (**Scheme 50**). At this point a recrystallisation was performed, so as to eliminate any impurities that may have poisoned the catalyst. Asymmetric hydrogenation of **190** in the presence of the commercially available rhodium catalyst **191** generated the (*R*)-enantiomer of **192** in 99% yield and 94% e.e. The ester was converted to the corresponding acid **193** with LiOH in 98% yield. Hydrogenation removed the Cbz-protecting group and the Boc-protecting group was then removed with HCl to give **195** in 49% overall yield.

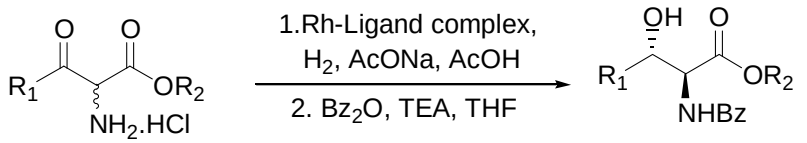


Scheme 50

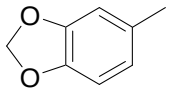
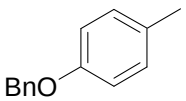
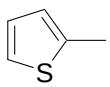
Dynamic kinetic resolution (DKR) is a powerful technique for synthesising one enantiomer from a racemic starting material with a labile stereocenter.[105] Noyori and co-workers originally described the ruthenium-catalysed DKR of α-substituted β-keto esters which yielded *syn*-β-hydroxy-α-amino acid esters.[106] In more recent times, Hamada and co-workers have demonstrated that a ruthenium-BINAP complex can catalyse the *anti*-

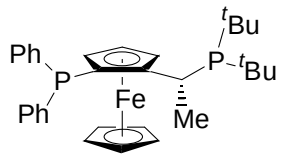
selective asymmetric hydrogenation of α-amino-β-keto ester hydrochlorides in the synthesis of *anti*-β-hydroxy-α-amino acid esters with high diastereoselectivities and enantiomeric excesses.[107] This will be discussed further within the 'ruthenium' section.

Recently, rhodium-catalysed asymmetric hydrogenation of α-amino-β-keto ester hydrochlorides through DKR was described by Hamada and co-workers.[108] This yields *anti*-β-hydroxy-α-amino acid esters. This had been previously described by two groups but gave low conversion and/or poor selectivity.[109] Following optimisation of the catalyst and reaction conditions, asymmetric hydrogenations were carried out on a number of aromatic substrates **196** (**Scheme 51**). While the yields achieved are moderate, good selectivity and enantioselectivies were obtained. The e.e.'s in **Scheme 51** refer to the α-stereocenter of the *anti*-β-hydroxy-α-amino acid esters



196 **197**

R_1	R_2	Yield	e.e.
	Et	61%	80%
	Me	53%	84%
	Et	66%	79%

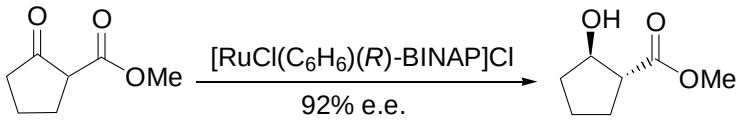
Ligand = 

Scheme 51

1.5.2 Ruthenium

As mentioned before, asymmetric hydrogenation is more often carried out with rhodium or ruthenium catalysts with diphosphine-cased chiral ligands. In 1986 a major breakthrough was made in ruthenium-BINAP chemistry when Noyori and co-workers prepared a ruthenium-BINAP dicarboxylate complex for asymmetric hydrogenation of various functionalised ketones.[110] Subsequently Noyori and co-workers also showed that ruthenium-BINAP/diamine complexes effectively catalyse the asymmetric hydrogenation of some unfunctionalised ketones.[111] Importantly, this system can selectively reduce ketones in the presence of carbon-carbon double bonds.[112]

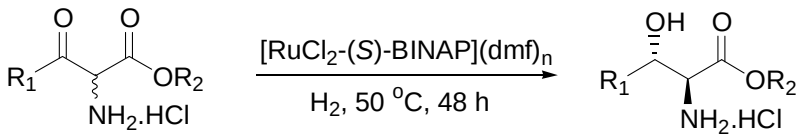
Noyori and co-workers originally described the ruthenium-catalysed DKR of α-substituted β-keto esters which yielded *syn*-β-hydroxy-α-amino acid esters.[106] The catalyst used was a ruthenium-(*R*)-BINAP complex. It was found that appropriate modification of the substrate, a simple 2-substitued 3-oxo-carboxylic ester, led to clear differentiation of *anti* and *syn* transition states. For example, the racemic cyclic ketone **198** was hydrogenated to give the corresponsing *trans*-hydroxy ester **199** in 92% e.e. (**Scheme 52**). In contrast, certain acyclic substrates bearing an amide or a carbamate group led to the *syn* products in excellent e.e.



198 **199**

Scheme 52

This combination of DKR with a ruthenium-(*S*)-BINAP catalyst was used more recently by Hamada and co-workers to synthesise β-hydroxy-α-amino acids from the corresponding β-keto-α-amino esters.[107] The 'β-hydroxy-α-amino' fragment can be found in many biologically active natural or unnatural products. Based on the methodolgy of Noyori, all four stereoisomers of 3-hydroxyleucine were synthesised previously.[113] Following optimisation of the reaction conditions, the hydrochloride salts of a number of β-keto-α-amino esters **196** were hydrogenated (**Scheme 53**). The substrates bearing a secondary alkyl carbon, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl substituent at the α-position of the ketone gave the *anti*-products **200** in high diastereoselectivity and enantioselectivity. However, a drawback of this hydrogenation was that the substrate scope was limited to those with alkyl groups at the C-4 position. The e.e's in **Scheme 53** refer to the α-stereocenter of the *anti*-products **200**.



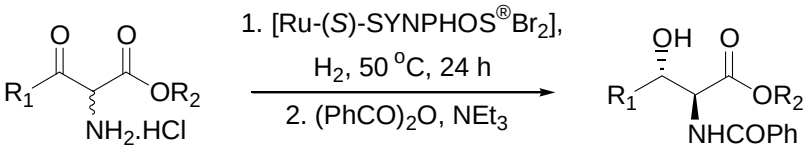
196 **200**

R_1	R_2	Yield	e.e.
C_5H_9	Bn	85%	95%
C_7H_{13}	Bn	86%	97%
^{n}Pr	Bn	88%	74%
Ph	Bn	93%	4%

Scheme 53

DKR has also been used by Genet and co-workers to synthesise *anti*-β-hydroxy-α-amino esters **201** *via* ruthenium-SYNPHOS®-catalysed hydrogenation.[114] Hydrochloride salts of

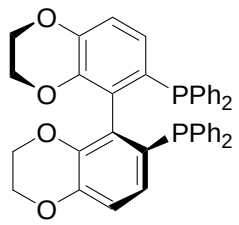
β-hydroxy-α-amino esters **196** were selectively hydrogenated under optimised conditions (**Scheme 54**). It was found that DCM with a small percentage of alcoholic solvent slowed the reaction rate and favoured better discrimination of the catalyst which in turn improved the chiral induction. Only 2 mol% of catalyst was required to ensure complete conversion. This combination worked well for both branched and unbranched substrates with excellent yields. High levels of *anti*-diastereoselectivity (86-99%) and enantioselectivity at the α-stereocenter (91-97%) were observed.



196 **201**

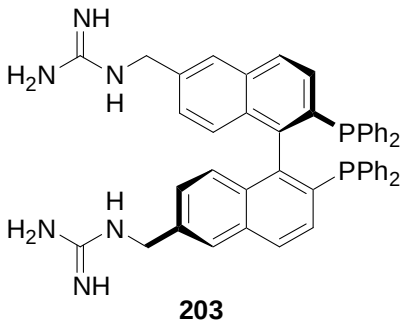
R_1	R_2	Yield	d.e.	e.e.
BnO-C_4H_8	Me	94%	92%	92%
$C_{15}H_{31}$	Me	83%	96%	96%
C_5H_{11}	Me	85%	93%	91%
^{i}Pr	Et	90%	99%	97%

202 (*S*)-SYNPHOS® =



Scheme **54**

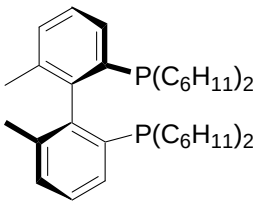
Very recently, Genet and co-workers have extended this work and reported a new synthesis of the marine natural product dolastatin 10.[115] The (*S*)-SYNPHOS® ligand **202** was used again and gave excellent diastereoselectivity of 98:2 (*R*):(*S*) in the ruthenium-catalysed hydrogenation of β-ketoesters. Of note is the recyclable catalyst (*R*)-Digm-BINAP **203** reported by Genet and co-workers in 2001 (**Figure 31**).[116] This catalyst is based on the very successful BINAP structure with guanidinium functionalisation. One of the main challenges in catalysis is the separation of product and catalyst and the subsequent recycling of the catalyst. Genet has also focused on the development of water-soluble catalysts. The ruthenium-catalysed asymmetric hydrogenation of β-keto esters in water gave e.e.'s of up to 62% which increased up to 99% in ethylene glycol. The catalyst was recovered and was recycled three times without loss of activity.



203

Figure 31

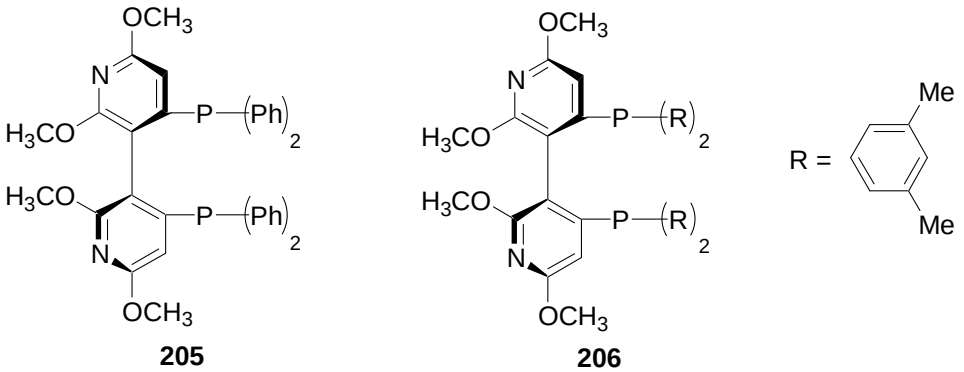
Based on the structure of BINAP, a new chiral bis(diarylphosphine) ligand known as BICHEP **204** was introduced by Miyashita and co-workers (**Figure 32**).[117] It was used in the ruthenium-catalysed asymmetric hydrogenation of prochiral olefins and ketones and very high enantioselectivites of up to >99% were achieved.



204

Figure 32

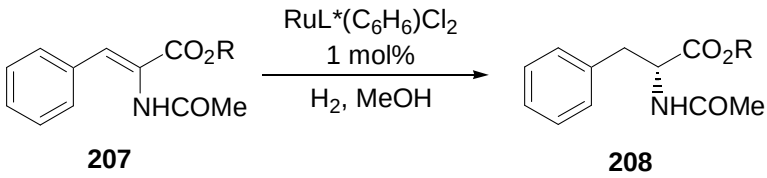
Subsequently, the group of Chan and co-workers introduced a new highly effective dipyridylphosphine ligand P-Phos **205** (**Figure 33**).[118] This new catalyst and its derivative, Xyl-P-Phos **206**, had been previously employed in the hydrogenation of 2-(6'-methoxy-2'-naphthyl)propenoic acid, β-ketoesters and aromatic ketones (**Figure 33**). The tuning of the original P-Phos ligand by the introduction of a 3,5-dimethyl group on each of the phenyl rings yielded Xyl-P-Phos, a much more effective ligand in the ruthenium-catalysed asymmetric hydrogenation of β-ketoesters. Another advantage of these catalysts is that they are air-stable even in solution state, in contrast to most air-sensitive metal phosphine catalysts.



205 **206**

Figure 33

These were applied in the ruthenium-catalysed asymmetric hydrogenation of the methyl esters of a variety of (*Z*)-2-acetamido-3-arylacrylic acids **207** (**Scheme 55**). After optimisation of the reaction conditions, it was found that the original catalyst Ru-(*R*)-P-Phos(C_6H_6)Cl_2 produced consistently higher enantioselectivity of up to 90% e.e. for the (*R*)-enantiomer **208**. Further studies on derivatives of the (*Z*)-2-acetamido-3-arylacrylic acids, where the phenyl ring was replaced by a range of other substituents, confirmed that the original catalyst consistently gave the higher enantioselectivities of up to 97% e.e.



207 **208**

R	L*	e.e	Time
Me	P-Phos	88%	2 h
Me	P-Phos	90%	3 h
Me	Xyl-P-Phos	73%	4 h

Scheme 55

1.6 Conclusions

The work presented here represents only a focused section from the recent literature in the field of α-amino acid synthesis. Other approaches not discussed here include enzymatic synthesis and use of the chiral pool. Many more chiral catalysts, both *in situ* generated catalysts and preformed catalysts are constantly being reported.

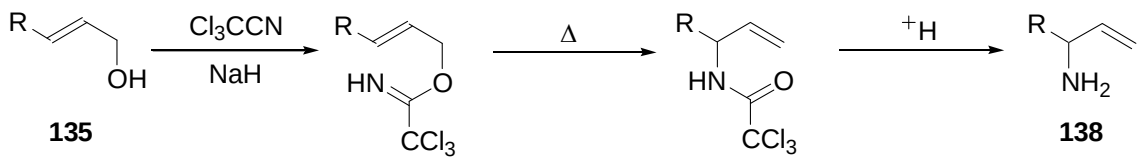
This thesis describes the use of some of the methods discussed above in order to synthesise α-amino acids such as the Overman rearrangement, α-amination and the use of the Schöllkopf bis-lactim ether as a chiral auxiliary.

2 Use of the 3,3-aza-Claisen Rearrangement

2.1 Introduction

The 3,3-sigmatropic aza-Claisen rearrangement of allylic trichloroacetimidates into allylic trichloroacetamides (also known as the Overman Rearrangement) has been widely used for the stereoselective synthesis of nitrogen-containing compounds including alkaloids, unnatural amino acids and antibiotics (over 180 publications report the use of this rearrangement).[80c,119] Natural products often suffer from hindered chemical environments during their synthesis and the use of intramolecular rearrangement reactions is a popular approach to enhance reactivity. The resulting allylic amine structures from aza-Claisen rearrangements can be transformed into many chemically and biologically important natural products, as they can generate defined, configured carbon centres and also complex carbon-heteroatom bonds.[120]

The general thermal rearrangement is shown below (**Scheme 56**). Reaction of an allylic alcohol **135** with sodium hydride and trichloroacetonitrile yields the rearrangement precursor **136**. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) can also be used as base in this reaction. The precursor **136** is then exposed to elevated temperatures and rearranges to give a racemic mixture of allylic trichloroacetamides **137**. Acidic or basic cleavage of the trichloroacetyl group yields the allylic amine **138**. Mumm and Möller first reported this thermal transformation in 1937.[121] The thermal rearrangement leads to a racemic mixture of trichloroacetamides which can be undesirable in pharmaceutical terms. Only one of the stereoisomers may have the desired beneficial effect and the other may have toxic properties. Currently, about 80% of drugs entering development are enantiomerically pure.[122]

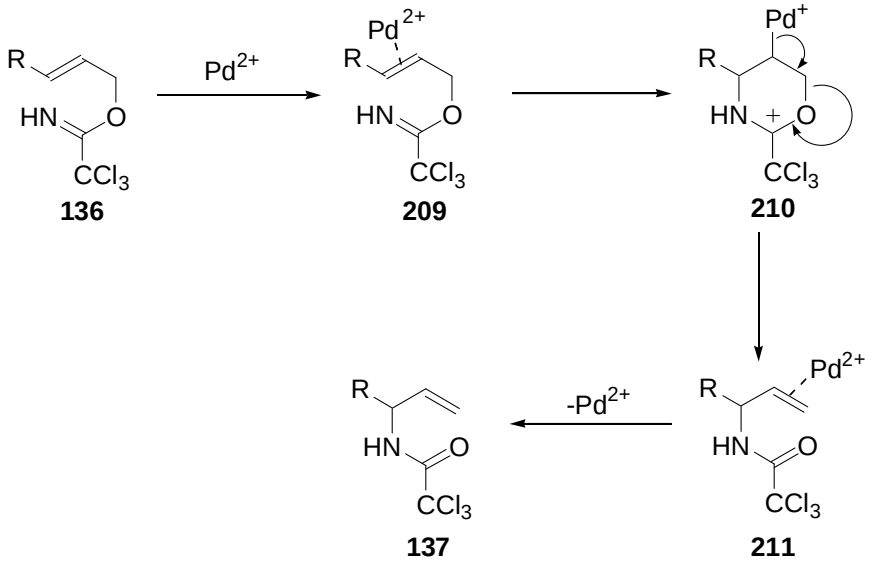


135 **136** **137** **138**

Scheme 56

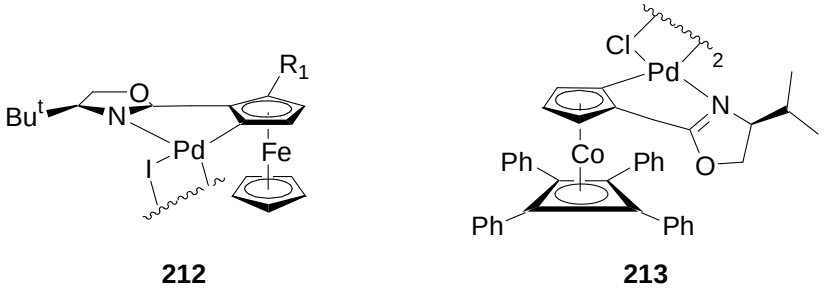
The rearrangement can also be carried out at room temperature in the presence of mercury(II) or palladium(II) catalysts.[80c,121] Overman reported that mercury(II) catalysed the reaction 10^{12} times faster than the thermal rearrangement.[80a] The driving force of ~14

kcal mol^{-1} for the imidate to amide reorganisation alleviates the problem of reversibility inherent in many sigmatropic rearrangements.[123] Henry originally proposed the cyclisation-induced rearrangement mechanism for the palladium(II)-catalysed acetate migration in allyl acetates.[124] This mechanism has subsequently been developed by Overman to explain, among others, the palladium(II)-catalysed aza-Claisen rearrangement (**Scheme 57**).[125] The catalyst is believed to activate the C-C bond for attack by the internal nitrogen nucleophile by coordinating to the allylic C-C π-bond to give the key cyclic carbocation intermediate **210**. Elimination of the palladium yields the trichloroacetamide **137** (thermodynamically favourable).[126]



Scheme 57

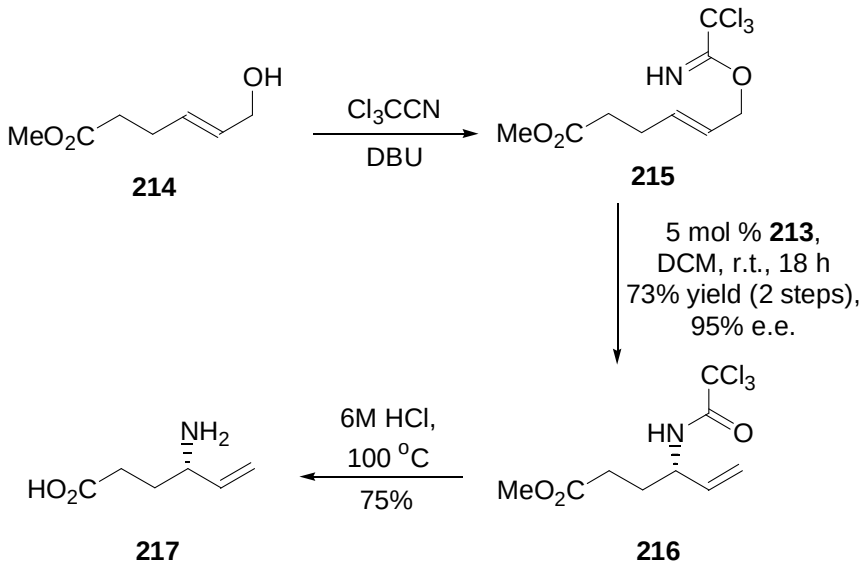
More recently, Overman has developed a number of chiral palladium(II) catalysts which allow for differentiation between the two faces of the palladium square plane, therefore effecting an enantioselective reaction. The catalyst coordinates to and blocks one face of the alkene, allowing attack of the internal nitrogen nucleophile solely at the unhindered face.[80b,80d] This asymmetric version of the rearrangement leads to the generation of predominantly one stereoisomer of the trichloroacetamide. Ferrocenyloxazoline (FOP) palladacycles **212** and cobaltocenyloxazoline (COP) palladacycles **213** have been used, leading to enantiomeric excesses of up to 99% (**Figure 34**).[127]



212 **213**

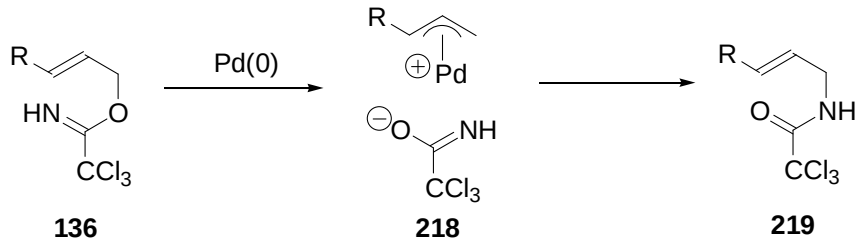
Figure 34

These catalysts were successfully employed in a number of rearrangements, an example of which is the synthesis of the anti-convulsant (*S*)-vigabatrin **217** (**Scheme 58**).[80c] This compound is a GABA aminotransaminase inhibitor and is used for the treatment of drug-resistant epilepsy, complex partial seizures and infantile spasms due to West Syndrome.[128] It is marketed as a racemic mixture under the name of Sabril® in Canada, Mexico and the United Kingdom, although only the (*S*)-isomer is pharmacologically active. The *E*-allylic alcohol **214** is converted to the trichloroacetimidate **215** using trichloroacetonitrile and DBU. The rearrangement is carried out using 5 mol % of COP-Cl catalyst **213** at room temperature and leads to the (*S*)-trichloroacetamide **216** in 73% yield over 2 steps and 95% e.e. Acidic cleavage of the trichloroacetyl and ester groups yields **217** in 75% yield. This synthesis illustrates the potential applications of this asymmetric rearrangement.



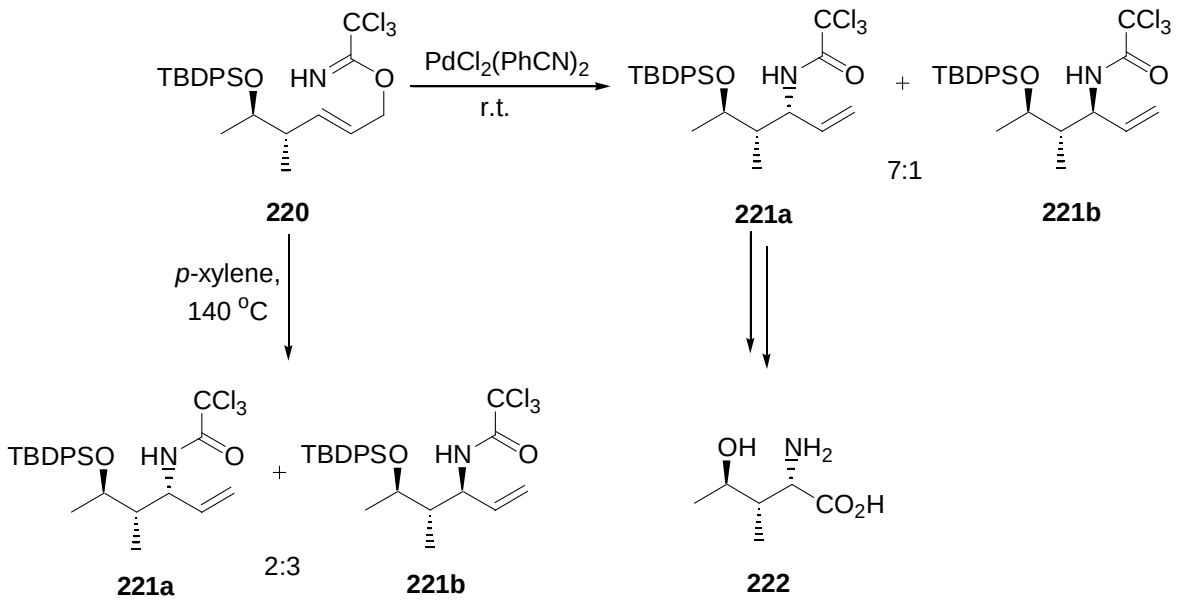
Scheme 58

It is also noted that the rearrangements have sometimes been unsuccessful due to competing elimination reactions, slow reaction rates and competing 1,3-rearrangements (anti-Claisen). 1,3-Rearrangements are known to be promoted by palladium(0) catalysts (**Scheme 59**).[80c]

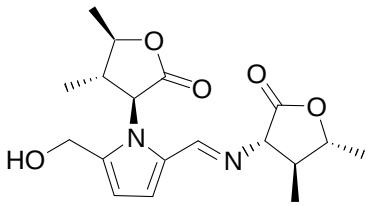


Scheme 59

Our group has recently reported the synthesis of (2*S*,3*S*,4*R*)-γ-hydroxyisoleucine **222** using a palladium(II)-catalysed aza-Claisen rearrangement to create the (3*S*)-stereogenic centre (**Scheme 60**).[2a] The rearrangement was also carried out under thermal conditions in *p*-xylene at 140 °C. This led to the undesired (3*R*)-isomer **221b** being the major product. Under the palladium(II)-catalysed conditions at room temperature, the desired (3*S*)-stereoisomer **221a** was favoured in a 7:1 ratio over the (3*R*)-stereoisomer. This was used to produce (2*S*,3*S*,4*R*)-γ-hydroxyisoleucine **222** which is the amino acid component of the natural product funebrine **223**, a pyrrole alkaloid (**Figure 35**).



Scheme 60



223

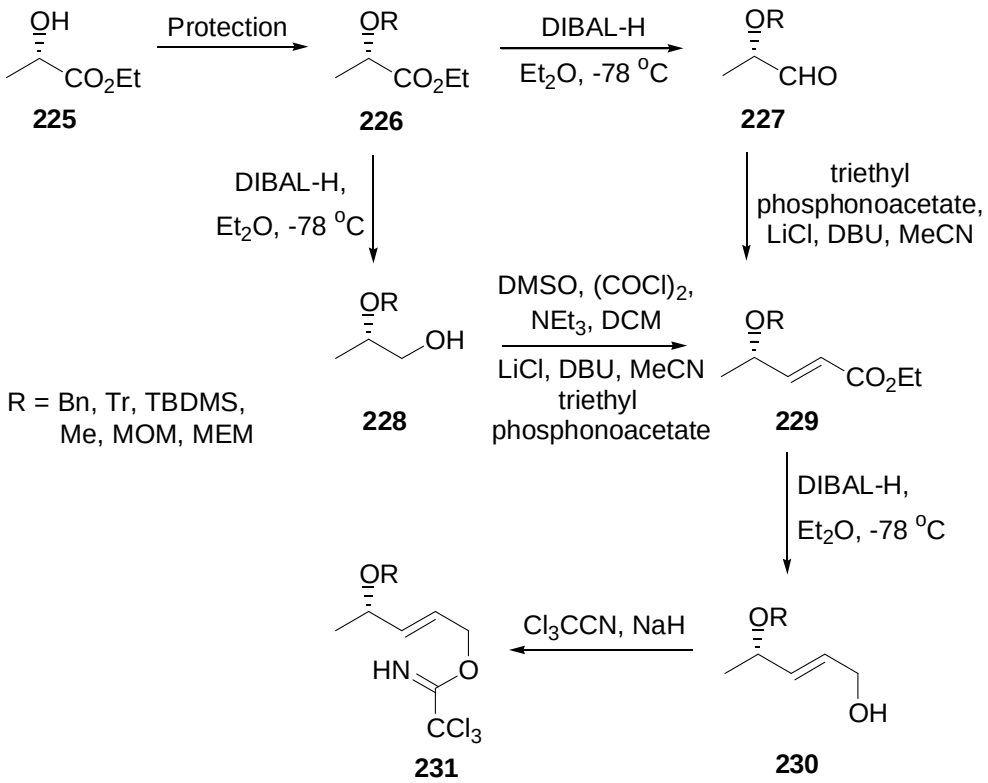
Figure 35

The stereoselectivity of this rearrangement can be explained by considering the transition states.[120,129] In both the thermal and palladium(II)-catalysed rearrangements, a chair-like transition state is formed in which the 1,3-allylic strain is minimised (**Figure 36**). In the case of the thermal rearrangement **224a**, intramolecular attack occurs at the least hindered face giving predominantly the (3*R*)-stereoisomer. With the palladium(II)-catalysed rearrangement **224b**, initial coordination of the catalyst to the least hindered face of the alkene blocks this from intramolecular attack of the internal nitrogen nucleophile.

Therefore, attack has to take place from the back face of the alkene, giving predominantly the (3*S*)-stereoisomer.

Figure 36

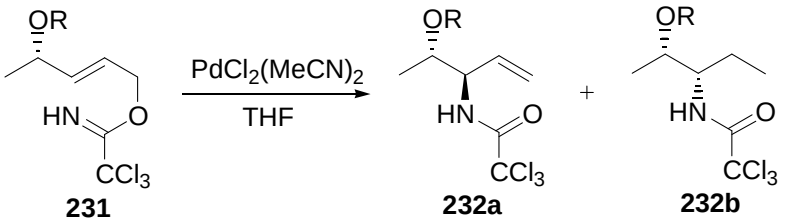
Following on from this work, our group also developed an ether-directed aza-Claisen rearrangement.[2b] It was thought that small, sterically unhindered groups could effectively coordinate to the catalyst and direct it towards a particular face of the alkene. A series of trichlororacetimidates **231** were prepared from ethyl (*S*)-lactate **225** (**Scheme 61**).



Scheme 61

The precursors were then subjected to a palladium(II)-catalysed rearrangement using bis(acetonitrile)palladium(II)-chloride catalyst. (**Scheme 62**) As was expected, the bulky ether groups such as TBDMS and benzyl gave low selectivities as they prevent effective coordination of the catalyst to the alkene. The smaller and less sterically hindered methyl

ether resulted in increased diastereoselectivity. It was then shown that the MOM ether, which contained a second oxygen, gave a diastereoselectivity of 10:1 *anti*:*syn*. A third oxygen was then introduced using the MEM ether in an attempt to further increase the directing effect and the selectivity. However, compared to the MOM-group, a decrease was observed in the selectivity to 8:1 *anti*:*syn*.

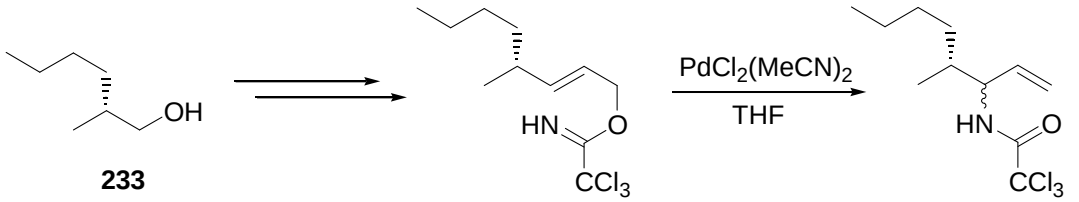


231 **232a** **232b**

R	Yield	Ratio *anti*:*syn*
TBDMS	68%	2:1
Tr	70%	3:1
Bn	62%	3:1
Me	49%	7:1
MOM	64%	10:1
MEM	60%	8:1

Scheme 62

To prove that the positive influence observed with the MOM-group stems from the presence of oxygen, a carbon analogue **234** was synthesised and subjected to the palladium(II)-catalysed rearrangement (**Scheme 63**). The major diastereomer was obtained in only a 2:1 ratio, showing that the oxygen is necessary for the directing effect.



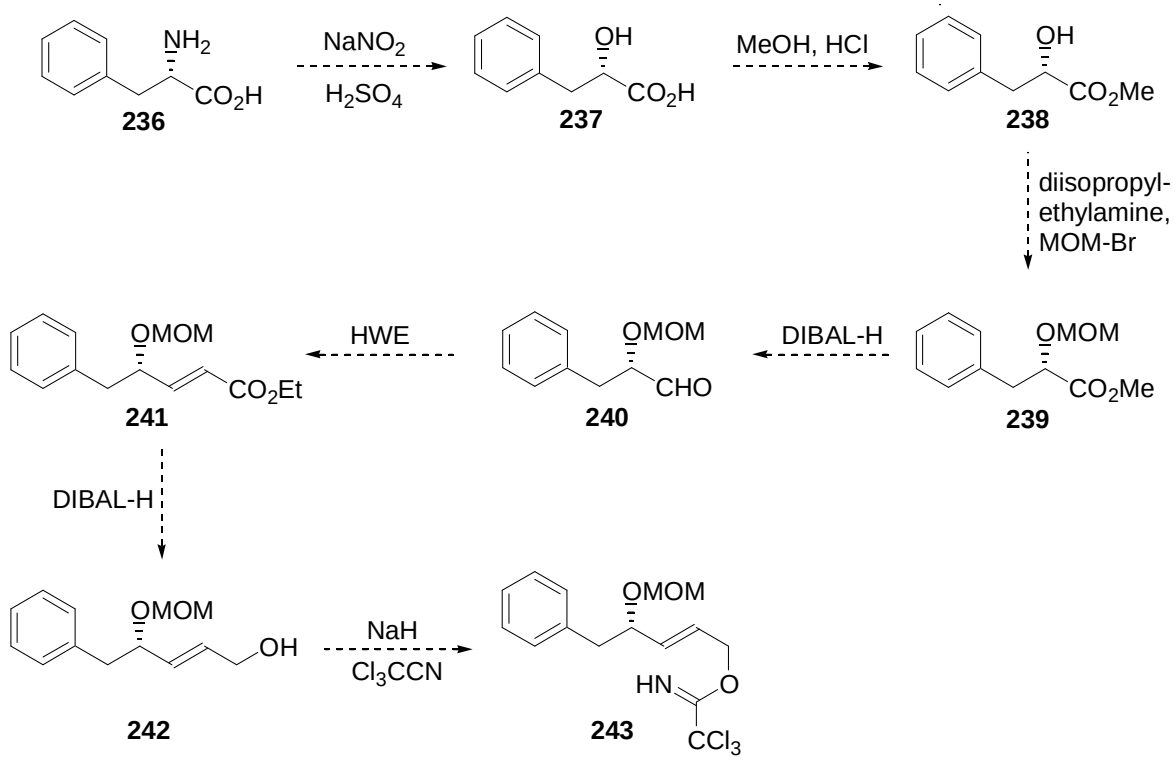
233 **234** 2:1 *anti*:*syn* **235**

Scheme 63

As this general scheme had worked well for the synthesis of trichloroacetimidates, we wanted to continue to use it in our work towards the synthesis of β-hydroxy-α-amino acids. We also wanted to use the general method to further investigate the effect of other directing groups on the rearrangement.

2.2 Use of the Directed Rearrangement for the Synthesis of β-hydroxy-α-amino acids

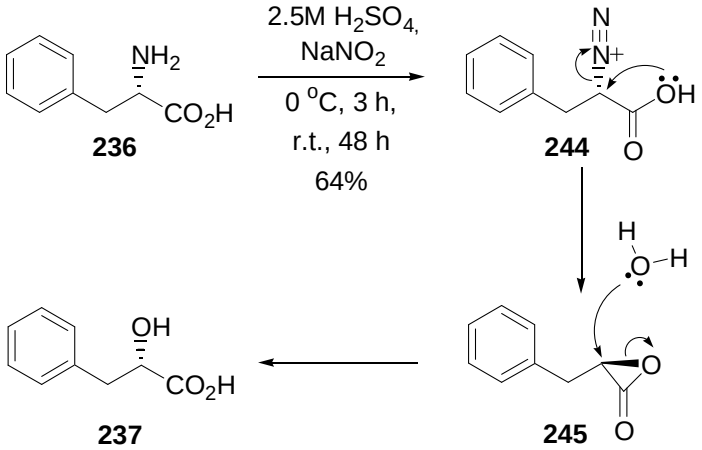
As discussed, preliminary studies have shown that chiral ether groups can be used to direct the stereoselectivity of these aza-Claisen rearrangements.[2b] We wanted to investigate the effects of other directing groups and additional stereogenic centres within the substrate to improve results already obtained. We wanted to incorporate a large bulky side chain and see what effect this would have on the stereoselective outcome of the rearrangement. We also wanted to continue to use the general flexible route which had previously been used to synthesise rearrangement precursors with great success. To this end, we modified the general route to derive the bulky side chain from L-phenylalanine **236** (**Scheme 64**). The synthesis begins with L-phenylalanine **236** and the amino acid is converted into the α-hydroxy analogue **237**. Following this, the acid is protected as the methyl ester to give **238**. The hydroxy group is then MOM-protected to give **239** and the methyl ester is reduced to the corresponding aldehyde **240**. Aldehyde **240** is transformed to the α,β-unsaturated ethyl ester **241** *via* a Horner-Wadsworth-Emmons reaction, and the subsequent ester is reduced to the *E*-allylic alcohol **242** using diisobutylaluminium hydride (DIBAL-H). Finally, the trichloroacetimidate group is incorporated to yield the rearrangement precursor **243**.



Scheme 64

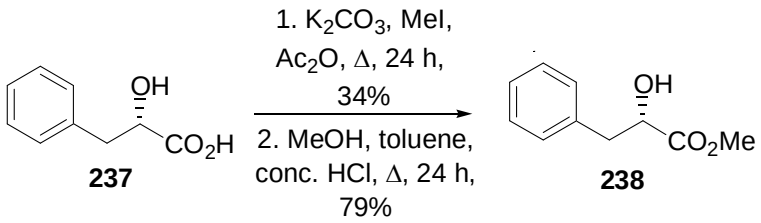
Thus, L-phenyalanine **236** was converted to the α-hydroxy analogue *via* the diazonium salt **244**, by reaction with sulfuric acid (H_2SO_4) and sodium nitrite (**Scheme 65**).[130] Initially,

1M H_2SO_4 was used and the mixture was stirred at 0 ^oC for 1 hour and then at room temperature for 12 hours, however this led to a complex mixture of compounds. Following optimisation, 2.5M H_2SO_4 was used and the reaction mixture was stirred at 0 ^oC for 3 hours and at room temperature for 48 hours. α-Hydroxy acid **237** was isolated in 64% yield as a crystalline solid and this was used in the next step without further purification. In the ^1H NMR spectrum of **237** the 3-CH_2 protons are seen as 2 separate signals, due to the influence of the adjacent chiral centre pushing these protons into non-equivalent chemical environments. These two doublet of doublets appear at 2.92 and 3.13 ppm in the ^1H NMR spectrum. This is a feature that is generally maintained throughout the ^1H NMR spectra of this series of compounds.



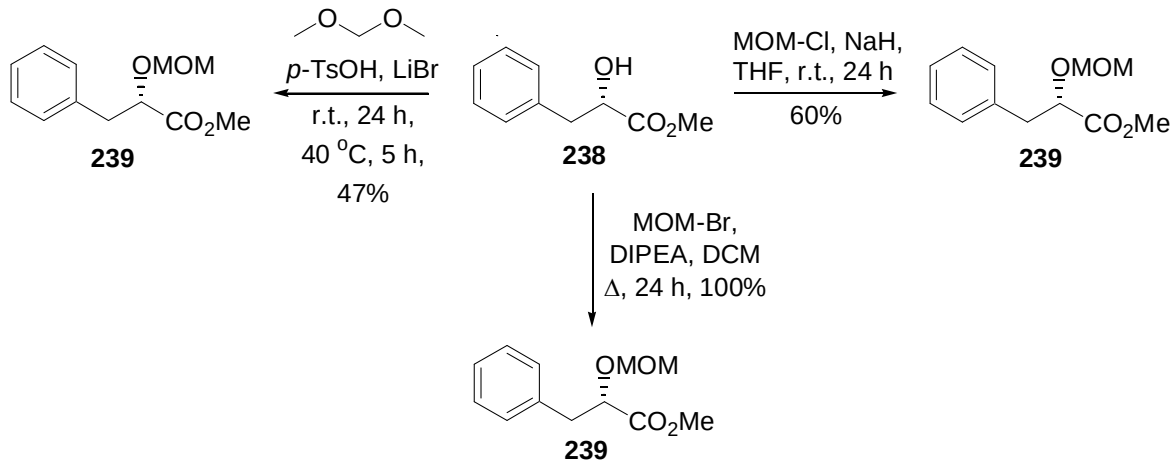
Scheme 65

α-Hydroxy acid **237** was used in the second step of the synthesis, which involved esterification of the acid. Two methods were used to attempt this conversion. Initially, we used potassium carbonate and methyl iodide in acetone and the reaction was heated under reflux for 24 hours (**Scheme 66**).[131] While this was successful to some degree, the maximum isolated yield of **238** following purification was 34%. The second method attempted was a modification of the method by Kano and co-workers.[132] Methanol, toluene and concentrated hydrochloric acid were heated under reflux with **237** for 24 hours. Following purification by Kugelrohr distillation, **238** was isolated in 79% yield, a significant improvement from before.



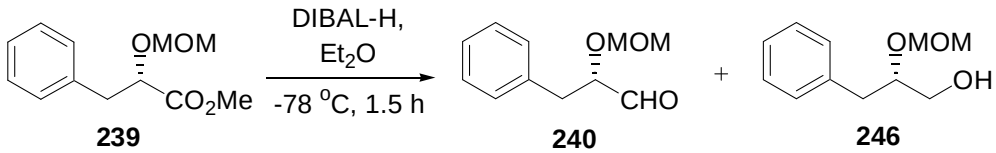
Scheme 66

MOM-protection of **238** was initially attempted by treating **238** with dimethoxymethane, lithium bromide and *p*-toluenesulfonic acid (**Scheme 67**).[133] The mixture was stirred at room temperature overnight and then, following TLC, warmed to 40 ^{o}C for 5 hours to drive the reaction to completion. Unfortunately, following purification by column chromatography, only 47% of **239** was isolated along with starting material. The reaction was attempted again by treating **238** with sodium hydride and chloromethylmethyl ether (MOM-Cl). This solution was stirred at room temperature for 24 hours and **239** was isolated in 60% yield. Due to difficulty in obtaining MOM-Cl and also the toxic nature of this reagent, a third method was attempted using more readily available and less volatile bromomethylmethyl ether (MOM-Br). Reaction of **238** with MOM-Br in the presence of diisopropylethylamine (DIPEA – Hünig's base) under reflux for 24 hours gave **239** in quantitative yield.



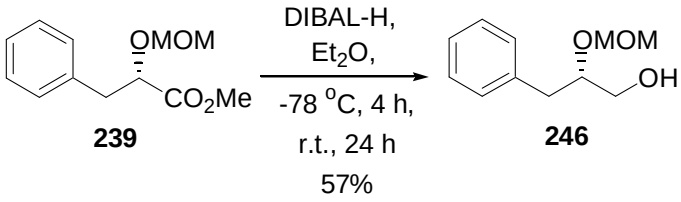
Scheme 67

Following protection of the hydroxy group, the next step was reduction of the methyl ester to the aldehyde **240**. This was initially attempted using approximately one molar equivalent of a DIBAL-H (**Scheme 68**). Unfortunately, the reaction was very difficult to control and resulted in mixtures of the aldehyde **240** and the corresponding alcohol **246**. In some reactions, some of the starting ester **239** was left unreduced. These compounds were very difficult to separate by column chromatography.



