

DEVELOPMENT OF NEW PREFORMED NITROGEN SOURCES FOR THE OSMIUM- CATALYSED AMINOHYDROXYLATION REACTION

A thesis submitted for the degree Doctor of Philosophy (PhD)
of the Australian National University

By

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THE AUSTRALIAN NATIONAL UNIVERSITY

RESEARCH SCHOOL OF CHEMISTRY
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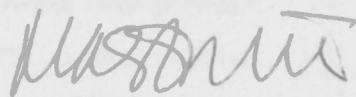
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Thesis Declaration

The material presented in this thesis represents the result of original work carried out by the author during the period July 2008 - January 2012 in the Research School of Chemistry, Australian National University. This thesis contains no material which has been accepted for the award of any degree in any university. To the best of my knowledge no other persons work has been used without due acknowledgement. This thesis is less than 100,000 words in length. Part of this thesis has been presented in poster format:

1. Masruri and McLeod, M. D., New nitrogen source for asymmetric aminohydroxylation reaction, RACI Organic 08 Symposium, Wrest Point, Hobart Tasmania, 7-12 December 2008 (Poster)
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Canberra, January 10th 2012

Masruri

Thesis Summary

The aim of this project was to develop new preformed nitrogen sources for the osmium-catalysed aminohydroxylation reaction. The goal was to overcome some limitations of the Sharpless asymmetric aminohydroxylation (AA) reaction. These included the requirement for a number of reagents in excess to generate nitrogen source. In some cases this is not “economic”, and the remaining reagent is not easily separated from the product. Secondly, the reaction requires strong basic conditions and in some substrates aminohydroxylation competes with Michael addition leading to by-products. Thirdly, chlorination of alkene substrates and amino alcohol products occurs as a result of using chlorinating reagents to generate nitrogen sources.

In this thesis, six *tert*-butyl carbamate-based preformed nitrogen sources **149-154** have been synthesised, evaluated, and optimised for performing the osmium-catalysed aminohydroxylation reaction. These first generation preformed nitrogen sources work under mildly acidic reaction conditions, and do not undergo reaction above pH 6. The best yields are afforded under acidic conditions. No diol was observed, but low enantioselectivity was afforded in the presence of chiral cinchona alkaloid ligands typically employed for the Sharpless AA reaction.

Five amino acid-based ligands were also synthesised. The aim was to prepare ligands that were able to work under mildly acidic conditions. Three ligands were derived from *L*-threonine with 4-toluenesulfonyl **185**, 4-nitrophenylsulfonyl **188**, and 4-methoxyphenylsulfonyl **189** *N*-protection. One was derived from *L*-serine with 4-toluenesulfonyl *N*-protection **190**, and one was derived from diamino acid (*R*)-2,3-bis(amino)propanoic acid with two-fold 4-toluenesulfonyl *N*-protection **191**. Although these ligands gave moderate stereoselectivity under literature conditions, they did not give similar induction in the osmium-catalysed aminohydroxylation reaction using preformed nitrogen sources.

A more base stable second generation of preformed nitrogen sources have also been synthesised, evaluated, and optimised for the osmium-catalysed aminohydroxylation reaction, including a study of substrate scope. These consisted of *tert*-butyl **153**, ethyl

201, benzyl **202**, 2,2,2-trichloroethyl **203**, and 2-(trimethylsilyl)ethyl **204** *N*-(4-toluenesulfonyloxy)carbamates. These preformed nitrogen sources worked under a wide range of pH conditions from pH 3 to 11, and gave excellent yields below pH 7 but decreased yields above pH 6. High yields were generally afforded with 1.2 equiv of preformed nitrogen source and 0.01 equiv of osmium catalyst. Low enantioselectivity was observed in the presence of chiral ligands typically employed for the Sharpless AA reaction.

More importantly, these preformed nitrogen sources worked by affording a high yield and a high regioselectivity for monosubstituted and 1,1-disubstituted alkenes. With 1,2-disubstituted alkenes a high yield was afforded but for unsymmetrical 1,2-disubstituted alkenes poor regioselectivity resulted. Good regioselectivity was afforded with 1,1,2-trisubstituted alkenes, but low yields were afforded. Reaction with preformed nitrogen sources *tert*-butyl **153**, benzyl **202**, and 2,2,2-trichloroethyl *N*-(4-toluenesulfonyloxy)-carbamate **203** consistently showed high yield products, while with ethyl **201** and 2-(trimethylsilyl)ethyl *N*-(4-toluenesulfonyloxy)carbamate **204** gave lower yields.

Benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** was selected as the preformed nitrogen source in a study of the diastereoselectivity of the aminohydroxylation reaction of allylic alcohols catalysed by osmium. Five conclusions were reached. First, reaction of monosubstituted allylic alcohols gave high yields, and the reaction was generally complete within 72 h. However these gave low diastereoselectivity. Protection of the allylic alcohol accelerated the reaction. Second, a moderate to high yield was afforded in terminal disubstituted allylic alcohols. The reaction gave higher diastereoselectivity but longer reaction times. Third, trisubstituted allylic alcohols did not reliably undergo reaction. They gave a low yield of product with 1,2,2-trisubstituted allylic alcohols in two examples. Fourth, the addition of methanesulfonamide and tetraethylammonium acetate did not give an acceleration of the reaction, or increase the yields. Finally, the rate determining-step of the catalytic cycle involved the addition to the double bond of alkenes.

List of Abbreviations

AA	asymmetric aminohydroxylation
AcNHBr	bromo acetamide
AcOH	acetic acid
AD	asymmetric dihydroxylation
AQN	anthraquinone
Ar	aryl
BF ₄ ⁻	boron tetrafluoride anion
Bn	benzyl
BnBr	benzyl bromide
BnCl	benzyl chloride
Boc	<i>tert</i> -butoxycarbonyl
bp	boiling point
C7	denotes carbon number 7
Cbz	benzyloxycarbonyl
CDCl ₃	deuterated chloroform
CDI	1,1'-carbonyldiimidazole
Chloramine-T	sodium <i>N</i> -chloro- <i>p</i> -toluenesulfonamide
Chloramine-M	sodium <i>N</i> -chloromethanesulfonamide
CN	cyano
δ	chemical shift (ppm)
<i>d</i>	doublet
<i>dd</i>	doublet-doublet
<i>dt</i>	doublet of triplets
(<i>D</i>)-	dextro-rotatory
DMA	dimethyl acetamide
DBI	dibromoisocyanuric acid or 1,3-dibromo-1,3,5-triazine-2,4,6-(1 <i>H</i> ,3 <i>H</i> ,5 <i>H</i>)-trione
DCM	dichloromethane
DHQ	dihydroquinine
DHQD	dihydroquinidine
(DHQ) ₂ PHAL	(8α,9 <i>R</i>)-(8''α,9'' <i>R</i>)-9,9''-[1,4-phthalazinediyl-bis(oxy)]bis[10,11-dihydro-6'-methoxycinchonan]
(DHQD) ₂ PHAL	9,9''-[1,4-phthalazinediylbis(oxy)]bis[10,11-dihydro-6'-methoxy-, (9 <i>S</i>)-(9'' <i>S</i>)-cinchonan
(DHQ) ₂ AQN	1,4-bis[[(8α,9 <i>R</i>)-10,11-dihydro-6'-methoxycinchonan-9-yl]oxy]- 9,10-anthracenedione
(DHQD) ₂ AQN	1,4-bis[(9 <i>S</i>)-10,11-dihydro-6'-methoxycinchonan-9-yl]-9,10-anthracenedione
DIBOC	di- <i>tert</i> -butyldicarbonate
2,2-DMP	2,2-dimethoxypropane
<i>d.r.</i>	diastereomeric ratio
EI	electron impact
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
EtO	ethoxy
Et ₃ N	triethylamine

Ether	diethyl ether
Et ₄ NOAc	tetraethylammonium acetate
Etoc	ethoxycarbonyl
e.e.	enantiomeric excess
ESI	electro-spray ionisation
ESI-MS	electro-spray ionisation-mass spectrometry
Fmoc	9-fluorenylmethoxycarbonyl
FTIR	fourrier transform infra-red
GABOB	gamma-aminohydroxybutyric acid
GCMS	gas chromatography – mass spectrometry
H6	denotes hydrogen attached at carbon number 6
Hex	hexyl, hexane
HPLC	high performance/pressure liquid chromatography
HRMS	high resolution mass spectrometry
Hydantoin	1,3-dichloro-5,5-dimethylhydantoin
Hz	Hertz
<i>i</i> -PrOH	isopropanol, 2-propanol
(<i>i</i> -Pr) ₂ EtN	diisopropylethylamine
IR	infra-red
<i>J</i>	coupling constant (Hz)
LAH	lithium aluminium hydride
LRMS	low resolution mass spectrometry
(<i>L</i>)-	levo-rotatory
<i>m</i>	multiplet
M	molarity
Ms	methanesulfonyl
Me	methyl
MeO	methoxy
MeCN	acetonitrile
Mes	mesityl or 2,4,6-trimethylphenyl-
mp	melting point
MS	mass spectrometry
<i>m/z</i>	mass to charge ratio
<i>n</i> -PrOH	<i>n</i> -propanol, 1-propanol
NMR	nuclear magnetic resonance
Ns	<i>p</i> -nitrophenylsulfonyl
NOE	nuclear Overhauser enhancement/effect
NOESY	nuclear Overhauser enhancement/effect spectroscopy
OH	hydroxyl
PFP	pentafluorophenyl
Ph	phenyl
pH	degree of acidity
PHAL	phthalazine
PMB	<i>p</i> -methoxybenzyl
PNB	<i>p</i> -nitrobenzyl
PNP	<i>p</i> -nitrophenyl
Pr	propyl
ppm	parts per million
ppb	parts per billion
PF ₆ ⁻	hexafluorophosphate anion

pyr	pyridine
<i>q</i>	quartet
<i>qn</i>	quintet
QN	quinine
RT	room temperature
Rh ₂ [tpa] ₄	rhodium(II) triphenylacetate dimer
(<i>R</i>)-	<i>R</i> - absolute configuration
(<i>R</i> [*])-	<i>R</i> - relative configuration
R	alkyl group
<i>s</i>	singlet
(<i>S</i>)-	<i>S</i> - absolute configuration
(<i>S</i> [*])-	<i>S</i> - relative configuration
<i>t</i>	triplet
TA	tethered aminohydroxylation reaction
Teoc	2-trimethylsilylethoxycarbonyl
Troc	2,2,2-trichloroethoxycarbonyl
t _R	retention time
Ts	tosyl, toluenesulfonyl
<i>t</i> -BuOH	<i>tert</i> -butylalcohol
TsCl	tosyl chloride, <i>p</i> -toluenesulfonyl chloride
<i>t</i> -BuOCl	<i>tert</i> -butyl hypochlorite
TBDMS	<i>tert</i> -butyldimethylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
tpa	triphenylacetate
Tf	triflate
THF	tetrahydrofuran
μm	micrometer, micron
v/v	volume/volume

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Chapter 1

The Osmium-Catalysed Aminohydroxylation Reaction

Summary

This chapter gives an introduction to the osmium-catalysed aminohydroxylation reaction, including (i) the mechanism of the Sharpless AA reaction, (ii) the chemo-, regio-, and enantio-selectivity of the aminohydroxylation reaction, (iii) nitrogen sources for the osmium-catalysed aminohydroxylation reaction, (iv) applications of the osmium-catalysed aminohydroxylation reaction in synthesis, and (v) aims of this research.

1.1 Introduction

The osmium-catalysed aminohydroxylation can be defined as a methodology to transform an olefin to the 1,2-amino alcohol functionality in a one step reaction catalysed by osmium.¹ Firstly, this reaction requires an osmium catalyst to promote the *syn*-addition of the amino-alcohol functionality to the double bond. Secondly, this method also requires the presence of reagents as the source for amino- and hydroxyl-functionality. An example is the transformation of olefin **1** catalysed by potassium osmate dihydrate, to afford amino alcohol products **2** and **3** (Figure 1.1). This is an example of the Sharpless asymmetric aminohydroxylation (AA) reaction.^{2,3} It uses carbamate reagents to generate amino functionality, and the hydroxyl-group is generated during the reaction after hydrolytic processes have occurred. In addition, an alcohol-water system is used as solvent and a cinchona alkaloid-derived ligand is applied to induce stereoselectivity.

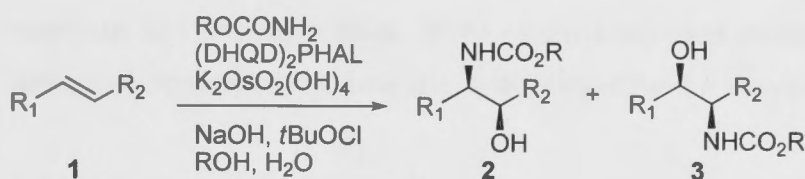


Figure 1.1

This methodology has been an ongoing focus of development^{4,5} and organic synthesis⁶ since it is an important functional group transformation from simple olefin substrates. The reaction can be generally classified into two types of reaction. First is the osmium-catalysed asymmetric aminohydroxylation (AA) reaction^{2,3,7} which uses a chiral ligand for osmium and affords asymmetric induction. Second is the simple osmium-catalysed aminohydroxylation reaction which provides racemic amino alcohol products.⁸⁻¹²

The Sharpless asymmetric aminohydroxylation (AA) reaction^{2,3,7} can afford high asymmetric induction. Cinchona alkaloid-derived ligands which have been developed for the asymmetric dihydroxylation^{13,14} (AD) reaction to induce enantioselectivity, were applied in the AA reaction and gave a similar asymmetric induction.³ Moreover, a diverse range of nitrogen sources have also been developed with different *N*-substituents affording products with protecting groups such as ethoxycarbonyl (Etoc),¹⁵

tert-butoxycarbonyl (Boc),¹⁶ benzyloxycarbonyl (Cbz),² and 2-(trimethylsilyl)ethoxycarbonyl (Teoc).¹⁵ On the other hand, the osmium-catalysed aminohydroxylation reaction which affords racemic amino alcohol products is a ligand-independent reaction.^{9,12} The addition of cinchona alkaloid ligands does not induce enantioselectivity even when added in excess amount. Representative examples of this type osmium-catalysed aminohydroxylation include reactions with α,β -unsaturated amide⁹ and α,β -unsaturated carboxylic acid¹² substrates. Applying the AA reaction procedure did not give enantioselectivity and both reactions afforded racemic product.

To give a detailed understanding of the osmium catalysed aminohydroxylation reaction, this chapter will describe; (i) the mechanism of the Sharpless asymmetric aminohydroxylation (AA) reaction including the *syn*-addition mechanism and catalytic cycle, (ii) the chemo-, enantio- and regio-selectivity of the osmium-catalysed aminohydroxylation reaction, (iii) nitrogen sources applied in both the AA and racemic reactions, and (iv) applications of the osmium-catalysed aminohydroxylation reaction including some of the problems and limitations of the AA reaction.

1.2 Mechanism of the AA reaction

The mechanism proposed for the Sharpless asymmetric aminohydroxylation (AA) reaction is basically adapted from that proposed for the asymmetric dihydroxylation (AD) reaction.^{13,14} The key step is *syn* or suprafacial addition of nitrogen and oxygen to the double bond of an alkene (**Figure 1.2**). Reddy and coworkers¹⁷ proposed that the imidotrioxosmium(VIII)-ligand complex **5** added to the alkenes in a stepwise manner starting with a [2+2] cycloaddition process at the more electrophilic osmium center. Formation of osmaazetidine **9** was favoured and an irreversible migration gave osmium(VI) azaglycolate **7**. Similarly, Sharpless and coworkers^{7,18} also reported a [2+2] cycloaddition to form osmaazetidine **8** from imidotrioxosmium(VIII) **4** and an alkene. Coordination between the ligand and osmaazetidine **8** formed species **9** which could trigger rearrangement giving osmium(VI) azaglycolate **7**. Furthermore both above reports gave similar arguments in underlining electronic factors controlling the regioselectivity. The nitrogen added to the carbon of the alkene further from the electron withdrawing group.

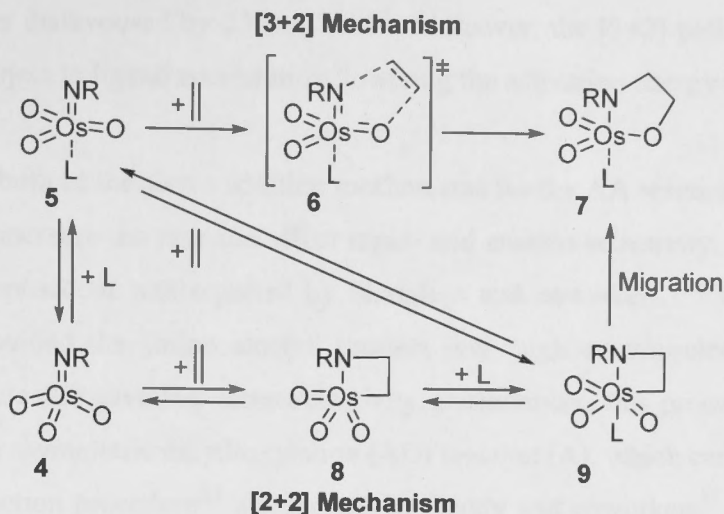


Figure 1.2

On the other hand, a [3+2] mechanism was proposed by Janda and coworkers.¹⁹ The formation of complex **5** which exists in equilibrium with the imidotrioxoosmium(VIII) species **4**. Complex **5** is rapidly transformed by a concerted [3+2] cycloaddition reaction with the alkene, via a transition state like **6** to give the osmium(VI) azaglycolate **7**. This model was analogous to what has been reported by Criegee²⁰ for the addition reaction of osmium tetroxide to olefins.

In fact both mechanisms above were still debatable due to the limited empirical evidence available. Even though stepwise [2+2] pathway was proposed to be electronically matched to the polarisation of Os-N bond, this could not rationalise effects such as the changes in regioselectivity associated with the use of anthraquinone (AQN) ligands.²¹ At the same time, the [3+2] cycloaddition was generally more accepted as the stereoselectivity could be more easily rationalised by the formation of complex **5**. The formation of complex **5** was also consistent with the phenomenon of ligand accelerated catalysis,²² and also ligand/substrate interaction controlling the regioselectivity via transition state **6**.^{23,24} Recently, a computational investigation reported by Strassner and coworkers²⁵ also supported the [3+2] instead of [2+2] pathway. Density functional theory (B3LYP/6-31G*) calculated the energy of transition state structures resulting from addition of ethylene and a cyano-substituted imidotrioxoosmium(VIII) compound in the gas phase. Compared to the [3+2] cycloaddition, the [2+2] mechanism

was disfavoured by 25 kcal mol⁻¹. Moreover, the [3+2] pathway was also found to be subject to ligand acceleration, lowering the activation energy by 2.7 kcal mol⁻¹.

In both of the above addition mechanisms for the AA reaction, the ligands played a role to increase the rate and affect regio- and enantio-selectivity. Two catalytic cycles were proposed. It was reported by Sharpless and coworkers,^{3,26} that the primary cycle (**B**) provided the amino alcohol product with high enantioselectivity, while a secondary cycle (**C**) gave low stereoselectivity. Furthermore, this process may also compete with the asymmetric dihydroxylation (AD) reaction (**A**), which can also occur during the AA reaction procedure^{2,3} as reported by Reddy and coworkers¹⁷ and illustrated in (**Figure 1.3**).

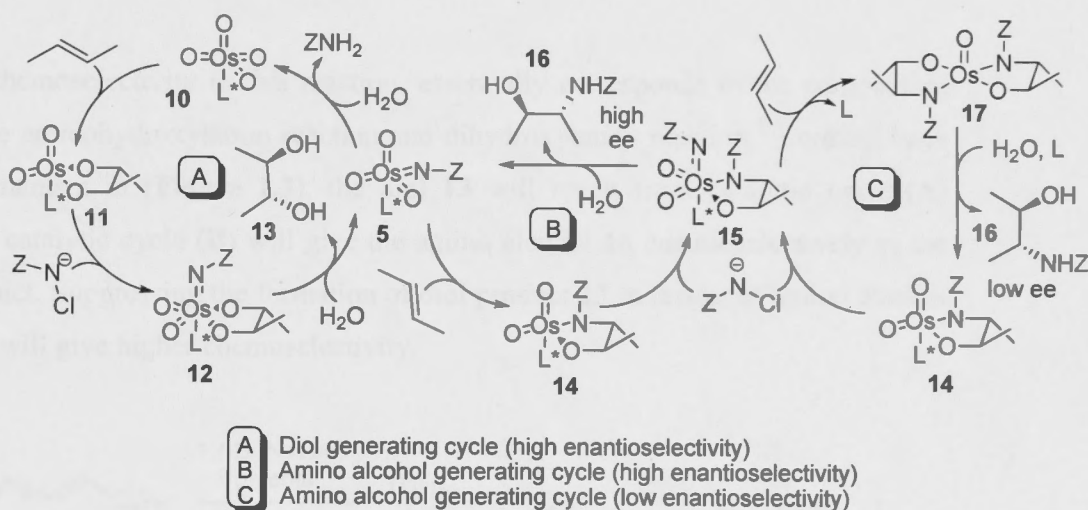


Figure 1.3

Three cycles have been proposed to occur simultaneously i.e. (i) following cycle (**A**) which gives the diol product with high enantioselectivity, (ii) cycle (**B**) provides the amino alcohol product with high enantioselectivity, and (iii) cycle (**C**) gives the amino alcohol product with low enantioselectivity.

Catalytic cycle (**A**) is basically an AD reaction. It is a very rapid process, initiated by formation of the glycolate ester **11** from osmium-ligand complex **10**. This is further oxidised by the nitrogen source to afford the osmate ester **12**, which is hydrolysed by water to provide the diol **13** and imidotrioxoosmium(VIII) species **5**. To continue

catalytic cycle (A) species imidotrioxoosmium(VIII) species **5** is hydrolysed with water giving osmium-ligand complex **10** and completing the catalytic cycle. However, complex **5** can also react with alkenes in the primary cycle (B) forming an osmium(VI) azaglycolate **14**. Oxidation of this species with nitrogen source forms an osmium(VIII) azaglycolate **15** which is hydrolysed by water giving amino alcohol product **16** enantioselectively. At the same time, complex **15** could further react with alkenes forming osmium(VI) bisazaglycolate **17** following the secondary catalytic cycle (C), and providing the amino alcohol product **16** with low enantioselectivity.

1.3 The chemo-, enantio- and regio-selectivity of the aminohydroxylation reaction

This sub chapter will give brief discussion on methods to control the chemo-, enantio- and regio-selectivity of the AA reaction.

The term chemoselectivity in this reaction, essentially corresponds to the competition between the aminohydroxylation reaction and dihydroxylation reaction.⁷ Looking back at the mechanism in (Figure 1.3), the diol **13** will result from catalytic cycle (A) meanwhile catalytic cycle (B) will give the amino alcohol **16** enantioselectively as the major product. Suppressing the formation of diol product **13** in favour of amino alcohol product **16** will give higher chemoselectivity.

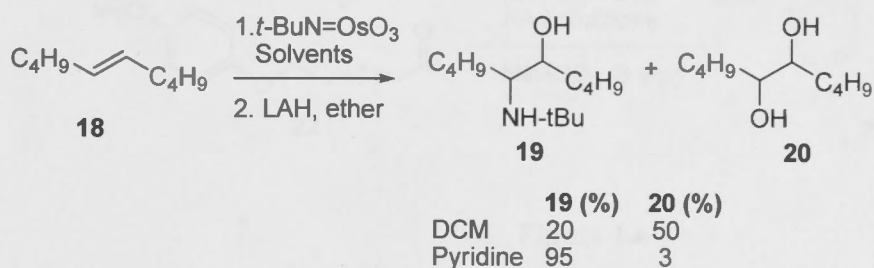


Figure 1.4

An example of controlling chemoselectivity occurred in the racemic oxyamination of (*E*)-dec-5-ene as **18** reported by Sharpless and coworkers.²⁷ The diol product **20** formed as a major product when the reaction was conducted in dichloromethane, but it gave 95% yield of amino alcohol product **19** when solvent was replaced with pyridine (Figure 1.4).

Another example reported by Reddy and coworkers¹⁷ showed that applying of higher loading of osmium tetroxide catalyst in the AA reaction tended to increase the diol product formed. This took place as the osmium tetroxide underwent an AD reaction first before entering the AA catalytic cycle (**B**). Using the osmium(VI) glycolate complex **21** as the osmium source, dramatically suppressed the diol formation (**Figure 1.5**).

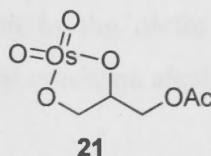


Figure 1.5

A different aspect of chemoselectivity involves the formation of by-products. McLeod and coworkers²⁴ reported that employing standard conditions for the AA reaction² with unsaturated ketone **22** resulted in Michael addition of the carbamate competing with aminohydroxylation. The amino alcohol product **23** was afforded as the major product after running the reaction under buffered conditions using (3 equiv.) of sodium hydrogen carbonate (**Figure 1.6**).

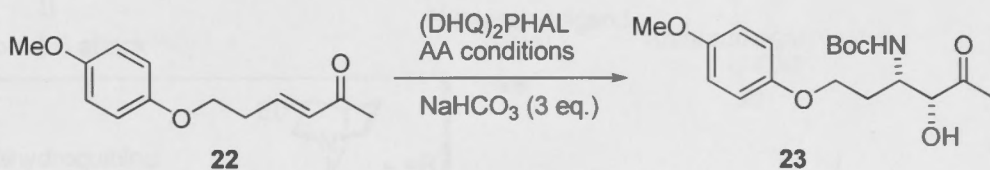


Figure 1.6

The enantioselectivity^{3,5,7} of the AA reaction can be controlled in similar manner to the AD reaction^{7,13,14,28,29} by applying ligands such as (DHQD)₂PHAL, (DHQD)₂AQN, (DHQ)₂PHAL, and (DHQ)₂AQN (**Figure 1.7**). Furthermore these ligands also exert some control over the regioselectivity^{3,6,21,24,30} of the AA reaction. Some experiments have probed the induction obtained in the presence of ligands. For example, Sharpless and coworkers³ discovered that for methyl cinnamate as substrate, good enantioselectivity was afforded by employing ligand. Moreover, with no ligand, two

regioisomers of amino alcohol product resulted with a ratio of 2:1. However, this increased to more than 5:1 in the presence of cinchona alkaloid ligand.

Considering the mechanism proposed by Reddy and coworkers¹⁷ (**Figure 1.3**), enantioselectivity can be achieved by controlling the addition step the AA reaction that operates in the primary catalytic cycle (**B**). The imidotrioxoosmium(VIII) complex **5** plays the central role to govern the addition to the olefin to afford the osmium azaglycolate species **14**. At this point, the chiral cinchona alkaloid ligand controls both enantio- and regio-selectivity.

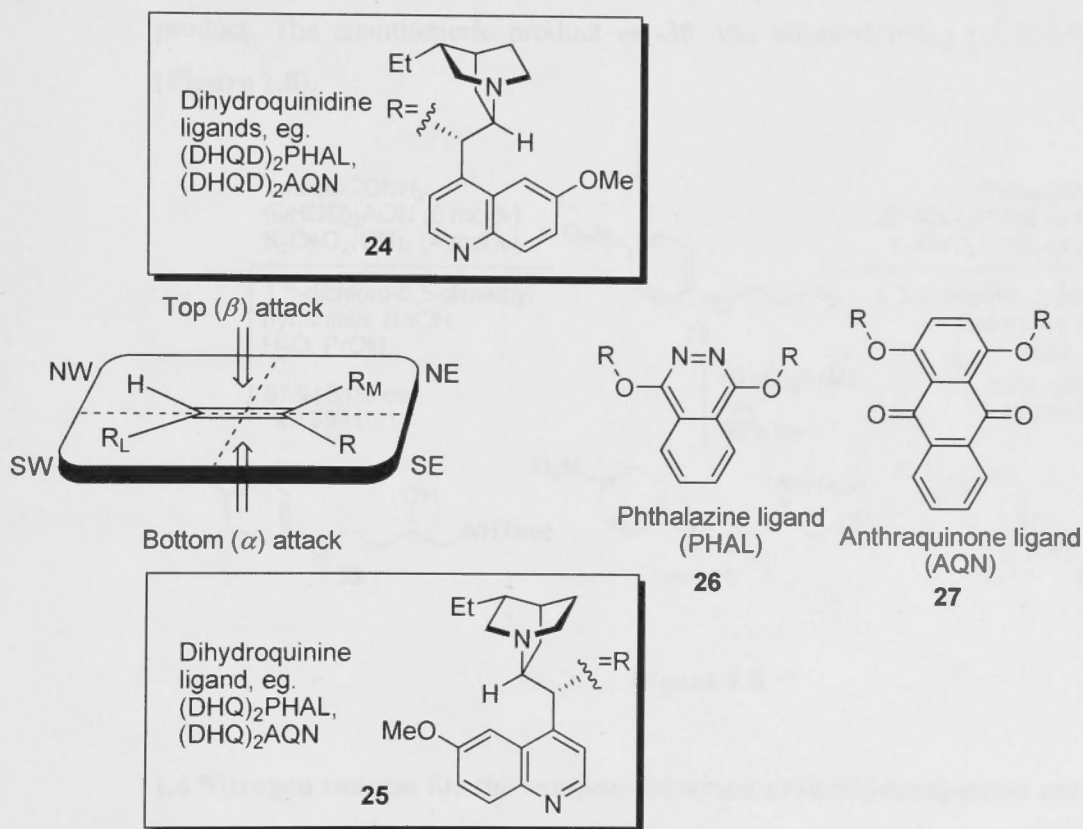


Figure 1.7

The Sharpless mnemonic^{7,13} (**Figure 1.7**) has been reported to predict the enantiofacial selectivity of the AD reaction using ligand such as (DHQD)₂PHAL, (DHQD)₂AQN, (DHQ)₂PHAL, and (DHQ)₂AQN. These ligands were also observed have similar effects on the AA reaction. Dihydroquinidine ligands such as (DHQD)₂PHAL and (DHQD)₂AQN induce addition to the β -face of alkenes. Dihydroquinine ligands such as

(DHQ)₂PHAL and (DHQ)₂AQN favour the addition to the α -face of alkenes. Applying the dihydroquinidine ligands in the AA reaction will favour the amino alcohol product which is the opposite enantiomer of that afforded by the dihydroquinine ligands.

In addition to this, control of regioselectivity was reported by Sharpless and coworkers²¹ on employing cinchona ligands with different spacers such as phthalazine (PHAL) and anthraquinone (AQN).²¹ Similar influences were also reported by McLeod and coworkers.⁶ Using 1-(but-3-enyloxy)-4-nitrobenzene **28** as substrate and phthalazine ligand (DHQD)₂PHAL gave the terminal alcohol **30** as the major product, whereas the anthraquinone ligand (DHQD)₂AQN afforded the terminal amine **29** as the major product. The enantiomeric product *ent*-**30** was afforded using (DHQ)₂PHAL ligand. (Figure 1.8).

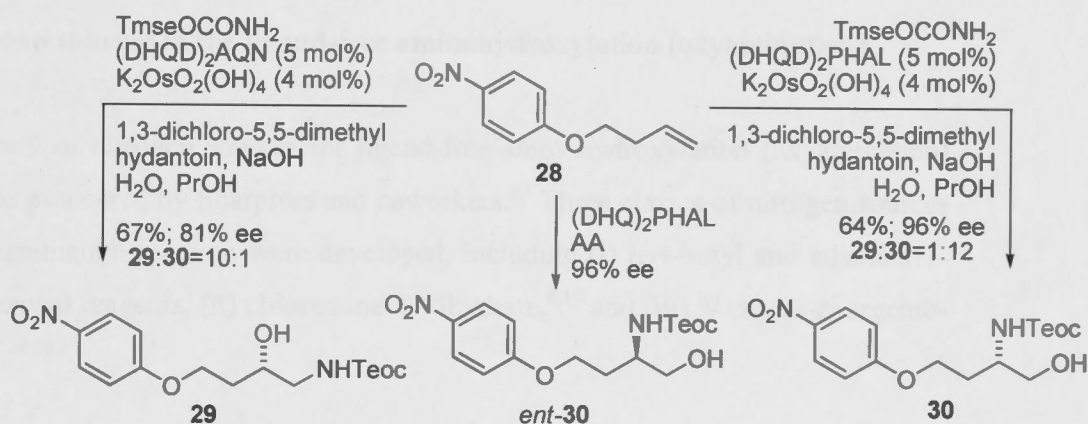
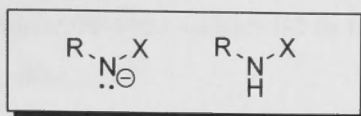


Figure 1.8

1.4 Nitrogen sources for the osmium-catalysed aminohydroxylation reaction

1.4.1 Role of the nitrogen source

A reactive nitrogen-based reagent serves as the source of nitrogen in generating the amino functional group in the oxyamination reaction. It can be represented schematically as **Figure 1.9**. The R-substituents function as an *N*-protecting group, while X-group will be released as leaving group as the reaction proceeds.



R, protecting group; X, leaving group

Figure 1.9

Until recent times, the R-*N*-group was mostly constructed from an alkyl amines,^{27,31,32} alkyl and aryl sulfonamides,^{8,10,26,33} carbamates,^{2,15,16,34,35} amides,³⁶ and heterocyclic amines.³⁷ Meanwhile the X-substituent was typically a chloride. The review below will describe the development of nitrogen sources for the osmium-catalysed ligand-free aminohydroxylation (oxyamination) reactions and the asymmetric aminohydroxylation reactions.

1.4.2 Nitrogen sources in the ligand-free aminohydroxylation (oxyamination) reaction

The discovery of nitrogen sources for ligand-free aminohydroxylation (oxyamination) reaction was pioneered by Sharpless and coworkers.²⁷ Three classes of nitrogen sources for the oxyamination reaction were developed, including (i) *tert*-butyl and adamant-1-yl-amine derived reagents, (ii) chloramine-T trihydrate,^{8,10} and (iii) *N*-chloro-*N*-argento-carbamates.^{34,38}

1.4.2.1 *tert*-Butylamine and adamant-1-yl-amine derived nitrogen sources

The first class of nitrogen sources developed for the oxyamination reaction was based on alkyl amines.^{27,31} *tert*-Alkyl amines react with stoichiometric osmium tetroxide to form an imidotrioxo osmium species. For example *tert*-butylimino-trioxoosmium **32** can be prepared from *tert*-butylamine **31** with equimolar osmium tetroxide using olefin-free pentane solvent²⁷ (**Figure 1.10**). Using a similar procedure, adamant-1-ylimino-trioxoosmium can also be synthesized from adamant-1-ylamine.

Addition of the imino osmium species **32** to an alkene formed the osmium azaglycolate **33**, and then a reductive cleavage process of this ester resulted in the amino alcohol³¹ **34**. Meanwhile, the diol product **13** resulted from addition of alkene to oxygens of the

tert-butyl-imino-trioxoosmium species **32** to form osmate ester **35** which was reduced to the corresponding diol.

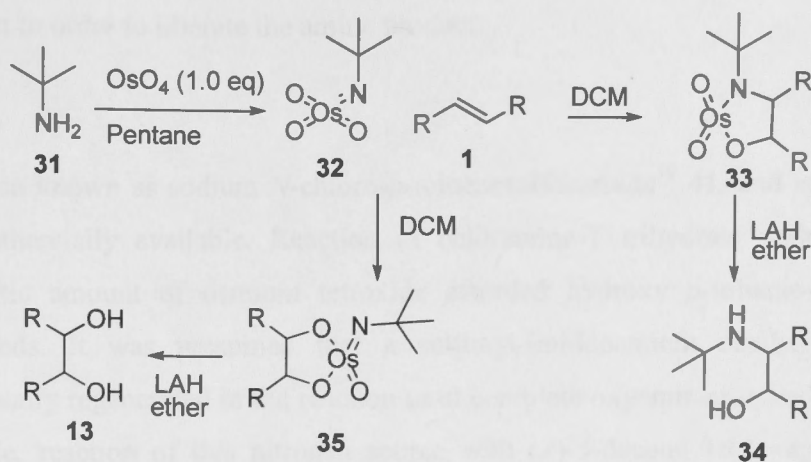
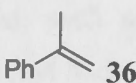
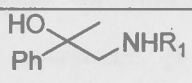
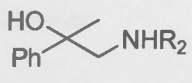
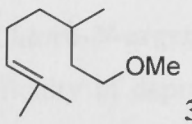
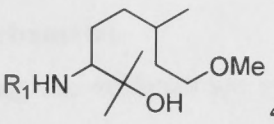


Figure 1.10

Reaction both *tert*-butyl- and adamant-1-yl-derived nitrogen sources with α -methyl styrene **36** using dichloromethane as a solvent afforded the amino alcohols **37** and **38** as the major product. The reaction of *tert*-butylamine-derived nitrogen source **31** with 8-methoxy-2,6-dimethyloct-2-ene **39** using dichloromethane as a solvent afforded diol as the major product. In this example the proportion of the amino alcohol product **40** increased when pyridine was used as a solvent²⁷ (Table 1.1)

Table 1.1

Olefins	Product	Solvent	Yield amino alcohol	Yield diol
 36	 37	CH_2Cl_2	92% ^a	<1%
	 38	CH_2Cl_2	62% ^b	-
 39	 40	CH_2Cl_2	0%	78%
		Pyridine	38% ^a	45%

Note: ^a R_1 : *tert*-butyl, ^b R_2 : adamant-1-yl

The main drawback of this method is the requirement for a stoichiometric amount of osmium reagent. In addition, the reaction is not controlled by chiral ligands and leads to the formation of racemic product from achiral alkenes. Finally, the *tert*-alkyl groups can be difficult to deprotect in order to liberate the amine product.

1.4.2.2 Chloramine-T

Chloramine-T^{8,10} is also known as sodium *N*-chloro-*p*-toluenesulfonamide³⁹ **41**, and is inexpensive and commercially available. Reaction of chloramine-T trihydrate with alkenes and a catalytic amount of osmium tetroxide afforded hydroxy *p*-toluenesulfonamide compounds. It was presumed that a sulfonyl-imidoosmium catalyst compound was continually regenerated in the reaction until complete oxyamination had occurred. For example, reaction of this nitrogen source with (*Z*)-5-decene **18** using osmium tetroxide (1.0 mol%) afforded the amino alcohol product **42**. It was also reported that silver nitrate affected the amino alcohol yield^{8,10} (Figure 1.11)

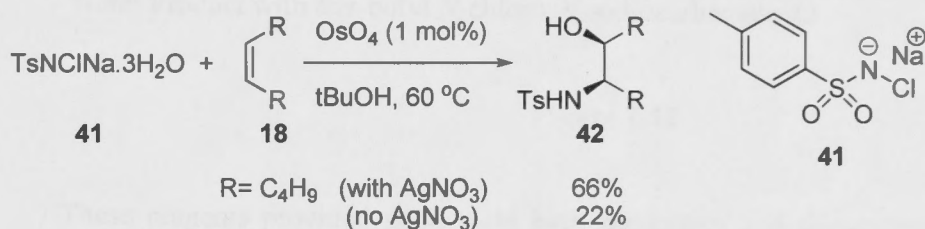


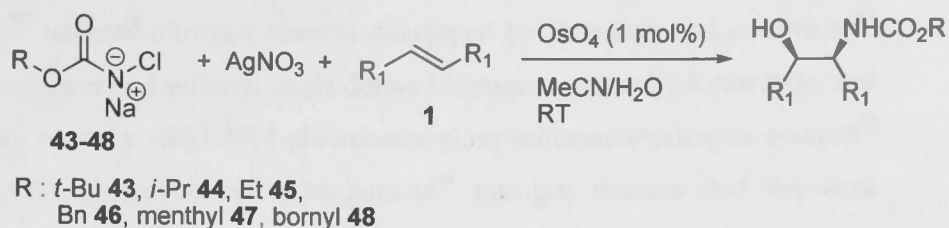
Figure 1.11

During the process, it was observed that the reaction was inhibited by chloride ion. In some substrates, especially mono-substituted olefins, addition of silver nitrate accelerated the reaction, but it sharply reduced the yield for unsymmetric di-substituted and tri-substituted olefins. Some other chloramine-T derivatives¹⁰ ($\text{ArSO}_2\text{NCINa}$) were also introduced, such as phenyl, *o*-toluene, *p*-chlorophenyl, *p*-nitrophenyl, and *o*-carboalkoxyphenyl *N*-chloro sulfonamide.

1.4.2.3 *N*-Chloro-*N*-argentocarbamates

Due to difficulty in deprotecting the sulfonamide group from the reaction products, nitrogen sources derived from alkyl and aryl carbamates were developed. They were

generated *in-situ* from *tert*-butyl, isopropyl, ethyl, benzyl, menthyl, and bornyl *N*-chloro-*N*-sodiocarbamates (**43-48**) with silver nitrate in acetonitrile³⁴ (**Figure 1.12**).



Olefins	Reaction Time	Yield amino alcohol product (%) ^a	
		Major	Minor
Styrene, 49	2 h	68.5	12
1-Decene, 50	6 h	61	9
(<i>E</i>)-stilbene, 51	10 h	87	
Dimethyl fumarate, 52	10 h	51	

*Note: Product with *tert*-butyl *N*-chloro-*N*-sodiocarbamate **43**

Figure 1.12

These reagents provided good yield both for mono- and di-substituted alkenes. Less reactive with tri-substituted alkenes, and with an electron deficient olefin dimethyl fumarate **52**, gave the reaction moderate yield. It was also reported that the use of 1-menthyl **47** and 1-bornyl *N*-chloro-*N*-sodiocarbamates **48** did not induce significant diastereoselectivity.³⁴

Some *N*-chloro-*N*-metallo carbamate³⁵ derivatives also have been developed using various metal salts such as HgCl₂, Hg(NO₃)₂, Hg(OAc)₂, AgNO₃, Zn(OAc)₂, Cd(OAc)₂, Cd(NO₃)₂, Cu(OAc)₂, Zn(NO₃)₂, CdCl₂, and ZnCl₂.

1.4.3 Nitrogen sources in the asymmetric aminohydroxylation reaction

The development of ligands to control the stereochemical outcome of the asymmetric dihydroxylation (AD) reaction by Sharpless and coworkers^{13,28} opened the path to control the stereoselectivity of catalytic aminohydroxylation reaction. Furthermore, the discovery of new and superior nitrogen sources was also reported.

Kolb and Sharpless⁴⁰ classify the nitrogen sources for asymmetric aminohydroxylation (AA) reaction into three forms of *N*-halogenated compound : (i) sulfonamide, (ii) carbamate and (iii) amide. In addition, there are other variants such as heterocyclic nitrogen sources,³⁷ tethered-nitrogen sources developed by Donohoe and coworkers⁴¹ including sulfamate ester and sulfanylamide derived nitrogen sources by Kenworthy and Taylor,⁴² and very recently alkyl *N*-(4-chlorobenzoyloxy)carbamate nitrogen sources⁴³ and alkyl *N*-(2,4,6-trichlorobenzoyloxy)carbamate⁴⁴ nitrogen sources that appeared during the course of this study.

1.4.3.1 *N*-Halogenated sulfonamide nitrogen sources : Chloramine-T, and -M

Chloramine-T⁴⁵ **41** was the first *N*-halogenated sulfonamide tested in the catalytic asymmetric aminohydroxylation reaction by Sharpless and coworkers,³ followed soon after by chloramine-M, **53**.²⁶ Chloramine-T was easily prepared and isolated while chloramine-M or sodium *N*-chloro-methanesulfonamide can be generated *in-situ* from methanesulfonamide with an equimolar amount of sodium hydroxide using chlorinating reagent *tert*-butyl hypochlorite.⁴⁶

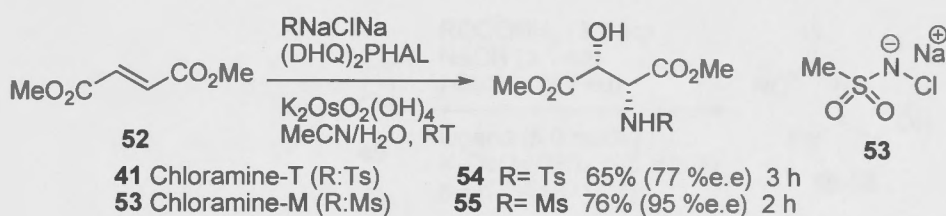


Figure 1.13

As indicated in **Figure 1.13** for dimethyl fumarate **52**, both chloramine-T and chloramine-M require 3.0 equiv. to give complete reaction. A higher yield and selectivity of **55** resulted from the use of chloramine-M rather than chloramine-T^{3,26} **41**. Both protecting groups require harsh conditions to be removed. Although chloramine-M can be cleaved with Red-Al in toluene, this method is incompatible with many functional groups.²⁶

Other variants of this class of nitrogen sources have been reported such as 2-(trimethylsilyl)ethyl sulfonamide^{26,40} which has reactivity comparable to chloramine-M,

and sodium *N*-chloro-*tert*-butylsulfonamide. This last nitrogen source provided good regioselectivity, however an evaluation using α,β -unsaturated amides gave low enantioselectivity.³³

1.4.3.2 *N*-Halogenated carbamate nitrogen sources

Carbamate-derived nitrogen sources have a greater scope than sulfonamides in synthetic applications. They are available in a broader range of variants than the sulfonamides, are easily deprotected to liberate the amino functional group under mild conditions,⁴⁷ and generally give better yields and selectivities.^{2,15,48}

Four variants are commonly used in the reaction derived from *tert*-butyl, ethyl, benzyl¹⁶ and 2-(trimethylsilyl)ethyl carbamates. All are commercially available with exception of 2-(trimethylsilyl)ethyl carbamate.¹⁵ The *N*-chloro-*N*-sodio-carbamate nitrogen source is generated *in-situ* by reacting parent carbamate with *tert*-butyl hypochlorite² (3.0 equiv.), or an other chlorinating reagent such as 1,3-dichloro-5,5-dimethylhydantoin or dichloroisocyanuric acid,⁴⁹ in basic conditions.

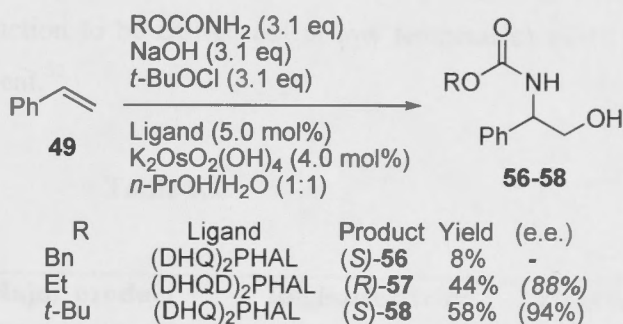


Figure 1.14

Reacting benzyl, ethyl and *tert*-butyl carbamate in the AA reaction using styrene **49** as substrate with the aim of preparing alkyl 2-hydroxy-1-phenylethylcarbamate as the major regioisomer **56-58**, O'Brien and coworkers¹⁶ found that *tert*-butyl carbamate gave the best results (Figure 1.14).

In another study, benzyl carbamate was shown to be less selective than 2-(trimethylsilyl)ethyl carbamate with methyl *p*-nitrocinnamate **59** as substrate. Benzyl

carbamate gave both regioisomers **60/61** (1:1), while 2-(trimethylsilyl)ethyl carbamate gave a 7:3 ratio with the α -amino isomer **62** as the major product⁵⁰ (**Figure 1.15**).

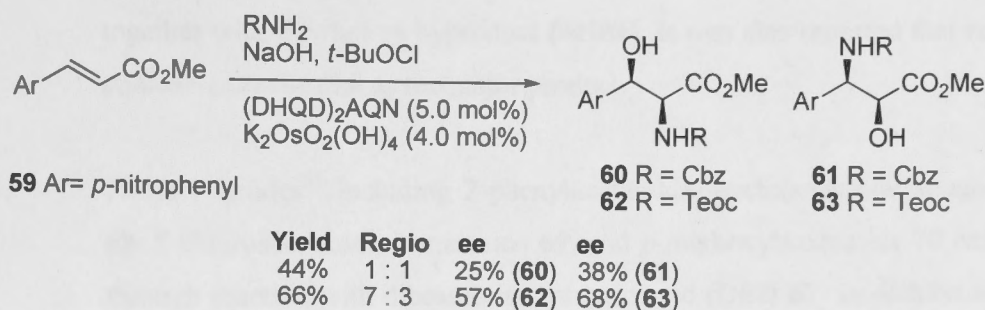


Figure 1.15

1.4.3.3 *N*-Halogenated amide nitrogen sources

Only two papers have been reported for *N*-halogenated amides as nitrogen sources, both were by Sharpless and coworkers.^{36,51} *N*-Bromoacetamide is commercially available and can be re-crystallised from chloroform/hexane. *N*-Halogenated primary amides can be generated from the corresponding amide with a suitable brominating reagent. Both of these variants required the reaction to be carried out at low temperature (4-10 °C) to suppress Hofmann rearrangement.⁵²

Table 1.2

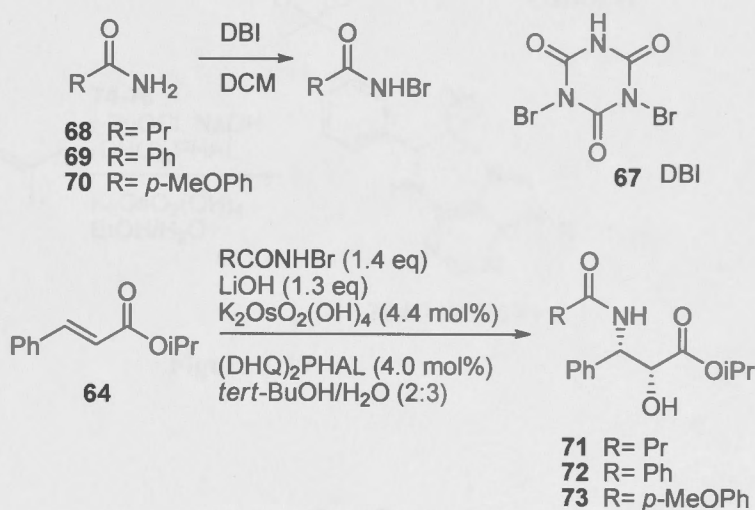
Olefins	Major product	Regioselectivity	Yield (e.e.)
$\text{Ph}-\text{CH}=\text{CH}-\text{CO}_2\text{iPr}$ 64	$\text{Ph}-\text{CH}(\text{NHAc})-\text{CH}(\text{OH})-\text{CO}_2\text{iPr}$ 65	>20 : 1	81% (99%)
$\text{Ph}-\text{CH}=\text{CH}-\text{Ph}$ 51	$\text{Ph}-\text{CH}(\text{NHAc})-\text{CH}(\text{OH})-\text{Ph}$ 66	-	50% (94%)

Conditions: Olefin (1.0 equiv.) AcNHBr (1.1 equiv.), LiOH (1.02 equiv.), K₂OsO₂(OH)₄ (4.0 mol%), (DHQD)₂PHAL (5.0 mol%), *tert*-BuOH/H₂O (2:3), 4 °C.

Examples of the reactions of *N*-bromoacetamide derived nitrogen sources include isopropyl cinnamate **64** and *trans*-stilbene **51** as substrates (**Table 1.2**). Reaction with

isopropyl cinnamate **64** using (DHQ)₂PHAL as ligand and potassium osmate dihydrate gave the β-amino-α-hydroxyl regioisomer **65** as the major product (>20:1) in excellent ee. Reaction with *trans*-stilbene gave amino alcohol **66** in moderate yield (94 %ee) together with the diol as byproduct (>10%). It was also reported that reaction with *cis*-stilbene gave the diol as the major product.

Primary amides⁵¹ including 2-phenylacetamide, cyclohexanecarboxamide, butyramide **68**, 2-chloroacetamide, benzamide **69**, and *p*-methoxybenzamide **70** can be brominated through reaction with dibromo-isocyanuric acid (DBI) **67** in dichloromethane (**Figure 1.16**). *N*-Bromobutyramide gave excellent results providing a 94% yield **71** (95 %e.e.) and high regioselectivity. In contrast, the aromatic amides gave lower yields and selectivity of **72** and **73**.



R	Product (%)	e.e. (%)	Regioselectivity
Pr	71 (94)	95	21:1
Ph	72 (38)	77	2.0:1
<i>p</i> -MeO-Ph	73 (42)	43	2.5:1

Figure 1.16

1.4.3.4 Heterocyclic nitrogen sources

In order to develop an improved strategy for accessing adenosine derivatives, Sharpless and coworkers⁵³ reported adenine-derivatives as nitrogen sources for the AA reaction. The *N*-chloro-*N*-sodio amine derivative was prepared from adenine derivatives **74-76** (3.0 equiv.) with *tert*-butyl hypochlorite and sodium hydroxide. The olefin 2-methyl-1-phenyl-1-propene **77** (1.0 equiv.) was reacted with these nitrogen sources, (DHQ)₂PHAL ligand (6.0 mol%) and potassium osmate dihydrate (5.0 mol%). Moderate to high yields (58% - 75%) of the amino alcohol products **78-80** was afforded with high regioselectivity. However, no enantioselectivity was observed (**Figure 1.17**).

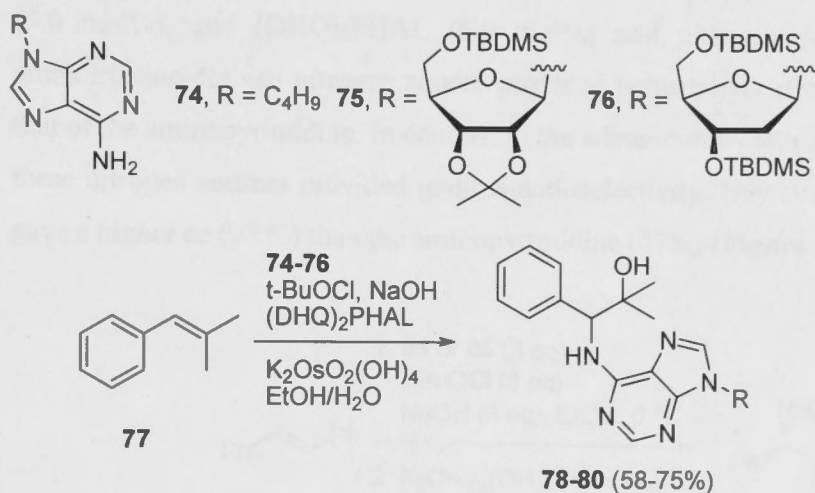


Figure 1.17

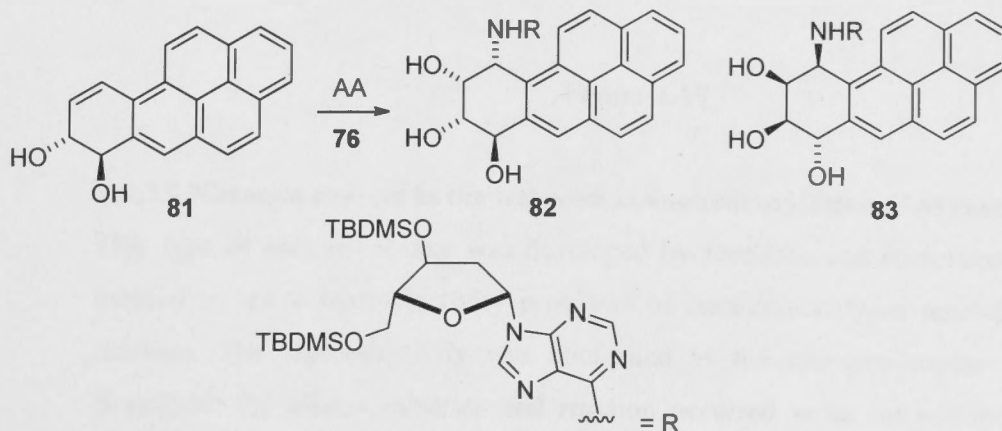


Figure 1.18

Previously, the nitrogen source generated from adenine derivative **76** had been reported by Jerina and coworkers,⁵³ who applied it to form polycyclic aromatic hydrocarbon (PAH) diol epoxide (DE) adducts **82** and **83**.⁵⁴ Using racemic substrate **81**, and (3.0 equiv.) of nitrogen source generated from adenosine **76**, ligand (DHQD)₂PHAL and K₂OsO₂(OH)₄ afforded both diastereomers of product **82** and **83** (1:1) in 85% yield (Figure 1.18).

Following the adenine derived nitrogen sources, aminotriazine **84** and aminopyrimidine **85** were also explored.³⁷ Their chloramine salts were prepared using *tert*-butyl hypochlorite with base at 0 °C. Using *trans*-stilbene **51**, potassium osmate dihydrate (5.0 mol%), and (DHQ)₂PHAL (6.0 mol%) and nitrogen source. It showed the aminotriazine-derived nitrogen source provided better yield of amino alcohol **86** than that of the aminopyrimidine. In contrast to the adenine-derived nitrogen sources, both of these nitrogen sources provided good enantioselectivity. However, aminotriazine form gave a higher ee (97 %) than the aminopyrimidine (87%) (Figure 1.19).

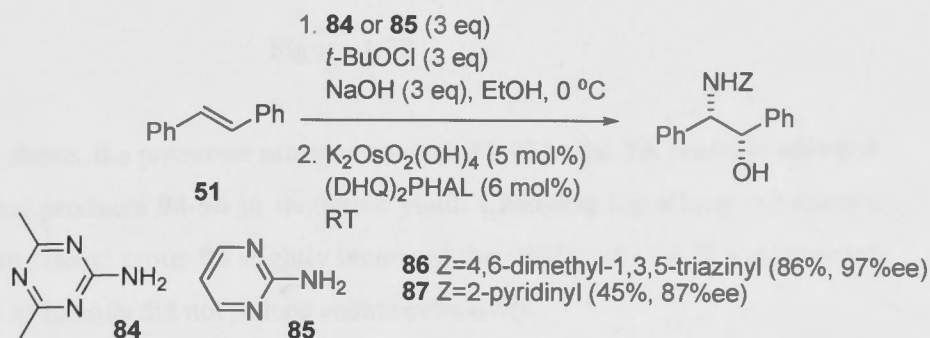


Figure 1.19

1.4.3.5 Nitrogen sources in the tethered-aminohydroxylation (TA) reaction

This type of nitrogen source was developed by Donohoe and coworkers⁴¹ as a novel method to solve regioselectivity problems of osmium-catalysed aminohydroxylation reaction. The regioselectivity was controlled as the nitrogen source was attached directly to the alkene substrate and reaction occurred in an intra-molecular fashion. Three classes of this nitrogen sources have been developed: (i) carbamate derived nitrogen sources including *N*-sulfonyloxy and *N*-acyloxy, (ii) sulfamate ester and sulfonamide-derived nitrogen sources, and (iii) amides.

1.4.3.5.1 Carbamate nitrogen sources in the TA reaction

The carbamate-tethered nitrogen source was the first reported.^{41,55,56} Its precursor was prepared from corresponding allylic alcohol by reacting with 2,2,2-trichloroacetyl isocyanate followed by potassium carbonate. For example, the precursor of the carbamate-tethered nitrogen source **92** was derived in two steps from (*E*)-hex-2-en-1-ol **89**. Reaction of alcohol **89** with 2,2,2-trichloroacetyl isocyanate, and then treatment with potassium carbonate afforded carbamate **92** in high yield. *In-situ* oxidation of carbamate **92** with *tert*-butyl hypochlorite⁴⁶ and sodium hydroxide afforded nitrogen source for TA reaction to give oxazolidinone product **95** (Figure 1.20).

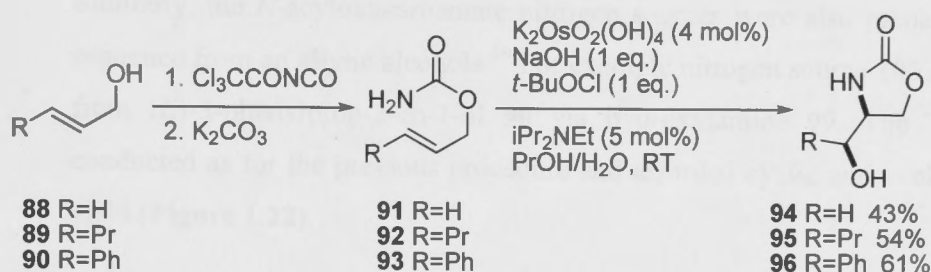


Figure 1.20

In the examples above, the precursor nitrogen sources **91-93** in the TA reaction afforded the amino alcohol products **94-96** in moderate yield. Changing the alkene substituent from proton **91** to phenyl group **93** slightly increased the yield to (61%). It was reported that the addition of ligands did not induce enantioselectivity.

Another report for this class of nitrogen source involved the *N*-sulfonyloxy and *N*-acyloxy- carbamates.^{57,58} The *N*-sulfonyloxycarbamate nitrogen source was not generated *in-situ* during the TA reaction. This was prepared in a pre-oxidised form and tethered in the alkene substrates in a two step sequence.⁵⁷ For example, nitrogen source **98** was prepared from prop-2-en-1-ol **88**, by reaction with 1,1'-carbonyldiimidazole (CDI) and then hydroxylamine followed by sulfonylation with mesitylsulfonyl chloride. A cyclic amino alcohol **94** was obtained in good yield in the following TA reaction (Figure 1.21).

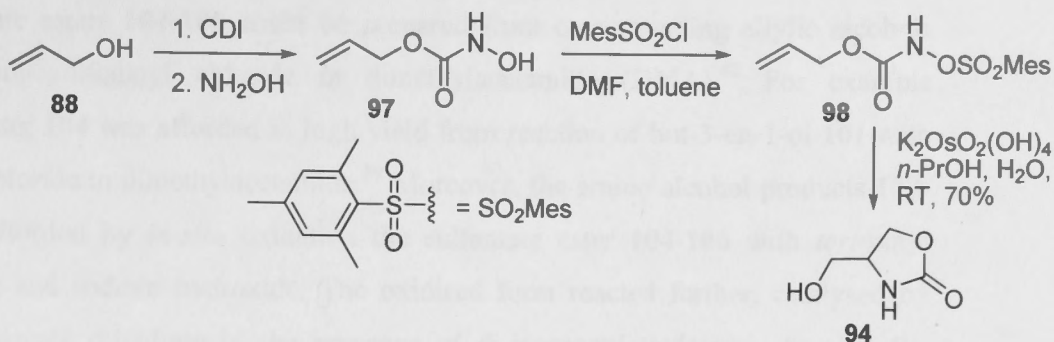


Figure 1.21

Similarly, the *N*-acyloxycarbamate nitrogen sources were also prepared in a two step sequence from an allylic alcohols.⁵⁸ For example nitrogen source **100** could be prepared from (*E*)-3-phenylprop-2-en-1-ol **90** via hydroxylamine **99**. The TA reaction was conducted as for the previous procedure and afforded cyclic amino alcohol **96** in good yield (Figure 1.22).

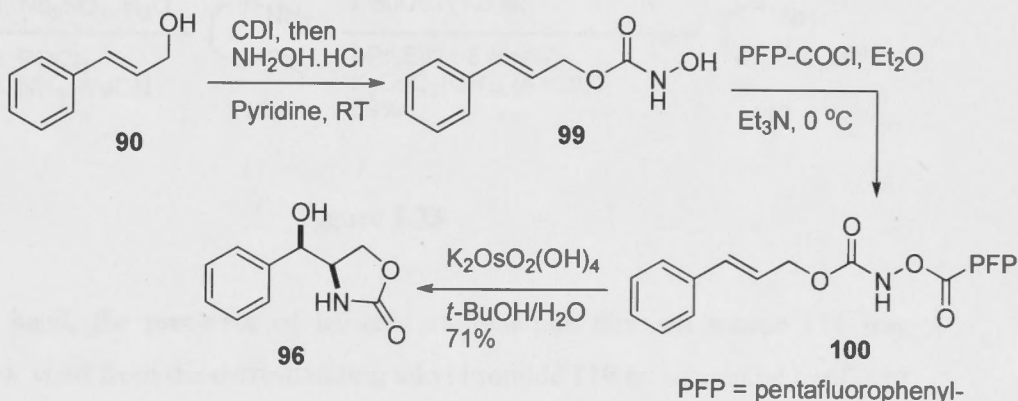


Figure 1.22

1.4.3.5.2 Sulfamate ester and sulfonamide nitrogen sources in the TA reaction

The sulfamate ester and sulfonamide tethered-nitrogen sources⁴¹ were reported by Kenworthy and Taylor.⁴² Both variant nitrogen sources were generated *in-situ* by reacting the tethered sulfamate esters **104-106** or sulfonamide compound **111** with *tert*-butyl hypochlorite and sodium hydroxide. The TA reaction was conducted with potassium osmate dihydrate and diisopropyl ethylamine (Figure 1.23).

The sulfamate esters **104-106** could be prepared from corresponding allylic alcohols **101-103** with sulfamoyl chloride in dimethylacetamide (DMA).⁴² For example sulfamate ester **104** was afforded in high yield from reaction of but-3-en-1-ol **101** with sulfamoyl chloride in dimethylacetamide.⁵⁹ Moreover, the amino alcohol products **107-109** were afforded by *in-situ* oxidation the sulfamate ester **104-106** with *tert*-butyl hypochlorite and sodium hydroxide. The oxidised form reacted further, catalysed by potassium osmate dihydrate in the presence of di-isopropylethylamine, to give the amino alcohol products **107-109** in good yield as a cyclic sulfamidate.

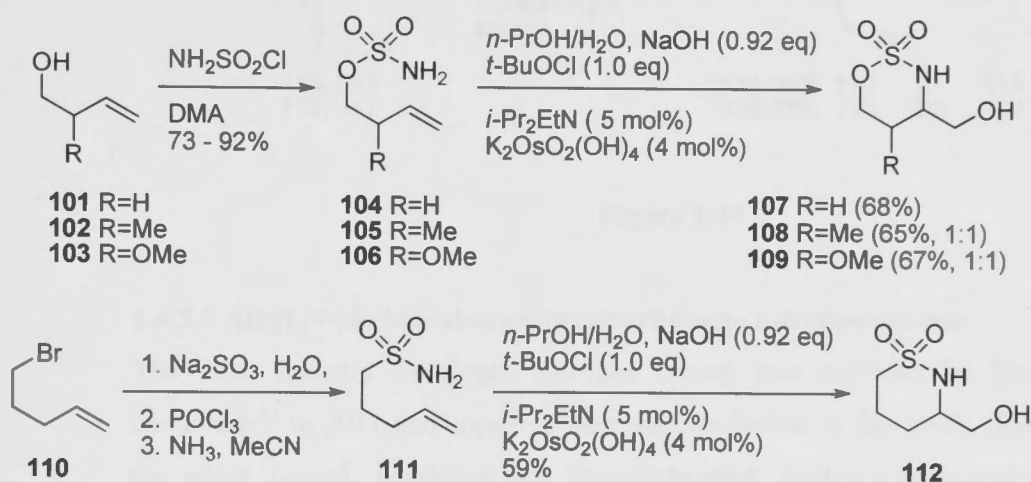


Figure 1.23

On the other hand, the precursor of tethered sulfonamide nitrogen source **111** was prepared in low yield from the corresponding alkyl bromide **110** by sequential treatment with sodium sulfite, phosphoryloxy chloride and ammonia.^{60,61} The *in-situ* generation of the nitrogen source from **111** then afforded a moderate yield of cyclic amino alcohol product **112**.

1.4.3.5.3 Amide nitrogen sources in the TA reaction

The amide tethered-nitrogen source for aminohydroxylation reaction was reported by Donohoe and coworkers.⁶² This amide nitrogen source was prepared in two steps from an olefinic acid **113**. This was transformed to its hydroxamic acid **114** using oxalyl chloride and a hydroxylamine and further reacted with trimethylbenzoyl chloride to afford the amide tethered-nitrogen source **115**. For example, the amide tethered nitrogen

sources **116** and **117** were subjected to TA reaction to afford cyclic amino alcohol products **118-121** in high yields (**Figure 1.24**).

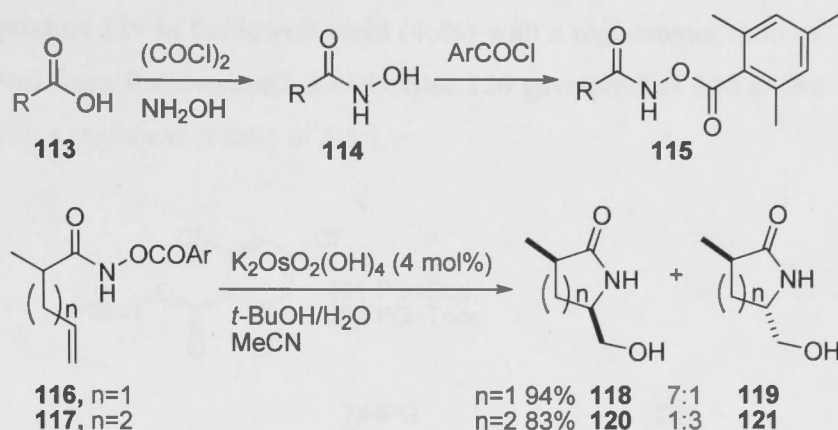


Figure 1.24

1.4.3.6 Alkyl *N*-(4-chlorobenzoyloxy)carbamate nitrogen sources

The most recently developed nitrogen source was reported by Luxenburger and coworkers⁴³ in 2011 and appeared near the conclusion of this study. They consisted of the ethyl, benzyl, *tert*-butyl and fluorenylmethyl *N*-(4-chlorobenzoyloxy)carbamates **123-126**. All could be prepared in two steps from corresponding chloroformate or dicarbonate reagent by reaction with hydroxylamine and a base, and followed by 4-chlorobenzoyl chloride to provide corresponding nitrogen sources **123-126** (**Figure 1.25**).

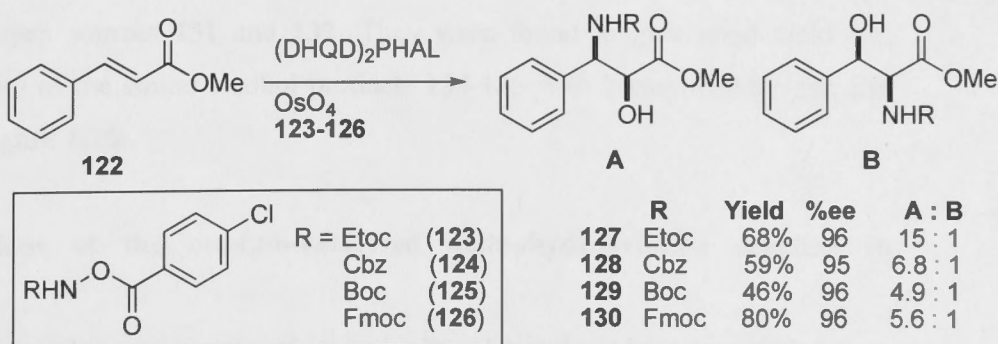


Figure 1.25

Evaluation with substrate methyl cinnamate **122**, and using (DHQD)₂PHAL ligand, OsO₄ catalyst provided low to good yield. The reactions gave two regioisomers with the β -amino compound as the major product. The nitrogen source derived from *tert*-butyl carbamate **125** gave product **129** in the lowest yield (46%) with a regioisomer ratio of 4.9:1, while that derived from fluorenylmethyl carbamate **126** gave product **130** in the highest yield (80%) with a regioisomer ratio of 5.6:1.

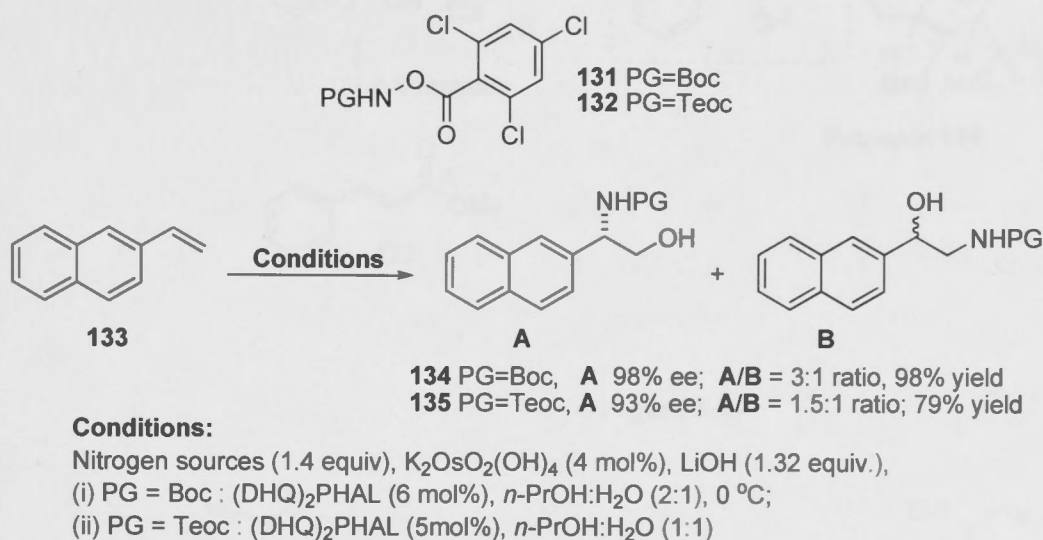


Figure 1.26

Another variant for this type was previously reported in a poster by Klauber et al.⁴⁴ and can be found cited in the footnote of the paper by Luxenburger and coworkers.⁴³ An intermolecular aminohydroxylation was performed using *N*-(2,4,6-trichlorobenzoyloxy) carbamate nitrogen sources **131** and **132**. They were found to give good yield and enantioselectivity of the amino alcohol products **134-135** with 2-vinylnaphthalene **133** as substrate (**Figure 1.26**).

1.5. Applications of the osmium-catalysed aminohydroxylation reaction in synthesis

Some applications of osmium-catalysed aminohydroxylation have been reported such as synthesis of C13 side-chain^{63,64} of paclitaxel **136**, a biologically active natural product with anti-leukemic and anti-tumor activity isolated from the bark of the Pacific yew (*Taxus brevifolia*).⁶⁵ This side-chain was essential for its biological activity^{66,67} and

practically, could be prepared on a large scale using the AA reaction from commercially available methyl *trans*-cinnamate⁶³ **122** or isopropyl *trans*-cinnamate⁶⁴ **64** (Figure 1.27).

