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

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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:

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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(amine)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
benzyl 202, 2,2,2-trichloroethyl 203, and 2-(trimethylsilyl)ethyl 204 N-(4-toluene-
sulfonyloxy)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.

Benzy l 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         tert-butoxycarbonyl
bp          boiling point
C7          denotes carbon number 7
Cbz         benzzyloxy carbonyl
CDCl$_3$    deuterated chloroform
CDI         1,1'-carbonyldiimidazole
Chloramine-T sodium N-chloro-p-toluene sulfonamide
Chloramine-M sodium N-chloromethanesulfonamide
CN          cyano
δ           chemical shift (ppm)
d           doublet
dd          doublet-doublet
dt          doublet of triplets
(D)-        dextro-rotatory
DMA         dimethyl acetamide
DBI         dibromo isocyanuric acid or 1,3-dibromo-1,3,5-triazine-2,4,6(1H,3H,5H)-trione
DCM         dichloromethane
DHQ         dihydroquinine
DHQD        dihydroquinidine
(DHQ)$_2$PHAL (8α,9R)-(8"α,9"R)-9,9"-[1,4-phthalazinediyi]bis(oxy))bis[10,11-dihydro-6'-methoxycinchonan]
(DHQD)$_2$PHAL 9,9"-[1,4-phthalazinediyi]bis(oxy))bis[10,11-dihydro-6'-methoxy-, (9S)-(9"S)-cinchonan
(DHQ)$_2$AQN 1,4-bis[[8α,9R]-10,11-dihydro-6'-methoxycinchonan-9-yl]oxy]-9,10-anthracenedione
(DHQD)$_2$AQN 1,4-bis[(9S)-10,11-dihydro-6'-methoxycinchonan-9-yl]oxy]-9,10-anthracenedione
DIBOC        di-tert-butyl dicarbonate
2,2-DMP      2,2-dimethoxy propane
d.r.         diastereomeric ratio
El           electron impact
Et           ethyl
EtOAc        ethyl acetate
EtOH         ethanol
EtO          ethoxy
Et$_3$N      triethylamine
<table>
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<tbody>
<tr>
<td>Ether</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>Et₄NOAc</td>
<td>tetraethylammonium acetate</td>
</tr>
<tr>
<td>Etoc</td>
<td>ethoxycarbonyl</td>
</tr>
<tr>
<td>e.e.</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>ESI</td>
<td>electro-spray ionisation</td>
</tr>
<tr>
<td>ESI-MS</td>
<td>electro-spray ionisation-mass spectrometry</td>
</tr>
<tr>
<td>Fmoc</td>
<td>9-fluorenylmethoxycarbonyl</td>
</tr>
<tr>
<td>FTIR</td>
<td>fourier transform infra-red</td>
</tr>
<tr>
<td>GABOB</td>
<td>gamma-aminohydroxybutyric acid</td>
</tr>
<tr>
<td>GCMS</td>
<td>gas chromatography – mass spectrometry</td>
</tr>
<tr>
<td>H6</td>
<td>denotes hydrogen attached at carbon number 6</td>
</tr>
<tr>
<td>Hex</td>
<td>hexyl, hexane</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance/pressure liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
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<td>Hydantoin</td>
<td>1,3-dichloro-5,5-dimethylhydantoin</td>
</tr>
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<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>i-PrOH</td>
<td>isopropanol, 2-propanol</td>
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<tr>
<td>(i-Pr)₂EtN</td>
<td>disopropylethylamine</td>
</tr>
<tr>
<td>IR</td>
<td>infra-red</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant (Hz)</td>
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<tr>
<td>LAH</td>
<td>lithium aluminium hydride</td>
</tr>
<tr>
<td>LRMS</td>
<td>low resolution mass spectrometry</td>
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<tr>
<td>(L)-</td>
<td>levo-rotatory</td>
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<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>M</td>
<td>molarity</td>
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<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
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<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeO</td>
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</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>Mes</td>
<td>mesityl or 2,4,6-trimethylphenyl-</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>m/z</td>
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<tr>
<td>n-ProOH</td>
<td>n-propanol, 1-propanol</td>
</tr>
<tr>
<td>NMR</td>
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</tr>
<tr>
<td>Ns</td>
<td>p-nitrophenylsulfonyl</td>
</tr>
<tr>
<td>NOE</td>
<td>nuclear Overhauser enhancement/effect</td>
</tr>
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<td>nuclear Overhauser enhancement/effect spectroscopy</td>
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<tr>
<td>OH</td>
<td>hydroxyl</td>
</tr>
<tr>
<td>PFP</td>
<td>pentafluorophenyl</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>pH</td>
<td>degree of acidity</td>
</tr>
<tr>
<td>PHAL</td>
<td>phthalazaine</td>
</tr>
<tr>
<td>PMB</td>
<td>p-methoxybenzyl</td>
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<td>PNB</td>
<td>p-nitrobenzyl</td>
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<tr>
<td>PNP</td>
<td>p-nitrophenyl</td>
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<tr>
<td>Pr</td>
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<tr>
<td>ppm</td>
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</tr>
<tr>
<td>ppb</td>
<td>parts per billion</td>
</tr>
<tr>
<td>PF₆⁻</td>
<td>hexafluorophosphate anion</td>
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pyr
q
qn
QN
RT
Rh₄(tpa)₄
(R)
(R̃)
R
s
(S)
(S̃)
t
TA
Teoc
Troc
tᵣ
Ts
BuOH
TsCl
t-BuOCl
TBDMS
TBS
tpa
Tf
THF
μm
v/v

pyridine
quartet
quintet
quinine
room temperature
rhodium(II) triphenylacetate dimer
R- absolute configuration
R- relative configuration
alkyl group
singlet
S- absolute configuration
S- relative configuration
triplet
tethered aminohydroxylation reaction
2-trimethylsilylethoxycarbonyl
2,2,2-trichloroethoxycarbonyl
retention time
tosyl, toluenesulfonyl
 tert-butylalcohol
tosyl chloride, p-toluenesulfonyl chloride
tert-butyl hypochlorite
 tert-butyldimethylsilyl
tert-butyldimethylsilyl
 triphenylacetate
 triflate
tetrahydrofuran
micrometer, micron
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](image)

This methodology has been an ongoing focus of development\(^4,5\) and organic synthesis\(^6\) 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), benzylxycarbonyl (Cbz), and 2-(trimethylsilyl)ethoxy-carbonyl (Teoc). On the other hand, the osmium-catalysed aminohydroxylation reaction which affords racemic amino alcohol products is a ligand-independent reaction. 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 \( \alpha,\beta \)-unsaturated amide and \( \alpha,\beta \)-unsaturated carboxylic acid 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 \( \text{syn} \)-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. The key step is \( \text{syn} \) or suprafacial addition of nitrogen and oxygen to the double bond of an alkene (Figure 1.2). Reddy and coworkers proposed that the imidotrioxoosmium(VIII)-ligand complex added to the alkenes in a stepwise manner starting with a [2+2] cycloaddition process at the more electrophilic osmium center. Formation of osmaazetidine was favoured and an irreversible migration gave osmium(VI) azaglycolate. Similarly, Sharpless and coworkers also reported a [2+2] cycloaddition to form osmaazetidine from imidotrioxoosmium(VIII) and an alkene. Coordination between the ligand and osmaazetidine formed species which could trigger rearrangement giving osmium(VI) azaglycolate. 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.
On the other hand, a [3+2] mechanism was proposed by Janda and coworkers. The formation of complex 5 which exists in equilibrium with the imidotrioxyosmium(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 Criegee 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. 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, and also ligand/substrate interaction controlling the regioselectivity via transition state 6. Recently, a computational investigation reported by Strassner and coworkers 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 imidotrioxyosmium(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 coworkers\(^{17}\) and illustrated in (Figure 1.3).

![Diagram](image)

**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](image)

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 coworkers\textsuperscript{17} 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](image)

A different aspect of chemoselectivity involves the formation of by-products. McLeod and coworkers\textsuperscript{24} reported that employing standard conditions for the AA reaction\textsuperscript{2} 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](image)

The enantioselectivity\textsuperscript{3,5,7} of the AA reaction can be controlled in similar manner to the AD reaction\textsuperscript{7,13,14,28,29} by applying ligands such as (DHQD)\textsubscript{2}PHAL, (DHQD)\textsubscript{2}AQN, (DHQ)\textsubscript{2}PHAL\textsubscript{,} and (DHQ)\textsubscript{2}AQN (Figure 1.7). Furthermore these ligands also exert some control over the regioselectivity\textsuperscript{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 coworkers\textsuperscript{3} 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 coworkers\(^\text{17}\) (Figure 1.3), enantioselectivity can be achieved by controlling the addition step the AA reaction that operates in the primary catalytic cycle (B). The imidotrioxosmium(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.

The Sharpless mnemonic\(^\text{7,13}\) (Figure 1.7) has been reported to predict the enantiofacial selectivity of the AD reaction using ligand such as (DHQD)$_2$PHAL, (DHQD)$_2$AQN, (DHQ)$_2$PHAL, and (DHQ)$_2$AQN. These ligands were also observed have similar effects on the AA reaction. Dihydroquinidine ligands such as (DHQD)$_2$PHAL and (DHQD)$_2$AQN induce addition to the $\beta$-face of alkenes. Dihydroquinine ligands such as
(DHQ)$_2$PHAL and (DHQ)$_2$AQN favour the addition to the $\alpha$-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 coworkers$^{21}$ 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)$_2$PHAL gave the terminal alcohol 30 as the major product, whereas the anthraquinone ligand (DHQD)$_2$AQN afforded the terminal amine 29 as the major product. The enantiomeric product ent-30 was afforded using (DHQ)$_2$PHAL 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.
Until recent times, the R-N-group was mostly constructed from an alkyl amines,$^{27,31,32}$ alkyl and aryl sulfonamides,$^{8,10,26,33}$ car bamates,$^{2,15,16,34,35}$ 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-argentocar bamates.$^{34,38}$

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 imidotrioxyo osmium species. For example tert-butylimino-trioxoosmium 32 can be prepared from tert-butylamine 31 with equimolar osmium tetroxide using olefin-free pentane solvent$^{27}$ (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 alcohol$^{31}$ 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 solvent\(^{27}\) (Table 1.1)

<table>
<thead>
<tr>
<th>Olefins</th>
<th>Product</th>
<th>Solvent</th>
<th>Yield amino alcohol</th>
<th>Yield diol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph(\equiv)</td>
<td>HO(\bigg\angle)NHR(_1)</td>
<td>CH(_2)Cl(_2)</td>
<td>92%(^a)</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ph(\equiv)</td>
<td>HO(\bigg\angle)NHR(_2)</td>
<td>CH(_2)Cl(_2)</td>
<td>62%(^b)</td>
<td>-</td>
</tr>
<tr>
<td>39</td>
<td>R(<em>1)HN(\bigg\angle)OH(\bigg\angle)O(</em>\text{Me})</td>
<td>CH(_2)Cl(_2)</td>
<td>0%</td>
<td>78%</td>
</tr>
<tr>
<td>40</td>
<td>R(<em>1)HN(\bigg\angle)O(</em>\text{Me})</td>
<td>Pyridine</td>
<td>38%(^a)</td>
<td>45%</td>
</tr>
</tbody>
</table>

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\textsuperscript{8,10} is also known as sodium \textit{N}-chloro-\textit{p}-toluenesulfonamide\textsuperscript{39 41}, and is inexpensive and commercially available. Reaction of chloramine-T trihydrate with alkenes and a catalytic amount of osmium tetroxide afforded hydroxy \textit{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 (\textit{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\textsuperscript{8,10} (Figure 1.11)

![Figure 1.11](image)

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 derivatives\textsuperscript{10} (ArSO\textsubscript{2}NCINa) were also introduced, such as phenyl, \textit{o}-toluene, \textit{p}-chlorophenyl, \textit{p}-nitrophenyl, and \textit{o}-carboalkoxyphenyl \textit{N}-chloro sulfonamide.

1.4.2.3 \textit{N}-Chloro-\textit{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 acetonitrile\textsuperscript{34} (Figure 1.12).

\[
\begin{align*}
\text{R} & : \text{i-Bu 43, i-Pr 44, Et 45, Bn 46, menthyl 47, bornyl 48} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Olefins</th>
<th>Reaction Time</th>
<th>Yield amino alcohol product (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Styrene, 49</td>
<td>2 h</td>
<td>Major: 68.5, Minor: 12</td>
</tr>
<tr>
<td>1-Decene, 50</td>
<td>6 h</td>
<td>Major: 61, Minor: 9</td>
</tr>
<tr>
<td>(E)-stilbene, 51</td>
<td>10 h</td>
<td>Major: 87, Minor: 9</td>
</tr>
<tr>
<td>Dimethyl fumarate, 52</td>
<td>10 h</td>
<td>Major: 51, Minor: 9</td>
</tr>
</tbody>
</table>

*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.\textsuperscript{34}

Some N-chloro-N-metalloocarbamate\textsuperscript{35} derivatives also have been developed using various metal salts such as HgCl\textsubscript{2}, Hg(NO\textsubscript{3})\textsubscript{2}, Hg(OAc)\textsubscript{2}, AgNO\textsubscript{3}, Zn(OAc)\textsubscript{2}, Cd(OAc)\textsubscript{2}, Cd(NO\textsubscript{3})\textsubscript{2}, Cu(OAc)\textsubscript{2}, Zn(NO\textsubscript{3})\textsubscript{2}, CdCl\textsubscript{2}, and ZnCl\textsubscript{2}.

**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\textsuperscript{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 Sharpless\textsuperscript{40} 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,\textsuperscript{37} tethered-nitrogen sources developed by Donohoe and coworkers\textsuperscript{41} including sulfamate ester and sulfanylamide derived nitrogen sources by Kenworthy and Taylor,\textsuperscript{42} and very recently alkyl N-(4-chlorobenzoyloxy)carbamate nitrogen sources\textsuperscript{43} and alkyl N-(2,4,6-trichlorobenzoyloxy)carbamate\textsuperscript{44} nitrogen sources that appeared during the course of this study.

