Investigation of A New Substrate Directed Aza-Claisen Rearrangement for Natural Product Synthesis.

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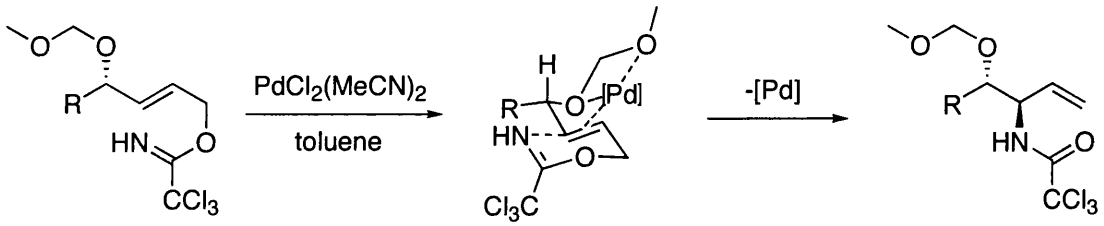
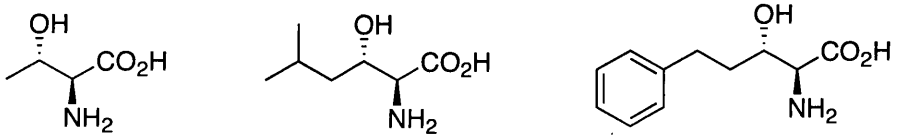
Abstract

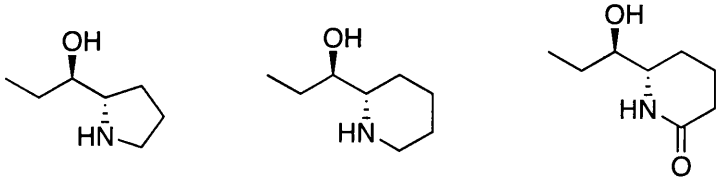
A novel substrate directed, palladium(II)-catalyst aza-Claisen rearrangement has been developed. Aza-Claisen rearrangement of a series of δ-ether substituted allylic trichloroacetimidates demonstrated that the oxygen atom in this position can effectively direct facial coordination of the palladium(II)-catalyst, with the MOM-ether substrate giving the most selective rearrangement reaction. An optimisation study was carried out using different catalysts and reaction conditions. The results from this study showed that bis(acetonitrile)palladium(II) chloride catalyst and non-coordinating solvents such as toluene give the most selective rearrangement resulting in the isolation of the *anti*-compound in up to 88% diastereomeric excess.



This methodology was used as the key step in the novel diastereoselective synthesis of β-hydroxy α-amino acids from enantiopure α-hydroxy acids. During the rearrangement step, a competing [1,3] pathway catalysed by palladium(0) was suppressed using *p*-benzoquinone as an *in-situ* oxidant in the reaction mixture.



A series of compounds based on the structure of the piperidine alkaloid (+)-α-conhydrine were synthesised using this newly developed ether-directed, palladium(II)-catalysed aza-Claisen rearrangement and a ring closing metathesis reaction as the key steps.



(+)-α-Conhydrine

Acknowledgements

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I would like to express my sincere gratitude to my supervisor, Dr Andrew Sutherland, for all his help, advice and support over the last three years. He has been an inspiration through his professionalism and has shaped me to be the chemist I am today. Also, my thanks goes to my second supervisor, Dr Richard C. Hartley, for his advice.

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Thank you to the other members of the Sutherland group and to the Hartley group for creating a professional yet relaxed environment in which to carry out my research.

Finally, I would like to thank my family and friends for their encouragement and support throughout my time at Glasgow University and also for their logistical assistance in the repeated relocation of my pink elephant.

Author's Declaration

This thesis represents the original work of Andrew George Jamieson unless explicitly stated otherwise in the text. The research upon which it is based was carried out at the University of Glasgow in the Loudon and Henderson laboratories, under the supervision of Dr Andrew Sutherland, during the period October 2003 to September 2006. Portions of the work described herein have been published elsewhere as listed below.

A. G. Jamieson, A. Sutherland, *Org. Biomol. Chem.*, 2005, **3**, 735.

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

A. G. Jamieson, A. Sutherland, *Org. Biomol. Chem.*, 2006, **4**, 2932.

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Abbreviations

Ar	aromatic
sec-BuLi	*sec*-Butyllithium
Bn	benzyl
Boc	*tert*-butoxycarbonyl
$(BMI)BF_4$	1-butyl-3-methylimidazolium tetrafluoroborate
BUS	*tert*-butylsulfonamide
Cat.	catalyst
CAN	Ceric Ammonium Nitrate
CI	Chemical Ionisation
COP	cobaltocenyloxazoline palladacycle
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
°C	degrees centigrade
DFT	Density Function Theory
d.e.	diastereomeric excess
DCM	dichloromethane
DDQ	dichlorodicyanoquinone
DCC	*N*,*N*'-dicyclohexylcarbodiimide
$(DHQD)_2AQN$	(diether hydroquinidine)anthraquinone-1,4-diyl
DMF	*N*,*N*'-dimethylformamide
DMSO	dimethyl sulfoxide
DIBAL-H	diisobutylaluminium hydride
d	doublet
EI	Electron Impact
e.e.	enantiomeric excess
$\Delta H^{\ddagger}$	enthalpy change
EtOAc	ethyl acetate
FIP	ferrocenylimidazoline palladacycle
FOP	ferrocenyloxazoline palladacycle
FTIR	Fourier Transform Infrared
g	gram(s)
GABA	gamma-aminobutyric acid
H	Hour(s)
HWE	Horner-Wadsworth-Emmons
kcal	kilocalorie(s)

LAB	lithium ammonia-borane
LDA	lithium diisopropylamine
LHMDS	lithium hexamethyldisilazide
mCBPA	*meta*-chloroperbenzoic acid
Ms	methane sulfonyl
M	Molar
MeBmt	(4*R*)-4-[(*E*)-2-butenyl]-4,*N*-dimethyl-L-threonine
MEM	Methoxyethylmethyl
MOM	Methoxymethyl
MTM	Methylthiomethyl
Me	Methyl
mg	milligram(s)
mL	millilitre(s)
MNDO-PM3	Modified neglect of differential overlap-parametric method 3
mol	mole(s)
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
Pd/C	Palladium on carbon
PMB	para-methoxybenzoic acid
PrOH	propanol
P	protecting group
ppm	parts per million
PS	Proton Sponge
^{1}H	proton
q	quartet
quin	quintet
RCM	Ring Closing Metathesis
RT	Room Temperature
sept	septet
sex	sextet
s	singlet
SAR	Structure-Activity-Relationship
TBDMS	*tert*-Butyldimethylsilyl
TBAF	*tetra-n*-butylammonium fluoride
THF	Tetrahydrofuran

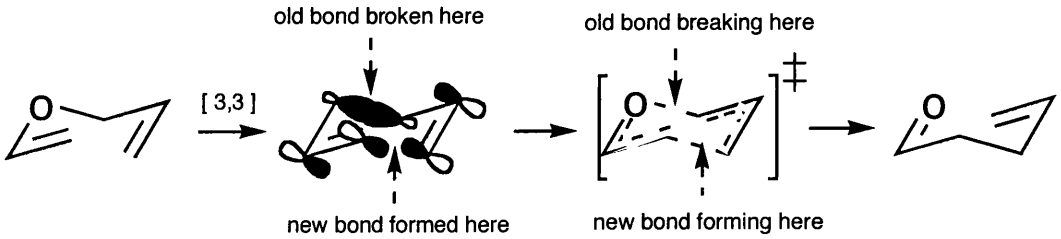
THP	Tetrahydropyranyl
TFA	Trifluoroacetic acid
$TeocNH_2$	2-Trimethylsilylethyl carbonate
t	triplet
Tr	trityl

1.0 Introduction

1.1 Introduction to [3,3] Sigmatropic Rearrangements.

The efficient synthesis of complex molecules is still a challenge in synthetic organic chemistry. This is the case because key components with defined stereochemistry must be generated as starting materials before the total synthesis of these complex molecules can be carried out.

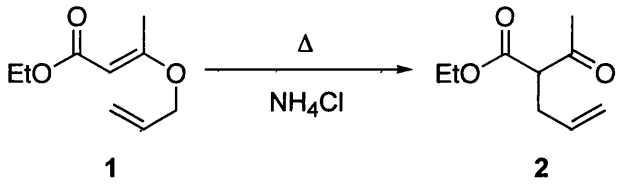
A subclass of pericyclic reactions, [3,3]-sigmatropic rearrangements have proven to be reliable reactions with which to generate defined stereogenic carbon-carbon and carbon-heteroatom bonds.[1] Sigmatropic rearrangments are so called because a σ-bond appears to move from one place to another (Scheme 1). For acyclic substrates the reaction occurs with a highly ordered chair-like transition state *via* a concerted, suprafacial reaction pathway which obeys the Woodward-Hoffman rules.[2]



Scheme 1: [3,3]-sigmatropic rearrangement.

The Woodward-Hoffman rules state that in a thermal pericyclic reaction the total number of $(4q + 2)_s$ and $(4r)_a$ components must be odd.[2] A component is a molecular orbital or bond participating in a pericyclic reaction. Thus, (4q + 2) and (4r) simply refer to the number of electrons in a component where q and r are integers. The suffix 's' stands for a suprafacial component (*i.e.* forms new bonds on the same face at both ends). On the other hand, the suffix 'a' stands for an antarafacial component (*i.e.* forms new bonds on opposite faces at both ends).

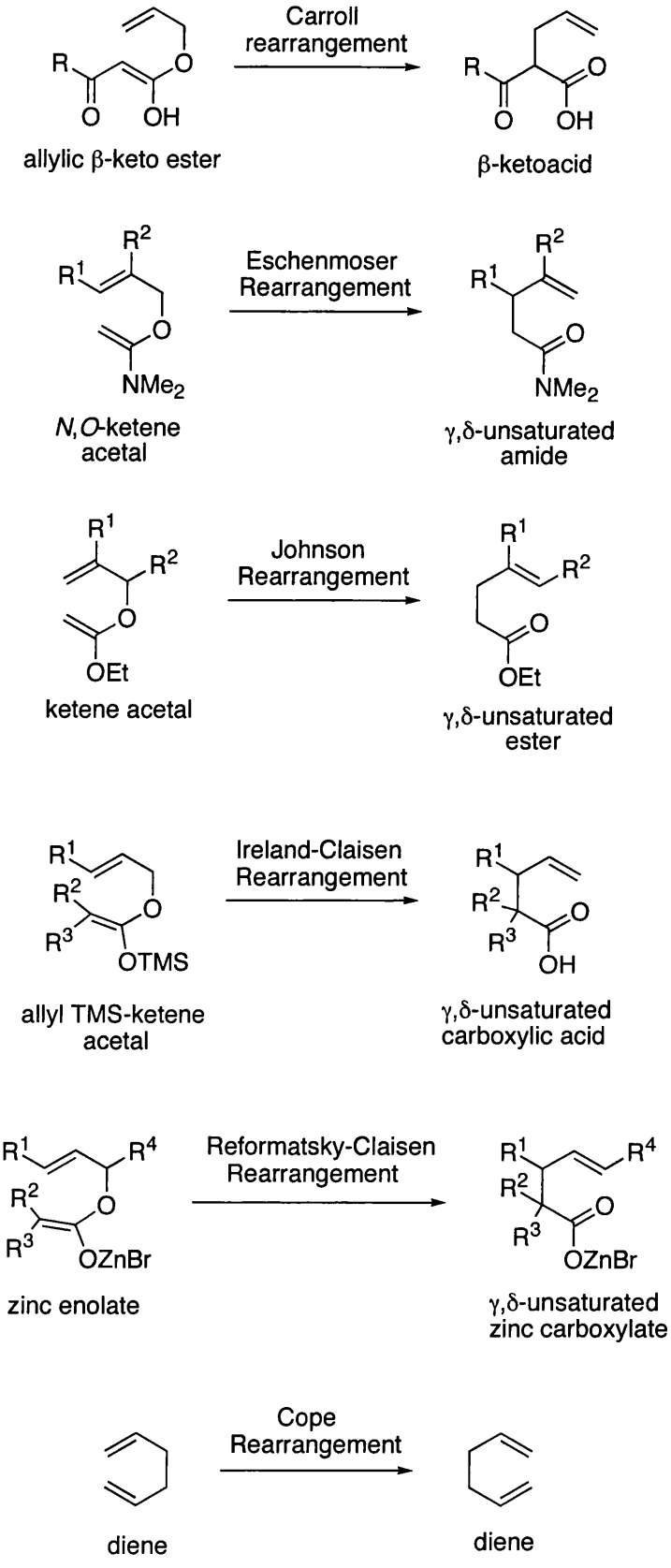
The first example of a [3,3]-sigmatropic rearrangement was reported by Ludwig Claisen in 1912.[3] Under thermal conditions, Claisen reacted ethyl 3-allyloxybut-2-enoate **1** in the presence of solid NH_4Cl and isolated the β-keto ester as the [3,3]-sigmatropic rearrangement product **2** (Scheme 2).



1 2

Scheme 2: Original Claisen rearrangement.

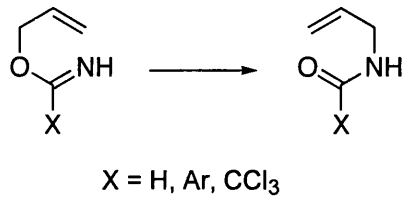
Since Claisen's original report nearly a century ago, the rearrangement now named after him has been developed to include numerous related [3,3]-sigmatropic rearrangements including the Carroll,[4] Eschenmoser,[5] Johnson,[6] Ireland-Claisen[7] and Reformatsky-Claisen[8] rearrangements as well as the Cope rearrangement[9] (Scheme 3).



Scheme 3: Common related [3,3]-rearrangements.

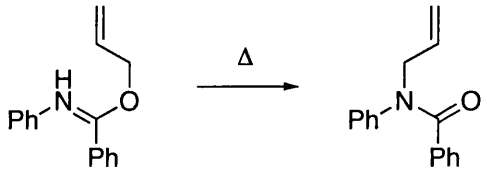
The [3,3]-sigmatropic rearrangement of six membered acyclic systems containing an oxygen and nitrogen atom is known as the aza-Claisen rearrangement.[10] Many examples of this type of rearrangement have been reported,[11] however the most predominant form is

the [3,3]-sigmatropic rearrangement of allylic imidates (occasionally called the "Claisen-imidate" rearrangement) (Scheme 4).[1a]



Scheme 4: [3,3] sigmatropic rearrangement of allylic imidates

The thermal [3,3]-sigmatropic rearrangement of allylic imidates was first described by Mumm & Möller in 1937 (Scheme 5).[12] Rearrangement of allylic benzimidate **3** was achieved at 210-125 °C to give allylic benzamide **4** in quantitative yield. The reaction is favoured due to the difference in enthalpy, 14 kcal/mol,[13] between dialkyl amide and a imidic ester in the liquid phase.

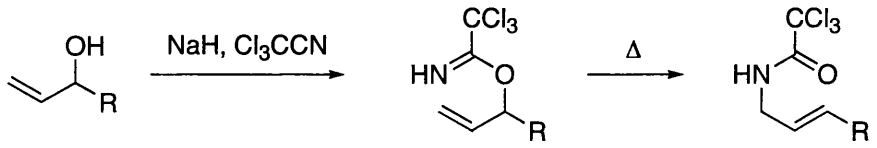


3 **4**

Scheme 5: The first example of a thermal [3,3]-sigmatropic rearrangement of an allylic imidate.

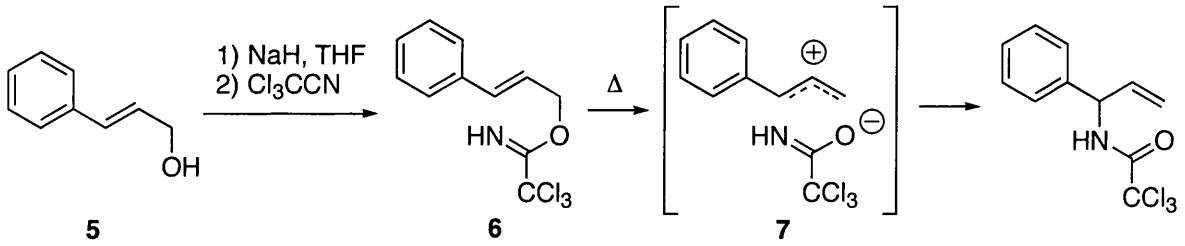
1.2 Thermal Rearrangement of Allylic Trichloroacetimidates.

Overman developed the aza-Claisen reaction in 1974 and found that the thermal [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates generates allylic trichloroamides (Scheme 6).[14] This reaction is now generally referred to as the Overman rearrangement. It was also reported that allylic trichloroacetimidates could be easily generated from readily available allylic alcohols and trichloroacetonitrile using sodium hydride as base.



Scheme 6: Preparation and rearrangement of trichloroacetimidates.

Thermal Overman rearrangements are carried out conveniently by dissolving the allylic trichloroacetimidate in an aprotic solvent (*e.g.* *p*-xylene) and heating the resulting solution under reflux. The rearrangements occur by an operationally concerted pericyclic mechanism with a negative change in enthalpy similar to that observed for the Claisen rearrangement. This results from the large enthalpic driving force associated with the conversion of the imidate to the amide functionality.[13] In order to obtain evidence for this mechanism, attempts have been made to detect an intermediate from the rearrangement. However, this has not been possible even in the case of the proposed highly stablised allylic carbocation **7** that would be formed during the rearrangement of trichloroacetimide **6**, prepared from cinnamyl alcohol **5** (Scheme 7).[15]

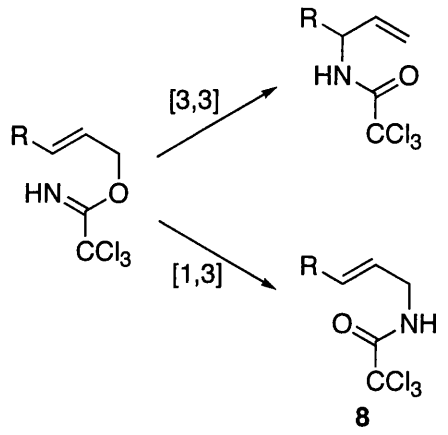


5 **6** **7**

Scheme 7: Rearrangement of cinnamyl alcohol derived trichloroacetimidate with no detection of highly delocalised intermediate.

However, a concerted mechanism was established for the rearrangement by investigation of regioselectivity, solvent effects, thermodynamic parameters and stereoselectivity.

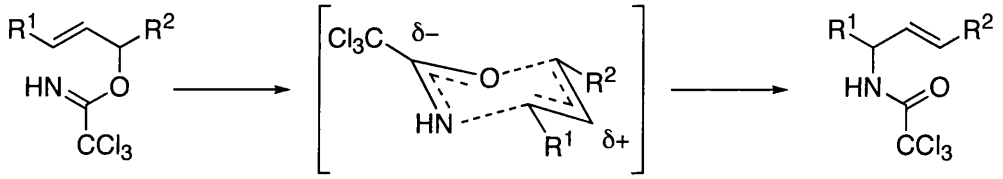
The regiochemical outcome of the thermal rearrangement supports a concerted mechanism. Complete oxygen-to-nitrogen transfer (aza-Claisen rearrangement) is observed while the formal [1,3]-rearrangement product **8** (anti-aza-Claisen rearrangement), arising from a non-concerted ionisation and recombination pathway, is rarely observed (Scheme 8).[16]



Scheme 8: [3,3] vs [1,3] pathways.

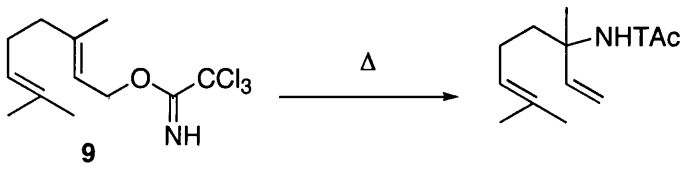
The thermal Overman rearrangement follows first order kinetics, with the rate of reaction influenced by both steric and electronic substituent effects.[15,17]

Stabilisation of the partial positive charge on the oxygen-bearing carbon atom (α-position) in the transition state causes trichloroacetimidates generated from doubly allylic alcohols to react at room temperature, tertiary alcohols at 80 °C ($t_{1/2}$ ~1 hour) and primary alcohols to react at 140 °C ($t_{1/2}$ ~1 hour).[15] Charge seperation in the transition state (*i.e.* partial negative charge on the electronegative HN=C(CCl_3)O fragment and partial positive charge on the all-carbon allyl fragment) is postulated for the reaction mechanism (Scheme 9).[15]



Scheme 9: Evidence for charge separation in transition state.

Evidence for this originates from solvent effects observed from Overman rearrangement of the trichloroacetimidate **9** prepared from geraniol (Scheme 10). Rearrangement at 132 °C gives a five fold rate enhancement with changing solvent from xylenes to the more polar solvent nitrobenzene.[15]

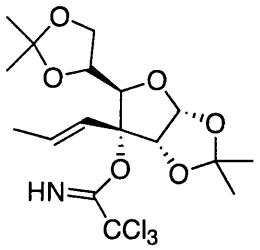


9

Xylene 10.8 (± 1.1) 10^5k,s^{-1}
Nitrobenzene 55.0 (± 4.7) 10^5k,s^{-1}

Scheme 10: Solvent effects in rearrangement of geraniol derived trichloroacetimidate.

Allylic trichloroacetimidates with *E*-alkene double bonds generally react faster than *Z*-alkenes. This is exemplified in the lower $\Delta H^{\ddagger}$ value for the *E*-isomer of imidate **10** compared to the *Z*-isomer **11** (Figure 1).[17]



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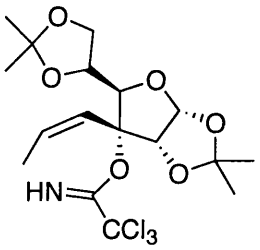
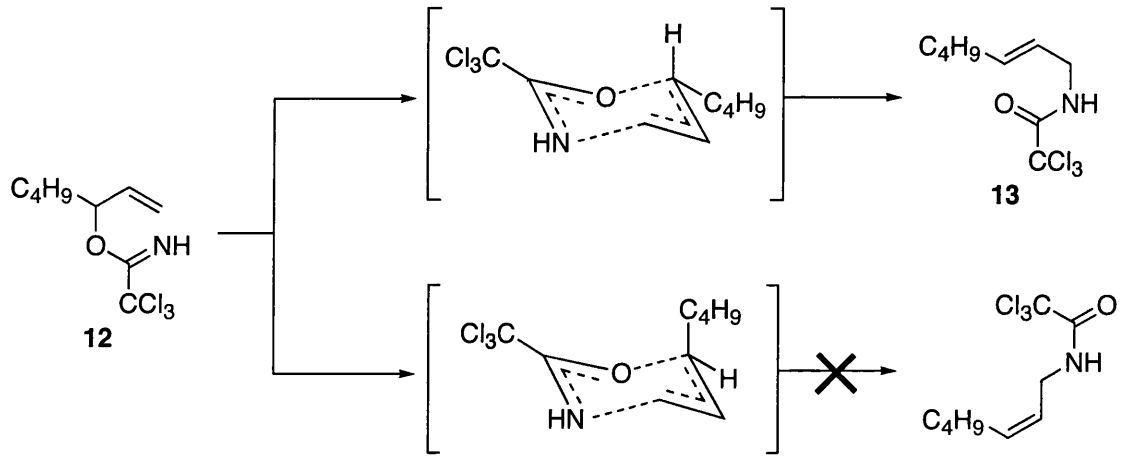


11

E $\Delta H^{\ddagger}$ = 25.6 kcal/mol *Z* $\Delta H^{\ddagger}$ = 28.3 kcal/mol

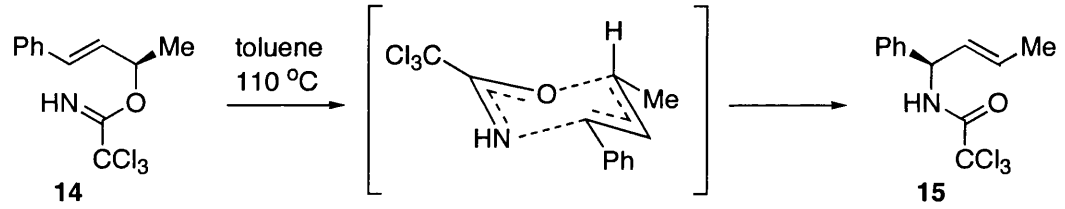
Figure 1: Lower $\Delta H^{\ddagger}$ value for *E*-isomer.

During the concerted, suprafacial transition state, substituents on the oxygen-bearing carbon prefer to adopt the equatorial postion and so effectively all thermal Overman rearrangements produce the allylic trichloroacetamide as the *E*-geometrical isomer. For example, rearrangement of trichloroacetimidate **12** gives *E*-geometric isomer **13** in 92% yield due to the *n*-butyl group being in the equatorial position (Scheme 11).[15]



Scheme 11: Formation of the *E*-geometric isomer.

Excellent stereoselectivity observed for the Overman rearrangement is attributed to the concerted, suprafacial reaction mechanism. For example, the preferred chair-like transition state explains the enantioselectivity observed for Overman rearrangement of allylic trichloroacetimidate **14** to (*R*,*E*)-trichloroacetamide **15** (Scheme 12).[18]

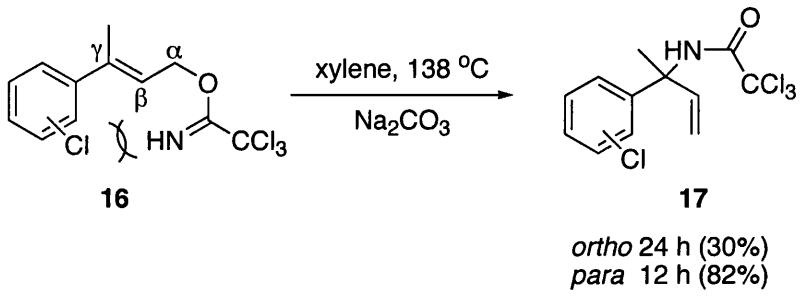


Scheme 12: Stereoselectivity attributed to concerted, suprafacial reaction mechanism.

Substituent effects are prevalent in the Overman rearrangement and also support the proposed development of charge separation in the transition state.

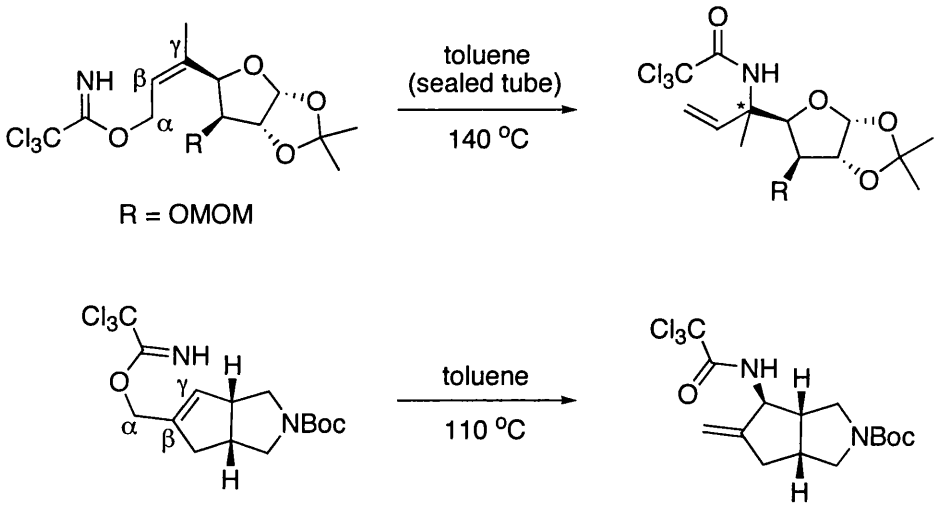
The thermal Overman rearrangement is particularly effected by substitution of the allylic carbon skeleton. Steric effects resulting from substitution at the α-position can, in general be overcome by increasing the temperature of reaction. As discussed previously, higher temperatures are required as electron-donating substituents are replaced by hydrogen. Therefore, primary trichloroacetimidates require temperatures as high as 130-160 °C and secondary and tertiary trichloroacetimidates require 80 °C or less.[15] Rearrangement of imidates with substitution at the γ-position do occur; however, problems have been encountered due to steric clash of these substituents and the nucleophilic nitrogen of the trichloroacetimidate during rearrangement. For example, rearrangement of trichloroacetimidate **16** with a chloro-substituent in the *ortho*-position requires 24 hours and gives trichloroacetamide **17** in only 30% yield. However, with the chloro-substituent

in the *para*-position the reaction is complete in 12 hours and gives the corresponding trichloroacetamide in 82% yield (Scheme 13).[19]



Scheme 13: Substitution at the γ-position.

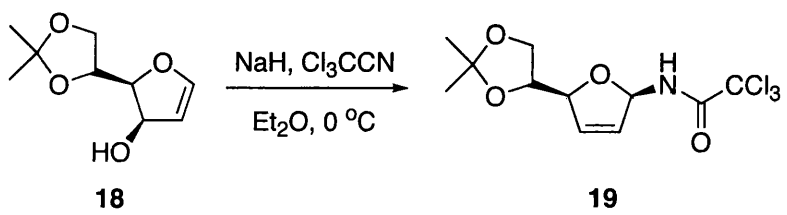
Several examples exist of rearrangements with trisubstituted allylic trichloroacetimidates having a second substituent at either the β- or γ-position (Scheme 14).[20] However, as mentioned previously, 1,2-disubstituted *Z* double bonds require higher temperatures and are therefore more susceptible to degradation and so give lower yields.



Scheme 14: Rearrangements with trisubstituted allylic trichloroacetimidates.

Overman rearrangements are also influenced by the electronic effects of substituents attached at the β- and γ-positions of the allylic system.

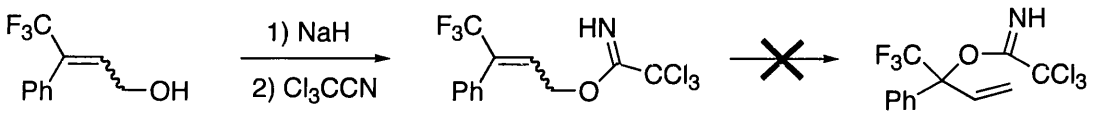
In general, electron-donating groups favour rearrangement by releasing electrons into the concerted transition state, thus increasing the rate of reaction. For example, reaction of allylic alcohol **18** with trichloroacetonitrile and sodium hydride at 0 °C yields the rearranged product allylic trichloroacetamide **19** directly with the intermediate imidate not being detected (Scheme 15).[21]



18 19

Scheme 15: Rearrangement with electron-donating substituent on allyl system.

Electron-withdrawing groups on the allylic system are problematic in the thermal rearrangement. For example, reaction of allylic alcohol **20** with trichloroacetonitrile and sodium hydride gives the allylic trichloroacetimidate **21** without incident, however thermal rearrangement fails (Scheme 16).[22]



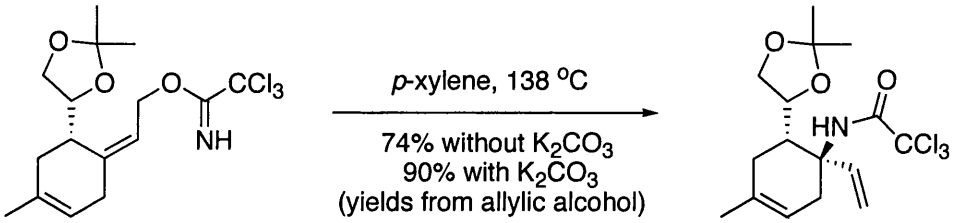
20 21

Scheme 16: Rearrangement with electron-withdrawing substituent on allyl system.

A density function theory (DFT) theoretical study and *ab-initio* study have yet to be carried out for the Overman rearrangement. Kakinuma and co-workers carried out MNDO-PM3 semi-empirical molecular orbital calculations for the template-based diastereoselective rearrangement of trichloroacetimidate derived from allyl alcohol.[17] It was found that the reaction occurs by an ion pair transition state with an enthalpy of formation of 11 kcal/mol. This value is 10 kcal/mol lower than that calculated by Overman for formation of the transition state in the [3,3]-sigmatropic reaction pathway.[15] However, all other experimental evidence supports a concerted suprafacial sigmatropic reaction mechanism.

The major competing pathway with the thermal Overman rearrangement is acid-catalysed decomposition of the allylic trichloroacetimidate before rearrangement can occur. The acidic conditions appear to result from decomposition of the solvent (*e.g.* xylenes) at high temperatures. *p*-Toluic acid has been detected (by ^{1}H NMR spectroscopy) in crude samples of reaction mixures which have been heated in xylene, under reflux, overnight.[23] During studies on the synthesis of tetrodotoxin, Isobe and co-workers found that the use of K_2CO_3 (2 mg/mL) as base, can trap any acid generated during the rearrangement and so addition of this reagent to the reaction mixture gives increased yields.[23] For example, the yield for rearrangement of trichloroacetimidate **22** can be increased from 74% to 90% with

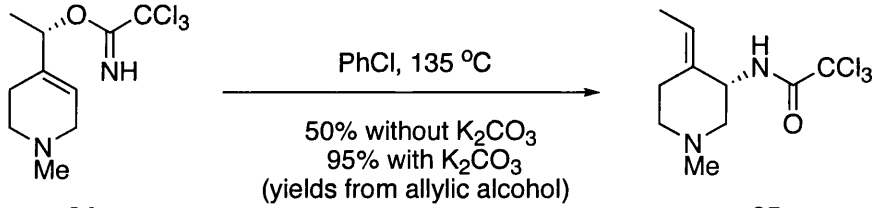
the addition of K_2CO_3 to the reaction mixture (Scheme 17).[23] Reactions have been carried out using this procedure on up to a 10 g scale with no decrease in yield of trichloroacetamide **23**.[23]



22 **23**

Scheme 17: Improved conditions for the Overman rearrangement.

Reilly and co-workers found a more dramatic increase in yield for rearrangement of trichloroacetimidate **24** using this improved procedure (Scheme 18).[24] The rearrangement was initially carried out in various solvents, however the desired product was only produced in refluxing chlorobenzene and in a disappointing 50% yield. Decomposition residues generated from the acid degradation of the trichloroacetimidate were observed in the crude reaction mixture. Thus, the reaction was repeated in the presence of K_2CO_3 and gave trichloroacetimidate **25** in an excellent 95% yield. Trichloroacetamide **25** was then used to complete the enantiospecific synthesis of (3*S*,4*R*)-3-amino-4-ethylpiperidine.[24]

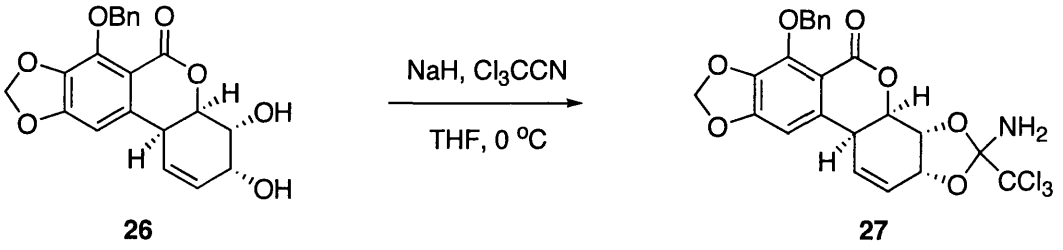


24 **25**

Scheme 18: Suppression of acid-catalysed degradation during the Overman rearrangement.

The popularity of thermal Overman rearrangements stems from the usefulness of the allylic trichloroacetamides produced from the reaction. The trichloroacetyl group is readly cleaved using sodium hydroxide and so this gives easy access to allylic amines. Therefore, the Overman rearrangement has been extensively used for the synthesis of nitrogen containing compounds and several excellent reviews exist covering this topic and so will not be covered.[1,11,25] An example in which the thermal Overman rearrangement has been utilised in the total synthesis of a complex natural product is Danishefsky's total synthesis

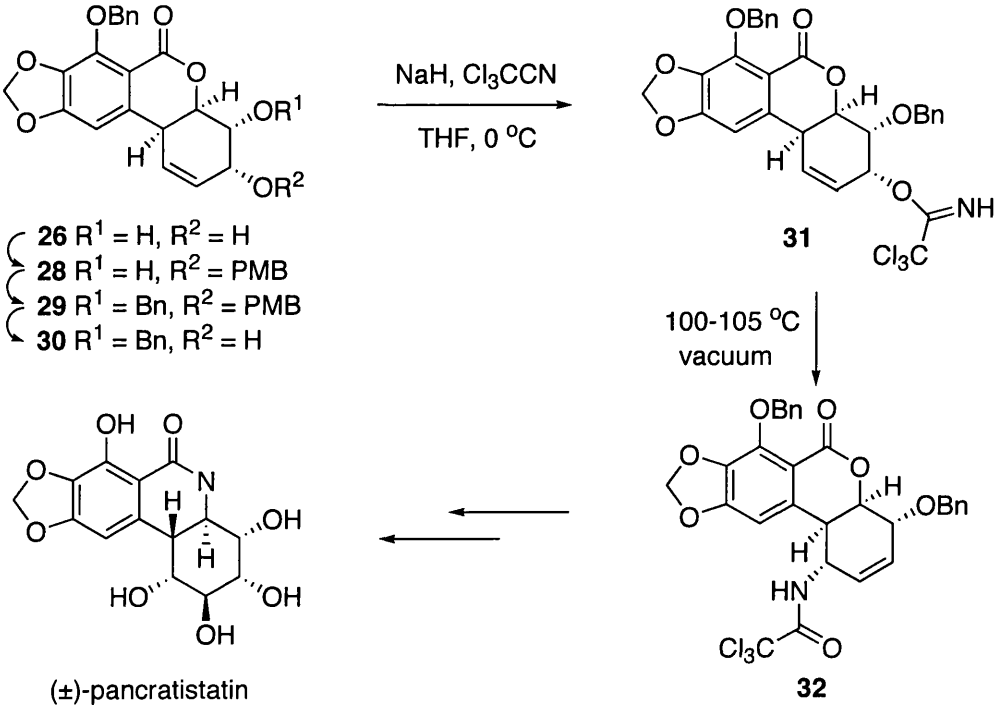
of (±)-pancratistatin.[26] Initially, synthesis of a trichloroacetimidate functional group on the less-hindered alcohol of diol **26** was attempted, however only orthoamide **27** was produced (Scheme 19).



26 **27**

Scheme 19: Problems encountered with trichloroacetimidate synthesis.

This problem was overcome by first protecting the less-hindered alcohol of diol **26** as a PMB ether, protecting the resulting mono-alcohol **28** as the benzyl ether **29** and then removing the PMB group with DDQ to give alcohol **30** (Scheme 20). The imidate **31** was then prepared using sodium hydride and trichloroacetonitrile. The thermal Overman rearrangement was best achieved by reaction of neat imidate **31** at 100-105 °C under high vacuum to give trichloroacetamide **32** in 56% yield. This synthesis elegantly utilized the suprafacial nature of the Overman rearrangement to give the desired chirality on the trichloroacetamide product which was taken on to complete the first total synthesis of (±)-pancratistatin.

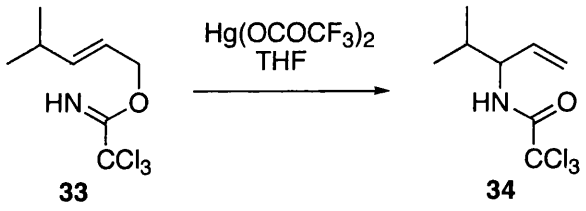


Scheme 20: Thermal Overman rearrangement in natural product synthesis.

1.3 Metal Catalysed aza-Claisen Rearrangement of Allylic Imidates.

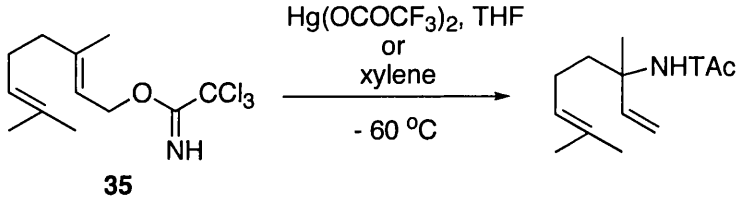
The thermal rearrangement of trichloroacetimidates has proven to be useful in the synthesis of nitrogen containing compounds. However, the harsh conditions (*e.g.* refluxing xylene) and long reaction times led to the development of a catalytic variant of the reaction. Several reviews on the metal catalysed rearrangement now exist.[27]

Overman's orginal paper on the thermal [3,3]-sigmatropic rearrangement of trichloroacetimidates also described the first known transition metal catalysed version of the reaction.[14] Mercury(II) salts were shown to catalyse the rearrangement of trichloroacetimidates derived from various C-3 substituted primary allylic alcohols. For example, mercury trifluoroacetate was added to a NMR tube containing trichloroacetimidate **33** in THF (Scheme 21). The spectrum was recorded immediately and only the rearranged trichloroacetamide **34** was detected.[14]



Scheme 21: Mercury catalysed aza-Claisen rearrangement.

By comparing the half-life of the catalytic rearrangement of trichloroacetimidate **35** at -60 °C and the extrapolated half-life for the corresponding thermal rearrangement in xylene at -60 °C, an estimate of 10^{12} was made for the rate enhancement (Scheme 22).[14]



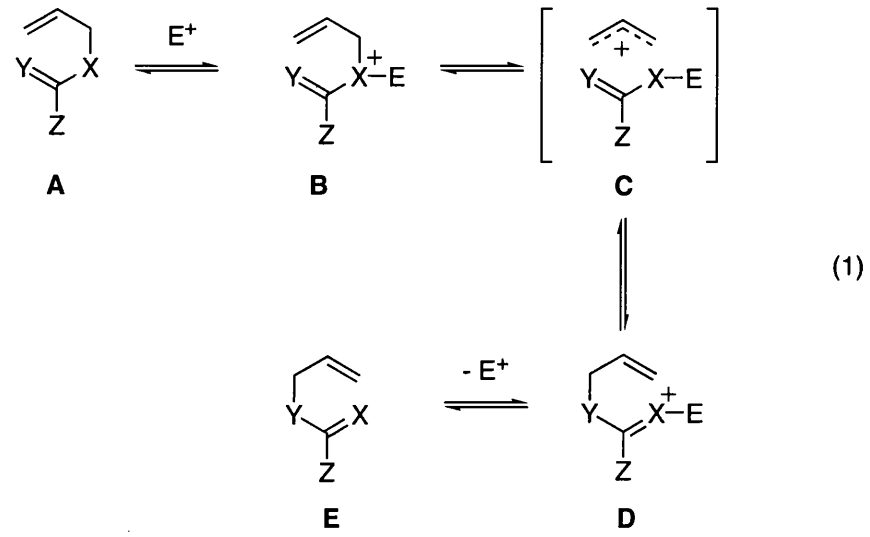
Scheme 22: Calculation of rate enhancement.

Three general mechanisms have been suggested for the metal catalysed aza-Claisen rearrangement which are catalysed by electrophiles (Scheme 23). In the *ionisation-recombination mechanism* (1)[28] the electrophile is believed to bind to the X atom to form **B**. The complex then undergoes heterolysis at the C-X bond to yield the intermediate **C**. This intermediate then recombines at the Y atom forming **D** and the electrophile leaves giving **E** as the product. With this mechanism, in compounds with X ≠ Y, we would expect to see mixtures of regioisomers. An example of a reaction, which is believed to occur by this mechanism, is the acid-catalysed rearrangement of allylic esters.[28]

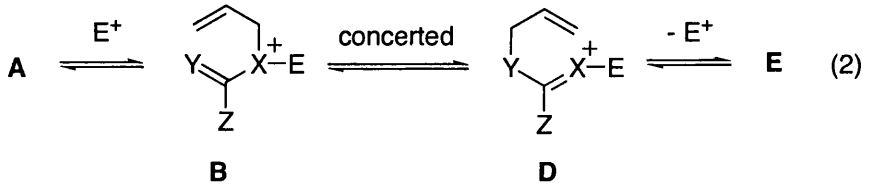
Another mechanism in which the electrophile binds to the substrate at the heteroatom X is the *concerted charge-induced* [3,3]-*sigmatropic rearrangement* (2). In this mechanism, proposed by Schmid, Hansen and co-workers,[29,30] complex **B** rearranges concertedly to give **D**. Catalysis would therefore be observed if this concerted rearrangement occurred more rapidly than the thermal uncomplexed rearrangement.[29] This mechanism is believed to occur in the rearrangement of allylaryl esters in trifluoroacetic acid.[30]

The third mechanism first suggested by Henry for palladium(II) catalysed reactions,[31] is called the *concerted cyclization-induced rearrangement* (3). This alternative mechanism occurs with the electrophile, instead of binding to the heteroatom X, coordinating to the allylic carbon-carbon π bond and so promotes an intermolecular cyclization to give the key cyclic carbocation intermediate **F**. The thermodynamically favoured fragmentation of this intermediate would then yield **E**, driving the equilibrium to the right. This mechanism was also proposed by Lutz for an alumina catalysed Cope rearrangement.[32]

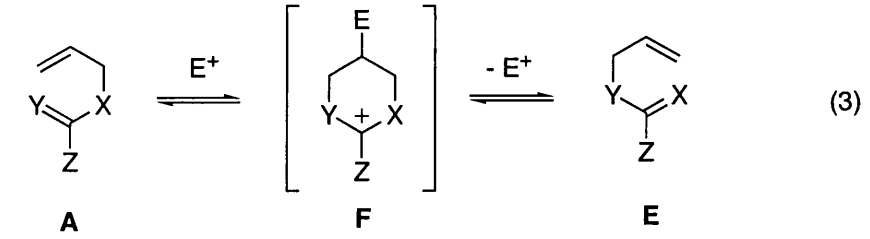
Ionisation-recombination rearrangement



Concerted charge-induced rearrangement

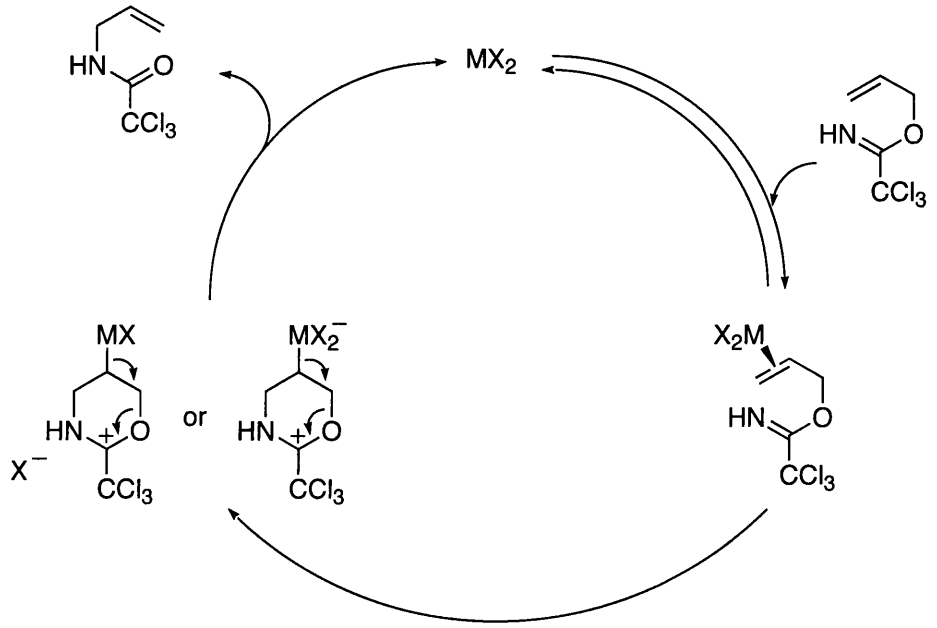


Concerted cyclization-induced rearrangement



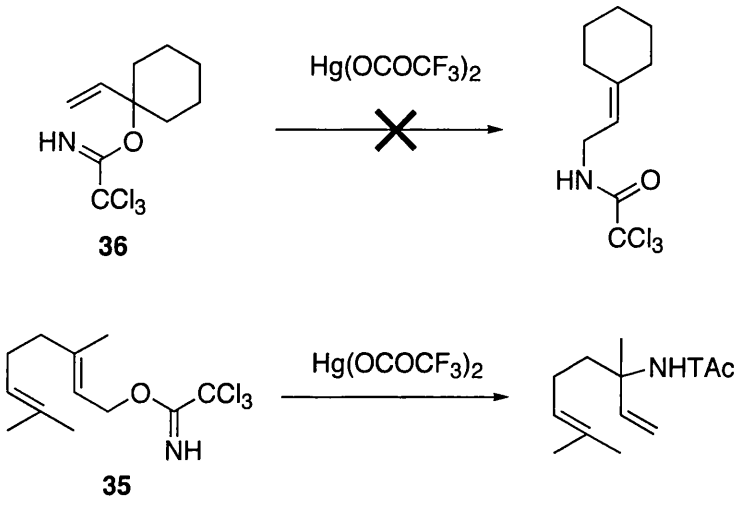
Scheme 23: Possible mechanisms for catalysed rearrangement.

Overman proposed that the mercury(II) catalysed rearrangement of trichloroacetimidates also occurs by a concerted cyclization-induced rearrangement mechanism (Scheme 24).[14] Initially, the electrophilic mercury(II) catalyst reversibly coordinates to the allylic carbon-carbon double bond, promoted by the aprotic solvent. Intramolecular attack of the nucleophilic imidate nitrogen at C-3 causes the formation of a mercury bound six-membered cyclic carbocation intermediate. The negative charge is believed to reside either on the mercury atom with both ligands still attached or as a free ligand anion. The intermediate then rapidly collapses exothermically to produce the trichloroacetimidate product and regenerate the catalyst.



Scheme 24: Mechanism of Hg(II)-catalysed rearrangement of trichloroacetimidates.

In a second paper published by Overman in 1976 it was detailed that the mechanism assignment was based on the fact that absolute regiospecificity is obtained for these rearrangement reactions.[15] It was also proposed that this mechanism explains the finite scope of the mercury(II) catalysed rearrangement.[15,27a] That is, substrates that do not favour attack of the nitrogen on C-3, such as imidate **36** are more likely to undergo elimination or attack at C-2. The reaction would therefore be restricted to substrates with substituents on C-3 that can assist attack at C-3 such as imidate **35** (Scheme 25).



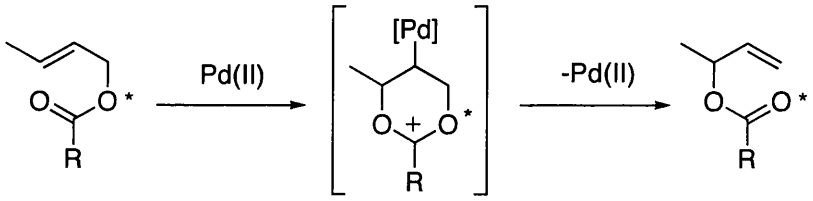
Scheme 25: Limitations of mercury(II)-catalysed rearrangement.

Although the concerted cyclization-induced rearrangement mechanism appears to be correct, the concerted charge-induced rearrangement mechanism could not be ruled out using the available experimental evidence.[15]

1.4 Palladium Catalysed aza-Claisen Rearrangement of Allylic Imidates.

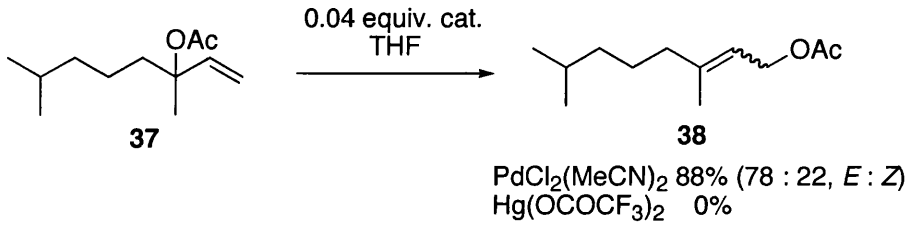
The first example of a palladium(II)-catalysed rearrangement by this mechanism was reported by Henry for the rearrangement of allylic esters (Scheme 26).[31]

Evidence for the proposed concerted cyclization-induced rearrangement mechanism was obtained from an ^{18}O labelling study in which a complete transfer of ^{18}O from ester to carbonyl was observed.[31] A 500 fold rate decrease on changing R from $-C_2H_5$ to $-CF_3$ provided further evidence for the proposed mechanism.[31]



Scheme 26: Pd(II)-catalysed rearrangement of allylic esters.

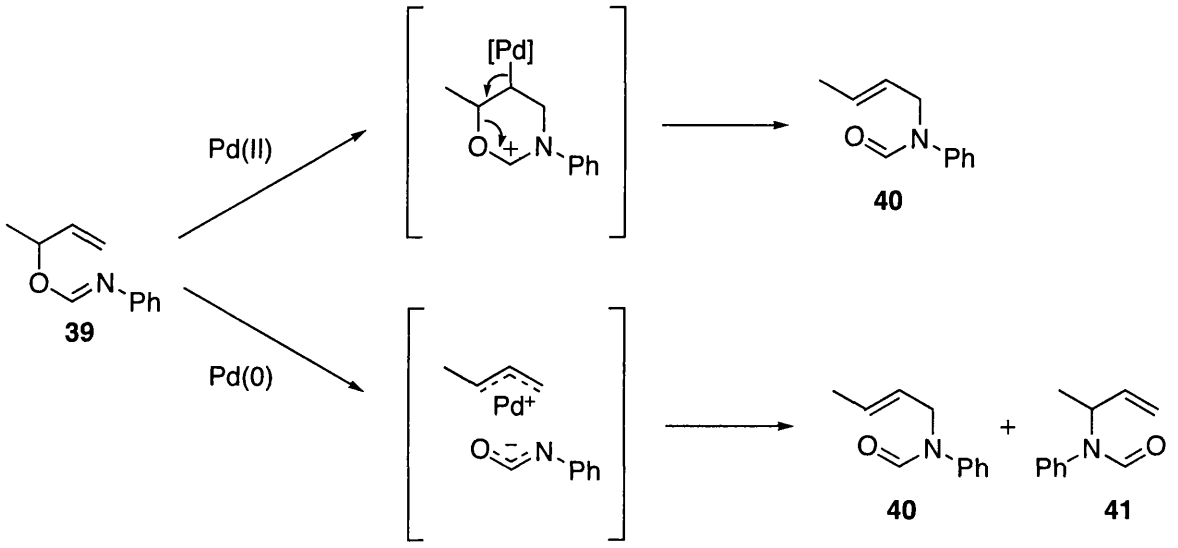
In 1979, Overman and Knoll developed the palladium(II)-catalysed rearrangement of allylic esters by using soluble palladium(II)-salts.[33] It was also shown that palladium(II)-salts are more effective than mercury(II)-salts at catalysing the rearrangement (Scheme 27). Rearrangement of acetate **37** in the presence of bis(acetonitrile)palladium chloride gave rearranged acetate **38** in 88% isolated yield. Reaction under the same conditions using mercury trifloroacetate failed to give any of the rearranged product. Rearrangement using the palladium(II)-catalyst also gave high selectivity for the *E*-geomeric isomer.



Scheme 27: $PdCl_2(MeCN)_2$ rearrangement of allylic esters.

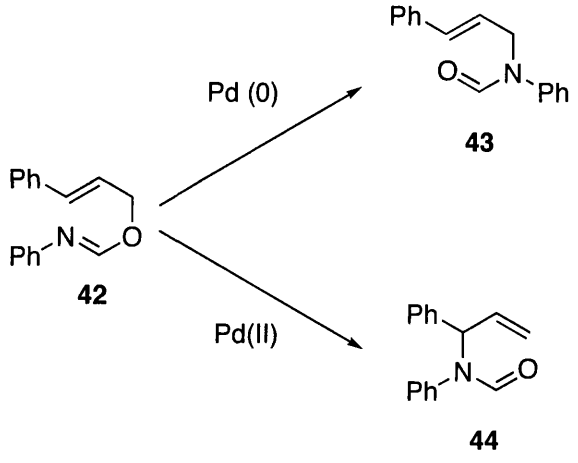
Ikariya and co-workers described the use of palladium complexes for the rearrangement of allylic *N*-phenylformimidates to form *N*-allyl-*N*-phenylformamides.[34] It was also reported that the reaction mechanism is dependent on the oxidation state of the palladium complexes used in the reaction. Rearrangement of allylic imidate **39** using $PdCl_2(MeCN)_2$ (*e.g.* a palladium(II)-complex) gave exclusively the formal [3,3]-rearrangement product,

amide **40**. However, rearrangement of imidate **39** using $Pd(PPh_3)_4$ (*e.g.* a palladium(0)-complex) gave a mixture of formal [3,3]-rearrangement product **40** and formal [1,3]-rearrangement product **41** (Scheme 28).[34] It was concluded that palladium(0) complexes catalyse the rearrangement by the ionisation-recombination reaction mechanism. Palladium(II)-complexes, on the other hand follow the cyclisation-induced rearrangement mechanism, thus explaining the regioselectivity observed.



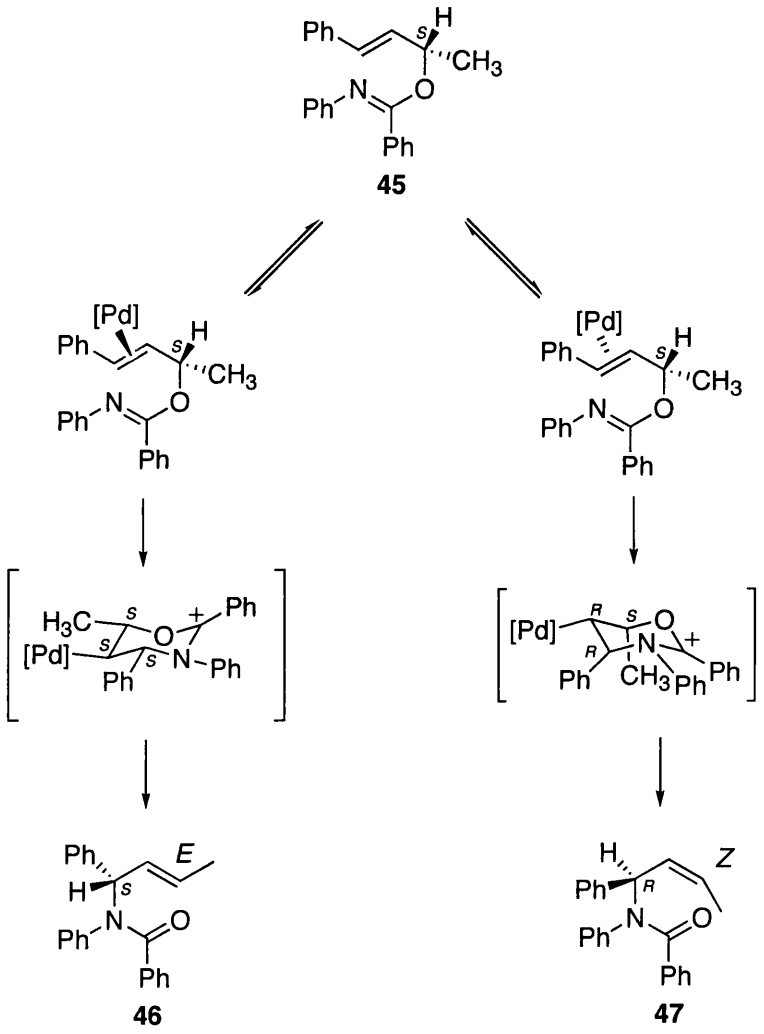
Scheme 28: Rearrangement with Pd(0) or Pd(II).

In 1985 Schenck and Bosnich provided further evidence for the palladium(II) versus palladium(0) selectivity for the rearrangement of allylic imidates.[27c] Rearrangement of 3-phenylallyl imidate **42** using palladium(0) was shown to give exclusively the formal [1,3]-rearrangement product **43** (Scheme 29).[27c] Palladium(II) on the other hand gave exclusively the [3,3]-rearrangement product **44** and thus is in agreement with Ikariya's assigned mechanisms.



Scheme 29: Rearrangement of 3-phenylallyl imidate **42** with Pd(0) or Pd(II).

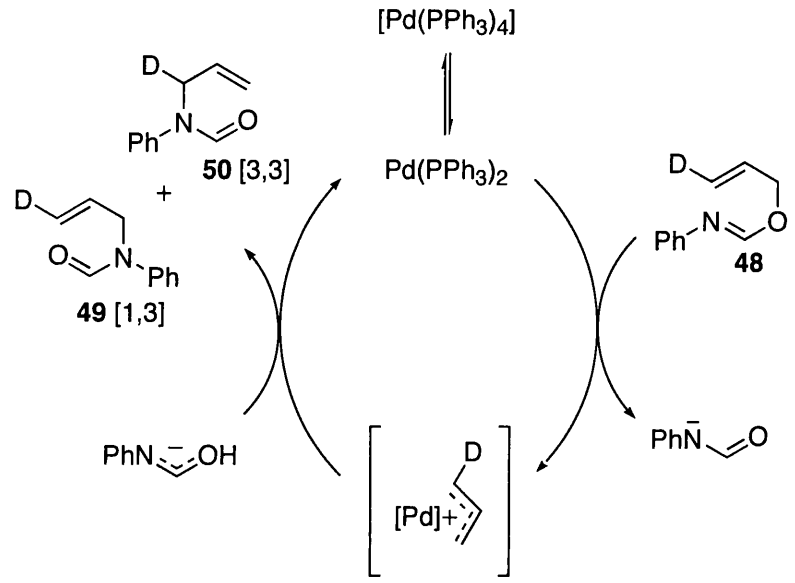
The mechanism for the palladium(II)-catalysed rearrangement was confirmed using chiral allylic imidates. Rearrangement of imidate **45** using $PdCl_2(MeCN)_2$ gave exclusively the [3,3]-rearrangement products **46** and **47** (77 : 22 ratio respectively) and so it was suggested that the reaction proceeds by a cyclization-induced mechanism with a metal-bound six membered carbocation intermediate. Furthermore, it was elegantly proposed that the intermediate forms a chair-like conformation in which palladium favours the equatorial position. Therefore, initial olefin facial attack on the palladium catalyst determines the stereochemical outcome of the reaction (Scheme 30).[27c]



Scheme 30: Proposed mechanism for the palladium catalysed rearrangement of a chiral allylic imidate.

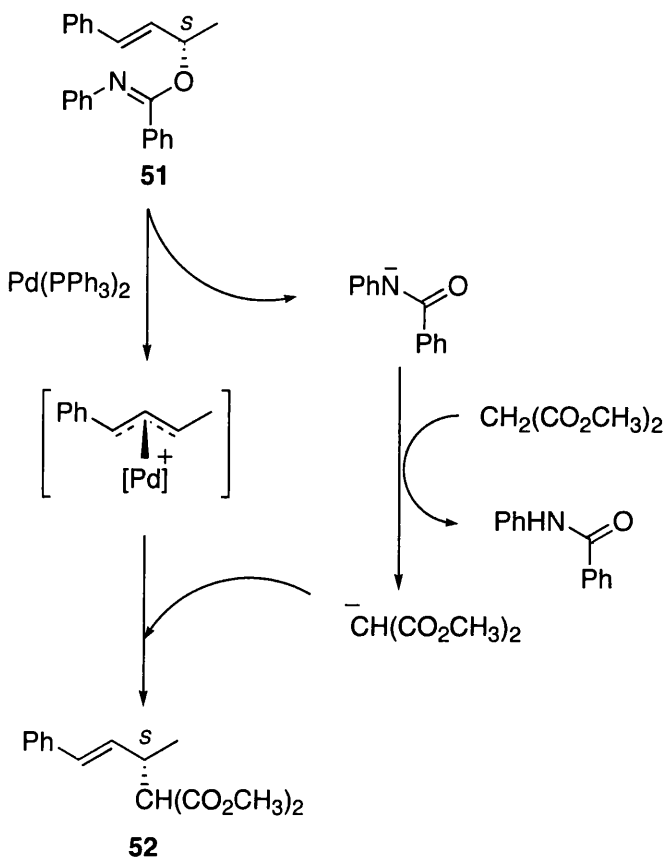
Evidence for the palladium(0)-catalysed mechanism was obtained from a deuterium labelling study (Scheme 31).[27c] Scrambling of deuterium labelled allylic imidate **48** confirmed that the reaction proceeds by an ionisation-recombination mechanism. Oxidative addition of the palladium(0)-catalyst to allylic imidate **48** gives a π-allyl

intermediate that can undergo scrambling if it has a sufficiently long half-life. Nucleophilic attack of the π-allyl intermediate by the amide anion gives a mixture of [1,3]-amide **49** and [3,3]-amide **50**.



Scheme 31: Deuterium labelling study of palladium(0)-catalysed rearrangement of allylic imidate **48**.

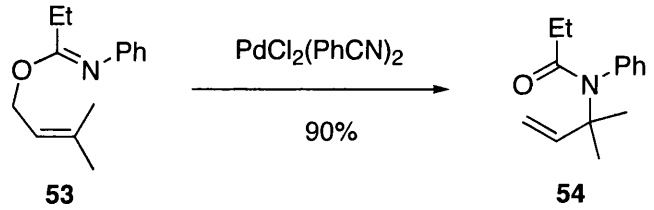
Further evidence for the palladium(0)-catalysed ionisation-recombination mechanism was obtained by trapping the π-allyl intermediate, formed from allylic imidate **51**, with dimethyl malonate anion to form diester **52** (Scheme 32).[27c]



Scheme 32: Trapping of π-allyl intermediate with dimethyl malate anion.

Finally, it was shown that rhodium(I)- and iridium(I)-complexes catalyse the rearrangement of allylic imidates, however by a different, unknown mechanism to that of the palladium(0)- and palladium(II)-catalysts.[27c]

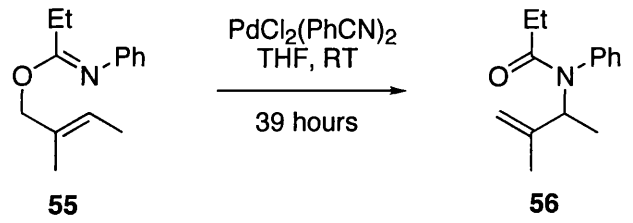
In a study by Metz and co-workers, the scope of the rearrangement of allylic imidates was broadened to include palladium(II)-catalysed rearrangement of *N*-allyl-*N*-phenylimidate **53** to form amide **54** with nitrogen bound to a tertiary carbon centre (Scheme 33).[27d]



Scheme 33: Rearrangement to form an amide bound to a tertiary carbon centre.