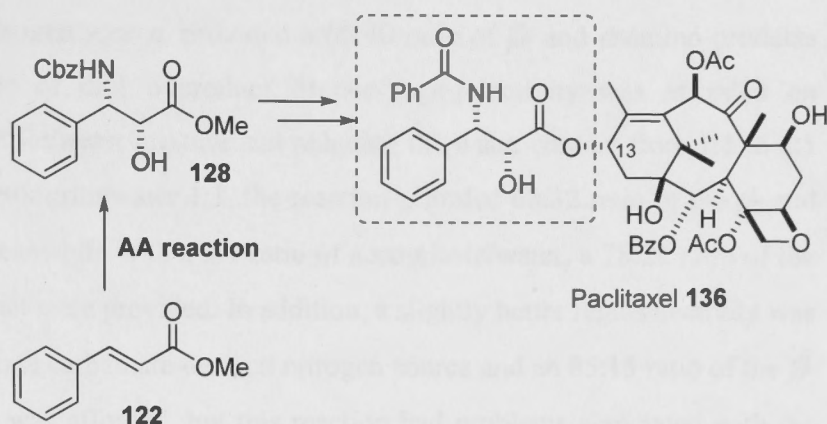


Figure 1.27

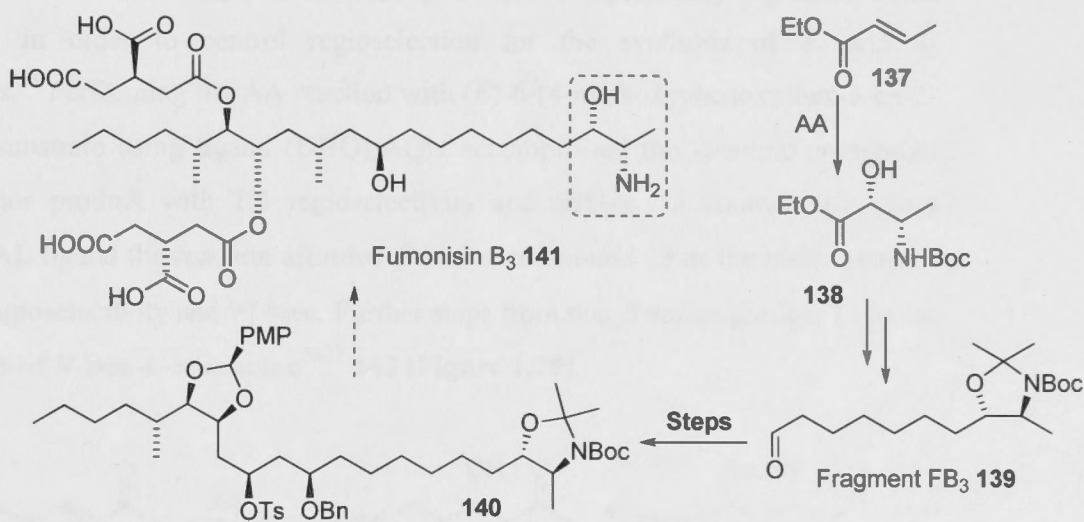


Figure 1.28

In the Mal McLeod research group, the AA reaction has been employed to achieve a synthesis of the C11-C20 fragment of Fumonisin B₃⁶⁸ **141**, a biologically active substance isolated from the fungus *Fusarium moniliforme* (Sheldon)⁶⁹ (Figure 1.28). The regioselectivity of the AA reaction was studied with (DHQ)₂PHAL ligand, and the

variation of the carbamate-derived nitrogen sources and solvent system was undertaken. The best conditions were applied to install β -amino ester structure **138** from ethyl crotonate **137**. It was reported that performing the reaction following the Sharpless AA reaction² procedure using *n*-propanol/water (1:1) as a solvent mixture and *tert*-butyl carbamate-derived nitrogen source, provided a 60:40 ratio of β - and α -amino products including 22% yields of diol byproduct. Better regioselectivity was afforded on employing an acetonitrile/water mixture and reducing the water content from 1:1 to 2:1 ratio. Ratio of the acetonitrile/water 1:1, the reaction afforded 68:32 ratio of the β - and α -amino products. Meanwhile with a 2:1 ratio of acetonitrile/water, a 78:22 ratio of the β - and α -amino product were provided. In addition, a slightly better regioselectivity was afforded on using benzyl carbamate-derived nitrogen source and an 85:15 ratio of the β - and α -amino product was afforded, but this reaction had problems associated with the separation of the diol byproduct and the remaining benzyl carbamate, besides the low yields isolated.⁶⁸

Another AA reaction study in the group involved optimising ligand/substrate interactions in order to control regioselection for the synthesis of 3- and 4-aminosugars.²⁴ Performing the AA reaction with (*E*)-6-(4-methoxyphenoxy)hex-3-en-2-one **22** as substrate using ligand (DHQ)₂AQN accomplished the α -amino compound **142** as major product with 1:5 regioselectivity and 68%ee. In contrast, by using (DHQ)₂PHAL ligand the reaction afforded β -amino compound **23** as the major product with 20:1 regioselectivity and 97 %ee. Further steps from this β -amino product **23** led to the synthesis of *N*-Boc-*L*-acosamine^{70,71} **143** (Figure 1.29).

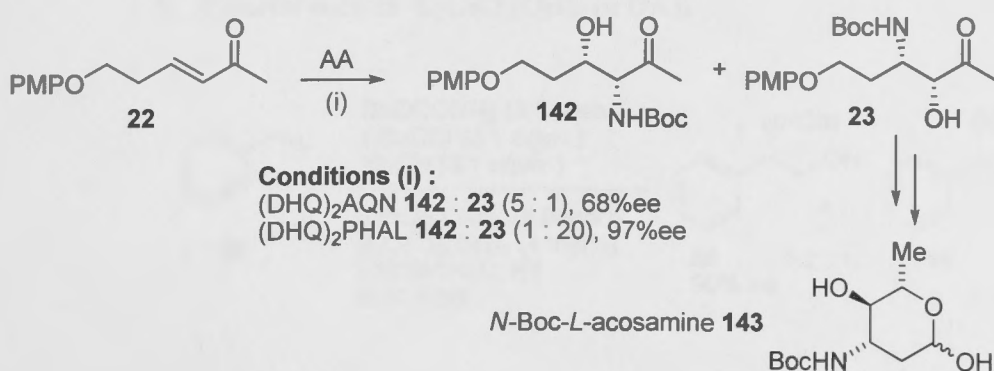


Figure 1.29

This result has underlined the fact that, a ligand with phthalazine (PHAL) spacer favorably furnished the β -amino product **23** in high yield, while the anthraquinone (AQN) spacer provided the α -amino product **142**. However, the AA reaction procedure for this purpose was accomplished by applying sodium hydrogen carbonate buffer. A good yield and high enantioselectivity was afforded when buffered with 3.0 equiv. of sodium hydrogen carbonate.²⁴ Performing reaction according to the standard AA reaction conditions² afforded the Michael adduct of *tert*-butyl carbamate addition to the β -carbon of (*E*)-6-(4-methoxyphenoxy)hex-3-en-2-one **22** as the major product.

Those examples above illustrate the value of the AA reaction for the introduction of vicinal-amino alcohol functional group regio- and enantio-selectively from the very simple and cheap substrates. However, the method still has some limitations^{72,73} such as requirement for a large number of different reagents^{2,7} to generate the nitrogen sources *in-situ*. Furthermore, chlorination of the AA product^{24,57,74} can result, and the strongly basic reaction conditions can lower the yields.²⁴

Under standard conditions, the Sharpless asymmetric aminohydroxylation (AA) reaction² requires the presence of five different reagents not including solvent. These are:

1. Precursor nitrogen source (3.1 equiv.), such as *tert*-butyl, or benzyl carbamate.
2. Chlorinating agent (3.1 equiv.), such as *tert*-butyl hypochlorite or 1,3-dichloro-5,5-dimethylhydantoin.
3. Base (3.1 equiv.), typically sodium hydroxide or sodium hydrogen carbonate
4. Ligand, such as (DHQ)₂PHAL, (DHQD)₂PHAL.
5. Catalyst such as K₂OsO₂(OH)₄ or OsO₄

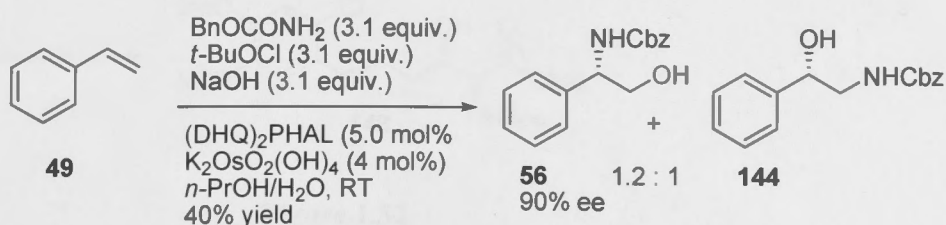


Figure 1.30

One representative example of the AA reaction under standard conditions was the reaction of styrene **49** as a substrate using the benzyl carbamate-derived nitrogen source to afford amino alcohol product **56**⁷⁵ (**Figure 1.30**). This reaction afforded a moderate yield and ratio (1.2:1) of the two regioisomers **56** and **144**. In addition, the benzyl *N*-chloro-*N*-sodiocarbamate **46** as nitrogen source was generated *in-situ*, and this reaction required 3.1 equivalents of benzyl carbamate **145**, 3.1 equivalents of freshly prepared of sodium hydroxide and 3.1 equivalents of *tert*-butyl hypochlorite (**Figure 1.31**). Finally, with 4 mol% of catalyst and ligand (5.0 mol%), styrene **49** was reacted in *n*-propanol/water solvent to give products **56** and **144**.

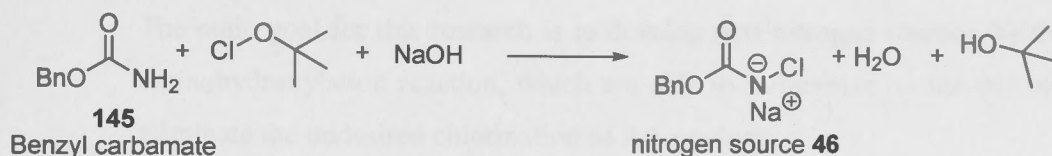


Figure 1.31

Employing a wide range of reagents to accomplish the AA reaction becomes an issue when applying the methodology of large scale such as industrial settings where issues of atom economy are of great importance. Future developments of the AA reaction should attempt to improve economy to reduce the usage of reagents.

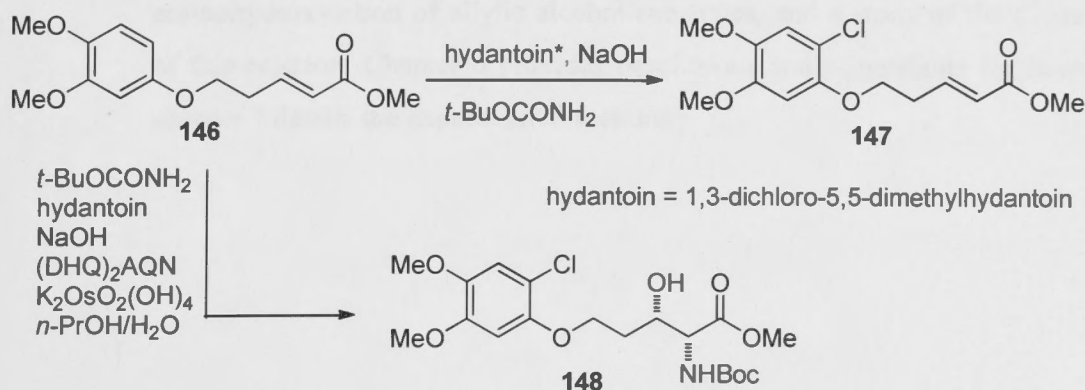


Figure 1.32

Another problem relates to the chlorination^{76,77} of the alkene substrates and the AA products in some cases.^{24,74} Chlorination occurs due to the use of chlorinating reagents

such as *tert*-butyl hypochlorite⁴⁶ or 1,3-dichloro-5,5-dimethylhydantoin⁷⁷ in generating the nitrogen sources. An example of the problems that arise during the standard AA reaction is given in **Figure 1.32**.⁷⁴ When the substrate **146** was reacted under standard AA reaction conditions, which generated the nitrogen source *in-situ* from *tert*-butyl carbamate and 1,3-dichloro-5,5-dimethylhydantoin, the reaction provided the chlorination product **148** in high yield. Indeed, further investigation provided evidence that complete chlorination also occurred from direct exposure of the substrate to the 1,3-dichloro-5,5-dimethylhydantoin under basic conditions.⁷⁴

1.6 Aims of the research

The main goal for this research is to develop new nitrogen sources for the asymmetric aminohydroxylation reaction, which are able to economise on the use of reagents and eliminate the undesired chlorination of AA products.

Chapter 2 describes the synthesis, evaluation, and optimisation of a first generation of pre-formed nitrogen sources. Chapter 3 presents the results on the investigation of amino acid-based ligands for controlling the enantio-selectivity of the reaction. Chapter 4 reports on the development of a second generation of preformed nitrogen sources and consists of the synthesis, evaluation and optimisation of these reagents. It also includes a study of the reaction scope for these reagents. Chapter 5 presents a study on the application of second generation preformed nitrogen sources for the osmium-catalysed aminohydroxylation of allylic alcohol substrates, and a study of the diastereoselectivity of this reaction. Chapter 6 provides conclusions and suggestions for future work, and chapter 7 details the experimental sections.

Chapter 2

tert-Butyl Carbamate-Based Preformed Nitrogen Sources for the Osmium-Catalysed Aminohydroxylation Reaction: Synthesis, Evaluation and Optimisation

Summary

This chapter contains an investigation of tert-butyl carbamate-based preformed nitrogen sources for the osmium-catalysed aminohydroxylation reaction. This includes (i) an introduction, (ii) synthesis of tert-butyl carbamate-based preformed nitrogen sources, (iii) evaluation of the tert-butyl carbamate-based preformed nitrogen sources, (iv) optimisation of the reaction conditions, including solvent system, catalyst and preformed nitrogen source loading and reaction pH, and (v) conclusion and future work.

Chapter 2

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2.1 Introduction

The carbamate functional group has been widely used as a protecting group in organic synthesis.⁷⁸ It has been used to protect many types of amines,⁴⁷ including in amino acid,⁷⁹ and carbohydrate synthesis.⁸⁰ The ease of deprotection using mild conditions^{79,81} to afford the free amine functionality is an important attribute. The *tert*-butyl carbamate is a widely-used example of this group. It is stable in neutral to basic conditions, and can be easily cleaved with trifluoroacetic acid (TFA), either neat or in dichloromethane solution.^{47,78} It can also be deprotected selectively in the presence of other ester groups by aqueous phosphoric acid⁸¹ or hydrochloric acid in ethyl acetate.⁸²

It has been reported by Sharpless and coworkers² that the AA reaction employs the *in-situ* preparation of nitrogen sources. The *N*-halocarbamate is prepared using the corresponding alkyl carbamate (3.10 equiv.), sodium hydroxide (3.05 equiv.) and *tert*-butyl hypochlorite (3.05 equiv.). The excess nitrogen source results in excess reagents at the end of the reaction that can not be separated easily using column chromatography. Besides that, it is less “green” in terms of atom economy and also requires basic conditions for the reaction to occur. It was hoped that the new preformed nitrogen sources would provide more efficient method of osmium-catalysed aminohydroxylation, free of chlorinating reagents and able to work under less basic conditions.

This chapter reports the development of *tert*-butyl carbamate-based preformed nitrogen sources for osmium-catalysed aminohydroxylation reaction which were synthesised free from chlorinating reagents. This consists of : (i) the synthesis of *tert*-butyl carbamate-based preformed nitrogen sources, (ii) an evaluation of these preformed reagents in the aminohydroxylation reaction, and (iii) an optimisation of the reaction conditions i.e. solvent, nitrogen source and catalyst loading, and the pH of the reaction.

2.2 Synthesis of *tert*-butyl carbamate-based preformed nitrogen sources

Six preformed nitrogen sources were investigated (**Figure 2.1**). Generally, the nitrogen source consisted of two parts. First was the *N*-protecting group part, which was based on *tert*-butyl carbamate. Second was the leaving group, which was formed from six different substituents with different properties such as bulkiness and electronic properties. This included two different classes of substituents, i.e. *N*-acyloxy- and *N*-sulfonyloxy-substituents.

The *N*-acyloxy-substituent as a leaving group consisted of pentafluorobenzoyloxy- **149** and 2-chloroacetoxy-groups **150**. Meanwhile the *N*-sulfonyloxy-substituent consisted of methanesulfonyloxy- **151**, mesitylsulfonyloxy- **152**, 4-toluenesulfonyloxy- **153**, and 4-nitrobenzene-sulfonyloxy-groups **154**, respectively.

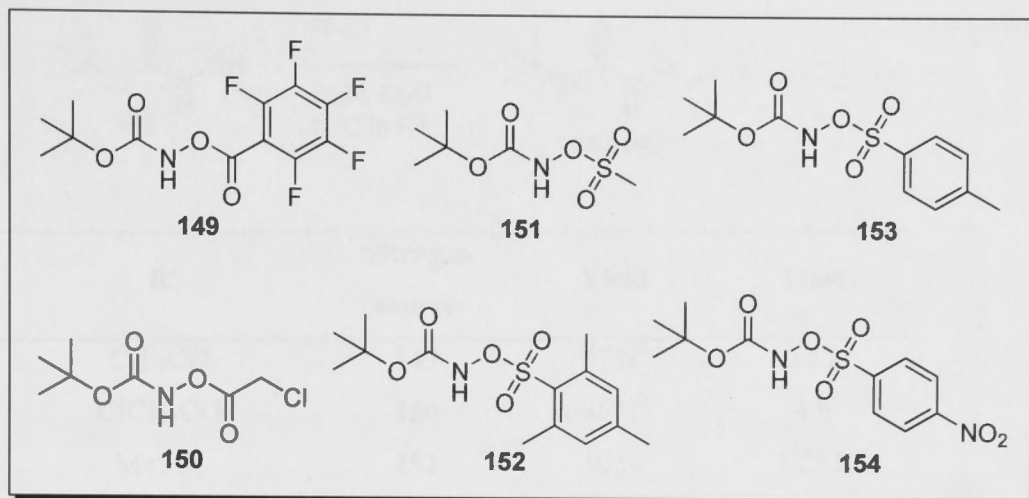


Figure 2.1

All of preformed nitrogen sources were synthesised from a common precursor, *tert*-butyl *N*-hydroxycarbamate⁸³ **156**. This precursor is commercially available, however it was cheaply and ready prepared on large scale and in excellent yield from di-*tert*-butyldicarbonate (DIBOC) **155** and hydroxylamine hydrochloride in diethyl ether-water⁸³ solvent (**Figure 2.2**). A first attempt using dichloromethane-water solvent and sodium hydrogen carbonate base only afforded the product in low yield⁸⁴ due to insolubility of the reagents.

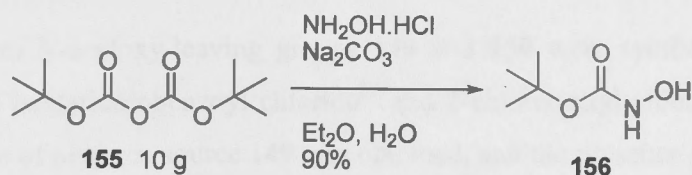
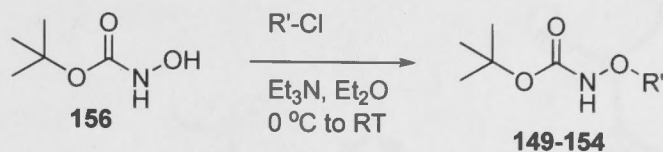


Figure 2.2

To afford the preformed nitrogen sources, *tert*-butyl *N*-hydroxycarbamate **156** was reacted to introduce various leaving groups as tabulated in **Figure 2.3**. This reaction was achieved by reacting compound **156** with the appropriate acyl or sulfonyl chloride in the presence of an amine as base.⁸⁴⁻⁸⁷



Entry	R'	Nitrogen source	Yield	Time
1	C ₆ F ₅ CO-	149	67% ^a	0.5 h
2	ClCH ₂ CO-	150	85% ^b	4 h
3	MeSO ₂ -	151	93%	1.25 h
4	2,4,6-Me ₃ C ₆ H ₂ SO ₂ -	152	58%	13 h
5	4-MeC ₆ H ₄ SO ₂ -	153	71%	17 h
6	4-NO ₂ C ₆ H ₄ SO ₂ -	154	51%	3.75 h

Note: ^aUsing dichloromethane as solvent; ^b(*i*-Pr)₂EtN used as a base.

Figure 2.3

In general, the *tert*-butyl carbamate based preformed nitrogen sources were synthesised in good to excellent yield, and this was accomplished in short reaction times, with exception of nitrogen sources **152** and **153** which were accomplished after an overnight reaction.

Two nitrogen sources with *N*-acyloxy-leaving groups **149** and **150** were synthesised from compound **156** with pentafluorobenzoyl chloride⁸⁴ and 2-chloroacetyl chloride.⁸⁵ The X-ray crystal structure of nitrogen source **149** was obtained, and the presence of the N8-O9-C10 bond confirmed the structure of *tert*-butyl *N*-pentafluorobenzoyloxy carbamate **149** (**Figure 2.4**). Four nitrogen sources with *N*-sulfonyloxy-leaving groups **151-154** were also afforded by reacting compound **156** with methanesulfonyl

chloride,^{84,88} mesitylsulfonyl chloride,⁸⁶ toluenesulfonyl chloride^{87,89} and 4-nitrobenzenesulfonyl chloride,^{87,90} respectively.

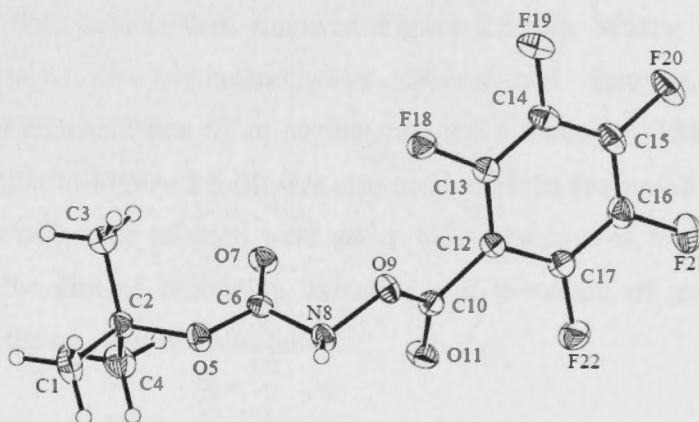


Figure 2.4 Structure of $C_{12}H_{10}F_5NO_4$ with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

After the preformed nitrogen sources had been synthesized, the next step was to investigate their reactivity in the osmium-catalysed aminohydroxylation reaction.

2.3 Evaluation of *tert*-butyl carbamate-based preformed nitrogen sources

Initial experiments used the simple substrate *trans*-stilbene **51**. It was found that the order of addition of the reagents strongly influenced the reaction (**Figure 2.5**).

In the first attempt a similar procedure to the AA reaction reported by Sharpless and coworkers³ was followed, using *tert*-butanol/water solvent. Preformed nitrogen source *tert*-butyl *N*-(4-toluenesulfonyloxy)carbamate **153** and ligand (DHQD)₂PHAL was mixed with *trans*-stilbene **51** and solvent *tert*-butanol/water (3:1), and finally, $K_2OsO_2(OH)_4$ catalyst was added. No reaction was observed (**Figure 2.5 (i)**). It was assumed this was due to solubility problem arising from the solvent system employed. The second attempt was similar to the first attempt (**Figure 2.5 (i)**), but *n*-propanol and water was used as solvent system, and the reaction mixture was warmed on a water bath until the reagents completely dissolved. After this, potassium osmate dihydrate in water was added. But the reaction still did not occur. This suggested it was not solubility

problem, but the nitrogen source did not effectively react with the catalyst to form imido-osmium species.

The order of addition of the reagents then followed **Figure 2.5 (ii)**. Mixing both nitrogen source and catalyst in *tert*-butanol/water solvent and then adding (DHQD)₂PHAL ligand and *trans*-stilbene **51** in *tert*-butanol, the reaction still did not occur. Another attempt similar to **Figure 2.5 (ii)** was also conducted. In this case a few drops of sodium hydrogen carbonate solution were added to the mixture of nitrogen source and catalyst with the aim of promoting oxidation and formation of imido-osmium species. However, the reaction still also failed.

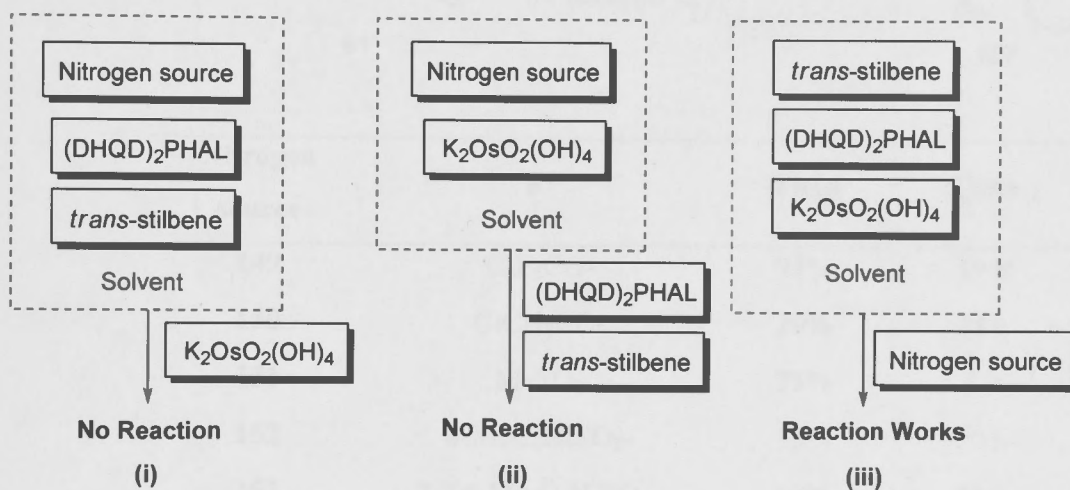
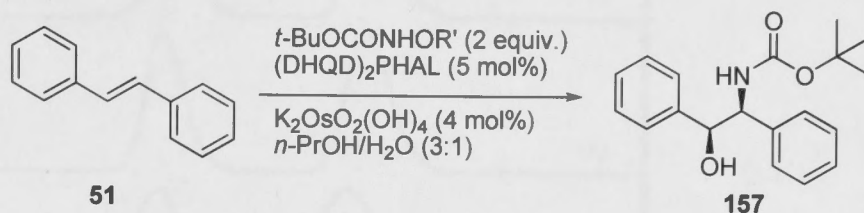


Figure 2.5

The reaction was observed to proceed with the order addition followed in **Figure 2.5 (iii)**. To a mixture of *trans*-stilbene **51**, potassium osmate dihydrate, and ligand in the solvent system was added a solution of the preformed nitrogen source **153**. This procedure was applied to each preformed nitrogen source as detailed below. Evaluation of *tert*-butyl carbamate-based preformed nitrogen sources in the osmium-catalysed aminohydroxylation reaction employing the order of addition specified above is shown in **Figure 2.6**.

In general, all of *tert*-butyl carbamate-based preformed nitrogen sources were able to deliver the desired reaction. The reaction afforded *tert*-butyl 2-hydroxy-1,2-diphenyl-

carbamate **157** as a product in low to good yield, with completion of the reaction after 4 to 30 h. High yields were afforded using *tert*-butyl *N*-(pentafluorobenzoyloxy)-carbamate **149**, *tert*-butyl *N*-(methanesulfonyloxy)carbamate **151** and *tert*-butyl *N*-(4-toluenesulfonyloxy)carbamate **152** as preformed nitrogen sources, while a low yield resulted from *tert*-butyl *N*-(chloroacetoxy)carbamate **150**. No diol byproduct was isolated from the reactions. However, no significant enantioselectivity observed, except for the reaction of nitrogen source **150** which afforded the product **157** in 27 %ee.



Nitrogen source	R'	Yield	Time	%e.e. [†]
149	C ₆ F ₅ CO-	71%	19 h	8
150	ClCH ₂ CO-	29%	24 h	27
151	MeSO ₂	75%	4 h	10
152	4-MeC ₆ H ₄ SO ₂ -	78%	30 h	6
153	2,4,6-Me ₃ C ₆ H ₂ SO ₂ -	59%	30 h	7
154	4-NO ₂ C ₆ H ₄ SO ₂ -	62%	9 h	0

[†]Enantiomeric excessive (%ee) value was calculated from HPLC peak area (Chiralcel OD-H, 10% isopropanol/*n*-hexane, 1.0 mL/min).

Figure 2.6

For preformed nitrogen sources which were constructed with the *N*-acyloxy-substituent as a leaving group, the pentafluorobenzoyloxy-group afforded the amino alcohol product in higher yield than the 2-chloroacetoxy-group. This suggested that this group was more reactive than the 2-chloroacetoxy-group. As a result, the reaction with nitrogen source **149** completed more rapidly. For preformed nitrogen sources which were constructed with *N*-sulfonyloxy-leaving groups, the reactions gave higher yields and shorter reaction times with smaller substituents such as methanesulfonyloxy and 4-

toluenesulfonyloxy as leaving group. In contrast, reaction gave slightly lower yield with 2,4,6-trimethylbenzenesulfonyloxy, and 4-nitrobenzenesulfonyloxy as leaving groups. It seemed that the electronic donating or withdrawing properties of the phenyl-substituent did not have a significant effect on the reaction.

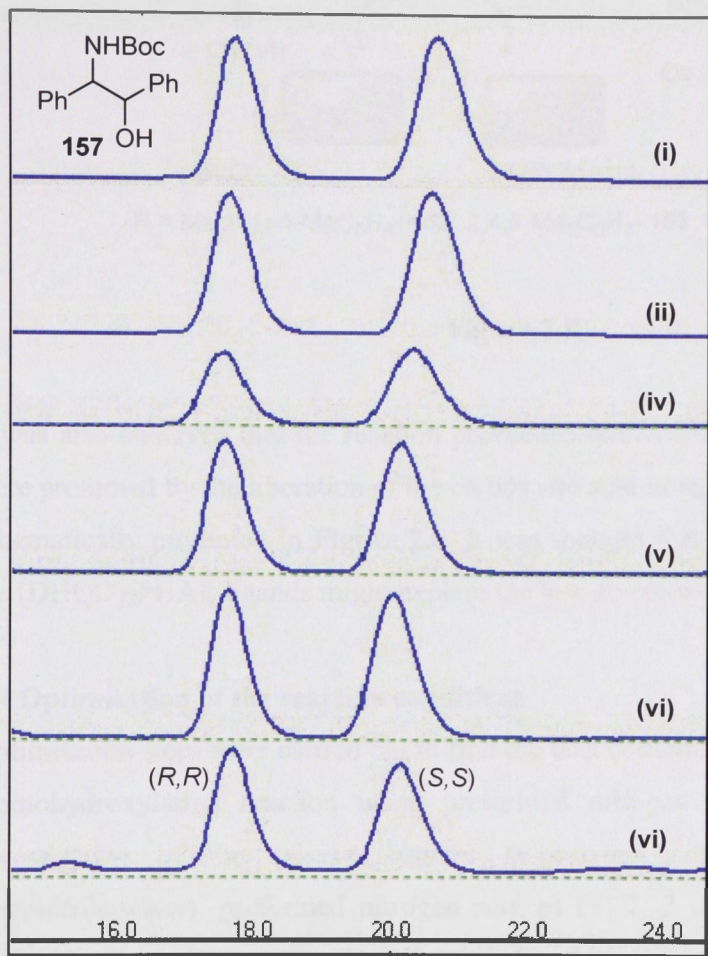


Figure 2.7 HPLC chromatogram of *tert*-butyl 2-hydroxy-1,2-diphenylethylcarbamate **157** (Sample from reaction with preformed nitrogen sources **149** (i), **150** (ii), **151** (iii), **152** (iv), **153** (v), and **154** (vi). HPLC conditions: Chiralcel OD-H, 10% isopropanol/hexane, 1.0 mL/min).

The enantioselectivity of each preformed nitrogen source reaction was analysed with HPLC and the chromatograms are presented in **Figure 2.7**. This result showed that the osmium-catalysed aminohydroxylation reaction with *tert*-butyl carbamate-based preformed nitrogen sources afforded near racemic product.

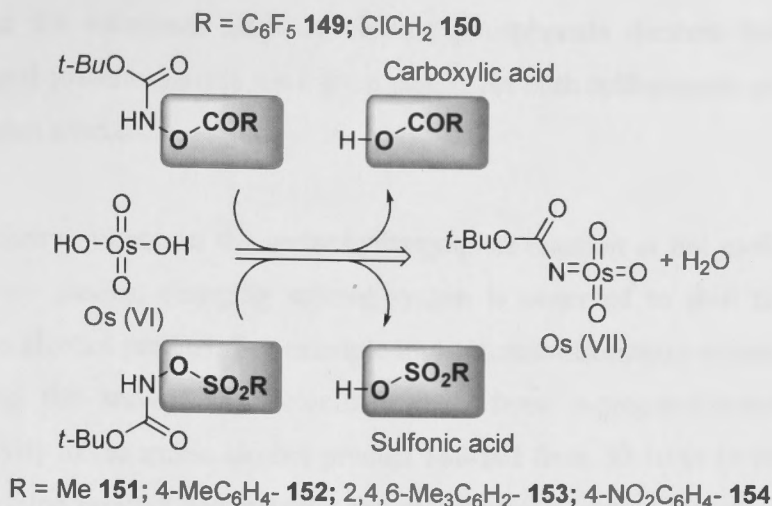


Figure 2.8

It was also observed that the reaction proceeded under mildly acidic conditions which were promoted by the liberation of the carboxylic acid or sulfonic acid leaving group, as schematically presented in **Figure 2.8**. It was thought that the resulting protonation of the (DHQD)₂PHAL ligands might explain the low enantioselectivity observed.

2.4 Optimisation of the reaction conditions

Optimisation steps were carried out to find the best conditions for the osmium-catalysed aminohydroxylation reaction using preformed nitrogen sources. This included an investigation of the solvent systems (*n*-propanol/water, *tert*-butanol/water, and acetonitrile/water), preformed nitrogen sources (1; 2; 3 equiv.) and catalyst (1; 2; 3 mol%) loading, and reaction pH (pH 1-11). For this purpose the high yielding *tert*-butyl *N*-(methanesulfonyloxy)carbamate **151** was used as the preformed nitrogen source.

2.4.1 Optimisation of the solvent

In past report of the Sharpless AA reaction,³ acetonitrile was found to suit sulfonamide based nitrogen sources affording high yields and selectivity, while *n*-propanol was best for the carbamate-based nitrogen sources.^{2,15,64} For substrates such as methyl *trans*-cinnamate using sulfonamide based nitrogen sources, acetonitrile/water solvent mixtures gave higher yields than *tert*-butanol/water.³ In contrast the reaction of vinylfuran and carbamate derived nitrogen sources in *tert*-butanol-water (1:1) solvent mixture gave better yields than in *n*-propanol/water or acetonitrile/water.⁹¹ These trends

were not universal and for substrates such as olefinic phosphonate diesters both acetonitrile and *n*-propanol solvent systems gave good results for both sulfonamide and carbamate-derived nitrogen sources.⁴⁸

The influence of the solvent system on the aminohydroxylation reaction is not easily predicted. In unsymmetric olefins, changing solvent system is observed to shift the regioselectivity of amino alcohol product. For example in 4-toluenesulfonyloxy-styrene substrate **158**, changing the solvent to acetonitrile/water from *n*-propanol/water, changed the regioselectivity of the amino alcohol product **160-161** from 50:50 to 14:86, in which the terminal amine product **161** become the major regioisomer.⁷⁵ However, under similar conditions, with 4-benzyloxy-styrene **159** as substrate, the regioisomer ratio shifted from 88:12 to 75:25, still favouring the terminal alcohol⁷⁵ **162** (Figure 2.9).

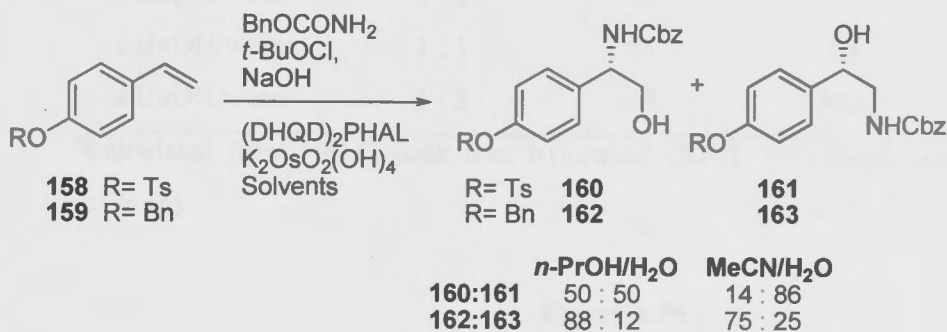
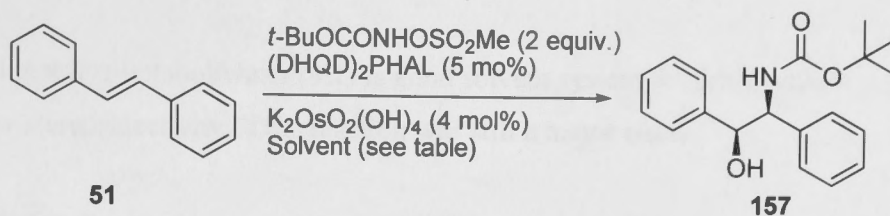


Figure 2.9

In the AA reaction, it has been suggested that increasing the water content of the solvent system accelerates hydrolysis of the osmium-azaglycolate complex **14** (Figure 1.3) to produce amino alcohol product and catalyst turnover, but also was able to hydrolyse the imido-osmium catalyst **5** itself releasing osmium tetroxide into the catalytic cycle.⁹² This results in increased diol product.⁷⁵ For carbamate derived nitrogen sources, using solvent mixture of *n*-propanol/water (1:1) afforded the amino alcohol product in the best yields.² However, in other examples, it is also found that the best chemoselectivity was achieved when using *n*-propanol/water (2:1).^{16,75} More recently, it was reported that applying acetonitrile/water (8:1) or *tert*-butanol/water (6:1) suppressed the diol by-product formation for alkyl *N*-(4-chlorobenzoyloxy)carbamate nitrogen sources.⁴³ Even though the *tert*-butyl carbamate-based preformed nitrogen source did not afford diol

product, the optimisation of solvent system may enhance the yield of amino alcohol product by increasing the rate or inhibiting side reactions such as decomposition.



Solvent	Composition	Yield (%)	e.e. (%) ^a	Time (h)
<i>n</i> -PrOH/water	3 : 1	75	8	4
MeCN/water	3 : 1	90	2	10
<i>t</i> -BuOH/water	3 : 1	99	8	4
<i>t</i> -BuOH/water	2 : 1	70	8	4.25
<i>t</i> -BuOH/water	1 : 1	63	10	5.25
<i>t</i> -BuOH/water	1 : 2	NR	ND	4.75

^aCalculated from HPLC peak area (Chiralcel OD-H, 10% isopropanol/*n*-hexane, 1.0 mL/min)

Figure 2.10

Solvent optimisation was carried out using *trans*-stilbene **51** (1.0 equiv.), *tert*-butyl *N*-(methanesulfonyloxy)carbamate **151** (2.0 equiv.), (DHQD)₂PHAL (5.0 mol%), and potassium osmate dihydrate (4.0 mol%) as catalyst (**Figure 2.10**).

Comparing the three solvent systems i.e. *n*-propanol/water, acetonitrile/water and *tert*-butanol/water with the same composition (3:1), most of them gave good to excellent yields. The best yield was afforded for *tert*-butanol/water system (99%), while acetonitrile/water and *n*-propanol/water gave lower yields. Moreover, in *tert*-butanol/water (3:1) and *n*-propanol/water system, the reaction was faster than in acetonitrile/water system. In terms of stereoselectivity, no significant difference in the enantioselectivity was observed.

For the *tert*-butanol/water system, increasing the water composition from 3:1 to 2:1, 1:1, and 1:2 lowered reaction yields and prolonged reaction time. In fact, with a composition of *tert*-butanol/water 1:2 the reaction did not occur.

It can be concluded that *tert*-butanol/water (3:1) is good solvent system for this reaction, even though the low stereoselectivity of the reaction was still a major issue.

2.4.2 Optimisation of the preformed nitrogen source and catalyst loading

To develop the highest efficiency is the goal of any optimisation study. Theoretically, one mole of olefin substrate can react with one mole of nitrogen source mediated by a tiny amount of osmium-catalyst. However, this is not easily achieved in practice.

As has been noted for the Sharpless AA reaction,^{2,3} the typical procedure requires excess (3.10 equiv.) nitrogen source to obtain a reasonable result.^{2,15} The nitrogen source must be generated with chlorinating reagent *tert*-butyl hypochlorite (3.05 equiv.) and a base sodium hydroxide (3.05 equiv.).² As a consequence, the remaining carbamate must be separated at the end of the reaction. Practically, this is a significant issue, since purification from the remaining carbamate is often not easily conducted using simple column chromatography. In contrast, the bromoacetamide-derived nitrogen source has been reported to require only a slight excess (1.10 equiv.) to react with substrate, when used with lithium hydroxide (1.02 equiv.) as a base.³⁶

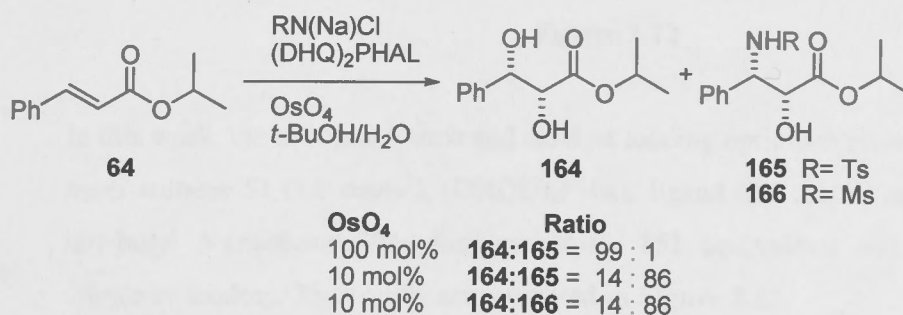


Figure 2.11

The function of the osmium catalyst in the aminohydroxylation reaction has been carefully studied, partly due to its ability to catalyse the dihydroxylation reaction at the

same time. It has been reported that the diol **164** formation becomes significant when the reaction employs a high loading of osmium tetroxide as catalyst^{5,17} (**Figure 2.11**). Conversely, reducing the amount of catalyst reduced the diol **164** product formation. Using isopropyl cinnamate **64** and chloramine-T **41**, with 100 mol% osmium tetroxide catalyst provided the diol **164** as the major product (**164:165** / 99:1). However, reducing the catalyst loading to 10 mol% afforded the amino alcohol **165** as the major product (**164:165** / 14:86). A similar result was observed on using Chloramine-M¹⁷ **53**. These results imply that reactive iminotrioxoosmium species only forms on reoxidation of osmium(VI) to osmium(VIII).

Another example using substrate **167** found similar results. Applying a higher catalyst loading increased the formation of the diol product **170**.^{93,94} The ratio of amino alcohol products **168** and **169** to diol **170** was greater with 3 mol% catalyst (52:21) than with 8 mol% (<5:73) (**Figure 2.12**).

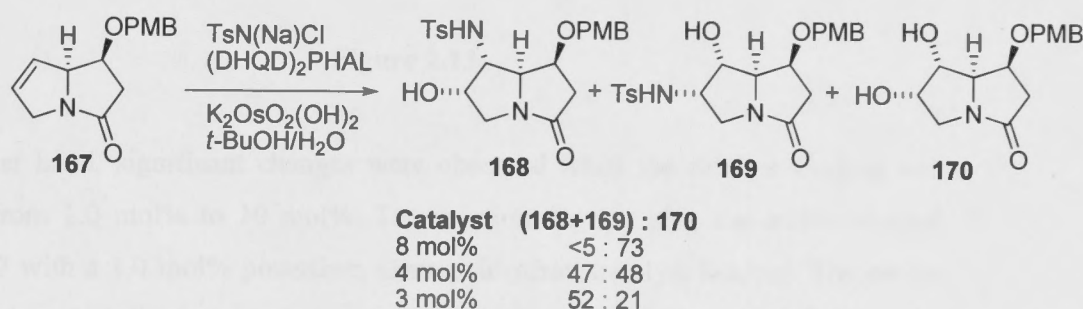
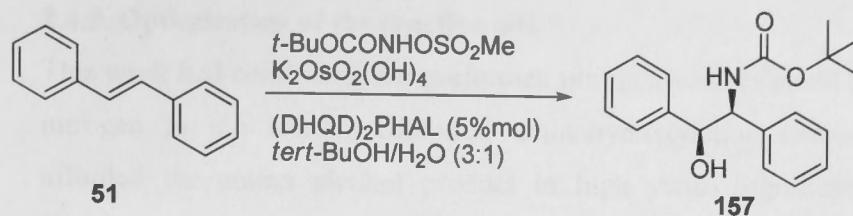


Figure 2.12

In this work, the nitrogen source and catalyst loading optimisation was carried out using *trans*-stilbene **51** (1.0 equiv.), (DHQD)₂PHAL ligand (5.0 mol%) and variation of both *tert*-butyl *N*-(methanesulfonyloxy)carbamate **151** equivalents and potassium osmate dihydrate loading. The results are presented in **Figure 2.13**.

In general, the reaction afforded amino alcohol product **157** in good to excellent yield. Increasing the preformed nitrogen source loading from 1.0 to 3.0 equivalents improved the yields. The reaction gave a sharp improvement in yield when two equivalents were employed.



Nitrogen source	Catalyst	Yield	e.e.*	Time
1 equiv.	4.0 mol%	65%	10%	4.5 h
2 equiv.	4.0 mol%	99%	8.0%	4 h
3 equiv.	4.0 mol%	89%	7.0%	2 h
2 equiv.	1.0 mol%	NR ^a	ND ^b	24 h
2 equiv.	5.0 mol%	81%	13%	4.25 h
2 equiv.	10 mol%	68%	10%	2 h

*Determined from HPLC chromatogram (Chiralcel OD-H, 10% isopropanol/*n*-hexane, 1.0 mL/min). ^aNR= no reaction; ^bND= not determined.

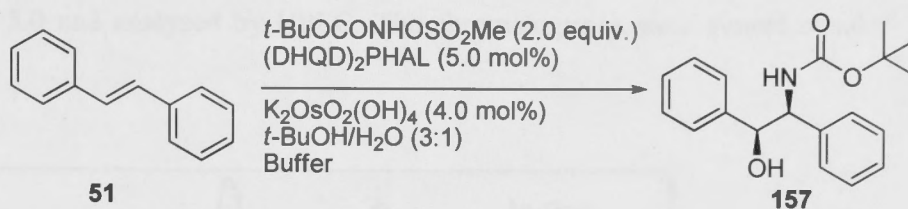
Figure 2.13

On the other hand, significant changes were observed when the catalyst loading was increased from 1.0 mol% to 10 mol%. The reaction did not give the amino alcohol product **157** with a 1.0 mol% potassium osmate dihydrate catalyst loading. The amino alcohol product **157** did form on increasing the catalyst loading from 4.0 mol% to 10 mol% and this change also made the reaction reach completion faster. However, the amino alcohol **157** yields declined with increasing catalyst loading. Previous results suggested that diol formation could be competing with aminohydroxylation, although the diol product was not observed in this reaction.

To conclude, it was found that the optimum conditions for aminohydroxylation reaction catalysed by osmium were 2.0 equiv. of *tert*-butyl *N*-(methanesulfonyloxy)carbamate **151** as preformed nitrogen source, and 4.0 mol% potassium osmate dihydrate as catalyst.

2.4.3. Optimisation of the reaction pH

This work had confirmed that preformed nitrogen sources could be used as a source of nitrogen in the osmium-catalysed aminohydroxylation reaction. In general, they afforded the amino alcohol product in high yield. Significantly, these preformed nitrogen sources required a slightly lower molar equivalent compared to that typically employed in the AA reaction,^{2,3} which uses 3.1 equivalents of nitrogen source.² However, the low enantioselectivity afforded by these preformed nitrogen sources remained an important limitation.



Buffer solution	pH	Yield	e.e.	Time
0.1 M	1	99.7%	1.3%	2 h
KCl/HCl	2	71%	6.2%	4.5 h
0.1 M Potassium	3	75%	ND ^b	6 h
hydrogen	4	55%	ND ^b	6 h
phthalate/NaOH	5	82%	8.8%	24 h
0.1 M KH ₂ PO ₄ /NaOH	6	NR ^a	ND ^b	2 d
	7	NR ^a	ND ^b	2 d
	8	NR ^a	ND ^b	52 h
0.1 M	9	NR ^a	ND ^b	23 h
Borax/NaOH	10	NR ^a	ND ^b	22 h
0.1 M NaHCO ₃ /NaOH	11	NR ^a	ND ^b	26.5 h

^aNR, no reaction; and ^bND, not determined.

Figure 2.14

To evaluate the possible influence of pH on enantioselectivity, the reaction was conducted under a range of pH conditions using *trans*-stilbene **51** (1.0 equiv.),

potassium osmate dihydrate (4.0 mol%), ligand (5.0 mol%), and *tert*-butyl *N*-(methanesulfonyloxy)carbamate **151** (2.0 equiv.). In place of water, a buffer pH range 1 to 11 was employed.⁹⁵ The results of this pH study are presented in **Figure 2.14**.

The reaction afforded amino alcohol product **157** below pH 6.0, meanwhile at pH 6.0 and above, the reaction did not proceed. Reducing pH from 5.0 to 1.0 increased the reaction yield, and reduced the reaction time from 24 to 2 h. The best yield was afforded at pH 1.0 and was completed in 2 h. No significant enantioselectivity was observed.

Figure 2.15 presents chromatogram of the amino alcohol product **157** from reactions at pH 1.0, 2.0, and 5.0 and analysed by HPLC. The chromatograms gave almost equal peak areas.

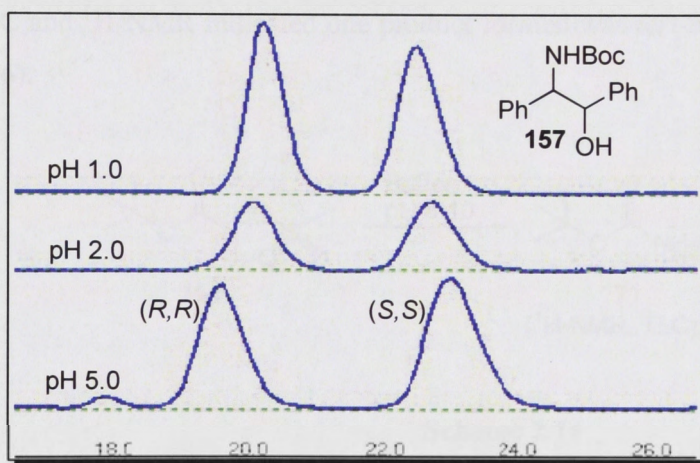
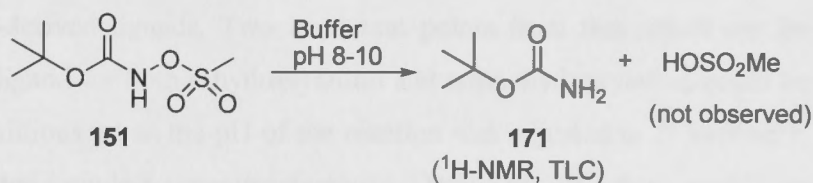


Figure 2.15 HPLC chromatogram of *tert*-butyl 2-hydroxy-1,2-diphenylethylcarbamate **157** (Chiralcel OD-H 5 μ m, 10% isopropanol/*n*-hexane, 1.0 mL/min).

The decrease of pH of the reaction to around 4-5 in the absence of buffer that resulted from the liberation of sulfonic acid or carboxylic acid as a byproduct of the preformed nitrogen source had previously been observed. It was assumed that the acid could protonate the tertiary-amine of the (DHQD)₂PHAL ligand, and preclude the ligand from controlling the enantioselectivity of the reaction. The Sharpless AA reaction^{2,3} is conducted under basic conditions. In some reports, employing ligands such as the cinchona alkaloid-derived ligand to control enantioselectivity requires basic conditions or a buffered reaction.⁹⁶⁻¹⁰⁰ Optimisation of the pH of the reaction was intended to find

the best pH conditions for the preformed nitrogen sources in the osmium-catalysed aminohydroxylation reaction. Importantly, the reaction does not proceed under basic conditions suggesting that cinchona alkaloid-derived ligands may not be suitable in controlling the enantioselectivity of the reaction.

As previously, no diol product was isolated from these reactions, and the product was formed with low enantioselectivity. The lack of product observed when conducting reaction at pH 6 or above suggested decomposition of the preformed nitrogen sources. A further test was undertaken by stirring a solution *tert*-butyl *N*-(methanesulfonyloxy)carbamate **151** alone in *tert*-butanol with buffer solution at pH 8, 9 and 10. The decomposition of this preformed nitrogen source was observed rapidly in each case by thin layer chromatography. Even though the mechanism of decomposition was unclear, TLC and $^1\text{H-NMR}$ indicated one product formed was *tert*-butyl carbamate **171** (Figure 2.16).



Scheme 2.16

2.5 Conclusions and future work

In conclusion six *tert*-butyl carbamate-based preformed nitrogen sources have been synthesised. They are *tert*-butyl *N*-(pentafluorobenzoyloxy)carbamate **149**, *tert*-butyl *N*-(2-chloroacetoxy)carbamate **150**, *tert*-butyl *N*-(methanesulfonyloxy)carbamate **151**, *tert*-butyl *N*-(4-toluenesulfonyloxy)carbamate **152**, *tert*-butyl *N*-(2,4,6-trimethylbenzene sulfonyloxy)carbamate **153**, and *tert*-butyl *N*-(4-nitrobenzenesulfonyloxy)carbamate **154**. All of these preformed nitrogen sources are able to perform the osmium-catalysed aminohydroxylation reaction in high yield, except for *tert*-butyl *N*-(2-chloroacetoxy)carbamate **150** which afforded low yield. The optimum reaction conditions for these preformed nitrogen sources, specifically *tert*-butyl *N*-(methanesulfonyloxy)carbamate **151** included preformed nitrogen source (2.0 equiv.), potassium osmate dihydrate (4.0

mol%) and *tert*-butanol/water (3:1) as solvent. No diol byproduct was isolated from the reactions, and the reaction worked efficiently under mildly acidic conditions.

Two main issues remain regarding the *tert*-butyl carbamate-based preformed nitrogen sources. Firstly, an evaluation of these preformed nitrogen sources in the osmium-catalysed aminohydroxylation reaction showed that addition of chiral cinchona alkaloid ligands such as (DHQD)₂PHAL does not induce significant enantioselectivity. It was assumed that the ligand was unable to interact with the imido-osmium intermediate and control the stereoselectivity due to the protonation state of the ligand. This is likely due to the mildly acidic pH of the reaction between pH 4 and 5.

Finding ligands which are able to work under slightly acidic conditions to control enantioselectivity will be a breakthrough for applying these preformed nitrogen sources in the osmium-catalysed aminohydroxylation reaction. Fokin and coworkers^{101,102} reported dihydroxylation and aminohydroxylation in the secondary cycle by applying *N*-protected amino acid-derived ligands. Two important points from this report can be underlined. First, the ligand for both dihydroxylation and aminohydroxylation could be used under acidic conditions when the pH of the reaction was adjusted to 5. Secondly, these ligands provided modest enantioselectivity. Building on this work, an investigation of amino acid-based ligands to induce enantioselectivity in the aminohydroxylation reaction catalysed by osmium using preformed nitrogen sources will be presented in chapter 3.

Secondly, these preformed nitrogen sources, especially *tert*-butyl *N*-(methanesulfonyloxy)carbamate **151** were able to deliver aminohydroxylation reaction to afford the amino alcohol product in high yields. The reaction required lower excess of preformed nitrogen source, and no diol product was isolated, but it was unable to undergo reaction under basic conditions (above pH 6). Finding more base-stable preformed nitrogen source derivatives for the reaction will be important, in order to apply them in the reaction following the Sharpless AA reaction procedure,^{2,3} using chiral cinchona alkaloid ligands to control the enantioselectivity. An investigation in the development of these preformed nitrogen sources will be presented in chapter 4.

Chapter 3

Amino Acid-Based Ligands : Synthesis and Evaluation in the Osmium- Catalysed Aminohydroxylation Reaction Using Preformed Nitrogen Sources

Summary

This chapter presents an investigation of amino acid-based ligands for the osmium-catalysed aminohydroxylation reaction. This includes (i) an introduction, (ii) the mechanism of the AA reaction and control of enantioselectivity, (iii) the secondary “racemic” cycle of the aminohydroxylation reaction, (iv) the synthesis of amino acid-based ligands for the osmium-catalysed aminohydroxylation reaction using preformed nitrogen sources, (v) an evaluation of amino acid based-ligand in the aminohydroxylation reaction, and (vi) conclusions and future work.

3.1 Introduction

Underlining what has been reviewed in the previous chapter, the aminohydroxylation reaction catalysed by osmium has opened new pathways to transform commercially available olefin substrates into important amino alcohol products.^{5,64,103-106} Since this method was invented in 1975 by Sharpless and coworkers²⁷ as a non-asymmetric oxyamination, it has undergone significant development including the introduction of the asymmetric aminohydroxylation reported in 1996.^{2,3} The progress of development of oxyamination chemistry has been recently reviewed.^{24,41,43,73,101,102}

In 2002, Sharpless and coworkers¹⁰² reported that the asymmetric aminohydroxylation (AA) reaction had some limitations in terms of generality and reliability, including problems relating to (i) low selectivity such as regio-, chemo- and enantio-selectivity, (ii) low substrate scope, and (iii) poor catalyst activity. These problems were highlighted by O'Brien in 1999,⁷² and also by Nilov and Reiser in 2002.⁷³

The reaction mechanism and the nature of some of these limitations will be discussed in this chapter including (i) a brief description of the mechanism of the AA reaction and control of the enantioselectivity, (ii) a brief review of the aminohydroxylation in the secondary "racemic" cycle and associated ligand development, and finally (iii) the development of amino acid-based ligands for application with the preformed nitrogen sources conducted as part of this work will be described and discussed.

3.2 Mechanism of the AA reaction and enantioselectivity

In the previous chapter (section 1.2 and 1.3) the proposed mechanism of the catalytic asymmetric aminohydroxylation (AA) reaction³ has been discussed. This mechanism is closely correlated to that of the asymmetric dihydroxylation (AD) reaction which had already been well studied.^{13,14} The success in controlling the enantioselectivity of the AD reaction by applying chiral cinchona alkaloid ligands also has parallels in the AA reaction, but with additional issue of regioselectivity in the AA reaction of unsymmetric-alkene as substrates.

In the AA reaction, two catalytic cycles have been proposed leading to the formation of amino alcohol products.^{5,102} First, the primary cycle is proposed to afford the amino alcohol product with high enantioselectivity (**Figure 3.1**). Achieving a high

enantioselectivity means ensuring the reaction undergoes only in the primary catalytic cycle where the ligand has an important role of governing the enantioselectivity of the reaction.^{3,13,107} Many factors are involved in controlling the enantioselectivity of the reaction such as accelerating the hydrolysis of imido-osmium-glycolate complex **15**,¹⁰² the electronic properties of the substrates,^{108,109} and the pH of the reaction.^{96,97,99,100}

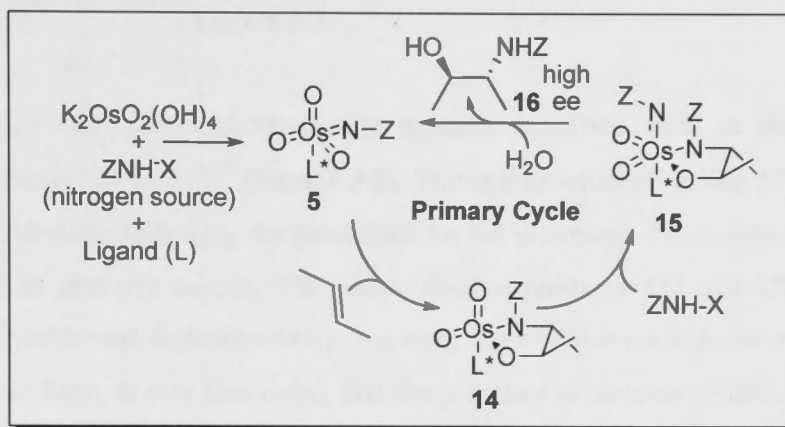


Figure 3.1

The secondary catalytic cycle is proposed to give the amino alcohol products with low enantioselectivity. It is also known as a ligand-free reaction or racemic aminohydroxylation reaction.¹² In some reports, addition of cinchona alkaloid ligands in large excess did not affect the enantioselectivity of induction.^{9,12} The next section will give a detailed discussion of the secondary cycle of the aminohydroxylation reaction.

3.3 The secondary “racemic” cycle of the aminohydroxylation reaction

Results in the previous chapter showed that the preformed nitrogen sources worked under mildly acidic conditions, and the amino alcohol product was afforded in high yield, but with low enantioselectivity in the presence of cinchona alkaloid-based ligands. Moreover, efforts to control the pH of the reaction to that used in the standard Sharpless AA reaction resulted in no amino alcohol product. It was assumed that the reaction at low pH was a ligand-independent reaction. Looking at the proposed aminohydroxylation mechanism (**Figure 1.3**) reported by Reddy and coworkers¹⁷ the reaction may proceed in the catalytic cycle [C], also known as the secondary catalytic cycle of the aminohydroxylation reaction in some reports.^{5,7,26}

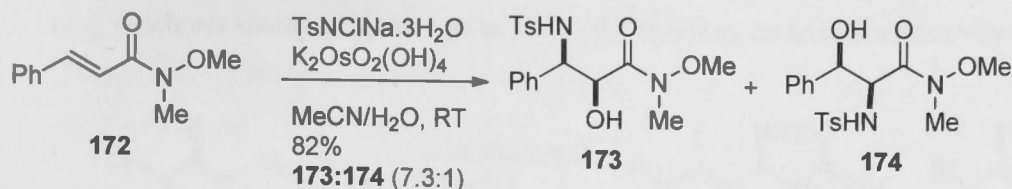


Figure 3.2

The secondary cycle has been proposed to operate in some reactions, such as that reported by Rubin and Sharpless in 1997⁹ (**Figure 3.2**). The α,β -unsaturated amide **172** had been employed as substrate following the procedure for the Sharpless AA reaction³ using chloramine-T **41** as nitrogen source. The amino alcohol products **173** and **174** were afforded in good yields and regioselectivity, but both the regioisomeric products were afforded in racemic form. It was also noted that the presence or absence of chiral cinchona alkaloid ligands gave similar reactivity.

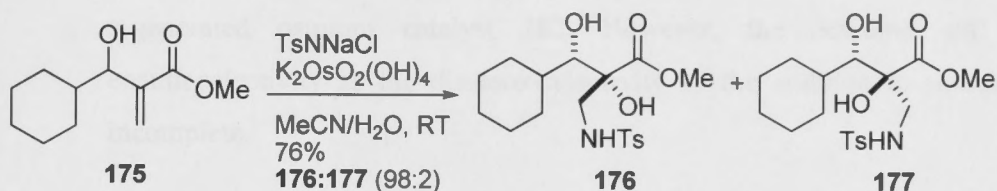


Figure 3.3

Pringle and Sharpless¹¹ also reported similar racemic products when using Bayliss-Hillman olefins **175** (**Figure 3.3**). The reaction was conducted using chloramine-T **41** as nitrogen source and proceeded smoothly to afford products **176** and **177** in high yield and diastereoselectivity (*anti/syn* = 98:2). On the addition of chiral cinchona alkaloid ligands, neither the yield, reaction rate, stereoselectivity was affected.

Finally, a report by Fokin and Sharpless¹² in 2001 employed α,β -unsaturated carboxylic acids **178** as substrates (**Figure 3.4**). The reaction was performed using chloramine-T **41** as nitrogen source with only water used as solvent, and the addition of sodium hydrogen carbonate in excess. The reaction was observed to be ligand-independent, and only

racemic products **179** and **180** were isolated. Even when a large excess of chiral-cinchona alkaloid ligand was added to the reaction, no enantioselectivity was observed.

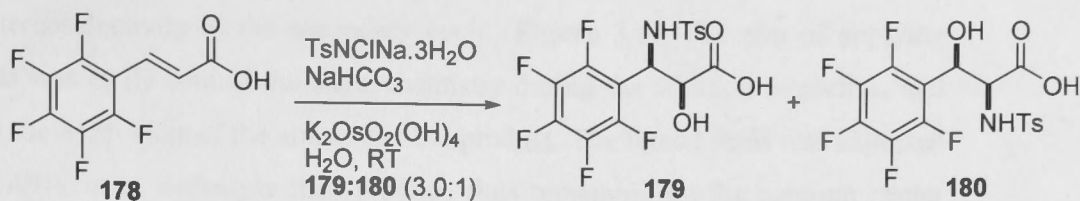


Figure 3.4

Recently, Muniz¹¹⁰ reported self-replication as a strategy to overcome the poor enantioselectivity of the secondary cycle (Figure 3.5). Compound **181** was reacted with an osmium(VI) species and sodium carbonate, and then further oxidized with chloramine-T **41** to form osmium(VIII) azaglycolate complex **182**. Sodium acrylate **183** and chloramine-T **41** were reacted with compound **182** to afford osmium(VIII) bisazaglycolate complex **184**. Hydrolysis of **184** provided amino alcohol **181** and regenerated osmium catalyst **182**. However, the outcome still afforded low enantioselectivity as the diastereoselectivity of the addition to sodium acrylate was incomplete.

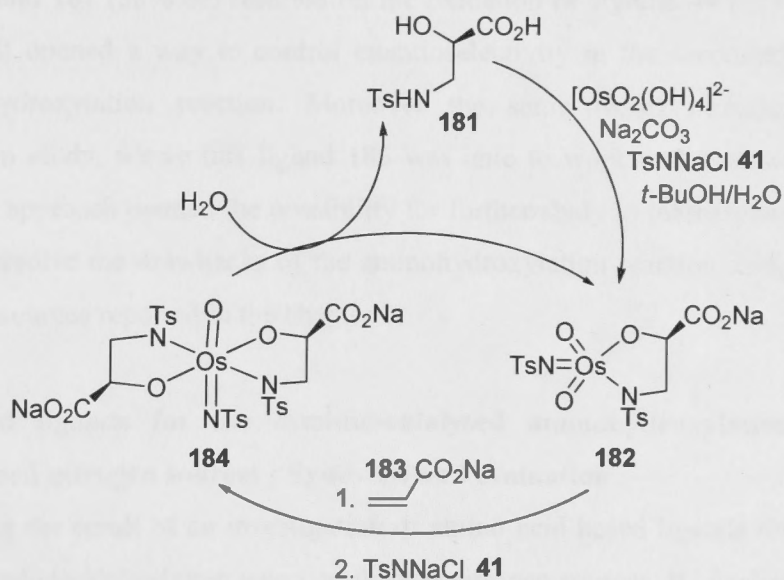


Figure 3.5

Another approach to controlling enantioselectivity in the secondary cycle was reported by Anderson et al.¹⁰² Hydroxyamino acid ligands such as compound **185** were applied to induce stereoselectivity in the secondary cycle (**Figure 3.6**). The aim of applying these ligands was to (i) control the stereochemistry during the addition to olefins, and (ii) promote the hydrolysis of the amino alcohol product. The ligand itself was expected to be more difficult to hydrolyse than product, thus remaining on the osmium center during the course of the reaction.

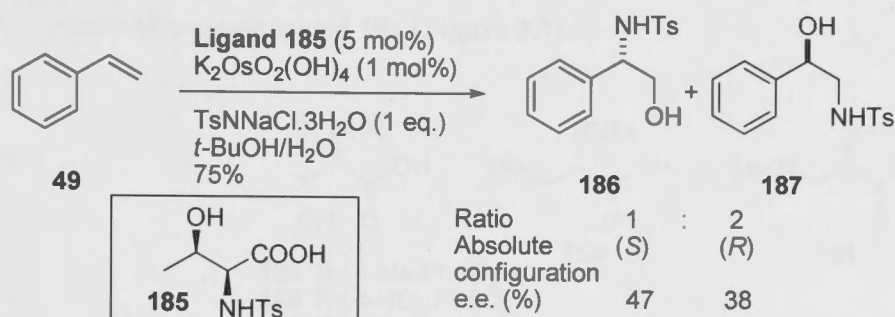


Figure 3.6

As shown in **Figure 3.6**, two regioisomers of enantiomerically enriched amino alcohol product **186** (47% ee) and **187** (38% ee) resulted on the oxidation of styrene **49** (75% conversion). This result opened a way to control enantioselectivity in the secondary cycle of the aminohydroxylation reaction. Moreover the same report included dihydroxylation reaction study, where this ligand **185** was able to work under acidic conditions (pH 5). This approach opened the possibility for further study to increase the enantioselectivity and resolve the drawbacks of the aminohydroxylation reaction using the preformed nitrogen sources reported in the chapter 2.

3.4 Amino acid-based ligands for the osmium-catalysed aminohydroxylation reaction using preformed nitrogen sources : Synthesis and evaluation

This section will present the result of an investigation of amino acid-based ligands for the osmium-catalysed aminohydroxylation using preformed nitrogen sources. It consists of (i) the synthesis of five amino acid based ligands, (ii) evaluation of the ligands in the aminohydroxylation reaction catalysed by osmium following procedure of Anderson et

al.,¹⁰² and (iii) evaluation of amino acid based ligand using preformed nitrogen sources reported in chapter 2.

3.4.1 Synthesis of amino acid-based ligands

Five amino acid based ligands were investigated in the current study. They consisted of; three ligands derived from *L*-threonine **192** i.e. *N*-(4-toluenesulfonyl)-*L*-threonine **185**, *N*-(4-nitrophenylsulfonyl)-*L*-threonine **188**, and *N*-(4-methoxyphenylsulfonyl)-*L*-threonine **189**; one ligand was derived from *L*-serine i.e. *N*-(4-toluenesulfonyl)-*L*-serine **190**; and one ligand was derived from a diamino acid i.e. (*R*)-*N,N'*-bis(4-toluenesulfonyl)propanoic acid **191** (Figure 3.7).

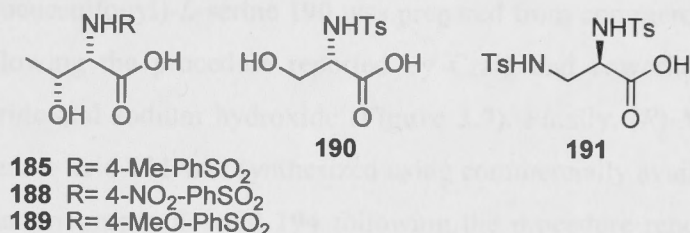


Figure 3.7

N-(4-Toluenesulfonyl)-(*L*)-threonine **185** as a ligand had been reported by Anderson et al.¹⁰² The synthesis of other *L*-threonine derived ligands was conducted from commercially available *L*-threonine **192** as shown in Figure 3.8.

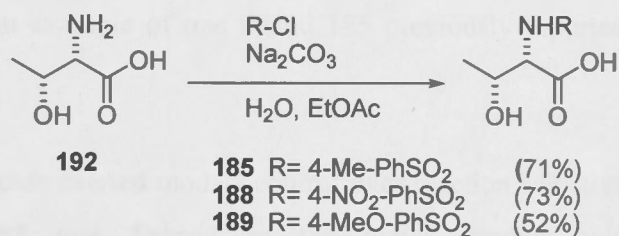


Figure 3.8

N-(4-Toluenesulfonyl)-*L*-threonine **185** was afforded in high yield (71%) by reaction of *L*-threonine with toluenesulfonyl chloride under basic conditions, following the procedure reported by Roemmele and Rapoport.¹¹¹ The other *L*-threonine derived

ligands **188** and **189** were afforded by similar procedures, and were isolated in good yields.

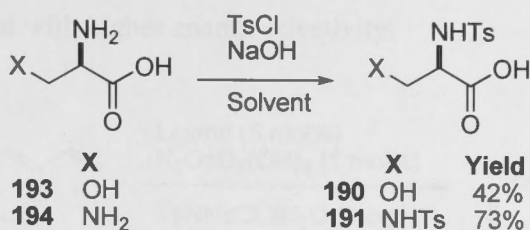


Figure 3.9

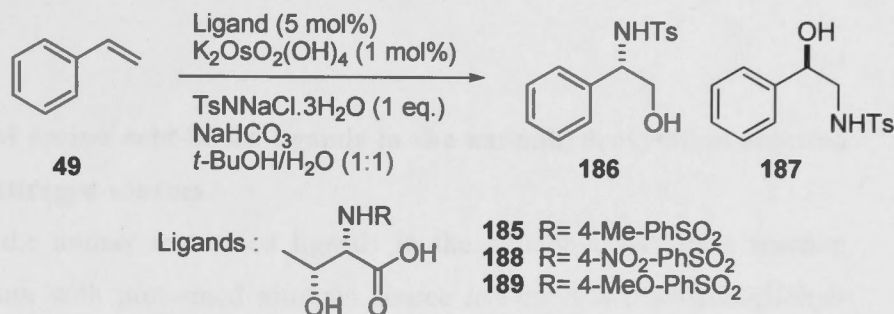
In similar manner, *N*-(4-toluenesulfonyl)-*L*-serine **190** was prepared from commercially available *L*-serine **193** following the procedure reported by Craig and coworkers¹¹² using toluenesulfonyl chloride and sodium hydroxide (**Figure 3.9**). Finally, (*R*)-*N,N'*-bis(4-toluenesulfonyl)propanoic acid **191** was synthesized using commercially available starting material (*R*)-2,3-diaminopropanoic acid **194** following the procedure reported by Bridger and coworkers (1996)¹¹³ using toluenesulfonyl chloride and sodium hydroxide.

3.4.2 Evaluation of *L*-threonine-derived ligands

To evaluate stereoselectivity of these ligands, the *L*-threonine-derived ligands were selected and evaluated following the procedure reported by Anderson et al.,¹⁰² using chloramine-T **41** as nitrogen source and styrene **49** as substrate. The results are reported in **Figure 3.10** and include an example of one ligand **185** previously reported in the literature.¹⁰²

The (*L*)-threonine derived ligands exerted modest control over reaction selectivity. The terminal amino product **187** was formed as the major product with low enantioselectivity. The minor terminal alcohol **186** was formed with higher, but still moderate enantioselectivity. The overall yield of products was moderate to low. In addition, the electron withdrawing and donating substituent on the ligands did not significantly affect the reaction yield or selectivity.

Compared to the literature,¹⁰² the *L*-threonine-derived ligand **185** afforded similar selectivity and yield. The terminal amino isomer **187** was the major product with low enantioselectivity. In contrast, the terminal alcohol **186** was provided as the minor product but with higher enantioselectivity.



Entry	Ligand	Yield (%)	Ratio (%) ^a 186 : 187	e.e. (%) ^b		Time
				(<i>S</i>)-186	(<i>R</i>)-187	
1	185	64	1 : 2.7	59	48	25 h
2 ^c	185	75 ^d	1 : 2.0	47	38	20 h
3	188	34	1 : 2.8	63	25	57 h
4	189	27	1 : 1.9	63	40	24 h

^aRegioisomer ratio was determined by integration of the ¹H-NMR spectrum; ^be.e. was calculated from peak area ratio determined by HPLC for each regioisomer; ^cLiterature result from Anderson et al.;¹⁰² ^dPercentage conversion.

Figure 3.10

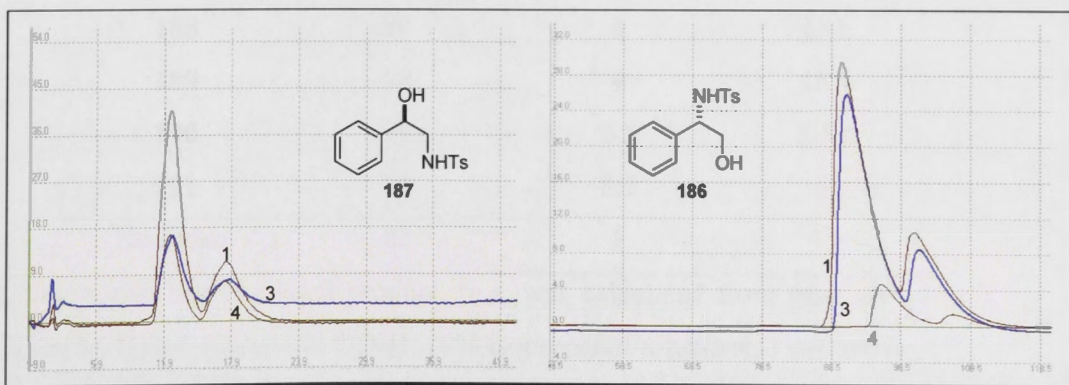
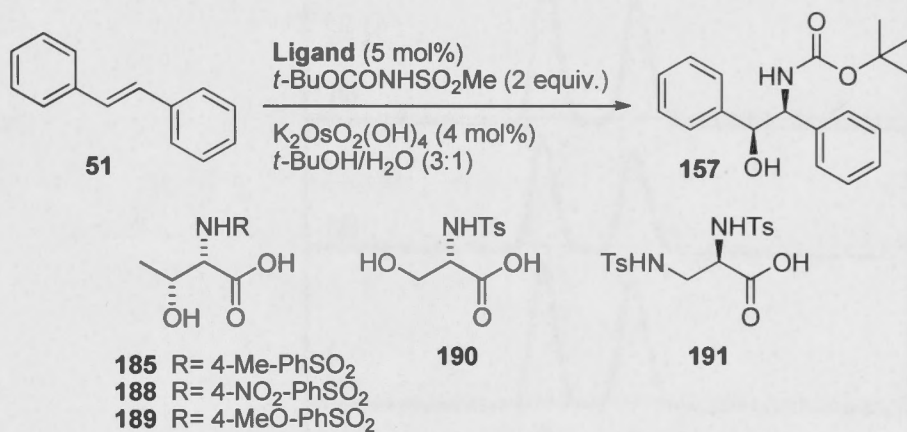


Figure 3.11

Figure 3.11 presents the chromatograms analysed by HPLC of the major product **187** (Chiralcel AS 5 μm , 30% isopropanol/*n*-hexane, 1.5 mL/min) and minor product **186** (Chiralcel OD-H 5 μm , 5% isopropanol/*n*-hexane, 0.6 mL/min). Numbering denotes a sample resulted from entries with ligand **185** (1), **188** (3), and **189** (4), with the absolute stereochemistry for each regioisomer was determined by comparison with literature retention times.¹⁰²

3.4.3 Evaluation of amino acid-based ligands in the aminohydroxylation reaction using preformed nitrogen sources

An evaluation of the amino acid-based ligands in the aminohydroxylation reaction catalysed by osmium with preformed nitrogen source *tert*-butyl *N*-(methanesulfonyl-oxy)carbamate **151** is presented in **Figure 3.12** and **3.13**.