1.4.3.1 \textit{N}-Halogenated sulfonamide nitrogen sources: Chloramine-T, and -M

Chloramine-T\textsuperscript{45} \textsuperscript{41} was the first \textit{N}-halogenated sulfonamide tested in the catalytic asymmetric aminohydroxylation reaction by Sharpless and coworkers,\textsuperscript{3} followed soon after by chloramine-M, \textsuperscript{53}\textsuperscript{26}. Chloramine-T was easily prepared and isolated while chloramine-M or sodium \textit{N}-chloro-methanesulfonamide can be generated \textit{in-situ} from methanesulfonamide with an equimolar amount of sodium hydroxide using chlorinating reagent \textit{tert}-butyl hypochlorite.\textsuperscript{46}

![Figure 1.13](image)

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\textsuperscript{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.\textsuperscript{26}

Other variants of this class of nitrogen sources have been reported such as 2-(trimethylsilyl)ethyl sulfonamide\textsuperscript{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](image)

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 product \(^{50}\) (Figure 1.15).

\[
\begin{align*}
\text{Ar} & \xrightarrow{\text{RNH}_2, \text{NaOH}, \text{t-BuOCl}} \text{Ar} \xrightarrow{\text{OH}} \text{Ar} \\
59 \text{ Ar} = \rho\text{-nitrophenyl} \\
\text{Yield} & \quad \text{Regio} & \quad \text{ee} & \quad \text{ee} \\
44\% & \quad 1:1 & 25\% & \text{ (60) 38\% (61)} \\
66\% & \quad 7:3 & 57\% & \text{ (62) 68\% (63)} \\
\end{align*}
\]

**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**

<table>
<thead>
<tr>
<th>Olefins</th>
<th>Major product</th>
<th>Regioselectivity</th>
<th>Yield (e.e.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph(\text{CO}_2\text{iPr})</td>
<td>NHAc</td>
<td>(\text{Ph} \xrightarrow{\text{CO}_2\text{iPr}} \text{OH} )</td>
<td>&gt;20 : 1</td>
</tr>
<tr>
<td>Ph(\text{Ph})</td>
<td>NHAc</td>
<td>(\text{Ph} \xrightarrow{\text{Ph}} \text{OH} )</td>
<td>-</td>
</tr>
</tbody>
</table>

Conditions: Olefin (1.0 equiv.) AcNHBr (1.1 equiv), LiOH (1.02 equiv.), \(\text{K}_2\text{OsO}_2\text{(OH)}_4\) (4.0 mol%), (DHQ)\(_2\)PHAL (5.0 mol%), tert-BuOH/H\(_2\)O (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 amides 51 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-Bromobutryramide 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.

![Reaction Scheme](image)

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

Figure 1.16
1.4.3.4 Heterocyclic nitrogen sources

In order to develop an improved strategy for accessing adenosine derivatives, Sharpless and coworkers\textsuperscript{53} 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)$_2$PHAL 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](image)

Figure 1.17

![Figure 1.18](image)

Figure 1.18
Previously, the nitrogen source generated from adenine derivative 76 had been reported by Jerina and coworkers, who applied it to form polycyclic aromatic hydrocarbon (PAH) diol epoxide (DE) adducts 82 and 83. Using racemic substrate 81, and (3.0 equiv.) of nitrogen source generated from adenosine 76, ligand (DHQD)$_2$PHAL and K$_2$OsO$_2$(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. 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)$_2$PHAL (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).

1.4.3.5 Nitrogen sources in the tethered-aminohydroxylation (TA) reaction
This type of nitrogen source was developed by Donohoe and coworkers 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.\textsuperscript{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 hypochlorite\textsuperscript{46} and sodium hydroxide afforded nitrogen source for TA reaction to give oxazolidinone product 95 (Figure 1.20).

\[ \text{R=H} \quad 88 \quad \text{R=Pr} \quad 89 \quad \text{R=Ph} \quad 90 \]

\[ \begin{align*}
88 & \quad \text{R=H} \\
89 & \quad \text{R=Pr} \\
90 & \quad \text{R=Ph}
\end{align*} \]

\[ \begin{align*}
91 & \quad \text{R=H} \\
92 & \quad \text{R=Pr} \\
93 & \quad \text{R=Ph}
\end{align*} \]

\[ \begin{align*}
94 & \quad \text{R=H} \quad 43\% \\
95 & \quad \text{R=Pr} \quad 54\% \\
96 & \quad \text{R=Ph} \quad 61\%
\end{align*} \]

**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-acloyloxy-carbamates.\textsuperscript{57,58} The N-sulfonyloxy carbamate 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.\textsuperscript{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).
Similarly, the \( N \)-acyloxy carbamate nitrogen sources were also prepared in a two step sequence from an allylic alcohols.\(^3^8\) 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).

\[
\text{Figure 1.22}
\]

1.4.3.5.2 Sulfamate ester and sulfonamide nitrogen sources in the TA reaction
The sulfamate ester and sulfonamide tethered-nitrogen sources\(^4^1\) were reported by Kenworthy and Taylor.\(^4^2\) 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). For example, sulfamate ester 104 was afforded in high yield from reaction of but-3-en-1-ol 101 with sulfamoyl chloride in dimethylacetamide. 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 permanganate dihydrate in the presence of di-isopropylethylamine, to give the amino alcohol products 107-109 in good yield as a cyclic sulfamidate.

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, phosphoryloxyl chloride and ammonia. 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. 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)$_2$PHAL ligand, OsO$_4$ catalyst provided low to good yield. The reactions gave two regioisomers with the $\beta$-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.

\[
\begin{align*}
\text{PG} & = \text{Boc} \\
\text{PG} & = \text{Teoc}
\end{align*}
\]

\[
\begin{align*}
\text{131} & \quad \text{132}
\end{align*}
\]

\[
\begin{align*}
\text{133} \xrightarrow{\text{Conditions}} & \quad \text{A} + \text{B} \\
\text{134} & \quad \text{PG} = \text{Boc}, \quad \text{A} \quad 98\% \text{ ee}; \quad \text{A/B} = 3:1 \text{ ratio}, \quad 98\% \text{ yield} \\
\text{135} & \quad \text{PG} = \text{Teoc}, \quad \text{A} \quad 93\% \text{ ee}; \quad \text{A/B} = 1.5:1 \text{ ratio}, \quad 79\% \text{ yield}
\end{align*}
\]

**Conditions:**
- Nitrogen sources (1.4 equiv), K$_2$OsO$_4$(OH)$_4$ (4 mol%), LiOH (1.32 equiv.),
- (i) PG = Boc : (DHQ)$_2$PHAL (6 mol%), n-PrOH:H$_2$O (2:1), 0 °C;
- (ii) PG = Teoc : (DHQ)$_2$PHAL (5mol%), n-PrOH:H$_2$O (1:1)

**Figure 1.26**

Another variant for this type was previously reported in a poster by Klauber et al. and can be found cited in the footnote of the paper by Luxenburger and coworkers. An intermolecular aminohydroxylation was performed using $N$-(2,4,6-trichlorobenzyloxy) 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 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). This side-chain was essential for its biological activity and
practically, could be prepared on a large scale using the AA reaction from commercially available methyl trans-cinnamate\textsuperscript{63} 122 or isopropyl trans-cinnamate\textsuperscript{64} 64 (Figure 1.27).

\[
\begin{align*}
\text{CbzHN} & \quad \text{O}\text{Me} \\
\text{128} & \quad \text{AA reaction} \\
\text{122} & \quad \text{HO} \\
\end{align*}
\]

Paclitaxel 136

\[
\begin{align*}
\text{HOOC} & \quad \text{EtO} \\
\text{137} & \quad \text{AA} \\
\text{138} & \quad \text{NHBOc} \\
\text{140} & \quad \text{NBOc} \\
\text{141} & \quad \text{Fumonisin B}_3 \\
\end{align*}
\]

Steps

Fragment FB\textsubscript{3} 139

In the Mal McLeod research group, the AA reaction has been employed to achieve a synthesis of the C11-C20 fragment of Fumonisins B\textsubscript{3}\textsuperscript{68} 141, a biologically active substance isolated from the fungus Fusarium moniliforme (Sheldon)\textsuperscript{69} (Figure 1.28). The regioselectivity of the AA reaction was studied with (DHQ)\textsubscript{2}PHAL 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 reaction\textsuperscript{2} procedure using \textit{n}-propanol/water (1:1) as a solvent mixture and \textit{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.\textsuperscript{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.\textsuperscript{24} Performing the AA reaction with (\textit{E})-6-(4-methoxyphenoxy)hex-3-en-2-one 22 as substrate using ligand (DHQ)\textsubscript{2}AQN accomplished the α-amino compound 142 as major product with 1:5 regioselectivity and 68%ee. In contrast, by using (DHQ)\textsubscript{2}PHAL 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 \textit{N}-Boc-\textit{L}-acosamine\textsuperscript{70,71} 143 (Figure 1.29).

\[\text{PMPO} \xrightarrow{(\text{i})} \text{AA} \rightarrow \text{PMPO} \quad \text{OH} \quad \text{O} \quad \text{NH} \quad \text{Boc} \quad \text{PMPO} \quad \text{OH} \]

\textbf{Conditions (i) :}
- (DHQ)\textsubscript{2}AQN 142 : 23 (5 : 1), 68%ee
- (DHQ)\textsubscript{2}PHAL 142 : 23 (1 : 20), 97%ee

\textit{N}-Boc-\textit{L}-acosamine 143

\textbf{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 limitations72,73 such as requirement for a large number of different reagents2,7 to generate the nitrogen sources in-situ. Furthermore, chlorination of the AA product24,57,74 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

\[
\begin{align*}
\text{BnOCONH₂ (3.1 equiv.)} & \quad (\text{DHQ})₂\text{PHAL (5.0 mol\%) K₂OsO₂(OH)₄ (4 mol\%) n-PrOH/H₂O, RT} \\
n-\text{BuOCl (3.1 equiv.)} & \quad 90\% \text{ ee} \\
\text{NaOH (3.1 equiv.)} & \quad 1.2 : 1 \\
\end{align*}
\]

**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\textsuperscript{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 \textit{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](image)

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](image)

Another problem relates to the chlorination\textsuperscript{76,77} of the alkene substrates and the AA products in some cases.\textsuperscript{24,74} Chlorination occurs due to the use of chlorinating reagents
such as tert-butyl hypochlorite\textsuperscript{46} or 1,3-dichloro-5,5-dimethylhydantoin\textsuperscript{77} in generating the nitrogen sources. An example of the problems that arise during the standard AA reaction is given in \textbf{Figure 1.32}.\textsuperscript{74} When the substrate 146 was reacted under standard AA reaction conditions, which generated the nitrogen source \textit{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.\textsuperscript{74}

\textbf{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 diastereselectivity 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 Aminoxygenation Reaction: Synthesis, Evaluation and Optimisation

Summary:

This chapter continues an investigation of tert-butyl carbamate-based preformed nitrogen sources for the osmium-catalysed aminoxygenation reaction. The project included (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, water, catalyst and preformed nitrogen source loading, and reaction pH, and (v) conclusion and future work.
Chapter 2

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

Summary

This chapter contains an investigation of \textit{tert}-butyl carbamate-based preformed nitrogen sources for the osmium-catalysed aminohydroxylation reaction. This includes (i) an introduction, (ii) synthesis of \textit{tert}-butyl carbamate-based preformed nitrogen sources, (iii) evaluation of the \textit{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 (vi) conclusion and future work.
2.1 Introduction

The carbamate functional group has been widely used as a protecting group in organic synthesis. It has been used to protect many types of amines, including in amino acid, and carbohydrate synthesis. The ease of deprotection using mild conditions 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. It can also be deprotected selectively in the presence of other ester groups by aqueous phosphoric acid or hydrochloric acid in ethyl acetate.

It has been reported by Sharpless and coworkers 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](image)

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-butyl dicarbonate (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](image)
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.  

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R'</th>
<th>Nitrogen source</th>
<th>Yield</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆F₅CO-</td>
<td>149</td>
<td>67%</td>
<td>0.5 h</td>
</tr>
<tr>
<td>2</td>
<td>ClCH₂CO-</td>
<td>150</td>
<td>85%</td>
<td>4 h</td>
</tr>
<tr>
<td>3</td>
<td>MeSO₂-</td>
<td>151</td>
<td>93%</td>
<td>1.25 h</td>
</tr>
<tr>
<td>4</td>
<td>2,4,6-Me₃C₆H₂SO₂-</td>
<td>152</td>
<td>58%</td>
<td>13 h</td>
</tr>
<tr>
<td>5</td>
<td>4-MeC₆H₄SO₂-</td>
<td>153</td>
<td>71%</td>
<td>17 h</td>
</tr>
<tr>
<td>6</td>
<td>4-NO₂C₆H₄SO₂-</td>
<td>154</td>
<td>51%</td>
<td>3.75 h</td>
</tr>
</tbody>
</table>

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 chloride and 2-chloroacetyl chloride. 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,\textsuperscript{84,88} mesitylsulfonyl chloride,\textsuperscript{86} toluenesulfonyl chloride\textsuperscript{87,89} and 4-nitrobenzenesulfonyl chloride,\textsuperscript{87,90} respectively.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{structure.png}
\caption{Structure of C_{12}H_{10}F_{3}NO_{4} with labeling of selected atoms. Anisotropic displacement ellipsoids show 30\% probability levels. Hydrogen atoms are drawn as circles with small radii.}
\end{figure}

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

\subsection*{2.3 Evaluation of tert-butyl carbamate-based preformed nitrogen sources}
Initial experiments used the simple substrate \textit{trans}-stilbene 51. It was found that the order of addition of the reagents strongly influenced the reaction (\textbf{Figure 2.5}).

In the first attempt a similar procedure to the AA reaction reported by Sharpless and coworkers\textsuperscript{3} was followed, using tert-butanol/water solvent. Preformed nitrogen source tert-butyl \textit{N}-(4-toluenesulfonyloxy)carbamate 153 and ligand (DHQD)$_{2}$PHAL was mixed with \textit{trans}-stilbene 51 and solvent tert-butanol/water (3:1), and finally, K$_{2}$OsO$_{4}$(OH)$_{4}$ catalyst was added. No reaction was observed (\textbf{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 (\textbf{Figure 2.5 (i)}), but \textit{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)$_2$PHAL 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](image)

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.

\[
\begin{array}{cccc}
\text{Nitrogen} & \text{R}^1 & \text{Yield} & \text{Time} & \%e.e.\
\text{source} & & & & \\
149 & \text{C}_6\text{F}_5\text{CO}^- & 71\% & 19 \text{ h} & 8 \\
150 & \text{ClCH}_2\text{CO}^- & 29\% & 24 \text{ h} & 27 \\
151 & \text{MeSO}_2 & 75\% & 4 \text{ h} & 10 \\
152 & 4-\text{MeC}_6\text{H}_4\text{SO}_2^- & 78\% & 30 \text{ h} & 6 \\
153 & 2,4,6-\text{Me}_3\text{C}_6\text{H}_2\text{SO}_2^- & 59\% & 30 \text{ h} & 7 \\
154 & 4-\text{NO}_2\text{C}_6\text{H}_4\text{SO}_2^- & 62\% & 9 \text{ h} & 0 \\
\end{array}
\]

\(\dagger\)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.