Furthermore, palladium(II)-catalysed rearrangement of an allylic imidate with substitution on C-2 was achieved for the first time.[27d] Surprisingly, rearrangement of imidate **55** was achieved to form, exclusively, [3,3]-product **56** in 75% yield (Scheme 34).[27d] The result from this reaction would at first sight appear to disagree with the proposed cyclisation-

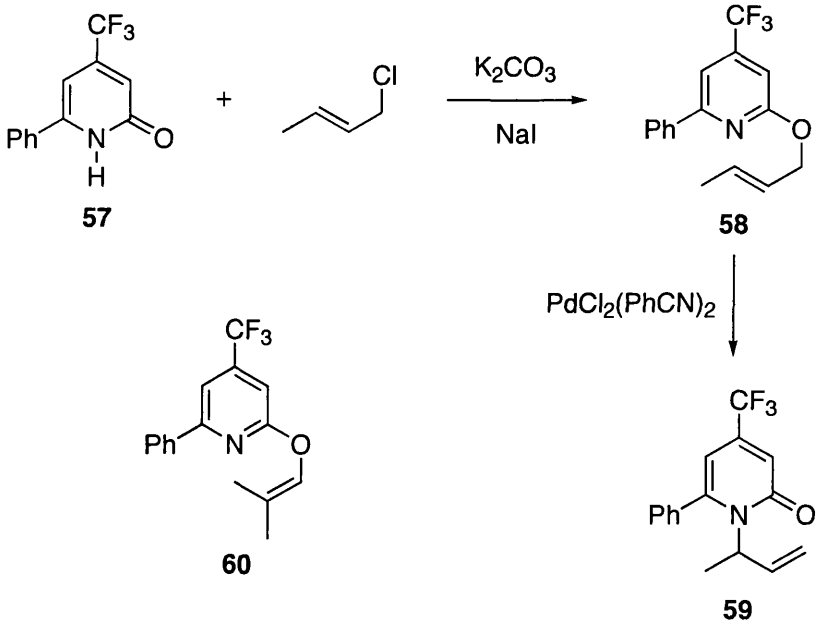
induced rearrangement mechanism for this type of reaction. In order for this reaction to occur, a σ-bond from the palladium catalyst to a tertiary carbon must be formed. The authors propose that this is still possible at room temperature and can be explained by counteracting the adverse steric stituation through stabilisation of the transition state by an electron donating group (*e.g.* C-3 = Me).



55 **56**

Scheme 34: Palladium(II)-catalysed rearrangement with substitution at C-2.

Venkataratnam and co-workers were able to synthesise, otherwise unattainable *N*-allylated pyridones using a palladium(II)-catalysed rearrangement (Scheme 35).[35] Imidate **58** was prepared by allylation of pyridone **57** under basic conditions. Palladium(II)-catalysed rearrangement of imidate **58** then gave exclusively [3,3]-rearrangement product **59**. Rearrangement of substrates with a methyl group at C-2 failed to give the [3,3]-rearrangement product and instead gave ionisation-recombination product **60**.

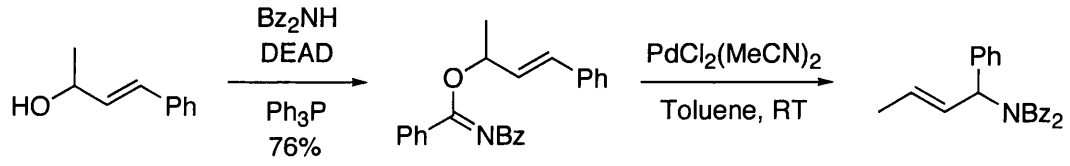


57 **58** **60** **59**

Scheme 35: *N*-Allylated pyridone synthesis using a palladium(II)-catalysed rearrangement.

Overman and Zipp have demonstrated that allylic dibenzamides can be prepared by palladium(II)-catalysed rearrangement of allylic *N*-benzoylbenzimidates (Scheme 36).[36]

The substrates for the rearrangement reaction are conveniently prepared by *O*-alkylation of primary or secondary allylic alcohols using dibenzamide under Mitsunobu conditions. Products arising from *N*-alkylation were only observed in 4% yield. Rearrangement of allylic *N*-benzoylbenzimidates was achieved within hours using 5 mol% $PdCl_2(MeCN)_2$ in toluene at room temperature to give allylic dibenzamides ([3,3]-products) in high yields. The authors also propose that since allylic *N*-benzoylbenzimidates are less basic than trichloroacetimidates they should be amendable to catalysis by a wider range of metals.



Scheme 36: Synthesis of allylic dibenzamides by palladium(II)-catalysed rearrangement.

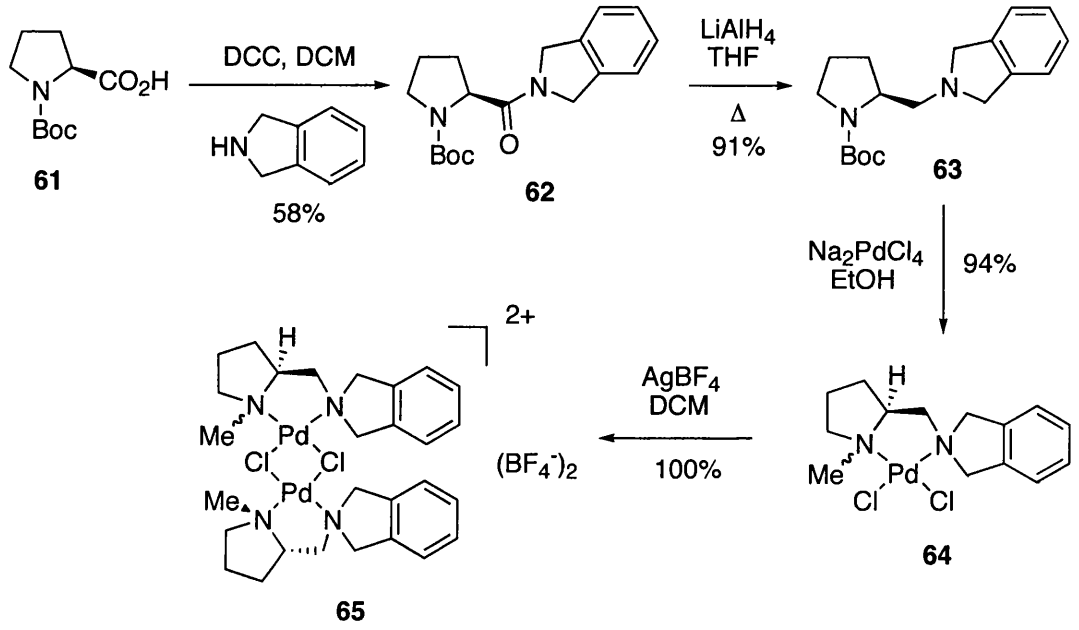
In summary, the mechanisms of both the palladium(0)- and palladium(II)-catalysed rearrangements of allylic imidates are now well understood. The palladium(II)-catalysed rearrangement follows a cyclisation-induced mechanism with a cyclic carbocation intermediate which adopts a chair-like transition state.

This therefore allows accurate prediction of both the regio- and stereochemical outcome of these reactions. In general, the palladium(II)-catalysed rearrangement of primary and secondary allylic imidates can be carried out at room temperature giving good yields and rate enhancements of $\sim 10^{12}$. Like the thermal rearrangement, the palladium(II)-catalysed version of the reaction gives complete suprafacial transfer of chirality and high selectivity for the amide as the *E*-geomeric isomer. The reaction is restricted by the requirement of a substituent on C-3 which favours attack of the imidate nitrogen and also the limited reactivity of imidates that have substitution on C-2.

1.5 Enantioselective Palladium(II)-Catalysed aza-Claisen Rearrangement of Allylic Imidates

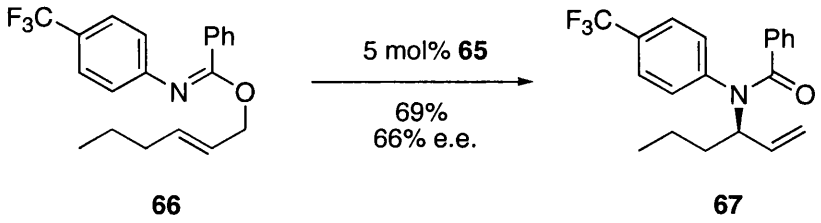
Given this understanding of the reaction mechanism and the use of a metal catalyst, the plausiblity of an asymmetric catalytic rearrangement of prochiral allylic imidates by a chiral metal complex has been the subject of most recent investigations.

While the use of palladium(II)-catalysts for the rearrangment of allylic imidates had been carried out, it was not until 1997 that the first enantioselective palladium(II)-catalysed rearrangement was demonstrated by Overman and co-workers.[37] Design of the catalyst was based on Bosnich's study of the rearrangement of chiral allylic amides (Scheme 30).[27c] In the study, complexation of the palladium(II)-catalyst to the alkene is reversible and showed face selectivity. Asymmetric induction of a catalytic reaction could therefore be determined from the cyclization step, which is the first irreversible enantiodifferentiating step. Initially, phosphine-containing palladium(II)-catalysts were screened, however these gave disappointing results due to the strong electron donating nature of the ligands. This inhibits nucleophilic attack of the alkene by the imidate nitrogen. Thus, a series of palladium(II) complexes containing chiral diamine ligands were prepared. The major issue with rearrangements using these catalysts was the formation of the [1,3]-product, *N*-4-trifluoromethylphenyl)benzamide, presumed to result form coordination of the cationic palladium complex to the imidate nitrogen, followed by ionisation-recombination. However, C_1 symmetric dimer **65** was found to be the best of these complexes and was easily prepared form *N*-Boc-L-proline **61** (Scheme 37).[37] *N*-Boc-L-proline **61** was coupled to 1,3-dihydroisoindole to give amide **62** in 58% yield. Reduction gave diamine **63** which was then complexed with Na_2PdCl_4 in ethanol to give palladium(II) complex **64** as a 10:1 mixture of diastereomers. The dichloride compounds were catalytically inactive and so the cationic dimers were prepared in order to increase lability of the palladium sphere. Reaction of dichloride **64** with silver tetrafluoroborate gave C_1 symmetric dimer **65** in quantitative yield.



Scheme 37: Synthesis of asymmetric tetraaminodipalladium(II)-catalyst.

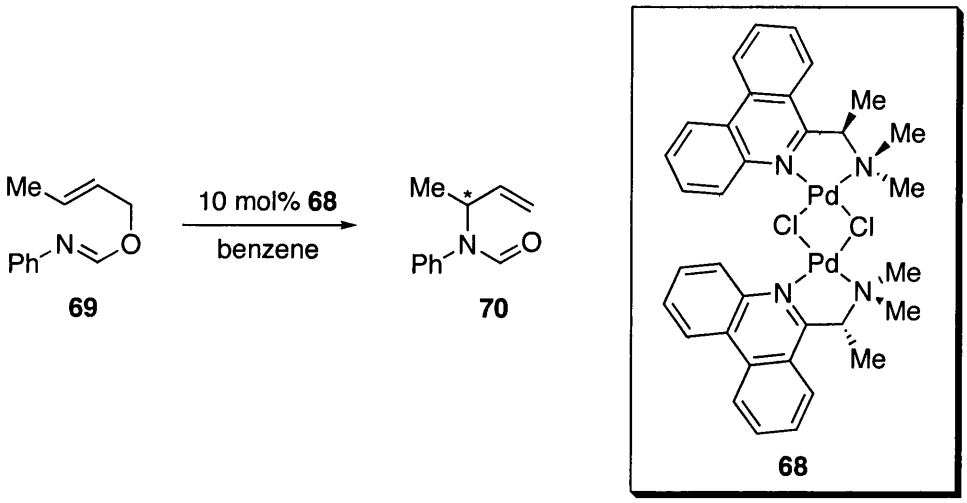
Rearrangement of allylic benzimidate **66** using palladium(II) complex **65** in CD_2Cl_2 at 40 °C gave benzamide **67** in 66% e.e. and 69% yield (Scheme 38).[37]



Scheme 38: Enantioselective tetraaminodipalladium(II)-catalysed rearrangement.

The *R* absolute configuration of amide **67** was determined by correlation with (*R*)-norvaline.[37] The authors then described that the major pathway of the catalysed cyclisation-induced rearrangement mechanism requires the palladium(II)-catalyst to coordinate to the *si*-face of the alkene forcing the imidate nitrogen to attack from the *re*-face.

Leung and co-workers have also reported that similar *ortho*-metallated complexes such as (*R*,*R*)-di-μ-chlorobis{9-[(1-dimethylamino)ethyl]-10-phenanthrenyl-*C*,*N*}dipalladium **68** can catalyse the enantioselective rearrangement of a non-activated allyl imidate **69** in up to 79% enantiomeric excess (Scheme 39).[38] However, no yields for the reactions are given and the absolute stereochemistry of the amide product **70** has yet to be determined. It was also reported that an electronically neutral palladium(II)-complex is required for this catalytic reaction.



Scheme 39: Enantioselective cyclopalladated-amine catalysed rearrangement.

The first examples of cyclopalladiated ferrocenyl amine complexes in enantioselective catalysis were reported by Overman and Hollis in 1997.[39] The design of these second generation catalysts was based on the superior yields and reaction times obtained for rearrangement with $PdCl_2(MeCN)_2$ compared to complex **65** (Scheme 37).[39] Also, $PdCl_2(MeCN)_2$ forms a neutral Pd-olefin complex and the Pd-olefin complex formed from catalyst **65** would be cationic. Thus, development of a neutral cyclopalladiated catalyst series led to cyclopalladated ferrocenyl trifluoroacetate amine complex **71** giving optimal results. Therefore, by using a neutral catalyst, suppression of the competing ionisation-recombination pathway was achieved. Rearrangement of allylic benzamide **66** was achieved with 5 mol% of catalyst **71** to give amide **67** in a modest 61% e.e. however in excellent 98% yield.

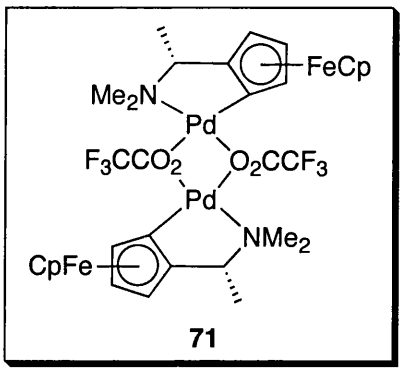
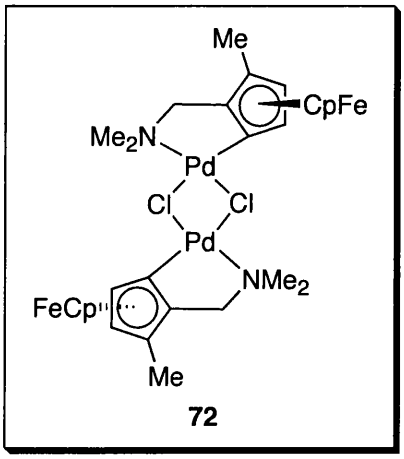


Figure 2: Enantioselective cyclopalladiated ferrocenyl amine catalyst.

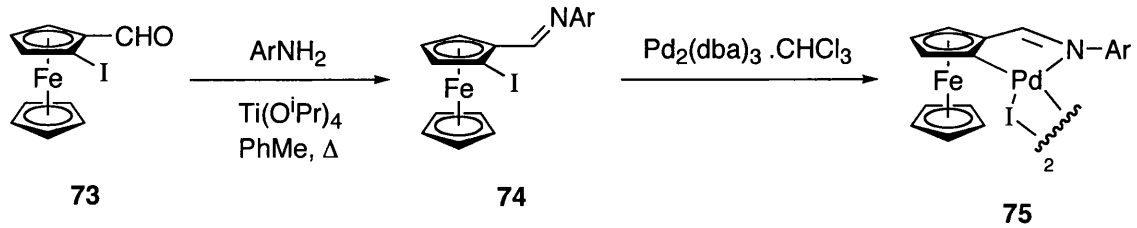
Overman and Cohen then went on to develop planar-chiral cyclopalladated ferrocenyl amine and imine catalysts (*i.e.* without substitution α to the coordinating nitrogen) for the enatioselective rearrangement of allylic imidates.[40] Initially, these catalysts were prepared as the cyclopalladated amines **72** (Figure 3). However, no improvement of the rate of reaction or enantioselectivity was observed compared with complex **71**.



72

Figure 3: Planar-chiral cyclopalladated ferrocenyl amine catalysts.

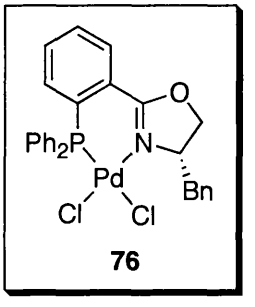
Thus, attention turned to cyclopalladated ferrocenyl imines. These ferrocenyl palladacycles were prepared from enantiopure iodoferrocenecarboxyaldehyde **73** in two steps (Scheme 40). Preparation of imines **74** was carried out by condensing aldehyde **73** with a range of anilines under reflux. These imines **74** were then reacted with $Pd_2(dba).CHCl_3$ in benzene at room temperature to give iodide-bridged dimer ferrocenyl palladacycles **75** in 22-57% yield over two steps. These iodide-bridged dimers did not catalyse the rearrangement of allylic benzimide **66** unlike the chloro-bridged amines. However, activation to the cationic palladium(II) complexes by dehalogenation using thalium triflate gave compounds which catalysed the rearrangement.



73 **74** **75**

Scheme 40: Synthesis of cyclopalladated ferrocenyl imine catalysts.

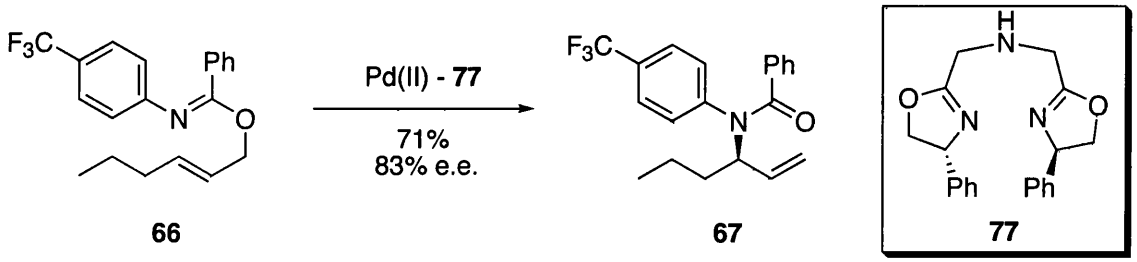
The rearrangement of benzimidate **66** was then carried out using these catalysts and although good yields of *R*-benzamide **67** were observed the enantioselectivities were inferior compared with earlier reported catalysts. Interestingly, rearrangement of the corresponding (*Z*)-allylic benzimidate gave the opposite absolute configuration of allylic benzamide **77** and in slightly higher enantioselectivity (*i.e.* *S*-benzamide **67** in 73% e.e.). Rearrangement of benzimidate **66** has also been carried out using a series of homochiral cationic palladium complexes by Hayashi and co-workers.[41] Rearrangement using the most enantioselective complex, prepared from $PdCl_2$[(*S*)-2-(2-diphenylphosphino)phenyl-4-benzyloxazoline] **76** (Figure 4) and silver tetrafluoroborate, gave *S*-allylic benzamides in enantioselectivities of up to 81%. However, significant amounts of the elimination product *N*-[4-(trifluoromethyl)phenyl]benzamide were obtained for this cationic catalysed rearrangement *via* the competing ionisation pathway and so yields of benzamide **67** were generally poor.



76

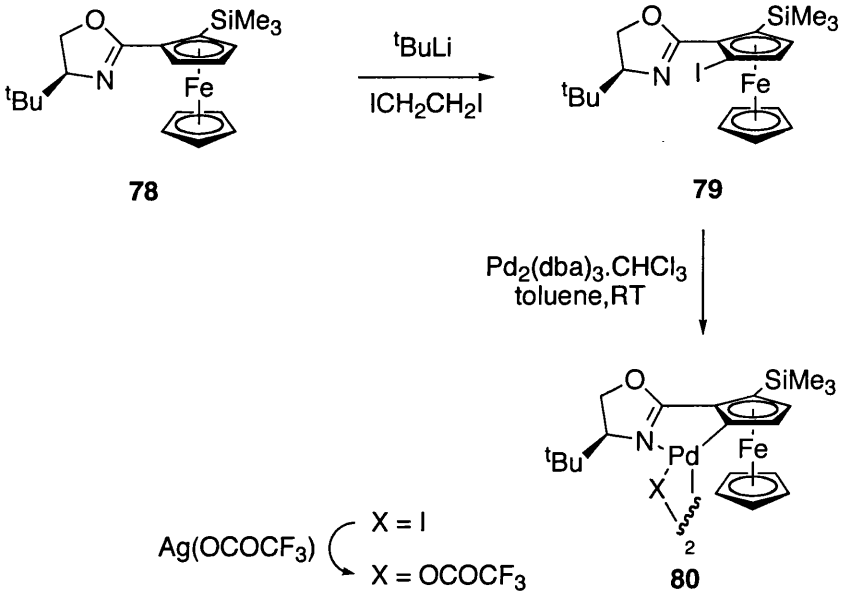
Figure 4: $PdCl_2$[(*S*)-2-(2-diphenylphosphino)phenyl-4-benzyloxazoline].

The first tridentate ligand for the enantioselective rearrangement of allylic imidates was reported by Zhang and co-workers in 1999.[42] A series of these ligands were prepared and reacted with $[Pd(MeCN)_4](BF_4)_2$ to form cationic palladium(II)-catalysts. These catalysts were then used for the rearrangement of a series of allylic imidates. The most enantioselective of these complexes was prepared from (*R*)-Ph-ambox (**77**, bis[4-(*R*)-phenyloxazolin-2-yl-methyl]amine) and gave *R*-allylic benzamide **67** in 83% e.e. and 71% yield (Scheme 41). However the elimination product and/or [1,3]-rearrangement product were obtained for rearrangement of the majority of other allylic imidates and so the scope of the rearrangement is severly limited with these cationic catalysts.



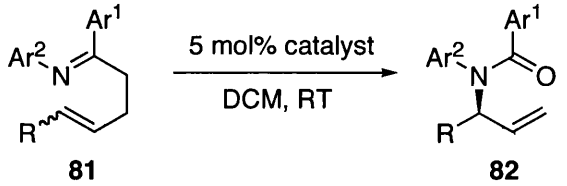
Scheme 41: Synthesis of cyclopalladated ferrocenyl imine catalysts.

Donde and Overman were able to significantly increase the enantioselectively of the rearrangement of allylic imidates using cyclopalladated catalysts containing ferrocenyloxazoline ligands.[43,44] The ligands were convienently prepared from enantioenriched oxazoline complex **78** (Scheme 42). Ortholithiation followed by reaction with diiodoethane gave a single stereoisomer of iodide **79** after recrystallisation. Oxidative addition of palladium(0) to these iodides gave iodide-bridged dimers **80**. Again, these iodide-bridged dimers proved to be inactive and so conversion to active trifluoroacetate catalysts was carried out by reaction with 2 equivalents of silver trifluoroacetate.



Scheme 42: Synthesis of ferrocenyloxazoline palladacycle (FOP) catalysts.

Rearrangement of benzimidates **81** to form *R*-benzamides **82** was achieved using 5 mol% of these ferrocenyloxazoline palladacyclic (FOP) catalysts with enantioselectivities of up to 96% being observed and in high yields (Scheme 42). In general, the *Z*-benzimidates gave higher enantioselectivities than the *E*-benzimidates.

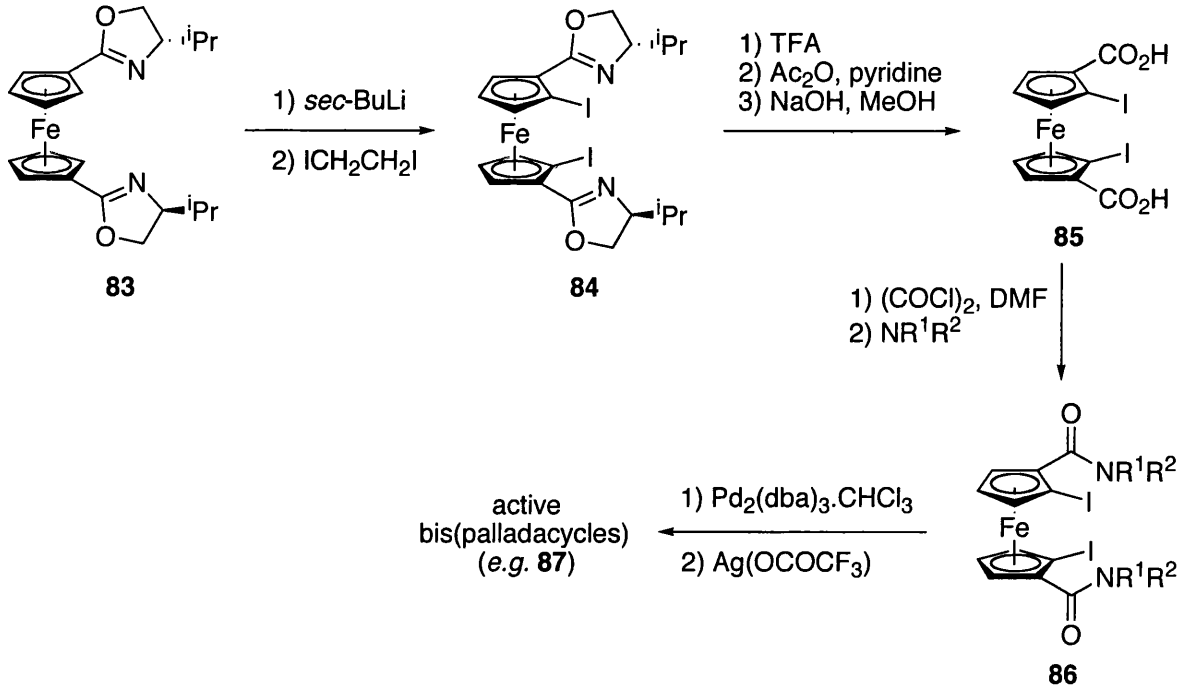


81 **82**

Scheme 43: Enantioselective cyclopalladated ferrocenyl-oxazoline catalysed rearrangement.

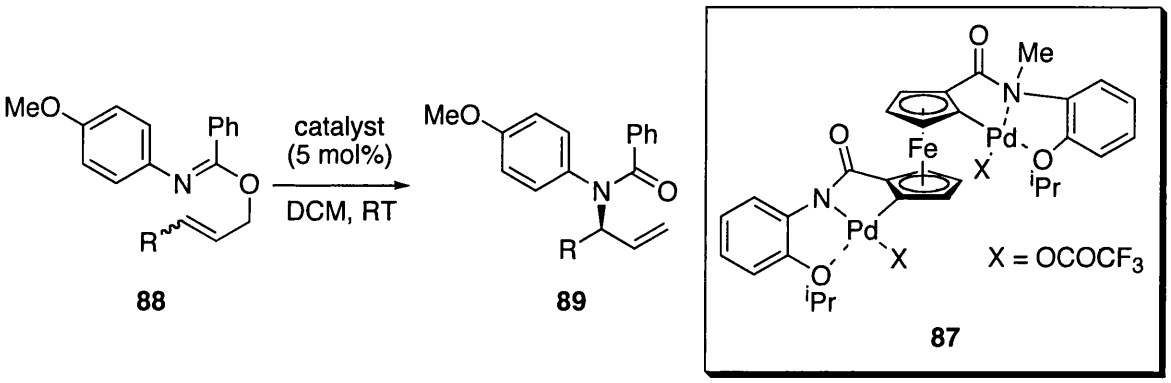
In order to improve the usefulness of the amides produced from these reactions, rearrangement using these cyclopalladated ferrocenyl-oxazoline catalysts was carried out with imidates that would result in amides with substituents on nitrogen that could be easily deprotected. FOP-catalysed rearrangement of (*E*)-3-hexenyl trichloroacetimidate gave the corresponding allylic trichloroacetamide in a disappointing 43% e.e. and with only 50% conversion after 6 days at 40 °C. Rearrangement of both (*Z*)-3-hexenyl *N*-benzoylbenzimidate and a *tert*-butylsulfonamide (BUS) nitrogen protected benzimidate was also attempted. However, the desired benzamide product was not observed for either substrate.

This type of catalyst was further developed by Kang and co-workers with the synthesis of bis(palladacycles) and their implementation in the aza-Claisen rearrangement of allylic benzimidates.[45] The complexes were designed to stabilise the palladacycle using tri-coordinating ligands. Synthesis of the palladacycles was carried out from chiral 1,1'-bis(oxazolinyl)-ferrocene **83** by ortholithiation followed by reaction with diiodoethane to give diiodide **84** (Scheme 44). Hydrolysis, acetylation and then saponification gave diacid **85** in good yields over the three-steps. Subsequent reaction with oxalyl chloride gave the corresponding acid chloride, which was converted to the corresponding tertiary amides **86** by reaction with a range of amines. Oxidative addition of $Pd(dba)_3.CHCl_3$ with these amides gave the desired bis(palladacycles), which were reacted with silver trifluoroacetate to give the catalytically active trifluoroacetate salts (*e.g.* **87**).



Scheme 44: Synthesis of bis(palladacycle) catalysts.

Enantioselective aza-Claisen rerrangement of a series of the allylic benzimidates **88** was then carried out to give allylic benzamides **89** in good yields (Scheme 45). Bis(palladacycle) **87** was found to be the most enantioselective (>95% e.e.). The selectivity is believed to be a result of conformational rigidity from the *o*-phenylene tether and steric bulk from the isopropoxy group generating a more chiral environment. Interestingly, the *E*/*Z* configuration of the imidate substrates does not significantly affect the enantioselectivity.



Scheme 45: Enantioselective bis(palladacycle) catalysed aza-Claisen rearrangement.

Following on from this work, Kang and co-workers reported the enantioselective aza-Claisen rearrangement of allylic benzimidates using a cobaltocenyl oxazoline palladacycle

(COP) **90**,[46] which was prepared in 7 steps from diphenylacetylene using a known synthesis (Figure 5).[47]

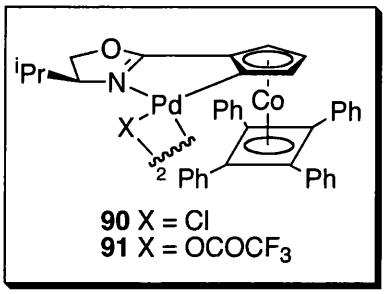
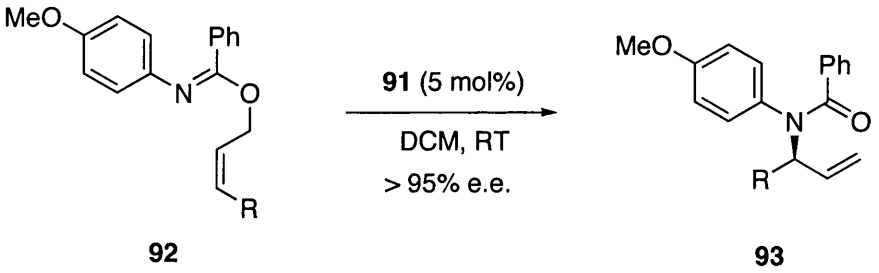


Figure 5: Cobaltocenyl oxazoline palladacycle (COP) catalysts.

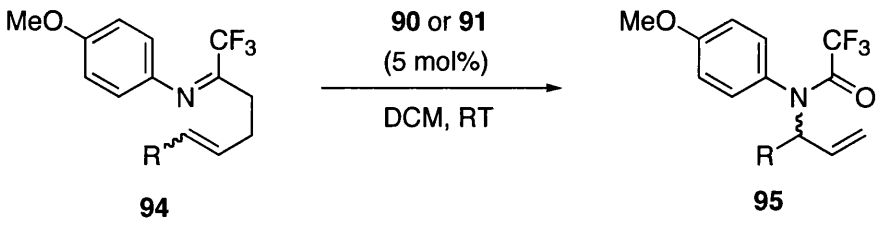
Compound **90** did not catalyse the rearrangement and so was activated to catalyst **91** using silver trifluoroacetate. Catalytic rearrangement of (*Z*)-allylic benzimidates **92** was then achieved to give (*R*)-allylic benzamides **93** in good yields and enantioselectivities of up to 95% (Scheme 46). However, rearrangement of (*E*)-allylic benzimidates gave poor enantioselectivities (*i.e.* 45-68% e.e.). The rational for these observations was a transition state in which the (η^4-tetraphenyl-cyclobutadiene)cobalt moiety blocks the *Si*-face of the olefin forcing the imidate nitrogen to attack the *Re*-face, thus producing the *R* product.



Scheme 46: Enantioselective activated cobaltocenyl oxazoline palladacycle catalysed aza-Claisen rearrangement.

Around the same time the Overman/Richards groups reported the enantioselective aza-Claisen rearrangement of allylic *N*-aryl trifluoroacetimidates using cobaltocenyl oxazoline palladacycle **90** (COP-Cl).[48] This methodology had two advantages over that reported by Kang and co-workers.[46] Rearrangement of (*E*)-allylic trifluoroimidates can be achieved using complex **90**, without being activated, to give excellent enantioselectivities and yields of (*S*)-allylic amides **95** (Scheme 47). Rearrangement of (*Z*)-allylic trifluoroimidates **94** can be achieved using the activated trifluoroacetate catalyst **91**, again in excellent

enantioselectivities and yields to give (*R*)-allylic amides **95**. Thus, either enantiomer of the allylic amide may be prepared with careful selection of substrate and catalyst.

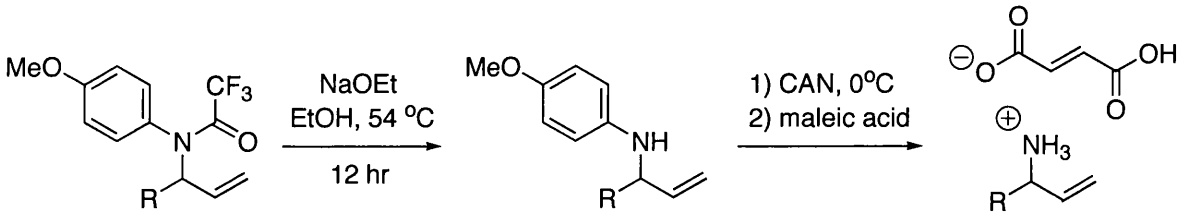


94 **95**

E-imidates > 92% yield, 92% e.e.(*S*)
Z-imidates > 77% yield, 97% e.e.(*R*)

Scheme 47: Enantioselective cobaltocenyl oxazoline palladacycle (COP-Cl) catalysed aza-Claisen rearrangements.

The second advantage of using trifluoroacetimidates as substrates for the rearrangement is the easy deprotection of the trifluoroacetamide functional group to give enantioenriched allylic amines (Scheme 48). Removal of the trifluoroacetamide group is achieved using sodium ethoxide to give amines **96**. Subsequent oxidative dearylation using ceric ammonium nitrite (CAN) followed by reaction with maleic acid gave salts **97** in good yields. Prochiral allylic alcohols can therefore be converted to highly desireable enantioenriched chiral allylic amines.

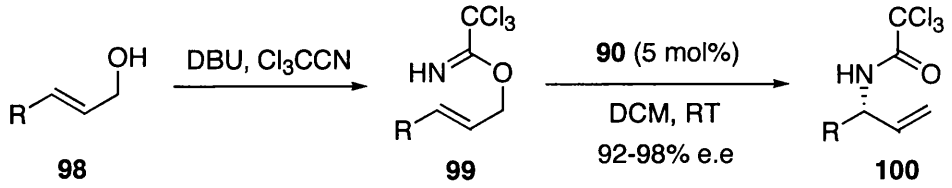


95 **96** **97**

Scheme 48: Synthesis of enantioenriched chiral allylic amines.

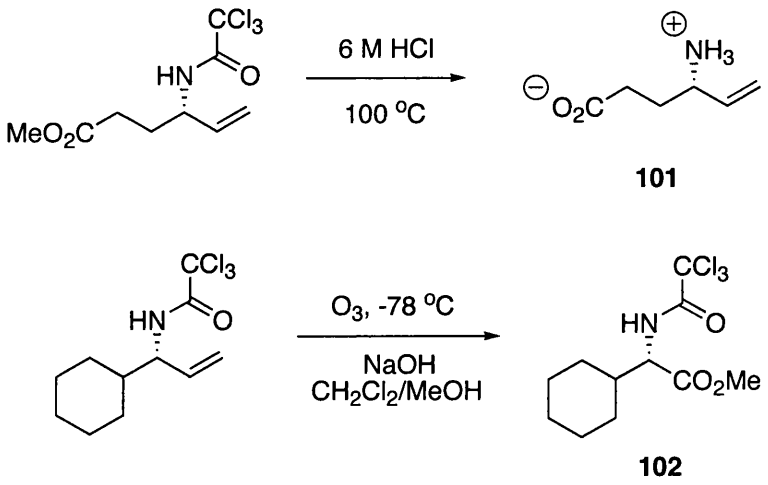
This methodology was further developed by Anderson and Overman in 2003 by using (*E*)-allylic trichloroacetimidates **99** which were easily prepared from allylic alcohols **98** using DBU and trichloroacetonitrile.[49] Subsequent enantioselective aza-Claisen rearrangement of these substrates using catalyst **90** gave the desired (*S*)-allylic trichloroacetamides **100** in high yield and excellent enantioselectivities (92-98% e.e.) (Scheme 49). However, rearrangement of (*Z*)-allylic trichloroacetimidates to give (*R*)-allylic trichloroacetamides generally gave low yields and enantioselectivities. Also, a study on functional group

tolerence in the rearrangement using the COP-Cl catalyst found that hydroxyl groups are tolerated in the allylic trichloroacetimidate structure although amine or thio groups are not.



Scheme 49: Synthesis and enantioselective cobaltocenyl oxazoline palladacycle (COP-Cl) catalysed aza-Claisen rearrangement of trichloroacetimidates.

Nevertheless, deprotection of the allylic trichloroacetimidate functional group was then easily achieved under acidic conditions to yield the corresponding enantioenriched allylic amines. The unity of this methodology was then demonstrated by the synthesis of the GABA aminotransaminase inhibitor (*S*)-vigabatrin **101** and also the protected (*S*)-α-amino ester **102** (Scheme 50).[49] This clearly illustrates that the trichloroacetimidate is easily cleaved and that functional group manipulation can be carried out in the precence of the protected amine.



Scheme 50: Synthesis of (*S*)-vigabatrin **101** and α-amino ester **102**.

In order to increase the solubility of the catalyst and thus allow solvents with varying polarity to be used for the aza-Claisen rearrangement of allyic trichloroacetimidates, Overman and co-workers developed COP-hfacac catalyst **103** (Figure 6).[50] The monomeric stucture of this catalyst was confirmed using single-crystal X-ray crystallography.

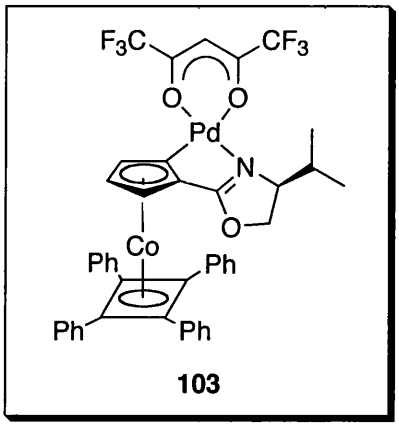
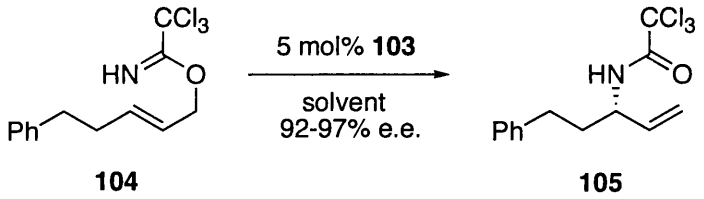


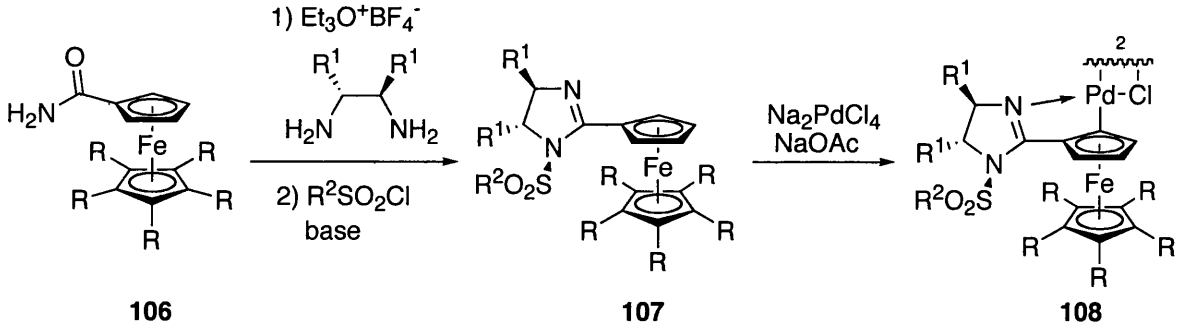
Figure 6: Monomeric COP-hfacac catalyst.

Rearrangement of allylic trichloroacetimidate **104** was achieved in a variety of solvents (*e.g.* cyclohexane, toluene, DCM, ethyl acetate, acetone, acetonitrile and THF to give allylic trichloroacetamide **105** in excellent yields and enantioselectivities (Scheme 51).



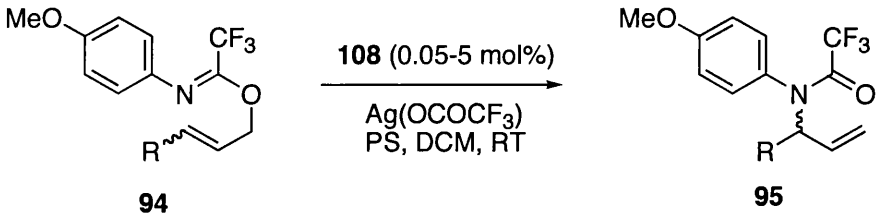
Scheme 51: Enantioselective COP-hfacac catalysed aza-Claisen rearrangement of trichloroacetimidate **102** in various solvents.

More recently Peters and co-workers described the use of ferrocenylimidazoline palladacycle (FIP) catalysts for the aza-Claisen rearrangement of *N-para*-methoxyphenyl trifluoroacetimidates.[51] The ferrocenylimidazoline ligands were conveniently prepared from amides **106** (Scheme 52). Activation as the iminium ethers, followed by sulfonylation gave imidazolines **107**. Subsequent cyclopalladation using Na_2PdCl_4 / NaOAc gave dimeric FIP-Cl complexes **108** in good yields.



Scheme 52: Synthesis of ferrocenylimidazoline palladacycle (FIP) catalysts.

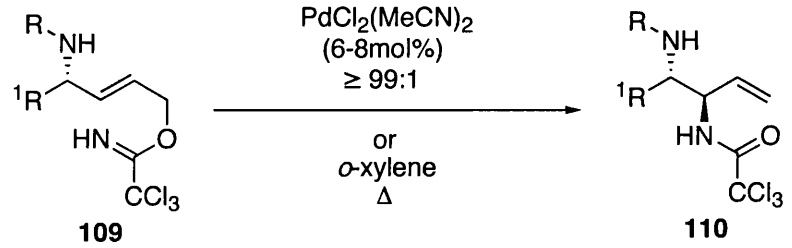
Enantioselective aza-Claisen rearrangement of a series of *N*-para-methoxyphenyl trifluoroacetimidates **94** was then carried out using these FIP-Cl catalysts (Scheme 53). Optimal results were obtained by activating the catalysts using silver trifluoroacetate and carrying out the reaction in DCM in the presence of a proton sponge (gave higher e.e. values and cleaner reactions). Enantioselectivities for all rearranged imidate substrates were improved from those reported using other catalysts. Interestingly, the *R*-enantiomers (>99.7% e.e.) of rearrangement products **95** were obtained by rearrangement of (*E*)-imidates and the *S*-enantiomers (>96% e.e.) from rearrangement of (*Z*)-imidates, the opposite from that observed by Overman / Richards for rearrangement of these substrates using the COP-Cl catalyst.[48]



Scheme 53: Enantioselective ferrocenylimidazoline palladacycle (FIP-Cl) catalysed aza-Claisen rearrangements.

Different methodology has also been used for the palladium(II)-catalysed rearrangement of allylic trichloroacetimidates. Heteroatom-directed reactions have been extensively utilised in asymmetric organic synthesis.[52] That is, reactions in which the incoming reagent (*e.g.* metal catalyst) is directed by the substrate, in a non-covalent manner, to influence the regio- or stereochemical outcome of the reaction.

Bellus and co-workers have used such a reaction for the diastereoselective synthesis of 1,2-diamines.[53] The key step in the synthesis was a heteroatom-directed palladium(II)-catalysed aza-Claisen rearrangement of chiral allylic trichloroacetimidates. These were prepared by chain elongation of the appropriate α-amino alcohol followed by reaction with sodium hydride and trichloroacetonitrile. Subsequent rearrangement under thermal conditions gave the corresponding trichloroacetamides **110** in good yield but low diastereoselectivity. However, rearrangement of the trichloroacetimidates **109** in the presence of bis(acetonitrile)palladium(II) chloride at room temperature gave the trichloroacetamides **109** in reasonable yield and excellent diastereoselectivity (≥ 99:1 in all cases) (Scheme 54). Inhibition of this diastereoselectivity was observed when the chiral nitrogen was doubly protected with either *tert*-butyl carbamate (*i.e.* Boc_2N), benzyl (*i.e.* Bn_2N) or a mixture of the two groups (*i.e.* BocNBn).



Scheme 54: Substrate directed palladium(II)-catalysed aza-Claisen rearrangements.

The diastereoselectivity observed for the palladium(II)-catalysed reaction was explained using transition state **111** (Figure 7). The substrate adopts a chair-like transition state minimising 1,3-diaxial interactions with the chiral amine group causing the olefin faces to be diastereotopic. The palladium(II)-catalyst coordinates to this chiral amine and is directed to the back face. The imidate nitrogen is then forced to attack the olefin from the front face. Thus, the *trans*-diastereomer is produced exclusively from this rearrangement.

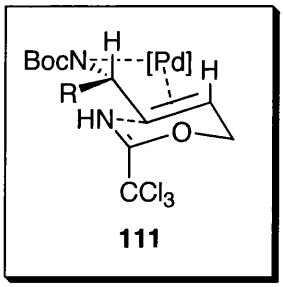
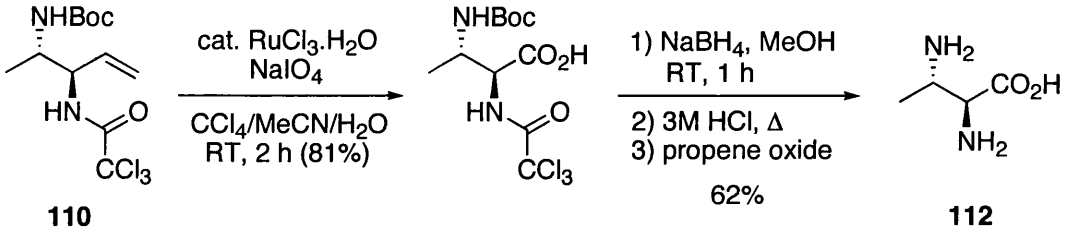


Figure 7: Transition state.

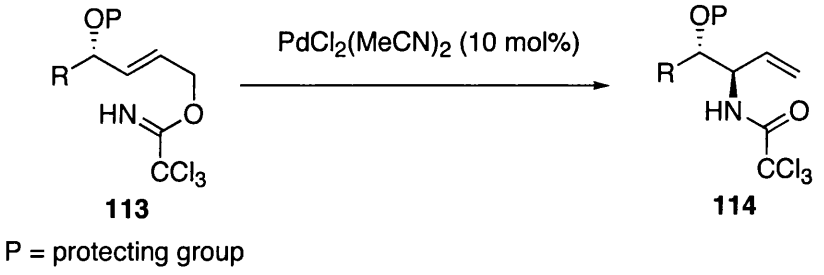
The usefulness of the rearrangement products was demonstrated by the synthesis of (2*S*,3*S*)-diaminobutanoic acid **112**, a component of several important biological molecules (Scheme 55).[53]



Scheme 55: Substrate directed palladium(II)-catalysed aza-Claisen rearrangements.

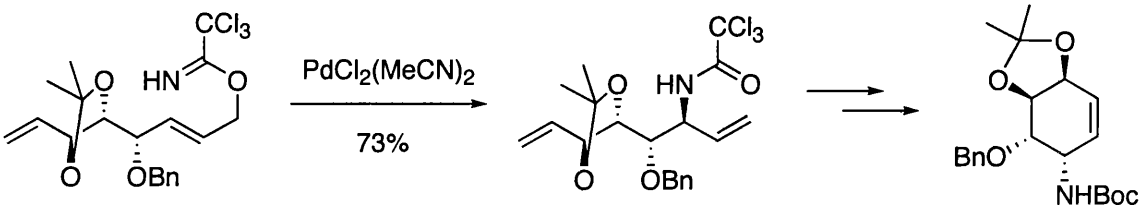
A similar study has been carried out by Doherty towards the synthesis of 3-aminodeoxystatine derivatives for use in a renin inhibitor program.[54] Initially thermal and mercury(II)-catalysed rearrangements of an allylic trichloroacetimidate with a nitrogen heteroatom in the δ-position gave a mixture of products and isomers. However, a subsequent palladium(II)-acetate catalysed rearrangement gave the desired allylic amide as a single isomer.

Ham and co-workers have carried out a study in which a diastereoselective aza-Claisen rearrangement of allylic trichloroacetimidates was used as the key step in the synthesis of allylic trichloroacetimidates **114** (Scheme 56).[55] The trichloroacetimidate substrates for the rearrangement reaction were prepared from the corresponding α-amino acid. Subsequent rearrangement of these allylic trichloroacetimidates **113** in the presence of bis(acetonitrile)palladium(II) chloride gave the trichloroacetamide **114** products with varying degrees of diastereoselectiviy (1.4:1 to 10:1). However, in contrast to the effect reported by Bellus for the corresponding amine compounds,[53] the authors explain that the diastereoselectivity observed is a result of the steric bulk of the substituents. Thus, the larger the chiral δ-ether protecting group and the smaller the R group, the more diastereoselective the rearrangement becomes.



Scheme 56: Steric bulk directed palladium(II)-catalysed aza-Claisen rearrangements.

The palladium(II)-catalysed rearrangement of allylic imidates has been used in the synthesis of a number of natural products and other medicinally important complex molecules. For example, the synthesis of highly functionalised carbocycles has been achieved by van Boom and co-workers utilising a palladium(II)-catalysed rearrangement (Scheme 57).[56] Trichloroacetimidate **115** underwent an aza-Claisen rearrangent in the presence of bis(acetonitrile)palladium(II) chloride to give trichloroacetamide **116** as a single diastereomer. Subsequent transformation of trichloroacetimidate **116** *via* ring closing metathesis gave the conduramine analogue **117**.



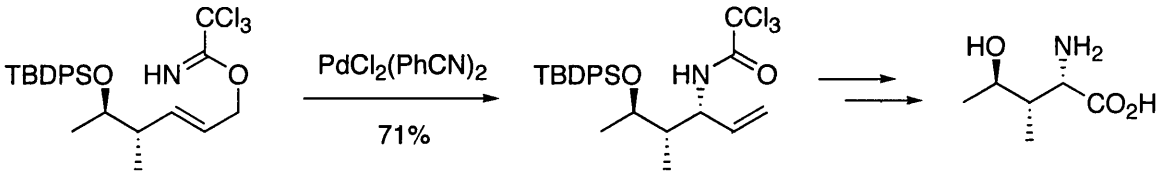
115 **116** **117**

Scheme 57: Diastereoselective synthesis of a conduramine analogue **117**.

As previously demonstrated by Bellus and co-workers,[53] the trichloroacetamides produced from the palladium catalysed aza-Claisen rearrangement can easily be converted to α-amino acids. Mehamandoust *et al.* have utilised this methodology for the enantioselective synthesis of (*E*)-β,γ-unsaturated α-amino acids.[57] Likewise, Salaün and co-workers used a palladium(II)-catalysed aza-Claisen rearrangement of *N*-aryl allylic imidates for the synthesis of 1-aminocyclopropane-carboxylic acids.[58]

Finally, Sutherland and co-workers carried out the first enantioselective synthesis of (2*S*,3*S*,4*R*)-γ-hydroxyisoleucine **120**, the amino acid constituent of the natural product, funebrine (Scheme 58).[59] Allylic trichloroacetimidate **118** was synthesised in 7 steps from poly (*R*)-hydroxybutanoate. Subsequent rearrangement under thermal conditions gave the corresponding trichloroacetamides in a diastereomeric ratio of 3 : 2, with the desired diastereomer being the minor isomer. However, catalysis using bis(benzonitrile)palladium(II) chloride, a switch in the diastereoselectivity was observed and the desired isomer **119** was obtained in a 7 : 1 ratio and in 71% yield. The diastereoselectivity for the palladium(II)-catalysed reaction was explained by the fact that the palladium catalyst coordinates to the less sterically hindered *Re*-face of the olefin and so the imidate nitrogen is forced to attack from the *Si*-face, thus giving the (3*S*)-isomer as

the major product. Subsequent oxidation then deprotection of the resulting trichloroacetamide completed the total synthesis of the enantiopure amino acid **120**.



118 **119** **120**

Scheme 58: Diastereoselective synthesis of (2*S*,3*S*,4*R*)-γ-hydroxyisoleucine **120**.

1.6 Conclusion

In 1912 the first thermal [3,3]-sigmatropic rearrangement was reported by Claisen.[3] The mechanism of the reaction has been determined by several studies on the regioselectivity, thermodynamic parameters, stereoselectivity and solvent effects. A negative change in enthalpy during the reaction was identified as the driving force and the concerted, suprafacial transition state gives the products as predominantly the *E*-geometrical isomer with excellent stereoselectivity. This reaction has subsequently been developed to include several related rearrangement reactions including the thermal rearrangement of allylic trichloroacetimidates.

Succeeding this, the development of a catalysed version of the reaction allowed the rearrangement to be carried out at room temperature with rate enhancements of up to 10^{12}.[14] Catalysis was initially carried out using mercury(II)-salts, however palladium(II)-salts proved to more effective catalysts for the rearrangements. Studies of these catalysed rearrangement reactions revealed a cyclisation-induced mechanism with a cyclic carbocation intermediate that readily collapses, exothermally, to give the amide products.

More recently, the enantioselective palladium(II)-catalysed rearrangement of allylic imidates has been the focus of most research in this area. Initially, cationic palladium diamine complexes were used to catalyse the rearrangement of allylic imidates, however these only gave moderate enantioselectivities and poor yields due to a competing ionisation pathway. The use of neutral cyclopalladated ferrocenyl catalysts suppressed these competing reactions and so gave increased yields. Enantioselectivities were increased using using planar chiral cyclopalladated ferrocenyl catalysts. Development of cobaltocenyl oxazoline palladacycle (COP) catalysts which when utilised for the rearrangement of allylic imidates further increased yields and enantioselectivities. More importantly, these compounds catalysed the rearrangement of trichloroacetimidates to give trichloroacetamides, which can be deprotected giving enantioenriched chiral amines. Ferrocenylimidazoline palladacycle (FIP) catalysts have also been shown to enantioselectively catalyse the rearrangement of allylic imidates to allylic amides which can be deprotected to form allylic amines.

The use of a heteroatom-directed palladium(II)-catalysed aza-Claisen rearrangement has been reported for the diastereoselective synthesis of 1,2-diamines. Also, the diastereoselective synthesis of *anti*-1,2-amino alcohols and γ-hydroxy α-amino acids has been achieved using steric effects in a palladium(II)-catalysed aza-Claisen rearrangement.

The development of these [3,3]-sigmatropic rearrangements has thus led to their use in the asymmetric synthesis of many medicinally important molecules and natural products.

Future developments in this area will no doubt lead to the more efficient asymmetric catalysis of the rearrangement of allylic imidates to allylic amides that can easily be deprotected and converted to more complex nitrogen containing compounds.

2.0 Results and Discussion

In order to investigate whether palladium(II)-catalysed aza-Claisen rearrangements can be influenced by stereogenic centres within the substrate, a program to synthesise and test a series of trichloroacetimidates with varying ether protecting groups was proposed. Oxygen was chosen as the heteroatom due to precedent that the rearrangement products could be converted to highly desirable β-hydroxy allylic amines.[59] It was also proposed that these allylic amines could then be converted to β-hydroxy α-amino acids or used for the synthesis of more complex nitrogen containing molecules.

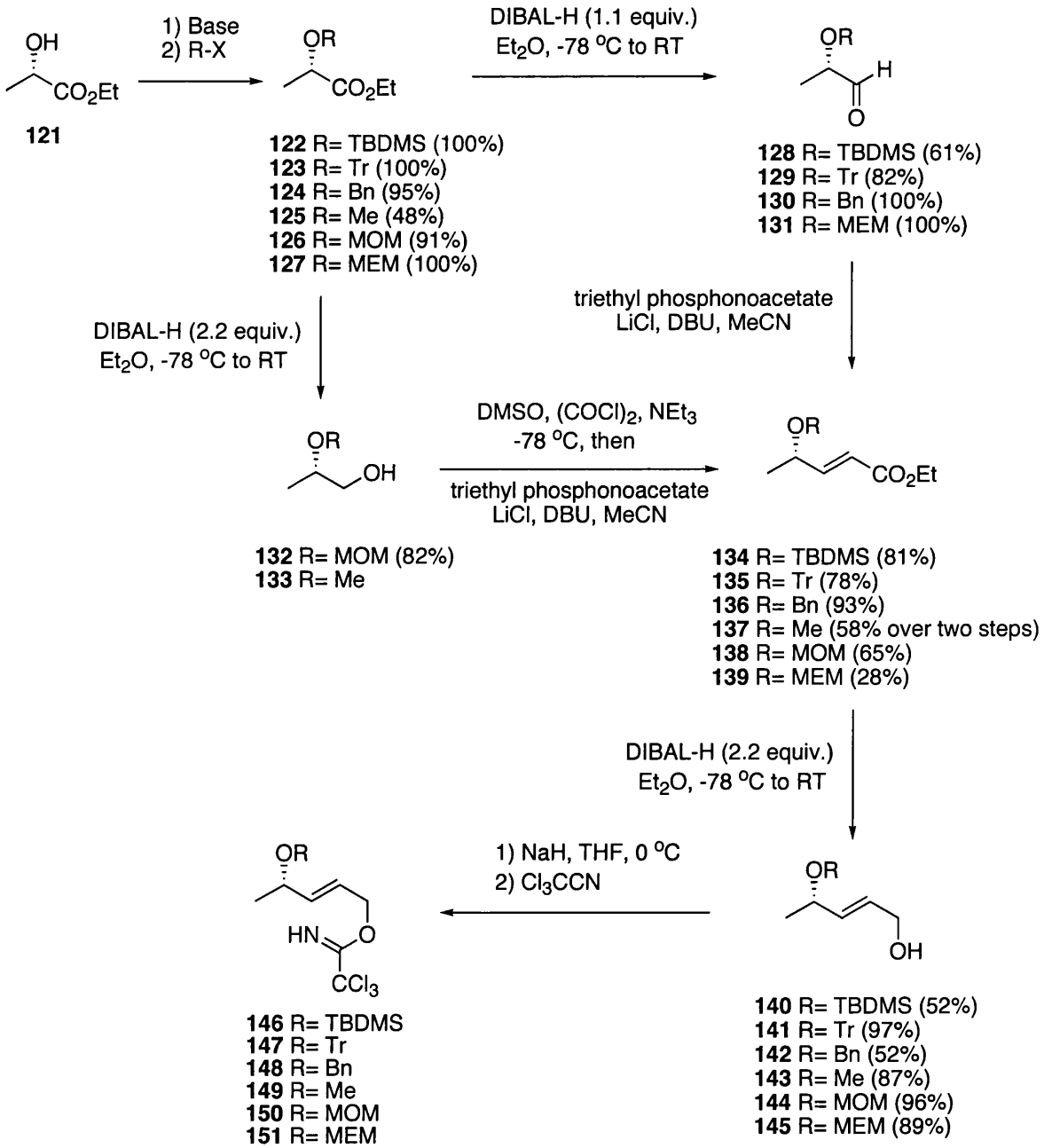
2.1 Studies of a Heteroatom Directing Effect.

2.1.1 Development of a Synthetic Route to Six Trichloroacetimidates with Varying Ether Protecting Groups.

The initial aim in this project was the development of a flexible efficient route for the synthesis of a series of *E*-allylic trichloroacetimidates (Scheme 59) from commercially available ethyl (*S*)-lactate **121**.

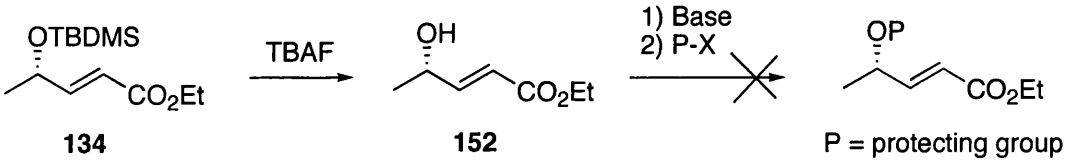
Protection of the secondary alcohol moiety of ethyl (*S*)-lactate **121** was achieved using the Williamson ether synthesis (sodium hydride, alkyl halide)[60] to yield compounds **124**, **125** and **127**. Compounds **122**, **123** and **126** were produced using imidazole, DBU and Hünig's base respectively.[60] Reduction of the ester functional group using 1.1 equivalents of DIBAL-H gave the aldehydes **128-131**.[60] Yields of the DIBAL-H reductions were significantly increased by changing the solvent from THF to diethyl ether. The method of work-up was also improved in order to optimise the yields. Rather than using methanol and Rochelle's salt, saturated ammonium chloride was used to quench the reaction. This produced a white precipitate, which could be filtered and washed with diethyl ether. Initially, the use of a stabilised phosphorus ylide in a Wittig reaction was investigated in order to produce preferentially the *E*-geometrical isomer of the α,β-unsaturated esters.[61] However, subsequent reaction with triethyl phosphonacetate under Horner-Wadsworth-Emmons (HWE) conditions gave α,β-unsaturated esters **134-136** and **139** with only the *E*-geometrical isomer observed by ^{1}H NMR spectroscopy.[61] Masamune-Roush conditions are used for all HWE reactions due to the mild conditions employed during this procedure.[62] Decomposition and volatility problems associated with the Me and MOM substituted aldehydes were overcome by reducing these compounds to the corresponding alcohols **132**

and **133** using 2.2 equivalents of DIBAL-H. A one-pot, Swern oxidation-HWE reaction[63] gave the (*E*)-α,β-unstaturated esters **137** and **138**. Reduction of all the (*E*)-α,β-unstaturated esters **134-139** to allylic alcohols **140-145** was achieved again using 2.2 equivalents of DIBAL-H.[61] Finally, reaction with sodium hydride and trichloroacetonitrile using an Overman group protocol[64] gave substrates **146-151** for the rearrangement reaction. Allylic trichloroacetimidates are known to be relatively unstable[15] and thus, the work-up and purification of these compounds involves simply washing the reaction mixture through a short pad of aluminium oxide followed by removal of the solvent *in vacuo*.[25b] Hence yields quoted for all rearrangements are calculated from the allylic alcohols **140-145** (over two steps).



Scheme 59: Synthesis of a series *E*-allylic trichloroacetimidates.

An approach was also attempted to prepare all six analogues *via* one route. This was tried by deprotecting the silyl group of α,β-unsaturated ester **134** and then reprotecting the resulting hydroxyl moiety (Scheme 60). Although deprotection was achieved without incident, the resulting allylic alcohol **152** could not be reprotected as either the methyl- or benzyl-ether. Protection of allylic alcohol **152** as the MOM-ether was also attempted, however gave low yield due to a MOM-ester by-product.



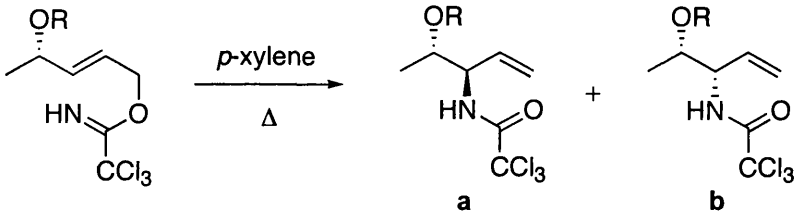
134 **152**

Scheme 60: Attempted deprotection and reprotection of α,β-unstaturated ester **134**.

2.1.2 Aza-Claisen rearrangements.

Allylic trichloroacetimidates **146-151** were initially subjected to thermal [3,3]-sigmatropic rearrangement in *p*-xylene (140 °C) for 24-120 hours.[15] In general, the ^{1}H NMR spectrum of the crude reaction mixture showed a 2:1 (3*R*:3*S*) ratio of diastereomers (Table 1). Rearrangement from the least hindered front face of the alkene is preferred, giving the (3*R*,4*S*) allylic amides **153a-158a** as the major products. The poor diastereoselectivity of this process can be explained by the small energy difference between the two possible reacting conformers at high temperatures. Purification of the reaction mixture by column chromatography gave the two diastereomers in very modest yields (21-44%) with a number of unidentifiable decomposition products. The low yields from these reactions are due to acid degradation of the trichloroacetimidates before rearrangement has occurred to the more stable trichloroamides.[23]

Table 1: Thermal [3,3]-sigmatropic rearrangement diastereoselectivities and yields

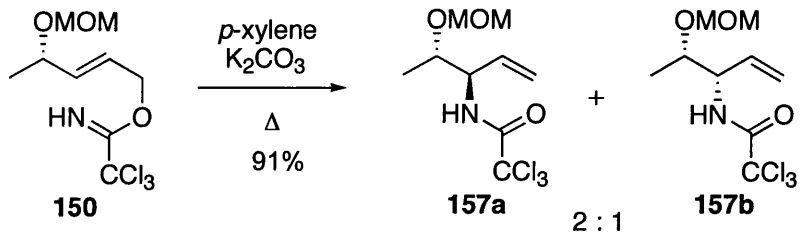


Entry	R	Yield[a] (%)	Ratio[b] (**a** : **b**)
1	TBDMS (**153**)	27%	1 : 1
2	Tr (**154**)	36%	2 : 1
3	Bn (**155**)	44%	2 : 1
4	Me (**156**)	38%	2 : 1
5	MOM (**157**)	21%	2 : 1
6	MEM (**158**)	37%	2 : 1

[a] Isolated combined yields of **a** and **b** from *E*-allylic alcohols **140-145**.
[b] Ratio in crude reaction mixture.

Using a modified thermal rearrangement procedure developed by Isobe and co-workers,[23] involving the addition of potassium carbonate to neutralise any acid formed during the

reaction, rearrangement of the lowest yielding imidate, the MOM-ether substrate was carried out giving the rearrangement products **157a** and **157b** in a much improved yield of 91% (Scheme 61).

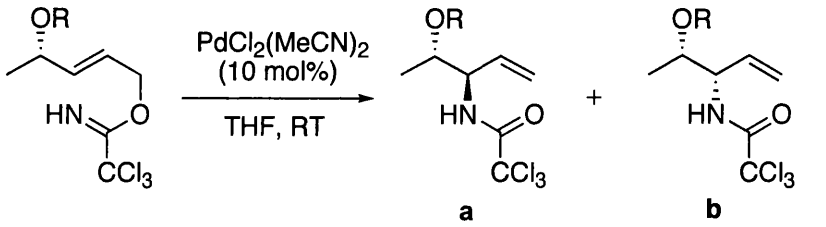


Scheme 61: Thermal rearrangement in presence of K_2CO_3.