Entry	Ligand	Yield (%) ^a	e.e. (%) ^b	Time
1	185	79	0	4 h
2	188	80	4	18 h
3	189	78	4	18 h
4	190	79	0.5	3.5 h
5	191	80	0.1	18 h
6	No ligand	82	1	4 h

^aYield was determined from isolated product. ^be.e. was calculated from peak area ratio determined by HPLC (Chiralcel OD-H, 10% isopropanol/*n*-hexane, 1 mL/min).

Figure 3.12

The reactions were conducted following the optimised aminohydroxylation procedure developed in the chapter 2. *trans*-Stilbene **51** (1.0 equiv.) was employed as substrate together with the amino acid-based ligands (5.0 mol%), potassium osmate dihydrate (4.0 mol%), and *tert*-butyl *N*-(methanesulfonyloxy)carbamate **151** (2.0 equiv.) as nitrogen source. In addition to this, one reaction was set up as a comparison using similar conditions but without the addition of a ligand.

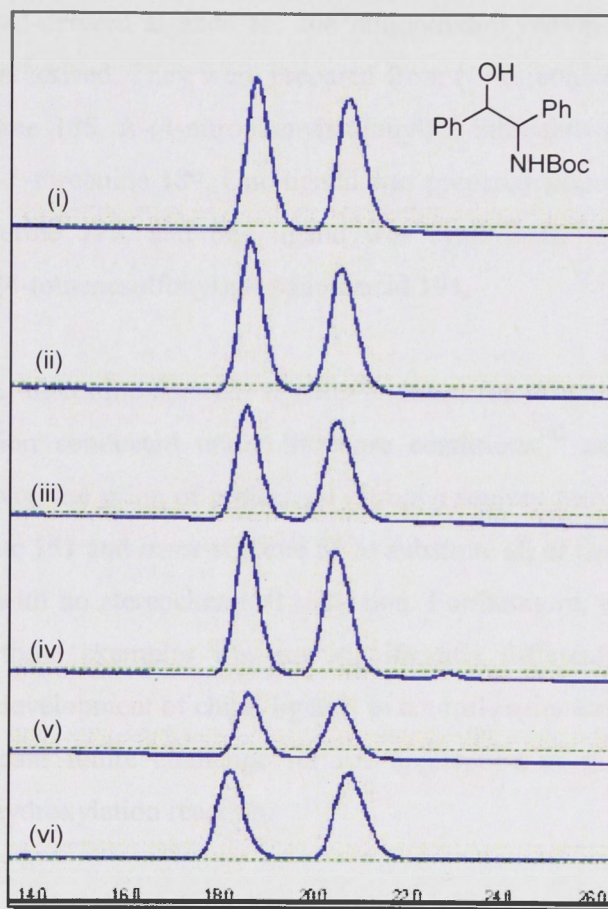


Figure 3.13 Chromatogram HPLC of product **157** (Reaction with ligand **185** (i), **188** (ii), **189** (iii), **190** (iv), **191** (v) and no ligand (vi). Conditions : Chiralcel OD-H 10% isopropanol/*n*-hexane, 1.0 mL/min)

In general, all the evaluation reactions gave high yields, both with and without the presence of ligand (78 to 82 %). These results were similar to those previously observed for the reaction of this preformed nitrogen source with *trans*-stilbene **51**. No diol

product was detected, and no significant enantioselectivity was observed under these conditions. Reactions conducted using ligand **185** and **190** gave similar reaction rate to that without a ligand with the reaction completed in 4 h. In contrast, reactions conducted using ligands **188**, **189**, and **191** were apparently slower. This indicated a possible decelerating effect of these ligands. Application of these amino acid-based ligands in the osmium-catalysed aminohydroxylation reaction was not further explored.

3.5 Conclusions and future work

In conclusion, five amino acid-derived ligands for the aminohydroxylation reaction catalysed by osmium were synthesised. They were prepared from (*L*)-threonine, i.e. *N*-(4-toluenesulfonyl)-(*L*)-threonine **185**, *N*-(4-nitrophenylsulfonyl)-*L*-threonine **188**, and *N*-(4-methoxyphenylsulfonyl)-*L*-threonine **189**. One ligand was prepared from *L*-serine i.e. *N*-(4-toluenesulfonyl)-*L*-serine **190**, and one ligand was synthesised from 2,3-diamino acid i.e. (*R*)-*N,N'*-bis(4-toluenesulfonyl)propanoic acid **191**.

The three derivatives of (*L*)-threonine-derived ligands induced moderate to low stereoselectivity in the reaction conducted under literature conditions¹⁰² and using styrene **49** as substrate. However, the using of preformed nitrogen sources *tert*-butyl *N*-(methanesulfonyloxy)carbamate **151** and *trans*-stilbene **51** as substrate all of the ligands provided excellent yield but with no stereochemical induction. Furthermore, the yield and selectivity observed in these examples was not significantly different to that observed without ligand. The development of chiral ligands to control regio- and stereoselectivity provides a significant future challenge for the application of preformed nitrogen sources in the aminohydroxylation reaction.

Even though the amino acid-derived ligands did not resolve the problem of stereoselectivity in the secondary cycle when using preformed nitrogen sources, investigation of broader variation of the preformed nitrogen sources with greater base stability and exploring substrate scope of these reagents will improve the knowledge of the aminohydroxylation reaction catalysed by osmium.

Chapter 4

Alkyl N-(4-Toluenesulfonyloxy)- Carbamates as Second Generation Preformed Nitrogen Sources for the Osmium-Catalysed Aminohydroxylation Reaction : Synthesis, Optimisation and Scope

Summary

This chapter describes the application of the alkyl N-(4-toluenesulfonyloxy) carbamates as second generation preformed nitrogen sources for the osmium-catalysed aminohydroxylation reaction. This includes (i) an introduction to N-(4-toluenesulfonyloxy)carbamate reagents, (ii) the synthesis of N-(4-toluenesulfonyloxy)carbamates as preformed nitrogen sources, (iii) an evaluation of alkyl N-(4-toluenesulfonyloxy)carbamates as preformed nitrogen sources in the osmium-catalysed aminohydroxylation reaction, (iv) a study of the stereoselectivity of the reaction, (v) a substrate scope study, and (vi) conclusions and future work.

4.1 Introduction

To summarize previous results, the first generation preformed nitrogen sources based on *tert*-butyl carbamate gave aminohydroxylation reactions in excellent yield (chapter 2). However, the use of chiral cinchona alkaloid ligands failed to induce stereoselectivity, and the low stereoselectivity was believed to arise as the preformed nitrogen sources only worked under acidic conditions. In contrast, the Sharpless AA reaction occurs under more basic conditions.^{2,3,114} Attempts to increase the pH of the reaction resulted in decomposition of the preformed nitrogen sources. The application of amino acid-based ligands which were expected work under more acidic reactions also failed to induce stereoselectivity (chapter 3).

The goal of this chapter was to generate a second generation of preformed nitrogen sources, with greater stability to basic reaction conditions. It was hoped that these new base stable nitrogen sources could be employed in the AA reaction. This chapter contains : (i) a brief review of *N*-(4-toluenesulfonyloxy)carbamate reagents, (ii) the synthesis of alkyl *N*-(4-toluenesulfonyloxy)carbamates as preformed nitrogen sources, (iii) the evaluation and optimisation of *N*-(4-toluenesulfonyloxy)carbamate derivatives as preformed nitrogen sources for the osmium-catalysed aminohydroxylation reaction, and (iv) a study of the scope of the osmium-catalysed aminohydroxylation reaction employing these second generation nitrogen sources.

4.2 *N*-(4-Toluenesulfonyloxy)carbamate reagents

In 2007, Huard and Lebel^{115,116} reported that *N*-(4-toluenesulfonyloxy)carbamate reagents could be used for C-H amination reactions catalysed by a rhodium (II) dimer complex. This reaction works under basic conditions and requires three equivalents of an inorganic base such as potassium carbonate. The resulting product was a carbamate-protected amine with potassium tosylate as a byproduct. For example 2,2,2-trichloroethyl *N*-(4-toluenesulfonyloxy)carbamate **203** reacted with cyclohexane **195** (5 equiv.), catalysed by [Rh₂(tpa)₄] (0.06 equiv.) to afford carbamate **196** in 80% yield (Figure 4.1).

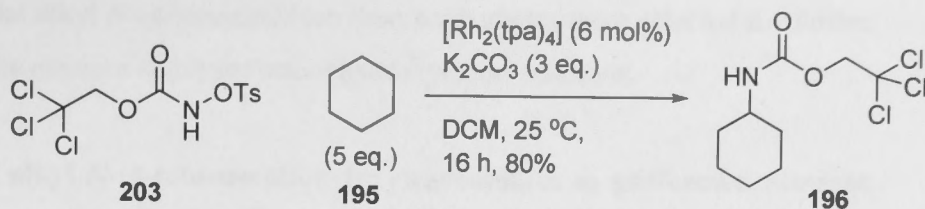


Figure 4.1

The reaction occurs through a metal-nitrene intermediate that was generated from *N*-(4-toluenesulfonyloxy)carbamate in the presence of rhodium dimer complex under basic conditions. Similar reagents were also applied in the intramolecular alkene-aziridination reactions of substrate **197** and **199** catalysed by rhodium⁸⁷ and copper,^{117,118} to give aziridine product **198** and **200**, respectively (**Figure 4.2**).

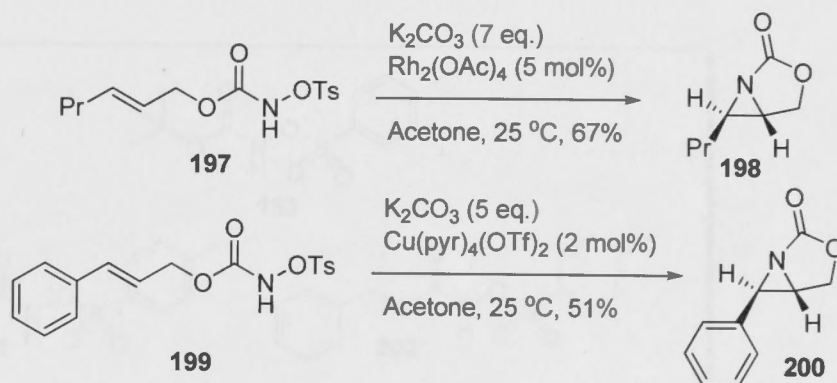


Figure 4.2

All these discoveries suggested *N*-(4-toluenesulfonyloxy)carbamates as a suitable second generation preformed nitrogen source for the aminohydroxylation reaction catalysed by osmium which would be able to work under basic conditions.

For the first generation of preformed nitrogen sources (chapter 2), three similar arylsulfonyloxy preformed nitrogen sources were evaluated. They were *tert*-butyl *N*-(mesitylsulfonyloxy)carbamate **152**, *tert*-butyl *N*-(4-toluenesulfonyloxy)carbamate **153**, and *tert*-butyl *N*-(4-nitrophenylsulfonyloxy)carbamate **154**. Giving consideration to the ease of access from commercial starting materials, simple purification from byproducts,

and stability,¹¹⁵ the alkyl *N*-(4-toluenesulfonyloxy)carbamates were selected for further investigation in the osmium-catalysed aminohydroxylation reactions.

4.3 Synthesis of alkyl *N*-(4-toluenesulfonyloxy)carbamates as preformed nitrogen sources for the osmium-catalysed aminohydroxylation reaction

Five derivatives of the *N*-(4-toluenesulfonyloxy)carbamates were proposed as second generation preformed nitrogen sources (**Figure 4.3**). The structures consist of two parts. First of these was the alkyl carbamate or *N*-protecting group. This was selected to afford common amine-protecting groups,^{78,119} and also provide variation in electronic and steric properties. They were *tert*-butyl **153**,^{89,120} ethyl **201**,¹²¹ benzyl **202**,^{116,120} 2,2,2-trichloroethyl **203**,¹¹⁶ and 2-(trimethylsilyl)ethyl **204** carbamates. Second was the leaving group part, which was comprised of a *N*-(4-toluenesulfonyloxy) unit. During the aminohydroxylation reaction, this leaving group is released as toluenesulfonic acid.

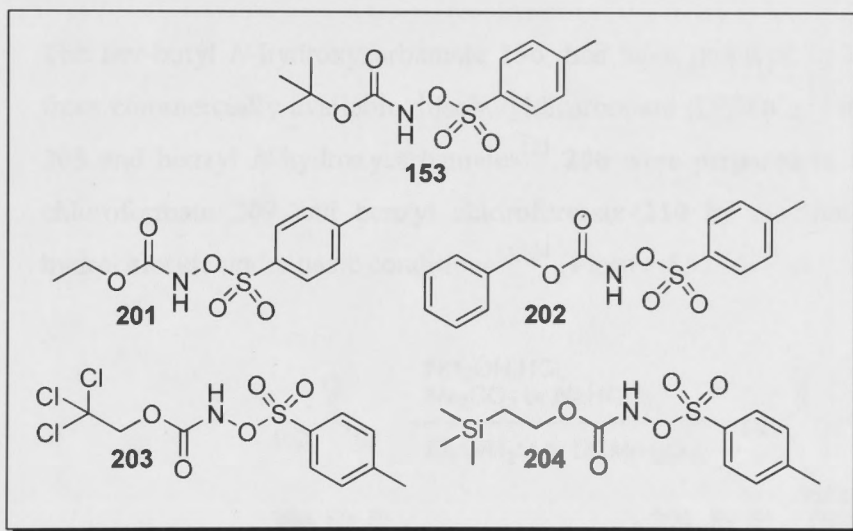


Figure 4.3

To synthesise these preformed nitrogen sources, two step sequence was followed: first, the synthesis of the alkyl *N*-hydroxycarbamate compound; and second, tosylation of the alkyl *N*-hydroxycarbamate.

4.3.1 Synthesis of alkyl *N*-hydroxycarbamates

The alkyl *N*-hydroxycarbamate precursors for the second generation preformed nitrogen sources are shown in **Figure 4.4**. They were *tert*-butyl *N*-hydroxycarbamate **156**, ethyl *N*-hydroxycarbamate¹²² **205**, benzyl *N*-hydroxycarbamate¹²³ **206**, 2,2,2-trichloroethyl *N*-hydroxycarbamate¹¹⁶ **207**, and 2-(trimethylsilyl)ethyl *N*-hydroxycarbamate **208**.

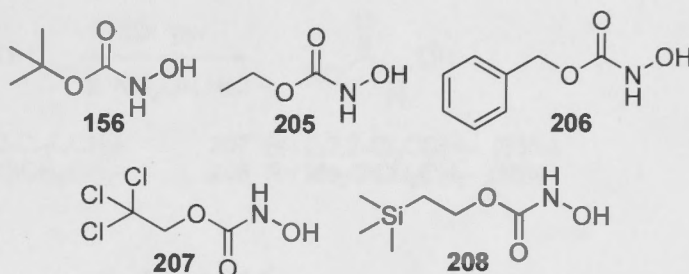


Figure 4.4

The *tert*-butyl *N*-hydroxycarbamate **156**, had been prepared in high yield (chapter 2) from commercially available diisobutyldicarbonate (DIBOC),⁸³ meanwhile the ethyl¹²² **205** and benzyl *N*-hydroxycarbamates¹²³ **206** were prepared in high yield from ethyl chloroformate **209** and benzyl chloroformate **210** by reaction with hydroxylamine hydrochloride under basic conditions^{83,124} (**Figure 4.5**).

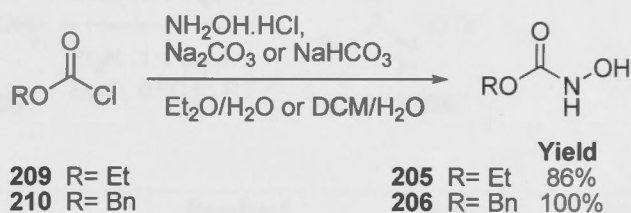


Figure 4.5

The 2,2,2-trichloroethyl *N*-hydroxycarbamate¹¹⁶ **207** and 2-(trimethylsilyl)ethyl *N*-hydroxycarbamate **208** were synthesised from the corresponding alcohol 2,2,2-trichloroethanol **211** and 2-(trimethylsilyl)ethanol **212** following the procedure reported by Donohoe and coworkers.¹²⁵ The alcohol **211** and **212** underwent carbonylation using 1,1'-carbonyldiimidazole (CDI), and then reacted with hydroxylamine hydrochloride to afford 2,2,2-trichloroethyl *N*-hydroxycarbamate **207** and 2-(trimethylsilyl)ethyl *N*-

hydroxycarbamate **208** in moderate yield (**Figure 4.6**). In addition, 2,2,2-trichloroethyl *N*-hydroxycarbamate **207** could also be prepared in high yield using commercially available succinimidyl 2,2,2-trichloroethyl carbonate and hydroxylamine hydrochloride under basic conditions.¹²⁵ With all of alkyl *N*-hydroxycarbamates **156**, **205-208** in hand, the tosylation reaction using toluenesulfonyl chloride could be performed.

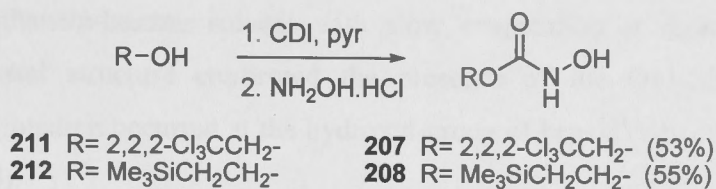
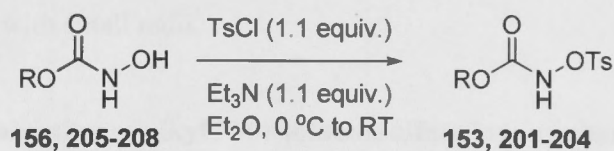


Figure 4.6

4.3.2 Tosylation of alkyl *N*-hydroxycarbamates

The tosylation reaction^{116,121,126} of all *N*-hydroxycarbamates was achieved under similar conditions. A solution of *N*-hydroxycarbamate was added to toluenesulfonyl chloride, and then triethylamine as a base was added at 0 °C. Formation of a suspension of triethyl-ammonium chloride indicated the reaction had occurred. The results of this process are presented in **Figure 4.7**.



Entry	R	Product	Yield	Time
1	<i>t</i> -Bu	153	71%	6 h
2	Et	201	72%	2 h
3	Bn	202	46%	2.5 h
4	2,2,2-trichloroethyl	203	78%	19 h
5	2-trimethylsilylethyl	204	76%	20 h

Figure 4.7

In general, the reaction of alkyl *N*-hydroxycarbamates **156**, **205-208** with toluenesulfonyl chloride afforded the products in moderate to high yield. Benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** was synthesised in moderate yield (46%), meanwhile *tert*-butyl **153**, ethyl **201**, 2,2,2-trichloroethyl **203**, and 2-(trimethylsilyl)-ethyl **204** *N*-(4-toluenesulfonyloxy)carbamates were afforded in high yield (71-78%). Benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** could be crystallised from dichloromethane/*n*-hexane solvent with slow evaporation at room temperature. The X-ray crystal structure confirmed the presence of the O11-S20 bond, which indicates sulfonation occurred at the hydroxyl-group of benzyl *N*-hydroxycarbamate **206** (Figure 4.8).

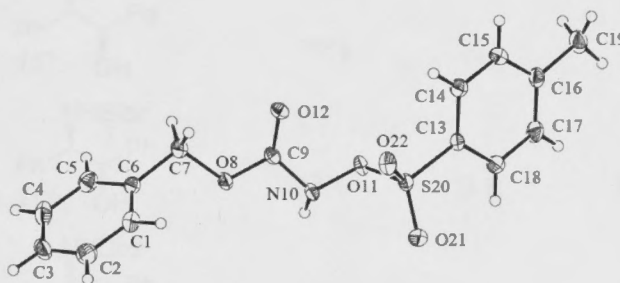


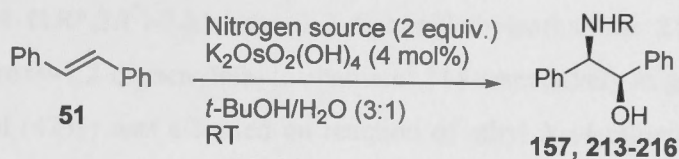
Figure 4.8 Structure of $C_{15}H_{15}NO_5S$ with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

4.4 Evaluation of alkyl *N*-(4-toluenesulfonyloxy)carbamates as preformed nitrogen sources

The aminohydroxylation of *trans*-stilbene **51** using *tert*-butyl *N*-(4-toluenesulfonyloxy)-carbamate **153** had previously been completed in chapter 2. Two points were noted from this study; (i) it was observed that the pH of the reaction was lowered to around 3, and (ii) the cinchona alkaloid ligand (DHQD)₂PHAL did not significantly induce stereoselectivity. It was believed that racemic product occurred due to the low pH as under these conditions the ligand was likely protonated. At the outset of this evaluation, the reactions were conducted without cinchona alkaloid ligands.

Figure 4.9 shows the results for the osmium-catalysed aminohydroxylation reaction with *N*-(4-toluenesulfonyloxy)carbamate-derived preformed nitrogen sources. Reactions

were conducted using *trans*-stilbene **51** as substrate alkene (1.0 equiv.), potassium osmate dihydrate catalyst (4.0 mol%), preformed nitrogen source (2.0 equiv.) and *tert*-butanol/water (3:1) solvent at room temperature.



Entry	Nitrogen source	Product	Yield	Time	pH _{obs}
1	153	 157	78%	20 h	~4
2	201	 213	42%	3 h	3-4
3	202	 214	61%	5 h	~3
4	203	 215	80%	6 h	~3
5	204	 216	50%	24 h	~3

Note: Boc = *tert*-butoxy carbonyl, Etoc = ethoxy carbonyl, Cbz = benzyloxy carbonyl, Troc = 2,2,2-trichloroethoxy carbonyl, and Teoc = 2-(trimethylsilyl)ethoxy carbonyl.

Figure 4.9

All of the *N*-(4-toluenesulfonyloxy)carbamate-based preformed nitrogen sources **153**, **201-204** were able to deliver osmium-catalysed aminohydroxylation reaction with *trans*-stilbene **51** to afford amino alcohol products **157**, **213-216**. The highest yield (78-80%) was afforded from *tert*-butyl *N*-(4-toluenesulfonyloxy)carbamate **153** and 2,2,2-trichloroethyl *N*-(4-toluenesulfonyloxy)carbamate **203** by producing *tert*-butyl

(1*R**,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate¹²⁷ **157** and 2,2,2-trichloroethyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate **215**, respectively. Reaction with preformed nitrogen source 2-(trimethylsilyl)ethyl *N*-(4-toluenesulfonyloxy)carbamate **204** and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** afforded 2-(trimethylsilyl)-ethyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate **216** and benzyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate² **214** respectively in good yield (50-61%). A lower yield (42%) was afforded on reaction of ethyl *N*-(4-toluenesulfonyloxy)carbamate **201** to give ethyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate³⁵ **213**.

It was observed that reaction of ethyl **201**, benzyl **202**, and 2,2,2-trichloroethyl **203** *N*-(4-toluenesulfonyloxy)carbamate was rapid compared to the reaction of *tert*-butyl and 2-(trimethylsilyl)ethyl *N*-(4-toluenesulfonyloxy)carbamates **153** and **204**. Furthermore, as the reaction proceeded the pH was observed to decrease to pH 3-4. This occurred as the reaction liberated toluenesulfonic acid as a by-product of the reaction.

4.5 Optimisation of the osmium-catalysed aminohydroxylation reaction

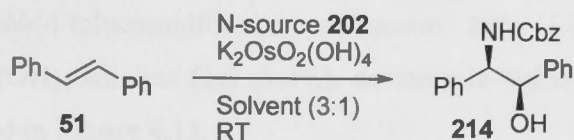
An optimisation study was undertaken using the preformed nitrogen source benzyl *N*-(4-toluenesulfonyloxy)carbamate **202**, and *trans*-stilbene **51**. The influence of solvent system, catalyst and preformed nitrogen source loading, and pH of the reaction was investigated. The main objective was to develop the best reaction conditions for this preformed nitrogen source, and investigate the stability of these reagents to the basic reaction conditions typically employed in the Sharpless AA reaction² procedures.

4.5.1 Optimisation of solvent, catalyst and preformed nitrogen source loading

Solvent optimisation was investigated with *tert*-butanol-water, *n*-propanol-water, acetonitrile-water, and dichloromethane-water using mixture (3:1). The majority of these solvents have been used previously in the aminohydroxylation reaction catalysed by osmium.^{3,27}

Solvent optimisation was conducted using *trans*-stilbene **51** (1.0 equiv.), potassium osmate dihydrate (4.0 mol%), and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (1.2 equiv.) in the indicated solvent system. The reaction gave benzyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate² product **214** in varying yields, with the best yield (80%) afforded in the acetonitrile-water as solvent system. This reaction resulted in clean

conversion with a small amount of preformed nitrogen source **202** still apparent at the end of the reaction. Using the *n*-propanol-water system, the reaction was completed in a similar time, but provided a lower yield. A similar yield was also afforded in solvent *tert*-butanol-water and using two equivalents of preformed nitrogen source **202**. The reaction in a biphasic dichloromethane-water mixture did not work, even after 96 h stirring. Some decomposition of the benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** and a large amount of unreacted *trans*-stilbene **51** was clearly observed by TLC.



Entry	Solvent	Catalyst	Nitrogen source	Yield (%)	Time
1	<i>t</i> -BuOH/H ₂ O	4 mol%	2.0 equiv.	61%	5 h
2	<i>n</i> -PrOH/H ₂ O	4 mol%	1.2 equiv.	62%	17.5 h
3	MeCN/H ₂ O	4 mol%	1.2 equiv.	80%	17 h
4	DCM/H ₂ O	4 mol%	1.2 equiv.	NR ^a	4 d
5	MeCN/H ₂ O	4 mol%	2.0 equiv.	81%	4 h
6	MeCN/H ₂ O	4 mol%	1.0 equiv.	71%	5 h
7	MeCN/H ₂ O	2 mol%	1.0 equiv.	71%	9 h
8	MeCN/H ₂ O	1 mol%	1.0 equiv.	88%	14 h
9	MeCN/H ₂ O	0.1 mol%	1.0 equiv.	55%	4 d

Note: ^aNR, no reaction.

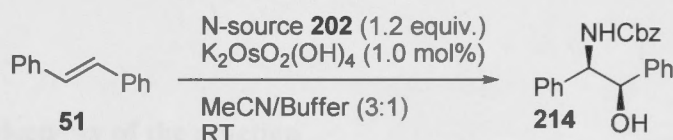
Figure 4.10

Optimisation of the osmium catalyst loading was then undertaken using acetonitrile-water solvent mixture, *trans*-stilbene **51** (1.0 equiv.), and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (1.0 equiv.). It was observed that reducing loading of K₂OsO₂(OH)₄ in the reaction from 4 mol% to 0.1 mol% still afforded benzyl (1*R*^{*},2*R*^{*})-2-hydroxy-1,2-diphenylethylcarbamate² **214** product. However, low loadings resulted in lower yields and increased the reaction times.

In summary the recommended conditions for osmium-catalysed aminohydroxylation reaction included 1.2 equivalents of nitrogen source and 1.0 mol% of osmium catalyst $K_2OsO_2(OH)_4$ in acetonitrile/water solvent mixture. These conditions resulted in smooth conversions, good yields, and few by-products or unreacted starting materials.

4.5.2 Optimisation of the reaction pH

Optimisation of the reaction pH was undertaken using buffer in the pH range from 3 to 11. Reactions were conducted using *trans*-stilbene **51** (1.0 equiv.) as olefin substrate, benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (1.2 equiv.) as nitrogen source, $K_2OsO_2(OH)_4$ catalyst (1.0 mol%), acetonitrile-buffer (3:1). Results of this study are presented in **Figure 4.11**.



Entry	Buffer solution	pH	Yield	Time
1	0.5 M Potassium hydrogen phthalate/NaOH	3 ^a	88%	14 h
2		4	94%	10 h
3		5	88%	10 h
4	0.5 M KH_2PO_4 /NaOH	6	80%	7.5 h
5		7	35%	5 h
6		8 ^a	56%	1.5 h
7	0.5 M Borax/HCl	9 ^a	53%	1.5 h
8	0.5 M Borax/NaOH	10 ^a	16%	5 h
9	0.5 M $NaHCO_3$ /NaOH	11 ^a	20%	5 h

Note: ^aReaction used 1.0 equiv. of preformed nitrogen source **202**.

Figure 4.11

It was observed that the preformed nitrogen source benzyl *N*-(4-toluenesulfonyloxy)-carbamate **202** delivered aminohydroxylation reaction at all pH values. Decreasing yields and reaction times were observed at increasing pH values. Two trends were

evident: the reactions afforded excellent yields under acidic conditions between pH 3 and 6; and under basic conditions (pH above 6), the reaction gave product in low to moderate yield. This decreasing yield appeared to correlate with pH. For example, the reaction at pH 8 gave 56% of product **214**, and this decreased to 16% yield at pH 10. The reactions under basic conditions were also not complete. Residual *trans*-stilbene **51** was observed but little preformed nitrogen source **202** remained suggesting decomposition.

In summary, preformed nitrogen source benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** could deliver reaction in a pH range between 3 and 11. It gave higher yields between pH 3 to 6, and gave an optimum yield at pH 4. Importantly, this preformed nitrogen source **202** also worked under basic conditions. However, it gave lower yields on increasing the basicity of the reaction.

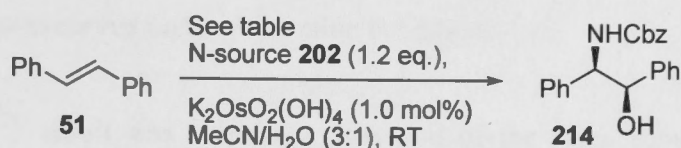
4.6 Evaluating the stereoselectivity of the reaction

The ability of benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** to participate in the osmium-catalysed aminohydroxylation reaction under basic conditions allowed for a further evaluation of ligand control of stereoselectivity. This investigation aimed to assess the stereoselectivity of the osmium-catalysed aminohydroxylation reaction by applying cinchona alkaloid ligand (DHQD)₂PHAL and the preformed nitrogen source benzyl *N*-(4-toluenesulfonyloxy)carbamate **202**. The reaction was conducted under buffered conditions at pH 9 using *trans*-stilbene **51** as substrate. As a comparison, the reaction was also performed without cinchona alkaloid ligand, without buffer, and without both ligand and buffer (**Figure 4.12**).

In general, the reaction afforded product benzyl (1*R*^{*},2*R*^{*})-2-hydroxy-1,2-diphenylethyl carbamate **214** from moderate to high yield. Unfortunately, the reaction also gave low stereoselectivity (2-5%ee). The presence of cinchona alkaloid ligand did not significantly induce stereoselectivity either in buffered or un-buffered reactions.

Two general trends could also be observed. The reactions conducted at pH 9 provided moderate yield and a relatively short reaction time. In addition, residual starting material *trans*-stilbene **51** was observed, decomposition of benzyl *N*-(4-toluenesulfonyloxy)-carbamate **202** was also detected by TLC. Reaction conducted without buffer afforded

amino alcohol product **214** in high yield, but required longer time to complete. In these instances only a small amount of preformed nitrogen source **202** and no *trans*-stilbene **51** could be observed (TLC) at the conclusion of the reaction.



Entry	Ligand ^a	Buffer	Yield	Time	e.e. (%) ^b
1	(DHQD) ₂ PHAL	pH 9	41%	6 h	5
2	(DHQD) ₂ PHAL	NO	93%	24 h	2
3 ^c	NO	pH 9	54%	7 h	4
4	NO	NO	88%	14 h	2

Note : ^aLigand quantity (4.0 mol%). ^bDetermined from HPLC peak area (Chiralpak AS-H, isocratic 20% isopropanol/*n*-hexane, 0.7 mL/min). ^cUsing **202** (2.0 equiv.).

Figure 4.12

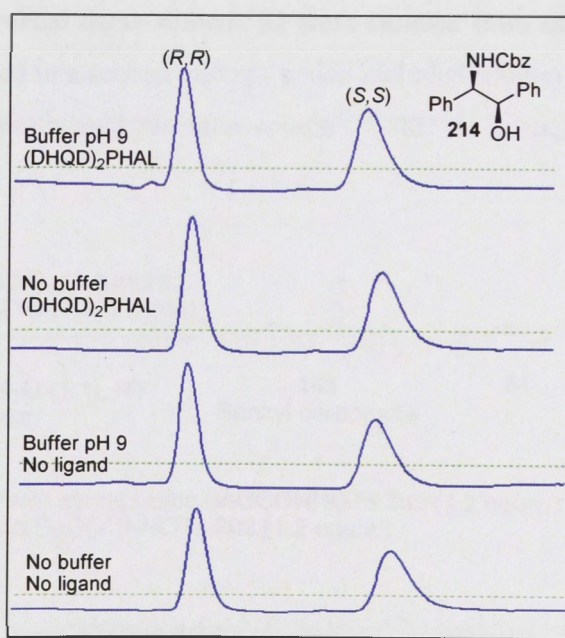


Figure 4.13 HPLC chromatogram of product **214** (Chiralpak AS-H, isocratic 20% isopropanol/*n*-hexane, 0.7 mL/min, (*R,R*)-**214** *t*_R 16.2 min, (*S,S*)-**214** *t*_R 21.6 min)

Figure 4.13 presents the HPLC chromatogram of benzyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethyl carbamate product **214** afforded from the reaction of benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** with *trans*-stilbene **51** in the stereoselectivity study. Similar peak area ratios were observed under all reaction conditions.

This ligand independent^{9,11,12} result was surprising. Reaction of the same substrate, *trans*-stilbene **51** using the standard Sharpless AA reaction² conditions gives excellent enantioselectivity (98%).² Using the preformed nitrogen source **202** under basic conditions to mimic the standard Sharpless AA reaction² still failed to induce stereoselectivity and the resulting product **214** was racemic. In contrast, the reaction worked well at low pH, was more reagent economic, and gave excellent yields.

One final investigation was attempted, conducting the reaction by slow addition of the preformed nitrogen source benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** using a syringe pump. Ligand (DHQD)₂PHAL (5.0 mol%), K₂OsO₂(OH)₄ catalyst (1.0 mol%), sodium hydroxide (2.0 equiv.), and *n*-propanol/water (1:1) solvent was used in the reaction. However, complete decomposition of nitrogen source took place in 3 h. Both benzyl carbamate **145** and unreacted *trans*-stilbene **51** were isolated from the reaction. A similar result was also afforded in a second attempt which included sodium hydroxide (2.0 equiv.) with addition of preformed nitrogen source^{96,97} **202** in a single portion (**Figure 4.14**).

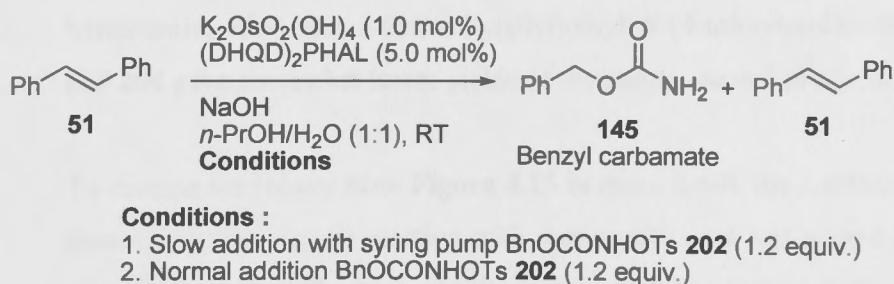


Figure 4.14

With the first generation preformed nitrogen sources (chapter 2), ligand independent reactions were predicted as the reaction only occurred under acidic conditions. This

would sequester the chiral cinchona alkaloid ligand by protonation, which as result, would not induce stereoselectivity. However, with the more base stable preformed nitrogen source benzyl *N*-(4-toluenesulfonyloxy)carbamate **202**, this assumption was not relevant. The application of chiral ligands was expected to induce stereoselectivity under basic conditions. No stereoselectivity was observed, and this may suggest the reaction proceeded through the secondary catalytic cycle (**Figure 1.3, chapter 1**). Despite this limitation, the second generation preformed nitrogen sources were capable of delivering efficient and high-yielding osmium-catalysed aminohydroxylation reactions. Further investigation was devoted to explore the substrate scope for these second generation preformed nitrogen sources.

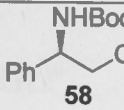
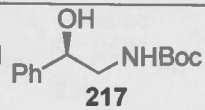
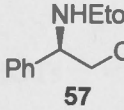
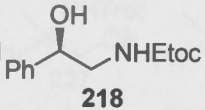
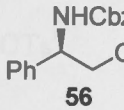
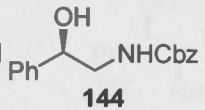
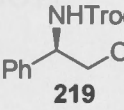
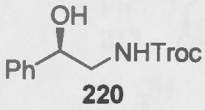
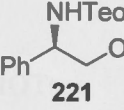
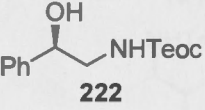
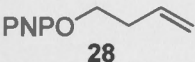
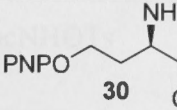
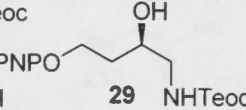
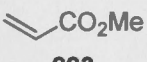
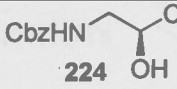
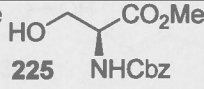
4.7 Substrate scope study

The osmium-catalysed aminohydroxylation reaction was performed on a range of alkenes to assess the influence of substrate steric and electronic properties on yield and regioselectivity. The optimised conditions were employed using alkenes (1.0 equiv.), potassium osmate dihydrate (1.0 mol%), preformed nitrogen sources (1.2 equiv.), and acetonitrile/water (3:1) as solvent mixture. Results are tabulated in **Figure 4.15**.

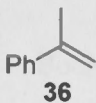
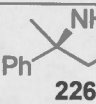
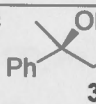
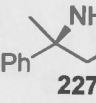
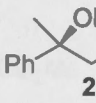
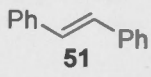
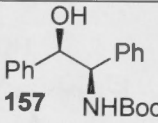
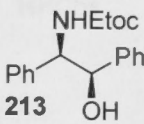
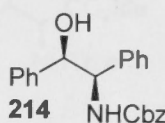
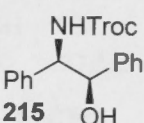
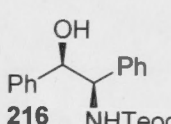
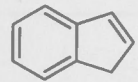
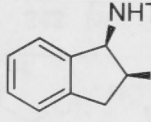
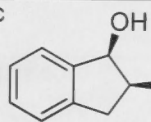
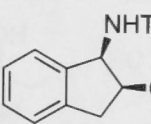
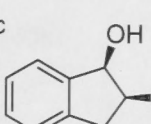
In general, all of the preformed nitrogen sources tested performed the reaction efficiently, especially with mono- and di-substituted alkenes. Reactivity decreased for trisubstituted alkenes. High regioselectivity was observed for terminal and trisubstituted alkenes. In general, the preformed nitrogen sources *tert*-butyl **153**, benzyl **202**, and 2,2,2-trichloroethyl **203** *N*-(4-toluenesulfonyloxy)carbamates gave high yields. Meanwhile, ethyl and 2-(trimethylsilyl)ethyl *N*-(4-toluenesulfonyloxy)carbamates **201** and **204** gave somewhat lower yields of the amino alcohol products.

To discuss the results from **Figure 4.15** in more detail, the reaction will be divided into three categories, i.e. (i) reaction with monosubstituted and related alkenes, (ii) reaction with disubstituted alkenes, and (iii) reaction with trisubstituted alkenes.

Figure 4.15

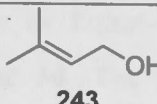
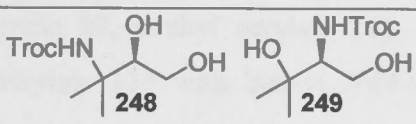
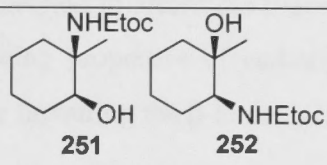
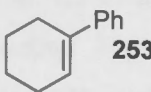
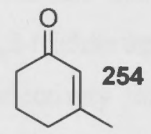
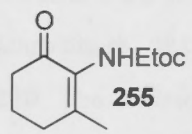
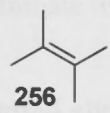
Alkenes	Nitrogen sources ⁱ	Product (A:B)	Yield	Time
 49	BocNHOTs ⁱⁱ	 58  217 (0 : 100)	83%	14 h
	EtocNHOTs	 57  218 (1 : 20)	76%	1 h
	CbzNHOTs	 56  144 (1 : 14.6)	89%	16 h
	TrocNHOTs	 219  220 (1 : 10.3)	100%	22 h
	TeocNHOTs	 221  222 (0 : 100)	39%	12 h
 28	TeocNHOTs	 30  29 (1 : 7.5)	81%	12 h
 223	CbzNHOTs	 224  225 (100 : 0)	68%	24 h

Continued of Figure 4.15

Alkenes	Nitrogen sources ⁱ	Product (A:B)	Yield	Time
 36	BocNHOTs ⁱⁱ	 226  37 (0 : 100)	68%	14 h
	TrocNHOTs	 227  228 (0 : 100)	91%	23 h
 51	BocNHOTs ⁱⁱ	 157	86%	16 h
	EtocNHOTs	 213	42%	1 h
	CbzNHOTs	 214	88%	14 h
	TrocNHOTs	 215	80%	6 h
	TeocNHOTs	 216	50%	24 h
 229	TrocNHOTs	 230  231 (1 : 1.1)	44%	56 h
	TeocNHOTs	 232  233 (1 : 2.1)	71%	22 h

Continued of Figure 4.15

Alkenes	Nitrogen sources ⁱ	Product (A:B)	Yield	Time
<chem>Ph-CH=CH-CO2Me</chem> 122	BocNHOTs ⁱⁱ	<chem>Ph-CH(OH)-CH(NHBoc)-CO2Me</chem> 129 <chem>Ph-CH(OH)-CH(NHBoc)-CO2Me</chem> 234 (1 : 1.6)	65%	16 h
	EtocNHOTs	<chem>Ph-CH(OH)-CH(NHEtOc)-CO2Me</chem> 127 <chem>Ph-CH(OH)-CH(NHEtOc)-CO2Me</chem> 235 (1 : 1.6)	82%	48 h
	CbzNHOTs ⁱⁱⁱ	<chem>Ph-CH(OH)-CH(NHCbz)-CO2Et</chem> 236 <chem>Ph-CH(OH)-CH(NHCbz)-CO2Et</chem> 237 (1 : 1.3)	82%	24 h
	TrocNHOTs	<chem>Ph-CH(OH)-CH(NHTroc)-CO2Me</chem> 238 <chem>Ph-CH(OH)-CH(NHTroc)-CO2Me</chem> 239 (1 : 1.3)	82%	46 h
	TeocNHOTs	<chem>Ph-CH(OH)-CH(NHTeoc)-CO2Me</chem> 240 <chem>Ph-CH(OH)-CH(NHTeoc)-CO2Me</chem> 241 (1 : 1.3)	50%	12 h
<chem>MeO2C-CH=CH-CO2Me</chem> 52	CbzNHOTs	<chem>MeO2C-CH(OH)-CH(NHCbz)-CO2Me</chem> 242	86%	14 h
<chem>Me2C=CH-CH2OH</chem> 243	BocNHOTs ⁱⁱ	<chem>Me2C(OH)-CH(OH)-CH2OH</chem> 244 <chem>Me2C(OH)-CH(OH)-CH2OH</chem> 245 (0 : 100)	64%	98 h
	CbzNHOTs	<chem>Me2C(OH)-CH(OH)-CH2OH</chem> 246 <chem>Me2C(OH)-CH(OH)-CH2OH</chem> 247 (0 : 100)	64%	72 h

Alkenes	Nitrogen sources ⁱ	Product (A:B)	Yield	Time
 243	TrocNHOTs	 248 249	trace	72 h
 250	EtocNHOTs	 251 252 (0 : 100)	74%	14 h
 253	EtocNHOTs	NR	-	-
 254	EtocNHOTs	 255	36%	72 h
 256	BocNHOTs ⁱⁱ	NR ^c	-	-

Note: (i) BocNHOTs = *tert*-butyl *N*-(4-toluenesulfonyloxy)carbamate **153**, EtocNHOTs = ethyl *N*-(4-toluenesulfonyloxy)carbamate **201**, CbzNHOTs = benzyl *N*-(4-toluenesulfonyloxy)carbamate **202**, TrocNHOTs = 2,2,2-trichloroethyl *N*-(4-toluenesulfonyloxy)carbamate **203**, and TeocNHOTs = 2-(trimethylsilyl)ethyl *N*-(4-toluenesulfonyloxy)carbamate **204**. (ii) Reaction with BocNHOTs was conducted with *tert*-butanol/water (3:1). (iii) Reaction with ethyl *trans*-cinnamate.

4.7.1 Monosubstituted and related alkenes

Reaction with monosubstituted alkenes was typified by the reaction with styrene **49**. In general, the reaction was accomplished in short times (below 24 h). The amino alcohol products were afforded in excellent yields, with exception of 2-(trimethylsilyl)ethyl *N*-(4-toluenesulfonyloxy)carbamate **204** which provided low yields.

Furthermore, all tested preformed nitrogen sources gave a strong regioselection by affording terminal amino product. For the reaction of styrene **49** with *tert*-butyl **153** and 2-(trimethylsilyl)ethyl *N*-(4-toluenesulfonyloxy)carbamate **204**, both nitrogen sources

gave a complete regioselection. The remaining preformed nitrogen sources **201-203** gave high regioselectivity (>10:1).

Similar trends were observed for the reaction of other terminal mono- and di-substituted alkenes such as 1-(but-3-enyloxy)-4-nitrobenzene **28**, methyl acrylate **223**, and α -methylstyrene **36**. The reaction of methyl acrylate **223** with benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** gave complete regioselection to afford the β -amino product **224**. This suggested that the electronic withdrawing properties of carbonyl-group in addition to steric effect might exert some influence favouring the β -amino product **224**.

The reaction of 1,1-disubstituted alkene α -methylstyrene **36** with *tert*-butyl **153** and 2,2,2-trichloroethyl *N*-(4-toluenesulfonyloxy)carbamate **203** gave the terminal amine products **37** and **228** with complete regioselectivity. In contrast, the reaction of styrene **49** with 2,2,2-trichloroethyl *N*-(4-toluenesulfonyloxy)carbamate **203** gave high but incomplete selectivity for the terminal amine product **220**. These observations suggest steric effect dominate in controlling the regioselectivity outcome.

4.7.2 Disubstituted alkenes

In general, reaction of symmetrical disubstituted alkenes with *N*-(4-toluenesulfonyloxy) carbamate preformed nitrogen sources afforded amino alcohol products in moderate to high yield, and were accomplished within 24 h. For example, the reaction of *trans*-stilbene **51** with *tert*-butyl **153**, benzyl **202**, and 2,2,2-trichloroethyl *N*-(4-toluenesulfonyloxy)carbamates **203** gave the product in 80-86% yields. Meanwhile, ethyl **201** and 2-(trimethylsilyl)ethyl *N*-(4-toluenesulfonyloxy)carbamates **204** gave somewhat lower yields. One example reaction of preformed nitrogen source benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** with dimethylfumarate **52** also gave high yield of the amino alcohol product **242**.

Furthermore, reaction of unsymmetrical 1,2-disubstituted alkenes 1*H*-indene **229** and methyl or ethyl cinnamate **122** generally afforded low regioselectivity. In the case of cinnamate esters, the α -amino isomer was isolated as the major product (1.3-1.6:1). This suggested that any electronic influence of the carbonyl-group over regioselectivity was modest.

4.7.3 Trisubstituted alkenes

For tri-substituted alkenes, the first reaction was conducted with isopropenol or 3-methylbut-2-en-1-ol **243**. Only two preformed nitrogen sources worked effectively with this alkene, i.e. *tert*-butyl *N*-(4-toluenesulfonyloxy)carbamate **153** and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202**. Both preformed nitrogen sources gave amino alcohol product in moderate yield (64%), with a long reaction time. Interestingly, this was a highly regioselective reaction providing one regioisomer of product **245** and **247**, and no secondary alcohol product **244** and **246** was detected. The reaction with 2,2,2-trichloroethyl *N*-(4-toluenesulfonyloxy)carbamate **203** afforded only traces of amino alcohol product.

Another study was conducted with cyclic tri-substituted alkenes, and the preformed nitrogen source ethyl *N*-(4-toluenesulfonyloxy)carbamate **201**. Reaction with 1-methylcyclohexene **250** afforded a high yield and regioselectivity to afford secondary amine product **252** dominantly. In contrast, no product was observed on reaction with 1-phenylcyclohexene **253**. Thus, it seemed the larger phenyl-group completely blocked the reaction. The presence of a carbonyl-group adjacent to the double bond such as in methylcyclohex-2-en-1-one **254** did not inhibit reaction. One regioisomer of product was produced but in this instance aminohydroxylation was followed by dehydration to afford ethyl 2-methyl-6-oxocyclohex-1-enyl carbamate **255** (36%). Finally, one reaction was attempted with tetrasubstituted alkenes 2,3-dimethylbut-2-ene **256** using preformed nitrogen source *tert*-butyl *N*-(4-toluenesulfonyloxy)carbamate **153**, however no aminohydroxylation reaction occurred.

4.8 Conclusion and future work

The second generation preformed nitrogen sources based on alkyl *N*-(4-toluenesulfonyloxy)carbamates have been investigated in the aminohydroxylation reaction catalysed by osmium. There are five important points that can be concluded in this chapter.

1. Five preformed nitrogen sources for the efficient osmium-catalysed aminohydroxylation reaction have been developed. They consist of *tert*-butyl **153**, ethyl **201**, benzyl **202**, 2,2,2-trichloroethyl **203**, and 2-(trimethylsilyl)ethyl **204** *N*-(4-toluenesulfonyloxy)carbamate.

2. These preformed nitrogen sources especially benzyl *N*-(4-toluenesulfonyloxy)-carbamate **202**, worked under broad range of reaction pH conditions. Performing the reaction in acidic conditions gave excellent yield, but the yield was slightly reduced under basic conditions.
3. Applying the chiral cinchona alkaloid-derived ligand (DHQD)₂PHAL failed to induce enantioselectivity, even under conditions similar to that employed for the Sharpless AA reaction.²
4. A substrate scope study of these preformed nitrogen sources indicates generality in the reactions of various differently substituted alkene substrates. The reagents work efficiently with mono- and di-substituted alkenes, and show decreased reactivity with trisubstituted alkenes.
5. Preformed nitrogen sources provide high yield and regioselectivity with terminal alkenes, high yield and low regioselectivity for unsymmetric 1,2-disubstituted alkenes, and moderate yield with high regioselectivity for trisubstituted alkenes.

The preformed nitrogen sources developed here provide efficient aminohydroxylation reactions and a broad substrate scope. However, application of these preformed nitrogen sources in the osmium-catalysed aminohydroxylation reaction still faces the important limitation of giving ligand-independent reactions. Controlling the reaction to afford high stereoselectivity will be a key aim for further investigation.

In some reports,^{87,115,117} similar structures to these preformed nitrogen sources have been exploited for their reactivity in generating metal nitrenes for C-H amination¹¹⁵ and aziridination.^{87,117} Further investigations for these reagents with different applications in methodology development or natural product synthesis will present other challenges for future work.

Chapter 5

Diastereoselectivity Study of the Osmium-Catalysed Aminohydroxylation Reaction of Allylic Alcohols with Benzyl *N*-(4-Toluenesulfonyloxy)carbamate

Summary

*This chapter presents a study of the diastereoselectivity of the osmium-catalysed aminohydroxylation reaction of allylic alcohol substrates with benzyl *N*-(4-toluenesulfonyloxy)carbamate. This includes (i) an introduction, (ii) the stereochemical induction in the addition reaction to allylic alcohols, (iii) the synthesis of allylic alcohols and derivatives, (iv) a diastereoselectivity study of the osmium-catalysed aminohydroxylation of allylic alcohols, (v) additive and competition reaction study, and (vi) conclusions.*

5.1 Introduction

In the previous substrate scope study, it was shown that the preformed nitrogen sources could react with 3-methylbut-2-en-1-ol **243** to give good yield and a high regioselectivity (**Figure 5.1**). For example, reaction of *tert*-butyl *N*-(4-toluenesulfonyloxy)carbamate **153** with 3-methylbut-2-en-1-ol **243** afforded (*S*^{*})-*tert*-butyl 1,3-dihydroxy-3-methylbutan-2-ylcarbamate **245** in 64% yield. Benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** reacted with the same alkene to afford (*S*^{*})-benzyl 1,3-dihydroxy-3-methylbutan-2-ylcarbamate **247** in 64% yield. However, reaction of 2,2,2-trichloroethyl *N*-(4-toluenesulfonyloxy)carbamate **203** with the same alkene **243** showed only traces of the amino alcohol product observed by mass spectrometry (MS).

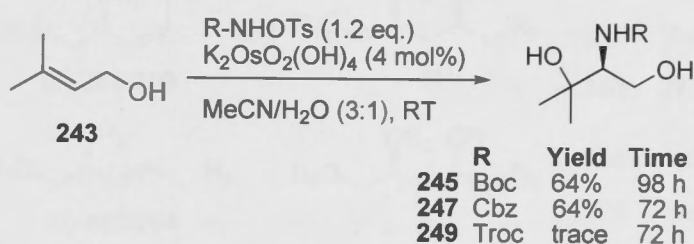


Figure 5.1

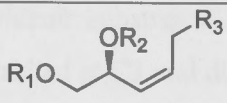
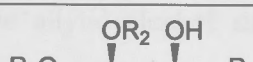
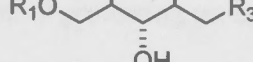
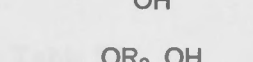
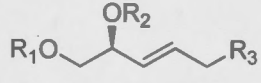
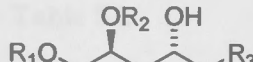
This was a very important result. Few reports have been published on the osmium-catalysed aminohydroxylation reaction using allylic alcohol as substrates. Besides that, the successful reaction of preformed nitrogen source *tert*-butyl **153** and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** on allylic alcohols suggested that manipulating the alkyl substituent adjacent to the carbon-carbon double bond and also potentially installing a different *O*-protecting group would be able to exert control on the face of addition.

This chapter will present the results of a diastereoselectivity study of the osmium-catalysed aminohydroxylation reaction of allylic alcohols using preformed nitrogen source benzyl *N*-(4-toluenesulfonyloxy)carbamate **202**. This includes (i) an introduction on the stereochemical induction in the addition reaction to allylic alcohols, (ii) synthesis of allylic alcohols and derivatives, (iii) the diastereoselectivity study of the osmium-catalysed aminohydroxylation reaction, (iv) additive and competition reaction studies of the osmium-catalysed aminohydroxylation reaction, and (v) conclusions.

5.2 Stereochemical induction in the addition reactions of allylic alcohols

The diastereoselectivity of the dihydroxylation reaction catalysed by osmium tetroxide with allylic alcohols as substrates has been investigated.¹²⁸⁻¹³¹ Given the mechanistic similarities between the aminohydroxylation⁷ and dihydroxylation^{13,14} reactions, the stereoselectivity of the aminohydroxylation reaction of allylic alcohols suggested itself as worthy of study.

Table 5.1

Substrate	Major product		R ₁	R ₂	R ₃	d.r.
 (Z)-257-259	 260	Bn	Bn	OH	7 : 1	
	 261	Bn	Bn	Et	8 : 1	
	 262	Ac	Ac	Et	2 : 1	
 (E)-263-264	 265	Bn	Bn	OH	3 : 1	
	 266	Bn	Bn	Et	6 : 1	

*Reaction was carried out under catalytic conditions with OsO₄ (0.05 equiv.), *N*-methylmorpholine *N*-oxide (2.0 equiv.), in water-acetone (1:8), RT.

Kishi and coworkers^{128,129} systematically studied the diastereoselectivity in the dihydroxylation of allylic alcohols catalysed by osmium tetroxide. It was reported that the relative stereochemistry of the new hydroxyl-group of the major product and the adjacent hydroxyl- or alkoxy-group was *anti*. The stereoselectivity of the reaction was slightly higher for (*Z*)-olefins than (*E*)-olefins. The existence of protecting group on hydroxyl had a limited affect on the stereoselectivity, except for acyl-groups which gave lower stereoselectivity. Some representative results are displayed in (Table 5.1).

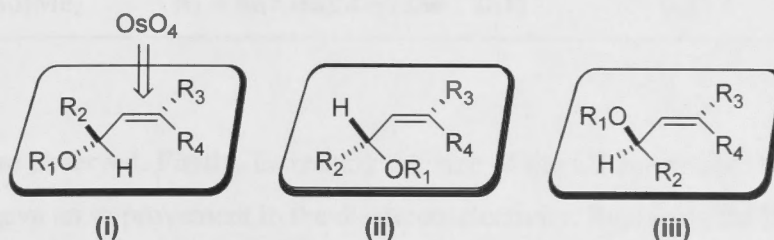
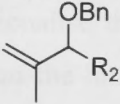
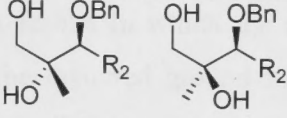
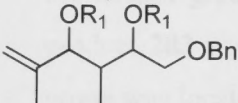
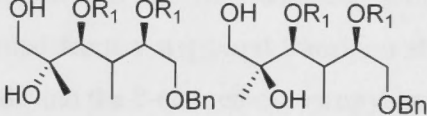


Figure 5.2

To rationalise these results, Kishi¹²⁸ proposed that the eclipsed conformations (i-iii) for these allylic alcohol systems would be most important, but conformation (i) was sterically favoured with the small hydrogen atom eclipsing the double bond substituent R₄. The osmium tetroxide would then add selectively to the carbon-carbon double bond face opposite to the hydroxyl- or alkoxy-group. In support of this model, the stereoselectivity of (*Z*)-alkenes was slightly higher than that from (*E*)-alkenes, suggesting conformation (i) was more strongly preferred over (ii) and (iii) (**Figure 5.2**).

In similar manner to Kishi,^{128,129} Evans and coworkers¹³⁰ reported the diastereoselectivity of the dihydroxylation reaction catalysed by osmium tetroxide using 1,1-disubstituted alkene substrates. These allylic alcohol substrates had different sized substituents attached at C3 and different *O*-protecting groups (**Table 5.2**).

Table 5.2

	Substrate	Product	Ratio (<i>anti</i> : <i>syn</i>)
1			
	267 R ₂ = Et	R ₂ = Et (268 : 269)	5.1 : 1
	270 R ₂ = <i>i</i> -Pr	R ₂ = <i>i</i> -Pr (271 : 272)	17 : 1
2			
	273 R ₁ = H	R ₁ = H (274 : 275)	35 : 1
	276 R ₁ = Ac	R ₁ = Ac (277 : 278)	16 : 1
	279 R ₁ = Si(<i>t</i> -Bu)Me ₂	R ₁ = Si(<i>t</i> -Bu)Me ₂ (280 : 281)	6.2 : 1

Two general trends were observed. Firstly, increasing the size of the C3 substituent for substrate **267** and **270** gave an improvement in the diastereoselectivity. Replacing the R₂ substituent from ethyl to isopropyl approximately tripled the diastereoselectivity. Secondly, steric rather than electronic factors were suggested for the influence of the *O*-

protecting groups. Introduction of acetate in compound **276** or silyl ether protecting group in substrate **279** gave lower selectivity. These results were not consistent with the model for selectivity proposed by Kishi,¹²⁸ but the trend followed that expected based on the transition-state model proposed by Houk and coworkers,^{132,133} and Vedejs and coworkers.^{134,135}

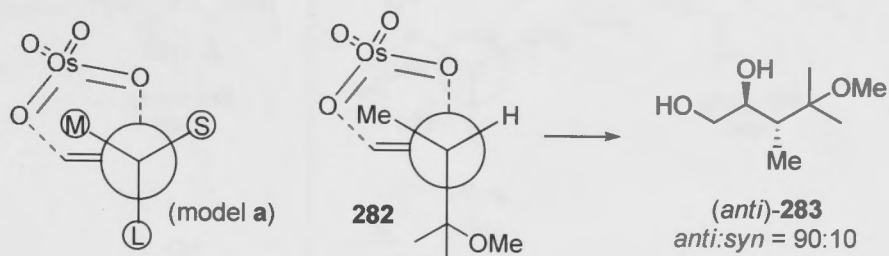


Figure 5.3

Houk and coworkers¹³² reported transition-state model¹³³ to explain the stereoselectivity of the cycloaddition reaction of nitrile oxides which also suited the dihydroxylation reaction catalysed by osmium tetroxide (**Figure 5.3**). This model was proposed to rationalise the experimental results in which the major product was always afforded from the hindered face of the favoured ground-state conformation of the alkene, and also increasing the size of alkyl-substituent improved diastereoselectivity of the reactions. The transition-state proposed involved a staggered structure (model **a**) where the largest group is placed *anti* and medium-sized group inside. For example, major product **283** was afforded from a staggered transition structure **282**, where the methyl group was located inside and the 2-(2-methoxy)propyl group located *anti*.

Furthermore, Vedejs and coworkers¹³⁵ also proposed a slightly different transition-state model to explain the dihydroxylation reaction in (*E*)- and (*Z*)-alkenes (**Figure 5.4**). The favoured transition-state for the reaction was affected by the size of substituent and the geometry of the alkenes. For example in (*Z*)-alkenes, major product (*anti*)-**289** was afforded from transition-state **288** with the small hydrogen positioned inside, and the alkyl substituent outside. The minor product (*syn*)-**291** from (*Z*)-alkenes were proposed following the transition-state **290**, where the hydrogen was located inside and alkyl-substituent *anti*. For (*E*)-alkenes, the favoured transition-state **284**, leading to the major

product **285** located the hydrogen at C2 close to the osmium centre. The transition-state **286** for the minor product (*syn*)-**287** of (*E*)-alkenes was proposed where the hydrogen was placed near to the osmium centre and the substituent-alkyl inside.

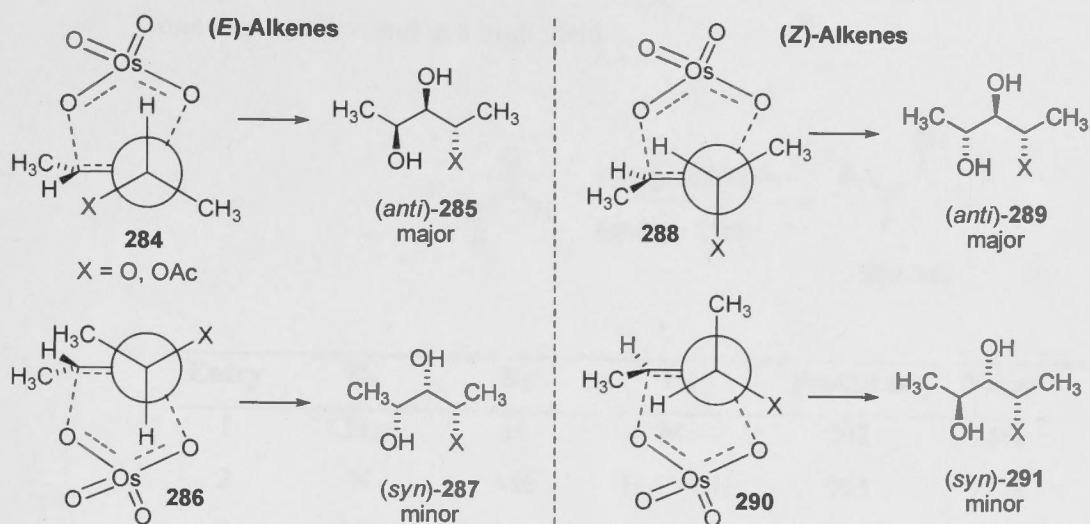


Figure 5.4

5.3 Synthesis of allylic alcohols and their derivatives

To study the diastereoselectivity of the osmium-catalysed aminohydroxylation reaction using the preformed nitrogen source benzyl *N*-(4-toluenesulfonyloxy)carbamate **202**, four types of allylic alcohol substrate would be used i.e. allylic alcohols which were constructed as (i) monosubstituted, (ii) 1,1-disubstituted, (iii) 1,1,2-trisubstituted and (iv) 1,2,2-trisubstituted (**Figure 5.5**). In each case the substitution pattern was expected to favour the formation of one regioisomer thus simplifying the task of evaluating diastereoselectivity.

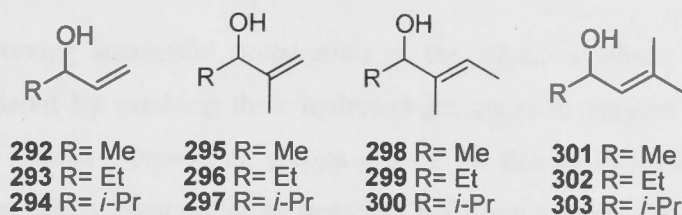
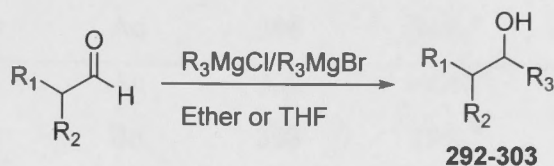


Figure 5.5

The twelve structures of allylic alcohols and their synthesis results are presented in **Figure 5.6**. Fourteen derivatives of these allylic alcohols and their preparation are summarised separately in **Table 5.3**. In general, the allylic alcohols¹³⁶⁻¹⁴⁰ were prepared from a commercially available aldehyde and a Grignard reagent. This was achieved in a one step reaction and in a high yield.



Entry	R ₁	R ₂	R ₃	Products	Yield	Time
1	CH ₂ =	H	Me	292	74%	2 h
2	H	Me	H ₂ C=CH	293	71%	1 h
3	Me	Me	H ₂ C=CH	294	65%	15 min
4	CH ₂ =	Me	Me	295	84%	30 min
5	CH ₂ =	Me	Et	296	100%	1 h
6	Me	Me	CH ₂ =C(Me)	297	71%	15 min
7	MeCH=	Me	Me	298	89%	1 h
8	MeCH=	Me	Et	299	68%	2 h
9	MeCH=	Me	<i>i</i> -Pr	300	91%	2 h
10	Me ₂ C=	H	Me	301	72%	15 h
11	Me ₂ C=	H	Et	302	88%	4 h
12	Me ₂ C=	H	<i>i</i> -Pr	303	71%	15 h

Figure 5.6

Following successful preparation of the allylic alcohols, a range of derivatives was prepared by masking their hydroxyl-groups with various different protecting groups. The hydroxyl-protecting groups chosen for this investigation consisted of acetyl (Ac), benzyl (Bn), *para*-methoxy-benzyl (PMB) and *tert*-butyldimethylsilyl (TBS) protecting groups. All these groups were already known as protecting groups for the hydroxyl functionality in organic synthesis,^{78,119} and also they had different electronic and steric properties.

Table 5.3

Entry	Substrate R ₂ = H	R ₁	R ₂	Product	Yield	Time
1		Me	Ac	304	36% ^a	15 h
2		Et	Ac	305	87% ^a	1 h
3		<i>i</i> -Pr	Ac	306	84% ^a	45 min
4		Me	Ac	307	100% ^a	1 h
5		Me	Bn	308	39% ^b	1 h
6		Me	PMB	309	10% ^c	16 h
7		Me	TBS	310	31% ^d	15 h
8		Et	Ac	311	41% ^a	15 min
9		Et	PMB	312	67% ^c	24 h
10		<i>i</i> -Pr	Ac	313	58% ^a	15 min
11		<i>i</i> -Pr	PMB	314	25% ^c	48 h
12		Et	Bn	315	100% ^b	1 h
13		Et	TBS	316	97% ^d	6 h
14		<i>i</i> -Pr	Bn	317	53% ^b	48 h

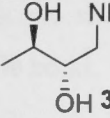
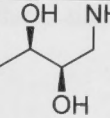
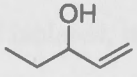
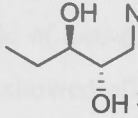
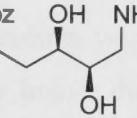
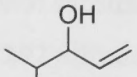
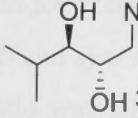
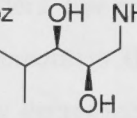
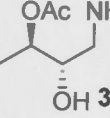
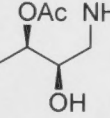
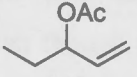
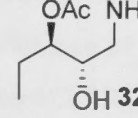
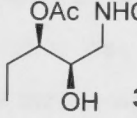
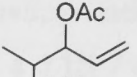
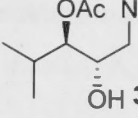
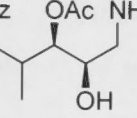
Note: ^aAc₂O (2.0 equiv. or as determined), Et₃N (2.0 equiv. or as determined); ^bBnBr (2.0 equiv. or as determined), NaH (4.0 equiv. or as determined), TBAI, DMF; ^cPMBCl (1.2 equiv. or as determined), NaH (4 equiv. or as determined), DCM or DMF; ^dTBSCl (2.0 equiv. or as determined), imidazole (4.0 equiv.), DMF.

Three derivatives of allylic alcohols¹⁴¹⁻¹⁴³ were prepared for monosubstituted alkenes. All of them contained the *O*-acetyl protecting group **304-306**, and were afforded in low to excellent yield. Eight derivatives of the 1,1-disubstituted allylic alcohol have been synthesised and consist of *O*-acetyl, *O*-*tert*-butyldimethylsilyl, and *O*-*p*-methoxy-benzyl groups **307-314**. They were afforded in low to quantitative yield. Two derivatives were prepared for the 1,1,2-trisubstituted allylic alcohol in excellent yield. They were with *O*-benzyl and *O*-*tert*-butyldimethylsilyl protecting groups **315-316**. Meanwhile for 1,2,2-trisubstituted allylic alcohols, one structure with *O*-benzyl protecting group **317** was prepared in good yield.

5.4 The diastereoselectivity of the osmium-catalysed aminohydroxylation in allylic alcohol substrates

5.4.1 Monosubstituted allylic alcohols

Table 5.4

Entry	Substrate	Product	Yield (<i>anti:syn</i>)	Time
1	 292	 318  319	79% 1.8:1 ^a	72 h
2	 293	 320  321	65% 2.1:1 ^a	72 h
3	 294	 322  323	73% 3.1:1 ^a	96 h
4	 304	 324  325	53% 1.2:1 ^b	2 h
5	 305	 326  327	71% 1.5:1 ^b	41 h
6	 306	 328  329	68% 2.4:1 ^b	72 h

Reaction conditions: Allylic alcohol (1.0 equiv.), $K_2OsO_2(OH)_4$ (4.0 mol%), BnOCONHOTs **202** (1.2 equiv.), MeCN/H₂O (3:1), RT. ^aRatio was determined from integration of ¹H-NMR. ^bRatio was determined from isolated yield.

Within this study, a similar procedure for evaluation of every allylic alcohol substrate was applied. A stirred solution of allylic alcohol or its derivative (1.0 equiv.) and potassium osmate dihydrate (0.04 equiv.) in acetonitrile/water (1 mL / 1 mL) at 0 °C was reacted with a solution of benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (1.2 equiv.) in acetonitrile (2 mL). This reaction mixture was further stirred until the reaction was complete at room temperature. The product was isolated after purification with

flash chromatography. Results of the diastereoselectivity study for these monosubstituted allylic alcohols are presented in **Table 5.4**.

Four trends were observed when applying monosubstituted allylic alcohols and their acetate esters as substrates. Firstly, the reaction afforded the amino alcohol product in good yield but it required long reaction times, except for acetate ester **304** which was completed in 2 h. Secondly, high regioselectivity was achieved, and the terminal amino product afforded from both *O*-protected and unprotected allylic alcohols. These results gave the same pattern as the substrate scope study, where nitrogen adds to the less substituted end of the carbon-carbon double bond.

Thirdly, in all products isolated, the yield of *anti*-diastereomer was higher than the *syn*-diastereomer. In addition, a trend also showed slightly higher diastereomer ratios for unprotected allylic alcohol substrates than for acetate esters. For example, reaction with substrate but-3-en-2-ol **292** afforded *anti*- and *syn*- diastereomers **318** and **319** with ratio of 1.8:1, respectively. The *anti* : *syn* ratio was slightly decreased to 1.2:1 for acetate ester **304**.

Finally, increasing the size of alkyl-substituent attached at C3 improved the diastereoselectivity. Even though the difference of the ratios was not large, it gave an increasing trend. For example, allylic alcohol **292** with methyl-substituent attached at C3 provided a 1.8:1 / *anti:syn* ratio. The reaction of allylic alcohol **294** with isopropyl substituent at C3 gave a 3.1:1 / *anti:syn* ratio. A similar trend was observed for the acetate ester substrates.

Analysing these results, the domination of the *anti*- over *syn*-diastereomer, and the improved diastereoselectivity also on increasing the size of C3 alkyl-substituent appeared similar in trend to the results of Evan and coworkers¹³⁰ who investigated the dihydroxylation reaction catalysed by osmium tetroxide with 1,1-disubstituted alkenes as substrates. In addition, it was also reported¹³⁰ that acetyl-protection of the allylic alcohol decreased the stereoselectivity.

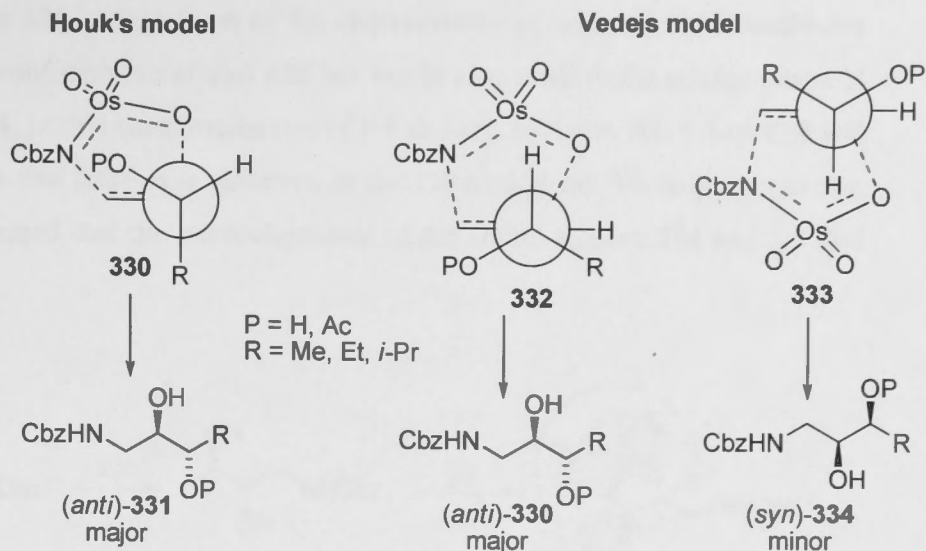


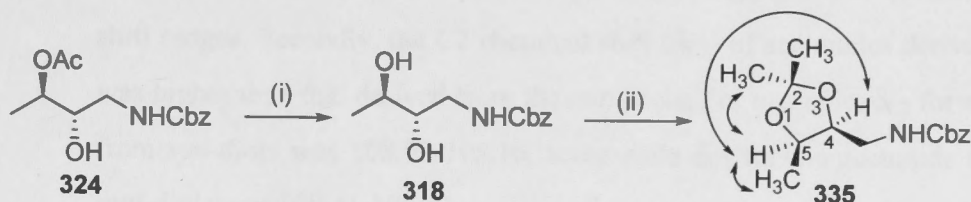
Figure 5.7

The major *anti*-product for these reactions seemed consistent with the Houk¹³² transition-state model for the dihydroxylation reaction catalysed by osmium tetroxide, where steric effects control the diastereoselectivity. This model positions the alkyl-groups (R) *anti* and OP-group inside (**Figure 5.7**). The reaction trend where increasing the size of R-group improved the diastereoselectivity would easily be predicted by this model. Moreover, the transition-state model developed by Vedejs and coworkers¹³⁵ could also explain this trend in diastereoselectivity. The terminal monosubstituted alkenes would resemble the (*E*)-alkenes of Vedejs model,¹³⁵ with the hydrogen placed near to the osmium to reduce the steric environment, and the large R-group located outside.