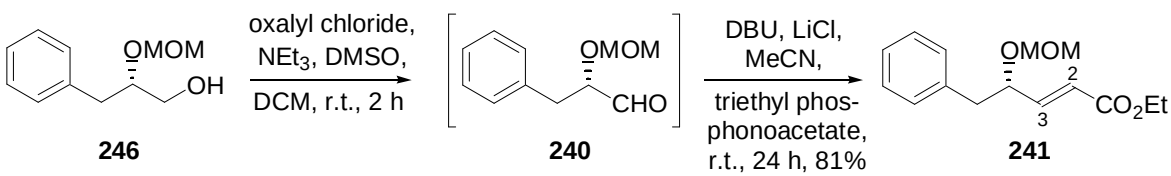
Scheme 68

Thus, it was decided that reduction of the ester **239** to the corresponding alcohol **246** would be easier to control. The alcohol **246** would then be re-oxidised to the aldehyde **240** and the Horner-Wadsworth-Emmons reaction could be carried out, as was planned initially. The reduction was carried out using 2.2 molar equivalents of DIBAL-H (**Scheme 69**). Following purification by column chromatography, **246** was isolated in 57% yield.



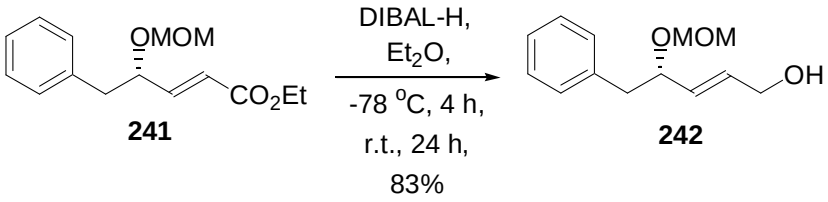
Scheme 69

To transform the alcohol **246** to the α,β-unsaturated ethyl ester **241** a one-pot Swern/Horner-Wadsworth-Emmons reaction was used so that the aldehyde **240** would not have to be isolated (**Scheme 70**). The Swern reaction was carried out under standard oxidation conditions with dimethyl sulfoxide, oxalyl chloride and triethylamine to give the aldehyde **240**. Following this, the Horner-Wadsworth-Emmons reaction was carried out under Masamune-Roush conditions.[134] These milder conditions are particularly useful for base-sensitive substrates, such as the aldehyde **240**. Standard Horner-Wadsworth-Emmons conditions use sodium hydride as base to deprotonate the phosphonate. However, Masamune-Roush conditions enable the use of DBU as base. Addition of lithium chloride enhances the acidity of the phosphonate and therefore, a weaker base and ambient temperature can be employed. The change in conditions does not affect the *E*-selectivity of the reaction. Following purification by column chromatography, **241** was isolated in 81%. In the ^{1}H NMR spectrum the signals for the CH_2 and CH_3 protons of the ethyl ester are observed at 4.23 and 1.32 ppm respectively. The protons of the *E*-alkene are seen as a doublet at 6.01 ppm for 2-H and a doublet of doublets at 6.90 ppm for 3-H. The coupling constant between these signals (15.6 Hz) confirms the formation of the *E*-alkene.



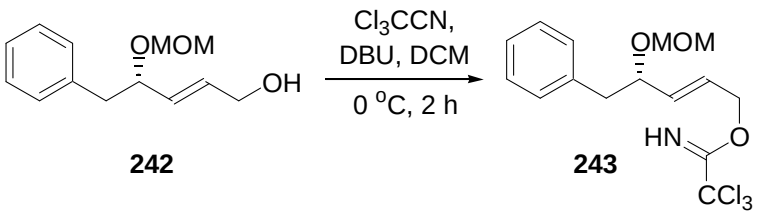
Scheme 70

The α,β-unsaturated ethyl ester **241** was then reduced to the corresponding *E*-allylic alcohol **242**. Just as with the reduction before, DIBAL-H was used and **242** was isolated in 83% yield (**Scheme 71**).



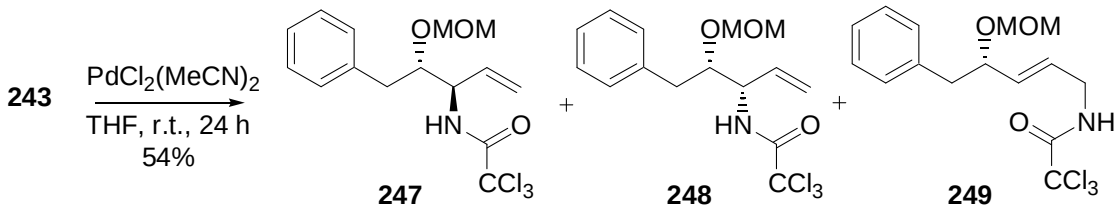
Scheme 71

The last step to synthesise the rearrangement precursor was incorporation of the trichloroacetimidate group. This was carried out by reaction of **242** with trichloroacetonitrile and DBU (**Scheme 72**). Initially, sodium hydride was used as the base, but it was found that DBU gave reliably higher yields. This was followed by flash column chromatography through a plug of silica. This gave **243** which was used immediately in the rearrangement without further purification, as **243** decomposes over a short period of time.



Scheme 72

The rearrangement was carried out by treating **243** with 0.1 molar equivalents of bis(acetonitrile)palladium(II) chloride catalyst in THF (**Scheme 73**). This was stirred at room temperature for 24 hours. The desired *anti*-product **247** was produced with a 12:1 diastereoselectivity, which is an excellent 85% d.e. The yield of the two diastereomers combined is 54% over 2 steps. The CH_2 and CH protons of the terminal alkene can be observed in the ^{1}H NMR spectrum of the *anti*-product at 5.43-5.45 and 5.93-6.02 ppm respectively. This was confirmed as the *anti*-product through correlation with previous spectra.[2b] The corresponding signals in the ^{1}H NMR spectrum of minor *syn*-product are observed at 5.25-5.29 and 5.55-5.60 ppm respectively. Also observed in trace amounts was the 1,3-rearrangement by-product **249**, normally seen when a palladium(0) catalyst is used.[135] It was believed that the palladium(0) was formed by a competing β-elimination process during the slow palladium(II)-catalysed rearrangement.



Scheme 73

The palladium catalyst coordinates to both oxygens in the MOM-group and also to the alkene as shown in **Figure 37.** This effectively blocks the back face of the alkene and directs the attack to take place from the front face.

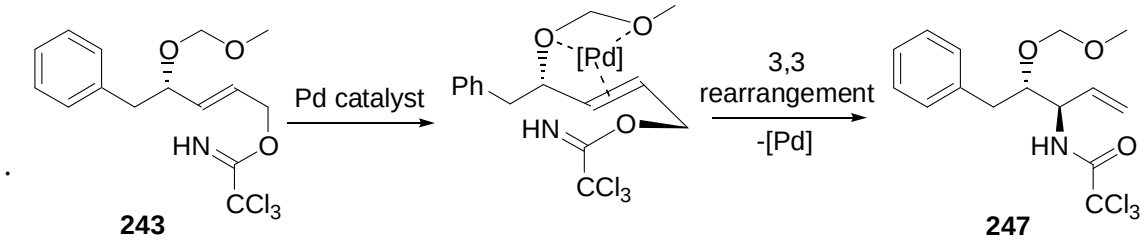
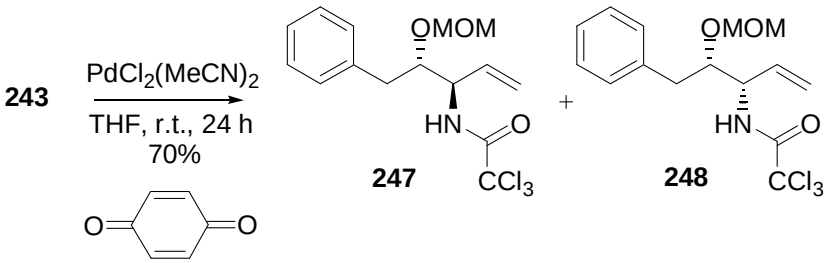


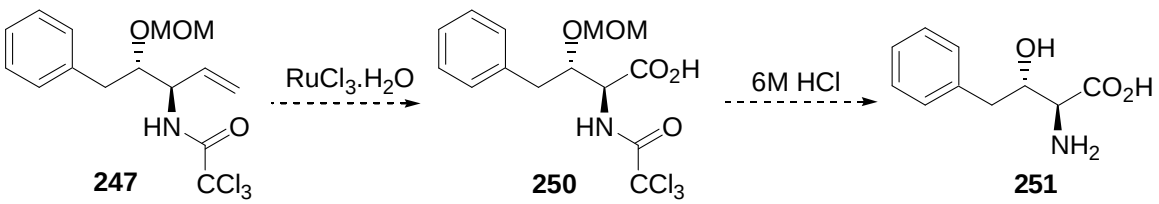
Figure 37

Addition of the mild oxidant *p*-benzoquinone to the reaction mixture effectively re-oxidised any palladium(0) formed back to palladium(II) (**Scheme 74**). This resulted in a greater yield of the 3,3-products though the stereoselectivity remains the same. The yield of **247** and **248** combined increased to 70% over 2 steps when the re-oxidant was used.



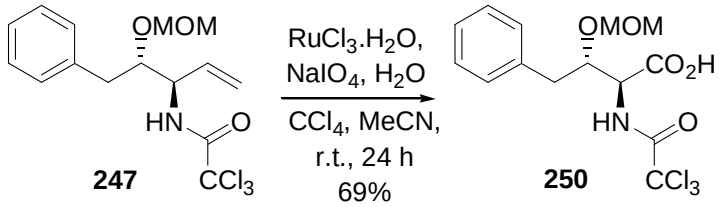
Scheme 74

The desired diastereomer **247** was then to be oxidised to the corresponding amino acid **251** (**Scheme 75**). To achieve this, the terminal double bond of **247** is oxidised to the acid using the method of Sharpless and then the trichloroacetamide and MOM-protecting groups are removed with 6M HCl.[136]



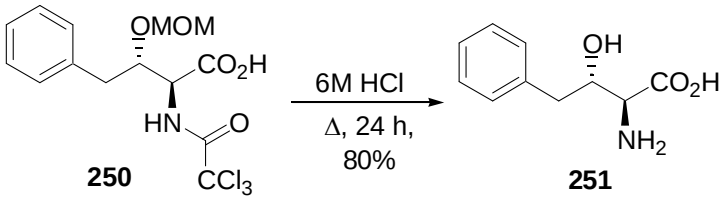
Scheme 75

Allylic amide **247** was therefore treated with ruthenium trichloride and sodium *m*-periodate at room temperature (**Scheme 76**). Following a short silica column to remove any ruthenium resides, **250** was isolated in 69% yield. In the ^{1}H NMR spectrum, the signals seen previously for the terminal alkene are no longer observed. In the ^{13}C NMR spectrum, a new quaternary peak is seen at 172.3 ppm which corresponds to the carbonyl carbon of the acid.



Scheme 76

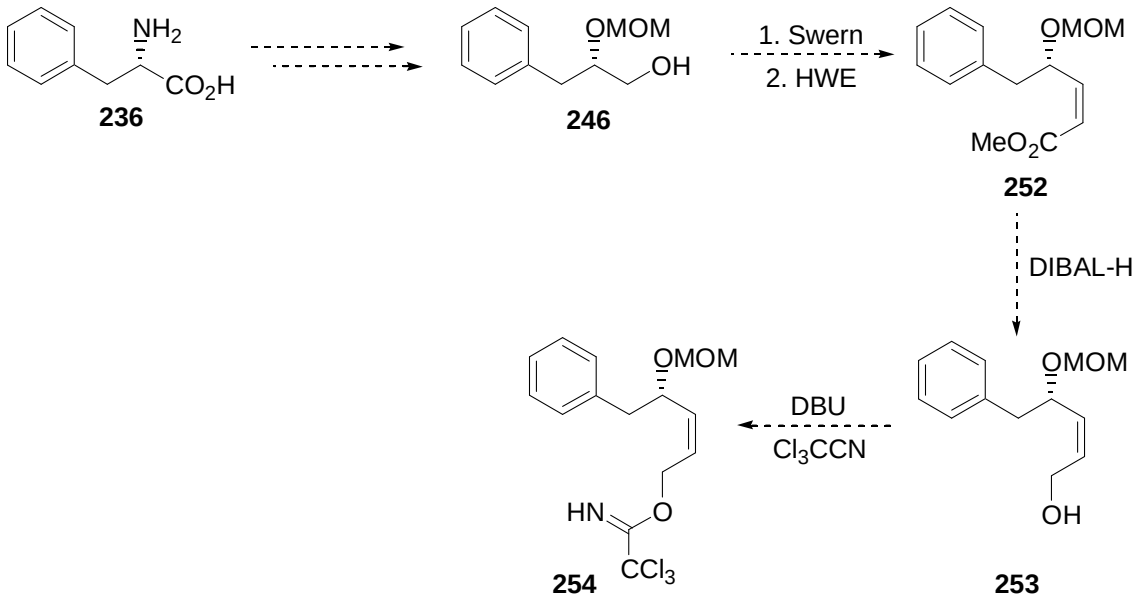
Removal of the trichloroacetamide and MOM-protecting groups was achieved by heating **250** and 6M HCl under reflux for 24 hours (**Scheme 77**). The amino acid **251** was isolated in 80% yield. The spectroscopic data and optical rotation for this amino acid corresponds to the literature data, confirming the stereochemical outcome of the rearrangement.[137]



Scheme 77

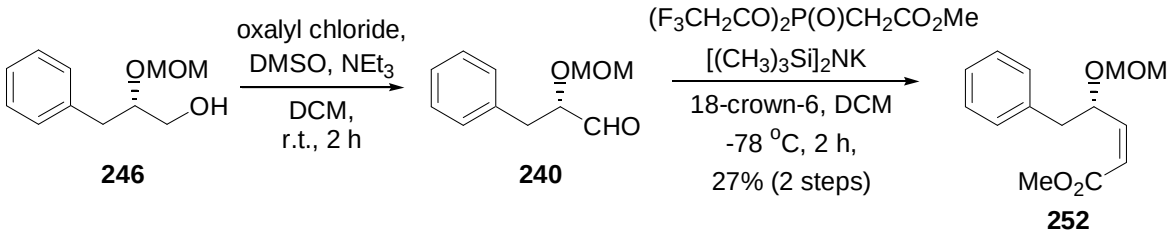
2.3 Investigation of New Substrates for the Directed Rearrangement

Due to the success of this route involving an *E*-alkene in the synthesis, it was decided to change this to a *Z*-alkene to see how this would affect the outcome of the rearrangement. The MOM-protecting group and the benzyl side chain were not changed. Thus, the synthesis begins with L-phenylalanine **236** again which is converted to the MOM-protected alcohol **246** as before (**Scheme 78**). This will be oxidised to the corresponding aldehyde **240** using a Swern reaction and then the α,β-unsaturated methyl ester **252** will be synthesised using a Horner-Wadsworth-Emmons reaction. Following the same steps as for the synthesis involving the *E*-alkene, the α,β-unsaturated ester **252** is reduced to the *Z*-allylic alcohol **253** using DIBAL-H and the trichloroacetimidate is incorporated to give the rearrangement precursor **254**.



Scheme 78

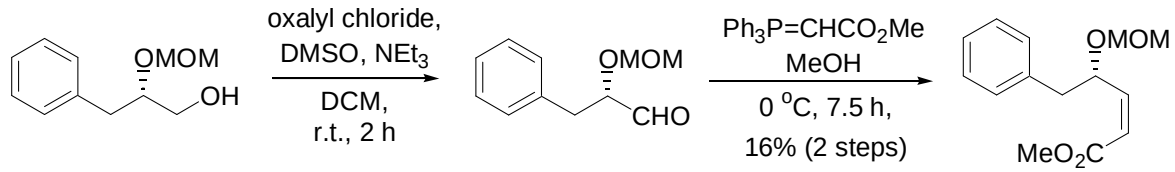
Therefore, **246** was treated with dimethyl sulfoxide, oxalyl chloride and triethylamine to give the aldehyde **240** as before (**Scheme 79**). To convert **240** to the corresponding *Z*-alkene, the Still modification of the Horner-Wadsworth-Emmons reaction was employed.[138] Using phosphonates with electron-withdrawing groups, such as trifluoroethyl, together with strongly dissociating conditions (such as KHMDS and 18-crown-6) favours rapid elimination and almost exclusive *Z*-alkene selectivity. Therefore, **240** was treated with 18-crown-6, bis(2,2,2-trifluoroethyl)(methoxycarbonylmethoxy)phosphonate and potassium-bis(trimethylsilyl)amide at -78 ^{o}C for 2 hours. Following purification by column chromatography, **252** was isolated in 27% over two steps. The coupling constant of 11.6 Hz between the alkene signals in the ^{1}H NMR spectrum, confirmed that the *Z*-alkene had been synthesised.



Scheme 79

Due to the rather low yield of this reaction, it was decided to attempt to synthesise **252** using a Swern and a Wittig reaction (**Scheme 80**). Thus, the Swern reaction was carried out as before to give **240**. The Wittig reaction can be carried out using stable ylides to give *E*-alkenes. More reactive (unstable) ylides give rapid reactions and subsequent rapid ring opening to give the *Z*-alkene. In our Wittig reaction, a stable ylide was used under kinetic

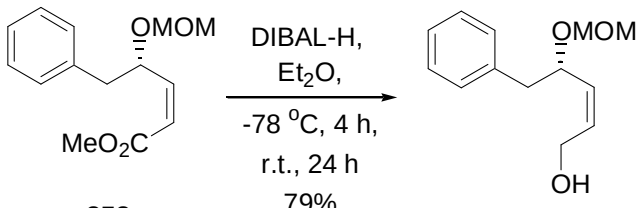
conditions to give the *Z*-alkene. The reason for this is that non-stabilised ylides tend to require strong base under inert conditions and this would not be suitable for our intermediate **240**. Thus, methyl (triphenylphosphoranylidene)acetate bromide was treated with NaOH to give the Wittig reagent, methyl (triphenylphosphoranylidene)acetate. The crude aldehyde **240** was then treated with the Wittig reagent in methanol at 0 ^{o}C for 7.5 hours.[139] After purification, **252** was isolated in just 16% yield.



246 **240** **252**

Scheme 80

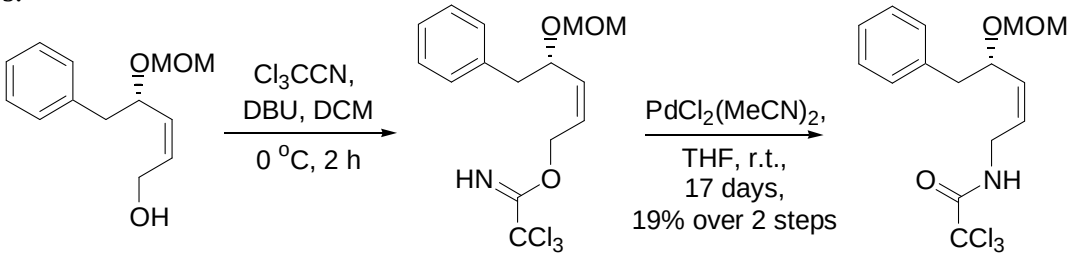
Despite neither of these reactions being particularly successful in terms of yield, at this point we had enough material to continue to the next step. Reduction of the α,β-unsaturated methyl ester **252** to the *Z*-allylic alcohol **253** was carried out using DIBAL-H (**Scheme 81**). Following work-up, **253** was isolated in 79% yield.



252 **253**

Scheme 81

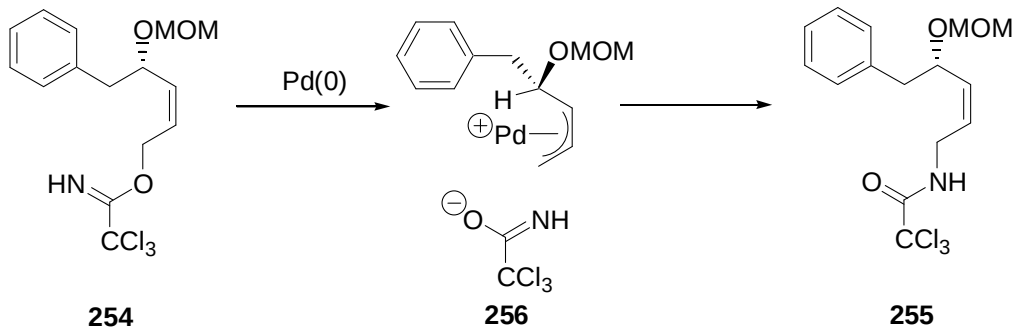
The allylic trichloroacetimidate was synthesised using the same method as before, with trichloroacetonitrile and DBU (**Scheme 82**). Again, **254** is unstable and prone to decomposition so it was used directly in the rearrangement step. This was carried out using the same catalyst as before, bis(acetonitrile)palladium(II) chloride. The reaction was stirred for 17 days (an extra 5 mol % of catalyst was added after 3 days). After purification, the major product isolated resulted from 1,3-rearrangment to give **255** in 19% yield over 2 steps.



253 **254** **255**

Scheme 82

As stated before, the 1,3-rearrangement is normally catalysed by palladium(0).[135] When the reaction progresses slowly, the palladium can be eliminated through competing β-elimination and reduce to palladium(0). Unusually, the stereochemistry of the *Z*-alkene was retained, as normally one would expect it to convert to the more stable *E*-configuration during the 1,3-rearrangement. This however, is prevented by the coordination of the palladium as can be seen in the transition state **256** (**Scheme 83**).

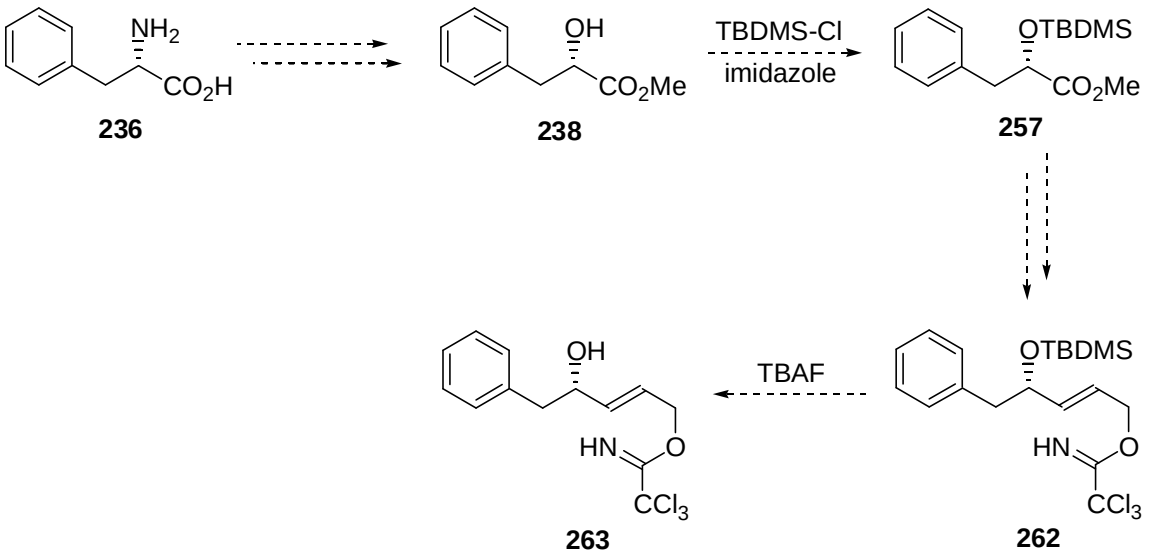


254 **256** **255**

Scheme 83

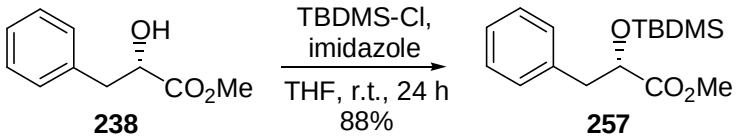
Following this interesting result, we progressed to another aspect of the rearrangement, namely substituting the MOM-protecting group for one that should coordinate to palladium more strongly. During the MOM-ether directed rearrangements, the MOM group coordinates to the catalyst and directs it towards to back face of the alkene. Due to the palladium(II) blocking this face of the alkene, the internal nitrogen nucleophile preferentially attacks at the less-hindered front face of the alkene. It was therefore proposed that a stronger bond to the palladium(II) catalyst may produce a more diastereoselective rearrangement.

Firstly, we investigated the outcome of the rearrangement of the unprotected hydroxy precursor **263**. The initial route to this rearrangement precursor is outlined below (**Scheme 84**). Again, we wanted to maintain the bulky side chain and so the synthesis began from L-phenylalanine **236**. It was decided to use the TBDMS-group throughout the synthetic scheme as it can be removed effectively and mildly when needed. As before, L-phenylalanine **236** is converted to the α-hydroxy acid **237** and then to the methyl ester **238**. The methyl ester **238** is protected with a TBDMS-group, by reaction with TBDMS-Cl and imidazole to give **257**. This is reduced to the alcohol **258** using DIBAL-H and this is then converted to the α,β-unsaturated ester **260** using a one-pot Swern/Horner-Wadsworth-Emmons reaction as before. Ester **260** is again reduced to the *E*-allylic alcohol **261** using DIBAL-H and the trichloroacetimidate group is incorporated to give **262**. The TBDMS-group is then removed using TBAF to give the unprotected rearrangement precursor **263**.



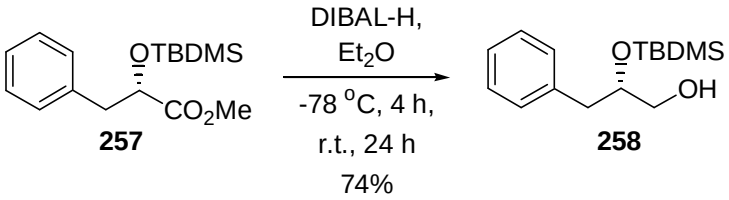
Scheme 84

Thus, L-phenylalanine was converted to the methyl ester **238** as before. Following this, **238** was protected with a TBDMS-group by treating **238** with TBDMS-Cl and imidazole (**Scheme 85**).[140] Following purification, **257** was isolated in 88% yield.



Scheme 85

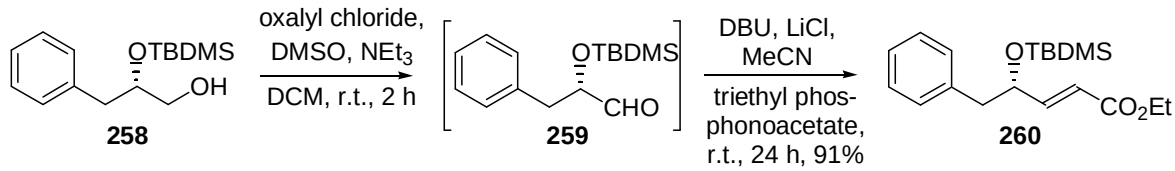
Following this, the methyl ester **257** was reduced to the alcohol **258** using DIBAL-H (**Scheme 86**). This reaction worked well and **258** was isolated in 74% yield.



Scheme 86

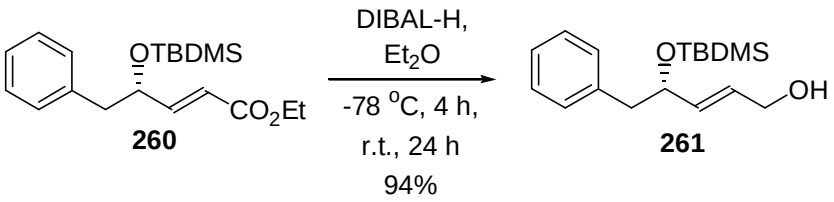
The alcohol **258** was converted to the α,β-unsaturated ethyl ester **260** without isolating the sensitive aldehyde **259** *via* a one-pot Swern/Horner-Wadsworth-Emmons reaction as before (**Scheme 87**). Standard Swern reaction conditions were used to synthesise the aldehyde, which was then converted to the α,β-unsaturated ethyl ester under Masamune-Roush conditions. Following purification by column chromatography, **260** was isolated in 91% yield. The signals in the ^{1}H NMR spectrum for the alkene protons are observed at

6.07 and 7.02 ppm. The coupling constant between these signals is 15.4 Hz, which confirms the formation of the *E*-alkene.



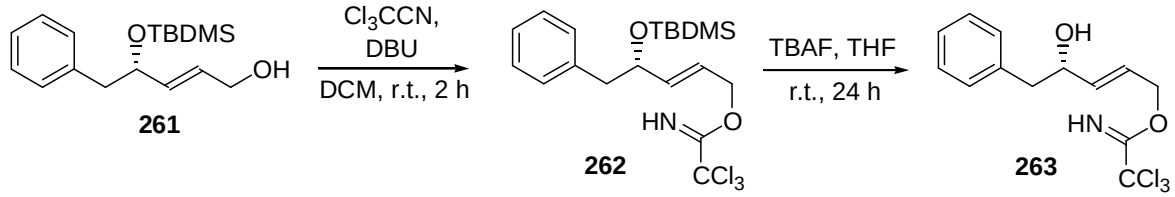
Scheme 87

The α,β-unsaturated ethyl ester **260** was reduced to the *E*-allylic alcohol **261** using DIBAL-H (**Scheme 88**). One of the concerns here was that there could be protecting group migration from the secondary to the primary alcohol but this was not observed. Following purification by column chromatography, **261** was isolated in an excellent 94% yield.



Scheme 88

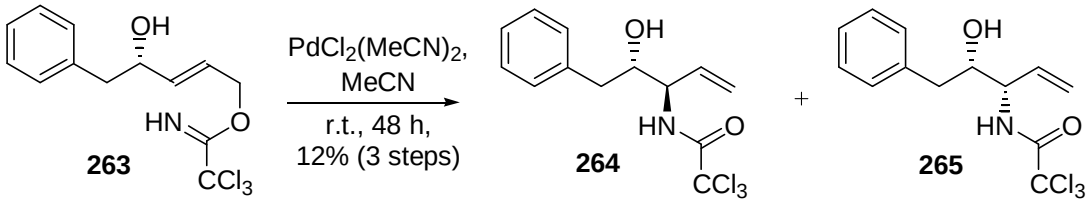
Following this, the remaining steps to the unprotected precursor involve addition of the trichloroacetimidate group and removal of the TBDMS-group. The allylic trichloroacetimidate was prepared as before, using trichloroacetonitrile and DBU (**Scheme 89**). The precursor **262** was used in the deprotection step without further purification. To remove the TBDMS-group, **262** was treated with TBAF. Again, **263** is not a particularly stable compound and is prone to decomposition and as such, it was passed through a short silica plug and used in the rearrangement without further purification.



Scheme 89

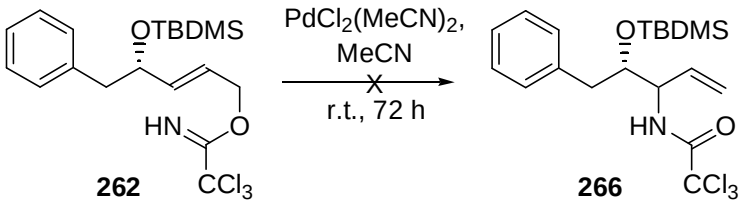
Finally, the hydroxy precursor **263** was subjected to a palladium(II)-catalysed rearrangement (**Scheme 90**). Allylic acetimidate **263** was treated with bis(acetonitrile)palladium(II) chloride in THF at room temperature for 48 hours. Following purification by column chromatography, it was found that ratio of *anti*:*syn* diastereomers is

6:1. This corresponds to a good 71% d.e. The yield of this reaction is 12% over three steps. The CH_2 and CH signals for the *anti*-product are observed in the ^1H NMR spectrum at 5.32-5.37 and 5.87-5.96 ppm respectively. The corresponding signals for the *syn*-product are seen at 5.22-5.27 and 5.74-5.85 ppm. This result shows that the MOM-group has a positive influence on the reaction as it increases the diastereoselectivity for the *anti*-diastereomer. Subsequent work has been carried out by our group which shows that the second oxygen in the MOM-group is critical for high diastereoselectivity.[2b] It is believed that the palladium(II) coordinates to both oxygens of the protecting group which then direct the catalyst to the back face of the alkene to give increased selectivity.



Scheme 90

Out of curiosity, we attempted the rearrangement of the TBDMS-protected precursor **262**, as we had already synthesised it during the route to the unprotected precursor **263**, even though it is a hindered ether. Thus, **262** was subjected to the rearrangement using the bis(acetonitrile)palladium(II) chloride catalyst as before (**Scheme 91**). Unfortunately, there was no reaction observed after 3 days at room temperature. In this case, it was thought that the combination of the bulky TBDMS-protecting group and the benzyl side chain was preventing the palladium(II) catalyst from coordinating to the alkene and inducing the rearrangement.

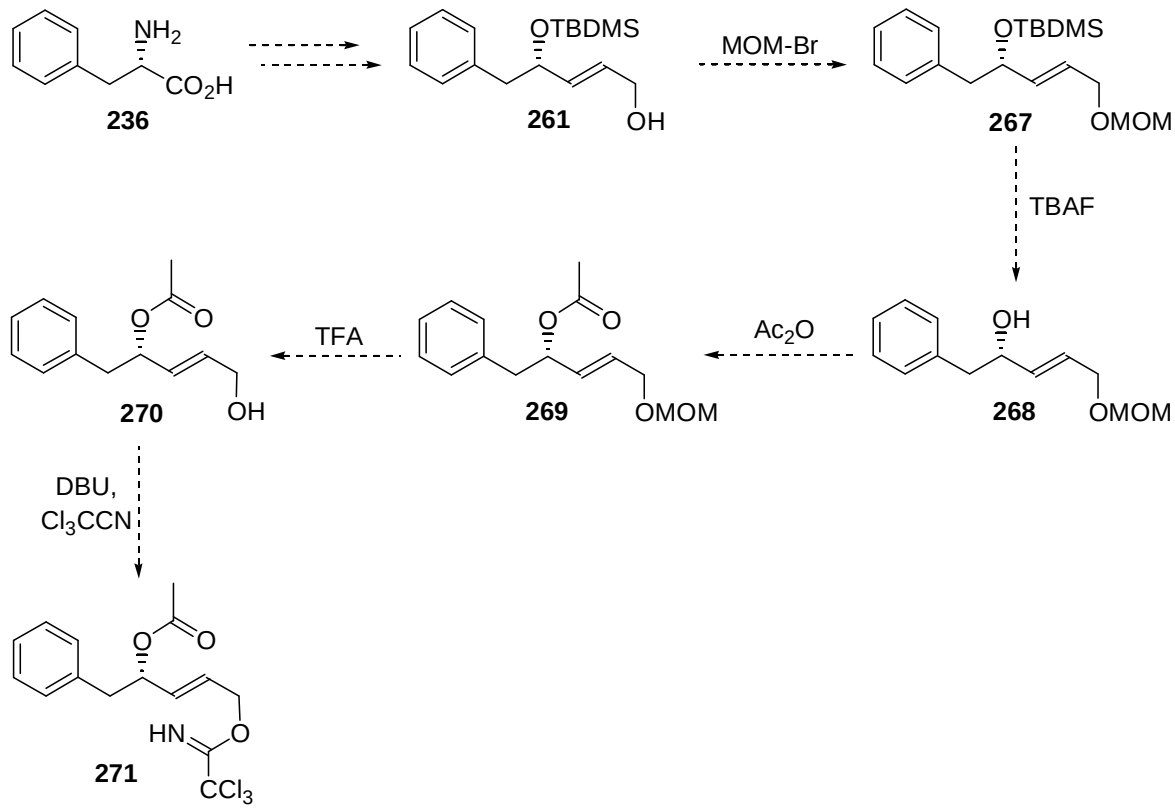


Scheme 91

Another protecting group was chosen with which to perform the rearrangement. We chose a group that was less bulky than the TBDMS-group and that had two oxygens in it. The acetate group fitted this profile well and its structure is quite similar to that of the MOM-group with which we had achieved excellent selectivity. Again, we wanted to use a variation on the optimised route we had already developed with some protecting group manipulation. Thus, it was decided that the acetate-protected rearrangement precursor **271** should be synthesised as outlined below (**Scheme 92**). The synthesis is the same as that

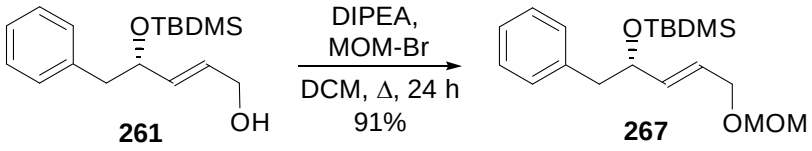
used to obtain the unprotected and TBDMS-protected precursors to the point where the trichloroacetimidate group is added. As stated before, the precursors for the rearrangement are unstable and prone to decomposition. Therefore, we wanted to incorporate the acetate group before we incorporated the trichloroacetimidate group, so we could proceed immediately to the rearrangement itself, without risking decomposition of the precursor.

Beginning from the TBDMS-protected allylic alcohol **261**, which was derived from L-phenylalanine **236** as before, the alcohol is MOM-protected to give **267**. The TBDMS-group is then removed using TBAF to give **268**. The exposed alcohol is re-protected with an acetate group using acetic anhydride to give **269**. The MOM-group can then be removed, in the presence of the acetate group, using trifluoroacetic acid to give the *E*-allylic alcohol **270**. The trichloroacetimidate is synthesised under the usual conditions to give the unstable rearrangement precursor **271**, which can be used immediately in the rearrangement step without the need for further manipulation.



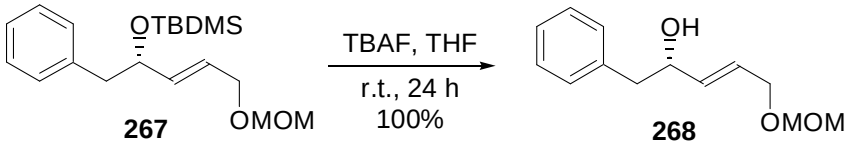
Scheme 92

Therefore, the *E*-allylic alcohol **261** was subjected to a MOM-protection using MOM-Br and DIPEA (**Scheme 93**). The solution was heated under reflux for 24 hours. Following purification, **267** was isolated in 91% yield.



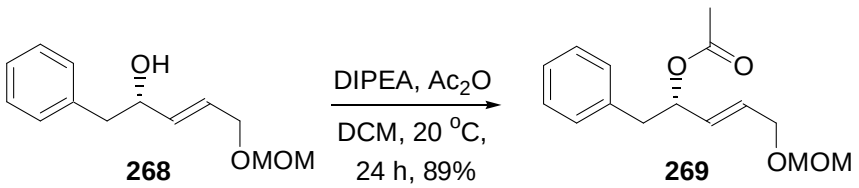
Scheme 93

Compound **267** was used in the next step, which involved removal of the TBDMS-group. Silyl ether **267** was treated with TBAF and the solution was then stirred at room temperature for 24 hours (**Scheme 94**). Following purification, **268** was isolated in a quantitative yield.



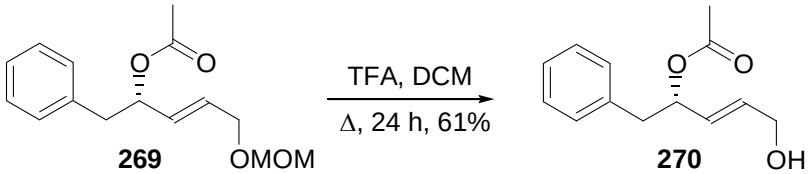
Scheme 94

The next step was re-protection of the hydroxy group with an acetate group. We performed this by modifying the method of Dauben and co-workers in which pyridine is used as a base.[141] In our case we used DIPEA, which is milder and less toxic. Thus, **268** was treated with acetic anhydride and DIPEA and stirred at 20 ^{o}C for 24 hours (**Scheme 95**). Following purification, **269** was isolated in 89% yield. The CH_3 of the acetate-protecting group is observed as a singlet at 2.03 ppm in the ^{1}H NMR spectrum. Also of note is the significant shift that has occurred with the 4-H proton moving from 4.46-4.52 to 5.49-5.53 ppm.



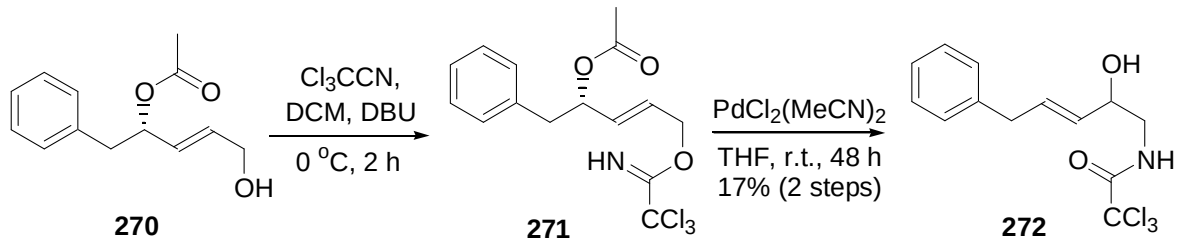
Scheme 95

The last protecting group manipulation that had to be carried out was removal of the MOM-group. This was achieved by treating **269** with trifluoroacetic acid and heating the solution under reflux for 24 hours (**Scheme 96**). Following purification, **270** was isolated in 61% yield.



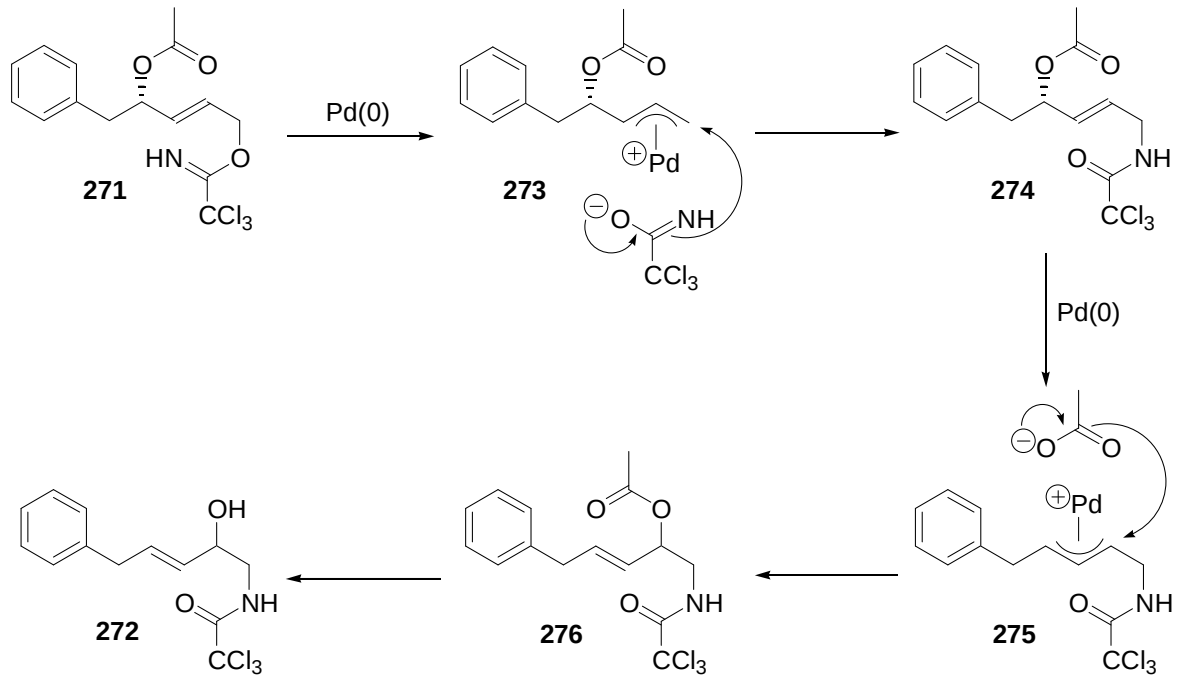
Scheme 96

The trichloroacetimidate **271** was synthesised using the same conditions as before (**Scheme 97**). The rearrangement was carried out using bis(acetonitrile)palladium(II) chloride catalyst. A very unusual and interesting result was obtained. **272** was isolated in 17% yield over two steps and this is believed to be the result of two 1,3 rearrangements followed by hydrolysis of the acetate group.