Allylic trichloroacetimidates **146-151** were then subjected to rearrangement conditions using bis(acetonitrile)palladium(II) chloride catalyst in THF for 24 hours at room temperature (Table 2).[59]

The results show that the larger sterically bulky ether groups (entries 1, 2 and 3) hinder the palladium(II)-catalyst from efficiently coordinating to the ether oxygen and so allylic trichloroacetamides **153-155** are produced with low diastereoselectivity. However, rearrangement of the smaller methyl ether group (entry 4) gives a significant increase in diastereoselectivity. This is a result of the palladium catalyst now being able to effectively coordinate to the ether oxygen than to the olefin, blocking the back face of the molecule and forcing the imidate nitrogen to attack the olefin from the front face. This result led to an investigation into whether having additional oxygen atoms within the ether side chain would further enhance this effect. Gratifingly, use of the MOM group (entry 5) gave **157a** and **157b** in an excellent 10:1 ratio. In an attempt to enhance this effect even further, rearrangement with a MEM-ether substrate (entry 6) containing three oxygen atoms, was attempted. Although this group gave a highly selective rearrangement, no improvement on the diastereoselectively observed for the MOM group was obtained. In the case of the MEM-ether derivative, which has three oxygens in the chain, the third oxygen is probably too far away to coordinate effectively with the palladium(II)-catalyst. The larger bulk of the MEM-ether compared to the MOM-ether is most likely the cause of the slightly decreased selectivity.

Table 2: Bis(acetonitrile)palladium(II) chloride catalysed aza-Claisen rearrangement diastereoselectivities and yields



Entry	R	Yield[a] (%)	Ratio[b] (**a** : **b**)
1	TBDMS (**153**)	68%	2 : 1
2	Tr (**154**)	70%	3 : 1
3	Bn (**155**)	62%	3 : 1
4	Me (**156**)	48%	7 : 1
5	MOM (**157**)	64%	10 : 1
6	MEM (**158**)	60%	8 : 1

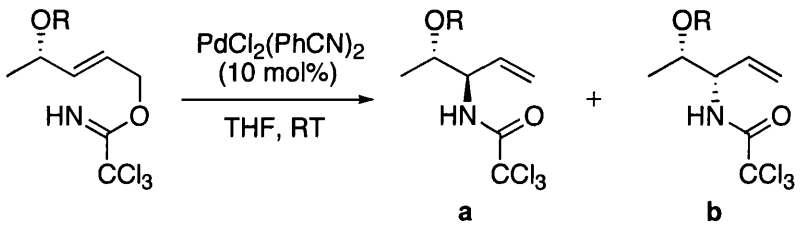
[a] Isolated combined yields of **a** and **b** from *E*-allylic alcohols **140-145**.
[b] Ratio in crude reaction mixture.

Allylic trichloroacetimidates **146-151** were then subjected to rearrangement conditions using bis(benzonitrile)palladium(II) chloride as catalyst in THF for 24 hours at room temperature.[59] As expected, bis(benzonitrile)palladium(II) chloride gave similar yields and ratio of diastereomers when treated with allylic trichloroacetimidates **146-151** (Table 3). On coordination of the catalyst with the MOM-ether and then the olefin both benzonitrile ligands are likely lost from the metal centre forming a similar intermediate as that for the acetonitrile catalyst.

Purification of the products generated from the bis(acetonitrile)palladium(II) chloride catalysed reaction proved easier due to co-eluting of benzonitrile derived compounds with the rearrangement products.

Overman and Knoll have also reported contamination of products from the rearrangement reaction with benzonitrile ligands originating from the bis(benzonitrile)palladium(II) chloride catalyst.[33]

Table 3: Bis(benzonitrile)palladium(II) chloride catalysed aza-Claisen rearrangement diastereoselectivities and yields.

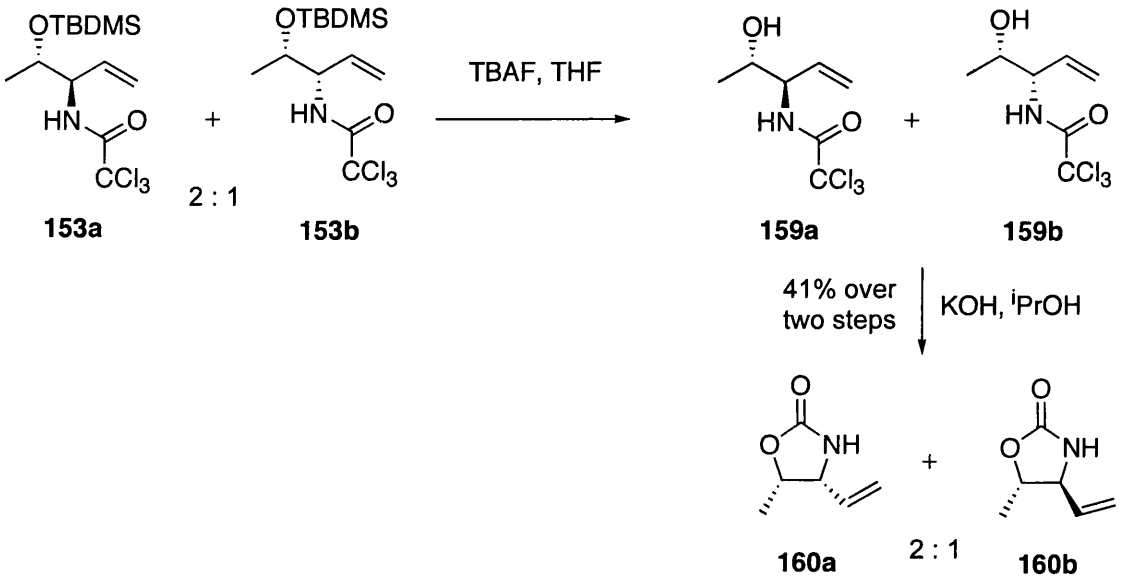


Entry	R	Yield[a] (%)	Ratio[b] (**a** : **b**)
1	TBDMS (**153**)	68%	2 : 1
2	Tr (**154**)	44%	3 : 1
3	Bn (**155**)	58%	4 : 1
4	Me (**156**)	48%	6 : 1
5	MOM (**157**)	57%	9 : 1
6	MEM (**158**)	52%	8 : 1

[a] Isolated combined yields of **a** and **b** from *E*-allylic alcohols **140-145**.
[b] Ratio in crude reaction mixture.

2.1.3 NOE study.

Oxazolidin-2-ones **160a** and **160b** were synthesised in order to prove the relative stereochemistry of the rearrangement products using nuclear Overhauser effect (NOE) experiments. The silyl ether protecting groups of trichloroacetamides **153a** and **153b** (2:1 ratio) were deprotected using tetra-*n*-butylammonium fluoride (TBAF) to give the secondary alcohols **159a** and **159b** (Scheme 62).[60] Reaction of these alcohols with potassium hydroxide in isopropanol gave the oxazolidin-2-ones **160a** and **160b** (2:1 ratio) in 41% yield over the two steps.



Scheme 62: Oxazolidin-2-ones synthesis.

The relative stereochemistry of the rearrangment products could then be determined using NOE experiments of these oxazolidin-2-ones (Figure 8).[65]

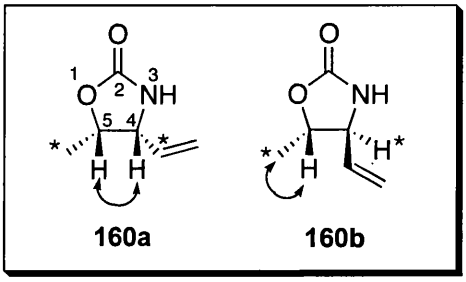


Figure 8: NOE experiments of these oxazolidin-2-ones.

Unfortunately oxazolidin-2-ones **160a** and **160b** could not be separated by column chromatography. However the ^{1}H NMR spectra of the 2:1 mixture of major and minor diastereomers clearly shows different peaks for the methyl substituents on C-5 (Figure 9). The peaks for the proton on C-4 of the minor diastereomer and the proton on C-5 of the major diastereomer are also very distinct.

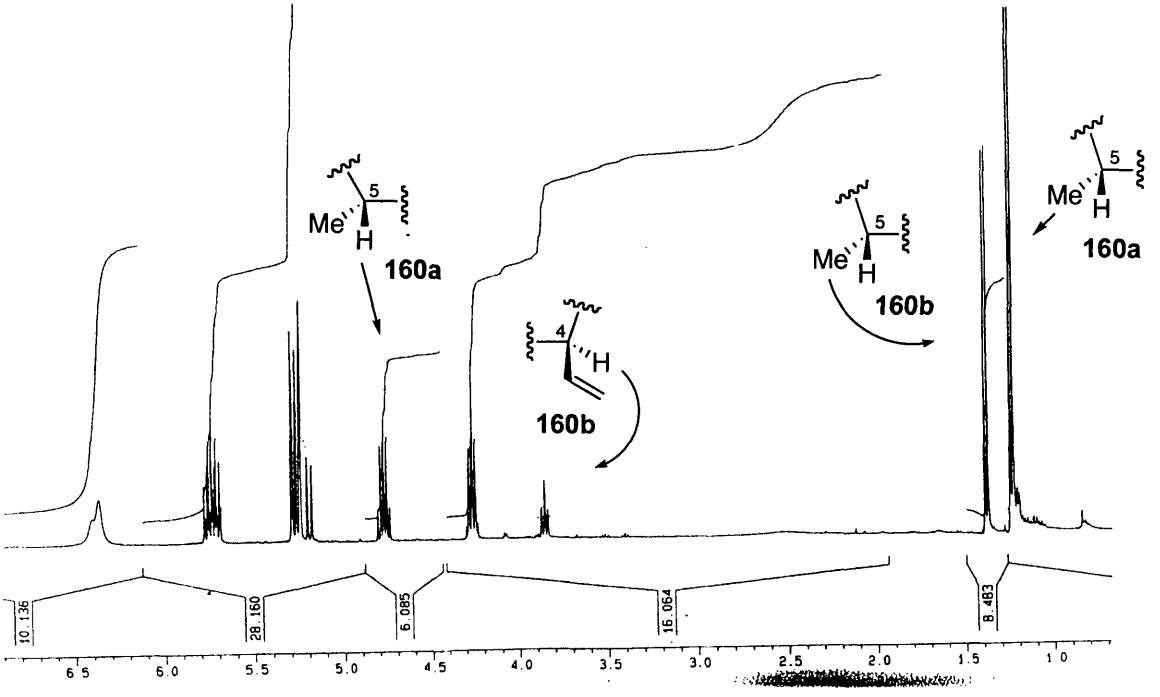


Figure 9: ^{1}H NMR spectra of the 2:1 mixture of major and minor oxazolidin-2-ones.

When the 5-H of the major diastereomer **160a** was irradiated, an increase in intensity of the peaks for both 4-H and 5-CH_3 was observed (Figure 10).

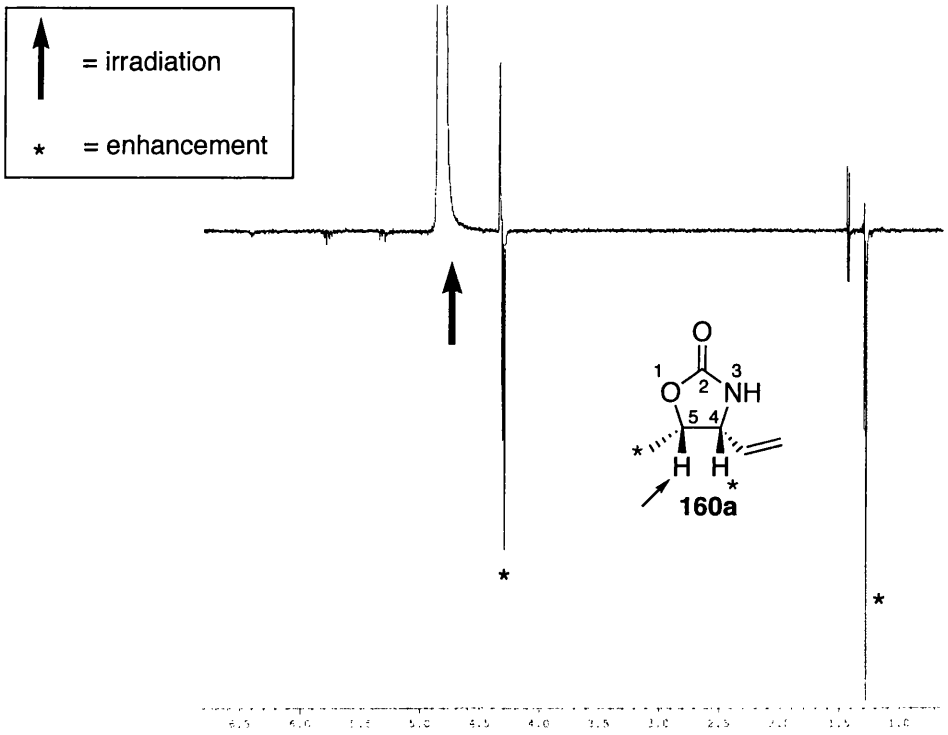


Figure 10: Irradiation of the 5-H on major diastereomer.

Irradiating the 5-CH_3 of the major diastereomer **160a** gave an increase in the intensity of both the 1'-H and 5-H peaks (Figure 11).

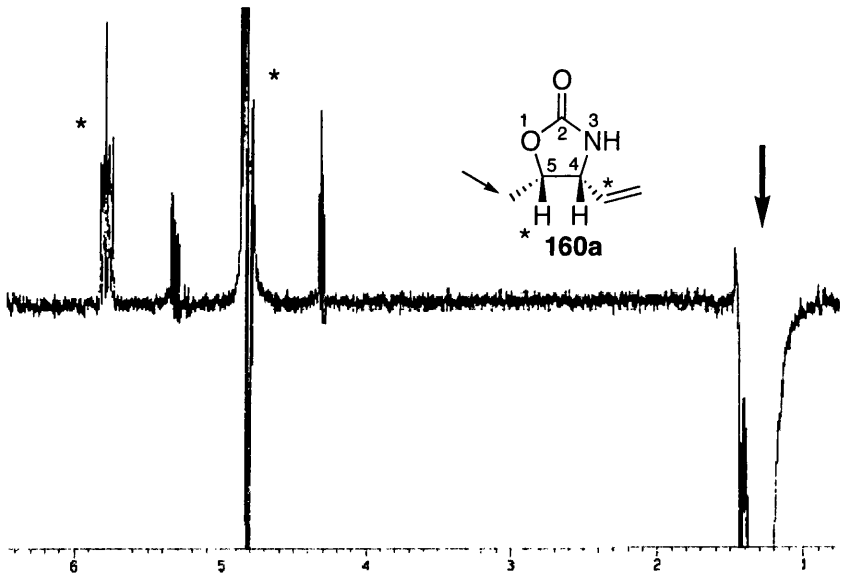


Figure 11: Irradiation of the 5-CH_3 of the major diastereomer.

Irradiating the 4-H of the minor diastereomer **160b** gave an increase in intensity of the 1'-H and 5-CH_3 peaks (Figure 12).

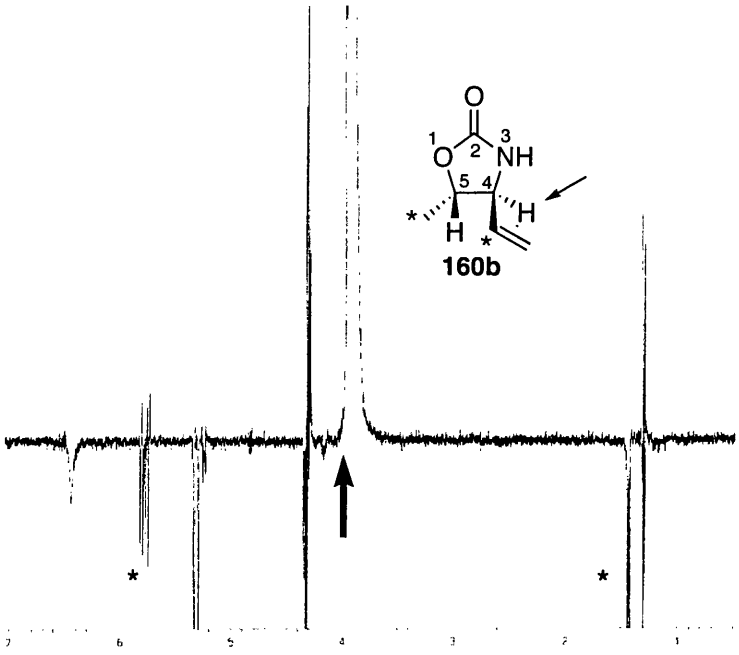


Figure 12: Irradiation of the 4-H on minor diastereomer.

Irradiation of the 5-CH_3 of the minor diastereomer **160b** gave an intensity increase for the 4-H peak and also the 5-H peak (Figure 13).

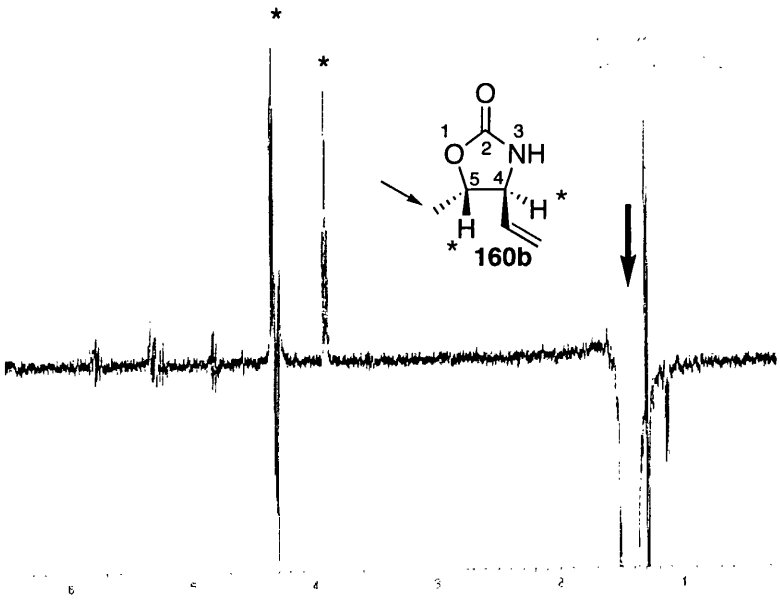


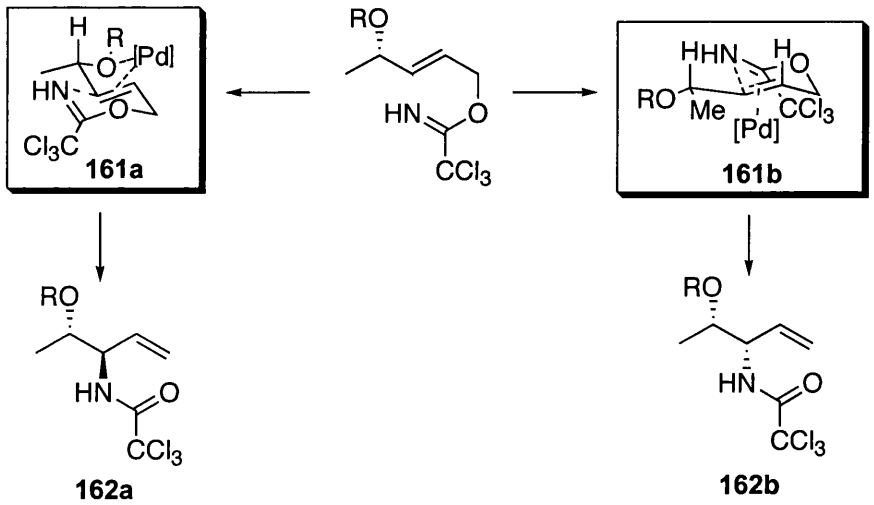
Figure 13: Irradiation of the 5-CH_3 of minor diastereomer.

These results confirmed that the 3*R*,4*S* diastereomer is the major compound obtained from these rearrangement reactions.

The diastereoselectivity for these reactions and the stereochemistry for the two products can be explained by the reacting conformations **161a** and **161b** (Scheme 63). The stereochemistry of the major compound **162a** can be explained by reacting confomer **161a**. The palladium(II)-catalyst initially coordinates to the ether oxygen and is then directed to the back face of the olefin. The trichloroacetimidate then adopts a chair-like conformation which minimises 1,3-allylic strain between the δ- and β-proton. The imidate nitrogen is then forced to attack the activated olefin from the front face and as a result the *anti*-diastereomer **162a** is produced.

The minor diastereomer **162b** produced in these reactions can be explained by reacting conformer **161b**. The catalyst coordinates to the less sterically hindered front face of the olefin which then adopts a chair-like conformation minimising 1,3-allylic strain. The imidate nitrogen is then forced to attack the activated olefin from the back face and the *syn*-diastereomer **162b** is produced.

Thus, for smaller protecting groups the palladium(II)-catalyst can efficiently coordinate to the ether oxygen and so diastereomer **162a** is the major product. However, with larger protecting groups the second pathway becomes more competitive and so low diastereoselectivity is observed for these substrates.



Scheme 63: Transition states resulting in major and minor diastereomers.

2.1.4 Catalyst Screen.

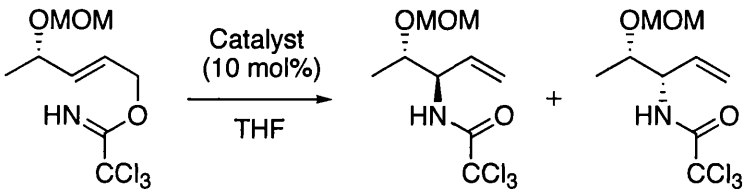
Having demonstrated the heteroatom-directing effect of the MOM-ether in the aza-Claisen rearrangement of allylic trichloroacetimidates with both bis(acetonitrile)palladium(II) chloride and bis(benzonitrile)palladium(II) chloride (Table 4, entries 1 and 2) giving greatly increased diastereoselectivities than the thermal rearrangement, other palladium catalysts were sought in order to further enhance the diastereoselectivity of the reaction.

A study was carried out using palladium(II) compounds with different sized ligands in order to observe what effect this would have on the selectivity of the reaction (Table 4). Palladium(II)-chloride, palladium(II)-bromide and palladium(II)-acetate gave high but similar ratios of diastereomers to that of the palladium(II) nitrile catalysts (entries 3-4 and 6). However, palladium(II)-iodide and palladium(II)-triflate showed no catalytic activity for this rearrangement (entries 5 and 7). Moreover, these palladium(II)-catalysts were only partially soluble in THF and thus, reaction times were considerably longer than for the reactions involving the palladium(II) nitrile catalysts. It is believed that these longer reaction times result in partial decomposition of allylic trichloroacetimidate **150** leading to lower yields of allylic trichloroacetamides **157a** and **157b**.

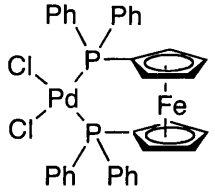
During Overman's initial studies on the enantioselective rearrangement of allylic imidates, phosphine-containing palladium(II)-catalysts were screened.[37] However, the catalysts gave disappointing results due to the electron-donating nature of the ligands inhibiting nucleophilic attack of the alkene by the imidate nitrogen. In order to investigate whether a similar effect would be observed for these substrates, reaction of allylic trichloroacetimidate **150** with dichloro[1,1'-bis(diphenylphosphino)ferrocene]-palladium(II) dichloromethane adduct was attempted (entry 8). As expected no catalytic activity for the rearrangement was observed.

Ikariya and co-workers have reported that the oxidation state of the palladium catalyst determines the regiochemical outcome of these rearrangement reactions with palladium(II) giving solely the [3,3] products and palladium(0) giving a mixture of [3,3] and [1,3] products.[34] Surprisingly, tetrakis(triphenylphosphine)palladium(0) showed no catalytic activity for the rearrangement of this substrate (entry 9).

Table 4: Rearrangement of allylic trichloroacetimidate **150** using palladium catalysts.



150 **157a** **157b**

Entry	Catalyst	Reaction time / h	Yield[a]	Ratio[b] (**157a : 157b**)
1	$PdCl_2(MeCN)_2$	24	64%	10 : 1
2	$PdCl_2(PhCN)_2$	24	57%	9 : 1
3	$PdCl_2$	120	45%	11 : 1
4	$PdBr_2$	72	44%	9 : 1
5[c]	PdI_2	----	----	----
6	$Pd(OAc)_2$	96	18%	9 : 1
7[c]	$Pd(OTf)_2$	----	----	----
8[c]		----	----	----
9[c]	$Pd(PPh_3)_4$	----	----	----

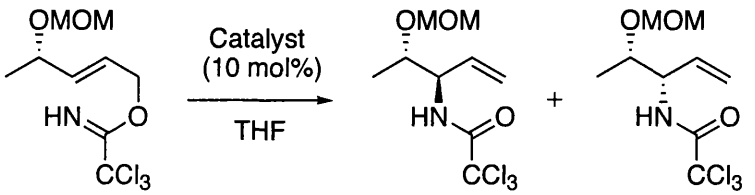
[a]Isolated combined yields of **157a** and **157b** from *E*-allylic alcohol **144**.
[b]Ratio in crude reaction mixture.
[c]No reaction after 120 hours.

A number of "soft" electrophilic transition metal catalysts have been used in the rearrangement of Claisen-type reactions.[27a,66] Some of these metal catalysts were screened for catalytic activity in the rearrangement of allylic trichloroacetimidate **150** and are listed in Table 5.

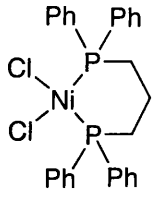
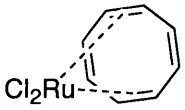
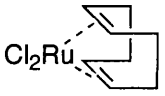
Complexes of nickel(II) and copper(II), residing in the fourth row of the periodic table, showed no catalytic activity for the rearrangment even after 5 days (entries 1-3). From the fifth row of the periodic table, complexes of ruthenium(II) proved to be catalytically inactive (entries 4-6). Since the electronic nature of the lanthanides resides between the

fifth and sixth rows of the periodic table, ytterbium(III) was tested, however it also showed no catalytic activity (entry 7).

Table 5: Rearrangement of allylic trichloroacetimidate **150** using electrophilic metal catalysts.



150 **157a** **157b**

Entry	Catalyst	Reaction time / h	Yield	Ratio (**157a : 157b**)
1[a]	$NiCl_2$	----	----	----
2[a]		----	----	----
3[a]	$CuCl_2$	----	----	----
4[a]	$Cl_2Ru(PPh_3)_3$	----	----	----
5[a]		----	----	----
6[a]		----	----	----
7[a]	$YbCl_3.H_2O$	----	----	----

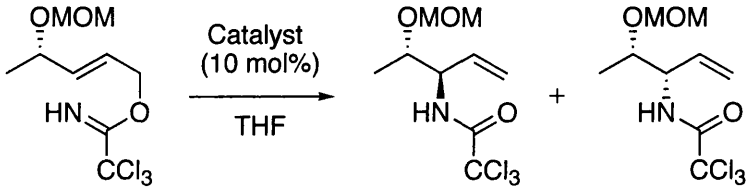
[a]No reaction after 120 hours.

The catalytic rearrangement of allylic trichloroacetimidates was first observed by Overman using mercury(II) salts.[14,15] However, these reactions were limited by the requirement of a substituent on C-3 that favours attack of the imidate nitrogen on the olefin (*i.e.* initiates 3-C to be δ+). Mercury(II)-triflate and mercury(II)-chloride, showed no activity for the rearrangement of **150** (Table 6, entries 1 and 2). This can therefore be explained by the

fact that the MOM-ether side chain does not exert an electron-withdrawing effect on C-3 and as a result C-3 is not δ+. Also residing in the sixth row of the periodic table, iridium(III) showed no catalytic activity for the rearrangement reaction (entry 3).

Finally, hydrogen tetrachloroaurate(III) hydrate and platinium(II)-chloride catalysed the rearrangement of allylic trichloroacetimidate **150** to give allylic trichloroacetamides **157a** and **157b** in good yields over the two steps (entries 4 and 5). However, the diastereoselectivity could not be improved on that observed for the palladium(II)-catalysts. In accordance with these results Jaunzeme and Jirgensons have also recently shown that platinum and gold catalyse the rearrangement of allylic trichloroacetimidates.[67]

Table 6: Rearrangement of allylic trichloroacetimidate **150** using sixth row transtion metal catalysts.



150 **157a** **157b**

Entry	Catalyst	Reaction time / h	Yield[a]	Ratio[b] (**157a : 157b**)
1[c]	$HgCl_2$	----	----	----
2[c]	$Hg(OTf)_2$	----	----	----
3[c]	$IrCl_3.3H_2O$	----	----	----
4	$HAuCl_2.3H_2O$	48	49%	6 : 1
5	$PtCl_2$	144	49%	10 : 1

[a]Isolated combined yields of **157a** and **157b** from *E*-allylic alcohol **144**.
[b]Ratio in crude reaction mixture.
[c]No reaction after 120 hours.

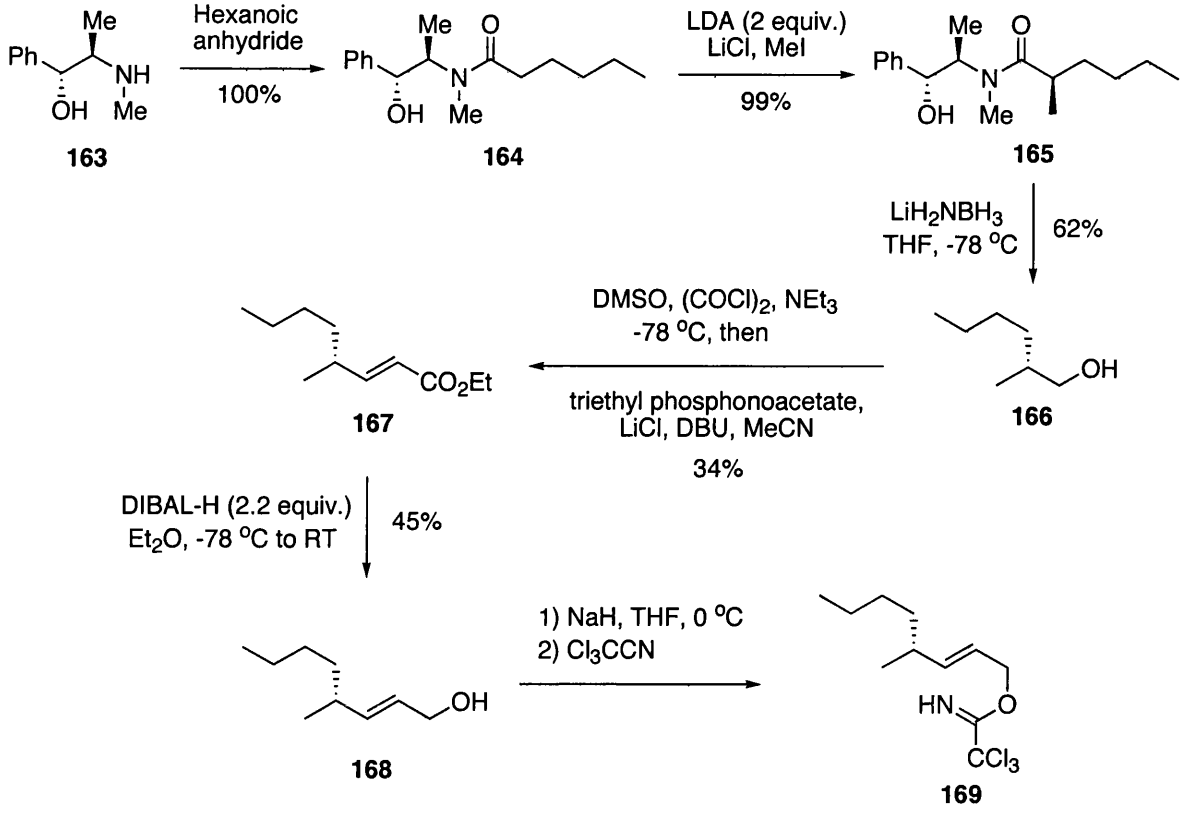
Thus, for optimal rate of reaction, ease of purification, high yield and high diastereoselectivity the preferred catalyst for this ether-directed rearrangement is bis(acetonitrile)palladium(II) chloride.

2.2 Further Evidence for the Directing Effect and Enhancement of Stereoselectivity

2.2.1 Synthesis and Rearrangement of MOM-ether Analogues.

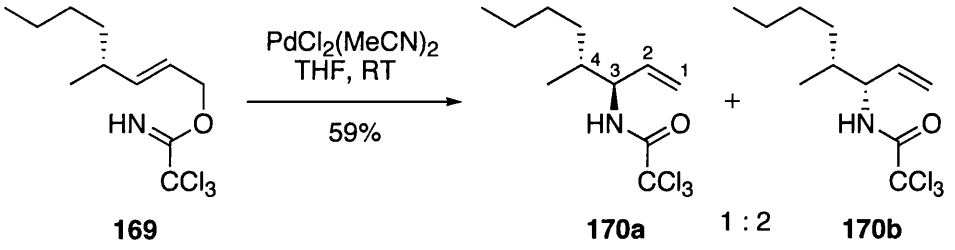
The results so far strongly suggest that the high diastereoselectivity observed in these rearrangement reactions are the result of the ether oxygen atoms coordinating to the palladium catalyst and directing it to one face of the olefin ultimately resulting in a highly selective reaction. However, further evidence for this effect was required and so an investigation of the palladium(II)-catalysed rearrangement of a carbon analogue of the most diastereoselective MOM-ether substrate was carried out.

This carbon analogue of the MOM-ether substrate was synthesised with the aid of Myer's pseudoephedrine chiral auxiliary (Scheme 64).[68] Acylation of (1*R*,2*R*)-(-)-pseudoephedrine **163** with hexanoic anhydride in THF produced amide **164** in quantitative yield. Myers reported a fast oxygen-nitrogen shift of the alkyl group and so only the desired product **164** was observed.[68] Amide **164** was then deprotonated at C-2 with lithium diisopropylamine (LDA). Two equivalents of LDA were required as the secondary alcohol is also deprotonated. Methylation of the resulting enolate with methyl iodide gave the desired 2*R* isomer **165** in 99% yield. Cleavage of the chiral auxiliary to give the primary alcohol **166** was then carried out using the milder variant of $LiAlH_4$, lithium ammonia-borane (LAB).[68] A subsequent one pot Swern oxidation-HWE reaction produced the α,β-unsaturated ester **167** regioselectively with only the *E*-geometrical isomer observed by ^1H NMR spectroscopy.[63] Reduction of the α,β-unsaturated ester **167** to the *E*-allylic alcohol **168** was carried out using 2.2 equivalents of DIBAL-H. Finally, reaction with sodium hydride and trichloroacetonitrile gave allylic trichloroacetimidate **169** for the rearrangement reaction.[64]



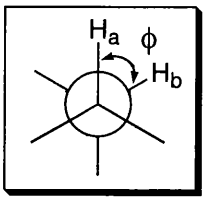
Scheme 64: Synthesis of MOM-ether carbon analogue.

The catalysed rearrangement reaction was carried out in THF at room temperature for 12 hours using bis(acetonitrile)palladium(II) chloride (10 mol%) producing the trichloroacetamides **170a** and **170b** in 59% combined yield, over two steps and in a ratio of 1:2 (3*R*:3*S*) (Scheme 65).[59]



Scheme 65: Rearrangement of MOM-ether carbon analogue.

The dihedral angle (ϕ) between two adjacent protons in a compound can be calculated theoretically using the Karplus equations (Figure 14) and the vicinal coupling constants J_{ab} obtained from the ^{1}H NMR spectra. This allows the assignment of relative stereochemistry of compounds such as **170a** and **170b**.[65]



$J_{ab} = J^{0} \cos^2 \phi - 0.28 \ (0^{o} \leq \phi \leq 90^{o})$
$J_{ab} = J^{180} \cos^2 \phi - 0.28 \ (90^{o} \leq \phi \leq 180^{o})$

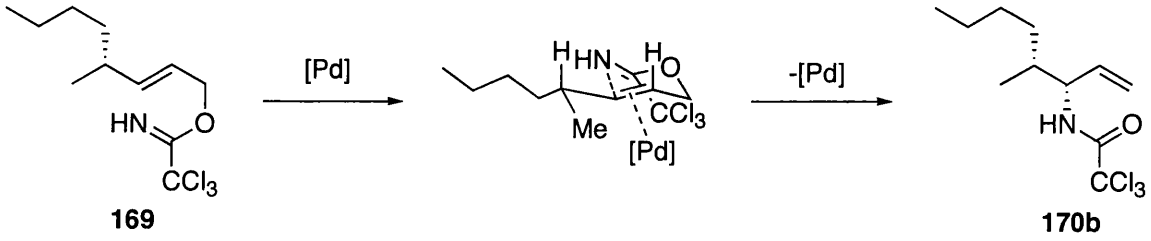
(J^{180} and J^{0} are constants which depend upon the substituents on the carbon atoms)

Figure 14: Karplus equations.

However the $J_{3,4}$ coupling constants could not be obtained from the ^{1}H NMR spectra of trichloroacetamides **170a** and **170b**, even using a variety of deuteriated solvents and so the *syn*- and *anti*-diastereomers could not be assigned using the Karplus equations.[65]

However, the diastereoselectivity observed for the MOM substrate (10:1) has been lost with the carbon analogue (1:2) and so this is additional proof that the rearrangement is an ether directed process and not directed by the steric bulk of the substituents on C-4.

This result demonstrates that without an ether oxygen in the δ-position to direct the palladium catalyst the reaction proceeds with low selectivity. The most likely major pathway for this reaction can be explained by reacting confomer (Scheme 66). Initially the palladium catalyst coordinates to the least hindered front face of the olefin, the trichloroacetimidate then adopts a chair-like configuration which minimises 1,3-allylic strain and the imidate nitrogen attacks the olefin from the back face to give the *syn*-isomer as the major product.

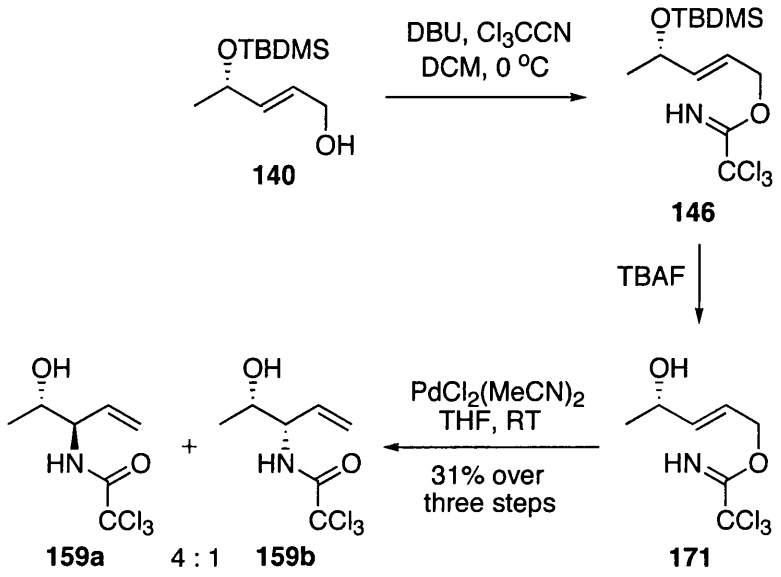


Scheme 66: Transition state for the non-coordinating aza-Claisen rearrangement.

During discussions about the ether-directed aza-Claisen rearrangement it was suggested that a hydroxyl functional group in place of the MOM-ether would coordinate more strongly to the palladium(II)-catalyst resulting in a more diastereoselective reaction.

Thus, our aim was the synthesis of δ-hydroxy substituted allylic trichloroacetimidate **171** (Scheme 67). Allylic alcohol **140** was synthesised as described above from ethyl (*S*)-lactate **121**. Subsequent reaction with DBU and trichloroacetonitrile gave

trichloroacetimidate **146**. This transformation can be carried out using sodium hydride as base.[64] However, it was found that the use of DBU as base and filtering the crude reaction mixture through a small plug of silica is more reliable, giving allylic trichloroacetimidates in higher yields.[57] The silyl ether protecting group was then removed using TBAF to give the desired allylic trichloroacetimidate **171**. The catalysed rearrangement reaction was carried out in THF at room temperature using bis(acetonitrile)palladium(II) chloride (10 mol%).[59] Trichloroamides **159a** and **159b** were produced in 31% yield over three steps, and in a ratio of 4:1 (3*R*,3*S*).



Scheme 67: Synthesis and rearrangement of hydroxyl compound.

The diastereoselectivity of this rearrangement (4:1) is significantly lower than that observed for the rearrangement of the MOM-ether substrate (10:1). This result therefore conflicts with the ideal that the free hydroxyl group would coordinate more strongly to the palladium(II)-catalyst and give a more selective reaction. Some other effect must therefore be assisting the MOM-ether in directing the palladium(II)-catalyst during the reaction. Thus, it was proposed that the oxygen in the 7-position of the MOM-ether substrate could be assisting coordination of the catalyst giving the observed enhancement of selectivity.

In order to specifically investigate this theory and, which of the oxygens in the MOM-ether group are responsible for coordinating to and directing the palladium(II)-catalyst during the rearrangement, the synthesis and rearrangement of two MOM-ether substrate analogues **172** and **173** was carried out (Figure 15). This would effectively show whether both of the oxygen atoms can bind to and coordinate the palladium(II)-catalyst independently and also whether both oxygen atoms are required for the enhanced selectivity observed for the MOM-ether substrate. Additionally, these two substrates, the carbon analogue and the

MOM-ether substrate are all of similar size. Therefore, if steric bulk is responsible for the selectivities in these rearrangements, very similar results in diastereoselectivity would be expected for all four substrates. However, if the directing effect is responsible, the diastereoselectivities should be very different. Thus, this study will conclusively demonstrate whether the selectivity for these rearrangement reactions is caused by a directing effect, or by steric bulk as proposed by Ham and co-workers.[55]

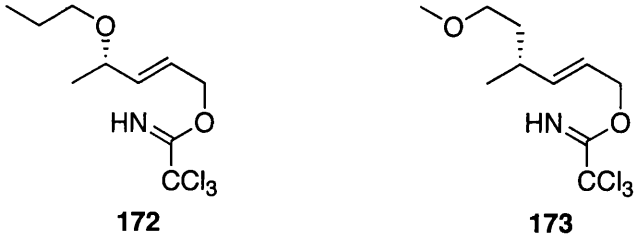
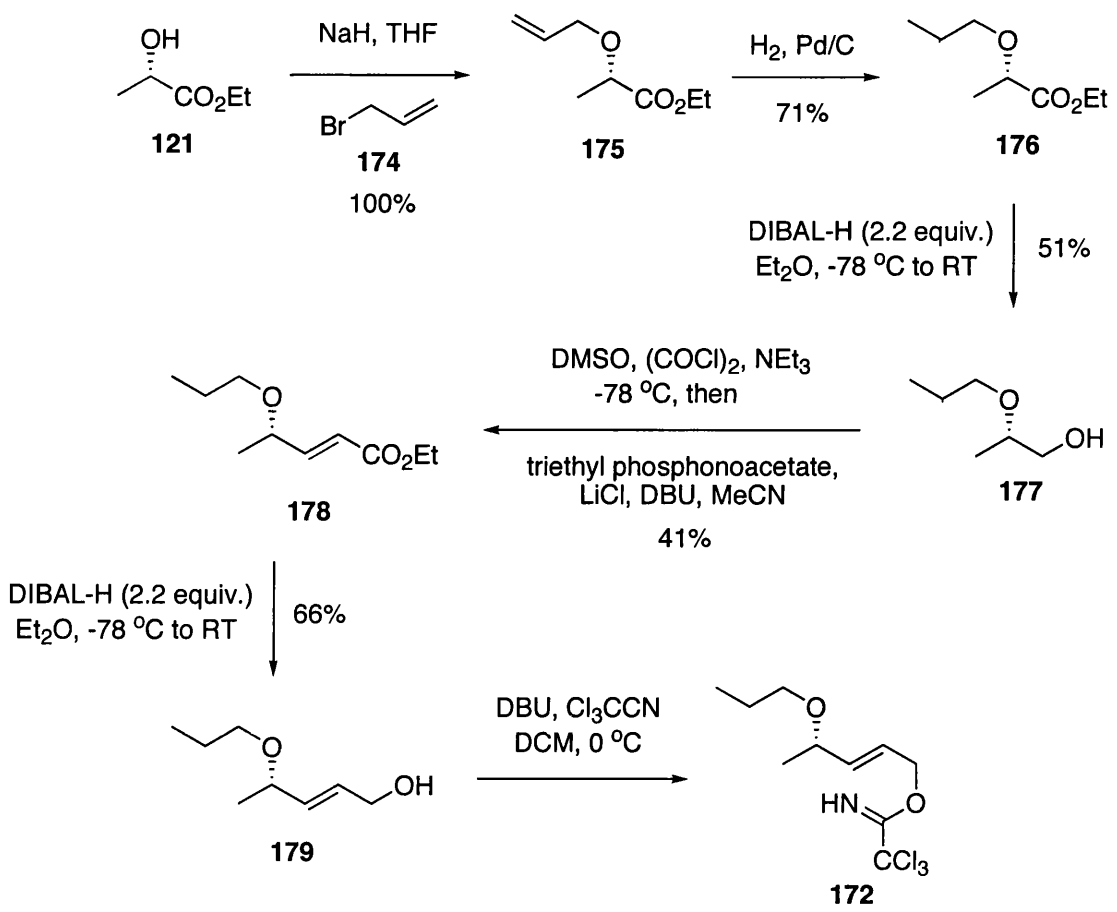


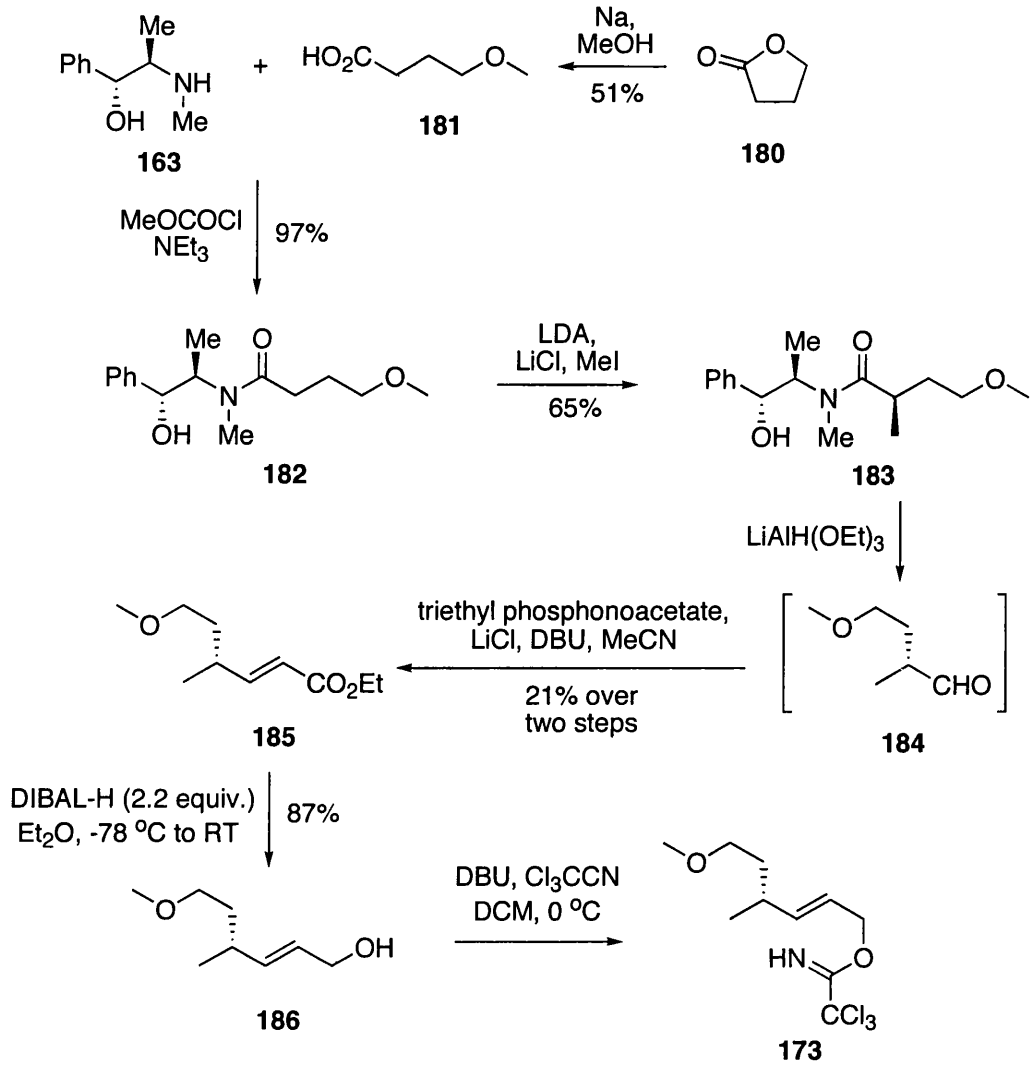
Figure 15: MOM-ether analogues.

The trichloroacetimidate analogue of the MOM-ether substrate containing the oxygen atom at the 5-position **172** was synthesised from ethyl (*S*)-lactate **121** in six steps (Scheme 68). Protection of alcohol **121** was carried out using sodium hydride and allyl bromide **174**. The alkene was then hydrogenated using hydrogen and 10% palladium on carbon to give the propyl protected lactate **176**.[69] Reduction of the ester moiety of **176** to the alcohol **177** was carried out using 2.2 equivalents of DIBAL-H.[61] A subsequent one pot Swern-HWE reaction, under Masamune-Roush conditions, produced the α,β-unsaturated ester **178**.[62,63] Reduction of the α,β-unsaturated ester **178** to allylic alcohol **179** was carried out again using 2.2 equivalents of DIBAL-H. Finally, trichloroacetimidate **172** was synthesised from alcohol **179** using DBU and trichloroacetonitrile.[57]



Scheme 68: Synthesis of MOM-ether analogue with oxygen in 5-position.

The trichloroacetimidate analogue of the MOM-ether substrate containing only the oxygen in the 7-position was synthesised with the aid of Myer's peusdoephedrine chiral auxiliary (Scheme 69).[68] γ-Butyrolactone **180** was reacted with sodium and methanol to give 4-methoxybutanoic acid **181**.[70] Carboxylic acid **181** was activated as the mixed anhydride and reacted with *N*-acetylation of (-)-(1*R*,2*R*)-peusdoephedrine **163** to give amide **182** in 97% yield over the two steps. Amide **182** was then deprotonated at C-2 with LDA. Methylation of the resulting enolate with methyl iodide gave the desired amide product **183** in 65% yield.[68] Reduction of the pseudoephedrine amide to form aldehyde **184** was achieved using Brown and Tsukamoto's lithium triethoxyaluminium hydride reagent.[71] The reaction was quenched with trifluoroacetic acid in 1M aqueous hydrochloric acid solution in order to complete the conversion of an aminal to the desired aldehyde.[68] Due to the volatile nature of the aldehyde produced it was reacted directly in a Horner-Wadsworth-Emmons reaction, under Masamune-Roush conditions,[62] producing α,β-unsaturated ester **185** with only the *E*-geometrical isomer observed by ^{1}H NMR spectroscopy. Reduction of α,β-unsaturated ester **185** to allylic alcohol **186** was carried out using 2.2 equivalents of DIBAL-H. Finally, trichloroacetimidate **173** was prepared from alcohol **186** using DBU and trichloroacetonitrile.[57]



Scheme 69: Synthesis of MOM-ether analogue with oxygen at 7-position.

With both allylic trichloroacetimidates in hand, the rearrangement reactions were carried out using bis(acetonitrile)palladium(II) chloride (10 mol%) in THF at room temperature (Table 7).[59]

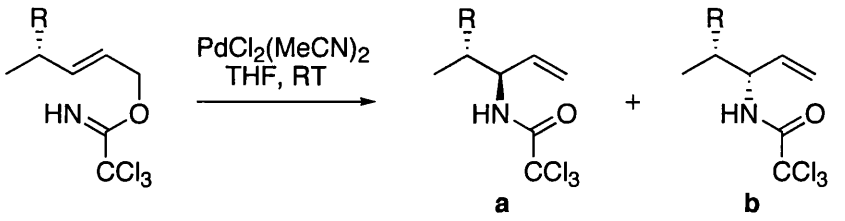
The allylic trichloroacetimidate substrate containing the oxygen atom at the 5-position underwent the rearrangement reaction to give the corresponding trichloroacetamide products **187a** and **187b** in 77% yield over the two steps from allylic alcohol **179** and in a ratio of 5:1 (3*R*,3*S*) (entry 3).

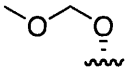
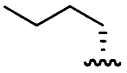
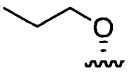
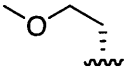
Rearrangement of the allylic trichloroacetimidate substrate containing the oxygen atom at the 7-position gave the allylic trichloroacetamide products **188a** and **188b** in 60% yield over the two steps and in a ratio of 1:2 (3*R*,3*S*) (entry 4).

Like the carbon analogue, allylic trichloroacetamides **188a** and **188b** could not be converted to the corresponding oxazolidin-2-ones in order to determine the relative stereochemistry using NOE. However, careful comparison of the ^{1}H NMR spectra of these

two products with the other allylic amides produced in this study shows clearly that the peaks for 1-H_2, 2-H and 5-H_3 are especially distinctive for the two diastereomers **a** and **b**. Therefore, diastereomer **b** was confirmed as the major compound produced from the rearrangement of the carbon analogue **168** and allylic trichloroacetimidate **173** by careful examination of the ^{1}H NMR spectra.

Table 7: Rearrangement of MOM-ether analogues.



Entry	R group	Yield[a] (%)	Ratio[b] (**a** : **b**)
1	 **(157)**	64%	10 : 1
2	 **(170)**	59%	1 : 2
3	 **(187)**	77%	5 : 1
4	 **(188)**	60%	1 : 2

[a] Isolated combined yields of **a** and **b** from *E*-allylic alcohols.
[b] Ratio in crude reaction mixture.

Rearrangement of allylic trichloroacetimidate **150** gave the allylic trichloroacetamide products **157a** and **157b** in an excellent 10:1 ratio (entry 1). On the other hand, the carbon analogue **169** produced the rearrangement products **170a** and **170b** in low diastereoselectivity (1:2) and so the directing effect has been lost (entry 2). This was also observed with the rearrangement of allylic trichloroacetimidate **173** to give rearrangement products **188a** and **188b**. Allylic trichloroacetimidate **172** gave a similar ratio of diastereomers as the hydroxyl compound **171** (5:1).

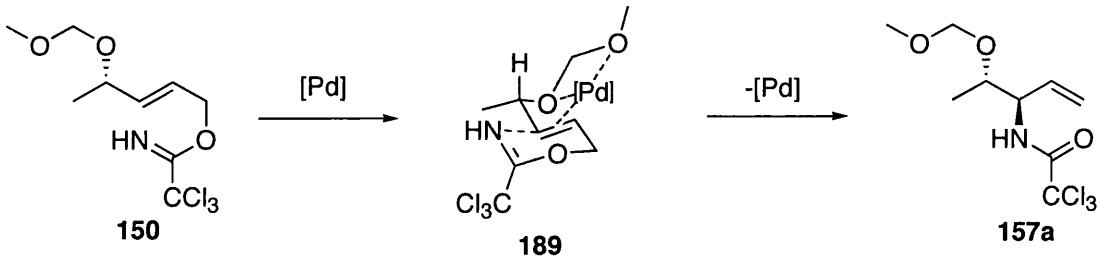
In the case of the carbon analogue no directing effect is observed and so the diastereoselective outcome of the rearrangement is controlled by the steric effects of the substituents on C-4. The catalyst therefore coordinates to the least sterically hindered front face of the olefin and forces the imidate nitrogen to attack the resulting activated olefin

from the back face (Scheme 66). The *syn*-diastereomer **b** is therefore produced as the major product.

The same diastereomeric ratio was obtained for the rearrangement of trichloroacetimidate **173** and so this suggests that the oxygen atom in the 7-position can not independently coordinate to and direct the palladium(II)-catalyst during the rearrangement reaction.

Rearrangement of allylic imidate **172** (5:1) and the hydroxyl substrate **171** (4:1) gave similar results, with the *anti*-diastereomer now being produced as the major product. This demonstrates that the oxygen atom in the 5-position effectively coordinates to the palladium(II)-catalyst and directs it to the back face of the olefin. Thus, the imidate is forced to attack the activated olefin from the front face and so the *anti*-diastereomer is produced as the major product (Scheme 63).

The same effect is observed with the MOM-ether substrate **150**. However, greatly increased selectivity is observed with this substrate (10:1). It is believed that the oxygen atom in the 7-position must therefore assist the oxygen atom in the 5-position in coordinating to and directing the palladium(II)-catalyst during the rearrangement of this substrate as shown in reacting confomation **189** and so an enhancement of selectivity is observed (Scheme 70).



Scheme 70: Transition state for the MOM-ether directed aza-Claisen rearrangement.

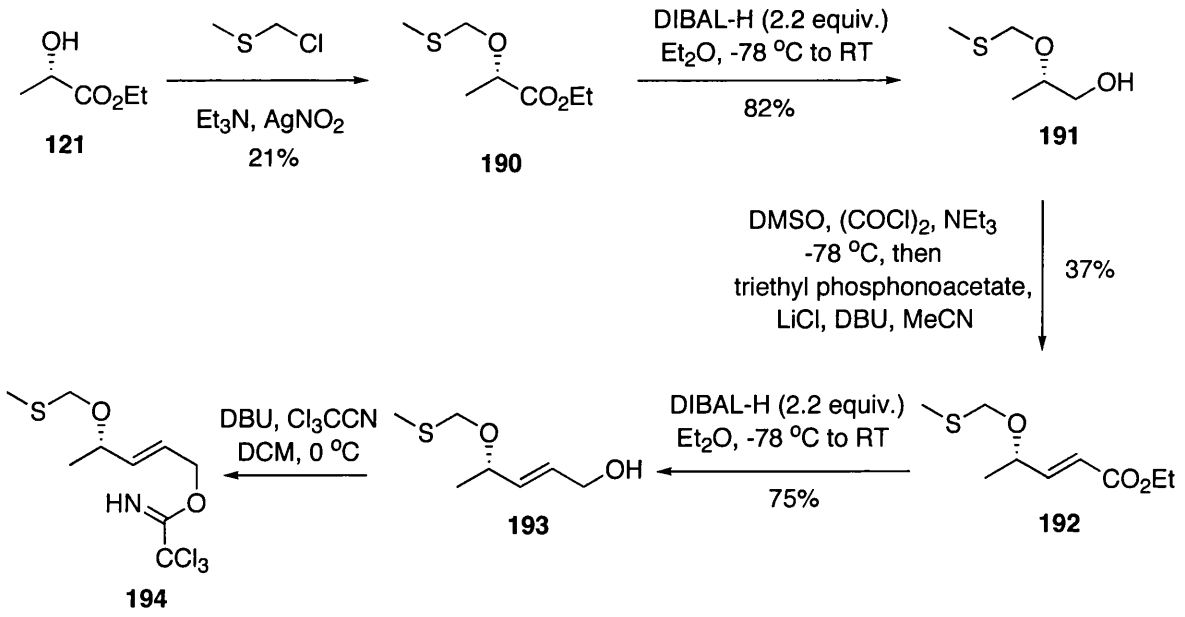
These four substrates are very similar in size and yet undergo palladium(II)-catalysed rearrangement to give very different diasteromeric ratios of the corresponding allylic trichloroacetamides. This, therefore, provides conclusive evidence that the diastereoselectivities observed for the palladium(II)-catalysed rearrangements of chiral allylic trichloroacetimidates, with a heteroatom α to the olefin, are the result of a heteroatom-directed process and not controlled by the steric bulk of the C-4 substituents.

Having demonstrated that both oxygen atoms in the MOM-ether substrate coordinate to the palladium(II)-catalyst leading to a highly selective reaction, a brief attempt was made to investigate whether other heteroatoms in the 7-position could enhance this selectivity.

A methylthiomethyl (MTM)-ether analogue of the MOM-ether substrate **150** was therefore prepared. The hypothesis for using this substrate was that the sulfur atom would

coordinate more strongly to the palladium(II)-catalyst, thus giving an enhancement of selectivity.

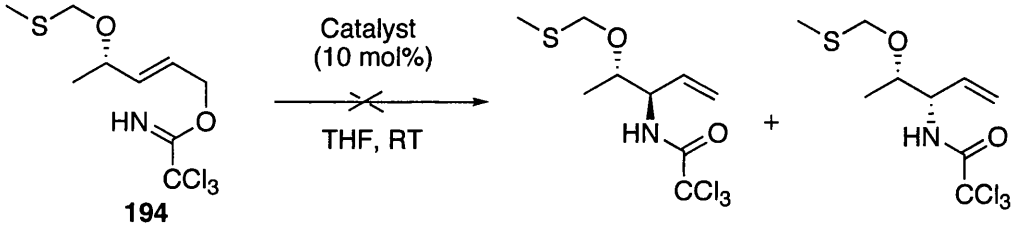
The MTM-ether allylic trichloroacetimidate **194** required for the rearrangement reaction was prepare from ethyl (*S*)-lactate **121** (Scheme 71). The MTM-ether **190** was synthesised from ethyl (*S*)-lactate **121** by reaction with chloromethylmethyl sulfide and silver nitrate in 21% yield.[72] Procedures for the efficient synthesis of MTM-ethers from primary and tertiary alcohols are known.[73] However the synthesis of MTM-ethers from secondary alcohols has previously been shown to be low yielding.[72] The reaction procedure involving silver nitrate was therefore carried out on a large enough scale to produce sufficient amounts of MTM-protected lactate **190** to complete the synthesis of allylic trichloroacetimidate **194**. The MTM protected lactate **190** was then reduced to the corresponding alcohol **191** using 2.2 equivalents of DIBAL-H.[61] (*E*)-α,β-Unsaturated ester **192** was then synthesised using a one-pot, Swern oxidation-HWE reaction.[63] Reduction, again using 2.2 equivalents of DIBAL-H gave the desired allylic alcohol **193**. Finally, treatment of allylic alcohol **193** with DBU and trichloroacetonitrile provided allylic trichloroacetimidate **194**.[57]



Scheme 71: Syntheis of MOM-ether thio-analogue.

The aza-Claisen rearrangement of allylic trichloroacetimidate **194** was attempted at room temperature using bis(acetonitrile)palladium(II) chloride (10 mol%) in THF (Scheme 72).[59] However, after 72 hours only starting material was observed by ^{1}H NMR spectroscopy. Having previously demonstrated that gold(III) and platinum(II) complexes can also catalyse this type of rearrangement, the reaction was repeated using platinum(II) chloride and hydrogen tetrachloroaurate(III) hydrate. However, in both these reactions, only

starting material was observed in the ^{1}H NMR spectra after 72 hours. Sulfur is known to poison heterogeneous catalysts and so inhibit catalysed reactions.[74] This may be the case with the MTM-substrate **194**.

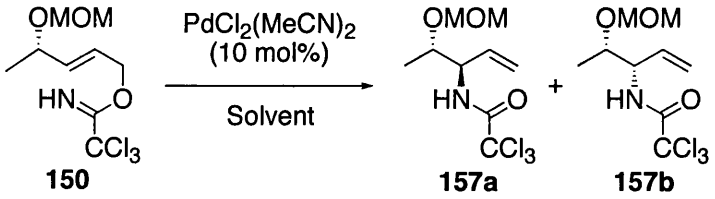


Scheme 72: Attempted rearrangement of MTM-substrate **194**.

2.2.2 Solvent Effects in the ether-directed, Palladium(II)-Catalysed aza-Claisen rearrangement.

Having conclusively shown that the rearrangements are ether-directed and since all the rearrangement reactions to date have been carried out in THF, it was suggested that as THF is an ether, this solvent may compete with the MOM group for the coordination of the Pd(II)-catalyst and thus restrict the directing effect. Using a non-coordinating solvent should therefore decrease this effect and lead to an enhancement of the diastereoselectivity observed. The rearrangement of **150** was therefore repeated with bis(acetonitrile)palladium(II) chloride and various solvents (Table 8). As mentioned above, bis(acetonitrile)palladium(II) chloride is soluble in organic solvents and so the reactions were complete in 24 h. Changing the solvent to diethyl ether and dichloromethane gave an increase in diastereoselectivity to 12:1. However, the largest increase in diastereoselectivity was observed with toluene as solvent. The reaction produced the allylic trichloroamides **157a** and **157b** in an excellent 15:1 ratio and in 56% yield. The reaction was also repeated using a highly coordinating solvent, the commercially available ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate. The increased viscosity of the ionic liquid compared with the other organic solvents led to a longer reaction time of 146 h. However, the allylic trichloroacetamides **157a** and **157b** were still isolated in 37% yield over the two steps and more importantly in a ratio of 5:1, effectively demonstrated that a strongly coordinating solvent can disrupt coordination of the palladium(II)-catalyst to the MOM-ether and decrease diastereoselectivity.

Table 8: Rearrangement of allylic trichloroacetimidate **150** using various solvents.



150 **157a** **157b**

Entry	Solvent	Reaction Time (h)	Yield[a]	Ratio[b] (**a** : **b**)
1	THF	24	64%	10 : 1
2	Et_2O	24	47%	12 : 1
3	MeCN	24	32%	9 : 1
4	CH_2Cl_2	24	49%	12 : 1
5	Toluene	24	56%	15 : 1
6	(BMI) BF_4	148	37%	5 : 1

[a] Isolated combined yields of **157a** and **157b** from *E*-allylic alcohol **144**.

[b] Ratio in crude reaction mixture.

In summary, conclusive evidence for the ether-directed, palladium(II)-catalysed aza-Claisen rearrangement has been obtained.

Rearrangement of a carbon analogue of the most diastereoselective MOM-ether substrate resulting in a loss of selectivity demonstrated that the diastereoselective rearrangement is an ether-directed process. Further more, by investigating the palladium(II)-catalysed rearrangement of two MOM-ether analogues and a hydroxyl substrate it was established that the oxygen atom in the 5-position is essential for this heteroatom-directed effect to be observed in the rearrangement. Also, the oxygen atom in the 7-position of the MOM-ether is able to assist the oxygen atom in the 5-position and so an enhancement in diastereoselectivity is observed for the palladium(II)-catalysed rearrangement of the MOM-ether substrate **150**.

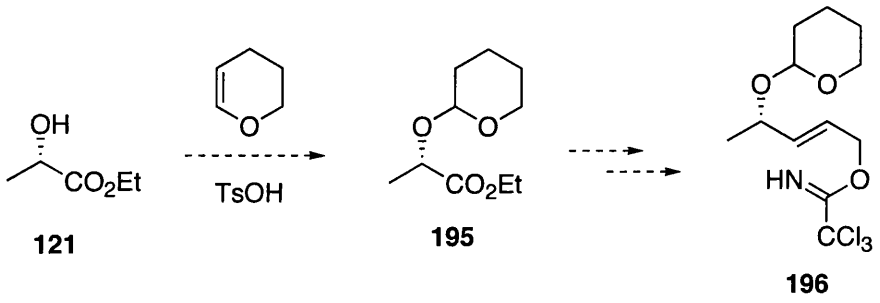
A brief investigation into the use of different heteroatoms was also attempted with the synthesis of a MTM-ether substrate. However, catalyst poisoning by the sulfur moiety prevented successful rearrangement.