Assignment of the amino alcohol diastereomers

The determination of *anti*- and *syn*-diastereomer identity was undertaken by NOE analysis of the 1,2-acetonide derivative formed from the corresponding 2,3-diol (**Figure 5.8**). The 2,3-diol was afforded directly from the aminohydroxylation of allylic alcohols or from hydrolysis of acetate ester of the amino alcohol product. For instance, the benzyl ((4*S**,5*R**)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methylcarbamate **335** was derived from 2,3-diol **318**. This diol was generated by hydrolysis of acetate ester of the amino alcohol product **324**. Reaction of this diol with 2,2-dimethoxypropane in the presence of camphorsulfonic acid (CSA) and *para*-toluenesulfonic acid (*p*TSA)

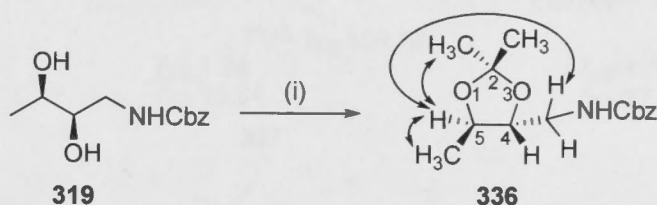
afforded acetonide **335**. Assignment of the configuration of acetonide **335** would not only confirm the configuration of diol **318** but would also confirm the configuration of amino alcohol **324**. In this case, irradiation of H5 showed NOEs to H4, C2-methyl and C5-methyl signals. No NOE was observed to the C4 methylene. These proton-proton correlations confirmed that the stereochemistry of the amino alcohol **324** and the diol **318** was *anti*.



Conditions: (i) K_2CO_3 , MeOH/H₂O (ii) 2,2-DMP, CSA, *p*-TSA, DCM

Figure 5.8

In similar way, the diol **319** could also be converted to benzyl ((4*R**,5*R**)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methylcarbamate **336**. Proton-proton interactions were also analysed by NOEs. Irradiation of H5 showed NOEs to C5-methyl, C2-methyl and one proton of the C4-methylene group. This analysis confirmed that the stereochemistry of the starting 2,3-diol was *syn* (**Figure 5.9**).



Conditions: (i) starting material **319** in mixture with **318** (1:1.8 ratio), 2,2-DMP, CSA, *p*-TSA, DCM, 83% purity of **336**.

Figure 5.9

In addition to NOE analysis the chemical shift data (δ) of C2, C6, H6, C7, and H7 was also diagnostic for *syn*- and *anti*-derived acetonides (**Figure 5.10**). In general, the group of acetonides that were derived from *syn*-diols had similar trend, and these trends were

different to those derived from the *anti*-diols. For *syn*-diol derived acetonides, chemical shifts of H6 (δ_{H6}) and H7 (δ_{H7}) as well as C6 (δ_{C6}) and C7 (δ_{C7}) showed values. For example acetonide **336**, **338**, and **340**, the δ_{H6} range was 1.37-1.39 and δ_{H7} range was 1.36-1.37. Meanwhile, the δ_{C6} range was 27.22-27.26 and δ_{C7} range was 26.97-27.10. In contrast, the acetonides derived from *anti*-diols such as **335**, **337**, and **339** had distinct, higher δ_{H6} (1.43-1.44) and lower δ_{H7} (1.33-1.34) chemical shift ranges. In addition, δ_{C6} showed slightly higher (28.26-28.55) and δ_{C7} slightly lower (25.51-25.86) chemical shift ranges. Secondly, the C2 chemical shift (δ_{C2}) of acetonides derived from *syn*-diols was higher than that derived from the *anti*-diols. For example, δ_{C2} for acetonide derived from *syn*-diols was 108.09-108.16, meanwhile δ_{C2} for the acetonide derived from the *anti*-diols was 108.41-108.53.

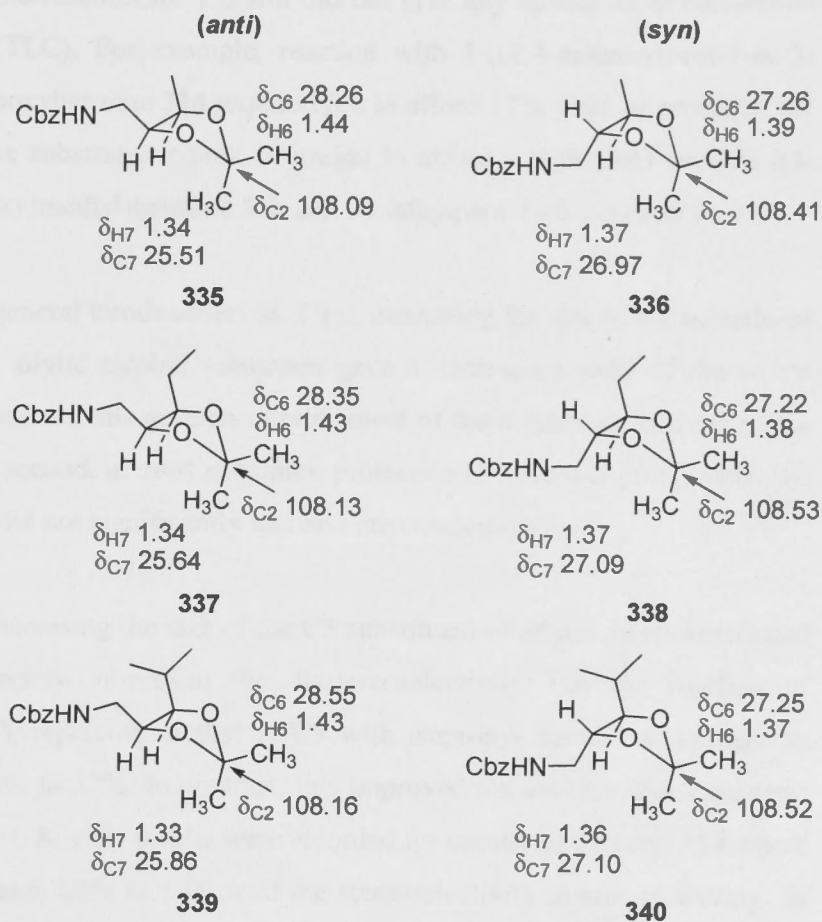


Figure 5.10

5.4.2 1,1-Disubstituted allylic alcohols

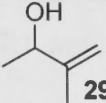
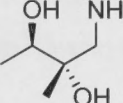
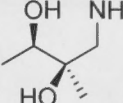
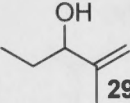
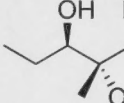
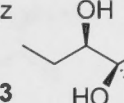
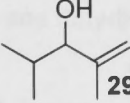
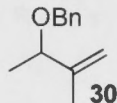
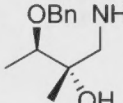
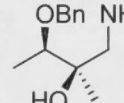
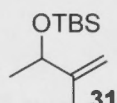
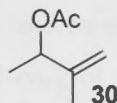
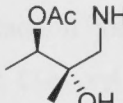
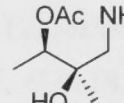
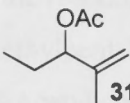
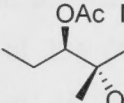
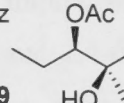
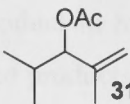
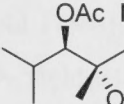
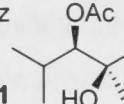
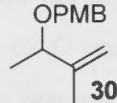
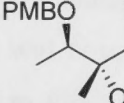
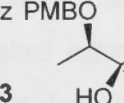
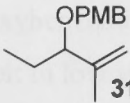
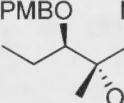
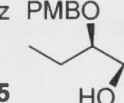
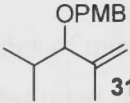
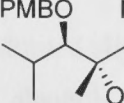
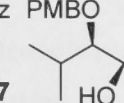
The diastereoselectivity of the osmium-catalysed aminohydroxylation reaction with 1,1-disubstituted allylic alcohols is presented in **Table 5.5**. There were eleven substrates which mostly consisted of allylic alcohols and their OAc, OPMB, OTBS, and OBn derivatives.

The reaction afforded amino alcohol products in diverse yields, from low to good yield, except for 2,4-dimethylpent-1-en-3-ol **297** and *tert*-butyldimethyl(3-methylbut-3-en-2-yloxy)silane **310**, which did not react. The lowest yield was afforded with 1-((2,4-dimethylpent-1-en-3-yloxy)methyl)-4-methoxybenzene **314** (17%), and the highest yield was afforded with ((3-methylbut-3-en-2-yloxy)methyl)benzene **308** (89%). Moreover, many reaction times were long, in two examples the reaction did not afford the product: stirring the reaction for 7 d still did not give any indication of conversion for compound **297** (TLC). For example, reaction with 1-((2,4-dimethylpent-1-en-3-yloxy)methyl)-4-methoxybenzene **314** required 8 d to afford 17% yield of products **357** and **358**. But, in some substrates it took overnight to afford a high yield such as ((3-methylbut-3-en-2-yloxy)methyl)benzene **309** and 2-methylpent-1-en-3-yl acetate **311**.

There were also two general trends observed. First, increasing the size of the substituent attached at C3 in all allylic alcohol substrates gave a decreasing yield of the amino alcohol isolated. In contrast, this gave an improvement of the diastereoselectivity of the product isolated. And second, in most examples, protection of hydroxyl-group increased the yield sharply, but did not significantly increase stereoselectivity.

It was observed that increasing the size of the C3 substituent of allylic alcohols reduced the yield, and conversely, improved the diastereoselectivity. For the reaction of substrate **307** and **313**, replacing methyl at C3 with isopropyl showed a decrease in product yield from 68% to 32%. In contrast, this improved the *anti:syn*-diastereomeric ratio from 2.5:1 to 3.4:1. Similar results were recorded for substrates **309** and **314** where the yields decreased from 69% to 17%, and the stereoselectivity improved sharply. In the case of allylic alcohol substrates **295-297**, conversion of C3-methyl to isopropyl completely shut down the reaction.

Table 5.5

Entry	Substrate	Product ^a	Yield (<i>anti:syn</i>)	Time
1		 341  342	44% 2.3:1 ^{a,b}	96 h
2		 343  344	40% 2.7:1 ^{a,b}	7 d
3		NP	-	7 d
4		 345  346	89% 2.5:1 ^{a,b}	15 h
5		NP	-	-
6		 347  348	68% 2.5:1 ^{b,c}	66 h
7		 349  350	75% 2.8:1 ^{b,c}	17 h
8		 351  352	32% 3.4:1 ^{b,c}	7 d
9		 353  354	69% 2.6:1 ^{a,b}	15 h
10		 355  356	44% 4.9:1 ^{a,b}	96 h
11		 357  358	17% 12.1:1 ^{a,b}	8 d

^aReaction conditions: substrate (1.0 equiv.), BnOCONHOTs **202** (1.2 equiv.), K₂OsO₂(OH)₄ (4.0 mol%), MeCN/H₂O (3:1), RT. ^bDiastereomers were determined from ¹H-NMR integration. ^cDiastereomers were determined from isolated product.

This similar phenomenon has also been reported by Evans and coworkers¹³⁰ for a dihydroxylation reaction catalysed by osmium tetroxide (**Figure 5.11**). Replacing C3-substituent from ethyl to isopropyl afforded better diastereoselectivity of the diol product. With R as ethyl the reaction gave a 5.1:1 *anti*-/*syn*-diastereomeric ratio, while R as isopropyl gave a 17:1 *anti*-/*syn*-diastereomeric ratio.

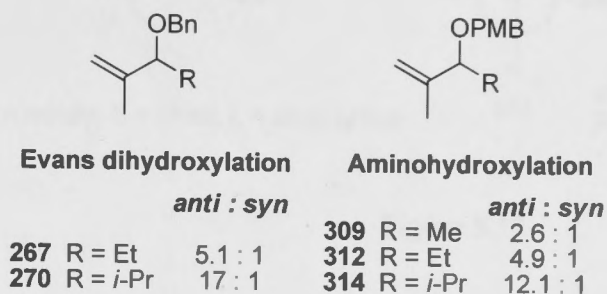


Figure 5.11

The last trend observed was that protection of hydroxyl-group of the allylic alcohol substrates significantly increased the reaction yield. For example, *O*-protection of substrate 3-methylbut-3-en-2-ol **295** with *O*-acetyl **307**, *O*-PMB **309**, and *O*-Bn **308**, significantly improved the reaction yields. Similar yield improvement was also recorded for the substrates 2-methylpent-1-en-3-ol **296** (40%) and 2,4-dimethylpent-1-en-3-ol **297** (no reaction). *O*-Acetyl protection of **296** gave ester **311** which afforded aminohydroxylation product in high yield (75%), meanwhile allylic alcohol **297** gave ester **313** which afforded products in 32% yield. However, protection of hydroxyl-group of the allylic alcohols did not significantly change the stereochemical induction in the products isolated. Both of *O*-protected and *O*-unprotected substrates afforded similar diastereoselectivity. The one exception to this trend was 1-((2,4-dimethylpent-1-en-3-yloxy)methyl)-4-methoxybenzene **314**, it gave a significant improvement in diastereoselectivity albeit in low yield.

Like the previous reactions of monosubstituted allylic alcohols and their derivatives, the reaction with 1,1-disubstituted allylic alcohols was also consistent with proposed transition-state models. Increasing the size of C3 alkyl substituent improved the diastereoselectivity affording the *anti*-diastereomer as the major product **360**. The transition-state model proposed by Houk and coworkers¹³² is consistent with this trend

The largest group is placed *anti*, meanwhile the medium group is placed inside **359** (Figure 5.12).

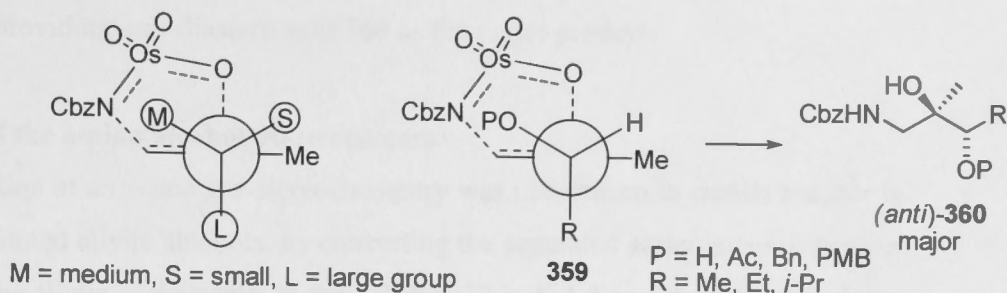


Figure 5.12

Furthermore, the transition-state model proposed by Vedejs and coworkers¹³⁵ was also consistent with these results. In this model, the steric interactions could be reduced by positioning the hydrogen near to the osmium in the transition-state leading to the major product. With 1,1-disubstituted allylic alcohol substrates, the transition-state model **361** and **362** presented in Figure 5.13 should be considered.

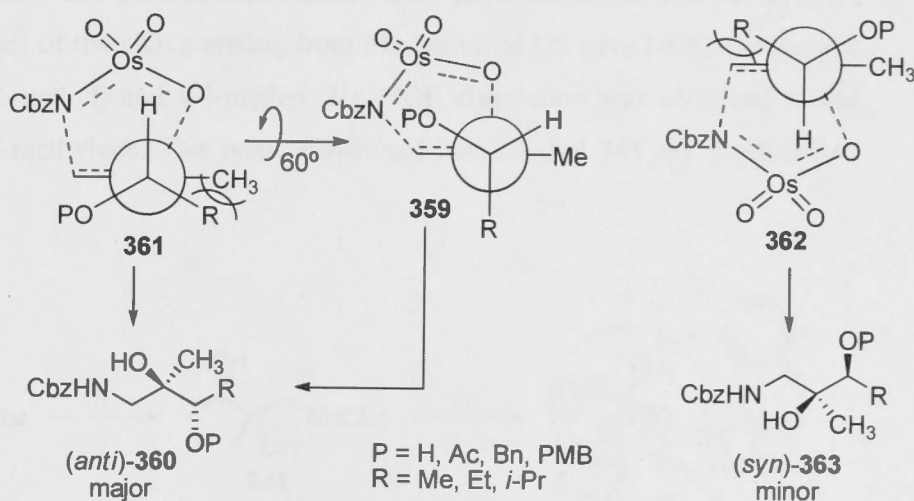


Figure 5.13

This model can rationalise the improving diastereoselectivity on increasing the size of the C3 alkyl substituent (R). The increasing size of the R-substituent would increase the A (1,3)-like interaction in transition structure **362**, thereby favouring transition structure

361. The increased A (1,2) strain associated with transition structure **361** could be alleviated by rotation leading to a transition structure similar to **359**. This would reduce the steric repulsion, and give a transition-state model **359** similar to the Houk and coworkers,¹³² providing *anti*-diastereomer **360** as the major product

Assignment of the amino alcohol diastereomers

The determination of *anti*- and *syn*-stereochemistry was undertaken in similar manner to the monosubstituted allylic alcohols, by converting the separated amino alcohol product derived from the allylic acetate ester to the 2,3-diol. This diol then was transformed into the 2,3-acetonide, allowing the *anti*- and *syn*-configuration to be established by NOESY. For the inseparable amino alcohol products derived from allylic alcohol substrates, the *anti*- and *syn*-stereochemistry was determined by ¹H-NMR integration.

Figure 5.14 presents the formation of acetonide **364** from amino alcohol product **347**. Selective deprotection of the acetyl-group of the amino alcohol product **347** was conducted with a solution of ammonia in methanol.¹⁴⁴ This afforded the 2,3-diol **341** in quantitative yield. Further treatment of 2,3-diol **341** with 2,2-dimethoxypropane, camphorsulfonic acid and *para*-toluenesulfonic acid gave acetonide **364** in excellent yield.^{119,145} Analysis of the NOEs arising from irradiation of H5 gave NOE correlations to C5-methyl, C2-methyl, and C4-methyl. No NOE correlation was observed to the protons of the C4-methylene. This result confirmed that 2,3-diol **341** and product **347** were *anti*.

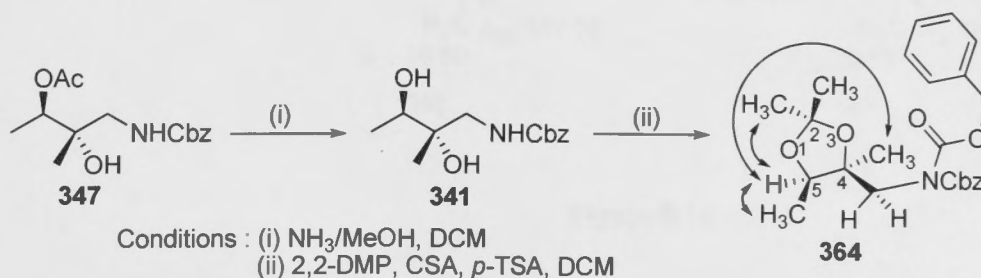


Figure 5.14

Using a similar procedure, hydrolysis of the minor diastereomer **348** afforded 2,3-diol **342**. Further treatment of diol **342** with 2,2-DMP, CSA, and *p*-TSA gave acetonide **365**

in high yield. The NOE analysis of acetonide **365** with irradiation of H5 gave NOE correlations with C5-methyl, C2-methyl, and a C4-methylene. No NOE correlation was observed to the C4-methyl (**Figure 5.15**). This result confirmed that amino alcohol product **348** and 2,3-diol **342** were *syn*.

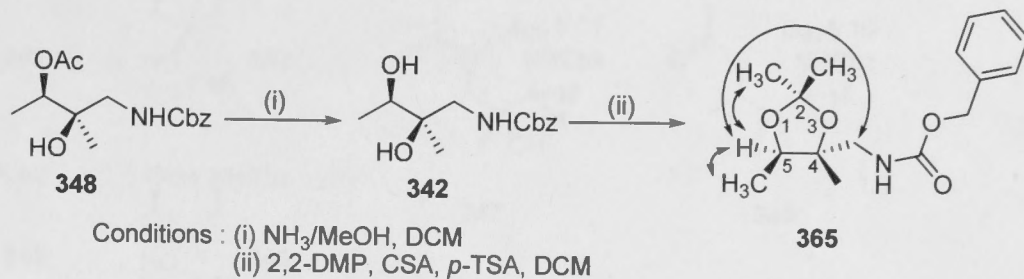


Figure 5.15

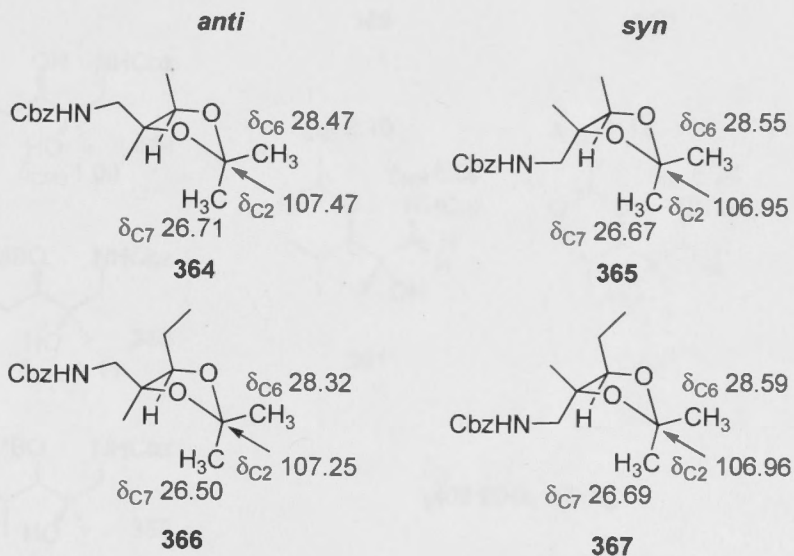


Figure 5.16

In addition to NOE analysis, the ^{13}C -NMR data was also diagnostic for *syn*- and *anti*-derived acetonides (**Figure 5.16**). The acetonide derived from the *anti*-diols generally had δ_{C_2} at higher field than that derived from the *syn*-diols. *Anti*-diol derived acetonides **364** and **366** gave δ_{C_2} 107.25-107.47, meanwhile *syn*-diol derived acetonides **365** and **367** showed δ_{C_2} 106.95-106.96. The δ_{C_6} and δ_{C_7} methyl chemical shifts showed similar

values. In this instance, both acetonides derived from *anti*- and *syn*-diols had similar values of δ_{C6} (28.32-28.59), meanwhile δ_{C7} gave slightly lower values (26.50-26.71).

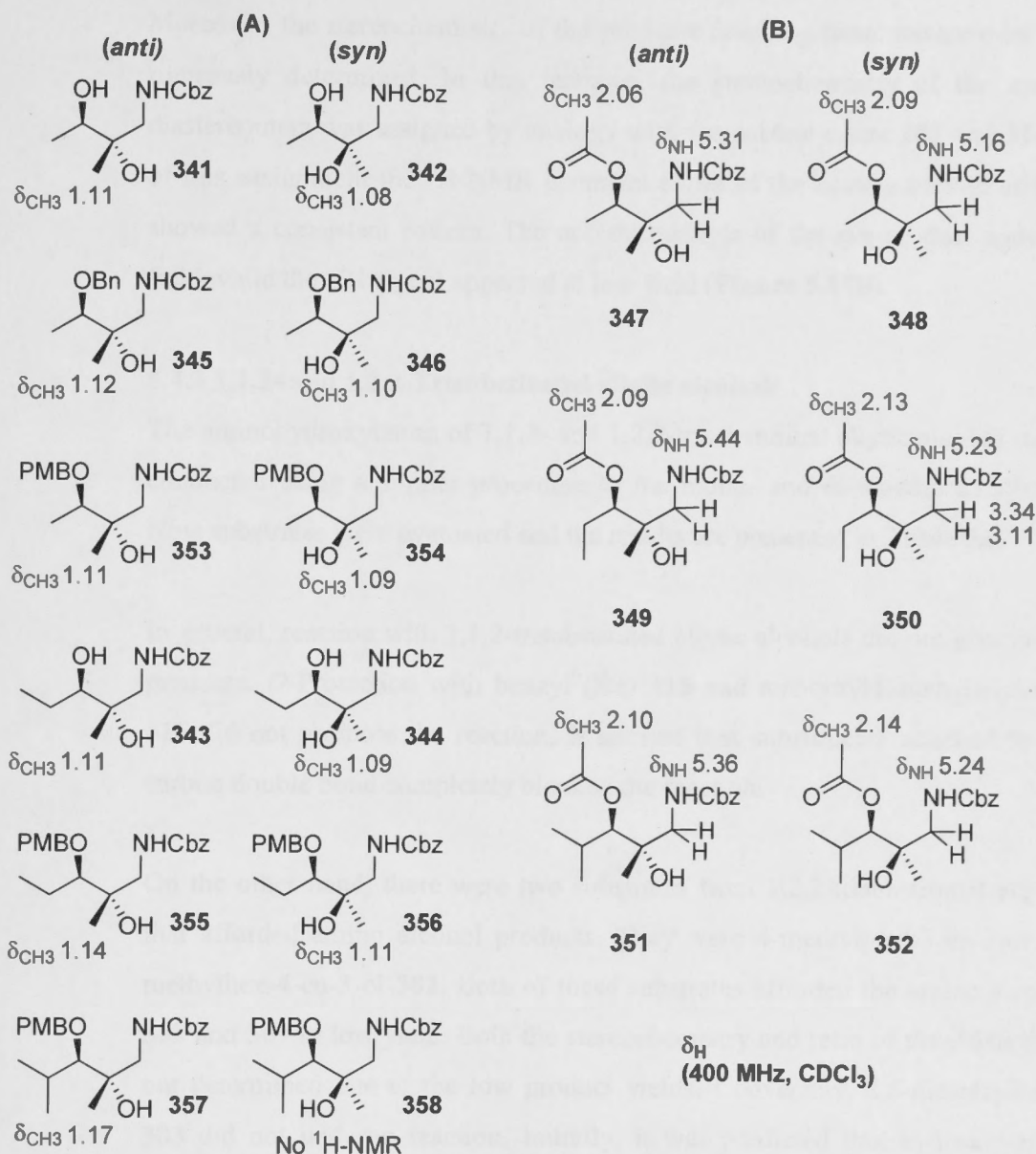


Figure 5.17

The stereochemistry of the products resulting from the allylic ethers **308**, **309**, **312** and **314** was not rigorously determined. In these instances the stereochemistry of *anti*- and *syn*-diastereomers was assigned by analogy with the results of the corresponding allylic alcohols. In support of this approach, the 1H -NMR chemical shift of proton C2-methyl

of the *syn*-diastereomer was consistently lower field than that of the *anti*-diastereomers (**Figure 5.17a**).

Moreover, the stereochemistry of the products resulting from acetate ester **313** was not rigorously determined. In this instance, the stereochemistry of the *anti*- and *syn*-diastereomers was assigned by analogy with the acetate esters **307** and **311**. In support of this assignment the ^1H -NMR chemical shifts of the acetate methyl and NH groups showed a consistent pattern. The acetate methyls of the *syn*-product appeared at high field while the NH signal appeared at low field (**Figure 5.17b**).

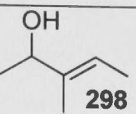
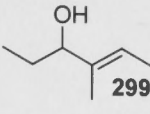
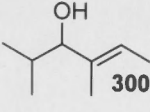
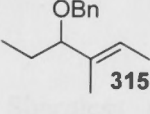
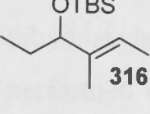
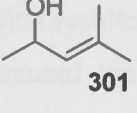
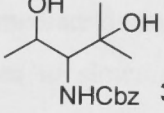
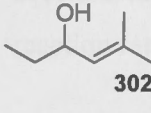
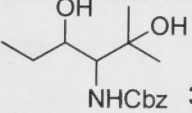
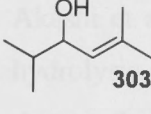
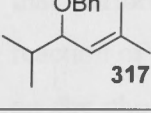
5.4.3 1,1,2- and 1,2,2-Trisubstituted allylic alcohols

The aminohydroxylation of 1,1,2- and 1,2,2-trisubstituted allylic alcohol substrates was conducted using a similar procedure to the mono- and di-substituted allylic alcohols. Nine substrates were evaluated and the results are presented in **Table 5.6**.

In general, reaction with 1,1,2-trisubstituted allylic alcohols did not give amino alcohol products. *O*-Protection with benzyl (Bn) **315** and *tert*-butyldimethylsilyl (TBS) ether **316** did not promote the reaction. It seemed that substituents attached to the carbon-carbon double bond completely blocked the reaction.

On the other hand, there were two substrates from 1,2,2-trisubstituted allylic alcohols that afforded amino alcohol products. They were 4-methylpent-3-en-2-ol **301** and 5-methylhex-4-en-3-ol **302**. Both of these substrates afforded the amino alcohol product **368** and **369** in low yield. Both the stereochemistry and ratio of the diastereomers were not determined due to the low product yields. Conversely, 2,5-dimethylhex-4-en-3-ol **303** did not undergo reaction. Initially, it was predicted that hydroxyl-groups might inhibit the reaction. However, *O*-protection of this allylic alcohol **303** as the benzyl ether **317** still did not promote the reaction.

Table 5.6

Entry	Substrate	Product	Yield (<i>anti:syn</i>)	Time
1		NP ^b	-	96 h
2		NP ^b	-	96 h
3		NP ^b	-	96 h
4		NP ^b	-	96 h
5		NP ^b	-	96 h
6			10% ^a	17 h
7			7.2% ^a	21 h
8		NP ^b	-	96 h
9		NP ^b	-	96 h

Reaction conditions: Substrate (1.0 equiv.), BnOCONHOTs **202** (1.2 equiv.), K₂OsO₂(OH)₄ (4.0 mol%), MeCN/H₂O (3:1), RT. ^aMixture two diastereomers. ^bNP: no amino alcohol product isolated.

5.5 Additive and competition reaction studies

5.5.1 Effect of methanesulfonamide and tetraethylammonium acetate (TEAA)

In some examples of the diastereoselectivity study, such as aminohydroxylation of 3-methylbut-3-en-2-yl acetate **307** and 2-methylpent-1-en-3-yl acetate **311**, the reaction afforded high yields and short reaction times. In contrast, with 3-methylbut-3-en-2-ol

295 and 2-methylpent-1-en-3-ol **296**, the reaction did not complete and afforded low yields (**Figure 5.18**). This suggested hydrogen bonding of the allylic alcohol to the osmate ester inhibited the hydrolysis step that afforded the amino alcohol product. This lower catalytic turnover led to lower rates and therefore yields.

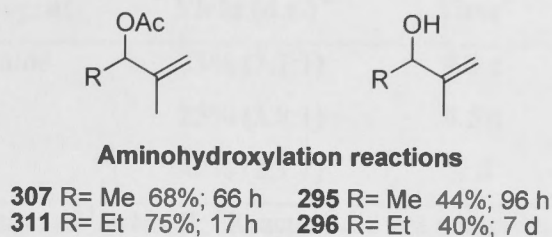
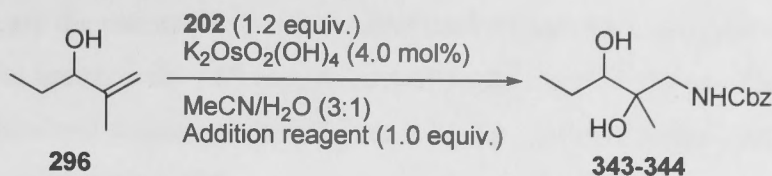


Figure 5.18

Sharpless and coworkers¹⁴⁶ reported a similar phenomenon in the asymmetric dihydroxylation of alkenes catalysed by osmium. The reaction gave lower yields when performed with more substituted alkenes or non-terminal alkenes. The osmate(VI) ester that resulted as an intermediate during the reaction could not easily be hydrolysed and caused the reaction rates to slow. Addition of methanesulfonamide in the reaction accelerated the hydrolysis of this osmate(VI) ester, and significantly increased the reaction rate up to 50 times.

Akashi et al.¹⁴⁷ reported the use of tetraethylammonium acetate (TEAA) to assist the hydrolysis process in the osmium-catalysed dihydroxylation of olefins. It was reported that performing reaction with cyclohexene gave a high yield of diol products, but reaction of cholesterol gave no conversion. The osmium catalyst was apparently trapped on the cholesterol substrate forming a strong osmate ester group that was not easily hydrolysed. Applying tetraethylammonium acetate as additive in the reaction provided greater turnover affording the diol products.

An attempt to accelerate the osmium-catalysed diastereoselective aminohydroxylation of allylic alcohols is presented in **Figure 5.19**.



Entry	Addition reagent	Yield (d.r.) ^a	Time ^b
1	Methanesulfonamide	23% (3.1:1)	4.5 d
2	TEAA	25% (3.8:1)	4.5 d
3	No addition	40% (2.7:1)	7 d

^aDetermined from integration of $^1\text{H-NMR}$; ^bReaction did not complete.

Figure 5.19

The reaction was undertaken using 2-methylpent-1-en-3-ol **296** (1.0 equiv.), benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (1.2 equiv.) and potassium osmate dihydrate (4.0 mol%) with solvent acetonitrile/water. Three different reactions were performed with addition of methanesulfonamide, tetraethylammonium acetate and no additive as a control. However, the addition of methanesulfonamide¹⁴⁶ and tetraethylammonium acetate¹⁴⁷ did not have a significant affect on the yields of the amino alcohol products **343** and **344**. For example, addition of methanesulfonamide gave amino alcohol product 23%. Similar yield was also afforded with addition of tetraethylammonium acetate.

To conclude, an attempt to accelerate the hydrolysis step of the osmium-catalysed aminohydroxylation in allylic alcohols did not succeed. Addition of methanesulfonamide and tetraethylammonium acetate in the reaction did not appear to accelerate the reaction.

5.5.2 Competition studies in the osmium-catalysed aminohydroxylation reaction

Final investigation involved a competition reaction in the aminohydroxylation reaction catalysed by osmium. In most substrates evaluated, it was found that the osmium-catalysed aminohydroxylation using preformed nitrogen sources worked faster and provided better yield in less substituted alkenes than in more substituted alkenes. This pattern of reactivity could be due to the differences in the rate of the addition step, alternatively the reaction rate could be dominated by the rate of hydrolysis. In another

case the reaction with 1,1-disubstituted alkenes such as allylic alcohol substrate **295** and its acetate ester **307** suggested a different reaction pattern. The reaction with the more hindered acetate ester **307** gave a higher yield and more rapid reaction than that with allylic alcohol **295**.

In **Figure 5.20** is described the catalytic aminohydroxylation reaction primary cycle that involves: (i) the addition step of imidotrioxoosmium(VIII) complex **13** to the alkene, to afford osmium(VI) azaglycolate **15**; and (ii) the hydrolysis step that provides amino alcohol product **17** following reoxidation of azaglycolate **15**.

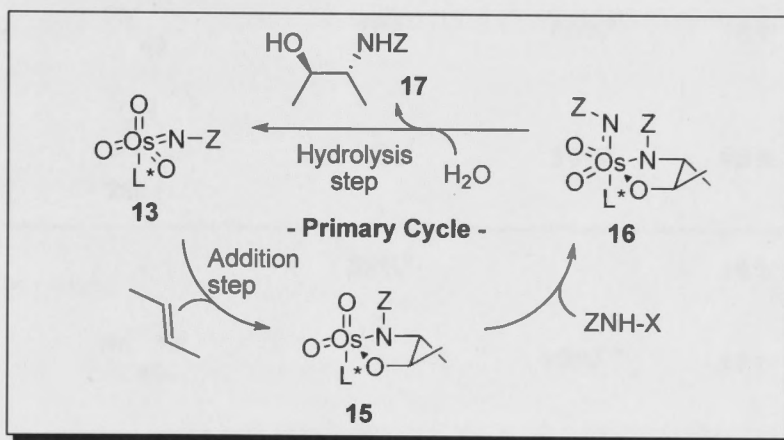
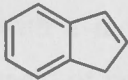
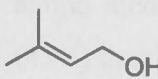
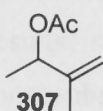
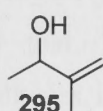
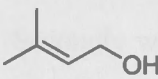
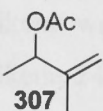
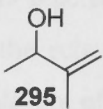


Figure 5.20

To understand better the reactivity of these different classes of alkenes and also find out whether the addition step or hydrolysis step was the rate determining step of the reaction, a set of competition experiments was performed. Two different types of alkenes were reacted with one equivalent of preformed nitrogen source benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** catalysed by osmium (4.0 mol%). Under these conditions the ratio of products would reflect the relative rate of addition to the double bond. Furthermore, the overall time for the reaction would reflect the rate of hydrolysis of the slowest component. Summary of the results were presented in **Table 5.7**.

Table 5.7

Entry	Substrates		Yield of product resulted		Time
			from alkenes		
	A	B	A	B	
1	 51	 49	43%	36% ^a	24 h
2	 229	 49	39% ^b	29% ^a	24 h
3	 243	 49	0%	66% ^b	16 h
4	 307	 295	16% ^c	34% ^c	96 h
5	 51	-	88% ^d	-	14 h
6	-	 49	-	89% ^{b,d}	16 h
7	 243	-	64% ^{a,d}	-	72 h
8	 307	-	68% ^{c,d}	-	66 h
9	-	 295	-	44% ^{c,d}	96 h

Note of reaction conditions: alkene A (1.0 equiv.), alkene B (1.0 equiv.), BnOCONHOTs **202** (1.0 equiv.), K₂OsO₂(OH)₄ (4.0 mol%), MeCN/H₂O (3:1), RT.

^aOne regioisomer was afforded; ^bTwo regioisomer was afforded; ^cTwo diastereomers were afforded. ^dUsing preformed nitrogen source **202** (1.2 equiv.).

In general the reactions afforded total product in good to excellent yield, and the reactions were completed in 16-96 h. For example, reaction between 3-methylbut-3-en-2-ol **295** and its acetate ester **307** afforded good yield and was completed over 96 h (entry 4). Meanwhile, reaction between 1*H*-indene **229** and styrene **49** afforded

excellent yield and was completed over 24 h (entry 2). The reaction only afforded styrene **49** products in competition between allylic alcohol **243** and styrene **49** (entry 3). Moreover, a high yield in total was afforded from competition between *trans*-stilbene **51** and styrene **49** (entry 1).

There were three groups of alkenes that gave different trends. First were the reactions in entry 1 and entry 2, which gave similar results when 1,2-disubstituted alkenes competed with a monosubstituted alkene. 1,2-Disubstituted alkenes afforded a slightly higher yield of product compared to the monosubstituted alkene. For example in entry 1, the amino alcohol resulting from *trans*-stilbene **51** was formed in slightly higher yield (43%) than that from styrene **49** (36%). The product resulting from 1*H*-indene **229** was formed in slightly higher yield (39%) than that from styrene **49** (29%) (entry 2). These results suggested that 1,2-disubstituted alkenes were more reactive than the monosubstituted alkenes in the addition step. Comparing the individual reactions of *trans*-stilbene **51** (entry 5) and styrene **49** (entry 6), both had similar yields and reaction rates. This suggested for mono- and 1,2-disubstituted alkenes there was little significant difference in the rate of addition or hydrolysis.

Secondly was the reaction in entry 3; the competition reaction between 3-methylbut-2-en-1-ol **243** and styrene **49**. This reaction showed that addition to the monosubstituted alkene was favoured strongly. No product from aminohydroxylation of trisubstituted alkene **243** was observed. If compared to the individual reactions (entry 6-7), it was clear that styrene **49** reacted faster and afforded higher yield than 3-methylbut-2-en-1-ol **243**. In this case the relative rate of addition controlled the product distribution and therefore the overall rate of reaction.

The final competition experiment is shown in entry 4. Previous results indicated that reaction of allylic acetate ester **307** (entry 8) worked in excellent yield with a shorter reaction time than its allylic alcohol **295** (entry 9). In contrast, competition of both substrate **307** and **295** found that allylic alcohol **295** afforded the product in higher yield than its acetate ester **307**. This implies addition to allylic alcohol **295** was faster than to the acetate ester **307** and suggests the low rate of addition is not responsible for the low yields afforded for allylic alcohol substrates. In comparing the individual rates, the acetate ester **307** reacted faster (66 h, 68%) than the allylic alcohol **295** (96 h, 44%).

This suggested that hydrolysis of the osmium(VIII) azaglycolate was rate determining in the reaction of allylic alcohol **295**, presumably due to the presence of the allylic alcohol functionality.

5.6 Conclusions

The diastereoselectivity study of the osmium-catalysed aminohydroxylation using benzyl *N*-(4-toluenesulfonyloxy) carbamate as preformed nitrogen source provided good yield and high regioselectivity with monosubstituted allylic alcohols and their acetate esters. The reaction worked but required long reaction times, and *O*-protection was observed to make reaction times shorter. The reaction diastereoselectivity was improved by increasing the size of C3 alkyl substituent adjacent to the double bond. Moreover, the transition-state model proposed by Houk and coworkers¹³² was consistent with the addition step affording *anti*-diastereomer as the major product.

Similar results were also provided with 1,1-disubstituted allylic alcohol substrates and their derivatives. Generally, low to high yields of amino alcohol products were afforded. Increasing the size of substituent attached at C3 in all substrates of allylic alcohols gave a decreasing yield of the amino alcohol product isolated. The *anti*-diastereomer was favoured over the *syn*-diastereomer, and increasing the size of substituent attached at C3 of the allylic alcohol afforded an improvement in the diastereoselectivity. Protection of hydroxyl-group increased the yield sharply, but did not give a significant increase in the diastereoselectivity. The transition-state models proposed by Houk and coworkers¹³² and Vedejs and coworkers¹³² were consistent with the diastereoselectivity of these reactions.

The diastereoselectivity study with trisubstituted allylic alcohols did not give significant results. Only two 1,2,2-disubstituted allylic alcohols afforded amino alcohol product, but in low yields. *O*-Protection of this class did not promote the reaction.

Another effort to accelerate the reaction by addition of methanesulfonamide¹⁴⁶ and tetraethylammonium acetate¹⁴⁷ gave no acceleration in the aminohydroxylation reaction catalysed by osmium with allylic alcohol substrates. Further investigation in competition reactions suggested both addition and hydrolysis could form the rate-determining step, depending on the nature of the substrate.

Chapter 6

General Discussion, Conclusion and Future Projects

Summary

This chapter will present a conclusion on the development of new preformed nitrogen sources for the osmium-catalysed aminohydroxylation reaction including suggestions for future work.

7.1 General discussion, conclusion and future prospects

The main objective of this project was to develop new nitrogen sources for osmium-catalysed aminohydroxylation reaction. This objective was derived from some limitations of the Sharpless asymmetric aminohydroxylation^{2,3} (AA) reaction especially the use of various and excessive reagents² to generate the nitrogen sources, chlorination of the substrates and amino alcohol products^{24,74} due to the chlorinating reagents used to generate the nitrogen sources. Besides that, the reaction requires basic conditions that are not suitable for some base-sensitive substrates.²⁴ This project also investigated ways to control the stereoselectivity of this reaction using preformed nitrogen sources.

In the chapter 2, six *tert*-butyl carbamate-based preformed nitrogen sources were synthesised, evaluated, and optimised for performing the aminohydroxylation reaction catalysed by osmium. These first generation preformed nitrogen sources consisted of *tert*-butyl *N*-(pentafluorobenzoyloxy)carbamates **149**, *tert*-butyl *N*-(2-chloroacetoxy)-carbamates **150**, *tert*-butyl *N*-(methanesulfonyloxy)carbamates **151**, *tert*-butyl *N*-(2,4,6-trimethylphenylsulfonyloxy)carbamates **152**, *tert*-butyl *N*-(4-toluenesulfonyloxy)-carbamates **153**, and *tert*-butyl *N*-(4-nitrophenylsulfonyloxy)carbamates **154**. Three important points can be concluded for these type preformed nitrogen sources: (i) these preformed nitrogen sources work under mildly acidic conditions (pH about 5), and did not work above that pH; (ii) the more acid the reaction conditions, the more products were afforded. These preformed nitrogen sources especially *tert*-butyl *N*-(methanesulfonyloxy)carbamate **151** still worked at reaction pH 1; (iii) this reaction works efficiently employing 2.0 equivalents of preformed nitrogen sources and 4.0 mol% osmium catalyst.

Employing chiral cinchona alkaloid ligand in the reaction using the first generation preformed nitrogen sources failed to afford enantioselectivity. Further efforts to control the stereoselectivity are an important avenue for further investigation. In addition, these nitrogen sources also work in mildly acidic reaction conditions. The acidic leaving group is responsible for the decreasing reaction pH. This leaves the way open to new preformed nitrogen sources with leaving groups suited for certain conditions and certain purposes. Exploring this methodology will be a good opportunity.

In the chapter 3, five ligands based on amino acid backbone have been developed for the aminohydroxylation reaction catalysed by osmium. They were *N*-(4-toluenesulfonyl)-*L*-threonine **185**, *N*-(4-nitrophenylsulfonyl)-*L*-threonine **188**, *N*-(4-methoxyphenylsulfonyl)-*L*-threonine **189**, *N*-(4-toluenesulfonyl)-*L*-serine **190**, and (*R*)-*N,N'*-bis(4-toluenesulfonyl)propanoic acid **191**. These ligands were able to induce stereoselectivity in the literature¹⁰² conditions. No stereoselectivity induction with preformed nitrogen sources was observed.

An important point that can be further explored in the future work, is expanding the conditions and substrate scope for these amino acid-based ligands. In the literature, this ligand could be employed under acidic pH (pH 5) for asymmetric dihydroxylation (AD) reaction. Investigating the best conditions for preformed nitrogen sources is suggested for future development.

In chapter 4 second generation preformed nitrogen sources were generated which were more base stable. The structure was constructed of *N*-(4-toluenesulfonyloxy) with various different alkyl carbamate groups, i.e. *tert*-butyl *N*-(4-toluenesulfonyloxy)-carbamate **153**, ethyl *N*-(4-toluenesulfonyloxy)carbamate **201**, benzyl *N*-(4-toluenesulfonyloxy)carbamate **202**, 2,2,2-trichloroethyl *N*-(4-toluenesulfonyloxy)carbamate **203**, and 2-(trimethyl-silyl)ethyl *N*-(4-toluenesulfonyloxy)carbamate **204**.

Four important points could be concluded. First, these second generation preformed nitrogen sources especially benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** are acidic and base stable. The osmium-catalysed aminohydroxylation reaction could be buffered from pH 1 to 11. However, the yield was observed to decrease with increasing reaction pH. Secondly, a near stoichiometric amount of the preformed nitrogen source (1.2 equiv.) provided good yields. Moreover, the reaction can work with 0.01 equivalents of potassium osmate dihydrate, and even 0.001 equivalents with prolonged reaction times. Both points make these preformed nitrogen sources more efficient than those typically used in the Sharpless AA reaction.

Third, the scope of this reaction with alkene substrates is wide. The reaction works well for mono- and di-substituted alkenes, giving high yields and regioselectivity. Reaction in trisubstituted alkenes decreased the yield and required longer reaction times but with

high regioselectivity. *tert*-Butyl **153**, benzyl **202**, and 2,2,2-trichloroethyl *N*-(4-toluenesulfonyloxy)carbamate **203** showed superiority and consistency as preformed nitrogen sources by providing high yield, meanwhile ethyl **201** and 2-(trimethylsilyl)ethyl *N*-(4-toluenesulfonyloxy)carbamate **204** gave lesser yield. Fourth, the reaction still affords low enantioselectivity. Finding new suitable ligands which are able to induce enantioselectivity for these preformed nitrogen sources is suggested for future work.

In the chapter 5, the diastereoselectivity of the osmium-catalysed aminohydroxylation reaction using benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** as preformed nitrogen source was studied on allylic alcohol substrates. Five results can be concluded. First, the reaction in monosubstituted allylic alcohols showed a high yield and moderate diastereoselectivity with reaction times generally below 72 h. Protection of the allylic alcohols accelerate the reaction. Second, a moderate to high yield and improved diastereoselectivity was afforded for 1,1-disubstituted allylic alcohols. *O*-Protection accelerated the reactions. Third, the reaction does not proceed well for trisubstituted allylic alcohols. The reaction gave low yields of product for two 1,2,2-allylic alcohols. Fourth, the addition of methanesulfonamide and tetraethylammonium acetate does not give acceleration of the reaction nor higher yields. And the last, the addition and hydrolysis steps were observed as rate determining steps of the osmium-catalysed aminohydroxylation reaction.

One point that deserves further investigation is applying terminal allylic alcohols with *O*-protection. The reactions with these type substrates gave a high yield and good diastereoselectivity. Further optimisation of the reaction conditions will allow applications in organic synthesis.

Chapter 7

Experimental Sections

Summary

This chapter presents a detailed description of the instrumentation and conditions used for this research, data and experimental procedures that make up this thesis, including (i) the experimental section chapter 2, (ii) the experimental section chapter 3, (iii) the experimental section chapter 4, and (iv) the experimental section chapter 5.

7.1 Instrumentation and conditions

Melting points were determined using Optimelt Automated Melting Point System MPA100 and are uncorrected. Infrared spectra were analysed on a Spectrum One Perkin Elmer spectrometer with samples prepared as a thin film on NaCl plates. Optical rotations were measured on a Perkin Elmer Polarimeter 241MC at the sodium D-line (589 nm).

Proton nuclear magnetic resonance spectra (^1H -NMR) were recorded on a Varian MR 400 MHz or Mercury 300 MHz spectrometer data and were reported relative to tetramethylsilane (0.00 ppm) or residual solvent used such as chloroform (7.26 ppm). Carbon nuclear magnetic resonance spectra (^{13}C -NMR) were recorded on a Varian MR 400 (100 MHz) or Mercury-300 (75.0 MHz) spectrometer and reported relative to residual solvent used such as chloroform (77.2 ppm).

High performance liquid chromatography (HPLC) was performed on an PDR Chiral System using an Agilent Technology 1200 series autosampler, isocratic pump with UV multi wavelength detector, using chiralcel OD-H ($\varnothing$ 0.46 mm, 25 cm length) or chiralpak AS-H ($\varnothing$ 0.46 mm, 25 cm length) columns. Preparative HPLC was performed on a Waters HPLC with diode array detector, Rheodyne TR5 injector, using a Waters SunFire Prep OBD Silica 5 μm 19x150 mm column.

Low resolution mass spectra were run on a Micromass ZMD ESI-Quad Mass Spectrometer and for high resolution work on a Waters LCT Premier XE ESI-TOF mass spectrometer. GC/MS were recorded on an Agilent 5973 mass selective detector / HP 6890 GC.

X-ray diffraction data sets from crystal samples were collected on a Nonius Kappa-CCD area-detector diffractometer equipped with an IFG capillary focusing collimator and Oxford Cryosystem crystal cooling device. The data were processed using Crystal and Rael's software packages.

Thin layer chromatography was run in pre-coated silica gel plates using Merck Silicagel 60 F₂₅₄ 0.2 mm and TLC spots were visualized with a UV detector lamp (254 and 265

nm) or stained with potassium permanganate dips. Flash chromatography was performed using Merck Silica Gel 60 (230-400 mesh) in the specified solvent systems.

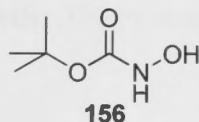
7.2 Experimental Section for Chapter 2

***tert*-Butyl carbamate based preformed nitrogen source for the osmium-catalysed aminohydroxylation reaction : Synthesis, optimisation and evaluation**

General procedure 2.1 : Synthesis first generation preform nitrogen sources

To a solution of *tert*-butyl *N*-hydroxycarbamate **156** in diethyl ether (15.0 mL) was added carboxylic acid chloride or sulfonyl chloride at 0 °C. To this reaction mixture was added triethylamine and the reaction was stirred at room temperature until complete. The reaction mixture was quenched with water and separated. The aqueous layer was extracted with dichloromethane (3 x), and the combined dichloromethane layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to afford crude product. Purification was conducted with flash chromatography using the specified solvents.

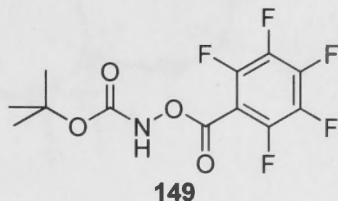
***tert*-Butyl *N*-hydroxycarbamate⁸³**



To a suspension of hydroxylamine hydrochloride (2.43 g, 35.0 mmol) and sodium carbonate (2.43 g, 23.0 mmol) in diethyl ether (15.0 mL) and water (1.0 mL) at 0 °C was added solution of di-*tert*-butyl dicarbonate, (5.02 g, 23.0 mmol) in diethyl ether (5.0 mL) over 30 min. The reaction mixture was stirred at room temperature until complete (3 h), quenched with solution sodium bicarbonate (5.0 mL, 1.0 M) and extracted with diethyl ether (10 mL). The aqueous layer was further extracted with diethyl ether (2 x 20 mL). The combined diethyl ether layers were washed with brine (10 mL), dried over magnesium sulfate and concentrated under reduced pressure to provide the title compound **156** as a white needles (2.68 g, 87%). R_f 0.47 (50% ethyl acetate/n-hexane), mp 55-56 °C (lit.⁸⁹ 58-59 °C). IR (thin film, cm^{-1}) 3285 (broad, O-H, N-H), 2980, 2937, 2923, 2867, 2844 (C-H), 1711 (C=O), 1646. $^1\text{H-NMR}$ (300 MHz, CDCl_3) 6.97 (1H, s,

NH), 6.22 (1H, s, OH), 1.48 (9H, s, C(CH₃)₃). ¹³C-NMR (100 MHz, CDCl₃) 158.83, 82.24, 28.18. LRMS (ESI+) 156 ([M+Na]⁺, 39%), 100 (100), 78 (35), 56 (33).

***tert*-Butyl *N*-(pentafluorobenzoyloxy)carbamate¹⁴⁸**



The reaction was conducted according to the General Procedure 2.1 with *tert*-butyl *N*-hydroxycarbamate **156** (666 mg, 5.00 mmol), pentafluorobenzoyl chloride (1.15 g, 5.00 mmol), and triethylamine (567 mg, 5.60 mmol). Purification by flash chromatography (15% ethyl acetate/*n*-hexane) afforded the title compound **149** as a yellow oil (1.10 g, 67%). *R*_f 0.53 (40% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3276 (N-H), 2985, 2938 (C-H), 1783, 1741 (C=O), 1653. ¹H-NMR (300 MHz, CDCl₃) 8.13 (1H, s, NH), 1.51 (9H, s, C(CH₃)₃). ¹³C-NMR (75 MHz, CDCl₃) 158.9, 155.3, 146.1 (d, *J* 267 Hz), 144.32 (d, *J* 261 Hz), 138.1 (d, *J* 257 Hz), 105.4, 84.3, 28.0. LRMS (ESI+) 350 ([M+Na]⁺, 8%), 294 (21), 268 (20), 266 (13), 228 (43), 195 (100), 167 (60), 135 (12), 119 (15), 100 (20), 72 (21), 57 (58). HRMS (ESI+) calcd. for C₁₂H₁₀NO₄F₅Na ([M+Na]⁺) 350.0428, found 350.0427.

Recrystallisation using *n*-hexane afforded a white crystal. The presence of O9-C10 bond from X-ray analysis confirmed the structure of *tert*-butyl *N*-(pentafluorobenzoyloxy)carbamate¹⁴⁸ **149** and the acylation had occurred at the hydroxyl-group of *tert*-butyl *N*-hydroxycarbamate (**Figure 7.2.1**).

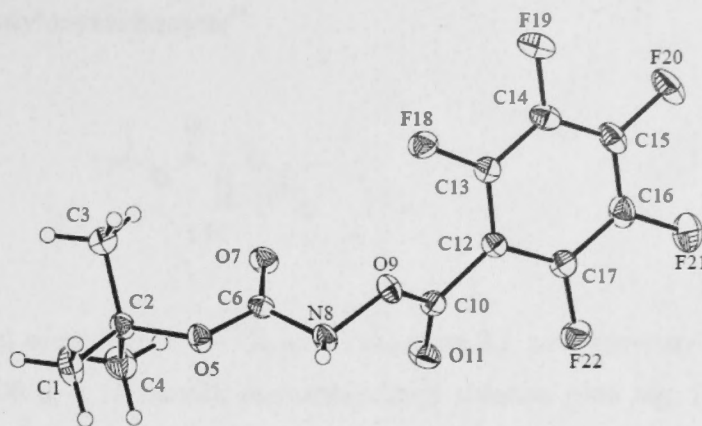
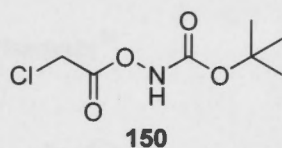


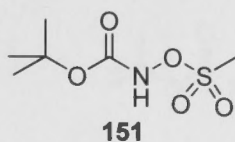
Figure 7.2.1 Structure of $C_{12}H_{10}F_5NO_4$ with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

***tert*-Butyl *N*-(2-chloroacetoxy)carbamate**



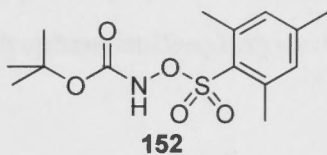
The reaction was conducted according to the General Procedure 2.1 with *tert*-butyl *N*-hydroxycarbamate **156** (98.0 mg, 0.74 mmol), chloroacetyl chloride (91.4 mg, 0.81 mmol), and diisopropyl ethylamine (105 mg, 0.81 mmol). Purification by flash chromatography (30% ethyl acetate/*n*-hexane) provided the title compound **150** as yellow oil (131 mg, 85%). R_f 0.33 (30% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3271 (N-H), 2982 (C-H), 1795, 1737 (C=O). 1H -NMR (300 MHz, $CDCl_3$) 8.14 (1H, s, NH), 4.20 (2H, s, CH_2), 1.47 (9H, s, $C(CH_3)_3$). ^{13}C -NMR (75 MHz, $CDCl_3$) 167.3, 155.2, 84.3, 38.9, 28.2. LRMS (EI+) 212 (M^{+}), 194 ($[M-CH_3]^+$), 154, 136, 115, 77, 58, 49, 43. HRMS (EI+) calcd. for $C_6H_9NO_4^{35}Cl$ ($[M-CH_3]^+$) 194.0220, found 194.0222; calcd. for $C_6H_9NO_4^{37}Cl$ ($[M-CH_3]^+$) 196.0191, found 196.0193.

***tert*-Butyl *N*-methanesulfonyloxycarbamate⁸⁸**



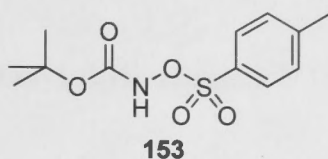
The reaction was conducted according to the General Procedure 2.1 with *tert*-butyl *N*-hydroxycarbamate **156** (1.00 g, 7.51 mmol), methanesulfonyl chloride (946 mg, 8.26 mmol), and triethylamine (836 mg, 8.26 mmol). The title compound **151** was afforded without purification as a white solid (1.47g, 93%), R_f 0.31 (40% ethyl acetate/*n*-hexane), mp 85-86 °C (lit.⁸⁸ 83-85 °C). IR (thin film, cm^{-1}) 3292 (N-H), 1741 (C=O). ^1H -NMR (300 MHz, CDCl_3) 7.92 (1H, s, NH), 3.17 (3H, s, CH_3), 1.51 (9H, s, $\text{C}(\text{CH}_3)_3$). ^{13}C -NMR (75 MHz, CDCl_3) 154.79, 85.02, 36.58, 28.21. LRMS (EI+) 196 ($[\text{M}-\text{CH}_3]^+$, 15%) 137 (49), 79 (100). HRMS (EI+) calcd. for $\text{C}_5\text{H}_{10}\text{NO}_5\text{S}$ ($[\text{M}-\text{CH}_3]^+$) 196.0280, found 196.0276.

***tert*-Butyl *N*-(2-mesitylenesulfonyloxy)carbamate⁸⁶**



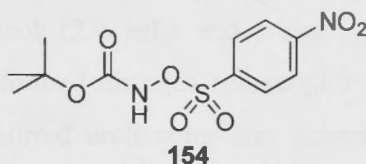
The reaction was conducted according to the General Procedure 2.1 with *tert*-butyl *N*-hydroxycarbamate **156** (399 mg, 3.00 mmol), mesitylsulfonyl chloride (729 mg, 3.06 mmol), and triethylamine (310 mg, 3.06 mmol). Purification by flash chromatography (20% ethyl acetate/*n*-hexane) provided the title compound **152** as a white solid (551 mg, 58%), R_f 0.24 (20% ethyl acetate/*n*-hexane), mp 99.5-102 °C (lit.⁸⁶ 104.0-105.5 °C). IR (thin film, cm^{-1}) 3292 (N-H), 1768, 1732, 1705 (C=O), 1603. ^1H -NMR (300 MHz, CDCl_3) 7.77 (1H, s, NH), 6.98 (2H, s, ArH), 2.66 (6H, s, 2x CH_3), 2.31 (3H, s, CH_3), 1.30 (9H, s, $\text{C}(\text{CH}_3)_3$). ^{13}C -NMR (75 MHz, CDCl_3) 154.5, 144.7, 142.2, 131.9, 128.7, 84.1, 27.9, 23.4, 21.4.

***tert*-Butyl *N*-(4-toluenesulfonyloxy)carbamate⁸⁹**



The reaction was conducted according to the General Procedure 2.1 with *tert*-butyl *N*-hydroxycarbamate **156** (1.96 g, 14.8 mmol), diethyl ether (60 mL), 4-toluenesulfonyl chloride (3.09 g, 16.2 mmol), and triethylamine (1.64 g, 16.2 mmol). Purification by flash chromatography (25% ethyl acetate/*n*-hexane) afforded the title compound **153** as a white solid (3.01 g, 71%), R_f 0.18 (25% ethyl acetate/*n*-hexane), mp 88-89 °C (lit.⁸⁹ 97 °C). IR (thin film, cm^{-1}) 3289 (N-H), 3071, 2982, 2934 (C-H), 1768, 1730, 1709 (C=O), 1597. $^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.89 (2H, d, J 8.10 Hz, ArH), 7.61 (1H, s, NH), 7.37 (2H, d, J 8.10 Hz, ArH), 2.47 (3H, s, CH_3), 1.30 (9H, s, $\text{C}(\text{CH}_3)_3$). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 154.06, 145.90, 130.53, 129.64, 129.60, 83.84, 27.67, 21.71. LRMS (ESI+) 310 ($[\text{M}+\text{Na}]^+$, 25%), 254 (100), 188 (29), 106 (87). HRMS (ESI+) calcd. for $\text{C}_{12}\text{H}_{17}\text{NO}_5\text{SNa}$ ($[\text{M}+\text{Na}]^+$) 310.0725, found 310.0719.

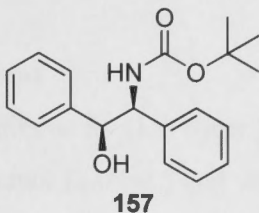
***tert*-Butyl *N*-(*p*-nitrophenylsulfonyloxy)carbamate⁹⁰**



The reaction was conducted according to the General Procedure 2.1 with *tert*-butyl *N*-hydroxycarbamate **156** (0.799 g, 6.00 mmol), diethyl ether (60 mL), *p*-nitrophenylsulfonyl chloride (1.34 g, 6.06 mmol), triethylamine (0.618 g, 6.11 mmol). Purification by flash chromatography (25% ethyl acetate/*n*-hexane) provided the title compound **154** as a white-yellow solid (0.881 g, 51%), R_f 0.58 (50% ethyl acetate/*n*-hexane), mp 95.5-97 °C (lit.⁹⁰ 91-92 °C). IR (thin film, cm^{-1}) 3306 (N-H), 3109 (C-H), 1733 (C=O). $^1\text{H-NMR}$ (300 MHz, CDCl_3) 10.35 (1H, s, NH), 8.55 (2H, d, J 9.0 Hz, ArH), 8.31 (2H, d, J 9.0 Hz, ArH), 1.30 (9H, s, $\text{C}(\text{CH}_3)_3$). $^{13}\text{C-NMR}$ (75 MHz, D_6 -

acetone) 27.26, 83.10, 124.53, 131.40, 139.73, 151.77, 154.71. LRMS (ESI+) 341 ([M+Na]⁺, 50%), 335 (68), 333 (30), 319 (46), 317 (100), 312 (40), 310 (48).

***tert*-Butyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate³⁸**



Mp 130-131 °C (lit.³⁸ 137-138 °C). IR (thin film, cm⁻¹) 3415 (brd, O-H, N-H), 3088, 3064, 3031, 3006, 2977, 2929 (C-H), 1691 (C=O), 1604, 1586; ¹H-NMR (300 MHz, CDCl₃) 7.23-7.31 (10H, m, ArH), 5.48 (1H, s, NH), 4.89 (2H, s, H1 and H2), 2.94 (1H, s, OH), 1.34 (9H, s, C(CH₃)₃). ¹³C-NMR (75 MHz, CDCl₃) 156.05, 140.83, 139.91, 128.48, 128.18, 127.66, 127.48, 126.93, 126.32, 79.83, 77.39, 60.72, 28.24. LRMS (ESI+) 336 ([M+Na]⁺, 100%), 320 (5), 280 (19), 240 (7), 236 (30), 196 (22). HRMS (ESI+) calcd. for C₁₉H₂₃NO₃Na ([M+Na]⁺) 336.1576, found 336.1572.

General procedure 2.2 : Evaluation of pre-formed nitrogen source

To a mixture of *trans*-stilbene **51** (1.0 equiv.), (DHQD)₂PHAL (5.0 mol%), K₂OsO₂(OH)₄ (4.0 mol%) in *n*-propanol (3.0 mL) and water (2.5 mL) at room temperature was added solution of preformed nitrogen source (2.0 eq) in *n*-propanol (4.0 mL). This reaction mixture was stirred until complete, quenched with solution sodium bisulfite (5.0 mL, 1.0 M) and stirred for 30 min. The mixture was filtered through celite and the filtrate was extracted with ethyl acetate (3 x 10 mL). The combined organic extract was washed with brine (10 mL), dried (Na₂SO₄), and concentrated under reduced pressure to afford crude product. Purification was conducted by flash chromatography to afford *tert*-butyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate **157**. The enantioselectivity for this product was determined by using HPLC (Chiralcell OD-H silica 5 μm 150 x 0.46 mm, 10% isopropanol/*n*-hexane, 1.0 mL/min).

Variation was performed on this procedure with different nitrogen sources : *tert*-butyl *N*-(pentafluorobenzoyloxy)carbamate **149**, *tert*-butyl *N*-(2-chloroacetoxy)carbamate **150**, *tert*-butyl *N*-(methanesulfonyloxy)carbamate **151**, *tert*-butyl *N*-(2-mesitylenesulfonyloxy)carbamate **152**, *tert*-butyl *N*-(4-toluenesulfonyloxy)carbamate **153**, and *tert*-butyl *N*-(4-nitrophenylsulfonyloxy)carbamate **154**.

Optimisation of solvent

To a mixture *trans*-stilbene **51** (1.0 equiv.), (DHQD)₂PHAL (5.0 mol%), K₂OsO₂(OH)₄ (4.0 mol%) in *n*-propanol (3.0 mL) and water (2.5 mL) at room temperature was added solution of *tert*-butyl *N*-(methanesulfonyloxy)carbamate **151** (2.0 equiv.) in *n*-propanol (4.0 mL). This reaction mixture was stirred until complete, quenched with aqueous sodium bisulfite solution (5.0 mL, 1.0 M) and stirred for 30 min. The mixture was filtered through celite, and extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate extract was washed with brine (10 mL), dried (Na₂SO₄), and concentrated under reduced pressure to afford crude product. Purification by flash chromatography afforded *tert*-butyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate **157**.

Variation was performed using series of solvents, i.e. acetonitrile/water (3:1), *tert*-butanol/water (3:1), *tert*-butanol/water (2:1), *tert*-butanol/water (1:1), and *tert*-butanol/water (1:2). The amino alcohol product was identified from IR spectrum, ¹H- and ¹³C-NMR spectrum and was compared to the reported data.

Optimisation of preformed nitrogen source and catalyst loading

To a mixture *trans*-stilbene **51** (1.0 equiv.), (DHQD)₂PHAL (5.0 mol%), K₂OsO₂(OH)₄ (4.0 mol%) in *tert*-butanol (3.0 mL) and water (2.5 mL) at room temperature was added solution of *tert*-butyl *N*-(methanesulfonyloxy)carbamate **151** (2.0 equiv.) in *tert*-butanol (4.0 mL). This reaction mixture was stirred until complete, quenched with aqueous sodium bisulfite solution (5.0 mL, 1.0 M) and stirred for 30 min. The mixture was filtered through celite, and extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate extract was washed with brine (10 mL), dried (Na₂SO₄), and concentrated under reduced pressure to afford crude product. Purification by flash chromatography afforded *tert*-butyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate **157**.

Variation was applied to above procedure using *tert*-butyl *N*-(methanesulfonyl-oxy)carbamate **151** 1.0 equiv., 1.5 equiv., and 3.0 equiv.; and potassium osmate dihydrate 1.0 mol%, 5.0 mol%, and 10 mol%.

Preparation of buffer solutions

Buffer solutions for each pH value was prepared by the addition of solution A to solution B and dilution with distilled water to 100 mL volume, as tabulated below.^{95,149}

pH	Solution A	Solution B
11.0	50 mL NaHCO ₃ 0.05 M	add NaOH 0.1 M until pH 11 (~23 mL), and diluted to 100 mL
10.0	50 mL Borax 0.025 M	Add NaOH 0.1 M until pH 10 (~18 mL), and diluted to 100 mL
9.0	50 mL Borax 0.025 M	Add HCl 0.1 M until pH 9.0 (~4.5 mL), and diluted to 100 mL
8.0	50 mL KH ₂ PO ₄ 0.1 M	Add NaOH 0.1 M until pH 8.0 (~ 46 mL), and diluted to 100 mL
7.0	50 mL KH ₂ PO ₄ 0.1 M	Add NaOH 0.1 M until pH 7.0 (~29 mL), and diluted to 100 mL
6.0	50 mL KH ₂ PO ₄ 0.1 M	Add NaOH 0.1 M until pH 6.0 (~5.6 mL), and diluted to 100 mL
5.0	50 mL Potassium hydrogen phthalate 0.1 M	Add NaOH 0.1 M until pH 5.0 (~ 22.5 mL) and diluted to 100 mL
4.0	50 mL Potassium hydrogen phthalate 0.1 M	Add NaOH 0.1 M until pH 4.0 (~ 2.0 mL) and diluted to 100 mL
3.0	50 mL Potassium hydrogen phthalate 0.1 M	Add HCl 0.1 M until pH 3.0 (~22.5 mL) and diluted to 100 mL
2.0	25 mL KCl 0.2 M	Add HCl 0.2 M until pH 2.0 (~ 6.0 mL) and diluted to 100 mL
1.0	25 mL KCl 0.2 M	Add HCl 0.2 M until pH 1.0 (~66 mL) and diluted to 100 mL

Optimisation of reactions pH

To a mixture of *trans*-stilbene **51** (1.0 equiv.), (DHQD)₂PHAL (5.0 mol%), potassium osmate dihydrate (4.0 mol%) in *tert*-butanol (4.5 mL) and water (2.5 mL) at 0 °C was added a solution *tert*-butyl *N*-(methanesulfonyloxy)carbamate **151** (2.0 eq.) in *tert*-butanol (3.0 mL) and pH 1 buffer (0.85 mL). This reaction mixture was stirred, and maintained at desired pH by addition of buffer solution, until complete. Sodium bicarbonate solution (5.0 mL, 2.0 M) was added and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extract was washed with brine (10 mL), dried (Na₂SO₄), and concentrated under reduced pressure. Product purification was conducted by flash chromatography to afford *tert*-butyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate **157**. The enantioselectivity for this product was determined by using HPLC (Chiralcel OD-H silica 5 µm 150 x 0.46 mm, solvent 10% isopropanol/*n*-hexane, flow rate 1.0 mL/min)

Using a similar procedure, a series of reactions were performed for pH 2 to 11. The amino alcohol product was identified from IR spectrum, ¹H- and ¹³C-NMR spectra and was compared to the reported data.

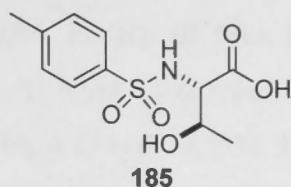
7.3 Experimental Section for Chapter 3

Amino acid based ligands : Synthesis and evaluation in the osmium-catalysed aminohydroxylation reaction using preformed nitrogen sources

General procedure 3.1 : Synthesis of amino acid-based ligands

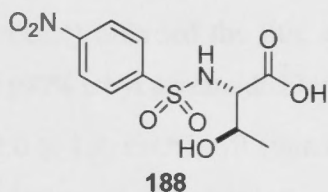
To the amino acid (1 equiv.) in a biphasic mixture of organic solvent and water was added sodium carbonate (2.5 equiv.), followed by the appropriate arenesulfonyl chloride (1.5 equiv.). The reaction mixture was stirred at room temperature until complete. The mixture was separated and the aqueous layer was acidified with hydrochloric acid 1 M. The precipitate that resulted was collected, or extracted with ethyl acetate (2 x 20 ml), dried (MgSO₄) and concentrated under reduced pressure to yield the product.

N-(4-Toluenesulfonyl)-*L*-threonine¹¹¹



The reaction was conducted according to general procedure 3.1 using *L*-threonine **192** (500 mg, 4.11 mmol), sodium carbonate (981 mg, 9.26 mmol), toluenesulfonyl chloride (863 mg, 4.52 mmol) and ethyl acetate/water (10 mL / 5 mL). The reaction mixture was extracted with ethyl acetate (3 x 20 mL), dried (MgSO₄) and concentrated under reduced pressure to provide the title compound **185** as a white solid (790 mg, 71%). *R*_f 0.26 (20% methanol/ethyl acetate), mp 131-134 °C (lit.¹¹¹ 100-102 °C), [α]_D²⁰ +11.1 (c 1.7, EtOH). IR (thin film, cm⁻¹) 3449 (O-H), 3259 (N-H), 3069, 2981, 2931 (C-H), 1728 (C=O), 1597 (C=C). ¹H-NMR (300 MHz, CD₃OD) 7.73 (2H, d, *J* 8.1, ArH), 7.33 (2H, d, *J* 7.8 Hz, ArH), 4.13 (1H, qd, *J* 6.3, 3.3 Hz, H3), 3.77 (1H, d, *J* 3.3 Hz, H2), 2.40 (3H, s, Ar-CH₃), 1.18 (3H, d, *J* 6.3 Hz, H4). ¹³C-NMR (75 MHz, CD₃OD) 171.87, 143.74, 137.91, 129.34, 127.13, 67.93, 61.68, 20.27, 19.02. LRMS (ESI+) 296 ([M+Na]⁺, 100%), 274 ([M+H]⁺, 12), 228 (34), 155 (16), 102 (12), 74 (46), 73 (42). HRMS (ESI+) calcd. for C₁₁H₁₅NO₅SNa ([M+Na]⁺) 296.0569, found 296.0568.

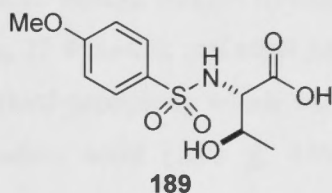
N-(4-Nitrophenylsulfonyl)-*L*-threonine



The reaction was conducted according to the general procedure 3.1 using *L*-threonine **192** (490 mg, 4.11 mmol), sodium carbonate (981 mg, 9.26 mmol), *p*-nitrobenzenesulfonyl chloride (1.82 g, 8.23 mmol), and benzene/water (10 mL / 5 mL). The reaction mixture was washed with benzene (2 x 20 mL) and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined ethyl acetate extract was dried (MgSO₄) and concentrated under reduced pressure to afford crude product. Purification

by flash chromatography (20% methanol/ethyl acetate) afforded the title compound **188** as a white solid (901 mg, 73%). R_f 0.26 (20% methanol/ethyl acetate), mp 126-128.4 °C, $[\alpha]_D^{20} +5.5$ (c 0.96, EtOH). IR (thin film, cm^{-1}) 3273 (N-H), 3106 (C-H), 1734 (C=O), 1602, 1527. $^1\text{H-NMR}$ (300 MHz, CD_3OD) 8.35 (2H, d, J 9.1 Hz, ArH), 8.10 (2H, d, J 9.1 Hz, ArH), 4.15 (1H, m, H3), 3.90 (1H, d, J 3.1 Hz), 1.23 (3H, d, J 6.39 Hz, H4) (OH not observed). $^{13}\text{C-NMR}$ (75 MHz, CD_3OD) 171.63, 150.17, 146.88, 128.53, 123.93, 67.75, 61.72, 19.17. HRMS (ESI+) calcd. for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_7\text{SNa}$ ($[\text{M}+\text{Na}]^+$) 327.0263, found 327.0257.