![Diagram](image)

**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.
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)$_2$PHAL 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, tert-butanol 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.\textsuperscript{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.\textsuperscript{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 alcohol\textsuperscript{75} 162 (Figure 2.9).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2_9.png}
\caption{Figure 2.9}
\end{figure}

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.\textsuperscript{92} This results in increased diol product.\textsuperscript{75} For carbamate derived nitrogen sources, using solvent mixture of n-propanol/water (1:1) afforded the amino alcohol product in the best yields.\textsuperscript{2} However, in other examples, it is also found that the best chemoselectivity was achieved when using n-propanol/water (2:1).\textsuperscript{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 \textit{N}-(4-chlorobenzoyloxy)carbamate nitrogen sources.\textsuperscript{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.

![Chemical Structures](image)

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

*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)$_2$PHAL (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, the typical procedure requires excess (3.10 equiv.) nitrogen source to obtain a reasonable result. The nitrogen source must be generated with chlorinating reagent tert-butyl hypochlorite (3.05 equiv.) and a base sodium hydroxide (3.05 equiv.) 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.

![Chemical Reaction](image)

**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\textsuperscript{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-M\textsuperscript{17} 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.\textsuperscript{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).

In this work, the nitrogen source and catalyst loading optimisation was carried out using trans-stilbene 51 (1.0 equiv.), (DHQD)$_2$PHAL 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.
<table>
<thead>
<tr>
<th>Nitrogen source</th>
<th>Catalyst</th>
<th>Yield</th>
<th>e.e.</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 equiv.</td>
<td>4.0 mol%</td>
<td>65%</td>
<td>10%</td>
<td>4.5 h</td>
</tr>
<tr>
<td>2 equiv.</td>
<td>4.0 mol%</td>
<td>99%</td>
<td>8.0%</td>
<td>4 h</td>
</tr>
<tr>
<td>3 equiv.</td>
<td>4.0 mol%</td>
<td>89%</td>
<td>7.0%</td>
<td>2 h</td>
</tr>
<tr>
<td>2 equiv.</td>
<td>1.0 mol%</td>
<td>NR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ND&lt;sup&gt;b&lt;/sup&gt;</td>
<td>24 h</td>
</tr>
<tr>
<td>2 equiv.</td>
<td>5.0 mol%</td>
<td>81%</td>
<td>13%</td>
<td>4.25 h</td>
</tr>
<tr>
<td>2 equiv.</td>
<td>10 mol%</td>
<td>68%</td>
<td>10%</td>
<td>2 h</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined from HPLC chromatogram (Chiralcel OD-H, 10% isopropanol/ gradient, 1.0 mL/min). <sup>b</sup>NR= no reaction; ND= 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,\textsuperscript{2,3} which uses 3.1 equivalents of nitrogen source.\textsuperscript{2} However, the low enantioselectivity afforded by these preformed nitrogen sources remained an important limitation.

\begin{center}
\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{Buffer solution} & \textbf{pH} & \textbf{Yield} & \textbf{e.e.} & \textbf{Time} \\
\hline
0.1 M KCl/HCl & 1 & 99.7\% & 1.3\% & 2 h \\
0.1 M Potassium hydrogen phthalate/NaOH & 2 & 71\% & 6.2\% & 4.5 h \\
0.1 M KH$_2$PO$_4$/NaOH & 3 & 75\% & ND\textsuperscript{b} & 6 h \\
0.1 M Borax/NaOH & 4 & 55\% & ND\textsuperscript{b} & 6 h \\
0.1 M NaHCO$_3$/NaOH & 5 & 82\% & 8.8\% & 24 h \\
0.1 M KH$_3$PO$_4$/NaOH & 6 & NR\textsuperscript{a} & ND\textsuperscript{b} & 2 d \\
0.1 M KH$_3$PO$_4$/NaOH & 7 & NR\textsuperscript{a} & ND\textsuperscript{b} & 2 d \\
0.1 M Borax/NaOH & 8 & NR\textsuperscript{a} & ND\textsuperscript{b} & 52 h \\
0.1 M NaHCO$_3$/NaOH & 9 & NR\textsuperscript{a} & ND\textsuperscript{b} & 23 h \\
0.1 M NaHCO$_3$/NaOH & 10 & NR\textsuperscript{a} & ND\textsuperscript{b} & 22 h \\
0.1 M NaHCO$_3$/NaOH & 11 & NR\textsuperscript{a} & ND\textsuperscript{b} & 26.5 h \\
\hline
\end{tabular}
\end{center}

\textsuperscript{a}NR, no reaction; and \textsuperscript{b}ND, 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-(methane-sulfonyloxy)carbamate 151 (2.0 equiv.). In place of water, a buffer pH range 1 to 11 was employed. 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 μm, 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)$_2$PHAL 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 $^1$H-NMR indicated one product formed was tert-butyl carbamate 171 (Figure 2.16).

![Scheme 2.16](image)

### 2.5 Conclusions and future work

In conclusion six tert-butyl carbamate-based preformed nitrogen sources have been synthesised. They are tert-butyl N-(pentafluorobenzoxyloxy)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)$_2$PHAL 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 enantioslectivity, (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.\textsuperscript{5,64,103-106} Since this method was invented in 1975 by Sharpless and coworkers\textsuperscript{27} as a non-asymmetric oxyamination, it has undergone significant development including the introduction of the asymmetric aminohydroxylation reported in 1996.\textsuperscript{2,3} The progress of development of oxyamination chemistry has been recently reviewed.\textsuperscript{24,41,43,73,101,102}

In 2002, Sharpless and coworkers\textsuperscript{102} 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,\textsuperscript{72} and also by Nilov and Reiser in 2002.\textsuperscript{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) reaction\textsuperscript{3} has been discussed. This mechanism is closely correlated to that of the asymmetric dihydroxylation (AD) reaction which had already been well studied.\textsuperscript{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.\textsuperscript{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.\textsuperscript{3,13,107} Many factors are involved in controlling the enantioselectivity of the reaction such as accelerating the hydrolysis of imido-osmium-glycolate complex \textbf{15},\textsuperscript{102} the electronic properties of the substrates,\textsuperscript{108,109} and the pH of the reaction.\textsuperscript{96,97,99,100}

![Diagram](image)

**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.\textsuperscript{12} In some reports, addition of cinchona alkaloid ligands in large excess did not affect the enantioselectivity of induction.\textsuperscript{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 coworkers\textsuperscript{17} the reaction may proceed in the catalytic cycle [C], also known as the secondary catalytic cycle of the aminohydroxylation reaction in some reports.\textsuperscript{5,7,26}
The secondary cycle has been proposed to operate in some reactions, such as that reported by Rubin and Sharpless in 1997\(^9\) (Figure 3.2). The \(\alpha\beta\)-unsaturated amide 172 had been employed as substrate following the procedure for the Sharpless AA reaction\(^3\) 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.

Pringle and Sharpless\(^{11}\) 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 (\textit{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 Sharpless\(^{12}\) in 2001 employed \(\alpha\beta\)-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, Muniz\(^{110}\) 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 chloromine-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.\textsuperscript{102} Hydroxyamino acid ligands such as compound 185 were applied to induce stereoselectivity in the secondary cycle (\textbf{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.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chemfig.png}
\caption{Figure 3.6}
\end{figure}

As shown in \textbf{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.

\textbf{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.,\textsuperscript{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 \textit{L}-threonine 192 i.e. \textit{N}-(4-toluenesulfonyl)\textit{L}-threonine 185, \textit{N}-(4-nitrophenylsulfonyl)\textit{L}-threonine 188, and \textit{N}-(4-methoxyphenylsulfonyl)\textit{L}-threonine 189; one ligand was derived from \textit{L}-serine i.e. \textit{N}-(4-toluenesulfonyl)\textit{L}-serine 190; and one ligand was derived from a diamino acid i.e. \textit{(R),\textit{N},\textit{N'}-bis(4-toluenesulfonyl)propanoic acid 191 (Figure 3.7).}

\[\begin{align*}
185 & \quad \text{R} = 4\text{-Me-PhSO}_2 \\
188 & \quad \text{R} = 4\text{-NO}_2\text{-PhSO}_2 \\
189 & \quad \text{R} = 4\text{-MeO-PhSO}_2
\end{align*}\]

\textbf{Figure 3.7}

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

\[\begin{align*}
&\begin{array}{c}
\text{NH}_2 \\
\text{OH} \\
\text{OH}
\end{array} \quad \text{R-Cl} \\
&\begin{array}{c}
\text{Na}_2\text{CO}_3 \\
\text{H}_2\text{O, EtOAc}
\end{array} \quad \begin{array}{c}
\text{NHR} \\
\text{OH}
\end{array}
\end{align*}\]

\[\begin{align*}
192 & \quad \begin{array}{c}
\text{R} = 4\text{-Me-PhSO}_2 \\
\text{R} = 4\text{-NO}_2\text{-PhSO}_2 \\
\text{R} = 4\text{-MeO-PhSO}_2
\end{array} \\
185 & \quad (71\%) \\
188 & \quad (73\%) \\
189 & \quad (52\%)
\end{align*}\]

\textbf{Figure 3.8}

\textit{N}-(4-Toluenesulfonyl)-\textit{L}-threonine 185 was afforded in high yield (71%) by reaction of \textit{L}-threonine with toluenesulfonyl chloride under basic conditions, following the procedure reported by Roemmele and Rapoport.\textsuperscript{111} The other \textit{L}-threonine derived
ligands 188 and 189 were afforded by similar procedures, and were isolated in good yields.

\[
\begin{array}{c}
\text{X} \quad \text{NH}_2 \\
\text{OH} & \text{NHTs} \\
\text{193} & \text{190} & \text{191}
\end{array}
\]

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 coworkers\(^\text{112}\) 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)\(^\text{113}\) 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.,\(^\text{102}\) 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.\(^\text{102}\)

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, 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.

\[
\begin{align*}
\text{Ligand (5 mol\%)} & \quad \text{K}_2\text{OsO}_2(\text{OH})_4 (1 \text{ mol\%}) \\
\text{TsNNaCl.3H}_2\text{O} (1 \text{ eq.}) & \quad \text{NaHCO}_3 \\
t\text{-BuOH/H}_2\text{O (1:1)} & \\
\end{align*}
\]

Ligands:

\[
\text{NHR} \quad \text{OH} \quad \text{OH} \]

\[
185 \quad R = 4\text{-Me-PhSO}_2 \\
188 \quad R = 4\text{-NO}_2\text{-PhSO}_2 \\
189 \quad R = 4\text{-MeO-PhSO}_2
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield (%)</th>
<th>Ratio (%) (^a)</th>
<th>e.e. (%) (^b)</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>185</td>
<td>64</td>
<td>1 : 2.7</td>
<td>59</td>
<td>48</td>
</tr>
<tr>
<td>2(^c)</td>
<td>185</td>
<td>75(^d)</td>
<td>1 : 2.0</td>
<td>47</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>188</td>
<td>34</td>
<td>1 : 2.8</td>
<td>63</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>189</td>
<td>27</td>
<td>1 : 1.9</td>
<td>63</td>
<td>40</td>
</tr>
</tbody>
</table>

\(^a\) Regioisomer ratio was determined by integration of the \(^1\text{H}\)-NMR spectrum; \(^b\) e.e was calculated from peak area ratio determined by HPLC for each regioisomer; \(^c\) Literature result from Anderson et al.; \(^d\) Percentage 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.\textsuperscript{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.

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield (%)\textsuperscript{a}</th>
<th>e.e. (%)\textsuperscript{b}</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>185</td>
<td>79</td>
<td>0</td>
<td>4 h</td>
</tr>
<tr>
<td>2</td>
<td>188</td>
<td>80</td>
<td>4</td>
<td>18 h</td>
</tr>
<tr>
<td>3</td>
<td>189</td>
<td>78</td>
<td>4</td>
<td>18 h</td>
</tr>
<tr>
<td>4</td>
<td>190</td>
<td>79</td>
<td>0.5</td>
<td>3.5 h</td>
</tr>
<tr>
<td>5</td>
<td>191</td>
<td>80</td>
<td>0.1</td>
<td>18 h</td>
</tr>
<tr>
<td>6</td>
<td>No ligand</td>
<td>82</td>
<td>1</td>
<td>4 h</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Yield was determined from isolated product. \textsuperscript{b}e.e. was calculated from peak area ratio determined by HPLC (Chiralcel OD-H, 10% isopropanol/n-hexane, 1 mL/min).
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 conditions sup 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 stereo-selectivity 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. 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 $[\text{Rh}_2(\text{tpa})_4]$ (0.06 equiv.) to afford carbamate 196 in 80% yield (Figure 4.1).
The reaction occurs through a metal-nitrene intermediate that was generated from \( N \)-\( (4 \)toluenesulfonfylloxy)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 rhodium\(^{87}\) and copper\(^{117,118}\) to give aziridine product 198 and 200, respectively (Figure 4.2).

All these discoveries suggested \( N \)-\( (4 \)toluenesulfonfylloxy)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 arylsulfonfylloxy preformed nitrogen sources were evaluated. They were \textit{tert}-butyl \( N \)-(mesitylsulfonfylloxy)carbamate 152, \textit{tert}-butyl \( N \)-(4-toluenesulfonfylloxy)carbamate 153, and \textit{tert}-butyl \( N \)-(4-nitrophensulfonfylloxy)carbamate 154. Giving consideration to the ease of access from commercial starting materials, simple purification from byproducts,
and stability, 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, and also provide variation in electronic and steric properties. They were tert-butyl 153, ethyl 201, benzyl 202, 2,2,2-trichloroethyl 203, 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](image)

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 $N$-hydroxycarbamate 205, benzyl $N$-hydroxycarbamate 206, 2,2,2-trichloroethyl $N$-hydroxycarbamate 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 diisobutylidicarbonate (DIBOC), meanwhile the ethyl 205 and benzyl $N$-hydroxycarbamates 206 were prepared in high yield from ethyl chloroformate 209 and benzyl chloroformate 210 by reaction with hydroxylamine hydrochloride under basic conditions (Figure 4.5).

![Figure 4.5]

The 2,2,2-trichloroethyl $N$-hydroxycarbamate 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. 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 succinimidyld 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.