Additionally, a study on the solvent utilised in the ether-directed, palladium(II)-catalysed aza-Claisen rearrangement revealed that the use of non-coordinating solvents such as toluene results in an enhancement of diastereoselectivity by minimising competition for coordination with the catalyst. Also, for the first time the rearrangement reaction was carried out using the highly coordinating ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate which disrupts binding of the palladium(II)-catalyst to the MOM-ether giving the allylic trichloroacetamide products with only moderate diastereoselectivity.

2.2.3 Future work on methodology development.

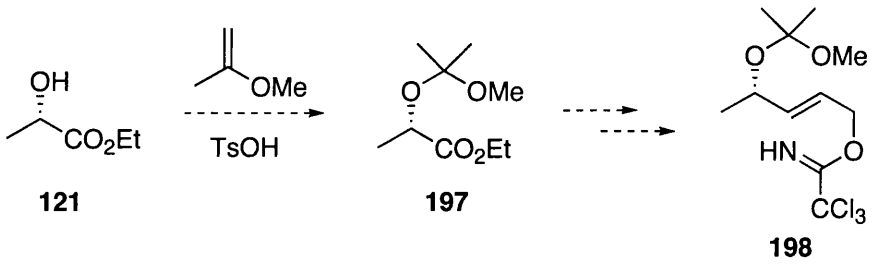
Future work on this project could be carried out towards the synthesis of allylic trichloroacetimidates containing ether protecting groups which give a more effective directing effect in the palladium(II)-catalysed aza-Claisen rearrangement.

For example, protection of ethyl (*S*)-lactate **121** using dihydropyran and toluenesulfonic acid would give tetrahydropyranyl (THP) ether lactate **195** which would be used in our general route to generate allylic trichloroacetimidate **196** (Scheme 73).[60] aza-Claisen rearrangement of allylic trichloroacetimidate **196** would show whether the rigidity of the ring can push the two oxygen atoms closer together and thus result in a more effective directing effect.



Scheme 73: Proposed synthesis of THP-substrate **196**.

Additionally, protection of ethyl (*S*)-lactate **121** using 2-methoxypropene and toluenesulfonic acid would yield compound **197** that would again be used in our general route to prepare allylic trichloroacetimidate **198** (Scheme 74).[60] Subsequent ether-directed, palladium(II)-catalysed aza-Claisen rearrangement would allow an investigation into whether the Thorpe-Ingold effect can force the two oxygen atoms together for a more effective directing effect.[75]



Scheme 74: Proposed synthesis of 1-methyl-1-methoxyethyl ether substrate **198**.

2.3 Application of Ether-directed, Pd(II)-catalysed aza-Claisen Rearrangement in Natural Product Synthesis.

Having developed an ether-directed, Pd(II)-catalysed aza-Claisen rearrangement it was decided to investigate the versatility of this reaction for the general synthesis of chiral allylic amides. The aim was to then utilise these compounds for the stereoselective synthesis of biologically important β-hydroxy-α-amino acids and alkaloids.

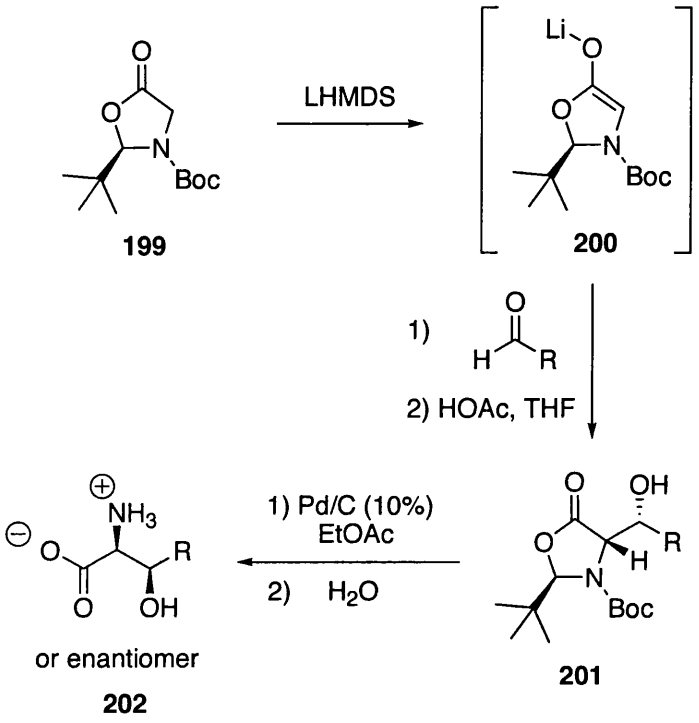
2.3.1 β-Hydroxy-α-amino acids.

β-Hydroxy-α-amino acids are an important class of molecules. They are defined as α-amino acids that contain a hydroxy group in the β-postion of the side chain. Not only are they classed as natural products in their own right, they are also found as constituents of more complex natural products and other biological and medicinally important molecules.[76] For example, β-hydroxytyrosine and β-hydroxyphenylalanine moieties are found in medicinally important glycopeptide antibiotics, such as vancomycin,[77] bouvardin,[78] and orienticins.[79] β-Hydroxyleucine is found in lysobactin and MeBmt in cyclosporine.[80] These highly functionalised small molecules have also been used as chiral building blocks for the asymmetric synthesis of β-lactams,[81] β-fluoro α-amino acids[82] and sugars.[83]

As a result of their importance, a number of different methodologies have been employed for the asymmetric synthesis of β-hydroxy-α-amino acids. These include, asymmetric aldol,[84] Sharpless asymmetric epoxidation,[85] Sharpless asymmetric dihydroxylation,[86] Sharpless asymmetric aminohydroxylations,[87] utilisation of chiral auxilaries such as oxazolidinones[80,88] and oxazolidines,[89] cycloaddition of chiral azomethine ylides,[90] enzymatic transformations,[91] stereoselective hydrolysis of aziridine carboxylate esters,[92] sulfonamide mediated asymmetric Strecker reactions,[93] imino [1,2]-Wittig rearrangements of hydroximates[94] and various others.[95] However, the majority of these methods involve the use of chiral auxiliaries or catalysts and involve multiple steps. Although most methods generate at least one of the chiral centres in an enantio-enriched form, few have also been able to generate a diastereoeselective reaction.

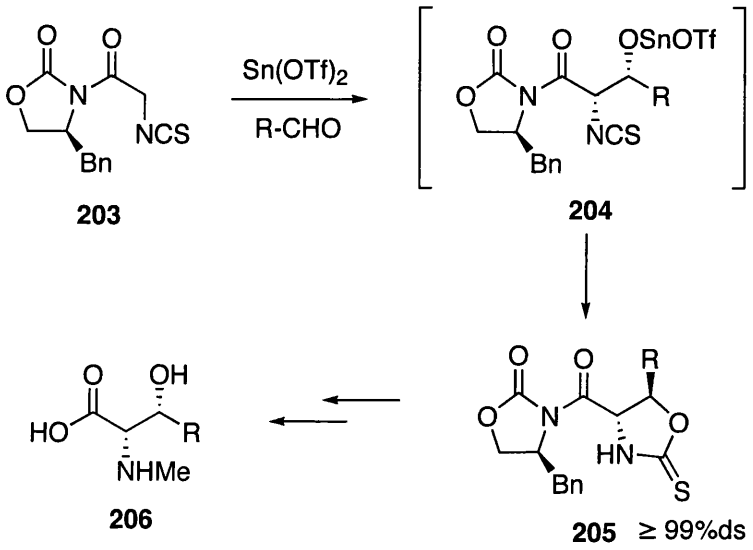
For example, Seebach and Blaser have synthesised a series of β-hydroxy-α-amino acids using a diastereoselective aldol reaction (Scheme 75).[84a] Reaction of oxazolidinone **199** with lithium hexamethyldisilazide (LHMDS) gave the lithium enolate **200** that rapidly undergoes aldol additions to aldehydes. Quenching the reaction with acetic acid gave

compounds **201** in excellent diastereoselectivity (typically >98% d.e.). Subsequent deprotection in ethyl acetate, addition of water and evaporation gave the corresponding β-hydroxy-α-amino acids **202**. However, although both the L and D α-amino acids may be prepared asymmetrically, synthesis of the *anti*-isomers is not possible and so this restricts the scope of this method.



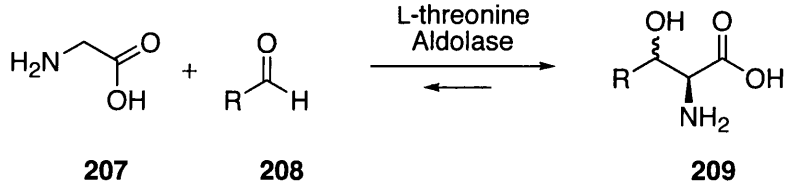
Scheme 75: β-Hydroxy-α-amino synthesis using asymmetric aldol.

Evans and Weber used a chiral auxiliary approach for the synthesis of cyclosporine's unusual β-hydroxy-α-amino, MeBmt **206**.[80] A stannous triflate mediated aldol reaction of compound **203** and a range of aldehydes gave the *syn* aldol product **204** which could be isolated as the oxazolidinthiones **205** in good yield and excellent diastereoselectivity after purification (> 99%) (Scheme 76). Oxazolidinethiones **205** were then converted to the corresponding β-hydroxy-α-amino acids **206** by transesterification, bismethylation and hydrolysis, giving the desired compounds in excellent yield. However, this methodology suffers from having multiple steps in order to reach the desired β-hydroxy-α-amino acids and only the *syn*-isomers may be prepared.



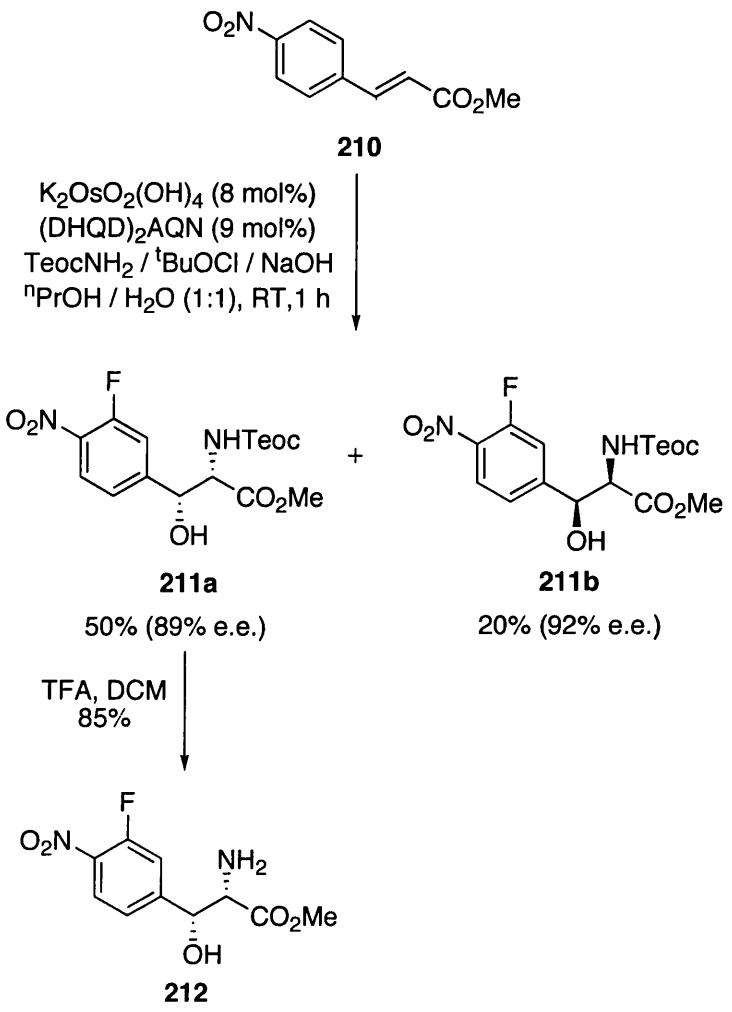
Scheme 76: β-Hydroxy-α-amino acid synthesis using chiral auxiliary approach.

Wong and co-workers have utilised L-threonine aldolase for the preparation of a series of novel β-hydroxy-α-amino acids.[91] Enzymatic aldol reaction of a series of aldehydes **208** with glycine **207** was achieved producing a range of L-α-amino acids **209** (Scheme 77). However, the new chiral center at the β-position was not generated stereoselectively in these reactions.



Scheme 77: β-Hydroxy-α-amino acid synthesis using an enzymatic aldol reaction.

Joullie and co-workers have utilised a regio- and diastereoselective asymmetric Sharpless aminohydroxylation strategy for the synthesis of a β-hydroxyphenylalanine derivative (Scheme 78).[87a] The 2-amino-3-hydroxyl functionality was inserted into α,β-unsaturated ester **210** using a Sharpless asymmetric aminohydroxylation to give regioisomers **211a** and **211b** in a 7:3 ratio and excellent enantioselectivity. Deprotection of isomer **211a** using trifluoroacetic acid (TFA) gave the desired β-hydroxy-α-amino acid **212** in 85% yield. Unfortunately, the aminohydroxylation reaction is highly substrate dependent and only the *syn*-isomers may be prepared using this methodology.



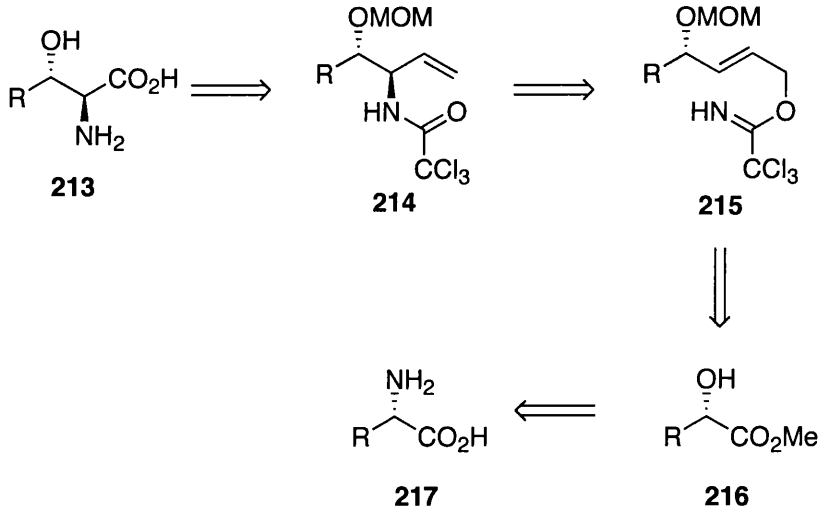
Scheme 78: β-Hydroxy-α-amino acid synthesis using Sharpless asymmetric aminohydroxylation.

In conclusion, β-hydroxy-α-amino acids are an important class of molecules. They are found as constituents of complex natural products and other biological and medicinally important compounds. As such, a variety of different methods have been developed for the synthesis of β-hydroxy-α-amino acids. However, a short synthesis that is regioselective, diastereoselective and can produce both *syn* and *anti* isomers of β-hydroxy-α-amino acids is still desired. Therefore, this is likely to be the subject of further research in this area.

2.3.2 Retrosynthetic Analysis of β-hydroxy-α-amino acids.

Since the products of the ether-directed, palladium(II)-catalysed rearrangement are protected 1,2-aminoalcohols, conversion to β-hydroxy-α-amino acids can easily be envisaged.

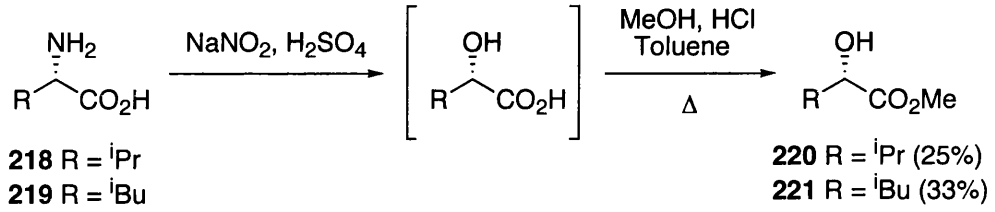
The proposed retrosynthetic analysis of β-hydroxy-α-amino acids **213** is shown in Scheme 79. Retrosynthesis of the β-hydroxy-α-amino acids **213** would lead back to the allylic trichloroacetamide **214** through oxidation of the alkene and deprotection of both the MOM-ether and trichloroacetamide groups. The C-3 chiral centre could then be generated asymmetrically by the ether-directed, palladium(II)-catalysed aza-Claisen rearrangement of allylic trichloroacetimidates **215**. These allylic trichloroacetimidates **215** would be prepared from α-hydroxy esters **216** using the previously described general route to these compounds (Scheme 59). Further retrosynthesis would lead back to the commercially available α-amino acids **217**. Not only would this constitute a new synthesis of these biologically important molecules, it would also allow the absolute stereochemistry of the rearrangement products to be confirmed.



Scheme 79: Retrosynthetic analysis of β-hydroxy-α-amino acids.

2.3.3 Synthesis of β-hydroxy-α-amino acids.

α-Hydroxy esters that could be taken through the general route to form the trichloroacetimidate substrates for the rearrangement reaction were prepared. Commercially available α-amino acids, L-valine **218** and L-leucine **219** were converted to α-hydroxy esters **220** and **221** through initial formation of the diazonium salts, intramolecular displacement by hydrolysis under aqueous conditions followed by esterification using hydrochloric acid and methanol (Scheme 80).[96] Carried out on a large scale this procedure gave sufficient quantities of product to complete the synthesis of the allylic trichloroacetimidates.

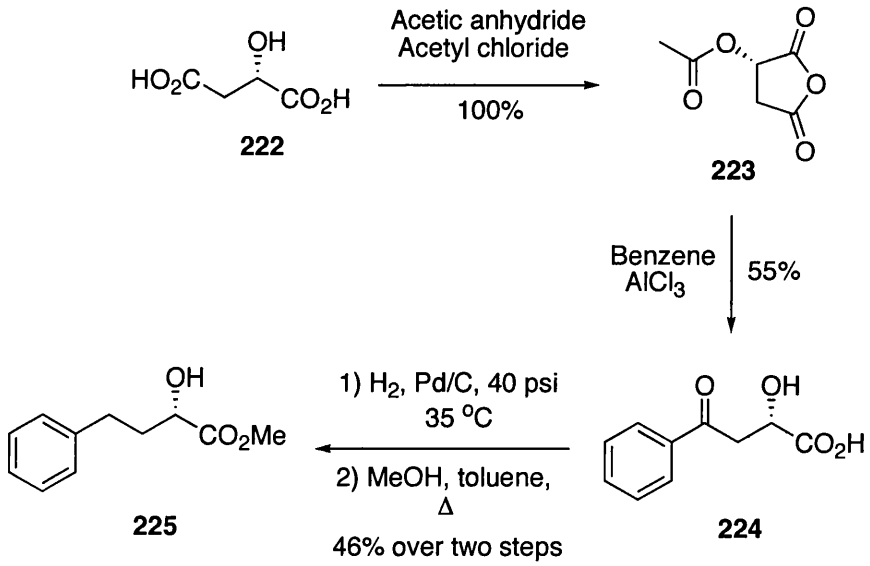


218 R = ^{i}Pr
219 R = ^{i}Bu

220 R = ^{i}Pr (25%)
221 R = ^{i}Bu (33%)

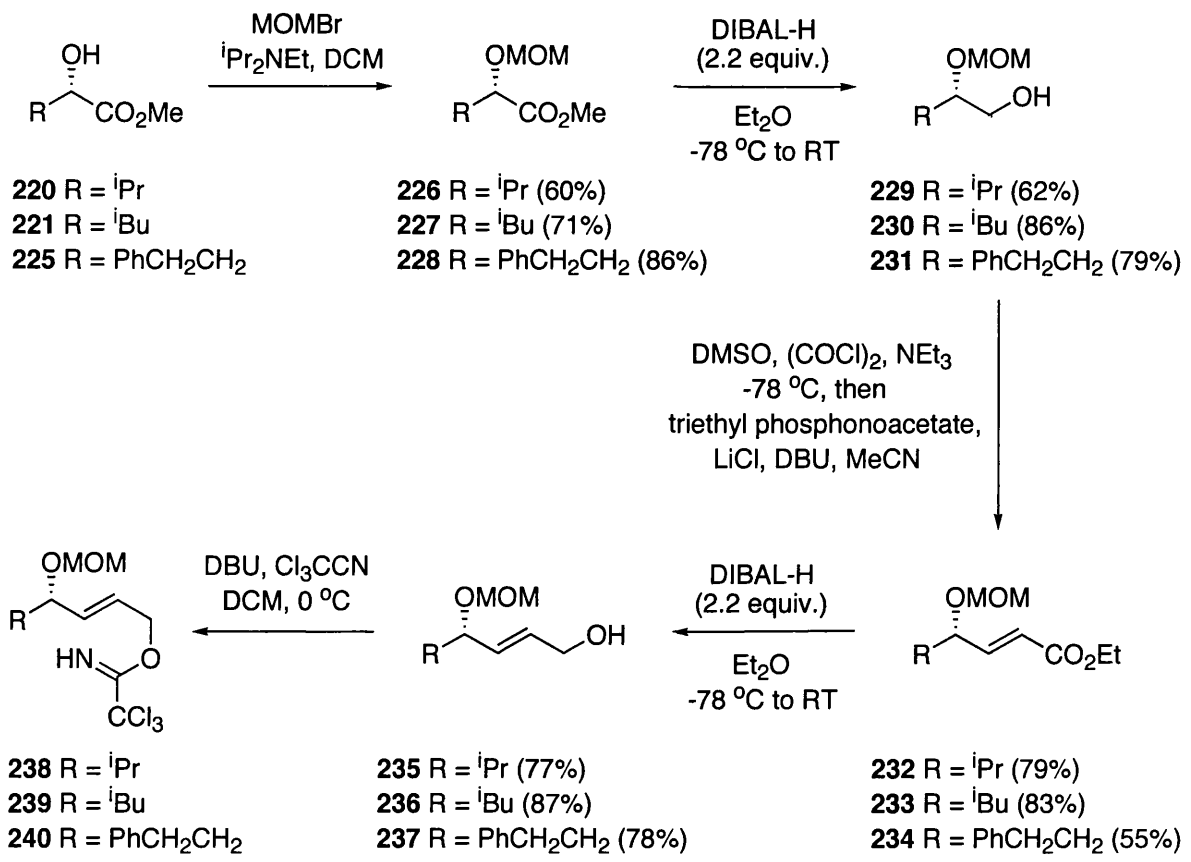
Scheme 80: Synthesis of α-hydroxy esters.

α-Hydroxy ester **225** was prepared from L-malic acid **222** in 25% yield over four steps as described by Mi and co-workers (Scheme 81).[97] Reaction of acetic anhydride, acetyl chloride and L-malic acid **222** gave (2*S*)-acetoxysuccinic anhydride **223** in quantitative yield. Friedel Crafts acylation gave α-hydroxy-carboxylic acid **224** with the desired 2*S* configuration. Hydrogenolysis of the benzyl ketone **224** and esterification of the carboxylic acid using hydrochloric acid and methanol gave (2*S*)-hydroxy ester **225** in 46% yield over the two steps.



Scheme 81: Synthesis of phenyl α-hydroxy ester.

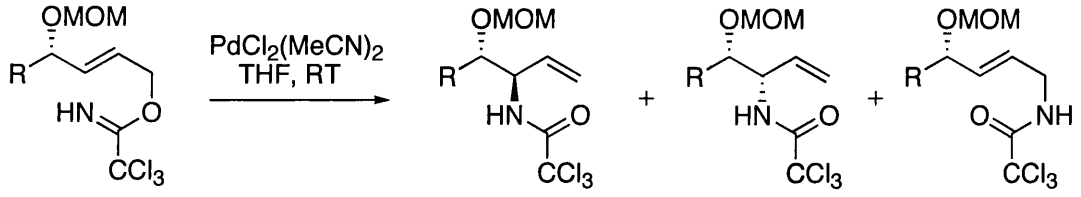
With the three α-hydroxy esters in hand, synthesis of the trichloroacetimidates **238-240** was achieved using the route described in scheme 82. MOM protection of α-hydroxy esters **220**, **221** and **225** was achieved using bromomethyl methyl ether and Hünig's base.[60] Previous reported examples of this protection were carried out using the Williamson methodology,[60] however this reaction uses less toxic reagents and gives higher yield. Protection of this alcohol was also attempted using methodology described by Gras *et al* using dimethoxymethane, lithium bromide and p-toluenesulfonic acid.[98] However, by varying the reaction conditions and equivalents of reagents no higher than 50% conversion was observed. The MOM protected α-hydroxy esters **226-228** were then reduced using 2.2 equivalents of DIBAL-H to give the corresponding alcohols **229-231** in good yields.[61] These were then converted to *E*-allylic esters **232-234** using a one-pot, Swern oxidation-HWE reaction.[63] Reduction, again using 2.2 equivalents of DIBAL-H gave allylic alcohols **235-237**. Finally, treatment with DBU and trichloroacetonitrile provided allylic trichloroacetimidates **238-240**, the substrates required for the directed aza-Claisen rearrangement.[57]



Scheme 82: Synthesis of amino acid derived trichloroacetimidates.

The aza-Claisen rearrangement of *E*-allylic trichloroacetimidates **238-240** was carried out at room temperature using bis(acetonitrile)palladium(II) chloride as catalyst (Table 9).[59]

Table 9: Rearrangement of amino acid derived trichloroacetimidates.



Entry	R group	Yield[a] (%)	Ratio[b] (**a** : **b** : **c**)
1	iPr (**241**)	58%	0 : 1 : 2
2	iBu (**242**)	60%	14 : 1 : 1
3	$PhCH_2CH_2$ (**243**)	65%	9 : 1 : 4

[a] Isolated combined yields of **a** and **b** from *E*-allylic alcohols.
[b] Ratio in crude reaction mixture.

As reported above, rearrangement of substrate **150** (R = Me) gives an excellent 10:1 ratio of diastereomers **157a** and **157b** ([3,3]-Claisen products) in 64% yield. However, the palladium(II)-catalysed rearrangement of allylic trichloroacetimidate **238** requires 48 hours for completion of the reaction and gave allylic trichloroacetamide **241b** and the [1,3]-rearrangement product **241c** (anti-Claisen) as the major products in a ratio of 1:2 respectively. Trace amounts of an elimination by-product were also observed by ^{1}H NMR spectroscopy. Unexpectedly, none of the usual (3*R*,4*S*)-diastereomer **241a** was produced from this rearrangement.

As described in the introduction chapter, the groups of Ikariya and Bosnich have investigated the mechanism of the aza-Claisen rearrangement using different palladium catalysts.[34,27c] Both groups found that palladium(0) complexes catalyse the rearrangement by a non-concerted ionisation mechanism to yield a mixture of [1,3]-product (anti-Claisen) and [3,3]-product (Claisen) (Scheme 28). The isolation of the [1,3]-product has also been reported by Overman and co-workers.[27a]

The relatively slow reaction rate and fomation of both the [1,3]-product and elimination by-product suggests that the ether-directed, palladium(II)-catalysed rearrangement of allylic trichloroacetimidate **238** is suppressed by the steric bulk of the isopropyl group (Figure 16).

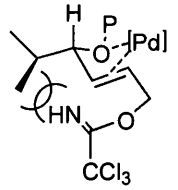
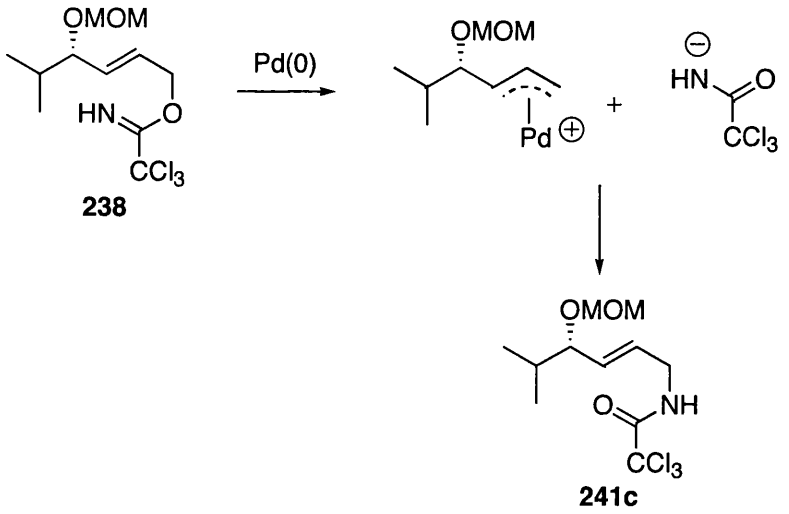


Figure 16: Suppresion of ether-directed, Pd(II)-catalysed rearrangement of allylic trichloroacetimidate.

This steric hinderence will also slow the rate of the pathway to the (3*S*,4*S*)-diastereomer **241b**. This isomer is produced when the palladium(II)-catalyst coordinates to the less sterically hindered front face of the olefin, forcing the imidate nitrogen to the back face of the now activated olefin, thus yielding the *syn*-diastereomer.

According to the work of Ikariya and Bosnich, the major product from this reaction must be produced from a palladium(0)-catalysed [1,3] rearrangement (Scheme 83).[34,27c] It is therefore proposed that trace amounts of a palladium(0) complex is produced *via* a competing β-elimination process during the slow palladium(II)-catalysed rearrangement of allylic trichloroacetimidate **238**. This palladium(0) complex can then very quickly catalyse the [1,3]-rearrangement to give compound **241c** as the major product from this reaction.



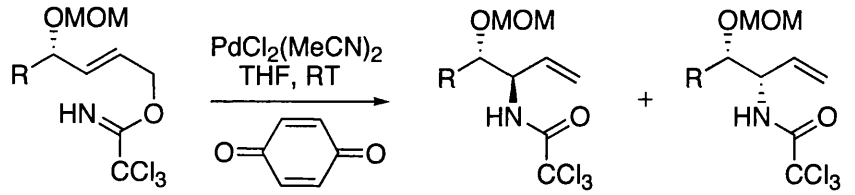
Scheme 83: Pd(0) catalysed allylic substitution reaction.

Fortunately, allylic trichloroacetimidates **239** and **240** underwent the ether-directed, palladium(II)-catalysed aza-Claisen rearrangement to give the desired allylic trichloroacetamides **242a** and **243a** in good yield and excellent diastereoselectivity (>14:1) (Table 9).

Unlike the valine derived substrate **238**, the sterically bulky moiety of the side chains in trichloroacetimidates **239** and **240** is far enough away that the ether-directed rearrangement can take place.

However, notable quantities of the [1,3] rearrangement products were still produced during these rearrangements. These reactions therefore, must be slow enough for trace amounts of palladium(0) to be produced and catalyse the [1,3] rearrangement. Therefore, in an attempt to optimise the yields of these reactions a suitably mild oxidising agent was required which could rapidly re-oxidise palladium(0) to palladium(II) before the [1,3] rearrangement could take place. In the palladium(II)-catalysed oxidation of alkenes, *p*-benzoquinone is used frequently for this purpose.[99,100] Thus, the palladium(II)-catalysed rearrangement of allylic trichloroacetimidates **239** and **240** were repeated in the presence of 2 equivalents of *p*-benzoquinone. Gratifingly, the [3,3]-products were produced with increased yields and again in excellent diastereoselectivity (Table 10).

Table 10: Rearrangements of with *p*-benzoquinone.



Entry	R group	Yield[a] (%)	Ratio[b] (**a** : **b**)
1	^{i}Bu (**242**)	73%	14 : 1
2	$PhCH_2CH_2$ (**243**)	69%	9 : 1

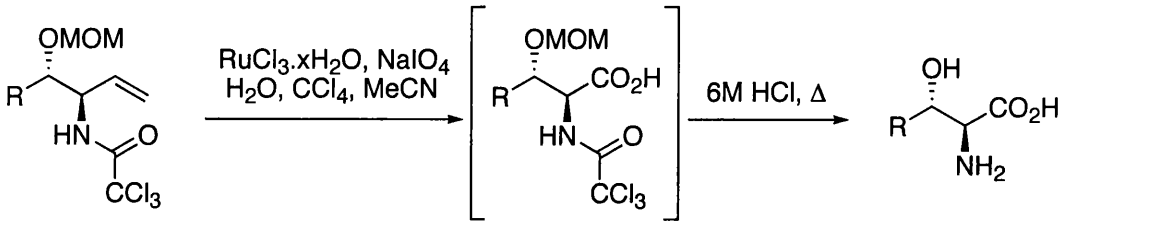
[a] Isolated combined yields of **a** and **b** from *E*-allylic alcohols.
[b] Ratio in crude reaction mixture.

These reactions not only demonstrate that palladium(0) is produced during the palladium(II)-catalysed rearrangement of these substrates, but also that the competing palladium(0)-catalysed [1,3] rearrangement can be suppressed by using *p*-benzoquinone as an additive in the reaction mixture.

The allylic amides produced from the MOM-ether directed, palladium(II)-catalysed aza-Claisen rearrangements were separated by column chromatography and the (3*R*,4*S*)-allylic amides **157a**, **242a** and **243a** were then converted to the corresponding (2*S*,3*S*)-β-hydroxy-α-amino acids **249**, **250** and **252** (Scheme 84). Allylic amide **243a** was prepared and converted to its corresponding (2*S*,3*S*)-β-hydroxy-α-amino acid **251** by a co-worker in the Sutherland group, Kate Fanning.[101] Initially oxidation of the allylic carbon-carbon double bonds was attempted by ozonolysis,[59] however this reaction failed to yield the desired products. Successful oxidation was carried out according to the Sharpless protocol using catalytic ruthenium(III) trichloride hydrate and sodium metaperiodate.[102] The carboxylic acids **245-248** were then heated under reflux in 6 M hydrochloric acid resulting in deprotection of both the MOM and trichloroacetamide protecting groups. The resulting β-hydroxy-α-amino acids **249-252** were purified by ion exchange chromatography giving the desired compounds in 48-67% yield over the two steps.[59]

The (2*S*,3*S*)-β-hydroxy-α-amino acids gave spectroscopic data which was consistent with literature reports.[103,104] The absolute stereochemistry of the major diastereomers produced from the ether-directed, palladium(II)-catalysed rearrangement could therefore be assigned as the (3*R*,4*S*)-diastereomers. This is therefore in agreement with previous stereochemical

assignment of the rearrangement products using NOE experiments on oxazolidin-2-one derivatives.



157a R = Me
242a R = ^{i}Bu
244a R = $PhCH_2$
243a R = $PhCH_2CH_2$

245 R = Me
246 R = ^{i}Bu
247 R = $PhCH_2$
248 R = $PhCH_2CH_2$

249 R = Me (67%)
250 R = ^{i}Bu (48%)
251 R = $PhCH_2$ (55%)
252 R = $PhCH_2CH_2$ (48%)

Scheme 84: Synthesis of β-hydroxy-α-amino acids.

In summary, a novel asymmetric synthesis of β-hydroxy-α-amino acids has been achieved. These molecules are natural products and are also found as constituents of both drugs and more complex natural products. They are therefore an important class of compounds due to their interesting biological properties. The key step in the synthesis is an ether-directed, palladium(II)-catalysed aza-Claisen rearrangement which occurs with excellent levels of diastereoselectivity (≥ 14:1). A limitation on the scope of this reaction was observed with the failed rearrangement of a valine derived substrate. The steric bulk of the isopropyl group hindering this ether-directed, palladium(II)-catalysed pathway. A competing [1,3]-rearrangement reaction catalysed *via* a palladium(0) pathway was suppressed using *p*-benzoquinone to re-oxidise palladium(0) back to palladium(II) thus resulting in higher yields for some substrates. Subsequent oxidation and deprotection of the rearrangement products completed this novel synthesis of the β-hydroxy-α-amino acids.

A limitation on the preparation of β-hydroxy-α-amino acids by this method is that only the *anti*-isomers may be synthesised. However, previous reported syntheses of β-hydroxy-α-amino acids have, in general, been for the *syn*-isomers and so this method complements previous reported methods for the synthesis of these natural products.

2.3.4 Piperidine Alkaloids and α-Conhydrine.

Alkaloids are one of the most important classes of natural products. These are compounds that are synthesised by secondary metabolism in living organisms. Piperidine alkaloids are one of the most common groups of alkaloids, thus one of the most frequently occuring structural motifs found in nature is the piperidine ring.[105] These structural building blocks have also been extensively utilised in the development of pharmacologically active agents.[105] For example, several alkaloids containing a 2-(1-hydroxyalkyl)piperidine moiety have been shown to exhibit potent glycosidase inhibitor, antiviral and antitumor properties.[106] Two such piperidine alkaloids are (+)-α-conhydrine **253** and (-)-β-conhydrine **254** (Figure 17). These natural products are found in the seeds and leaves of the poisonous Hemlock plant, *Conium maculatum* L.[107]

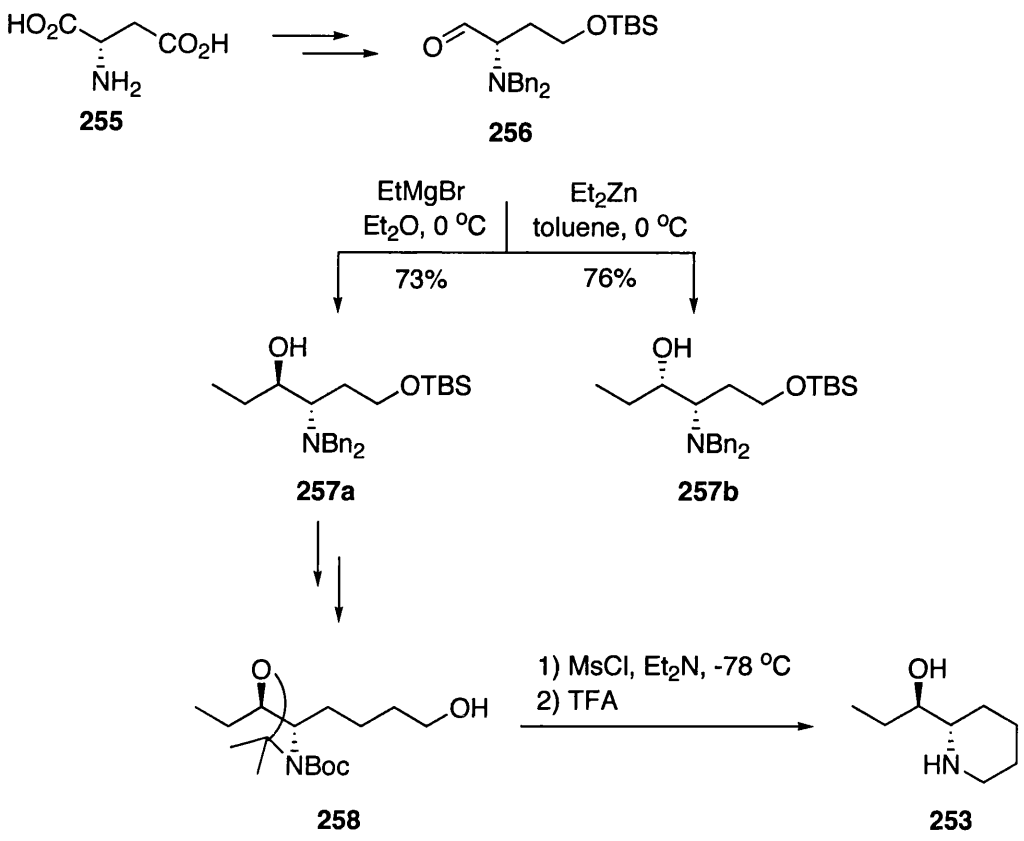
(+)-α-Conhydrine **253**

(-)-β-Conhydrine **254**

Figure 17: Piperidine alkaloids (+)-α-conhydrine and (-)-β-conhydrine.

The biological and medicinal importance of these compounds has lead to a variety of synthetic methods being developed for their preparation and are mainly based on auxiliary-supported or chiral pool strategies.[108,109]

For example, Kumar and co-workers reported a stereoselective synthesis of (+)-α-conhydrine and (-)-β-conhydrine from L-aspartic acid (Scheme 85).[109a] Amino aldehyde **256** was prepared from L-aspartic acid **255** using literature procedures.[110] Diastereoselective alkylation of amino aldehyde **256** was then achieved using ethylmagnesium bromide to yield *anti*-diastereomer **257a**. On the other hand, the *syn*-diastereomer **257b** was prepared as a single isomer by reaction of amino aldehyde **256** with diethylzinc. Subsequent protecting group manipulation, chain extension and reduction gave alcohol **258**. Finally, cyclisation using methanesulfonyl chloride and triethylamine followed by Boc deprotection completed the synthesis of (+)-α-conhydrine **253**. (-)-β-conhydrine **254** was synthesised following the same route using the *syn*-diastereomer **257b**.

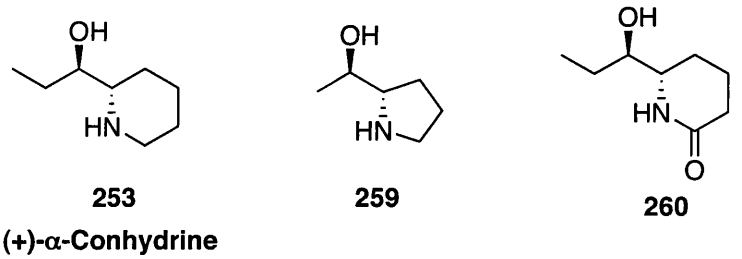


Scheme 85: Kumar and co-worker's synthesis of (+)-α-conhydrine.

This therefore constituents a practical and stereocontrolled synthesis of both (+)-α-conhydrine and (-)-β-conhydrine. Nevertheless, new stereoselective routes that can also be utilised to synthesise analogues of this important structural motif are still required.

2.3.5 Retrosynthetic Analysis of α-Conhydrine.

Having developed an ether directed, Pd(II)-catalysed aza-Claisen rearrangement and used it as the key step in a novel synthesis of β-hydroxy-α-amino acids, it was proposed that this chemistry could be used for the asymmetric synthesis of a series of nitrogen containing heterocycles including the piperidine alkaloid natural product (+)-α-conhydrine **253** (Figure 18).



253
(+)-α-Conhydrine

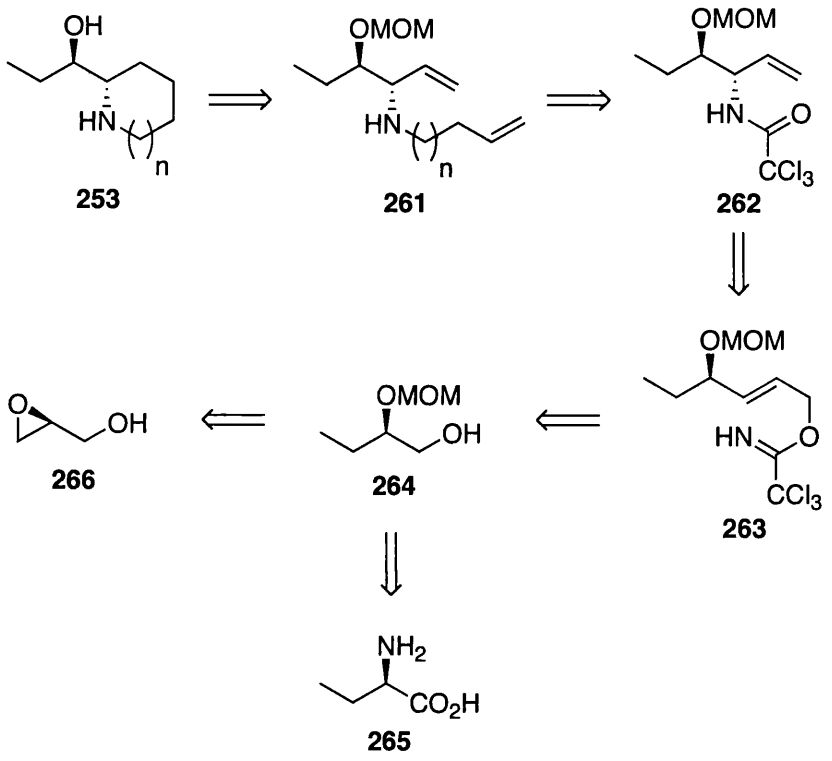
259

260

Figure 18: Target alkaloid compounds.

The proposed retrosynthetic analysis of the piperidine alkaloid (+)-α-conhydrine **253** is shown in Scheme 86. Retrosynthesis of (+)-α-conhydrine **253** would lead back to allylic amine **261** *via* a ring closing metathesis (RCM) reaction. Trichloroacetamides **262** could be deprotected to the secondary amine and alkylated to give allylic amines **261**. Derivatisation could be envisaged at this step by alkylation using different alkyl chains. The C-3 chiral centre could then be generated asymmetrically by the ether-directed, palladium(II)-catalysed aza-Claisen rearrangement of allyic trichloroacetimidate **263**. The allyic trichloroacetimidate **263** could be prepared from alcohol **264** using the previously described general route to these compounds (Scheme 59). Further retrosynthesis would lead back to either the commercially available α-amino acid **265** or (*S*)-glycidol **266**. However, previous studies revealed that the preparation of compounds similar to alcohol **264** from α-amino acids are low yielding and so the synthetic route from (*S*)-glycidol **266** was chosen for this investigation.

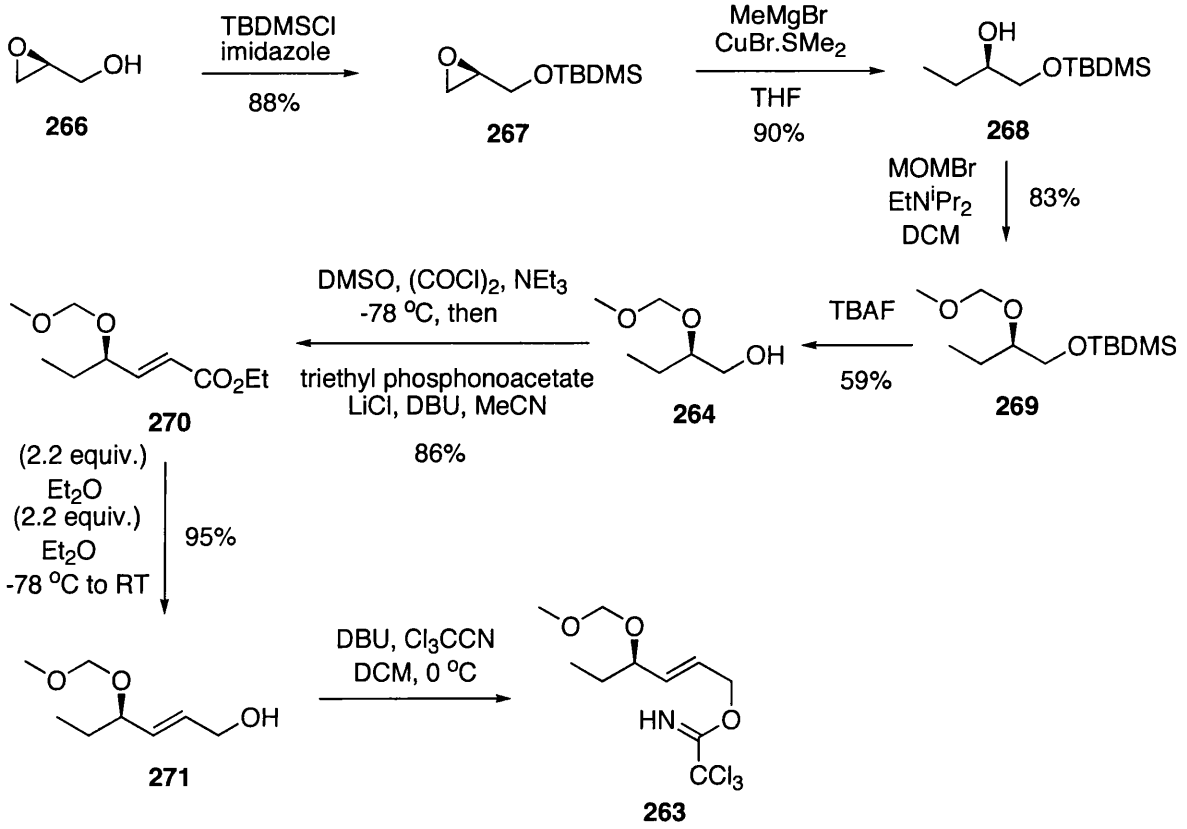
The key steps in this synthesis was therefore an ether-directed, palladium catalysed aza-Claisen rearrangement reation to generate a new chiral centre and a RCM reaction to form the piperidine ring moiety. Not only would this constitute a new synthesis of this biologically important molecule, it would also allow for the synthesis of a series of analogues of (+)-α-conhydrine to be prepared.



Scheme 86: Retrosynthetic analysis of the piperidine alkaloid (+)-α-conhydrine **253**.

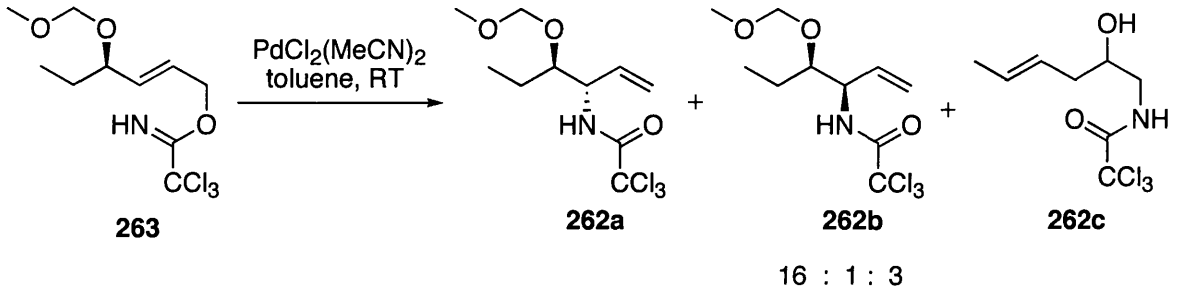
2.3.6 Synthesis of α-Conhydrine and Other Nitrogen Containing Heterocyclic Analogues.

The substrate for the directed rearrangement reaction, trichloroacetimidate **263** was prepared from (*S*)-glycidol **266** (Scheme 87). Silyl protection of (*S*)-glycidol **266** gave epoxide **267** which was reacted with methylmagnesium bromide and copper(I) bromide-dimethyl sulfide complex resulting in a regioselective copper Grignard epoxide ring-opening reaction giving alcohol **268**, with the desired 2*R* stereocentre.[111] The copper Grignard reagent preferentially attacks the least hindered carbon of the epoxide and so the C-2 methyl isomer was not observed by ^{1}H NMR spectroscopy. Protection of the alcohol moiety using bromomethyl methyl ether and Hünig's base gave MOM-ether **269** in 83% yield.[60] The silyl protecting group was removed using TBAF to give alcohol **264** in 59% yield.[60] A one-pot Swern oxidation-HWE reaction gave (*E*)-α,β-unsaturated ester **270** in 86% yield.[63] Reduction of the ester functional group with 2.2 equivalents of DIBAL-H then gave allylic alcohol **271**.[61] Finally, trichloroacetimidate **263** was prepared using trichloroacetonitrile and DBU.[57]



Scheme 87: Synthesis of (*S*)-glycidol derived trichloroacetimidate.

Rearrangement of allylic trichloroacetimidate **263** was carried out at room temperature using the optimised conditions of bis(acetonitrile)palladium(II) chloride catalyst in toluene (Scheme 88). Trichloroacetamides **262a** and **262b** were produced in an excellent 16:1 ratio and in 54% yield from the allylic alcohol **271**. However, significant amounts (15% yield) of impurity **262c** were produced during the reaction.



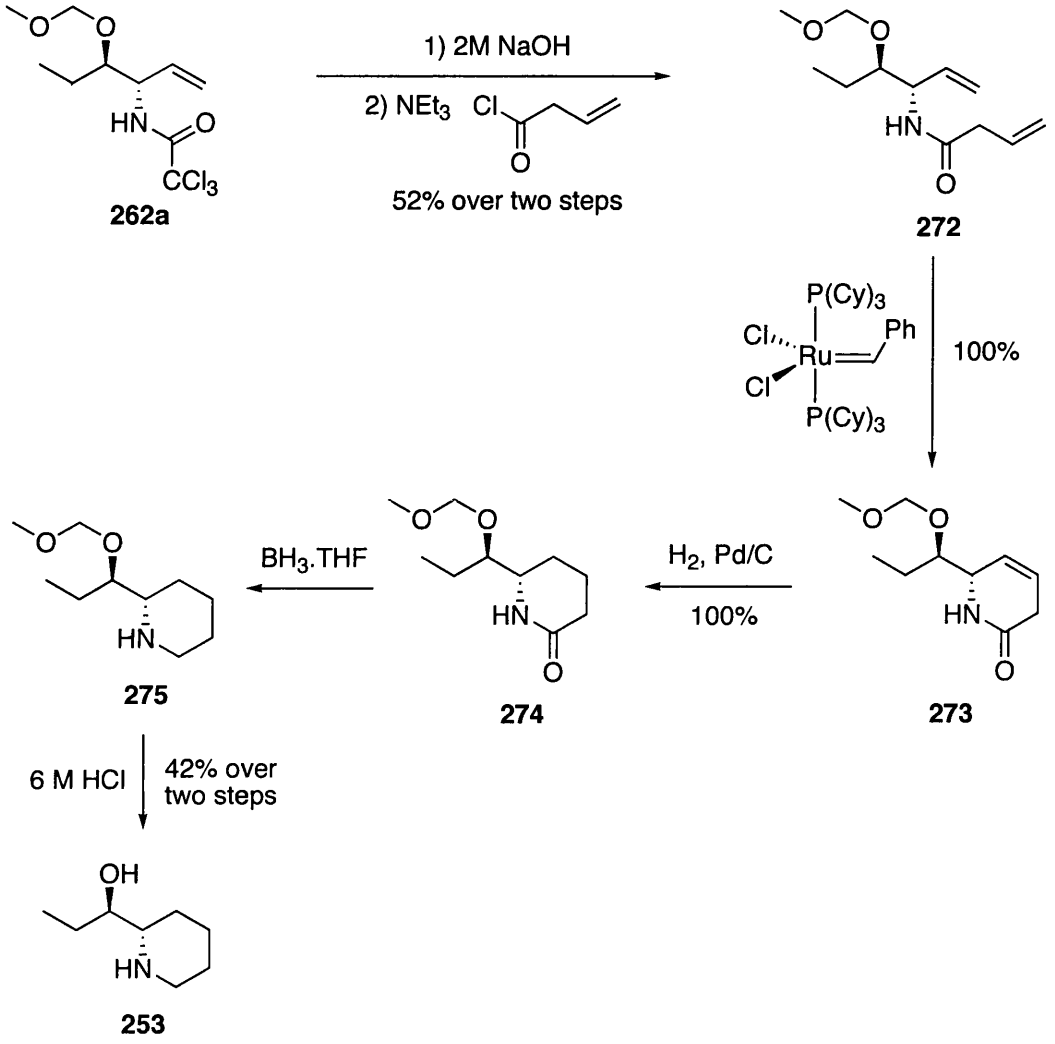
Scheme 88: Rearrangement of (*S*)-glycidol derived trichloroacetimidate.

Trichloroacetimidates **242** and **243** could be rearranged with the suppression of the 1,3 (anti-Claisen) rearrangement by addition of *p*-benzoquinone. This additive was able to reoxidise palladium(0), produced during the reaction, back to palladium(II). However, the addition of *p*-benzoquinone did not suppress the formation of this impurity. This suggests that this impurity, produced by an unknown elimination pathway does not involve palladium(0).

The products of the rearrangement were separated by column chromatography and trichloroacetamide **262a** was used to complete the synthesis of α-conhydrine **253** (Scheme 89).

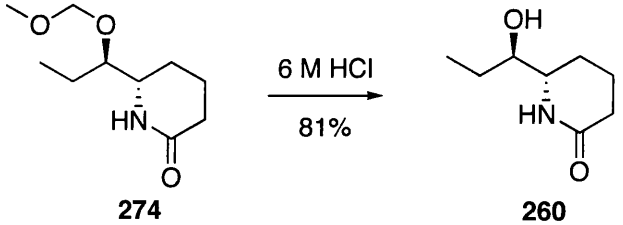
Hydrolysis of the trichloroamide functional group using cesium carbonate in DMF was attempted,[112] however optimal yields were achieved using sodium hydroxide. Initially, attempts were made to alkylate the resulting amine using 4-bromobutene, however none of the desired product was produced. Further attempts were then made using the triflate derivative of 3-buten-1-ol. Even under various conditions, successful alkylation of this amine could not be achieved. The synthetic strategy was therefore modified and acylation of the amine was attempted. This change in strategy was deemed acceptable because it would allow for a further derivative of α-conhydrine to be prepared (discussed later). Acylation was successfully achieved *via* hydrolysis of the trichloroacetamide functional group using 2 M sodium hydroxide solution to give the secondary amine that was subsequently coupled to 3-butenoyl chloride using triethylamine as base to give amide **272** in 52% yield over two steps (Scheme 89). Ring closing metathesis using Grubbs' first generation catalyst gave unsaturated lactam **273** in quantitative yield.[113] Hydrogenation

under standard conditions gave lactam **274**. Finally, reduction of the amide functional group using boron-THF complex,[114] followed by deprotection under acidic conditions completed the synthesis of (+)-α-conhydrine **253**.



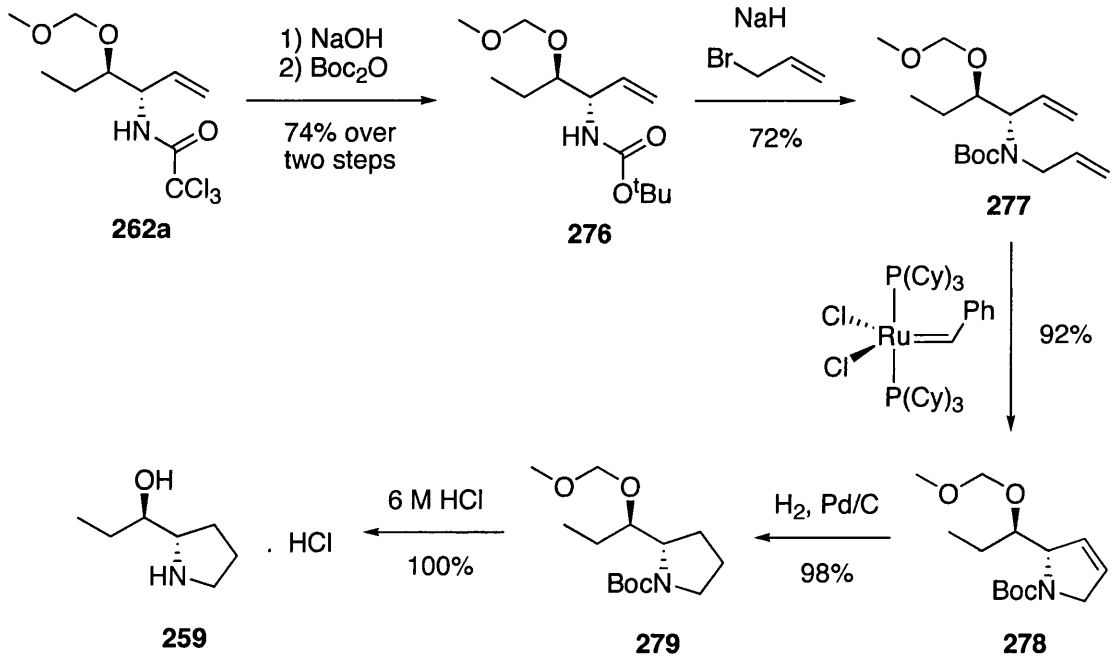
Scheme 89: Synthesis of (+)-α-conhydrine **253**.

This alternative synthesis of (+)-α-conhydrine *via* δ-lactam **274** allowed for the synthesis of a new analogue. Thus, the removal of the MOM-group of δ-lactam **274** gave δ-lactam **260** (Scheme 90).



Scheme 90: Synthesis of δ-lactam analogue of (+)-α-conhydrine.

The pyrrolidine analogue of α-conhydrine was prepared in 6 steps from trichloroacetamide **262a** (Scheme 91). Hydrolysis of the trichloroacetamide functional group, again using sodium hydroxide solution followed by reprotection using di-*tert*-butyl dicarbonate gave carbamate **276** in 74% over two steps. Alkylation was achieved by a procedure developed by Hartley and co-workers in which sodium hydride was added portionwise to a solution of allyl bromide and carbamate **276** in DMF to give **277** in 72% yield.[115] Ring closing metathesis using Grubbs' first generation catalyst then gave dihydropyrrole **278**.[113] Hydrogenation under standard conditions gave pyrrolidine **279** in good yield. Finally, removal of both the Boc- and MOM-protecting groups completed the synthesis of α-hydroxy-pyrrolidine **259**. α-Hydroxy-pyrrolidine **259** was prepared as the hydrochloride salt for ease of purification and handling.

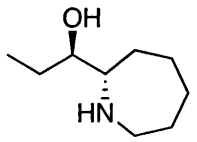


Scheme 91: Synthesis of pyrrolidine analogue of (+)-α-conhydrine.

In summary, the piperidine ring motif is one of the most common structural building blocks found in nature and has been extensively used in the development of pharmacologically active agents. A novel synthesis of the piperidine alkaloid (+)-α-conhydrine, along with two analogues of this compound has been achieved. The key steps in the synthesis of these compounds are an ether-directed, palladium catalysed aza-Claisen rearrangement reation which generated a new stereogenic centre with excellent diastereoselecitvity (16:1) and a RCM reaction which formed the heterocyclic ring.

2.3.7 Future work.

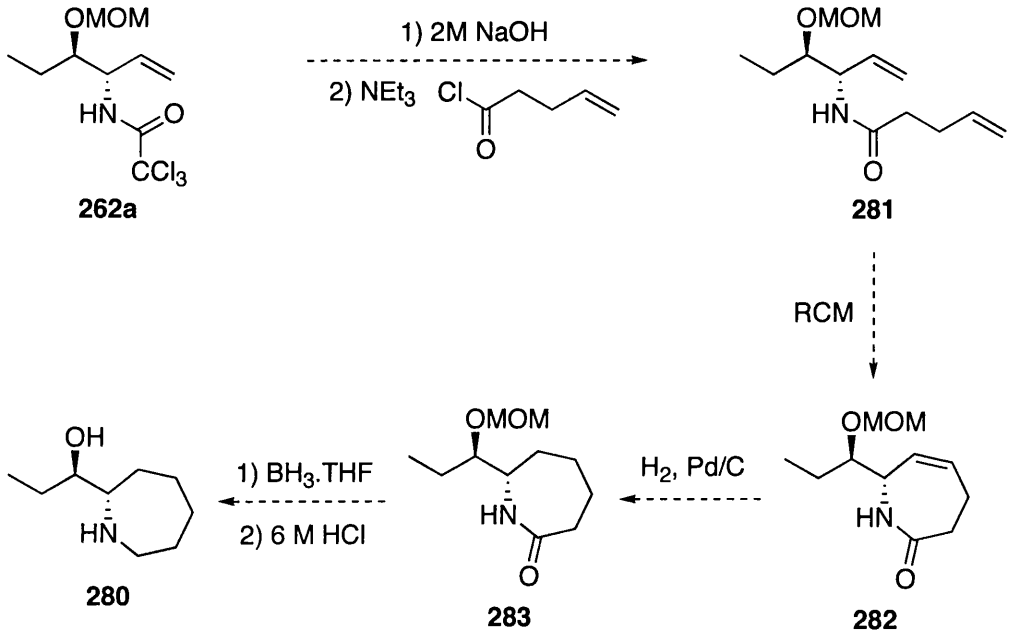
Future work on this project would include the synthesis of a 7-membered ring analogue of α-conhydrine (Figure 19). Pyrrolidine **259**, α-conhydrine **253** and aza-cycloheptane analogue **280** could then be used in a structure-activity-relationship (SAR) study into the biological effect observed with varying ring size in these nitrogen containing heterocycles.



280

Figure 19: Future target compound.

Preparation of aza-cycloheptane analogue of α-conhydrine could be envisaged from trichloroacetamide **262a** (Scheme 92). Acetylation of trichloroacetamide **262a** with 4-pentenoyl chloride would afford amide **281** which would undergo ring closing metathesis using either Grubbs' first or second generation catalysts to give 7-membered lactam **282**.[113] Hydrogenation under standard conditions would give the saturated lactam **283**. Finally, reduction followed by deprotection under acidic conditions would give aza-cycloheptane **280**.[114]



Scheme 92: Proposed synthesis of aza-cycloheptane analogue of α-conhydrine.

Other further future work in this area will be toward the stereoselective synthesis of polyhydroxylated pyrrolidines. This project will investigate a new approach for the synthesis of four polyhydroxylated pyrrolidines (Figure 20). Three of these **284-286** are known compounds and have been shown be potent inhibitors of mannosidases.[116] The fourth compound **287** is a novel polyhydroxylated pyrrolidine.

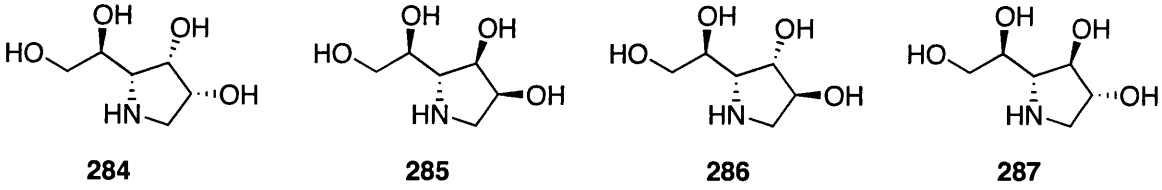
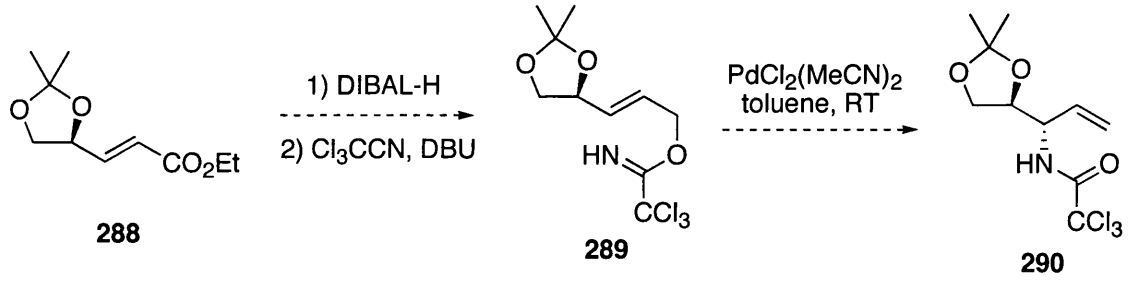


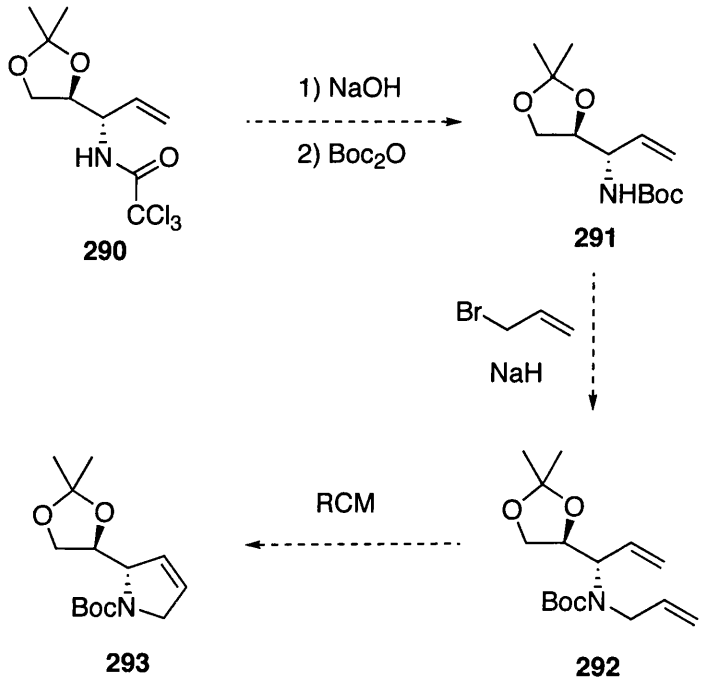
Figure 20: Target polyhydroxylated pyrrolidines.