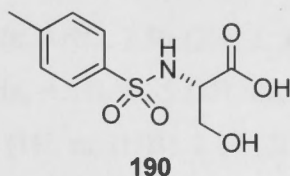
N-(4-Methoxyphenylsulfonyl)-*L*-threonine¹¹¹



The reaction was conducted according to general procedure 3.1 with minor modification using *L*-threonine **192** (100 mg, 0.84 mmol), sodium carbonate (174 mg, 2.10 mmol), *p*-methoxybenzenesulfonyl chloride (226 mg, 1.09 mmol) and tetrahydrofuran/water (8 mL / 8 mL). The reaction mixture was washed with benzene (6.0 mL), acidified with concentrated phosphoric acid, and extracted with ethyl acetate (3 x 10 mL). The combined organic extract was dried (MgSO_4) and concentrated under reduced pressure to afford crude product. Purification by flash chromatography (90% ethyl acetate/dichloromethane) afforded the title compound **189** as a colorless solid (125.6 mg, 52%). R_f 0.22 (90% ethyl acetate/dichloromethane), mp 143.0-144.5 °C (lit.¹¹¹ 139-141 °C), $[\alpha]_D^{20} +12.0$ (c 1.2, EtOH). IR (thin film, cm^{-1}) 3455 (O-H), 3296 (N-H), 3104, 3078, 2980, 2943, 2843 (C-H), 1729 (C=O), 1596 (C=C). $^1\text{H-NMR}$ (300 MHz, d_6 -acetone) 7.81 (2H, d, J 9.3 Hz, ArH), 7.05 (2H, d, J 9.0 Hz, ArH), 6.21 (1H, d, J 9.3 Hz, NH), 4.21 (1H, m, H3), 3.87 (3H, s, CH_3), 3.82 (1H, d, J 9.3 Hz, H2), 1.19 (3H, d, J 6.3 Hz, H4) (OH not observed). $^{13}\text{C-NMR}$ (75 MHz, d_6 -acetone) 171.03, 162.99, 133.02, 129.47, 114.14, 67.97, 61.31, 55.39, 19.76. LRMS (ESI+) 312 ($[\text{M}+\text{Na}]^+$, 80%), 290 ($[\text{M}+\text{H}]^+$, 10), 244 (8), 171 (20), 102 (55), 74 (100), 56 (22). HRMS (ESI+) calcd. for

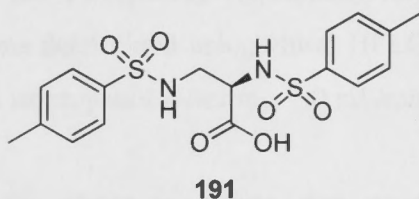
$C_{11}H_{16}NO_6S$ ($[M+H]^+$) 290.0698, found 290.0698; calcd. for $C_{11}H_{15}NO_6SNa$ ($[M+Na]^+$) 312.0518, found 312.0518.

***N*-(4-Toluenesulfonyl)-*L*-serine¹¹²**



The reaction was conducted according to the general procedure 3.1 with minor modification using *L*-serine **193** (1.00 g, 9.52 mmol), sodium hydroxide (1.03 mg, 25.7 mmol), *p*-toluenesulfonyl chloride (2.36 g, 12.4 mmol), and ethyl acetate/water (13 mL / 7 mL). The mixture was acidified to afford precipitate which was dried *in vacuo* to afford the title compound **190** as a white solid (1.03 g, 42%). R_f 0.20 (20% methanol/ethyl acetate), $[\alpha]_D^{20} +11.4$ (c 1.6, MeOH), mp 219.0-220.5 °C (lit.¹¹² 236 °C). IR (thin film, cm^{-1}) 3404 (broad, O-H, N-H), 3280 (C-H), 1732 (C=O). 1H -NMR (300 MHz, d_6 -acetone) 7.78 (2H, d, J 8.2 Hz, ArH), 7.37 (2H, d, J 8.0 Hz, ArH), 6.53 (1H, s, broad, NH), 3.97 (1H, m, H2), 3.88-3.71 (2H, m, H3), 2.40 (3H, s, CH₃) (OH not observed). ^{13}C -NMR (75 MHz, d_6 -acetone) 171.69, 143.52, 137.99, 129.40, 127.06, 63.07, 58.06, 20.27. LRMS (ESI+) 282 ($[M+Na]^+$, 100%). HRMS (ESI+) calcd. for $C_{10}H_{14}NO_5S$ ($[M+H]^+$) 260.0593, found 260.0593.

(2*R*)-*N,N'*-Bis(4-toluenesulfonyl)-2,3-diaminopropanoic acid¹¹³



The reaction was conducted according to the general procedure 3.1 with minor modification using (2*R*)-2,2-diaminopropanoic acid **194** (100 mg, 0.71 mmol), sodium hydroxide (71.1 mg, 1.78 mmol), *p*-toluenesulfonyl chloride (339 mg, 1.78 mmol), and 1,4-dioxane/water (3.5 mL / 3.5 mL). The reaction was acidified and extracted with

ethyl acetate (3 x 10 mL). The combined organic extract was dried (MgSO₄) and concentrated *in vacuo* to afford the title compound **191** as a colorless solid (212.1 mg, 72%). R_f 0.4 (30% methanol/ethyl acetate), mp 228-229 °C (lit¹¹³ 227-228 °C), [α]_D²⁰ -35.8 (c 1.1, EtOH). IR (thin film, cm⁻¹) 3435 (broad, O-H, N-H), 2886 (C-H), 1661 (C=O). ¹H-NMR (400 MHz, d₆-DMSO) 7.99 (1H, d, *J* 9.6 Hz, NH), 7.68 (1H, m, NH), 7.62 (2H, d, *J* 8.4 Hz, ArH), 7.55 (2H, d, *J* 8.0 Hz, ArH), 7.37 (2H, d, *J* 8.4 Hz, ArH), 7.33 (2H, d, *J* 8.0 Hz, ArH), 3.85 (1H, dd, *J* 15.2, 8.8 Hz, H₂), 3.35 (1H, s, OH), 2.82 (1H, m, H_{3A}), 2.66 (1H, m, H_{3B}), 2.37 (3H, s, CH₃), 2.38 (3H, s, CH₃). ¹³C-NMR (100 MHz, d₆-DMSO) 170.61, 142.85, 142.67, 138.13, 136.76, 129.64, 129.48, 126.54, 126.49, 55.60, 44.20, 20.99 (2C). LRMS (ESI+) 451 ([M+K]⁺, 50%), 435 ([M+Na]⁺, 100), 413 (10), 367 (8), 213 (10), 57 (18). HRMS (ESI+) calcd. for C₁₇H₂₀N₂O₆NaS₂ ([M+Na]⁺) 435.0661, found 435.0666.

General procedure 3.2 : Evaluation of amino acid-based ligands in the aminohydroxylation reaction catalysed by osmium

To a mixture of *trans*-stilbene **51** (1.0 equiv.), *N*-(4-toluenesulfonyl)-*L*-threonine **185** (0.05 equiv.), and potassium osmate dihydrate (4.0 mol%) in *tert*-butanol (4.0 mL) and water (2.5 mL) at 0 °C was added solution *tert*-butyl *N*-(methanesulfonyloxy)carbamate **151** (1.2 equiv.) in *tert*-butanol (3.0 mL). This reaction mixture was stirred at room temperature until complete, aqueous sodium bisulfite solution (5.0 mL, 1.0 M) was added and the mixture was stirred for 30 min. The mixture was filtered through celite and the filtrate was extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate extract was washed with brine (10 mL), dried (Na₂SO₄) and concentrated under reduced pressure to afford crude product. Purification by flash chromatography provided pure *tert*-butyl (1*R**,2*S**)-2-hydroxy-1,2-diphenylethylcarbamate **157**. Enantioselectivity of the reaction was determined using chiral HPLC (Chiralcel OD-H Silica 5 μm, 150 x 0.46 mm, 10% isopropanol/*n*-hexane, 1.0 mL/min).

Variation to the above procedure was conducted using alternate ligands *N*-(4-nitrophenylsulfonyl)-*L*-threonine **188**, *N*-(4-methoxyphenylsulfonyl)-*L*-threonine **189**, *N*-(4-toluenesulfonyl)-*L*-serine **190**, (2*R*)-*N,N'*-bis(4-toluenesulfonyl)-2,3-diaminopropanoic acid **191** and without ligand.

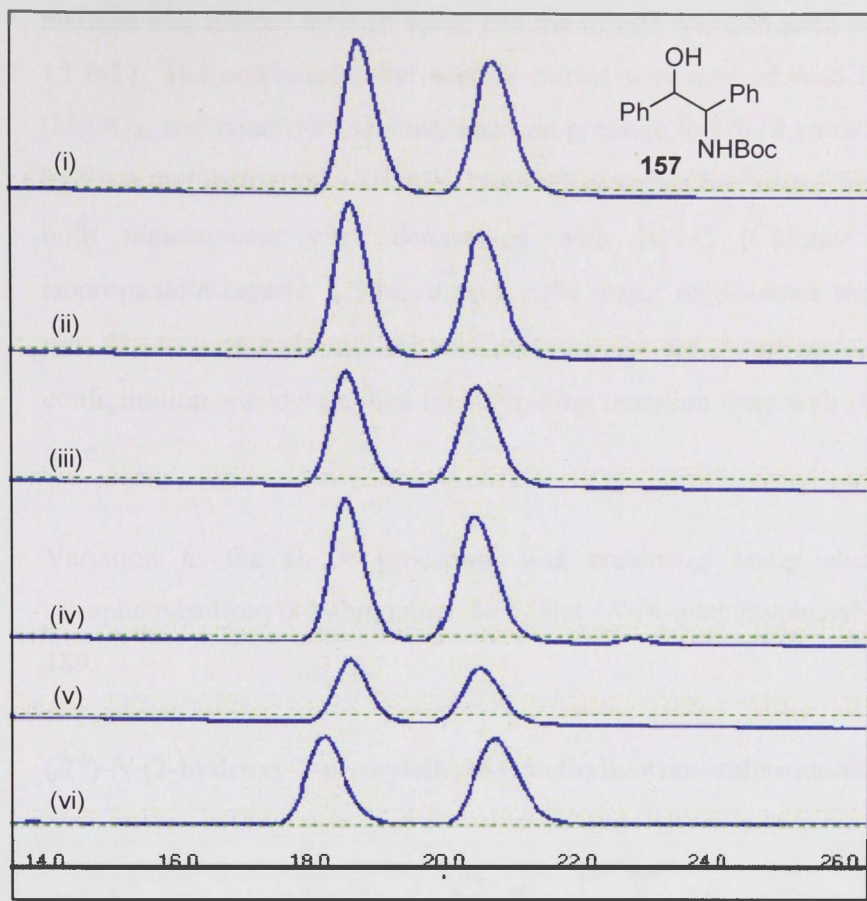


Figure 7.3.1 HPLC chromatogram of *tert*-butyl 2-hydroxy-1,2-diphenylethylcarbamate **157**. Sample from reaction with ligands (i) *N*-(4-toluenesulfonyl)-*L*-threonine **185**, (ii) *N*-(4-nitrophenyl-sulfonyl)-*L*-threonine **188**, (iii) *N*-(4-methoxyphenylsulfonyl)-*L*-threonine **189**, (iv) *N*-(4-toluene sulfonyl)-*L*-serine **190**, (v) (2*R*)-*N,N'*-bis(*p*-toluenesulfonyl)-2,3-diaminopropanoic acid **191**, and (vi) without ligand (HPLC conditions: Chiralcel OD-H Silica 5 μ m, 150 x 0.46 mm, 10% isopropanol/*n*-hexane, 1.0 mL/min).

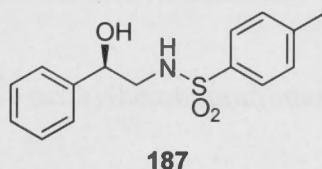
General procedure 3.3 : Evaluation of the *N*-protected *L*-threonine-based ligands using substrate styrene

To a mixture of *N*-(4-toluenesulfonyl)-*L*-threonine **185** (5.0 mol%) and sodium bicarbonate (5.0 mol%) in *tert*-butanol (1.0 mL) and water (1.0 mL) at room temperature was added styrene **49** (1.0 equiv.), chloramine-T **41** (1.0 equiv.) and potassium osmate dihydrate (0.01 equiv.). This reaction mixture was stirred until complete, quenched with sodium sulfite (10 mL, 1.0 M) and stirred for 30 min. The

mixture was filtered through celite and the filtrate was extracted with ethyl acetate (2 x 15 mL). The combined ethyl acetate extract was washed with brine (10 mL), dried (MgSO_4) and concentrated under reduced pressure to afford crude product. Purification by flash chromatography afforded two regioisomeric products. The enantioselectivity of both regioisomers were determined with HPLC (Chiralcel AS 5 μm , 30% isopropanol/*n*-hexane, 1.5 mL/min) for the major regioisomer and (Chiralcel OD-H 5 μm , 5% isopropanol/*n*-hexane, 0.6 mL/min) for the minor regioisomer. The absolute configuration was determined by comparing retention time with the literature retention time.

Variation to the above procedure was conducted using alternate ligands *N*-(4-nitrophenylsulfonyl)-*L*-threonine **188** and *N*-(4-methoxyphenylsulfonyl)-*L*-threonine **189**.

(*R)-*N*-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide¹⁰¹**



R_f 0.39 (23% ethyl acetate/dichloromethane). IR (thin film, cm^{-1}) 3433 (O-H), 3270 (N-H), 3065, 3032, 2923, 2858 (C-H), 1598. ^1H -NMR (400 MHz, CDCl_3) 7.72 (2H, d, J 8.2 Hz, ArH), 7.26-7.31 (7H, m, ArH), 5.53 (1H, s, NH), 4.79 (1H, dd, J 9.0, 3.6 Hz, H2), 3.20 (1H, m, H1A), 3.11 (1H, s, OH), 2.99 (1H, dd, J 12.6, 8.7 Hz, H1B), 2.40 (3H, s, CH_3). ^{13}C -NMR (100 MHz, CDCl_3) 143.61, 140.83, 136.52, 129.81, 128.59, 128.13, 127.09, 125.90, 72.74, 50.28, 21.55 LRMS (ESI+) 314 ($[\text{M}+\text{Na}]^+$, 100%), 274 (76), 155 (48), 118 (38), 91 (12). HRMS (ESI+) calcd. for $\text{C}_{15}\text{H}_{17}\text{NO}_3\text{SNa}$ ($[\text{M}+\text{Na}]^+$) 314.0827, found 314.0829.

Absolute configuration was determined from HPLC (*R*)-**187** t_R 12.5 min, (*S*)-**187** t_R 17.4 min. (Chiralcel AS 5 μm , 30% isopropanol/*n*-hexane, 1.5 mL/min) and was determined by comparing to the literature.¹⁰²

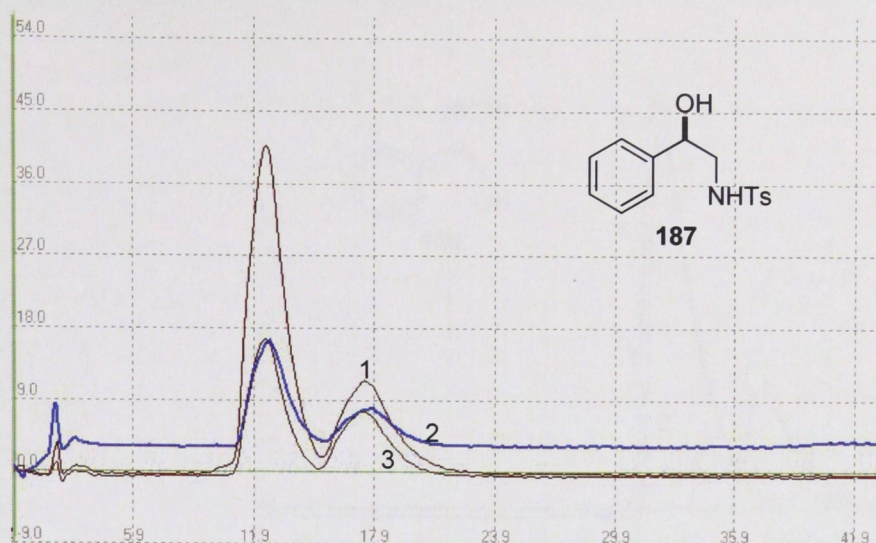
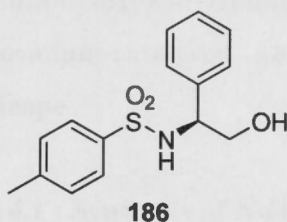


Figure 7.3.2 HPLC chromatogram of product **187** afforded using ligand *N*-(4-toluenesulfonyloxy)-*L*-threonine **185** (1), *N*-(4-nitrophenylsulfonyl)-*L*-threonine **188** (2), and *N*-(4-methoxyphenylsulfonyl)-*L*-threonine **189** (3). (HPLC conditions: Chiralcel AS 5 μ m, 30% isopropanol/*n*-hexane, 1.5 mL/min)

(*S)-*N*-(2-hydroxy-1-phenylethyl)-4-methylbenzenesulfonamide**^{101,150}



R_f 0.28 (23% ethyl acetate/dichloromethane). IR (thin film, cm^{-1}) 3496 (O-H), 3277 (N-H), 3064, 3032, 2926, 2876 (C-H), 1598. ^1H -NMR (400 MHz, CDCl_3) 7.59 (2H, d, J 8.1 Hz, ArH), 7.06-7.17 (7H, m, ArH), 6.00 (1H, m, NH), 4.44 (1H, m, H1A), 3.72 (2H, m, H1B), 3.67 (1H, s, OH), 2.34 (3H, s, CH_3) ^{13}C -NMR (100 MHz, CDCl_3) 143.30, 137.52, 137.03, 129.41, 128.51, 127.75, 127.14, 126.91, 66.15, 59.74, 21.49

Absolute configuration was determined from HPLC (*S*)-**186** t_R 90.0 min, (*R*)-**186** t_R 100.1 min. (Chiralcel OD-H 5 μ m, 5% isopropanol/*n*-hexane, 0.6 mL/min) and was determined by comparing to the literature.¹⁰²

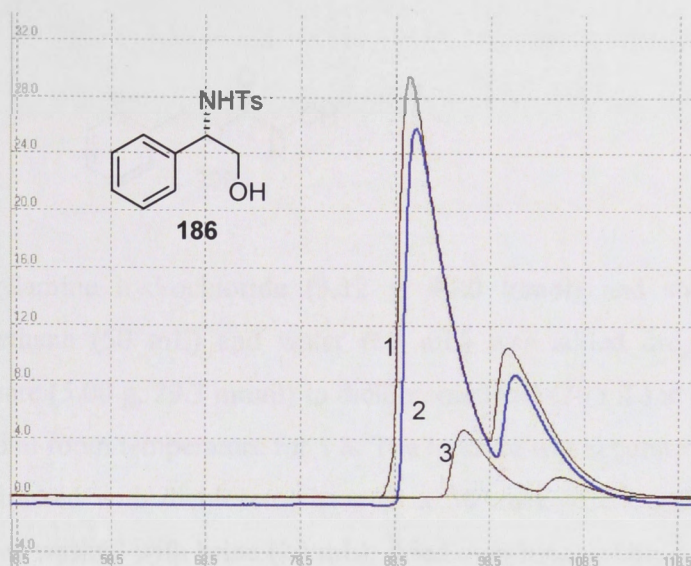


Figure 7.3.3 HPLC chromatogram of product **186** afforded using ligand *N*-(4-toluenesulfonyloxy)-*L*-threonine **185** (1), *N*-(4-nitrophenylsulfonyl)-*L*-threonine **188** (2), and *N*-(4-methoxyphenylsulfonyl)-*L*-threonine **189** (3). (HPLC conditions: Chiralcel OD-H 5 μ m, 5% isopropanol/*n*-hexane, and 0.6 mL/min).

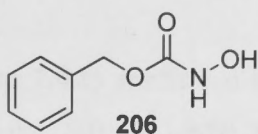
7.4 Experimental Section for Chapter 4

Alkyl *N*-(4-toluenesulfonyloxy)carbamate as second generation preformed nitrogen sources for the osmium-catalysed aminohydroxylation reaction : Synthesis, Optimisation and Scope

General procedure 4.1 : Synthesis of *N*-(4-toluenesulfonyloxy)carbamate preformed nitrogen sources¹²¹

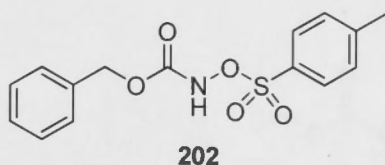
To a mixture of *N*-hydroxycarbamate (1.0 equiv.) in diethyl ether (30.0 mL) was added toluenesulfonyl chloride (1.0 equiv. or as specified) and triethylamine (1.0 equiv. or as specified) at 0 °C. This reaction mixture was stirred at room temperature until complete. The mixture was filtered, the filtrate was extracted with diethyl ether (3 x 20 mL or as specified), washed with brine (20 mL), dried over magnesium sulfate and concentrated under reduced pressure to afford crude product. Purification was conducted by flash chromatography using the specified solvents.

Benzyl *N*-hydroxycarbamate¹²³



To a mixture of hydroxylamine hydrochloride (3.12 g, 44.0 mmol) and sodium bicarbonate in dichloromethane (50 mL) and water (60 mL) was added dropwise solution benzyl chloroformate (5.00 g, 29.3 mmol) in dichloromethane (20 mL) at 0 °C, and the reaction was stirred at room temperature for 1 h. The mixture was separated and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The Combined dichloromethane extract was washed with brine (20 mL), dried over magnesium sulfate and evaporated under reduced pressure to produce the title compound **206** as a white solid (4.90 g, 100%), mp 59-62 °C (lit¹²³ 62-64 °C). IR (thin film, cm⁻¹) 3300 (broad, O-H, N-H), 3061, 3030, 2977, 2952, 2897 (C-H), 1708 (C=O), 1504. ¹H-NMR (300 MHz, CDCl₃) 7.65 (1H, s, NH), 7.32-7.37 (5H, m, ArH), 5.13 (2H, s, CH₂) (OH not observed). ¹³C- NMR (75 MHz, CDCl₃) 159.41, 135.38, 128.61, 128.50, 128.33, 67.86.

Benzyl *N*-(4-toluenesulfonyloxy)carbamate¹²⁶



The reaction was conducted according to the general procedure 4.1 with benzyl *N*-hydroxycarbamate **206** (936 mg, 5.60 mmol), toluenesulfonyl chloride (1.20 g, 6.72 mmol) and triethylamine (680 mg, 6.72 mmol). Purification by flash chromatography (30% ethyl acetate/*n*-hexane) provided the title compound **202** as a white solid (814 mg, 46%), mp 119-121 °C (lit¹²⁶ 120-123 °C), *R*_f value 0.11 (80% dichloromethane/*n*-hexane). IR (thin film, cm⁻¹) 3282 (N-H), 3067, 3035, 2957 (C-H), 1774, 1743 (C=O), 1597. ¹H-NMR (300 MHz, CDCl₃) 8.19 (1H, s, NH), 7.81 (2H, d, *J* 8.10 Hz, ArH), 7.14-7.34 (7H, m, ArH), 5.01 (2H, s, CH₂Ar), 2.42 (3H, s, CH₃). ¹³C-NMR (75 MHz, CDCl₃) 155.51, 146.12, 134.51, 130.04, 129.72, 129.54, 128.67, 128.56, 128.33, 68.58,

21.84. LRMS (ESI+) 344 ($[M+Na]^+$, 100%). HRMS (ESI+) calcd. for $C_{15}H_{15}NO_5NaS$ ($[M+Na]^+$) 344.0569, found 344.0568.

X-ray spectra (**Figure 7.4.1**) confirmed the structure of benzyl *N*-(4-toluenesulfonyl-oxy)carbamate **202**, the N10-O11-S20 bonding shows sulfonation occurred in the hydroxyl-group of benzyl *N*-hydroxycarbamate **206**.

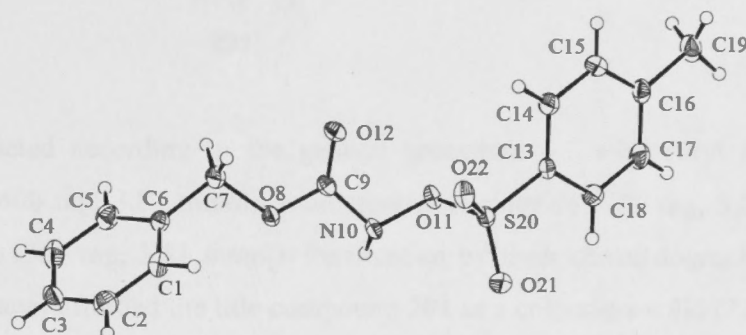
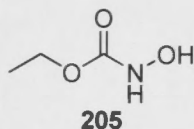


Figure 7.4.1 Structure of $C_{15}H_{15}NO_5S$ with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

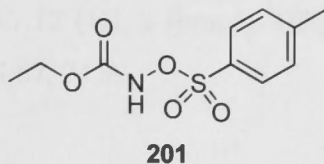
Ethyl *N*-hydroxycarbamate¹²²



To a solution of sodium carbonate (24.4 g, 231 mmol) in water (75 mL) and diethyl ether (50 mL) was added hydroxylamine hydrochloride (12.8 g, 184 mmol) at room temperature. To this reaction mixture was added ethyl chloroformate (8.80 mL, 92.2 mmol) and the reaction was stirred until complete (4 h), quenched with aqueous hydrochloric acid (20 mL, 1.0 M), and extracted with diethyl ether (4 x 250 mL). The combined diethyl ether extract was washed with brine (100 mL), dried over magnesium sulfate and concentrated under reduced pressure to afford the title compound **205** as colorless oil (8.30 g, 86%). IR (thin film, cm^{-1}) 3304 (broad, O-H, N-H), 2986, 2938, 2914 (C-H), 1716 (C=O). 1H -NMR (400 MHz, $CDCl_3$) 7.79 (2H, s, broad, NH and

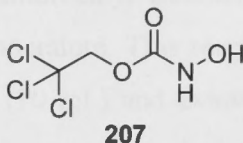
OH), 4.15 (2H, q, J 7.6 Hz, CH₂), 1.23 (3H, t, J 7.2 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 159.62, 62.24, 14.32.

Ethyl *N*-(4-toluenesulfonyloxy)carbamate¹²¹



The reaction was conducted according to the general procedure 4.1 with ethyl *N*-hydroxycarbamate **205** (400 mg, 3.81 mmol), toluenesulfonyl chloride (726 mg, 3.81 mmol) and triethylamine (389 mg, 3.81 mmol). Purification by flash chromatography (30% ethyl acetate/*n*-hexane) afforded the title compound **201** as a colourless solid (715 mg, 72%). R_f 0.22 (30% ethyl acetate/*n*-hexane), mp 61-64 °C (lit.¹²¹ 58-59 °C). IR (thin film, cm⁻¹) 3282 (N-H), 1773, 1744 (C=O), 1597. ¹H-NMR (300 MHz, CDCl₃) 8.64 (1H, s, NH), 7.79 (2H, d, J 8.40 Hz, Ar-H), 7.31 (2H, d, J 8.10 Hz, Ar-H), 3.97 (2H, q, J 7.0 Hz, CH₂), 2.38 (3H, s, CH₃), 1.04 (3H, t, J 7.4 Hz, CH₃). ¹³C-NMR (75 MHz, CDCl₃) 156.03, 146.20, 130.18, 129.70, 129.46, 63.13, 21.67, 13.92. LRMS (ESI⁺) 282 ([M+Na]⁺, 100%). HRMS (ESI⁺) calcd. for C₁₀H₁₃NO₅NaS [M+Na]⁺ 282.0412, found 282.0412.

2,2,2-Trichloroethyl *N*-hydroxycarbamate¹¹⁶



To a mixture of hydroxylamine hydrochloride (1.80 g, 27.0 mmol) and sodium hydrogen carbonate (1.13 g, 13.5 mmol) in dichloromethane (7.0 mL) and water (7.0 mL) at 0 °C was added a solution of succinimidyl 2,2,2-trichloroethyl carbonate (2.00 g, 6.75 mmol) in dichloromethane (5.0 mL). This reaction mixture was stirred at room temperature until complete, acidified to pH 5 with concentrated hydrochloric acid, and extracted with dichloromethane (3 x 20 mL). The combined dichloromethane extract

was washed with brine (15 mL), dried over magnesium sulfate and concentrated under reduced pressure to afford crude product. Purification by flash chromatography (10% ethyl acetate/dichloromethane) afforded the title compound **207** as a white solid (953 mg, 75%), mp 88-89 °C (lit.¹¹⁵ 86-88 °C), R_f 0.25 (10% ethyl acetate/dichloromethane). IR (thin film, cm^{-1}) 3366 (O-H), 3264 (N-H), 1709 (C=O). ^1H -NMR (300 MHz, CDCl_3) 7.61 (1H, s, NH), 7.12 (1H, s (broad), OH), 4.72 (2H, s, CH_2). ^{13}C -NMR (75 MHz, CDCl_3) 157.19, 94.67, 74.89.

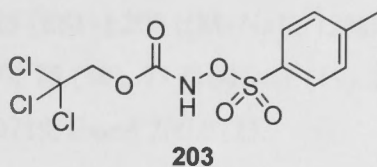
Procedure 2:¹²⁵

To a solution of trichloroethylethanol (500 mg, 3.31 mmol) in pyridine (4.0 mL) was added 1,1'-carbonyldiimidazole (1.34 g, 8.25 mmol) at room temperature, and the reaction was stirred for 15 h at 40 °C. To this reaction mixture was added hydroxylamine hydrochloride (921 mg, 13.3 mmol) and stirring was continued for 32 h at 40 °C. The mixture was acidified to pH 2 with aqueous hydrochloric acid (2.0 M), and extracted with diethyl ether (5 x 20 mL). The combined organic extract was washed with potassium bicarbonate (15 mL), dried over magnesium sulfate and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (10% ethyl acetate/dichloromethane) provided the title compound **207** as white solid (365 mg, 53%). All data matched that above.

Procedure 3:

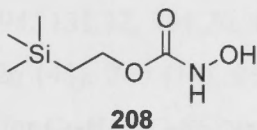
To a mixture of hydroxylamine hydrochloride (281 mg, 4.05 mmol) and sodium bicarbonate (172 mg, 2.02 mmol) in water (2.5 mL) was added solution of succinimidyl-2,2,2-trichloroethyl carbonate (309 mg, 1.01 mmol) in dichloromethane (2.5 mL) at room temperature. This reaction mixture was stirred until complete (5 h), quenched with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic extract was washed with brine (10 mL), dried over magnesium sulfate and concentrated under reduced pressure to afford the title compound **207** as white solid (138 mg, 66%). All data matched that above.

2,2,2-Trichloroethyl *N*-(4-toluenesulfonyloxy)carbamate¹¹⁶



The reaction was conducted according to the general procedure 4.1 with 2,2,2-trichloroethyl *N*-hydroxycarbamate¹¹⁶ **207** (900 mg, 4.32 mmol), toluenesulfonyl chloride (915 mg, 4.75 mmol) and triethylamine (437 mg, 4.32 mmol). Purification by flash chromatography (20% ethyl acetate/*n*-hexane) afforded the title compound **203** as a white solid (1.23 g, 79%), R_f value 0.25 (20% ethyl acetate/*n*-hexane), mp 133-135 °C (lit.¹¹⁶ 123 °C). IR (thin film, cm^{-1}) 3259 (N-H), 3009 (C-H), 1764 (C=O), 1595. ^1H -NMR (300 MHz, CDCl_3) 8.25 (1H, s, NH), 7.90 (2H, d, J 7.50 Hz, ArH), 7.36 (2H, d, J 8.10 Hz, ArH), 4.65 (2H, s, CH_2), 2.45 (3H, s, CH_3). ^{13}C -NMR (75 MHz, CDCl_3) 153.66, 146.57, 136.83, 129.88, 129.73, 94.08, 75.03, 21.84. LRMS (ESI+) 384 ($[\text{M}+\text{Na}]^+$, 100%). HRMS (ESI+) calcd. for $\text{C}_{10}\text{H}_{10}\text{NO}_5\text{NaSCl}_3$ ($[\text{M}+\text{Na}]^+$) 383.9243, found 383.9238.

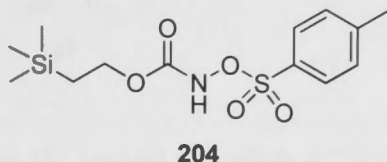
2-(Trimethylsilyl)ethyl *N*-hydroxycarbamate



To a solution of 2-trimethylsilyl ethanol **212** (1.0 g, 8.4 mmol) in pyridine (8.0 mL) was added *N,N'*-carbonyl diimidazole (3.39 g, 20.9 mmol) at room temperature. This reaction mixture was stirred for 13 h at 40 °C. Hydroxylamine hydrochloride (2.33 g, 33.5 mmol) was added and stirred until complete (6 h). The reaction mixture was concentrated, acidified to pH 2 with aqueous hydrochloric acid (2.0 M), and extracted with diethyl ether (5 x 20 mL). The combined organic extract was washed with brine (20 mL), dried over magnesium sulfate and concentrated under reduced pressure to afford the title compound **208** as a colorless liquid (0.82 g, 55%), R_f 0.45 (80% ethyl acetate/dichloromethane). IR (thin film, cm^{-1}) 3282 (N-H), 1773, 1744 (C=O), 1597.

$^1\text{H-NMR}$ (300 MHz, CDCl_3) 7.81 (1H, s, NH), 7.52 (1H, s, OH), 4.20 (2H, m, CH_2), 0.98 (2H, m, CH_2), 0.0 (9H, s, $\text{Si}(\text{CH}_3)_3$). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) 161.40 66.19, 19.10, 0.0. LRMS (ESI+) 200 ($[\text{M}+\text{Na}]^+$, 12%), 172 (10%), 150 (8), 132 (20), 105 (12), 100 (19), 90 (19), 75 (30), 73 (100), 61 (19). HRMS (ESI+) calcd. for $\text{C}_6\text{H}_{15}\text{NO}_3\text{NaSi}$ ($[\text{M}+\text{Na}]^+$) 200.0719, found 200.0723.

2-(Trimethylsilyl)ethyl *N*-(4-toluenesulfonyloxy)carbamate



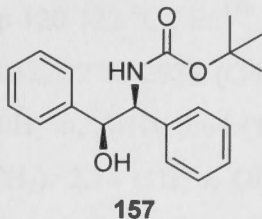
The reaction was conducted according to the general procedure 4.1 with 2-(trimethylsilyl)ethyl *N*-hydroxycarbamate **208** (761 mg, 4.29 mmol), toluenesulfonyl chloride (900 mg, 4.72 mmol) and triethylamine (434 mg, 4.29 mmol). Purification by flash chromatography (20% ethyl acetate/*n*-hexane) afforded the title compound **204** as a colourless oil (1.08 g, 76%), R_f 0.21 (20% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3287 (N-H), 1741, 1711 (C=O), 1597. $^1\text{H-NMR}$ (300 MHz, CDCl_3) 8.29 (1H, s, NH), 7.87 (2H, d, J 8.10 Hz, ArH), 7.36 (2H, d, J 8.40 Hz, ArH), 4.08 (2H, m, CH_2), 2.46 (3H, s, CH_3), 0.84 (2H, m, CH_2), 0.00 (9H, s, $\text{Si}(\text{CH}_3)_3$). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) 157.49, 147.65, 131.94, 131.32, 131.20, 67.40, 23.38, 18.94, 0.0. LRMS (ESI+) 354 ($[\text{M}+\text{Na}]^+$, 100%), 326 (48), 260 (12), 254 (22), 229 (10), 217 (8), 139 (12), 73 (8). HRMS (ESI+) calcd. for $\text{C}_{13}\text{H}_{21}\text{NO}_5\text{SSiNa}$ ($[\text{M}+\text{Na}]^+$) 354.0807, found 354.0804.

General Procedure 4.2 : Evaluation of *N*-(4-toluenesulfonyloxy)carbamate-based preformed nitrogen sources in the aminohydroxylation reaction

To a mixture of *trans*-stilbene **51** (1.0 equiv.) and potassium osmate dihydrate (4.0 mol%) in *tert*-butanol (4.0 mL) and water (2.5 mL) was added a solution of preformed nitrogen source (1.2 equiv.). The reaction mixture was stirred at room temperature until complete, quenched with aqueous sodium bisulfite (5.0 mL, 1.0 M), stirred for 30 min, and filtered through celite. The filtrate was extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate extract was dried (Na_2SO_4) and concentrated under reduced

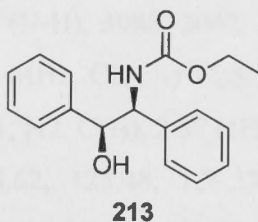
pressure to afford crude product. Purification was performed by flash chromatography using the specified solvents.

***tert*-Butyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate¹²⁷**



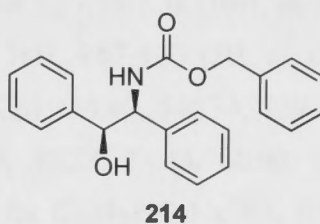
The reaction was conducted according to the general procedure 4.2 using *trans*-stilbene **51** (60.0 mg, 0.33 mmol), potassium osmate dihydrate (4.90 mg, 0.01 mmol), *tert*-butyl *N*-(4-toluenesulfonyloxy)carbamate **153** (287 mg, 0.67 mmol) with *tert*-butanol/water (3:1). Purification by flash chromatography (1:9:5 ethyl acetate/dichloromethane/*n*-hexane) afforded the title compound **157** as a white solid (89.9 mg, 78%). R_f 0.15 (1:9:5 of ethyl acetate/dichloromethane/*n*-hexane), mp 129.9-131.3 °C (lit³⁸ 137-138 °C). IR (thin film, cm^{-1}) 3415 (brd, O-H, N-H), 3088, 3064, 3031, 3006, 2977, 2929 (C-H), 1691 (C=O), 1604, 1586. ^1H -NMR (300 MHz, CDCl_3) 7.23-7.31 (10H, m, ArH), 5.48 (1H, s, NH), 4.89 (2H, s, H1 and H2), 2.94 (1H, s, OH), 1.34 (9H, s, $\text{C}(\text{CH}_3)_3$). ^{13}C -NMR (75 MHz, CDCl_3) 156.05, 140.83, 139.91, 128.48, 128.18, 127.66, 127.48, 126.93, 126.32, 79.83, 77.39, 60.72, 28.24. LRMS (ESI+) 336 ($[\text{M}+\text{Na}]^+$, 100%), 320 (5), 280 (19), 240 (7), 236 (30), 196 (22). HRMS (ESI+) calcd. for $\text{C}_{19}\text{H}_{23}\text{NO}_3\text{Na}$ ($[\text{M}+\text{Na}]^+$) 336.1576, found 336.1572.

Ethyl (1*R,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate¹⁵¹**



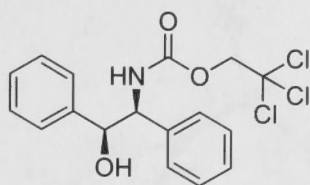
The reaction was conducted according to the general procedure 4.2 using *trans*-stilbene **51** (30.0 mg, 0.17 mmol), potassium osmate dihydrate (2.5 mg, 0.01 mmol), solvent *tert*-butanol/water (3:1) and ethyl *N*-(4-toluenesulfonyloxy)carbamate **201** (86.3 mg, 0.33 mmol). Purification by flash chromatography (10% dichloromethane/*n*-hexane) provided the title compound **213** as white solid (20.1 mg, 42%). R_f 0.23 (20% ethyl acetate/*n*-hexane); mp 120-122 °C (lit.¹⁵¹ 122-123.5 °C). IR (thin film, cm^{-1}) 3346 (brd, O-H, N-H), 3062, 3032, 2978, 2922 (C-H), 1686 (C=O), 1533. ^1H -NMR (300 MHz, CDCl_3) 7.28-7.31 (10H, m, ArH), 5.64 (1H, d, J 6.90 Hz, NH), 4.91 (2H, m, H1 and H2), 4.00 (2H, m, CH_2), 2.74 (1H, s, OH), 1.56 (3H, m, CH_3). ^{13}C -NMR (75 MHz, CDCl_3) 156.63, 140.65, 139.90, 128.54, 128.25, 127.80, 127.58, 126.86, 126.22, 77.00, 61.07, 61.01, 14.49. LRMS (ESI+) 308 ($[\text{M}+\text{Na}]^+$, 100%), 268 (11), 224 (15), 196 (23). HRMS (ESI+) calcd. for $\text{C}_{17}\text{H}_{19}\text{NO}_3\text{Na}$ ($[\text{M}+\text{Na}]^+$) 308.1263, found 308.1258.

Benzyl (1*R,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate**¹⁵²



The reaction was conducted according to the general procedure 4.2 using *trans*-stilbene **51** (100 mg, 0.56 mmol), potassium osmate dihydrate (8.2 mg, 0.02 mmol), benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (357 mg, 1.11 mmol), and *tert*-butanol/water (3:1). Purification by flash chromatography (10% ethyl acetate/dichloromethane) afforded the title compound **214** as white solid (116.3 mg, 61%). R_f value 0.22 (20% ethyl acetate/dichloromethane), mp 147.7-149.7 °C (lit.² 149-151 °C). IR (thin film, cm^{-1}) 3574 (O-H), 3353 (N-H), 3088, 3062, 3031, 2941 (C-H), 1689 (C=O), 1603, 1587, 1535. ^1H -NMR (300 MHz, CDCl_3) 7.28-7.37 (15H, m, ArH), 5.76 (1H, d, J 6.90 Hz, NH), 4.98 (4H, m, H1, H2, CH_2), 2.57 (1H, s, OH). ^{13}C -NMR (75 MHz, CDCl_3) 156.32, 140.54, 136.31, 128.62, 128.48, 128.33, 128.18, 128.10, 128.04, 127.87, 127.67, 126.85, 126.16, 66.99, 66.85, 61.04. LRMS (ESI+) 370 ($[\text{M}+\text{Na}]^+$, 100%), 286 (14), 91 (41). HRMS (ESI+) calcd. for $\text{C}_{22}\text{H}_{21}\text{NO}_3\text{Na}$ ($[\text{M}+\text{Na}]^+$) 370.1419, found 370.1420.

2,2,2-Trichloroethyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate



215

The reaction was conducted according to the general procedure 4.2 using *trans*-stilbene **51** (50.0 mg, 0.28 mmol), potassium osmate dihydrate (4.10 mg, 0.01 mmol), 2,2,2-trichloroethyl *N*-(4-toluenesulfonyloxy)carbamate **203** (201 mg, 0.56 mmol), and *tert*-butanol/water (3:1). Purification by flash chromatography (1:3:6 ethyl acetate/dichloromethane/*n*-hexane) provided the title compound **215** as white solid (85.4 mg, 80%), R_f 0.20 (1:3:6 ethyl acetate/dichloromethane/*n*-hexane); mp 117.7-120.7 °C. IR (thin film, cm^{-1}) 3423 (brd, O-H, N-H), 3088, 3063, 3031, 3006, 2953, 2925 (C-H), 1720 (C=O), 1603, 1586, 1509. ^1H -NMR (300 MHz, CDCl_3) 7.28-7.38 (10H, m, ArH), 5.93 (1H, d, J 6.30 Hz, NH), 5.04-4.99 (2H, m, H1 and H2), 4.67-4.57 (2H, m, CH_2), 2.19 (1H, d, J 2.70 Hz, OH). ^{13}C -NMR (75 MHz, CDCl_3) 154.40, 140.34, 139.35, 128.67, 128.44, 127.99, 127.83, 126.76, 126.06, 109.99, 77.28, 74.44, 60.96. LRMS (ESI+) 410 ($[\text{M}+\text{Na}]^+$, 100%). HRMS (ESI+) calcd. for $\text{C}_{17}\text{H}_{16}\text{NO}_3\text{Na}^{35}\text{Cl}_3$ ($[\text{M}+\text{Na}]^+$) 410.0093, found 410.0090.

Recrystallisation using the solvents dichloromethane/*n*-hexane with slow evaporation at room temperature afforded white crystals, and X-ray crystallography confirmed the structure of 2,2,2-trichloroethyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate **215** (Figure 7.4.2).

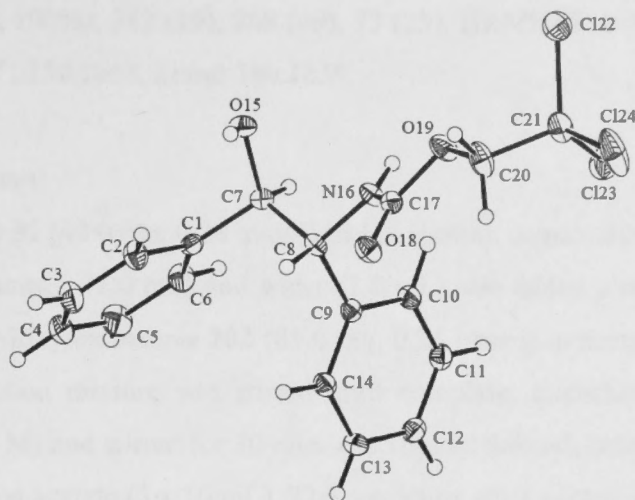
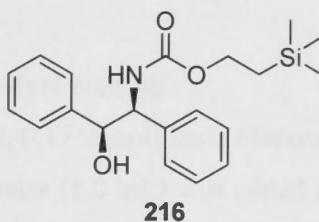


Figure 7.4.2 Structure of $C_{17}H_{16}Cl_3NO_3$ with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

2-(Trimethylsilyl)ethyl (1*R,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate**



The reaction was conducted according to the general procedure 4.2 using *trans*-stilbene **51** (95.0 mg, 0.53 mmol), potassium osmate dihydrate (7.70 mg, 0.02 mmol), 2-(trimethylsilyl)ethyl *N*-(4-toluenesulfonyloxy)carbamate **204** (175 mg, 0.53 mmol), and *tert*-butanol/water (3:1). Purification by flash chromatography (1:6:3 ethyl acetate/dichloromethane/*n*-hexane) afforded the title compound **216** as a white solid (93.3 mg, 50%). R_f 0.34 (1:7:2 ethyl acetate/dichloromethane/*n*-hexane), mp 133.7–134.7 °C. IR (thin film, cm^{-1}) 3339 (brd, O-H, N-H), 3063, 3029, 2954, 2897 (C-H), 1689 (C=O), 1602, 1586, 1537. 1H -NMR (300 MHz, $CDCl_3$) 7.25–7.30 (10H, m, ArH), 5.61 (1H, d, *J* 7.80 Hz, NH), 4.93 (2H, s, H1 and H2), 4.04 (2H, m, CH_2), 2.72 (1H, s, OH), 0.91 (2H, m, CH_2), 0.00 (9H, s, $Si(CH_3)_3$). ^{13}C -NMR (75 MHz, $CDCl_3$) 158.23, 142.14, 141.44, 130.06, 129.77, 129.28, 129.08, 128.35, 127.68, 78.47, 64.84, 62.44, 19.11, 0.00.

LRMS (ESI+) 380 ($[M+Na]^+$, 100%), 312 (19), 268 (49), 73 (23). HRMS (ESI+) calcd. for $C_{20}H_{27}NO_3NaSi$ ($[M+Na]^+$) 380.1658, found 380.1659.

Optimisation of solvent system

To a mixture of *trans*-stilbene **51** (40.0 mg, 0.28 mmol) and potassium osmate dihydrate (3.2 mg, 0.01 mmol) in acetonitrile (1.0 mL) and water (1.0 mL) was added a solution of benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (85.6 mg, 0.26 mmol) in acetonitrile (2.0 mL) at 0 °C. This reaction mixture was stirred until complete, quenched with sodium bisulfite (5.0 mL, 1.0 M) and stirred for 30 min, and filtered through celite. The filtrate was extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate extract was washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford crude product. Purification by flash chromatography (10% ethyl acetate/dichloromethane) afforded benzyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate **214** as a white solid.

Variation was conducted using solvents *tert*-butanol/water (3:1), *n*-propanol/water (3:1), and dichloromethane/water (3:1).

Optimisation of nitrogen source and catalyst loading

To a mixture of *trans*-stilbene **51** (30.3 mg, 0.17 mmol) and potassium osmate dihydrate (4.0 mol%) in acetonitrile (1.0 mL) and water (1.0 mL) was added a solution of benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (1.0 equiv., 53.5 mg, 0.17 mmol) in acetonitrile (2.0 mL). This reaction mixture was stirred at room temperature until complete, quenched with aqueous sodium bisulfite (5.0 mL, 1.0 M), stirred for 30 min, and filtered through celite. The filtrate was extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate extract was washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford crude product. Purification by flash chromatography (10% ethyl acetate/dichloromethane) afforded pure benzyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate **214** as a white solid.

Variation was performed using benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (1.2 equiv.), and (2.0 equiv.). Variation was also performed using of potassium osmate dihydrate 2.0 mol%, 1.0 mol% and 0.1 mol%.

Preparation of buffer solution

Buffer solutions (0.5 M) were prepared according to the procedure in the experimental section for chapter 2.

Optimisation of reaction pH

To a mixture of *trans*-stilbene **51** (50.0 mg, 0.277 mmol) and potassium osmate dihydrate (1.00 mg, 0.003 mmol) in acetonitrile (1.0 mL) and pH 3 buffer (1.0 mL, 0.5 M) at 0 °C was added solution benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (107 mg, 0.33 mmol) in acetonitrile (2.0 mL). This reaction mixture was stirred and maintained at the desired pH by addition of buffer solution until complete. Sodium bicarbonate solution (5.0 mL, 2.0 M) was added and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extract was washed with brine (10 mL), dried (Na₂SO₄), and concentrated under reduced pressure. Product purification was conducted by flash chromatography (10% ethyl acetate/dichloromethane) to afford benzyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethyl carbamate **214** as white solid.

Using a similar procedure, a series of reactions were performed for pH 4 to 11.

Procedure to evaluate stereoselectivity using ligand (DHQD)₂PHAL

A mixture of *trans*-stilbene **51** (50.2 mg, 0.28 mmol), ligand (DHQD)₂PHAL (8.60 mg, 0.01 mmol) and potassium osmate dihydrate (2.00 mg, 0.01 mmol) in acetonitrile (2.0 mL) at 0 °C was adjusted to pH 9 with buffer solution. A solution of benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (107 mg, 0.33 mmol) in acetonitrile (1.0 mL) was added. This reaction mixture was stirred at room temperature until complete, quenched with aqueous hydrochloric acid (5.0 mL, 2.0 M) and extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate extract was washed with brine (10 mL), dried (MgSO₄), and concentrated under reduced pressure to give the crude product. Purification by flash chromatography (10% ethyl acetate/dichloromethane) afforded benzyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethylcarbamate **214** as a white solid (39.9 mg, 41%).

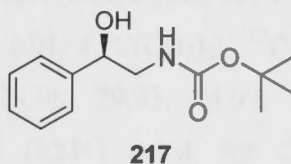
Using the above procedure, similar reaction was also conducted without the addition of buffer solution. Pure product **214** was afforded as colorless solid (93%, 89.7 mg) after

flash chromatography. As a comparison, a reaction buffered at pH 9, and without ligand was also completed.

General procedure 4.3 : Substrate scope study

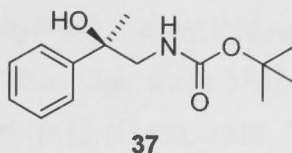
To a mixture of alkene (1.0 equiv.) and potassium osmate dihydrate (1.0 mol% or as specified) in the solvent of (3:1 acetonitrile/water or as specified) at 0 °C was added solution of preformed nitrogen source (1.2 equiv. or as specified). The reaction mixture was stirred at room temperature until complete, quenched with aqueous sodium bisulfite (5.0 mL, 1.0 M), stirred for 30 min and then filtered through celite. The filtrate was extracted with ethyl acetate (3 x 5 ml). The combined ethyl acetate extract was washed brine (10 mL), dried (Na₂SO₄) and concentrated under reduced pressure to afford crude product. Purification was performed by flash chromatography using the specified solvents.

tert-Butyl (*R**)-2-hydroxy-2-phenylethylcarbamate¹⁵³



The reaction was conducted according to general procedure 4.3 using styrene **49** (40.0 mg, 0.38 mmol), *tert*-butyl *N*-(4-toluenesulfonyloxycarbamate **153** (132 mg, 0.46 mmol), potassium osmate dihydrate (4.0 mol%, 5.7 mg, 0.015 mmol) in *tert*-butanol/water (3:1). Purification by flash chromatography (2:2:6 ethyl acetate/dichloromethane/*n*-hexane) afforded the title compound **217** as white solid (75.6 mg, 83%). *R*_f 0.20 (2:2:6 ethyl acetate/dichloromethane/*n*-hexane), mp 120-121 °C (lit.¹⁵⁴ 120-121 °C). IR (thin film, cm⁻¹) 3339 (N-H), 3048, 2978, 2927 (C-H), 1687 (C=O), 1535. ¹H-NMR (400 MHz, CDCl₃) 7.27-7.37 (5H, m, ArH), 4.92 (1H, d, *J* 1.60 Hz, NH), 4.84 (1H, m, H₂), 3.48 (1H, m, H1A), 3.26 (1H, m, H1B), 3.01 (1H, s, OH), 1.45 (9H, s, C(CH₃)₃). ¹³C-NMR (100 MHz, CDCl₃) 156.99, 141.78, 128.48, 127.79, 125.86, 79.87, 74.05, 48.37, 28.34. LRMS (ESI⁺) 260 ([M+Na]⁺, 100%), 204 (30), 164 (40), 119 (70). HRMS (ESI⁺) calcd. for C₁₃H₂₀NO₃ ([M+H]⁺) 238.1143, found 238.1448; calcd. for C₁₃H₁₉NO₃Na ([M+Na]⁺) 260.1263, found 260.1266.

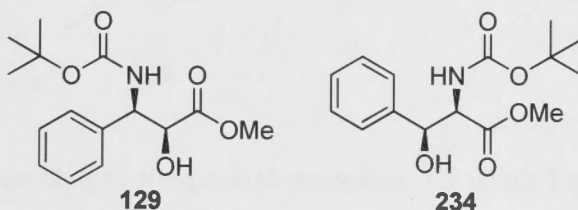
***tert*-Butyl (*R*^{*})-2-hydroxy-2-phenylpropylcarbamate**



The reaction was conducted according to general procedure 4.3 using α -methyl styrene **36** (45.0 mg, 0.38 mmol), potassium osmate dihydrate (5.60 mg, 0.02 mmol), *tert*-butyl *N*-(4-toluenesulfonyloxy)carbamate **153** (131 mg, 0.46 mmol) and *tert*-butanol/water (3:1). Purification by flash chromatography (2:2:6 ethyl acetate/dichloromethane/*n*-hexane) afforded the title compound **37** as a colorless solid (65.1 mg, 68%). *R*_f 0.22 (2:2:6 ethyl acetate/dichloromethane/*n*-hexane), mp 122-124 °C. IR (thin film, cm⁻¹) 3354 (N-H, O-H), 2974, 2925 (C-H), 1691 (C=O), 1533. ¹H-NMR (400 MHz, CDCl₃) 7.45 (2H, m, ArH), 7.36 (2H, m, ArH), 7.28 (1H, m, ArH), 4.76 (1H, s, NH), 3.52 (1H, dd, *J* 14.0, 7.2 Hz, H1A), 3.32 (1H, dd, *J* 14.4, 5.6 Hz, H1B), 3.14 (1H, s, OH), 1.54 (3H, s, CH₃), 1.41 (9H, s, C(CH₃)₃). ¹³C-NMR (100 MHz, CDCl₃) 157.27, 145.66, 128.30, 126.95, 124.98, 79.83, 74.97, 51.99, 28.26, 27.47. LRMS (ESI⁺) 274 ([M+Na]⁺). HRMS (ESI⁺) calcd. for C₁₄H₂₁NO₃Na ([M+Na]⁺) 274.1419, found 274.1419.

Methyl (2*S*^{*},3*R*^{*})-2-(*tert*-butoxycarbonylamino)-3-hydroxy-3-phenyl-propanoate¹⁵⁵

Methyl (2*S*^{*},3*R*^{*})-3-(*tert*-butoxycarbonylamino)-2-hydroxy-3-phenyl-propanoate¹⁵⁶

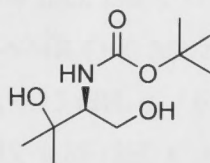


The reaction was conducted according to the general procedure 4.3 using *trans*-methyl cinnamate **122** (40.0 mg, 0.25 mmol), *tert*-butyl *N*-(4-toluenesulfonyloxy)carbamate **153** (85.10 mg, 0.296 mmol), potassium osmate dihydrate (3.600 mg, 0.001 mmol) and *tert*-butanol/water (3:1). Purification by flash chromatography (2:2:6 ethyl acetate/

dichloromethane/*n*-hexane) afforded an inseparable mixture of two regioisomers, R_f 0.23 (2:2:6 ethyl acetate/dichloromethane/*n*-hexane). Separation with preparative HPLC (SunFire Silica 10 μ m, 2% isopropanol/*n*-hexane, 10 mL/min.) afforded methyl (2*S**,3*R**)-3-(*tert*-butoxycarbonylamino)-2-hydroxy-3-phenylpropanoate **129** at t_R 12.8 min as a white solid (17.5 mg, 37%). IR (thin film, cm^{-1}) 3707 (O-H), 3401 (N-H), 3061, 2979, 2952, 2872 (C-H), 1738, 1719, 1685 (C=O), 1517. ^1H -NMR (400 MHz, CDCl_3) 7.37-7.27 (5H, m, ArH), 5.38 (1H, d, J 10.0 Hz, NH), 5.22 (1H, d, J 9.2 Hz, H3), 4.47 (1H, s, H2), 3.84 (3H, s, CH_3), 3.12 (1H, d, J 4.2 Hz, OH), 1.42 (9H, s, $3\times\text{CH}_3$). ^{13}C -NMR (100 MHz, CDCl_3) 173.41, 155.09, 139.05, 128.61, 127.73, 126.68, 79.93, 73.48, 56.00, 53.09, 28.22. LRMS (ESI+) 318 ($[\text{M}+\text{Na}]^+$, 100%). HRMS (ESI+) calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_5\text{Na}$ ($[\text{M}+\text{Na}]^+$) 318.1317, found 318.1317.

A second fraction (t_R 21.0 minute) afforded methyl (2*S**,3*R**)-2-(*tert*-butoxycarbonylamino)-3-hydroxy-3-phenyl-propanoate¹⁵⁵ **234** as colorless solid (29.7 mg, 63%). IR (thin film, cm^{-1}) 3719 (O-H), 3431 (N-H), 3062, 2979, 2953, 2880 (C-H), 1754, 1719 1694 (C=O), 1511. ^1H -NMR (400 MHz, CDCl_3) 7.39-7.28 (5H, m, ArH), 5.32 (1H, d, J 7.6 Hz, NH), 5.24 (1H, s, H3), 4.54 (1H, d, J 8.4 Hz, H2), 3.76 (3H, s, CH_3), 2.69 (1H, s, OH), 1.34 (9H, s, $3\times\text{CH}_3$). ^{13}C -NMR (100 MHz, CDCl_3) 171.33, 155.57, 139.67, 128.39, 128.07, 125.96, 80.09, 73.98, 59.35, 52.54, 28.14.

***tert*-Butyl (*S**)-1,3-dihydroxy-3-methylbutan-2-ylcarbamate¹⁵⁷**



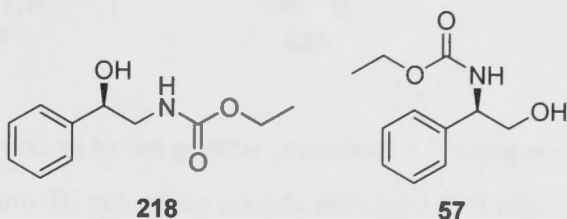
245

The reaction was conducted according to the general procedure 4.3 using 3-methyl-2-buten-1-ol **243** (40.0 mg, 0.41 mmol), potassium osmate dihydrate (5.90 mg, 16.0 μ mol), and *tert*-butyl *N*-(4-toluenesulfonyloxy)carbamate **153** (140 mg, 0.49 mmol). Purification by flash chromatography (5/2/3 ethyl acetate/ dichloromethane/*n*-hexane) afforded the title compound **245** as a violet oil (55.8 mg, 63%). R_f 0.25 (5/2/3 ethyl acetate/dichloromethane/*n*-hexane). IR (thin film, cm^{-1}) 3368 (O-H, N-H), 2977, 2930,

2855 (C-H), 1689 (C=O), 1511. $^1\text{H-NMR}$ (400 MHz, CDCl_3) 5.44 (1H, d, J 8.8 Hz, NH), 4.00 (1H, d, J 10.8 Hz, H1A), 3.78 (1H, d, J 10.8 Hz, H1B), 3.45 (1H, m, H2), 3.03 (2H, s, 2xOH), 1.44 (9H, s, 3xCH₃), 1.34 (3H, s, CH₃), 1.23 (3H, s, CH₃). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 156.40, 79.55, 73.73, 63.44, 57.66, 28.35, 27.51, 27.34. LRMS (ESI+) 242 ($[\text{M}+\text{Na}]^+$, 100%). HRMS (ESI+) calcd. for $\text{C}_{10}\text{H}_{21}\text{NO}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$) 242.1368, found 242.1366.

Ethyl (*R)-2-hydroxy-2-phenylethylcarbamate**¹⁵⁸

Ethyl (*R)-2-hydroxy-1-phenylethylcarbamate**¹⁵⁹



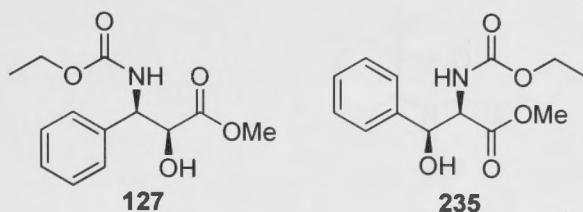
The reaction was conducted according to the general procedure 4.3 using styrene **49** (40.0 mg, 0.38 mmol), potassium osmate dihydrate (1.4 mg, 4.0 μmol), ethyl *N*-(4-toluenesulfonyloxy)carbamate **201** (79.7 mg, 0.31 mmol) and acetonitrile/water (3:1). Purification by flash chromatography (2:3:5 ethyl acetate/dichloromethane/*n*-hexane) afforded ethyl (*R**)-2-hydroxy-2-phenylethyl carbamate **218** in the first fraction as a white solid (46.7 mg, 73%). R_f 0.23 (40% ethyl acetate/*n*-hexane), mp 84.7-85.6 $^{\circ}\text{C}$ (lit¹⁵⁸ 85-87 $^{\circ}\text{C}$). IR (thin film, cm^{-1}) 3315 (O-H, N-H), 3062, 3032, 2974, 2930 (C-H), 1693 (C=O), 1554. $^1\text{H-NMR}$ (300 MHz, CDCl_3) 7.38-7.30 (5H, m, ArH), 5.04 (1H, s, NH), 4.85 (1H, m, H2), 4.13 (2H, q, J 6.90 Hz, CH₂), 3.55 (1H, m, H1A), 3.31 (1H, m, H1B), 2.78 (1H, s, OH), 1.25 (3H, t, J 7.20 Hz, CH₃). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 157.49, 141.61, 128.53, 127.90, 125.86, 73.71, 61.13, 48.48, 14.57. LRMS (ESI+) 232 ($[\text{M}+\text{Na}]^+$, 100%), 229 (10), 103 (19), 62 (18). HRMS (ESI+) calcd. $\text{C}_{11}\text{H}_{15}\text{NO}_3\text{Na}$ for $[\text{M}+\text{Na}]^+$ 232.0950 found 232.0952.

A second fraction afforded ethyl (*R**)-2-hydroxy-1-phenylethylcarbamate¹⁵⁹ **57** as colorless solid (2.3 mg, 3%), R_f 0.13 (40% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3585 (O-H), 3345 (N-H), 2924, 2852 (C-H), 1688 (C=O), 1604, 1527. $^1\text{H-NMR}$ (300 MHz, CDCl_3) 7.30-7.39 (5H, m, ArH), 5.34 (1H, s, NH), 4.84 (1H, d, J 7.20 Hz, H1),

4.12 (2H, q, J 7.0 Hz, CH₂), 3.90-3.86 (2H, m, H₂), 2.10 (1H, s, OH), 1.25 (3H, t, J 7.5 Hz, CH₃). LRMS (ESI+) 232 ([M+Na]⁺, 100%), 102 (18), 61 (17). HRMS (ESI+) calcd. for C₁₁H₁₅NO₃Na ([M+Na]⁺) 232.0950, found 232.0951.

Methyl (2*S,3*R**)-3-(ethoxycarbonylamino)-2-hydroxy-3-phenylpropanoate**⁴³

Methyl (2*S,3*R**)-2-(ethoxycarbonylamino)-3-hydroxy-3-phenylpropanoate**¹⁵¹

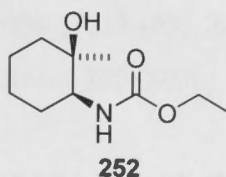


The reaction was conducted according to the general procedure 4.3 using *trans*-methyl cinnamate **122** (40.0 mg, 0.25 mmol), potassium osmate dihydrate (0.9 mg, 3.0 μmol), and ethyl *N*-(4-toluenesulfonyloxy)carbamate **201** (116 mg, 0.62 mmol). Purification by flash chromatography (40% ethyl acetate/*n*-hexane) gave a mixture regioisomers, R_f 0.22 (40% ethyl acetate/*n*-hexane). Further separation with preparative HPLC (SunFire Silica 10 μm, 2% isopropanol/*n*-hexane, 10 mL/min.) afforded methyl (2*S**,3*R**)-3-(ethoxycarbonylamino)-2-hydroxy-3-phenylpropanoate **127** (t_R 22.42 min) as colorless solid (20.4 mg, 31%). IR (thin film, cm⁻¹) 3370 (O-H, N-H), 3066, 3019, 2980, 2954 (C-H), 1735, 1720, 1701 (C=O), 1697, 1603, 1586, 1522. ¹H-NMR (400 MHz, CDCl₃) 7.38-7.29 (5H, m, ArH), 5.56 (1H, d, J 9.2 Hz, NH), 5.25 (1H, d, J 9.2 Hz, H₃), 4.48 (1H, s, H₂), 4.08 (2H, q, J 7.2, 6.8 Hz, CH₂), 3.85 (3H, s, CH₃), 3.19 (1H, d, J 4.0 Hz, OH), 1.22 (3H, t, J 6.8 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 173.27, 155.88, 138.97, 128.63, 127.84, 126.69, 73.40, 61.19, 56.32, 53.13, 14.45. LRMS (ESI+) 290 ([M+Na]⁺, 100%), 119 (14), 91 (52), 62 (20). HRMS (ESI+) calcd. for C₁₃H₁₇NO₅Na ([M+Na]⁺) 290.1004, found 290.1005.

A second fraction (t_R 30.03 min.) afforded methyl (2*S**,3*R**)-2-(ethoxycarbonylamino)-3-hydroxy-3-phenylpropanoate **235** as colorless solid (33.3 mg, 51%). IR (thin film, cm⁻¹) 3401 (O-H, N-H), 3020, 2955, 2931, 2851 (C-H), 1720, 1701 (C=O), 1622, 1516. ¹H-NMR (400 MHz, CDCl₃) 7.36-7.34 (5H, m, ArH), 5.48 (1H, d, J 8.4 Hz, NH), 5.25 (1H, m, H₃), 4.57 (1H, d, J 7.6 Hz, H₂), 4.01-4.00 (2H, m, CH₂), 3.76 (3H, s, CH₃), 2.81

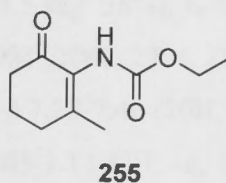
(1H, s, OH), 1.16 (3H, t, J 7.2 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 171.23, 156.47, 139.59, 128.40, 128.14, 125.88, 73.70, 61.29, 59.69, 52.60, 14.39. LRMS (ESI+) 290 ([M+Na]⁺, 95%), 218 (29), 190 (30), 172 (100), 144 (38), 118 (50), 116 (18), 60 (18). HRMS (ESI+) calcd. for C₁₃H₁₇NO₅Na ([M+Na]⁺) 290.1004, found 290.1004.

Ethyl (1*S,2*R**)-2-hydroxy-2-methylcyclohexylcarbamate¹⁵¹**



The reaction was conducted according to the general procedure 4.3 using 1-methylcyclohex-1-ene **250** (50.0 mg, 0.50 mmol), potassium osmate dihydrate (7.43 mg, 0.02 mmol), ethyl *N*-(4-toluenesulfonyloxy)carbamate **201** (162 mg, 0.62 mmol). Purification by flash chromatography (15% ethyl acetate/*n*-hexane) provided the title compound **252** as brown oil (75.1 mg, 74%). R_f 0.22 (2:2:6 ethyl acetate/dichloromethane/*n*-hexane). IR (thin film, cm⁻¹) 3436 (O-H), 3395 (N-H), 2931, 2855 (C-H), 1696 (C=O), 1515. ¹H-NMR (400 MHz, CDCl₃) 5.01 (1H, d, J 6.72 Hz, NH), 4.10 (2H, q, J 6.8 Hz, CH₂), 3.40 (1H, m, H1), 1.68-1.73 (4H, m, H4 and H5), 1.53 (1H, s, OH), 1.39-1.51 (4H, m, H3, and H6), 1.22-1.25 (6H, m, 2xCH₃). ¹³C-NMR (100 MHz, CDCl₃) 156.59, 71.36, 60.65, 56.03, 38.96, 29.12, 27.69, 24.75, 21.04, 14.60. LRMS (ESI+) 224 ([M+Na]⁺, 100%), 185 (23), 102 (10). HRMS (ESI+) calcd. for C₁₀H₁₉NO₃Na ([M+Na]⁺) 224.1263, found 224.1258.

Ethyl 2-methyl-6-oxocyclohex-1-enylcarbamate¹⁶⁰

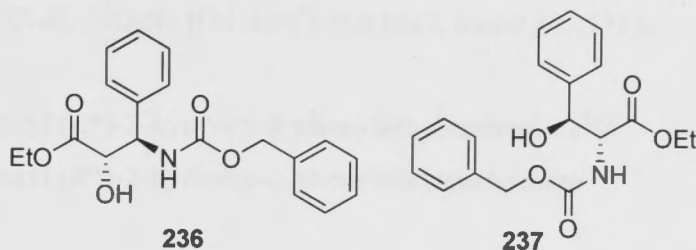


The reaction was conducted according to the general procedure 4.3 using 3-methylcyclohex-2-enone **254** (58.2 mg, 0.53 mmol), potassium osmate dihydrate (7.79

mg, 0.02 mmol), and ethyl *N*-(4-toluenesulfonyloxy)carbamate **201** (166 mg, 0.64 mmol). Purification by flash chromatography (15% ethyl acetate/*n*-hexane) provided the title compound **255** as brown viscous oil (37.4 mg, 36%). R_f 0.42 (60% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3317 (N-H), 2925, 2852 (C-H), 1727 (C=O), 1672, 1639. ^1H -NMR (400 MHz, CDCl_3) 6.42 (1H, s, NH), 4.13 (2H, q, J 6.9 Hz, OCH_2), 2.44-2.49 (4H, m, H3 and H5), 1.94-1.99 (5H, m, H4 and CH_3), 1.26 (3H, t, J 7.0 Hz, CH_3). ^{13}C -NMR (100 MHz, CDCl_3) 194.81, 154.29, 151.74, 129.55, 61.35, 36.76, 32.20, 29.66, 21.26, 14.46. LRMS (ESI+) 220 ($[\text{M}+\text{Na}]^+$, 100%), 153 (65), 126 (32). HRMS (ESI+) calcd. for $\text{C}_{10}\text{H}_{15}\text{NO}_3\text{Na}$ ($[\text{M}+\text{Na}]^+$) 220.0950, found 220.0950.

Ethyl (2*S,3*R**)-3-(benzyloxycarbonylamino)-2-hydroxy-3-phenylpropanoate**¹⁶¹

Ethyl (2*R,3*S**)-2-(benzyloxycarbonylamino)-3-hydroxy-3-phenyl-propanoate**¹⁶²



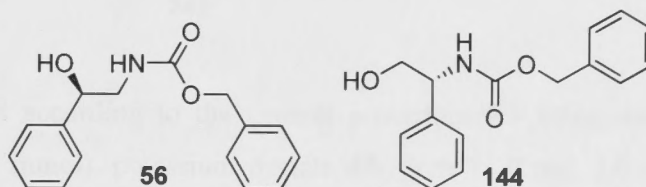
The reaction was conducted according to general procedure 4.3 using *trans*-ethyl cinnamate **368** (50.0 mg, 0.284 mmol), potassium osmate dihydrate (1.1 mg, 3.0 μmol), and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (110 mg, 0.34 mmol). Purification by flash chromatography (2:2:6 ethyl acetate/dichloromethane/*n*-hexane) afforded a mixture of two regioisomers. R_f 0.33 (3:2:5 of ethyl acetate/dichloromethane/*n*-hexane). Further purification with preparative HPLC (SunFire Silica 10 μm , 1% isopropanol/*n*-hexane, 10 mL/min) provided ethyl (2*S**,3*R**)-3-(benzyloxycarbonylamino)-2-hydroxy-3-phenyl propanoate **236** as a white solid (34.5 mg, 35%), t_R 9.20 min. IR (thin film, cm^{-1}) 3367 (broad, O-H, N-H), 3089, 3064, 2981, 2960, 2934, 2851 (C-H), 1730 (C=O), 1604, 1586, 1519. ^1H -NMR (400 MHz, CDCl_3) 7.28-7.40 (10H, m, ArH), 5.69 (1H, d, J 9.2 Hz, NH), 5.29 (1H, d, J 8.8 Hz, H3), 5.03-5.12 (2H, m, CH_2), 4.47 (1H, s, H2), 4.23-4.29 (2H, m, CH_2), 3.19 (1H, d, J 4.0 Hz, OH), 1.28 (3H, t, J 6.8 Hz, CH_3). ^{13}C -NMR (100 MHz, CDCl_3) 127.70, 155.61, 138.90, 136.25, 128.61, 128.47, 128.13, 128.07, 127.84, 126.72, 73.41, 66.98, 62.60, 56.39, 14.00. LRMS (ESI+) 366

($[M+Na]^+$, 100%), 300 (10), 91 (10). HRMS (ESI+) calcd. for $C_{19}H_{22}NO_5$ ($[M+H]^+$) 344.1498, found 344.1496; calcd. for $C_{19}H_{21}NO_5Na$ ($[M+Na]^+$) 366.1317, found 366.1317.

A second fraction afforded ethyl (2*S**,3*R**)-2-(benzyloxycarbonylamino)-3-hydroxy-3-phenylpropanoate **237** as white solid (45.7 mg, 47%), t_R 14.68 min. IR (thin film, cm^{-1}) 3423 (O-H, N-H), 3064, 3032, 2981, 2962, 2937 (C-H), 1726 (C=O), 1605, 1518. 1H -NMR (400 MHz, $CDCl_3$) 7.27-7.37 (10H, m, ArH), 5.59 (1H, d, J 8.8 Hz, NH), 5.25 (1H, s, H3), 5.01 (2H, s, CH_2), 4.59 (1H, d, J 6.8 Hz, H2), 4.16-4.24 (2H, m, CH_2), 2.73 (1H, d, J 3.2 Hz, OH), 1.24 (3H, t, J 6.8 Hz, CH_3). ^{13}C -NMR (100 MHz, $CDCl_3$) 170.54, 156.25, 139.55, 136.19, 128.42, 128.16, 128.06 (2C), 127.90, 125.95, 73.84, 66.97, 61.82, 59.87, 14.00. LRMS (ESI+) 366 ($[M+Na]^+$, 100%), 344 (14), 326 (11), 91 (18). HRMS (ESI+) calcd. for $C_{19}H_{22}NO_5$ ($[M+H]^+$) 344.1498, found 344.1498; calcd. for $C_{19}H_{21}NO_5Na$ ($[M+Na]^+$) 366.1317, found 366.1317.