![Chemical reaction diagram]

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.

![Chemical reaction diagram with data table]

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

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](image.png)

**Figure 4.8** Structure of C15H15NO3S 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)$_2$PHAL 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.

![Chemical Reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitrogen source</th>
<th>Product</th>
<th>Yield</th>
<th>Time</th>
<th>pH&lt;sub&gt;obs&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>153</td>
<td><img src="image" alt="Product 157" /></td>
<td>78%</td>
<td>20 h</td>
<td>~4</td>
</tr>
<tr>
<td>2</td>
<td>201</td>
<td><img src="image" alt="Product 213" /></td>
<td>42%</td>
<td>3 h</td>
<td>3-4</td>
</tr>
<tr>
<td>3</td>
<td>202</td>
<td><img src="image" alt="Product 214" /></td>
<td>61%</td>
<td>5 h</td>
<td>~3</td>
</tr>
<tr>
<td>4</td>
<td>203</td>
<td><img src="image" alt="Product 215" /></td>
<td>80%</td>
<td>6 h</td>
<td>~3</td>
</tr>
<tr>
<td>5</td>
<td>204</td>
<td><img src="image" alt="Product 216" /></td>
<td>50%</td>
<td>24 h</td>
<td>~3</td>
</tr>
</tbody>
</table>

Note: Boc = *tert*-butyloxy 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$R^*,2R^*$)-2-hydroxy-1,2-diphenylethylcarbamate$^{127}$ 157 and 2,2,2-trichloroethyl (1$R^*,2R^*$)-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$R^*,2R^*$)-2-hydroxy-1,2-diphenylethylcarbamate 216 and benzyl (1$R^*,2R^*$)-2-hydroxy-1,2-diphenylethylcarbamate$^2$ 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$R^*,2R^*$)-2-hydroxy-1,2-diphenylethylcarbamate$^{35}$ 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 reaction$^2$ 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$R^*,2R^*$)-2-hydroxy-1,2-diphenylethylcarbamate$^2$ 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.

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Nitrogen source</th>
<th>Yield (%)</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-BuOH/H₂O</td>
<td>4 mol%</td>
<td>2.0 equiv.</td>
<td>61%</td>
<td>5 h</td>
</tr>
<tr>
<td>2</td>
<td>n-PrOH/H₂O</td>
<td>4 mol%</td>
<td>1.2 equiv.</td>
<td>62%</td>
<td>17.5 h</td>
</tr>
<tr>
<td>3</td>
<td>MeCN/H₂O</td>
<td>4 mol%</td>
<td>1.2 equiv.</td>
<td>80%</td>
<td>17 h</td>
</tr>
<tr>
<td>4</td>
<td>DCM/H₂O</td>
<td>4 mol%</td>
<td>1.2 equiv.</td>
<td>NR³</td>
<td>4 d</td>
</tr>
<tr>
<td>5</td>
<td>MeCN/H₂O</td>
<td>4 mol%</td>
<td>2.0 equiv.</td>
<td>81%</td>
<td>4 h</td>
</tr>
<tr>
<td>6</td>
<td>MeCN/H₂O</td>
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<td>1.0 equiv.</td>
<td>71%</td>
<td>5 h</td>
</tr>
<tr>
<td>7</td>
<td>MeCN/H₂O</td>
<td>2 mol%</td>
<td>1.0 equiv.</td>
<td>71%</td>
<td>9 h</td>
</tr>
<tr>
<td>8</td>
<td>MeCN/H₂O</td>
<td>1 mol%</td>
<td>1.0 equiv.</td>
<td>88%</td>
<td>14 h</td>
</tr>
<tr>
<td>9</td>
<td>MeCN/H₂O</td>
<td>0.1 mol%</td>
<td>1.0 equiv.</td>
<td>55%</td>
<td>4 d</td>
</tr>
</tbody>
</table>

Note: *NR, 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 (1R⁺,2R⁺)-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 K₂OsO₂(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-toluenesulfonyleoxy)carbamate 202 (1.2 equiv.) as nitrogen source, K₂OsO₂(OH)₄ catalyst (1.0 mol%), acetonitrile-buffer (3:1). Results of this study are presented in Figure 4.11.

![Chemical structure of reactions](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Buffer solution</th>
<th>pH</th>
<th>Yield</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5 M Potassium</td>
<td>3a</td>
<td>88%</td>
<td>14 h</td>
</tr>
<tr>
<td>2</td>
<td>hydrogen phthalate/NaOH</td>
<td>4</td>
<td>94%</td>
<td>10 h</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>5</td>
<td>88%</td>
<td>10 h</td>
</tr>
<tr>
<td>4</td>
<td>0.5 M KH₂PO₄/NaOH</td>
<td>6</td>
<td>80%</td>
<td>7.5 h</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>7</td>
<td>35%</td>
<td>5 h</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>8a</td>
<td>56%</td>
<td>1.5 h</td>
</tr>
<tr>
<td>7</td>
<td>0.5 M Borax/HCl</td>
<td>9a</td>
<td>53%</td>
<td>1.5 h</td>
</tr>
<tr>
<td>8</td>
<td>0.5 M Borax/NaOH</td>
<td>10a</td>
<td>16%</td>
<td>5 h</td>
</tr>
<tr>
<td>9</td>
<td>0.5 M NaHCO₃/NaOH</td>
<td>11a</td>
<td>20%</td>
<td>5 h</td>
</tr>
</tbody>
</table>

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

**Figure 4.11**

It was observed that the preformed nitrogen source benzyl *N*-(4-toluenesulfonyleoxy)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)$_2$PHAL 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 (1R$^*$,2R$^*$)-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.

\[
\begin{align*}
\text{Ph} & \quad \text{See table N-source 202 (1.2 eq.),} \\
\text{Ph} & \quad K_{2}O_{3}O_{2}(OH)_{4} (1.0 \text{ mol%)},} \\
\text{Ph} & \quad \text{MeCN/H}_{2}O (3:1) \text{, RT} \\
\text{Ph} & \quad \text{NHCbz} \\
\text{Ph} & \quad \text{214}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (^a)</th>
<th>Buffer</th>
<th>Yield</th>
<th>Time</th>
<th>e.e. (%) (^b)</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>(DHQD)(_2)PHAL</td>
<td>pH 9</td>
<td>41%</td>
<td>6 h</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>(DHQD)(_2)PHAL</td>
<td>NO</td>
<td>93%</td>
<td>24 h</td>
<td>2</td>
</tr>
<tr>
<td>3(^c)</td>
<td>NO</td>
<td>pH 9</td>
<td>54%</td>
<td>7 h</td>
<td>4</td>
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<tr>
<td>4</td>
<td>NO</td>
<td>NO</td>
<td>88%</td>
<td>14 h</td>
<td>2</td>
</tr>
</tbody>
</table>

Note: \(^a\)Ligand quantity (4.0 mol%). \(^b\)Determined from HPLC peak area (Chiralpak AS-H, isocratic 20% isopropanol/n-hexane, 0.7 mL/min). \(^c\)Using 202 (2.0 equiv.).
Figure 4.13 presents the HPLC chromatogram of benzyl (1R*,2R*)-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 independent⁹¹,¹² 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 source⁹⁶,⁹⁷ 202 in a single portion (Figure 4.14).

\[ \text{Conditions:} \]
1. Slow addition with syringe pump BnOCONHOTs 202 (1.2 equiv.)
2. Normal addition BnOCONHOTs 202 (1.2 equiv.)

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.
<table>
<thead>
<tr>
<th>Alkenes</th>
<th>Nitrogen sources</th>
<th>Product (A:B)</th>
<th>Yield</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph(\rightarrow)</td>
<td>BocNHOTs(^{ii})</td>
<td>NH(\rightarrow)OH(\rightarrow)NH(\rightarrow)O(\rightarrow)Boc</td>
<td>83%</td>
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<td>49</td>
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</tr>
<tr>
<td>EtocNHOTs</td>
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<td>NHEt(\rightarrow)OH(\rightarrow)NHEt(\rightarrow)oc</td>
<td>76%</td>
<td>1 h</td>
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<tr>
<td></td>
<td></td>
<td>218</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CbzNHOTs</td>
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<td>NH(\rightarrow)Cbz(\rightarrow)OH(\rightarrow)NHCbz</td>
<td>89%</td>
<td>16 h</td>
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<td>144</td>
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<tr>
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<td>NHTroc(\rightarrow)OH(\rightarrow)NHTroc</td>
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<td>PNPOn(\rightarrow)</td>
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<td>PNPO(\rightarrow)NHTeoc(\rightarrow)OH</td>
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<td>CbzHN(\rightarrow)CO(_2)Me(\rightarrow)OH(\rightarrow)CO(_2)Me</td>
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</tr>
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<td>223</td>
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<td>224</td>
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<td>225</td>
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Continued of Figure 4.15

<table>
<thead>
<tr>
<th>Alkenes</th>
<th>Nitrogen sources&lt;sup&gt;i&lt;/sup&gt;</th>
<th>Product (A:B)</th>
<th>Yield</th>
<th>Time</th>
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</tr>
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<td></td>
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</tr>
<tr>
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<td>(1 : 2.1)</td>
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</tbody>
</table>
Continued of Figure 4.15

<table>
<thead>
<tr>
<th>Alkenes</th>
<th>Nitrogen sources(^i)</th>
<th>Product (A:B)</th>
<th>Yield</th>
<th>Time</th>
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</tr>
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<td>129 234</td>
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<td>CbzNHOT(^{iii})</td>
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<td></td>
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<td></td>
<td>NHCbz</td>
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</tr>
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<td>98 h</td>
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<td>246 247</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Continued of Figure 4.15

<table>
<thead>
<tr>
<th>Alkenes</th>
<th>Nitrogen sources(^i)</th>
<th>Product (A:B)</th>
<th>Yield</th>
<th>Time</th>
</tr>
</thead>
</table>
| \(\text{cis-C}2\)-OH | Troc\text{NHOTs} | \begin{align*} &\text{TrocN}2\text{H}2\text{OH} \quad \text{OH} \quad \text{HO} \quad \text{NH}\text{Troc} \\
 &\text{248} \quad \text{249} \end{align*} | trace | 72 h |
| \(\text{cis-C}2\) | \begin{align*} &\text{Etoc}\text{NHOTs} \quad \text{NHEtoc} \\
 &\text{250} \quad \text{251} \quad \text{252} \end{align*} | 74\% | 14 h |
| \(\text{cis-C}2\) | \begin{align*} &\text{Etoc}\text{NHOTs} \quad \text{NHEtoc} \\
 &\text{253} \quad \text{254} \quad \text{255} \end{align*} | NR | - |
| \(\text{cis-C}2\) | \begin{align*} &\text{Boc}\text{NHOTs}\^{ii} \quad \text{NR}\^{c} \\
 &\text{256} \quad \text{257} \end{align*} | - | - |

Note: (i) Boc\text{NHOTs} = \text{tert-butyl} \(N\)-(4-toluenesulfonyloxy)carbamate \(153\), Etoc\text{NHOTs} = \text{ethyl} \(N\)-(4-toluenesulfonyloxy)carbamate \(201\), Cbz\text{NHOTs} = \text{benzyl} \(N\)-(4-toluenesulfonyloxy)carbamate \(202\), Troc\text{NHOTs} = 2,2,2-trichloroethyl \(N\)-(4-toluenesulfonyloxy)carbamate \(203\), and Teoc\text{NHOTs} = 2-(trimethylsilyl)ethyl \(N\)-(4-toluenesulfonyloxy)carbamate \(204\). (ii) Reaction with Boc\text{NHOTs} was conducted with \text{tert}-butanol/water (3:1). (iii) Reaction with ethyl \text{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 \text{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-toluene-sulfonyloxy)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-toluene-sulfonyloxy)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-toluene-sulfonyloxy)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-toluene-sulfonyloxy) 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-toluene-sulfonyloxy)carbamates 203 gave the product in 80-86% yields. Meanwhile, ethyl 201 and 2-(trimethylsilyl)ethyl N-(4-toluene-sulfonyloxy)carbamates 204 gave somewhat lower yields. One example reaction of preformed nitrogen source benzyl N-(4-toluene-sulfonyloxy)carbamate 202 with dimethylfumarate 52 also gave high yield of the amino alcohol product 242.

Furthermore, reaction of unsymmetrical 1,2-disubstituted alkenes 1H-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 \textbf{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)$_2$PHAL 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 amination$^{115}$ 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-toluenesulfonyl-oxy)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-toluenesulfonyl-oxy)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-toluenesulfonyl-oxy)carbamate 203 with the same alkene 243 showed only traces of the amino alcohol product observed by mass spectrometry (MS).

![Chemical structure](image)

**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-toluenesulfonyl-oxy)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-toluenesulfonyl-oxy)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.\textsuperscript{128-131} Given the mechanistic similarities between the aminohydroxylation\textsuperscript{7} and dihydroxylation\textsuperscript{13,14} reactions, the stereoselectivity of the aminohydroxylation reaction of allylic alcohols suggested itself as worthy of study.