The synthesis of these compounds will again utilise the ether-directed, palladium(II)-catalysed aza-Claisen rearrangement to generate a new chiral centre and a RCM reaction to prepare the pyrrolidine ring system. The allylic trichloroacetimidate substrate **289** for the rearrangement reaction will be prepared in two steps from known compound **288** by DIBAL-H reduction to give the corresponding allylic alcohol, followed by treatment with DBU and trichloroacetonitrile to give the desired substrate **289** (Scheme 93). Based on our previous studies, allylic trichloroacetimidate **289** will undergo a highly diastereoselective ether-directed, palladium(II)-catalysed aza-Claisen rearrangement to yield predominantly diastereomer **290**.



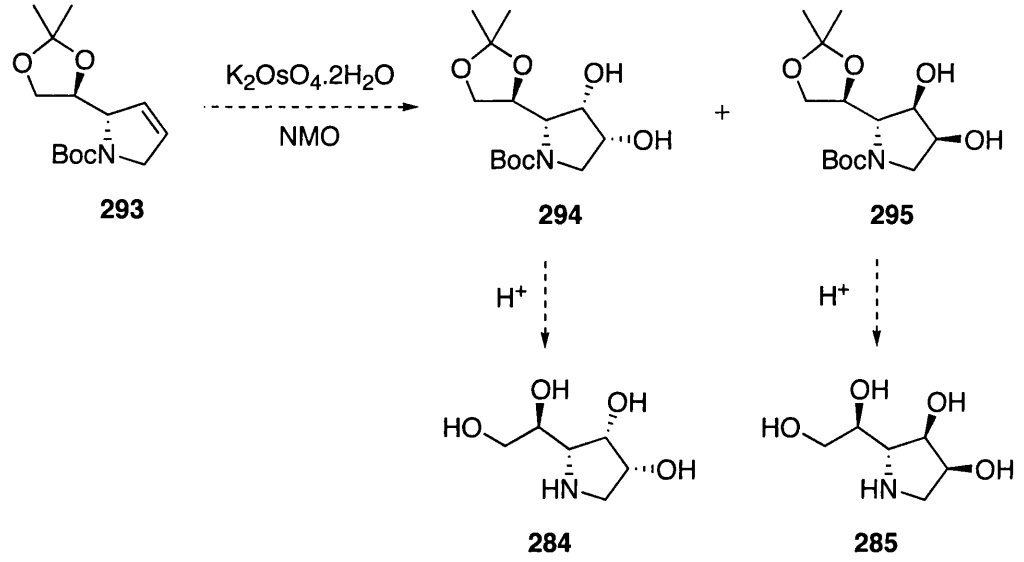
Scheme 93: Proposed synthesis of allylic amide **290**.

The trichloroacetamide group of allylic amide **290** will then be cleaved and the resulting amine reprotected to give the carbamate **291** (Scheme 94). Subsequent alkylation using allyl bromide and sodium hydride would give tertiary amine **292**.[115] A RCM reaction using Grubbs' first generation catalyst will then yield alkene **293**, which is the key intermediate for the synthesis of all four polyhydroxylated pyrrolidines.



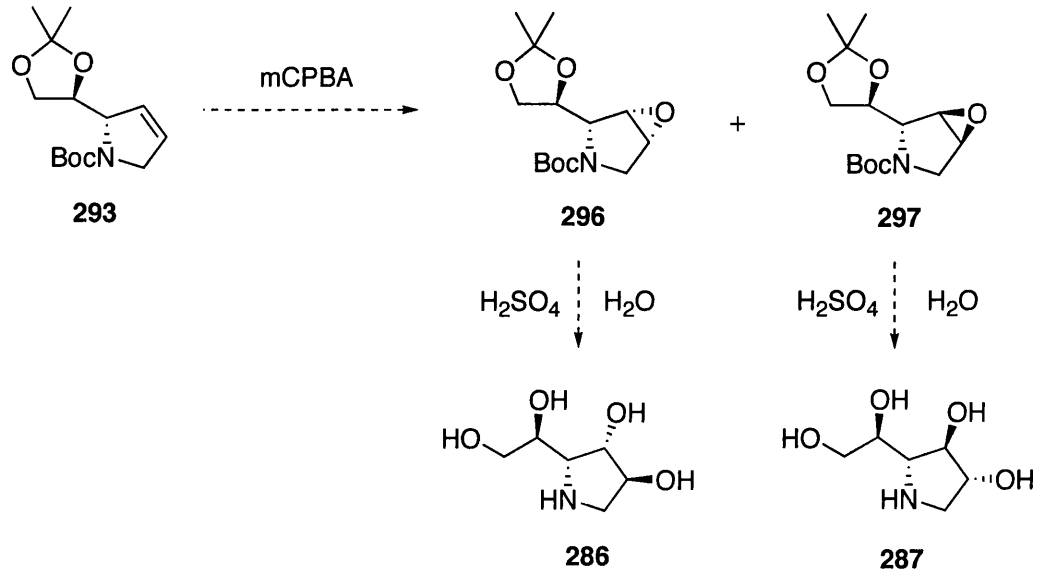
Scheme 94: Proposed synthesis of alkene **293**.

Dihydroxylation of alkene **293** would then yield diols **294** and **295** which would then undergo acid deprotection to complete the synthesis of the two *syn*-diol-pyrrolidine compounds **284** and **285** (Scheme 95).[117]



Scheme 95: Proposed synthesis of *syn*-diol pyrrolidine compounds **284** and **285**.

Similarly, oxidation of alkene **293** using MCBPA would give the corresponding epoxides **297** and **298** (Scheme 96).[118] A one-pot ring opening and deprotection procedure would then complete the synthesis of the two *anti*-diol pyrrolidine compounds **287** and **288**.



Scheme 96: Proposed synthesis of *anti*-diol-pyrrolidine compounds **286** and **287**.

2.4 Conclusions

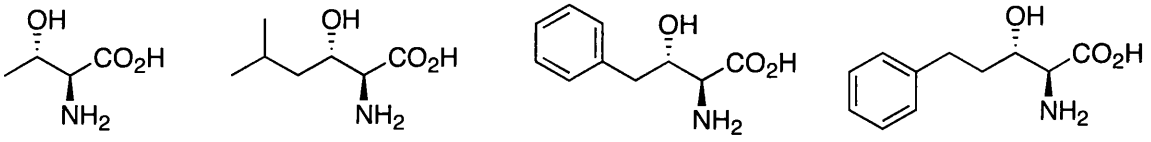
Synthesis and rearrangement of six chiral allylic trichloroacetimidates with various ether protecting groups in the δ-position demonstrated that the oxygen atom in this position can effectively direct facial coordination of the palladium(II)-catalyst during the aza-Claisen rearrangement with the MOM-ether substrate giving the most selective rearrangement reaction (10:1). The relative stereochemistry of the rearrangement products was then determined by a NOE study on oxazolidin-2-ones derived from the TBDMS-ether allylic trichloroacetamides produced from the directed rearrangement reaction.

Following this a range of electrophilic catalysts were screened in an attempt to enhance the stereoselectivity observed in these rearrangements. Bis(acetonitrile)palladium(II) chloride proved to be the best catalyst for this ether-directed, palladium(II)-catalysed aza-Claisen rearrangement on the basis of optimal rate of reaction, ease of purification, high yield and high diastereoselectivity.

Further evidence for the ether-directing effect was then obtained by the rearrangement of a series of chiral δ-substituted allylic trichloroacetimidate analogues of the most selective MOM-ether substrate. These experiments demonstrated that the diastereoselectivity of the reaction is controlled by the directing effect of an oxygen atom in the 5-position and not by steric bulk of substituents on C-4. Furthermore, the oxygen atom in the 7-position of the MOM-ether substrate can also coordinate to the palladium(II)-catalyst and so enhances the directing effect leading to a highly diastereoselective process (Scheme 70).

In order to further investigate the mechanism of this ether-directed rearrangement reaction a range of solvents were screened. An enhancement of stereoselectivity was observed using non-coordinating solvents such as toluene, which can minimise the competition between the solvent and ether group for coordination of the catalyst and also provides further evidence for the directing effect.

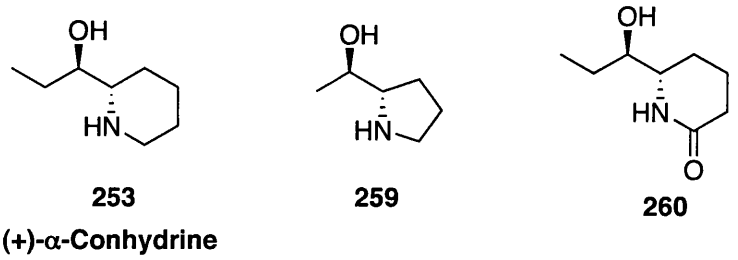
This methodology was then used as the key step in the novel diastereoselective synthesis of β-hydroxy α-amino acids from enantiopure α-hydroxy acids (Figure 21). During the rearrangement step, a competing [1,3] pathway catalysed by palladium(0) was suppressed using *p*-benzoquinone as an additive in the reaction mixture.



249 **250** **251** **252**

Figure 21: Successfully synthesised β-hydroxy α-amino acids.

Finally, a novel synthesis of the piperidine alkaloid (+)-α-conhydrine along with two analogues of this compound has been achieved using the ether-directed, palladium catalysed aza-Claisen rearrangement reaction as a key step in which to generated a new stereogenic centre with excellent diastereoselecitvity (16:1) (Figure 22). A RCM reaction was also used as a key step in this synthesis with which to form the heterocyclic ring moieties.



253
(+)-α-Conhydrine

259

260

Figure 22: Successfully synthesised alkaloid and analogues.

The ether-directed, palladium(II)-catalysed aza-Claisen rearrangement of allylic imidates with chiral heteroatoms in the δ-position is a highly diastereoselective process which occurs through a cyclisation induced mechanism. As such, the reaction is likely to be utilised in the synthesis of other complex natural products and medicinally important molecules.

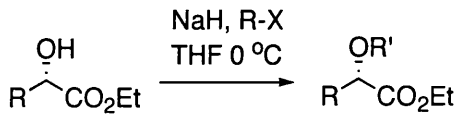
Experimental Data and Characterisation of Compounds

General Experimental

All reactions were performed under a nitrogen atmosphere unless otherwise noted. Reagents and starting materials were obtained from commercial sources and used as received. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium and benzophenone. Dichloromethane (DCM) and toluene are distilled from calcium hydride. Petroleum ether refers to petroleum ether (40-60). Lithium chloride was oven dried (110 °C) for at least 12 h before use. Brine refers to a saturated solution of sodium chloride.
Flash column chromatography was carried out using Fisher Matrex 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 $KMnO_4$.
^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to residual chloroform (δ_H 7.28 & δ_C 77.2) as standard. *J* values are given in Hz. Infrared spectra were recorded using Golden Gate apparatus on a JASCO FTIR 410 spectrometer and mass spectra were obtained using a JEOL JMS-700 spectrometer. 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 $10^{-1}degcm^2g^{-1}$.

1) Development of a synthetic route to six trichloroacetimidates with varying ether protecting groups.

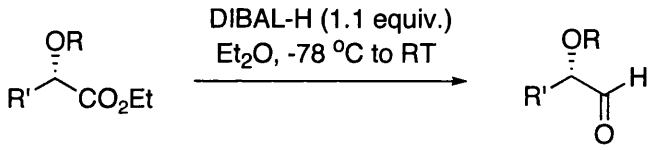
General procedure 1: Williamson ether protection of ethyl (*S*)-lactate.[60]



Sodium Hydride (60% in mineral oil) (1.2 equiv.) was washed with petroleum ether (3 x 3 mL). The grey powder was then suspended in THF and cooled to 0 °C. Ethyl (*S*)-lactate (1 equiv.) was then added dropwise and the solution was allowed to stir for 0.5 h. The alkyl halide (1.4 equiv.) was added and, after 0.75 h, the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was concentrated, acidified with 2 M hydrochloric acid (20 mL) and extracted with ethyl acetate (2 x 40 mL).

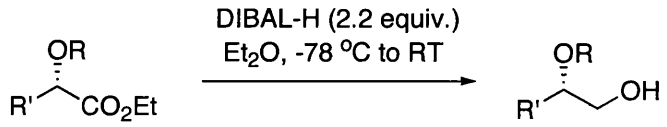
The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography using diethyl ether / petroleum ether as eluent.

General procedure 2a: DIBAL-H reduction to the aldehyde.[61]



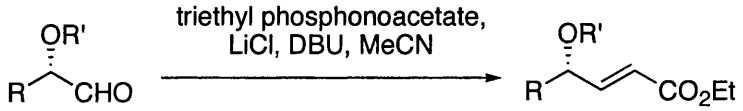
The ester (1.0 equiv.) was dissolved in diethyl ether (30 mL) and cooled to -78 °C. DIBAL-H (1 M in hexane) (1.1 equiv.) was added dropwise and the reaction mixture was allowed to stir at -78 °C for 1 h then for 12 h at room temperature. The reaction mixture was cooled to 0 °C before being quenched by the addition of a saturated solution of ammonium chloride (20 mL), diluted with diethyl ether (30 mL) and warmed to room temperature with vigorous stirring over 1 h, producing a white precipitate. The precipitate was filtered through a pad of Celite® and washed with diethyl ether (3 x 100 mL). The filtrate was then dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography using diethyl ether / petroleum ether as eluent.

General procedure 2b: DIBAL-H reduction to the alcohol.[61]



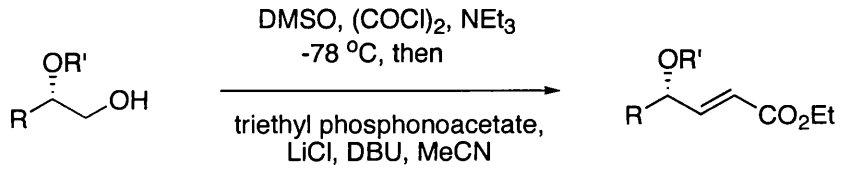
The ester (1.0 equiv.) was dissolved in diethyl ether (30 mL) and cooled to -78 °C. DIBAL-H (1 M in hexane) (2.2 equiv.) was added dropwise and the reaction mixture was allowed to stir at -78 °C for 1 h then overnight at room temperature. The reaction mixture was cooled to 0 °C before being quenched by the addition of a saturated solution of ammonium chloride (20 mL), diluted with diethyl ether (30 mL) and warmed to room temperature with vigorous stirring over 1 h, producing a white precipitate. The precipitate was filtered through a pad of Celite® and washed with diethyl ether (3 x 100 mL). The filtrate was then dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography using diethyl ether / petroleum ether as eluent.

General procedure 3a: Horner-Wadsworth-Emmons reaction.[61]



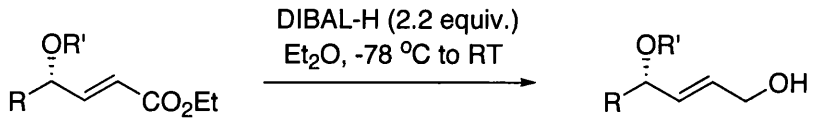
A suspension of lithium chloride (1.5 equiv.), triethyl phosphonoacetate (1.5 equiv.) and 1,8-diazabicyclo(5,4,0)undec-7-ene (1.5 equiv.) in acetonitrile (30 mL) was stirred for 0.5 h before being added to a solution of the aldehyde (1.0 equiv.) in acetonitrile (40 mL) and the reaction mixture was allowed to stir for 2 h at room temperature. The reaction mixture was concentrated *in vacuo*. The resulting residue was dissolved in ethyl acetate (100 mL), washed with water (2 x 70 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography using diethyl ether / petroleum ether as eluent.

General procedure 3b: One-pot Swern-Horner-Wadsworth-Emmons reaction.[62,63]



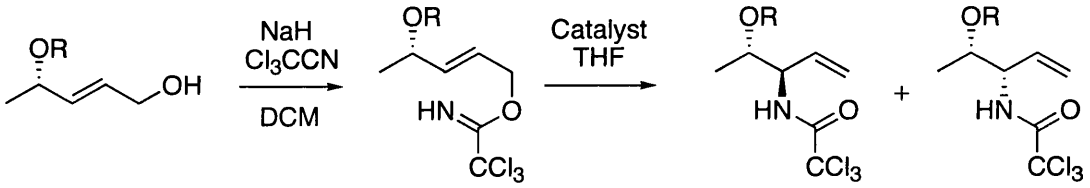
Methyl sulfoxide (2.4 equiv.) was added to a stirred solution of oxalyl chloride (1.2 equiv.) in DCM (20 mL) at -78 °C. This mixture was stirred for 0.25 h before the alcohol (1 equiv.) in DCM (30 mL) was added. The mixture was stirred for a further 0.25 h before triethylamine (5 equiv.) was added. This reaction mixture was then allowed to stir for 2 h. Meanwhile, a solution of lithium chloride (1.5 equiv.), triethyl phosphonoacetate (1.5 equiv.) and 1,8-diazabicyclo[5,4,0]undec-7-ene (1.5 equiv.) in acetonitrile (30 mL) was prepared and stirred for 0.5 h. The ylide mixture was added to the Swern solution and the reaction mixture was allowed to stir at room temperature for 12 h. The reaction was quenched with brine (50 mL) then concentrated to give an orange residue. This residue was extracted with diethyl ether (5 x 50 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated to give an orange liquid. Purification was carried out by flash column chromatography using diethyl ether / petroleum ether as eluent.

General procedure 4: DIBAL-H reduction to allylic alcohol.[61]



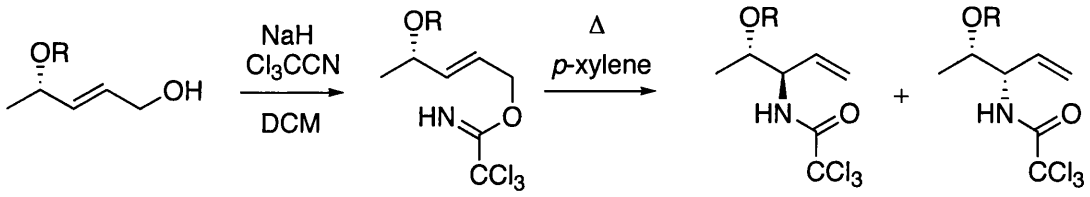
The α,β-unsaturated ester (1.0 equiv.) was dissolved in diethyl ether (20 mL) and cooled to -78 °C. DIBAL-H (1 M in hexane) (2.2 equiv.) was added dropwise and the reaction mixture was allowed to warm to room temperature with stirring for 4 h. The reaction was cooled to 0 °C before being quenched by the addition of a saturated solution of ammonium chloride (20 mL), diluted with diethyl ether (30 mL) and warmed to room temperature with vigorous stirring over 1 h producing a white precipitate. The precipitate was filtered through a pad of Celite® and washed with diethyl ether (3 x 100 mL). The filtrate was then dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography eluting with diethyl ether / petroleum ether.

General procedure 5: Allylic trichloroacetimidate synthesis using NaH and subsequent metal catalysed rearrangement.[64]



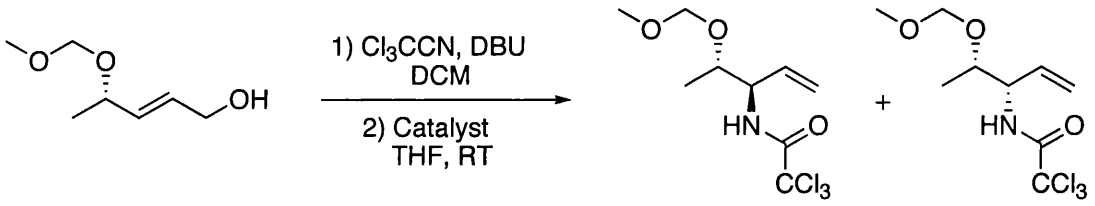
Sodium hydride (60% in mineral oil) (1.2 equiv.) was washed with petroleum ether (40-60) (3 x 3 mL), suspended in THF (20 mL) and cooled to 0 °C. A solution of the allylic alcohol (1.0 equiv.) in THF (6 mL) was then added slowly. After 0.5 h trichloroacetonitrile (1.2 equiv.) was added causing the formation of a light yellow colour. After 1 h the reaction mixture was warmed to room temperature and filtered through a short pad of aluminium oxide (neutral). This was washed with diethyl ether (20 mL) and the combined filtrate was concentrated *in vacuo* to give the desired allylic trichloroacetimidate, which was used without further purification. The allylic trichloroacetimidate was dissolved in THF (10 mL). Catalyst (10 mol%) was then added and the reaction mixture stirred for 24-48 h. Concentration *in vacuo* followed by purification by flash column chromatography eluting with diethyl ether / petroleum ether gave all products as brown oils.

General procedure 6: Allylic trichloroacetimidate synthesis and subsequent thermal rearrangement.[59]



Sodium hydride (60% in mineral oil) (1.2 equiv.) was washed with petroleum ether (40-60) (3 x 3 mL), suspended in THF (20 mL) and cooled to 0 °C. A solution of the allylic alcohol (1.0 equiv.) in THF (6 mL) was then added slowly. After 0.5 h trichloroacetonitrile (1.2 equiv.) was added causing the formation of a light yellow colour. After 1 h the reaction mixture was warmed to room temperature and filtered through a short pad of aluminium oxide (neutral). This was washed with diethyl ether (20 mL) and the combined filtrate was concentrated *in vacuo* to give the desired allylic trichloroacetimidate, which was used without further purification. The crude trichloroacetimidate was dissolved in *p*-xylene (20 mL) and heated to 140 °C for 24 h. The reaction mixture was concentrated *in vacuo* to give a brown oil. Purification by chromatography eluting with diethyl ether / petroleum ether gave the target compounds as brown oils.

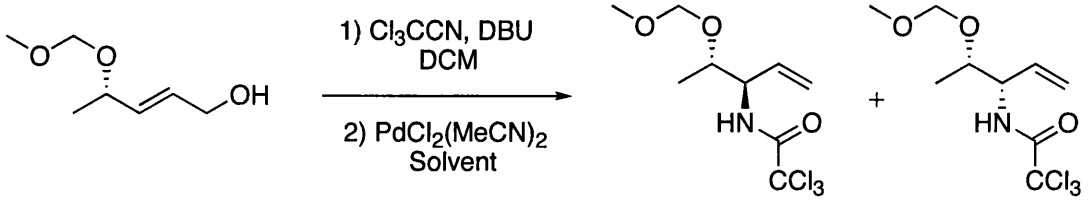
General procedure 7: Allylic trichloroacetimidate synthesis using DBU and subsequent metal catalysed rearrangement in THF as solvent.[57,59]



(2*E*,4*S*)-4-Methoxymethoxypent-2-en-1-ol (2 mmol) was dissolved in DCM (10 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5,4,0]undec-7-ene (1.2 equiv.) and trichloroacetonitrile (1.5 equiv.) were then added and the mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was then filtered through a dry silica plug and the filtrate was concentrated *in vacuo* to give an orange liquid. The product was used without further purification. The allylic trichloroacetimidate was dissolved in THF (10 mL). Catalyst (10 mol%) was then added and the reaction mixture was stirred and monitored to completion by ^{1}H NMR spectroscopy. Concentration *in vacuo* followed by purification by

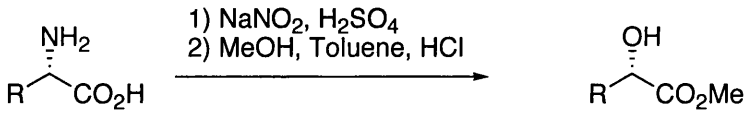
flash column chromatography eluting with 20% diethyl ether / petroleum ether gave the target compounds.

General procedure 8: Allylic trichloroacetimidate synthesis using DBU and subsequent bis(acetonitrile)palladium(II) chloride catalysed rearrangement in varying solvents.[57,59]



(2*E*,4*S*)-4-Methoxymethoxypent-2-en-1-ol (0.34 mmol) was dissolved in DCM (10 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5,4,0]undec-7-ene (1.2 equiv.) and trichloroacetonitrile (1.5 equiv.) were then added and the mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was then filtered through a dry silica plug and the filtrate was concentrated *in vacuo* to give an orange liquid. The product was used without further purification. The allylic trichloroacetimidate was dissolved in solvent (10 mL). Bis(acetonitrile)palladium(II) chloride (10 mol%) was then added and the reaction mixture was stirred and monitored to completion by ^{1}H NMR spectroscopy. Concentration *in vacuo* followed by purification by flash column chromatography eluting with 20% diethyl ether / petroleum ether gave the target compounds.

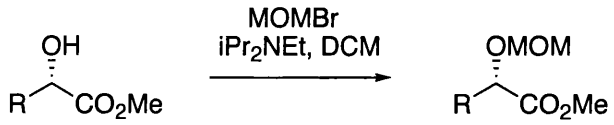
General procedure 9: Synthesis of α-hydroxy methyl esters.[96]



L-Amino acid (5 mmol) was dissolved in 2.5 M sulphuric acid (7.5 mmol) and then cooled to 0 °C. Sodium nitrite (7.5 mmol) in water (20 mL) was then added dropwise and the mixture was allowed to stir at room temperature for 12 h. The reaction mixture was then extracted using diethyl ether (3 x 50 mL) and also chloroform (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give the α-hydroxy acid as a white solid. The α-hydroxy acid (5 mmol) was dissolved in toluene (40 mL) and methanol (25 mL). Concentrated hydrochloric acid (1 mL) was added and the reaction mixture was heated under reflux for 12 h. The reaction mixture was cooled to room

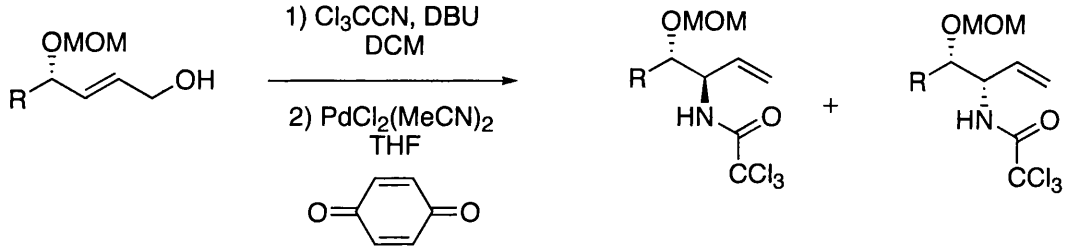
temperature and concentrated *in vacuo*. The resulting residue was neutralised with saturated sodium hydrogen carbonate solution (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by Kugelrohr distillation gave the α-hydroxy esters as colourless oils.

General procedure 10: Preparation of methoxymethyl ethers using Hünig's base.[60]



N,*N*-Diisopropylethylamine (1.5 equiv.) and bromomethyl methyl ether (1.5 equiv.) were added to a solution of the α-hydroxy ester (5 mmol) in DCM (20 mL). The reaction mixture was then heated under reflux for 12 h before being diluted with DCM (50 mL) and washed with 2 M hydrochloric acid solution (25 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography using diethyl ether / petroleum ether to give the desired compounds as colourless oils.

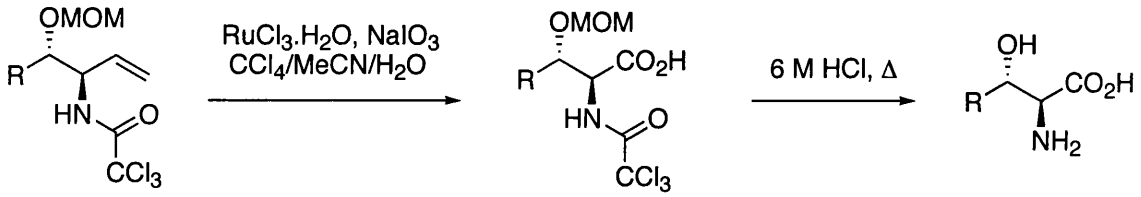
General procedure 11: Allylic trichloroacetimidate synthesis and subsequent rearrangement with bis(acetonitrile)palladium(II) chloride and *p*-benzoquinone.



The allylic alcohol (2 mmol) was dissolved in DCM (20 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5,4,0]undec-7-ene (0.2 equiv.) and trichloroacetonitrile (1.5 equiv.) were then added and the mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was then filtered through a dry silica plug and the filtrate was concentrated *in vacuo* to give an orange liquid. The product was used without further purification. The allylic trichloroacetimidate was dissolved in THF (10 mL). Bis(acetonitrile)palladium(II) chloride (10 mol%) and *p*-benzoquinone (2.0 equiv.) were then added and the reaction mixture was stirred for 24 h. Concentration *in vacuo* followed

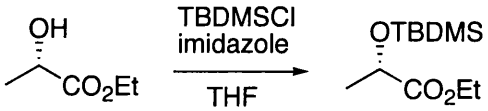
by purification by flash column chromatography eluting with diethyl ether / petroleum ether gave the target compounds as colourless oils.

General procedure 12: Ruthenium trichloride oxidation to carboxylic acids and deprotection to β-hydroxy-α-amino-acids.[102]



Sodium metaperiodate (4.1 equiv.) was dissolved in water (21 mL) and added to a solution of the trichloroacetamide (1 mmol) in carbon tetrachloride (14 mL) and acetonitrile (14 mL). Ruthenium trichloride hydrate (5 mol%) was added and the mixture was stirred vigorously for 6 h before a further portion of sodium metaperiodate (1 equiv.) was added. The reaction mixture was then stirred vigorously for 12 h and then extracted with DCM (3 x 40 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated to give a viscous oil. The product was used without further purification. The carboxylic acid (1 mmol) was dissolved in 6 M hydrochloric acid (20 mL) and heated under reflux for 12 h. The reaction mixture was then cooled before being extracted with diethyl ether (2 x 10 mL). The aqueous layer was concentrated to give a brown liquid. Purification was carried out using an ion exchange column with Dowex® 50WX8-100 (20 g per mmol of substrate), eluting with 25% ammonia solution. Concentration gave the β-hydroxy-α-amino-acids as white solids.

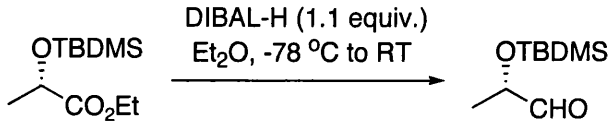
Ethyl (2*S*)-2-*tert*-butyldimethylsilyloxypropanoate (122).[119]



A mixture of ethyl (*S*)-lactate **121** (6.2 mL, 55.1 mmol), *tert*-butyldimethylsilyl chloride (9.98 g, 66.1 mmol) and imidazole (5.61 g, 82.6 mmol) in THF (65 mL) were stirred for 12 h at room temperature forming a white precipitate. The precipitate was filtered and washed with ethyl acetate (20 mL). The combined filtrate was concentrated and purified by flash column chromatography (5% ethyl acetate / petroleum ether) giving ethyl (2*S*)-2-*tert*-butyldimethylsilyloxypropanoate **122** (12.7 g, 100%) as a white liquid. $[\alpha]_D^{20}$ -31.1 (*c* 1.0,

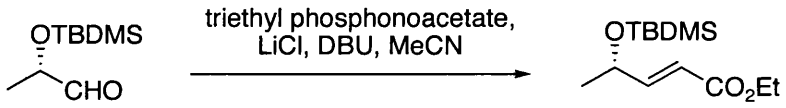
$CHCl_3$), (Lit.[119] $[\alpha]_D^{20}$ -28.2 (*c* 0.6, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 0.00 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.26 (3H, t, *J* 7.2, OCH_2CH_3), 1.38 (3H, d, *J* 6.8 Hz, 3-H_3), 4.16 (2H, m, OCH_2CH_3) and 4.30 (1H, q, *J* 6.8, 2-H); *m/z* (CI) 233 (MH^+, 100%), 217 (7), 192 (5), 175 (6) and 134 (5).

(2*S*)-2-*tert*-Butyldimethylsilyloxypropan-1-al (128).[119]



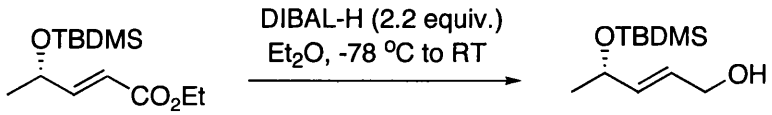
The reaction was carried out according to general procedure 2a using ethyl (2*S*)-2-*tert*-butyldimethylsilyloxypropanoate **122** (13.8 g, 59.5 mmol) giving (2*S*)-2-*tert*-butyldimethylsilyloxypropanal **128** (6.82 g, 61%) which was used without further purification. δ_H (400 MHz, $CDCl_3$) 0.00 (3H, s, $SiCH_3$), 0.01 (3H, s, $SiCH_3$), 0.83 (9H, s, $SiC(CH_3)_3$), 1.18 (3H, d, *J* 6.8, 3-H_3), 3.99 (1H, q, *J* 6.8, 2-H) and 9.51 (1H, m, CHO).

Ethyl (2*E*,4*S*)-4-*tert*-butyldimethysilyloxypent-2-enoate (134).[120]



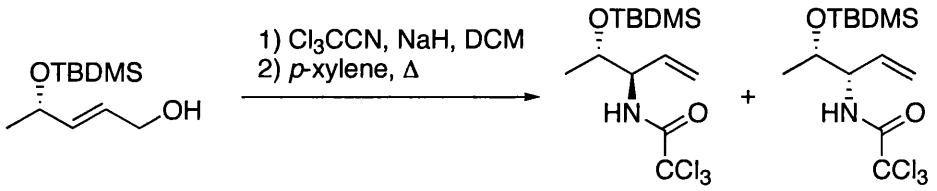
The reaction was carried out according to general procedure 3a using (2*S*)-2-*tert*-butyldimethylsilyloxypropan-1-al **128** (6.82 g, 36.3 mmol). Purification was carried out by flash column chromatography (5% ethyl acetate / petroleum ether) giving ethyl (2*E*,4*S*)-4-*tert*-butyldimethysilyloxypent-2-enoate **134** (7.59 g, 81%) as a colourless oil. $[\alpha]_D^{21}$ +4.4 (*c* 1.0, $CHCl_3$), (Lit.[120] $[\alpha]_D^{22}$ +4.4 (*c* 1.2, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 0.08 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$), 0.93 (9H, s, $SiC(CH_3)_3$), 1.28 (3H, d, *J* 6.4, 5-H_3), 1.31 (3H, t, *J* 7.2, OCH_2CH_3), 4.21 (2H, m, OCH_2CH_3), 4.47 (1H, m, 4-H), 6.00 (1H, dd, *J* 15.6, 2.0, 2-H) and 6.94 (1H, dd, *J* 15.6, 4.0, 3-H); *m/z* (EI) 258.1652 (M^+. $C_{13}H_{26}O_3Si$ requires 258.1651), 243 (9%), 201 (70), 173 (46), 103 (58) and 82 (100).

(2*E*,4*S*)-4-*tert*-Butyldimethysilyloxypent-2-en-1-ol (140).[121]



The reaction was carried out according to general procedure 4 using ethyl (2*E*,4*S*)-4-*tert*-butyldimethysilyloxypent-2-enoate **134** (0.10 g, 0.4 mmol). Purification was carried out by flash column chromatography (50% ethyl acetate / hexane) to give (2*E*,4*S*)-4-*tert*-butyldimethysilyloxypent-2-en-1-ol **140** (0.05 g, 52%) as a colourless oil. $[\alpha]_D^{23}$ +5.9 (*c* 1.0, $CHCl_3$), (Lit.[121] $[\alpha]_D^{19}$ +3.7 (*c* 2.9, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3343 (OH), 2928 (CH), 1720, 1252, 1080, 829 and 772; δ_H (400 MHz, $CDCl_3$) 0.08 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.24 (3H, d, *J* 6.3, 5-H_3), 1.43 (1H, br s, OH), 4.16 (2H, d, *J* 6.0, 1-H_2), 4.27 (1H, m, 4-H) and 5.72-5.84 (2H, m, 2-H and 3-H); δ_C (100 MHz, $CDCl_3$) -4.4 (CH_3), -4.2 (CH_3), 18.7 (C), 24.7 (CH_3), 26.3 (CH_3), 63.6 (CH_2), 68.9 (CH), 127.6 (CH) and 136.8 (CH); *m/z* (CI) 217.1626 (MH^+. $C_{11}H_{25}O_2Si$ requires 217.1624), 175 (2%), 159 (8) and 133 (12).

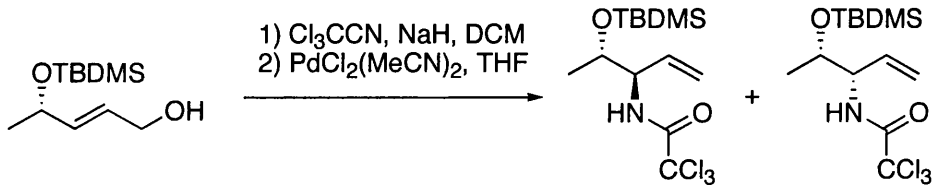
(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(*tert*-butyldimethylsilyloxy)penta-1-ene (153a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(*tert*-butyldimethylsilyloxy)penta-1-ene (153b) from thermal rearrangement.



The reactions were carried out according to general procedure 6 using (2*E*,4*S*)-4-(*tert*-butyldimethylsilyloxy)pent-2-en-1-ol **140** (0.28 g, 1.33 mmol). Purification was carried out by flash column chromatography (30% ethyl acetate / petroleum ether) giving the title compounds **153a** and **153b** (0.13 g, 27% over two steps) as a yellow oil, in a ratio of 1 : 1 (3*R* : 3*S*). υ_{max}/cm^{-1} (neat) 3426 (NH), 2929 (CH), 1721 (CO), 1498, 1255, 837 and 777; (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(*tert*-butyldimethylsilyloxy)penta-1-ene **153a** (major compound): δ_H (400 MHz, $CDCl_3$) 0.12 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$), 0.93 (9H, s, $SiC(CH_3)_3$), 1.19 (3H, d, *J* 6.4, 5-H_3), 4.06 (1H, m, 4-H), 4.29 (1H, m, 3-H), 5.33 (2H, m, 1-H), 5.86 (1H, m, 2-H) and 7.13 (1H, br d, *J* 6.4, NH); δ_C (100 MHz, $CDCl_3$) -4.5 (CH_3), -3.9 (C), -3.5 (CH_3), 18.2 (C), 20.6 (CH_3), 26.1 (CH_3), 59.7 (CH), 69.8 (CH), 119.8

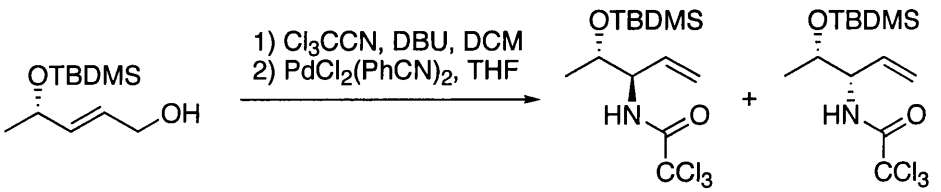
(CH_2), 132.0 (CH) and 161.2 (C); (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(*tert*-butyldimethylsilyloxy)penta-1-ene **153b** (minor compound): δ_H (400 MHz, $CDCl_3$) 0.09 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.23 (3H, d, *J* 6.4, 5-H_3), 3.78 (1H, m, 4-H), 4.31 (1H, m, 3-H), 5.27 (2H, m, 1-H_2), 5.79 (1H, m, 2-H) and 7.23 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) -4.4 (CH_3), -3.9 (CH_3), -3.5 (C), 21.7 (CH_3), 18.4 (C), 26.2 (CH_3), 58.9 (CH), 70.1 (CH), 116.9 (CH_2), 135.8 (CH) and 162.8 (C); *m/z* (CI) 360.0722 (MH^+. $C_{13}H_{25}O_2NSi^{35}Cl_3$ requires 360.0720), 290 (54%), 255 (33), 199 (100), 159 (27) and 133 (48).

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(*tert*-butyldimethylsilyloxy)penta-1-ene (153a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(*tert*-butyldimethylsilyloxy)penta-1-ene (153b) from bis(acetonitrile)palladium(II) chloride catalysed aza-Claisen rearrangement.



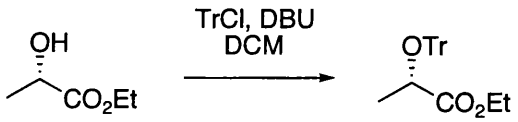
The reactions were carried out according to general procedure 5 using (2*E*,4*S*)-4-(*tert*-butyldimethylsilyloxy)pent-2-en-1-ol **140** (0.29 g, 1.32 mmol) then bis(acetonitrile)palladium(II) chloride (10 mol%) in THF (10 mL). Purification was carried out by flash column chromatography (30% ethyl acetate / petroleum ether) giving the title compounds **153a** and **153b** (0.32 g, 68% over two steps) as a yellow oil, in a ratio of 2 : 1 (3*R* : 3*S*). Spectroscopic data as above.

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(*tert*-butyldimethylsilyloxy)penta-1-ene (153a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(*tert*-butyldimethylsilyloxy)penta-1-ene (153b) from bis(benzonitrile)palladium(II) chloride catalysed aza-Claisen rearrangement.



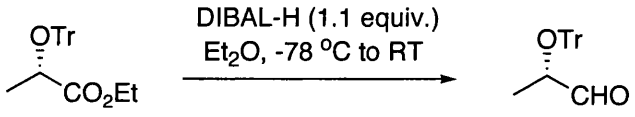
The reactions were carried out according to general procedure 5 using (2*E*,4*S*)-4-(tert-butyldimethylsilyloxy)pent-2-en-1-ol **140** (0.29 g, 1.33 mmol) then bis(benzonitrile)palladium(II) chloride (10 mol%) in THF (10 mL). Purification was carried out by flash column chromatography (30% ethyl acetate / petroleum ether) giving the title compounds **153a** and **153b** (0.33 g, 68% over two steps) as a yellow oil, in a ratio of 2 : 1 (3*R* : 3*S*). Spectroscopic data as above.

Ethyl (2*S*)-2-trityloxypropanoate (123).[122]



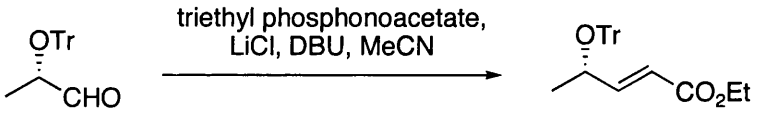
Ethyl (*S*)-lactate **121** (3.5 g, 29.7 mmol) was added to a solution of triphenylmethyl chloride (9.9 g, 35.6 mmol) and 1,8-diazabicyclo(5,4,0)undec-7-ene (6.2 mL, 41.5 mmol) in DCM (130 mL). The reaction mixture was allowed to stir for 48 h before being quenched with water (100 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 x 50 mL). The combined organic layers were then dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (50% ethyl acetate / petroleum ether) gave ethyl (2*S*)-2-trityloxypropionate **123** (10.7 g, 100%) as a white solid. $[\alpha]_D^{22}$ -32.4 (*c* 1.4, $CHCl_3$), (Lit.[122] $[\alpha]_D^{24}$ -32.4 (*c* 1.44, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.07 (3H, t, *J* 7.1, OCH_2CH_3), 1.38 (3H, d, *J* 6.7, 3-H_3), 3.70 (2H, m, OCH_2CH_3), 4.19 (1H, q, *J* 6.7, 2-H) and 7.23-7.51 (15H, m, 3 x Ph); *m/z* (EI) 360.1725 (M^+. $C_{24}H_{24}O_3$ requires 360.1725), 283 (21%), 243 (100), 183 (15) and 165 (76).

(2*S*)-2-Trityloxypropanal (129).[122]



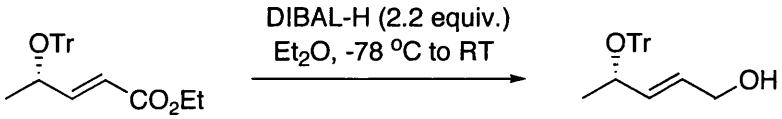
The reaction was carried out according to general procedure 2a using ethyl (2*S*)-2-trityloxypropanoate **123** (10.67 g, 29.7 mmol) giving (2*S*)-2-trityloxypropanal **129** (7.66 g, 82%) as a white solid, which was used without further purification. δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.9, 3-H_3), 4.03 (1H, qd, *J* 6.9, 3.1, 2-H), 7.21-7.54 (15H, m, 3 x Ph) and 8.71 (1H, d, *J* 3.1, CHO).

Ethyl (2*E*,4*S*)-4-trityloxypent-2-enoate (135).



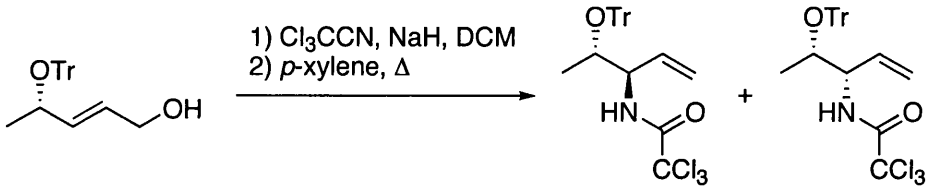
The reaction was carried out according to general procedure 3a using (2*S*)-trityloxypropanal **129** (8.99 g, 28.4 mmol). Purification was carried out by flash column chromatography (50% ethyl acetate / petroleum ether) giving ethyl (2*E*,4*S*)-4-(trityloxy)pent-2-enoate **135** (8.51 g, 78%) as a white solid. mp 112-114 °C (from EtOAc / petroleum ether); $[\alpha]_D^{19}$ -33.6 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2979 (CH), 1714 (CO), 1664 (C=C), 1448, 1251, 1177, 1058 and 1015; δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.4, 5-H_3), 1.27 (3H, t, *J* 7.1, OCH_2CH_3), 4.12 (2H, q, *J* 7.1, OCH_2CH_3), 4.25 (1H, m, 4-H), 5.48 (1H, dd, *J* 15.7, 1.1, 2-H), 6.54 (1H, dd, *J* 15.7, 6.1, 3-H) and 7.21-7.53 (15H, m, 3 x Ph); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3), 22.5 (CH_3), 60.4 (CH_2), 70.0 (CH), 87.7 (C), 118.3 (CH), 127.5 (CH), 128.2 (CH), 129.2 (CH), 145.0 (C), 150.8 (CH) and 166.8 (C); *m/z* (EI) 386.1880 (M^+, $C_{26}H_{26}O_3$ requires 386.1882), 309 (3%), 243 (100), 183 (39) and 165 (37).

(2*E*,4*S*)-4-Trityloxypent-2-en-1-ol (141).



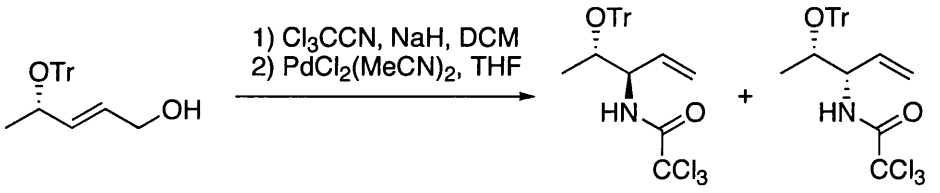
The reaction was carried out according to general procedure 4 using ethyl (2*E*,4*S*)-4-(trityloxy)pent-2-enoate **135** (3.0 g, 7.8 mmol). Purification was carried out by flash column chromatography (50% ethyl acetate / hexane) to gave (2*E*,4*S*)-4-trityloxypent-2-en-1-ol **141** (2.59g, 97%) as a viscous oil. $[\alpha]_D^{18}$ +11.6 (*c* 1.6, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3348 (OH), 2926 (CH), 1596 (C=C), 1447, 1051, 1022 and 966; δ_H (400 MHz, $CDCl_3$) 0.69 (1H, t, *J* 6.0, OH), 1.15 (3H, d, *J* 6.4, 5-H_3), 3.77 (2H, m, 1-H_2), 4.16 (1H, quin., *J* 6.4, 4-H), 5.24 (1H, dt, *J* 15.6, 6.0, 2-H), 5.34 (1H, dd, *J* 15.6, 6.4, 3-H) and 7.22-7.54 (15H, m, 3 x Ph); δ_C (100 MHz, $CDCl_3$) 23.6 (CH_3), 63.3 (CH_2), 70.8 (CH), 87.4 (C), 126.8 (CH), 127.2 (CH), 128.1 (CH), 129.4 (CH), 136.2 (CH) and 145.5 (C); *m/z* (CI) 327 (MH^+ - H_2O, 8%), 243 (100), 183 (80) and 145 (35).

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(trityloxy)penta-1-ene (154a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(trityloxy)penta-1-ene (154b) from thermal rearrangement.



The reactions were carried out according to general procedure 6 using (2*E*,4*S*)-4-trityloxypent-2-en-1-ol **141** (0.54 g, 1.58 mmol). Purification was carried out by flash column chromatography (30% diethyl ether / petroleum ether) giving the title compounds **154a** and **154b** (0.28 g, 36% over two steps) as a yellow oil, in a ratio of 2 : 1 (3*R* : 3*S*). υ_{max}/cm^{-1} (neat) 3411 (NH), 3021 (CH), 1713 (CO), 1597 (C=C), 1490, 1447, 1001, 818 and 698; (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(trityloxy)penta-1-ene **154a** (major compound): δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.4, 5-H_3), 3.41 (1H, qd, *J* 6.4, 3.1, 4-H), 4.06 (1H, m, 3-H), 5.34 (2H, m, 1-H_2), 6.06 (1H, m, 2-H) and 7.12-7.56 (15H, m, 3 x Ph); δ_C (100 MHz, $CDCl_3$) 18.1 (CH_3), 58.6 (CH), 71.6 (CH), 87.2 (C), 118.9 (CH_2), 127.5 (CH), 128.1 (CH), 128.8 (CH), 132.8 (CH), 144.8 (C), 147.0 (C), 161.0 (C); (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(trityloxy)penta-1-ene **154b** (minor compound): δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.4, 5-H_3), 3.61 (1H, m, 4-H), 3.94 (1H, m, 3-H), 5.16 (2H, m, 1-H_2), 6.25 (1H, m, 2-H) and 7.12-7.56 (15H, m, 3 x Ph); *m/z* (CI) 490 (MH^+, 1%), 452 (1), 387 (1), 285 (3) and 243 (100).

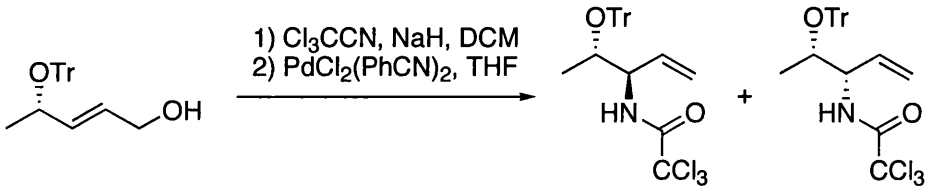
(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(trityloxy)penta-1-ene (154a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(trityloxy)penta-1-ene (154b) from bis(acetonitrile)palladium(II) chloride catalysed aza-Claisen rearrangement.



The reactions were carried out according to general procedure 5 using (2*E*,4*S*)-4-trityloxypent-2-en-1-ol **141** (1.22 g, 3.6 mmol) and bis(acetonitrile)palladium(II) chloride (10 mol%). Purification was carried out by flash column chromatography (30% diethyl

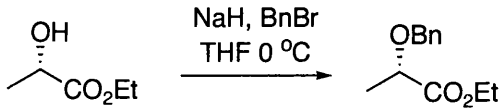
ether / petroleum ether) giving the title compounds **154a** and **154b** (1.22 g, 70% over two steps) as a yellow oil, in a ratio of 3 : 1 (3*R* : 3*S*). Spectroscopic data as above.

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(trityloxy)penta-1-ene (154a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(trityloxy)penta-1-ene (154b) from bis(benzonitrile)palladium(II) chloride catalysed aza-Claisen rearrangement.



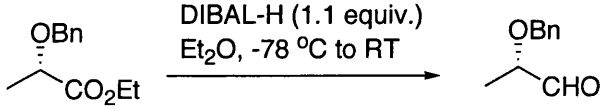
The reactions were carried out according to general procedure 5 using (2*E*,4*S*)-4-trityloxypent-2-en-1-ol **141** (0.55 g, 1.60 mmol) and bis(benzonitrile)palladium(II) chloride (10 mol%). Purification was carried out by flash column chromatography (30% diethyl ether / petroleum ether) giving the title compounds **154a** and **154b** (0.34 g, 44% over two steps) as a yellow oil, in a ratio of 3 : 1 (3*R* : 3*S*). Spectroscopic data as above.

Ethyl (2*S*)-2-benzyloxypropanoate (124).[123]



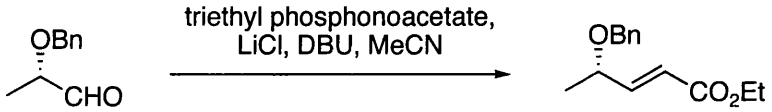
The reaction was carried out according to general procedure 1 using ethyl (*S*)-lactate **121** (5.0 mL, 44.5 mmol) giving ethyl (2*S*)-2-benzyloxypropanoate **124** (8.77g, 95%) as a colourless oil. $[\alpha]_D^{25}$ -69.3 (*c* 1.0, $CHCl_3$), (Lit.[123] $[\alpha]_D^{22}$ -87.0 (*c* 2.5, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.1, OCH_2CH_3), 1.42 (3H, d, *J* 6.8, 3-H_3), 4.04 (1H, q, *J* 6.8, 2-H), 4.19 (2H, m, OCH_2CH_3), 4.42 (1H, d, *J* 11.6, PhC*H*H), 4.68 (1H, d, *J* 11.6, PhCH*H*) and 7.21-7.49 (5H, m, Ph); *m/z* (CI) 209.1178 (MH^+. $C_{12}H_{17}O_3$ requires 209.1178), 179 (11%), 174 (13), 119 (7) and 91 (100).

(2*S*)-2-Benzyloxypropan-1-al (130).



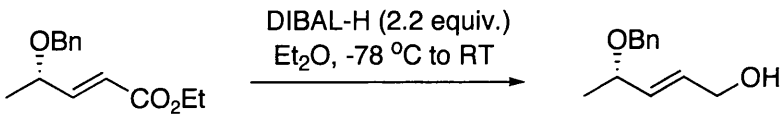
The reaction was carried out according to general procedure 2a using ethyl (2*S*)-2-benzyloxypropanoate **124** (3.0 g, 14.4 mmol) giving (2*S*)-2-benzyloxypropan-1-al **130** (2.37 g, 100%) as a yellow oil, which was used without further purification. δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 6.9, 3-H_3), 3.89 (1H, qd, *J* 6.9, 3.2, 2-H), 4.10 (1H, d, *J* 11.7, PhC*H*H), 4.62 (1H, d, *J* 11.7, PhCH*H*), 7.24 (5H, m, Ph) and 9.61 (1H, d, *J* 3.2, CHO).

Ethyl (2*E*,4*S*)-4-benzyloxypent-2-enoate (136).[121]



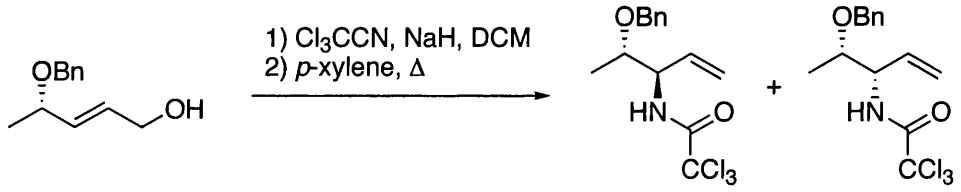
The reaction was carried out according to general procedure 3a using (2*S*)-2-benzyloxypropanal **130** (2.37 g, 14.4 mmol). Purification by flash column chromatography (40% ethyl acetate / petroleum ether) gave ethyl (2*E*,4*S*)-4-benzyloxypent-2-enoate **136** (3.14 g, 93%) as an oil. $[\alpha]_D^{23}$ -50.4 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.2 (6H, m, OCH_2CH_3 and 5-H_3), 4.10 (1H, m, 4-H), 4.20 (2H, q, *J* 6.3, OCH_2CH_3), 4.42 (1H, d, *J* 11.8, PhC*H*H), 4.56 (1H, d, *J* 11.8, PhCH*H*), 6.04 (1H, dd, *J* 15.7, 1.3, 2-H), 6.91 (1H, dd, *J* 15.7, 6.0, 3-H) and 7.29-7.46 (5H, m, Ph); *m/z* (CI) 235.1334 (MH^+. $C_{14}H_{19}O_3$ requires 235.1334), 189 (10%), 145 (5), 107 (12) and 91 (31).

(2*E*,4*S*)-4-Benzyloxypent-2-en-1-ol (142).[121]



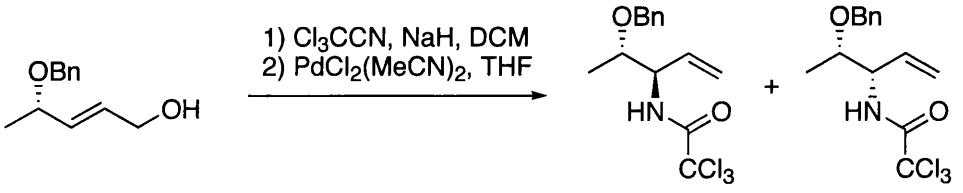
The reaction was carried out according to general procedure 4 using ethyl (2*E*,4*S*)-4-benzyloxypent-2-enoate **136** (1.99 g, 8.5 mmol). Purification was carried out by flash column chromatography (50% ethyl acetate / hexane) to give (2*E*,4*S*)-4-benzyloxypent-2-en-1-ol **142** (0.85 g, 52%). $[\alpha]_D^{22}$ -38.1 (*c* 1.0, $CHCl_3$), (Lit.[121] $[\alpha]_D^{25}$ -39.2 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.4, 5-H_3), 1.39 (1H, br t, *J* 6.4, OH), 4.00 (1H, quin, *J* 6.4, 4-H), 4.20 (2H, t, *J* 5.2, 1-H_2), 4.42 (1H, d, *J* 12.0, PhC*H*H), 4.57 (1H, d, *J* 12.0, PhCH*H*), 5.6 (1H, dd, *J* 15.6, 6.4, 3-H), 5.7 (1H, dt, *J* 15.6, 5.2, 2-H) and 7.15-7.56 (5H, m, Ph); *m/z* (CI) 175.1121 (MH^+ - H_2O. $C_{12}H_{15}O$ requires 175.1123), 157 (66%), 131 (50), 91 (51) and 85 (50).

(3*R*,4*S*)-3-(Trichloromethanecarbonylamino)-4-(benzyloxy)penta-1-ene (155a) and (3*S*,4*S*)-3-(trichloromethanecarbonylamino)-4-(benzyloxy)penta-1-ene (155b) from thermal rearrangement.



The reactions were carried out according to general procedure 6 using (2*E*,4*S*)-4-benzyloxypent-2-en-1-ol **142** (0.20 g, 1.04 mmol). Purification was carried out by flash column chromatography (20% ethyl acetate / hexane) giving the title compounds **155a** and **155b** (0.15 g, 44% over two steps) as a brown oil, in a ratio of 2 : 1 (3*R* : 3*S*). υ_{max}/cm^{-1} (neat) 3415 (NH), 2869 (CH), 1714 (CO), 1598 (C=C), 1497, 1454, 1068, 924 and 818; (3*R*,4*S*)-3-(trichloromethanecarbonylamino)-4-(benzyloxy)penta-1-ene **155a** (major compound): δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.4, 5-H_3), 3.74 (1H, m, 4-H), 4.36 (1H, m, 3-H), 4.67 (2H, s, $PhCH_2$), 5.29 (2H, m, 1-H_2), 5.87 (1H, m, 2-H) and 7.24-7.39 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 15.8 (CH_3), 57.8 (CH), 70.8 (CH_2), 75.0 (CH), 92.7 (C), 116.9 (CH_2), 127.7 (CH), 128.0 (CH), 128.6 (CH), 131.7 (CH), 137.8 (C) and 161.0 (C); (3*S*,4*S*)-3-(trichloromethanecarbonylamino)-4-(benzyloxy)penta-1-ene **155b** (minor compound): δ_H (400 MHz, $CDCl_3$) 1.24 (1H, d, *J* 6.4, 5-H_3), 3.93 (1H, m, 4-H), 4.29 (1H, m, 3-H), 4.42 (1H, d, *J* 11.6, PhC*H*H), 4.66 (1H, d, *J* 11.6, PhCH*H*), 5.24 (2 H, m, 1-H_2), 5.68 (1H, m, 2-H) and 7.24-7.39 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 16.7 (CH_3), 58.0 (CH), 71.1 (CH_2), 75.3 (CH), 92.9 (C), 119.4 (CH_2), 127.9 (CH), 128.0 (CH), 128.3 (CH), 135.0 (CH), 137.9 (C) and 161.8 (C); *m/z* (CI) 338 (MH^+, 25%), 302 (22), 218 (15), 181 (70) and 105 (100).

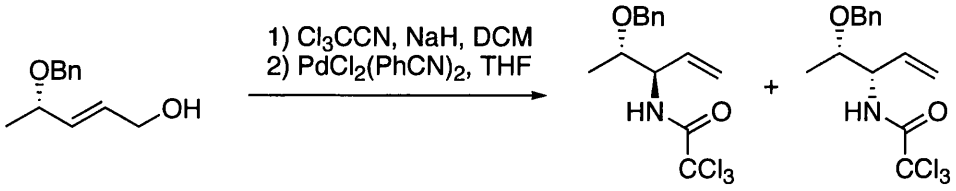
(3*R*,4*S*)-3-(Trichloromethanecarbonylamino)-4-(benzyloxy)penta-1-ene (155a) and (3*S*,4*S*)-3-(trichloromethanecarbonylamino)-4-(benzyloxy)penta-1-ene (155b) from bis(acetonitrile)palladium(II) chloride catalysed aza-Claisen rearrangement.



The reactions were carried out according to general procedure 5 using (2*E*,4*S*)-4-benzyloxypent-2-en-1-ol **142** (0.15 g, 0.8 mmol) and bis(acetonitrile)palladium(II)

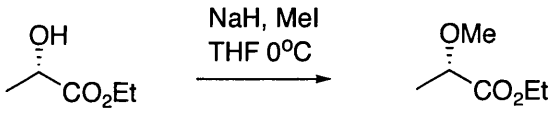
chloride (10 mol%). Purification was carried out by flash column chromatography (20% ethyl acetate / hexane) giving the title compounds **155a** and **155b** (0.16 g, 62% over two steps) as a brown oil, in a ratio of 3 : 1 (3*R* : 3*S*). Spectroscopic data as above.

(3*R*,4*S*)-3-(Trichloromethanecarbonylamino)-4-(benzyloxy)penta-1-ene (155a) and (3*S*,4*S*)-3-(trichloromethanecarbonylamino)-4-(benzyloxy)penta-1-ene (155b) from bis(benzonitrile)palladium(II) chloride catalysed aza-Claisen rearrangement.



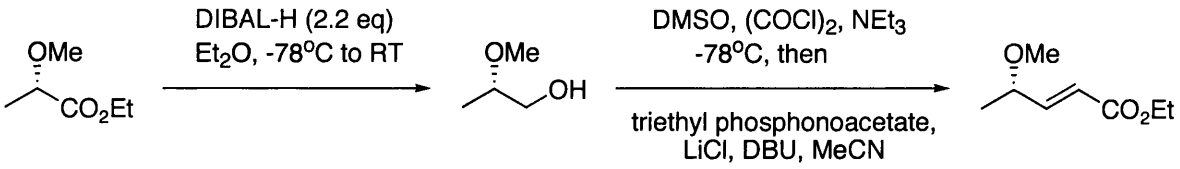
The reactions were carried out according to general procedure 5 using (2*E*,4*S*)-4-benzyloxypent-2-en-1-ol **142** (0.35 g, 1.04 mmol) and bis(benzonitrile)palladium(II) chloride (10 mol%). Purification was carried out by flash column chromatography (20% ethyl acetate / hexane) giving the title compounds **155a** and **155b** (0.20 g, 58% over two steps) as a brown oil, in a ratio of 4 : 1 (3*R* : 3*S*). Spectroscopic data as above.

Ethyl (2*S*)-2-methoxypropanoate (125).[124]



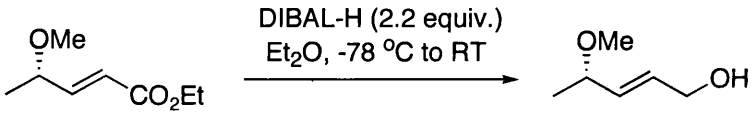
The reaction was carried out according to general procedure 1 using ethyl (*S*)-lactate **121** (7.7 mL, 67.8 mmol). Purification was carried out by flash column chromatography (50% ethyl acetate / petroleum ether) to give ethyl (2*S*)-2-methoxypropanoate **125** (4.29 g, 48%) as a pale liquid. $[\alpha]_D^{22}$ -115.3 (*c* 1.0, $CHCl_3$), (Lit.[124] $[\alpha]_D^{25}$ –115.9 (*c* 1.1, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7.1, OCH_2CH_3), 1.33 (3H, d, *J* 6.8, 3-H_3), 3.33 (3H, s, OMe), 3.80 (1H, q, *J* 6.8, 2-H) and 4.14 (2H, q, *J* 7.1, OCH_2CH_3); *m/z* (CI) 133.0869 (MH^+. $C_6H_{13}O_3$ requires 133.0865), 128 (3%), 85 (4) and 71 (4).