Benzyl (*R)-2-hydroxy-2-phenylethylcarbamate**¹⁶³

Benzyl (*R)-2-hydroxy-1-phenylethylcarbamate**¹⁶⁴

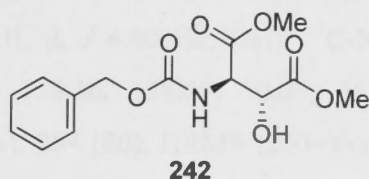


The reaction was conducted according to the general procedure 4.3 using styrene **49** (30.0 mg, 0.29 mmol), potassium osmate dihydrate (1.1mg, 3.0 μ mol), and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (111 mg, 0.35 mmol). Purification by flash chromatography (2:3:5 ethyl acetate/dichloromethane/*n*-hexane) provided benzyl (*R**)-2-hydroxy-2-phenylethylcarbamate **56** as white solid (61.7 mg, 80%), R_f 0.25 (2:3:5 ethyl acetate/dichloromethane/*n*-hexane), mp 109-111 $^{\circ}C$ (lit¹⁶⁵ 120-121 $^{\circ}C$). IR (thin film, cm^{-1}) 3369 (O-H), 3283 (N-H), 2927 (C-H), 1693 (C=O). 1H -NMR (300 MHz, $CDCl_3$) 7.29-7.37 (10H, m, ArH), 5.12 (2H, s, CH_2), 4.86 (1H, d, J 3.90 Hz, NH), 3.58 (1H, m, H2), 3.29-3.38 (2H, m, CH_2), 2.61 (1H, s, OH). ^{13}C -NMR (75 MHz, $CDCl_3$) 157.11, 141.47, 136.32, 128.58, 128.54, 128.18, 128.12, 127.99, 125.84, 73.67, 66.96,

48.51; LRMS (ESI+) 294 ($[M+Na]^+$, 100%), 261 (15), 185 (20). HRMS (ESI+) calcd. for $C_{16}H_{17}NO_3Na$ ($[M+Na]^+$) 294.1106, found 294.1108.

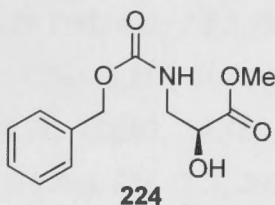
A second fraction afforded benzyl (*R**)-2-hydroxy-1-phenylethylcarbamate **144** as a white solid (4.2 mg, 5%), R_f 0.16 (2:3:5 ethyl acetate/dichloromethane/*n*-hexane), mp 80.5-82.4 °C (lit.³⁴ 83.0-84.5 °C). IR (thin film, cm^{-1}) 3311 (O-H, N-H), 2923, 2852 (C-H), 1700 (C=O), 1539. 1H -NMR (300 MHz, $CDCl_3$) 7.29-7.20 (10H, m, ArH), 5.42 (1H, d, J 6.90 Hz, NH), 5.00-5.08 (2H, m, CH_2), 4.78 (1H, m, H1), 3.80 (2H, s, CH_2), 1.98 (1H, s, OH). ^{13}C -NMR (100 MHz, $CDCl_3$) 156.35, 139.01, 136.21, 128.85, 128.52, 128.18, 127.90, 126.53, 125.84, 67.03, 66.58, 57.10. LRMS (ESI+) 294 ($[M+Na]^+$, 100%), 277 (10), 261 (18), 185 (35), 122 (20). HRMS (ESI+) calcd. for $C_{16}H_{17}NO_3Na$ ($[M+Na]^+$) 294.1106, found 294.1107.

Dimethyl (2*R**,3*R**)-2-(benzyloxycarbonylamino)-3-hydroxysuccinate²



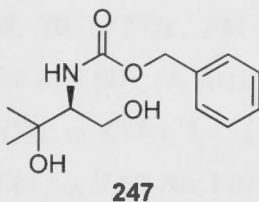
The reaction was conducted according to the general procedure 4.3 using dimethyl fumarate **52** (40.5 mg, 0.28 mmol), potassium osmate dihydrate (1.0 mg, 3.0 μ mol), benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (108 mg, 0.33 mmol). Purification by flash chromatography (40% ethyl acetate/*n*-hexane) provided the title compound **242** as white solid (74.6 mg, 86%), R_f 0.23 (50% ethyl acetate/*n*-hexane), mp 124.4-126.3 °C. IR (thin film, cm^{-1}) 3370 (O-H, N-H), 3064, 3033, 2956, 2924, 2853 (C-H), 1742 (C=O). 1H -NMR (300 MHz, $CDCl_3$) 7.27-7.35 (5H, m, ArH), 5.50 (1H, d, J 9.0 Hz, NH), 5.10 (2H, s, CH_2), 4.85 (1H, d, J 9.90 Hz, H2), 4.71 (1H, d, J 5.40 Hz, H3), 3.81 (6H, s, 2x CH_3), 3.15 (1H, d, J 5.10 Hz, OH). ^{13}C -NMR (75 MHz, $CDCl_3$) 172.24, 169.63, 156.02, 136.01, 128.51, 128.21, 127.98, 70.94, 67.26, 56.46, 53.30, 53.04. LRMS (ESI+) 334 ($[M+Na]^+$, 100%). HRMS (ESI+) calcd. for $C_{14}H_{17}NO_7Na$ ($[M+Na]^+$) 334.0903, found 334.0903.

Methyl (*S*^{*})-3-(benzyloxycarbonylamino)-2-hydroxypropanoate¹⁶⁶



The reaction was conducted according to the general procedure 4.3 using methyl acrylate **223** (31.4 mg, 0.37 mmol), potassium osmate dihydrate (1.3 mg, 4.0 μ mol), and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (135 mg, 0.42 mmol). Purification by flash chromatography (3:2:5 ethyl acetate/dichloromethane/*n*-hexane) provided the title compound **224** as colorless oil (60.2 mg, 68%). R_f 0.11 (3:2:5 ethyl acetate/dichloromethane/*n*-hexane). IR (thin film, cm^{-1}) 3583 (O-H), 3373 (N-H), 2929 (C-H), 1721 (C=O). ^1H -NMR (300 MHz, CDCl_3) 7.34-7.37 (5H, m, ArH), 5.16 (1H, s (broad), NH), 5.09 (2H, s, CH_2), 4.28 (1H, dd, J 9.60, 5.10 Hz, H2), 3.78 (3H, s, CH_3), 3.54-3.59 (2H, m, H3), 3.21 (1H, d, J 4.80 Hz, OH). ^{13}C -NMR (75 MHz, CDCl_3) 173.42, 156.67, 136.28, 128.51, 128.16, 128.09, 70.07, 66.97, 52.81, 44.22. LRMS (ESI+) 276 ($[\text{M}+\text{Na}]^+$, 100%), 254 (20). HRMS (ESI+) calcd. $\text{C}_{12}\text{H}_{16}\text{NO}_5$ for ($[\text{M}+\text{H}]^+$) 254.1028, found 254.1029; calcd. $\text{C}_{12}\text{H}_{15}\text{NO}_5\text{Na}$ for ($[\text{M}+\text{Na}]^+$) 276.0848, found 276.0855.

Benzyl (*S*^{*})-1,3-dihydroxy-3-methylbutan-2-ylcarbamate¹⁶⁷

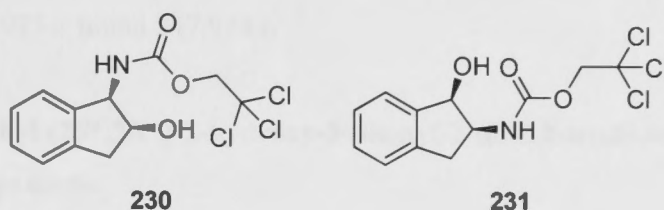


The reaction was conducted according to the general procedure 4.3 using 3-methyl-2-buten-1-ol **243** (64.3 mg, 0.75 mmol), potassium osmate dihydrate (9.2 mg, 0.03 mmol), and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (200 mg, 0.62 mmol). Purification by flash chromatography (3:2:5 ethyl acetate/dichloromethane/*n*-hexane) provided the title compound **247** as yellow oil (101 mg, 64%), R_f 0.13 (3:2:5 ethyl acetate/dichloromethane/*n*-hexane). IR (thin film, cm^{-1}) 3403 (O-H), 3373 (N-H), 3090, 3066, 3034,

2976, 2929, 2825 (C-H), 1690 (C=O) 1533. $^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.28-7.34 (5H, m, ArH), 5.79 (1H, d, J 8.8 Hz, NH), 5.12-5.06 (2H, m, CH_2), 3.98 (1H, d, J 11.2 Hz, H1A), 3.78 (1H, d, J 11.2 Hz, H1B), 3.51 (1H, ddd, J 9.2, 3.2, 3.2 Hz, H2), 3.20 (1H, s, OH), 3.16 (1H, s, OH), 1.32 (3H, s, CH_3), 1.21 (3H, s, CH_3). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 156.86, 136.34, 128.51, 128.14, 128.02, 73.56, 66.91, 63.18, 58.26, 27.45, 27.32. LRMS (ESI+) 276 ($[\text{M}+\text{Na}]^+$, 100%), 236 (20), 203 (10), 185 (40), 125 (8). HRMS (ESI+) calcd. for $\text{C}_{13}\text{H}_{19}\text{NO}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$) 276.1212, found 276.1212.

2,2,2-Trichloroethyl ($1R^*$, $2S^*$)-2-hydroxy-2,3-dihydro-1H-inden-1-ylcarbamate¹⁶⁸

2,2,2-Trichloroethyl ($1R^*$, $2S^*$)-1-hydroxy-2,3-dihydro-1H-inden-2-ylcarbamate

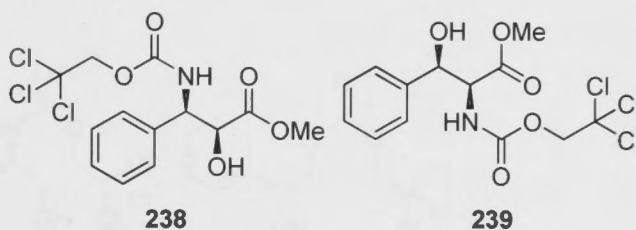


The reaction was conducted according to the general procedure 4.3 using 1H-indene **229** (30.0 mg, 0.25 mmol), potassium osmate dihydrate (0.9 mg, 3.0 μmol), and 2,2,2-trichloroethyl *N*-(4-toluenesulfonyloxy)carbamate **203** (110 mg, 0.31 mmol). Purification by flash chromatography using (20% ethyl acetate/*n*-hexane) provided 2,2,2-trichloroethyl ($1R^*$, $2S^*$)-2-hydroxy-2,3-dihydro-1H-inden-1-ylcarbamate **230** as colorless oil (17.5 mg, 21%). R_f 0.2 (30% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3411 (O-H), 3350 (N-H), 3074, 3045, 3028, 2952, 2926, 2853 (C-H), 1717 (C=O), 1599, 1514. $^1\text{H-NMR}$ (300 MHz, CDCl_3) 7.28-7.37 (4H, m, ArH), 5.73 (1H, brd, J 7.50 Hz, NH), 5.09 (1H, t, J 5.10 Hz), 4.71-4.80 (2H, m, CH_2), 4.45 (1H, m, H2), 3.31 (1H, dd, J 15.90, 7.20 Hz, H3A), 2.95 (1H, dd, J 15.60, 7.50 Hz, H3B), 1.91 (1H, d, J 5.10 Hz, OH). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 154.59, 141.71, 140.82, 129.50, 127.46, 125.32, 125.08, 95.6, 74.62, 74.55, 55.01, 36.65. LRMS (ESI+) 346 ($[\text{M}+\text{Na}]^+$, 40%), 308 (30), 306 (28), 176 (38), 159 (100), 130 (13). HRMS (ESI+) calcd. $\text{C}_{12}\text{H}_{12}^{35}\text{ClNO}_3^{23}\text{Na}$ for ($[\text{M}+\text{Na}]^+$) 345.9780, found 345.9768; calcd. $\text{C}_{12}\text{H}_{12}^{35}\text{Cl}_2^{37}\text{ClNO}_3^{23}\text{Na}$ for ($[\text{M}+\text{Na}]^+$) 347.9751, found 347.9756.

A second fraction afforded 2,2,2-trichloroethyl (1*R**,2*S**)-1-hydroxy-2,3-dihydro-1*H*-inden-2-ylcarbamate **231** as a colorless solid (18.3 mg, 22%), *R*_f 0.16 (30% ethyl acetate/*n*-hexane), mp 112-115 °C. IR (thin film, cm⁻¹) 3404 (O-H), 3328 (N-H), 3072, 3026, 2925, 2849 (C-H), 1714 (C=O), 1611, 1514. ¹H-NMR (300 MHz, CDCl₃) 7.46-7.38 (4H, m, ArH), 5.70 (1H, d, *J* 8.10 Hz, NH), 5.18 (1H, dd, *J* 8.70, 5.10 Hz, H₂), 4.88 (1H, d, *J* 11.70 Hz, CH_AH_B), 4.76 (1H, d, *J* 12.30 Hz, CH_AH_B), 4.67 (1H, m, H₁), 3.19 (1H, dd, *J* 16.5, 4.80 Hz, H_{3A}), 2.96 (1H, d, *J* 16.5 Hz, H_{3B}), 1.90 (1H, d, *J* 4.20 Hz, OH). ¹³C-NMR (100 MHz, CDCl₃) 155.02, 140.03, 139.49, 128.50, 127.36, 125.46, 124.53, 95.54, 74.69, 73.54, 59.33, 39.67. LRMS (ESI+) 348 ([M+Na]⁺, 24%), 346 (25), 158 (15), 133 (100), 62 (18). HRMS (ESI+) calcd. for C₁₂H₁₂³⁵Cl₃NO₃²³Na ([M+Na]⁺) 345.9780, found 345.9773; calcd. for C₁₂H₁₂³⁵Cl₂³⁷ClNO₃²³Na ([M+Na]⁺) 347.9751, found 347.9743.

Methyl (2*S,3*R**)-3-hydroxy-3-phenyl-2-((2,2,2-trichloroethoxy)carbonylamino)-propanoate**

Methyl (2*S,3*R**)-2-hydroxy-3-phenyl-3-((2,2,2-trichloro-ethoxy)carbonylamino)-propanoate**¹⁶⁹



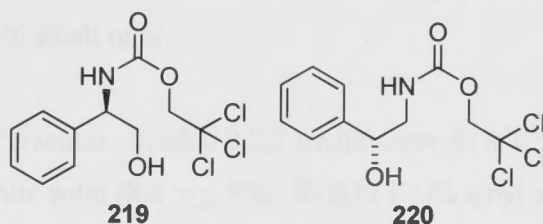
The reaction was conducted according to the general procedure 4.3 using *trans*-methyl cinnamate **122** (40.0 mg, 0.25 mmol), potassium osmate dihydrate (0.9 mg, 3.0 μmol), and 2,2,2-trichloroethyl *N*-(4-toluenesulfonyloxy)carbamate **203** (107 mg, 0.30 mmol). Purification by flash chromatography (25% ethyl acetate/*n*-hexane) afforded a mixture of two regioisomers. *R*_f 0.22 (30% ethyl acetate/*n*-hexane). Further separation with preparative HPLC (SunFire silica 10 μm, 4% isopropanol/*n*-hexane, 10 mL/min.) provided methyl (2*S**,3*R**)-2-hydroxy-3-phenyl-3-((2,2,2-trichloroethoxy)carbonylamino)propanoate **238** as a colorless oil (33.1 mg, 44%), *t*_R 7.82 min. IR (thin film, cm⁻¹) 3351 (O-H, N-H), 3066, 3020, 2955, 2855 (C-H), 1735 (C=O), 1522. ¹H-NMR (400 MHz, CDCl₃) 7.38-7.29 (5H, m, ArH), 5.91 (1H, d, *J* 9.2 Hz, NH), 5.29 (1H, dd, *J* 9.2,

1.6 Hz, H₃), 4.67-4.75 (2H, m, CH₂), 4.53 (1H, dd, *J* 4.4, 2.4 Hz, H₂), 3.85 (1H, s, CH₃), 3.23 (1H, d, *J* 4.00 Hz, OH). ¹³C-NMR (100 MHz, CDCl₃) 172.96, 153.99, 138.26, 128.74, 128.09, 126.68, 95.41, 74.59, 73.15, 56.62, 53.24. LRMS (ESI⁺) 396 ([M+Na]⁺, 18%), 394 (50), 392 (53), 179 (20), 119 (30), 91 (100). HRMS (ESI⁺) calcd. for C₁₃H₁₄Cl₃NO₅Na ([M+Na]⁺) 391.9835, found 391.9834.

A second fraction (*t_R* 10.22 min) afforded methyl (2*S**,3*R**)-3-hydroxy-3-phenyl-2-((2,2,2-trichloroethoxy)carbonylamino)propanoate **239** as a colorless oil (42.2 mg, 56%). IR (thin film, cm⁻¹) 3431 (O-H, N-H), 3065, 3029, 2955 (C-H), 1733 (C=O), 1606, 1521. ¹H-NMR (400 MHz, CDCl₃) 7.37-7.28 (5H, m, ArH), 5.85 (1H, d, *J* 9.6 Hz, NH), 5.35 (1H, t, *J* 3.2 Hz, H₃), 4.61-4.66 (2H, m, CH_AH_B), 4.55 (1H, d, *J* 12.0 Hz, CH_AH_B), 3.80 (3H, s, CH₃), 2.67 (1H, d, *J* 4.0 Hz, OH). ¹³C-NMR (100 MHz, CDCl₃) 170.61, 154.47, 139.26, 128.51, 128.27, 125.83, 95.21, 74.55, 73.46, 59.85, 52.81. LRMS (ESI⁺) 396 ([M+Na]⁺, 23%), 394 (98), 392 (100), 172 (92). HRMS (ESI⁺) calcd. for C₁₃H₁₄³⁵Cl₃NO₅Na ([M+Na]⁺) 391.9835, found 391.9835.

2,2,2-Trichloroethyl (*R**)-2-hydroxy-2-phenylethylcarbamate

2,2,2-Trichloroethyl (*R**)-2-hydroxy-1-phenylethylcarbamate



The reaction was conducted according to the general procedure 4.3 using styrene **49** (30.0 mg, 0.29 mmol), potassium osmate dihydrate (1.1 mg, 3.0 μmol), and 2,2,2-trichloroethyl *N*-(4-toluenesulfonyloxy)carbamate **203** (125 mg, 0.35 mmol). Purification by flash chromatography (30% ethyl acetate/*n*-hexane) afforded 2,2,2-trichloroethyl (*R**)-2-hydroxy-2-phenylethylcarbamate **220** as a white solid (82.1 mg, 91%). *R_f* 0.24 (30% ethyl acetate/*n*-hexane). Recrystallisation using chloroform/*n*-hexane (slow evaporation) at room temperature provided white crystals, mp 116-118 °C. IR (thin film, cm⁻¹) 3397 (O-H), 3317 (N-H), 3085, 3062, 2960, 2894 (C-H), 1710 (C=O). ¹H-NMR (400 MHz, CDCl₃) 7.31-7.36 (5H, d, *J* 4.40 Hz, ArH), 5.37 (1H, s,

NH), 4.87 (1H, m, H2), 4.72 (2H, s, CH₂), 3.61 (1H, ddd, *J* 14.0, 7.6, 4.0 Hz H1A), 3.36 (1H, ddd, *J* 13.2, 8.0, 4.8 Hz, H1B), 2.37 (1H, d, *J* 3.60 Hz, OH). ¹³C-NMR (100 MHz, CDCl₃) 155.09, 141.14, 128.67, 128.21, 125.84, 77.19, 74.61, 73.36, 48.41. LRMS (ESI+) 334 ([M+Na]⁺, 100%), 146 (93), 120 (78). HRMS (ESI+) calcd. for C₁₁H₁₂³⁵Cl₃NO₃²³Na ([M+Na]⁺) 333.9787, found 333.9780; calcd. for C₁₁H₁₂³⁵Cl₂³⁷ClNO₃²³Na ([M+Na]⁺) 335.9756, found 335.9751.

X-ray crystallography confirmed the structure of 2,2,2-trichloroethyl (*R*^{*})-2-hydroxy-2-phenylethylcarbamate **220** (Figure 7.4.3).

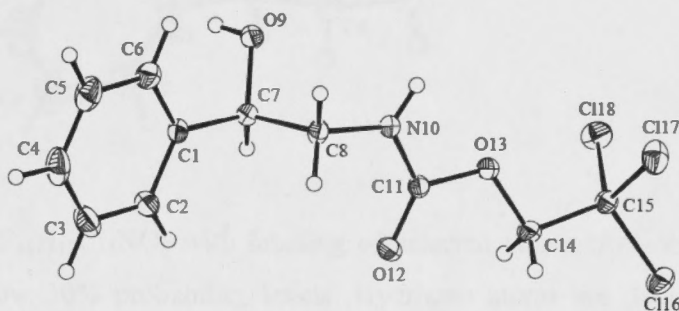


Figure 7.4.3 Structure of C₁₁H₁₂Cl₃NO₃ with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

A second fraction afforded 2,2,2-trichloroethyl (*R*^{*})-2-hydroxy-1-phenylethylcarbamate **219** as white solid (8.0 mg, 9%), *R*_f 0.11 (30% ethyl acetate/*n*-hexane). Recrystallisation using chloroform/*n*-hexane (slow evaporation) at room temperature afforded white crystal, mp 135-137 °C. IR (thin film, cm⁻¹) 3322 (O-H), 3204 (N-H), 3052, 2951, 2927, 2853 (C-H), 1706 (C=O), 1560. ¹H-NMR (400 MHz, CDCl₃) 7.32-7.40 (5H, m, ArH), 5.76 (1H, s, broad, NH), 4.73 (2H, s, CH₂), 3.93 (2H, m, H2), 1.82 (1H, s, OH). ¹³C-NMR (100 MHz, CDCl₃) 154.42, 138.49, 128.92, 128.06, 126.49, 95.60, 74.65, 66.19, 57.05. LRMS (ESI+) 336 ([M+Na]⁺, 100%), 194 (32), 154 (45), 121 (58), 103 (43). HRMS (ESI+) calcd. for C₁₁H₁₂³⁵Cl₃NO₃²³Na ([M+Na]⁺) 333.9782, found 333.9780; calcd. for C₁₁H₁₂³⁵Cl₂³⁷ClNO₃²³Na ([M+Na]⁺) 335.9749, found 335.9751.

X-ray crystallography confirmed the structure of 2,2,2-trichloroethyl (*R*^{*})-2-hydroxy-1-phenylethylcarbamate **219** (Figure 7.4.4).

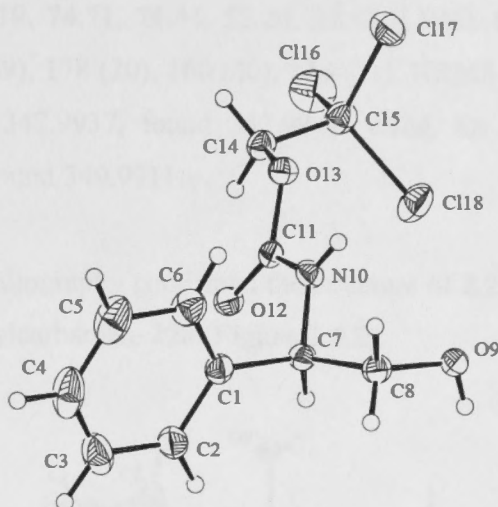
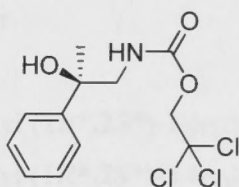


Figure 7.4.4 Structure of $C_{11}H_{12}Cl_3NO_3$ with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

2,2,2-Trichloroethyl (*R*^{*})-2-hydroxy-2-phenylpropylcarbamate



228

The reaction was conducted according to the general procedure 4.3 using α -methyl styrene **36** (30.0 mg, 0.25 mmol), potassium osmate dihydrate (0.9 mg, 3.0 μ mol), and 2,2,2-trichloroethyl *N*-(4-toluenesulfonyloxy)carbamate **203** (111 mg, 0.31 mmol). Purification by flash chromatography (25% ethyl acetate/*n*-hexane) provided the title compound **228** as colorless solid (75.6 mg, 91%). R_f 0.22 (30% ethyl acetate/*n*-hexane). Recrystallisation using chloroform/*n*-hexane (slow evaporation) at room temperature provided colorless crystal, mp 131-133 °C. IR (thin film, cm^{-1}) 3422 (O-H), 3331 (N-H), 3062, 3002, 2935, 2851 (C-H), 1716 (C=O). 1H -NMR (400 MHz, $CDCl_3$) 7.45 (2H, m,

ArH), 7.36 (2H, m, ArH), 7.26 (1H, m, ArH), 5.22 (1H, s, NH), 4.65-4.72 (2H, m, CH₂), 3.60 (1H, dd, *J* 14.0, 6.8 Hz, H1A), 3.45 (1H, dd, *J* 14.0, 5.6 Hz, H1B), 2.23 (1H, s, OH), 1.53 (3H, s, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 155.43, 144.95, 128.48, 127.34, 124.86, 77.19, 74.71, 74.54, 52.20, 27.51. LRMS (ESI+) 350 ([M+Na]⁺, 100%), 348 (98), 310 (39), 178 (20), 160 (40), 134 (71). HRMS (ESI+) calcd. for C₁₂H₁₄Cl₃NO₃Na ([M+Na]⁺) 347.9937, found 347.9941; calcd. for C₁₂H₁₄³⁵Cl₂³⁷ClNO₃Na ([M+Na]⁺) 349.9907, found 349.9911.

X-ray crystallography confirmed the structure of 2,2,2-trichloroethyl (*R*^{*})-2-hydroxy-2-phenylpropylcarbamate **228** (Figure 7.4.5).

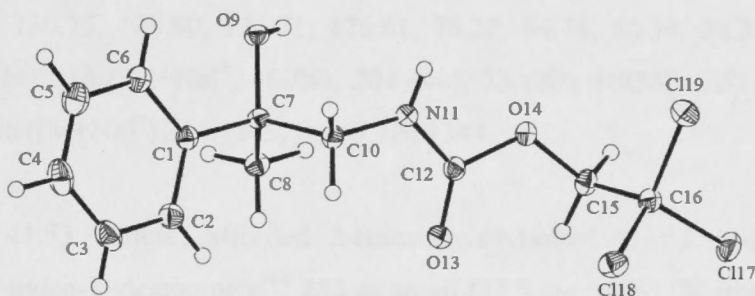
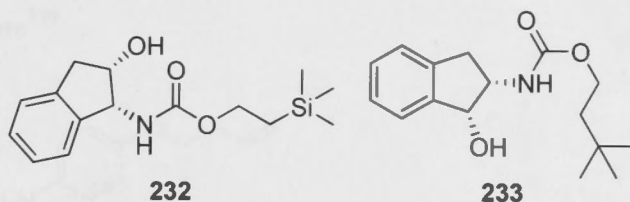


Figure 7.4.5 Structure of C₁₂H₁₄Cl₃NO₃ with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii

2-(Trimethylsilyl)ethyl (1*R*^{*},2*S*^{*})-1-hydroxy-2,3-dihydro-1*H*-inden-2-yl carbamate
2-(Trimethylsilyl)ethyl (1*R*^{*},2*S*^{*})-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl
carbamate¹⁶⁸

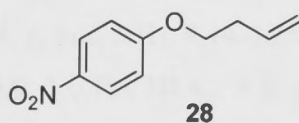


The reaction was conducted according to the general procedure 4.3 using 1*H*-indene **229** (40.0 mg, 0.34 mmol), potassium osmate dihydrate (4.9 mg, 0.01 mmol), and 2-

(trimethylsilyl)ethyl *N*-(4-toluenesulfonyloxy)carbamate **204** (148 mg, 0.45 mmol). Purification by flash chromatography (30% ethyl acetate/*n*-hexane) afforded an inseparable mixture of two regioisomers. *R*_f 0.38 (2:2:6 ethyl acetate/dichloromethane/*n*-hexane). Further separation using preparative HPLC (SunFire silica 10 μm, 1% isopropanol/*n*-hexane, 8 mL/min.) provided 2-(trimethylsilyl)ethyl (1*R**,2*S**)-1-hydroxy-2,3-dihydro-1*H*-inden-2-ylcarbamate **233** (*t*_R 33.81 min) as an oil (47.8 mg, 48%). IR (thin film, cm⁻¹) 3413 (O-H, N-H), 3071, 3046, 2952, 2897, (C-H), 1718, 1691 (C=O), 1512. ¹H-NMR (400 MHz, CDCl₃) 7.38 (1H, d, *J* 6.8 Hz, NH), 7.20-7.28 (4H, m, ArH), 5.25 (1H, s, H1), 5.00 (1H, s), 4.38 (1H, s, brd), 4.14 (2H, t, *J* 8.4 Hz, CH₂), 3.20 (1H, dd, *J* 16.0, 7.6 Hz, H3A), 2.84 (1H, dd, *J* 16.0, 7.6 Hz, H3B), 1.91 (1H, s, OH), 0.96 (2H, t, *J* 8.4 Hz, CH₂), 0.00 (9H, s, 3xCH₃). ¹³C-NMR ((100 MHz, CDCl₃) 158.35, 143.53, 142.50, 130.75, 128.80, 126.71, 126.61, 76.22, 64.74, 56.34, 38.30, 19.24, 0.00. LRMS (ESI+) 316 ([M+Na]⁺, 100%), 204 (40), 73 (20). HRMS (ESI+) calcd. for C₁₅H₂₃NO₃SiNa ([M+Na]⁺) 316.1345, found 316.1344.

A second fraction (*t*_R 41.53 minute) afforded 2-(trimethylsilyl)ethyl (1*R**,2*S**)-2-hydroxy-2,3-dihydro-1*H*-inden-1-ylcarbamate¹⁶⁸ **232** as an oil (22.5 mg, 32%). IR (thin film, cm⁻¹) 3408 (O-H), 3323 (N-H), 3047, 2952, 2897 (C-H), 1720, 1694 (C=O), 1609, 1518. ¹H-NMR (400 MHz, CDCl₃) 7.24-7.26 (1H, m, ArH), 7.18-7.20 (3H, m, ArH), 5.18 (1H, s, NH), 5.09 (1H, s, H1), 4.57 (1H, m, H2), 4.18 (2H, t, *J* 7.6 Hz, CH₂), 3.09 (1H, dd, *J* 16.4, 5.2 Hz, H3A), 2.88 (1H, dd, *J* 16.4, 2.0 Hz, H3B), 1.94 (1H, s, OH), 0.98 (2H, m, CH₂), 0.00 (9H, s, 3xCH₃). ¹³C-NMR (100 MHz, CDCl₃) 158.63, 142.02, 141.24, 129.76, 128.67, 126.86, 125.90, 75.11, 64.99, 60.66, 40.92, 19.21, 0.00. LRMS (ESI+) 316 ([M+Na]⁺, 100%), 288 (10), 172 (18), 73 (9). HRMS (ESI+) calcd. for C₁₅H₂₃NO₃SiNa ([M+Na]⁺) 316.1345, found 316.1344.

1-(But-3-enyloxy)-4-nitrobenzene¹⁷⁰

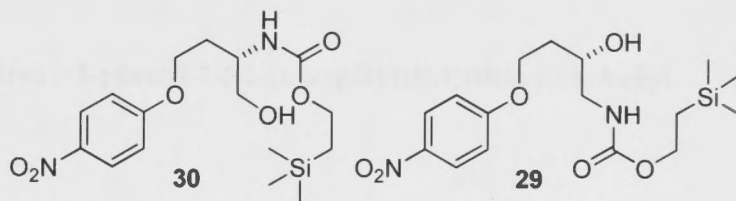


Procedure follow lit.¹⁷¹ To a solution of 4-nitrophenol (1.0 g, 7.2 mmol) and potassium carbonate (2.48 g, 18.0 mmol) in acetonitrile (50.0 mL) was added 4-bromobutene (1.46

mL, 14.4 mmol) at room temperature. This reaction mixture was stirred until complete (18 h). The mixture was filtered and concentrated under reduced pressure. The crude mixture was dissolved in dichloromethane (100 mL), washed with water (2 x 10 mL), dried (MgSO₄), and concentrated to afford the title compound **28** as pale-yellow oil (1.30 g, 94%). IR (thin film, cm⁻¹) 3083, 2937 (C-H), 2448, 1642, 1594. ¹H-NMR (300 MHz, CDCl₃) 8.18 (2H, d, *J* 8.80 Hz, ArH), 6.95 (2H, d, *J* 9.60 Hz, ArH), 5.89 (1H, ddt, *J* 16.8, 10.0, 6.8 Hz, H3), 5.12-5.22 (2H, m, H4), 4.11 (2H, t, *J* 6.4 Hz, H1), 2.59 (2H, m, H2). ¹³C-NMR (75 MHz, CDCl₃) 164.10, 141.34, 133.67, 125.81, 117.56, 114.43, 67.97, 33.27. LRMS (EI+) 193 ([M]⁺, 50%), 165 (49), 152 (32), 122 (23), 139 (13), 122 (23), 109 (18), 92 (15), 76 (30), 63 (30), 55 (100), 39 (58). HRMS (EI+) calcd. for C₁₀H₁₁NO₃ ([M]⁺) 193.0739, found 193.0739.

2-(Trimethylsilyl)ethyl (*S*^{*})-2-hydroxy-4-(4-nitrophenoxy)butylcarbamate⁶

2-(Trimethylsilyl)ethyl (*S*^{*})-1-hydroxy-4-(4-nitrophenoxy)butan-2-ylcarbamate⁶



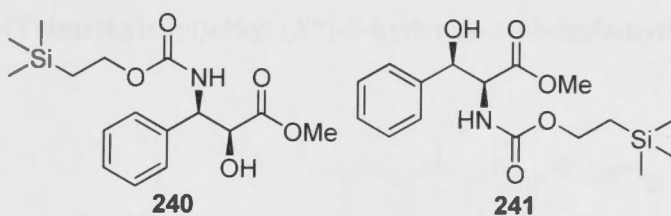
The reaction was conducted according to the general procedure 4.3 using 1-(but-3-enyloxy)-4-nitrobenzene **28** (65.0 mg, 0.34 mmol), potassium osmate dihydrate (4.90 mg, 14.0 μmol), and 2-(trimethylsilyl)ethyl *N*-(4-toluenesulfonyloxy)carbamate **204** (133.8 mg, 0.404 mmol). Purification by flash chromatography (50% ethyl acetate/*n*-hexane) afforded 2-(trimethylsilyl)ethyl (*S*^{*})-2-hydroxy-4-(4-nitrophenoxy)butylcarbamate **29** as a colourless oil (88.8 mg, 71%), *R*_f 0.5 (70% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3408 (O-H, N-H), 3114, 3086, 2953, 2898, 2854 (C-H), 1693 (C=O), 1607, 1593. ¹H-NMR (400 MHz, CDCl₃) 8.18 (2H, d, *J* 9.20 Hz, ArH), 6.95 (2H, d, *J* 9.60 Hz, ArH), 5.09 (1H, s, brd, NH), 4.14-4.28 (4H, m, H4, CH₂), 4.01 (1H, m, H2), 3.39 (1H, ddd, *J* 14.1, 5.9, 3.0 Hz, H1A), 3.21 (1H, m, H1B), 2.95 (1H, s, OH), 1.89-2.04 (2H, m, H3), 0.89 (2H, m, CH₂), 0.03 (9H, s, Si(CH₃)₃). ¹³C-NMR (100 MHz, CDCl₃) 165.26, 159.41, 143.06, 127.43, 115.93, 70.27, 67.13, 65.09, 48.59, 35.18, 19.23, 0.00. LRMS (ESI+) 393 ([M+Na]⁺, 100%) 371 ([M+H]⁺, 10), 343 (90), 325 (20), 212 (47),

192 (28), 146 (22), 70 (48). HRMS (ESI+) calcd. for $C_{16}H_{26}N_2O_6SiNa$ ($[M+Na]^+$) 393.1458, found 393.1452.

A second fraction afforded 2-(trimethylsilyl)ethyl (*S*^{*})-1-hydroxy-4-(4-nitrophenoxy)-butan-2-ylcarbamate^{6,109} **30** as a colourless oil (11.9 mg, 10%), R_f 0.36 (70% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3577 (O-H), 3385 (N-H), 2954, 2924, 2853 (C-H), 1691 (C=O), 1607, 1593, 1514. 1H -NMR (400 MHz, $CDCl_3$) 8.18 (2H, d, J 9.6 Hz, ArH), 6.93 (2H, d, J 9.3 Hz, ArH), 4.95 (1H, m, NH), 4.09-4.17 (4H, m, H4, CH_2), 3.94 (1H, m, H2), 3.67-3.77 (2H, m, H1), 1.95-2.16 (3H, m, H3 and OH), 0.95 (2H, m, CH_2), 0.00 (9H, s, $Si(CH_3)_3$). ^{13}C -NMR (100 MHz, $CDCl_3$) 165.10, 159.41, 143.18, 127.97, 127.45, 67.40, 66.73, 64.95, 51.97, 31.20, 19.22, 0.00. LRMS (ESI+) 393 ($[M+Na]^+$, 100%), 343 (24), 212 (21), 204 (28), 73 (15). HRMS (ESI+) calcd. for $C_{16}H_{26}N_2O_6SiNa$ ($[M+Na]^+$) 393.1458, found 393.1456.

Methyl (2*S*^{*},3*R*^{*})-2-hydroxy-3-phenyl-3-((2-(trimethylsilyl) ethoxy)carbonyl-amino)propanoate¹⁷²

Methyl (2*S*^{*},3*R*^{*})-3-hydroxy-3-phenyl-2-((2-(trimethylsilyl)ethoxy)carbonyl-amino)propanoate

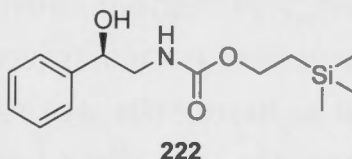


The reaction was conducted according to the general procedure 4.3 using *trans*-methyl cinnamate **122** (56.0 mg, 0.35 mmol), potassium osmate dihydrate (5.00 mg, 14.0 μ mol), and 2-(trimethylsilyl)ethyl *N*-(4-toluenesulfonyloxy)carbamate **204** (147.4 mg, 0.445 mmol). Purification by flash chromatography (2:2:6 ethyl acetate/dichloromethane/*n*-hexane) provided an inseparable mixture of two regioisomers. R_f 0.22 (2:2:6 ethyl acetate/ dichloromethane/*n*-hexane). Further separation with preparative HPLC (SunFire silica 10 μ m, 2% isopropanol/*n*-hexane, 10 mL/min) afforded methyl (2*S*^{*},3*R*^{*})-2-hydroxy-3-phenyl-3-((2-(trimethylsilyl)ethoxy)carbonylamino)propanoate **240** as a colorless oil (22.3 mg, 19%), t_R 12.2 min. IR (thin film, cm^{-1}) 3370 (brd, O-H,

N-H), 3067, 3021, 2953 (C-H), 1721, 1697 (C=O), 1603, 1514. ^1H -NMR (400 MHz, CDCl_3) 7.28-7.36 (5H, m, ArH), 5.51 (1H, d, J 9.0 Hz, NH), 5.25 (1H, d, J 9.3 Hz, H3), 4.49 (1H, m, H2), 4.12 (2H, m, CH_2) 3.85 (3H, s, CH_3), 3.15 (1H, s, OH), 0.96 (2H, m, CH_2), 0.00 (9H, s, $3\times\text{CH}_3$). ^{13}C -NMR (100 MHz, CDCl_3) 174.81, 157.51, 140.54, 130.18, 129.37, 128.19, 74.91, 64.99, 57.77, 54.73, 19.11, 0.00. LRMS (ESI+) 362 ($[\text{M}+\text{Na}]^+$, 100%), 134 (32), 118 (34), 91 (44), 73 (35). HRMS (ESI+) calcd. for $\text{C}_{16}\text{H}_{25}\text{NO}_5\text{SiNa}$ ($[\text{M}+\text{Na}]^+$) 362.1400, found 362.1400.

A second fraction (t_{R} 19.87 min.) afforded methyl (2*S**,3*R**)-3-hydroxy-3-phenyl-2-((2-(trimethylsilyl)ethoxy)carbonylamino)propanoate **241** as a colorless oil (34.9 mg, 30%). IR (thin film, cm^{-1}) 3401 (O-H, N-H), 3065, 3029, 2953, 2898 (C-H), 1752, 1724, 1701 (C=O), 1606, 1513. ^1H -NMR (400 MHz, CDCl_3) 7.26-7.38 (5H, m, ArH), 5.42 (1H, d, J 8.4 Hz, NH), 5.26 (1H, m, H3), 4.58 (1H, d, J 7.2 Hz, H2), 4.03-4.06 (2H, m, CH_2), 3.76 (3H, s, CH_3) 2.76 (1H, s, OH), 0.91 (2H, t, J 7.6 Hz, CH_2), 0.00 (9H, s, $3\times\text{CH}_3$). ^{13}C -NMR (100 MHz, CDCl_3) 172.82, 158.12, 141.14, 129.98, 129.70, 127.44, 75.27, 65.15, 61.20, 54.16, 19.09, 0.00. LRMS (ESI+) 362 ($[\text{M}+\text{Na}]^+$, 100%), 118 (60), 73 (16). HRMS (ESI+) calcd. for $\text{C}_{16}\text{H}_{25}\text{NO}_5\text{SiNa}$ ($[\text{M}+\text{Na}]^+$) 362.1400, found 362.1400; calcd. for $\text{C}_{16}\text{H}_{26}\text{NO}_5\text{Si}$ ($[\text{M}+\text{H}]^+$) 340.1580, found 362.1580.

2-(Trimethylsilyl)ethyl (*R**)-2-hydroxy-2-phenylethylcarbamate



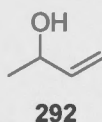
The reaction was conducted according to the general procedure 4.3 using styrene **49** (35.0 mg, 0.34 mmol), potassium osmate dihydrate (4.9 mg, 13 μmol), and 2-(trimethylsilyl)ethyl *N*-(4-toluenesulfonyloxy)carbamate **204** (137 mg, 0.41 mmol). Purification by flash chromatography (2:2:6 ethyl acetate/dichloromethane/*n*-hexane) provided the title compound **222** as a colorless solid (37.1 mg, 39%). R_f 0.23 (2:2:6 of ethyl acetate/dichloromethane/*n*-hexane), mp 75-77 $^{\circ}\text{C}$. IR (thin film, cm^{-1}) 3361 (O-H), 3266 (N-H), 3072, 2953, 2929, 2899 (C-H), 1679 (C=O), 1554. ^1H -NMR (400 MHz, CDCl_3) 7.27-7.37 (5H, m, ArH), 5.03 (1H, s, NH), 4.84 (1H, m, H1), 4.17 (2H, m,

CH₂), 3.54 (1H, m, H1A), 3.30 (1H, ddd, *J* 14.0, 8.4, 5.6 Hz, H1B), 2.88 (1H, s, OH), 0.98 (2H, m, CH₂), 0.09 (9H, s, Si(CH₃)₃). ¹³C-NMR (100 MHz, CDCl₃) 159.16, 143.11, 130.04, 129.40, 127.34, 75.37, 64.91, 50.02, 19.20, 0.00. LRMS (ESI+) 304 ([M+Na]⁺, 100%). HRMS (ESI+) calcd. for C₁₄H₂₃NO₃SiNa ([M+Na]⁺) 304.1345, found 304.1345.

7.5 Experimental Section for Chapter 5

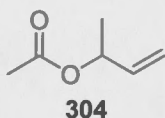
Diastereoselectivity study of the osmium-catalysed aminohydroxylation reaction of allylic alcohols with benzyl *N*-(4-toluenesulfonyloxy)carbamate

But-3-en-2-ol¹³⁶



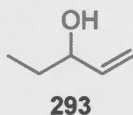
To a stirred solution of methylmagnesium bromide (41.7 mL, 3.0 M, 125 mmol) in diethyl ether was added acrolein (5.40 g, 96.3 mmol) at 0 °C under nitrogen. The reaction mixture was stirred until complete, quenched with aqueous hydrochloric acid solution (50 mL, 1.0 M) and then extracted with diethyl ether (3 x 50 mL). The combined organic extract was washed with brine (10 mL), dried over magnesium sulfate and concentrated. Purification by distillation afforded the title compound **292** as a colourless oil (5.12 g, 74%), bp 80 °C (760 mmHg) (lit.¹⁷³ 97 °C, 760 mmHg). IR (thin film, cm⁻¹) 3372 (O-H), 3089, 2978, 2929, 2876 (C-H), 1647 (C=C). ¹H-NMR (400 MHz, CDCl₃) 5.90 (1H, ddd, *J* 17.2, 10.4, 6.0 Hz, H3) 5.20 (1H, m, H4A), 5.05 (1H, m, H4B), 4.30 (1H, m, H2), 1.72 (1H, s, OH), 1.27 (3H, d, *J* 6.4 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 142.3, 113.6, 69.0, 23.0.

But-3-en-2-yl acetate¹⁴¹



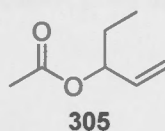
To a stirred solution of but-3-en-2-ol **292** (202 mg, 2.81 mmol) in dichloromethane (7.5 mL) was added pyridine (244 mg, 3.09 mmol) and acetyl chloride (231 mg, 2.95 mmol) at 0 °C under nitrogen. The reaction mixture was stirred until complete, quenched with water (15 mL) and then extracted with diethyl ether (3 x 10 mL). The combined organic extract was washed with brine (10 mL), dried over magnesium sulfate and concentrated to afford the title compound **304** as a colourless oil (117 mg, 36%). R_f 0.51 (20% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3090, 2985, 2935 (C-H), 1737 (C=O). $^1\text{H-NMR}$ (400 MHz, CDCl_3) 5.84 (1H, ddd, J 16.4, 10.4, 6.0 Hz, H3), 5.34 (1H, m, H2), 5.24 (1H, m, H4A), 5.14 (1H, m, H4B), 2.05 (3H, s, CH_3), 1.31 (3H, d, J 6.4 Hz, H1). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 170.29, 137.66, 115.71, 70.96, 21.30, 19.88.

Pent-1-en-3-ol¹⁷⁴



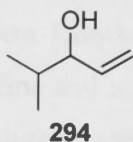
To a stirred solution of vinylmagnesium bromide (25.1 mL, 1.0 M, 25.1 mmol) in tetrahydrofuran was added propanal (970 mg, 16.7 mmol) at 0 °C under nitrogen. The reaction mixture was stirred until complete, quenched with aqueous hydrochloric acid solution (10 mL, 1.0 M) and then extracted with diethyl ether (3 x 50 mL). The combined organic extract was washed with brine (20 mL), dried over sodium sulfate and concentrated. Purification by distillation afforded the title compound **293** as a colourless oil (1.02 g, 71%), bp 30 °C (12 mmHg) (lit.¹⁷⁴ 114-116 °C, 760 mmHg). IR (thin film, cm^{-1}) 3368 (O-H), 2080, 2964, 2934, 2876 (C-H), 1646 (C=C). $^1\text{H-NMR}$ (400 MHz, CDCl_3) 5.85 (1H, ddd, J 17.2, 10.4, 6.4 Hz, H2), 5.22 (1H, m, H1A), 5.11 (1H, m, H1B), 4.03 (1H, dt, J 6.4, 6.4 Hz, H3), 1.65 (1H, s, OH), 1.52-1.60 (2H, m, H4), 0.92 (3H, t, J 7.2 Hz, CH_3). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 140.90, 114.70, 74.50, 29.80, 9.50.

Pent-1-en-3-yl acetate¹⁴²



To a stirred solution of pent-1-en-3-ol **293** (150 mg, 1.74 mmol) in dichloromethane (8.0 mL) was added pyridine (179 mg, 2.26 mmol) and acetyl chloride (178 mg, 2.26 mmol) at 0 °C under nitrogen. The reaction mixture was stirred until complete, quenched with water (10 mL) and then extracted with diethyl ether (3 x 10 mL). The combined organic extract was washed with brine (30 mL), dried over magnesium sulfate and concentrated to afford the title compound **305** as a colourless oil (194 mg, 87%). R_f 0.48 (20% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3086, 2972, 2939, 2881 (C-H), 1739 (C=O), 1647 (C=C). $^1\text{H-NMR}$ (400 MHz, CDCl_3) 5.77 (1H, ddd, J 16.8, 10.0, 6.4 Hz, H2), 5.14-5.25 (3H, m, H1 and H3), 2.07 (3H, s, CH_3), 1.64 (2H, m, H4), 0.90 (3H, t, J 8.0 Hz, H5). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 170.42, 136.27, 116.67, 75.99, 27.14, 21.22, 9.35.

4-Methylpent-1-en-3-ol¹⁷⁵

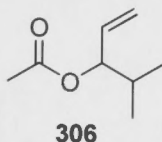


To a stirred magnesium (1.96 g, 80.5 mmol) in diethyl ether (100 mL) was added 2-bromopropane (10.0 g, 80.5 mmol) at 0 °C. This mixture was warmed to 25 °C, and stirred until the magnesium was consumed. The temperature was adjusted to 0 °C, and acrolein (2.00 g, 35.7 mmol) was added. The reaction mixture was stirred until complete, quenched with aqueous hydrochloric acid (50 mL, 1.0 M) and then extracted with diethyl ether (3 x 100 mL). The combined organic extract was washed with brine (20 mL), and dried over magnesium sulfate. Purification by distillation provided the title compound **294** as a colourless oil (510 mg, 14%), bp 125 °C (760 mmHg) (lit.¹⁷⁶ 134-137 °C, 760 mmHg). IR (cm^{-1}) 3368 (O-H), 3080, 2957, 2927, 2870 (C-H), 1648 (C=C). $^1\text{H-NMR}$ (300 MHz, CDCl_3) 5.85 (1H, ddd, J 17.1, 10.5, 6.6 Hz, H2), 5.12-5.25 (2H, m, H1), 3.86 (1H, t, J 6.0 Hz, H3), 1.72 (1H, m, H4) 1.63 (1H, s, OH), 0.93 (3H, d, J 7.2 Hz, CH_3), 0.90 (3H, d, J 6.9 Hz, CH_3). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 139.4, 115.6, 78.2, 33.5, 18.1, 17.7.

Procedure 2:

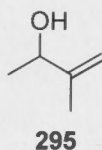
To a stirred solution of vinylmagnesium bromide (6.24 mL, 1.00 M, 6.24 mmol) in tetrahydrofuran was added isobutyraldehyde (300 mg, 4.16 mmol) at 0 °C under nitrogen. The reaction mixture was stirred until complete, quenched with aqueous hydrochloric acid solution (10 mL, 1.0 M) and then extracted with diethyl ether (3 x 10 mL). The combined organic extract was washed with brine (10 mL), dried over sodium sulfate and concentrated to afford the title compound **294** as a colourless oil (273 mg, 65%). The spectroscopic data agreed with that above.

4-Methylpent-1-en-3-yl acetate¹⁴³



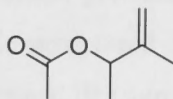
To a stirred of 4-methylpent-1-en-3-ol **294** (200 mg, 2.00 mmol) in dichloromethane (7.0 mL) was added pyridine and acetyl chloride (235 mg, 3.00 mmol) at 0 °C under nitrogen. The reaction mixture was stirred until complete, quenched with water (10 mL) and then extracted with diethyl ether (3 x 10 mL). The combined organic extract was washed with brine (10 mL), dried over sodium sulfate and concentrated to afford the title compound **306** as a colourless oil (237.3 mg, 84%), R_f 0.55 (20% ethyl acetate/*n*-hexane). ¹H-NMR (400 MHz, CDCl₃) 5.75 (1H, ddd, J 17.2, 10.4, 6.4 Hz, H₂), 5.24-5.18 (2H, m, H₁) 5.09 (1H, dd, J 6.4, 1.2 Hz, H₃), 2.07 (3H, s, CH₃), 1.86 (1H, m, H₄), 0.89-0.92 (6H, m, 2xCH₃). ¹³C-NMR (100 MHz, CDCl₃) 170.38, 134.75, 117.46, 79.37, 31.76, 21.16, 17.96, 17.93.

3-Methylbut-3-en-2-ol¹⁷⁷



To a solution of methylmagnesium bromide (21.4 mL, 3.00 M, 64.0 mmol) in diethyl ether was added a solution methacrolein (4.28 g, 61.0 mmol) in diethyl ether (10 mL) at 0 °C under nitrogen. This mixture was stirred until complete (30 min), quenched with aqueous solution ammonium chloride (50 mL, 1.0 M), and extracted with diethyl ether (3 x 50 mL). The combined organic extract was washed with brine (10 mL), dried over magnesium sulfate and evaporated to afford the title compound **295** as a colorless oil (4.39 g, 84%). IR (thin film, cm^{-1}) 3370 (O-H), 3020, 2961, 2931, 2856 (C-H), 1623 (C=C). ^1H -NMR (300 MHz, CDCl_3) 4.96 (1H, d, J 1.8 Hz, H4A), 4.79 (1H, d, J 1.8 Hz, H4B), 4.25 (1H, q, J 5.7 Hz, H2), 1.75 (3H, s, CH_3), 1.51 (1H, s, broad, OH), 1.28 (3H, d, J 6.9 Hz, H1). ^{13}C -NMR (100 MHz, CDCl_3) 148.95, 109.52, 71.57, 21.73, 17.84.

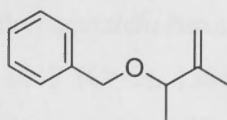
3-Methylbut-3-en-2-yl acetate¹⁷⁸



307

A mixture of 3-methylbut-3-en-2-ol **295** (100 mg, 1.16 mmol), triethylamine (235 mg, 2.32 mmol), 4-dimethylaminopyridine (14.2 mg, 0.12 mmol) and acetic anhydride (237 mg, 2.32 mmol) at room temperature was stirred until complete. Then, this mixture was quenched with aqueous sodium hydrogen carbonate (5 mL, 2 M), and extracted with diethyl ether (3 x 10 mL). The combined diethyl ether layer was washed with brine (10 mL), dried over sodium sulfate and concentrated under reduced pressure to afford the title compound **307** as a colourless oil (254 mg, 100%). IR (thin film, cm^{-1}) 3115, 3042, 2921, 2852, 2815 (C-H), 1739 (C=O), 1649 (C=C), 1598. ^1H -NMR (300 MHz, CDCl_3) 5.27 (1H, q, J 7.2 Hz, H2), 4.95 (1H, m, H4A), 4.85 (1H, m, H4B), 2.06 (3H, s, CH_3), 1.74 (3H, s, CH_3), 1.31 (3H, d, J 6.6 Hz, H1). ^{13}C -NMR (100 MHz, CDCl_3) 170.30, 144.52, 111.46, 73.32, 21.28, 19.06, 18.30

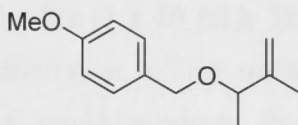
((3-Methylbut-3-en-2-yloxy)methyl)benzene¹⁷⁹



308

To a stirred solution of 3-methylbut-3-en-2-ol **295** (100 mg, 1.16 mmol) in dimethylformamide (3 mL) and sodium hydride (111 mg, 4.64 mmol) was added benzyl bromide (397 mg, 2.32 mmol), and tetrabutylammonium iodide (4.30 mg, 0.01 mmol) at room temperature under nitrogen. The reaction was stirred until complete, quenched with methanol (1 mL) and water (2 mL), and extracted with ethyl acetate (2 x 5 mL). The combined organic extract was washed with brine (5 mL), dried over sodium sulfate and concentrated to afford crude product. Flash chromatography (60% diethyl ether/*n*-hexane) afforded the title compound **308** as a colourless oil (90.8 mg, 39%), R_f 0.67 (80% diethyl ether/*n*-hexane). IR (thin film, cm^{-1}) 3068, 3031, 2978, 2933, 2862 (C-H), 1650 (C=C). $^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.23-7.35 (5H, m, ArH), 4.91-4.93 (2H, m, H4), 4.48 (1H, d, J 12.0 Hz, $\text{CH}_A\text{H}_B\text{Ph}$), 4.27 (1H, d, J 12.4 Hz, $\text{CH}_A\text{H}_B\text{Ph}$), 3.91 (1H, q, J 6.4 Hz, H2), 1.72 (3H, s, CH_3), 1.27 (3H, d, J 6.8 Hz, CH_3). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 146.02, 138.80, 128.31, 127.67, 127.37, 112.50, 78.71, 69.82, 20.18, 16.53.

1-Methoxy-4-((3-methylbut-3-en-2-yloxy)methyl)benzene¹⁸⁰

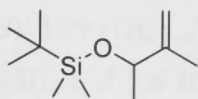


309

To a stirred suspension of hexane-washed sodium hydride (111 mg, 4.64 mmol) and 3-methylbut-3-en-2-ol **295** (200 mg, 2.32 mmol) in dichloromethane (2 mL) at 0 °C under nitrogen was added a solution of *p*-methoxybenzyl chloride (400 mg, 2.55 mmol) in dichloromethane (3 mL). The reaction was stirred overnight, quenched with aqueous sodium hydrogen carbonate (5.0 mL, 1.0 M) and the layers were separated. The aqueous layer was further extracted with dichloromethane (3 x 10 mL). The combined organic extract was washed with brine (10 mL), dried over sodium sulfate, and concentrated

under reduced pressure to provide the crude product. Purification by flash chromatography (10% diethyl ether/petroleum ether) afforded the title compound **309** as a colourless oil (50 mg, 10%), R_f 0.44 (20% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3071, 2976, 2933, 2859, 2836 (C-H), 1649, 1612 (C=C), 1586. ^1H -NMR (400 MHz, CDCl_3) 7.24 (2H, d, J 8.4 Hz, ArH), 6.85 (2H, m, ArH), 4.92-4.89 (2H, m, H₄), 4.40 (1H, d, J 11.6 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.20 (1H, d, J 11.2 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 3.90 (1H, q, J 6.4 Hz, H₂), 3.78 (3H, s, CH_3), 1.71 (3H, s, CH_3), 1.25 (3H, d, J 6.4 Hz, H₁). ^{13}C -NMR (100 MHz, CDCl_3) 159.00, 146.13, 130.91, 129.26, 113.72, 112.35, 78.40, 69.46, 55.25, 20.19, 16.54. LRMS (EI⁺) 206 (M^+ , 1%), 176 (2), 161 (4), 137 (60), 121 (100), 109 (10), 91 (5), 77 (8), 70 (5), 41 (3). HRMS (EI⁺) calcd. for $\text{C}_{13}\text{H}_{18}\text{O}_2$ (M^+) 206.1307, found 206.1312.

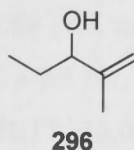
***tert*-Butyldimethyl(3-methylbut-3-en-2-yloxy)silane¹⁸¹**



310

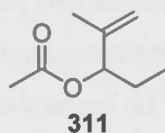
To a stirred solution of 3-methylbut-3-en-2-ol **295** (100 mg, 1.16 mmol) in dimethylformamide (2 mL) was added 1*H*-imidazole (316 mg, 4.64 mmol) and *tert*-butyldimethylsilyl chloride (350 mg, 2.32 mmol) at 0 °C under nitrogen. The reaction was stirred until complete (2 h), quenched with aqueous sodium hydrogen carbonate (1.0 M, 5 mL), and extracted with diethyl ether (3 x 10 mL). The combined organic extract was washed with brine (10 mL), dried over sodium sulfate, and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (2% diethyl ether/*n*-hexane) provided pure product *tert*-butyldimethyl-(3-methylbut-3-en-2-yloxy)silane **310** as a colourless oil (73 mg, 31%), R_f 0.67 (10% diethyl ether/*n*-hexane). IR (thin film, cm^{-1}) 3074, 2957, 2930, 2887, 2858 (C-H), 1652 (C=C). ^1H -NMR (300 MHz, CDCl_3) 4.89 (1H, s, H_{4A}), 4.71 (1H, s, H_{4B}), 4.20 (1H, q, J 6.0 Hz, H₂), 1.69 (3H, s, CH_3), 1.21 (3H, d, J 6.3 Hz, CH_3), 0.89 (9H, s, 3x CH_3), 0.05 (3H, s, CH_3), 0.03 (3H, s, CH_3). ^{13}C -NMR (100 MHz, CDCl_3) 149.20, 108.90, 72.19, 25.82, 23.17, 18.26, 17.65, -4.93, -5.02. HRMS (ESI⁺) calcd. for $\text{C}_{11}\text{H}_{24}\text{ONaSi}$ ($[\text{M}+\text{Na}]^+$) 223.1494, found 223.1493.

2-Methylpent-1-en-3-ol¹⁸²



To a stirred solution of ethyl magnesium bromide (25.4 mL, 3.00 M, 76.0 mmol) in diethyl ether was added a solution of methacrolein (4.84 g, 69.1 mmol) in diethyl ether (5 mL) at 0 °C under nitrogen. The reaction was stirred until complete, quenched with aqueous hydrochloric acid (50 mL, 1.0 M), and then extracted with diethyl ether (3 x 50 mL). The combined organic extract was washed with brine (20 mL), dried over magnesium sulfate and concentrated to afford title compound **296** as a yellowish oil (6.91 g, 100%), R_f 0.5 (40% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3369 (O-H), 3074, 2963, 2935, 2876 (C-H), 1651 (C=C). $^1\text{H-NMR}$ (400 MHz, CDCl_3) 4.93 (1H, m, H1A), 4.84 (1H, m, H1B), 3.99 (1H, t, J 6.4 Hz, H3), 1.71 (3H, m, CH_3), 1.49-1.64 (3H, m, H4 and OH), 0.89 (3H, t, J 7.6 Hz, H5). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 147.25, 111.08, 77.18, 27.68, 17.43, 9.74. LRMS (EI+) 100 (M^+ , 15%), 83 (70), 71 (100), 58 (28), 55 (58). HRMS (EI+) calcd. for $\text{C}_6\text{H}_{12}\text{O}$ (M^+) 100.0888, found 100.0888.

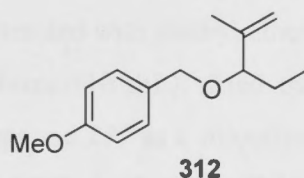
2-Methylpent-1-en-3-yl acetate¹⁸³



To a stirred solution of 2-methylpent-1-en-3-ol **296** (480 mg, 4.79 mmol), triethylamine (970 mg, 9.58 mmol) and 4-dimethylaminopyridine (58.6 mg 0.48 mmol) was added acetic anhydride (980 mg, 9.58 mmol) at room temperature under nitrogen. This reaction mixture was stirred until complete, quenched with aqueous sodium hydrogen carbonate (2 mL, 1 M), and then extracted with diethyl ether (4 x 5 mL). The combined organic extract was washed with brine (10 mL), dried over magnesium sulfate and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (10% diethyl ether/*n*-hexane) provided the title compound **311** as a

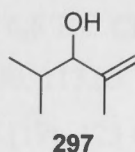
colourless oil (278 mg, 41%). R_f 0.5 (20%) ethyl acetate/*n*-hexane. IR (thin film, cm^{-1}) 3079, 2963, 2935, 2876 (C-H), 1742 (C=O), 1653 (C=C). $^1\text{H-NMR}$ (400 MHz, CDCl_3) 5.10 (1H, t, J 6.4 Hz, H3), 4.94 (1H, m, H1A), 4.89 (1H, m, H1B), 2.06 (3H, s, CH_3), 1.71 (3H, s, CH_3), 1.65 (2H, m, H4), 0.87 (3H, t, J 7.6 Hz, H5). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 170.39, 142.88, 112.71, 78.53, 25.49, 21.17, 18.05, 9.59. LRMS (EI+) 142 (M^+ , 10%), 135 (48), 124 (12), 111 (30), 100 (100), 95 (20), 83 (70), 77 (12), 69 (45), 55 (64). HRMS (EI+) calcd. for $\text{C}_8\text{H}_{14}\text{O}_2$ for (M^+) 142.0994, found 142.0996.

1-Methoxy-4-((2-methylpent-1-en-3-yloxy)-methyl)-benzene



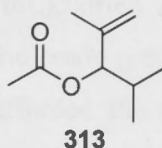
To a stirred solution of 2-methylpent-1-en-3-ol **296** (800 mg, 7.99 mmol) and sodium hydride (383 mg, 16.0 mmol) in dichloromethane (5.0 mL) at 0 °C under nitrogen was added *p*-methoxybenzyl chloride (1.38 g, 8.79 mmol). The reaction mixture was stirred at room temperature until complete (24 h), quenched with aqueous sodium bicarbonate (5.0 mL, 1.0 M), and the layers were separated. The aqueous layers were further extracted with dichloromethane (3 x 5 mL). The combined organic extract was washed with brine (10 mL), dried over sodium sulfate and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (2% ethyl acetate/*n*-hexane) afforded the title compound **312** as a colourless oil (1.18 mg, 67%), R_f 0.27 (5% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3071, 3034, 2963, 2936, 2874, 2836 (C-H), 1649, 1613 (C=C), 1586, 1513. $^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.23-7.26 (2H, m, ArH), 6.84-6.87 (2H, m, ArH), 4.89-4.96 (2H, m, H1), 4.43 (1H, d, J 11.2 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.18 (1H, d, J 11.6 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 3.79 (3H, s, CH_3), 3.59 (1H, t, J 6.8 Hz, H3), 1.42-1.68 (5H, m, H4 and CH_3), 0.89 (3H, t, J 7.6 Hz, H5). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 158.99, 144.55, 130.99, 129.31, 113.72, 113.69, 84.55, 69.48, 55.24, 26.45, 16.46, 10.22. LRMS (EI+) 220 (M^+ , 5%), 137 (62), 121 (100), 109 (8), 91 (6), 84 (20), 77 (15), 69 (19), 65 (4), 55 (10). HRMS (EI+) calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_2$ (M^+) 220.1463, found 220.1466.

2,4-Dimethylpent-1-en-3-ol¹⁸⁴



A stirred suspension of magnesium (1.21 g, 49.6 mmol) and 2-bromopropene (6.00 g, 49.6 mmol) in diethyl ether (50 mL) under nitrogen was warmed at 30 °C for 30 min. To this reaction mixture was added isobutyraldehyde (3.00 g, 41.6 mmol) at 0 °C and the reaction was stirred until complete, quenched with aqueous hydrochloric acid (25 mL, 1.0 M), and extracted with diethyl ether (3 x 50 mL). The combined organic extract was washed with brine (10 mL), dried over magnesium sulfate and concentrated to afford the title compound **297** as a colourless oil (2.4 g, 51%). IR (thin film, cm^{-1}) 3406 (O-H), 3070, 2969, 2959, 2923, 2873 (C-H), 1650 (C=C). ^1H -NMR (400 MHz, CDCl_3) 4.91 (1H, m, H1A), 4.86 (1H, m, H1B), 3.70 (1H, d, J 7.2 Hz, H3), 1.77 (1H, m, H4), 1.70 (3H, s, CH_3), 0.95 (3H, d, J 6.8 Hz, CH_3), 0.86 (3H, d, J 7.2 Hz, CH_3). ^{13}C -NMR (100 MHz, CDCl_3) 146.69, 112.04, 81.69, 30.84, 19.37, 17.62, 17.52.

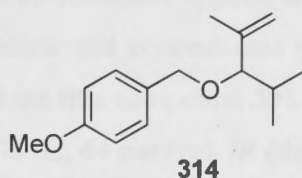
2,4-Dimethylpent-1-en-3-yl acetate¹⁸⁵



To a stirred solution of 2,4-dimethylpent-1-en-3-ol **297** (800 mg, 7.01 mmol), triethylamine (1.42 g, 14.0 mmol), and 4-dimethylamino pyridine (85.6 mg, 0.70 mmol) was added acetic anhydride (1.43 g, 14.0 mmol) in dichloromethane (7.5 mL) at room temperature under nitrogen. This reaction mixture was stirred until complete, quenched with aqueous sodium hydrogen carbonate (3.0 mL, 1.0 M) and extracted with diethyl ether (3 x 5 mL). The combined organic extract was washed with brine (10 mL), dried over magnesium sulfate and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (5% ethyl acetate/*n*-hexane) afforded the title compound **313** as a colourless oil (632 mg, 58%), R_f 0.22 (5% ethyl acetate/*n*-

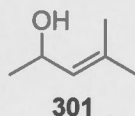
hexane). IR (thin film, cm^{-1}) 3080, 2966, 2941, 2876 (C-H), 1742 (C=O), 1653 (C=C). ^1H -NMR (400 MHz, CDCl_3) 4.89-4.92 (3H, m, H1 and H3), 2.07 (3H, s, CH_3), 1.90 (1H, m, H4), 1.70 (3H, m, CH_3), 0.90 (3H, d, J 6.8 Hz, CH_3), 0.87 (3H, d, J 6.8 Hz, CH_3). ^{13}C -NMR (100 MHz, CDCl_3) 170.40, 142.30, 113.63, 82.34, 29.60, 21.07, 18.94, 18.27, 17.84. LRMS (EI+) 156 (M^+ , 21%), 135 (19), 123 (30), 111 (90), 97 (76), 83 (40), 71 (60), 60 (25), 55 (100). HRMS (EI+) calcd. for $\text{C}_9\text{H}_{16}\text{O}_2$ (M^+) 156.1150, found 156.1151.

1-((2,4-Dimethylpent-1-en-3-yloxy)methyl)-4-methoxybenzene



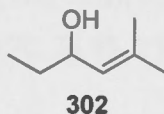
To a stirred suspension of 2,4-dimethylpent-1-en-3-ol **297** (480 mg, 4.20 mmol) and sodium hydride (202 mg, 8.41 mmol) in dimethyl-formamide (3.0 mL) was added *p*-methoxybenzyl chloride (988 mg, 6.31 mmol) at room temperature under nitrogen. This reaction mixture was stirred until complete, quenched with aqueous sodium bicarbonate (5.0 mL, 1.0 M) and extracted with dichloromethane (3 x 10 mL). The combined organic extract was washed with brine (10 mL), dried over sodium sulfate and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (2% ethyl acetate/*n*-hexane) afforded the title compound **314** as a colourless oil (243 mg, 25%), R_f 0.23 (5% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3070, 2957, 2870, 2836 (C-H), 1649, 1613, 1586 (C=C), 1514. ^1H -NMR (400 MHz, CDCl_3) 7.23 (2H, d, J 7.6 Hz, ArH), 6.84-6.86 (2H, m, ArH), 4.98 (1H, m, H1A), 4.85 (1H, m, H1B), 4.42 (1H, d, J 11.6 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.13 (1H, d, J 11.6 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 3.79 (3H, s, CH_3), 3.20 (1H, d, J 8.8 Hz, H3), 1.76 (1H, m, H4), 1.66 (3H, s, CH_3), 0.99 (3H, d, J 6.4 Hz, CH_3), 0.74 (3H, d, J 6.8 Hz, CH_3). ^{13}C -NMR (100 MHz, CDCl_3) 143.78, 142.33, 131.06, 129.36, 114.82, 113.62, 89.30, 69.63, 55.23, 30.12, 19.51, 19.13, 16.61. LRMS (EI+) 234 (M^+ , 100%), 228 (80), 213 (12), 204 (22), 197 (54), 191 (70). HRMS (EI+) calcd. for $\text{C}_{15}\text{H}_{22}\text{O}_2$ (M^+) 234.1620, found 234.1619.

4-Methylpent-3-en-2-ol¹⁸⁶



To a stirred solution of methylmagnesium bromide (8.49 mL, 3.00 M, 25.5 mmol) in diethyl ether was added solution of 3-methylbut-2-enal (1.95 g, 23.2 mmol) in diethyl ether (12 mL) at 0 °C under nitrogen. The reaction mixture was stirred until complete, quenched with aqueous ammonium chloride (50 mL, 1.0 M) and extracted with diethyl ether (3 x 50 mL). The combined organic extract was washed with brine (20 mL), dried over magnesium sulfate and concentrated to afford the crude product. Purification by distillation afforded the title compound **301** as a colourless oil (1.67 g, 72%), b.p. 50 °C (16 mmHg) (lit.¹⁸⁶ 71 °C, 44 mmHg). IR (thin film, cm⁻¹) 3344 (O-H), 2970, 2928, 2874 (C-H), 1676 (C=C). ¹H-NMR (400 MHz, CDCl₃) 5.21 (1H, m, H₂), 4.56 (1H, m, H₃), 1.71 (3H, s, CH₃), 1.68 (3H, s, CH₃), 1.32 (1H, s, broad, OH), 1.23 (3H, d, *J* 6.4 Hz, H₁). ¹³C-NMR (100 MHz, CDCl₃) 134.21, 129.31, 64.79, 25.64, 23.59, 17.99.

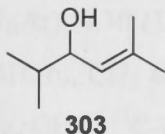
5-Methylhex-4-en-3-ol¹³⁷



To a stirred solution of ethylmagnesium bromide (18.0 mL, 3.00 M, 54.1 mmol) in diethyl ether was added 3-methylbut-2-enal (3.79 g, 45.1 mmol) at 0 °C under nitrogen. The reaction mixture was stirred until complete, quenched with aqueous ammonium chloride (60 mL, 1.0 M), and extracted with diethyl ether (3 x 100 mL). The combined organic extract was washed with brine (20 mL), dried over magnesium sulfate and concentrated to afford the crude product. Purification by distillation afforded the title compound **302** as a colourless oil (4.50 g, 88%), b.p. 30 °C (12 mmHg) (lit.¹³⁷ 60 °C, 12 mmHg). IR (thin film, cm⁻¹) 3349 (O-H), 2968, 2930, 2877 (C-H), 1678 (C=C). ¹H-NMR (400 MHz, CDCl₃) 5.15 (1H, m, H₄), 4.26 (1H, ddd, *J* 10.8, 6.4, 3.2 Hz, H₃), 1.73 (3H, s, CH₃), 1.69 (3H, s, CH₃), 1.60 (1H, m, H₂B), 1.40 (1H, m, H₂A), 1.33 (1H,

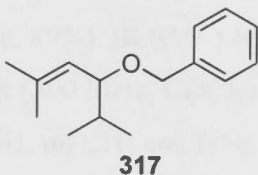
d, J 4.0 Hz, OH), 0.89 (3H, t, J 7.6 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 135.28, 127.92, 70.08, 30.54, 25.75, 18.22, 9.73.

2,5-Dimethylhex-4-en-3-ol¹³⁷



To a stirred solution of isopropylmagnesium bromide (25.7 mL, 2.90 M, 74.5 mmol) in methyltetrahydrofuran was added a solution of 3-methylbut-2-enal (5.23 g, 62.1 mmol) in tetrahydrofuran (25 mL) at 0 °C under nitrogen. The reaction mixture was stirred until complete, quenched with aqueous ammonium chloride (50 mL, 1.0 M) and extracted with diethyl ether (3 x 100 mL). The combined organic extract was washed with brine (20 mL), dried over magnesium sulfate and concentrated to provide the crude product. Purification by distillation afforded the title compound **303** as a colourless oil (5.65 g, 71%), b.p. 98 °C (12 mmHg) (lit.¹³⁷ 59 °C, 12 mmHg). IR (thin film, cm⁻¹) 3368 (O-H), 2958, 2929, 2873 (C-H), 1675 (C=C). ¹H-NMR (400 MHz, CDCl₃) 5.18 (1H, m, H₄), 4.04 (1H, dd, J 8.8, 6.8 Hz, H₃), 1.74 (3H, s, CH₃), 1.63-1.71 (4H, m, H₂ and CH₃), 1.30 (1H, s, broad, OH), 0.95 (3H, d, J 6.8 Hz, CH₃), 0.85 (3H, d, J 7.2 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 135.67, 126.36, 73.70, 34.39, 25.88, 18.33, 18.29, 18.06.

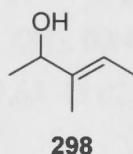
((2,5-Dimethylhex-4-en-3-yloxy)methyl)benzene



To a stirred suspension of 2,5-dimethylhex-4-en-3-ol **303** (200 mg, 1.56 mmol) and sodium hydride (74.9 mg, 3.12 mmol) in dimethylformamide (5.0 mL) was added benzyl bromide (320 mg, 1.87 mmol) at 0 °C under nitrogen. The reaction mixture was stirred at room temperature until complete, quenched with water (50 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic extract was washed with brine

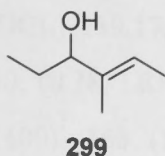
(10 mL), dried over magnesium sulfate and concentrated to afford the crude product. Purification by flash chromatography (1% diethyl ether/*n*-hexane) provided the title compound **317** as a colourless oil (180 mg, 53%), R_f 0.5 (20% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3088, 3064, 3030, 2930, 2957, 2929, 2869 (C-H), 1673, 1605 (C=C). $^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.30-7.23 (5H, m, ArH), 5.10 (1H, m, H3), 4.60 (1H, d, J 12.0 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.30 (1H, d, J 12.0 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 3.70 (1H, dd, J 9.1, 7.2 Hz, H4), 1.73-1.81 (4H, m, CH_3 and H2), 1.62 (3H, m, H6), 0.96 (3H, d, J 6.8 Hz, H1), 0.84 (3H, d, J 6.4 Hz, CH_3). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 139.41, 136.43, 128.16, 127.62, 127.15, 124.74, 80.18, 69.52, 33.19, 26.01, 18.99, 18.51, 18.27. LRMS (ESI+) 241 ($[\text{M}+\text{Na}]^+$, 5%), 145 (5), 105 (10), 91 (45), 69 (100). HRMS (ESI+) calcd. for $\text{C}_{15}\text{H}_{22}\text{ONa}$ ($[\text{M}+\text{Na}]^+$) 241.1568, found 241.1569.