Scheme 97

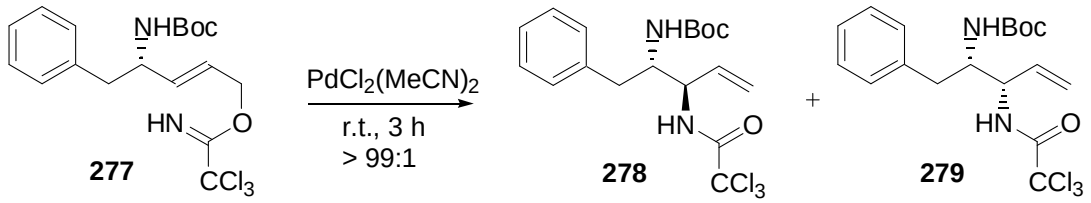
The mechanism of this rearrangement is thought to be that shown below (**Scheme 98**). As previously stated, a slow reaction can cause the palladium(II) to eliminate and form palladium(0), which is known to catalyse the 1,3-rearrangement.[135] The 1,3-rearrangement takes place initially between the trichloroacetimidate group and the alkene. If it happened between the acetate and the alkene first, the double bond would then not be available for the second rearrangement. After this 1,3-rearrangement, the alkene is perfectly positioned to undergo a 1,3-rearrangement with the acetate group. Finally, hydrolysis occurs to leave the rearranged product **272** which was confirmed by COSY NMR spectroscopy.



Scheme 98

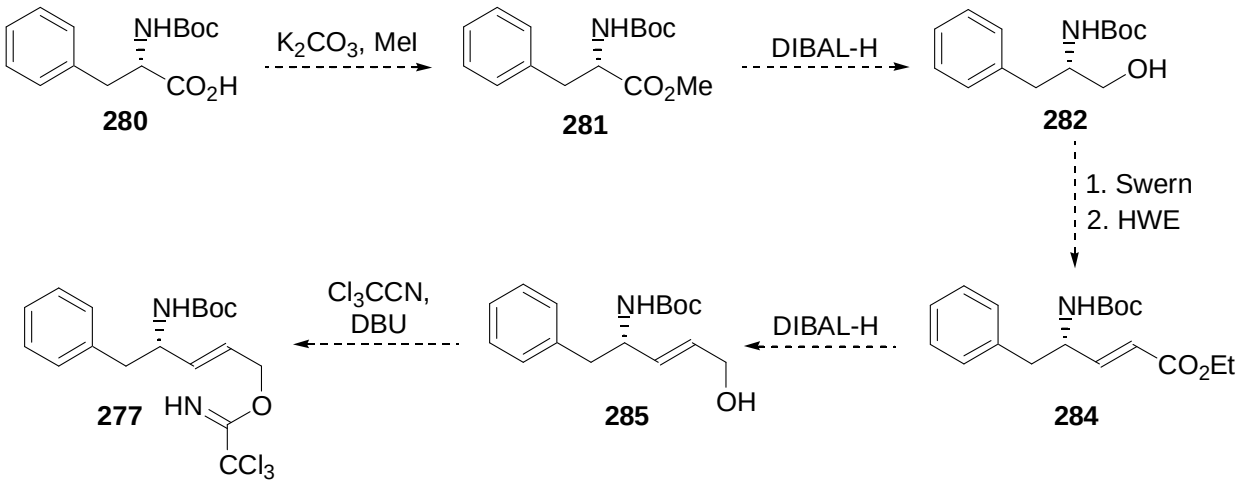
2.4 Use of Nitrogen for the Directed Rearrangement

During our studies on ether-directed rearrangements, it had come to our attention that Belluš and co-workers had performed a similar rearrangement to us, using instead a Boc-protected amine **277**.[142] For them, this gave a selectivity of ≥ 99:1 for the *anti*-diastereomer (**Scheme 99**). The best result we had achieved using a protected alcohol group and the bulky L-phenylalanine side chain was 12:1 *anti*:*syn* selectivity. Thus, we decided to synthesise the Boc-protected amine precursor, again using a variation of our optimised route and rearrange this using the same conditions as before.



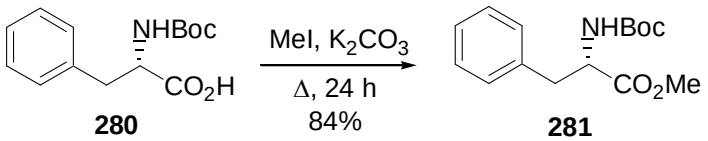
Scheme 99

The variation of the optimised route to **277** is outlined below (**Scheme 100**). We began the synthesis from *N*-Boc-phenylalanine **280** as it is commercially available, though it can easily be derived from L-phenylalanine **236**. This mono-protected compound is then converted to the methyl ester **281** using potassium carbonate and iodomethane.[131] The ester is reduced to the corresponding alcohol **282** using DIBAL-H. Following this, the carbon chain is elongated using a one-pot Swern/Horner-Wadsworth-Emmons reaction to give the α,β-unsaturated ethyl ester **284**. Ester **284** is reduced to the *E*-allylic alcohol **285** using DIBAL-H and the trichloroacetimidate group is introduced as before, using trichloroacetonitrile and DBU to give the rearrangement precursor **277**.



Scheme 100

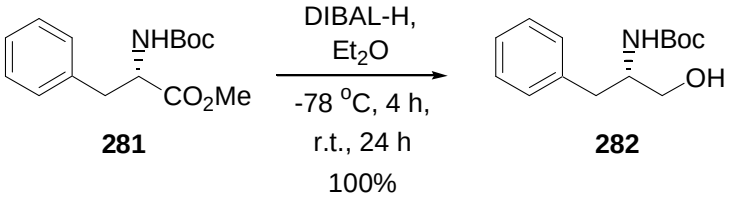
Thus, the acid group of **280** was converted to the corresponding methyl ester to give **281**. This was achieved by reacting **280** with potassium carbonate and iodomethane (**Scheme 101**). After purification by column chromatography, **281** was isolated in 84% yield.



280 **281**

Scheme 101

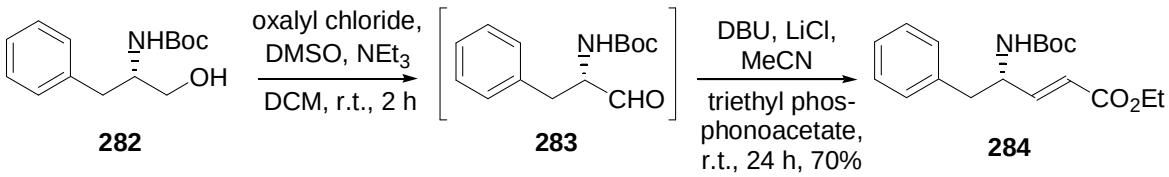
This ester was then reduced to the alcohol **282** using DIBAL-H (**Scheme 102**). After purification, **282** was isolated in a quantitative yield.



281 **282**

Scheme 102

The alcohol **282** was used in the one-pot Swern/Horner-Wadsworth-Emmons reaction to give the α,β-unsaturated ethyl ester **284** (**Scheme 103**). The Swern reaction was carried out first, as detailed previously, followed by the Horner-Wadsworth-Emmons reaction using Masamune-Roush conditions.[134] Following purification, **284** was isolated in 70% yield. It was expected that the *E*-alkene would be produced due to these conditions and from the ^{1}H NMR spectrum, it can be seen that indeed the expected alkene is the one that has been formed. The signals for 2-H and 3-H, the protons on either side of the alkene, are seen at 5.88 (doublet) and 6.93 ppm (doublet of doublet) respectively. The coupling constant between these signals is 15.6 Hz, which confirms that the *E*-alkene has been synthesised.

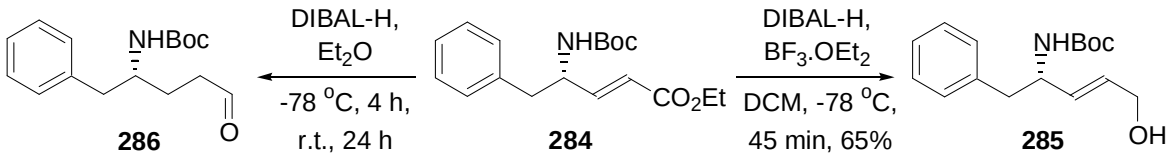


282 **283** **284**

Scheme 103

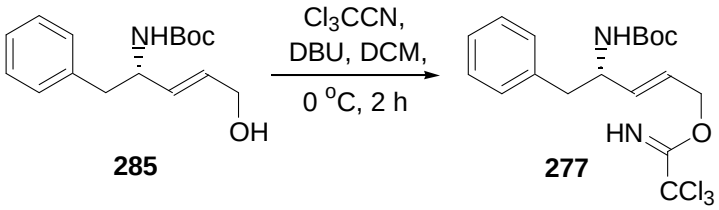
The α,β-unsaturated ethyl ester **284** was reduced to the *E*-allylic alcohol **285** using DIBAL-H (**Scheme 104**). However, with this approach the DIBAL-H was coordinating to both the ethyl ester and the alkene and thus, was inducing a 1,4-conjugate addition to give **286**, as well as 1,2-addition to give the alcohol **285**. A combination of boron trifluoride diethyl etherate and DIBAL-H was then used, as the Lewis acid should coordinate to the Boc-

protected amino group and allow the DIBAL-H to cleanly react with the ester, to give the desired 1,2-addition.[143] This solution was allowed to stir at -78 ^{o}C for 45 minutes. Using this approach, the *E*-allylic alcohol **285** was isolated cleanly in 65% yield.



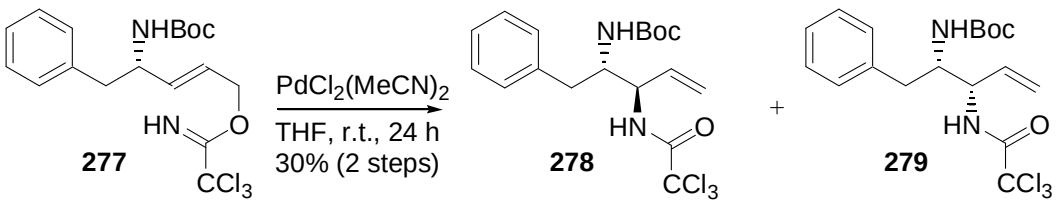
Scheme 104

The rearrangement precursor **277** was synthesised as described before and was used in the rearrangement step without further purification (**Scheme 105**).



Scheme 105

The rearrangement was carried out using bis(acetonitrile)palladium(II) chloride (**Scheme 106**). The reaction was allowed to stir at room temperature for 24 hours. Following purification, the major *anti*-diastereomer **278** was isolated in 30% yield over 2 steps. The CH_2 and CH signals of the terminal alkene are observed in the ^{1}H NMR spectrum at 5.28-5.36 and 5.68-5.77 ppm respectively. The corresponding signals for the *syn*-diastereomer are observed at 5.28-5.32 and 5.62-5.66 ppm. These siganls however, are obscured in the ^{1}H NMR spectrum of the crude mixture by side products, thus giving the appearance of only one diastereomer. We found the ratio of *anti*:*syn* distereomers to be 3:1 following purification and separation and not ≥ 99:1, as Belluš and co-workers found.[142] We believe that perhaps Belluš and co-workers determined their ratio from the ^{1}H NMR spectrum of the crude reaction mixture.



Scheme 106

In conclusion, a number of rearrangements were attempted and some unusual results were obtained. The table below summarises the protecting groups used and the outcome of the rearrangements (**Table 1**). The most successful protecting group used was the MOM-group

in conjunction with an E-alkene. With this substrate we obtained 12:1 selectivity for the *anti*-diastereomer **247** and a 70% yield over 2 steps. No rearrangement occurred with the TBDMS-protected substrate. This was due to the size and bulky nature of the protecting group and sidechain. The most unusual result was obtained with the acetate protecting group, in which two 1,3-rearrangements and then hydrolysis of the acetate group occured to give **272** in 17% yield over 2 steps. This rearrangement is being further investigated by our group. The amino acids this rearrangement can produce are very valuable in the field of natural product synthesis, as they contain defined and configured carbon centres, that otherwise, may be difficult to introduce.

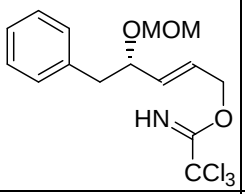
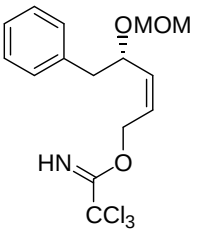
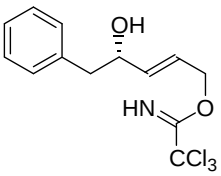
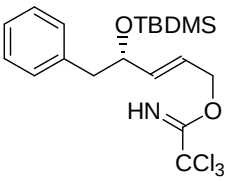
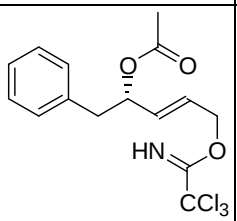
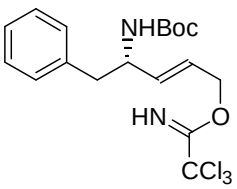
Rearrangement Precursor	**Outcome of Rearrangement**	**Yield over 2 steps**
243 	12:1 *anti*:*syn*	70%
254 	1,3-rearrangement	19%
263 	6:1 *anti*:*syn*	12%
262 	No rearrangement	n/a
271 	2 x 1,3-rearrangement	17%
277 	3:1 *anti*:*syn*	30%

Table 1

3 The Synthesis of (*S*)-Gizzerosine

3.1 Introduction

Black vomit is a serious disease in chickens and is a problem in poultry production all over the world.[144] This disease is accompanied by gizzard erosion and, in severe cases, gizzard ulceration and mortality. Other effects are decreased weight gain and feed consumption.[145] Although the condition was described as early as 1930, fish meal was only implicated in the pathogenesis since 1971.[144a]

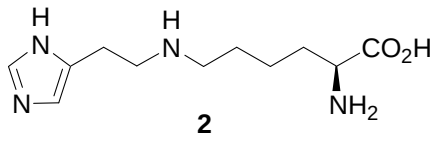
Pelagic fish and cannery waste (heads, tails and guts) that are unfit for human consumption are converted into meal with high nutritional value for use in animal feed. The meal produced is added to chicken feed in level of 3-10% and is considered an irreplaceable component due to the unique amino acid composition. There are high levels of free lysine, which animals cannot synthesise themselves, found in the fish muscle.[146] The meal is normally blended with proteins and carbohydrates from vegetable origin and the biggest exporters are Peru, Chile and Denmark.[147,148]

To produce meal, fish is exposed to steam in the cooker and then heat in the dryer until it can be ground down. Drying is the vulnerable part of the process and scorching can occur. Elevated temperatures (130 ^{o}C or higher) also give rise to undesirable side reactions and can increase levels of biogenic amines such as histamine (derived from histidine), putrescine and cadaverine. Biogenic amines are derived from the corresponding amino acid when the carboxylic acid is removed by decarboxylase enzymes present in bacteria (e.g. *Proteus morganii, Pseudomonas sp. etc*.).[149]

Levels of histamine above 100 mg kg^{-1} show that the fish have been mishandled during storage and/or processing. The presence of histamine at high levels has been shown to be toxic and the presence of putrescine and cadaverine can potentiate the effects of histamine *in vivo* by inhibiting intestinal histamine-catabolising enzymes. However a relatively large amount of histamine (0.4-0.5%) needs to be included in feeds to induce gizzard erosion and Naito and co-workers realised this during their investigations in 1983.[150]

The active substance named gizzerosine **2** (**Figure 38**) was produced in a model system by heating casein with histidine and was isolated from the protein fraction (2 mg from 10 kg of mackerel meal). It is produced during the heat treatment of fish meal.[150,151] Further

studies have proved that only the (*S*)-isomer is active (**Figure 38**).[152] It was found to be 300 times more potent than histamine at inducing gizzard erosion in 3-day old chicks on a diet including 6.25 ppm of the amino acid.[153] (*S*)-Gizzerosine **2** is also metabolised and secreted at a far slower rate than histamine, thus having a more prolonged effect.[154]



2

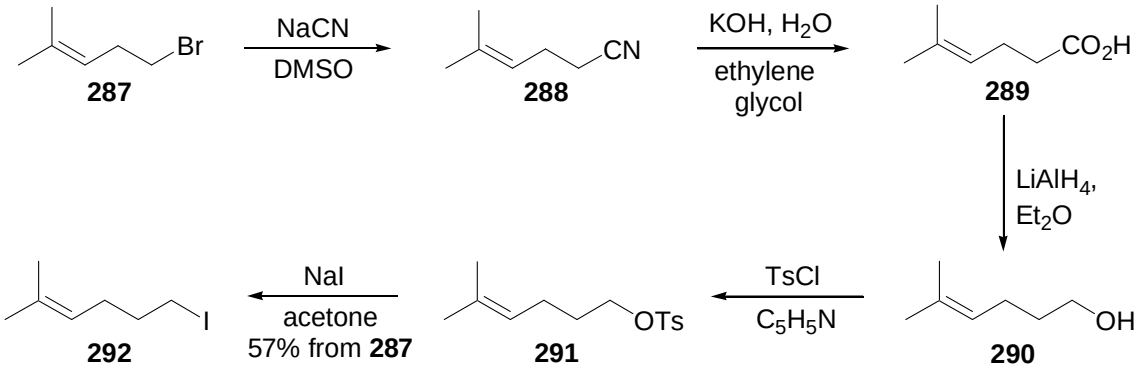
Figure 38

(*S*)-Gizzerosine **2** is a potent agonist for the H_2-receptor of histamine. On binding, it stimulates the release of cyclic adenosine-3',5'-monophosphatase (cAMP). The increase in cAMP in turn stimulates the secretion of excess gastric acid from the proventricular gland, which degrades the protective lining of the gizzard. This leaves the mucosal cells exposed to the hyperacidic conditions, causing ulceration.[155]

Unusually, (*S*)-gizzerosine **2** did not show any visible effects on rat stomach, though the gastric secretions had been promoted.[150,156] This biological profile suggests that **2** could be a possible drug candidate for conditions such as gastric achlorhydria (lack of HCl in stomach fluid) and osteoporosis. With osteoporosis, an acid-alkaline balance is vital as too much stomach acid can encourage calcium loss and too little acid promotes excessive calcium storage.

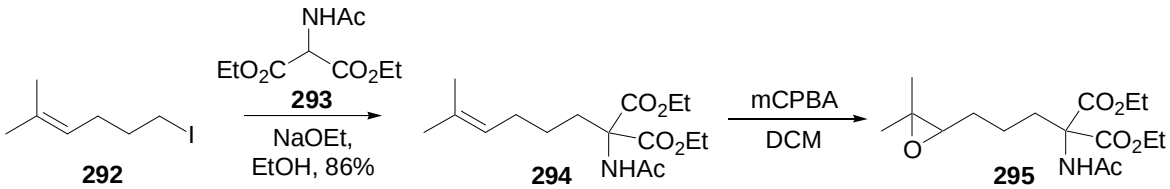
3.2 Previous Syntheses

The first synthesis of both the racemic and optically active forms of gizzerosine was carried out by Mori and co-workers.[152] 4-Methyl-3-pentenyl bromide **287** was treated with sodium cyanide to give **288** (**Scheme 107**). Alkaline hydrolysis of this nitrile **288** gave the acid **289** which was subjected to a reduction with lithium aluminium hydride to give the alcohol **290**. This was converted to the corresponding tosyl group to give **291** and to the iodide **292** using sodium iodide in acetone (57% yield from 4-methyl-3-pentenyl bromide **287**).



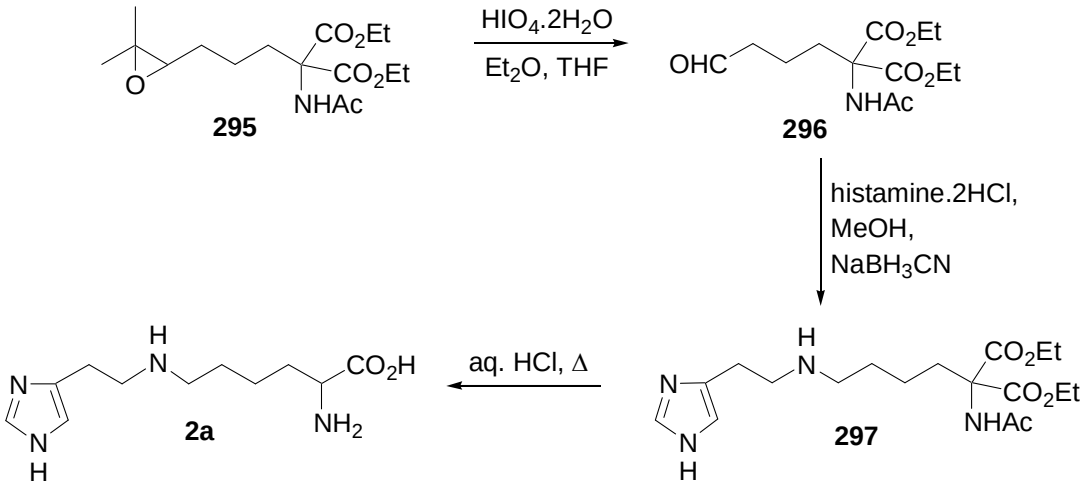
Scheme 107

Alkylation of diethyl acetaminomalonate **293** with **292** in the presence of sodium ethoxide and ethanol gave the alkylated product **294** in 86% yield (**Scheme 108**). This was then oxidised to the epoxide **295** with *m*-chloroperbenzoic acid.



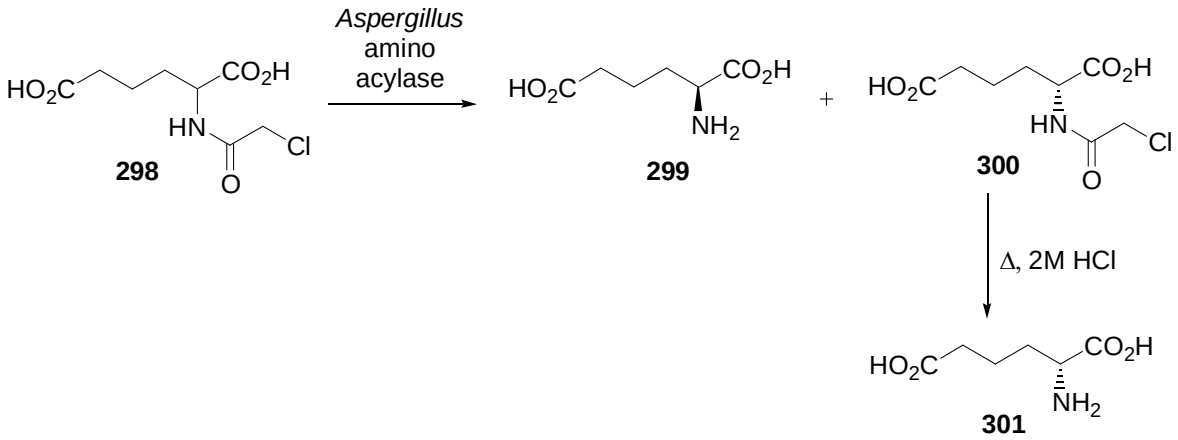
Scheme 108

The epoxide **295** was treated with hydrated hydrogen *m*-periodate to give the somewhat unstable aldehyde **296** in a quantitative yield over 2 steps (**Scheme 109**). The aldehyde **296** was subjected to a reductive amination with histamine dihydrochloride and sodium cyanoborohydride to give the coupled diester **297** in 87% crude yield. Following hydrolysis with aqueous hydrochloric acid which concurrently results in decarboxylation of the di-acid, the amino acid was purified to give (±)-gizzerosine **2a**.



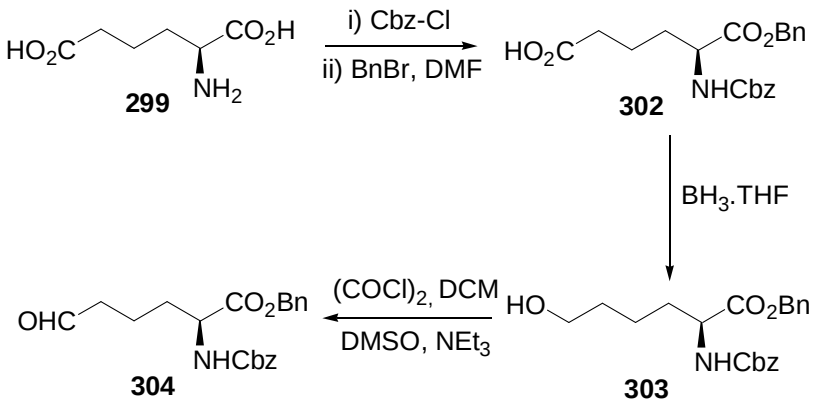
Scheme 109

To produce the optically active form of gizzerosine, Mori and co-workers started with (*S*)-2-aminoadipic acid **299** shown below, which was obtained by enzymatic resolution from the racemic precursor **298** (**Scheme 110**).



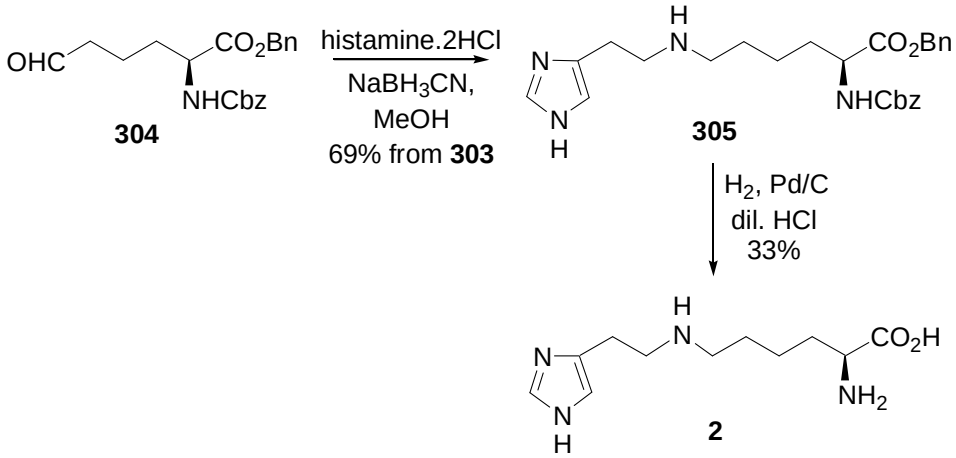
Scheme 110

(*S*)-2-aminoadipic acid **299** was protected with a Cbz group (**Scheme 111**) and the α-acid was converted to the benzyl ester **302** using the procedure of Baldwin and co-workers.[157] The side-chain acid was reduced to the alcohol **303** using borane.THF and then oxidised to the unstable aldehyde **304** using a Swern reaction.[158]



Scheme 111

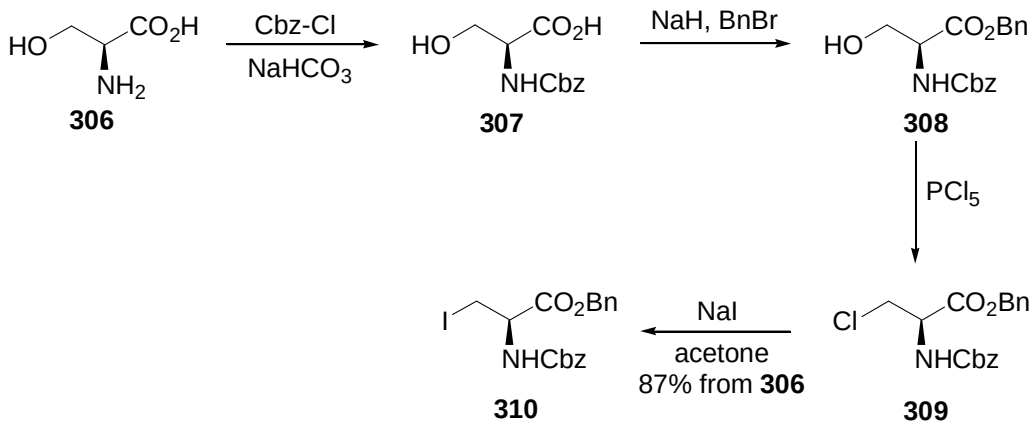
This was used immediately in the reductive amination step, again using histamine dihydrochloride and sodium cyanoborohydride to give the coupled product **305** in 69% yield from the alcohol **303** (**Scheme 112**). Hydrogenation over palladium/carbon followed by acidification using hydrochloric acid gave the salt which was recrystallised from methanol to give pure (*S*)-gizzerosine **2** in 33% yield from the coupled product **305**.



Scheme 112

Similarly, the (*R*)-enantiomer was prepared from **301** and bioassays were carried out on both enantiomers. The (*R*)-enantiomer caused no damage to chicks when added to their diets in 3 or 6 ppm, whereas (*S*)-gizzerosine caused severe gizzard erosion, clearly indicating it is the active form.

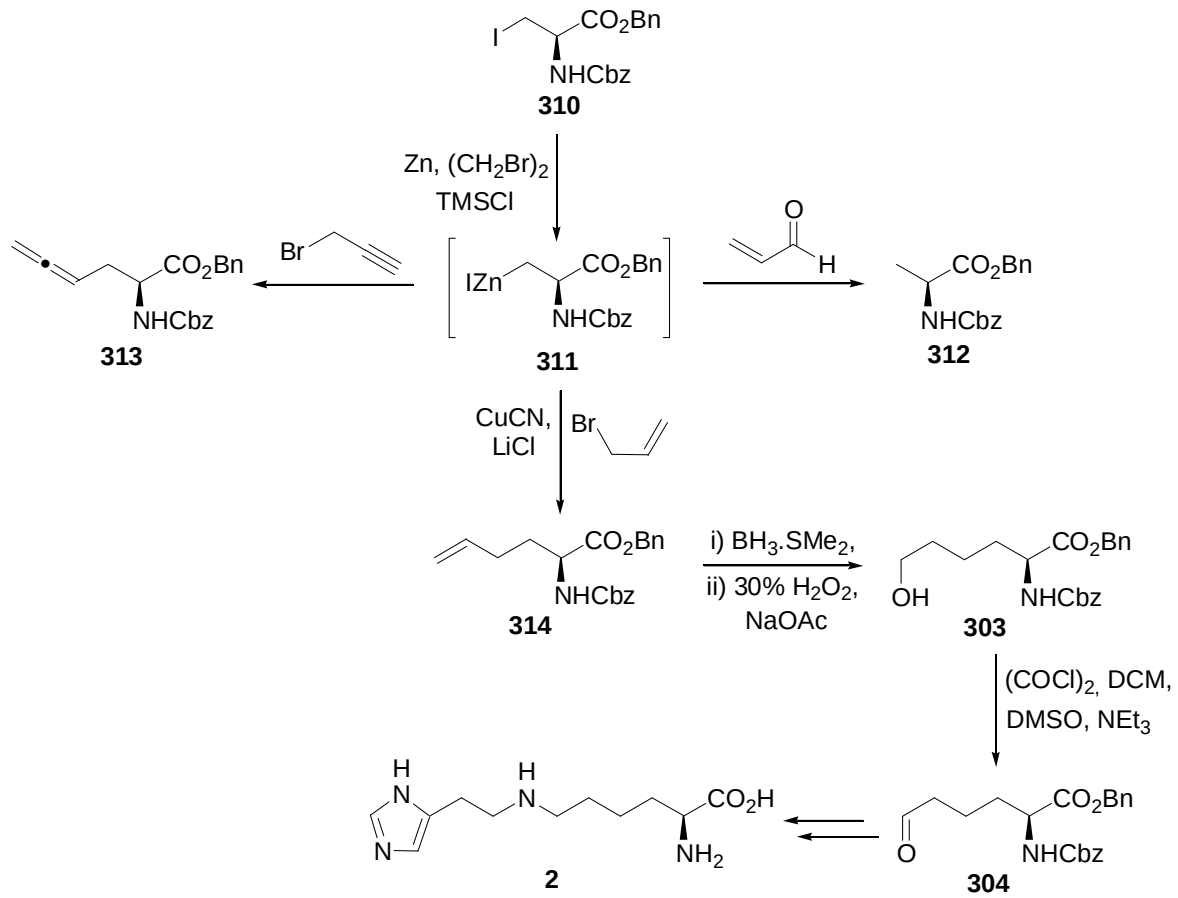
The second synthesis of (*S*)-gizzerosine **2** was carried out by Kiyota and co-workers using successive zinc and palladium-mediated coupling reactions.[3,159] Both the alcohol **303** and unstable aldehyde **304** from Mori's earlier synthesis were targeted. Beginning from (*S*)-serine **306**, the iodide **310** was produced in 4 steps and 87% yield (**Scheme 113**).[160]



Scheme 113

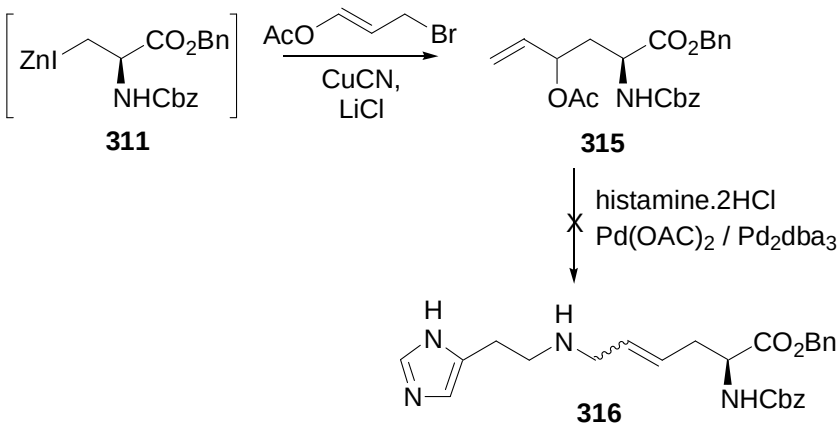
The iodide **310** was then converted to Mori's aldehyde **304** *via* a zinc-mediated coupling reaction. This reaction was attempted with acrolein, however only the corresponding alanine derivative **312** could be isolated (**Scheme 114**). Use of propargyl bromide gave the undesired allenyl compound **313**, but reaction with allyl bromide afforded the desired olefin **314** (**Scheme 114**). Hydroboration-oxidation of **314** gave **304** which was converted

to (*S*)-gizzerosine **2** using Mori's procedure.[152] The target compound was achieved in 58% yield from (*S*)-serine **306**.



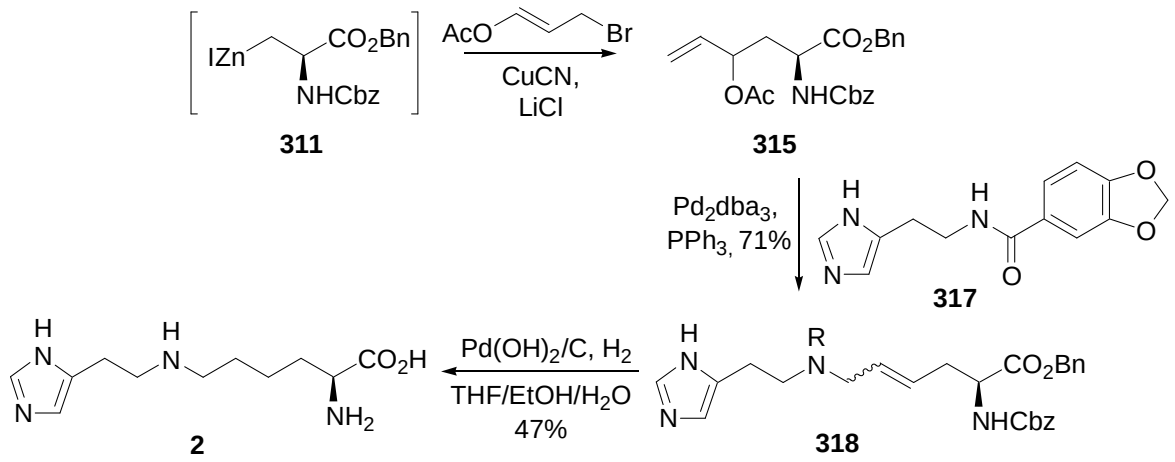
Scheme 114

While preparing the aldehyde **304**, it was noticed that the coupling of the organozinc iodide **311** with 3-bromo-1-propenyl acetate gave the allylic acetate **315** as a 2:1 diastereomeric mixture at the 4-position in 98% yield (**Scheme 115**). This was expected to be a good substrate for the palladium-catalysed coupling with nitrogen nucleophiles such as histamine, but this was not the case.



Scheme 115

Histamine was protected with a number or electron withdrawing/donating protecting groups. Unsuccessful protection through nucleophilic substitution led to protection *via* reductive amination. The coupled product **318** was achieved using piperonyl-protected histamine **317**, in 71% yield, when a mixture of triphenylphosphine and palladium(II) was used (**Scheme 116**). Hydrogenation and hydrolysis using an excess of palladium hydroxide/carbon gave (*S*)-gizzerosine **2** in 47% yield, and 26% overall yield in seven steps from (*S*)-serine **306**.



Scheme 116

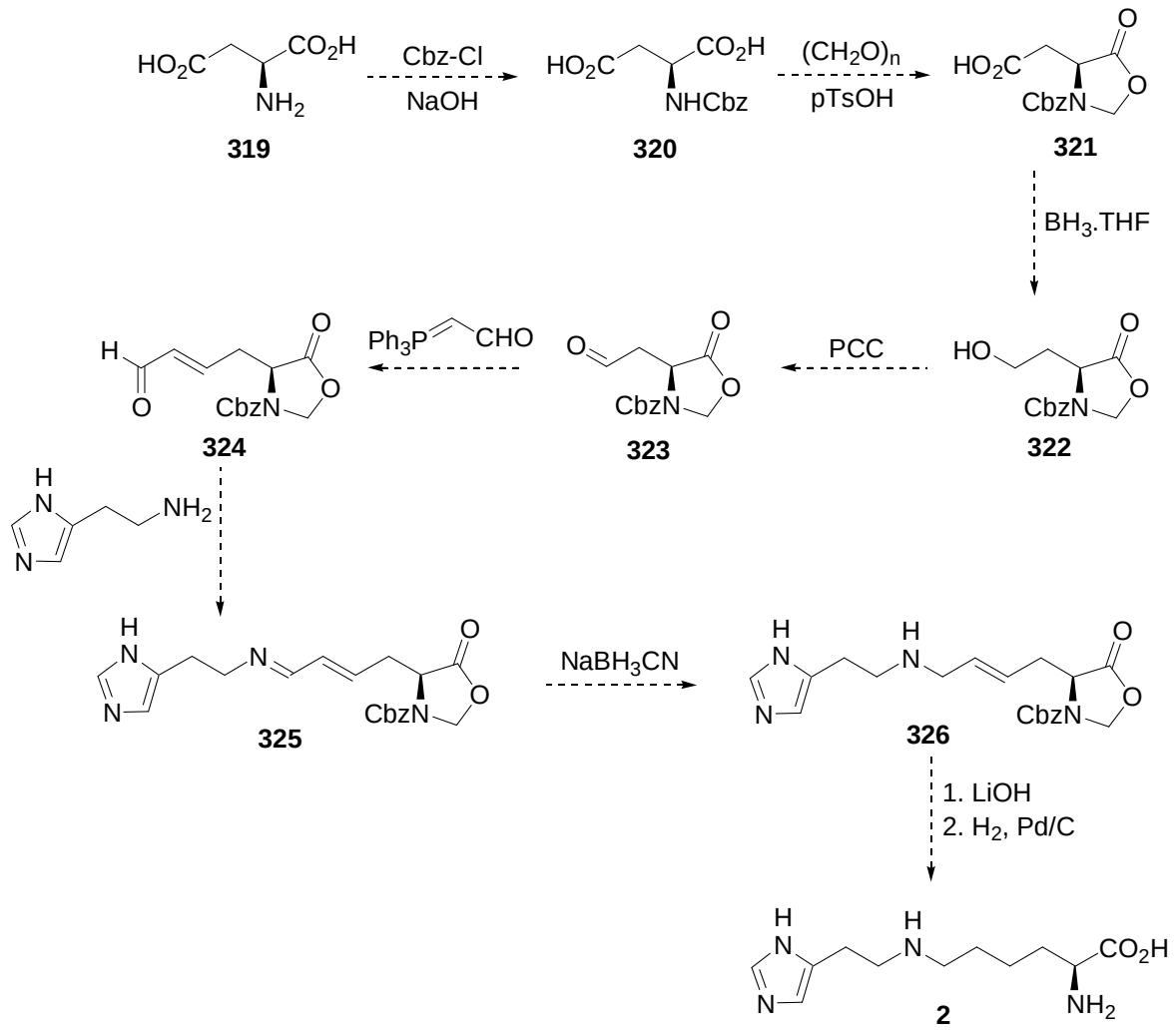
3.3 Aims

As (*S*)-gizzerosine **2** can only be isolated from brown fishmeal in very small amounts (0.2 mg per kg), a chemical approach is needed to facilitate further biological testing.[150] We wanted to generate a novel synthetic approach that is more efficient than those already published. Also, we were interested in eliminating very toxic reagents from the scheme, such as the cyanides in Mori's synthesis.[152]

Our approach was designed with flexibility in mind, and to this end, we have proposed the introduction of the histamine side chain late in the synthesis (**Scheme 117**). This allows for introduction of other amino acids in place of histamine and thus, the synthesis of a library of (*S*)-gizzerosine analogues that could be used for drug discovery. Also of note is the fact that the histamine in the proposed synthesis is unprotected. This will mean less deprotection steps and hopefully a higher overall yield for this synthetic route. It also avoids problems that could arise when attempting to introduce other protected amines at this point in a library synthesis, such as incompatibility of those protecting groups.