Ethyl (*2E*,4*S*)-4-methoxypent-2-enoate (137).[125]



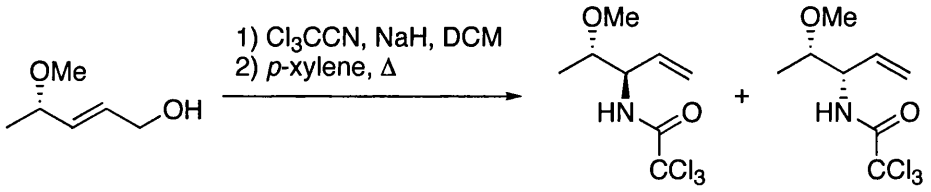
The reactions were carried out according to general procedure 2b and then 3b using ethyl (*S*)-2-methoxypropanoate **125** (5.2 g, 39.4 mmol). Purification by flash column chromatography (30% ethyl acetate / petroleum ether) gave ethyl (*2E*,4*S*)-4-methoxypent-2-enoate **137** (3.61 g, 58% over three steps) as a brown oil. $[\alpha]_D^{22}$ -34.1 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2981 (CH), 1716 (CO), 1659 (C=C), 1260, 1176 and 1086; δ_H(400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.4, 5-H_3), 1.32 (3H, t, *J* 7.2, OCH_2CH_3), 3.34 (3H, s, OMe), 3.91 (1H, dq, *J* 6.4, 1.8, 4-H), 4.22 (2H, q, *J* 7.1, OCH_2CH_3), 5.98 (1H, dd, *J* 15.7, 1.3, 2-H) and 6.84 (1H, dd, *J* 15.7, 6.4, 3-H); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3), 20.7 (CH_3), 57.0 (CH_3), 60.8 (CH_2), 76.5 (CH), 121.7 (CH), 149.3 (CH) and 166.7 (C); *m/z* (CI) 159.1021 (MH^+. $C_8H_{15}O_3$ requires 159.1021), 150 (2%), 138 (9), and 127 (5).

(*2E*,4*S*)-4-Methoxypent-2-en-1-ol (143).[126]



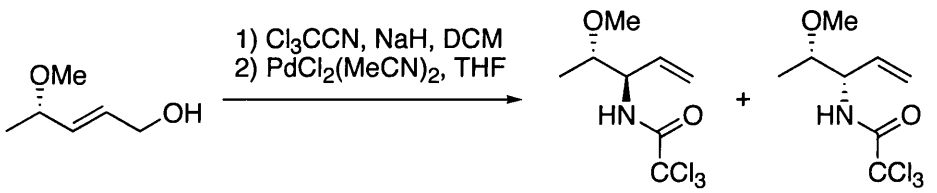
The reaction was carried out according to general procedure 4 using ethyl (*2E*,4*S*)-4-methoxypent-2-enoate **137** (0.88 g, 5.57 mmol). Purification was carried out by flash column chromatography (50% ethyl acetate / petroleum ether) to give (*2E*,4*S*)-4-methoxypent-2-en-1-ol **143** (0.56 g, 87%) as a yellow liquid. $[\alpha]_D^{21}$ -35.6 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3363 (OH), 2931 (CH), 1673 (C=C), 1087, 970 and 842; δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.4, 5-H_3), 1.50 (1H, br t, *J* 5.3, OH), 3.30 (3H, s, OMe), 3.78 (1H, quin, *J* 6.4, 4-H), 4.19 (2H, d, *J* 5.3, 1-H_2), 5.63 (1H, dd, *J* 15.5, 6.4, 3-H) and 5.84 (1H, dt, *J* 15.5 and 5.3, 2-H); δ_C (100 MHz, $CDCl_3$) 21.4 (CH_3), 56.3 (CH_3), 63.3 (CH_2), 77.6 (CH), 131.3 (CH) and 133.5 (CH); *m/z* (CI) 117.0918 (MH^+. $C_6H_{13}O_2$ requires 117.0916), 99 (35%), 85 (100) and 79 (3).

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxy)penta-1-ene (156a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxy)penta-1-ene (156b) from thermal rearrangement.



The reactions were carried out according to general procedure 6 using (2*E*,4*S*)-4-methoxypent-2-en-1-ol **143** (0.08 g, 0.65 mmol). Purification was carried out by flash column chromatography (30% ethyl acetate / petroleum ether) to give the title compounds **156a** and **156b** (0.07 g, 38% over two steps) as a brown oil, in a ratio of 2 : 1 (3*R* : 3*S*). υ_{max}/cm^{-1} (neat) 3339 (NH), 1705 (CO), 1598 (C=C), 1498, 1087, 927 and 817; (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxy)penta-1-ene **156a** (major compound): δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.4, 5-H_3), 3.38 (3H, s, OMe), 3.55 (1H, m, 4-H), 4.38 (1H, m, 3-H), 5.28 (2H, m, 1-H_2), 5.77-5.94 (1H, m, 2-H) and 7.10 (1H, br d, *J* 6.4, NH); δ_C (100 MHz, $CDCl_3$) 15.6 (CH_3), 57.2 (CH), 58.0 (CH_3), 77.9 (CH), 93.2 (C), 119.5 (CH_2), 132.0 (CH) and 161.4 (C); (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxy)penta-1-ene **156b** (minor compound): δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.4, 5-H_3), 3.37 (3H, s, OMe), 3.40 (1H, m, 4-H), 4.42 (1H, m, 3-H), 5.19 (2H, m, 1-H_2), 5.72 (1H, m, 2-H) and 6.96 (1H, br d, *J* 6.4, NH); δ_C (100 MHz, $CDCl_3$) 16.5 (CH_3), 57.5 (CH), 58.1 (CH_3), 77.8 (CH), 93.3 (C), 117.2 (CH_2), 134.9 (CH) and 162.1 (C); *m/z* (CI) 274 (MH^+, 4%), 260 (75), 226 (17), 190 (100).

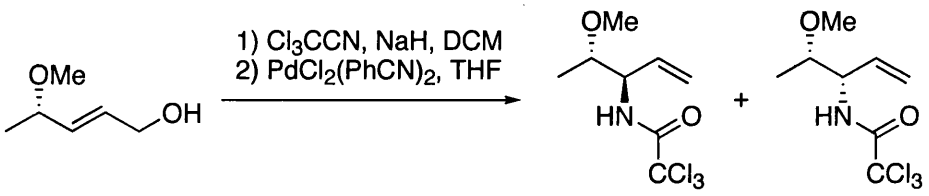
(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxy)penta-1-ene (156a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxy)penta-1-ene (156b) from bis(acetonitrile)palladium(II) chloride catalysed aza-Claisen rearrangement.



The reactions were carried out according to general procedure 5 using (2*E*,4*S*)-4-methoxypent-2-en-1-ol **143** (0.06 g, 0.52 mmol) and bis(acetonitrile)palladium(II) chloride (10 mol%). Purification was carried out by flash column chromatography (30% ethyl

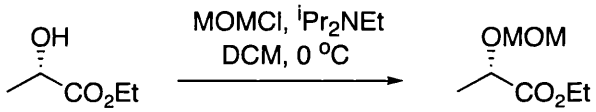
acetate / petroleum ether) to give the title compounds **156a** and **156b** (0.07 g, 48% over two steps) as a brown oil, in a ratio of 7 : 1 (3*R* : 3*S*). Spectroscopic data as above.

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxy)penta-1-ene (156a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxy)penta-1-ene (156b) from bis(benzonitrile)palladium(II) chloride catalysed aza-Claisen rearrangement.



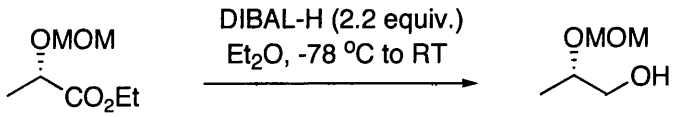
The reactions were carried out according to general procedure 5 using (2*E*,4*S*)-4-methoxypent-2-en-1-ol **143** (0.03 g, 0.22 mmol) and bis(benzonitrile)palladium(II) chloride (10 mol%). Purification was carried out by flash column chromatography (30% ethyl acetate / petroleum ether) to give the title compounds **156a** and **156b** (0.03 g, 48% over two steps) as a brown oil, in a ratio of 6 : 1 (3*R* : 3*S*). Spectroscopic data as above.

Ethyl (2*S*)-2-methoxymethoxypropanoate (126).[127]



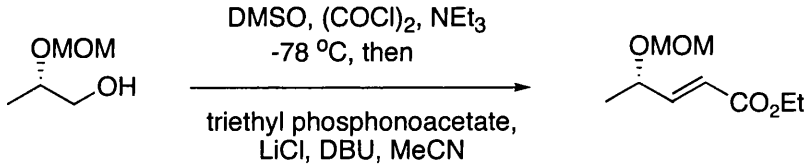
N,*N*'-Diisopropylethylamine (12.4 mL, 71.2 mmol) and chloromethyl methyl ether (6.8 mL, 89.0 mmol) were added dropwise to a solution of ethyl (*S*)-lactate **121** (7.0 g, 59.3 mmol) in DCM (70 mL) at 0 °C. The reaction mixture was allowed to stir for 1 h, then heated under reflux for 12 h. The reaction mixture was then cooled to room temperature, quenched with 2 M hydrochloric acid solution (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification was carried out by flash column chromatography (40% diethyl ether / petroleum ether) to give ethyl (2*S*)-2-methoxymethoxypropanoate **126** (8.7 g, 91%) as a yellow liquid. $[\alpha]_D^{23}$ -105.7 (*c* 1.0, $CHCl_3$), (Lit.[127] $[\alpha]_D^{25}$ –92.3 (*c* 1.0, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.0, OCH_2CH_3), 1.43 (3H, d, *J* 7.0, 3-H_3), 3.39 (3H, s, OMe), 4.21 (2H, q, *J* 7.0, OCH_2CH_3), 4.24 (1H, q, *J* 7.0, 2-H), 4.69 (1H, d, *J* 7.0, OC*H*HO) and 4.72 (1H, d, J 7.0, OCH*H*O); *m/z* (CI) 163.0969 (MH^+. $C_7H_{15}O_4$ requires 163.0970), 131 (100%), 119 (3) and 85 (4).

(2*S*)-2-Methoxymethoxypropan-1-ol (132).[127]



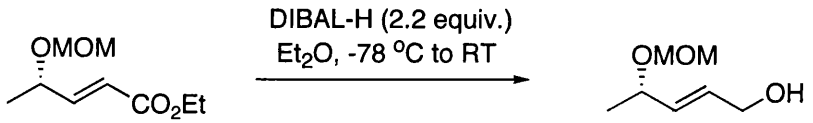
The reaction was carried out according to general procedure 2b using ethyl (2*S*)-2-methoxymethoxypropanoate **126** (1.0 g, 6.2 mmol). Purification by flash column chromatography (90% diethyl ether / petroleum ether) gave (2*S*)-2-methoxymethoxypropanol **132** (0.61 g, 82%) as a colourless oil. $[\alpha]_D^{25}$ +80.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.4, 3-H_3), 2.60 (1H, br s, OH), 3.43 (3H, s, OMe), 3.46 (1H, dd, *J* 11.8, 7.3, 1-*H*H), 3.57 (1H, dd, *J* 11.8, 2.8, 1-H*H*), 3.70 (1H, m, 2-H), 4.71 (1H, d, *J* 6.9, OC*H*HO) and 4.76 (1H, d, *J* 6.9 Hz, OCH*H*O); *m/z* (CI) 121.0866 (MH^+. $C_5H_{13}O_3$ requires 121.0865), 119 (8%), 89 (100), and 87 (19).

Ethyl (2*E*,4*S*)-4-methoxymethoxypent-2-enoate (138).



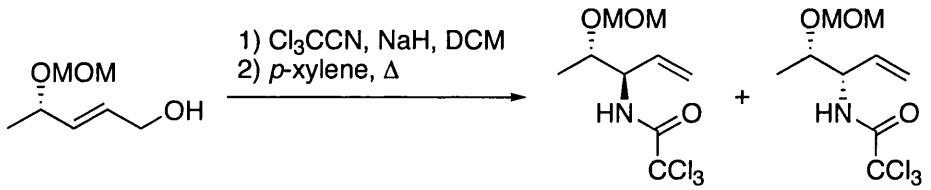
The reaction was carried out according to general procedure 3b using (2*S*)-2-methoxymethoxypropan-1-ol **132** (2.58 g, 21.5 mmol). Purification by flash column chromatography (40% diethyl ether / petroleum ether) gave ethyl (2*E*,4*S*)-4-methoxymethoxypent-2-enoate **138** (2.64 g, 65% over two steps) as a brown oil.
$[\alpha]_D^{21}$-80.0 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2981 (CH), 1720 (CO), 1660 (C=C), 1271, 1099, 1032 and 920; δ_H (400 MHz, $CDCl_3$) 1.27 (6H, m, OCH_2CH_3 and 5-H_3), 3.37 (3H, s, OMe), 4.20 (2H, q, *J* 7.1, OCH_2CH_3), 4.35 (1H, quin d, *J* 6.5, 2.1, 4-H), 4.62 (2H, s, OCH_2O), 5.99 (1H, dd, *J* 15.7, 2.1, 2-H) and 6.87 (1H, dd, *J* 15.7, 6.5, 3-H); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3), 20.9 (CH_3), 55.8 (CH_3), 60.8 (CH_2), 71.4 (CH), 94.8 (CH), 121.4 (CH), 149.1 (CH) and 166.7 (C); *m/z* (CI) 189.1125 (MH^+. $C_9H_{17}O_4$ requires 189.1127), 175 (3%), 159 (42), 143 (49) and 127 (61).

(2*E*,4*S*)-4-Methoxymethoxypent-2-en-1-ol (144).



The reaction was carried out according to general procedure 4 using ethyl (2*E*,4*S*)-4-methoxymethoxypent-2-enoate **138** (2.56 g, 13.6 mmol). Purification was carried out by flash column chromatography (80% diethyl ether / petroleum ether) to give (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol **144** (1.90 g, 96%) as a colourless oil. $[\alpha]_D^{23}$ -117.9 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3404 (OH), 2931 (CH), 1446 (C=C), 1373, 1217 and 1026; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.4, 5-H_3), 2.21 (H, br s, OH), 3.37 (3H, s, OMe), 4.14 (2H, dd, *J* 5.1, 1.6, 1-H_2), 4.16 (1H, quin, *J* 6.4, 4-H), 4.57 (1H, d, *J* 6.7, OC*H*HO), 4.66 (1H, d, *J* 6.7, OCH*H*O), 5.63 (1H, ddt, *J* 15.0, 6.8, 1.6, 3-H) and 5.81 (1H, dt, *J* 15.0, 5.1, 2-H); δ_C (100 MHz, $CDCl_3$) 21.3 (CH_3), 55.3 (CH_3), 63.0 (CH_2), 72.0 (CH), 93.8 (CH_2), 130.9 (CH) and 132.8 (CH); *m/z* (CI) 121.0866 (MH^+ - H_2O. $C_7H_{13}O_2$ requires 121.0865), 99 (35%), 85 (100) and 79 (3).

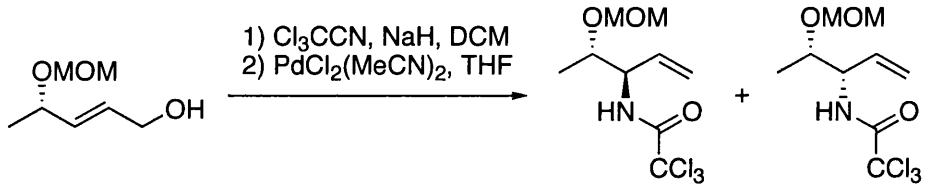
(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157b) from thermal rearrangement.



The reactions were carried out according to general procedure 6 using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol **144** (0.08 g, 0.53 mmol). Purification was carried out by flash column chromatography (20% diethyl ether / petroleum ether) to give the title compounds **157a** and **157b** (0.03 g, 21% over two steps) as an orange oil, in a ratio of 2 : 1 (3*R* ; 3*S*). υ_{max}/cm^{-1} (neat) 3302 (NH), 2935 (CH), 1712 (CO), 1643 (C=C), 1511, 1148, 1028 and 819; (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157a** (major compound): δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.4, 5-H_3), 3.43 (3H, s, OMe), 3.88 (1H, qd, *J* 6.4, 3.0, 4-H), 4.35 (1H, m, 3-H), 4.69 (1H, d, *J* 6.8, OC*H*HO) 4.71 (1H, d, *J* 6.8, OCH*H*O), 5.36 (2H, m, 1-H_2), 5.89 (1H, m, 2-H) and 7.89 (1H, br d, *J* 6.4, NH); δ_C (100 MHz, $CDCl_3$) 18.4 (CH_3), 56.2 (CH), 58.1 (CH_3), 77.7 (CH), 92.1 (C), 97.0

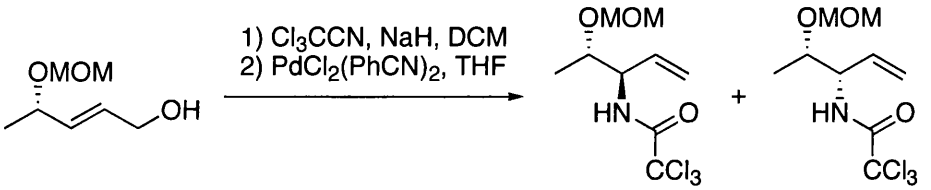
(CH_2), 119.6 (CH_2), 131.8 (CH) and 161.7 (C); (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157b** (minor compound): δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.4, 5-H_3), 3.39 (3H, s, OMe), 3.93 (1H, qd, *J* 6.4, 3.0, 4-H), 4.43 (1H, m, 3-H), 4.63 (1H, d, *J* 6.8, OC*H*HO) 4.79 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.27 (2H, m, 1-H_2), 5.89 (1H, m, 2-H) and 7.10 (1H, br d, *J* 6.4, NH); δ_C (100 MHz, $CDCl_3$) 17.8 (CH_3), 56.1 (CH), 58.2 (CH_3), 74.1 (CH), 94.3 (C), 95.3 (CH_2), 117.3 (CH_2), 135.3 (CH) and 161.7 (C); *m/z* (CI) 290.0127 (MH^+. $C_9H_{15}O_3N^{35}Cl_3$ requires 290.0118), 258 (81%), 246 (22), 214 (37) and 196 (72).

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157b) from bis(acetonitrile)palladium(II) chloride catalysed aza-Claisen rearrangement.



The reactions were carried out according to general procedure 5 using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol **144** (0.44 g, 3.7 mmol) and bis(acetonitrile)palladium(II) chloride (10 mol%). Purification was carried out by flash column chromatography (20% diethyl ether / petroleum ether) to give the title compounds **157a** and **157b** (0.68 g, 64% over two steps) as an orange oil, in a 10 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as above.

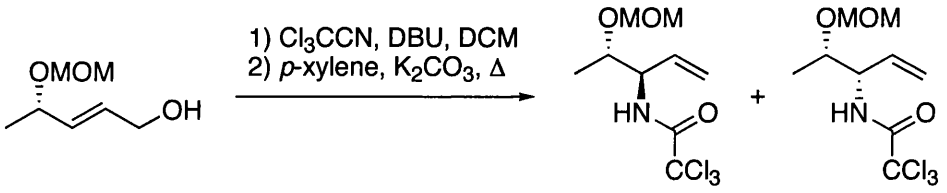
(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157b) from bis(benzonitrile)palladium(II) chloride catalysed aza-Claisen rearrangement.



The reactions were carried out according to general procedure 5 using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol **144** (0.06 g, 0.42 mmol) and

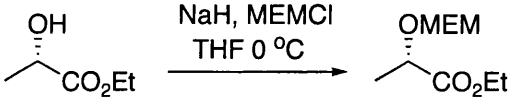
bis(benzonitrile)palladium(II) chloride (10 mol%). Purification was carried out by flash column chromatography (20% diethyl ether / petroleum ether) to give the title compounds **157a** and **157b** (0.10 g, 57% over two steps) as an orange oil, in a ratio of 9 : 1 (3*R* : 3*S*). Spectroscopic data as above.

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157b) from thermal rearrangement with K_2CO_3.



(2*E*,4*S*)-4-Methoxymethoxypent-2-en-1-ol **144** (0.10 g, 0.69 mmol) was dissolved in DCM (10 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5,4,0]undec-7-ene (0.10 g, 0.69 mmol) and trichloroacetonitrile (0.1 mL, 1.03 mmol) were then added and the mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was then filtered through a dry silica plug and the filtrate was concentrated *in vacuo* to give an orange liquid. The product was used without further purification. The allylic trichloroacetimidate and potassium carbonate (0.20 g) were dissolved in *p*-xylene (10 mL) and heated under reflux for 72 h. The mixture was then concentrated to give a brown liquid. Purification was carried out by flash column chromatography (20% diethyl ether / petroleum ether) to give the title compounds **157a** and **157b** (0.18 g, 91% over two steps) as an orange oil, in a 2 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

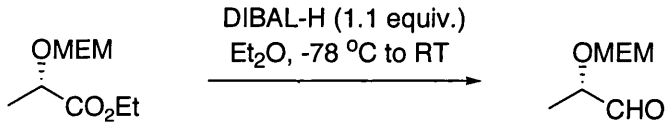
Ethyl (2*S*)-2-methoxyethoxymethoxypropanoate (127).[128]



The reaction was carried out according to general procedure 1 using ethyl (*S*)-lactate **121** (4.8 mL, 42.4 mmol). Purification was carried out by flash column chromatography (20% diethyl ether / petroleum ether) to give ethyl (2*S*)-2-methoxyethoxymethoxypropionate **127** (8.73 g, 100%) as a colourless oil. $[\alpha]_D^{23}$ -62.7 (*c* 2.0, $CHCl_3$), (Lit.[128] $[\alpha]_D^{20}$ -66.7 (*c* 1.2, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1, OCH_2CH_3), 1.43 (3H, d, *J* 6.8, 3-H_3), 3.40 (3H, s, OMe), 3.54 (2H, m, OCH_2CH_2O), 3.75 (2H, m, OCH_2CH_2O), 4.18 (2H, q, *J*

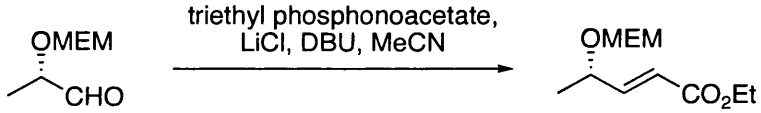
7.1, OCH_2CH_3), 4.25 (1H, q, *J* 6.8, 2-H), 4.80 (2H, s, OCH_2O); *m/z* (CI) 207.1232 (MH^+. $C_9H_{18}O_3$ requires 207.1232), 203 (30%), 179 (3), 131 (100) and 89 (80).

(2*S*)-2-Methoxyethoxymethoxypropan-1-al (131).



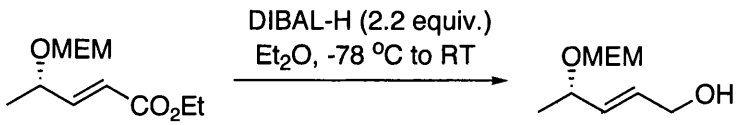
The reaction was carried out according to general procedure 2a using ethyl (2*S*)-2-methoxyethoxymethoxypropanoate **127** (5.0 g, 24.3 mmol) giving (2*S*)-2-methoxyethoxymethoxypropan-1-al **131** (3.93 g, 100%) as a yellow oil, which was used without further purification. δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 7.1, 3-H_3), 3.38 (3H, s, OMe), 3.48-3.90 (4H, m, OCH_2CH_2O), 4.1 (1H, qd, *J* 7.1, 1.9, 2-H), 4.81 (2H, s, OCH_2O) and 9.62 (1H, d, *J* 1.9, CHO).

Ethyl (2*E*,4*S*)-4-methoxyethoxymethoxypent-2-enoate (139).



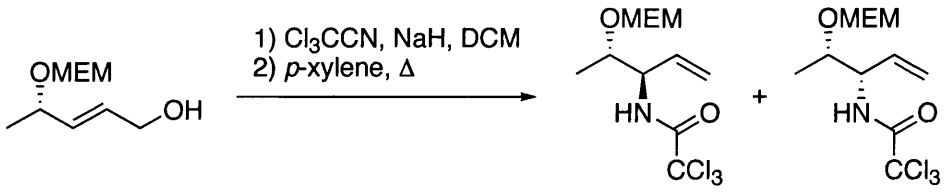
The reaction was carried out according to general procedure 3a using (2*S*)-2-methoxyethoxymethoxypropan-1-al **131** (4.20 g, 25.9 mmol). Purification was carried out by flash column chromatography (30% ethyl acetate / petroleum ether) giving ethyl (2*E*,4*S*)-4-methoxyethoxymethoxypent-2-enoate **139** (1.69 g, 28%) as a yellow liquid. $[\alpha]_D^{21}$ -53.5 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2983 (CH), 1748 (CO), 1656 (C=C), 1180, 1029 and 750; δ_H (400 MHz, $CDCl_3$) 1.28 (6H, m, OCH_2CH_3 and 5-H_3), 3.39 (3H, s, OMe), 3.54-3.78 (4H, m, OCH_2CH_2O), 4.15 (2H, q, *J* 7.2, OCH_2CH_3), 4.42 (1H, qd, *J* 6.8, 1.6 Hz, 4-H), 4.70 (1H, d, *J* 6.8, OC*H*HO), 4.73 (1H, d, *J* 6.8, OCH*H*O), 5.99 (1H, dd, *J* 15.6, 1.6, 2-H), 6.84 (1H, dd, *J* 15.6, 6.8, 3-H); δ_C (100 MHz, $CDCl_3$) 14.4 (CH_3), 20.7 (CH_3), 59.2 (CH_2), 66.7 (CH), 67.1 (CH_2), 71.2 (CH_3), 71.9 (CH_2), 93.6 (CH_2), 121.2 (CH), 149.0 (CH) and 166.6 (C); *m/z* (CI) 233.1390 (MH^+. $C_{11}H_{21}O_5$ requires 233.1389), 203 (10%), 157 (19), 127 (64) and 89 (100).

(2*E*,4*S*)-4-Methoxyethoxymethoxypent-2-en-1-ol (145).



The reaction was carried out according to general procedure 4 using ethyl (2*E*,4*S*)-4-methoxyethoxymethoxypent-2-enoate **139** (1.04 g, 4.48 mmol). Purification was carried out by flash column chromatography (90% ethyl acetate / petroleum ether) giving (2*E*,4*S*)-4-methoxyethoxymethoxypent-2-en-1-ol **145** (0.76 g, 89%) as a yellow liquid. $[\alpha]_D^{24}$ -73.0 (*c* 2.1, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3418 (OH), 2928 (CH), 1290, 1247, 1036, 778 and 734; δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.4, 5-H_3), 1.63 (1H, br s, OH), 3.44 (3H, s, OMe), 3.51 (2H, m, OCH_2CH_2O), 3.60 (2H, m, OCH_2CH_2O), 4.16 (2H, dd, *J* 6.5, 1.2, 1-H_2), 4.23 (1H, q, *J* 6.4, 4-H), 4.70 (1H, d, *J* 7.0, OC*H*HO), 4.77 (1H, d, *J* 7.0, OCH*H*O), 5.61 (1H, m, 3-H) and 5.85 (1H, m, 2-H); δ_C (100 MHz, $CDCl_3$) 21.6 (CH_3), 59.4 (CH_3), 63.2 (CH_2), 67.1 (CH_2), 72.2 (CH_2), 73.0 (CH), 93.6 (CH_2), 131.1 (CH) and 133.3 (CH); *m/z* (CI) 158 (MH^+ - CH_3 and H_2O, 7%), 129 (12), 123 (7) and 89 (100).

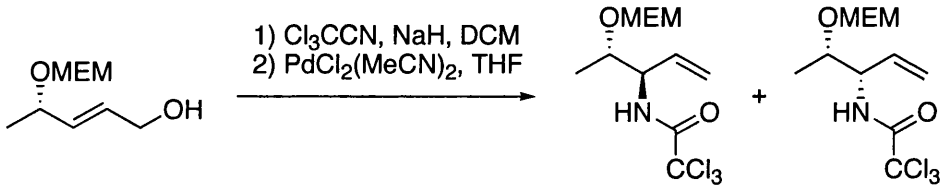
(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxyethoxymethoxy)penta-1-ene (158a) and (3*S*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxyethoxymethoxy)penta-1-ene (158b) from thermal rearrangement.



The reactions were carried out according to general procedure 6 using (2*E*,4*S*)-4-methoxyethoxymethoxypent-2-en-1-ol **145** (0.29 g, 1.50 mmol). Purification was carried out by flash column chromatography (30% ethyl acetate / petroleum ether) giving the title compounds **158a** and **158b** (0.19 g, 37% over two steps) as a yellow oil, in a ratio of 2 : 1 (3*R* : 3*S*). υ_{max}/cm^{-1} (neat) 3289 (NH), 2930 (CH), 1708 (C=O), 1601 (C=C), 1514, 1034 and 820; (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxyethoxymethoxy)penta-1-ene **158a** (major compound): δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.4, 5-H_3), 3.39 (3H, s, OMe), 3.56-3.78 (4H, m, OCH_2CH_2O), 3.91 (1H, qd, *J* 6.4, 2.8, 4-H), 4.41 (1H, m, 3-H), 4.80 (1H, d, *J* 7.2, OC*H*HO), 4.82 (1H, d, *J* 7.2, OCH*H*O), 5.35 (2H, m, 1-H_2), 5.90 (1H, m, 2-H) and 7.73 (1H, br d, *J* 6.4, NH); δ_C (100 MHz, $CDCl_3$) 18.0 (CH_3), 58.3 (CH), 59.4

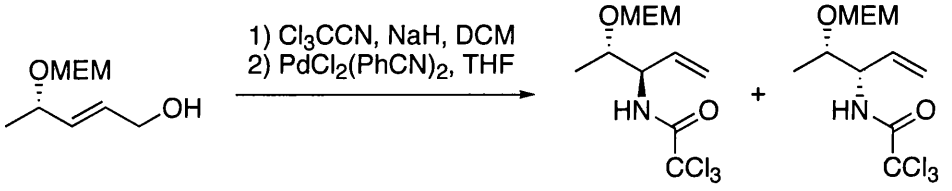
(CH), 68.0 (CH_2), 72.0 (CH_2), 77.4 (CH_3), 93.8 (C), 95.7 (CH_2), 119.6 (CH_2), 131.9 (CH) and 162.2 (C); (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxyethoxymethoxy)penta-1-ene **158b** (minor compound): δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.4, 5-H_3), 3.41 (3H, s, OMe), 3.56-3.78 (4H, m, OCH_2CH_2O), 4.03 (1H, qd, *J* 6.4, 2.4, 4-H), 4.27 (1H, m, 3-H), 4.72 (1H, d, *J* 7.2, OC*H*HO), 4.74 (1H, d, *J* 7.2, OCH*H*O), 5.26 (2H, m, 1-H_2), 5.70 (1H, m, 2-H) and 7.15 (1H, br d, *J* 6.4, NH); *m/z* (CI) 334 (MH^+, 5%), 306 (6), 260 (95), 258 (100), 214 (22) and 162 (40).

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxyethoxymethoxy)penta-1-ene (158a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxyethoxymethoxy)penta-1-ene (158b) from bis(acetonitrile)palladium(II) chloride catalysed aza-Claisen rearrangement.



The reactions were carried out according to general procedure 5 using (2*E*,4*S*)-4-methoxyethoxymethoxypent-2-en-1-ol **145** (0.52 g, 2.7 mmol) and bis(acetonitrile)palladium(II) chloride (10 mol%). Purification was carried out by flash column chromatography (30% ethyl acetate / petroleum ether) giving the title compounds **158a** and **158b** (0.54 g, 60% over two steps) as a yellow oil, in a ratio of 8 : 1 (3*R* : 3*S*). Spectroscopic data as above.

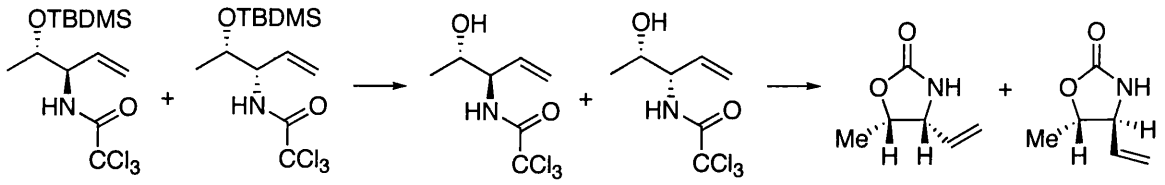
(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxyethoxymethoxy)penta-1-ene (158a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxyethoxymethoxy)penta-1-ene (158b) from bis(benzonitrile)palladium(II) chloride catalysed aza-Claisen rearrangement.



The reactions were carried out according to general procedures 5 using (2*E*,4*S*)-4-methoxyethoxymethoxypent-2-en-1-ol **145** (0.30 g, 1.55 mmol) and

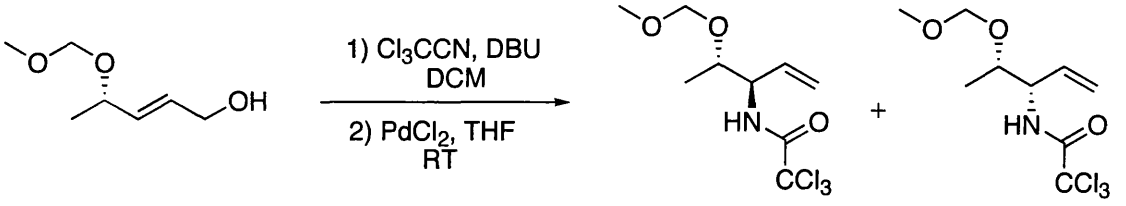
bis(benzonitrile)palladium(II) chloride (10 mol%). Purification was carried out by flash column chromatography (30% ethyl acetate / petroleum ether) giving the title compounds **158a** and **158b** (0.27 g, 52% over two steps) as a yellow oil, in a ratio of 8 : 1 (3*R* : 3*S*). Spectroscopic data as above.

(4*R*,5*S*)-4-Vinyl-5-methyl-oxazolidin-2-one (160a) and (4*S*,5*S*)-4-vinyl-5-methyl-oxazolidin-2-one (160b).



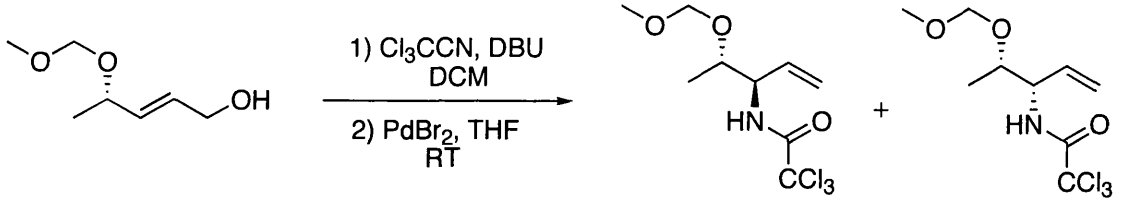
A mixture of (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(*tert*-butyldimethylsilyloxy)penta-1-ene **153a** and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(*tert*-butyldimethylsilyloxy)penta-1-ene **153b** (0.11 g, 0.3 mmol) and tetra-*n*-butylammonium fluoride (1.0 M solution in THF) (0.32 mL, 0.32 mmol) in THF (5 mL) was allowed to stir at room temperature for 0.5 h. The reaction mixture was then concentrated and the resulting residue was taken up in ethyl acetate (20 mL), washed with water (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (70% ethyl acetate / petroleum ether) gave a yellow oil. The oil was added to a solution of potassium hydroxide (0.12 g, 2.22 mmol) in isopropanol (5 mL) and the reaction mixture was allowed to stir at room temperature for 12 h. The mixture was then concentrated and the resulting residue was dissolved in water (10 mL) and extracted with ethyl acetate (5 x 10 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compounds **160a** and **160b** (16 mg, 41% over two steps) as a colourless oil, in a ratio of 2 : 1 (4*R* : 4*S*). υ_{max}/cm^{-1} (neat) 3280 (NH), 2984 (CH), 1733 (CO), 1645 (C=C), 1383, 1227 and 1056; (4*R*,5*S*)-4-vinyl-5-methyl-oxazolidin-2-one **160a** (major compound): δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.5, 5-CH_3), 4.33 (1H, t, *J* 6.1, 4-H), 4.82 (1H, dq, *J* 7.9, 6.5, 5-H), 5.30 (2H, m, 4-CH=CH_2) and 5.78 (1H, m, 4-C*H*=CH_2); δ_C (100 MHz, $CDCl_3$) 16.4 (CH_3), 58.8 (CH), 76.7 (CH), 119.6 (CH_2), 133.4 (CH) and 160.1 (C); (4*S*,5*S*)-4-vinyl-5-methyl-oxazolidin-2-one **160b** (minor compound): δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* 6.2, 5-CH_3), 3.90 (1H, t, *J* 7.2, 4-H), 4.33 (1H, qd, *J* 7.9, 6.2, 5-H), 5.24 (2H, m, 4-CH=CH_2) and 5.78 (1H, m, 4-C*H*=CH_2); δ_C (100 MHz, $CDCl_3$) 19.3 (CH_3), 63.3 (CH), 79.2 (CH), 119.3 (CH_2), 135.7 (CH) and 160.0 (C); *m/z* (CI) 128.0711 (MH^+. $C_6H_{10}O_2N$ requires 128.0712), 126 (2%), 112 (1) and 84 (1).

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157b) from palladium (II) chloride catalysed aza-Claisen rearrangement.



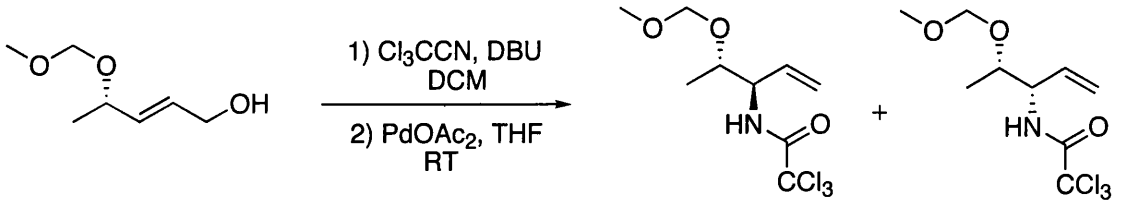
The reactions were carried out according to general procedure 7 for 120 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol **144** (100 mg, 0.69 mmol) then palladium(II) chloride (12 mg, 10 mol%) to give (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157a** and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157b** (90 mg, 45% over two steps) as a brown oil, in a 11 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157b) from palladium (II) bromide catalysed aza-Claisen rearrangement.



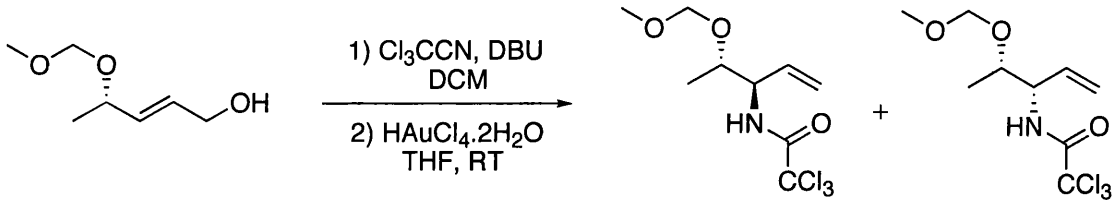
The reaction was carried out according to general procedure 7 for 72 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol **144** (100 mg, 0.69 mmol) then palladium(II) bromide (18 mg, 10 mol%) to give (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157a** and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157b** (87 mg, 44% over two steps) as a brown oil, in a 9 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157b) from palladium(II) acetate catalysed aza-Claisen rearrangement.



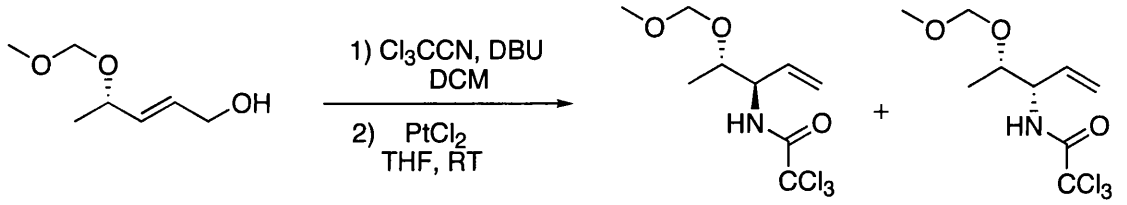
The reactions were carried out according to general procedure 7 for 96 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol **144** (72 mg, 0.49 mmol) then palladium(II) acetate (18 mg, 10 mol%) to give (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157a** and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157b** (25 mg, 18% over two steps) as a brown oil, in a 9 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157b) from hydrogen tetrachloroaurate(III) hydrate catalysed aza-Claisen rearrangement.



The reactions were carried out according to general procedure 7 for 48 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol **144** (100 mg, 0.69 mmol) then hydrogen tetrachloroaurate(III) hydrate (24 mg, 10 mol%) to give (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157a** and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157b** (98 mg, 49% over two steps) as a brown oil, in a 6 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

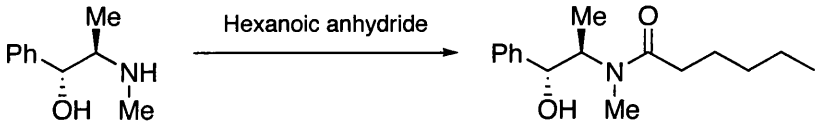
(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157b) from platinium(II) chloride catalysed aza-Claisen rearrangement.



The reactions were carried out according to general procedure 7 for 144 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol **144** (50 mg, 0.34 mmol) then platinium chloride (9 mg, 10 mol%) to give (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157a** and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157b** (49 mg, 49% over two steps) as a brown oil, in a 10 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

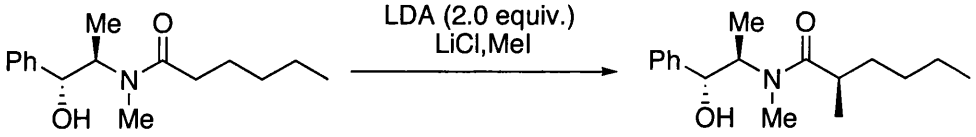
2.0 Further Evidence for the Directing Effect and Enhancement of Stereoselectivity

(1*R*,2*R*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylhexanamide (164).[68]



Hexanoic anhydride (6.0 mL, 25.9 mmol) was added dropwise over several minutes to a solution of (1*R*,2*R*)-(-)-pseudoephedrine **163** (4.0 g, 24.2 mmol) in THF (60 mL). The reaction mixture was stirred at room temperature for 0.5 h before the excess anhydride was quenched by the addition of a saturated solution of aqueous sodium bicarbonate solution (50 mL). The reaction mixture was then extracted with ethyl acetate (3 x 50 mL). The organic layers were then combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (50% ethyl acetate / petroleum ether) gave (1*R*,2*R*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylhexanamide **164** (6.4 g, 100%). $[\alpha]_D^{21}$ -87.2 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.81 (3H, t, *J* 7.0, 6'-H_3), 0.91 (1H, d, *J* 6.7, OH), 1.01 (2H, d, *J* 7.0, 1-CH_3), 1.24 (4H, m, 4'-H_2, 5'-H_2), 1.43 (2H, m, 3'-H_2), 2.14 (2H, dt, *J* 15.5, 7.8, 2'-H_2), 2.71 (3H, s, NCH_3), 4.31 (1H, m, 1-H), 4.41 (1H, m, 2-H) and 7.08-7.35 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3), 14.5 (CH_3), 15.3 (CH_3), 22.5 (CH_2), 24.7 (CH_2), 31.5 (CH_2), 34.4 (CH_2), 58.3 (CH), 75.5 (CH), 126.3 (CH), 127.6 (CH), 128.3 (CH), 142.5 (C) and 175.7 (C); *m/z* (CI) 264.1965 (MH^+. $C_{16}H_{26}NO_2$ requires 264.1964), 256 (5%), 186 (2) and 156 (4).

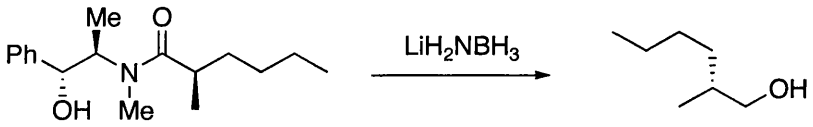
(1*R*,2*R*,2'*R*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-2',*N*-dimethylhexanamide (165).[68]



A solution of lithium chloride (3.3 g, 77.6 mmol) and diisopropylamine (4.4 mL, 31.7 mmol) in THF (25 mL) was cooled to -78 °C before *n*-butyllithium (2.4 M in hexane, 12.3 mL, 29.5 mmol) was added. The solution was warmed briefly to 0 °C, then was cooled to -78 °C and stirred for 0.5 h. A solution of (1*R*,2*R*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylhexanamide **164** (3.4 g, 12.9 mmol) in THF (35 mL), cooled to 0 °C, was transferred to the reaction flask and the resulting solution was stirred at -78 °C for 1 h, 0 °C

for 0.25 h and at room temperature for 5 min. The reaction mixture was then cooled to 0 °C and methyl iodide (2.95 mL, 19.4 mmol) was added. After 1 h, the reaction was quenched with a saturated solution of aqueous ammonium chloride solution (50 mL). The two phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (50% ethyl acetate / petroleum ether) gave (1*R*,2*R*,2'*R*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-2',*N*-dimethylhexanamide **165** (3.54 g, 99%). $[\alpha]_D^{21}$ -122.6 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3377 (OH), 2931 (CH), 1613 (CO), 1454, 1407, 1109 and 1050; (1*R*,2*R*,2'*R*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-2',*N*-dimethylhexanamide **165** exists as a 3 : 1 mixture of rotomers, signals for the major rotamer are: δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.2, 6'-H_3), 1.04 (3H, d, *J* 6.8, 2'-CH_3), 1.12 (1H, d, *J* 7.2, OH), 1.16-1.42 (8H, m, 3'-*H*H, 4'-H_2, 5'-H_2, 1-CH_3), 1.68 (1H, m, 3'-H*H*), 2.59 (1H, sex, *J* 6.8, 2'-H), 2.81 (3H, s, N-CH_3), 4.31 (1H, m, 1-H), 4.67 (1H, t, *J* 7.2, 2-H) and 7.25-7.57 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 14.4 (CH_3), 17.4 (CH_3), 17.7 (CH_3), 22.7 (CH_2), 29.6 (CH_2), 33.7 (CH_2), 36.0 (CH), 58.1 (CH), 76.5 (CH_3), 126.2 (CH), 127.4 (CH), 128.2 (CH), 142.6 (C) and 179.1 (C); *m/z* (CI) 278.2119 (MH^+. $C_{17}H_{28}NO_2$ requires 278.2120), 169 (25%) and 106 (8).

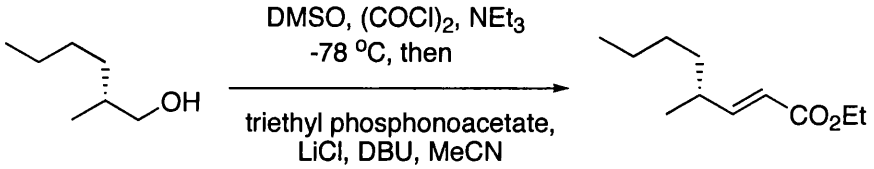
(2*R*)-2-Methylhexan-1-ol (166).[129]



n-Butyllithium (2.4 M in hexane, 20 mL, 47.3 mmol) was added to a solution of di-isopropylamine (7.2 mL, 50.9 mmol) in THF at -78 °C. The resulting solution was stirred at -78 °C for 10 min, then warmed to 0 °C for 10 min. Borane-ammonia complex (90%, 1.67 g, 48.51 mmol) was added in one portion and the suspension was cooled to -78 °C before a solution of (1*R*,2*R*,2'*R*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-2',*N*-dimethylhexanamide **165** (3.36 g, 48.5 mmol) in THF (35 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was then cooled to 0 °C before 2 M hydrochloric acid (120 mL) was carefully added and allowed to stir for 0.5 h. The organic layer was then separated followed by extraction of the aqueous layer with ether (4 x 45 mL). The combined organic layers were washed sequentially with 2 M hydrochloric acid (20 mL), 1 M sodium hydroxide solution (20 mL) and brine (20 mL). The diethyl ether extracts were dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (40% diethyl ether /

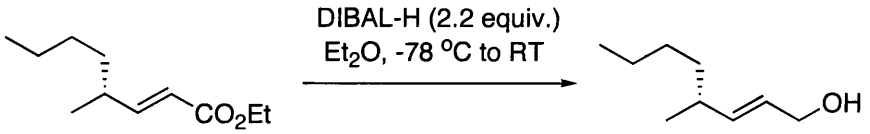
petroleum ether) gave (2*R*)-2-methylhexan-1-ol **166** (0.86 g, 62%) as a colourless liquid. $[\alpha]_D^{21}$ +12.8 (*c* 1.0, $CHCl_3$) (Lit.[129] $[\alpha]_D^{21}$ +12.8 (*c* 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89-0.99 (6H, m, 2-CH_3, 6-H_3), 1.09-1.48 (7H, m, 3-H_2, 4-H_2, 5-H_2, OH), 1.63 (1H, m, 2-H), 3.44 (1H, dd, *J* 10.4, 6.4, 1-*H*H) and 3.54 (1H, dd, *J* 10.4, 6.4, 1-H*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 16.6 (CH_3), 23.0 (CH_2), 29.2 (CH_2), 32.9 (CH_2), 35.8 (CH) and 68.5 (CH_2); *m/z* (CI) 85 (MH^+ - CH_2OH, 100%), 79 (67) and 73 (19).

Ethyl (2*E*,4*R*)-4-methyloctan-2-enoate (167).



The reactions were carried out according to general procedure 3b using (2*R*)-2-methylhexan-1-ol **166** (0.1 g, 0.9 mmol). Purification by flash column chromatography (30% ether / petroleum ether) gave ethyl (2*E*,4*R*)-4-methyloctan-2-enoate **167** (0.05 g, 34%) as a colourless oil. $[\alpha]_D^{23}$ -30.8 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2959 (CH), 1717 (CO), 1651 (C=C), 1263 and 1177; δ_H (400 MHz, $CDCl_3$) 0.81 (3H, t, *J* 6.8, OCH_2CH_3), 0.97 (3H, d, *J* 6.8, 4-CH_3), 1.16-1.38 (9H, m, 5-H_2, 6-H_2, 7-H_2, 8-H_3), 2.21 (1H, m, 4-H), 4.11 (2H, q, *J* 6.8, OCH_2CH_3), 5.70 (1H, dd, *J* 16.0, 1.2, 2-H) and 6.79 (1H, dd, *J* 16.0, 7.6, 3-H); δ_C (100 MHz, $CDCl_3$) 13.0 (CH_3), 13.3 (CH_3), 18.4 (CH_3), 21.7 (CH_2), 28.4 (CH_2), 34.7 (CH_2), 35.5 (CH), 59.1 (CH), 118.5 (CH), 153.8 (CH) and 166.0 (C); *m/z* (EI) 184.1464 (MH^+. $C_{11}H_{20}O_2$ requires 184.1463), 169 (1%), 155 (1), 142 (11), 84 (65) and 82 (100).

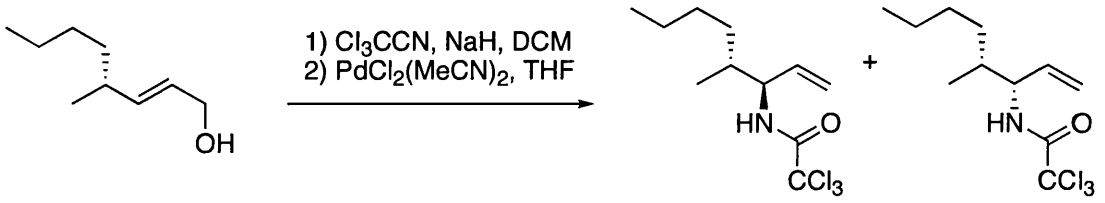
(2*E*,4*R*)-4-Methyloctan-2-en-1-ol (168).



The reaction was carried out according to general procedure 4 using ethyl (2*E*,4*R*)-4-methyloctan-2-enoate **167** (0.4 g, 2.2 mmol). Purification by flash column chromatography (30% diethyl ether / petroleum ether) gave (2*E*,4*R*)-4-methyloctan-2-en-1-ol **168** (0.14 g, 45%) as a clear liquid. $[\alpha]_D^{19}$ -15.7 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3296 (OH), 2921 (CH), 1675 (C=C), 1455, 1380 and 969; δ_H (400 MHz, $CDCl_3$) 0.84-0.95 (5H, m, 7-H_2, 8-H_3), 0.99 (3H, d, *J* 6.4, 4-CH_3), 1.22-1.56 (4H, m, 5-H_2, 6-H_2), 2.14 (1H, quin, *J*

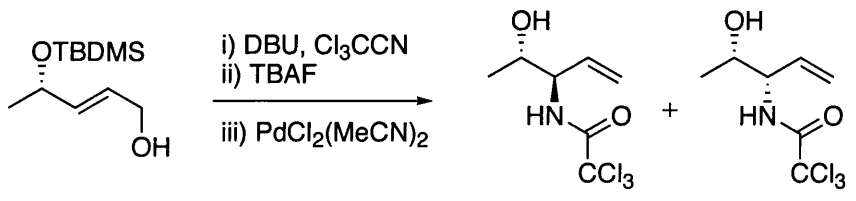
6.4, 4-H), 3.49 (1H, m, OH), 4.12 (2H, m, 1-H_2) and 5.60 (2H, m, 2-H, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 20.4 (CH_3), 22.8 (CH_2), 29.5 (CH_2), 36.3 (CH), 36.6 (CH_2), 64.0 (CH_2), 127.0 (CH) and 139.4 (CH); *m/z* (CI): 125 (MH^+ - H_2O, 100%), 99 (10) and 83 (11).

(3*S*,4*R*)-3-(Trichloromethylcarbonylamino)-4-methylocta-1-ene (170a) and (3*R*,4*R*)-3-(trichloromethylcarbonylamino)-4-methylocta-1-ene (170b).



The reactions were carried out according to general procedure 5 using (2*E*,4*R*)-4-methyloctan-2-en-1-ol **168** (0.16 g, 1.1 mmol) then bis(acetonitrile)palladium(II) chloride (10 mol%). Purification by chromatography (50% diethyl ether / petroleum ether) gave the target compounds **170a** and **170b** (0.19 g, 59%) as a colourless oil, in a ratio of 1 : 2 (3*R* : 3*S*). υ_{max}/cm^{-1} (neat) 3330 (NH), 2959 (CH), 1694 (CO), 1513 and 817; (3*R*,4*R*)-3-(trichloromethylcarbonylamino)-4-methylocta-1-ene **170a** (major isomer): δ_H (400 MHz, $CDCl_3$) 0.81-1.02 (6H, m, 4-CH_3, 8-H_3), 1.21-1.46 (6H, m, 5-H_2, 6-H_2, 7-H_2), 2.05 (1H, m, 4-H), 4.42 (1H, m, 3-H), 5.26 (2H, m, 1-H_2), 5.82 (1H, m, 2-H) and 6.63 (1H, br s, NH); (3*S*,4*R*)-3-(trichloromethylcarbonylamino)-4-methylocta-1-ene **170b** (minor isomer): δ_H (400 MHz, $CDCl_3$) 0.81-1.02 (6H, m, 4-CH_3, 8-H_3), 1.21-1.46 (6H, m, 5-H_2, 6-H_2, 7-H_2), 1.91 (1H, m, 4-H), 4.48 (1H, m, 3-H), 5.18 (2H, m, 1-H_2), 5.82 (1H, m, 2-H) and 6.48 (1H, br s, NH); *m/z* (CI) 286 (MH^+, 26%), 216 (12), 167 (6), 125 (12) and 104 (5).

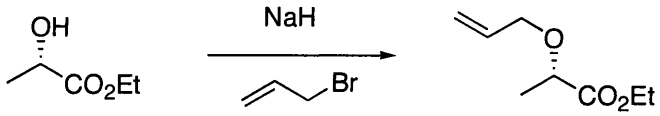
(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-hydroxypenta-1-ene (159a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-hydroxypenta-1-ene. (159b)



(2*E*,4*S*)-4-(*tert*-Butylldimethylsilyloxy)-pent-2-en-1-ol **140** (0.8 g, 3.7 mmol) was dissolved in DCM (20 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5,4,0]undec-7-ene (0.6 mL, 4.4 mmol) and trichloroacetonitrile (0.6 mL, 5.6 mmol) were then added and the mixture was allowed to warm to room temperature and stirred for 2 h. The reaction

mixture was then filtered through a dry silica plug and the filtrate was concentrated *in vacuo* to give an orange liquid. The product was used without further purification. The allylic trichloroacetimidate and tetra-*n*-butylammonium fluoride (TBAF) (1M soln in THF) (6.7 mL, 6.7 mmol) in THF (20 mL) was allowed to stir at room temperature for 24 h. The reaction mixture was concentrated and the resulting residue was taken up in ethyl acetate (30 mL), washed with water (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The product was used without further purification. The allylic trichloroacetimidate was dissolved in THF (10 mL). Bis(acetonitrile)palladium(II) chloride (10 mol%) was then added and the reaction mixture stirred for 24 h. Concentration *in vacuo* followed by purification by flash column chromatography (40% ethyl acetate / petroleum ether) gave (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-hydroxypenta-1-ene **159a** and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-hydroxypenta-1-ene **159b** (0.28 g, 31% over three steps) as a yellow oil, in a ratio of 4 : 1 (3*R*,3*S*). υ_{max}/cm^{-1} (neat): 3403 (OH and NH), 2979 (CH), 1693 (CO), 1644 (C=C), 1513, 1131, 929 and 822; (3*R*,4*S*)-3-(trichloromethyl carbonylamino)-4-hydroxypenta-1-ene **159a**: δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.4, 5-H_3), 1.97 (1H, br d, *J* 5.6, OH), 4.05 (1H, m, 4-H), 4.38 (1H, m, 3-H), 5.39 (2H, m, 1-H_2), 5.90 (1H, m, 2-H) and 7.24 (1H, br d, *J* 6.4, NH); δ_C (100 MHz, $CDCl_3$) 20.0 (CH_3), 58.6 (CH), 68.9 (CH), 92.7 (C), 119.6 (CH_2), 131.1 (CH) and 161.4 (C); (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-hydroxypenta-1-ene **159b**: δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.4, 5-H_3), 2.04 (1H, br s, OH), 4.05 (1H, m, 4-H), 4.38 (1H, m, 3-H), 5.33 (2H, m, 1-H_2), 5.90 (1H, m, 2-H) and 7.13 (1H, br d, *J* 6.4, NH); δ_C (100 MHz, $CDCl_3$) 20.0 (CH_3), 58.2 (CH), 68.6 (CH), 92.7 (C), 117.4 (CH_2), 134.7 (CH) and 162.0 (C); *m/z* (CI) 245.9852 (MH^+. $C_7H_{11}O_2N^{35}Cl_3$ requires 245.9855), 228 (10%), 212 (7) and 172 (4).

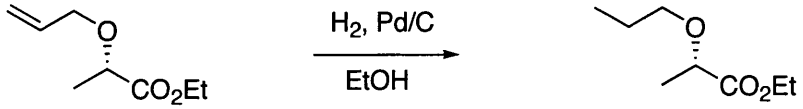
Ethyl (2*S*)-2-(propyloxy-2-ene)propanoate (175).[130]



The reaction was carried out according to general procedure 1 using ethyl (*S*)-lactate **121** (10.0 g, 84.8 mmol). Purification by flash column chromatography (40% diethyl ether / petroleum ether) gave ethyl (2*S*)-2-(propyloxy-2-ene)propanoate **175** (13.4 g, 100%) as a yellow liquid. $[\alpha]_D^{25}$ -67.8 (*c* 2.0, MeOH) (Lit.[130] $[\alpha]_D^{25}$ -70.7 (*c* 2.7, MeOH)); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.2, OCH_2CH_3), 1.44 (3H, d, *J* 6.8, 3-H_3), 3.96 (1H, ddt, *J* 12.8, 6.8, 1.2, OC*H*HCHCH_2), 4.02 (1H, q, *J* 6.8, 2-H), 4.16 (1H, ddt, *J* 12.8, 5.6 and 1.2, OCH*H*CHCH_2), 4.23 (2H, m, OCH_2CH$_3$), 5.20-5.34 (2H, m, OCH_2CHCH_2) and 5.89-5.99

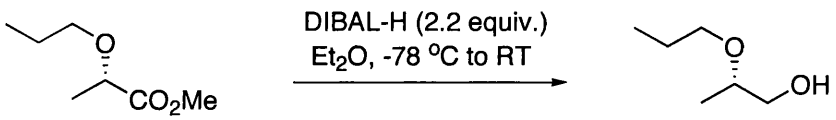
(1H, m, OCH_2CHCH_3); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 18.7 (CH_3), 60.8 (CH_2), 71.1 (CH_2), 74.1 (CH), 117.7 (CH_2), 134.2 (CH) and 173.3 (C); *m/z* (CI) 159.1018 (MH^+. $C_8H_{15}O_3$ requires 159.1021), 157 (2%) and 119 (2).

Ethyl (2*S*)-2-propyloxypropanoate (176).[131]



Ethyl (2*S*)-2-(propyloxy-2-ene)propanoate **175** (12.9 g, 81.6 mmol) was dissolved in ethanol (50 mL) before palladium (10% on carbon) (50 mg) was added. The reaction vessel was flushed with hydrogen then allowed to stir under an atmosphere of hydrogen for 72 h. The reaction mixture was filtered through a short pad of Celite®, which was then washed with chloroform. The combined filtrates were concentrated and purified by flash chromatography (15% diethyl ether / petroleum ether) to give ethyl (2*S*)-2-propyloxypropanoate **176** (9.21 g, 71% yield) as a yellow liquid. $[\alpha]_D^{25}$ -98.3 (neat), (Lit.[131] $[\alpha]_D^{20}$ -100.9 (neat)); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.2, $OCH_2CH_2CH_3$), 1.31 (3H, t, *J* 7.2, OCH_2CH_3), 1.42 (3H, d, *J* 6.8, 3-H_3), 1.64 (2H, sex, *J* 7.2, $OCH_2CH_2CH_3$), 3.34 (1H, dt, *J* 8.8, 7.2, $OCHHCH_2CH_3$), 3.54 (1H, dt, *J* 8.8, 7.2, $OCHHCH_2CH_3$) 3.96 (1H, q, *J* 6.8, 2-H) and 4.22 (2H, m, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 10.5 (CH_3), 14.3 (CH_3), 18.7 (CH_3), 23.0 (CH_2), 60.7 (CH_2), 72.0 (CH_2), 75.0 (CH) and 173.6 (C); *m/z* (CI) 161.1176 (MH^+. $C_8H_{17}O_3$ requires 161.1178), 228 (10%), 212 (7) and 172 (4).

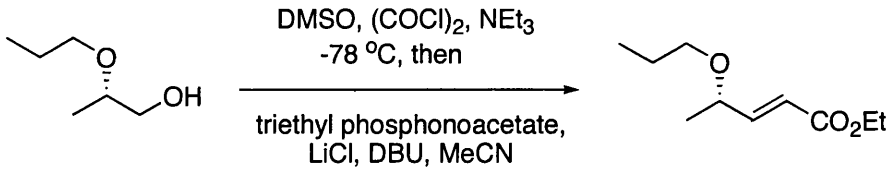
(2*S*)-2-Propyloxypropan-1-ol (177).[132]



The reaction was carried out according to general procedure 2b using ethyl (2*S*)-2-propyloxypropanoate **176** (5.0 g, 31.3 mmol). Purification was carried out by flash column chromatography (50% diethyl ether / petroleum ether) to give (2*S*)-2-propyloxypropan-1-ol **177** (1.83 g, 51%) as clear liquid. $[\alpha]_D^{24}$ +17.8° (*c* 1.0, $CHCl_3$), (Lit.[132] $[\alpha]_D^{20}$ +26.1 (neat); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.6, $OCH_2CH_2CH_3$), 1.12 (3H, d, *J* 6.0, 3-H_3), 1.61 (2H, m, $OCH_2CH_2CH_2$), 2.08 (1H, br s, OH), 3.34 (1H, dt, *J* 8.8, 6.8, $OCHHCH_2CH_2$) and 3.41-3.61 (4H, m, 1-H_2, 2-H and $OCHHCH_2CH_3$); δ_C (100 MHz, $CDCl_3$) 10.6 (CH_3), 15.9

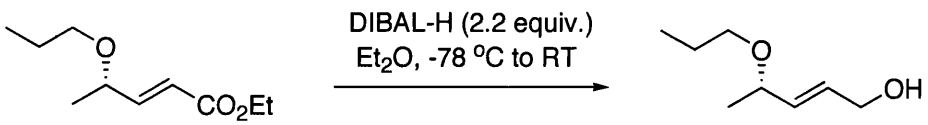
(CH_3), 23.3 (CH_2), 66.4 (CH_2), 70.5 (CH_2) and 75.7 (CH); *m/z* (CI) 119.1074 (MH^+. $C_6H_{15}O_2$ requires 119.1072), 113 (3%) and 85 (4).

Ethyl (2*E*,4*S*)-4-propyloxypent-2-enoate (178).



The reactions were carried out according to general procedure 3b using (2*S*)-propyloxypropan-1-ol **177** (1.8 g, 15.3 mmol). Purification was carried out by flash column chromatography (40% diethyl ether / petroleum ether) to give ethyl (2*E*,4*S*)-4-propyloxypent-2-enoate **178** (1.15 g, 41% over two steps). $[\alpha]_D^{24}$ -10.0 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat): 2977 (CH), 1719 (CO), 1658 (C=C), 1271, 1180, 1097 and 982; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.0, $OCH_2CH_2CH_3$), 1.30 (3H, d, *J* 6.4, 5-H_3), 1.32 (3H, t, *J* 7.2, OCH_2CH_3), 1.61 (2H, sex, *J* 7.0, $OCH_2CH_2CH_3$), 3.34 (1H, dt, *J* 8.8, 7.0, $OCHHCH_2CH_3$), 3.41 (1H, dt, *J* 8.8, 7.0, $OCHHCH_2CH_3$), 4.01 (1H, quin d, *J* 6.4, 1.2, 4-H), 4.22 (2H, q, *J* 7.2, OCH_2CH_3), 5.99 (1H, dd, *J* 15.6, 1.2, 2-H) and 6.87 (1H, dd, *J* 15.6, 6.4, 3-H); δ_C (100 MHz, $CDCl_3$) 10.6 (CH_3), 14.3 (CH_3), 20.7 (CH_3), 23.1 (CH_2), 60.4 (CH_2), 70.8 (CH_2), 74.6 (CH), 120.8 (CH), 149.8 (CH) and 166.5 (C); *m/z* (CI) 187.1336 (MH^+. $C_{10}H_{18}O_3$ requires 187.1334), 186 (1%), 127 (12) and 117 (1).