(*E*)-3-Methylpent-3-en-2-ol¹⁴⁰



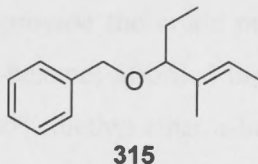
To a stirred solution of methylmagnesium chloride (4.19 mL, 3.00 M, 12.8 mmol) in tetrahydrofuran was added (*E*)-2-methyl-2-butenal (882 mg, 10.5 mmol) at 0 °C under nitrogen. The reaction mixture was stirred until complete, quenched with aqueous ammonium chloride (20 mL, 1.0 M) and extracted with diethyl ether (3 x 50 mL). The combined organic extract was washed with brine (20 mL), dried over sodium sulfate and concentrated under reduced pressure to afford the title compound **298** as a colourless oil (939 mg, 89%). IR (thin film, cm^{-1}) 3357 (O-H), 2974, 2921, 2864 (C-H), 1673 (C=C). $^1\text{H-NMR}$ (300 MHz, CDCl_3) 5.48 (1H, q, J 6.6 Hz, H4), 4.21 (1H, q, J 6.3 Hz, H2), 1.59-1.62 (6H, m, CH_3 and H5), 1.41 (1H, s, OH), 1.24 (3H, d, J 6.3 Hz, H1). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) 139.20, 119.28, 73.45, 21.51, 13.01, 11.08.

(*E*)-4-Methylhex-4-en-3-ol¹³⁸



To a stirred solution of ethylmagnesium bromide (14.0 mL, 3.00 M, 41.9 mmol) in diethyl ether was added (*E*)-2-methyl-2-butenal (2.94 g, 35.0 mmol) at 0 °C under nitrogen. The reaction mixture was stirred until complete, quenched with aqueous ammonium chloride (10 mL, 1.0 M) and extracted with diethyl ether (3 x 50 mL). The combined organic extract was washed with brine (20 mL), dried over sodium sulfate and concentrated under reduced pressure to afford the title compound **299** as a colourless oil (2.72 g, 68%). IR (thin film, cm⁻¹) 3350 (O-H), 2963, 2934, 2876 (C-H), 1671 (C=C). ¹H-NMR (300 MHz, CDCl₃) 5.46 (1H, m, H5), 3.90 (1H, t, *J* 6.6 Hz, H3), 1.50-1.62 (8H, m, H6, CH₃ and H2), 1.42 (1H, s, OH), 0.84 (3H, t, *J* 7.8 Hz, H1). ¹³C-NMR (75 MHz, CDCl₃) 137.60, 121.00, 79.54, 27.63, 13.02, 10.73, 10.15.

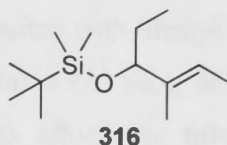
(*E*)-((4-Methylhex-4-en-3-yloxy)-methyl)-benzene



To a stirred solution of (*E*)-4-methylhex-4-en-3-ol **299** (200 mg, 1.75 mmol) in dimethyl-formamide (3.0 mL) and sodium hydride (168 mg, 7.01 mmol) at 0 °C under nitrogen was added benzyl bromide (359 mg, 2.10 mmol). This reaction mixture was stirred until complete, quenched with water (20 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extract was washed with brine (20 mL), dried over sodium sulfate and concentrated to provide the crude product. Purification by flash chromatography (1% ethyl acetate/*n*-hexane) afforded the title compound **315** as a colourless oil (358 mg, 100%), *R*_f 0.12 (100% *n*-hexane). IR (thin film, cm⁻¹) 3088, 3064, 3030, 2963, 2934, 2874, 2860 (C-H), 1669, 1606 (C=C), 1586. ¹H-NMR (400 MHz, CDCl₃) 7.29-7.36 (5H, m, ArH), 5.41 (1H, m, H5), 4.44 (1H, d, *J* 11.6 Hz,

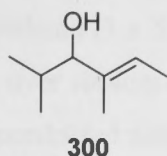
$\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.21 (1H, d, J 11.6 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 3.52 (1H, t, J 6.8 Hz, H3), 1.60-1.71 (4H, m, CH_3 and H2A), 1.42-1.57 (4H, m, H6 and H2B), 0.82 (3H, t, J 6.9 Hz, H1). ^{13}C -NMR (100 MHz, CDCl_3) 139.17, 135.02, 128.23, 127.73, 127.22, 123.17, 86.77, 69.50, 26.45, 13.06, 10.40, 10.18. LRMS (EI+) 205 ($[\text{M}+\text{H}]^+$, 10%), 204 ($\text{M}^{+\bullet}$, 5), 181 (10), 175 ($[\text{M}-\text{C}_2\text{H}_5]^+$, 100), 163 (10). HRMS (EI+) calcd. for $\text{C}_{14}\text{H}_{20}\text{O}$ ($[\text{M}]^{+\bullet}$) 204.1514, found 204.1519.

(*E*)-*tert*-Butyldimethyl(4-methylhex-4-en-3-yloxy)silane



To a stirred solution of (*E*)-4-methylhex-4-en-3-ol **299** (100 mg, 0.88 mmol) and 1*H*-imidazole (238 mg, 3.50 mmol) in acetonitrile (3 mL) was added solution of *tert*-butyldimethylsilyl chloride (158 mg, 1.05 mmol) in acetonitrile (2 mL). The reaction mixture was stirred until complete, quenched with aqueous sodium hydrogen carbonate (5 mL, 1 M) and extracted with diethyl ether (3 x 15 mL). The combined organic extract was washed with brine (10 mL), dried over sodium sulfate and concentrated under reduced pressure to provide the crude product. Purification by flash chromatography (10% diethyl ether/*n*-hexane) afforded the title compound **316** as a colourless oil (194 mg, 97%), R_f 0.67 (80% diethyl ether/*n*-hexane). IR (thin film, cm^{-1}) 2958, 2930, 2858, 2855 (C-H), 1671 (C=C). ^1H -NMR (300 MHz, CDCl_3) 5.33 (1H, m, H5), 3.83 (1H, t, J 7.2 Hz, H3), 1.58 (3H, m, H6), 1.38-1.53 (5H, m, H2 and CH_3), 0.87 (9H, s, 3x CH_3), 0.79 (3H, t, J 6.2 Hz, CH_3), -0.01 (3H, s, CH_3), -0.03 (3H, s, CH_3). ^{13}C -NMR (100 MHz, CDCl_3) 138.16, 119.39, 80.09, 29.05, 25.85, 18.24, 12.87, 10.67, 10.28, -4.72, -5.03. LRMS (ESI+) 229 ($[\text{M}+\text{H}]^+$, 25%), 217 (18), 214 (100), 201 (25), 193 (10). HRMS (ESI+) calcd. for $\text{C}_{13}\text{H}_{29}\text{OSi}$ ($[\text{M}+\text{H}]^+$) 229.1988, found 229.1986.

(*E*)-2,4-Dimethylhex-4-en-3-ol¹³⁹



To a stirred solution of isopropylmagnesium chloride (8.39 mL, 2.00 M, 16.8 mmol) in tetrahydrofuran was added (*E*)-2-methyl-2-butenal (1.18 g, 14.0 mmol) at 0 °C under nitrogen. The reaction mixture was stirred until complete, quenched with aqueous ammonium chloride (20 mL, 1.0 M) and extracted with diethyl ether (3 x 50 mL). The combined organic extract was washed with brine (20 mL), dried over sodium sulfate and concentrated under reduced pressure to afford the title compound **300** as a colourless oil (1.64 g, 91%). IR (thin film, cm⁻¹) 3368 (O-H), 2956, 2922, 2871 (C-H), 1670 (C=C). ¹H-NMR (300 MHz, CDCl₃) 5.46 (1H, q, *J* 6.6 Hz, H5), 3.57 (1H, d, *J* 8.1 Hz, H3), 1.76 (1H, m, H2), 1.58-1.62 (6H, m, 2xCH₃), 1.44 (1H, s, broad, OH), 0.98 (3H, d, *J* 6.6 Hz, CH₃), 0.76 (3H, d, *J* 7.2 Hz, H1). ¹³C-NMR (75 MHz, CDCl₃) 137.23, 121.81, 84.25, 31.09, 19.40, 18.70, 12.99, 10.90.

General procedure 5.1: Diastereoselectivity study of the osmium-catalysed aminohydroxylation reaction

To a stirred solution of allylic alcohols (1.0 equiv.) and potassium osmate dihydrate (0.04 equiv.) in acetonitrile/water (1:1 mL/mL) was added a solution of benzyl *N*-(4-toluensulfonyloxy)carbamate **202** (1.2 equiv.) in acetonitrile (2 mL) at 0 °C. The reaction mixture was stirred at room temperature until complete, quenched with aqueous sodium hydrogen sulfite (5.00 mL, 0.05 M.) and stirred for 30 min. The mixture was filtered through celite and extracted with ethyl acetate (3 x 10 mL). The combined organic extract was washed with brine (10 mL), dried over sodium sulfate and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography was conducted to afford the target compounds.

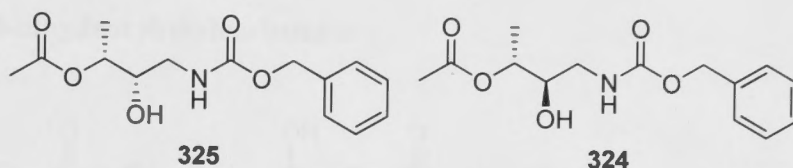
General procedure 5.2: Acetonide formation

To a stirred solution of diol (1.0 equiv.) in dichloromethane (3 mL) and 2,2-dimethoxy propane (4.0 equiv.) at room temperature was added camphorsulfonic acid (0.04 equiv.)

and *p*-toluenesulfonic acid (0.04 equiv.). The reaction mixture was stirred until complete, quenched with aqueous sodium hydrogen carbonate (3.0 mL, 1.0 M), and extracted with dichloromethane (3 x 5 mL). The combined organic extract was washed with brine (5 mL), dried over sodium sulfate and concentrated under reduced pressure. Further purification was conducted using flash chromatography.

(2*R,3*S**)-4-(Benzyloxycarbonylamino)-3-hydroxybutan-2-yl acetate**

(2*R,3*R**)-4-(Benzyloxycarbonylamino)-3-hydroxybutan-2-yl acetate**



The reaction was conducted according to General Procedure 5.1 with but-3-en-2-yl acetate **304** (60.0 mg, 0.53 mmol), potassium osmate dihydrate (7.00 mg, 0.02 mmol) and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (221 mg, 0.69 mmol). Purification by flash chromatography (30% ethyl acetate/*n*-hexane) afforded (2*R**,3*S**)-4-(benzyloxy-carbonylamino)-3-hydroxybutan-2-yl acetate **325** as a colourless oil (42.4 mg, 29%) in the first fraction, *R*_f 0.44 (70% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3369 (O-H, N-H), 3066, 3034, 2981, 2925, 2825 (C-H), 1717 (C=O), 1533. ¹H-NMR (400 MHz, CDCl₃) 7.29-7.38 (5H, m, ArH), 5.29 (1H, s, NH), 5.07-5.13 (2H, m, CH₂Ar), 4.90 (1H, m, H₂), 3.70 (1H, m, H₃), 3.50 (1H, m, H_{4A}), 3.11 (1H, m, H_{4B}), 3.01 (1H, s, OH), 2.05 (3H, s, CH₃), 1.27 (3H, d, *J* 6.8 Hz, H₁). ¹³C-NMR (100 MHz, CDCl₃) 170.83, 156.93, 136.26, 128.54, 128.19, 128.11, 73.08, 71.56, 66.96, 43.48, 21.19, 16.23. LRMS (ESI⁺) 304 ([M+Na]⁺, 100%), 238 (5), 178 (5), 120 (6), 91 (64). HRMS (ESI⁺) calcd. for C₁₄H₂₀NO₅ ([M+H]⁺) 282.1341, found 282.1339; calcd. for C₁₄H₁₉NO₅Na ([M+Na]⁺) 304.1161, found 304.1159.

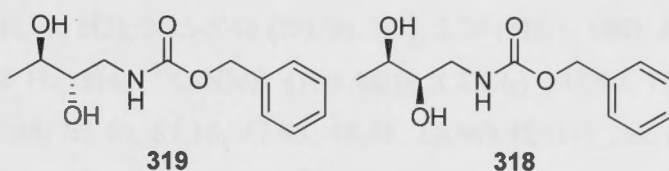
A second fraction afforded (2*R**,3*R**)-4-(benzyloxycarbonylamino)-3-hydroxy-butan-2-yl acetate **324** as a colourless oil (36.6 mg, 25%), *R*_f 0.40 (70% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3400 (O-H, N-H), 3066, 3034, 2982, 2940 (C-H), 1721 (C=O), 1533. ¹H-NMR (400 MHz, CDCl₃) 7.30-7.38 (5H, m, ArH), 5.24 (1H, s, NH), 5.10 (2H, s, CH₂Ar), 4.91 (1H, m, H₂), 3.74 (1H, m, H₂), 3.66 (2H, m, H_{4A}), 3.28 (1H, m, H_{4B}),

2.60 (1H, s, OH), 2.08 (3H, s, CH₃), 1.28 (3H, d, *J* 6.8 Hz, H1). ¹³C-NMR (100 MHz, CDCl₃) 170.84, 157.48, 136.22, 128.54, 128.20, 128.12, 73.28, 71.62, 67.05, 42.95, 21.21, 15.63. LRMS (ESI+) 304 ([M+Na]⁺, 100%), 218 (4), 120 (6), 91 (56). HRMS (ESI+) calcd. for C₁₄H₁₉NO₅Na ([M+Na]⁺ 304.1161, found 304.1161.

The *anti*- and *syn*-diastereomeric structures were confirmed by NOESY_1D analysis of their acetonide derivatives.

Benzyl (2*S,3*R**)-2,3-dihydroxybutylcarbamate**

Benzyl (2*R,3*R**)-2,3-dihydroxybutylcarbamate**



The reaction was conducted according to General Procedure 5.1 with 3-buten-2-ol **292** (45.9 mg, 0.64 mmol), potassium osmate dihydrate (9.40 mg, 0.03 mmol) and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (246 mg, 0.76 mmol). Purification by flash chromatography (gradient from 50% to 100% ethyl acetate/*n*-hexane) afforded an inseparable mixture of two diastereomers as a colourless oil (121 mg, 79%), *R*_f 0.11 (60% ethyl acetate/*n*-hexane). Integration of the NH signal in the 400 MHz ¹H-NMR spectrum provided a 1.8:1 ratio of benzyl (2*S**,3*R**)-2,3-dihydroxybutylcarbamate **319** and benzyl (2*R**,3*R**)-2,3-dihydroxybutylcarbamate **318**. IR (thin film, cm⁻¹) 3347 (broad, O-H, N-H), 3088, 3065, 3033, 2956, 2924, 2853 (C-H), 1695 (C=O), 1533. ¹H-NMR (400 MHz, CDCl₃) 7.29-7.38 (5H, m, ArH), 5.21 (1H, s, NH) 5.12 (2H, s, CH₂Ar), 3.74 (1H, m, H3) and 4.12* (1H, m, H3), 3.56 (1H, m, H2) and 4.04* (1H, m, H2), 3.38-3.44 (2H, m, H1) and 3.19-3.24* (2H, m, H1), 1.92 (2H, s, broad, 2xOH), 1.25 (3H, d, *J* 6.4 Hz, H4) and 1.20* (3H, d, *J* 6.0 Hz, H4). ¹³C-NMR (100 MHz, CDCl₃) 157.85 (157.42*), 136.19, 128.54, 128.22, 128.10, 74.94 (74.65*), 68.48 (68.12*), 67.11 (67.04), 42.84 (43.82*), 18.34 (19.30*). LRMS (ESI+) 262 ([M+Na]⁺, 72%), 196 (28), 181 (9), 120 (5), 90 (100). HRMS (ESI+) calcd. for C₁₂H₁₇NO₄Na ([M+Na]⁺) 262.1055, found 262.1049. (* Indicates signals for the minor diastereomer).

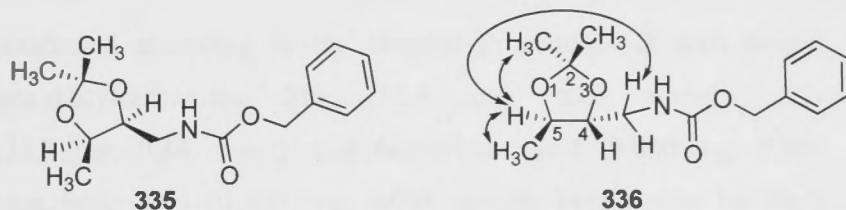
Procedure 2:

To a solution of (2*R**,3*S**)-4-(benzyloxycarbonylamino)-3-hydroxybutan-2-yl acetate **325** (20.0 mg, 0.07 mmol) was added a solution of potassium carbonate (23.1 mg, 0.18 mmol) in methanol (3 mL) and water (1 mL) at 20 °C. This mixture was stirred at room temperature until complete (2 h), quenched with aqueous hydrochloric acid (1.0 mL, 1.0 M), washed with brine (5 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic extract was dried over sodium sulfate and concentrated under reduced pressure afforded benzyl (2*S**,3*R**)-2,3-dihydroxybutylcarbamate **319** as a colorless oil (17.0 mg, 100%), *R*_f 0.18 (70% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3341 (O-H), 3065, 3034, 2970, 2926 (C-H), 1695 (C=O), 1534. ¹H-NMR (400 MHz, CDCl₃) 7.30-7.38 (5H, m, ArH), 5.30 (1H, s, NH), 5.11 (2H, s, CH₂Ar), 3.75 (1H, m, H₃), 3.55 (1H, m, H₂), 3.35-3.43 (2H, m, H₁), 2.79 (1H, s, OH), 1.70 (1H, s, OH), 1.22 (3H, d, *J* 6.4 Hz, H₄). ¹³C-NMR (100 MHz, CDCl₃) 157.90, 136.16, 128.55, 128.25, 128.13, 75.05, 68.40, 67.15, 42.83, 18.41. LRMS (ESI⁺) 262 ([M+Na]⁺, 62%), 259 (6), 196 (10), 181 (5), 120 (4), 91 (100), 60 (6). HRMS (ESI⁺) calcd. for C₁₂H₁₇NO₄Na ([M+Na]⁺) 262.1055, found 262.1053.

The *anti*- and *syn*-diastereomeric structures were confirmed by NOESY_1D analysis of their acetonide derivatives.

Benzyl ((4*S**,5*R**)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methylcarbamate

Benzyl ((4*R**,5*R**)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methylcarbamate

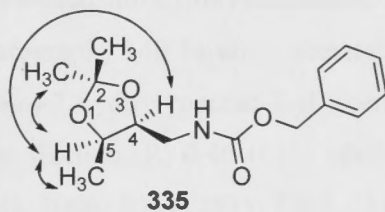


The reaction was conducted according to the General Procedure 5.2 with mixture of benzyl (2*S**,3*R**)-2,3-dihydroxybutylcarbamate **319** and benzyl (2*R**,3*R**)-2,3-dihydroxy-butylcarbamate **318** (1.8:1 / *anti*:*syn* ratio) (53.6 mg, 0.22 mmol), 2,2-dimethoxy-propane (233 mg, 2.24 mmol), camphorsulfonic acid (2.10 mg, 0.01 mmol) and *p*-toluene sulfonic acid (1.50 mg, 0.01 mmol). Purification by flash chromatography

(20% ethyl acetate/*n*-hexane) afforded an inseparable mixture of diastereomers (15.0 mg, 24%), R_f 0.23 (30% ethyl acetate/*n*-hexane). Integration of the H5 signals in the 400 MHz ^1H -NMR spectrum showed a 1:4.8 ratio of benzyl ((4*S**,5*R**)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methylcarbamate **335** and benzyl ((4*R**,5*R**)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methylcarbamate **336**. IR (thin film, cm^{-1}) 3339 (N-H), 3033, 2983, 2926, 2853 (C-H), 1724 (C=O), 1537. ^1H -NMR (400 MHz, CDCl_3) 7.30-7.37 (5H, m, ArH), 5.08-5.12 (3H, m, NH and CH_2Ar), 3.82 (1H, m, H5), 3.64 (1H, m, H4), 3.48 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{NH}$), 3.30 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{NH}$), 1.39 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.29 (3H, d, J 6.4 Hz, CH_3). ^{13}C -NMR (100 MHz, CDCl_3) 156.50, 136.39, 128.51, 128.16, 128.09, 108.41, 81.22, 73.84, 66.87, 41.55, 27.26, 26.97, 17.42. LRMS (ESI+) 302 ($[\text{M}+\text{Na}]^+$, 100%), 91 (30). HRMS (ESI+) calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$) 302.1368, found 302.1366.

The NOE interactions for product benzyl ((4*R**,5*R**)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methylcarbamate **336** were determined by NOESY_1D.

Benzyl ((4*S**,5*R**)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methylcarbamate



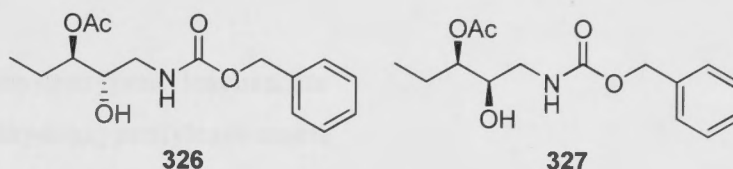
The reaction was conducted according to the General Procedure 5.2 with benzyl (2*S**,3*R**)-2,3-dihydroxybutylcarbamate **319** (16.4 mg, 0.07 mmol), 2,2-dimethoxypropane (35.7 mg, 0.34 mmol), camphorsulfonic acid (0.600 mg, 0.003 mmol) and *p*-toluenesulfonic acid (0.500 mg, 0.003 mmol). Purification by flash chromatography (20% ethyl acetate/*n*-hexane) afforded benzyl ((4*S**,5*R**)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methylcarbamate compound **335** as a colourless oil (10.1 mg, 53%). IR (thin film, cm^{-1}) 3340 (N-H), 3065, 3034, 2985, 2936 (C-H), 1722 (C=O), 1532. ^1H -NMR (400 MHz, CDCl_3) 7.30-7.37 (5H, m, ArH), 5.11 (2H, s, CH_2Ar), 5.07 (1H, s, NH), 4.33 (1H, m, H5), 4.11 (1H, m, H4), 3.48 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{NH}$), 3.05 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{NH}$), 1.44 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.23 (3H, d, J 6.4 Hz, CH_3). ^{13}C -

NMR (100 MHz, CDCl₃) 156.39, 136.45, 128.49, 128.11, 128.10, 108.09, 76.63, 72.61, 66.80, 41.59, 28.26, 25.51, 14.45. LRMS (ESI⁺) 302 ([M+Na]⁺, 88%), 222 (5), 181 (6), 149 (4), 91 (100). HRMS (ESI⁺) calcd. for C₁₅H₂₁NO₄Na ([M+Na]⁺) 302.1368, found 302.1368.

The NOE interactions for product benzyl ((4*S**,5*R**)-2,2,5-trimethyl-1,3-dioxolan-4-yl) methylcarbamate **335** were determined by NOESY_1D.

(2*S,3*R**)-1-(Benzyloxycarbonylamino)-2-hydroxypentan-3-yl acetate**

(2*R,3*R**)-1-(Benzyloxycarbonylamino)-2-hydroxypentan-3-yl acetate**



The reaction was conducted according to the General Procedure 5.1 with pent-1-en-3-yl acetate **305** (53.9 mg, 0.42 mmol), potassium osmate dihydrate (6.00 mg, 0.02 mmol) and benzyl *N*-(4-toluensulfonyloxy)carbamate **202** (165 mg, 0.51 mmol). Purification by flash chromatography (40 % ethyl acetate/*n*-hexane) afforded (2*S**,3*R**)-1-(benzyloxycarbonylamino)-2-hydroxypentan-3-yl acetate **326** as a colourless oil (53.1 mg, 43%) in the first fraction, *R*_f 0.46 (65% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3400 (O-H, N-H), 3066, 3034, 2935, 2882, 2853 (C-H), 1713, 1701 (C=O), 1537. ¹H-NMR (400 MHz, CDCl₃) 7.30-7.36 (5H, m, ArH), 5.29 (1H, s, NH), 5.07-5.14 (2H, m, CH₂Ar), 4.82 (1H, m, H3), 3.73 (1H, m, H2), 3.54 (1H, m, H1A), 3.06 (1H, m, H1B), 2.99 (1H, s, OH), 2.08 (3H, s, CH₃), 1.62-1.76 (2H, m, H4), 0.93 (3H, t, *J* 7.2 Hz, H5). ¹³C-NMR (400 MHz, CDCl₃) 171.55, 157.63, 136.23, 128.53, 128.19, 128.11, 76.32, 72.26, 67.05, 42.90, 23.31, 21.01, 9.69. LRMS (ESI⁺) 318 ([M+Na]⁺, 100%), 270 (5), 184 (6), 120 (8), 91 (68), 84 (8), 69 (4). HRMS (ESI⁺) calcd. for C₁₅H₂₁NO₅Na ([M+Na]⁺) 318.1317, found 318.1318.

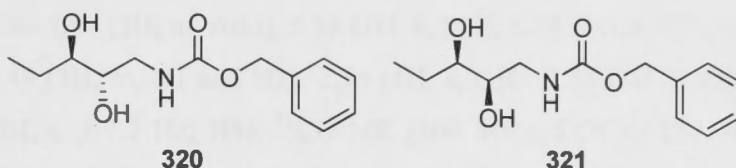
A second fraction afforded (2*R**,3*R**)-1-(benzyloxycarbonylamino)-2-hydroxypentan-3-yl acetate **327** as a colourless oil (34.8 mg, 28%), *R*_f 0.36 (65% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3369 (O-H, N-H), 3034, 2924, 2853 (C-H), 1713 (C=O), 1537. ¹H-

NMR (400 MHz, CDCl_3) 7.29-7.38 (5H, m, ArH), 5.33 (1H, s, NH), 5.09-5.10 (2H, m, CH_2Ar), 4.81 (1H, m, H3), 3.74 (1H, m, H2), 3.60 (1H, m, H1A), 3.26 (1H, m, H1B), 2.68 (1H, m, OH), 2.05-2.11 (3H, m, CH_3), 1.62-1.72 (2H, m, H4), 0.90 (3H, t, J 6.8 Hz, H5). ^{13}C -NMR (100 MHz, CDCl_3) 171.35 (170.91*), 157.22 (156.95*), 136.29 (136.16*), 128.53, 128.27, 128.17, 75.86 (74.11*), 71.52 (71.40*), 67.14 (66.92*), 43.71 (40.91*), 25.91 (23.45*), 20.99 (20.89*), 10.21 (9.75*). LRMS (ESI+) 318 ($[\text{M}+\text{Na}]^+$, 90%), 91 (100). HRMS (ESI+) calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_5\text{Na}$ ($[\text{M}+\text{Na}]^+$) 318.1317, found 318.1318. (* indicates peaks of a minor impurities).

The *anti*- and *syn*-diastereomeric structures were confirmed by NOESY_1D analysis of their acetonide derivatives.

Benzyl (2*S,3*R**)-2,3-dihydroxypentylcarbamate**

Benzyl (2*R,3*R**)-2,3-dihydroxypentylcarbamate**



The reaction was conducted according to the General Procedure 5.1 with 1-penten-3-ol **293** (36.0 mg, 0.42 mmol), potassium osmate dihydrate (6.20 mg, 16.8 μmol) and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (148 mg, 0.46 mmol). Purification by flash chromatography (60% ethyl acetate/*n*-hexane) afforded an inseparable a mixture of two diastereomers as a white solid (58.9 mg, 65%), R_f 0.19 (60% ethyl acetate/*n*-hexane). Integration of the NH signals in the 400 MHz ^1H -NMR spectrum provided a 2.1:1 ratio of benzyl (2*S**,3*R**)-2,3-dihydroxypentylcarbamate **320** and benzyl (2*R**,3*R**)-2,3-dihydroxypentylcarbamate **321**. IR (thin film, cm^{-1}) 3327 (O-H, N-H), 3064, 3035, 2960, 2925, 2876, 2853 (C-H), 1689 (C=O), 1548. ^1H -NMR (400 MHz, CDCl_3) 7.30-7.37 (5H, m, ArH), 5.32 (1H, s, NH) and 5.25* (1H, s, NH*), 5.11 (2H, m, CH_2Ar), 3.58 (1H, m, H3), 3.46-3.52 (1H, m H2), 3.39-3.43 (2H, m, H1) and 3.22* (1H, m, H1B*), 2.49 (2H, s, broad, 2xOH) and overlap with minor product, 1.51-1.60 (2H, m, H4) and 1.42-1.49* (2H, m, H4*), 1.00 (3H, t, J 7.6 Hz, H5) and 0.97* (3H, t, J 7.6 Hz, H5*). ^{13}C -NMR (100 MHz, CDCl_3) 157.92, 136.19, 128.54, 128.23, 128.11, 73.91

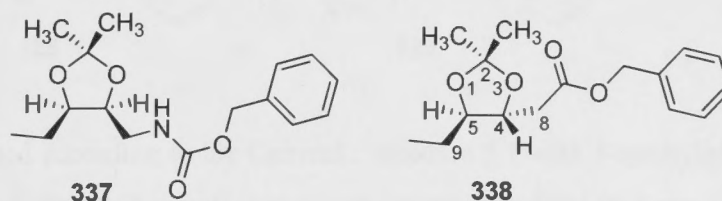
(73.20*), 73.77 (72.71*), 67.12 (67.07*), 42.85 (44.05*), 25.49 (26.25*), 10.13 (10.04*). LRMS (ESI+) 276 ([M+Na]⁺, 100%), 262 (5), 210 (8), 190 (5), 105 (5), 90 (43). HRMS (ESI+) calcd. for C₁₃H₁₉NO₄Na ([M+Na]⁺) 276.1212, found 276.1213. (* indicates peaks for the minor product)

Procedure 2:

To a solution of (2*S**,3*R**)-1-(benzyloxycarbonylamino)-2-hydroxypentan-3-yl acetate **326** (20.0 mg, 0.07 mmol) was added a solution of potassium carbonate (23.1 mg, 0.17 mmol) in methanol (3.0 mL) and water (1.0 mL) at 20 °C. This reaction mixture was stirred until complete (2 h), quenched with aqueous hydrochloric acid (1.0 mL, 1.0 M) and extracted with dichloromethane (3 x 10 mL). The combined organic extract was washed with brine (5 mL), dried over sodium sulfate and concentrated under reduced pressure to afford benzyl (2*S**,3*R**)-2,3-dihydroxypentylcarbamate **320** as a colourless oil (15.1 mg, 88%), *R*_f 0.37 (70% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3330 (broad, O-H, N-H), 2961, 2926 (C-H), 1689 (C=O), 1547. ¹H-NMR (400 MHz, CDCl₃) 7.30-7.37 (5H, m, ArH), 5.19 (1H, s, NH), 5.12 (2H, s, CH₂Ar), 3.59 (1H, m, H3), 3.39-3.49 (3H, m, H1 and H2), 2.58 (1H, s, OH), 2.51 (1H, s, OH), 1.47 (2H, m, H4), 1.01 (3H, t, *J* 7.2 Hz, H5). ¹³C-NMR (100 MHz, CDCl₃) 157.94, 136.17, 128.54, 128.24, 128.13, 73.86, 73.78, 67.14, 42.83, 25.49, 10.14. LRMS (ESI+) 276 ([M+Na]⁺, 100%), 181 (7), 149 (12), 120 (4), 107 (5), 91 (68). HRMS (ESI+) calcd. for C₁₃H₁₉NO₄Na ([M+Na]⁺) 276.1212, found 276.1212.

Benzyl ((4*S,5*R**)-5-ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)methylcarbamate**

Benzyl ((4*R,5*R**)-5-ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)methylcarbamate**

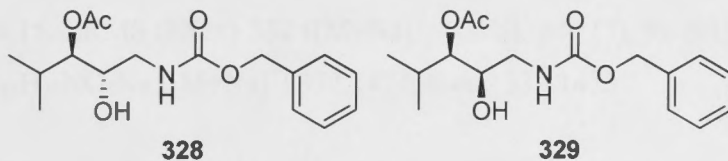


The reaction was conducted according to the General Procedure 5.2 with a mixture of benzyl (2*S**,3*R**)-2,3-dihydroxypentylcarbamate **320** and benzyl (2*R**,3*R**)-2,3-dihydroxypentylcarbamate **321** (2.1:1 / *anti:syn* ratio) (66.1 mg, 0.26 mmol), 2,2-

dimethoxypropane (272 mg, 2.61 mmol), camphorsulfonic acid (2.40 mg, 0.01 mmol) and *p*-toluenesulfonic acid (1.80 mg, 0.01 mmol). Purification by flash chromatography (30% ethyl acetate/*n*-hexane) afforded inseparable mixture of benzyl ((4*S**,5*R**)-5-ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)-methylcarbamate **337** and benzyl ((4*R**,5*R**)-5-ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)methylcarbamate **338** as a colourless oil (62.3 mg, 81%). Integration of the H8 signal in the 400 MHz ¹H-NMR spectrum showed a 1.7:1 ratio of **337** and **338**. IR (thin film, cm⁻¹) 3338 (N-H), 3065, 3035, 2984, 2936, 2880 (C-H), 1724 (C=O), 1533. ¹H-NMR (400 MHz, CDCl₃) 7.30-7.36 (5H, m, ArH), 5.10 (3H, broad, s, NH and CH₂Ar), 4.12 (1H, m, H4) and 3.74* (1H, ddd, *J* 8.8, 6.0, 3.2 Hz, H4*), 4.05 (1H, ddd, *J* 11.2, 8.8, 5.6 Hz, H5) and 3.64* (1H, ddd, *J* 14.0, 8.0, 5.6 Hz, H5*), 3.49 (1H, m, H8A) and overlap with (H8A*), 3.03 (1H, m, H8B) and 3.27* (1H, m, H8B*), 1.56-1.63 (2H, m, H9) and 1.47-1.54* (2H, m, H9*), 1.43 (3H, s, CH₃) and 1.38* (3H, s, CH₃*), 1.34 (3H, s, CH₃) and 1.37* (3H, s, CH₃*), 1.02 (3H, t, *J* 6.8 Hz, H10) and 1.00* (3H, t, *J* 6.8 Hz, H10*). ¹³C-NMR (100 MHz, CDCl₃) 156.42, 136.46, 128.49, 128.21, 128.09, 108.13 (108.53*), 78.56 (79.56*), 76.41 (79.22*), 66.77 (67.10*), 41.46 (42.47*), 28.35 (27.22*), 25.64 (27.09*), 22.04 (25.75*), 10.86 (10.05*). LRMS (ESI+) 316 ([M+Na]⁺, 46%), 276 (38), 236 (4), 91 (100%). HRMS (ESI+) calcd. for C₁₆H₂₃NO₄Na ([M+Na]⁺) 316.1525, found 316.1530. (*denotes peaks of the minor product).

(2*S,3*R**)-1-(Benzyloxycarbonylamino)-2-hydroxy-4-methylpentan-3-yl acetate**

(2*R,3*R**)-1-(Benzyloxycarbonylamino)-2-hydroxy-4-methylpentan-3-yl acetate**



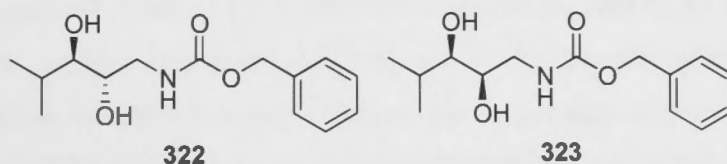
The reaction was conducted according to the General Procedure 5.1 with 4-methylpent-1-en-3-yl acetate **306** (60.0 mg, 0.42 mmol), potassium osmate dihydrate (6.2 mg, 0.02 mmol) and benzyl *N*-(4-toluensulfonyloxy)carbamate **202** (163 mg, 0.51 mmol). Purification by flash chromatography (30% ethyl acetate/*n*-hexane) afforded separable diastereomer with a 2.4:1 / **328** : **329** ratio. First fraction was afforded a colourless liquid (62.2 mg, 48%), *R*_f 0.55 (65% ethyl acetate/*n*-hexane). Further purification by

HPLC (SunFire Prep Silica OBD 5 μ m, 3% isopropanol 97% *n*-hexane, flow rate 1.0 mL/min) provided (2*S**,3*R**)-1-(benzyloxycarbonylamino)-2-hydroxy-4-methylpentan-3-yl acetate **328**, t_R 8.9 min. IR (thin film, cm^{-1}) 3407 (O-H, N-H), 3090, 3066, 3034, 2965, 2938, 2878 (C-H), 1721 (C=O), 1530. ^1H -NMR (400 MHz, CDCl_3) 7.29-7.36 (5H, m, ArH), 5.35 (1H, s, NH), 5.06-5.15 (2H, m, CH_2Ar), 4.75 (1H, dd, J 6.8, 4.8 Hz, H3), 3.79 (1H, m, H2), 3.59 (1H, m, H1A), 2.99 (1H, m, H1B), 2.03-2.11 (4H, m, H4 and CH_3), 1.66 (1H, s, OH), 0.93-0.94 (6H, m, $2\times\text{CH}_3$). ^{13}C -NMR (100 MHz, CDCl_3) 171.80, 157.89, 136.22, 128.52, 128.18, 128.10, 78.46, 70.53, 67.07, 42.99, 28.20, 20.88, 19.54, 16.65. LRMS (ESI+) 332 ($[\text{M}+\text{Na}]^+$, 98%), 293 (10), 266 (5), 250 (6), 232 (7), 188 (8), 120 (11), 91 (100), 81 (8). HRMS (ESI+) calcd. for $\text{C}_{16}\text{H}_{24}\text{NO}_5$ ($[\text{M}+\text{H}]^+$) 310.1654, found 310.1654; HRMS (ESI+) calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_5\text{Na}$ ($[\text{M}+\text{Na}]^+$) 332.1474, found 332.1474.

A second fraction afforded (2*R**,3*R**)-1-(benzyloxycarbonylamino)-2-hydroxy-4-methylpentan-3-yl acetate **329** as a colourless oil (26.1 mg, 20%), R_f 0.29 (65% ethyl acetate/*n*-hexane). Further purification by HPLC (column SunFire Preparative Silica 5 μ m, 5% isopropanol 95% *n*-hexane, flow rate 10 mL/min) afforded pure product t_R 14.7 min. IR (thin film, cm^{-1}) 3406 (O-H, N-H), 3065, 3033, 2966, 2877 (C-H), 1718 (C=O), 1528. ^1H -NMR (400 MHz, CDCl_3) 7.30-7.36 (5H, m, ArH), 5.26 (1H, s, NH), 5.10 (2H, s, CH_2Ar), 4.64 (1H, dd, J 7.6, 3.2 Hz, H3), 3.87 (1H, m, H2), 3.27 (1H, m, H1A), 3.14 (1H, m, H1B), 2.35 (1H, d, J 7.2 Hz, OH), 2.06-2.14 (4H, m, H4 and CH_3), 0.95 (3H, d, J 6.8 Hz, CH_3), 0.91 (3H, d, J 7.2 Hz, H5). ^{13}C -NMR (100 MHz, CDCl_3) 171.49, 156.91, 136.29, 128.52, 128.16, 128.09, 78.99, 70.10, 66.92, 44.13, 28.61, 20.84, 19.08, 18.15. LRMS (ESI+) 332 ($[\text{M}+\text{Na}]^+$, 100%), 246 (5), 91 (21). HRMS (ESI+) calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_5\text{Na}$ ($[\text{M}+\text{Na}]^+$) 332.1474, found 332.1473.

Benzyl (2*R,3*S**)-2,3-dihydroxy-4-methylpentylcarbamate**

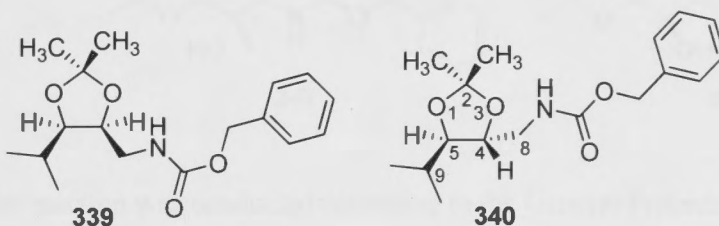
Benzyl (2*R,3*R**)-2,3-dihydroxy-4-methylpentylcarbamate**



The reaction was conducted according to the General Procedure 5.1 with 4-methyl-1-penten-3-ol **294** (41.7 mg, 0.42 mmol), potassium osmate dihydrate (6.1 mg, 16.6 μ mol) and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (161 mg, 0.50 mmol). Purification by flash chromatography (50% ethyl acetate/*n*-hexane) afforded an inseparable mixture of two diastereomers as a colourless oil (81.3 mg, 73%). Integration of NH signal of 400 MHz ^1H -NMR spectrum showed a 3.1:1 ratio of benzyl (2*R**,3*S**)-2,3-dihydroxy-4-methylpentylcarbamate **322** and benzyl (2*R**,3*R**)-2,3-dihydroxy-4-methylpentylcarbamate **323**. IR (thin film, cm^{-1}) 3405 (O-H, N-H), 3067, 3034, 2960, 2930, 2875 (C-H), 1695 (C=O), 1532. ^1H -NMR (400 MHz, CDCl_3) 7.29-7.37 (5H, m, ArH), 5.40 (1H, m, NH) and 5.30* (1H, s, NH*), 5.07-5.14 (2H, m, CH_2Ar), 3.70 (1H, m, H3), 3.36-3.42 (2H, m, H2 and H1A), 3.31 (1H, m, H1B), 2.88 (1H, s, OH), 2.76 (1H, s, OH), 1.82 (1H, m, H4), 0.96 (3H, s, CH_3) and 0.93* (3H, s, CH_3), 0.95 (3H, s, H5) and 0.91* (3H, s, H5*). ^{13}C -NMR (100 MHz, CDCl_3) 157.93 (157.48*), 136.22, 128.54, 128.22, 128.11, 77.16, 71.61 (70.64*), 67.09, 42.90 (44.41*), 29.31 (29.66*), 19.33, 17.10 (18.03*). LRMS (ESI+) 290 ($[\text{M}+\text{Na}]^+$, 100%), 91 (38). HRMS (ESI+) calcd. for $\text{C}_{14}\text{H}_{21}\text{NO}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$) 290.1368, found 290.1360. (* indicates peaks of the minor product).

Benzyl ((4*S,5*R**)-5-isopropyl-2,2-dimethyl-1,3-dioxolan-4-yl)methylcarbamate**

Benzyl ((4*R,5*R**)-5-isopropyl-2,2-dimethyl-1,3-dioxolan-4-yl)methylcarbamate**

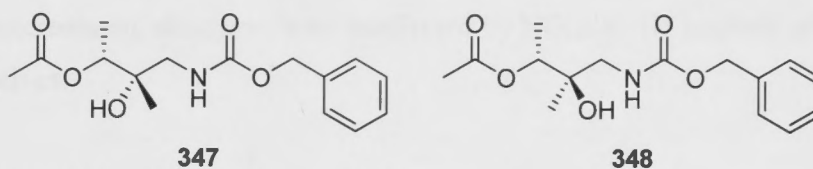


The reaction was conducted according to the General Procedure 5.2 with a mixture of benzyl (2*R**,3*S**)-2,3-dihydroxy-4-methylpentylcarbamate **322** and benzyl (2*R**,3*R**)-2,3-dihydroxy-4-methylpentylcarbamate **323** (3.1:1 / *anti:syn* ratio) (71.3 mg, 0.27 mmol), 2,2-dimethoxypropane (278 mg, 2.67 mmol), camphorsulfonic acid (2.50 mg, 0.01 mmol) and *p*-toluene sulfonic acid (1.80 mg, 0.01 mmol). Purification by flash chromatography (20% ethyl acetate/*n*-hexane) afforded an inseparable mixture of benzyl ((4*S**,5*R**)-5-isopropyl-2,2-dimethyl-1,3-dioxolan-4-yl)methylcarbamate **339** and benzyl ((4*R**,5*R**)-5-isopropyl-2,2-dimethyl-1,3-dioxolan-4-yl)methylcarbamate **340** as

a colourless oil (27.5 mg, 34%), R_f 0.24 (20% ethyl acetate/*n*-hexane). Integration of the H8B signal in the 400 MHz ^1H -NMR spectrum showed a 1:1.6 / *anti:syn* ratio. IR (thin film, cm^{-1}) 3338 (N-H), 3065, 3035, 2984, 2936, 2880 (C-H), 1724 (C=O), 1533. ^1H -NMR (400 MHz, CDCl_3) 7.30-7.36 (5H, m, ArH), 5.11-5.15 (3H, m, NH and CH_2Ar), 3.88 (1H, ddd, J 9.6, 7.2, 2.8 Hz, H4) and 4.09* (1H, m, H4*), 3.44 (1H, dd, J 7.2, 7.2 Hz, H5) and 3.70* (1H, dd, J 10, 5.6 Hz, H5*), 3.54 (1H, m, H8A), 3.22 (1H, ddd, J 12.4, 6.4, 5.2 Hz, H8B) and 3.00* (1H, ddd, J 12.8, 10.0, 2.4 Hz, H8B*), 1.78 (1H, m, H9), 1.37 (3H, s, CH_3) and 1.43* (3H, s, CH_3^*), 1.37 (3H, s, CH_3) and 1.33* (3H, s, CH_3^*), 1.04 (3H, d, J 6.8 Hz, H5) and 1.00* (3H, d, J 6.8 Hz, H5*), 0.96 (3H, d, J 7.2 Hz, CH_3) and 0.93* (3H, d, J 7.6 Hz, CH_3^*). ^{13}C -NMR (100 MHz, CDCl_3) 156.46, 136.50 (136.44*), 128.48, 128.11, 128.07, 108.52 (108.16*), 83.16 (83.01*), 78.23 (76.27*), 66.79 (66.78*), 43.82 (41.29*), 31.20 (28.55*), 27.25 (27.15*), 27.11 (25.86*), 20.47 (19.13*), 18.63. LRMS (ESI+) 330 ($[\text{M}+\text{Na}]^+$, 100%). HRMS (ESI+) calcd. for $\text{C}_{17}\text{H}_{25}\text{NO}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$) 330.1681, found 330.1680. (*Indicates peaks of the minor product).

(2*R,3*S**)-4-(Benzyloxycarbonylamino)-3-hydroxy-3-methylbutan-2-yl acetate**

(2*R,3*R**)-4-(Benzyloxycarbonylamino)-3-hydroxy-3-methylbutan-2-yl acetate**



The reaction was conducted according to the General Procedure 5.1 with 3-methylbut-3-en-2-yl acetate **307** (27.1 mg, 0.21 mmol), potassium osmate dihydrate (3.10 mg, 0.01 mmol) and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (81.6 mg, 0.25 mmol). Purification by flash chromatography (gradient eluent 60% to 100% diethyl ether/*n*-hexane) afforded separable of two diastereomers with a 2.5:1 / **347**:**348** ratio. The (2*R**,3*S**)-4-(benzyloxycarbonylamino)-3-hydroxy-3-methylbutan-2-yl acetate **347** was afforded as a colourless oil (30.4 mg, 49%), R_f 0.14 (80% diethyl ether/*n*-hexane). IR (thin film, cm^{-1}) 3415 (N-H, O-H), 3090, 3066, 3034, 2985, 2943 (C-H), 1724 (C=O), 1532. ^1H -NMR (400 MHz, CDCl_3) 7.29-7.36 (5H, m, ArH), 5.31 (1H, s, broad, NH), 5.07-5.15 (2H, m, CH_2Ar), 4.90 (1H, q, J 6.4 Hz, H2), 3.34 (1H, dd, J 14.0, 7.2 Hz,

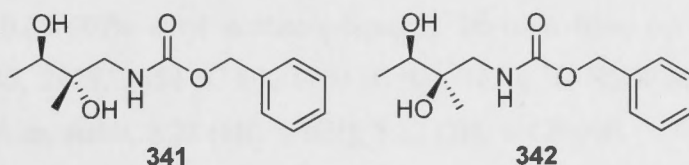
H4A), 3.15 (1H, dd, J 14.4, 5.6 Hz, H4B), 2.50 (1H, s, OH), 2.06 (3H, s, CH₃), 1.25 (3H, d, J 6.0 Hz, H1), 1.16 (3H, s, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 170.75, 157.76, 136.26, 128.51, 128.16, 128.10, 73.78, 73.30, 67.08, 47.39, 21.23, 20.57, 14.29. LRMS (ESI⁺) 318 ([M+Na]⁺, 100%), 92 (5), 91 (35). HRMS (ESI⁺) calcd. for C₁₅H₂₂NO₅ ([M+H]⁺) 296.1498, found 296.1499; calcd. for C₁₅H₂₁NO₅Na ([M+Na]⁺) 318.1317, found 318.1318.

A second fraction afforded (2*R**,3*R**)-4-(benzyloxycarbonylamino)-3-hydroxy-3-methylbutan-2-yl acetate **348** as a colourless oil (12.1 mg, 19%), R_f 0.09 (80% diethyl ether/*n*-hexane). IR (thin film, cm⁻¹) 3584 (O-H), 3419 (N-H), 3090, 3066, 3033, 2984, 2942 (C-H), 1722 (C=O), 1529. ¹H-NMR (400 MHz, CDCl₃) 7.29-7.38 (5H, m, ArH), 5.16 (1H, s, NH), 5.08-5.14 (2H, m, CH₂Ar), 4.89 (1H, q, J 6.4 Hz, H2), 3.34 (1H, dd, J 13.6, 6.0 Hz, H4A), 3.17 (1H, dd, J 14.0, 6.0 Hz, H4B), 2.09 (3H, s, CH₃) 1.44 (1H, s, OH), 1.25 (3H, d, J 6.4 Hz, H1), 1.16 (3H, s, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 170.81, 157.04, 136.33, 128.52, 128.16, 128.09, 74.31, 74.11, 66.97, 47.77, 30.29, 20.43, 14.75. LRMS (ESI⁺) 319 (20%), 318 ([M+Na]⁺, 100), 91 (60). HRMS (ESI⁺) calcd. for C₁₅H₂₂NO₅ ([M+H]⁺) 296.1498, found 296.1498; calcd. for C₁₅H₂₁NO₅Na ([M+Na]⁺) 318.1317, found 318.1317.

The *anti*- and *syn*-diastereomeric structures were confirmed by NOESY_1D analysis of their acetonide derivatives.

Benzyl (2*S**,3*R**)-2,3-dihydroxy-2-methylbutylcarbamate

Benzyl (2*R**,3*R**)-2,3-dihydroxy-2-methylbutylcarbamate



The reaction was conducted according to the General Procedure 5.1 with 3-methylbut-3-en-2-ol **295** (48.5 mg, 0.56 mmol), potassium osmate dihydrate (8.30 mg, 0.02 mmol) and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (217 mg, 0.68 mmol). Purification by flash chromatography (40% ethyl acetate/*n*-hexane) afforded a mixture of two

diastereomers as a colourless oil (64.6 mg, 45%), R_f 0.27 (70% ethyl acetate/*n*-hexane). Integration of the NH signal of the 400 MHz ^1H -NMR spectrum showed a 2.4:1 ratio of benzyl (2*S**,3*R**)-2,3-dihydroxy-2-methylbutylcarbamate **341** and benzyl (2*R**,3*R**)-2,3-dihydroxy-2-methylbutylcarbamate **342**. IR (thin film, cm^{-1}) 3401 (O-H, N-H), 3066, 3033, 2976, 2924, 2853 (C-H), 1697 (C=O), 1534. ^1H -NMR (400 MHz, CDCl_3) 7.30-7.38 (5H, m, ArH), 5.39 (1H, s, NH) and 5.25* (1H, s, NH*), 5.11 (2H, s, CH_2Ar), 3.66 (1H, q, J 6.4 Hz, H3) and 3.67* (1H, q, J 6.4 Hz, H3*), 3.48 (1H, dd, J 14.4, 6.0 Hz, H1A) and 3.37* (1H, dd, J 14.0, 7.2 Hz, H1A*), 3.11 (1H, dd, J 14.0, 7.2 Hz, H1B) and 3.09* (1H, dd, J 14.8, 7.6 Hz, H1B*), 2.63 (1H, s, OH), 1.43 (1H, s, OH), 1.18 (3H, d, J 6.8 Hz, H4), 1.11 (3H, s, CH_3) and 1.08* (3H, s, CH_3 *). ^{13}C -NMR (100 MHz, CDCl_3) 158.10, 136.16, 128.55, 128.25, 128.13, 74.00, 71.31 (70.01*), 67.18, 47.07 (48.56*), 20.62 (20.14*), 16.63. LRMS (ESI+) 276 ($[\text{M}+\text{Na}]^+$, 100%), 91 (5). HRMS (ESI+) calcd. for $\text{C}_{13}\text{H}_{19}\text{NO}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$) 276.1212, found 276.1213; calcd. for $\text{C}_{13}\text{H}_{20}\text{NO}_4$ ($[\text{M}+\text{H}]^+$) 254.1392, found 254.1392; calcd. for $\text{C}_{13}\text{H}_{19}\text{NO}_4\text{K}$ ($[\text{M}+\text{K}]^+$) 292.0951, found 292.0954 (* indicates peaks of the minor product).

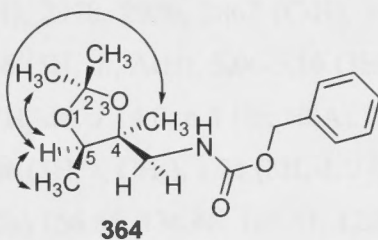
Procedure 2:

To a solution of (2*R**,3*S**)-4-(benzyloxycarbonylamino)-3-hydroxy-3-methyl-butan-2-yl acetate **347** (20.0 mg, 0.07 mmol) in methanol (0.5 mL) and dichloromethane (3.0 mL) was added a freshly prepared solution of ammonia in methanol (2.0 mL, 10%). This reaction mixture was stirred at room temperature until complete (9 h), quenched with aqueous hydrochloric acid (3.0 mL, 1.0 M) and extracted with dichloromethane (3 x 10 mL). The combined dichloromethane extract was washed with brine (5 mL), dried over sodium sulfate and concentrated under reduced pressure to afford benzyl (2*S**,3*R**)-2,3-dihydroxy-2-methylbutylcarbamate **341** as a yellow oil (17.0 mg, 99%), R_f 0.35 (80% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3401 (O-H, N-H), 3066, 3033, 2925, 2854 (C-H), 1700 (C=O), 1525. ^1H -NMR (400 MHz, CDCl_3) 7.30-7.38 (5H, m, ArH), 5.28 (1H, s, NH), 5.12 (2H, s, CH_2Ar), 3.68 (1H, q, J 6.8 Hz, H3), 3.50 (1H, dd, J 14.8, 6.0 Hz, H1A), 3.12 (1H, dd, J 14.4, 6.4 Hz, H1B), 2.29 (1H, m, OH), 2.05 (1H, m, OH), 1.19 (3H, d, J 6.8 Hz, H4), 1.13 (3H, s, CH_3). ^{13}C -NMR (100 MHz, CDCl_3) 158.07, 136.17, 128.55, 128.25, 128.13, 74.68, 71.34, 67.19, 47.09, 20.67, 16.66. LRMS (ESI+) 276 ($[\text{M}+\text{Na}]^+$, 100%), 190 (4), 91 (23), 74 (4). HRMS (ESI+) calcd. for $\text{C}_{13}\text{H}_{19}\text{NO}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$) 276.1212, found 276.1213.

Procedure 3:

To a solution of (2*R**,3*R**)-4-(benzyloxycarbonylamino)-3-hydroxy-3-methyl butan-2-yl acetate **348** (20 mg, 0.07 mmol) in dichloromethane (3.0 mL) and methanol (0.5 mL) was added a freshly prepared solution of ammonia in methanol (2.0 mL, 10%). This reaction mixture was stirred at room temperature, quenched with aqueous hydrochloric acid (3.0 mL, 1.0 M) and extracted with dichloromethane (3 x 5 mL). The combined dichloromethane extract was washed with brine (5 mL), and dried over sodium sulfate. Purification by flash chromatography (50% ethyl acetate/*n*-hexane) afforded benzyl (2*R**,3*R**)-2,3-dihydroxy-2-methyl-butyl-carbamate **342** as a colourless liquid (10.1 mg, 59%), *R*_f 0.33 (80% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3368 (O-H, N-H), 3066, 3033, 2976, 2923, 2853 (C-H), 1700 (C=O), 1649 (C=C), 1538. ¹H-NMR (300 MHz, CDCl₃) 7.32-7.37 (5H, m, ArH), 5.12 (3H, s, broad, NH and CH₂Ar), 3.67 (1H, q, *J* 4.5 Hz, H3), 3.40 (1H, dd, *J* 14.1, 7.2 Hz, H1A), 3.09 (1H, dd, *J* 14.1, 5.7 Hz, H1B), 2.97 (1H, s, OH), 2.62 (1H, s, OH), 1.17 (3H, d, *J* 6.6 Hz, H4), 1.09 (3H, s, CH₃). ¹³C-NMR (75 MHz, CDCl₃) 157.79, 136.12, 128.59, 128.32, 128.16, 74.36, 69.90, 67.23, 48.63, 20.19, 16.61. LRMS (ESI⁺) 276 ([M+Na]⁺, 25%), 91 (45). HRMS (ESI⁺) calcd. for C₁₃H₁₉NO₄Na ([M+Na]⁺) 276.1212, found 276.1214.

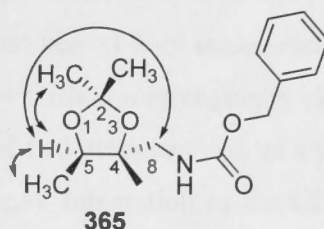
Benzyl ((4*S**,5*R**)-2,2,4,5-tetramethyl-1,3-dioxolan-4-yl)methylcarbamate



The reaction was conducted according to the General Procedure 5.2 with benzyl (2*S**,3*R**)-2,3-dihydroxy-2-methylbutylcarbamate **341** (15.0 mg, 0.06 mmol), 2,2-dimethoxypropane (67.0 mg, 0.67 mmol), camphorsulfonic acid (0.600 mg, 0.003 mmol) and *p*-toluenesulfonic acid (0.500 mg, 0.003 mmol). Purification by flash chromatography (20% ethyl acetate/*n*-hexane) afforded the title compound **364** as a colourless oil (14.5 mg, 84%), *R*_f 0.18 (20% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3345 (N-H), 3036, 2983, 2933, 2869 (C-H), 1724 (C=O), 1513. ¹H-NMR (400 MHz, CDCl₃) 7.30-7.37 (5H, m, ArH), 5.11 (2H, s, CH₂Ar), 5.06 (1H, d, *J* 8.4 Hz, NH), 4.00

(1H, q, J 6.4 Hz, H5), 3.32 (1H, dd, J 12.8, 8.8 Hz, H8A), 3.10 (1H, m, H8B), 1.41 (3H, s, CH₃), 1.35 (3H, s, CH₃), 1.24 (3H, d, J 6.4 Hz, H9), 1.22 (3H, s, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 157.00, 142.92, 136.72, 128.66, 128.25, 107.47, 81.43, 78.70, 66.95, 45.24, 28.48, 26.71, 21.34, 12.99. LRMS (ESI+) 316 ([M+Na]⁺, 100%), 236 (3), 120 (3), 92 (4), 91 (30). HRMS (ESI+) calcd. for C₁₆H₂₄NO₄ ([M+H]⁺) 294.1705, found 294.1700; calcd. for C₁₆H₂₃NO₄Na ([M+Na]⁺) 316.1525, found 316.1518.

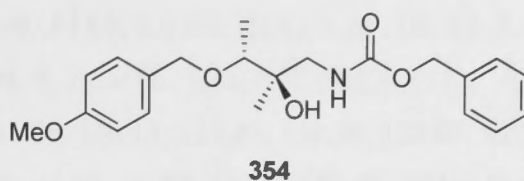
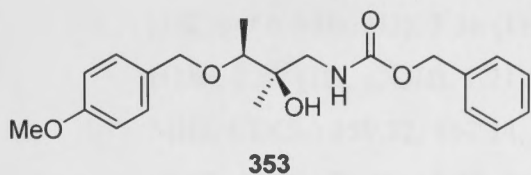
Benzyl ((4*R,5*R**)-2,2,4,5-tetramethyl-1,3-dioxolan-4-yl)methylcarbamate**



The reaction was conducted according to the General Procedure 5.2 with benzyl (2*R**,3*R**)-2,3-dihydroxy-2-methylbutylcarbamate **342** (15.0 mg, 0.06 mmol), 2,2-dimethoxypropane (61.9 mg, 0.60 mmol), camphorsulfonic acid (0.600 mg, 0.002 mmol) and *p*-toluenesulfonic acid (0.500 mg, 0.003 mmol). The title compound **365** was afforded without further purification as a colourless oil (14.5 mg, 84%). IR (thin film, cm⁻¹) 3347 (N-H), 2978, 2926, 2862 (C-H), 1717 (C=O), 1537. ¹H-NMR (400 MHz, CDCl₃) 7.30-7.36 (5H, m, ArH), 5.06-5.16 (3H, m, NH and CH₂Ar), 3.95 (1H, q, J 6.0 Hz, H5), 3.31 (1H, dd, J 14.0, 6.8 Hz, H8A), 3.19 (1H, dd, J 14.0, 5.2 Hz, H8B), 1.32 (3H, s, CH₃), 1.26 (3H, s, CH₃), 1.21 (3H, d, J 6.4 Hz, H9), 1.08 (3H, s, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 156.65, 136.46, 128.51, 128.14, 128.05, 106.95, 85.50, 82.13, 66.84, 46.14, 28.55, 26.67, 19.61, 14.13. LRMS (ESI+) 316 ([M+Na]⁺, 88%), 236 (5), 120 (5), 91 (100). HRMS (ESI+) calcd. for C₁₆H₂₃NO₄Na 316.1525, found 316.1523.

Benzyl (2*R,3*S**)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylbutyl carbamate**

Benzyl (2*R,3*R**)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylbutyl carbamate**



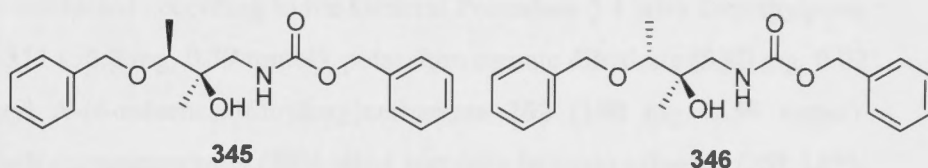
The reaction was conducted according to the General Procedure 5.1 with 1-methoxy-4-((3-methylbut-3-en-2-yloxy)methyl)benzene **309** (35.0 mg, 0.17 mmol), potassium osmate dihydrate (2.50 mg, 0.01 mmol) and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (65.4 mg, 0.20 mmol). Purification by flash chromatography (30% ethyl acetate/*n*-hexane) afforded an inseparable mixture of two diastereomers as a yellow oil (43.6 mg, 69 %), R_f 0.23 (40% ethyl acetate/*n*-hexane). Integration of the C2-CH₃ signals in the 400 MHz ¹H-NMR spectrum showed a 2.6:1 ratio of benzyl (2*R**,3*S**)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylbutyl carbamate **353** and benzyl (2*R**,3*R**)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylbutyl carbamate **354**. Further separation by preparative HPLC (column μ Porasil silica 10 μ m, 3.9 x 300 mm, solvent 1% isopropanol/*n*-hexane, flow rate 0.7 mL/min) afforded benzyl (2*R**,3*R**)-2-hydroxy-3-(4-methoxybenzyl-oxy)-2-methylbutylcarbamate **354** at t_R 31.81 min as a colourless liquid. IR (thin film, cm⁻¹) 3419 (N-H, O-H), 3066, 3033, 2976, 2936, 2837 (C-H), 1717 (C=O), 1612, 1586 (C=C), 1514. ¹H-NMR (400 MHz, CDCl₃) 7.29-7.36 (5H, m, ArH), 7.24 (2H, d, J 8.4 Hz, ArH), 6.87 (2H, d, J 8.4 Hz, ArH), 5.10 (3H, s, broad, NH and CH₂), 4.60 (1H, d, J 10.8 Hz, CH_AH_BAr), 4.31 (1H, d, J 11.2 Hz, CH_AH_BAr), 3.79 (3H, s, OCH₃), 3.42 (1H, q, J 6.4 Hz, H3), 3.31 (1H, dd, J 13.6, 5.6 Hz, H1A), 3.20 (1H, dd, J 13.6, 6.6 Hz, H1B), 2.65 (1H, s, OH), 1.19 (3H, d, J 6.4 Hz, H4), 1.09 (3H, s, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 159.31, 156.82, 136.58, 130.14, 129.42, 128.48, 128.06, 128.01, 113.89, 77.95, 74.24, 70.79, 66.70, 55.24, 47.75, 20.22, 13.57. LRMS (ESI⁺) 396 ([M+Na]⁺, 75%), 121 (100). HRMS (ESI⁺) calcd. for C₂₁H₂₇NO₅Na ([M+Na]⁺) 396.1787, found 396.1790.

A second fraction afforded benzyl (2*R**,3*S**)-2-hydroxy-3-(4-methoxybenzyl-oxy)-2-methylbutylcarbamate **353** at t_R 36.40 min as a colourless oil. IR (thin film, cm⁻¹) 3418 (N-H, O-H), 3065, 3033, 2975, 2936, 2874, 2837 (C-H), 1705 (C=O), 1612, 1586

(C=C), 1513. $^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.29-7.38 (5H, m, ArH), 7.23 (2H, d, J 8.4 Hz, ArH), 6.86 (2H, d, J 8.8 Hz, ArH), 5.08 (3H, s, broad, NH and CH_2Ar), 4.60 (1H, d, J 10.8 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.30 (1H, d, J 11.6 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 3.77 (3H, s, OCH_3), 3.46 (1H, q, J 6.0 Hz, H3), 3.36 (1H, dd, J 14.0, 8.0 Hz, H1A), 3.20 (1H, dd, J 13.6, 3.6 Hz, H1B), 2.89 (1H, s, OH), 1.21 (3H, d, J 6.0 Hz, H4), 1.11 (3H, s, CH_3). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 159.32, 157.34, 136.55, 130.13, 129.39, 128.47, 128.03, 127.98, 113.92, 79.37, 73.98, 70.76, 66.73, 55.23, 46.88, 21.05, 13.50. LRMS (ESI+) 396 ($[\text{M}+\text{Na}]^+$, 75%), 121 (100). HRMS (ESI+) calcd. for $\text{C}_{21}\text{H}_{27}\text{NO}_5\text{Na}$ ($[\text{M}+\text{Na}]^+$) 396.1787, found 396.1788).

Benzyl (2*R,3*S**)-3-(benzyloxy)-2-hydroxy-2-methylbutylcarbamate**

Benzyl (2*R,3*R**)-3-(benzyloxy)-2-hydroxy-2-methylbutylcarbamate**

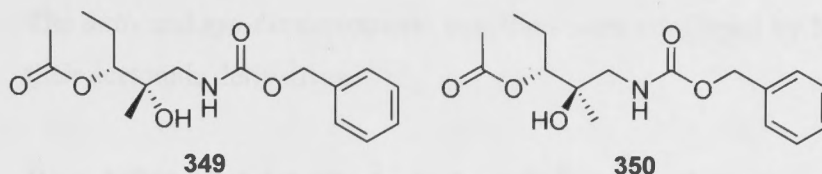


The reaction was conducted according to the General Procedure 5.1 with ((3-methylbut-3-en-2-yloxy)methyl)benzene **308** (50.0 mg, 0.28 mmol), potassium osmate dihydrate (4.20 mg, 0.01 mmol) and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (109 mg, 0.34 mmol). Purification by flash chromatography (25% ethyl acetate/*n*-hexane) afforded an inseparable mixture of benzyl (2*R**,3*S**)-3-(benzyloxy)-2-hydroxy-2-methylbutylcarbamate **345** and benzyl (2*R**,3*R**)-3-(benzyloxy)-2-hydroxy-2-methylbutylcarbamate **346** as a colourless liquid (86.3 mg, 89%), R_f 0.23 (40% ethyl acetate/*n*-hexane). Integration of H3 signal of the 400 MHz $^1\text{H-NMR}$ spectrum showed a 2.5:1 / **345** : **346** ratio. IR (thin film, cm^{-1}) 3421 (O-H), 3352 (N-H), 3088, 3064, 3031, 2977, 2938, 2875 (C-H), 1707 (C=O), 1604 (C=C), 1586. $^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.28-7.37 (10H, m, ArH), 5.17 (1H, m, NH), 5.09-5.11 (2H, m, CH_2Ar), 4.67 (1H, d, J 11.6 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 4.38 (1H, d, J 11.2 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$), 3.49 (1H, q, J 7.6 Hz, H3) and 3.46* (1H, q, J 6.4 Hz, H3*), 3.39 (1H, dd, J 14.0, 8.0 Hz, H1A) and 3.34* (1H, dd, J 13.6, 6.0 Hz, H1A*), 3.24 (1H, dd, J 6.8, 3.6 Hz, H1B) and 3.21* (1H, dd, J 10.0, 6.4 Hz, H1B*), 2.74 (1H, s, broad, OH), 1.21 (3H, d, J 6.4 Hz, H4) and 1.19* (3H, d, J 6.4 Hz, H4*), 1.12 (3H, s, CH_3) and 1.10* (3H, s, CH_3 *). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 157.36, 138.09,

136.53, 128.51, 128.48, 128.06, 128.00, 127.84, 127.75, 79.88, 74.05, 71.16, 66.75, 46.88, 21.03, 13.53. LRMS (ESI+) 366 ($[M+Na]^+$, 100%), 300 (10), 181 (20), 120 (13), 90 (55). HRMS (ESI+) calcd. for $C_{20}H_{25}NO_4Na$ ($[M+Na]^+$) 366.1681, found 366.1681. (*Indicates peaks of the minor product).

(2*S,3*R**)-1-(Benzyloxycarbonylamino)-2-hydroxy-2-methylpentan-3-yl acetate**

(2*R,3*R**)-1-(Benzyloxycarbonylamino)-2-hydroxy-2-methylpentan-3-yl acetate**



The reaction was conducted according to the General Procedure 5.1 with 2-methylpent-1-en-3-yl acetate **311** (56.0 mg, 0.39 mmol), potassium osmate dihydrate (5.80 mg, 0.02 mmol) and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (190 mg, 0.59 mmol). Purification by flash chromatography (30% ethyl acetate/*n*-hexane) afforded (2*S**,3*R**)-1-(benzyloxycarbonylamino)-2-hydroxy-2-methylpentan-3-yl acetate **349** in the first fraction as a colourless oil (67.0 mg, 55%). R_f 0.33 (50% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3744 (O-H), 3414 (N-H), 3066, 3033, 2974, 2938, 2879 (C-H), 1722 (C=O), 1524. 1H -NMR (400 MHz, $CDCl_3$) 7.29-7.36 (5H, m, ArH), 5.44 (1H, s, NH), 5.07-5.16 (2H, m, CH_2Ar), 4.80 (1H, dd, J 10.4, 2.0 Hz, H3), 3.38 (1H, dd, J 14.0, 8.0 Hz, H1A), 3.01 (1H, dd, J 14.4, 4.8 Hz, H1B), 2.82 (1H, s, OH), 2.09 (3H, s, CH_3), 1.80 (1H, m, H4A), 1.54 (1H, m, H4B), 1.15 (3H, s, CH_3), 0.90 (3H, t, J 7.6 Hz, H5). ^{13}C -NMR (100 MHz, $CDCl_3$) 171.68, 158.03, 136.28, 128.51, 128.14, 128.09, 78.16, 73.99, 67.08, 47.60, 21.66, 20.99, 20.92, 10.70. LRMS (ESI+) 332 ($[M+Na]^+$, 100%), 272 (5), 91 (34). HRMS (ESI+) calcd. for $C_{16}H_{23}NO_5Na$ ($[M+Na]^+$) 332.1474, found 332.1487; calcd. for $C_{16}H_{24}NO_5$ ($[M+H]^+$) 310.1654, found 310.1654.

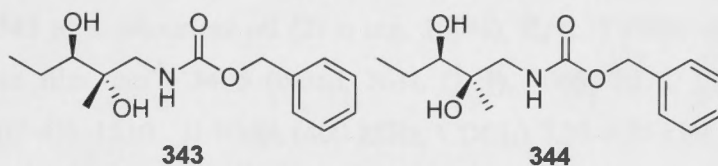
A second fraction afforded (2*R**,3*R**)-1-(benzyloxycarbonyl-amino)-2-hydroxy-2-methylpentan-3-yl acetate **350** as a colourless oil (23.8 mg, 20%), R_f 0.26 (50% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3748 (O-H), 3401 (N-H), 3066, 3033, 2973, 2936, 2879 (C-H), 1717 (C=O), 1529. 1H -NMR (400 MHz, $CDCl_3$) 7.30-7.36 (5H, m, ArH), 5.23 (1H, s, NH), 5.11 (2H, s, CH_2Ar), 4.82 (1H, dd, J 10.4, 2.4 Hz, H3), 3.34

(1H, dd, J 14.0, 6.8 Hz, H1A), 3.11 (1H, dd, J 14.0, 6.4 Hz, H1B), 2.43 (1H, s, OH), 2.13 (3H, s, CH₃), 1.71 (1H, m, H4A), 1.58 (1H, m, H4B), 1.15 (3H, s, CH₃), 0.89 (3H, t, J 7.2 Hz, H5). ¹³C-NMR (100 MHz, CDCl₃) 171.78, 157.06, 136.37, 128.51, 128.13, 128.06, 79.05, 74.45, 66.93, 48.08, 22.16, 20.92, 20.63, 10.48. LRMS (ESI⁺) 332 ([M+Na]⁺, 100%), 284 (4), 272 (4), 91 (30). HRMS (ESI⁺) calcd. for C₁₆H₂₃NO₅K ([M+K]⁺) 348.1213, found 348.1214; calcd. for C₁₆H₂₃NO₅Na ([M+Na]⁺) 332.1474, found 332.1474.

The *anti*- and *syn*-diastereomeric structures were confirmed by NOESY_1D analysis of their acetonide derivatives.

Benzyl (2*S,3*R**)-2,3-dihydroxy-2-methylpentylcarbamate**

Benzyl (2*R,3*R**)-2,3-dihydroxy-2-methylpentylcarbamate**



The reaction was conducted according to the General Procedure 5.1 with 2-methylpent-1-en-3-ol **296** (63.5 mg, 0.63 mmol), potassium osmate dihydrate (9.40 mg, 0.03 mmol) and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (245 mg, 0.76 mmol). Purification by flash chromatography (30% ethyl acetate/*n*-hexane) afforded an inseparable mixture of benzyl (2*S**,3*R**)-2,3-dihydroxy-2-methyl-pentylcarbamate **343** and benzyl (2*R**,3*R**)-2,3-dihydroxy-2-methylpentylcarbamate **344** as a colourless oil (67.2 mg, 40%), R_f 0.36 (70% ethyl acetate/*n*-hexane). Integration of C2-CH₃ signal of the 400 MHz ¹H-NMR spectrum showed a 2.7:1 ratio of **343** and **344**. IR (thin film, cm⁻¹) 3401 (O-H, N-H), 3066, 2966, 2932, 2877 (C-H), 1697 (C=O), 1529. ¹H-NMR (400 MHz, CDCl₃) 7.29-7.38 (5H, m, ArH), 5.40 (1H, s, NH) and 5.26* (1H, s, NH*), 5.08-5.15 (2H, m, CH₂Ar), 3.48 (1H, dd, J 14.4, 6.4 Hz, H3) and 3.36* (1H, dd, J 14.0, 6.8 Hz, H3*), 3.30 (1H, m, H1A), 3.12 (1H, dd, J 15.2, 6.8 Hz, H1B) and 3.07* (1H, dd, J 14.4, 6.4 Hz, H1B*), 2.61 (1H, s, OH), 1.78 (1H, s, OH), 1.58 (1H, m, H4A), 1.33 (1H, m, H4B), 1.11 (3H, s, CH₃) and 1.08* (3H, s, CH₃*), 1.02 (3H, t, J 6.8 Hz, H5). ¹³C-NMR (100 MHz, CDCl₃) 158.07 (157.66*), 136.22, 128.54, 128.23, 128.10, 77.23 (75.88*),

74.63 (74.48*), 67.14, 47.51 (48.58*), 23.50, 20.76 (20.24*), 11.48 (11.03*). LRMS (ESI+) 290 ($[M+Na]^+$, 90%), 288 (4), 244 (4), 181 (10), 120 (4), 91 (100). HRMS (ESI+) calcd. for $C_{14}H_{21}NO_4Na$ ($[M+Na]^+$) 290.1368, found 290.1368; calcd. for $C_{14}H_{21}NO_4K$ ($[M+K]^+$) 306.1108, found 306.1108 (*Indicates signal of the minor product).