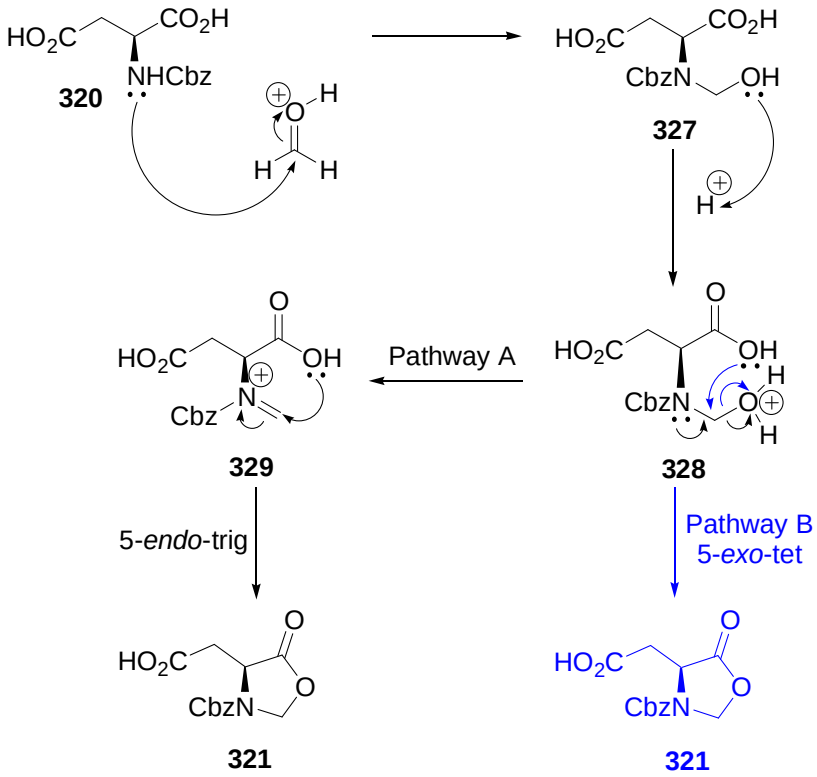
3.4 The Synthesis of (*S*)-Gizzerosine

The initially proposed scheme for the synthesis is outlined below (**Scheme 117**). As with other projects discussed in this thesis, the scheme was designed around a key semi-aldehyde intermediate which could be a focal point for new divergent syntheses to other non-proteinogenic amino acids. The semi-aldehyde intermediate in the synthesis of gizzerosine could be obtained in four steps from commercially available L-aspartic acid Starting from L-aspartic acid **319**, the amino acid functionality is fully protected as an oxazolidinone ring with a benzyloxycarbonyl (Cbz) protecting group. This will allow for manipulation of the β-acid without compromising the α-acid or the amino group. Following borane reduction of the acid to the alcohol **322** and PCC oxidation to the semi-aldehyde intermediate **323**, chain elongation will be performed using a Wittig reaction to yield the α,β-unsaturated aldehyde **324**. The molecule is then ideally suited to a reductive amination with unprotected histamine to yield the coupled product **325**, which after reduction of the imine, hydrogenation and hydrolysis will yield (*S*)-gizzerosine **2**.



Scheme 117

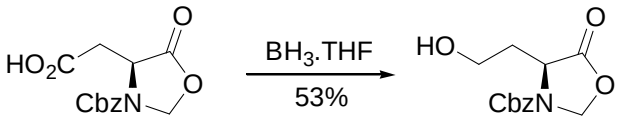
Commercially available Cbz-protected L-aspartic acid **320** was reacted in benzene, paraformaldehyde and a catalytic amount of *p*-TsOH, the mechanism of which is shown below (**Scheme 118**). There are two potential pathways that this reaction could follow. In the first, Pathway A, the lone pair on nitrogen attacks the bond next to it and displaces water to give **329**. The lone pair on oxygen then attacks the iminium species to cyclise to the oxazolidinone **321**. This, according to Baldwin's guidelines, is a 5-*endo*-trig cyclisation, as a five-membered ring is formed, the bond being broken is inside the ring (*endo*) and the electrophilic carbon is trigonal (sp^2). Due to orbital overlap requirements, this is an unfavoured cyclisation. In Pathway B, the lone pair on oxygen attacks the carbon adjacent to nitrogen and water is displaced to give **321**. This is classed as a 5-*exo*-tet cyclisation as a 5-membered ring is formed, the bond being broken is outside the ring (*exo*) and the electrophilic carbon is tetrahedral (sp^3). This is a favoured reaction according to Baldwin's guidelines and thus, this is the most likely mechanism. The water that was generated was removed by azeotropic distillation using a Dean-Stark apparatus, hence pushing the equilibrium towards the oxazolidinone **321** in 87% yield.



Scheme 118

Oxazolidinone **321** was then subjected to a borane reduction to the alcohol **322** using a 1M solution of borane.THF complex.[161] Initially, the reaction was brought back to room temperature after addition of the reductant at -15 °C. This however resulted in degradation of **322**. When the reaction was maintained at -4 °C for 20 hours, **322** was recovered in a

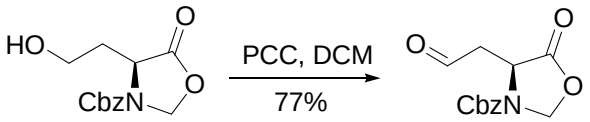
moderate 53% yield following purification by silica gel column chromatography (**Scheme 119**). The ^{1}H NMR spectrum shows two sets of signals for the new CH_2 due to the stereogenic centre. These signals appear at 4.84 and 4.96 ppm and the single proton attatched to the chiral centre has shifted upfield by approximately 0.4 ppm.



321 **322**

Scheme 119

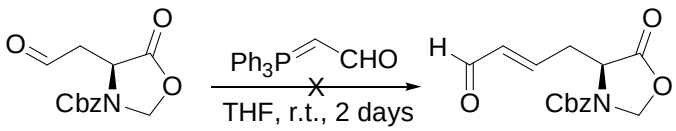
The alcohol **322** was then oxidised to the key aldehyde intermediate **323** using PCC in DCM and a 77% yield was achieved after purification by column chromatography (**Scheme 120**). The ^{1}H NMR spectrum clearly showed a new signal for the aldehyde proton at 9.26 ppm.



322 **323**

Scheme 120

The aldehyde **323** was then reacted with (triphenylphosphoranylidene)acetaldehyde in THF at room temperature in a Wittig reaction but only starting material was recovered (**Scheme 121**). An attempt was also made to react **323** with carbomethoxymethylene triphenylphosphorane, initially thinking that our original ylide had decomposed. Once again, only the aldehyde **323** was recovered. It was believed then that the inability of **323** to undergo a Wittig reaction was due to both the Cbz-protecting group and the oxazolidinone ring sterically hindering the aldehyde.

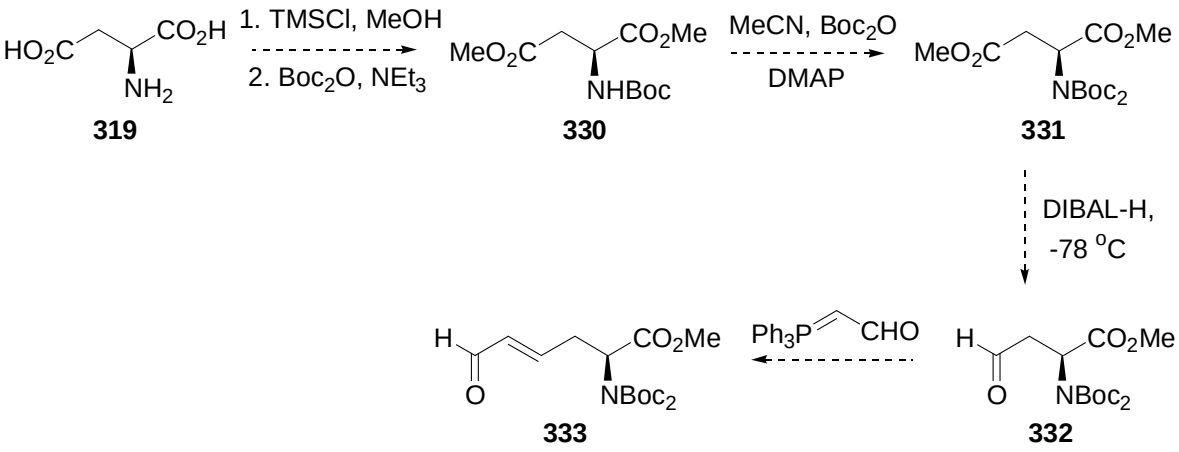


323 **324**

Scheme 121

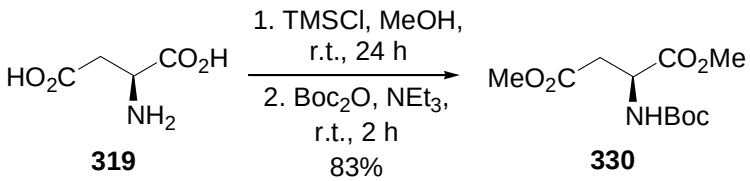
A new strategy was therefore needed in order to prepare a semi-aldehyde intermediate which would undergo a Wittig reaction with (triphenylphosphoranylidene)acetaldehyde. It was decided to make an analogous L-aspartic acid compound without the oxazolidinone ring, where it was believed part of the problem lay. In the new scheme, the amino acid functionalities will be protected separately, with a Boc-group and an ester respectively,

instead of incorporating them into a ring (**Scheme 122**). It was hoped that this strategy would leave the aldehyde more exposed to react with the ylide. Starting with L-aspartic acid, the acid groups are methylated and the amine is mono-protected as before to give **330**. The amine is then fully protected with a second Boc-group to yield **331**. The addition of the second Boc-group is necessary, not only to fully protect the amide, but also to provide selectivity during the reduction step. The β-ester will be converted to an aldehyde in a DIBAL-H reduction as before, to give the key intermediate **332** for the Wittig reaction.



Scheme 122

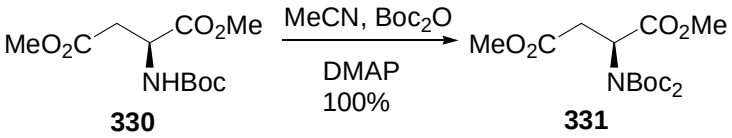
In the first step, L-aspartic acid **319** was reacted with TMSCl to yield the di-ester (**Scheme 123**).[162] After 24 hours at room temperature, NEt_3 and Boc_2O were added to mono-protect the amine.[163] This reaction was complete after 2 hours and **330** was isolated in 83% yield. The experimental data corresponds well with that from the literature.[164] Due to the adjacent stereogenic centre, the 3-H_2 protons are therefore in chemically different environments, and thus appear as two separate doublet of doublet peaks in the ^{1}H NMR spectrum, instead of a single peak integrating for 2 protons.



Scheme 123

The di-Boc protected amino acid **331** was then prepared in quantitative yield using Boc_2O and DMAP (**Scheme 124**).[165] This reaction was stirred for 24 hours at room temperature. The NH peak seen at 5.5 ppm in the ^{1}H NMR spectrum for **330** is now not observed and the peak for the ^{t}butyl groups now integrates for 18 protons. The optical rotation obtained corresponds exactly with the literature.[164] The second protection step is necessary in order

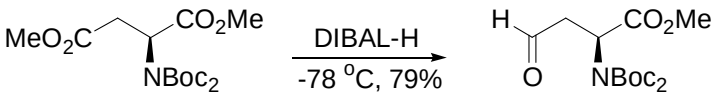
to make the following reduction regioselective for the β-ester.[164,166] The added bulk of the second Boc-group effectively shields the α-ester, thus only leaving the β-ester exposed during the reduction.



330 **331**

Scheme 124

The reduction of **331** to **332** was carried out using 1.4 equivalents of DIBAL-H at -78 ^{o}C (**Scheme 125**). Initially, the reaction was stirred at -78 ^{o}C for between 5 minutes and 2 hours (according to literature), but both of these attempts led to a mixture of **331** and **332**. Next, the reaction was also allowed to warm to room temperature overnight but this led to partial over-reduction of the β-ester to the corresponding alcohol and these mixtures were extremely difficult to separate. Following a number of attempts, the optimum conditions were found to be maintenance of the reaction at -78 ^{o}C for 24 hours. This ensured that no starting material remained and that there was no over-reduction of the β-ester to the corresponding alcohol. The semi-aldehyde intermediate **332** was isolated in 79%. The experimental data corresponded well with that obtained from literature.[164] A new peak for the aldehyde proton was seen at 9.82 ppm in the ^{1}H NMR spectrum and at 198.5 ppm in the ^{13}C NMR spectrum.



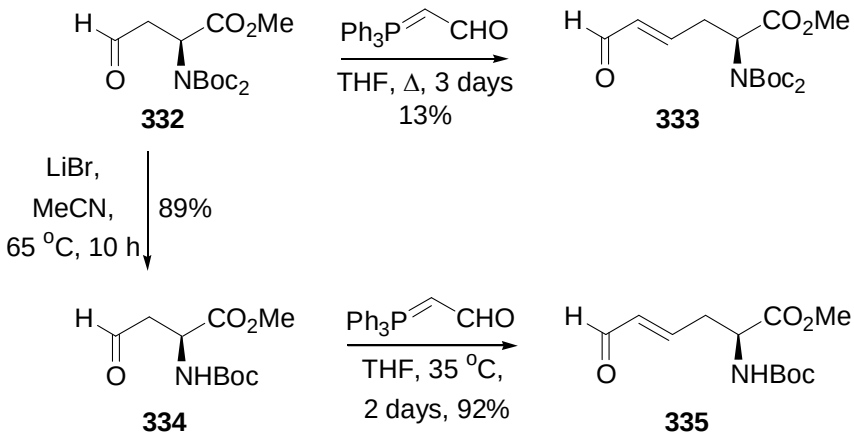
331 **332**

Scheme 125

This aldehyde **332** was then reacted with (triphenylphosphoranylidene)acetaldehyde in a Wittig reaction to extend the carbon chain in preparation for coupling with histamine (**Scheme 126**). The reaction proceeded very slowly and after 3 days under reflux, only 13% of the α,β-unsaturated aldehyde **333** was isolated. The new aldehyde proton peak appeared at 9.50 ppm in the ^{1}H NMR spectrum. A stabilised ylide was used to produce the *E*-alkene. The coupling constants prove this has been formed, with $J_{4H\text{-}5H}$ equal to 15.6 Hz. It was believed that the reaction was slow, and therefore low yielding, due to the steric hindrance of the two Boc-protecting groups on the amino functionality.

Recently, Martín and co-workers have shown that LiBr can be used for selective cleavage of one Boc-group in *N*,*N*-di-protected amino compounds.[167] It was decided to use this

procedure to selectively remove one of the Boc-groups that was believed to be slowing the Wittig reaction. Aldehyde **332** was therefore reacted with LiBr in MeCN to yield the less hindered mono-protected semi-aldehyde **334** in 89% yield (**Scheme 126**). A broad signal is seen in the ^{1}H NMR spectrum at 5.41 ppm, corresponding to the new NH. Also, the signal for the α-proton, which shifted downfield to 5.57 ppm when the second Boc-group was added, has moved upfield again to approximately 4.63 ppm. This new semi-aldehyde **334** was subjected to a Wittig reaction at 35 ^{o}C for 2 days using the same ylide as before, (triphenylphosphoranylidene)acetaldehyde. The α,β-unsaturated aldehyde **335** was isolated in 92% yield, a vast improvement on the previous Wittig reaction. Again, the *E*-alkene was produced as expected, with $J_{4H\text{-}5H}$ equal to 15.4 Hz (**Figure 39**).



Scheme 126

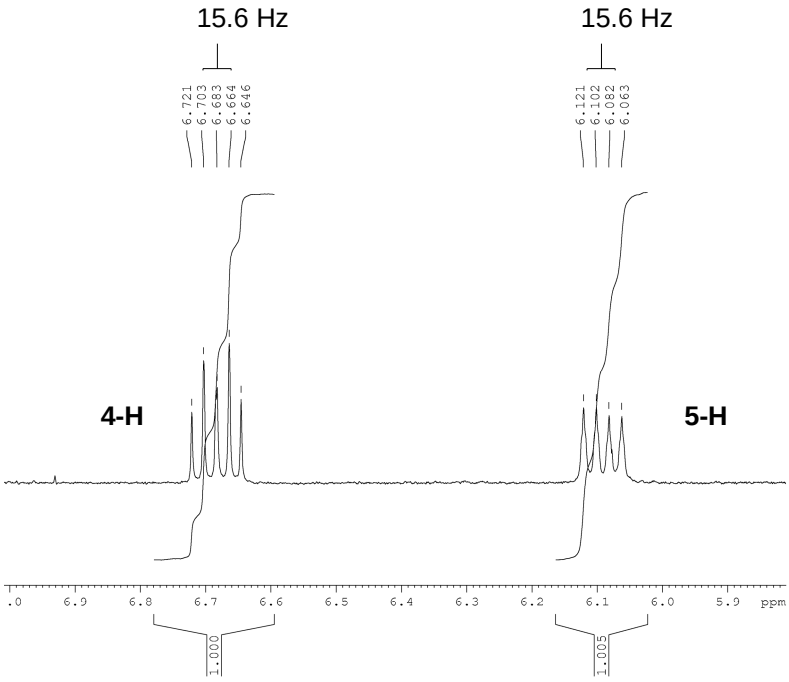
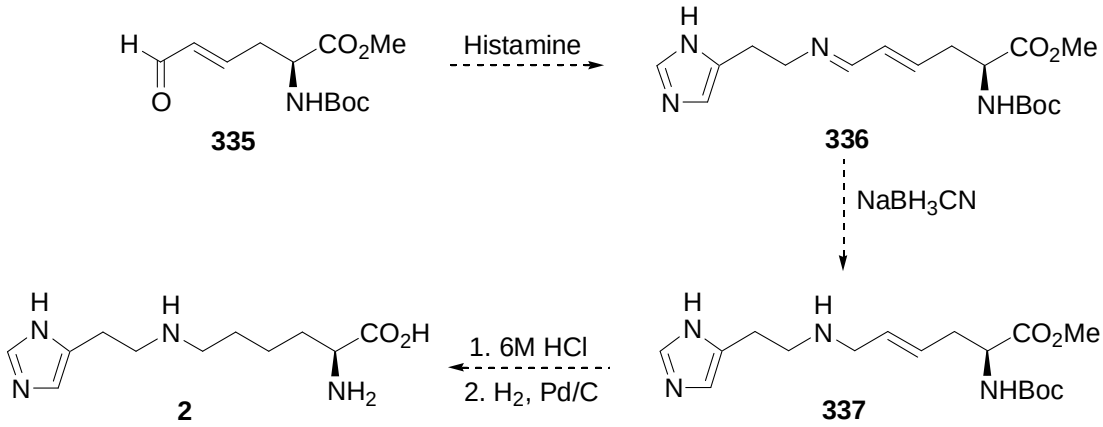


Figure 39

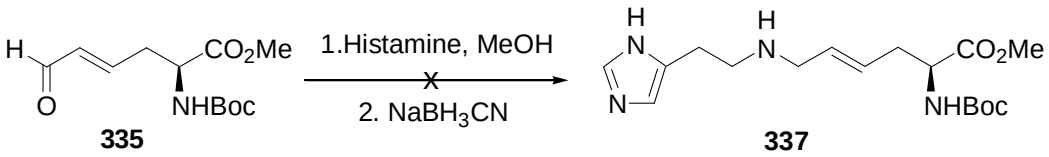
In previous syntheses of (*S*)-gizzerosine **2**, both Mori and co-workers and Kiyota and co-workers have used a reductive amination with histamine in the latter stages, with much

success, to make the backbone of the target material.[3,152] Following this, both groups used $NaBH_4$ to reduce the imine double bond formed. Due to this literature precedent, the next stage of our synthesis required reductive amination of **335** with histamine and reduction of the imine double bond with $NaBH_3CN$ (**Scheme 127**). Finally, reduction of the alkene and deprotection will give (*S*)-gizzerosine **2**.



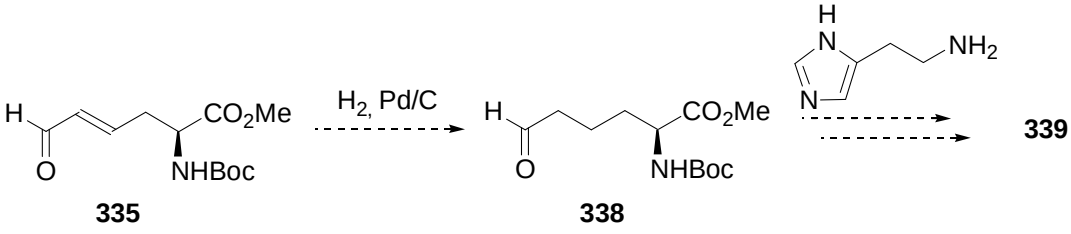
Scheme 127

The coupling reaction was attempted with the α,β-unsaturated aldehyde **335** and histamine, using $MgSO_4$ to ensure a dry reaction.[168] However, only **335** was recovered. The reductive amination was then attempted in the presence of $NaBH_3CN$ to reduce the imine formed *in situ* (**Scheme 128**).[152] 4Å Molecular sieves were also added to the reaction to eliminate any water, however, again only starting material **335** was recovered.



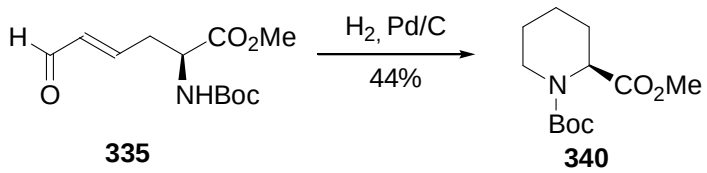
Scheme 128

As this approach had failed, an alternative route was proposed in which the double bond of the α,β-unsaturated aldehyde is reduced by hydrogenation to corresponding saturated aldehyde **338** prior to the reductive amination with histamine to yield the saturated coupled compound **339** (**Scheme 129**).



Scheme 129

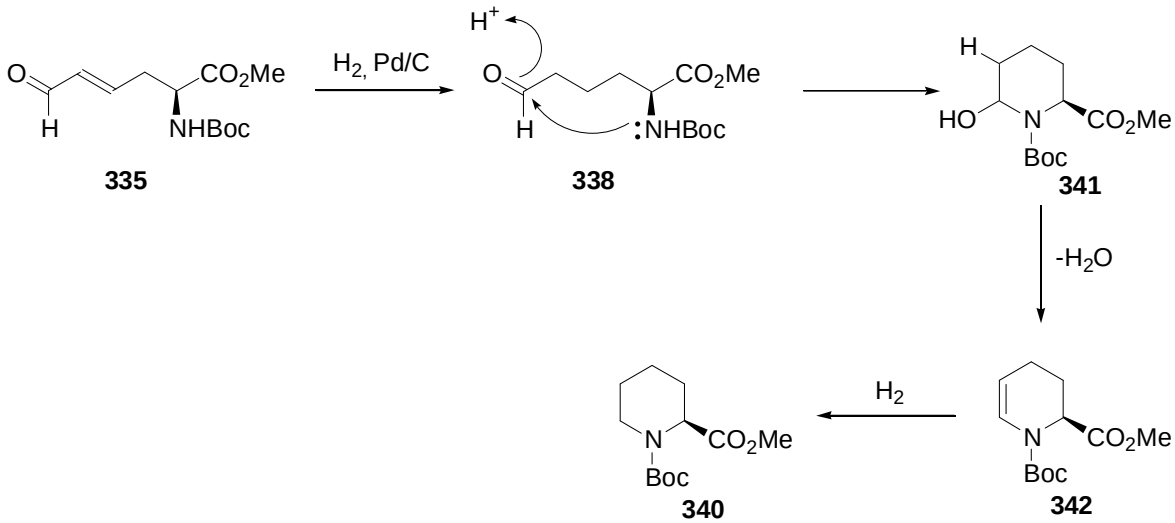
The hydrogenation was carried out on α,β-unsaturated aldehyde **335** using 10% palladium on carbon as catalyst. Hydrogen was bubbled through the solution and then the reaction was placed under a hydrogen atmosphere for 24 hours. Unfortunately, following isolation by column chromatography, the desired saturated aldehyde **338** was not produced. Instead the major product observed was the cyclised piperidine **340** which was isolated in 44% yield (**Scheme 130**).[169] The broad peak for the NH stretch seen previously in the IR spectrum is no longer observed and the ^{1}H NMR spectrum is broad with rotamers (2 sets) normally seen in cyclic *N*-carbamate-protected compounds. These peaks were resolved to some degree using high temperature ^{1}H NMR experiments. All other experimental data for **340** corresponds well with the literature data.[169]



335 **340**

Scheme 130

We believe that when the double bond is reduced during the hydrogenation, it introduces a large degree of flexibility into the carbon chain. This allows the lone pair on the nitrogen to attack the aldehyde *via* a condensation reaction which forms the enamine **342**. Further hydrogenation during the reaction leads to reduction of the enamine to give **340** (**Scheme 131**).

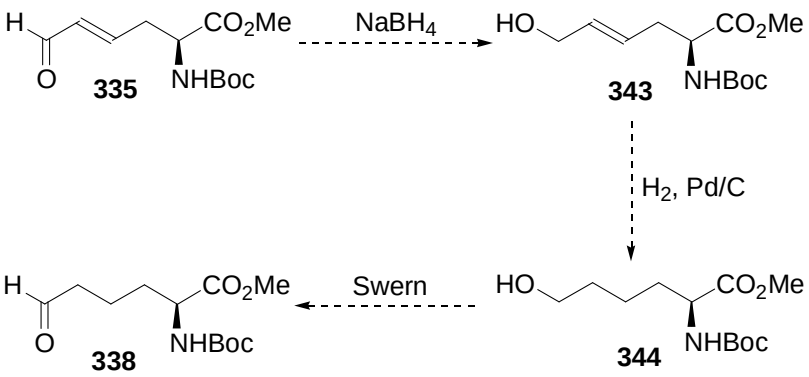


335 **338** **341** **342** **340**

Scheme 131

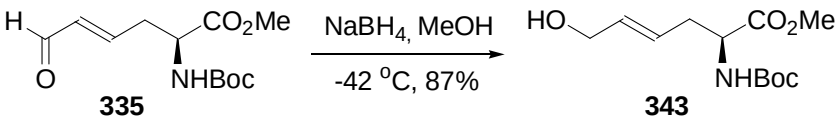
To overcome this issue, a variation on the scheme was proposed in order to synthesise the saturated aldehyde **338** (**Scheme 132**). It was proposed that reduction of the α,β-unsaturated aldehyde **335** using $NaBH_4$ would give the allylic alcohol **343**.[170] Following

this, hydrogenation of the double bond and oxidation of the alcohol to the aldehyde should yield the saturated aldehyde **338**.



Scheme 132

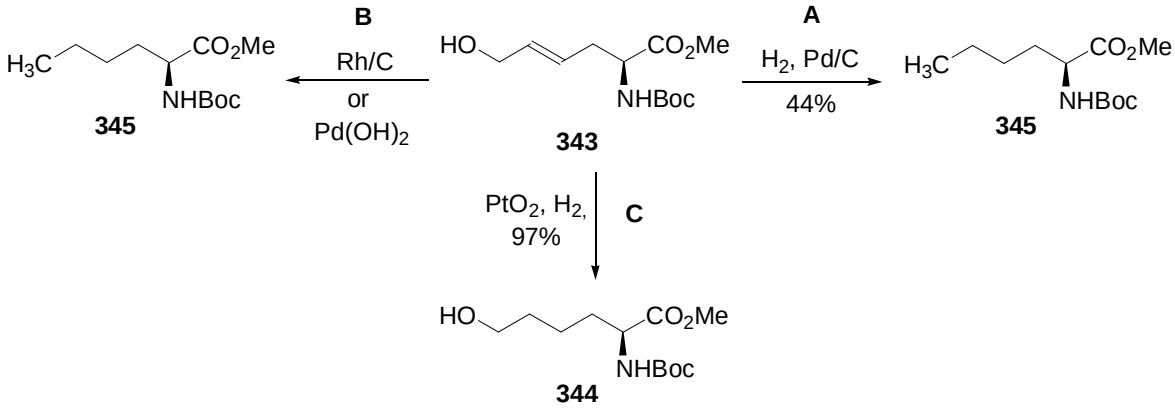
Thus, **335** was reduced to the unsaturated alcohol **343** using $NaBH_4$. The reaction was stirred for 2 hours at -42 ^{o}C (MeCN/dry ice bath) and **343** was isolated in 87% yield (**Scheme 133**). The ^{1}H NMR showed a new signal, integrating for 2 protons at 4.03 ppm, which corresponds to C*H*$_2$OH. Also, the protons of the double bond (5-H and 4-H) have shifted upfield, from 6.1 and 6.65-6.72 ppm respectively, to 5.68 and 5.48-5.56 ppm. This is because the electron withdrawing effect of the aldehyde group is lost to these protons.



Scheme 133

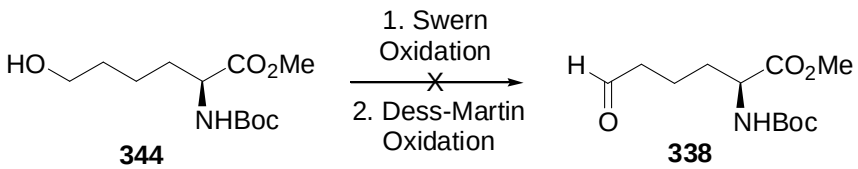
Removal of the double bond to yield the saturated alcohol **344** was carried out in a standard hydrogenation reaction using 0.2 molar equivalents of 10% palladium on carbon catalyst over 24 hours. Surprisingly, although not unknown, the hydroxyl group of the allylic alcohol **343** was also reduced during the course of the reaction, and following purification by column chromatography the major product isolated was **345** in 44% yield (**Scheme 134** – Route A).[171] This reduction was attempted using both 5% rhodium on carbon and palladium hydroxide catalysts, but again, the major product recovered was **345** (**Scheme 134** – Route B).[172] The ^{1}H NMR spectrum has a characteristic triplet (integrating for 3 protons) for the new terminal CH_3 at 0.90 ppm. There is also a new peak at 1.30-1.36 ppm, integrating for 4 protons, for 4-H_2 and 5-H_2. All other experimental data are consistent with the literature.[173]

The reduction was then carried out using 0.05 molar equivalents of platinum oxide and fortunately, this reaction yielded the desired saturated alcohol **344** in 97% yield after 2 hours at room temperature (**Scheme 134** – Route C).[174] The ^{1}H NMR spectrum shows a triplet (integrating for 2 protons) at 3.64 ppm, and all other experimental data are in keeping with the literature values.[175]



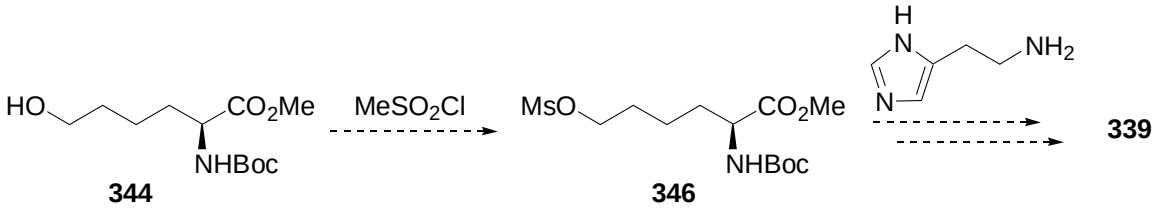
Scheme 134

The last stage of the synthesis involved re-oxidation of the saturated alcohol **344** to the saturated aldehyde **338**, followed by reductive amination of this aldehyde with histamine. A standard Swern oxidation was employed for conversion of the alcohol to the aldehyde, stirring for 18 hours at room temperature (**Scheme 135**). However, only starting material was recovered. It was thought that possibly the oxalyl chloride has decomposed somewhat, giving HCl and this was interfering with our acid-sensitive compound. The oxalyl chloride was distilled, yet the same result was produced. This was very unusual, as this reaction had been carried out previously in the literature with a similar compound (protected with a Cbz-group) and a 91% yield was achieved.[158] This oxidation was also attempted with Dess-Martin periodinone, stirring at room temperature for 3 hours, but a similar result was achieved (**Scheme 135**).[176]



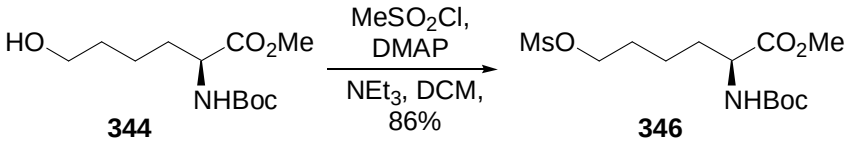
Scheme 135

Another approach was needed to couple our compound with histamine. In a publication by Gokel and co-workers histamine was coupled with a mesylate-protected macrocycle in a moderate yield.[177] Thus, it was decided to activate the saturated alcohol **344** with a mesylate group in order to make it a better leaving group, and then react this directly with histamine to yield the saturated coupled compound **337** (**Scheme 136**).



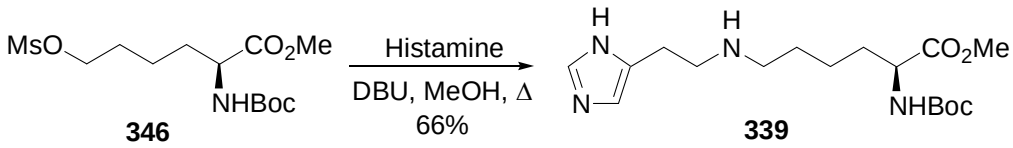
Scheme 136

The mesylation was performed under standard conditions using $MeSO_2Cl$ and the reaction was allowed to stir at room temperature for 24 hours. Following purification by column chromatography, **346** was isolated in 86% yield (**Scheme 137**). A new singlet peak is seen at 3.01 ppm (integrating for 3 protons) in the ^1H NMR spectrum, corresponding to the mesylate.



Scheme 137

Initially, **346** was coupled with histamine using sodium carbonate in MeOH and this reaction was stirred at room temperature for 13 hours. In this case, only starting material was recovered. The reaction was repeated, heating the mixture to 50 ^oC for 24 hours but again, only **346** was recovered. The solvent was changed to EtOH because of the higher boiling point, and the reaction was heated under reflux for 24 hours. However, this led to hydrolysis of the α-ester. The base was switched from sodium carbonate to milder DBU and the solvent was also changed to MeOH (**Scheme 138**). Again, the reaction was heated under reflux for 24 hours. This was successful and gave the saturated coupled product **339** in 66% yield.

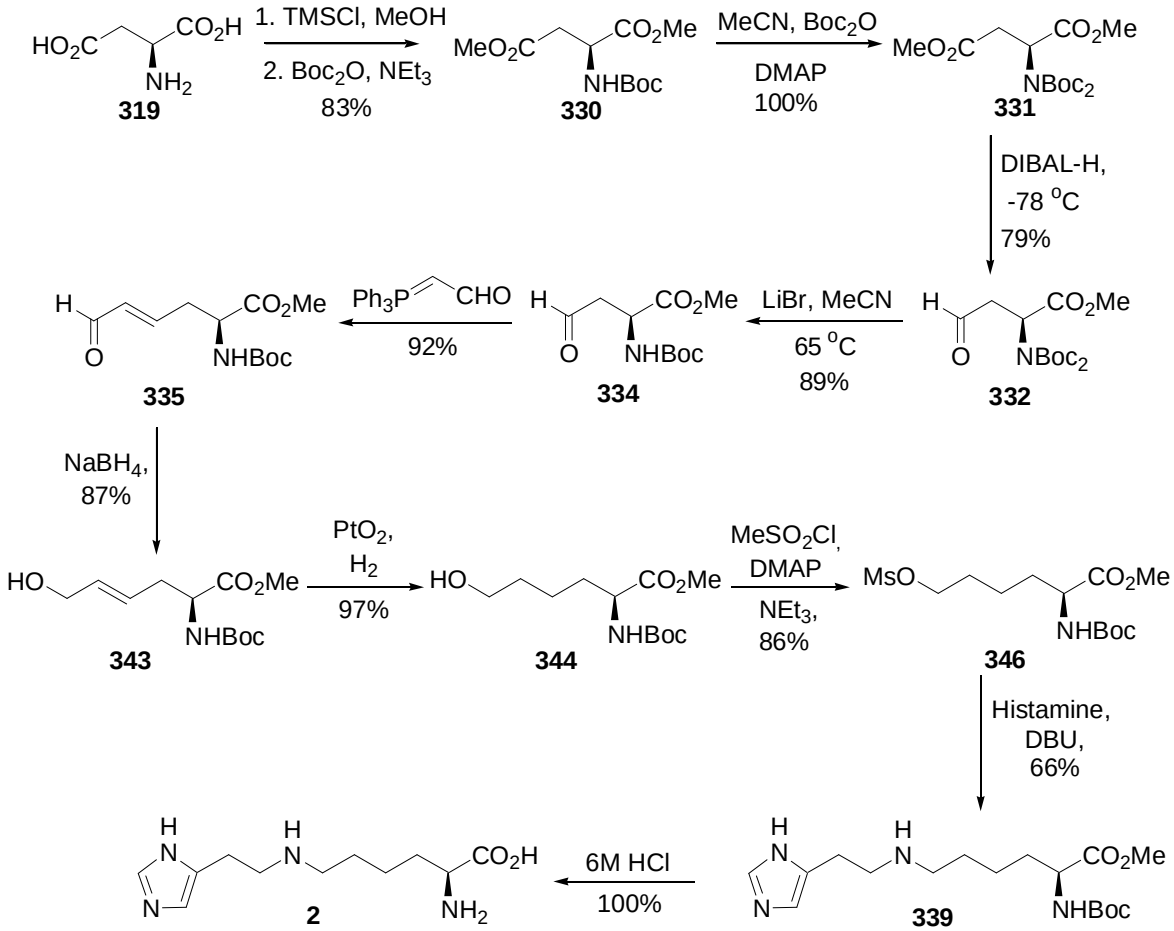


Scheme 138

Finally, deprotection of **339** by reflux in 6M hydrochloric acid for 24 hours, gave (*S*)-gizzerosine **2** in quantitative yield (**Scheme 139**). A Dowex® 55WX ion-exchange column was used for purification with a 5% ammonia solution as eluent. The optical rotation obtained ($[\alpha]_D^{23}$ +10.0 (*c* 0.2, H_2O)) is almost identical to the literature value (lit.[152] $[\alpha]_D^{22}$ +10.3 (*c* 1.3, H_2O)). All other experimental data obtained correlates well with that from the literature.[3,152]

Scheme 139

To summarise, (*S*)-gizzerosine **2** was prepared from commercially available L-aspartic acid **319** in 10 steps and 31% overall yield (**Scheme 140**). This optimised scheme could be used to prepare a number of other unusual amino acids, with two areas having scope for diversity. The key semi-aldehyde intermediate can be generated from a number of readily available amino acids (e.g. L-glutamic acid) and histamine in the case of (*S*)-gizzerosine could also be substituted for a number of other nucleophiles. Other advantages of this synthesis are the use of less toxic materials and the lack of any inefficient late-stage enzymatic resolution, as discussed previously.

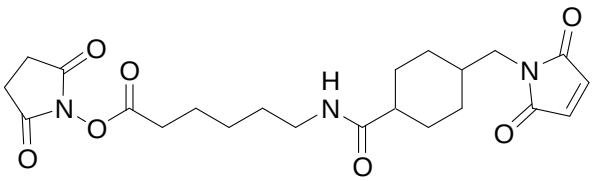


Scheme 140

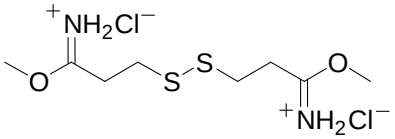
4 The Synthesis of Photo-Acids

4.1 Detecting Protein-Protein Interactions

Protein-protein interactions are key to organising cellular processes in space and time. They are involved in viral fusion or in growth factor signalling and so are promising targets for antiviral or anticancer drugs.[178] There are a number of methods to detect these interactions, each of which has strengths and weaknesses. An example is co-immunoprecipitation, where endogenous proteins are isolated with a specific antibody. Interaction partners that stick to the protein are identified by western blotting. However this method can only verify suspected interactions and is not a screening process. Another method often used is chemical cross-linking. Protein interactions are 'fixed' in place before trying to isolate and identify the interacting partners. Common cross-linkers used include the non-cleavable, membrane-permeable *N*-hydroxysuccinimide ester LC-SMCC **347** and the cleavable imidoester dimethyl dithiobispropionimidate (DTBP) **348** (**Figure 40**). Unfortunately, chemical cross-linking often results in smears on the gel or unresolvable aggregates during western blotting.



347



348

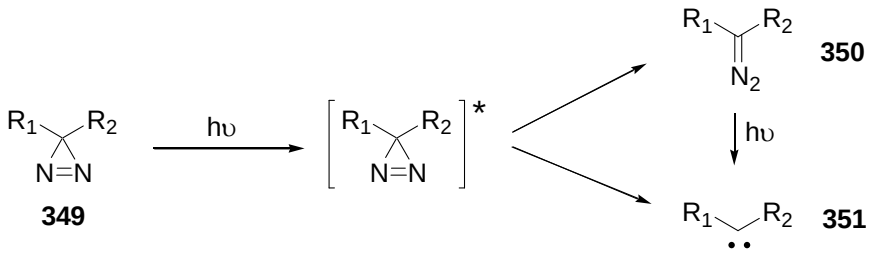
Figure 40

Photo cross-linking is one of the most informative biochemical approaches in studying interactions of biological molecules and was initially put forward by Westheimer and his group.[179] Photo cross-linking requires the introduction of a photoactivatable (photoreactive or photolabile) group into a protein to produce a precursor, which upon irradiation with ultraviolet light generates highly reactive species *in situ*. This photoactivatable group needs to be stable to peptide synthesis and must not disturb the interaction of the protein with the receptor. The precursor should photolyse at wavelengths clear of protein absorption.[180] Upon irradiation, the photoactivatable group incorporated into the molecule transforms into a highly reactive species (nitrene, carbene or radical) which attacks neighbouring groups to produce a covalent bond. The covalent bond formed must be stable to proteolysis and chemical degradation. Also, high yielding cross-linking reactions are needed with

picomole amounts of receptor. The covalently cross-linked interacting proteins can then be detected with high specificity using simple western blotting.

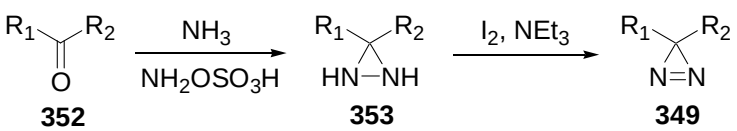
4.2 Photo Cross-Linking With Diazirines

Diazirines were first proposed as potential reagents for photo cross-linking by Smith and Knowles in 1973.[180] The diazirine functionality is surprisingly inert and stable; acid and alkali have no effect on the group at room temperature. Irradiation of a diazirine precursor **349** has been shown to produce a reactive carbene **351** after the light induced loss of nitrogen *via* the corresponding diazo compound **350** (**Scheme 141**).[4] Because of their electron deficiency, the (singlet) species are powerful electrophiles and reactions with double bonds or heteroatoms possessing non-bonding electron pairs are extremely rapid.[181] Cross-linking is also very specific due to the short half-life of the activated carbene.

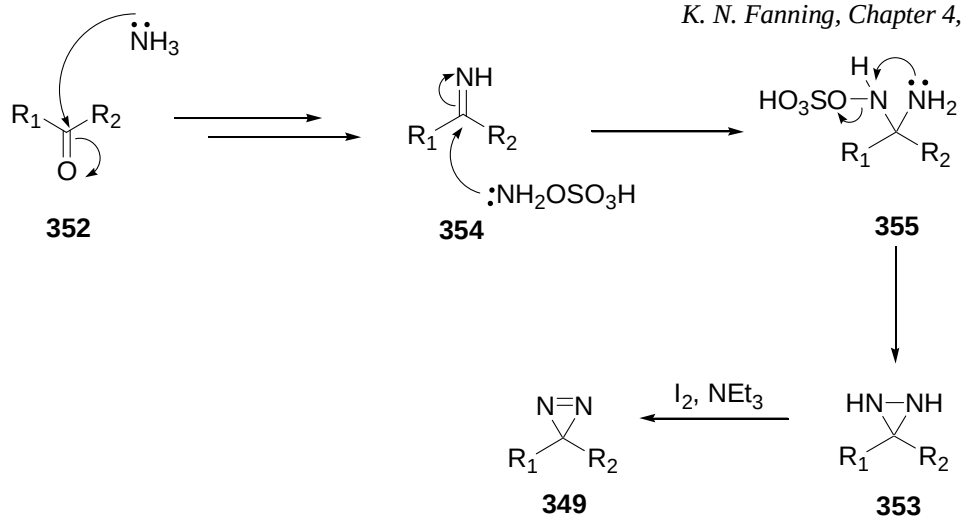


Scheme 141

The diazirine group is generally introduced by oxidation of the diaziridine obtained from the corresponding ketone **352** by treatment with ammonia and hydroxylamine-*O*-sulfonic acid or chloramine (**Scheme 142**).[182] Previously, the oxidation was effected using silver oxide. However, certain functional groups such as amines can interfere with the reagent and the reaction is often sluggish due to competing side reactions. It also forms a silver mirror with potential explosive character on the inside of the reaction vessel as the oxidation proceeds. In 1970, Church and Weiss reported that iodine as an oxidant (in basic media) produced a faster, cleaner and safer reaction. The mechanism for the formation of the diazirine is shown in **Scheme 143**.