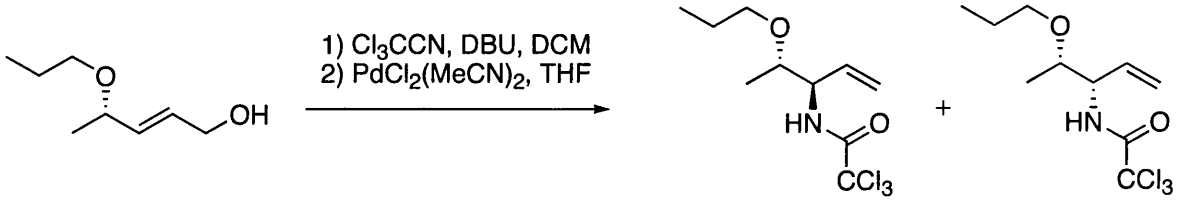
(2*E*,4*S*)-4-Propyloxypent-2-en-1-ol (179).



The reaction was carried out according to general procedure 4 using ethyl (2*E*,4*S*)-4-propyloxypent-2-enoate **178** (1.1 g, 5.8 mmol). Purification was carried out by flash column chromatography (50% diethyl ether / petroleum ether) to give (2*E*,4*S*)-4-propyloxypent-2-en-1-ol **179** (0.55 g, 66%) as a clear liquid. $[\alpha]_D^{24}$ -11.0 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat): 3367 (OH), 2970 (CH), 1653 (C=C), 1558, 1541, 1456, 1086 and 971; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.2, $CH_2CH_2CH_3$), 1.26 (3H, d, *J* 6.4, 5-H_3), 1.41 (1H, t, *J* 6.4, OH), 1.60 (2H, sex, *J* 7.2, $CH_2CH_2CH_3$), 3.30 (1H, dt, *J* 8.8, 7.2, $CHHCH_2CH_3$), 3.42 (1H, dt, *J* 8.8, 7.2, $CHHCH_2CH_3$), 3.88 (1H, quin, *J* 6.4, 4-H), 4.18 (2H, m, 1-H_2), 5.66 (1H, ddt, *J* 15.2, 6.4, 1.2, 3-H) and 5.81 (1H, dt, *J* 15.2, 5.6, 2-H); δ_C (100 MHz,

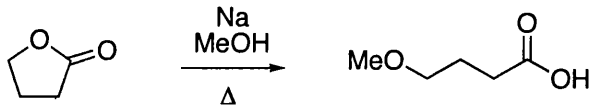
$CDCl_3$) 10.6 (CH_3), 21.3 (CH_3), 23.1 (CH_2), 63.1 (CH_2), 70.1 (CH_2), 75.5 (CH), 130.2 (CH) and 134.0 (CH); *m/z* (CI) 145.1223 (MH^+. $C_8H_{17}O_2$ requires 145.1229), 127 (44%) and 85 (100).

(3*R*,4*S*)-Trichloromethylcarbonylamino-4-propyloxypenta-1-ene (187a) and (3*S*,4*S*)-trichloromethylcarbonylamino-4-propyloxypenta-1-ene (187b).



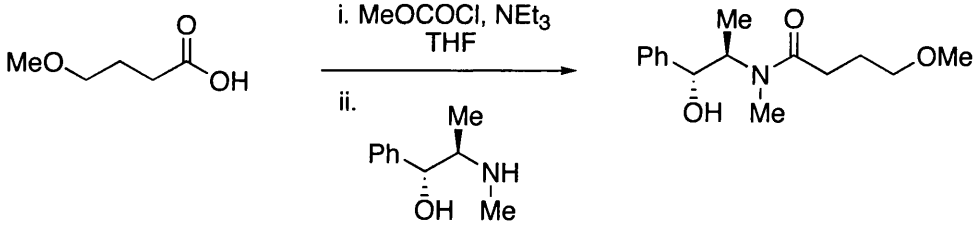
The reactions were carried out according to general procedure 7 using (2*E*,4*S*)-4-propyloxypent-2-en-1-ol **179** (0.2 g, 1.4 mmol) and bis(acetonitrile)palladium(II) chloride (10 mol%). Purification was carried out by flash column chromatography (30% diethyl ether / petroleum ether) to give the title compounds **187a** and **187b** (0.25 g, 77%) as a brown oil in a ratio of 5 : 1 (3*R*,3*S*). υ_{max}/cm^{-1} (neat): 3331 (NH), 2931 (CH), 1715 (CO), 1652 (C=C), 1518, 1114 and 822; (3*R*,4*S*)-trichloromethylcarbonylamino-4-propyloxypenta-1-ene **187a**: δ_H (400 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.7, $CH_2CH_2CH_3$), 1.18 (3H, d, *J* 6.4, 5-H_3), 1.54-1.65 (2H, m, $CH_2CH_2CH_3$), 3.29 (1H, dt, *J* 8.8, 6.4, $CHHCH_2CH_3$), 3.62-3.67 (2H, m, 4-H and $CHHCH_2CH_3$), 4.32-4.39 (1H, m, 3-H), 5.31-5.36 (2H, m, 1-H_2) and 5.82-5.91 (1H, m, 2-H); δ_C (100 MHz, $CDCl_3$) 10.8 (CH_3), 16.0 (CH_3), 23.1 (CH_2), 57.9 (CH), 70.8 (CH_2), 75.8 (CH), 92.5 (C), 119.2 (CH_2), 131.8 (CH) and 161.0 (C); (3*S*,4*S*)-trichloromethylcarbonylamino-4-propyloxypenta-1-ene **187b**: δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.6, $CH_2CH_2CH_3$), 1.21 (3H, d, *J* 6.4, 5-H_3), 1.57-1.66 (2H, m, $CH_2CH_2CH_3$), 3.34 (1H, dt, *J* 8.8, 6.8, $CHHCH_2CH_3$), 3.54-3.60 (2H, m, 4-H and $CHHCH_2CH_3$), 4.32-4.39 (1H, m, 3-H), 5.23-5.28 (2H, m, 1-H_2) and 5.87-5.95 (1H, m, 2-H); δ_C (100 MHz, $CDCl_3$) 10.7 (CH_3), 17.0 (CH_3), 23.1 (CH_2), 58.1 (CH), 71.1 (CH_2), 75.8 (CH), 88.4 (C), 116.9 (CH_2), 135.1 (CH) and 161.4 (C); *m/z* (CI) 288.0328 (MH^+. $C_{10}H_{17}O_2N^{35}Cl_3$ requires 288.0325), 254 (20%) and 218 (100).

4-Methoxybutanoic acid (181).[133]



γ-Butyrolactone **180** (10.0 g, 116.3 mmol) was added dropwise to a solution of sodium (8.0 g, 348.8 mmol) in methanol at 0 °C. The reaction mixture was then heated under reflux for 48 h, cooled and concentrated. The resulting white residue was acidified to pH 2 with 2 M hydrochloric acid solution and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give 4-methoxybutanoic acid **181** (7.0 g, 51%) as a clear oil. δ_H (400 MHz, $CDCl_3$) 1.90 (2H, m, 3-H_2), 2.48 (2H, t, *J* 7.2, 2-H_2), 3.36 (3H, s, OMe) and 3.45 (2H, t, *J* 6.0, 4-H_2); δ_C (100 MHz, $CDCl_3$) 24.6 (CH_3), 30.8 (CH_2), 58.6 (CH_3), 71.5 (CH_2) and 178.9 (C); *m/z* (CI) 119.0710 (MH^+. $C_5H_{11}O_3$ requires 119.0708), 101 (38%) and 87 (21).

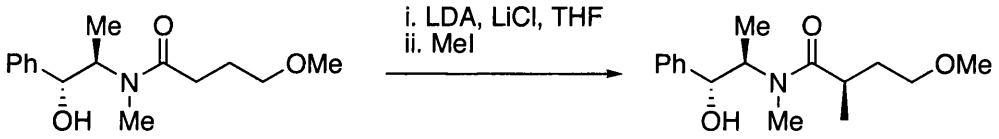
(1*R*,2*R*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-4'-methyloxy-*N*-methylbutyramide (182).



4-Methoxybutanoic acid **181** (2.36 g, 20.0 mmol) was dissolved in THF (50 mL) and cooled to 0°C. Triethylamine (3.1 mL, 22.0 mmol) and methyl chloroformate (1.7 mL, 22.0 mmol) were then added producing a white precipitate. This suspension was stirred for 1 h before a solution of (1*R*,2*R*)-(-)-pseudoephedrine (3.63 g, 22.0 mmol) in THF (20 mL) was added and the mixture was allowed to stir at room temperature for 12 h. The reaction was quenched with brine (50 mL), concentrated and then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give a clear liquid. Purification was carried out by flash column chromatography (50% ethyl acetate / petroleum ether) to give (1*R*,2*R*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-4'-methyloxy-*N*-methylbutyramide **182** (5.1 g, 97%) as a clear liquid. $[\alpha]_D^{21}$ –91.8 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3390 (OH), 2932 (CH), 1623 (CO), 1453 (C=C), 1118, 756 and 703; (1*R*,2*R*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-4'-methyloxy-*N*-methylbutyramide **182** exists as a 3 : 1 mixture of rotomers, signals for the

major rotamer are: δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.8, 1-CH_3), 1.92 (2H, m, 3'-H_2), 2.40 (2H, m, 2'-H_2), 2.85 (3H, s, NMe), 3.34 (3H, s, OMe), 3.43 (2H, t, *J* 6.0, 4'-H_2), 4.27 (1H, br s, 2-OH), 4.47 (1H, m, 1-H), 4.56-4.63 (1H, m, 2-H) and 7.33-4.40 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.5 (CH_3), 25.1 (CH_2), 30.9 (CH_2), 58.6 (CH_3), 71.8 (CH_2), 76.6 (CH_3), 126.4 (CH), 127.0 (CH), 127.7 (CH), 128.4 (CH), 128.7 (CH), 142.3 (C) and 175.1 (C); *m/z* (CI) 266.1755 (MH^+. $C_{15}H_{24}O_3N$ requires 266.1756), 248 (3%) and 234 (2).

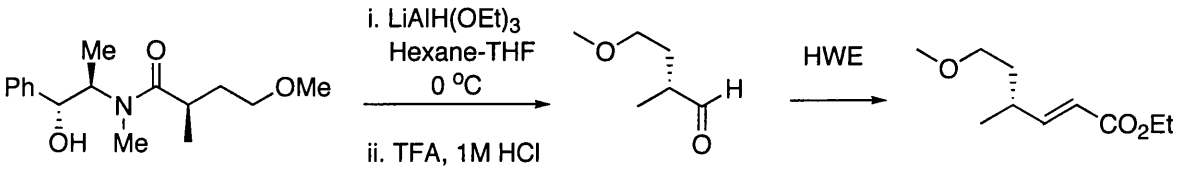
(1*R*,2*R*,2'*R*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4'-methoxy-2',*N*-dimethylbutyramide (183).



A solution of lithium chloride (0.09 g, 2.15 mmol) and diisopropylamine (0.11 mL, 0.81 mmol) in THF (5 mL) was cooled to -78 °C before *n*-butyllithium (2.5 M in hexane, 0.3 mL, 0.75 mmol) was added. The solution was warmed briefly to 0 °C, then was cooled to -78 °C and stirred for 0.5 hr. A solution of (1*R*,2*R*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-4'-methyloxy-*N*-methylbutyramide **182** (95 mg, 0.35 mmol) in THF (10 mL), cooled to 0 °C, was transferred to the reaction flask and the resulting solution was stirred at -78 °C for 1 hr, 0 °C for 0.25 hr and at room temperature for 5 min. The reaction mixture was then cooled to 0 °C, where upon methyl iodide (0.08 mL, 0.54 mmol) was added. After 3 h the reaction was quenched with saturated aqueous ammonium chloride solution (20 mL). The aqueous layer was separated and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a yellow liquid. Purification by chromatography (50 % ethyl acetate / petroleum ether) gave (1*R*,2*R*,2'*R*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4'-methoxy-2',*N*-dimethylbutyramide **183** (0.1 g, 65%) as a yellow liquid. $[\alpha]_D^{23}$ -96.2 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3364 (OH), 2973 (CH), 1612 (CO) 1451, 1111, 750 and 700; (1*R*,2*R*,2'*R*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4'-methoxy-2',*N*-dimethylbutyramide **183** exists as a 3:1 mixture of rotamers, signals for major rotamer are: δ_H (400 MHz, $CDCl_3$) 1.06 (3H, d, *J* 6.8, 1-CH_3), 1.13 (3H, d, *J* 6.8, 2'-CH_3), 1.62 (1H, m, 3'-*H*H), 1.89-2.05 (2H, m, 2'-H and 3'-H*H*), 2.87 (3H, s, NMe), 3.31 (3H, s, OMe), 3.38 (2H, m, 4'-H_2), 4.45 (1H, br s, OH), 4.55-4.64 (2H, m, 1-H and 2-H) and 7.35 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.4 (CH_3), 17.7 (CH_3), 33.4 (CH), 34.1 (CH_2), 58.6 (CH_3), 70.6 (CH_2), 76.3 (CH_3), 126.3 (CH), 126.5 (CH), 127.0

(CH), 127.6 (CH), 128.7 (CH), 142.4 (C) and 178.7 (C); *m/z* (CI) 280.1911 (MH^+. $C_{16}H_{26}O_6N$ requires 280.1913), 262 (16%) and 248 (11).

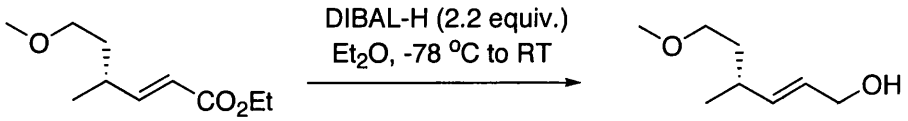
Ethyl (2*E*,4*S*)-4-methyl-6-methoxyhex-2-enoate (185).



Lithium aluminium hydride (0.22 g, 5.86 mmol) was suspended in anhydrous hexanes (20 mL) and cooled to 0 °C. Anhydrous ethyl acetate (0.85 mL. 8.70 mmol) was added dropwise over 0.5 h and the solution was allowed to stir for a further 1 h before being cooled to -78 °C. (1*R*,2*R*,2'*R*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4'-methoxy-2',*N*-dimethylbutyramide **183** (0.71 g, 2.55 mmol) in THF (15 mL) was added to the $LiAlH(OEt)_3$ solution with the evolution of H_2 gas. The reaction mixture was then allowed to stir for 0.25 h at -78 °C, then at 0 °C for 5 h. The reaction was quenched with a solution of trifluoroacetic acid (1.9 mL, 25.5 mmol) in aqueous 1 M hydrochloric acid solution (10 mL). Separation of the organic layer was followed by extraction of the aqueous layer with diethyl ether (3 x 20 mL). The combined organic layers were then neutralized to pH 7 with sodium hydrogen carbonate solution (30 mL). The aqueous layer was extracted with diethyl ether (2 x 20 mL) and the combined organic layers were dried ($MgSO_4$). The aldehyde was used without further purification. A solution of lithium chloride (0.16 mg, 3.8 mmol), triethyl phosphonoacetate (0.76 mL, 3.8 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (0.57 mL, 3.8 mmol) in acetonitrile (10 mL) was prepared and stirred for 0.5 h. The ylide mixture was added to the aldehyde solution and the reaction mixture was allowed to stir at room temperature 12 h. The reaction was quenched with brine (50 mL) then concentrated to give an orange residue. This residue was extracted with diethyl ether (5 x 50 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated to give an orange liquid. Purification by flash column chromatography (50% diethyl ether / petroleum ether) gave ethyl (2*E*,4*S*)-4-methyl-6-methoxyhex-2-enoate **185** (0.1 mL, 21% over two steps) as a colourless oil. $[\alpha]_D^{22}$ -27.5 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2931 (CH), 1719 (CO), 1651 (C=C), 1270, 1179 and 1120; δ_H (400 MHz, $CDCl_3$) 1.09 (3H, d, *J* 6.8, 4-CH_3), 1.31 (3H, t, *J* 7.2, OCH_2CH_3), 1.66 (2H, q, *J* 6.8, 5-H_2), 2.50 (1H, m, 4-H), 3.33 (3H, s, OMe), 3.35-3.41 (2H, m, 6-H_2), 4.20 (2H, q, *J* 7.2, OCH_2CH_3), 5.81 (1H, dd, *J* 15.6, 1.2, 2-H) and 6.87 (1H, dd, *J* 15.6, 8.0, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 19.4 (CH_3), 33.3 (CH), 35.7 (CH_2), 58.6 (CH_3), 60.2 (CH_3), 70.3

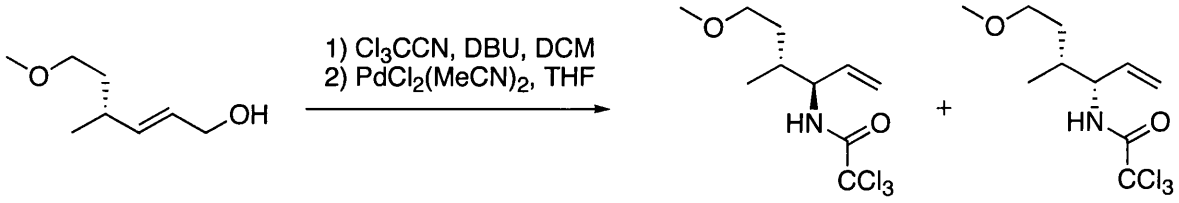
(CH_2), 120.0 (CH), 153.8 (CH) and 166.8 (C); *m/z* (CI) 187.1329 (MH^+. $C_{10}H_{19}O_3$ requires 187.1334), 232 (2%) and 187 (100).

(2*E*,4*S*)-4-Methyl-6-methoxyhex-2-en-1-ol (186).



The reaction was carried out according to general procedure 4 using ethyl (2*E*,4*S*)-4-methyl-6-methoxyhex-2-enoate **185** (0.8 g, 0.4 mmol). Purification was carried out by flash column chromatography (50% diethyl ether / petroleum ether) to give (2*E*,4*S*)-4-methyl-6-methoxyhex-2-en-1-ol **186** (0.5 g, 87%) as a colourless oil. $[\alpha]_D^{21}$ -22.7 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat): 3382 (OH), 2929 (CH), 1456 (C=C), 1116, 972 and 669; δ_H (400 MHz, $CDCl_3$) 1.03 (3H, d, *J* 6.8, 4-CH_3), 1.36 (1H, br s, OH), 1.59 (2H, q, *J* 6.4, 5-H_2), 2.32 (1H, m, 4-H), 3.34 (3H, s, OMe), 3.39 (2H, t, *J* 6.4, 6-H_2), 4.12 (2H, m, 1-H_2) and 5.56-5.68 (2H, m, 2-H and 3-H); δ_C (100 MHz, $CDCl_3$) 20.4 (CH_3), 33.2 (CH), 36.4 (CH_2), 58.6 (CH_3), 63.8 (CH_2), 70.8 (CH_2), 127.6 (CH) and 138.2 (CH); *m/z* (CI) 127.1125 (MH^+ - H_2O. $C_8H_{15}O$ requires 127.1123), 95 (19%) and 85 (3).

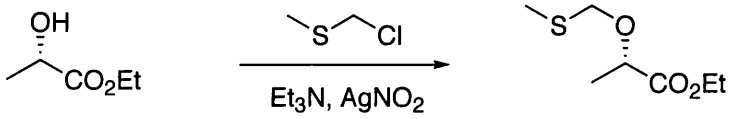
(3*R*,4*R*)-(Trichloromethylcarbonylamino)-4-methyl-6-methoxyhexa-1-ene (188a) and (3*S*,4*R*)-3-(trichloromethylcarbonylamino)-4-methyl-6-methoxyhexa-1-ene (188b).



The reactions were carried out according to general procedure 7 using (2*E*,4*S*)-4-methyl-6-methoxyhex-2-en-1-ol **186** (0.05 g, 0.4 mmol) and bis(acetonitrile)palladium(II) chloride (10 mol%). Purification by flash column chromatography (30% diethyl ether / petroleum ether) gave (3*R*,4*R*)-(trichloromethylcarbonylamino)-4-methyl-6-methoxyhexa-1-ene **188a** and (3*S*,4*R*)-3-(trichloromethylcarbonylamino)-4-methyl-6-methoxyhexa-1-ene **188b** (0.06 mg, 60% over two steps) as a brown oil, in a ratio of 1 : 2 (3*R* : 3*S*). (Found: C, 41.7; H, 5.6; N, 4.7, $C_{10}H_{16}O_2NCl_3$ requires C, 41.6; H, 5.6; N, 4.9%); υ_{max}/cm^{-1} (neat): 3331 (NH), 2931 (CH), 1715 (CO), 1652 (C=C), 1518, 1114 and 822; (3*R*,4*R*)-(trichloromethylcarbonylamino)-4-methyl-6-methoxyhexa-1-ene **188a**: δ_H (400 MHz,

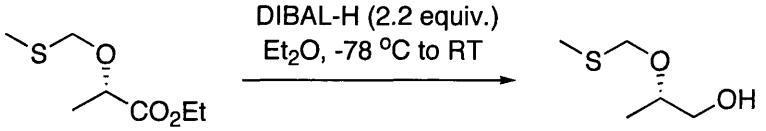
$CDCl_3$) 1.00 (3H, d, *J* 6.8, 4-CH_3), 1.66 (2H, m, 5-H_2), 1.97 (1H, m, 4-H), 3.37 (3H, s, OMe), 3.45 (2H, m, 6-H_2), 4.39 (1H, m, 3-H), 5.26 (2H, m, 1-H_2), 5.81 (1H, m, 2-H) and 7.67 (1H, br d, *J* 7.2, NH); (C); δ_C (100 MHz, $CDCl_3$) 17.5 (CH_3), 32.6 (CH_2), 35.3 (CH), 57.2 (CH_3), 58.8 (CH), 71.2 (CH), 93.3 (C), 117.0 (CH), 134.3 (CH) and 161.4 (C); (3*S*,4*R*)-3-(trichloromethylcarbonylamino)-4-methyl-6-methoxyhexa-1-ene **188b**: δ_H (400 MHz, $CDCl_3$) 1.02 (3H, d, *J* 6.8, 4-CH_3), 1.66 (2H, m, 5-H_2), 2.05 (1H, m, 4-H), 3.36 (3H, s, OMe), 3.51 (2H, m, 6-H_2), 4.39 (1H, m, 3-H), 5.22 (2H, m, 1-H_2), 5.79 (1H, m, 2-H) and 7.76 (1H, br d, *J* 6.0, NH); δ_C (100 MHz, $CDCl_3$) 16.3 (CH_3), 31.2 (CH_2), 34.6 (CH), 57.7 (CH_3), 58.9 (CH), 69.5 (CH), 93.3 (C), 116.0 (CH), 135.9 (CH) and 161.7; *m/z* (CI) 290 (MH^+, 89%), 254 (20), 220 (36), 218 (100) and 184 (8).

Ethyl (2*S*)-2-(methylsulfanylmethoxy)propanoate (190).



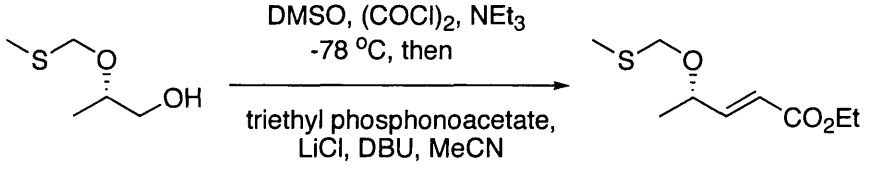
A solution of ethyl (*S*)-lactate **121** (0.50 g, 4.24 mmol) and chloromethylmethyl sulfide (0.43, 5.09 mmol) in THF (15 mL) was added to a solution of silver nitrate (0.79 mg, 4.66 mmol) and triethylamine (0.71 mL, 5.09 mmol) in THF (10 mL). The reaction mixture was allowed to stir at room temperature for 4 h before being heated to 80 °C and stirred for 5 days. The mixture was then filtered through Celite® then washed with saturated ammonium chloride solution (20 mL), saturated sodium hydrogen carbonate solution (20 mL) and water (20 mL). The organic layer was then dried ($MgSO_4$) and concentrated to give a brown liquid. Purification was carried out by flash column chromatography (30% diethyl ether / petroleum ether) to give ethyl (2*S*)-2-(methylsulfanylmethoxy)propanoate **190** (0.16 g, 21%). $[\alpha]_D^{21}$ -166.0 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2984 (CH), 1746 (CO), 1201, 1109, 1063 and 1024; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.2, OCH_2CH_3), 1.44 (3H, d, *J* 7.0, 3-H_3), 2.18 (3H, s, SMe), 4.22 (2H, qd, *J* 7.2, 1.2, OCH_2CH_3), 4.37 (1H, q, *J* 7.0, 2-H), 4.66 (1H, d, *J* 11.6, OC*H*HS) and 4.79 (1H, d, *J* 11.6, OCH*H*S); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 14.2 (CH_3), 18.4 (CH_3), 61.0 (CH_2), 71.2 (CH), 74.3 (CH_2) and 172.9 (C); *m/z* (CI) 179.0740 (MH^+. $C_7H_{15}O_3S$ requires 179.0742) 163 (3%), 147 (3), 131 (61), 119 (4) and 102 (8).

(2*S*)-2-Methylsulfanylmethoxypropan-1-ol (191).



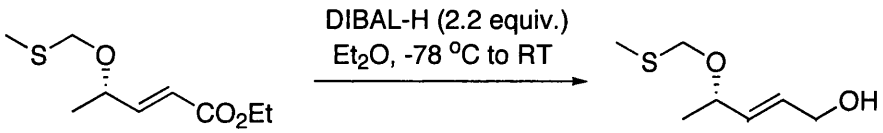
The reaction was carried out according to general procedure 2b using ethyl (2*S*)-2-(methylsulfanylmethoxy)propanoate **190** (1.58 g, 8.87 mmol). Purification by flash column chromatography (40% diethyl ether / petroleum) gave (2*S*)-2-methylsulfanylmethoxypropan-1-ol **191** (0.75 g, 82%) as colourless oil. $[\alpha]_D^{19}$ +146.9 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3418 (OH), 2922 (CH), 1436, 1301, 1060 and 681; δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.4, 3-H_3), 2.13 (1H, m, OH), 2.20 (3H, s, SMe), 3.52 (1H, dd, *J* 11.6 and 6.8, 1-*H*H), 3.64 (1H, dd, *J* 11.6 and 3.2, 1-H*H*), 3.90 (1H, m, 2-H), 4.65 (1H, d, *J* 11.2, OC*H*HS) and 4.77 (1H, d, *J* 11.2, OCH*H*S); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 15.9 (CH_3), 66.2 (CH_2), 73.3 (CH_2) and 74.0 (CH); *m/z* (CI) 137.0517 (MH^+. $C_5H_{13}O_2S$ requires 137.0636) 118 (12%), 105 (22), 89 (100) and 75 (35).

Ethyl (2*E*,4*S*)-4-methylsulfanylmethoxypent-2-enoate (192).



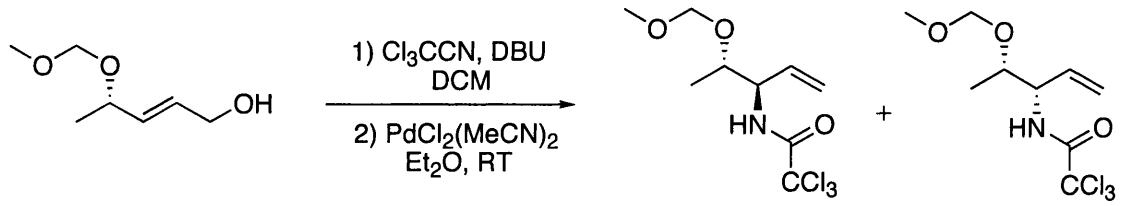
The reactions were carried out according to general procedure 3b using (2*S*)-2-methylsulfanylmethoxypropan-1-ol **191** (0.55 g, 5.28 mmol). Purification was carried out by flash column chromatography (30% diethyl ether / petroleum ether) to give ethyl (2*E*,4*S*)-4-methylsulfanylmethoxypent-2-enoate **192** (0.4 g, 37%) as colourless oil. $[\alpha]_D^{21}$ -232.4 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2980 (CH), 1716 (CO), 1659 (C=C), 1300, 1266, 1180 and 1051; δ_H (400 MHz, $CDCl_3$) 1.29 (6H, m, OCH_2CH_3 and 5-H_3), 2.17 (3H, s, SMe), 4.22 (2H, q, *J* 6.8, OCH_2CH_3), 4.48 (1H, quin d, *J* 6.2, 1.2, 4-H), 4.55 (1H, d, *J* 11.6, OC*H*HS), 4.70 (1H, d, *J* 11.6, OCH*H*S), 6.01 (1H, dd, *J* 15.6, 1.2, 2-H) and 6.84 (1H, dd, *J* 15.6, 6.2, 3-H); δ_C (100 MHz, $CDCl_3$) 13.8 (CH_3), 14.3 (CH_3), 20.3 (CH_3), 60.5 (CH_2), 70.9 (CH), 72.8 (CH_2), 121.6 (CH), 148.4 (CH) and 166.3 (C); *m/z* (CI) 205.0896 (MH^+. $C_9H_{17}O_3S$ requires 205.0898) 175 (10%), 157 (100) and 127 (35).

(2*E*,4*S*)-Methylsulfanylmethoxypent-2-en-1-ol (193).



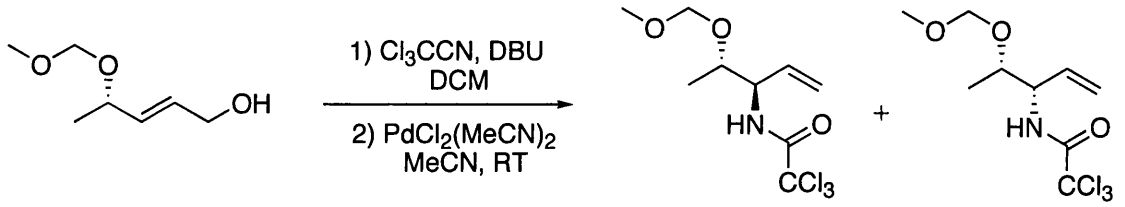
The reaction was carried out according to general procedure 4 using (2*E*,4*S*)-4-methylsulfanylmethoxypent-2-enoate **192** (0.34 g, 1.79 mmol). Purification was carried out by flash column chromatography using (50% diethyl ether / petroleum ether) to give (2*E*,4*S*)-methylsulfanylmethoxypent-2-en-1-ol **193** (0.22 mg, 75%) as a colourless oil. $[\alpha]_D^{21}$ -250.3 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3403 (OH), 2975 (CH), 1671 (C=C), 1433, 1374, 1300 and 1057; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.4, 5-H_3), 1.47 (1H, br s, OH), 2.18 (3H, s, SMe), 4.19 (2H, dd, *J* 5.2, 1.6, 1-H_2), 4.33 (1H, m, 4-H), 4.55 (1H, d, *J* 11.6, OC*H*HS), 4.67 (1H, d, *J* 11.6, OCH*H*S), 5.63 (1H, ddt, *J* 15.6, 7.6 and 1.6, 3-H) and 5.86 (1H, dtd, *J* 15.6, 5.2, 0.8, 2-H); δ_C (100 MHz, $CDCl_3$) 13.8 (CH_3), 21.1 (CH_3), 62.9 (CH_2), 72.0 (CH_2), 72.1 (CH), 131.7 (CH) and 132.3 (CH); *m/z* (CI) 145.0685 (MH^+ - H_2O. $C_7H_{13}OS$ requires 145.0688) 145 (38%), 133 (100), 115 (32) and 85 (67).

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157b) from bis(acetonitrile)palladium(II) chloride in diethyl ether as solvent.



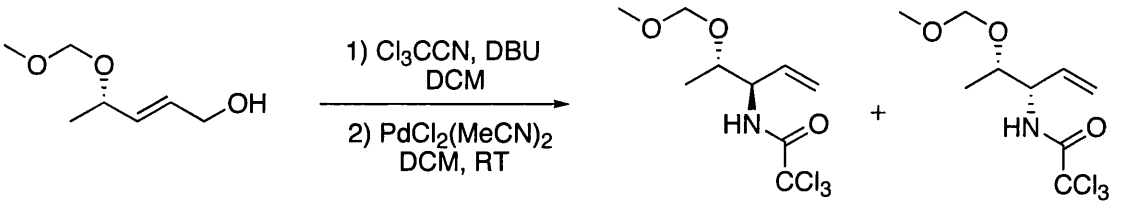
The reaction was carried out according to general procedure 8 for 24 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol **144** (50 mg, 0.34 mmol) then bis(acetonitrile)palladium(II) chloride (8 mg, 10 mol%) in diethyl ether (10 mL) to give (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157a** and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157b** (47 mg, 47% over two steps) as a brown oil, in a 12 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157b) from bis(acetonitrile)palladium(II) chloride in acetonitrile as solvent.



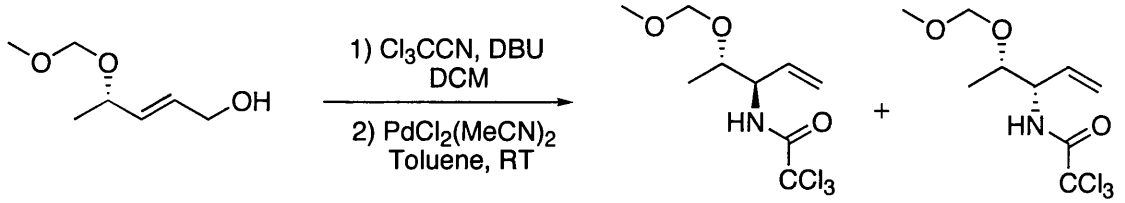
The reaction was carried out according to general procedure 8 for 24 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol **144** (100 mg, 0.69 mmol) then bis(acetonitrile)palladium(II) chloride (18 mg, 10 mol%) in acetonitrile (10 mL) to give (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157a** and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157b** (64 mg, 32% over two steps) as a brown oil, in a 9 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157b) from bis(acetonitrile)palladium(II) chloride in DCM as solvent.



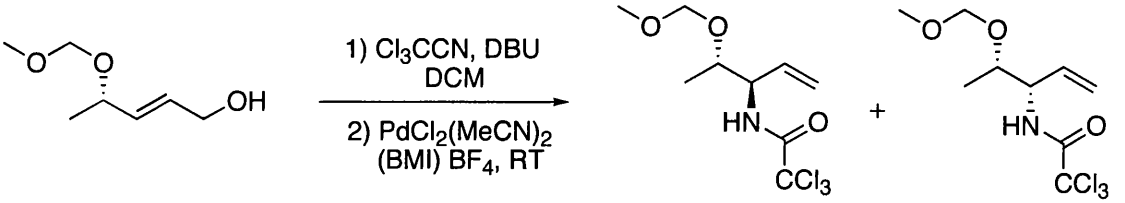
The reaction was carried out according to general procedure 8 for 24 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol **144** (50 mg, 0.34 mmol) then bis(acetonitrile)palladium(II) chloride (8 mg, 10 mol%) in DCM (10 mL) to give (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157a** and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157b** (47 mg, 49% over two steps) as a brown oil, in a 12 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157b) from bis(acetonitrile)palladium(II) chloride in toluene as solvent.



The reaction was carried out according to general procedure 8 for 24 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol **144** (50 mg, 0.34 mmol) then bis(acetonitrile)palladium(II) chloride (8 mg, 10 mol%) in toluene (10 mL) to give (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157a** and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157b** (56 mg, 56% over two steps) as a brown oil, in a 15 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

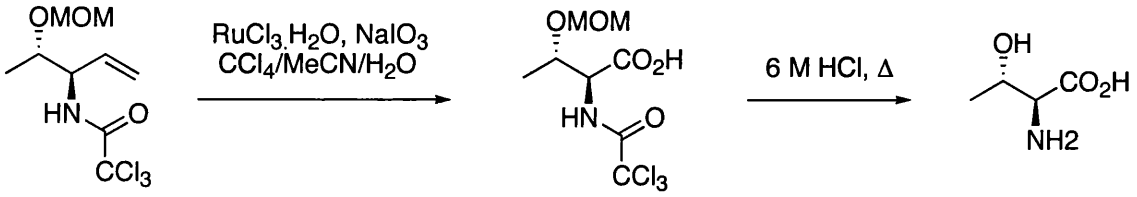
(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157a) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (157b) from bis(acetonitrile)palladium(II) chloride in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate as solvent.



The reaction was carried out according to general procedure 8 for 148 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol **144** (100 mg, 0.69 mmol) then bis(acetonitrile)palladium(II) chloride (18 mg, 10 mol%) in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (3 mL) to give (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157a** and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene **157b** (74 mg, 37% over two steps) as a brown oil, in a 5 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

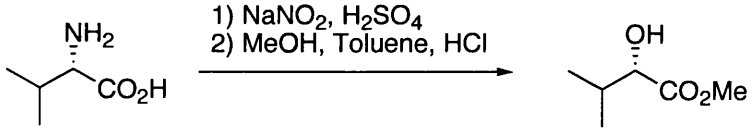
3.0 Application of Ether Directed, Pd(II)-Catalysed aza-Claisen Rearrangement for Natural Product Synthesis.

(2*S*,3*S*)-2-Amino-3-hydroxybutanoic acid (249).[103]



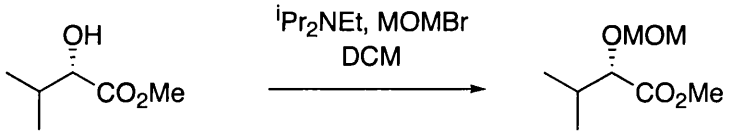
The reactions were carried out according to general procedure 12 using (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)pent-1-ene **157a** (0.7 g, 2.4 mmol) to give (2*S*,3*S*)-2-amino-3-hydroxybutanoic acid **249** (0.19 mg, 67% over two steps). $[\alpha]_D^{21}$ +8.0 (*c* 1.0, H_2O); Lit.[103] $[\alpha]_D^{22}$ +8.6 (*c* 0.1, H_2O); δ_H (400 MHz, D_2O) 1.17 (3H, d, *J* 6.8, 4-H_3), 3.98 (1H, d, *J* 3.6, 2-H) and 4.24 (1H, qd, *J* 6.8, 3.6, 3-H); δ_C (100 MHz, D_2O) 16.1 (CH_3); 59.6 (CH), 65.3 (CH) and 171.9 (C); *m/z* (CI) 119.0539 (MH^+. $C_4H_9O_3N$ requires 119.0582), 117 (11%), 85 (4), 81 (74) and 79 (100).

Methyl (2*S*)-2-hydroxy-3-methylbutanoate (220).[134]



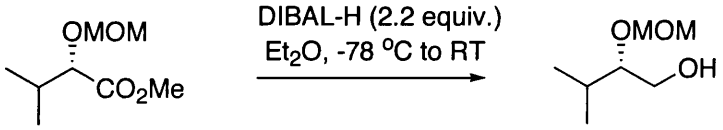
The reaction was carried out according to general procedure 9 using L-valine **218** (7.0 g, 59.8 mmol). Purification by Krugelrohr distillation gave methyl (2*S*)-2-hydroxy-3-methylbutanoate **220** (1.96 g, 25%). $[\alpha]_D^{21}$ +24.3 (*c* 1.0, $CHCl_3$); Lit.[134] $[\alpha]_D^{25}$ +23.1 (*c* 2.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.8, 3-CH_3), 1.03 (3H, d, *J* 6.8, 4-H_3), 2.02 (1H, sept of d, *J* 6.8, 3.6, 3-H), 2.66 (1H, d, *J* 6.4, OH), 3.80 (3H, s, OMe), 4.05 (1H, dd, *J* 6.4, 3.6, 2-H); δ_C (100 MHz, $CDCl_3$) 16.0 (CH_3), 18.8 (CH_3), 32.1 (CH), 52.4 (CH_3), 75.0 (CH), 175.4 (C); *m/z* (CI) 133.0872 (MH^+. $C_6H_{13}O_3$ requires 133.0865), 105 (8%) and 73 (7).

Methyl (2*S*)-2-methoxymethoxy-3-methylbutanoate (226).



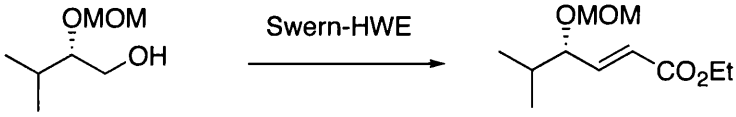
The reaction was carried out according to general procedure 10 using methyl (2*S*)-2-hydroxy-3-methylbutanoate **220** (1.96 g, 14.9 mmol). Purification was carried out by flash column chromatography (30% diethyl ether / petroleum ether) to give methyl (2*S*)-2-methoxymethoxy-3-methyl-butanoate **226** (1.33 g, 60%). $[\alpha]_D^{20}$ -76.0 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2965 (CH), 1748 (CO), 1201, 1152, 1041 and 916; δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.8, 3-CH_3), 0.99 (3H, d, *J* 6.8, 4-H_3), 2.04-2.15 (1H, m, 3-H), 3.39 (3H, s, OMe), 3.75 (3H, s, OMe), 3.89 (1H, d, *J* 5.6, 2-H), 4.66 (1H, d, *J* 7.2, OC*H*HO) and 4.68 (1H, d, *J* 7.2, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 17.7 (CH_3), 18.8 (CH_3), 31.5 (CH), 51.7 (CH_3), 56.1 (CH_3), 80.7 (CH), 96.5 (CH_2) and 172.9 (C); *m/z* (CI) 177.1126 (MH^+. $C_8H_{17}O_4$ requires 177.1127), 145 (100%), 117 (34) and 79 (38).

(2*S*)-2-Methoxymethoxy-3-methylbutan-1-ol (229).



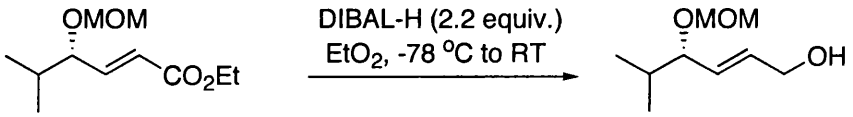
The reaction was carried out according to general procedure 2b using methyl (2*S*)-2-methoxymethoxy-3-methylbutanoate **226** (0.5 g, 3.2 mmol). Purification was carried out by flash column chromatography (50% diethyl ether / petroleum ether) to give (2*S*)-methoxymethoxy-3-methylbutan-1-ol **229** (0.3 g, 62%) as a yellow liquid. $[\alpha]_D^{19}$ +80.3 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3423 (OH), 2957 (CH), 1152, 1095, 1026 and 916; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.8, 3-CH_3), 0.95 (3H, d, *J* 6.8, 4-H_3), 1.78-1.90 (1H, m, 3-H), 3.17 (1H, dd, *J* 9.2, 3.2, OH), 3.29 (1H, m, 2-H), 3.45 (3H, s, OMe), 3.61 (1H, m, 1-*H*H), 3.61 (1H, ddd, *J* 12.0, 9.2, 2.4, 1-H*H*), 4.66 (1H, d, *J* 6.8, OC*H*HO) and 4.76 (1H, d, *J* 6.8, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 18.2 (CH_3), 18.9 (CH_3), 30.3 (CH), 55.7 (CH_3), 63.9 (CH_2), 88.2 (CH) and 97.8 (CH_2); *m/z* (CI) 149.1174 (MH^+. $C_7H_{17}O_3$ requires 149.1178), 117 (100%), 87 (20) and 71 (18).

Ethyl (2*E*,4*R*)-4-methoxymethoxy-5-methylhex-2-enoate (232).



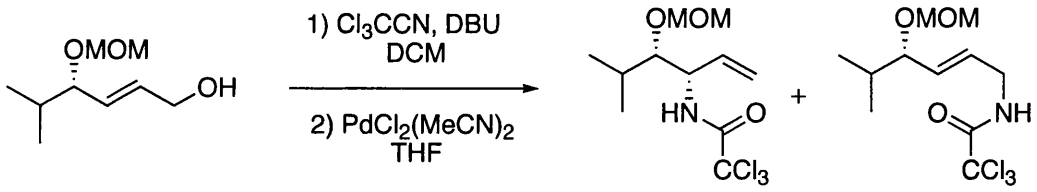
The reactions were carried out according to general procedure 3b using (2*S*)-methoxymethoxy-3-methylbutan-1-ol **229** (1.0 g, 6.13 mmol). Purification was carried out by flash column chromatography (10% diethyl ether / petroleum ether) to give ethyl (2*E*,4*R*)-4-methoxymethoxy-5-methylhex-2-enoate **232** (1.0 g, 79% over two steps) as a yellow liquid. $[\alpha]_D^{19}$ -96.2 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2965 (CH), 1718 (CO), 1656 (C=C), 1249, 1153, 1029, 986 and 920; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.8, 5-CH_3), 0.98 (3H, d, *J* 6.8, 6-H_3), 1.31 (3H, t, *J* 7.2, OCH_2CH_3), 1.82-1.93 (1H, m, 5-H), 3.38 (3H, s, OMe), 3.95 (1H, m, 4-H), 4.18 (2H, q, *J* 7.2, OCH_2CH_3), 4.58 (1H, d, *J* 6.8, OC*H*HO), 4.63 (1H, d, *J* 6.8, OCH*H*O), 5.98 (1H, dd, *J* 15.6, 1.2, 2-H) and 6.82 (1H, dd, *J* 15.6, 6.8, 3-H); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 18.2 (CH_3), 18.3 (CH_3), 32.6 (CH_3), 55.7 (CH), 60.5 (CH_2), 80.2 (CH_3), 94.7 (CH_2), 123.0 (CH), 146.5 (CH) and 166.2 (C); *m/z* (CI) 217.1441 (MH^+. $C_{11}H_{21}O_4$ requires 217.1440), 187 (17%), 155 (100) and 127 (5).

(2*E*,4*R*)-4-Methoxymethoxy-5-methylhex-2-en-1-ol (235).



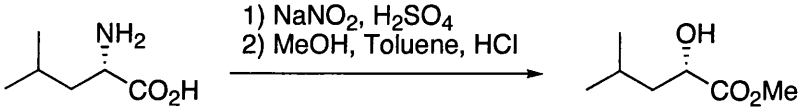
The reaction was carried out according to general procedure 4 using ethyl (2*E*,4*R*)-4-methoxymethoxy-5-methylhex-2-enoate **232** (1.0 g, 4.6 mmol). Purification was carried out by flash column chromatography (50% diethyl ether / petroleum ether) to give (2*E*,4*R*)-4-methoxymethoxy-5-methylhex-2-en-1-ol **235** (0.6 g, 77%) as a yellow liquid. $[\alpha]_D^{20}$ -124.3 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3386 (OH), 2958 (CH), 1469, 1152, 1089, 1030, 973 and 920; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.8, 5-CH_3), 0.96 (3H, d, *J* 6.8, 6-H_3), 1.71 (1H, sept, *J* 6.8, 5-H), 1.86 (1H, m, OH), 3.37 (3H, s, OMe), 3.73 (1H, dd, *J* 7.6, 6.8, 4-H), 4.16 (2H, dd, *J* 5.6, 4.4, 1-H_2), 4.51 (1H, d, *J* 6.8, OC*H*HO), 4.69 (1H, d, *J* 6.8, OCH*H*O), 5.54 (1H, ddt, *J* 15.6, 7.6, 1.6, 3-H) and 5.79 (1H, dt, *J* 15.6, 5.6, 2-H); δ_C (100 MHz, $CDCl_3$) 18.5 (CH_3), 18.6 (CH_3), 32.7 (CH), 55.5 (CH), 62.9 (CH_2), 81.5 (CH_3), 93.7 (CH_2), 129.6 (CH) and 133.3 (CH); *m/z* (CI) 145.1227 (MH^+ - CH_2O. $C_8H_{17}O_2$ requires 145.1229), 125 (8%), 113 (38), 95 (100) and 85 (11).

(3*S*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-methylhexa-1-ene (241b) and (2*E*,4*S*)-1-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-methylhexa-2-ene (241c).



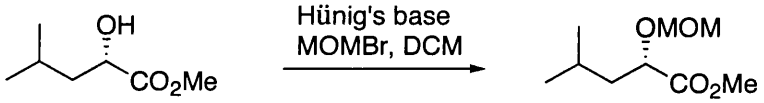
The reactions were carried out according to general procedures 7 using (2*E*,4*R*)-methoxymethoxy-5-methylhex-2-en-1-ol **235** (0.6 g, 3.5 mmol) then bis(acetonitrile)palladium(II) chloride (10 mol%). Purification by flash column chromatography (15% diethyl ether/ petroleum ether) gave (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-methylhexa-1-ene **241b** and (2*E*,4*S*)-1-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-methylhexa-2-ene **241c** (0.65 g, 58% combined yield, over two steps) in a 1 : 2 ratio respectively. (2*E*,4*S*)-1-(Trichloromethylcarbonylamide)-4-(methoxymethoxy)-5-methylhexa-2-ene **241c**: $[\alpha]_D^{18}$ -89.7 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3422 (OH), 2853 (CH), 1655, 1037, 992 and 793; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.8, 5-CH_3), 0.97 (3H, d, *J* 6.8, 6-H_3), 1.74-1.84 (1H, m, 5-H), 3.38 (3H, s, OMe), 3.76 (1H, t, *J* 6.8, 4-H), 4.08 (2H, d, *J* 6.8, 1-H_2), 4.53 (1H, d, *J* 6.8, OC*H*HO), 4.69 (1H, d, *J* 6.8, OCH*H*O), 5.64 (1H, dd, *J* 15.6, 6.8, 3-H) and 5.79 (1H, m, 2-H); δ_C (100 MHz, $CDCl_3$) 17.3 (CH_3), 17.5 (CH_3), 31.6 (CH), 43.3 (CH_2), 54.5 (CH_3), 76.2 (C), 79.7 (CH), 92.9 (CH_2), 128.5 (CH), 132.3 (CH) and 161.8 (C); *m/z* (CI) 276 (MH^+ - CH_3OCH_2, 11%), 240 (11), 204 (5) and 168 (6); (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-methylhexa-1-ene **241b**: $[\alpha]_D^{25}$ +61.8 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3422 (NH), 2862 (CH), 1680, 1041 and 995; δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.8, 5-CH_3), 1.00 (3H, d, *J* 6.8, 6-H_3), 1.77-1.86 (1H, m, 5-H), 3.13 (1H, dd, *J* 10.0, 1.6, 4-H), 3.44 (3H, s, OMe), 4.56 (1H, m, 3-H), 4.62 (1H, d, *J* 6.4, OC*H*HO), 4.79 (1H, d, *J* 6.4, OCH*H*O), 5.31 (1H, d, *J* 10.0, 1-*H*H), 5.36 (1H, d, *J* 17.2, 1-H*H*) 5.80 (1H, ddd, *J* 17.2, 10.0, 6.8, 2-H) and 8.49 (1H, br d, *J* 6.8, NH); δ_C (100 MHz, $CDCl_3$) 18.9 (CH_3), 19.6 (CH_3), 31.0 (CH), 54.7 (CH), 55.8 (CH), 90.9 (CH_3), 93.0 (C), 99.3 (CH_2), 118.8 (CH_2), 131.5 (CH) and 161.5 (C), *m/z* (CI) 276 (MH^+ - CH_3OCH_2, 12%), 240 (5), 204 (3) and 168 (2).

Methyl (2*S*)-2-hydroxy-4-methylpentanoate (221).[134]



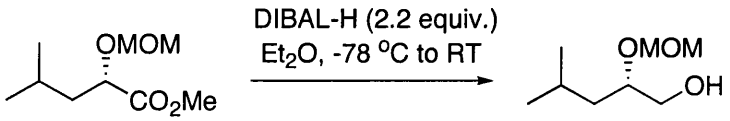
The reactions were carried out according to general procedure 9 using L-leucine **219** (7.0 g, 53 mmol). Purification by Krugelrohr distillation gave methyl (2*S*)-hydroxy-4-methyl-pentanoate **221** (2.6 g, 33%) as a clear liquid. $[\alpha]_D^{20}$ +3.9 (*c* 1.0, $CHCl_3$); Lit.[134] $[\alpha]_D^{21}$ +2.2 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.8, 5-H_3), 0.94 (3H, d, *J* 6.8, 4-CH_3), 1.54-1.60 (2H, m, 3-H_2), 1.83 (1H, m, 4-H), 2.63 (1H, d, *J* 6.0, OH), 3.79 (3H, s, OMe) and 4.19 (1H, td, *J* 7.6, 6.0, 2-H); δ_C (100 MHz, $CDCl_3$) 21.6 (CH_3), 23.3 (CH), 24.4 (CH_3), 43.5 (CH_2), 52.5 (CH_3), 69.1 (CH) and 176.4 (C); *m/z* (CI) 147.1023 (MH^+. $C_7H_{15}O_3$ requires 147.1021), 143 (8%) and 119 (11).

Methyl (2*S*)-methoxymethoxy-4-methylpentanoate (227).



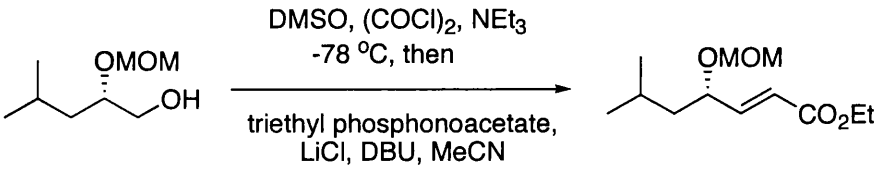
The reaction was carried out according to general procedure 10 using methyl (2*S*)-hydroxy-4-methylpentanoate **221** (2.2 g, 15.1 mmol). Purification was carried out by flash column chromatography (50% diethyl ether / petroleum ether) to give methyl (2*S*)-methoxymethoxy-4-methylpentanoate **227** (2.0 g, 71%) as an orange liquid. $[\alpha]_D^{20}$ -66.0 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2956 (CH), 1750 (CO), 1203, 1158, 1026 and 917; δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.4, 5-H_3), 0.96 (3H, d, *J* 6.4, 4-CH_3), 1.50-1.57 (1H, m, 3-C*H*H), 1.67-1.76 (1H, m, 3-CH*H*), 1.78-1.87 (1H, m, 4-H), 3.40 (3H, s, OMe), 3.75 (3H, s, OMe), 4.16 (1H, dd, *J* 9.2, 4.4, 2-H), 4.66 (1H, d, *J* 6.8, OC*H*HO) and 4.69 (1H, d, *J* 6.8, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 21.5 (CH_3), 23.2 (CH), 24.4 (CH_3), 41.8 (CH_2), 51.9 (CH_3), 56.1 (CH_3), 74.3 (CH), 96.4 (CH_2) and 173.7 (C); *m/z* (CI) 191.1289 (MH^+. $C_9H_{19}O_4$ requires 191.1283) and 159 (100%).

(2*S*)-2-Methoxymethoxy-4-methylpentan-1-ol (230).



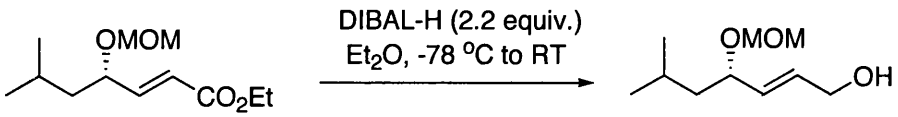
The reaction was carried out according to general procedure 2b using methyl (2*S*)-methoxymethoxy-4-methylpentanoate **227** (2.45 g, 12.90 mmol). Purification was carried out by flash column chromatography (60% diethyl ether / petroleum ether) to gave (2*S*)-2-methoxymethoxy-4-methylpentan-1-ol **230** (1.78 g, 86%) as a yellow liquid. $[\alpha]_D^{19}$ +57.1 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3402 (OH), 2951 (CH), 1469, 1099, 1029 and 917; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.8, 5-H_3), 0.92 (3H, d, *J* 6.8, 4-CH_3), 1.20 (1H, ddd, *J* 14.0, 8.4, 5.2, 3-*H*H), 1.47 (1H, ddd, *J* 14.0, 8.4, 5.6, 3-H*H*), 1.68-1.77 (1H, m, 4-H), 3.26 (1H, dd, *J* 9.2, 3.6, OH), 3.44 (3H, s, OMe), 3.47 (1H, m, 2-H), 3.55-3.65 (2H, m, 1-H_2), 4.68 (1H, d, *J* 6.8, OC*H*HO) and 4.73 (1H, d, *J* 6.8, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 22.2 (CH_3), 23.2 (CH), 24.4 (CH_3), 40.7 (CH_2), 55.7 (CH), 66.2 (CH_2), 81.0 (CH_3) and 97.1 (CH_2); *m/z* (CI) 163.1333 (MH^+. $C_8H_{19}O_3$ requires 163.1334), 131 (100%), 101 (29) and 83 (21).

Ethyl (2*E*,4*R*)-4-methoxymethoxy-6-methylhepta-2-enoate (233).



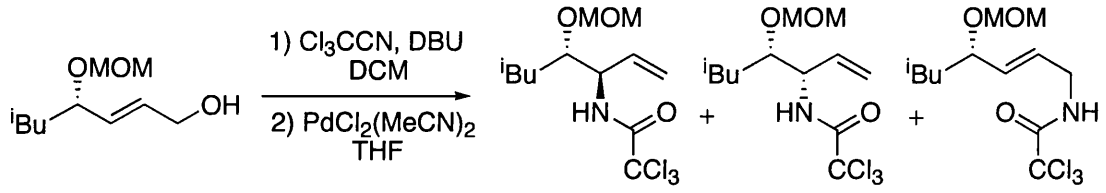
The reactions were carried out according to general procedure 3b using (2*S*)-methoxymethoxy-4-methylpentan-1-ol **230** (1.79 g, 10.98 mmol). Purification was carried out by flash column chromatography (30% diethyl ether / petroleum ether) to give ethyl (2*E*,4*R*)-4-methoxymethoxy-6-methylhept-2-enoate **233** (2.01 g, 83% over two steps) as a yellow liquid. $[\alpha]_D^{21}$ -125.6 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2954 (CH), 1718 (CO), 1659 (C=C), 1266, 1161, 984 and 919; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.4, 6-CH_3), 0.95 (3H, d, *J* 6.4, 7-H_3), 1.30 (3H, t, *J* 7.2, OCH_2CH_3), 1.34 (1H, m, 5-C*H*H), 1.58 (1H, ddd, *J* 14.0, 8.4, 6.0, 5-CH*H*), 1.73-1.84 (1H, m, 6-H), 3.39 (3H, s, OMe), 4.20 (2H, q, *J* 7.2, OCH_2CH_3), 4.27 (1H, m, 4-H), 4.57 (1H, d, *J* 6.8, OC*H*HO), 4.64 (1H, d, *J* 6.8, OCH*H*O), 5.97 (1H, dd, *J* 15.6, 1.2, 2-H) and 6.81 (1H, dd, *J* 15.6, 6.8, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 22.1 (CH_3), 23.1 (CH_3), 24.3 (CH), 44.2 (CH_2), 55.7 (CH), 60.5 (CH_2), 73.6 (CH_3), 94.6 (CH_2), 121.7 (CH), 148.2 (CH) and 166.3 (C); *m/z* (CI) 231.1594 (MH^+. $C_{12}H_{23}O_4$ requires 231.1596), 201 (63%), 169 (100) and 129 (6).

(2*E*,4*R*)-4-Methoxymethoxy-6-methylhept-2-en-1-ol (236).



The reaction was carried out according to general procedure 4 using ethyl (2*E*,4*R*)-4-methoxymethoxy-6-methylhept-2-enoate **233** (2.1 g, 9.13 mmol). Purification was carried out by flash column chromatography (60% diethyl ether / petroleum ether) to give (2*E*,4*R*)-4-methoxymethoxy-6-methylhept-2-en-1-ol **236** (1.48 g, 87%) as a yellow liquid. $[\alpha]_D^{19}$ -126.4 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3332 (OH), 2952 (CH), 1560, 1092, 1029, 971 and 916; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.4, 6-CH_3), 0.94 (3H, d, *J* 6.4, 7-H_3), 1.12 (1H, m, OH), 1.29 (1H, m, 5-*H*H), 1.56 (1H, m, 5-H*H*), 1.69-1.81 (1H, m, 6-H), 3.38 (3H, s, OMe), 4.12 (1H, m, 4-H), 4.15 (2H, ddd, *J* 6.4, 5.2, 1.2, 1-H_2), 4.52 (1H, d, *J* 6.8, OC*H*HO), 4.71 (1H, d, *J* 6.8, OCH*H*O), 5.55 (1H, ddt, *J* 15.6, 8.0, 1.2, 3-H) and 5.79 (1H, dt, *J* 15.6, 5.2, 2-H); δ_C (100 MHz, $CDCl_3$) 22.3 (CH_3), 23.0 (CH_3), 24.3 (CH), 44.8 (CH_2), 55.5 (CH), 63.0 (CH_2), 74.4 (CH_3), 93.6 (CH_2), 131.8 (CH) and 131.9 (CH); *m/z* (CI) 143 (MH^+ - CH_2O, 19%), 127 (100), 109 (92) and 85 (42).

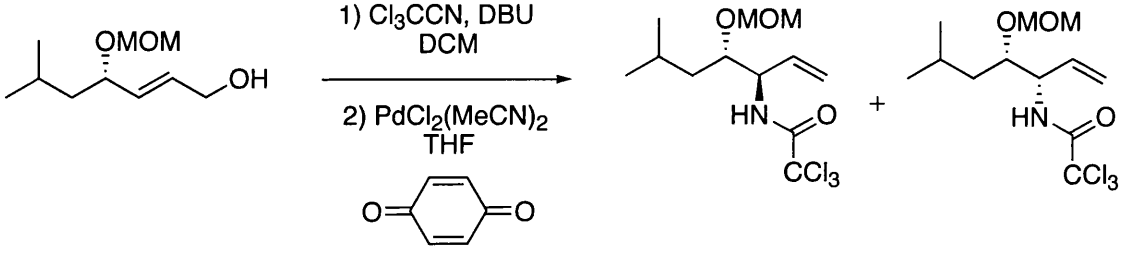
(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-methylhept-1-ene (242a), (3*S*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-methylhept-1-ene (242b) and (2*E*,4*S*)-1-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-methylhept-2-ene (242c).



The reactions were carried out according to general procedure 7 using (2*E*,4*R*)-methoxymethoxy-6-methylhept-2-en-1-ol **236** (1.48 g, 7.87 mmol) then bis(acetonitrile)palladium(II) chloride (10 mol%). Purification by flash column chromatography (20% diethyl ether / petroleum ether) gave (2*E*,4*S*)-1-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-methylhepta-2-ene **242c**. Further elution (25% diethyl ether / petroleum ether) gave (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-methylhept-1-ene **242a** followed by (30% diethyl ether / petroleum ether) (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-

(methoxymethoxy)-6-methylhept-1-ene **242b** (1.56 g, 60% combined yield, over two steps) in a 14 : 1 : 1 ratio, as a brown oil. (2*E*,4*S*)-1-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-methylhepta-2-ene **242c**: $[\alpha]_D^{20}$ -91.1 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2594 (CH), 1769 (CO), 1468, 1154, 1096 and 1035; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.4, 6-CH_3), 0.93 (3H, d, *J* 6.4, 7-H_3), 1.25 (1H, ddd, *J* 13.6, 8.2, 5.6, 5-*H*H), 1.51 (1H, m, 5-H*H*), 1.70-1.81 (1H, m, 6-H), 3.37 (1H, s, OMe), 4.05 (2H, d, *J* 6.8, 1-H_2), 4.11 (1H, m, 4-H), 4.51 (1H, d, *J* 6.8, OC*H*HO), 4.68 (1H, d, *J* 6.8, OCH*H*O), 5.62 (1H, dd, *J* 15.2, 7.6, 3-H) and 5.81 (1H, dt, *J* 15.2, 6.8, 2-H); δ_C (100 MHz, $CDCl_3$) 22.2 (CH_3), 23.0 (CH), 24.2 (CH_3), 44.3 (CH_2), 44.6 (CH_2), 55.5 (CH_3), 73.9 (CH), 93.8 (CH_2), 96.2 (C), 128.3 (CH), 135.2 (CH) and 161.9 (C); *m/z* (CI) 288 (MH^+ - CH_3OCH_2, 32%), 254 (10) and 218 (7); (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-methylhept-1-ene **242a**: $[\alpha]_D^{19}$ +37.0 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3263 (NH), 2951 (CH), 1713 (CO), 1625 (C=C), 1517, 1032, 823 and 680; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.4, 6-CH_3), 0.94 (3H, d, *J* 6.4, 7-H_3), 1.25 (1H, ddd, *J* 12.8, 9.2, 4.4, 5-*H*H), 1.53 (1H, ddd, *J* 12.8, 9.2, 6.4, 5-H*H*), 1.68-1.80 (1H, m, 6-H), 3.44 (1H, s, OMe), 3.66 (1H, ddd, *J* 9.2, 4.4, 1.6, 4-H), 4.37 (1H, m, 3-H), 4.66 (1H, d, *J* 6.8, OC*H*HO), 4.75 (1H, d, *J* 6.8, OCH*HO*), 5.31 (2H, d, *J* 1.6, 1-*H*H), 5.35 (1H, m, 1-*H*H), 5.78-5.91 (1H, m, 2-H) and 8.36 (1H, br d, *J* 6.8, NH); δ_C (100 MHz, $CDCl_3$) 22.2 (CH), 23.2 (CH_3), 24.4 (CH_3), 42.0 (CH_2), 56.0 (CH), 56.9 (CH), 82.2 (CH_3), 93.0 (C), 98.2 (CH_2), 118.9 (CH_2), 131.7 (CH) and 161.5 (C); *m/z* (CI) 332.0578 (MH^+. $C_{12}H_{21}O_3N^{35}Cl_3$ requires 332.0587), 300 (42%), 262 (100), 238 (18), 202 (21) and 167 (49). Unable to isolate (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-methylhept-1-ene **242b** for characterisation.

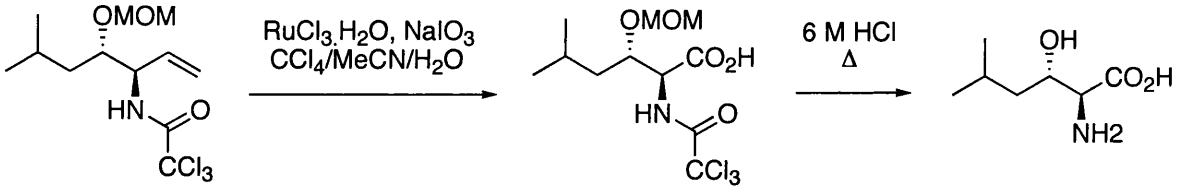
(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-methylhept-1-ene (242a) and (3*S*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-methylhept-1-ene (242b).