Procedure 2:¹⁸⁷

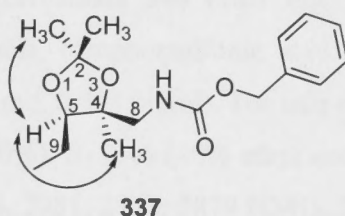
To (2*S**,3*R**)-1-(benzyloxycarbonylamino)-2-hydroxy-2-methylpentan-3-yl acetate **349** (25.0 mg, 0.08 mmol) was added a freshly prepared solution of potassium carbonate (22.4 mg, 0.16 mmol) in methanol (3 mL) and water (1 mL) at 20 °C. The reaction mixture was stirred until complete (1 h), quenched with aqueous hydrochloric acid (5.0 mL, 1.0 M), and extracted with dichloromethane (3 x 10 mL). The combined dichloromethane extract was washed with brine (10 mL), dried over sodium sulfate and concentrated under reduced pressure to afford benzyl (2*S**,3*R**)-2,3-dihydroxy-2-methylpentyl carbamate **343** as a colourless oil (21.6 mg, 100%), R_f 0.37 (70% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3405 (broad, N-H, O-H), 3065, 3033, 2966, 2933, 2877 (C-H), 1696 (C=O), 1530. 1H -NMR (400 MHz, $CDCl_3$) 7.30-7.37 (5H, m, ArH), 5.28 (1H, s, NH), 5.09-5.16 (2H, m, CH_2Ar), 3.50 (1H, dd, J 14.8, 6.4 Hz, H3), 3.31 (1H, m, H1A), 3.09 (1H, dd, J 14.4, 6.0 Hz, H1B), 2.96 (1H, s, OH), 2.40 (1H, s, OH), 1.60 (1H, m, H4A), 1.35 (1H, m, H4B), 1.12 (3H, s, CH_3), 1.03 (3H, t, J 8.0 Hz, H5). ^{13}C -NMR (100 MHz, $CDCl_3$) 158.08, 136.22, 128.54, 128.23, 128.10, 77.24, 74.62, 67.13, 47.50, 23.51, 20.75, 11.48. LRMS (ESI+) 290 ($[M+Na]^+$, 100%), 204 (7), 91 (9). HRMS (ESI+) calcd. for $C_{14}H_{21}NO_4Na$ ($[M+Na]^+$) 290.1368, found 290.1360; calcd. for $C_{14}H_{22}NO_4$ ($[M+H]^+$) 268.1549, found 268.1544.

Procedure 3:¹⁸⁷

To (2*R**,3*R**)-1-(benzyloxycarbonylamino)-2-hydroxy-2-methylpentan-3-yl acetate **350** (20.0 mg, 0.065 mmol) was added a freshly prepared of solution potassium carbonate (17.9 mg, 0.129 mmol) in methanol (3 mL) and water (1 mL) at 20 °C. The reaction mixture was stirred until complete (1 h), quenched with aqueous hydrochloric acid (5.0 mL, 1.0 M) and extracted with dichloromethane (3 x 10 mL). The combined dichloromethane extract was washed with brine (10 mL), dried over sodium sulfate and concentrated under reduced pressure to afford benzyl (2*R**,3*R**)-2,3-dihydroxy-2-methylpentylcarbamate **344** as a colourless oil (16.7 mg, 97%), R_f 0.36 (70% ethyl

acetate/*n*-hexane). IR (thin film, cm^{-1}) 3400 (broad, N-H, O-H), 3066, 3033, 2964, 2931, 2876 (C-H), 1697 (C=O), 1530. ^1H -NMR (400 MHz, CDCl_3) 7.30-7.38 (5H, m, ArH), 5.22 (1H, s, NH), 5.11 (2H, s, CH_2Ar), 3.37 (1H, dd, J 14.0, 6.8 Hz, H3), 3.32 (1H, m, H1A), 3.12 (1H, dd, J 14.4, 6.0 Hz, H1B), 2.91 (1H, s, OH), 2.77 (1H, s, OH), 1.54 (1H, m, H4A), 1.40 (1H, m, H4B), 1.09 (3H, s, CH_3), 1.00 (3H, t, J 7.2 Hz, H5). ^{13}C -NMR (100 MHz, CDCl_3) 157.65, 136.22, 128.54, 128.24, 128.10, 75.85, 74.45, 67.12, 48.60, 23.45, 20.24, 11.03. LRMS (ESI+) 290 ($[\text{M}+\text{Na}]^+$, 100%), 204 (4), 91 (5). HRMS (ESI+) calcd. for $\text{C}_{14}\text{H}_{22}\text{NO}_4$ ($[\text{M}+\text{H}]^+$) 268.1549, found 268.1541; calcd. for $\text{C}_{14}\text{H}_{21}\text{NO}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$) 290.1368, found 290.1364.

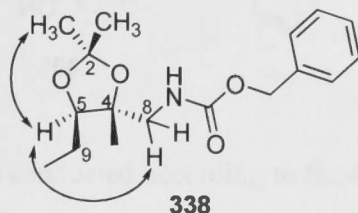
Benzyl ((4*S,5*R**)-5-ethyl-2,2,4-trimethyl-1,3-dioxolan-4-yl)methylcarbamate**



The reaction was conducted according to the General Procedure 5.2 with benzyl (2*S**,3*R**)-2,3-dihydroxy-2-methylpentylcarbamate **343** (21.8 mg, 0.08 mmol), 2,2-dimethoxypropane (42.5 mg, 0.41 mmol), camphorsulfonic acid (0.800 mg, 0.003 mmol) and *p*-toluenesulfonic acid (0.600 mg, 0.003 mmol). The title compound **337** was afforded without further purification as a yellowish oil (25.1 mg, 100%), R_f 0.51 (40% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3350 (N-H), 3066, 3033, 2981, 2935, 2878 (C-H), 1725 (C=O), 1513. ^1H -NMR (400 MHz, CDCl_3) 7.30-7.37 (5H, m, ArH), 5.11 (2H, s, CH_2Ar), 5.07 (1H, s, NH), 3.73 (1H, dd, J 8.8, 4.0 Hz, H5), 3.31 (1H, dd, J 13.2, 8.8 Hz, H8A), 3.09 (1H, dd, J 13.6, 2.0 Hz, H8B), 1.46-1.65 (2H, m, H9), 1.40 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.23 (3H, s, CH_3), 1.05 (3H, t, J 7.2 Hz, H10). ^{13}C -NMR (100 MHz, CDCl_3) 156.81, 136.60, 128.46, 128.10, 128.03, 107.25, 84.62, 81.05, 66.73, 45.23, 28.32, 26.50, 21.70, 21.08, 11.44. LRMS (ESI+) 330 ($[\text{M}+\text{Na}]^+$, 100%), 91 (9). HRMS (ESI+) calcd. for $\text{C}_{17}\text{H}_{26}\text{NO}_4$ ($[\text{M}+\text{H}]^+$) 308.1862, found 308.1865; calcd. for $\text{C}_{17}\text{H}_{25}\text{NO}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$) 330.1681, found 330.1678.

The NOE interactions for product benzyl ((4*S**,5*R**)-5-ethyl-2,2,4-trimethyl-1,3-dioxolan-4-yl)methylcarbamate **337** were determined by NOESY_1D.

Benzyl ((4*R,5*R**)-5-ethyl-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl carbamate**

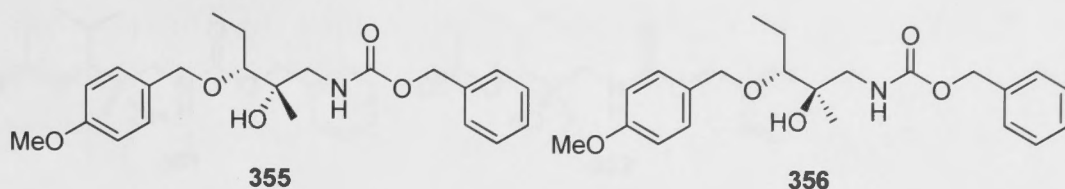


The reaction was conducted according to the General Procedure 5.2 with benzyl (2*R**,3*R**)-2,3-dihydroxy-2-methylpentylcarbamate **344** (16.7 mg, 0.06 mmol), 2,2-dimethoxypropane (32.5 mg, 0.31 mmol), camphorsulfonic acid (0.600 mg, 0.003 mmol) and *p*-toluenesulfonic acid (0.500 mg, 0.003 mmol). The title compound **338** was afforded as a yellowish oil (19.2 mg, 100%), R_f 0.46 (40% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3350 (N-H), 3066, 3034, 2981, 2933, 2879 (C-H), 1725 (C=O), 1516. ^1H -NMR (400 MHz, CDCl_3) 7.30-7.37 (5H, m, ArH), 5.11 (3H, s, broad, NH and CH_2Ar), 3.66 (1H, dd, J 9.2, 4.0 Hz, H5), 3.31 (1H, dd, J 14.0, 6.8 Hz, H8A), 3.20 (1H, dd, J 14.4, 5.6 Hz, H8B), 1.57 (1H, m, H9A), 1.47 (1H, m, H9B), 1.41 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.01 (3H, t, J 7.2 Hz, H10). ^{13}C -NMR (100 MHz, CDCl_3) 156.60, 136.57, 128.47, 128.09, 128.01, 106.96, 81.83, 80.56, 66.77, 46.69, 28.60, 26.69, 22.42, 19.68, 11.18. LRMS (ESI+) 330 ($[\text{M}+\text{Na}]^+$, 100%), 91 (52). HRMS (ESI+) calcd. for $\text{C}_{17}\text{H}_{26}\text{NO}_4$ ($[\text{M}+\text{H}]^+$) 308.1862, found 308.1861; calcd. for $\text{C}_{17}\text{H}_{25}\text{NO}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$) 330.1681, found 330.1681; calcd. for $\text{C}_{17}\text{H}_{25}\text{NO}_4\text{K}$ ($[\text{M}+\text{K}]^+$) 346.1421, found 346.1420.

The NOE interactions for product benzyl ((4*R**,5*R**)-5-ethyl-2,2,4-trimethyl-1,3-dioxolan-4-yl)methylcarbamate **338** were determined by NOESY_1D.

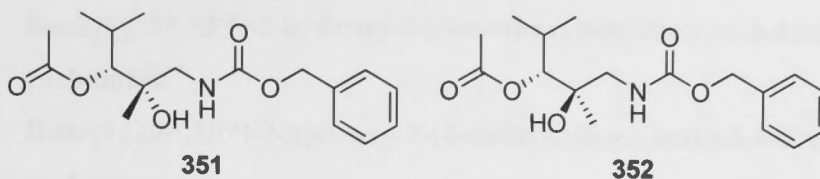
Benzyl (2*S,3*R**)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylpentylcarbamate**

Benzyl (2*R,3*R**)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylpentylcarbamate**



The reaction was conducted according to the General Procedure 5.1 with 1-methoxy-4-((2-methylpent-1-en-3-yloxy)methyl)benzene **312** (65.0 mg, 0.30 mmol), potassium osmate dihydrate (4.40 mg, 0.01 mmol) and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (114 mg, 0.35 mmol). Purification by flash chromatography (20% ethyl acetate/*n*-hexane) afforded an inseparable mixture of benzyl (2*S**,3*R**)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylpentylcarbamate **355** and benzyl (2*R**,3*R**)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylpentylcarbamate **356** as a colourless oil (49.9 mg, 44%), R_f 33 (40% ethyl acetate/*n*-hexane). Integration of the C2-CH₃ signal of the 400 MHz ¹H-NMR spectrum showed a 4.9:1 ratio of **355** and **356**. IR (thin film, cm⁻¹) 3401 (O-H, N-H), 3066, 3033, 2966, 2932, 2877 (C-H), 1697 (C=O), 1529. ¹H-NMR (400 MHz, CDCl₃) 7.27-7.37 (5H, m, ArH), 7.25 (2H, d, *J* 8.4 Hz, ArH), 6.86 (2H, d, *J* 8.8 Hz, ArH), 5.21 (1H, s, NH), 5.09-5.12 (2H, m, ArCH₂), 4.65 (1H, d, *J* 10.4 Hz, CH_AH_B), 4.50 (1H, d, *J* 11.2 Hz, CH_AH_B), 3.78 (3H, s, OCH₃), 3.35 (1H, dd, *J* 14.0, 8.0 Hz, H3), 3.26 (1H, dd, *J* 8.8, 3.6 Hz, H1A), 3.21 (1H, dd, *J* 13.6, 3.6 Hz, H1B), 2.69 (1H, s, OH), 1.69 (1H, m, H4A), 1.55 (1H, m, H4B), 1.14 (3H, s, CH₃) and 1.11* (3H, s, CH₃*), 1.07 (3H, t, *J* 7.6 Hz, H5) and 1.04* (3H, t, *J* 7.6 Hz, H5*). ¹³C-NMR (100 MHz, CDCl₃) 159.34 (157.31*), 136.57, 130.39, 129.39, 128.47, 128.03, 127.97, 113.94, 86.90 (84.54*), 74.51, 74.42, 66.73 (66.94*), 55.24, 47.30 (48.08*), 23.69 (23.48*), 21.93 (20.70*), 11.82 (11.29*). LRMS (ESI+) 410 ([M+Na]⁺, 100%), 121 (16). HRMS (ESI+) calcd. for C₂₂H₂₉NO₅Na ([M+Na]⁺) 410.1943, found 410.1938. (*Indicates signals of the minor product)

(2*S,3*R**)-1-(Benzyloxycarbonylamino)-2-hydroxy-2,4-dimethylpentan-3-yl acetate**
(2*R,3*R**)-1-(Benzyloxycarbonylamino)-2-hydroxy-2,4-dimethylpentan-3-yl acetate**



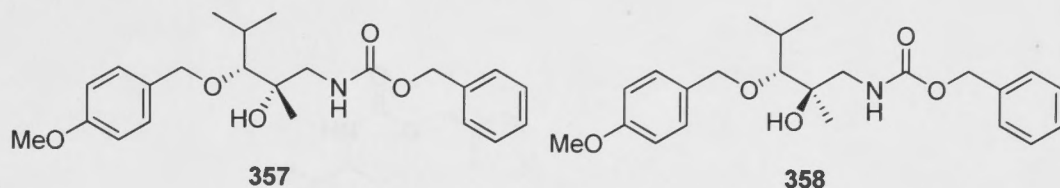
The reaction was conducted according to the General Procedure 5.1 with 2,4-dimethylpent-1-en-3-yl acetate **313** (60.0 mg, 0.38 mmol), potassium osmate dihydrate (5.70 mg, 15.5 μ mol) and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (148 mg, 0.46 mmol). Purification by flash chromatography (30% ethyl acetate/*n*-hexane) afforded (2*S**,3*R**)-1-(benzyloxycarbonylamino)-2-hydroxy-2,4-dimethylpentan-3-yl acetate **351** as a colourless oil (31.0 mg, 25%) in the first fraction, R_f 0.34 (40% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3416 (O-H, N-H), 3064, 3033, 2965, 2936, 2877 (C-H), 1722 (C=O), 1525. ^1H -NMR (400 MHz, CDCl_3) 7.29-7.37 (5H, m, ArH), 5.36 (1H, s, NH), 5.08-5.16 (2H, m, CH_2Ar), 4.70 (1H, d, J 4.4 Hz, H3), 3.36 (1H, dd, J 14.4, 8.0 Hz, H1A), 3.04 (1H, dd, J 14.4, 4.4 Hz, H1B), 2.70 (1H, s, OH), 2.10-2.16 (4H, m, CH_3 and H4), 1.19 (3H, s, CH_3), 1.00 (3H, d, J 6.8 Hz, CH_3), 0.94 (3H, d, J 6.4 Hz, H5). ^{13}C -NMR (100 MHz, CDCl_3) 171.35, 157.87, 136.34, 128.48, 128.11, 128.04, 79.95, 74.67, 67.03, 48.37, 28.14, 21.91, 21.53, 20.85, 18.27. LRMS (ESI+) 346 ($[\text{M}+\text{Na}]^+$, 100%), 286 (5), 91 (11). HRMS (ESI+) calcd. for $\text{C}_{17}\text{H}_{25}\text{NO}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$) 346.1630, found 346.1623.

A second fraction afforded (2*R**,3*R**)-1-(benzyloxycarbonylamino)-2-hydroxy-2,4-dimethylpentan-3-yl acetate **352** as a colourless oil (8.9 mg, 7%), R_f 0.20 (40% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3400 (O-H, N-H), 3066, 3033, 2963, 2929, 2874 (C-H), 1721 (C=O), 1522. ^1H -NMR (400 MHz, CDCl_3) 7.30-7.36 (5H, m, ArH), 5.24 (1H, s, NH), 5.11 (2H, s, CH_2Ar), 4.76 (1H, d, J 3.2 Hz, H3), 3.31 (1H, dd, J 14.0, 6.4 Hz, H1A), 3.02 (1H, dd, J 14.4, 6.4 Hz, H1B), 2.27 (1H, s, OH), 2.08-2.14 (4H, m, CH_3 and H4), 1.21 (3H, s, CH_3), 0.99 (3H, d, J 7.2 Hz, CH_3), 0.94 (3H, d, J 6.4 Hz, H5). ^{13}C -NMR (100 MHz, CDCl_3) 171.45, 157.04, 136.40, 128.50, 128.12, 128.07, 79.95, 74.95, 66.89, 48.56, 28.32, 21.90, 21.31, 20.77, 17.04. LRMS (ESI+) 346 ($[\text{M}+\text{Na}]^+$, 100%),

286 (7), 260 (5), 91 (8). HRMS (ESI+) calcd. for $C_{17}H_{25}NO_4Na$ ($[M+Na]^+$) 346.1630, found 346.1630.

Benzyl (2*S,3*R**)-2-hydroxy-3-(4-methoxybenzyloxy)-2,4-dimethylpentyl-carbamate**

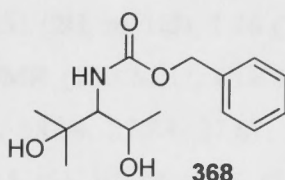
Benzyl (2*R,3*R**)-2-hydroxy-3-(4-methoxybenzyloxy)-2,4-dimethylpentyl-carbamate**



The reaction was conducted according to the General Procedure 5.1 with 1-((2,4-dimethylpent-1-en-3-yloxy)methyl)-4-methoxybenzene **314** (84.5 mg, 0.36 mmol), potassium osmate dihydrate (5.30 mg, 0.02 mmol) and benzyl *N*-(4-toluenesulfonyloxy) carbamate **202** (139 mg, 0.43 mmol). Purification by flash chromatography (30% ethyl acetate/*n*-hexane) afforded an inseparable mixture of two diastereomer as a colourless oil (25.2 mg, 17%) with d.r. 12.1:1. Purification with preparative HPLC (column μ Porasil silica 10 μ m, 3.9x300 mm, 1% isopropanol/*n*-hexane, flow rate 0.7 mL/min) afforded benzyl (2*S**,3*R**)-2-hydroxy-3-(4-methoxybenzyloxy)-2,4-dimethylpentyl carbamate **357** at t_R 23.71 min. IR (thin film, cm^{-1}) 3421 (O-H, N-H), 3065, 3032, 2959, 2874, 2837 (C-H), 1702 (C=O), 1612, 1586 (C=C), 1514. 1H -NMR (400 MHz, $CDCl_3$) 7.29-7.38 (5H, m, ArH), 7.26 (2H, d, J 8.4 Hz, ArH), 6.86 (2H, d, J 8.4 Hz, ArH), 5.16 (1H, s, NH), 5.09 (2H, s, CH_2Ar), 4.68 (1H, d, J 10.8 Hz, CH_AH_BAr), 4.46 (1H, d, J 10.8 Hz, CH_AH_BAr), 3.78 (3H, s, OCH_3), 3.37 (1H, dd, J 13.6, 8.0 Hz, H1A), 3.21 (1H, d, J 2.8 Hz, H3), 3.19 (1H, dd, J 11.6, 3.6 Hz, H1B), 2.68 (1H, s, OH), 1.99 (1H, m, H4), 1.17 (3H, s, CH_3), 1.12 (3H, d, J 6.8 Hz, CH_3), 1.03 (3H, d, J 6.8 Hz, H5). ^{13}C -NMR (100 MHz, $CDCl_3$) 159.32, 157.28, 136.58, 130.36, 129.27, 128.47, 128.02, 127.96, 113.92, 89.27, 75.34, 74.90, 66.72, 55.23, 47.56, 28.96, 24.07, 22.18, 17.65. LRMS (ESI+) 424 ($[M+Na]^+$, 100%), 121 (90). HRMS (ESI+) calcd. for $C_{23}H_{31}NO_5Na$ ($[M+Na]^+$) 424.2100, found 424.2102; calcd. for $C_{23}H_{32}NO_5$ ($[M+H]^+$) 402.2280, found 424.2290.

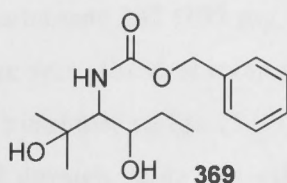
A second fraction (t_R 21.33 min) afforded benzyl (2*R**,3*R**)-2-hydroxy-3-(4-methoxybenzyl-oxy)-2,4-dimethylpentyl carbamate **358** as a colourless oil (1.8 mg, 7%). IR (thin film, cm^{-1}) 3401 (O-H, N-H), 3031, 2958, 2925, 2872, 2852 (C-H), 1705 (C=O), 1612, 1587 (C=C), 1514. LRMS (ESI+) 424 ($[\text{M}+\text{Na}]^+$, 100%), 413 (11), 302 (32), 181 (8), 149 (18), 121 (65), 91 (42). HRMS (ESI+) calcd. for $\text{C}_{23}\text{H}_{31}\text{NO}_5\text{Na}$ ($[\text{M}+\text{Na}]^+$) 424.2100, found 424.2099.

Benzyl 2,4-dihydroxy-2-methylpentan-3-ylcarbamate



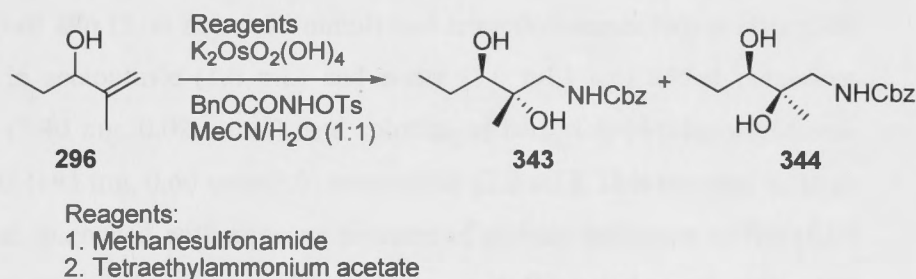
The reaction was conducted according to the General Procedure 5.1 with 4-methylpent-3-en-2-ol **301** (45.0 mg, 0.45 mmol), potassium osmate dihydrate (6.60 mg, 0.02 mmol) and benzyl *N*-(4-toluensulfonyloxy)carbamate **202** (173 mg, 0.54 mmol). Purification by flash chromatography (80% diethyl ether/*n*-hexane) afforded the title compound **368** as a brown slurry (11.3 mg, 10%), R_f 0.14 (80% diethyl ether/*n*-hexane). IR (thin film, cm^{-1}) 3414 (broad, O-H, N-H), 3067, 3033, 2956, 2923, 2852 (C-H), 1721, 1699 (C=O), 1513. ^1H -NMR (400 MHz, CDCl_3) 7.31-7.37 (5H, m, ArH), 5.56 (1H, d, J 9.6 Hz, NH), 5.14 (2H, s, CH_2Ar), 4.42 (1H, m, H4), 3.37 (1H, d, J 9.2 Hz, H3), 2.59 (2H, s, broad, 2xOH), 1.38 (3H, s, CH_3), 1.24 (3H, s, H1), 1.18 (3H, d, J 6.4 Hz, H5). ^{13}C -NMR (100 MHz, CDCl_3) 157.35, 136.57, 128.50, 128.06, 127.86, 74.49, 67.16, 66.84, 60.54, 27.87, 27.65, 20.56. LRMS (ESI+) 290 ($[\text{M}+\text{Na}]^+$, 85%), 272 (28), 245 (11), 232 (5), 177 (5), 149 (6), 132 (10), 91 (100), 89 (9), 57 (5). HRMS (ESI+) calcd. for $\text{C}_{14}\text{H}_{21}\text{NO}_3\text{Na}$ ($[\text{M}+\text{Na}]^+$) 290.1368, found 290.1367.

Benzyl 2,4-dihydroxy-2-methylhexan-3-ylcarbamate



The reaction was conducted according to the General Procedure 5.1 with 5-methylhex-4-en-3-ol **302** (50.0 mg, 0.44 mmol), potassium osmate dihydrate (6.50 mg, 0.02 mmol) and benzyl *N*-(4-toluensulfonyloxy)carbamate **202** (169 mg, 0.53 mmol). Purification by flash chromatography (80% diethyl ether/*n*-hexane) afforded the title compound **369** as a brown slurry (8.2 mg, 7.0%), R_f 0.33 (80% diethyl ether/*n*-hexane). IR (thin film, cm^{-1}) 3406 (broad, O-H, N-H), 2970, 2934 (C-H), 1694 (C=O), 1515. ^1H -NMR (400 MHz, CDCl_3) 7.29-7.36 (5H, m, ArH), 5.52 (1H, d, J 10.0 Hz, NH), 5.09-5.16 (2H, m, CH_2Ar), 4.08 (1H, t, J 7.2 Hz, H4), 3.47 (1H, dd, J 9.6, 1.6 Hz, H3), 2.67 (1H, s, OH), 2.54 (1H, s, OH), 1.51 (2H, m, H5), 1.38 (3H, s, CH_3), 1.25 (3H, s, H1), 0.95 (3H, t, J 7.6 Hz, H6). ^{13}C -NMR (100 MHz, CDCl_3) 157.22, 136.57, 128.48, 128.05, 127.87, 74.60, 72.92, 66.82, 58.84, 27.84, 27.67, 27.32, 9.98. LRMS (ESI+) 304 ($[\text{M}+\text{Na}]^+$, 100%), 286 (4), 145 (5), 91 (84), 85 (5). HRMS (ESI+) calcd. for $\text{C}_{15}\text{H}_{23}\text{NO}_3\text{Na}$ ($[\text{M}+\text{Na}]^+$) 304.1525, found 304.1526.

Procedure to accelerate the osmium-catalysed aminohydroxylation reaction of allylic alcohols



Addition methanesulfonamide

The reaction procedure was adopted from Sharpless and coworkers.¹⁴⁶ To a stirred mixture of methanesulfonamide (48.7 mg, 0.50 mmol), 2-methylpent-1-en-3-ol **296** (48.7 mg, 0.49 mmol) and potassium osmate dihydrate (7.30 mg, 0.02 mmol) in acetonitrile (1.0 mL) and water (3.0 mL) was added a solution of benzyl *N*-(4-toluensulfonyloxy)carbamate **202** (193 mg, 0.60 mmol) in acetonitrile (2.0 mL) at 0 °C. This reaction mixture was stirred at room temperature for 4 d, quenched with aqueous solution of sodium hydrogen sulfite (5.00 mL, 0.05 M.) and stirred for 30 min. The mixture was filtered through celite and extracted with ethyl acetate (3 x 10 mL). The

combined ethyl acetate extract was washed with brine (10 mL), dried over sodium sulfate and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (40% ethyl acetate/*n*-hexane) afforded an inseparable mixture of benzyl (2*S**,3*R**)-2,3-dihydroxy-2-methylpentylcarbamate **343** and benzyl (2*R**,3*R**)-2,3-dihydroxy-2-methylpentylcarbamate **344** as a colourless oil (30.2 mg, 23%), *R*_f 0.37 (70% ethyl acetate/*n*-hexane). Integration of C2-methyl in the 400 MHz ¹H-NMR spectrum showed a 3.1:1 / **343** : **344** ratio. IR (thin film, cm⁻¹) 3406 (O-H, N-H), 3066, 3032, 2966, 2933, 2877 (C-H), 1697 (C=O), 1534. ¹H-NMR (400 MHz, CDCl₃) 7.30-7.36 (5H, m, ArH), 5.30 (1H, s, NH) and 5.17* (1H, s, NH*), 5.09-5.16 (2H, m, CH₂Ar), 3.49 (1H, m, H3), 3.31 (1H, dd, *J* 10.8, 1.6 Hz, H1A) and 3.38* (1H, dd, *J* 14.4, 2.9 Hz, H1A*), 3.09 (1H, m, H1B), 2.60 (2H, s, broad, 2xOH), 1.59 (1H, m, H4A), 1.35 (1H, m, H4B), 1.12 (3H, s, CH₃) and 1.09* (3H, s, CH₃*), 1.03 (3H, t, *J* 7.6 Hz, H5) and 1.01* (3H, t, *J* 9.6 Hz, H5*) ¹³C-NMR (100 MHz, CDCl₃) 158.07 (157.67*), 136.22, 128.54, 128.23, 128.11, 77.23 (75.84*), 74.64 (74.46*), 67.16, 47.53 (48.62*), 23.52, 20.80 (20.26*), 11.48 (11.03*). *Denotes the signals for the minor product.

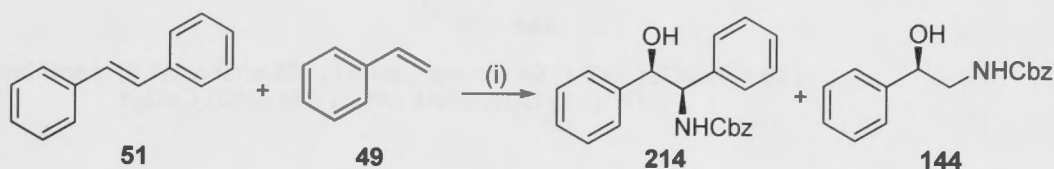
Addition tetraethylammonium acetate

The reaction procedure was adopted from Akashi et al.¹⁴⁷ To a stirred mixture of 2-methylpent-1-en-3-ol **296** (5.00 mg, 0.50 mmol) and tetraethylammonium acetate (130 mg, 0.50 mmol) in acetonitrile (1.0 mL) and water (3.0 mL) was added potassium osmate dihydrate (7.40 mg, 0.02 mmol), and solution of benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (193 mg, 0.60 mmol) in acetonitrile (2.0 mL). This reaction mixture was stirred for 4 d, quenched with aqueous solution of sodium hydrogen sulfite (5.00 mL, 0.05 M.) and stirred for 30 min. The mixture was filtered through celite and extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate extract was washed with brine (10 mL), dried over sodium sulfate and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (40% ethyl acetate/*n*-hexane) afforded an inseparable mixture of benzyl (2*S**,3*R**)-2,3-dihydroxy-2-methylpentylcarbamate **343** and benzyl (2*R**,3*R**)-2,3-dihydroxy-2-methylpentylcarbamate **344** as a colourless oil (33.7 mg, 25%), *R*_f 0.37 (70% ethyl acetate/*n*-hexane). Integration of C2-methyl in the 400 MHz ¹H-NMR spectrum showed a 3.8:1 / **343** : **344** ratio. The spectroscopic data agreed with that reported above.

General procedure 5.3: Competition reactions

To a mixture alkene A (1.0 equiv.), alkene B (1.0 equiv.) and potassium osmate dihydrate (4.0 mol%) in acetonitrile (1.0 mL) and water (1.0 mL) was added solution benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (1.0 equiv.) in acetonitrile (2.0 mL). This reaction mixture was stirred until complete, quenched with aqueous sodium hydrogen sulfite (5.0 mL, 0.05 M) and stirred for 30 min. The mixture was filtered through celite and extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate extract was washed with brine (10 mL), dried (Na₂SO₄) and concentrated to afford the crude product. Purification by flash chromatography was conducted to afford the target compounds.

Competition between *trans*-stilbene and styrene



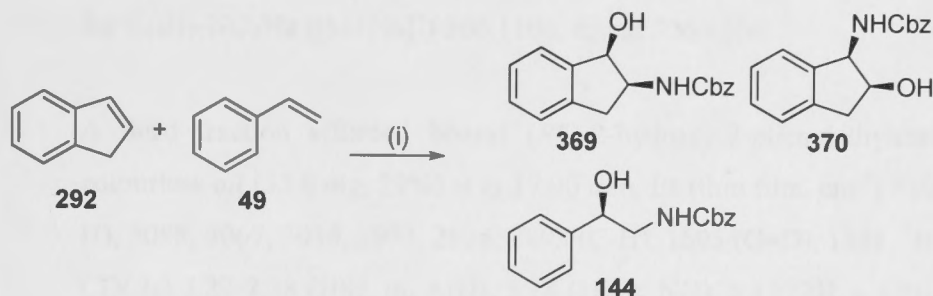
Conditions: (i) *trans*-stilbene (1.0 eq.), styrene (1.0 eq.), **202** (1.0 eq.), K₂OsO₂(OH)₄ (4.0 mol%), MeCN/H₂O (3:1), RT

The reaction was conducted according to the General Procedure 5.3 with *trans*-stilbene **51** (70.5 mg, 0.39 mmol), styrene **49** (40.5 mg, 0.39 mmol), potassium osmate dihydrate (5.40 mg, 14.7 μ mol) and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (125 mg, 0.39 mmol). Purification by flash chromatography (25% ethyl acetate/*n*-hexane) afforded benzyl (1*R**,2*R**)-2-hydroxy-1,2-diphenylethyl-carbamate **214** as a white solid (58.2 mg, 43%), *R*_f 0.23 (30% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3748 (O-H), 3350 (N-H), 3087, 3063, 3032, 2941, 2909 (C-H), 1688 (C=O), 1536. ¹H-NMR (400 MHz, CDCl₃) 7.27-7.35 (15 H, m, ArH), 5.67 (1H, s, NH), 4.98-5.06 (4H, m, CH₂Ar, H1 and H2), 2.38 (1H, s, OH). ¹³C-NMR (100 MHz, CDCl₃) 156.30, 140.54, 139.70, 136.33, 129.05, 128.58, 128.45, 128.30, 128.03, 127.84, 127.65, 126.84, 126.15, 76.93, 66.82, 61.03.

A second fraction afforded benzyl (*R**)-2-hydroxy-2-phenylethyl-carbamate **144** as a colorless oil (37.7 mg, 36%), *R*_f 0.14 (30% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹)

3366 (O-H), 3272 (N-H), 3065, 2962, 2929, 2885 (C-H), 1692 (C=O), 1548. ^1H -NMR (400 MHz, CDCl_3) 7.29-7.37 (10H, m, ArH), 5.12 (3H, m, broad, NH and CH_2Ar), 4.86 (1H, m, H2), 3.57 (1H, m, H1A), 3.33 (1H, ddd, J 12.8, 8.0, 5.2 Hz, H1B), 2.64 (1H, s, OH). ^{13}C -NMR (100 MHz, CDCl_3) 157.13, 141.49, 136.33, 128.56, 128.53, 128.17, 128.11, 127.96, 125.85, 73.59, 66.95, 48.51.

Competition between 1*H*-indene and styrene



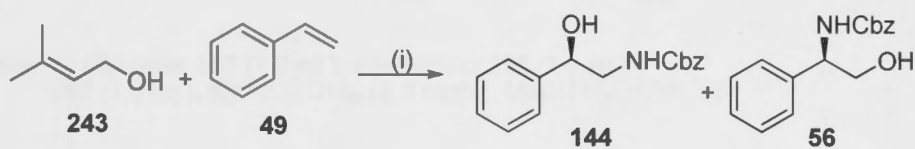
Conditions: (i) 1*H*-indene **292** (1.0 eq.), styrene **49** (1.0 eq.), **202** (1.0 eq.), $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4.0 mol%), MeCN/ H_2O (3:1), RT

The reaction was conducted according to the General Procedure 5.3 with 1*H*-indene **229** (49.0 mg, 0.42 mmol), styrene **49** (43.9 mg, 0.42 mmol), potassium osmate dihydrate (5.40 mg, 0.02 mmol) and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (135.6 mg, 0.42 mmol). Purification by flash chromatography (20% ethyl acetate/*n*-hexane) afforded inseparable mixture of two regioisomers from 1*H*-indene and one regioisomer from styrene. Further separation with preparative HPLC (column SunFire prep silica 5 μm , 2% isopropanol/*n*-hexane, flow rate 0.7 mL/min) afforded benzyl (1*R**,2*S**)-1-hydroxy-2,3-dihydro-1*H*-inden-2-ylcarbamate **369** as an orange oil (26.8 mg, 22%) at t_R 8.57 min. IR (thin film, cm^{-1}) 3405 (O-H, N-H), 3070, 3030, 2933 (C-H), 1695 (C=O), 1611, 1586 (C=C), 1514. ^1H -NMR (400 MHz, CDCl_3) 7.21-7.40 (9H, m, ArH), 5.49 (1H, d, J 8.0 Hz, H1), 5.08-5.14 (2H, m, CH_2Ar), 5.02 (1H, m, NH), 4.42 (1H, m, H2), 3.23 (1H, dd, J 15.6, 6.8 Hz, H3A), 2.88 (1H, dd, J 16.0, 7.2 Hz, H3B), 2.15 (1H, s, OH). ^{13}C -NMR (100 MHz, CDCl_3) 156.46, 141.98, 140.97, 136.39, 136.73, 129.29, 128.56, 128.18, 127.32, 125.23, 125.13, 74.65, 66.88, 54.93, 36.77. LRMS (ESI+) 306 ($[\text{M}+\text{Na}]^+$, 85%), 304 (38), 266 (5), 235 (8), 222 (20), 205 (5), 174 (4), 91 (100). HRMS (ESI+) calcd. for $\text{C}_{17}\text{H}_{17}\text{NO}_3\text{Na}$ ($[\text{M}+\text{Na}]^+$) 306.1106, found 306.1105.

A second fraction afforded benzyl (1*R**,2*S**)-2-hydroxy-2,3-dihydro-1*H*-inden-1-ylcarbamate **370** as an orange oil (20.1 mg, 17%) at *t_R* 13.44 min. IR (thin film, cm^{-1}) 3408 (O-H, N-H), 3070, 3032, 2941 (C-H), 1694 (C=O), 1515. ^1H -NMR (400 MHz, CDCl_3) 7.23-7.38 (10H, m, ArH), 5.41 (1H, s, NH), 5.09-5.19 (3H, m, H1 and CH_2Ar), 4.61 (1H, m, H2), 3.13 (1H, dd, *J* 16.8, 4.8 Hz, H3A), 2.91 (1H, dd, *J* 16.8, 16.8 Hz, H3B), 2.03 (1H, s, OH). ^{13}C -NMR (100 MHz, CDCl_3) 156.78, 140.42, 139.69, 136.29, 128.56, 128.30, 128.21, 128.14, 127.20, 125.37, 124.46, 73.56, 67.08, 59.28, 39.48. LRMS (ESI+) 306 ($[\text{M}+\text{Na}]^+$, 100%), 220 (6), 133 (8), 91 (84). HRMS (ESI+) calcd. for $\text{C}_{17}\text{H}_{17}\text{NO}_3\text{Na}$ ($[\text{M}+\text{Na}]^+$) 306.1106, found 306.1106.

A third fraction afforded benzyl (*R**)-2-hydroxy-2-phenylethylcarbamate **144** as a colourless oil (33.6 mg, 29%) at *t_R* 17.90 min. IR (thin film, cm^{-1}) 3308 (broad, O-H, N-H), 3088, 3067, 3034, 2953, 2928, 2893 (C-H), 1695 (C=O), 1551. ^1H -NMR (400 MHz, CDCl_3) 7.27-7.38 (10H, m, ArH), 5.18 (1H, s, NH), 5.11 (2H, s, CH_2Ar), 4.85 (1H, dd, *J* 7.6, 3.2 Hz, H2), 3.57 (1H, m, H1A), 3.32 (1H, ddd, *J* 13.2, 7.6, 4.8 Hz, H1B), 2.51 (1H, s, OH). ^{13}C -NMR (100 MHz, CDCl_3) 157.14, 141.48, 136.33, 128.56, 128.54, 128.17, 128.11, 127.97, 125.85, 73.58, 66.96, 48.51.

Competition between 3-methylbut-2-en-1-ol and styrene



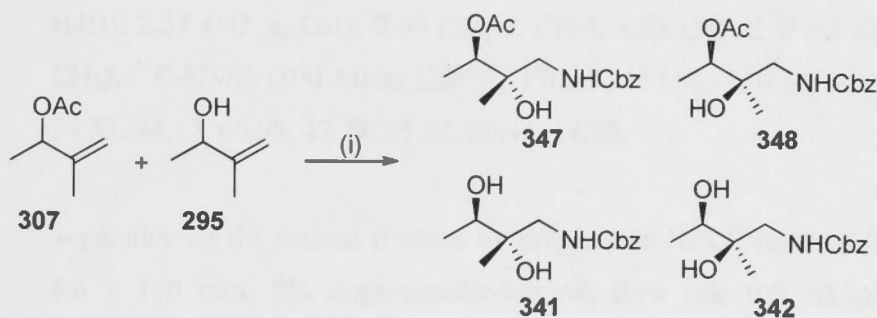
Conditions: (i) 3-methylbut-2-en-1-ol **243** (1.0 eq.), styrene **49** (1.0 eq.), **202** (1.0 eq.), $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4.0 mol%), $\text{MeCN}/\text{H}_2\text{O}$ (3:1), RT

The reaction was conducted according to the General Procedure 5.3 with 3-methylbut-2-en-1-ol **243** (39.1 mg, 0.44 mmol), styrene **49** (45.9 mg, 0.44 mmol), potassium osmate dihydrate (5.100 mg, 0.014 mmol) and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (142 mg, 0.44 mmol). Purification by flash chromatography (gradient from 25% to 50% ethyl acetate/*n*-hexane) afforded benzyl (*R**)-2-hydroxy-2-phenylethylcarbamate **144** as a colourless solid (70.3 mg, 59%) in the first fraction, *R_f* 0.26 (40% ethyl acetate/*n*-hexane). IR (thin film, cm^{-1}) 3307 (broad, O-H, N-H), 3087, 3065, 3034, 2952, 2928, 2892 (C-H), 1696 (C=O), 1556. ^1H -NMR (400 MHz, CDCl_3) 7.27-7.38 (10H, m, ArH),

5.21 (1H, s, NH), 5.11 (2H, s, CH₂Ar), 4.83 (1H, m, H₂), 3.56 (1H, m, H_{1A}), 3.31 (1H, ddd, *J* 13.6, 7.6, 4.8 Hz, H_{1B}), 2.84 (1H, s, OH). ¹³C-NMR (100 MHz, CDCl₃) 157.12, 141.48, 136.33, 128.56, 128.54, 128.16, 128.12, 127.98, 125.85, 73.59, 66.95, 48.51.

A second fraction afforded benzyl (*R*^{*})-2-hydroxy-1-phenylethylcarbamate **56** as a colourless oil (6.8 mg, 7.0%), *R*_f 0.13 (40% ethyl acetate/*n*-hexane). IR (thin film, cm⁻¹) 3329 (broad, O-H, N-H), 3063, 3031, 2926 (C-H), 1695 (C=O), 1513. ¹H-NMR (400 MHz, CDCl₃) 7.28-7.38 (10H, m, ArH), 5.54 (1H, s, NH) and 5.36^{*} (1H, s, NH^{*}), 5.06-5.16 (2H, m, CH₂Ar), 4.85 (1H, s, OH), 4.53 (1H, m, H₁), 3.81-3.90 (2H, m, H₂). ¹³C-NMR (100 MHz, CDCl₃) 156.39, 136.22, 129.06, 128.83, 128.51, 128.30, 128.17, 127.87, 126.55, 72.81, 67.03, 57.12.

Competition between 3-methylbut-3-en-2-yl acetate and 3-methylbut-3-en-2-ol



Conditions: (i) allyl ester **307** (1.0 eq.), allyl alcohol **295** (1.0 eq.), **202** (1.0 eq.), K₂OsO₂(OH)₄ (4.0 mol%), MeCN/H₂O (3:1), RT

The reaction was conducted according to the General Procedure 5.3 with 3-methylbut-3-en-2-ol **295** (30.0 mg, 0.35 mmol), 3-methylbut-3-en-2-yl acetate **307** (44.6 mg, 0.35 mmol), potassium osmate dihydrate (5.100 mg, 0.014 mmol) and benzyl *N*-(4-toluenesulfonyloxy)carbamate **202** (112 mg, 0.35 mmol). Purification by flash chromatography (40% ethyl acetate/*n*-hexane) afforded a separable mixture of **347** and **348** as a colorless oil (15.9 mg) in the first fraction, and **341** and **342** as a colorless oil (29.8 mg) in the second fraction.

Further separation of the first fraction by preparative HPLC (column SunFire silica 5 μm, 4.6 x 150 mm, 5% isopropanol/*n*-hexane, flow rate 0.6 mL/min) afforded

(2*R**,3*S**)-4-(benzyloxycarbonylamino)-3-hydroxy-3-methylbutan-2-yl acetate **347** as a colourless liquid (11.2 mg, 11%) at t_R 9.64 min. IR (thin film, cm^{-1}) 3358 (broad, O-H, N-H), 3090, 3065, 3034, 2984, 2943 (C-H), 1712 (C=O), 1605 (C=C), 1530. $^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.29-7.36 (5H, m, ArH), 5.30 (1H, s, NH), 5.06-5.15 (2H, m, CH_2Ar), 4.91 (1H, q, J 6.0 Hz, H2), 3.35 (1H, dd, J 14.4, 7.6 Hz, H4A), 3.16 (1H, dd, J 14.0, 5.2 Hz, H4B), 2.74 (1H, s, OH), 2.06 (3H, s, CH_3), 1.25 (3H, d, J 6.4 Hz, H1), 1.16 (3H, s, CH_3). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 170.77, 157.80, 136.28, 128.54, 128.19, 128.13, 73.80, 73.32, 67.10, 47.41, 21.25, 20.59, 14.31.

(2*R**,3*R**)-4-(Benzyloxycarbonylamino)-3-hydroxy-3-methylbutan-2-yl acetate **348** was afforded as a colorless oil (4.7 mg, 5%) at t_R 12.98 min. IR (thin film, cm^{-1}) 3391 (broad, O-H, N-H), 3066, 3033, 2952, 2924, 2852 (C-H), 1713 (C=O), 1532. $^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.30-7.36 (5H, m, ArH), 5.08-5.14 (3H, m, NH and CH_2Ar), 4.89 (1H, q, J 6.8 Hz, H2), 3.34 (1H, dd, J 13.6, 6.4 Hz, H4A), 3.17 (1H, dd, J 14.4, 6.4 Hz, H4B), 2.37 (1H, s, OH), 2.09 (3H, s, CH_3), 1.25 (3H, d, J 6.0 Hz, H1), 1.16 (3H, s, CH_3). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 170.83, 157.06, 136.34, 128.54, 128.18, 128.10, 74.33, 74.12, 66.99, 47.79, 21.22, 20.44, 14.76.

Separation of the second fraction by preparative HPLC (column SunFire silica 5 μm , 4.6 x 150 mm, 5% isopropanol/*n*-hexane, flow rate 0.6 mL/min) afforded benzyl (2*S**,3*R**)-2,3-dihydroxy-2-methylbutylcarbamate **341** as a colourless oil (24.4 mg, 28%) at t_R 23.60 min. IR (thin film, cm^{-1}) 3371 (broad, O-H, N-H), 3092, 3065, 3035, 2972, 2924, 2854 (C-H), 1695 (C=O), 1532. $^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.31-7.37 (5H, m, ArH), 5.27 (1H, s, NH), 5.12 (2H, s, CH_2Ar), 3.68 (1H, q, J 6.0 Hz, H3), 3.50 (1H, dd, J 14.4, 5.6 Hz, H1A), 3.12 (1H, dd, J 14.4, 6.8 Hz, H1B), 2.93 (1H, s, OH), 2.43 (1H, s, OH), 1.19 (3H, d, J 6.8 Hz, H4), 1.13 (3H, s, CH_3). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) 158.09, 136.19, 128.57, 128.27, 128.14, 74.70, 71.36, 67.21, 47.11, 20.69, 16.67.

Benzyl (2*R**,3*R**)-2,3-dihydroxy-2-methylbutylcarbamate **342** was afforded as a colourless oil (5.4 mg, 6%) at t_R 25.69 min. IR (thin film, cm^{-1}) 3401 (O-H, N-H), 3066, 3034, 2975, 2927 (C-H), 1697 (C=O), 1532. $^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.30-7.36 (5H, m, ArH), 5.36 (1H, s, NH), 5.11 (2H, s, CH_2Ar), 3.67 (1H, q, J 6.8 Hz, H3), 3.48 (1H, dd, J 14.4, 6.0 Hz, H1A), 3.12 (1H, dd, J 14.0, 7.2 Hz, H1B), 2.59 (2H, s, 2 x OH),

1.18 (3H, d, J 6.8 Hz, H₄), 1.12 (3H, s, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 158.08, 136.18, 128.54, 128.24, 128.12, 74.67, 71.34, 67.18, 47.08, 20.64, 16.65.

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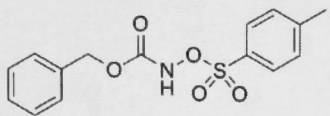
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Appendix

Appendix A.1

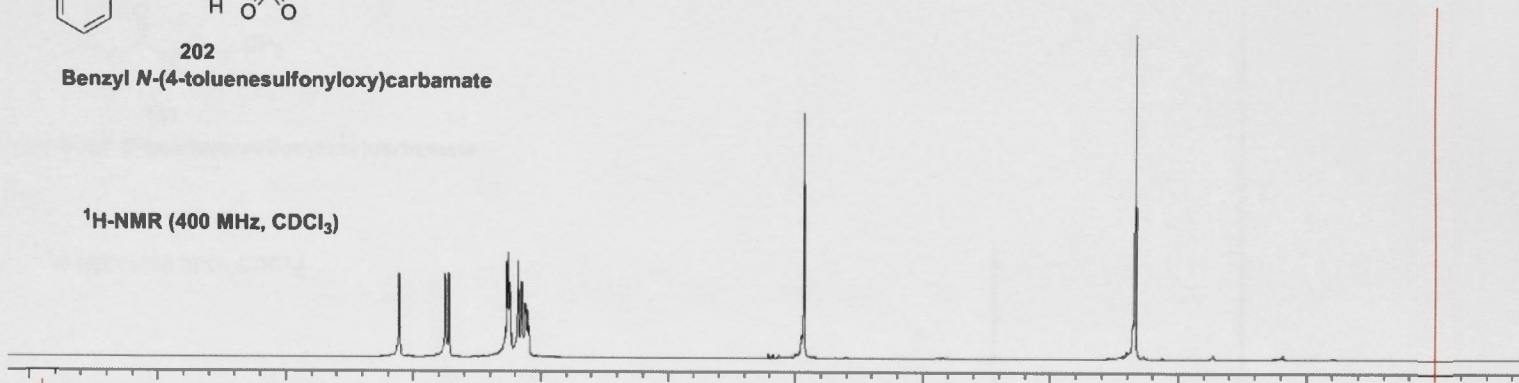
Example spectra ^1H - and ^{13}C -NMR of preformed nitrogen source 202



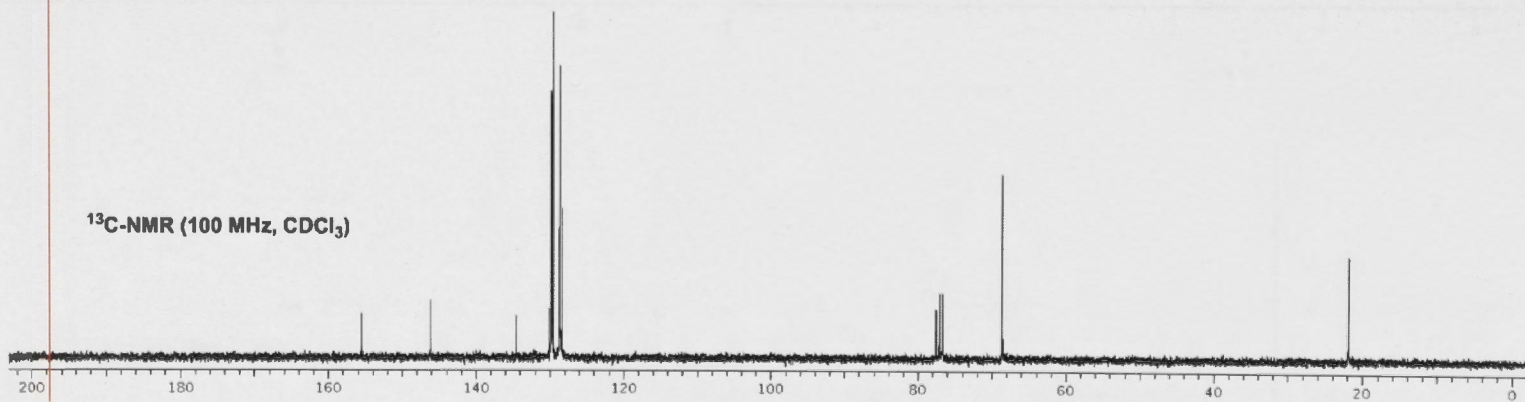
202

Benzyl *N*-(4-toluenesulfonyloxy)carbamate

^1H -NMR (400 MHz, CDCl_3)

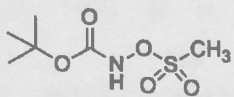


^{13}C -NMR (100 MHz, CDCl_3)



Appendix A.2

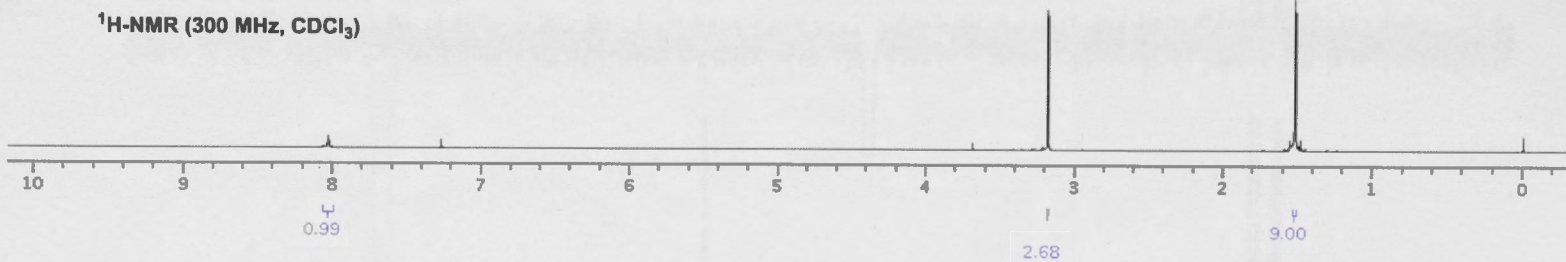
Example spectra ^1H - and ^{13}C -NMR of preformed nitrogen source 151



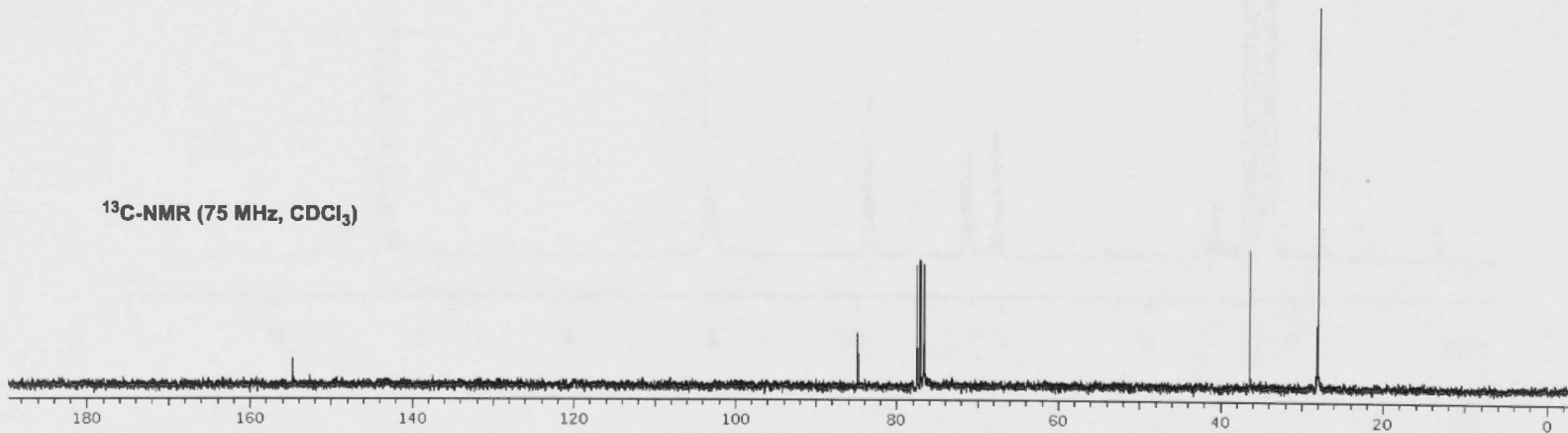
151

tert-Butyl *N*-(methanesulfonyloxy)carbamate

^1H -NMR (300 MHz, CDCl_3)

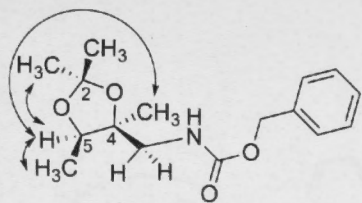


^{13}C -NMR (75 MHz, CDCl_3)



Appendix A.3

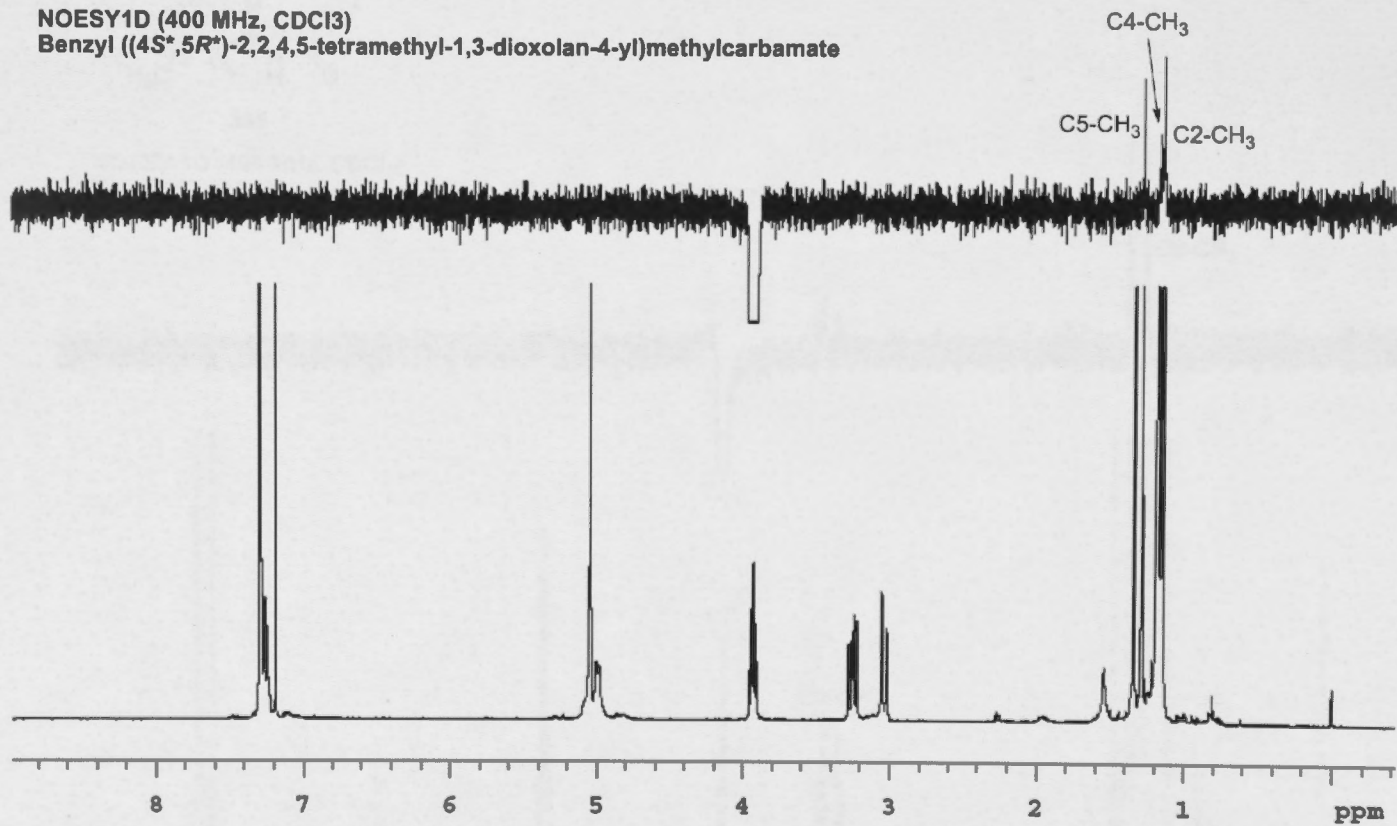
Example of NOESY spectra of acetone 364



364

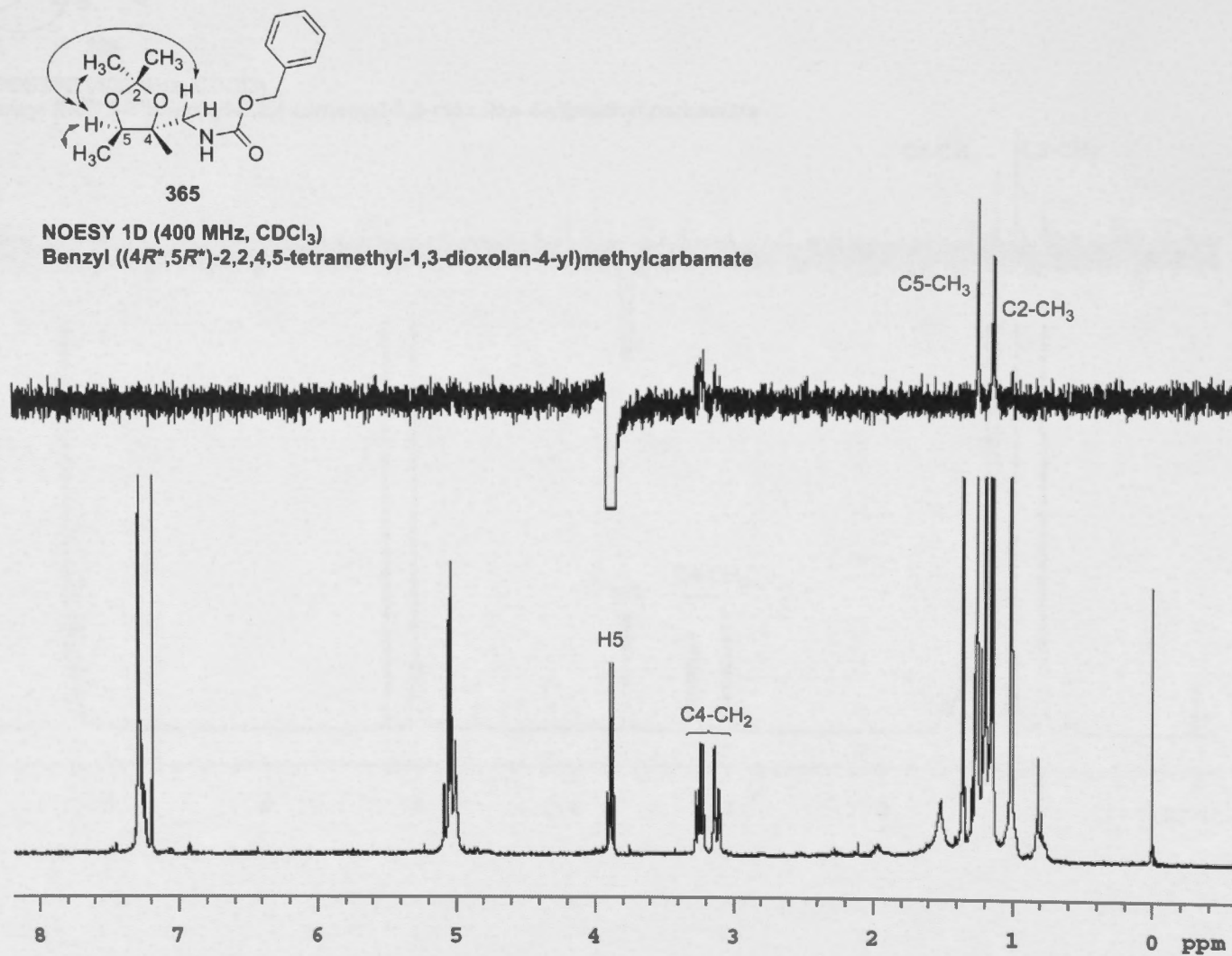
NOESY1D (400 MHz, CDCl₃)

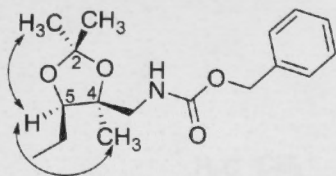
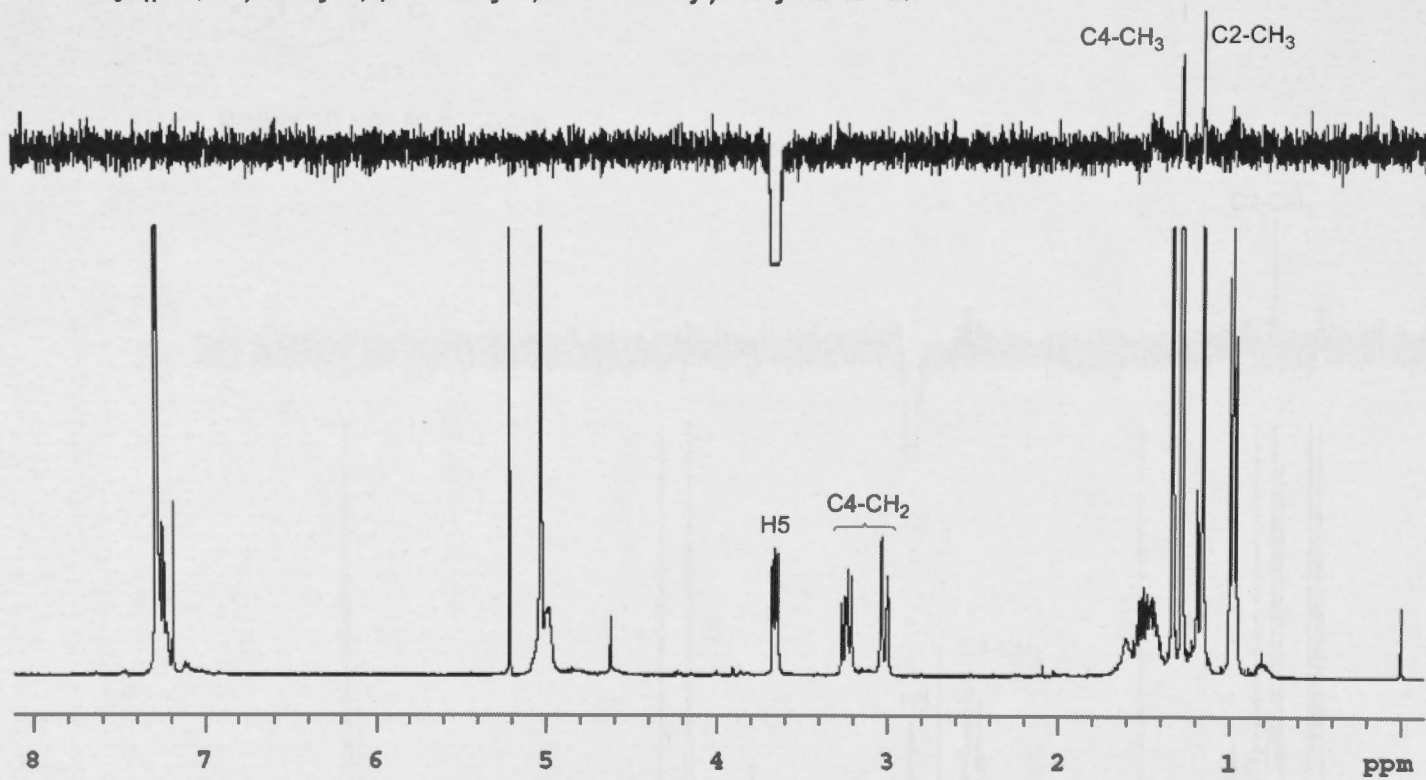
Benzyl ((4*S**,5*R**)-2,2,4,5-tetramethyl-1,3-dioxolan-4-yl)methylcarbamate



Appendix A.4

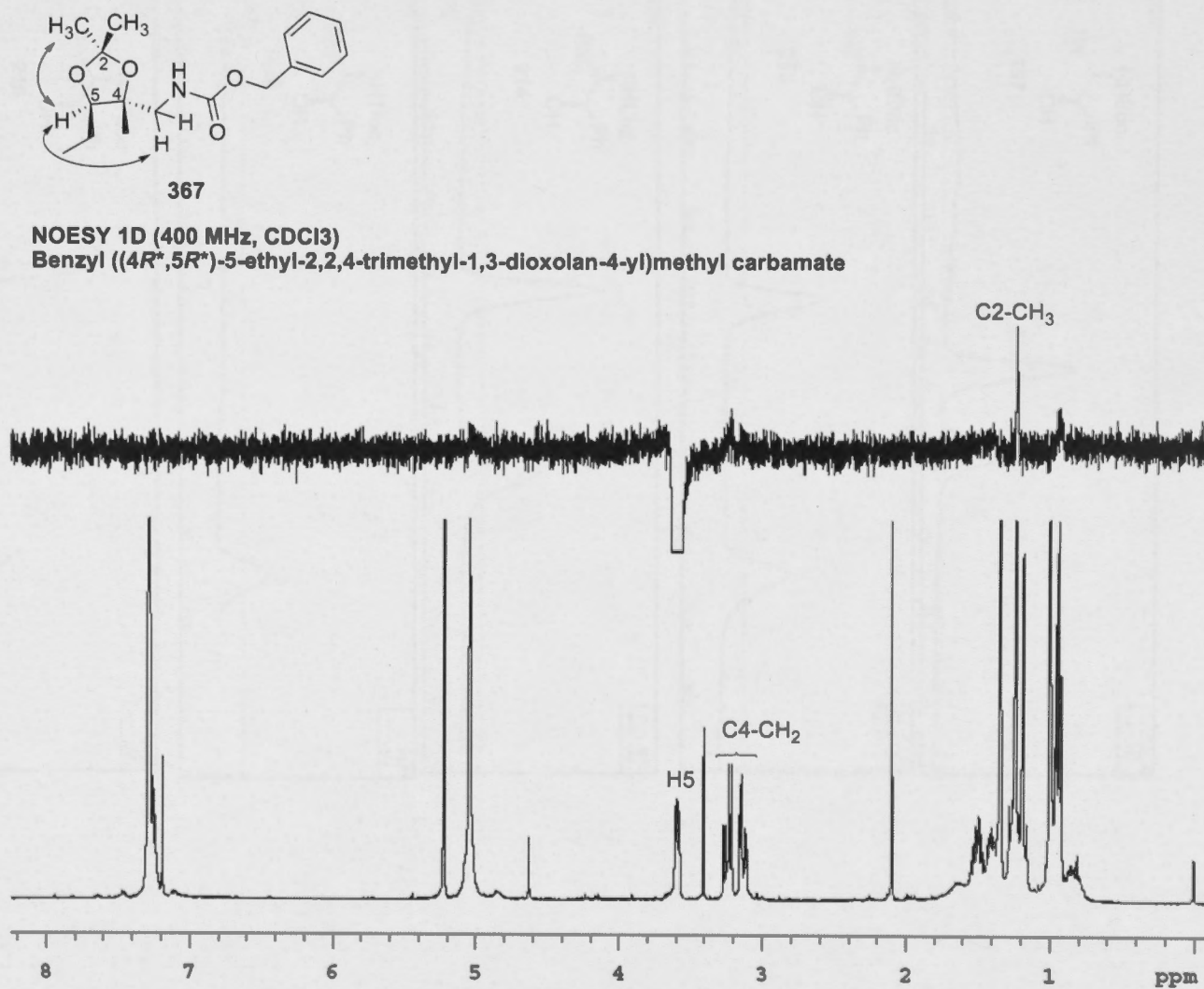
Example of NOESY spectra of acetone 365



NOESY1D (400 MHz, CDCl₃)Benzyl ((4*S**,5*R**)-5-ethyl-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl carbamate

Appendix A.6

Example of NOESY spectra of acetone 367



Appendix A.7

Chromatogram HPLC from evaluation of the second generation preformed nitrogen sources

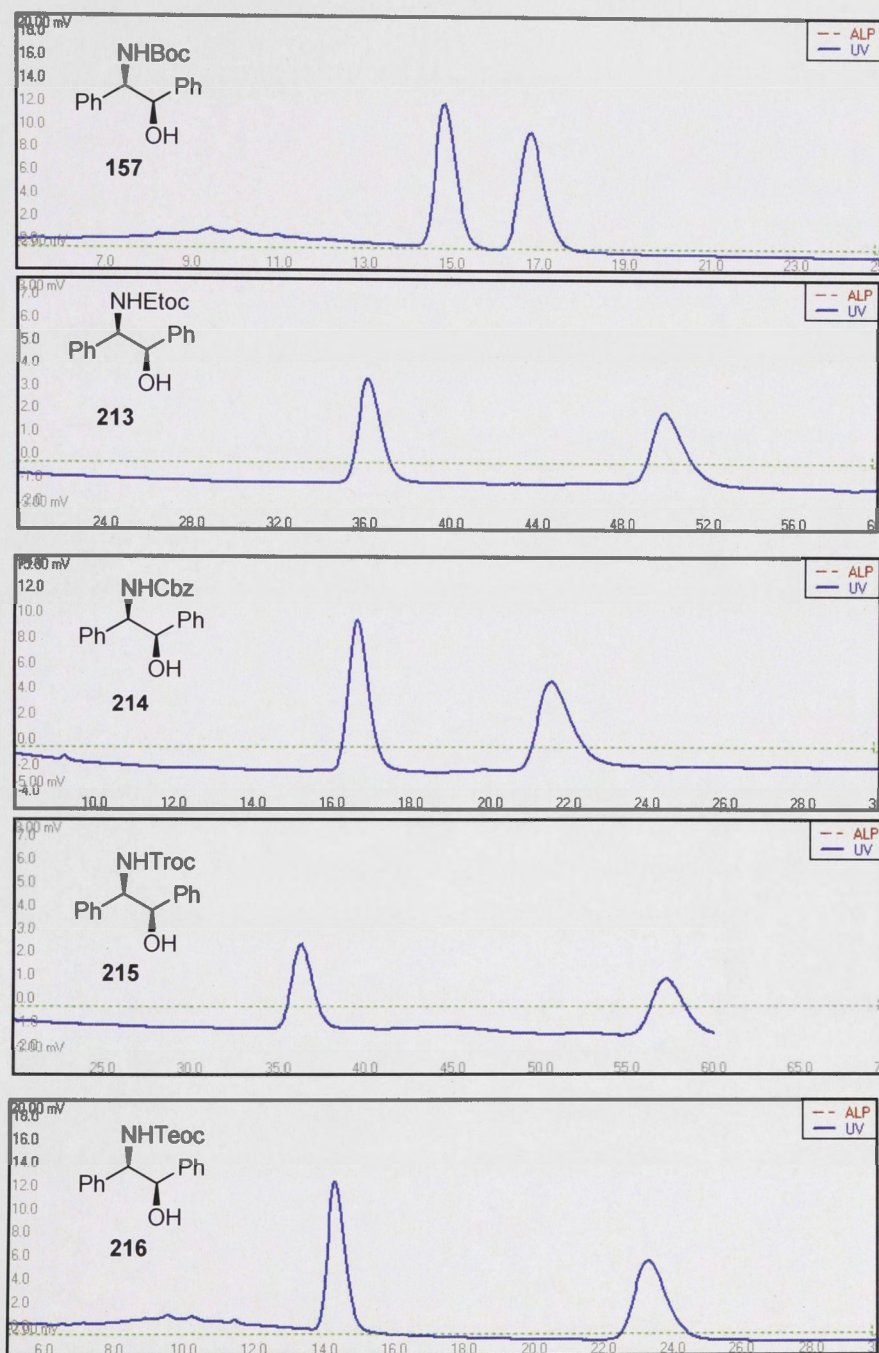


Figure A.5 (HPLC conditions: Chiralpak AS-H, flow rate 1 mL/min, isocratic solvent 10% isopropanol/*n*-hexane).