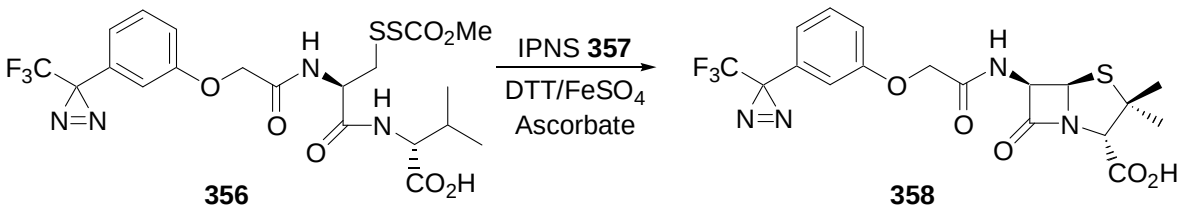


Scheme 142



Scheme 143

The diazirine functionality has been used previously to detect a number of protein-protein interactions. Balwin and co-workers have used the diazirinyl-containing substrate 2-[3-(3-trifluoro-methyl-3*H*-diazirin-3-yl)-phenoxy]acetyl-(*S*)-methyloxycarbonylsulphenyl-L-cysteinyl-D-valine (DCV) **356** in a study with the enzyme isopenicillin N synthetase (IPNS) **357** (**Scheme 144**).[183] The enzyme has been shown to catalyse the conversion of a number of substrates into the corresponding β-lactams, thereby providing routes to a new range of antibiotics. The selective, light-dependant covalent incorporation of the radiolabelled [^{14}C]DCV into IPNS was demonstrated, although the low specific radioactivity of the [^{14}C]DCV made it impracticable to localise the point of insertion.



Scheme 144

4.3 Photo Cross-Linking With Photoacids

Chemical synthesis of large proteins bearing a photoactivatable group is generally not viable due to the complexity involved. Since amino acids are the building blocks for proteins, if instead the tRNA of a cell is supplied with only an amino acid that is modified with a photoactivatable group, these groups can be easily incorporated into larger proteins that are not amenable to chemical synthesis. The modified amino acids are so similar, both in structure and in properties, to the unmodified ones, they can escape the stringent identity

control mechanisms during protein synthesis. Examples of this are rare and usually confined to bacteria.[181]

This method has previously been applied, using a photoactivatable diazirine ring, to discover a direct interaction of the progesterone-binding membrane protein PGRMC1 with Insig-1, a key regulator of cholesterol homeostasis.[4] The three modified amino acids used to identify this interaction are photo-leucine **3**, photo-isoleucine **359** and photo-methionine **360**, so called because of their similarity to the natural amino acids (**Figure 41**).

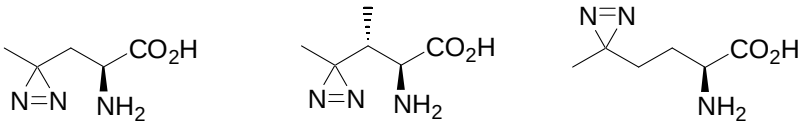
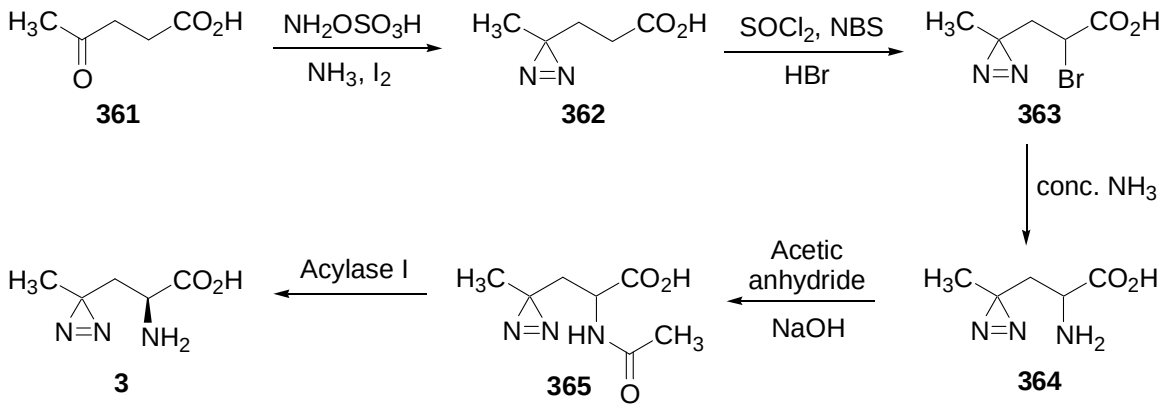


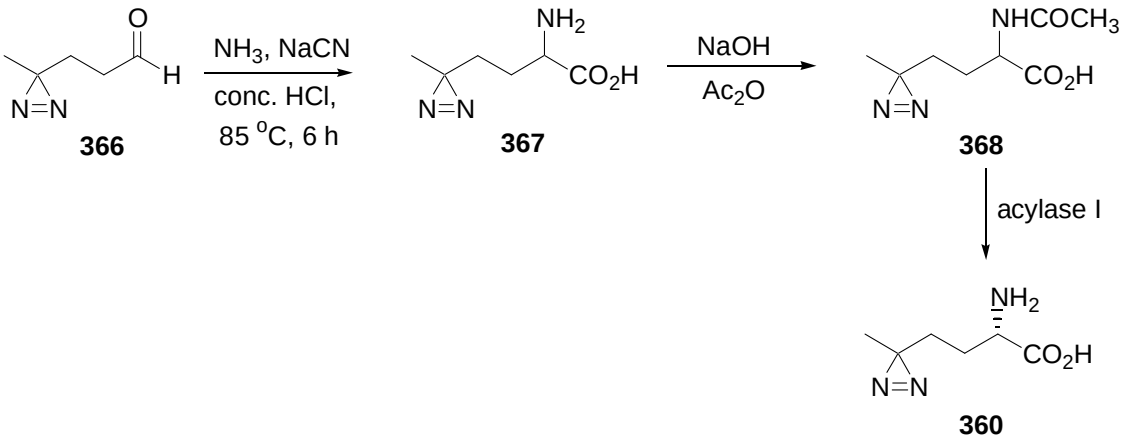
Figure 41

Photo-leucine **3** was obtained by α-bromination of the respective azi-carboxylic acid **362** according to the procedure described by Haarp and co-workers (**Scheme 145**).[184] This was followed by aminolysis of the azi-bromo-carboxylic acid **363**. Acetylation followed by enzymatic kinetic resolution using porcine kidney acylase I gave L-photo-leucine **3**.



Scheme 145

The corresponding azi-carboxylic acid **367** for photo-methionine was achieved by Strecker synthesis. This was followed again by acetylation and enzymatic kinetic resolution to yield L-photo-methionine **360** (**Scheme 146**). In the case of photo-isoleucine **359**, the azi-carboxylic acid was produced by the procedure of Church and Weiss.[182] This was followed again by bromination and aminolysis but no attempt was made to resolve the enantiomers of photo-isoleucine.



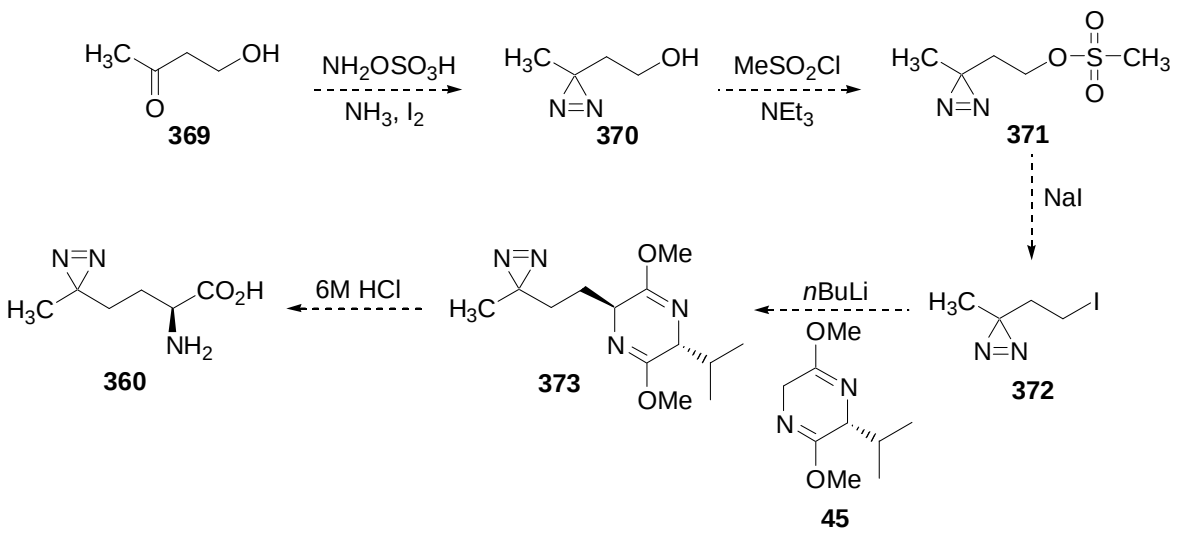
Scheme 146

Following radio-labelling to determine the uptake of modified amino acids, it was concluded that there were 3-4 photoactivatable positions in an average 500-amino acid protein. It was also found that the photo-acids do not affect cell viability or impair the function of the proteins. The PGRMC1 and the Insig-1 were cultured with and without photo-methionine and were cross-linked. When cells were grown in the absence of photo-methionine, no cross-linked band was detected by western blotting. In cells grown with photo-methionine, a strong band appeared at the expected molecular weight of the Insig-1-PGRMC1 cross-linked complex.

We wanted to develop a stereoselective flexible new route to diazirine-containing amino acids that would allow the synthesis of many different analogues using the same general pathway. We also wanted to generate an approach that had no highly toxic reagents, such as the hydrogen bromide or cyanides used by Thiele and co-workers (**Scheme 145** and **146**).[4] It was important to increase the overall yield of the scheme by not using inefficient kinetic resolution, where the maximum yield for the desired enantiomer is only 50%. The three photo-acids initially synthesised were to be used by Dr. Fraser Rixon in the Department of Virology, who was going to incorporate them into viral proteins and then investigate viral protein-protein interactions through photo cross-linking.

4.4 Progress Towards the Synthesis of Photo-Acids

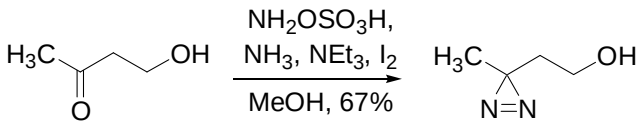
As stated before, we wanted to develop a flexible route to these photo-acids and, with this in mind, the initial route used is outlined below (**Scheme 147**). This route uses the commercially available Schöllkopf bis-Lactim ether ((2*R*)-(-)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine) **45** as a chiral auxiliary to insert the amino acid functionality, with the required chirality, at the desired position on the compound. This scheme focuses on the synthesis of photo-methionine **360**, due to the commercial availability of the starting alcohol, 3-ketobutanol **369**. This will be converted to the corresponding diazirine **370** using the procedure of Church and Weiss.[182] The alcohol will then be mesylated using methanesulfonyl chloride and triethylamine. The mesylate **371** will be converted to the iodide **372** using sodium iodide, in order to make it more labile during the reaction with the chiral auxiliary. Following alkylation of the auxiliary, hydrolysis with 6M HCl should furnish the desired photo-acid. This scheme could then be manipulated for the synthesis of the other two photo-acids, photo-leucine and photo-isoleucine, simply by changing the starting alcohol.



Scheme 147

3-Ketobutanol **369** was converted to the corresponding diazirine **370** using Church and Weiss' conditions (**Scheme 148**).[182] The alcohol was dissolved in MeOH and cooled to -78 ^{o}C. Liquid NH_3 was condensed into the flask and this was then allowed to stir at -78 ^{o}C for 4 hours. Hydroxylamine-*O*-sulfonic acid was added and the mixture was allowed to warm to room temperature for 1 hour, with a dry ice condenser. This gave the diaziridine which was then re-dissolved in MeOH and triethylamine and solid iodine were added to oxidise the diaziridine to the diazirine. This gave **370** in 67% yield after purification. In the ^{1}H NMR spectrum of **370**, the signal corresponding to 3-CH_3 has shifted upfield from 2.20

ppm to 1.48 ppm. In the ^{13}C NMR spectrum, the characteristic quaternary peak of diazirines is observed at 24.3 ppm.

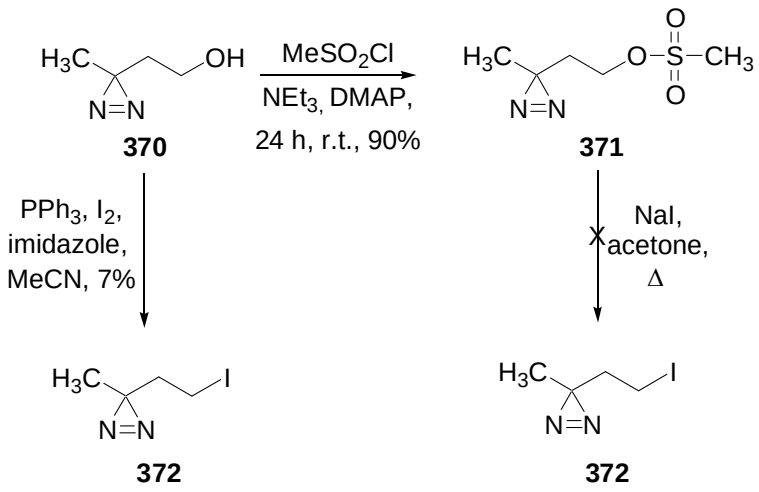


369 **370**

Scheme 148

From here the alcohol **370** was mesylated using methanesulfonyl chloride, triethylamine and DMAP, to hopefully enable more facile conversion to the iodide, which is a better leaving group for reaction with the chiral auxiliary (**Scheme 149**). The reaction mixture was stirred at room temperature for 24 hours and following purification by dry flash column chromatography, **371** was isolated in 90% yield. New signals, integrating for 3 protons, are observed at 3.09 ppm in the ^{1}H NMR spectrum corresponding to the mesylate CH_3. Also, the signals for 1-H_2 have shifted downfield from 3.54 ppm to 4.14 ppm, showing the increased electron withdrawing effect of the new mesylate group.

The next step involved conversion of the mesylate **371** to the corresponding iodide **372**. This reaction was first carried out using sodium iodide in acetone (**Scheme 149**).[185] The reaction was heated under reflux for 24 hours. Unfortunately, none of the desired iodide was isolated from this reaction. Due to the lack of reactivity of the mesylate in this particular reaction, it was attempted to perform a halogenation with the alcohol **370** to give the iodide **372** directly, missing out the mesylate **371**. This was performed using triphenylphosphine, imidazole and iodine (**Scheme 149**). The reaction mixture was stirred at room temperature for 2 hours and following purification, 7% of the iodide **372** was isolated. Unfortunately, despite repeating this reaction numerous times, no more of the iodide was isolated.

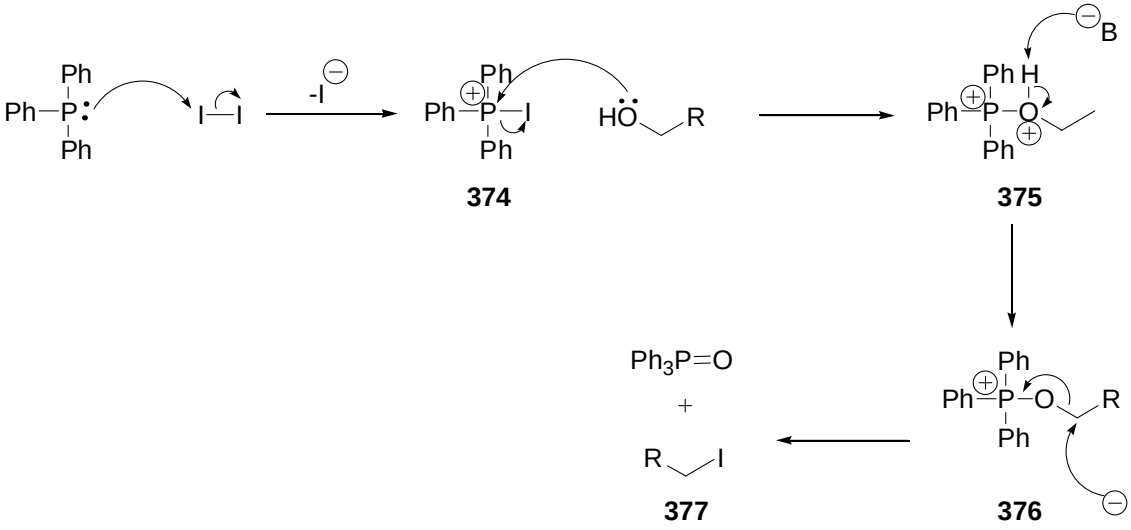


370 **371**

372 **372**

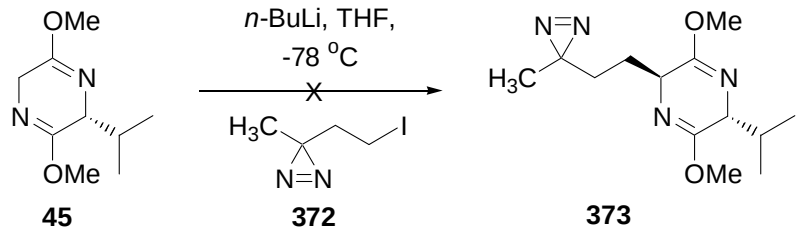
Scheme 149

The mechanism for this conversion is a variation of the Appel reaction (**Scheme 150**). The initial step is formation of the phosphonium salt pair **370** through reaction of PPh_3 with iodine. The alcohol displaces the iodine to give **375**. With primary and secondary alcohols, the iodide anion reacts in an S_N2 process to form the desired alkyl halide **377**.



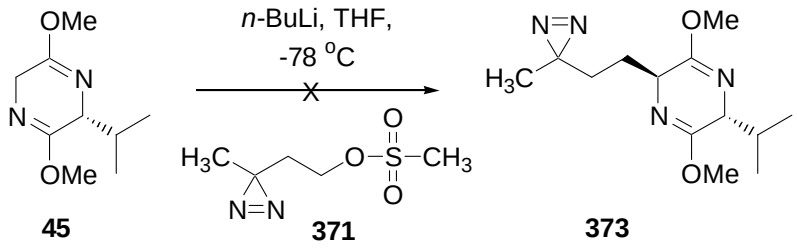
Scheme 150

The iodide **372** that was isolated from the reaction with PPh_3, imidazole and iodine was used in the next step, where the chiral auxiliary was to be attached. This was attempted by reacting **372** with the (*R*)-Schöllkopf bis-lactim ether **45**, and *n*-BuLi in THF at -78 ^oC (**Scheme 151**).[186] The reaction was allowed to stir at -78 ^oC for 5 hours. Unfortunately, none of the desired product **373** was isolated from this reaction.



Scheme 151

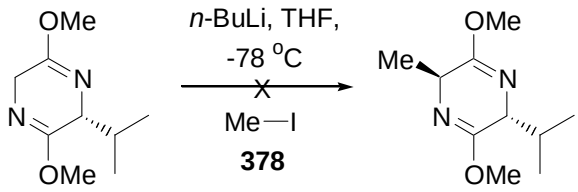
At this point, it was decided to couple the mesylate **371** directly with the chiral auxiliary **45**, due to both the low yield of the iodination reaction and the fact that no success was achieved when attempting to react the iodide with the chiral auxiliary. This reaction was attempted with the chiral auxiliary and *n*-BuLi in THF at -78 ^oC (**Scheme 152**). The reaction was maintained at -78 ^oC for 24 hours. Unfortunately, none of the coupled product **373** was isolated.



45 **371** **373**

Scheme 152

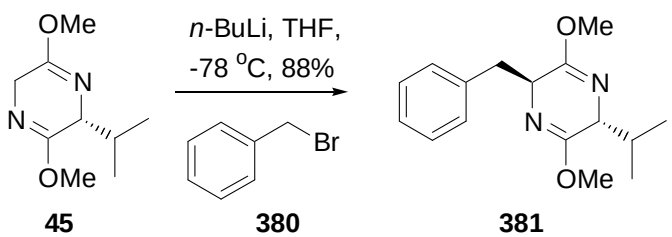
Due to the lack of success with the coupling reactions, some test procedures were carried out to check the reactivity of the Schöllkopf bis-lactim ether **45**. Methyl iodide **378**, a very simple substrate with the same leaving group as before, was reacted with the chiral auxiliary under the same conditions used previously (**Scheme 153**). Unusually, none of the coupled product **379** was isolated.



45 **378** **379**

Scheme 153

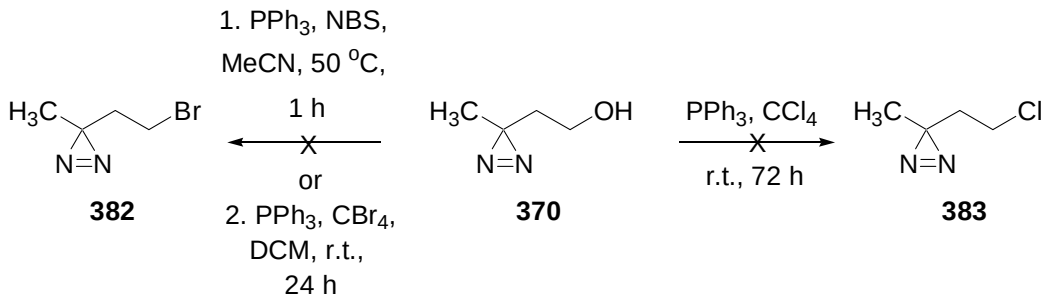
Another coupling reaction was attempted using benzyl bromide **380** as the substrate. The conditions used were the same as before. Again, none of the desired product **381** was isolated. It was thought that the chiral auxiliary had decomposed slightly and that these decomposition products were preventing the coupling of the auxiliary and the substrate. Therefore, the auxiliary was purified by column chromatography using 30% ethyl acetate in petroleum ether as the eluent. This purified auxiliary was then used in a coupling reaction with benzyl bromide as before (**Scheme 154**). The desired product **381** was isolated in 88% yield after purification. This was confirmed by the ^{1}H NMR spectrum in which the 5-H appears as a triplet at 4.26 ppm, showing that it is now adjacent to a CH_2. The molecular ion was also observed in the high resolution mass spectrum.



45 **380** **381**

Scheme 154

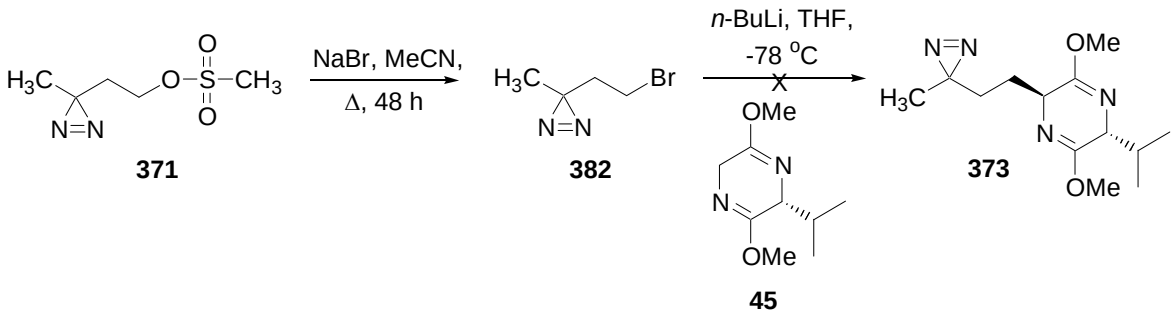
The reaction of the iodide **372** was then re-attempted, this time with the purified auxiliary (see **Scheme 151**). Unfortunately, there was still no reaction. Due to the success of the reaction with the benzyl bromide, it was attempted to convert the alcohol **370** to the corresponding bromide **382** and chloride **383**, and use these substrates in the coupling reaction with the chiral auxiliary (**Scheme 155**). To synthesise the bromide, two sets of conditions were used. Initially, the alcohol **370** was reacted with triphenylphosphine and *N*-bromosuccinimide in MeCN.[187] This mixture was warmed to 50 ^{o}C for 1 hour, but no product was isolated following work-up. Another method was attempted to synthesise the bromide using triphenylphosphine and carbon tetrabromide in DCM but again, none of the desired bromide **382** was isolated.[188] For the chloride, the alcohol **370** was reacted with triphenylphosphine in carbon tetrachloride.[188] This reaction mixture was stirred at room temperature for 72 hours but unfortunately, none of the desired chloride **383** was isolated from this reaction.



Scheme 155

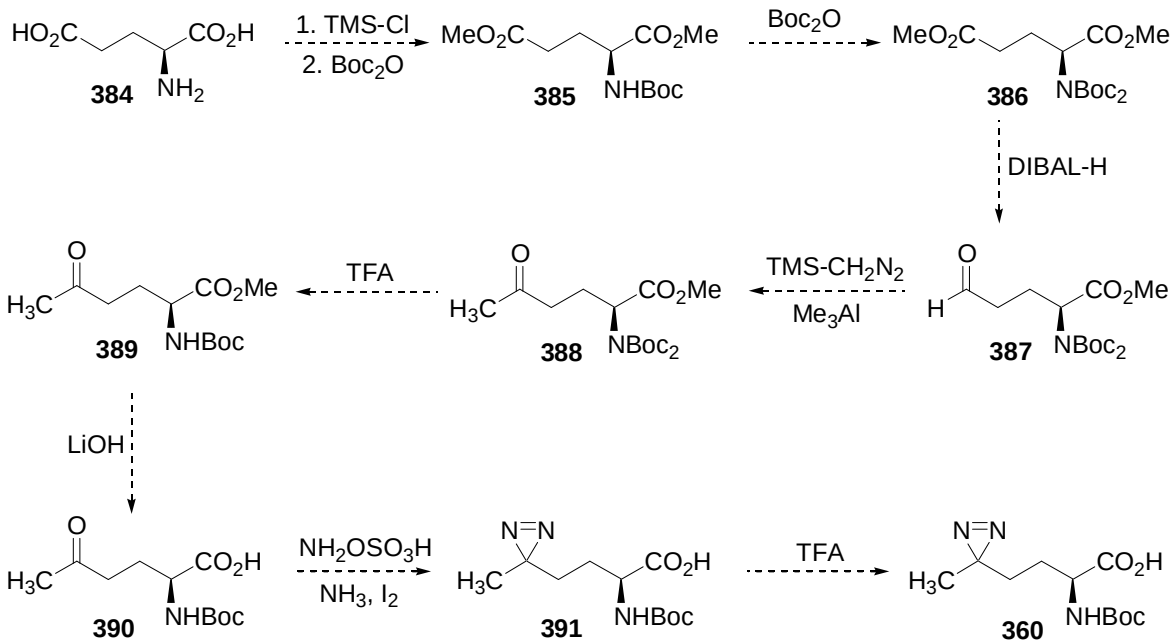
In order to synthesise the bromide **382** for reaction with the chiral auxiliary, it was decided to return to the mesylate **371** and attempt to exchange the leaving group for bromine. Therefore, the mesylate **371** was treated with sodium bromide in acetone and heated under reflux. After two days at reflux, a small amount product was observed when the ^{1}H NMR spectrum of the crude mixture was analysed, but the majority of the starting material remained. The reaction was attempted again using a solvent with a higher boiling point, hoping that the elevated temperature would drive the reaction to completion. The mesylate **371** was reacted with sodium bromide using MeCN as solvent (**Scheme 156**). This was heated under reflux at 70 ^{o}C for 24 hours and then at 95 ^{o}C for 24 hours. The ^{1}H NMR spectrum of the crude material showed that the reaction had gone to completion and the crude bromide **382** was taken on to the coupling step with the chiral auxiliary without further purification. The reaction was carried out under the same conditions as before, but unfortunately, none of the desired coupled product **373** was obtained. This particular route using the iodide **372** has very recently been successfully employed in the synthesis of photo-methionine by Kent and co-workers.[189] One of the reasons that this was not

successful for us could be the purity of the iodide that was isolated. It was likely that it was contaminated with residual iodine which may have interfered with the coupling.



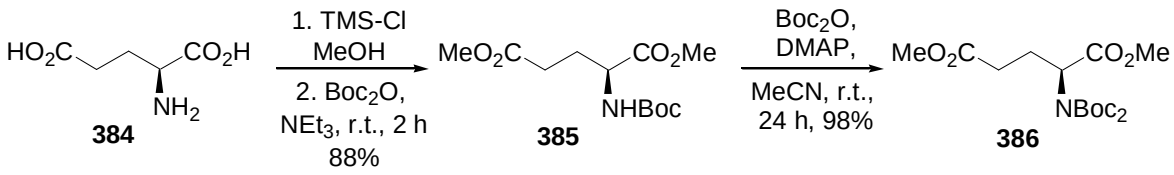
Scheme 156

At this point, despite attempting numerous reactions and routes, progress had not been made towards the target molecule and it was decided to modify the synthetic scheme. We still wanted to begin with a commercially available substrate that could be easily substituted to create all three photo-acids. The decision was also taken to introduce the diazirine ring late in the synthesis, to minimise any problems that this group may be causing. To this end, a new route was devised and is shown below for photo-methionine (**Scheme 157**). The route begins with commercially available L-glutamic acid **384**, which is then protected as the di-ester di-Boc analogue **386**. This is selectively reduced to the aldehyde **387**.[164,166] This aldehyde **387** is then converted to the methyl ketone **388** using trimethylsilyldiazomethane . Following this, one of the Boc-groups is selectively removed to yield **389** and the ester is hydrolysed to the acid, so as to limit any interference at the aziridination step. Compound **390** is then aziridinated to give the diazirine **391** which is deprotected to give photo-methionine **360**.



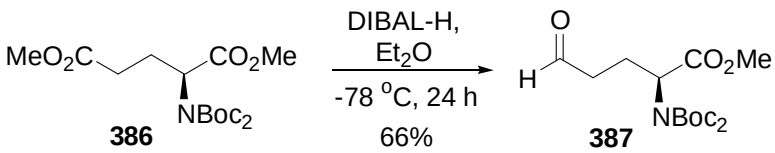
Scheme 157

L-Glutamic acid **384** was treated with trimethylsilyl chloride, triethylamine and di-^{t}butyl dicarbonate and this first step proceeded well, with **385** being isolated in 88% yield (**Scheme 158**).[162,163] In the ^{1}H NMR spectrum of **385**, two sets of signals, each integrating for three protons, can be observed at 3.71 and 3.77 ppm, corresponding to the two esters. Also, a singlet integrating for 9 protons is observed at 1.47 ppm, corresponding to the Boc-protecting group. Compound **385** was then protected with a second Boc-group by treating it with DMAP and di-*tert*-butyl dicarbonate and stirring at room temperature for 24 hours (**Scheme 158**). After purification by column chromatography, **386** was isolated in an excellent 98% yield. The singlet at 1.52 ppm in the ^{1}H NMR spectrum now integrates for 18 protons and corresponds to the two Boc-groups. Also, the doublet seen previously for NH at 5.14 ppm in the ^{1}H NMR spectrum of **385** is no longer observed.



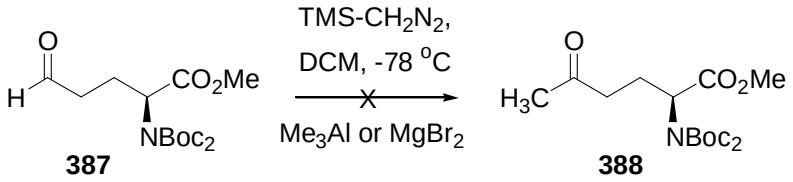
Scheme 158

Following this, the reduction of **386** to **387** was attempted using 1.4 equivalents of DIBAL-H at -78 ^{o}C (**Scheme 159**). Initially, the reaction was stirred at -78 ^{o}C for between 5 minutes and 2 hours (according to the literature), but both of these attempts led to a mixture of **386** and **387**. Next, the reaction was allowed to warm to room temperature overnight following addition of the DIBAL-H and a period at -78 ^{o}C, but this led to over-reduction to the corresponding alcohol and these mixtures were extremely difficult to separate. Following a number of attempts, the optimum conditions were found to be maintenance of the reaction at -78 ^{o}C for 24 hours. This ensured that no starting material remained and that there was no over-reduction to the corresponding alcohol. Interestingly, there was no reduction of the second ester observed in these reactions, showing complete regioselectivity was achieved. The semi-aldehyde intermediate **387** was isolated in 66% yield. Of note in the ^{1}H NMR spectrum is the triplet peak, integrating for one proton at 9.81 ppm. This corresponds to the new aldehyde proton. In the ^{13}C spectrum, a new peak for CH is observed at 201.0 ppm, corresponding to the carbon of the aldehyde.



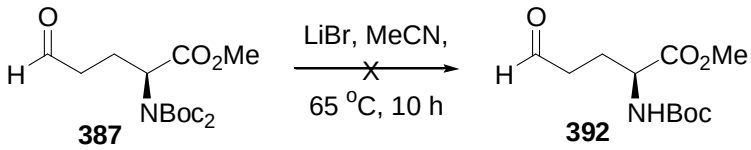
Scheme 159

The next step involved conversion of the key semi-aldehyde **387** to the methyl ketone **388** (**Scheme 160**). This conversion was attempted by treating **387** with trimethylsilyldiazomethane and trimethylaluminium in DCM at -78 ^{o}C.[190] Unfortunately, none of the desired compound **388** was isolated from this reaction. The Lewis acid was changed to magnesium bromide and the reaction attempted again, however, a similar result was achieved.[191]



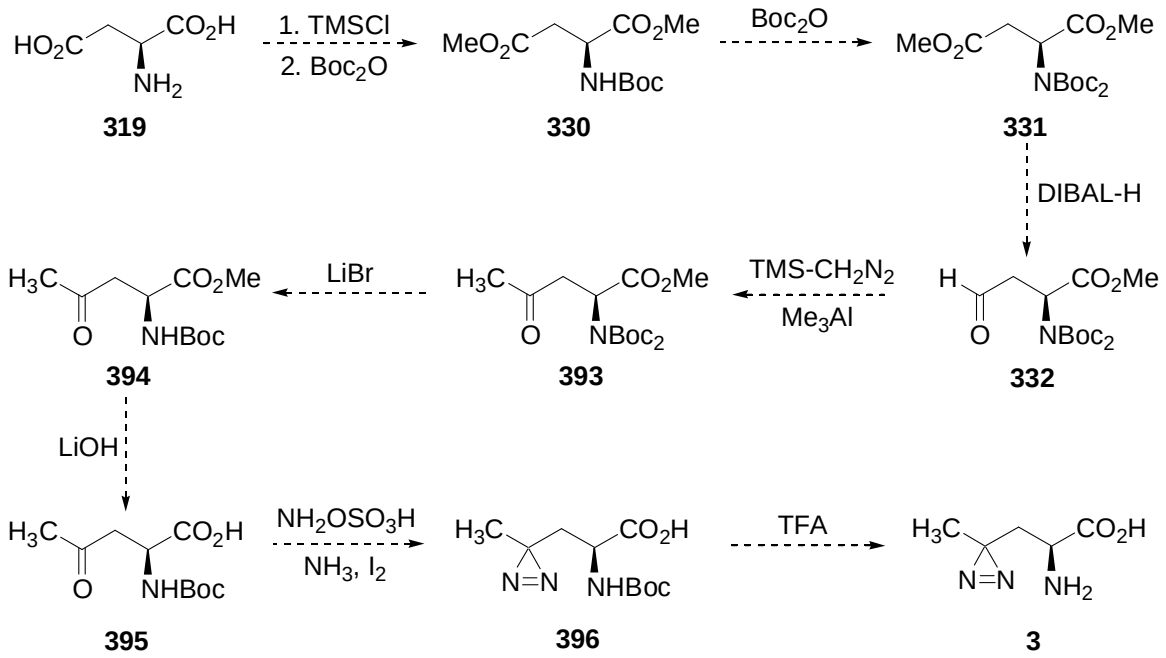
Scheme 160

It came to our attention that Martín and co-workers had used lithium bromide to selectively remove one Boc-group from a number of di-protected compounds.[167] It was now believed that the second Boc-group was hindering the conversion of **387** to **392**. Thus, **387** was treated with lithium bromide in MeCN and heated to 65 ^{o}C for 10 hours as previously reported (**Scheme 161**). Unfortunately, **392** was not isolated from this reaction and the ^{1}H NMR spectrum of the crude material showed a mixture of di-protected **387** with a trace amount of mono-protected **392** and a number of unknown peaks.



Scheme 161

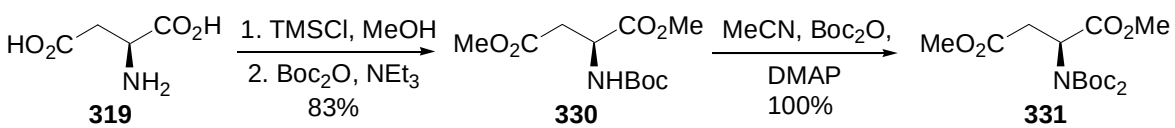
Work was concurrently being carried out to prepare photo-leucine **3**. As this proved more successful and due to limited time, our focus shifted to the synthesis of **3**. The new proposed route for the synthesis of photo-leucine **3** is shown below (**Scheme 162**). This is the same general scheme as used initially for photo-methionine **360**. In the case of photo-leucine, L-aspartic acid **319** is protected as the di-ester and the amino functionality is protected with two Boc-groups to give **331**. As before, this provides the necessary selectivity during the reduction of the β-ester to the aldehyde **332**. This aldehyde **332** is then converted to the methyl ketone **393** with trimethylsilyldiazomethane and trimethylaluminium. Following this, one of the Boc-groups is removed with lithium bromide and the ester is hydrolysed to the acid, so as to limit any interference at the aziridination step. The aziridination is then carried out to give **396** which is deprotected to give photo-leucine **3**.



319 **330** **331** **394** **393** **332** **395** **396** **3**

Scheme 162

Thus, L-aspartic acid **319** was treated with trimethylsilyl chloride in MeOH to yield the di-ester (**Scheme 163**).[162] After 24 hours at room temperature, triethylamine and di-*tert*-butyl dicarbonate were added to mono-protect the amine.[163] This reaction was complete after 2 hours and **330** was isolated in 83% yield. The experimental data collected correlates well with the literature data.[164] Due to the adjacent stereogenic centre, the 3-H_2 protons are in chemically different environments, and thus appear as two separate doublet of doublet peaks at 2.85 and 3.03 ppm in the ^{1}H NMR spectrum. The di-Boc-protected amino acid **331** was then prepared in quantitative yield using di-*tert*-butyl dicarbonate and DMAP (**Scheme 163**).[165] This reaction mixture was stirred for 24 hours at room temperature. The NH signals observed at 5.50 ppm in the ^{1}H NMR spectrum for **330** are now not seen and the peak for the Boc-groups at 1.53 ppm now integrates for 18 protons. The optical rotation obtained ($[\alpha]_D^{25}$ -61.0 (*c* 2.0, $CHCl_3$)) corresponds exactly with the literature ($[\alpha]_D^{25}$ -61.0 (*c* 2.0, $CHCl_3$)).[164]

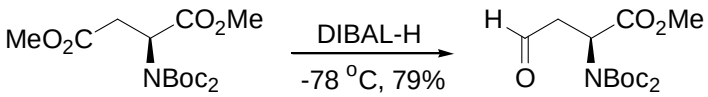


319 **330** **331**

Scheme **163**

The reduction of **331** to **332** was carried out using 1.4 equivalents of DIBAL-H at -78 ^{o}C (**Scheme 164**). These were the optimum conditions used when this reduction was carried out with the glutamic analogue in the synthesis of photo-methionine. The semi-aldehyde

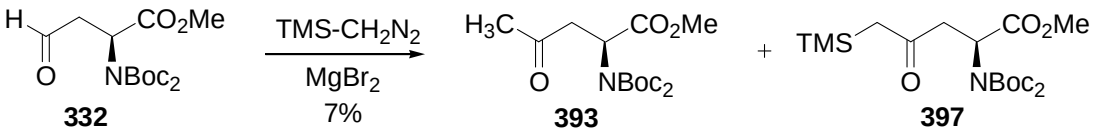
intermediate **332** was isolated in 79% after purification. The experimental data correlates well with that obtained from the literature.[164] A new signal for the aldehyde proton is seen at 9.82 ppm in the ^{1}H NMR spectrum and at 198.5 ppm in the ^{13}C NMR spectrum.



331 **332**

Scheme 164

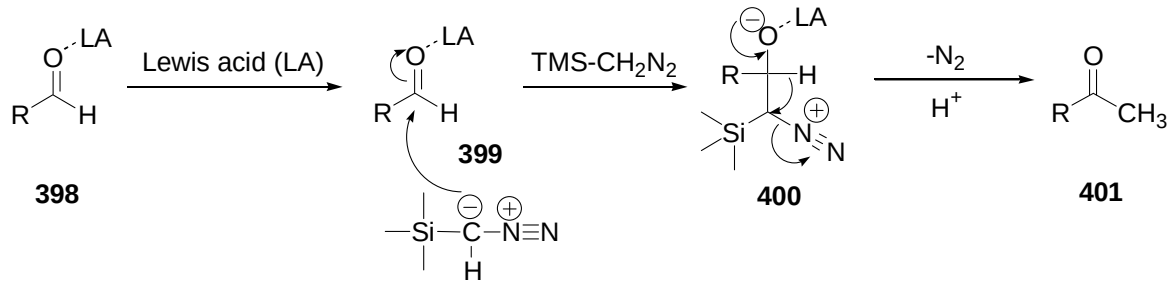
The next step was to convert the semi-aldehyde **332** to the methyl ketone **393** (**Scheme 165**). Initially, this was attempted using a method that was used for the same reaction in the synthesis of photo-methionine i.e. trimethylsilyldiazomethane with magnesium bromide.[191] While this reaction did work, the methyl ketone **393** was isolated in only 7% yield. A new CH_3 singlet is observed in the ^{1}H NMR spectrum at 2.09 ppm and the aldehyde signals, previously at 9.82 ppm, are no longer observed. Also, in the ^{13}C NMR spectrum, there is a new quaternary signal at 206.5 ppm. One of the main products formed was the TMS-protected methyl ketone **397**. This is characterised by two doublets for 5-H_2, observed at 2.08 and 2.13 ppm in the ^{1}H NMR spectrum.