Table 5.1

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Major product</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>R&lt;sub&gt;3&lt;/sub&gt;</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R&lt;sub&gt;1&lt;/sub&gt;O(\text{OR}_2)(\text{OR}_3)</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;O(\text{OR}_2)(\text{OH})</td>
<td>260 Bn</td>
<td>Bn</td>
<td>OH</td>
<td>7 : 1</td>
</tr>
<tr>
<td>(Z)-257-259</td>
<td>261 Bn</td>
<td>Bn</td>
<td>Et</td>
<td>8 : 1</td>
<td></td>
</tr>
<tr>
<td>(Z)-257-259</td>
<td>262 Ac</td>
<td>Ac</td>
<td>Et</td>
<td>2 : 1</td>
<td></td>
</tr>
<tr>
<td>R&lt;sub&gt;1&lt;/sub&gt;O(\text{OR}_2)(\text{OR}_3)</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;O(\text{OR}_2)(\text{OH})</td>
<td>265 Bn</td>
<td>Bn</td>
<td>OH</td>
<td>3 : 1</td>
</tr>
<tr>
<td>(E)-263-264</td>
<td>266 Bn</td>
<td>Bn</td>
<td>Et</td>
<td>6 : 1</td>
<td></td>
</tr>
</tbody>
</table>

*Reaction was carried out under catalytic conditions with OsO<sub>4</sub> (0.05 equiv.), N-methylmorpholine N-oxide (2.0 equiv.), in water-acetone (1:8), RT.*

Kishi and coworkers\textsuperscript{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 \textit{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, Kishi\textsuperscript{128} 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 R\textsubscript{4}. 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,\textsuperscript{128,129} Evans and coworkers\textsuperscript{130} 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>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Ratio (anti : syn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>267 ( R_2 = \text{Et} )</td>
<td>( R_2 = \text{Et (268 : 269)} )</td>
<td>5.1 : 1</td>
</tr>
<tr>
<td>270 ( R_2 = \text{i-Pr} )</td>
<td>( R_2 = \text{i-Pr (271 : 272)} )</td>
<td>17 : 1</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>273 ( R_1 = \text{H} )</td>
<td>( R_1 = \text{H (274 : 275)} )</td>
<td>35 : 1</td>
</tr>
<tr>
<td>276 ( R_1 = \text{Ac} )</td>
<td>( R_1 = \text{Ac (277 : 278)} )</td>
<td>16 : 1</td>
</tr>
<tr>
<td>279 ( R_1 = \text{Si}(\text{t-Bu})\text{Me}_2 )</td>
<td>( R_1 = \text{Si}(\text{t-Bu})\text{Me}_2 (280 : 281) )</td>
<td>6.2 : 1</td>
</tr>
</tbody>
</table>

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 \( R_2 \) 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,\textsuperscript{128} but the trend followed that expected based on the transition-state model proposed by Houk and coworkers,\textsuperscript{132,133} and Vedejs and coworkers.\textsuperscript{134,135}

![Figure 5.3](image)

Houk and coworkers\textsuperscript{132} reported transition-state model\textsuperscript{133} 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 \textit{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 \textit{anti}.

Furthermore, Vedejs and coworkers\textsuperscript{135} 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 (\textit{anti})-289 was afforded from transition-state 288 with the small hydrogen positioned inside, and the alkyl substituent outside. The minor product (\textit{syn})-291 from (Z)-alkenes were proposed following the transition-state 290, where the hydrogen was located inside and alkyl-substituent \textit{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.

![Diagram of alkenes and their reactions](image)

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 regiosomer thus simplifying the task of evaluating diastereoselectivity.

![Diagram of allylic alcohols](image)

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 alcohols\(^{136-140}\) were prepared from a commercially available aldehyde and a Grignard reagent. This was achieved in a one step reaction and in a high yield.

![Reaction mechanism]

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R_1)</th>
<th>(R_2)</th>
<th>(R_3)</th>
<th>Products</th>
<th>Yield</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{CH}_2)(=)</td>
<td>(H)</td>
<td>(\text{Me})</td>
<td>292</td>
<td>74%</td>
<td>2 h</td>
</tr>
<tr>
<td>2</td>
<td>(H)</td>
<td>(\text{Me})</td>
<td>(\text{H}_2\text{C}=-\text{CH})</td>
<td>293</td>
<td>71%</td>
<td>1 h</td>
</tr>
<tr>
<td>3</td>
<td>(\text{Me})</td>
<td>(\text{Me})</td>
<td>(\text{H}_2\text{C}=-\text{CH})</td>
<td>294</td>
<td>65%</td>
<td>15 min</td>
</tr>
<tr>
<td>4</td>
<td>(\text{CH}_2)(=)</td>
<td>(\text{Me})</td>
<td>(\text{Me})</td>
<td>295</td>
<td>84%</td>
<td>30 min</td>
</tr>
<tr>
<td>5</td>
<td>(\text{CH}_2)(=)</td>
<td>(\text{Me})</td>
<td>(\text{Et})</td>
<td>296</td>
<td>100%</td>
<td>1 h</td>
</tr>
<tr>
<td>6</td>
<td>(\text{Me})</td>
<td>(\text{Me})</td>
<td>(\text{CH}_2\text{C}(\text{Me}))</td>
<td>297</td>
<td>71%</td>
<td>15 min</td>
</tr>
<tr>
<td>7</td>
<td>(\text{MeCH}=)</td>
<td>(\text{Me})</td>
<td>(\text{Me})</td>
<td>298</td>
<td>89%</td>
<td>1 h</td>
</tr>
<tr>
<td>8</td>
<td>(\text{MeCH}=)</td>
<td>(\text{Me})</td>
<td>(\text{Et})</td>
<td>299</td>
<td>68%</td>
<td>2 h</td>
</tr>
<tr>
<td>9</td>
<td>(\text{MeCH}=)</td>
<td>(\text{Me})</td>
<td>(\text{i-Pr})</td>
<td>300</td>
<td>91%</td>
<td>2 h</td>
</tr>
<tr>
<td>10</td>
<td>(\text{Me}_2\text{C}=)</td>
<td>(\text{H})</td>
<td>(\text{Me})</td>
<td>301</td>
<td>72%</td>
<td>15 h</td>
</tr>
<tr>
<td>11</td>
<td>(\text{Me}_2\text{C}=)</td>
<td>(\text{H})</td>
<td>(\text{Et})</td>
<td>302</td>
<td>88%</td>
<td>4 h</td>
</tr>
<tr>
<td>12</td>
<td>(\text{Me}_2\text{C}=)</td>
<td>(\text{H})</td>
<td>(\text{i-Pr})</td>
<td>303</td>
<td>71%</td>
<td>15 h</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate R₂ = H</th>
<th>R₁</th>
<th>R₂</th>
<th>Product</th>
<th>Yield</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Ac</td>
<td></td>
<td>304</td>
<td>36%ᵃ</td>
<td>15 h</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>Ac</td>
<td></td>
<td>305</td>
<td>87%ᵃ</td>
<td>1 h</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>Ac</td>
<td></td>
<td>306</td>
<td>84%ᵃ</td>
<td>45 min</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>Ac</td>
<td></td>
<td>307</td>
<td>100%ᵃ</td>
<td>1 h</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>Bn</td>
<td></td>
<td>308</td>
<td>39%ᵇ</td>
<td>1 h</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>PMB</td>
<td></td>
<td>309</td>
<td>10%ᶜ</td>
<td>16 h</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>TBS</td>
<td></td>
<td>310</td>
<td>31%ᵈ</td>
<td>15 h</td>
</tr>
<tr>
<td>8</td>
<td>Et</td>
<td>Ac</td>
<td></td>
<td>311</td>
<td>41%ᵃ</td>
<td>15 min</td>
</tr>
<tr>
<td>9</td>
<td>Et</td>
<td>PMB</td>
<td></td>
<td>312</td>
<td>67%ᶜ</td>
<td>24 h</td>
</tr>
<tr>
<td>10</td>
<td>i-Pr</td>
<td>Ac</td>
<td></td>
<td>313</td>
<td>58%ᵃ</td>
<td>15 min</td>
</tr>
<tr>
<td>11</td>
<td>i-Pr</td>
<td>PMB</td>
<td></td>
<td>314</td>
<td>25%ᶜ</td>
<td>48 h</td>
</tr>
<tr>
<td>12</td>
<td>Et</td>
<td>Bn</td>
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<td>1 h</td>
</tr>
<tr>
<td>13</td>
<td>Et</td>
<td>TBS</td>
<td></td>
<td>316</td>
<td>97%ᵈ</td>
<td>6 h</td>
</tr>
<tr>
<td>14</td>
<td>i-Pr</td>
<td>Bn</td>
<td></td>
<td>317</td>
<td>53%ᵇ</td>
<td>48 h</td>
</tr>
</tbody>
</table>

Note: ᵃAc₂O (2.0 equiv. or as determined), Et₃N (2.0 equiv. or as determined); ᵄBnBr (2.0 equiv. or as determined), NaH (4.0 equiv. or as determined), TBAI, DMF; ᵅPMBCl (1.2 equiv. or as determined), NaH (4 equiv. or as determined), DCM or DMF; ᵆTBSCl (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-butyltrimethylsilyl, 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-butyltrimethylsilyl 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>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (anti:syn)</th>
<th>Time</th>
</tr>
</thead>
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<td>1</td>
<td></td>
<td>OH</td>
<td>OH</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>292</td>
<td>NHCbz</td>
<td>OH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OH</td>
<td>NHCbz</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>OH</td>
<td>OH</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>293</td>
<td>NHCbz</td>
<td>OH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OH</td>
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<td>73%</td>
</tr>
<tr>
<td></td>
<td>294</td>
<td>NHCbz</td>
<td>OH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OH</td>
<td>NHCbz</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>OAc</td>
<td>OAc</td>
<td>53%</td>
</tr>
<tr>
<td></td>
<td>304</td>
<td>NHCbz</td>
<td>OAc</td>
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<td>NHCbz</td>
<td></td>
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<td>OAc</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td>305</td>
<td>NHCbz</td>
<td>OAc</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OAc</td>
<td>NHCbz</td>
<td></td>
</tr>
<tr>
<td>6</td>
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<td>OAc</td>
<td>68%</td>
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<tr>
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<td>306</td>
<td>NHCbz</td>
<td>OAc</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OAc</td>
<td>NHCbz</td>
<td></td>
</tr>
</tbody>
</table>

Reaction conditions: Allylic alcohol (1.0 equiv.), K<sub>2</sub>O<sub>2</sub>SO<sub>4</sub>(OH)<sub>4</sub> (4.0 mol%), BnOCONHOTs 202 (1.2 equiv.), MeCN/H<sub>2</sub>O (3:1), RT. <sup>a</sup>Ratio was determined from integration of <sup>1</sup>H-NMR. <sup>b</sup>Ratio 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 coworkers\textsuperscript{130} who investigated the dihydroxylation reaction catalysed by osmium tetroxide with 1,1-disubstituted alkenes as substrates. In addition, it was also reported\textsuperscript{130} that acetyl-protection of the allylic alcohol decreased the stereoselectivity.
The major anti-product for these reactions seemed consistent with the Houk\textsuperscript{132} transition-state model for the dihydroxylation reaction catalysed by osmium tetroxide, where steric effects control the diastereoselectivity. This model positions the alkylgroups (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 coworkers\textsuperscript{135} could also explain this trend in diastereoselectivity. The terminal monosubstituted alkenes would resemble the (E)-alkenes of Vedejs model,\textsuperscript{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 ((4S\text{*},5R\text{*})-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 (pTSA)
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.

![Chemical structure](image)

**Figure 5.8**

In similar way, the diol 319 could also be converted to benzyl ((4R*,5R*)-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).

![Chemical structure](image)

**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.
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-yl)oxy)silane 310, which did not react. The lowest yield was afforded with 1-((2,4-dimethylpent-1-en-3-yl)oxy)methyl)-4-methoxybenzene 314 (17%), and the highest yield was afforded with ((3-methylbut-3-en-2-yl)oxy)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-yl)oxy)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-yl)oxy)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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product$^a$</th>
<th>Yield (anti:syn)</th>
<th>Time</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>OH 295</td>
<td>OH NHCbz</td>
<td>44%</td>
<td>96 h</td>
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<td></td>
<td></td>
<td>OH 341</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OH 342</td>
<td>2.3:1$^{ab}$</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>OH 296</td>
<td>OH NHCbz</td>
<td>40%</td>
<td>7 d</td>
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<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td>OH 344</td>
<td>2.7:1$^{ab}$</td>
<td></td>
</tr>
<tr>
<td>3</td>
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<td>-</td>
<td>7 d</td>
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<td>OAc NHCbz</td>
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</tr>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OAc 346</td>
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</tr>
<tr>
<td>5</td>
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<td>-</td>
<td></td>
</tr>
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<td>OAc 307</td>
<td>OAc NHCbz</td>
<td>68%</td>
<td>66 h</td>
</tr>
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<td></td>
<td></td>
<td>OAc 347</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td>OAc 348</td>
<td>2.5:1$^{bc}$</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>OAc 311</td>
<td>OAc NHCbz</td>
<td>75%</td>
<td>17 h</td>
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<td></td>
<td></td>
<td>OAc 349</td>
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<td></td>
</tr>
<tr>
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<td></td>
<td>OAc 350</td>
<td>2.8:1$^{bc}$</td>
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</tr>
<tr>
<td>8</td>
<td>OAc 313</td>
<td>OAc NHCbz</td>
<td>32%</td>
<td>7 d</td>
</tr>
<tr>
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<td></td>
<td>OAc 351</td>
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</tr>
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<td>OAc 352</td>
<td>3.4:1$^{bc}$</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>OPMB 309</td>
<td>PMBO NHCbz</td>
<td>69%</td>
<td>15 h</td>
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<tr>
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<td></td>
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<td></td>
<td></td>
<td>PMBO 354</td>
<td>2.6:1$^{ab}$</td>
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</tr>
<tr>
<td>10</td>
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<td>PMBO NHCbz</td>
<td>44%</td>
<td>96 h</td>
</tr>
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<td></td>
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</tr>
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<td></td>
<td>PMBO 356</td>
<td>4.9:1$^{ab}$</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>OPMB 314</td>
<td>OPMB NHCbz</td>
<td>17%</td>
<td>8 d</td>
</tr>
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</tr>
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<td></td>
<td>OPMB 358</td>
<td>12.1:1$^{ab}$</td>
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</table>

$^a$Reaction conditions: substrate (1.0 equiv.), BnOCONHOTs 202 (1.2 equiv.), K$_2$OsO$_2$(OH)$_4$ (4.0 mol%), MeCN/H$_2$O (3:1), RT. $^b$Diastereomers were determined from $^1$H-NMR integration. $^c$Diastereomers were determined from isolated product.
This similar phenomenon has also been reported by Evans and coworkers\textsuperscript{130} 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 \textit{anti}/\textit{syn}-diastereomeric ratio, while R as isopropyl gave a 17:1 \textit{anti}/\textit{syn}-diastereomeric ratio.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure5.11}
\caption{Evans dihydroxylation and Aminohydroxylation}
\end{figure}

The last trend observed was that protection of hydroxyl-group of the allylic alcohol substrates significantly increased the reaction yield. For example, \textit{O}-protection of substrate 3-methylbut-3-en-2-ol 295 with \textit{O}-acetyl 307, \textit{O}-PMB 309, and \textit{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). \textit{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 \textit{O}-protected and \textit{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 \textit{anti}-diastereomer as the major product 360. The transition-state model proposed by Houk and coworkers\textsuperscript{132} 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 coworkers\(^{135}\) 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,\textsuperscript{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 \textsuperscript{1}H-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.\textsuperscript{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-toluensulfonic acid gave acetonide 364 in excellent yield.\textsuperscript{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](image)

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.