The reactions were carried out according to general procedure 11 using (2*E*,4*R*)-methoxymethoxy-6-methylhept-2-en-1-ol **236** (0.1 g, 0.53 mmol). Purification was carried

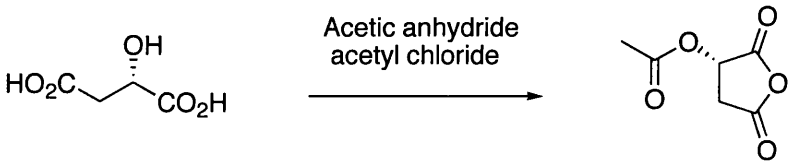
out by flash column chromatography (10% diethyl ether / petroleum ether) to give (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-methylhept-1-ene **242a** and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-methylhept-1-ene **242b** (0.13 g, 73% combined yield, over two steps) in a 14 : 1 ratio (3*R*,3*S*), as a brown oil. Spectroscopic data as above.

(2*S*,3*S*)-2-Amino-3-hydroxy-5-methyl hexanoic acid (250).[104]



The reactions were carried out according to general procedure 12 using (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-methyl-hept-1-ene **242a** (0.7 g, 2.1 mmol) to give (2*S*,3*S*)-2-amino-3-hydroxy-5-methyl hexanoic acid **250** (0.16 g, 48%). $[\alpha]_D^{20}$ +13.7 (*c* 1.0, 1 M HCl); Lit.[104] $[\alpha]_D^{25}$ +14.6 (*c* 1.0, 1 M HCl); υ_{max}/cm^{-1} (neat) 3033 (OH and NH), 2960 (CH), 1617 (CO), 1405, 1339, 1136 and 1053; δ_H (400 MHz, D_2O) 0.82 (3H, d, *J* 6.8, 6-H_3), 0.86 (3H, d, *J* 6.8, 5-CH_3), 1.11 (1H, ddd, *J* 14.0, 10.0, 2.8, 4-*H*H), 1.43 (1H, ddd, *J* 14.0, 10.0, 4.4, 4-H*H*), 1.63-1.71 (3H, m, 5-H), 3.75 (3H, m, 2-H) and 4.12 (1H, m, 3-H); δ_C (100 MHz, D_2O) 20.3 (CH_3) 22.7 (CH_3), 23.9 (CH), 39.6 (CH_2), 59.8 (CH), 67.5 (CH), and 171.7 (C); *m/z* (CI) 145 (M^+ - NH_2, 20%), 131 (50), 117 (49) and 113 (100).

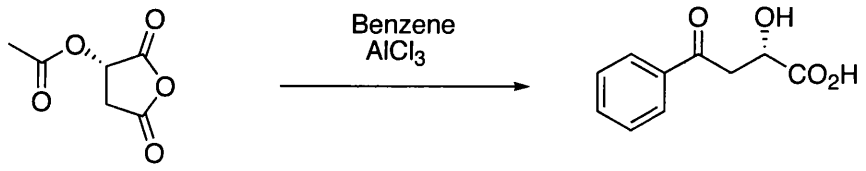
(2*S*)-Acetoxysuccinic anhydride (223).[135]



L-Malic acid **222** (10.0 g, 74.6 mmol) was added to a solution of acetic anhydride (10.5 mL, 111.9 mmol) and acetyl chloride (10.2 mL, 141.8 mmol), which had been cooled to 0 °C. The reaction mixture was allowed to stir at 0 °C for 5 minutes then for 1.5 h at 50 °C. The reaction mixture was cooled to room temperature and excess acetic anhydride and acetyl chloride were distilled off under reduced pressure at 50 °C to give (2*S*)-acetoxysuccinic anhydride **223** (11.7 g, 100%). mp 55-57 °C; Lit.[135] mp 56-58 °C; δ_H (400

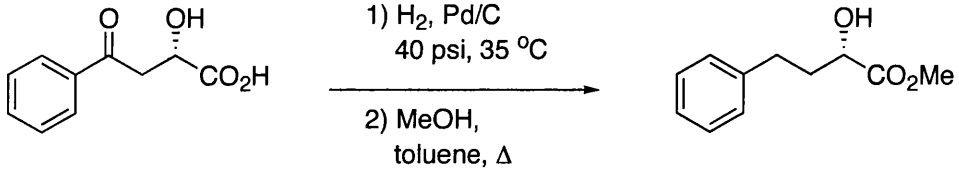
MHz, $CDCl_3$) 2.19 (3H, s, CH_3), 3.00 (1H, dd, *J* 19.2, 6.4, C*H*H), 3.35 (1H, dd, *J* 19.2, 9.2, CH*H*) and 5.52 (1H, dd, *J* 9.2, 6.4, CH); δ_C (100 MHz, $CDCl_3$) 20.2 (CH_3), 53.1 (CH_2), 67.6 (CH), 166.3 (C), 167.8 (C) and 169.7 (C); *m/z* (CI) 159.0292 (MH^+. $C_6H_7O_5$ requires 159.0293), 131 (3%), 113 (6) and 99 (37).

(2*S*)-2-Hydroxy-4-oxo-4-phenylbutanoic acid (224).[135]



Anhydrous aluminium chloride (1.3 g, 9.5 mmol) was added to a solution of (2*S*)-acetoxysuccinic anhydride **223** (0.5 g, 3.2 mmol) in anhydrous benzene (8 mL) which had been cooled to 0 °C. The reaction mixture was then was heated under reflux with vigorous stirring for 4 h then poured into a mixture of crushed ice (10 g) and conc. hydrochloric acid (10 mL). The mixture was stirred for 2 h and then extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by recrystallisation from ethyl acetate / petroleum ether to give (2*S*)-2-hydroxy-4-oxo-4-phenylbutanoic acid **224** (0.33 g, 55%) as white crystals. mp 139-141 °C; Lit.[135] mp 142-144 °C; δ_H (400 MHz, $CDCl_3$) 3.53 (2H, dd, *J* 18.4, 6.4, 3-H_2), 3.86 (1H, br s, OH), 4.72 (1H, dd, *J* 6.4, 4.4, 2-H), 7.49 (2H, m, Ph), 7.63 (1H, m, Ph) and 7.98 (2H, m, Ph); δ_C (100 MHz, $CDCl_3$) 41.7 (CH_2), 66.9 (CH), 128.4 (CH), 128.9 (CH), 134.4 (CH), 135.6 (C), 174.4 (C) and 199.3 (C); *m/z* (EI) 194 (M^+, 2%), 176 (8), 149 (8), 131 (4) and 105 (100).

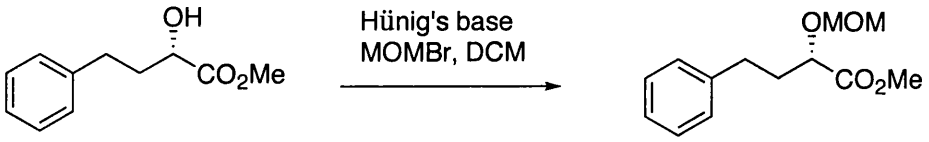
Methyl-(2*S*)-2-hydroxy-4-phenylbutanoate (225).[136]



(2*S*)-2-Hydroxy-4-oxo-4-phenylbutanoic acid **224** (7.3 g, 37.6 mmol) was dissolved in acetic acid (100 mL) with heating. 10% Palladium on carbon (0.75 g) was added and the reaction mixture was shaken at 35 °C and under 40 psi of pressure of H_2 for 48 h. The reaction mixture was filtered through Celite® and concentrated to give a white solid. This solid carboxylic acid was dissolved in toluene (40 mL) and methanol (20 mL) before

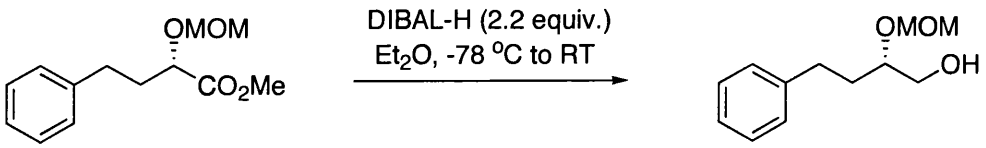
concentrated hydrochloric acid (4 mL) was added and the reaction mixture was heated under reflux for 12 h. The reaction mixture was concentrated, then the resulting residue was dissolved in sodium hydrogen carbonate solution (50 mL) and extracted into ethyl acetate (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography (30% ethyl acetate / petroleum ether) to give methyl (2*S*)-2-hydroxy-4-phenylbutanoate **225** (3.4 g, 46% over two steps) as a liquid. $[\alpha]_D^{19}$ +23.7 (*c* 1.0, $CHCl_3$); Lit.[136] $[\alpha]_D^{25}$ +30.9 (*c* 2.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.94 (1H, m, 3-*H*H), 2.11 (1H, m, 3-H*H*), 2.77 (2H, m, 4-H_2), 2.82 (1H, d, *J* 5.2, OH), 3.78 (1H, s, OMe), 4.20 (1H, ddd, *J* 9.2, 5.2, 4.4, 2-H), 7.21 (5H, m, Ph); *m/z* (CI) 194.0941 (MH^+. $C_{11}H_{14}O_3$ requires 194.0943), 176 (7%), 163 (4), 135 (6), 117 (20), 105 (60) and 90 (100).

Methyl (2*S*)-2-methoxymethoxy-4-phenylbutanoate (228).



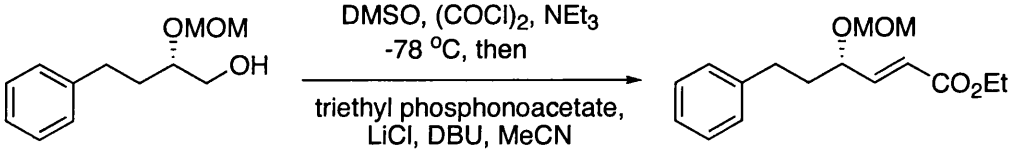
The reaction was carried out according to general procedure 10 using methyl (2*S*)-2-hydroxy-4-phenylbutanoate **225** (3.3 g, 17.1 mmol). Purification was carried out by flash column chromatography (30% diethyl ether / petroleum ether) to give methyl (2*S*)-2-methoxymethoxy-4-phenylbutanoate **228** (3.2 g, 86%) as an oil. $[\alpha]_D^{18}$ -28.6 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2949 (CH), 1749 (CO), 1655 (C=C), 1644 and 1028; δ_H (400 MHz, $CDCl_3$) 2.10 (2H, td, *J* 8.4, 6.4, 3-H_2), 2.68-2.84 (2H, m, 4-H_2), 3.42 (3H, s, OMe), 3.74 (3H, s, OMe), 4.15 (1H, t, *J* 6.4, 2-H), 4.68 (1H, d, *J* 6.8, OC*H*HO), 4.72 (1H, d, *J* 6.8, OCH*H*O) and 7.18-7.31 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 31.4 (CH_2), 34.5 (CH_2), 52.0 (CH_3), 56.2 (CH), 75.1 (CH_3), 96.5 (CH_2), 126.1 (CH), 128.5 (CH), 141.0 (C) and 173.0 (C); *m/z* (CI) 207.1015 (MH^+ - CH_3OH. $C_{12}H_{15}O_3$ requires 207.1021), 189 (89%), 147 (52) and 105 (23).

(2*S*)-2-Methoxymethoxy-4-phenylbutan-1-ol (231).



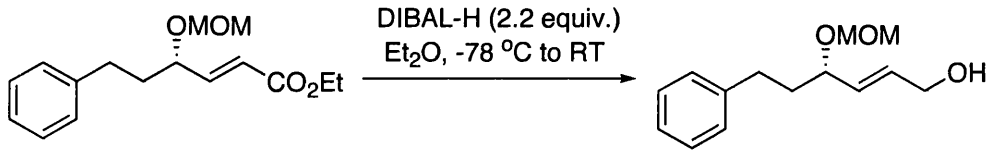
The reaction was carried out according to general procedure 2b using methyl (2*S*)-2-methoxymethoxy-4-phenylbutanoate **228** (2.99 g, 13.46 mmol). Purification was carried out by flash column chromatography (50% diethyl ether / petroleum ether) to give (2S)-2-methoxymethoxy-4-phenylbutan-1-ol **231** (2.24 g, 79%). $[\alpha]_D^{18}$ +47.5 (*c* 1.0, $CHCl_3$); (Found: C, 68.4; H, 8.6. $C_{12}H_{18}O_3$ requires C, 68.5; H, 8.6%); υ_{max}/cm^{-1} (neat) 3421 (OH), 2934 (CH), 1146, 1101, 1024 and 916; δ_H (400 MHz, $CDCl_3$) 1.82-1.92 (2H, m, 3-H_2), 2.64-2.83 (2H, m, 4-H_2), 3.48 (3H, s, OMe), 3.56-3.64 (3H, m, 2-H and 1-H_2), 4.69 (1H, d, *J* 6.8, OCH*H*O), 4.79 (1H, d, *J* 6.8, OC*H*HO), 7.20-7.35 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 31.7 (CH_2), 33.3 (CH_2), 55.7 (CH_2), 65.8 (CH_2), 81.9 (CH_3), 97.2 (CH_2), 126.0 (CH), 128.4 (CH), 128.5 (CH) and 141.6 (C); *m/z* (CI) 211 (MH^+, 7%), 179 (92), 161 (100), 131 (55) and 105 (17).

Ethyl (2*E*,4*S*)-4-methoxymethoxy-6-phenyl-2-hexa-2-enoate (234).



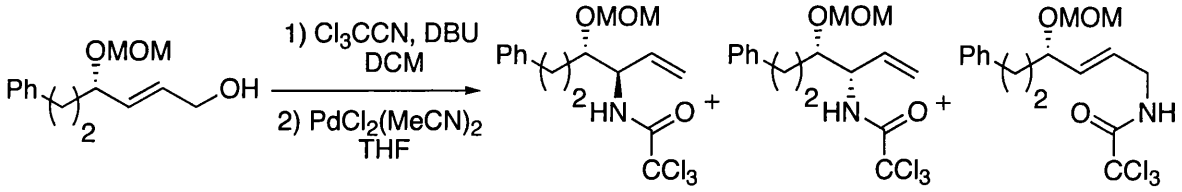
The reactions were carried out according to general procedure 3b using (2*S*)-2-methoxymethoxy-4-phenylbutan-1-ol **231** (2.16 g, 10.28 mmol). Purification was carried out by flash column chromatography (50% diethyl ether / petroleum ether) to give ethyl (2*E*,4*S*)-4-methoxymethoxy-6-phenyl-2-hexanoate **234** (1.57 g, 55%). $[\alpha]_D^{19}$ -52.0 (*c* 1.0, $CHCl_3$); (Found: C, 68.8; H, 8.0. $C_{16}H_{22}O_4$ requires C, 69.0; H, 8.0%); υ_{max}/cm^{-1} (neat) 2944 (CH), 1717 (CO), 1658 (C=C), 1265, 1147 and 1020; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.2, OCH_2CH_3), 1.86-2.02 (2H, m, 5-H_2), 2.67-2.82 (2H, m, 6-H_2), 3.41 (3H, s, OMe), 4.21 (2H, q, *J* 7.2, OCH_2CH_3), 4.25 (1H, m, 4-H), 4.62 (1H, d, *J* 6.8, OC*H*HO), 4.67 (1H, d, *J* 6.8, OCH*H*O), 6.01 (1H, dd, *J* 15.6, 1.6, 2-H), 6.86 (1H, dd, *J* 15.6, 6.0, 3-H) and 7.18-7.32 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 31.4 (CH_2), 36.6 (CH_2), 55.8 (CH), 60.6 (CH_2), 74.9 (CH_3), 94.8 (CH_2), 122.2 (CH), 126.0 (CH), 128.4 (CH), 128.5 (CH), 141.5 (C), 147.6 (CH) and 166.2 (C); *m/z* (CI) 279 (MH^+, 52%), 247 (50), 217 (100), 216 (7) and 173 (6).

(2*E*,4*S*)-Methoxymethoxy-6-phenylhex-2-en-1-ol (237).



The reaction was carried out according to general procedure 4 using ethyl (2*E*,4*S*)-4-methoxymethoxy-6-phenyl-2-hexanoate **234** (1.28 g, 4.60 mmol). Purification was carried out by flash column chromatography (50% diethyl ether / petroleum ether) to give (2*E*,4*S*)-methoxymethoxy-6-phenyl-hex-2-en-1-ol **237** (0.87 g, 78%). $[\alpha]_D^{16}$ +93.7 (*c* 1.0, $CHCl_3$); (Found: C, 71.0; H, 8.6. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.6%); υ_{max}/cm^{-1} (neat) 3408 (OH), 2927 (CH), 1603 (C=C), 1146, 1093, 1028, 972, 917 and 699; δ_H (400 MHz, $CDCl_3$) 1.41 (1H, br s, OH), 1.80-2.03 (2H, m, 5-H_2), 2.63-2.81 (2H, m, 6-H_2), 3.40 (3H, s, OMe), 4.09 (1H, q, *J* 7.2, 4-H), 4.17 (2H, dd, *J* 5.2, 1.6, 1-H_2), 4.57 (1H, d, *J* 6.8, OC*H*HO), 4.72 (1H, d, *J* 6.8, OCH*H*O), 5.61 (1H, ddt, *J* 15.6, 7.2, 1.6, 3-H), 5.84 (1H, dt, *J* 15.6, 5.2, 2-H) and 7.17-7.32 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 31.7 (CH_2), 37.2 (CH_2), 55.6 (CH), 62.9 (CH_2), 75.9 (CH_3), 93.9 (CH_2), 125.9 (CH), 128.4 (CH), 128.4 (CH), 131.2 (CH), 132.4 (CH) and 142.0 (C); *m/z* (CI) 219 (MH^+ - H_2O, 12%), 199 (15), 175 (96), 157 (100) and 131 (86).

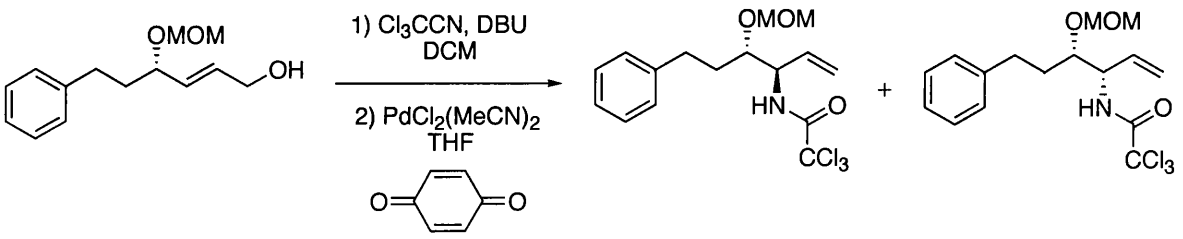
(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-phenylhexa-1-ene (243a), (3*S*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-phenylhexa-1-ene (243b) and (2*E*,4*S*)-1-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-phenylhexa-2-ene (243c).



The reactions were carried out according to general procedure 7 using (2*E*,4*R*)-methoxymethoxy-6-phenylhex-2-en-1-ol **237** (0.99 g, 2.60 mmol) then bis(acetonitrile)palladium(II) chloride (10 mol%). Purification was carried out by flash column chromatography (10% diethyl ether / petroleum ether) to give (2*E*,4*S*)-1-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-phenylhexa-2-ene **243c**. Further elution (15% diethyl ether / petroleum ether) gave (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-phenylhexa-1-ene **243a** followed

by (20% diethyl ether / petroleum ether) (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-phenylhexa-1-ene **243b** (0.64 g, 65% combined yield, over two steps) in a 9 : 1 : 4 ratio, as a brown oil. (2*E*,4*R*)-1-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-phenylhexa-2-ene **243c**: $[\alpha]_D^{20}$ -82.1 (*c* 1.0, $CDCl_3$); υ_{max}/cm^{-1} (neat) 3085 (NH), 2947 (CH), 1718 (CO), 1656 (C=C), 1496, 1148, 1098, 1030 and 970; δ_H (400 MHz, $CDCl_3$) 1.83-2.04 (2H, m, 5-H_2), 2.73-2.83 (2H, m, 6-H_2), 3.43 (3H, s, OMe), 4.10 (3H, m, 4-H and 1-H_2), 4.61 (1H, d, *J* 6.8, OC*H*HO), 4.74 (1H, d, *J* 6.8, OCH*H*O), 5.72 (1H, dd, *J* 15.2, 7.2, 3-H), 5.86 (1H, dt, *J* 15.2, 6.4, 2-H), 7.23-7.35 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 31.6 (CH_2), 37.1 (CH_2), 44.3 (CH_2), 55.6 (CH), 75.4 (CH_3), 94.1 (CH_2), 94.2 (C), 126.0 (CH), 128.4 (CH), 128.5 (CH), 128.8 (CH), 134.7 (CH), 141.8 (C) and 163.1 (C); *m/z* (CI) 321 (MH^+ - CH_3CH_2O, 6%), 284 (11), 225 (12), 193 (62) and 157 (100). (3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-phenylhexa-1-ene **243a**: $[\alpha]_D^{18}$ +58.8 (*c* 1.0, $CHCl_3$); (Found: C, 50.5; H, 5.3; N, 3.7. $C_{16}H_{20}Cl_3NO_3$ requires C, 50.5; H, 5.3, N, 3.7%); υ_{max}/cm^{-1} (neat) 3277 (NH), 2939 (CH), 1713 (CO), 1514, 1141, 1031 and 821; δ_H (400 MHz, $CDCl_3$) 1.81-1.91 (1H, m, 5-*H*H), 1.95 (1H, m, 5-H*H*), 2.63-2.71 (1H, m, 6-*H*H), 2.79-2.86 (1H, m, 6-H*H*), 3.48 (3H, s, OMe), 3.59 (1H, ddd, *J* 8.6, 4.4, 2.0, 4-H), 4.43 (1H, br t, *J* 8.6, 3-H), 4.65 (1H, d, *J* 6.8, OC*H*HO), 4.81 (1H, d, *J* 6.8, OCH*H*O), 5.34 (1H, m, 1-*H*H), 5.38 (1H, m, 1-*H*H), 5.89 (1H, ddd, *J* 17.2, 10.4, 8.6, 2-H), 7.19-7.39 (5H, m, Ph), 8.37 (1H, br d, *J* 8.6, NH); δ_C (100 MHz, $CDCl_3$) 31.9 (CH_2), 34.8 (CH_2), 56.0 (CH), 56.9 (CH), 83.5 (CH_3), 93.0 (C), 98.4 (CH_2), 119.2 (CH_2), 126.2 (CH), 128.4 (CH), 128.6 (CH), 131.5 (CH), 141.0 (C), 161.5 (C); *m/z* (CI) 380 (MH^+, 100%), 310 (63), 286 (12), 244 (16), 187 (66) and 157 (58). Unable to isolate (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-phenylhexa-1-ene **243b** for characterisation.

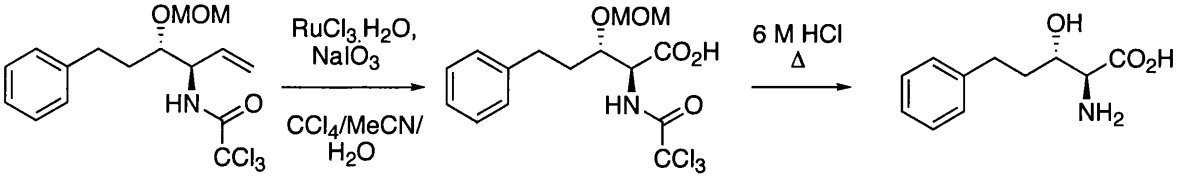
(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-phenylhexa-1-ene (243a) and (3*S*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-phenylhexa-1-ene (243b).



The reactions were carried out according to general procedure 11 using (2*E*,4*R*)-methoxymethoxy-6-phenylhex-2-en-1-ol **237** (0.1 g, 0.42 mmol). Purification was carried

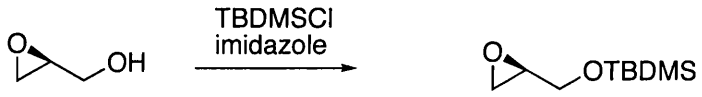
out by flash column chromatography (10% diethyl ether / petroleum ether) to give (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-phenylhexa-1-ene **243a** and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-phenylhexa-1-ene **243b** (0.11 g, 69% combined yield, over two steps) in a 9 : 1 ratio (3*R*,3*S*), as a brown oil. Spectroscopic data as above.

(2*S*,3*S*)-2-Amino-3-hydroxy-5-phenylpentanoic acid (252).



The reactions were carried out according to general procedures 12 using (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-phenylhexa-1-ene **243a** (0.77 g, 0.20 mmol) and gave (2*S*,3*S*)-2-amino-3-hydroxy-5-phenylpentanoic acid **252** (0.03 g, 48% over two steps) as a brown solid. $[\alpha]_D^{19}$ +14.7 (*c* 0.4, 2 M HCl); υ_{max}/cm^{-1} (neat) 3388 (NH, OH), 2913 (CH), 1729 (CO), 1495, 1218 and 1036; δ_H (400 MHz, D_2O) 1.73-1.83 (2H, m, 4-CH_2), 2.53-2.63 (1H, m, 5-*H*H), 2.74 (1H, ddd, *J* 14.0, 8.8, 5.2, 5-H*H*), 3.89 (1H, d, *J* 3.6, 2-H), 3.93 (1H, dt, *J* 8.8, 3.6, 3-H) and 7.09-7.26 (5H, m, Ph); δ_C (100 MHz, D_2O) 31.2 (CH_2), 33.2 (CH_2), 58.1 (CH), 68.6 (CH), 126.2 (CH), 128.5 (CH), 128.7 (CH), 141.3(C) and 169.9 (C); *m/z* (CI) 210 (MH^+, 12%), 175 (100), 144 (28) and 113 (34).

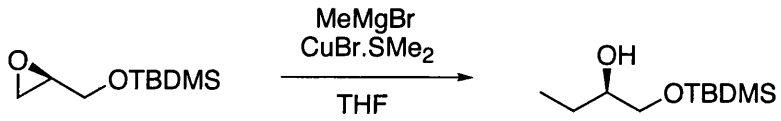
(2*R*)-3-(*tert*-Butyldimethylsilyloxy)-1,2-epoxypropane (267).[137]



A mixture of (*S*)-glycidol **266** (5.0 g, 65.4 mmol), *tert*-butyldimethylsilyl chloride (14.8 g, 98.1 mmol) and imidazole (6.7 g, 98.1 mmol) in THF (70 mL) were stirred for 12 h at room temperature forming a white precipitate. The precipitate was filtered and washed with diethyl ether (50 mL). The combined filtrate was concentrated and purified by flash column chromatography (10% diethyl ether / petroleum ether) to give (2*R*)-3-(*tert*-butyldimethylsilyloxy)-1,2-epoxypropane **267** (10.8 g, 88%) as a clear white liquid. $[\alpha]_D^{24}$ +2.7 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat): 2929 (CH), 1472, 1255, 1098 and 838; δ_H (400 MHz, $CDCl_3$) 0.09 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 2.66 (1H, dd, *J* 4.6, 2.4, 3-*H*H), 2.79 (1H, dd, *J* 5.2, 4.6, 3-H*H*), 3.12 (1H, m, 2-H), 3.68 (1H, dd, *J* 11.8,

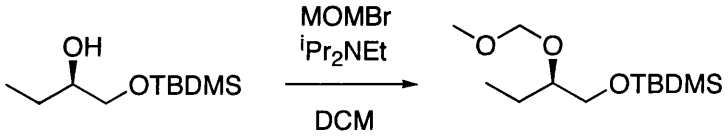
4.8, 1-*H*H), 3.87 (1H, dd, *J* 11.8, 3.2, 1-H*H*); δ_C (100 MHz, $CDCl_3$) -5.3 (CH_3), -5.4 (CH_3), 19.0 (C), 26.0 (CH_3), 45.0 (CH_2), 52.5 (CH) and 63.9 (CH_2); *m/z* (CI) 189.1307 (MH^+. $C_9H_{21}O_2Si$ requires 189.1311), 145 (5%), 131 (6), 113 (4) and 73 (25).

(2*R*)-1-(*tert*-Butyldimethylsilyloxy)butan-2-ol (268).[111]



Methylmagnesium bromide (3 M in diethyl ether) (28.7 mL, 86.2 mmol) was added dropwise to a solution of copper(I) bromide-dimethyl sulfide complex (0.60 g, 2.9 mmol) in THF (50 mL) at -78 °C and the white suspension was stirred for 0.5 h. (2*R*)-3-(*tert*-Butyldimethylsilyloxy)-1,2-epoxypropane **267** (10.8 g, 57.5 mmol) in THF (50 mL) was then added and the reaction mixture was warmed to 0 °C and stirred for 2 h. The reaction was quenched by the addition of a saturated ammonium chloride solution (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography (20% diethyl ether / petroleum ether) to give (2*R*)-1-(*tert*-butyldimethylsilyloxy)butan-2-ol **268** (10.5 g, 90%) as a clear liquid. $[\alpha]_D^{21}$ -61.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.09 (6H, s, $Si(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 0.98 (3H, t, *J* 7.2, 4-H_3), 1.47 (2H, m, 3-H_2), 2.39 (1H, br s, OH), 3.41 (1H, dd, *J* 9.8, 7.6, 1-*H*H), 3.57 (1H, m, 2-H) and 3.65 (1H, dd, *J* 9.8, 3.2, 1-H*H*); δ_C (100 MHz, $CDCl_3$) -5.5 (CH_3), 10.2 (CH_3), 18.5 (C), 26.0 (CH_2), 26.1 (CH_3), 67.1 (CH_2) and 73.4 (CH); *m/z* (CI) 205 (MH^+, 37%), 198 (100), 187 (10) and 172 (25).

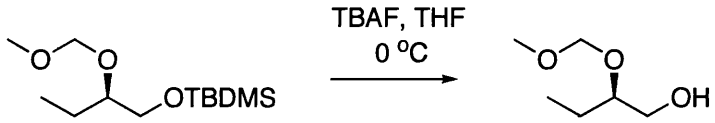
(2*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-(methoxymethoxy)butane (269).



The reaction was carried out according to general procedure 10 using (2*R*)-1-(*tert*-butyldimethylsilyloxy)butan-2-ol **268** (9.41 g, 46.1 mmol). Purification was carried out by flash column chromatography (20% diethyl ether / petroleum ether) to give (2*R*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)butane **269** (3.2 g, 86%) as a clear oil. $[\alpha]_D^{20}$ +54.3 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (NaCl): 2930 (CH), 1464, 1255, 1107, 838 and 777; δ_H (400 MHz, $CDCl_3$) 0.10 (6H, s, $Si(CH_3)_2$), 0.91 (9H, s, $SiC(CH_3)_3$), 0.96 (3H, t, *J* 7.2, 4-H_3), 1.55 (2H, m, 3-H_2), 3.41 (3H, s, OMe), 3.57 (3H, m, 1-H_2 and 2-H), 4.68 (1H, d, *J* 6.8, OC*H*HO) and 4.80 (1H, d, *J* 6.8, OCH*H*O); δ_C (100 MHz, $CDCl_3$) -5.2 (CH_3), 10.0 (CH_3),

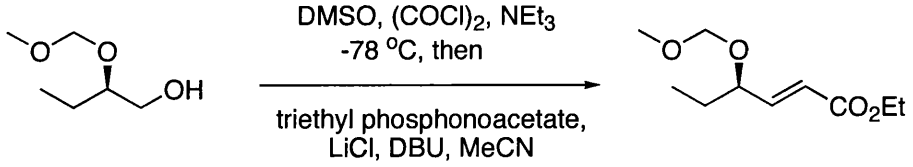
18.5 (C), 24.7 (CH_2), 26.1 (CH_3), 55.6 (CH_3), 65.7 (CH_2), 79.7 (CH) and 96.4 (CH_2); *m/z* (CI) 217.1616 (M^+ - CH_3O, $C_{11}H_{25}O_2Si$ requires 217.1624), 171 (33%) and 73 (25).

(2*R*)-2-(Methoxymethoxy)butan-1-ol (264).



Tetra-*n*-butylammonium fluoride (1.0 M solution in THF) (45.4 mL, 45.4 mmol) was added to a solution of (2*R*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)butane **269** (9.4 g, 37.9 mmol) in THF (90 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 12 h and then concentrated. The resulting residue was taken up in ethyl acetate (20 mL), washed with water (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (40% diethyl ether / petroleum ether) gave (2*R*)-2-(methoxymethoxy)butan-1-ol **264** (3.0 g, 59%) as yellow oil. $[\alpha]_D^{22}$ -60.5 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat): 3442 (OH), 2936 (CH), 1465, 1135, 1033 and 918; δ_H (400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.6, 4-H_3), 1.54 (2H, m, 3-H_2), 3.08 (1H, br s, OH), 3.44 (3H, s, OMe), 3.46-3.63 (3H, m, 1-H_2 and 2-H), 4.71 (1H, d, *J* 7.0, OC*H*HO) and 4.76 (1H, d, *J* 7.0, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 10.1 (CH_3), 24.7 (CH_2), 55.8 (CH), 65.5 (CH_2), 83.6 (CH) and 97.1 (CH_2); *m/z* (CI) 135.1016 (MH^+. $C_6H_{15}O_3$ requires 135.1021), 121 (3%), 103 (100) 89 (13) and 73 (29).

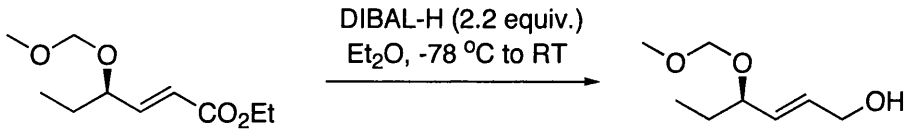
Ethyl (2*E*,4*S*)-4-(methoxymethoxy)hex-2-enoate (270).



The reactions were carried out according to general procedure 3b using (2*R*)-2-(methoxymethoxy)butan-1-ol **264** (1.43 g, 10.7 mmol). Purification by flash column chromatography (50% ether / petroleum ether) gave ethyl (2*E*,4*S*)-4-(methoxymethoxy)hex-2-enoate **270** (1.9 g, 86%) as a yellow liquid. $[\alpha]_D^{23}$ +104.8 (*c* 1.0, $CHCl_3$); (Found: C, 59.3; H, 9.1. $C_{10}H_{18}O_4$ requires C, 59.4; H, 9.0%); υ_{max}/cm^{-1} (neat): 2937 (CH), 1722 (CO), 1660 (C=C), 1273, 1178 and 1034; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.2, 6-H_3), 1.30 (3H, t, *J* 7.2, OCH_2CH_3), 1.65 (2H, m, 5-H_2), 3.39 (3H, s, OMe), 4.14 (1H, ddd, *J* 12.8, 6.0, 1.2, 4-H), 4.21 (2H, q, *J* 7.2, OCH_2CH_3), 4.60 (1H, d, *J* 6.8,

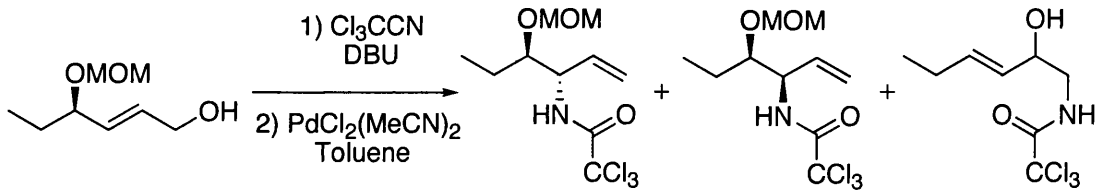
OC*H*HO), 4.65 (1H, d, *J* 6.8, OCH*H*O), 5.99 (1H, dd, *J* 16.0, 1.2, 2-H) and 6.82 (1H, dd, *J* 16.0, 6.0, 3-H); δ_C (100 MHz, $CDCl_3$) 9.7 (CH_3), 14.4 (CH_3), 27.9 (CH), 55.8 (CH_3), 60.6 (CH_2), 76.6 (CH), 94.8 (CH_2), 122.2 (CH), 147.9 (CH) and 166.4 (C); *m/z* (CI) 203.1281 (MH^+. $C_{10}H_{19}O_4$ requires 203.1283), 173 (43%), 171 (25), 141 (100) and 113 (2).

(2*E*,4*S*)-4-(Methoxymethoxy)hex-2-en-1-ol (271).



The reaction was carried out according to general procedure 4 using ethyl (2*E*,4*S*)-4-(methoxymethoxy)hex-2-enoate **270** (1.85 g, 9.16 mmol). Purification by flash column chromatography (50% ether / petroleum ether) gave (2*E*,4*S*)-4-(methoxymethoxy)hex-2-en-1-ol **271** (1.4 g, 95%) as a yellow liquid. $[\alpha]_D^{24}$ -146.5 (*c* 1.0, $CHCl_3$); (Found: C, 59.7; H, 10.2. $C_8H_{16}O_3$ requires C, 60.0; H, 10.1%); υ_{max}/cm^{-1} (neat): 3708 (OH), 2935 (CH), 1673 (C=C), 1158, 1097 and 1034; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.2, 6-H_3), 1.60 (2H, m, 5-H_2), 1.70 (1H, br s, OH), 3.39 (3H, s, OMe), 3.96 (1H, dt, *J* 7.2, 6.8, 4-H), 4.17 (2H, dd, *J* 5.2, 1.2, 1-H_2), 4.55 (1H, d, *J* 6.8, OC*H*HO), 4.72 (1H, d, *J* 6.8, OCH*H*O), 5.57 (1H, ddt, *J* 15.6, 7.2, 1.2, 3-H) and 5.83 (1H, dt, *J* 15.6, 5.2, 2-H); δ_C (100 MHz, $CDCl_3$) 10.0 (CH_3), 28.6 (CH_2), 55.5 (CH_3), 63.1 (CH_2), 77.8 (CH), 93.9 (CH_2), 131.4 (CH) and 132.4 (CH); *m/z* (CI) 143 (MH^+ - H_2O, 25%), 131 (55), 115 (23) and 99 (100).

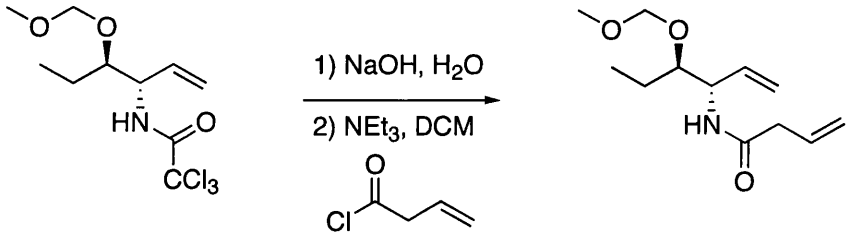
(3*S*,4*R*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)hexa-1-ene (262a), (3*R*,4*R*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)hexa-1-ene (262b) and (3*E*)-1-(trichloromethylcarbonylamino)-2-hydroxyhexa-3-ene (262c).



The reaction was carried out according to general procedure 8 using (2*E*,4*S*)-4-(methoxymethoxy)hex-2-en-1-ol **271** (0.1 g, 0.6 mmol) then bis(acetonitrile)palladium(II) chloride (10 mol%) in toluene (10 mL). Purification was carried out by flash column chromatography (10% diethyl ether / petroleum ether) to give (3*E*)-1-(trichloromethylcarbonylamino)-2-hydroxyhexa-3-ene **262c** (28 mg, 15% over two steps).

δ_H (400 MHz, $CDCl_3$) 1.03 (3H, t, *J* 7.6, 6-H_3), 1.27 (1H, br s, NH), 2.11 (2H, m, 5-H_2), 4.31 (2H, dd, *J* 8.4, 8.0, 1-H_2), 4.77 (1H, d, *J* 8.4, OH), 4.84 (1H, dt, *J* 8.4, 7.6, 2-H), 5.47 (1H, ddt, *J* 15.6, 7.6, 1.6, 3-H) and 5.88 (1H, dt, *J* 15.6, 6.4, 4-H); δ_C (100 MHz, $CDCl_3$) 13.1 (CH_3), 25.3 (CH_2), 68.8 (CH), 76.3 (CH_2), 87.8 (C), 126.4 (CH), 136.9 (CH) and 162.8 (C); *m/z* (CI) 260.0014 (MH^+. $C_8H_{13}O_2N^{35}Cl_3$ requires 260.0012), 242 (50%), 226 (35) 190 (23) and 162 (16). Further elution (20% diethyl ether / petroleum ether) gave (3*S*,4*R*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)hexa-1-ene **262a** and (3*R*,4*R*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)hexa-1-ene **262b** (0.1 g, 54% combined yield, over two steps) in a ratio of 16 : 1 (3*S* : 3*R*), as a colourless oil. (3*S*,4*R*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)hexa-1-ene **262a**: $[\alpha]_D^{27}$ -72.9 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat): 3285 (NH), 2938 (CH), 1715 (CO), 1644 (C=C), 1518, 1036 and 823; δ_H (400 MHz, $CDCl_3$) 0.98 (3H, t, *J* 7.6, 6-H_3), 1.61 (2H, m, 5-H_2), 3.44 (3H, s, OMe), 3.50 (1H, ddd, *J* 8.4, 5.6, 2.0, 4-H), 4.41 (1H, dd, *J* 8.4, 6.4, 3-H), 4.67 (1H, d, *J* 6.8, OC*H*HO), 4.76 (1H, d, *J* 6.8, OCH*H*O), 5.34 (2H, m, 1-H_2), 5.85 (1H, ddd, *J* 17.2, 10.4, 6.4, 2-H) and 8.26 (1H, br d, *J* 6.4, NH); δ_C (100 MHz, $CDCl_3$) 10.2 (CH_3), 25.9 (CH_2), 55.9 (CH), 56.4 (CH_3), 85.2 (CH), 93.0 (C), 98.2 (CH_2), 118.9 (CH_2), 131.6 (CH) and 161.4 (C); (3*R*,4*R*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)hexa-1-ene **262b**: $[\alpha]_D^{25}$ +13.2 (*c* 4.5, $CHCl_3$), δ_H (400 MHz, $CDCl_3$) 0.98 (3H, t, *J* 7.6, 6-H_3), 1.63 (2H, m, 5-H_2), 3.40 (3H, s, OMe), 3.69 (1H, ddd, *J* 7.6, 5.6, 2.4, 4-H), 4.55 (1H, m, 3-H), 4.66 (1H, d, *J* 6.8, OC*H*HO), 4.70 (1H, d, *J* 6.8, OCH*H*O), 5.29 (2H, m, 1-H_2), 5.90 (1H, ddd, *J* 17.2, 10.8, 5.2, 2-H), 7.16 (1H, br d, *J* 6.4, NH); δ_C (100 MHz, $CDCl_3$) 9.9 (CH_3), 24.7 (CH_2), 55.1 (CH), 56.0 (CH_3), 80.1 (CH), 93.0 (C), 96.0 (CH_2), 116.7 (CH_2), 135.3 (CH) and 161.7 (C); *m/z* (CI) 304.0281 (MH^+. $C_{10}H_{17}O_3N^{35}Cl_3$ requires 304.0274), 272 (100%), 234 (23), 214 (46) and 174 (19).

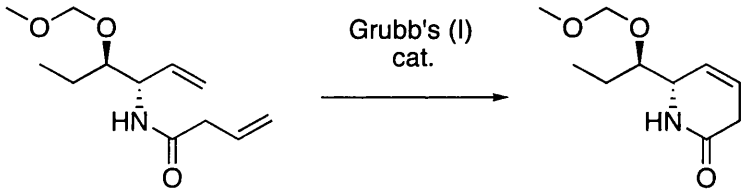
(3*S*,4*R*)-3-(But-3'-enoylamino)-4-(methoxymethoxy)hexa-1-ene (272).



(3*S*,4*R*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)hexa-1-ene **262a** (1.14 g, 3.73 mmol) was suspended in 2 M sodium hydroxide solution (10 mL) and stirred vigorously for 12 h. The solution was extracted with DCM (3 x 15 mL) and ethyl acetate (3 x 15 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*

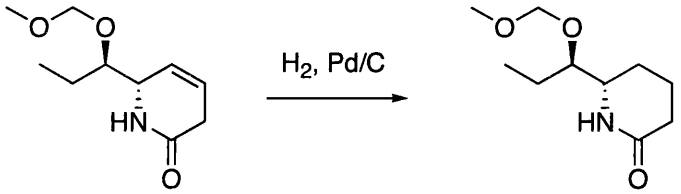
to give the amine as a yellow liquid. The amine was dissolved in DCM (10 mL) and cooled to 0 °C. Triethylamine (2.6 mL, 18.7 mmol) was added and the solution was stirred for 0.5 h. 3-Butenoyl chloride (0.8 mL, 7.5 mmol) was added and the reaction mixture was allowed to stir for 1 h. Concentration *in vacuo* followed by purification by flash column chromatography (100% diethyl ether / petroleum ether) gave (3*S*,4*R*)-3-(but-3'-enoylamino)-4-(methoxymethoxy)hexa-1-ene **272** (0.44 g, 52% over two steps). $[\alpha]_D^{24}$ -86.4 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat): 3308 (NH), 2937 (CH), 1655 (CO), 1540 (C=C), 1036 and 919; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.2, 6-H_3), 1.45-1.67 (2H, m, 5-H_2), 3.05 (2H, dt, *J* 7.2, 1.2, 2'-H_2), 3.42 (3H, s, OMe), 3.43-3.46 (1H, m, 3H), 4.52-4.56 (1H, m, 4-H), 4.65 (1H, d, *J* 6.8, OC*H*HO), 4.73 (1H, d, *J* 6.8, OCH*H*O), 5.22-5.27 (4H, m, 1-H_2 and 4'-H_2), 5.82 (1H, m, 2-H), 5.98 (1H, m, 3'-H) and 6.85 (1H, br d, *J* 6.8, NH); δ_C (100 MHz, $CDCl_3$) 10.2 (CH_3), 25.6 (CH_2), 42.0 (CH_2), 53.8 (CH), 55.9 (CH_3), 85.2 (CH), 97.9 (CH_2), 117.5 (CH_2), 119.4 (CH_2), 131.4 (CH), 133.3 (CH) and 169.8 (C); *m/z* (CI) 228.1609 (MH^+. $C_{12}H_{22}NO_3$ requires 228.1600), 196 (31%), 169 (5), 127 (6) and 113 (28).

(1'*R*,6*S*)-6-[1'-(Methoxymethoxy)propyl]-3,6-dihydro-1*H*-pyridin-2-one (273).



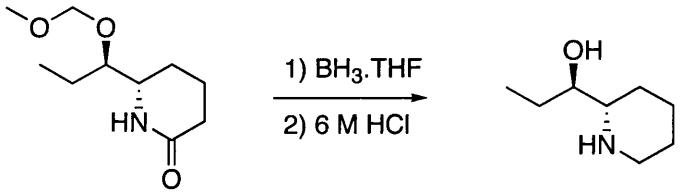
(3*S*,4*R*)-3-(But-3'-enoylamino)-4-(methoxymethoxy)hexa-1-ene **272** (0.13 g, 0.44 mmol) and bis(tricyclohexylphosphine) benzylidine ruthenium(IV) chloride (18 mg, 0.02 mmol) were dissolved in DCM (10 mL) and heated under reflux for 12 h. Concentration *in vacuo* followed by purification by flash column chromatography (100% ethyl acetate) gave (1'*R*,6*S*)-6-[1'-(methoxymethoxy)propyl]-3,6-dihydro-1*H*-pyridin-2-one **273** (0.09 g, 100%) as brown liquid. $[\alpha]_D^{25}$ -2.1 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3253 (NH), 2936 (CH), 1716 (CO), 1653 (C=C), 1457 and 1034; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 6.8, 3'-H_3), 1.38-1.55 (2H, m, 2'-H_2), 2.91 (2H, m, 3-H_2), 3.38 (3H, s, OMe), 3.50 (1H, dt, *J* 8.4, 3.6, 1'-H), 4.31 (1H, m, 6-H), 4.65 (1H, d, *J* 6.8, OC*H*HO), 4.71 (1H, d, *J* 6.8, OCH*H*O), 5.58-5.61 (1H, m, 5-H), 5.80-5.85 (1H, m, 4-H) and 6.44 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 10.3 (CH_3), 22.1 (CH_2), 31.6 (CH_2), 56.0 (CH_3), 57.1 (CH), 81.6 (CH), 96.5 (CH_2), 121.9 (CH), 123.9 (CH) and 169.7 (C); *m/z* (CI) 200.1286 (MH^+. $C_{10}H_{18}NO_3$ requires 200.1287), 168 (9%), 141 (3) and 113 (4).

(1'*R*,6*S*)-6-[1'-(Methoxymethoxy)propyl]piperidin-2-one (274).



(1'*R*,6*S*)-6-[1'-(Methoxymethoxy)propyl]-3,6-dihydro-1*H*-pyridin-2-one **273** (0.13 g, 0.65 mmol) and 10% palladium on carbon (0.07 g, 0.07 mmol) were dissolved in ethyl acetate (10 mL) and stirred under an atmosphere of hydrogen for 17 h. The reaction mixture was then filtered through a short pad of Celite® and the filtrate concentrated *in vacuo*. Purification was carried out by flash column chromatography (100% ethyl acetate) to give (1'*R*,6*S*)-6-[1'-(methoxymethoxy)propyl]piperidin-2-one **274** (0.17 g, 100%) as a clear liquid. $[\alpha]_D^{24}$ -14.6 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3429 (NH), 2966 (CH), 1636 (CO), 1481, 1105 and 1033; δ_H (400 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.2, 3'-H_3), 1.43-2.00 (6H, m, 2'-H_2, 4-H_2 and 5-H_2), 2.23-2.46 (2H, m, 3-H_2), 3.40 (3H, s, OMe), 3.42-3.46 (1H, m, 1'-H), 3.65 (1H, dt, *J* 10.4, 4.0, 6-H), 4.66 (1H, d, *J* 7.2, OC*H*HO), 4.69 (1H, d, *J* 7.2, OCH*H*O) and 5.92 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 10.2 (CH_3), 20.1 (CH_2), 22.4 (CH_2), 24.0 (CH_2), 31.6 (CH_2), 55.5 (CH), 55.9 (CH_3), 80.8 (CH), 96.3 (CH_2) and 172.4 (C); *m/z* (CI) 202.1441 (MH^+. $C_{10}H_{20}NO_3$ requires 202.1443), 188 (3%), 170 (8), 156 (15) and 143 (3).

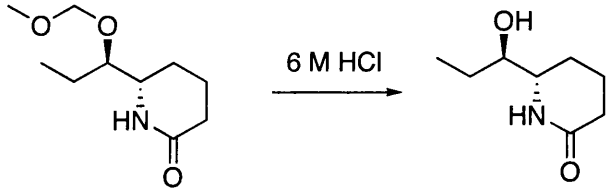
(1'*R*,2*S*)-2-[1'-(Hydroxy)propyl]piperidine (253).[138]



(1'*R*,6*S*)-6-[1'-(Methoxymethoxy)propyl]piperidin-2-one **274** (0.07 g, 0.32 mmol) was dissolved in THF (10 mL) and cooled to 0 °C. Borane-THF complex (1 M in THF) (5 mL) was added and the reaction mixture was heated under reflux for 4 h. The reaction was quenched with water (3 mL), concentrated and the resulting residue dissolved in ethyl acetate (10 mL). This solution was washed with 6 M hydrochloric acid solution, dried ($MgSO_4$) and concentrated *in vacuo*. The amine (0.32 mmol) was then dissolved in 6 M hydrochloric acid solution (3 mL) and stirred at room temperature for 2 h. The reaction mixture was neutralized with saturated sodium hydrogen carbonate solution and extracted

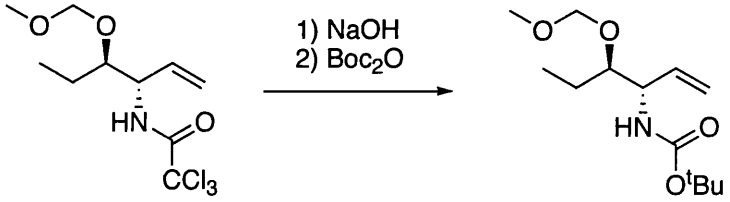
with DCM (3 x 10 mL) and ethyl acetate (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography (10% methanol / ethyl acetate) to give (1'*R*,2*S*)-2-[1'-(hydroxy)propyl]piperidine **253** (0.02 g, 42% over two steps) as a white solid. $[\alpha]_D^{25}$ +4.0 (*c* 1.7, EtOH), (Lit.[138] $[\alpha]_D^{27}$ +8.9 (EtOH)); δ_H (400 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.2, 3'-H_3), 1.27-1.65 (7H, m, 2'-H_2, 3-H_2, 4-*H*H and 5-H_2), 1.86 (1H, m, 4-H*H*), 2.51 (2H, br s, NH and OH), 2.60-2.65 (1H, m, 2-H), 2.72 (1H, td, *J* 12.0, 2.8, 6-*H*H), 3.17 (1H, m, 6-H*H*) and 3.49 (1H, m, 1'-H); δ_C (100 MHz, $CDCl_3$) 10.5 (CH_3), 24.5 (CH_2), 25.2 (CH_2), 25.4 (CH_2), 26.5 (CH_2), 47.1 (CH_2), 60.1 (CH) and 76.0 (CH); *m/z* (CI) 144.1387 (MH^+. $C_8H_{18}NO$ requires 144.1388), 126 (10%), 113 (29), 85 (88) and 71 (100).

(1'*R*,6*S*)-6-[1'-(Hydroxy)propyl]piperidin-2-one (260).



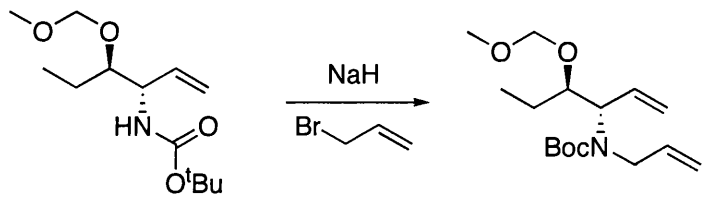
(1'*R*,6*S*)-6-[1'-(Methoxymethoxy)propyl]piperidin-2-one **274** (40 mg, 0.20 mmol) was dissolved in 6 M hydrochloric acid solution (3 mL) and stirred at room temperature for 2 h. The reaction mixture was neutralized with saturated sodium hydrogen carbonate solution and extracted with DCM (3 x 10 mL) and ethyl acetate (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography (10% methanol / ethyl acetate) to give (1'*R*,6*S*)-6-[1'-(hydroxy)propyl]piperidin-2-one **260** (25 mg, 81%) as a white solid. $[\alpha]_D^{25}$ -53.5 (*c* 0.6, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3406 (OH and NH), 2963 (CH), 1638 (CO), 1482, 1413, 1330 and 733; δ_H (400 MHz, $CDCl_3$) 1.02 (3H, t, *J* 7.2, 3'-H_3), 1.45-1.95 (6H, m, 2'-H_2, 4-H_2 and 5-H_2), 2.21-2.42 (2H, m, 3-H_2), 3.03 (1H, br s, OH), 3.48 (1H, m, 6-H), 3.54 (1H, m, 1'-H), 6.78 (1H, br s, OH); δ_C (100 MHz, $CDCl_3$) 10.7 (CH_3), 19.9 (CH_2), 22.4 (CH_2), 24.7 (CH_2), 31.6 (CH_2), 57.9 (CH), 74.6 (CH) and 173.9 (C); *m/z* (CI) 158.1180 (MH^+. $C_8H_{16}NO_2$ requires 158.1181), 139 (5%), 127 (5), 113 (30) and 97 (30).

(3*S*,4*R*)-3-(*tert*-Butoxycarbonylamino)-4-(methoxymethoxy)hexa-1-ene (276).



(3*S*,4*R*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)hexa-1-ene **262a** (0.4 g, 1.3 mmol) was dissolved in 2 M sodium hydroxide solution and stirred vigorously for 12 h at room temperature. Di-*tert*-butyl dicarbonate (0.72 g, 3.28 mmol) was added and the solution was stirred for 6 h before a further portion of Di-*tert*-butyl dicarbonate (0.72 g, 3.28 mmol) was added and the reaction mixture stirred for a further 12 h. The reaction mixture was then extracted with ethyl acetate (4 x 15 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography (30% diethyl ether / petroleum ether) to give (3*S*,4*R*)-3-(*tert*-butoxycarbonylamino)-4-(methoxymethoxy)hexa-1-ene **276** (0.25 g, 74% over two steps) as a yellow liquid. $[\alpha]_D^{25}$ -45.0 (*c* 4.7, $CHCl_3$); (Found: C, 60.2; H, 9.8; N, 5.4. $C_{13}H_{25}NO_4$ requires C, 60.2; H, 9.7; N, 5.3%); υ_{max}/cm^{-1} (neat) 3358 (NH), 2975 (CH), 1716 (CO), 1509, 1366, 1171 and 1039; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.2, 6-H_3), 1.45 (9H, s, $OC(CH_3)_3$), 1.43-1.65 (2H, m, 5-H_2), 3.41 (3H, s, OMe), 3.49 (1H, m, 4-H), 4.19 (1H, m, 3-H), 4.66 (1H, d, *J* 6.8, OC*H*HO), 4.71 (1H, d, *J* 6.8, OCH*H*O), 5.24 (2H, m, 1-H_2), 5.43 (1H, br d, *J* 6.4, NH), 5.81 (1H, ddd, *J* 17.2, 10.8, 6.4, 2-H); δ_C (100 MHz, $CDCl_3$) 10.1 (CH_3), 25.0 (CH_2), 28.4 (CH_3), 55.3 (CH), 55.8 (CH_3), 79.2 (C), 83.7 (CH), 97.2 (CH_2), 117.0 (CH_2), 134.2 (CH) and 155.4 (C); *m/z* (CI) 260 (MH^+, 19%), 228 (4), 204 (100), 172 (35), 145 (13) and 128 (10).

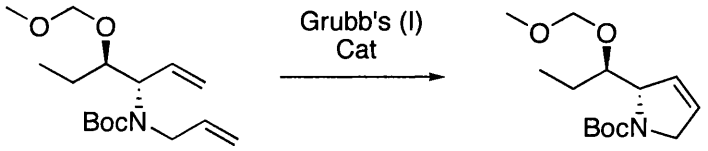
(3*S*,4*R*)-3-(Prop-2-ene-*tert*-butoxycarbonylamino)-4-(methoxymethoxy)hexa-1-ene (277).



(3*S*,4*R*)-3-(*tert*-Butoxycarbonylamino)-4-(methoxymethoxy)hexa-1-ene **276** (0.22 g, 0.85 mmol) and allyl bromide (0.15 mL, 1.7 mmol) were dissolved in DMF (20 mL) and cooled to 0 °C. Sodium hydride (60% in mineral oil) (0.07 g, 1.7 mmol) was added portionwise

over 3 h. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction was quenched by the addition of water (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with water (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography (30% diethyl ether / petroleum ether) to give (3*S*,4*R*)-3-(prop-2-ene-*tert*-butoxycarbonylamino)-4-(methoxymethoxy)hexa-1-ene **277** (0.18 g, 72%) as a yellow liquid. $[\alpha]_D^{23}$ -8.0 (*c* 1.0, $CHCl_3$); (Found: C, 64.4; H, 10.0; N, 4.8. $C_{16}H_{29}NO_4$ requires C, 64.2; H, 9.8; N, 4.7%); υ_{max}/cm^{-1} (neat): 2975 (CH), 1695 (CO), 1658 (C=C), 1396, 1165, 1040 and 910; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.6, 6-H_3), 1.47 (9H, s, $OC(CH_3)_3$), 1.54 (2H, m, 5-H_2), 3.38 (3H, s, OMe), 3.83 (2H, m, 4-H and 3-H), 3.84-4.31 (2H, m, 1'-H_2), 4.62 (1H, d, *J* 6.8, OC*H*HO), 4.66 (1H, d, *J* 6.8, OCH*H*O), 5.09 (2H, m, 3'-H_2), 5.25 (2H, d, *J* 10.4, 1-H_2), 5.80 (1H, m, 2'-H) and 6.03 (1H, m, 2-H); δ_C (100 MHz, $CDCl_3$) 9.2 (CH_3), 24.3 (CH_2), 28.5 (CH_3), 48.0 (CH_2), 55.9 (CH_3), 61.4 (CH), 79.9 (C), 80.3 (CH), 96.8 (CH_2), 115.8 (CH_2), 118.8 (CH_2), 134.5 (CH), 135.6 (CH) and 155.2 (C); *m/z* (CI) 300 (MH^+, 100%), 268 (19), 244 (98), 212 (46) and 168 (65).

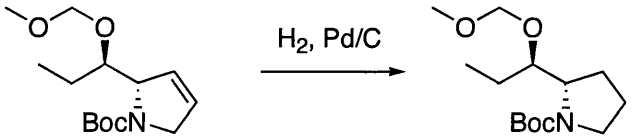
(2*S*,1'*R*)-2-(1'-(Methoxymethoxy)propyl)-*N*-(*tert*-butoxycarbonyl)-2,5-dihydropyrrole (278).



(3*S*,4*R*)-3-(Prop-2-ene-*tert*-butoxycarbonylamino)-4-(methoxymethoxy)hexa-1-ene **277** (0.1 g, 0.34 mmol) and bis(tricyclohexylphosphine) benzylidine ruthenium(IV) chloride (17 mg, 0.02 mmol) were dissolved in DCM (10 mL) and heated under reflux for 20 h. Concentration *in vacuo* followed by purification by flash column chromatography (30% diethyl ether / petroleum ether) gave (2*S*,1'*R*)-2-(1'-(methoxymethoxy)propyl)-*N*-(*tert*-butoxycarbonyl)-2,5-dihydropyrrole **278** (0.09 g, 92%) as a brown liquid. $[\alpha]_D^{26}$ -116.7 (*c* 1.0, $CHCl_3$); (Found: C, 62.0; H, 9.3; N, 5.0. $C_{14}H_{25}NO_4$ requires C, 62.0; H, 9.3; N, 5.2%); υ_{max}/cm^{-1} (neat) 2970 (CH), 1700 (CO), 1627 (C=C), 1400, 1366, 1174, 1124, 1108 and 1038; (2*S*,1'*R*)-2-(1'-(methoxymethoxy)propyl)-*N*-(*tert*-butoxycarbonyl)-2,5-dihydropyrrole **278** exists as a 8 : 7 mixture of rotamers, signals for major rotamer are: δ_H (400 MHz, $CDCl_3$) 1.03 (3H, t, *J* 7.2, 3'-H_3), 1.48 (9H, s, $OC(CH_3)_3$), 1.60 (2H, m, 2'-H_2), 3.33 (3H, s, OMe), 3.96-4.27 (3H, m, 1'-H and 5-H_2), 4.34-4.64 (3H, m, 2-H and OCH_2O) and 5.57-5.97 (2H, m, 3-H and 4-H); δ_C (100 MHz, $CDCl_3$) 10.67 (CH_3), 25.4 (CH_2), 28.49

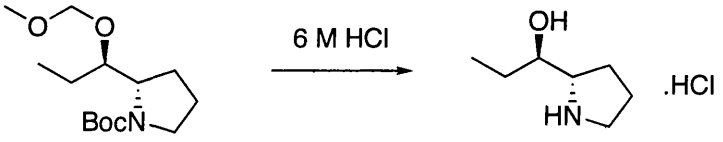
(CH_3), 53.8 (CH_2), 55.5 (CH_3), 67.0 (CH), 78.5 (CH_3), 79.8 (C), 96.3 (CH_2), 125.3 (CH), 127.3 (CH) and 153.9 (C); *m/z* (CI) 272 (MH^+, 9%), 256 (6), 240 (5), 216 (63) and 69 (100).

(2*S*,1'*R*)-2-(1'-(Methoxymethoxy)propyl)-*N*-(*tert*-butoxycarbonyl)pyrrolidine (279).



(2*S*,1'*R*)-2-(1'-(Methoxymethoxy)propyl)-*N*-(*tert*-butoxycarbonyl)-2,5-dihydropyrrole **278** (0.15 g, 0.55 mmol) and 10% palladium on carbon (0.06 g, 0.06 mmol) were dissolved in ethyl acetate (10 mL) and stirred under an atmosphere of hydrogen for 12 h. The reaction mixture was then filtered through Celite® and the filtrate concentrated *in vacuo*. Purification was carried out by flash column chromatography (30% diethyl ether / petroleum ether) to give (2*S*,1'*R*)-2-(1'-(methoxymethoxy)propyl)-*N*-(*tert*-butoxycarbonyl)pyrrolidine **279** (0.15 g, 98%) as a colourless oil. $[\alpha]_D^{24}$ -77.0 (*c* 1.0, $CHCl_3$); (Found: C, 61.6; H, 10.0; N, 5.2. $C_{14}H_{27}NO_4$ requires C, 61.5; H, 10.0; N, 5.1%); υ_{max}/cm^{-1} (neat) 2972 (CH), 1695 (CO), 1395, 1168 and 1037; (2*S*,1'*R*)-2-(1'-(methoxymethoxy)propyl)-*N*-(*tert*-butoxycarbonyl)pyrrolidine **279** exists as an 8 : 6 mixture of rotamers, signals for major rotamer are: δ_H (400 MHz, $CDCl_3$) 0.98 (3H, m, 3'-H_3), 1.49 (9H, s, $OC(CH_3)_3$), 1.50 (2H, m, 2'-H_2), 1.82 (2H, m, 4-H_2), 1.97 (2H, m, 3-H_2), 3.27-3.54 (2H, m, 5-H_2), 3.35 (3H, s, OMe), 3.81 (1H, m, 2-H), 4.02 (1H, m, 1'-H) and 4.61 (2H, m, OCH_2O); δ_C (100 MHz, $CDCl_3$) 10.5 (CH_3), 24.7 (CH_2), 25.7 (CH_2), 28.6 (CH_3), 46.9 (CH_2), 55.4 (CH_3), 59.4 (CH), 78.9 (CH), 79.4 (C), 96.1 (CH_2), 97.0 (CH_2) and 153.9 (C); *m/z* (CI) 274 (MH^+, 65%), 242 (12), 218 (100) and 186 (36).

(2*S*,1'*R*)-2-(1'-(Hydroxy)propyl)pyrrolidine hydrochloride (259).[139]



(2*S*,1'*R*)-2-(1'-(Methoxymethoxy)propyl)-*N*-(*tert*-butoxycarbonyl)pyrrolidine **279** (0.15 g, 0.42 mmol) was dissolved in 6 M hydrochloric acid (10 mL) and stirred at room temperature for 12 h. Concentration *in vacuo* give (2S,1'R)-2-(1'-(hydroxy)propyl)pyrrolidine hydrochloride **259** (0.07 g, 100%) as a white solid. $[\alpha]_D^{29}$ -

41.0 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3347 (OH and NH), 2917 (CH), 1396, 1316 and 965; δ_H (400 MHz, D_2O) 1.01 (3H, t, *J* 7.2, 3'-H_3), 1.56 (2H, m, 2'-H_2), 2.00 (4H, m, 3-H_2 and 4-H_2), 3.36 (2H, t, *J* 6.4, 5-H_2), 3.71 (1H, m, 2-H_2) and 3.90 (1H, m, 1'-H); δ_C (100 MHz, D_2O) 9.4 (CH_3), 23.1 (CH_2), 23.4 (CH_2), 26.7 (CH_2), 45.8 (CH_2), 63.4 (CH) and 70.3 (CH); *m/z* (CI) 130.1233 (MH^+. $C_7H_{16}ON$ requires 130.1232), 128 (22%), 112 (17) and 100 (6).

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