332 **393** **397**

Scheme 165

The mechanism for this transformation is shown in **Scheme 166**. The Lewis acid coordinates to the aldehyde **398** through the oxygen of the carbonyl group. The trimethylsilyldiazomethane can then attack the electrophilic carbon of the carbonyl group **399**. Following a 1,2-hydride shift, N_2 is displaced to yield the TMS-protected methyl ketone. The TMS-group is normally removed with an acidic workup.



398 **399** **400** **401**

Scheme 166

Due to the low yield of the reaction when using magnesium bromide as the Lewis acid, other methods were investigated. **Table 2** shows the other conditions used to convert the semi-aldehyde **332** into the methyl ketone **393**. The Lewis acid was changed to trimethylaluminium, as before, and a stronger acid was used in the work-up, as in reaction 2 of **Table 2**, in an effort to decompose any **397** which had formed during the reaction.[190] This led to an increased yield of 20% of the methyl ketone **393**. Unfortunately, when the concentration of the acid was increased to 2M HCl, as in reaction 3, the major product isolated was **397** in 71% yield. It was then attempted to remove the TMS-group from **397** by repeated washings with 6M HCl as in reaction 4. While this was successful to a degree, only 21% of **393** was isolated. We then reverted to milder 0.1M HCl in the work-up and maintained the reaction at -78 ^{o}C, as in reaction 5, to give **397** as the major product in 14% yield. Finally, the Lewis acid was changed to tin dichloride and the reaction stirred at room temperature for 30 minutes, as in reaction 6.[190] Unfortunately, no product was isolated in this reaction.

Reagent	Lewis Acid	Conditions	Work-up	Product
1. TMS-CH_2N_2	$MgBr_2$	0 ^{o}C for 1 h r.t. for 4 h	0.1M HCl	7% **393**
2. TMS-CH_2N_2	Me_3Al	-78 ^{o}C for 1 h -40 ^{o}C for 1 h	1M HCl	20% **393**
3. TMS-CH_2N_2	Me_3Al	-78 ^{o}C for 1 h -40 ^{o}C for 1 h	2M HCl	71% **397**
4. TMS-CH_2N_2	Me_3Al	-78 ^{o}C for 1 h -40 ^{o}C for 1 h	6M HCl, repeated washings	21% **393**
5. TMS-CH_2N_2	Me_3Al	-78 ^{o}C for 5 h	0.1M HCl	14% **397**
6. TMS-CH_2N_2	$SnCl_2$	r.t. for 30 min	0.1M HCl	No product

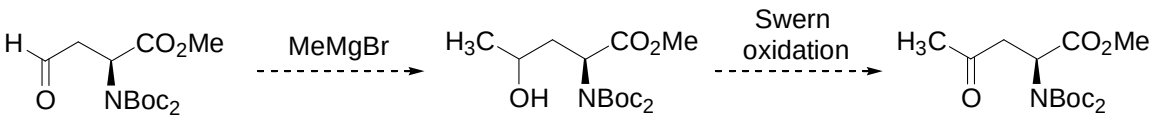
Table 2

It was then attempted to deprotect the TMS-protected methyl ketone **397** in a separate reaction, as it seemed to be the major product recovered in a lot of the reactions (**Scheme 167**). Compound **397** was reacted with TBAF in DMF at room temperature for 2 hours.[192] Unfortunately, no product was isolated from this reaction.

397 **393**

Scheme 167

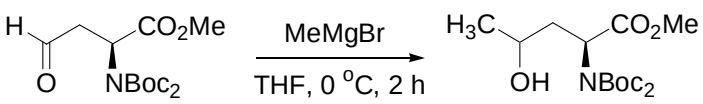
As this approach did not allow the preparation of the methyl ketone **393** in larger quantities, another method was attempted (**Scheme 168**). The semi-aldehyde **332** would be converted to the methyl alcohol **402** using a Grignard reaction.[193,194] Following this, the methyl alcohol **402** would be re-oxidised to the methyl ketone **393**, and from here, the initial **Scheme 162** could continue to produce the target molecule.



332 **402** **393**

Scheme 168

A solution of methyl magnesium bromide (1.4M in THF) was used for the Grignard reaction and this was stirred at 0 ^{o}C for 2 hours (**Scheme 169**). It was quenched with a saturated solution of NaCl and following purification by column chromatography, **402** was isolated in 15%. A new doublet signal, integrating for 3 protons, is observed at 1.22 ppm in the ^{1}H NMR spectrum, corresponding to the terminal methyl group. The aldehyde signal, previously seen at 9.82 ppm, is now not observed and instead, a doublet signal for the hydroxyl proton is seen at 5.21 ppm in the ^{1}H NMR spectrum. Despite the low yield, the methyl alcohol **402** was taken to the oxidation step.

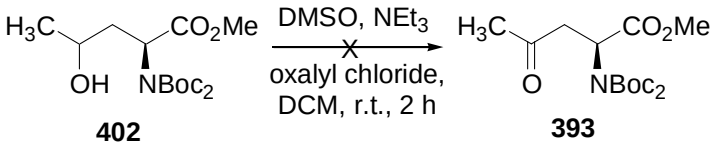


332 **402**

Scheme 169

A Swern oxidation was employed to convert the methyl alcohol **402** to the methyl ketone **393** (**Scheme 170**). Compound **402** was reacted with DMSO, triethylamine and oxalyl

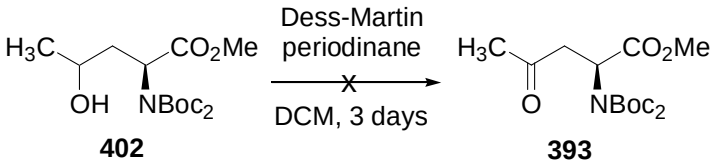
chloride at room temperature for 2 hours. Following purification by column chromatography only starting material was recovered.



402 **393**

Scheme 170

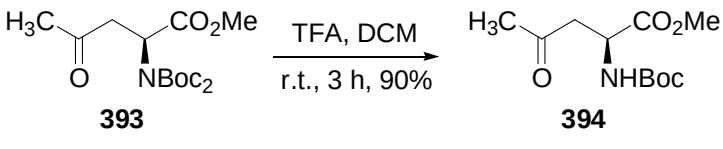
Another oxidation method was attempted; the Dess-Martin oxidation (**Scheme 171**).[193] The methyl alcohol **402** was reacted with Dess-Martin periodinane at room temperature for 3 days. Once again though, this reaction did not work and none of the methyl ketone **393** was isolated.



402 **393**

Scheme 171

At this point we had limited quantities of the methyl ketone **393** as the only reaction to yield **393** was the methylation of **332** with trimethylsilyldiazomethane. Despite this, one of the Boc-protecting groups was removed by reacting **393** with trifluoroacetic acid in DCM (**Scheme 172**). The crude material was purified immediately by column chromatography to yield 90% of the mono-Boc protected methyl ketone **394**. A new doublet signal for the amine is observed in the ^{1}H NMR spectrum at 5.53 ppm and the peak for the Boc-group at 1.47 ppm, previously integrating for 18 protons, now integrates for 9 protons, showing that one Boc-group has been removed.

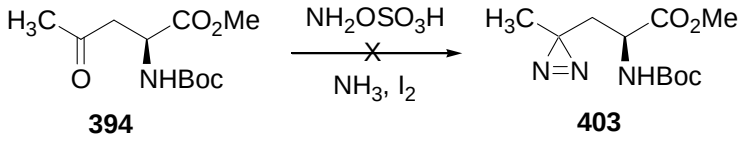


393 **394**

Scheme 172

This compound was used in the next step of the scheme where the diazirine ring is introduced. Hydrolysis of the ester was not performed due to the limited quantities of **394**. This reaction was carried out according to the procedure of Church and Weiss, using solid iodine as the oxidant (**Scheme 173**).[182] **394** was reacted with anhydrous liquid ammonia in MeOH at -78 ^{o}C for 4 hours. Hydroxylamine-*O*-sulfonic acid was dissolved in MeOH and added slowly to the flask to give the diaziridine. This was allowed to warm to room

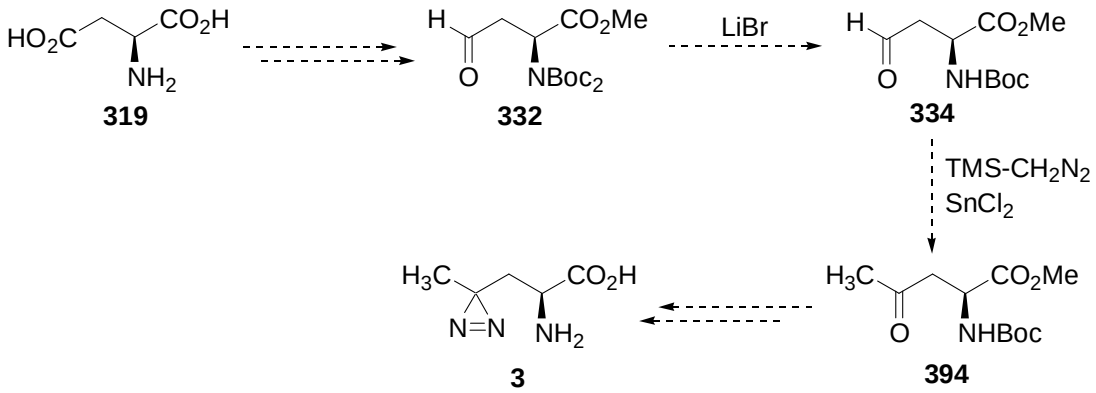
temperature overnight to evaporate the ammonia (boiling point: -33 °C). The residue was re-dissolved in MeOH and triethylamine was added followed by solid iodine to oxidise the diaziridine to the diazirine. Unfortunately, there was no product isolated from this reaction and we no longer had any of the methyl ketone **394** to continue to investigate this reaction.



394 **403**

Scheme 173

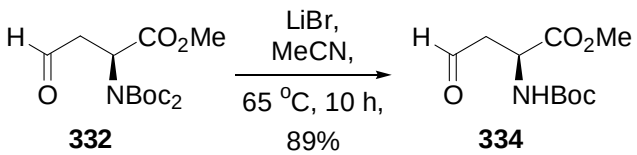
Again, a re-think of the synthesis was carried out and it was decided that, perhaps in the second Boc-group was hindering the conversion of the semi-aldehyde **332** to the methyl ketone **393**. As discussed for photo-methionine, Martín and co-workers have successfully used lithium bromide to selectively remove one Boc-group from a number of di-protected compounds.[167] It was therefore decided to employ this reaction again as shown below in **Scheme 174** but the remainder of the route was to remain similar to that in **Scheme 162**.



319 **332** **334** **394** **3**

Scheme 174

The semi-aldehyde **332** was treated with lithium bromide in MeCN and heated to 65 °C for 10 hours (**Scheme 175**). Following immediate purification by column chromatography, **334** was isolated in 89% yield. In the ^{1}H NMR spectrum, a new doublet signal is observed at 5.41 ppm, corresponding to NH. Also, the singlet at 1.47 ppm corresponding to the Boc-group now integrates for only 9 protons, indicating that one of the groups has been removed.

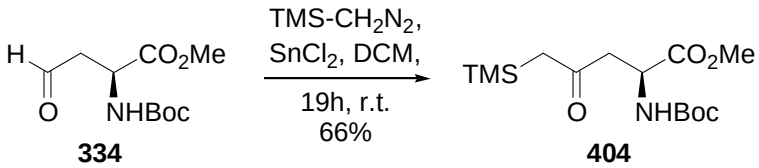


332 **334**

Scheme 175

Following this successful result, **334** was used in the next step where the methyl ketone would be introduced. Previously, this reaction was attempted using a number of methods and reagents, however, due to literature precedent, it was decided to use tin dichloride as the Lewis acid for this reaction.[190] Our tin dichloride was complexed with water but the reaction requires completely anhydrous conditions. Thus, the reagent was placed in an oven at 110 ^{o}C for 48 hours and then heated to 100 ^{o}C under vacuum for 3 hours, to remove all the water. This anhydrous reagent was then reacted with **334**, trimethylsilyldiazomethane and DCM at room temperature. Unfortunately, this reaction produced mixtures of **334**, the TMS-protected analogue **404** and the desired methyl ketone **394**. As the TMS-protected methyl ketone **404** was generally the major fraction, it was decided to optimise the reaction for the synthesis of this compound and then remove the TMS-group after isolation.

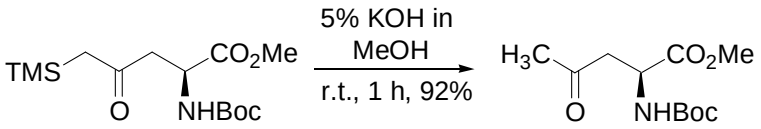
Thus, the optimised reaction conditions involved stirring the anhydrous tin dichloride and trimethylsilyldiazomethane with the semi-aldehyde **334** in DCM at room temperature for 19 hours (**Scheme 176**). During purification, it was found that the desired compound **404** decomposes when exposed to the silica gel on a column for extended periods. Purification therefore involved a short silica column and the crude mixture was passed through very quickly. Following this, **404** was isolated in 66% yield. A new singlet is observed in the ^{1}H NMR spectrum, integrating for 9 protons, at 0.0 ppm corresponding to the TMS-group. Also, the triplet for the aldehyde proton previously observed at 9.76 ppm is now not seen. Instead, a new singlet, integrating for 2 protons, is seen at 2.08 ppm corresponding to 5-H_2.



334 **404**

Scheme 176

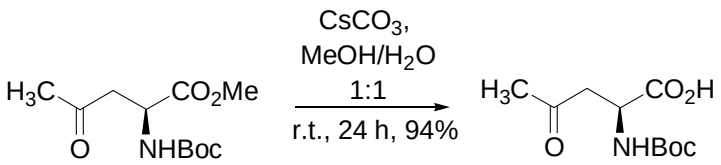
The next step was removal of the TMS-group to yield the methyl ketone **394**. This was carried out by reacting **404** with a solution of 5% potassium hydroxide in MeOH at room temperature for 1 hour (**Scheme 177**). This gave the desired methyl ketone **394** in an excellent 92% yield, without the need for further purification. In the ^{1}H NMR spectrum, the singlet for the TMS-group at 0.0 ppm is no longer observed and the peak at 2.08 ppm for 5-H_2 has now shifted to 2.20 ppm and integrates for 3 protons (5-H_3).



404 **394**

Scheme **177**

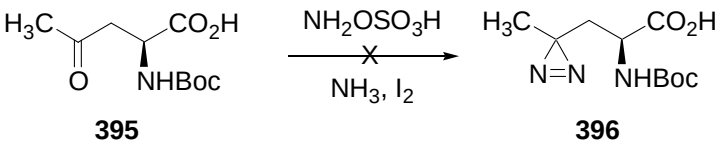
Following this, **394** was used in the next step, where the methyl ester is hydrolysed to the acid. This was carried out in an effort to prevent any reaction with ammonia during the aziridination step. Initially, **394** was reacted with a 1M NaOH solution at 0 ^{o}C for 1 hour.[195] Unfortunately, none of the desired product **395** was isolated from this reaction. It was then attempted to react **394** with another base, lithium hydroxide, in THF at 0 ^{o}C for 4 hours.[196] Again, no product was isolated from this reaction. We then decided that a larger counter-ion, such as cesium, would have a more diffuse charge and accordingly, would have looser ionic interactions and therefore would not interfere with the nucleophilic properties of the hydroxide ion. Thus, **394** was treated with cesium carbonate in MeOH:H_2O 1:1 at room temperature for 24 hours (**Scheme 178**). Acid **395** was isolated in 94% yield without the need for further purification. The singlet for the OMe group, which previously appeared at 3.76 ppm in the ^{1}H NMR spectrum, is no longer observed.



394 **395**

Scheme 178

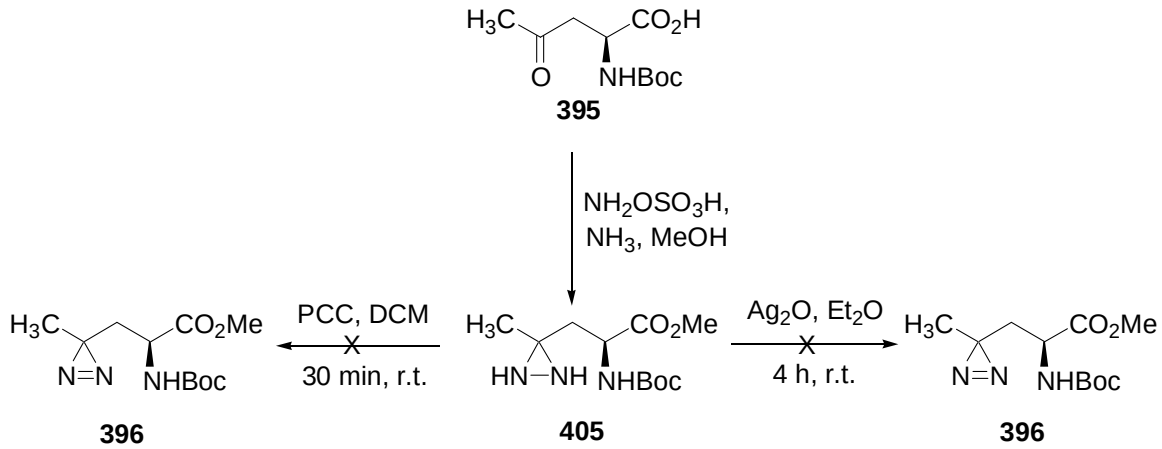
Acid **395** was used in the penultimate step of the scheme, where the diazirine ring is introduced. This procedure was attempted initially using Church and Weiss' conditions (**Scheme 179**).[182] Unfortunately, no product was isolated from this reaction. We decided to analyse the reaction as it progressed, by isolating the diaziridine **405** before the oxidation to the desired compound **396**. From the crude ^{1}H NMR spectrum, diaziridine **405** was present. Thus, a second oxidation was attempted, instead of using solid iodine as is used in Church and Weiss' procedure.



395 **396**

Scheme 179

We assumed 100% conversion to the diaziridine **405** had taken place and attempted an oxidation using PCC at room temperature for 30 minutes (**Scheme 180**).[197] Unfortunately, no product was isolated from this reaction. A final attempt was made to oxidise the diaziridine to the diazirine **396**, using silver oxide (**Scheme 180**).[198] This procedure had been used prior to Church and Weiss using solid iodine for the oxidation.[182] The silver oxide was freshly prepared by adding a 1M NaOH solution to a 1M boiling solution of silver nitrate. The precipitated silver oxide was then filtered off and washed with H_2O, acetone and ether and used immediately. The silver oxide was added to a solution of the diaziridine in diethyl ether and this mixture was stirred in the dark for 4 hours. Again, unfortunately, no product was isolated from this reaction.



Scheme **180**

Due to time constraints, this reaction could not be investigated further, although significant progress has been made towards a stereoselective route that is flexible and high-yielding.

Although the desired diazirine-containing amino acids were not synthesised during this study, an interesting keto-silyl derived amino acid was unexpectedly isolated and this is now being used to investigate the Peterson reaction of these compounds.

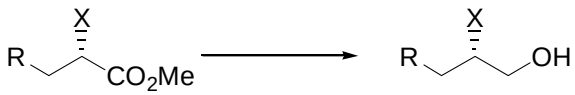
5 Experimental

5.1 General Experimental

All reactions were performed under an atmosphere of nitrogen or argon unless otherwise noted. Reagents and starting materials were obtained from common commercial sources and used as received. THF and Et_2O were distilled from sodium and benzophenone. Lithium bromide was oven dried (110 ^oC) for at least 12 h before use. ^1H NMR and ^{13}C NMR spectra were recorded on a DPX 400 spectrometer with chemical shift values in ppm relative to residual chloroform (δ_H 7.28 and δ_C 77.2) as standard. Infrared spectra were recorded using Golden Gate apparatus on a JASCO FT/IR 410 spectrometer and mass spectra obtained using a JEOL JMS-700 spectrometer. Flash column chromatography was carried out using Fisher Matrix silica 60. Macherey-Nagel aluminium backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by staining with basic potassium permanganate solution. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using an AA series Automatic polarimeter. $[\alpha]_D$ values are given in units $10^{-1}degcm^2g^{-1}$.

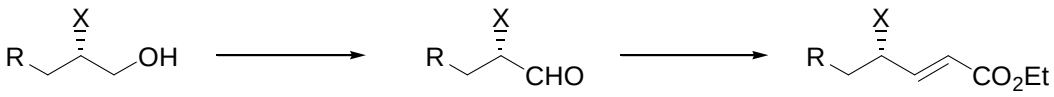
5.2 Chapter 2

General Procedure 1: DIBAL-H Reduction



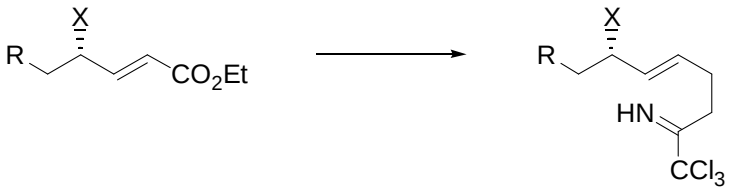
DIBAL-H (1M solution in Et_2O, 2.2 equiv.) was added dropwise to a solution of the ester (1.0 equiv.) in Et_2O (30 mL) at -78 ^oC. The reaction mixture was allowed to stir at -78 ^oC for 4 h before being allowed to warm to room temperature overnight. The flask was then cooled with an ice-bath and a saturated solution of NH_4Cl was added to quench the reaction. The flask was allowed again to warm to room temperature. A white precipitate was produced which was filtered through a pad of Celite® and washed multiple times with Et_2O. The filtrate was then concentrated *in vacuo* and purified using flash column chromatography.

General Procedure 2: One-Pot Swern/Horner-Wadsworth-Emmons



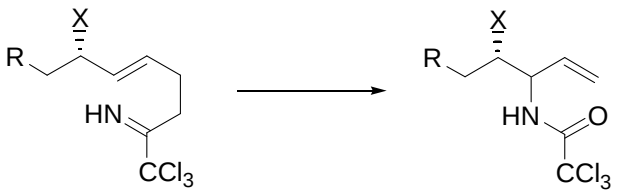
DMSO (2.4 equiv.) was added dropwise to a solution of oxalyl chloride (1.2 equiv.) in DCM at -78 ^{o}C. This was allowed to stir for 15 min before the alcohol (1.0 equiv.) was added and the solution allowed to stir for another 15 min. Triethylamine (5.0 equiv.) was added and the reaction mixture allowed to stir at room temperature for 2 h. Meanwhile, LiCl (2.0 equiv.) was added to MeCN and allowed to stir for 15 min. Triethyl phosphonoacetate (2.0 equiv.) and DBU (2.0 equiv.) were added and the solution allowed to stir for 30 min. This phosphonoacetate solution was added to the alcohol solution and the reaction allowed to stir overnight. Saturated NaCl solution was added to quench the reaction, the solvent was removed and the product extracted with Et_2O (3 x 50 mL). The extracts were combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification was achieved using flash column chromatography.

General Procedure 3: Trichloroacetimidate Synthesis



The allylic alcohol (1.0 equiv.) was dissolved in DCM and cooled to 0 ^{o}C. Trichloroacetonitrile (1.5 equiv.) was added followed by DBU (1.2 equiv.) and the reaction mixture allowed to stir at 0 ^{o}C for 2 h. Flash column chromatography through a plug of silica and multiple washings with Et_2O yielded a filtrate which was concentrated and taken onto the rearrangement step without further purification.

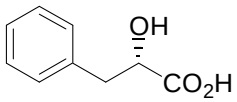
General Procedure 4: $PdCl_2(MeCN)_2$-catalysed rearrangement



The trichloroacetimidate (1.0 equiv.) was dissolved in THF before bis(acetonitrile)palladium(II) chloride (0.1 equiv.) was added and the reaction stirred for 24

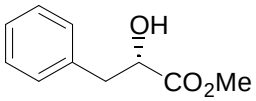
h. Flash chromatography through a plug of silica and multiple washings with Et_2O yielded a filtrate which was concentrated *in vacuo*. The product was purified using flash column chromatography through silica.

(2*S*)-2-Hydroxy-3-phenylpropanoic acid (237)[131]



L-Phenylalanine (10.0 g, 60.6 mmol) was dissolved in 2.5M H_2SO_4 (50 mL) and the solution was cooled in an ice-bath. A solution of $NaNO_2$ (8.36 g, 121.2 mmol) in water (50 mL) was added dropwise and the reaction mixture was left to stir at 0 ^oC for 3 h, then at room temperature for 48 h, followed by extraction with Et_2O (3 x 50 mL) and chloroform (3 x 50 mL). The combined extracts were washed with a saturated NaCl solution and dried ($MgSO_4$). The solvent was removed *in vacuo* to give beige crystals (6.44 g, 64%), which were suspended in petroleum ether and dried by suction filtration. ν_{max}/cm^{-1} (neat) 3435 (OH), 2929 (CH), 1724 (CO), 1455, 1300, 1239, 1189, 1088, 1066, 794, 699; $[\alpha]_D^{21}$ -17.5 (*c* 1.0, EtOH) (lit.[199] $[\alpha]_D^{20}$ -17.8 (*c* 0.5, MeOH)); δ_H (400 MHz, CD_3OD) 2.92 (1H, dd, *J* 13.8, 8.0 Hz, 3-*H*H), 3.13 (1H, dd, *J* 13.8, 4.4 Hz, 3-H*H*), 3.33 (1H, s, 2-OH), 4.35 (1H, dd, *J* 8.0, 4.4 Hz, 2-H), 7.27-7.32 (5H, m, Ph); δ_c (100 MHz, CD_3OD) 41.6 (CH_2), 78.2 (CH), 127.5 (CH), 129.3 (CH), 130.6 (CH), 138.9 (C), 177.2 (C); *m/z* (EI) 166.0628 (M^+. $C_9H_{10}O_3$ requires 166.0630), 148 (19%), 103 (10), 91 (100) and 77 (8).

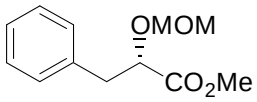
Methyl (2*S*)-2-hydroxy-3-phenylpropanoate (238)[132]



A stirred mixture of (2*S*)-2-hydroxy-3-phenylpropanoic acid (**237)** (2.69 g, 16.2 mmol), MeOH (50 mL), toluene (30 mL) and concentrated HCl (4 mL) were heated under reflux for 24 h. The mixture was neutralised with 5% $NaHCO_3$ solution and the solvent removed *in vacuo*. The resulting residue was extracted with EtOAc (3 x 50 mL), washed with water (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by Kugelrohr distillation to give **238** as a colourless oil (2.32 g, 79%). ν_{max}/cm^{-1} (neat) 3260 (OH), 2947 (CH), 2362, 1748 (CO), 1428, 1258, 1173, 1096, 1018 (OH); $[\alpha]_D^{21}$ -5.9 (*c* 1.0, $CHCl_3$) (lit.[200] $[\alpha]_D^{20}$ -7.3 (*c* 1.0, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 2.74 (1H, br s, 2-OH), 3.00 (1H, dd, *J* 14.0, 6.8 Hz, 3-*H*H), 3.17 (1H, dd, *J* 14.0, 4.4 Hz, 3-H*H*), 3.81 (3H, s,

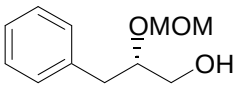
CO_2Me), 4.49 (1H, dd, *J* 6.8, 4.4 Hz, 2-H), 7.23-7.36 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) 40.6 (CH_2), 52.5 (CH_3), 71.3 (CH), 126.9 (CH), 128.5 (CH), 129.5 (CH), 136.3 (CH), 174.6 (CH); *m/z* (EI) 188.0786 (M^+. $C_{10}H_{12}O_3$ requires 188.0786), 162 (34%), 150 (7), 121 (16) and 91 (100).

Methyl (2*S*)-2-methoxymethoxy-3-phenylpropanoate (239)



DIPEA (10.6 mL, 61.0 mmol) and methyl (2*S*)-2-hydroxy-3-phenylpropanoate **(238)** (5.49 g, 30.5 mmol) were stirred at 0 ^oC for 10 min in DCM (100 mL). MOM-Br (5 mL, 61.0 mmol) was added dropwise and the solution was heated under reflux overnight. DCM was added for dilution and the solution was washed with dilute HCl (20 mL). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The yellow oil was purified by flash column chromatography (70% EtOAc/petroleum ether) to give **239** (6.83 g, quant.). ν_{max}/cm^{-1} (neat) 2952 (CH), 1747 (CO), 1435, 1279, 1205, 1147, 1110, 1017, 916, 699; $[\alpha]_D^{21}$ -56.6 (*c* 1.0, $CHCl_3$) (lit.[201] $[\alpha]_D$ +55.7 (c 0.8, $CHCl_3$)) for opposite enantiomer); δ_H (400 MHz, $CDCl_3$) 3.01 (1H, dd, *J* 14.0, 9.2 Hz, 3-*H*H), 3.09 (3H, s, OMe), 3.13 (1H, dd, *J* 14.0, 4.4 Hz, 3-H*H*), 3.76 (3H, s, CO_2Me), 4.37 (1H, dd, *J* 9.2, 4.4 Hz, 2-H), 4.54 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.66 (1H, d, *J* 6.8 Hz, OCH*H*O), 7.24-7.37 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) 38.2 (CH_2), 52.1 (CH_3), 55.7 (CH_3), 76.3 (CH), 96.0 (CH_2), 126.8 (CH), 128.4 (CH), 129.5 (CH), 137.0 (C), 172.6 (C); *m/z* (CI) 225.1124 (MH^+. $C_{12}H_{17}O_4$ requires 225.1127), 193 (100%), 162 (12), 133 (39) and 85 (22).

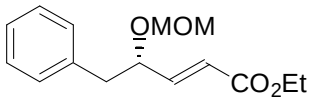
(2*S*)-2-Methoxymethoxy-3-phenylpropan-1-ol (246)



The reaction was carried out according to General Procedure 1 using methyl (2*S*)-2-methoxymethoxy-3-phenylpropanoate **(239)** (2.89 g, 12.9 mmol). Purification by flash column chromatography (60% EtOAc/petroleum ether) gave **246** as an oil (1.43 g, 56%). ν_{max}/cm^{-1} (neat) 3386 (OH), 2930 (CH), 1494, 1454, 1145, 1104, 1028, 913, 699; $[\alpha]_D^{21}$ +20.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.79-2.94 (3H, m, 3-H_2 and 1-OH), 3.37 (3H, s, OMe), 3.53-3.58 (1H, m, 1-*H*H), 3.65-3.70 (1H, m, 1-H*H*), 3.82-3.92 (1H, m, 2-H), 4.59

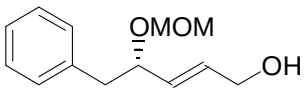
(1H, d, *J* 7.2 Hz, OC*H*HO), 4.70 (1H, d, *J* 7.2 Hz, OCH*H*O), 7.24-7.38 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) 38.2 (CH_2), 55.6 (CH_3), 64.9 (CH_2), 82.1 (CH), 96.7 (CH_2), 126.4 (CH), 128.4 (CH), 129.4 (CH), 138.0 (C); *m/z* (CI) 197.1179 (MH^+. $C_{11}H_{17}O_3$ requires 197.1178), 165 (76%), 147 (100), 136 (12), 117 (15) and 105 (12).

Ethyl (2*E*,4*S*)-4-methoxymethoxy-5-phenylpent-2-enoate (241)



The reaction was carried out according to General Procedure 2 using (2*S*)-2-methoxymethoxy-3-phenylpropan-1-ol **(246)** (3.07 g, 15.7 mmol). Purification using flash column chromatography (50% EtOAc/petroleum ether) yielded **241** as a viscous oil (3.35 g, 81%). ν_{max}/cm^{-1} (neat) 2924 (CH), 2087, 1716 (CO), 1267, 1149, 1016, 699; $[\alpha]_D^{21}$ -56.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 2.92 (2H, d, *J* 6.8 Hz, 5-H_2), 3.08 (3H, s, OMe), 4.23 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 4.43-4.49 (2H, m, 4-H and OC*H*HO), 4.61 (1H, d, *J* 6.8 Hz, OCH*H*O), 6.01 (1H, dd, *J* 15.6, 1.2 Hz, 2-H), 6.90 (1H, dd, *J* 15.6, 6.0 Hz, 3-H), 7.32-7.41 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) 14.3 (CH_3), 41.6 (CH_2), 55.4 (CH_3), 60.6 (CH_2), 75.9 (CH), 94.5 (CH_2), 122.1 (CH), 126.6 (CH), 128.4 (CH), 129.6 (CH), 137.4 (C) 147.1 (CH), 166.2 (C); *m/z* (EI) 264.1363 (M^+. $C_{15}H_{20}O_4$ requires 264.1362), 203 (2%), 173 (21), 85 (63), 83 (100).

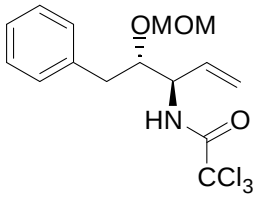
***(2E,4S)*-4-Methoxymethoxy-5-phenylpent-2-en-1-ol (242)**



The reaction was carried out according the General Procedure 1 using ethyl (2*E*,4*S*)-4-methoxymethoxy-5-phenylpent-2-enoate (1.15 g, 4.4 mmol) **(241)**. Purification using flash column chromatography (50% EtOAc/petroleum ether) gave **242** as a colourless oil (0.8 g, 83%). ν_{max}/cm^{-1} (neat) 3370 (OH), 2887 (CH), 1635 (C=C), 1495, 1453, 1092, 1027, 699; $[\alpha]_D^{21}$ -86.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.42 (1H, s, OH), 2.86 (1H, dd, *J* 13.6, 5.6 Hz, 5-*H*H), 2.92 (1H, dd, *J* 13.6, 8.0 Hz, 5-H*H*), 3.08 (3H, s, OMe), 4.17 (2H, d, *J* 5.2 Hz, 1-H_2), 4.28-4.34 (1H, m, 4-H), 4.46 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.68 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.66 (1H, ddt, *J* 15.4, 7.6, 1.2 Hz, 3-H), 5.83 (1H, dt, *J* 15.4, 5.2 Hz, 2-H), 7.27-7.36 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) 42.3 (CH_2), 55.2 (CH_3), 62.9 (CH_2), 76.8 (CH),

93.6 (CH_2), 126.3 (CH), 128.2 (CH), 129.7 (CH), 130.9 (CH), 132.3 (CH), 138.2 (C); *m/z* (CI) 205 ($MH^+ - H_2O$, 32%), 175 (21), 161 (69), 143 (100) and 129 (8).

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-methoxymethoxy-5-phenylpent-1-ene (247)



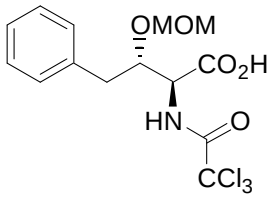
Method A

The reaction was carried out according to General Procedures 3 and 4 using *(*2*E*,4*S*)-4-methoxymethoxy-5-phenylpent-2-en-1-ol **(242)** (1.17 g, 5.3 mmol). Purification using flash column chromatography (20% EtOAc/petroleum ether) gave **247** as a colourless oil (0.7 g, 54%). ν_{max}/cm^{-1} (neat) 3273 (NH), 2943 (CH), 2102, 1711 (CO), 1512 (C=C), 1143, 1026, 820, 699; $[\alpha]_D^{21}$ +59.1 (*c* 1.7, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 2.82 (1H, dd, *J* 14.0, 5.2 Hz, 5-*H*H), 2.93 (1H, dd, *J* 14.0, 8.8 Hz, 5-H*H*), 3.39 (3H, s, OMe), 3.86 (1H, ddd, *J* 8.4, 4.8, 2.0 Hz, 4-H), 4.36 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.45 (1H, br dt, *J* 7.6 Hz, 3-H), 4.60 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.42 (1H, d, *J* 7.6 Hz, 1-*H*H), 5.45 (1H, br s, 1-H*H*), 5.92-6.02 (1H, m, 2-H), 7.21-7.36 (5H, m, Ph), 8.19 (1H, d, *J* 7.6 Hz, NH); δ_c (100 MHz, $CHCl_3$) 39.4 (CH_2), 55.8 (CH), 56.7 (CH), 84.4 (CH_3), 92.9 (CCl_3), 98.1 (CH_2), 119.7 (CH_2), 126.8 (CH), 128.6 (CH), 129.3 (CH), 131.4 (CH), 137.4 (C), 161.4 (C); *m/z* (CI) 366.0431 (MH^+. $C_{15}H_{19}O_3N^{35}Cl_3$ requires 366.0431), 334 (100%), 300 (25), 272 (26), 236 (19) and 173 (33).

Method B (with *p*-benzoquinone)

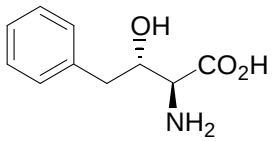
The allylic trichloroacetimidate was prepared according to General Procedure 3 using *(*2*E*,4*S*)-4-methoxymethoxy-5-phenylpent-2-en-1-ol **(242)** (0.80 g, 2.2 mmol). The allylic trichloroacetimidate was dissolved in THF (15 mL) and bis(acetonitrile)palladium(II) chloride (0.05 g, 0.2 mmol) and *p*-benzoquinone (0.47 g, 4.4 mmol) were added. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo* followed by flash column chromatography (20% EtOAC/petroleum ether) gave **247** as a colourless oil (0.56 g, 70%). Characterisation data is consisitent with that shown above.

(2*R*,3*S*)-2-(Trichloromethylcarbonylamino)-3-methoxymethoxy-4-phenylbutanoic acid (250)[137]



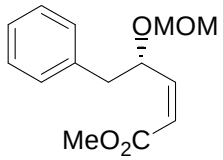
$NaIO_4$ (0.33 g, 1.7 mmol) was dissolved in water (5 mL) and added to a stirred solution of (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-methoxymethoxy-5-phenylpent-1-ene **(247)** (0.15 g, 0.4 mmol) in CCl_4 (3.7 mL) and MeCN (3.7 mL). Ruthenium trichloride (4.6 mg, 0.02 mmol) was added and the mixture stirred vigorously for 6 h before a further portion of $NaIO_4$ (0.16 g, 0.8 mmol) was added and the solution allowed to stir for 24 h. The solution was filtered through a short column of silica to remove ruthenium residues. The acid was extracted with DCM (3 x 20 mL), the organic layers combined, dried ($MgSO_4$) and concentrated *in vacuo* to give **250** (0.1 g, 69%). This was used without further purification.

(2*R*,3*S*)-2-Amino-3-hydroxy-4-phenylbutanoic acid (251)



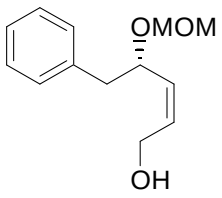
(2*R*,3*S*)-2-(Trichloromethylcarbonylamino)-3-methoxymethoxy-4-phenylbutanoic acid **(250)** (0.20 g, 0.5 mmol) was dissolved in 6M HCl (13 mL) and heated under reflux for 24 h. The reaction mixture was extracted with Et_2O (2 x 10 mL) and the aqueous layer was concentrated *in vacuo* to give the amino acid **251** as a cream solid (0.09 g, 80%). ν_{max}/cm^{-1} (neat) 3364 (NH and OH), 2489 (CH), 1719 (CO), 1197, 1068, 747, 696; $[\alpha]_D^{21}$ +8.6 (*c* 1.0, 1M HCl) (lit.[137] $[\alpha]_D$ +9.1 (*c* 1.0, 1M HCl)); δ_H (400 MHz, $CDCl_3$) 2.83 (1H, dd, *J* 14.0, 9.2 Hz, 4-*H*H), 2.93 (1H, dd, *J* 14.0, 4.8 Hz, 4-H*H*), 4.03 (1H, d, *J* 2.8 Hz, 2-H), 4.19-4.24 (1H, m, 3-H), 7.18-7.32 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) 38.5 (CH_2), 57.0 (CH), 71.0 (CH), 126.9 (CH), 128.7 (CH), 129.3 (CH), 137.3 (C), 169.6 (C); *m/z* (CI) 196.0974 (MH^+. $C_{10}H_{13}O_3N$ requires 196.0974), 167 (16%), 139 (37) and 121 (21).

Methyl (2*Z*,4*S*)-4-methoxymethoxy-5-phenylpent-2-enoate (252)



DMSO (0.9 mL, 12.9 mmol) was added dropwise to a solution of oxalyl chloride (0.6 mL, 6.4 mmol) in DCM (30 mL) at -78 ^{o}C. This was allowed to stir for 15 min before (2*S*)-2-methoxymethoxy-3-phenylpropan-1-ol **(246)** (1.05 g, 5.4 mmol) was added and the solution allowed to stir for another 15 min. NEt_3 (3.7 mL, 26.8 mmol) was added and the reaction mixture allowed to stir at room temperature for 2 h. After TLC, the reaction was quenched with a saturated solution of $NaHCO_3$ (20 mL) and the solvent was removed *in vacuo* to give (2*S*)-2-methoxymethoxy-3-phenylpropionaldehyde (1.04 g, 5.4 mmol). Methyl (triphenylphosphoranylidene)acetate bromide (4.45 g, 10.7 mmol) was dissolved in DCM. NaOH (0.86 g, 21.4 mmol) was dissolved in water and this was added to the DCM solution to give methyl (triphenylphosphoranylidene)acetate. To a solution of (2*S*)-2-methoxymethoxy-3-phenylpropionaldehyde (1.04 g, 5.4 mmol) in MeOH (25 mL) was added methyl (triphenylphosphoranylidene)acetate (3.71 g, 11.1 mmol) at 0 ^{o}C. This mixture was allowed to stir at 0 ^{o}C for 7.5 h before the solvent was evaporated to give a tan solid. Flash column chromatography (30% EtOAc/petroleum ether) gave **252** as an oil (0.21 g, 16%). ν_{max}/cm^{-1} (neat) 2939 (CH), 1717 (CO), 1436, 1398, 1177, 1097, 1041, 917, 826, 700; $[\alpha]_D^{21}$ -30.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.85 (1H, dd, *J* 13.6, 8.8 Hz, 5-*H*H), 2.97 (1H, dd, *J* 13.6, 3.6 Hz, 5-H*H*), 3.05 (3H, s, OMe), 3.76 (3H, s, CO_2Me), 4.44 (1H, d, *J* 6.6 Hz, OC*H*HO), 4.58 (1H, d, *J* 6.6 Hz, OCH*H*O), 5.43-5.49 (1H, m, 4-H), 5.91 (1H, d, *J* 11.6 Hz, 2-H), 6.26 (1H, dd, *J* 11.6, 8.0 Hz, 3-H), 7.26-7.39 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) 41.3 (CH_2), 51.5 (CH_3), 55.2 (CH_3), 74.2 (CH), 95.2 (CH_2), 120.3 (CH), 126.3 (CH), 128.2 (CH), 129.7 (CH), 138.1 (C), 150.8 (CH), 166.1 (C); *m/z* (EI) 189 (M^+ − OCH_2OCH_3, 26%), 173 (35), 130 (62) and 61 (100).