![Diagram](image)

**Figure 5.15**

\[
\text{ Conditions: (i) } \text{NH}_3/\text{MeOH, DCM (ii) 2,2-DMP, CSA, p-TSA, DCM} \\
\]

\[
\text{anti} \\
\text{syn}
\]

\[
\begin{align*}
\delta_{C2} & : 28.47 \\
\delta_{C6} & : 107.47 \\
\delta_{C7} & : 26.71 \\
\end{align*}
\]

**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 $\delta_{C2}$ at higher field than that derived from the syn-diols. Anti-diol derived acetonides 364 and 366 gave $\delta_{C2}$ 107.25-107.47, meanwhile syn-diol derived acetonides 365 and 367 showed $\delta_{C2}$ 106.95-106.96. The $\delta_{C6}$ and $\delta_{C7}$ methyl chemical shifts showed similar
values. In this instance, both acetonides derived from anti- and syn-diols had similar values of $\delta_{C6}$ (28.32-28.59), meanwhile $\delta_{C7}$ gave slightly lower values (26.50-26.71).

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 $^1$H-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 $^1$H-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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (anti:syn)</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>298</td>
<td>NP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>96 h</td>
</tr>
<tr>
<td>2</td>
<td>299</td>
<td>NP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>96 h</td>
</tr>
<tr>
<td>3</td>
<td>300</td>
<td>NP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>96 h</td>
</tr>
<tr>
<td>4</td>
<td>315</td>
<td>NP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>96 h</td>
</tr>
<tr>
<td>5</td>
<td>316</td>
<td>NP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>96 h</td>
</tr>
<tr>
<td>6</td>
<td>301</td>
<td>368</td>
<td>10%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17 h</td>
</tr>
<tr>
<td>7</td>
<td>302</td>
<td>369</td>
<td>7.2%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>21 h</td>
</tr>
<tr>
<td>8</td>
<td>303</td>
<td>NP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>96 h</td>
</tr>
<tr>
<td>9</td>
<td>317</td>
<td>NP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>96 h</td>
</tr>
</tbody>
</table>

Reaction conditions: Substrate (1.0 equiv.), BnOCONHOTs 202 (1.2 equiv.), K₂OsO₂(OH)₄ (4.0 mol%), MeCN/H₂O (3:1), RT. *Mixture two diastereomers. <sup>b</sup>NP: 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.

\[
\text{OAc} \\
R \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \q
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 methanesulfonylamide, tetraethylammonium acetate and no additive as a control. However, the addition of methanesulfonylamide\(^{146}\) and tetraethylammonium acetate\(^{147}\) did not have a significant affect on the yields of the amino alcohol products 343 and 344. For example, addition of methanesulfonylamide 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 methanesulfonylamide 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.

![Chemical Diagram](image)

**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>
<thead>
<tr>
<th>Entry</th>
<th>Substrates</th>
<th>Yield of product resulted from alkenes</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Ph−CHPh</td>
<td>Ph−CH</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td>51</td>
<td>49</td>
<td>36%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Ph−CH2</td>
<td>Ph−CH</td>
<td>39%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>229</td>
<td>49</td>
<td>29%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>CH−OH</td>
<td>Ph−CH</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>243</td>
<td>49</td>
<td>66%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>CH−OAc</td>
<td>CH−OH</td>
<td>16%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>307</td>
<td>295</td>
<td>34%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>Ph−CHPh</td>
<td>-</td>
<td>88%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>Ph−CH</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>89%&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>16 h</td>
</tr>
<tr>
<td>7</td>
<td>CH−OH</td>
<td>-</td>
<td>64%&lt;sup&gt;a,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>CH−OAc</td>
<td>-</td>
<td>68%&lt;sup&gt;c,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>CH−OH</td>
<td>44%&lt;sup&gt;c,d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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. <sup>a</sup>One regioisomer was afforded; <sup>b</sup>Two regioisomers were afforded. <sup>c</sup>Two diastereomers were afforded. <sup>d</sup>Using 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 1H-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 1H-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 that 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 aminohydroxylolation 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 tetaethylammonium acetate147 gave no acceleration in the aminohydroxylolation 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 Prospects

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 reagents\(^2\) to generate the nitrogen sources, chlorination of the substrates and amino alcohol products\(^2^4,^7^4\) 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.\(^2^4\) 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 \( N-(4\text{-toluenesulfonyl})-L\text{-threonine 185}, N-(4\text{-nitrophenylsulfonyl})-L\text{-threonine 188}, N-(4\text{-methoxyphenylsulfonyl})-L\text{-threonine 189}, N-(4\text{-toluenesulfonyl})-L\text{-serine 190}, \) and \((R)-N,N'\text{-bis(4-toluenesulfonyl)}\text{propanoic acid 191}\. These ligands were able to induce stereoselectivity in the literature\(^{102}\) 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 \( N-(4\text{-toluenesulfonyloxy}) \) with various different alkyl carbamate groups, i.e. tert-butyl \( N-(4\text{-toluenesulfonyloxy})\text{-carbamate 153}, \) ethyl \( N-(4\text{-toluenesulfonyloxy})\text{carbamate 201, benzyl N-(4-toluenesulfonyloxy)}\text{carbamate 202, 2,2,2-trichloroethyl N-(4-toluenesulfonyloxy)}\text{carbamate 203, and 2-(trimethyl-silyl)ethyl N-(4-toluenesulfonyloxy)}\text{carbamate 204.} \)

Four important points could be concluded. First, these second generation preformed nitrogen sources especially benzyl \( N-(4\text{-toluenesulfonyloxy})\text{carbamate 202} \) 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-toluene-sulfonyloxy)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 (¹³C-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 (Ø 0.46 mm, 25 cm length) or chiralpak AS-H (Ø 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 Raels 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.

\[
\text{tert-Butyl N-hydroxycarbamate}^{83}
\]

\[\text{O} \quad \text{N} \quad \text{OH} \quad \text{156}\]

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%). R₂ 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. ¹H-NMR (300 MHz, CDCl₃) 6.97 (1H, s,
NH), 6.22 (1H, s, OH), 1.48 (9H, s, C(CH$_3$)$_3$). $^{13}$C-NMR (100 MHz, CDCl$_3$) 158.83, 82.24, 28.18. LRMS (ESI+) 156 ([M+Na]$^+$, 39%), 100 (100), 78 (35), 56 (33).

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

![Chemical Structure](image)

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. $^1$H-NMR (300 MHz, CDCl$_3$) 8.13 (1H, s, NH), 1.51 (9H, s, C(CH$_3$)$_3$). $^{13}$C-NMR (75 MHz, CDCl$_3$) 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 C$_{12}$H$_{10}$NO$_4$F$_3$Na ([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-(pentafluorobenzoyl-oxy)carbamate 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_{5}NO_{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**

![Chemical structure](image)

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, CDCl₃) 8.14 (1H, s, NH), 4.20 (2H, s, CH₂), 1.47 (9H, s, C(CH₃)₃). ¹³C-NMR (75 MHz, CDCl₃) 167.3, 155.2, 84.3, 38.9, 28.2. LRMS (EI⁺) 212 (M⁺), 194 ([M-CH₃]⁺), 154, 136, 115, 77, 58, 49, 43. HRMS (EI⁺) calced. for C₆H₉NO₄Cl⁻ 194.0220, found 194.0222; calcd. for C₆H₉NO₄Cl⁻ 196.0191, found 196.0193.
**tert-Butyl N-methanesulfonyloxy carbamate**

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 (1.47 g, 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). $^1$H-NMR (300 MHz, CDCl$_3$) 7.92 (1H, s, NH), 3.17 (3H, s, CH$_3$), 1.51 (9H, s, C(CH$_3$)$_3$). $^{13}$C-NMR (75 MHz, CDCl$_3$) 154.79, 85.02, 36.58, 28.21. LRMS (EI+) 196 ([M-CH$_3$]$^+$, 15%) 137 (49), 79 (100). HRMS (EI+) calcd. for C$_5$H$_{10}$NO$_5$S ([M-CH$_3$]$^+$) 196.0280, found 196.0276.

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

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. $^1$H-NMR (300 MHz, CDCl$_3$) 7.77 (1H, s, NH), 6.98 (2H, s, ArH), 2.66 (6H, s, 2xCH$_3$), 2.31 (3H, s, CH$_3$), 1.30 (9H, s, C(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-toluensulfonyloxy)carbamate**\(^{89}\)

![Structure 153](image)

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-toluensulfonyl 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. \(^1\)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, C(CH\(_3\))\(_3\)). \(^{13}\)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 ([M+Na]\(^+\), 25%), 254 (100), 188 (29), 106 (87). HRMS (ESI+) calcd. for C\(_{12}\)H\(_{17}\)NO\(_5\)SNa ([M+Na]\(^+\)) 310.0725, found 310.0719.

**tert-Butyl N-(p-nitrophenylsulfonyloxy)carbamate**\(^{90}\)

![Structure 154](image)

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). \(^1\)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, C(CH\(_3\))\(_3\)). \(^{13}\)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 (1R*,2R*)-2-hydroxy-1,2-diphenylethylcarbamate\textsuperscript{38}

![Chemical Structure Image]

Mp 130-131 °C (lit.\textsuperscript{38} 137-138 °C). IR (thin film, cm\textsuperscript{-1}) 3415 (brd, O-H, N-H), 3088, 3064, 3031, 3006, 2977, 2929 (C-H), 1691 (C=O), 1604, 1586; \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{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, C(CH\textsubscript{3})\textsubscript{3}). \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{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 ([M+Na]+, 100%), 320 (5), 280 (19), 240 (7), 236 (30), 196 (22). HRMS (ESI+) calcd. for C\textsubscript{19}H\textsubscript{23}NO\textsubscript{3}Na ([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)\textsubscript{2}PHAL (5.0 mol%), K\textsubscript{2}OsO\textsubscript{2}(OH)\textsubscript{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 (Na\textsubscript{2}SO\textsubscript{4}), and concentrated under reduced pressure to afford crude product. Purification was conducted by flash chromatography to afford tert-butyl (1R*,2R*)-2-hydroxy-1,2-diphenylethylcarbamate 157. The enantioselectivity for this product was determined by using HPLC (Chiralcell OD-H silica 5 \(\mu\)m 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-(methanesulfonyl oxy)carbamate 151, tert-butyl N-(2-mesitylenesulfonyl oxy)carbamate 152, tert-butyl N-(4-toluenesulfonylox y)carbamate 153, and tert-butyl N-(4-nitrophenyl sulfonyloxy)carbamate 154.

Optimisation of solvent
To a mixture trans-stilbene 51 (1.0 equiv.), (DHQD)$_2$PHAL (5.0 mol%), K$_2$OsO$_2$(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 (Na$_2$SO$_4$), and concentrated under reduced pressure to afford crude product. Purification by flash chromatography afforded tert-butyl (1R*,2R*)-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, $^1$H- and $^{13}$C-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)$_2$PHAL (5.0 mol%), K$_2$OsO$_2$(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-(methanesulfonylox y)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 (Na$_2$SO$_4$), and concentrated under reduced pressure to afford crude product. Purification by flash chromatography afforded tert-butyl (1R*,2R*)-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:

<table>
<thead>
<tr>
<th>pH</th>
<th>Solution A</th>
<th>Solution B</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.0</td>
<td>50 mL NaHCO$_3$ 0.05 M</td>
<td>add NaOH 0.1 M until pH 11 (~23 mL), and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diluted to 100 mL</td>
</tr>
<tr>
<td>10.0</td>
<td>50 mL Borax 0.025 M</td>
<td>Add NaOH 0.1 M until pH 10 (~18 mL), and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diluted to 100 mL</td>
</tr>
<tr>
<td>9.0</td>
<td>50 mL Borax 0.025 M</td>
<td>Add HCl 0.1 M until pH 9.0 (~4.5 mL), and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diluted to 100 mL</td>
</tr>
<tr>
<td>8.0</td>
<td>50 mL KH$_2$PO$_4$ 0.1 M</td>
<td>Add NaOH 0.1 M until pH 8.0 (~46 mL), and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diluted to 100 mL</td>
</tr>
<tr>
<td>7.0</td>
<td>50 mL KH$_2$PO$_4$ 0.1 M</td>
<td>Add NaOH 0.1 M until pH 7.0 (~29 mL), and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diluted to 100 mL</td>
</tr>
<tr>
<td>6.0</td>
<td>50 mL KH$_2$PO$_4$ 0.1 M</td>
<td>Add NaOH 0.1 M until pH 6.0 (~5.6 mL), and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diluted to 100 mL</td>
</tr>
<tr>
<td>5.0</td>
<td>50 mL Potassium hydrogen phthalate 0.1 M</td>
<td>Add NaOH 0.1 M until pH 5.0 (~22.5 mL) and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diluted to 100 mL</td>
</tr>
<tr>
<td>4.0</td>
<td>50 mL Potassium hydrogen phthalate 0.1 M</td>
<td>Add NaOH 0.1 M until pH 4.0 (~2.0 mL) and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diluted to 100 mL</td>
</tr>
<tr>
<td>3.0</td>
<td>50 mL Potassium hydrogen phthalate 0.1 M</td>
<td>Add HCl 0.1 M until pH 3.0 (~22.5 mL) and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diluted to 100 mL</td>
</tr>
<tr>
<td>2.0</td>
<td>25 mL KCl 0.2 M</td>
<td>Add HCl 0.2 M until pH 2.0 (~6.0 mL) and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diluted to 100 mL</td>
</tr>
<tr>
<td>1.0</td>
<td>25 mL KCl 0.2 M</td>
<td>Add HCl 0.2 M until pH 1.0 (~66 mL) and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diluted to 100 mL</td>
</tr>
</tbody>
</table>
Optimisation of reactions pH

To a mixture of trans-stilbene 51 (1.0 equiv.), (DHQD)$_2$PHAL (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 (Na$_2$SO$_4$), and concentrated under reduced pressure. Product purification was conducted by flash chromatography to afford tert-butyl (1R*,2R*)-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, $^1$H- and $^{13}$C-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 (MgSO$_4$) and concentrated under reduced pressure to yield the product.
$N$-(4-Toluenesulfonyl)-$L$-threonine

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 (MgSO$_4$) 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), $[\alpha]_{D}^{20}$ +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). $^1$H-NMR (300 MHz, CD$_3$OD) 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-CH$_3$), 1.18 (3H, d, J 6.3 Hz, H4). $^{13}$C-NMR (75 MHz, CD$_3$OD) 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 C$_{11}$H$_{15}$NO$_5$SNa ([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 (MgSO$_4$) 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%). Rf 0.26 (20% methanol/ethyl acetate), mp 126-128.4 °C, [α]D20 +5.5 (c 0.96, EtOH). IR (thin film, cm⁻¹) 3273 (N-H), 3106 (C-H), 1734 (C=O), 1602, 1527. ¹H-NMR (300 MHz, CD₃OD) 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). ¹³C-NMR (75 MHz, CD₃OD) 171.63, 150.17, 146.88, 128.53, 123.93, 67.75, 61.72, 19.17. HRMS (ESI+) calcd. for C₁₀H₁₂N₂O₇SNa ([M+Na]⁺) 327.0263, found 327.0257.

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

![Chemical structure of N-(4-Methoxyphenylsulfonyl)-L-threonine](image)

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 (MgSO₄) 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%). Rf 0.22 (90% ethyl acetate/dichloromethane), mp 143.0-144.5 °C (lit.¹¹¹ 139-141 °C), [α]D20 +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). ¹H-NMR (300 MHz, d₆-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, CH₃), 3.82 (1H, d, J 9.3 Hz, H2), 1.19 (3H, d, J 6.3 Hz, H4) (OH not observed). ¹³C-NMR (75 MHz, d₆-acetone) 171.03, 162.99, 133.02, 129.47, 114.14, 67.97, 61.31, 55.39, 19.76. LRMS (ESI+) 312 ([M+Na]⁺, 80%), 290 ([M+H]⁺, 10), 244 (8), 171 (20), 102 (55), 74 (100), 56 (22). HRMS (ESI+) calcd. for
C_{11}H_{16}NO_{6}S ([M+H]^+) 290.0698, found 290.0698; calcd. for C_{11}H_{16}NO_{6}SNa ([M+Na]^+) 312.0518, found 312.0518.

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

![Chemical structure](image1)

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), [α]_D^{20} +11.4 (c 1.6, MeOH), mp 219.0-220.5 °C (lit.\textsuperscript{112} 236 °C). IR (thin film, cm\textsuperscript{-1}) 3404 (broad, O-H, N-H), 3280 (C-H), 1732 (C=O). \textsuperscript{1}H-NMR (300 MHz, d6-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). \textsuperscript{13}C-NMR (75 MHz, d6-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_{6}S ([M+H]^+) 260.0593, found 260.0593.

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

![Chemical structure](image2)

The reaction was conducted according to the general procedure 3.1 with minor modification using (2R)-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%). Rₙ 0.4 (30% methanol/ethyl acetate), mp 228-229 °C (lit 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). H-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, H3A), 2.66 (1H, m, H3B), 2.37 (3H, s, CH₃), 2.38 (3H, s, CH₃). C-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 C₁₂H₂₀N₂O₆NaS₂ ([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 (1R*,2S*)-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, (2R)-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\text{-toluenesulfonyl})\-L\text{-threonine 185, (ii) } N\-(4\text{-nitrophenyl-sulfonyl})\-L\text{-threonine 188, (iii) } N\-(4\text{-methoxyphenylsulfonyl})\-L\text{-threonine 189, (iv) } N\-(4\text{-toluene sulfonyl})\-L\text{-serine 190, (v) } (2R)\cdot N,N\-'\text{bis(p-toluenesulfonyl)}\-2,3\text{-diaminopropanoic acid 191, and (vi) without ligand (HPLC conditions: Chiralcel OD-H Silica 5 \( \mu \text{m, 150 x 0.46 mm, 10\% isopropanol/n-hexane, 1.0 mL/min).}}\)

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

To a mixture of \( N\-(4\text{-toluenesulfonyl})\-L\text{-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 (MgSO₄) 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-methylbenzenesulfonamide

\[ \text{187} \]

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, CDCl₃) 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, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 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 ([M+Na]^+, 100%), 274 (76), 155 (48), 118 (38), 91 (12). HRMS (ESI+) calcd. for C₁₅H₁₇NO₃SNa ([M+Na]^+) 314.0827, found 314.0829.

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

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

\[
\begin{align*}
\text{R}_f \ 0.28 \ (23\% \ \text{ethyl acetate/dichloromethane}). \ IR \ (\text{thin film, cm}^{-1}) \ 3496 \ (\text{O-H}), \ 3277 \ (\text{N-H}), \ 3064, \ 3032, \ 2926, \ 2876 \ (\text{C-H}), \ 1598. \ ^1\text{H-NMR} \ (400 \ \text{MHz, CDCl}_3) \ 7.59 \ (2\text{H, d, J} \ 8.1 \ \text{Hz, ArH}), \ 7.06-7.17 \ (7\text{H, m, ArH}), \ 6.00 \ (1\text{H, m, NH}), \ 4.44 \ (1\text{H, m, H1A}), \ 3.72 \ (2\text{H, m, H1B}), \ 3.67 \ (1\text{H, s, OH}), \ 2.34 \ (3\text{H, s, CH}_3) \ ^{13}\text{C-NMR} \ (100 \ \text{MHz, CDCl}_3) \ 143.30, \ 137.52, \ 137.03, \ 129.41, \ 128.51, \ 127.75, \ 127.14, \ 126.91, \ 66.15, \ 59.74, \ 21.49
\end{align*}
\]

Absolute configuration was determined from HPLC \((S)\)-186 \(t_R\) 90.0 min, \((R)\)-186 \(t_R\) 100.1 min. (Chiralcel OD-H 5 \(\mu\)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 \(\mu\)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 sources\[^{[21]}\]

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-hydroxycarbamate\textsuperscript{123}

\[ \text{206} \]

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 \textbf{206} as a white solid (4.90 g, 100%), mp 59-62 °C (lit\textsuperscript{123} 62-64 °C). IR (thin film, cm\textsuperscript{-1}) 3300 (broad, O-H, N-H), 3061, 3030, 2977, 2952, 2897 (C-H), 1708 (C=O), 1504. \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}) 7.65 (1H, s, NH), 7.32-7.37 (5H, m, ArH), 5.13 (2H, s, CH\textsubscript{2}) (OH not observed). \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}) 159.41, 135.38, 128.61, 128.50, 128.33, 67.86.

\[ \text{206} \]

Benzyl N-(4-toluenesulfonyloxy)carbamate\textsuperscript{126}

The reaction was conducted according to the general procedure 4.1 with benzyl N-hydroxycarbamate \textbf{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 \textbf{202} as a white solid (814 mg, 46%), mp 119-121 °C (lit\textsuperscript{126} 120-123 °C), R\textsubscript{f} value 0.11 (80% dichloromethane/n-hexane). IR (thin film, cm\textsuperscript{-1}) 3282 (N-H), 3067, 3035, 2957 (C-H), 1774, 1743 (C=O), 1597. \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}) 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, CH\textsubscript{2}Ar), 2.42 (3H, s, CH\textsubscript{3}). \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}) 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_{3}S ([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](image_url) Structure of C_{15}H_{15}NO_{3}S with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

**Ethyl \( N \)-hydroxycarbamate**

![Structure](image_url)

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). \(^1\)H-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)carbamate**

![Structure of 201](image)

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%). Rf 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 C₁₀H₁₃NO₃NaS [M+Na]⁺ 282.0412, found 282.0412.

**2,2,2-Trichloroethyl N-hydroxycarbamate**

![Structure of 207](image)

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. 86-88 °C), Rf 0.25 (10% ethyl acetate/dichloromethane). IR (thin film, cm⁻¹) 3366 (O-H), 3264 (N-H), 1709 (C=O). ¹H-NMR (300 MHz, CDCl₃) 7.61 (1H, s, NH), 7.12 (1H, s (broad), OH), 4.72 (2H, s, CH₂). ¹³C-NMR (75 MHz, CDCl₃) 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)carbamate\textsuperscript{116}

![Chemical Structure](image)

203

The reaction was conducted according to the general procedure 4.1 with 2,2,2-trichloroethyl \( N \)-hydroxycarbamate\textsuperscript{116} 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.\textsuperscript{116} 123 °C). IR (thin film, cm\(^{-1}\)) 3259 (N-H), 3009 (C-H), 1764 (C=O), 1595. \textsuperscript{1}H-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\(_3\)). \textsuperscript{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 ([M+Na\textsuperscript{+}], 100%). HRMS (ESI+) calcd. for C\(_{10}\)H\(_{10}\)NO\(_5\)NaScI\(_3\) ([M+Na\textsuperscript{+}]\) 383.9243, found 383.9238.

2-(Trimethylsilyl)ethyl \( N \)-hydroxycarbamate

![Chemical Structure](image)

208

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.
\(^1\)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, Si(CH\(_3\))\(_3\)). \(^1\)C-NMR (75 MHz, CDCl\(_3\)) 161.40 66.19, 19.10, 0.0. LRMS (ESI+) 200 ([M+Na]\(^+\), 12%), 172 (10%), 150 (8), 132 (20), 105 (12), 100 (19), 90 (19), 75 (30), 73 (100), 61 (19). HRMS (ESI+) calcd. for C\(_6\)H\(_{15}\)NO\(_3\)NaSi ([M+Na]\(^+\)) 200.0719, found 200.0723.

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

![Structural formula of 2-(Trimethylsilyl)ethyl N-(4-toluenesulfonyloxy)carbamate](image)

204

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. \(^1\)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, Si(CH\(_3\))\(_3\)). \(^1\)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 ([M+Na]\(^+\), 100%), 326 (48), 260 (12), 254 (22), 229 (10), 217 (8), 139 (12), 73 (8). HRMS (ESI+) calcd. for C\(_{13}\)H\(_{21}\)NO\(_3\)SSiNa ([M+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\(_2\)SO\(_4\)) and concentrated under reduced
pressure to afford crude product. Purification was performed by flash chromatography using the specified solvents.

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

![](image)

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%). Rf 0.15 (1:9:5 of ethyl acetate/dichloromethane/n-hexane), mp 129.9-131.3 °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. \(^1\)H-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, C(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 ([M+Na]\(^+\), 100%), 320 (5), 280 (19), 240 (7), 236 (30), 196 (22). HRMS (ESI+) calcd. for C\(_{19}\)H\(_{23}\)NO\(_3\)Na ([M+Na]\(^+\)) 336.1576, found 336.1572.

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

![](image)
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)carbamatc 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\textsubscript{f} 0.23 (20% ethyl acetate/n-hexane); mp 120-122 °C (lit.\textsuperscript{1} 122-123.5 °C). IR (thin film, cm\textsuperscript{-1}) 3346 (brd, O-H, N-H), 3062, 3032, 2978, 2922 (C-H), 1686 (C=O), 1533. \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{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\textsubscript{2}), 2.74 (1H, s, OH), 1.56 (3H, m, CH\textsubscript{3}). \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{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 ([M+Na]\textsuperscript{+}, 100%), 268 (11), 224 (15), 196 (23). HRMS (ESI+) calcd. for C\textsubscript{17}H\textsubscript{16}NO\textsubscript{3}Na ([M+Na]\textsuperscript{+}) 308.1263, found 308.1258.

**Benzyl (1R*,2R*)-2-hydroxy-1,2-diphenylethylcarbamate**\textsuperscript{152}

![214]

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\textsubscript{f} value 0.22 (20% ethyl acetate/dichloromethane), mp 147.7-149.7 °C (lit.\textsuperscript{2} 149-151 °C). IR (thin film, cm\textsuperscript{-1}) 3574 (O-H), 3353 (N-H), 3088, 3062, 3031, 2941 (C-H), 1689 (C=O), 1603, 1587, 1555. \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}) 7.28-7.37 (15H, m, ArH), 5.76 (1H, d, J 6.90 Hz, NH), 4.98 (4H, m, H1, H2, CH\textsubscript{2}), 2.57 (1H, s, OH). \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{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 ([M+Na]\textsuperscript{+}, 100%), 286 (14), 91 (41). HRMS (ESI+) calcd. for C\textsubscript{22}H\textsubscript{21}NO\textsubscript{3}Na ([M+Na]\textsuperscript{+}) 370.1419, found 370.1420.
2,2,2-Trichloroethyl (1R*,2R*)-2-hydroxy-1,2-diphenylethylcarbamate

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%), Rf 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. \(^1\)H-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+) calcd. for C\(_{17}\)H\(_{16}\)NO\(_2\)Na\(^{35}\)Cl\(_3\) ([M+Na]\(^{+}\)) 410 (100%). HRMS (ESI+) calcd. for C\(_{17}\)H\(_{16}\)NO\(_2\)Na\(^{35}\)Cl\(_3\) ([M+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 (1R*,2R*)-2-hydroxy-1,2-diphenylethylcarbamate 215 (Figure 7.4.2).
Figure 7.4.2 Structure of C\textsubscript{17}H\textsubscript{16}Cl\textsubscript{3}NO\textsubscript{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\textit{R}\textdagger,2\textit{R}\textdagger)-2-hydroxy-1,2-diphenylethylcarbamate

![Chemical structure](image)

The reaction was conducted according to the general procedure 4.2 using \textit{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 \textit{tert}-butanol/water (3:1). Purification by flash chromatography (1:6:3 ethyl acetate/dichloromethane/\textit{n}-hexane) afforded the title compound 216 as a white solid (93.3 mg, 50\%). R\textsubscript{f} 0.34 (1:7:2 ethyl acetate/dichloromethane/\textit{n}-hexane), mp 133.7-134.7 °C. IR (thin film, cm\textsuperscript{-1}) 3339 (brd, O-H, N-H), 3063, 3029, 2954, 2897 (C-H), 1689 (C=O), 1602, 1586, 1537. \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{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\textsubscript{2}), 2.72 (1H, s, OH), 0.91 (2H, m, CH\textsubscript{2}), 0.00 (9H, s, Si(CH\textsubscript{3})\textsubscript{3}). \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{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_{3}NaSi ([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 × 10 mL). The combined ethyl acetate extract was washed with brine (10 mL), dried (Na_{2}SO_{4}) and concentrated under reduced pressure to afford crude product. Purification by flash chromatography (10% ethyl acetate/dichloromethane) afforded benzyl (1R*,2R*)-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 × 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 (1R*,2R*)-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 (1R*,2R*)-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 (1R*,2R*)-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-phenylethylcarbamate**

![Structure](image)

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%). Rₜ 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+Na]⁺) 238.1143, found 238.1448; calcd. for C₁₃H₁₉NO₃Na ([M+Na]⁺) 260.1263, found 260.1266.
**tert-Butyl (R*)-2-hydroxy-2-phenylpropylcarbamate**

![Chemical Structure of tert-Butyl (R*)-2-hydroxy-2-phenylpropylcarbamate](image)

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 C₁₄H₂₁NO₅Na ([M+Na]⁺) 274.1419, found 274.1419.