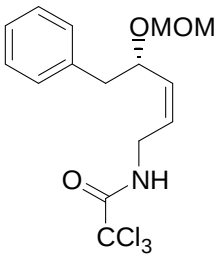
(2*Z*,4*S*)-4-Methoxymethoxy-5-phenylpent-2-en-1-ol (253)



The reaction was carried out according to General Procedure 1 using methyl (2*Z*,4*S*)-4-methoxymethoxy-5-phenylpent-2-enoate **(252)** (0.15 g, 0.6 mmol). The colourless oil **253**

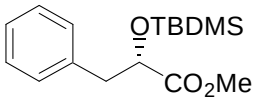
(0.11 g, 79%) was characterised without further purification. ν_{max}/cm^{-1} (neat) 3372 (OH), 2925 (CH), 2110, 1495, 1454, 1145, 1094, 1023, 917, 698; $[\alpha]_D^{21}$ -88.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.48 (1H, s, 1-OH), 2.59 (1H, dd, *J* 13.6, 7.0 Hz, 5-*H*H), 2.83 (1H, dd, *J* 13.6, 6.6 Hz, 5-H*H*), 3.07 (3H, s, OMe), 3.59-3.66 (1H, m, 1-*H*H), 3.87-3.93 (1H, m, 1-H*H*), 4.35 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.44-4.49 (1H, m, 4-H), 4.54 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.25-5.31 (1H, m, 2-H), 5.58-5.95 (1H, m, 3-H); δ_c (100 MHz, $CHCl_3$) 42.0 (CH_2), 55.2 (CH_3), 58.2 (CH_2), 72.1 (CH), 93.6 (CH_2), 126.5 (CH), 128.3 (CH), 129.7 (CH), 131.6 (CH), 132.4 (CH), 137.8 (C); *m/z* (EI) 161.0965 (M^+ – OCH_2OCH_3 requires 161.0966), 205 (20%), 161 (22), 143 (46), 91 (100), 69 (59) and 45 (69).

(2*Z*,4*S*)-1-(Trichloromethylcarbonylamino)-4-methoxymethoxy-5-phenylpent-2-ene (255)



The reaction was carried out according to General Procedures 3 and 4 using (2*Z*,4*S*)-4-methoxymethoxy-5-phenylpent-2-en-1-ol **(253)** (0.09 g, 0.4 mmol). The reaction mixture was allowed to stir for 17 days. Flash column chromatography was performed to give **255** as an oil (0.04 g, 19%). ν_{max}/cm^{-1} (neat) 2924 (CH), 2154, 1727 (CO), 1495, 1454, 1253, 1145, 1095, 1022, 915, 778, 745, 699; $[\alpha]_D^{21}$ -57.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.72 (1H, dd, *J* 13.4, 6.0 Hz, 5-*H*H), 2.88 (1H, dd, *J* 13.4, 7.4 Hz, 5-H*H*), 3.05 (3H, s, OMe), 3.75-3.38 (1H, m 1-*H*H), 3.84-3.89 (1H, m 1-H*H*), 4.39 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.49-4.56 (1H, m, 4-H), 4.55 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.41-5.46 (1H, m, 3-H), 5.68-5.77 (1H, m, 2-H), 7.11-7.24 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) 39.0 (CH_2), 41.9 (CH_2), 55.3 (CH_3), 71.5 (CH), 93.7 (CH_2), 126.5 (CH), 128.3 (CH), 128.8 (CH), 129.7 (CH), 133.6 (CH), 135.6 (C); *m/z* (CI) 306 (MH^+ - OCH_3OCH_2, 1%), 214 (11), 173 (27), 143 (43), 91 (26) and 81 (85).

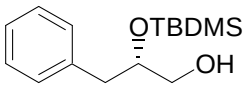
Methyl (2*S*)-2-(*tert*-butyldimethylsilyloxy)-3-phenylpropanoate (257)



Methyl (2*S*)-2-hydroxy-3-phenylpropanoate **(238)** (2.0 g, 11.1 mmol) was dissolved in THF (40 mL). TBDMS-Cl (2.0 g, 13.3 mmol) and imidazole (1.89 g, 27.8 mmol) were

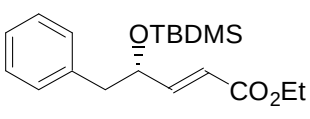
added and the reaction mixture allowed to stir for 24 h. The reaction mixture was filtered and the solid formed was washed with Et_2O. The solvent was removed *in vacuo* and purification by flash column chromatography (10% Et_2O /petroleum ether) yielded **257** as a pale yellow oil (2.88 g, 88%). ν_{max}/cm^{-1} (neat) 3360, 2928 (CH), 2855, 2156, 1756 (CO), 1436, 1251, 1120, 1022, 942, 830, 778, 696; $[\alpha]_D^{21}$ -27.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.01 (3H, s, SiC*H*$_3$CH$_3$), 0.08 (3H, s, SiCH$_3$C*H*$_3$), 1.01 (9H, s, Si^{t}Bu), 3.10 (1H, dd, *J* 13.4, 9.2 Hz, 3-*H*H), 3.30 (1H, dd, *J* 13.4, 3.8 Hz, 3-H*H*), 3.95 (3H, s, CO_2Me), 4.56 (1H, dd, *J* 9.2, 3.8 Hz, 2-H), 7.40-7.57 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) -5.5 (CH_3), -5.4 (CH_3), 18.4 (C), 26.0 (CH_3), 41.8 (CH_2), 52.1 (CH_3), 74.0 (CH), 126.8 (CH), 128.4 (CH), 130.0 (CH), 137.6 (C), 173.8 (CH); *m/z* (CI) 295.1727 (MH^+. $C_{16}H_{26}O_3Si$ requires 295.1729), 279 (5%), 327 (10) and 163 (4).

(2*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-phenylpropan-1-ol (258)



The reaction was carried out according to General Procedure 1 using methyl (2*S*)-2-(*tert*-butyldimethylsilyloxy)-3-phenylpropanoate **(257)** (3.57 g, 12.1 mmol). Purification was achieved by flash column chromatography (50% EtOAc/petroleum ether) to give **258** as a colourless oil (2.39 g, 74%). ν_{max}/cm^{-1} (neat) 3390 (OH), 2857 (CH), 2162, 2092, 1254, 1033, 835, 774, 697; $[\alpha]_D^{21}$ -15.3 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.01 (3H, s, SiC*H*$_3$CH$_3$), 0.08 (3H, s, SiCH$_3$C*H*$_3$), 1.01 (9H, s, Si^{t}Bu), 2.04-2.07 (1H, br s, 1-OH), 2.78 (1H, dd, *J* 13.6, 3.2 Hz, 3-*H*H), 2.81 (1H, dd, *J* 13.6, 3.6 Hz, 3-H*H*), 3.45 (1H, dd, *J* 11.2, 4.4 Hz, 1-*H*H), 3.53 (1H, dd, *J* 11.2, 3.6 Hz, 1-H*H*), 3.88-3.94 (1H, m, 2-H), 7.31-7.47 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) -4.8 (CH_3), -4.7 (CH_3), 18.2 (C), 26.0 (CH_3), 40.7 (CH_2), 65.8 (CH_2), 74.3 (CH), 126.5 (CH), 128.5 (CH), 129.8 (CH), 138.5 (C); *m/z* (CI) 367.1782 (MH^+. $C_{15}H_{26}O_2Si$ requires 267.1780), 249 (10%), 135 (31) and 117 (23).

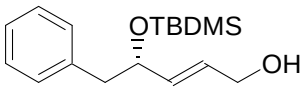
Ethyl (2*E*,4*S*)-4-(*tert*-butyldimethylsilyloxy)-5-phenylpent-2-enoate (260)



The reaction was carried out according to General Procedure 2 using (2*S*)-2-(*tert*-butyldimethylsilyloxy)-3-phenylpropan-1-ol **(258)** (1.23 g, 4.6 mmol). Purification by flash

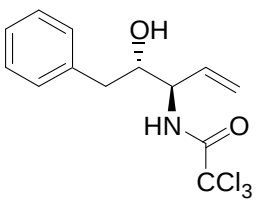
column chromatography (40% EtOAc/petroleum ether) gave **260** as a colourless oil (1.40 g, 91%). ν_{max}/cm^{-1} (neat) 2929 (CH), 2857, 1721 (CO), 1659, 1471, 1366, 1258, 1115; $[\alpha]_D^{21}$ -2.3 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) -0.25 (3H, s, $SiCH_3CH_3$), -0.08 (3H, s, $SiCH_3CH_3$), 0.86 (9H, s, Si^{t}Bu), 1.30 (3H, t, *J* 7.4 Hz, OCH_2CH_3), 2.85 (2H, dd, *J* 13.4, 7.8 Hz, 5-*H*H), 2.93 (1H, dd, *J* 13.4, 5.6 Hz, 5-H*H*), 4.25-4.33 (2H, m, OCH_2CH_3), 4.50-4.55 (1H, m, 4-H), 6.07 (1H, d, *J* 15.4 Hz, 2-H), 7.02 (1H, dd, *J* 15.4, 4.4 Hz, 3-H), 7.26-7.45 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) -5.3 (CH_3), -4.7 (CH_3), 14.4 (CH_3), 18.3 (C), 26.0 (CH_3), 44.5 (CH_2), 60.5 (CH_2), 73.3 (CH), 120.2 (CH), 126.7 (CH), 128.4 (CH), 130.1 (CH), 137.9 (C), 150.5 (CH), 166.9 (CH); *m/z* (CI) 335.2041 (MH^+. $C_{19}H_{30}O_3Si$ requires 335.2042), 277 (6%), 203 (20) and 133 (11).

(2*E*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-phenylpent-2-en-1-ol (261)



This reaction was carried out according to General Procedure 1 using methyl (2*E*,4*S*)-4-(*tert*-butyldimethylsilyloxy)-5-phenylpent-2-enoate **(260)** (2.05 g, 6.2 mmol). Purification by flash column chromatography (50% EtOAc/petroleum ether) gave **261** as a colourless oil (1.68 g, 94%). ν_{max}/cm^{-1} (NaCl) 3336 (OH), 3028, 2928 (CH), 1603, 1471, 1361, 1254, 1092, 941; $[\alpha]_D^{21}$ -1.8 (*c* 0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) -0.13 (3H, s, $SiCH_3CH_3$), 0.00 (3H, s, $SiCH_3CH_3$), 0.94 (9H, s, Si^{t}Bu), 1.35 (1H, t, *J* 6.8 Hz, 1-OH), 2.86 (2H, d, *J* 6.8 Hz, 5-H_2), 4.21-4.23 (2H, m, 1-H_2), 4.38-4.42 (1H, m, 4-H), 5.84-5.87 (2H, m, 2-H and 3-H), 7.27-7.39 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) -5.3 (CH_3), -4.7 (CH_3), 18.2 (C), 25.9 (CH_3), 45.2 (CH_2), 63.2 (CH_2), 74.0 (CH), 126.2 (CH), 128.1 (CH), 128.6 (CH), 129.9 (CH), 134.7 (CH), 138.6 (C); *m/z* (CI) 275.1828 (MH^+ - OH, $C_{17}H_{27}OSi$ requires 275.1831), 293 (4%), 235 (6), 201 (8), 161 (11) and 143 (26).

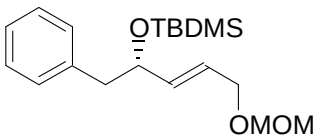
(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-hydroxy-5-phenylpent-1-ene (264)



The allylic trichloroacetimidate was prepared according to General Procedure 3 using (2*E*,4*S*)-4-(*tert*-butyldimethylsilyloxy)-5-phenylpent-2-en-1-ol **(261)** (0.20 g, 0.7 mmol). To remove the TBDMS-group before the rearrangement, (2*E*,4*S*)-4-(*tert*-

butyldimethylsilyloxy)-5-phenyl-2-pentene-1-yl trichloroethanimidate **(262)** (0.31 g, 0.7 mmol) was dissolved in THF (10 mL) and cooled to 0 ^{o}C. TBAF (0.3 mL, 1.1 mmol) was slowly added and the solution returned to room temperature and allowed to stir for 2 h. The reaction was monitored by TLC every 30 min. After 2 h, TBAF (0.1 mL, 0.4 mmol) was added and the reaction left to stir for 24 h. The solvent was removed *in vacuo* and the residue was dissolved in EtOAc. This was washed with water and then the aqueous layers were extracted with EtOAc. The organic layers were combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude precursor was passed through a short silica plug (15% EtOAc/petroleum ether) to give **263** which was taken to the rearrangement without further purification. The rearrangement was carried out according to General Procedure 4 using (2*E*,4*S*)-1-(trichloromethylcarbonylamino)-4-hydroxy-5-phenylpenta-2-ene **(263)**. The reaction was allowed to stir for 48 h. Flash chromatography through silica (15% Et_2O/petroleum ether) gave **264** as an oil (0.04 g, 12%). ν_{max}/cm^{-1} (neat) 3315 (OH), 2922 (CH), 1685 (CO), 1495, 1227, 1051 (OH), 925, 817, 740; $[\alpha]_D^{29}$ +15.9 (*c* 0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.85 (1H, s, OH), 2.66 (1H, dd, *J* 13.6, 9.4 Hz, 5-*H*H), 2.77 (1H, dd, *J* 13.6, 4.0 Hz, 5-H*H*), 3.96-3.97 (1H, m, 4-H), 4.37-4.42 (1H, m, 3-H), 5.32-5.37 (2H, m, 1-H_2), 5.87-5.96 (1H, m, 2-H), 7.13-7.28 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) 40.6 (CH_2), 57.4 (CH), 73.7 (CH), 120.1 (CH_2), 127.1 (CH), 128.9 (CH), 129.4 (CH), 131.1 (CH), 137.0 (C), 161.2 (C); *m/z* (CI) 324.0137 (MH^+. $C_{13}H_{15}O_2N^{35}Cl_2{}^{37}Cl$ requires 324.0140), 304 (50%), 201 (77), 166 (91), 143 (60) and 91 (67).

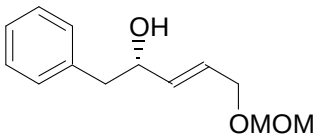
(2*E*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-phenyl-1-methoxymethoxypent-2-ene (267)



(2*E*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-phenylpent-2-en-1-ol **(261)** (3.88 g, 13.3 mmol) was dissolved in DCM (70 mL) and cooled to 0 ^{o}C. DIPEA (4.6 mL, 26.5 mmol) was added and the mixture stirred at 0 ^{o}C for 15 mins. MOM-Br (2.2 mL, 26.5 mmol) was added dropwise and the reaction heated under reflux for 24 h. DCM (25 mL) and HCl (25 mL) were added. Following extraction with Et_2O (3 x 50 mL), removal of solvent *in vacuo* and purification by flash column chromatography (10% EtOAc/petroleum ether) gave **267** as a pale yellow oil (4.08 g, 91%). ν_{max}/cm^{-1} (neat) 2927 (CH), 1471, 1361, 1254, 1041, 833, 775, 698; $[\alpha]_D^{25}$ +0.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) -0.13 (3H, s, SiC*H*$_3$CH$_3$), 0.00 (3H, s, SiCH$_3$C*H*$_3$), 1.66 (9H, s, Si^{t}Bu), 2.86 (2H, d, *J* 6.4 Hz, 5-H_2), 3.46 (3H, s, OMe), 4.14 (2H, d, *J* 5.2 Hz, 1-H_2), 4.37-4.42 (1H, m, 4-H), 4.71 (2H, s, OCH_2O), 5.78

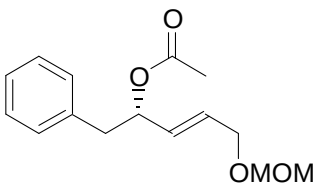
(1H, dt, *J* 15.2, 5.2 Hz, 2-H), 5.87 (1H, dd, *J* 15.2, 5.2 Hz, 3-H), 7.26-7.38 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) -5.3 (CH_3), -4.7 (CH_3), 18.2 (C), 25.8 (CH_3) 45.2 (CH_2), 55.2 (CH_3), 67.2 (CH_2), 74.1 (CH), 95.3 (CH_2), 125.7 (CH), 126.1 (CH), 128.0 (CH), 129.9 (CH), 136.2 (CH), 138.6 (C); *m/z* (CI) 275.1832 (MH^+ - OCH_2OCH_3 requires 275.1831), 245 (66%), 213 (92), 143 (75), 89 (73) and 73 (100).

(2*E*,4*S*)-4-Hydroxy-5-phenyl-1-methoxymethoxypent-2-ene (268)



(2*E*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-phenyl-1-methoxymethoxypent-2-ene **(267)** (0.1 g, 0.3 mmol) was dissolved in THF (3 mL) and cooled to 0 ^oC. TBAF (0.6 mL, 0.6 mmol) was slowly added, the solution allowed to return to room temperature and stirred for 24 h. The solvent was removed *in vacuo* and the residue was dissolved in EtOAc. This was washed with water and then extracted with EtOAc (3 x 15 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent removed. Following flash column chromatography to purify (25% EtOAc/petroleum ether), **268** was obtained as a colourless oil (0.07 g, quant.). ν_{max}/cm^{-1} (neat) 3392 (OH), 2882 (CH), 1494, 1455, 1147, 1104, 1028, 970, 918, 747, 700; $[\alpha]_D^{25}$ +7.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.78 (1H, s, OH), 2.89 (1H, dd, *J* 13.6, 8.0 Hz, 5-*H*H), 2.98 (1H, dd, *J* 13.6, 4.8 Hz, 5-H*H*), 3.47 (3H, s, OMe), 4.17 (2H, d, *J* 1.2 Hz, 1-H_2), 4.46-4.52 (1H, m, 4-H), 4.72 (2H, s, OCH_2O), 5.90-5.94 (2H, m, 2-H and 3-H), 7.31-7.44 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) 43.9 (CH_2), 55.3 (CH_3), 67.1 (CH_2), 72.8 (CH), 95.6 (CH_2), 126.6 (CH), 127.0 (CH), 128.6 (CH), 129.5 (CH), 135.0 (C), 137.7 (CH); *m/z* (CI) 205.1227 (MH^+- OH requires 205.1229), 173 (100%), 161 (35), 143 (52) and 129 (42).

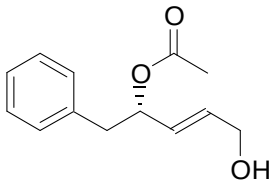
(2*E*,4*S*)-4-Acetyl-5-phenyl-1-methoxymethoxypent-2-ene (269)



(2*E*,4*S*)-4-Hydroxy-5-phenyl-1-methoxymethoxypent-2-ene **(268)** (0.1 g, 0.5 mmol) was dissolved in DCM (5 mL) and stirred at 20 ^oC. Acetic anhydride (0.1 mL, 0.7 mmol) was added dropwise followed by DIPEA (0.2 mL, 1.4 mmol) and the reaction allowed to stir

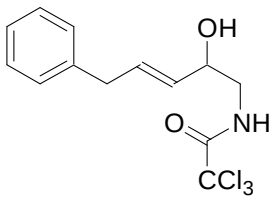
for 24 h. The solvent was removed *in vacuo* and the product purified by flash column chromatography (25% EtOAc/petroleum ether) to give **269** as a colourless oil (0.1 g, 89%). ν_{max}/cm^{-1} (neat) 3050, 1780 (CO), 1585, 1481, 1419, 1103, 891; $[\alpha]_D^{24}$ +10.2 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.03 (3H, s, $COCH_3$), 2.91 (1H, dd, *J* 13.6, 6.0 Hz, 5-*H*H), 2.99 (1H, dd, *J* 13.6, 7.2 Hz, 5-H*H*), 3.36 (3H, s, OMe), 4.04 (2H, d, *J* 3.6 Hz, 1-H_2), 4.62 (2H, s, OCH_2O), 5.49-5.53 (1H, m, 4-H), 5.75-5.77 (2H, m, 2-H and 3-H), 7.21-7.33 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) 21.2 (CH_3), 41.0 (CH_2), 55.3 (CH_3), 66.8 (CH_2), 74.3 (CH), 95.6 (CH_2), 126.6 (CH), 128.3 (CH), 129.2 (CH), 129.5 (CH), 130.3 (CH), 136.9 (C), 170.1 (C); *m/z* (CI) 205.1228 (MH^+- OAc requires 205.1229), 173 (100%), 143 (22) and 129 (33).

(2*E*,4*S*)-4-Acetyl-5-phenylpent-2-en-1-ol (270)



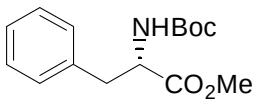
(2*E*,4*S*)-4-Acetyl-5-phenyl-1-methoxymethoxypent-2-ene **(269)** (0.21 g, 0.8 mmol) was dissolved in DCM (20 mL). TFA (0.09 mL, 1.2 mmol) was added dropwise and the mixture heated under reflux for 24 h. The solvent was removed *in vacuo* and the residue was dissolved in Et_2O and washed with a saturated solution of $NaHCO_3$. This was then dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification was achieved by flash column chromatography (15% Et_2O/petroleum ether) to give **270** (0.11 g, 61%). ν_{max}/cm^{-1} (neat) 3028 (OH), 2157 (CH), 1738 (CO), 1346, 1220, 1141, 1023, 968, 699; $[\alpha]_D^{26}$ +0.6 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.96 (3H, s, $COCH_3$), 2.79 (1H, dd, *J* 13.6, 6.4 Hz, 5-*H*H), 2.91 (1H, dd, *J* 13.6, 7.2 Hz, 5-H*H*), 4.69 (2H, d, *J* 5.6 Hz, 1-H_2), 5.41 (1H, ddd, *J* 7.2, 6.4, 6.2 Hz, 4-H), 5.65 (1H, dt, *J* 15.6, 5.6 Hz, 2-H), 5.77 (1H, dd, 15.6, 6.4 Hz, 3-H), 7.06-7.28 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) 21.1 (CH_3), 40.7 (CH_2), 67.2 (CH_2), 73.6 (CH), 123.8 (CH), 126.8 (CH), 128.4 (CH), 129.5 (CH), 134.6 (CH), 136.2 (C), 169.8 (C); *m/z* (CI) 203.1070 (MH^+ - OH requires 203.1072) and 143 (100%).

(3*E*)-1-(Trichloromethylcarbonylamino)-2-hydroxy-5-phenylpent-3-ene (272)



The reaction was carried out according to General Procedures 3 and 4 using (2*E*,4*S*)-4-acetate-5-phenyl-2-pentene-1-ol **(270)** (0.08 g, 0.4 mmol). Purification by flash column chromatography (10% EtOAc/petroleum ether) yielded **272** as a colourless oil (0.02 g, 17% yield over 2 steps). ν_{max} /cm^{-1} (neat) 3407 (OH and NH), 2926 (CH), 2854, 2253, 1714 (CO), 1597 (C=C); $[\alpha]_D^{18}$ + 0.9 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.58 (1H, br s, OH), 3.36 (2H, d, *J* 6.8 Hz, 5-H_2), 3.70 (1H, dd, *J* 11.0, 4.2 Hz, 1-*H*H), 3.75 (1H, dd, *J* 11.0, 3.4 Hz, 1-H*H*), 4.44-4.49 (1H, m, 2-H), 5.47 (1H, dd, *J* 15.2, 6.2 Hz, 3-H), 5.88 (1H, dt, *J* 15.2, 6.8 Hz 4-H), 7.01 (1H, s, NH), 7.14-7.25 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) 38.6 (CH_2), 54.4 (CH), 64.3 (CH_2), 92.9 (C), 126.4 (CH), 128.6 (CH), 128.7 (CH), 133.46 (CH), 139.3 (C), 161.7 (C); *m/z* (CI) 322.0172 (MH^+. $C_{13}H_{15}O_2N^{35}Cl_3$ requires 322.0168), 288 (30%), and 162 (31).

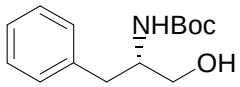
Methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-3-phenylpropanoate (281)[131]



(2*S*)-2-(*tert*-Butoxycarbonylamino)-3-phenylpropionic acid (7.38 g, 27.8 mmol) was dissolved in acetone (150 mL). K_2CO_3 (7.69 g, 55.7 mmol) was added and the reaction allowed to stir at room temperature for 1 h. MeI (4.2 mL, 66.8 mmol) was added and the reaction heated under reflux for 24 h. The mixture was filtered and the solvent removed *in vacuo*. The residue was acidified with 2M HCl (40 mL) and extracted using EtOAc (3 x 50 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (25% EtOAc/petroleum ether) gave **281** as a white solid (6.51 g, 84%). ν_{max}/cm^{-1} (NaCl) 3182 (NH), 1774 (CO), 1628, 1412, 1319, 1111, 964; $[\alpha]_D^{18}$ +52.8 (*c* 1.4, $CHCl_3$) (lit.[173] $[\alpha]_D^{27}$ -51.4 (*c* 1.7, $CHCl_3$) for opposite enantiomer); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, ^{t}Bu), 3.07 (1H, dd, *J* 14.0, 6.2 Hz, 3-*H*H), 3.13 (1H, dd, *J* 14.0, 5.8 Hz, 3-H*H*), 3.73 (3H, s, OMe), 4.61 (1H, dd, *J* 6.2, 5.8 Hz, 2-H), 4.97 (1H, s, NH), 7.14-7.34 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) 28.3 (CH_3), 38.4 (CH_2), 52.2 (CH_3), 54.4 (CH), 80.0 (C), 127.0 (CH), 128.6 (CH), 129.3 (CH), 136.0 (C), 155.1

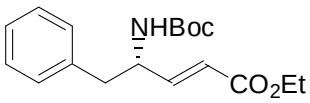
(C), 172.4 (C); *m/z* (EI) 279.1472 (M^+. $C_{15}H_{21}O_4N$ requires 279.1471), 179 (9%), 162 (100), 120 (27) and 91 (50).

(2*S*)-2-(*tert*-Butoxycarbonylamino)-3-phenylpropan-1-ol (282)



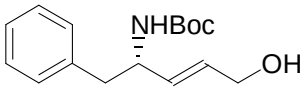
The reaction was carried out according to General Procedure 1 using methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-3-phenylpropanoate **(281)** (6.40 g, 22.9 mmol). Purification by flash column chromatography (30% EtOAc/petroleum ether) gave **282** as a colourless oil (5.76 g, 100%). ν_{max}/cm^{-1} (neat) 3351 (OH), 2976 (CH), 1684 (CO), 1525, 1365, 1165, 1004, 699; $[\alpha]_D^{20}$ -19.4 (*c* 0.8, $CHCl_3$) (lit.[202] $[\alpha]_D^{26}$ -19.5 (*c* 1.0, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, ^{t}Bu), 2.23 (1H, s, OH), 2.86 (2H, d, *J* 7.2 Hz, 3-H_2), 3.58 (1H, dd, *J* 11.0, 5.4 Hz, 1-*H*H), 3.69 (1H, dd, *J* 11.0, 3.6 Hz, 1-H*H*), 3.85-3.93 (1H, m, 2-H), 4.79 (1H, s, NH), 7.26-7.36 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) 28.4 (CH_3), 37.4 (CH_2), 53.7 (CH), 64.1 (CH_2), 79.7 (C), 126.5 (CH), 128.5 (CH), 129.4 (CH), 137.9 (C), 156.2 (C), *m/z* (EI) 251.1521 (M^+. $C_{14}H_{21}O_3N$ requires 251.1519), 220 (61%), 134 (40), 120 (100) and 91 (98).

Ethyl (2*E*,4*S*)-4-(*tert*-butoxycarbonylamino)-5-phenylpent-2-enoate (284)



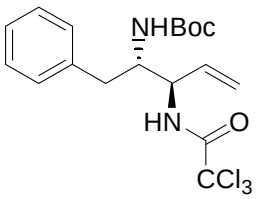
The reaction was carried out according the General Procedure 2 using (2*S*)-2-(*tert*-butoxycarbonylamino)-3-phenylpropan-1-ol **(282)** (5.94 g, 23.7 mmol). Purification was achieved using flash column chromatography (40% EtOAc/petroleum ether) to yield **284** as a pale yellow oil (5.54 g, 70%). ν_{max}/cm^{-1} (neat) 3357 (NH), 2977 (CH), 1694 (CO), 1495 (C=C), 1365, 1246, 1158, 1030, 698; $[\alpha]_D^{20}$ +20.5 (*c* 0.8, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, ^{t}Bu), 1.59 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 2.91-2.96 (2H, m, 5-H_2), 4.20 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 4.46-4.56 (1H, m, 4-H), 4.63 (1H, br s, NH), 5.88 (1H, d, *J* 15.6 Hz, 2-H), 6.93 (1H, dd, *J* 15.6, 5.2 Hz, 3-H), 7.18-7.39 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) 14.2 (CH_3), 20.1 (CH), 28.3 (CH_3), 40.1 (CH_2), 60.5 (CH_2), 121.1 (CH), 126.9 (CH), 128.6 (CH), 129.4 (CH), 136.4 (C), 147.6 (CH), 154.9 (C), 166.2 (C); *m/z* (CI) 320.1860 (MH^+. $C_{18}H_{25}O_4N$ requires 320.1862), 264 (100%), 220 (41) and 174 (11).

(2*E*,4*S*)-4-(*tert*-Butoxycarbonylamino)-5-phenylpent-2-en-1-ol (285)



Ethyl (2*E*,4*S*)-4-(*tert*-butoxycarbonylamino)-5-phenylpent-2-enoate **(284)** (0.12 g, 0.3 mmol) was dissolved in DCM (4 mL) and was stirred for 10 min at -78 ^{o}C. Boron trifluoride diethyl etherate (0.05 mL, 0.4 mmol) was added and the reaction was allowed to stir for 30 min at -78 ^{o}C. DIBAL-H (0.9 mL, 0.9 mmol) was added and the reaction was allowed to stir at -78 ^{o}C for 45 min. The reaction was quenched with a 5M DCM solution of acetic acid (0.6 mL) and allowed to warm to room temperature. The mixture was poured into 10% aqueous tartaric acid before being extracted with DCM (3 x 10 mL). The organic layers were combined, washed with a saturated $NaHCO_3$ solution and then a saturated NaCl solution, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/petroleum ether) yielded **285** as a colourless oil (0.04 g, 43%). ν_{max}/cm^{-1} (neat) 3318 (NH and OH), 2976 (CH), 1684 (CO), 1496 (C=C), 1365, 1247, 1163, 1012, 699; $[\alpha]_D^{20}$ -3.5 (*c* 0.9, $CHCl_3$) (lit.[203] $[\alpha]_D^{29}$ -4.8 (*c* 1.0, MeOH)); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, ^{t}Bu), 2.84 (2H, d, *J* 6.4 Hz, 5-H_2), 4.11 (2H, d, *J* 3.6 Hz, 1-H_2), 4.44 (1H, s, OH), 4.58-4.63 (1H, m, 4-H), 5.67 (1H, dd, *J* 15.4, 4.4 Hz, 3-H), 5.73 (1H, dt, *J* 15.4, 3.6 Hz, 2-H), 7.18-7.32 (5H, m, Ph); δ_c (100 MHz, $CHCl_3$) 28.4 (CH_3), 41.9 (CH_2), 63.0 (CH_2), 126.5 (CH), 128.4 (CH), 129.5 (CH), 129.7 (CH), 131.6 (CH), 137.4 (C), 155.2 (C); *m/z* (FAB) 278.1740 (MH^+. $C_{16}H_{23}O_3N$ requires 278.1756), 222 (42%), 204 (100), 186 (36) and 131 (37).

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(*tert*-butoxycarbonylamino)-5-phenylpent-1-ene (278)

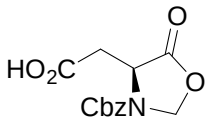


The reaction was carried out according to General Procedures 3 and 4 using (2*E*,4*S*)-4-(*tert*-butoxycarbonylamino)-5-phenylpent-2-en-1-ol **(285)** (0.06 g, 0.2 mmol). Flash chromatography through silica (15% Et_2O/petroleum ether) gave **278** as a pale yellow oil (0.03 g, 30%). ν_{max}/cm^{-1} (neat) 3345 (NH), 2929 (CH), 1683 (CO), 1529, 1442, 1170, 832; $[\alpha]_D^{20}$ +17.3 (*c* 0.55, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.33 (9H, s, ^{t}Bu), 2.68 (1H, dd, *J* 14.2, 7.6 Hz, 5-*H*H), 2.80 (1H, dd, *J* 14.2, 7.6 Hz, 5-H*H*), 4.15 (1H, dd, *J* 14.0, 6.6 Hz, 3-H),

4.26-4.29 (1H, m, 4-H), 4.46 (1H, s, 3-NH), 5.28-5.36 (1H, m, 1-H_2), 5.68-5.77 (1H, m, 2-H), 7.12-7.28 (5H, m, Ph), 8.52 (1H, d, *J* 6.6 Hz, 4-NH); δ_c (100 MHz, $CHCl_3$) 8.5 (CH), 28.2 (CH_3), 38.4 (CH_2), 54.4 (CH), 57.8 (CH), 80.8 (C), 92.8 (C), 119.9 (CH_2), 127.2 (CH), 128.6 (CH), 136.3 (C), 157.1 (C), 161.5 (C); *m/z* (CI) 423.0825 (MH^+. $C_{18}H_{24}O_3N_2{}^{35}Cl_2{}^{37}Cl$ requires 423.0822), 367 (100%), 323 (75), 287 (30) and 164 (60).

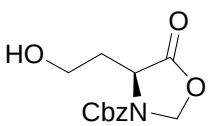
5.3 Chapter 3

2-(*N*-Benzyloxycarbonyloxazolidin-5-on-4-yl)ethanoic acid (321)[204]



N-Benzyloxycarbonyl-L-aspartic acid (10.0 g, 37.5 mmol) was dissolved in benzene (125 mL). Paraformaldehyde (22.5 g, 0.8 mmol) was added along with a catalytic amount of *p*-TsOH (0.36 g, 1.9 mmol). The reaction was heated under reflux for 6 h using a Dean-Stark apparatus to remove water. The reaction was cooled and concentrated *in vacuo*. The resulting residue was dissolved in EtOAc, washed twice with both water and a saturated solution of $NaHCO_3$ and the basic layer acidified to pH 2 using 6M HCl. This was then extracted with EtOAc, dried ($MgSO_4$) and concentrated to give **321** as a white solid (9.1 g, 87%). This was taken to the next step without further purification. ν_{max}/cm^{-1} (NaCl) 3255 (OH), 2924 (CH), 1717 (CO), 1419, 1176, 751; $[\alpha]_D{}^{25}$ +96.2 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.09-3.13 (2H, m, 2-H_2), 3.38-3.45 (1H, m, 2-CH_2CH), 4.39 (1H, s, OH), 5.22 (2H, s, CH_2Ph), 5.31-5.37 (1H, m, NC*H*HO), 5.52-5.62 (1H, m, NCH*H*O), 7.38-7.43 (10H, m, 2 x Ph); δ_c (100 MHz, $CDCl_3$) 34.0 (CH_2), 51.4 (CH), 68.3 (CH_2), 78.4 (CH_2), 128.2 (CH), 128.4 (CH), 128.8 (CH), 135.1 (C), 152.8 (C), 171.5 (C), 174.5 (C); *m/z* (CI) 280.0819 (MH^+. $C_{13}H_{15}O_5N$ requires 280.0821), 236 (100%), 178 (5) and 91 (22).

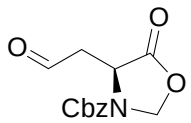
2-(*N*-Benzyloxycarbonyloxazolidin-5-on-4-yl)ethanol (322)[161]



2-(*N*-Benzyloxycarbonyloxazolidin-5-on-4-yl)ethanoic acid **(321)** (0.2 g, 0.7 mmol) was dissolved in THF (10 mL) and cooled to -15 ^oC. 1M Borane.THF complex (1.4 mL, 1.4 mmol) was added dropwise over 10 min and the solution was then stirred at 4 ^oC for 20 h.

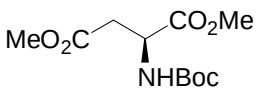
The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with saturated solutions of $NaHCO_3$ and NaCl. It was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (30% EtOAc/petroleum ether) yielded **322** as a colourless viscous oil (0.1 g, 53%). ν_{max}/cm^{-1} (NaCl) 3446 (OH), 2957 (CH), 1699 (CO), 1540, 1256, 1024; $[\alpha]_D^{25}$ -6.8 (*c* 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.41-2.58 (2H, m, 2-H_2), 3.67-3.88 (1H, m, 2-CH_2CH), 4.18-4.31 (1H, m, 1-*H*H), 4.55 (1H, m, 1-H*H*), 4.84 (1H, d, *J* 11.6 Hz, NC*H*HO), 4.96 (1H, d, *J* 11.6 Hz, NCH*H*O), 5.20 (2H, s, CH_2Ph), 7.32-7.40 (5H, m, Ph); δ_c (100 MHz, $CDCl_3$) 27.3 (CH_2), 56.3 (CH), 66.0 (CH_2), 68.2 (CH_2), 71.8 (CH_2), 128.2 (CH), 128.5 (CH), 128.8 (CH), 135.6 (C), 155.1 (C), 175.2 (C); *m/z* (EI) 265.0952 (M^+. $C_{13}H_{15}O_5N$ requires 265.0950), 235 (41%), 203 (97), 130 (20), 108 (97), 91 (100) and 65 (83).

2-(*N*-Benzyloxycarbonyloxazolidin-5-on-4-yl)ethanal (323)



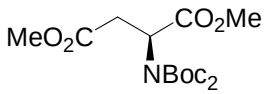
2-(*N*-Benzyloxycarbonyloxazolidin-5-on-4-yl)ethanol **(322)** (0.1 g, 0.4 mmol) was dissolved in DCM (15 mL) and cooled to 0 ^oC. PCC (0.12 g, 0.6 mmol) was added and the reaction was allowed to stir at room temperature for 3 h. The reaction was then concentrated *in vacuo*. The resulting residue was dissolved in EtOAc and washed through a pad of silica. The organic layer was washed with $NaHCO_3$, dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (40% EtOAc/petroleum ether) yielded **323** as a colourless oil (0.08 g, 77%). ν_{max}/cm^{-1} (NaCl) 2966 (CH), 1698 (CO), 1218, 1019, 754; $[\alpha]_D^{25}$ -26.1 (*c* 1.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.51-2.56 (2H, m, 2-H_2), 4.25-4.37 (1H, m, 2-CH_2CH), 4.52-5.27 (1H, br m, NCH_2O), 5.33-5.37 (2H, m, CH_2Ph), 7.40-7.47 (5H, m, Ph), 9.26 (1H, s, 1-H); δ_c (100 MHz, $CDCl_3$) 25.9 (CH_2), 65.6 (CH_2), 70.0 (CH_2), 77.3 (CH), 128.8 (CH), 128.9 (CH), 129.2 (CH), 133.8 (C), 161.8 (CH), 172.6 (C); *m/z* (EI) 263.0793 (M^+. $C_{13}H_{13}O_5N$ requires 263.0794), 118 (77%), 107 (66), 91 (100) and 65 (54).

Dimethyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-aminobutane-1,4-dioate (330)[164]



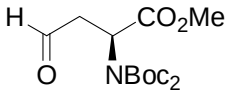
To a stirred suspension of L-aspartic acid (5.0 g, 37.6 mmol) in MeOH (100 mL), TMS-Cl (21.2 mL, 165.4 mmol) was added slowly at 0 ^{o}C. The reaction was allowed to stir for 1 h at 0 ^{o}C and then at room temperature for 24 h. NEt_3 (34.0 mL, 244.4 mmol) and Boc_2O (9.02 g, 41.4 mmol) were added slowly and the reaction stirred for 2 h. The reaction mixture was concentrated *in vacuo* and the resulting residue dissolved in Et_2O and filtered to remove the white precipitate. The filtrate was concentrated *in vacuo* and purified using flash column chromatography (35% EtOAc/petroleum ether) to yield **330** as a white solid (7.46 g, 76%). ν_{max}/cm^{-1} (NaCl) 3406 (NH), 2927 (CH), 2360, 1704 (CO), 1458, 1159, 1045; $[\alpha]_D^{25}$ +35.8 (*c* 1.0, $CHCl_3$), (lit.[164] $[\alpha]_D$ +30.8 (*c* 2.1, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, ^{t}Bu), 2.85 (1H, dd, *J* 16.8, 4.2 Hz, 3-*H*H), 3.03 (1H, dd, *J* 16.8, 4.2 Hz, 3-H*H*), 3.72 (3H, s, OMe), 3.78 (3H, s, OMe), 4.58-4.61 (1H, m, 2-H), 5.50 (1H, br s, NH); δ_c (100 MHz, $CDCl_3$) 28.3 (CH_3), 36.7 (CH_2), 49.9 (CH), 52.1 (CH_3), 52.8 (CH_3), 80.2 (C), 155.4 (C), 171.5 (C), 171.6 (C); *m/z* (CI) 262.1293 (MH^+. $C_{11}H_{20}O_6N$ requires 262.1291), 206 (100%), 162 (36) and 85 (13).

Dimethyl (2*S*)-*N*,*N*-di-(*tert*-butoxycarbonyl)-2-aminobutane-1,4-dioate (331)[164]



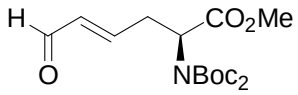
Dimethyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-aminobutane-1,4-dioate (0.9 g, 3.5 mmol) **(330)** was dissolved in MeCN (50 mL). DMAP (0.08 mg, 0.7 mmol,) and Boc_2O (0.8 g, 3.8 mmol) were added and the reaction was allowed to stir at room temperature for 3 h. Boc_2O (0.4 g, 1.9 mmol) was added and the reaction was allowed to stir at room temperature for 24 h. The solvent was removed *in vacuo* and the crude product was purified using flash column chromatography (20% EtOAc/petroleum ether) to yield **331** as a white solid (1.25 g, 100%). ν_{max}/cm^{-1} (NaCl) 2857 (CH), 1747 (CO), 1458, 1375, 1145; $[\alpha]_D^{25}$ -61.0 (*c* 2.0, $CHCl_3$), (lit.[164] $[\alpha]_D^{25}$ -61.0 (*c* 2.0, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.53 (18H, s, 2 x ^{t}Bu), 2.77 (1H, dd, *J* 16.4, 6.4 Hz, 3-*H*H), 3.29 (1H, dd, *J* 16.4, 7.2 Hz, 3-H*H*), 3.73 (3H, s, OMe), 3.76 (3H, s, OMe), 5.48 (1H, dd, *J* 7.2, 6.4 Hz, 2-H); δ_c (100 MHz, $CDCl_3$) 27.9 (CH_3), 35.7 (CH_2), 51.9 (CH_3), 52.5 (CH_3), 54.9 (CH), 83.6 (C), 151.6 (C), 170.3 (C), 171.1 (C); *m/z* (CI) 362.1817 (MH^+. $C_{16}H_{28}O_8N$ requires 362.1815), 306 (38%), 250 (33), 206 (100) and 162 (50).

Methyl (2*S*)-*N*,*N*-di-(*tert*-butoxycarbonyl)-2-amino-4-oxobutanoate (332)[205]



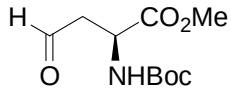
Dimethyl (2*S*)-*N*,*N*-di-(*tert*-butoxycarbonyl)-2-aminobutane-1,4-dioate **(331)** (6.9 g, 19.1 mmol) was dissolved in Et_2O (150 mL) and cooled to -78 ^oC. DIBAL-H (26.8 mL, 26.8 mmol) was added dropwise and the solution was allowed to stir at -78 ^oC for 24 h. A saturated NH_4Cl solution was added (40 mL) and the reaction allowed to warm to room temperature. It was filtered through a pad of Celite® with Et_2O and concentrated *in vacuo*. Following purification by column chromatography (10% EtOAC/petroleum ether) **332** was obtained as a colourless oil (5.0 g, 79%). ν_{max}/cm^{-1} (NaCl) 3132, 2796 (CH), 1782 (CO), 1678, 1199, 1072; $[\alpha]_D^{26}$ -49.2 (*c* 3.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.53 (18H, s, 2 x ^{t}Bu), 2.86 (1H, ddd, *J* 18.0, 6.0, 1.2 Hz, 3-*H*H), 3.45 (1H, ddd, *J* 18.0, 6.8, 1.2 Hz, 3-H*H*), 3.76 (3H, s, OMe), 5.57 (1H, dd, *J* 6.8, 6.0 Hz, 2-H), 9.82 (1H, dd, *J* 1.2, 1.2 Hz, 4-H); δ_c (100 MHz, $CDCl_3$) 27.9 (CH_3), 45.0 (CH_2), 52.6 (CH_3), 52.9 (CH), 83.7 (C), 151.7 (C), 170.2 (C), 198.4 (C); *m/z* (CI) 332.1708 (MH^+. $C_{15}H_{26}O_7N$ requires 332.1709), 276 (60%), 236 (51), 220 (100), 192 (98), 176 (100) and 132 (26).

Methyl (2*S*)-*N*,*N*-di-(*tert*-butoxycarbonyl)-2-aminohexan-4-enoate (333)



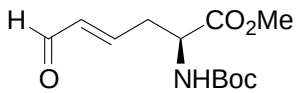
Methyl (2*S*)-*N*,*N*-di-(*tert*-butoxycarbonyl)-2-amino-4-oxobutanoate **(332)** (0.1 g, 0.3 mmol) was dissolved in THF and triphenylphosphoranylidene-acetaldehyde (0.14 g, 0.4 mmol) was added. The mixture was heated under reflux for 3 days. Purification by column chromatography gave **333** as a colourless oil (14 mg, 13%). ν_{max}/cm^{-1} (NaCl) 3378, 2979 (CH), 1746 (CO), 1458, 1368, 1252, 1163, 853; $[\alpha]_D^{27}$ -16.2 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.49 (18H, s, 2 x ^{t}Bu), 2.92-3.02 (1H, m, 3-*H*H), 3.11-3.18 (1H, m, 3-H*H*), 3.75 (3H, s, OMe), 5.11 (1H, dd, *J* 10.4, 5.4 Hz, 2-H), 6.15 (1H, dd, *J* 15.6, 7.6 Hz, 5-H), 6.84 (1H, ddd, *J* 15.6, 8.8, 6.4 Hz, 4-H), 9.50 (1H, d, *J* 7.6 Hz, 6-H); δ_c (100 MHz, $CDCl_3$) 27.9 (CH_3), 33.6 (CH_2), 52.5 (CH_3), 56.7 (CH), 83.7 (C), 135.2 (CH), 151.9 (C), 153.3 (CH), 170.1 (C), 193.6 (CH); *m/z* (CI) 358.1863 (MH^+. $C_{17}H_{28}O_7N$ requires 358.1866), 258 (26%), 222 (81), 202 (66) and 140 (100).

Methyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-amino-4-oxobutanoate (334)[167]



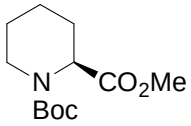
Methyl (2*S*)-*N*,*N*-di-(*tert*-butoxycarbonyl)-2-amino-4-oxobutanoate **(332)** (2.7 g, 8.1 mmol) was dissolved in MeCN (150 mL) and LiBr was added (2.1 g, 24.3 mmol). The mixture was warmed to 65 ^{o}C for 10 h. The solvent was then removed *in vacuo*. Purification by column chromatography (20% EtOAc/petroleum ether) gave **334** as a colourless oil (1.7 g, 89%). ν_{max}/cm^{-1} (NaCl) 3364 (NH), 2978 (CH), 1717 (CO), 1507, 1166, 860; $[\alpha]_D^{25}$ +33.2 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, ^{t}Bu), 3.05 (1H, dd, *J* 18.4, 5.2 Hz, 3-*H*H), 3.15 (1H, dd, *J* 18.4, 4.8 Hz, 3-H*H*), 3.78 (3H, s, OMe), 4.61-4.65 (1H, m, 2-H), 5.41 (1H, d, *J* 7.6 Hz, NH), 9.76 (1H, s, 4-H); δ_c (100 MHz, $CDCl_3$) 28.3 (CH_3), 46.1 (CH_2), 48.6 (CH), 52.8 (CH_3), 80.3 (C), 155.4 (C), 171.5 (C), 199.5 (CH); *m/z* (CI) 232.1181 (MH^+. $C_{10}H_{18}O_5N$ requires 232.1185), 176 (100%) and 132 (79).

Methyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-aminohexan-4-enoate (335)



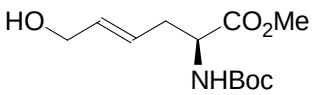
Methyl (2*S*)-*N*,*N*-di-(*tert*-butoxycarbonyl)-2-amino-4-oxobutanoate **(334)** (0.6 g, 2.7 mmol) was dissolved in THF (50 mL) and triphenylphosphoranylidene-acetaldehyde (1.2 g, 4.0 mmol) was added. The reaction mixture was allowed to stir at 35 ^{o}C for 2 days. The reaction mixture was concentrated *in vacuo* and purification by flash column chromatography (25% EtOAc/petroleum ether) gave **335** as a colourless oil (0.6 g, 92%). ν_{max}/cm^{-1} (NaCl) 3369 (NH), 2926 (CH), 1698 (CO), 1507, 1165; $[\alpha]_D^{25}$ +48.2 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, ^{t}Bu), 2.60-2.68 (1H, m, 3-*H*H), 2.82-2.87 (1H, m, 3-H*H*), 3.71 (3H, s, OMe), 4.47-4.49 (1H, m, 2-H), 5.08 (1H, d, *J* 6.0 Hz, NH), 6.10 (1H, dd, *J* 15.4, 8.0 Hz, 5-H), 6.65-6.72 (1H, dt, *J* 15.4, 7.2 Hz, 4-H), 9.44 (1H, d, *J* 8.0 Hz, 6-H); δ_c (100 MHz, $CDCl_3$) 27.2 (CH_3), 34.9 (CH_2), 51.3 (CH_3), 51.7 (CH), 79.4 (C), 134.5 (CH), 150.6 (CH), 154.1 (C), 170.7 (C), 192.5 (CH); *m/z* (CI) 258.1333 (MH^+. $C_{12}H_{20}O_5N$ requires 258.1341), 240 (52%), 176 (100), 140 (98) and 132 (53).

Methyl (2*S*)-1-(*tert*-butoxycarbonyl)piperidine-2-carboxylate (340)



Methyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-aminohexan-4-enoate **(335)** (0.3 g, 1.2 mmol) was dissolved in EtOAc (10 mL). 10% Palladium on carbon (0.25 g, 0.2 mmol) was added and H_2 gas was allowed to bubble though the solution. The reaction mixture was then placed under a H_2 atmosphere and allowed to stir at room temperature for 24 h. The reaction mixture was filtered through Celite® with EtOAc and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc/petroleum ether) gave **340** as a colourless oil (0.13 g, 44%). The ^{1}H NMR spectrum showed significant rotamers which were resolved to some degree using high temperature (55 ^{o}C) NMR spectroscopy. ν_{max}/cm^{-1} (NaCl) 2941 (CH), 1747 (CO), 1393, 1158, 1045, 876; $[\alpha]_D^{26}$ -45.9 (*c* 1.1, $CHCl_3$) (lit.[169] $[\alpha]_D^{20}$ -48.1 (*c* 1.1, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.26-1.34 (2H, m, 4-H_2), 1.48 (9H, s, ^{t}Bu), 1.65-1.74 (3H, m, 5-H_2 and 3-*H*H), 2.20-2.23 (1H, m, 3-H*H*), 2.94-3.03 (1H, m, 6-*H*H), 3.75 (3H, s, OMe), 3.96-4.02 (1H, m, 6-H*H*), 4.79-4.85 (1H, br m, 2-H); δ_c (100 MHz, $CDCl_3$) 20.8 (CH_2), 24.8 (CH_2), 26.8 (CH_2), 28.4 (CH_3), 42.1 (CH_2), 52.1 (CH_3), 53.8 (CH), 80.0 (C), 155.6 (C), 172.5 (C); *m/z* (CI) 244.1547 (MH^+. $C_{12}H_{22}O_4N$ requires 244.1549), 188 (100%), 144 (50), 137 (16), 107 (16) and 85 (25).

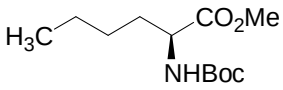
Methyl (2*S*)-*N*-(^{t}butoxycarbonyl)-2-aminohexan-4-en-6-ol (343)



Methyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-aminohexan-4-enoate **(335)** (1.55 g, 6.0 mmol) was dissolved in MeOH (100 mL) and $NaBH_4$ (0.25 g, 6.6 mmol) was added. The reaction was allowed to stir at room temperature for 2 h. The reaction was quenched with water (20 mL) and the mixture extracted with EtOAc. This was dried ($MgSO_4$) and concentrated *in vacuo* to give **343** as a colourless oil (1.36 g, 87%). No further purification was required. ν_{max}/cm^{-1} (NaCl) 3371 (NH and OH), 2978 (CH), 1714 (CO), 1517, 1367, 1169, 1021; $[\alpha]_D^{27}$ +18.2 (*c* 1.9, $CHCl_3$) (lit.[205] $[\alpha]_D^{22}$ -22.3 (*c* 1.4, $CHCl_3$) for opposite enantiomer); δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, ^{t}Bu), 2.36-2.42 (1H, m, 3-*H*H), 2.46-2.53 (1H, m, 3-H*H*), 3.68 (3H, s, OMe), 4.03 (2H, d, *J* 5.4 Hz, 6-H_2), 4.28-4.33 (1H, m, 2-H), 5.04 (1H, d, *J* 8.0 Hz, NH), 5.48-5.56 (1H, m, 4-H), 5.68 (1H, dt, *J* 15.6, 5.4 Hz, 5-H); δ_c (100 MHz, $CDCl_3$) 28.3

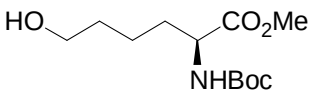
(CH_3), 35.4 (CH_2), 52.4 (CH_3), 53.1 (CH), 63.1 (CH_2), 80.1 (C), 125.7 (CH), 133.7 (CH), 155.3 (C), 172.6 (C); *m/z* (CI) 260.1495 (MH^+. $C_{12}H_{22}O_5N$ requires 260.1498), 204 (74%), 186 (100) and 160 (11).

Methyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-aminohexanoate (345)[173]



Methyl (2*S*)-*N*-(^{t}butoxycarbonyl)-2-aminohexan-4-en-6-ol **(343)** (0.6 g, 2.5 mmol) was dissolved in EtOAc (15 mL). 10% Palladium on carbon (0.5 g, 0.5 mmol) was added and H_2 gas was allowed to bubble though the solution. The reaction was then placed under a H_2 atmosphere and allowed to stir at room temperature for 24 h. The reaction mixture was filtered through Celite® with EtOAc and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc/petroleum ether) gave **345** as a colourless oil (0.27 g, 44%). $[\alpha]_D^{27}$ -5.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.0 Hz, 6-H_3), 1.30-1.36 (4H, m, 4-H_2 and 5-H_2), 1.47 (9H, s, ^{t}Bu), 1.56-1.78 (4H, m, 3-H_2), 3.74 (3H, s, OMe), 4.24-4.34 (1H, m, 2-H), 4.97-5.00 (1H, d, *J* 8.4 Hz, NH); δ_c (100 MHz, $CDCl_3$) 13.9 (CH_3), 22.3 (CH_2), 27.4 (CH_2), 28.3 (CH_3), 32.5 (CH_2), 52.2 (CH_3), 53.4 (CH), 80.0 (C), 155.4 (C), 173.6 (C); *m/z* (CI) 246.1703 (MH^+. $C_{12}H_{24}O_4N$ requires 246.1705), 190 (100%), 188 (21) and 146 (13).

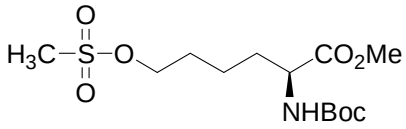
Methyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-aminohexan-6-ol (344)



Methyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-aminohexan-4-en-6-ol **(343)** (0.47 g, 1.8 mmol) was dissolved in EtOAc (15 mL). PtO_2 (0.02 g, 0.09 mmol) was added and H_2 gas was allowed to bubble though the solution. The reaction mixture was then placed under a H_2 atmosphere and allowed to stir at room temperature for 24 h. The reaction mixture was filtered through Celite® with EtOAc and concentrated *in vacuo*. Purification by column chromatography (15% EtOAc/petroleum ether) gave **344** as a colourless oil (0.46 g, 97%). ν_{max}/cm^{-1} (NaCl) 3368 (NH and OH), 2936 (CH), 2360, 1699 (CO), 1522, 1367, 1167, 1023; $[\alpha]_D^{25}$ -4.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, ^{t}Bu), 1.54-1.84 (6H, m, 3-H_2, 4-H_2 and 5-H_2), 3.64 (2H, t, *J* 6.4 Hz, 6-H_2), 3.74 (3H, s, OMe), 4.30 (1H, dd, *J* 12.8,

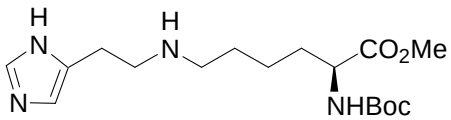
7.4 Hz, 2-H), 5.10 (1H, d, *J* 7.4 Hz, NH); δ_c (100 MHz, $CDCl_3$) 21.6 (CH_2), 28.3 (CH_3), 32.1 (CH_2), 32.6 (CH_2), 52.3 (CH_3), 53.3 (CH), 62.4 (CH_2), 80.0 (C), 155.5 (C), 173.4 (C); *m/z* (CI) 262.1652 (MH^+. $C_{12}H_{24}O_5N$ requires 262.1654), 206 (100%), 162 (85) and 146 (10).

Methyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-amino-6-(methylsulfonyloxy)hexanoate (346)



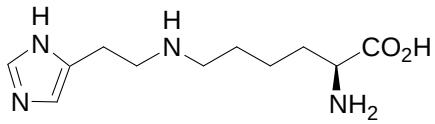
Methyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-aminohexan-6-ol **(343)** (0.03 g, 0.1 mmol) was dissolved in DCM (10 mL). NEt_3 (0.02 mL, 0.15 mmol) was added followed by DMAP (0.01 g, 0.02 mmol) and $MeSO_2Cl$ (0.01 mL, 0.12 mmol). The reaction was allowed to stir at room temperature for 24 h. The reaction was washed with 0.1M HCl and extracted with DCM. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (30% EtOAc/petroleum ether) gave **346** as a colourless oil (0.03 g, 86%). ν_{max}/cm^{-1} (NaCl) 3383 (NH), 2977 (CH), 1711 (CO), 1517, 1353, 1172, 936; $[\alpha]_D^{25}$ +4.4 (*c* 0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, ^{t}Bu), 1.63-1.92 (6H, m, 3-H_2, 4-H_2 and 5-H_2), 3.01 (3H, s, OSO_2CH_3), 3.75 (3H, s, OMe), 4.24 (2H, t, *J* 6.4 Hz, 6-H_2), 4.39-4.40 (1H, m, 2-H), 5.05 (1H, br s, NH); δ_c (100 MHz, $CDCl_3$) 21.4 (CH_2), 28.3 (CH_3), 28.6 (CH_2), 32.2 (CH_2), 37.4 (CH_3), 52.4 (CH_3), 53.0 (CH), 69.5 (CH_2), 80.0 (C), 155.4 (C), 173.1 (C); *m/z* (CI) 340.1431 (MH^+. $C_{13}H_{26}O_7NS$ requires 340.1430), 284 (100%), 240 (100), 180 (28) and 144 (26).

Methyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-amino-9-(4-imidazolyl)-7-azanonanoate (339)



Methyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-amino-6-(methylsulfonyl)hexanoate **(346)** (0.1 g, 0.3 mmol) was dissolved in MeOH (10 mL) and DBU (0.07 mL, 0.5 mmol) and histamine (0.1 g, 0.8 mmol) were added. The mixture was heated under reflux for 24 h. The reaction was concentrated *in vacuo* and the residue was dissolved in EtOAc, washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to give **339** as a pale yellow oil (0.07 g, 66%). This was used in the next step without further purification.

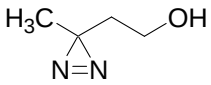
(2*S*)-2-Amino-9-(4-imidazolyl)-7-azanonanoic acid ((*S*)-Gizzerosine), (2))



Methyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-amino-9-(4-imidazolyl)-7-azanonanoate **(339)** (0.07 g, 0.2 mmol) was dissolved in 6M HCl and heated under reflux for 24 h. The reaction mixture was extracted with EtOAc and the aqueous layer was concentrated *in vacuo* to give **2** as a colourless oil (0.05 mg, 100%). $[\alpha]_D^{23}$ +10.0 (*c* 0.2, H_2O) (lit.[152] $[\alpha]_D^{22}$ +10.3 (*c* 1.3,H_2O)); δ_H (400MHz, D_2O) 1.28-1.36 (2H, m, 4-H_2), 1.48-1.58 (2H, m, 3-H_2), 1.66-1.78 (2H, m, 5-H_2), 2.84 (2H, t, *J* 7.0 Hz, 6-H_2) 2.90 (2H, t, *J* 7.6 Hz, 8-H_2), 3.15 (2H, t, *J* 7.6 Hz, 9-H_2), 3.47 (1H, t, *J* 6.0 Hz, 9-CHCN*H*), 3.83-3.91 (1H, m, 2-H), 6.90 (1H, s, 9-CC*H*N), 7.58 (1H, s, 9-CNHC*H*); δ_c (100 MHz, D_2O) 21.6 (CH_2), 23.7 (CH_2), 25.3 (CH_2), 31.0 (CH_2), 46.9 (CH_2), 47.1 (CH_2), 54.7 (CH), 115.8 (CH), 133.7 (C), 136.3 (CH), 177.2 (C); *m/z* (FAB) 241 (MH^+. 1%), 190 (50), 96 (100) and 76 (41).

5.4 Chapter 4

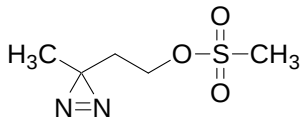
3,3'-Azo-butanol (370)[182]



3-Ketobutanol (l4.9 mL, 56.8 mmol) was dissolved in MeOH (100 mL) and cooled to -78 ^oC. Liquid NH_3 (100 mL) was added and the solution was stirred at -78 ^oC for 4 h. NH_2OSO_3H (7.38 g, 65.3 mmol) was added, the cooling bath was removed and the solution was heated under reflux with a dry ice condenser for 1 h. The NH_3 was then allowed to evaporate overnight. The resulting slurry was filtered and the filter cake was washed with MeOH. The filtrate was reduced *in vacuo*, diluted with MeOH and cooled to 0 ^oC. NEt_3 (15 mL) was added and the solution was brought to room temperature. Solid iodine was added until the red colour persisted. The solution was concentrated *in vacuo*, diluted with a saturated solution of NaCl (50 mL) to twice the volume and extracted with Et_2O (3 x 75 mL). The organic layer was washed with $Na_2S_2O_3$, dried ($MgSO_4$) and concentrated. The crude product was purified using column chromatography (25% EtOAc/petroleum ether) to yield **370** as a colourless oil (2.2 g, 39%). ν_{max}/cm^{-1} (NaCl) 3325 (OH), 2928 (CH), 1589, 1387, 1052, 862; δ_H (400 MHz, $CDCl_3$) 1.08 (3H, s, 4-H_3),

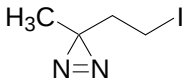
1.65 (3H, m, 2-H_2 and OH), 3.54 (2H, t, *J* 6.4 Hz, 1-H_2); δ_c (100 MHz, $CDCl_3$) 20.3 (CH_3), 24.3 (C), 36.9 (CH_2), 57.8 (CH_2); *m/z* (CI) 101.0703 (MH^+. $C_4H_9ON_2$ requires 101.0715).

3,3'-Azo-1-(methylsulfonyloxy)butane (371)



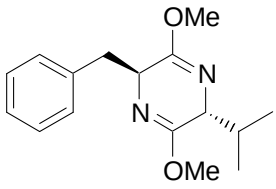
3,3-Azo-butanol **(370)** (0.1 g, 1.0 mmol) was dissolved in DCM (10 mL). NEt_3 (0.2 mL, 1.5 mmol) was added followed by DMAP (0.02 g, 0.2 mmol) and $MeSO_2Cl$ (0.1 mL, 1.2 mmol). The reaction was allowed to stir at room temperature for 24 h. The reaction was washed with 2M HCl and extracted with DCM. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by dry flash column chromatography using EtOAc gave **371** as a yellow oil (0.16 g, 90%). ν_{max}/cm^{-1} (NaCl) 2928 (CH), 1717, 1353, 1175, 960, 806; δ_H (400 MHz, $CDCl_3$) 1.11 (3H, s, 4-H_3), 1.81 (2H, t, *J* 6.2 Hz, 2-H_2), 3.09 (3H, s, OSO_2CH_3), 4.14 (2H, t, *J* 6.2 Hz, 1-H_2); δ_c (100 MHz, $CDCl_3$) 19.9 (CH_3), 23.4 (C), 34.3 (CH_2), 37.7 (CH_3), 64.4 (CH_2); *m/z* (CI) 179.0491 (MH^+. $C_5H_{11}O_3N_2S$ requires 179.0490), 169 (53%), 151 (100) and 113 (17).

3, 3'-Azo-1-iodo-butane (372)



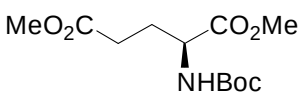
3,3'-Azo-butanol **(370)** (0.5 g, 5.0 mmol) was dissolved in MeCN (50 mL) and Et_2O (50 mL). PPh_3 (1.1 g, 20 mmol) and imidazole (1.4 g, 20 mmol) were added and the reaction mixture allowed to stir for 10 min. Iodine (3.8 g, 15 mmol) was added and the reaction was stirred at room temperature for 2 h. It was then washed with a saturated $Na_2S_2O_3$ solution, the organic layer dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (20% EtOAc/petroleum ether) gave **372** as a brown oil (0.08 g, 7%). ν_{max}/cm^{-1} (NaCl) 2924 (CH), 1652, 1172, 842; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, s, 4-H_3), 1.68 (2H, t, *J* 6.4 Hz, 2-H_2), 3.57 (2H, t, *J* 6.4 Hz, 1-H_2); δ_c (100 MHz, $CDCl_3$) 20.3 (CH_3), 24.5 (C), 37.0 (CH_2), 57.8 (CH_2); *m/z* (EI) 83 (M^+ – I, 100%), 127 (19) and 41 (88).

(2*R*,5*S*)-2-Isopropyl-3,6-dimethoxy-5-benzyl-2,5-dihydropyrazine (381)



(2*R*,5*S*)-2-Isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (0.1 mL, 0.6 mmol) was added to a dry flask followed by THF (5 mL). This was cooled to -40 ^{o}C and BuLi (2.5M in hexanes) (0.3 mL, 0.7 mmol) was added and the reaction allowed to stir at -40 ^{o}C for 1 h. BnBr (1.0 mL, 0.7 mmol) was dissolved in THF (3 mL) and cooled to -40 ^{o}C. This was added to the BuLi solution which had been cooled to -78 ^{o}C. The reaction was then allowed to stir at -78 ^{o}C for 5 h and at room temperature for 24 h. The solvent was removed *in vacuo* and the residue was dissolved in Et_2O. This was then washed with water and extracted with Et_2O (2 x 5 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (25% EtOAc/petroleum ether) yielded **381** as a yellow oil (0.14 g, 88%). ν_{max}/cm^{-1} (NaCl) 2960 (CH), 1696, 1437, 1239, 1014, 701; $[\alpha]_D^{25}$ +33.4 (*c* 2.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.53 (3H, d, *J* 6.8 Hz, 2-CHC*H*$_3$CH$_3$), 0.87 (3H, d, *J* 6.8 Hz, 2-CHCH$_3$C*H*$_3$), 2.07 (1H, septet of d, *J* 6.8, 3.2 Hz, 2-C*H*$(CH_3)_2$), 3.02 (2H, d, *J* 4.8 Hz, 5-C*H*$_2$Ph), 3.20 (1H, d, *J* 3.2 Hz, 2-H), 3.61 (3H, s, OMe), 3.65 (3H, s, OMe), 4.26 (1H, t, *J* 4.8 Hz, 5-H), 6.93-7.20 (5H, m, Ph); δ_c (100 MHz, $CDCl_3$) 16.4 (CH_3), 19.0 (CH_3), 31.2 (CH), 40.0 (CH_2), 52.2 (CH_3), 52.4 (CH_3), 56.6 (CH), 60.2 (CH), 126.3 (CH), 127.8 (CH), 130.0 (CH), 137.0 (C), 162.1 (C), 163.8 (C); *m/z* (CI) 275.1757 (MH^+. $C_{16}H_{22}O_2N_2$ requires 275.1760), 243 (4%), 183 (9) and 141 (5).

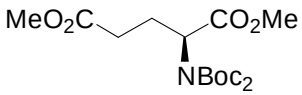
Dimethyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-aminopentan-1,4-dioate (385)[164]



To a stirred suspension of L-glutamic acid (5.0 g, 34.0 mmol) in MeOH (100 mL), TMS-Cl (19.2 mL, 149.6 mmol) was added slowly at 0 ^{o}C. The reaction was allowed to stir for 1 h at 0 ^{o}C and then at room temperature for 24 h. NEt_3 (30.7 mL, 221.1 mmol) and Boc_2O (8.16 g, 37.4 mmol) were added slowly and the reaction stirred for 2 h. The reaction mixture was concentrated *in vacuo* and the resulting residue dissolved in Et_2O and filtered to remove the white precipitate. The filtrate was concentrated *in vacuo* and purified using flash column chromatography (30% EtOAc/petroleum ether), to give **385** as a white solid

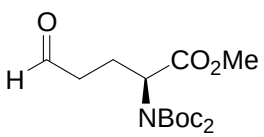
(8.2 g, 88%). ν_{max}/cm^{-1} 2986 (CH), 1778 (CO), 1753 (CO), 1731 (CO), 1368, 1135, 1082, 853; $[\alpha]_D^{27}$ -37.3 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, ^{t}Bu), 1.91-2.02 (1H, m, 3-*H*H), 2.17-2.26 (1H, m, 3-H*H*), 2.43 (2H, dd, *J* 15.6, 7.6 Hz, 4-H_2), 3.71 (3H, s, OMe), 3.77 (3H, s, OMe), 4.34-4.39 (1H, m, 2-H), 5.14 (1H, d, *J* 8.0 Hz, NH); δ_c (100 MHz, $CDCl_3$) 27.8 (CH_2), 28.3 (CH_3), 30.1 (CH_2), 51.8 (CH_3), 52.4 (CH_3), 52.9 (CH), 80.1 (C), 155.4 (C), 172.7 (C), 173.2 (C); *m/z* (CI) 276.1445 (MH^+. $C_{12}H_{22}O_6N$ requires 276.1447), 220 (100%) and 176 (17).

Dimethyl (2*S*)-*N*,*N*-di-(*tert*-butoxycarbonyl)-2-aminopentan-1,4-dioate (386)[164]



Dimethyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-aminopentan-1,4-dioate **(385)** (8.70 g, 31.8 mmol) was dissolved in MeCN (180 mL). DMAP (0.78 g, 6.4 mmol) and Boc_2O (7.63 g, 35.0 mmol) were added and the reaction was allowed to stir at room temperature for 3 h. Boc_2O (3.47 g, 15.9 mmol) was added and the reaction was allowed to stir at room temperature for 24 h. The solvent was removed *in vacuo* and the crude product was purified using flash column chromatography (20% EtOAc/petroleum ether) to give **386** as a white solid (11.7 g, 98%). ν_{max}/cm^{-1} 2981 (CH), 2360, 1795 (CO), 1747 (CO), 1369, 1142; $[\alpha]_D^{27}$ -35.6 (*c* 0.7, $CHCl_3$); (lit.[164] $[\alpha]_D^{25}$ -37.2 (*c* 2.2, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.52 (18H, s, 2 x ^{t}Bu), 2.16-2.26 (1H, m, 3-*H*H), 2.38-2.47 (2H, m, 4-H_2), 2.48-2.55 (1H, m, 3-H*H*), 3.69 (3H, s, OMe), 3.74 (3H, s, OMe), 4.96 (1H, dd, *J* 9.6, 4.8 Hz, 2-H); δ_c (100 MHz, $CDCl_3$) 25.2 (CH_2), 27.9 (CH_3), 30.6 (CH_2), 51.7 (CH_3), 52.2 (CH_3), 57.3 (CH), 83.3 (C), 151.9 (C), 170.8 (C), 173.1 (C); *m/z* (CI) 376 (MH^+. 8%), 338 (46), 320 (41), 276 (40), 220 (98), 176 (100) and 128 (93).

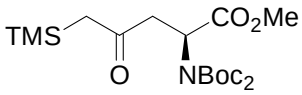
Methyl (2*S*)-*N*,*N*-di-(*tert*-butoxycarbonyl)-2-amino-4-oxopentanoate (387)[164]



Dimethyl (2*S*)-*N*,*N*-di-(*tert*-butoxycarbonyl)-2-aminopentan-1,4-dioate **(386)** (1.0 g, 2.8 mmol) was dissolved in Et_2O (50 mL) and cooled to -78 ^oC. DIBAL-H (3.9 mL, 3.9 mmol) was added dropwise and the solution was allowed to stir at -78 ^oC for 24 h. A saturated NH_4Cl solution was added (10 mL) and the reaction was allowed to warm to room temperature. It was filtered through a pad of Celite® with Et_2O and concentrated *in vacuo*.

Following purification by column chromatography (15% EtOAC/petroleum ether) **387** was obtained as a colourless oil (0.6 g, 68%). ν_{max}/cm^{-1} 2981 (CH), 1793 (CO), 1734 (CO), 1367, 1125, 854; $[\alpha]_D^{27}$ -49.0 (*c* 0.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.53 (18H, s, 2 x ^{t}Bu), 2.15-2.23 (1H, m, 3-*H*H), 2.49-2.67 (3H, m, 3-H*H* and 4-H_2), 3.76 (3H, s, OMe), 4.92 (1H, dd, *J* 9.6, 5.0 Hz, 2-H), 9.81 (1H, t, *J* 1.2, 5-H); δ_c (100 MHz, $CDCl_3$) 22.5 (CH_2), 28.0 (CH_3), 40.5 (CH_2), 52.3 (CH), 57.3 (CH_3), 83.5 (C), 151.9 (C), 170.8 (C), 201.0 (CH); *m/z* (CI) 346.1865 (MH^+. $C_{16}H_{28}O_7N$ requires 346.1866), 345 (38), 228 (55), 207 (74) and 128 (100).

Methyl (2*S*)-*N*,*N*-di-(*tert*-butoxycarbonyl)-2-amino-5-(trimethylsilyl)-4-oxopentanoate (397)



Method A[190]

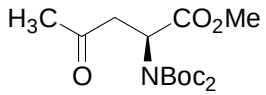
Methyl (2*S*)-*N*,*N*-di-(*tert*-butoxycarbonyl)-2-amino-4-oxobutanoate **(332)** (0.1 g, 0.3 mmol) was added to a solution of Me_3Al (0.2 mL, 0.4 mmol) in DCM (10 mL) at -78 ^{o}C. TMS-CH_2N_2 (0.2 mL, 0.3 mmol) was added and the reaction mixture stirred at -78 ^{o}C for 1 h and then at -40 ^{o}C for 1 h. The solution was then poured into 2M HCl and extracted using DCM (3 x 15 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give **397** as a pale yellow oil (0.09 g, 71%). ν_{max}/cm^{-1} (NaCl) 2980 (CH), 1795 (CO), 1747 (CO), 1144, 853; $[\alpha]_D^{25}$ -72.5 (*c* 0.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.01 (9H, s, ^{t}Bu), 1.56 (18H, s, 2 x ^{t}Bu), 2.08 (1H, d, *J* 10.4 Hz, 5-*H*H), 2.13 (1H, d, *J* 10.4 Hz, 5-H*H*), 2.62 (1H, dd, *J* 18.0, 5.6 Hz, 3-*H*H), 3.22 (1H, dd, *J* 18.0, 6.8 Hz, 3-H*H*), 3.56 (3H, s, OMe), 5.35-5.40 (1H, m, 2-H); δ_c (100 MHz, $CDCl_3$) 0.0 (CH_3), 24.1 (CH_3), 39.3 (CH_2), 46.7 (CH_2), 52.5 (CH), 55.2 (CH_3), 84.4 (C), 152.9 (C), 171.9 (C), 206.2 (C); *m/z* (CI) 418.2262 (MH^+. $C_{19}H_{36}NO_7Si$ requires 418.2261), 346 (53%), 318 (78), 262 (95), 234 (99), 218 (25), 190 (100) and 146 (89).

Method B[190]

Methyl (2*S*)-*N*,*N*-di-(*tert*-butoxycarbonyl)-2-amino-4-oxobutanoate **(332)** (0.1 g, 0.3 mmol) was dissolved in DCM (10 mL). $SnCl_2$ (2.9 mg, 0.02 mmol) and TMS-CH_2N_2 (0.15 mL, 0.3 mmol) were added and the solution was allowed to stir at room temperature for 30 min. The reaction was quenched with 0.1M HCl and extracted with DCM (20 mL). The organic layers were combined, washed with a saturated solution of NaCl, dried ($MgSO_4$)

and concentrated *in vacuo*. **397** was the main product isolated (89 mg, 85%). Characterisation data for this product was consistent with that shown above.

Methyl (2*S*)-*N*,*N*-di-(*tert*-butoxycarbonyl)-2-amino-4-oxopentanoate (393)



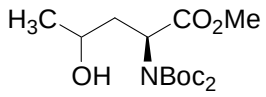
Method A[192]

Methyl (2*S*)-*N*,*N*-di-(*tert*-butoxycarbonyl)-2-amino-4-oxobutanoate **(332)** (0.1 g, 0.3 mmol) was dissolved in Et_2O (10 mL) and cooled to 0 ^oC. $MgBr_2$ (0.08 g, 0.45 mmol) was added followed by TMS-CH_2N_2 (2M solution in Et_2O) (0.2 mL, 0.4 mmol) and the reaction mixture was then stirred at 0 ^oC for 30 min and at room temperature for 4 h. The reaction mixture was cooled again to 0 ^oC, MeOH (3 mL) and 0.1M HCl (3 mL) were added and it was warmed to room temperature. The mixture was diluted with Et_2O (50 mL), washed with water (50 mL) and the organic layer dried ($MgSO_4$) and concentrated *in vacuo*. Following purification by column chromatography (10% EtOAc/petroleum ether), **393** was obtained as a dark yellow oil (7.5 mg, 7%). ν_{max}/cm^{-1} 2980 (CH), 1749 (CO), 1368, 1236, 1144, 1044, 866; $[\alpha]_D^{27}$ -77.1 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.38 (18H, s, 2 x ^{t}Bu), 2.09 (3H, s, 5-H_3), 2.56 (1H, dd, *J* 17.6, 4.8 Hz, 3-*H*H), 3.34 (1H, dd, *J* 17.6, 7.6 Hz, 3-H*H*), 3.58 (3H, s, OMe), 5.38 (1H, dd, *J* 7.6, 4.8 Hz, 2-H); δ_c (100 MHz, $CDCl_3$) 29.7 (CH_3), 31.9 (CH_3), 46.2 (CH_2), 54.2 (CH), 55.9 (CH_3), 85.2 (C), 153.5 (C), 172.4 (C), 206.5 (C); *m/z* (FAB) 346.1867 (MH^+. $C_{16}H_{28}O_7N$ requires 346.1866), 290 (28%), 234 (61), 190 (50), 147 (100) and 89 (30).

Method B[190]

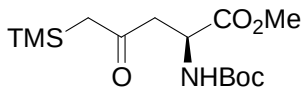
Methyl (2*S*)-*N*,*N*-di-(*tert*-butoxycarbonyl)-2-amino-4-oxobutanoate **(332)** (0.1 g, 0.3 mmol) was added to a solution of Me_3Al (0.2 mL, 0.4 mmol) in DCM (10 mL) at -78 ^oC. The reaction mixture was stirred at -78 ^oC for 1 h and at -40 ^oC for 1 h. The mixture was poured into 1M HCl and extracted with DCM (3 x 15 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (30% EtOAc/petroleum ether) gave **393** as a dark yellow oil (0.02 g, 21%). Characterisation data for this product was consistent with that shown above.

Methyl (2*S*)-*N*,*N*-di-(*tert*-butoxycarbonyl)-2-amino-4-hydroxy-pentanoate (402)



Methyl (2*S*)-*N*,*N*-di-(*tert*-butoxycarbonyl)-2-amino-4-oxobutanoate **(332)** (0.1 g, 0.3 mmol) was dissolved in THF (10 mL) and cooled to 0 ^{o}C. The solution was treated with MeMgBr (0.2 mL, 0.3 mmol) and stirred for 2 h. The reaction was quenched with a saturated solution of NaCl and extracted with EtOAc (3 x 15 mL). The organic layers were combined, washed with a saturated solution of $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (15% EtOAc/petroleum ether) gave **402** as a dark yellow oil (0.02 g, 15%). ν_{max}/cm^{-1} 3377 (OH), 2980 (CH), 1742 (CO), 1500, 1283, 1165, 945, 734; $[\alpha]_D^{25}$ +28.9 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.4 Hz, 5-H_3), 1.37 (9H, s, ^{t}Bu), 1.41 (9H, s, ^{t}Bu), 1.92-1.98 (1H, m, 3-*H*H), 2.00-2.11 (1H, m, 3-H*H*), 3.68 (3H, s, OMe), 4.31 (1H, dd, *J* 13.2, 6.0 Hz, 2-H), 4.71-4.79 (1H, m, 4-H), 5.21 (1H, d, *J* 7.6 Hz, OH); δ_c (100 MHz, $CDCl_3$) 20.2 (CH_3), 27.8 (CH_3), 38.2 (CH_2), 50.8 (CH), 52.4 (CH_3), 70.0 (CH), 80.0 (C), 152.8 (C), 172.5 (C); *m/z* (CI) 348.2019 (MH^+. $C_{16}H_{30}O_7N$ requires 348.2022), 292 (22%), 236 (100), 192 (23), 174 (45) and 148 (17).

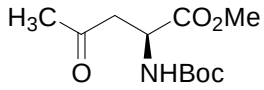
Methyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-amino-4-oxo-5-trimethylsilylpentanoate (404)



$SnCl_2$ (5 mg, 0.02 mmol) was placed in a round bottomed flask and dried in an oven at 100 ^{o}C for 48 h. It was then heated to 100 ^{o}C under vacuum for 3 h and cooled under an argon atmosphere. TMS-CH_2N_2 (0.2 mL, 0.4 mmol) was added to the flask followed by methyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-amino-4-oxobutanoate **(334)** (0.1 g, 0.4 mmol) dissolved in DCM (5 mL). This was allowed to stir at room temperature for 19 h. The reaction was quenched with 0.1M HCl (3 mL) and extracted with Et_2O (3 x 10 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by a short silica column (30% EtOAc/petroleum ether) gave **404** as a pale yellow oil (0.07 g, 66%). ν_{max}/cm^{-1} (NaCl) 3370 (NH), 2956 (CH), 1718 (CO), 1499, 1167, 854; $[\alpha]_D^{27}$ +30.3 (*c* 0.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.0 (9H, s, $(CH_3)_3Si$), 1.31 (9H, s, ^{t}Bu), 2.08 (2H, s, 5-H_2), 2.79 (1H, dd, *J* 18.4, 4.0 Hz, 3-*H*H), 3.02 (1H, dd, *J* 18.4, 4.0 Hz, 3-H*H*), 3.60 (3H, s, OMe), 4.28-4.31 (1H, m, 2-H), 5.43 (1H, d, *J* 8.4 Hz, NH); δ_c (100 MHz, $CDCl_3$) 0.0 (CH_3), 29.5 (CH_3), 39.2 (CH_2), 47.2 (CH_2), 50.1 (CH), 53.7 (CH_3), 81.0 (C), 156.7 (C),

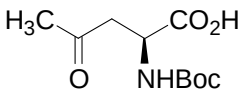
173.2 (C), 208.4 (C); *m/z* (CI) 318.1738 (MH^+. $C_{14}H_{28}O_5NSi$ requires 318.1737), 279 (31%), 262 (100), 218 (46), 207 (71) and 146 (21).

Methyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-amino-4-oxopentanoate (394)



Methyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-amino-4-oxo-5-trimethylsilylpentanoate **(404)** (0.1 g, 0.3 mmol) was dissolved in a 5% KOH in MeOH (10 mL). This mixture was allowed to stir at room temperature for 1 h. The solvent was then removed *in vacuo*. The residue was dissolved in EtOAc, dried ($MgSO_4$) and concentrated. Immediate purification by column chromatography (50% EtOAc/petroleum ether) gave **394** as a pale yellow oil (67 mg, 92%). $[\alpha]_D^{25}$ +25.5 (*c* 2.1, $CHCl_3$) (lit.[195] $[\alpha]_D^{22}$ +32.7 (*c* 1.0, $CHCl_3$)); ν_{max}/cm^{-1} 3420 (NH), 3082 (CH), 1774 (CO), 1612, 1466, 1111, 945; δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, ^{t}Bu), 2.20 (3H, s, 5-H_3), 2.98 (1H, dd, *J* 18.4, 4.2 Hz, 3-*H*H), 3.22 (1H, dd, *J* 18.4, 4.4 Hz, 3-H*H*), 3.76 (3H, s, OMe), 4.49-4.54 (1H, m, 2-H), 5.53 (1H, d, *J* 8.4 Hz, NH); δ_c (100 MHz, $CDCl_3$) 28.3 (CH_3), 29.9 (CH_3), 45.4 (CH_2), 49.4 (CH), 52.7 (CH_3), 80.1 (C), 155.6 (C), 171.9 (C), 206.7 (C); *m/z* (FAB) 246.1343 (MH^+. $C_{11}H_{20}O_5N$ requires 246.1341), 190 (100%), 147 (67) and 89 (23).

(2*S*)-*N*-(*tert*-butoxycarbonyl)-2-amino-4-oxopentanoic acid (395)



Methyl (2*S*)-*N*-(^{t}butoxycarbonyl)-2-amino-4-oxopentanoate **(394)** (0.2 g, 0.7 mmol) was dissolved in MeOH:water 1:1 (20 mL). $CsCO_3$ (0.3 g, 0.9 mmol) was added and the reaction mixture stirred at room temperature for 24 h. The mixture was acidified with 1M HCl and extracted with DCM. The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give **395** as a colourless oil (0.15 g, 94%). No further purification was required. ν_{max}/cm^{-1} 3357 (NH), 3030 (CH), 1743 (CO), 1688, 1456, 1138; $[\alpha]_D^{27}$ +26.1 (*c* 0.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, ^{t}Bu), 2.13 (3H, s, 5-H_3), 2.88 (1H, dd, *J* 18.2, 4.8 Hz, 3-*H*H), 3.14 (1H, dd, *J* 18.2, 3.6 Hz, 3-H*H*), 4.46 (1H, ddd, *J* 8.4, 4.8, 3.6 Hz, 2-H), 5.48 (1H, d, *J* 8.4 Hz, NH); δ_c (100 MHz, $CDCl_3$) 28.3 (CH_3), 30.0 (CH_3), 45.1

(CH_2), 49.3 (CH), 80.5 (C), 155.8 (C), 175.1 (C), 207.3 (C); *m/z* (CI) 232.1189 (MH^+. $C_{10}H_{18}O_5N$ requires 232.1185), 176 (100%), 158 (33), 132 (95), 130 (36) and 73 (40).

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