**Methyl (2S*,3R*)-2-(tert-butoxycarbonylamino)-3-hydroxy-3-phenyl-propanoate**¹⁵⁵

**Methyl (2S*,3R*)-3-(tert-butoxycarbonylamino)-2-hydroxy-3-phenyl-propanoate**¹⁵⁶

![Chemical Structures of Methyl (2S*,3R*)-2-(tert-butoxycarbonylamino)-3-hydroxy-3-phenyl-propanoate and Methyl (2S*,3R*)-3-(tert-butoxycarbonylamino)-2-hydroxy-3-phenyl-propanoate](image)

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, Rf 0.23 (2:2:6 ethyl acetate/dichloromethane/n-hexane). Separation with preparative HPLC (SunFire Silica 10 μm, 2% isopropanol/n-hexane, 10 mL/min.) afforded methyl (2S*,3R*)-3-(tert-butoxycarbonylamino)-2-hydroxy-3-phenylpropanoate 129 at tR 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, CDCl₃) 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, CH₃), 3.12 (1H, d, J 4.2 Hz, OH), 1.42 (9H, s, 3xCH₃). ¹³C-NMR (100 MHz, CDCl₃) 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 ([M+Na]+, 100%). HRMS (ESI+) calcd. for C₁₃H₂₁NO₅Na ([M+Na]+) 318.1317, found 318.1317.

A second fraction (tR 21.0 minute) afforded methyl (2S*,3R*)-2-(tert-butoxycarbonylamino)-3-hydroxy-3-phenyl-propanoate \(^{155}\) 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, CDCl₃) 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, CH₃), 2.69 (1H, s, OH), 1.34 (9H, s, 3xCH₃). ¹³C-NMR (100 MHz, CDCl₃) 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-ylcarbamate \(^{157}\)

![Image of the compound](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 μmol), and tert-butyl N-(4-toluenesulfonyl)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%). Rf 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. $^1$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, 3xCH$_3$), 1.34 (3H, s, CH$_3$), 1.23 (3H, s, CH$_3$). $^{13}$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 ([M+Na]$^+$, 100%). HRMS (ESI+) calcd. for C$_{16}$H$_{21}$NO$_4$Na ([M+Na]$^+$) 242.1368, found 242.1366.

**Ethyl (R*)-2-hydroxy-2-phenylethylcarbamate**$^{158}$

**Ethyl (R*)-2-hydroxy-1-phenylethylcarbamate**$^{159}$

![218](image1)

![57](image2)

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-phenylethylcarbamate 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 $^\circ$C (lit$^{158}$ 85-87 $^\circ$C). IR (thin film, cm$^{-1}$) 3315 (O-H, N-H), 3062, 3032, 2974, 2930 (C-H), 1693 (C=O), 1554. $^1$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, CH$_2$), 3.55 (1H, m, H1A), 3.31 (1H, m, H1B), 2.78 (1H, s, OH), 1.25 (3H, t, $J$ 7.20 Hz, CH$_3$). $^{13}$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 ([M+Na]$^+$, 100%), 229 (10), 103 (19), 62 (18). HRMS (ESI+) calcd. C$_{11}$H$_{13}$NO$_3$Na for [M+Na]$^+$ 232.0950 found 232.0952.

A second fraction afforded ethyl (R*)-2-hydroxy-1-phenylethylcarbamate$^{159}$ 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. $^1$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 C₁₁H₁₃NO₃Na ([M+Na]⁺) 232.0950, found 232.0951.

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

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

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, Rf 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 (2S*,3R*)-3-(ethoxycarbonylamino)-2-hydroxy-3-phenylpropanoate 127 (tR 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. H-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). C-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 C₁₃H₁₃NO₃Na ([M+Na]⁺) 290.1004, found 290.1005.

A second fraction (tR 30.03 min.) afforded methyl (2S*,3R*)-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. H-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). $^{13}$C-NMR (100 MHz, CDCl$_3$) 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 C$_{13}$H$_{17}$NO$_5$Na ([M+Na]$^+$) 290.1004, found 290.1004.

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

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. $^1$H-NMR (400 MHz, CDCl$_3$) 5.01 (1H, d, J 6.72 Hz, NH), 4.10 (2H, q, J 6.8 Hz, CH$_2$), 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, 2xCH$_3$). $^{13}$C-NMR (100 MHz, CDCl$_3$) 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 C$_{10}$H$_{19}$NO$_3$Na ([M+Na]$^+$) 224.1263, found 224.1258.

**Ethyl 2-methyl-6-oxocyclohex-1-enylcarbamate**

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%). Rf 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, CDCl₃) 6.42 (1H, s, NH), 4.13 (2H, q, J 6.9 Hz, OCH₂), 2.44-2.49 (4H, m, H3 and H5), 1.94-1.99 (5H, m, H4 and CH₃), 1.26 (3H, t, J 7.0 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 194.81, 154.29, 151.74, 129.55, 61.35, 36.76, 32.20, 29.66, 21.26, 14.46. LRMS (ESI⁺) 220 ([M+Na]⁺, 100%), 153 (65), 126 (32). HRMS (ESI⁺) calcd. for C₁₀H₁₅NO₃Na ([M+Na]⁺) 220.0950, found 220.0950.

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

Ethyl (2R*,3S*)-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. Rf 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 (2S*,3R*)-3-(benzyloxycarbonylamino)-2-hydroxy-3-phenyl propanoate 236 as a white solid (34.5 mg, 35%), tᵣ 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, CDCl₃) 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, CH₂), 4.47 (1H, s, H2), 4.23-4.29 (2H, m, CH₂), 3.19 (1H, d, J 4.0 Hz, OH), 1.28 (3H, t, J 6.8 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 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_3Na (M+Na)^+ 366.1317, found 366.1317.

A second fraction afforded ethyl (2S^*,3R^*)-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. \(^1\)H-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\(_3\)). \(^1\)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_3Na ([M+Na]^+) 366.1317, found 366.1317.

**Benzyl (R\(^*\))-2-hydroxy-2-phenylethylcarbamate\(^{163}\)**

**Benzyl (R\(^*\))-2-hydroxy-1-phenylethylcarbamate\(^{164}\)**

\[\text{HO-}\text{NH-}\text{O-} \quad \text{HO-}\text{NH-O-} \]

\[\text{56} \quad \text{144} \]

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 \(\mu\)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 (lit\(^{165}\) 120-121 \(^\circ\)C). IR (thin film, cm\(^{-1}\)) 3369 (O-H), 3283 (N-H), 2927 (C-H), 1693 (C=O). \(^1\)H-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). \(^1\)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,
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.\(^3\) 83.0-84.5 °C). IR (thin film, cm\(^{-1}\)) 3311 (O-H, N-H), 2923, 2852 (C-H), 1700 (C=O), 1539. \(^1\)H-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\(_3\)Na ([M+Na]\(^+\)) 294.1106, found 294.1107.

**Dimethyl (2\(R^*,3R^*\))-2-(benzyloxycarbonylamino)-3-hydroxysuccinate**

![Image of the molecule 242]

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 \(\mu\)mol), benzyl \(N\)-(4-toluenesulfonloyloxy)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). \(^1\)H-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, 2xCH\(_3\)), 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\(_7\)Na ([M+Na]\(^+\)) 334.0903, found 334.0903.
**Methyl (S*)-3-(benzyloxy carbonylamino)-2-hydroxypropanoate**

![Chemical Structure](image)

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 μmol), 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%). Rf 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, CDCl₃) 7.34-7.37 (5H, m, ArH), 5.16 (1H, s (broad), NH), 5.09 (2H, s, CH₂), 4.28 (1H, dd, J 9.60, 5.10 Hz, H2), 3.78 (3H, s, CH₃), 3.54-3.59 (2H, m, H3), 3.21 (1H, d, J 4.80 Hz, OH). ¹³C-NMR (75 MHz, CDCl₃) 173.42, 156.67, 136.28, 128.51, 128.16, 128.09, 70.07, 66.97, 52.81, 44.22. LRMS (ESI⁺) 276 ([M+Na]⁺, 100%), 254 (20). HRMS (ESI⁺) calcd. C₁₂H₁₆NO₅ for ([M+H]⁺) 254.1028, found 254.1029; calcd. C₁₂H₁₅NO₅Na for ([M+Na]⁺) 276.0848, found 276.0855.

**Benzyl (S*)-1,3-dihydroxy-3-methylbutan-2-ylcarbamate**

![Chemical Structure](image)

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%), Rf 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. $^1$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$_3$). $^{13}$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 ([M+Na]$^+$, 100%), 236 (20), 203 (10), 185 (40), 125 (8). HRMS (ESI+) calcd. for C$_{13}$H$_{16}$NO$_4$Na ([M+Na]$^+$) 276.1212, found 276.1212.

2,2,2-Trichloroethyl (1$R^*,2S^*$)-2-hydroxy-2,3-dihydro-1H-inden-1-ylcarbamate$^{168}$

2,2,2-Trichloroethyl (1$R^*,2S^*$)-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 (1$R^*,2S^*$)-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. $^1$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). $^{13}$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 ([M+Na]$^+$, 40%), 308 (30), 306 (28), 176 (38), 159 (100), 130 (13). HRMS (ESI+) calcd. C$_{12}$H$_{12}^{35}$ClNO$_3^{23}$Na for ([M+Na]$^+$) 345.9780, found 345.9768; calcd. C$_{12}$H$_{12}^{35}$Cl$_2^{37}$ClNO$_3^{23}$Na for ([M+Na]$^+$) 347.9751, found 347.9756.
A second fraction afforded 2,2,2-trichloroethyl (1R*,2S*)-1-hydroxy-2,3-dihydro-1H-inden-2-ylcarbamate 231 as a colorless solid (18.3 mg, 22%), Rf 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, CH₃H), 4.76 (1H, d, J 12.30 Hz, CH₃H), 4.67 (1H, m, H1), 3.19 (1H, dd, J 16.5, 4.80 Hz, H3A), 2.96 (1H, d, J 16.5 Hz, H3B), 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 C₁₂H₁₂⁵Cl₃⁷ClNO₃²³Na ([M+Na]+) 347.9751, found 347.9743.

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

Methyl (2S*,3R*)-2-hydroxy-3-phenyl-3-((2,2,2-trichloroethoxy)carbonylamino)-propanoate¹⁶⁹

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. Rf 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 (2S*,3R*)-2-hydroxy-3-phenyl-3-((2,2,2-trichloroethoxy)carbonylamino)propanoate 238 as a colorless oil (33.1 mg, 44%), tᵣ 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, 4.2 Hz, OH).
A second fraction ($t_R$ 10.22 min) afforded methyl (25*,3R*)-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. $^1$H-NMR (400 MHz, CDCl$_3$) 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$_2$H$_2$), 4.55 (1H, d, J 12.0 Hz, CH$_2$H$_2$), 3.80 (3H, s, CH$_3$), 2.67 (1H, d, J 4.0 Hz, OH). $^{13}$C-NMR (100 MHz, CDCl$_3$) 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 C$_{13}$H$_{14}$Cl$_3$NO$_3$Na ([M+Na]$^+$) 391.9835, found 391.9834.

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-toluenesulfonyl)oxy)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). $^1$H-NMR (400 MHz, CDCl$_3$) 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). $^{13}$C-NMR (100 MHz, CDCl$_3$) 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 C$_{11}$H$_{12}$Cl$_3$NO$_3$Na $^{23}$Na ([M+Na]$^+$) 333.9787, found 333.9780; calcd. for C$_{11}$H$_{12}$Cl$_3$Na $^{23}$Cl $^{37}$ClNO$_3$Na ([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 C$_{11}$H$_{12}$Cl$_3$NO$_3$ with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.](image)

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 ºC. IR (thin film, cm$^{-1}$) 3322 (O-H), 3204 (N-H), 3052, 2951, 2927, 2853 (C-H), 1706 (C=O), 1560. $^1$H-NMR (400 MHz, CDCl$_3$) 7.32-7.40 (5H, m, ArH), 5.76 (1H, s, broad, NH), 4.73 (2H, s, CH$_2$), 3.93 (2H, m, H2), 1.82 (1H, s, OH). $^{13}$C-NMR (100 MHz, CDCl$_3$) 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 C$_{11}$H$_{12}$Cl$_3$NO$_3$Na $^{23}$Na ([M+Na]$^+$) 333.9782, found 333.9780; calcd. for C$_{11}$H$_{12}$Cl$_3$Na $^{23}$Cl $^{37}$ClNO$_3$Na ([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).

![Structure of C\(_{11}\)H\(_{12}\)Cl\(_3\)NO\(_3\) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.](image)

**Figure 7.4.4** Structure of C\(_{11}\)H\(_{12}\)Cl\(_3\)NO\(_3\) 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

![Structure of 228](image)

228

The reaction was conducted according to the general procedure 4.3 using \(\alpha\)-methyl styrene 36 (30.0 mg, 0.25 mmol), potassium osmate dihydrate (0.9 mg, 3.0 \(\mu\)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). \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 7.45 (2H, m, 160
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 (1R*,2S*)-1-hydroxy-2,3-dihydro-1H-inden-2-yl carbamate 2-(Trimethylsilyl)ethyl (1R*,2S*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl carbamate¹⁶⁸

The reaction was conducted according to the general procedure 4.3 using 1H-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. Rf 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 (1R*,2S*)-1-hydroxy-2,3-dihydro-1H-inden-2-ylcarbamate 233 (tr 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, Ht), 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 (tr 41.53 minute) afforded 2-(trimethylsilyl)ethyl (1R*,2S*)-2-hydroxy-2,3-dihydro-1H-inden-1-ylcarbamate²⁶² 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), 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

![1-(But-3-enyloxy)-4-nitrobenzene](image)

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 C₁₀H₁₁N₂O₃ ([M]⁺) 193.0739, found 193.0739.

2-(Trimethylsilyl)ethyl (S⁰)-2-hydroxy-4-(4-nitrophenoxy)butylcarbamate

2-(Trimethylsilyl)ethyl (S⁰)-1-hydroxy-4-(4-nitrophenoxy)butan-2-ylcarbamate

![Chemical Structures](image)

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 (S⁰)-2-hydroxy-4-(4-nitrophenoxy)butylcarbamate 29 as a colourless oil (88.8 mg, 71%), Rᵣ 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, C₂H₂), 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, C₂H₂), 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), 163
A second fraction afforded 2-(trimethylsilyl)ethyl \((S^*)\)-1-hydroxy-4-(4-nitrophenoxy)butan-2-ylcarbamate\(^{6,10^9}\) \(30\) 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. \(^1\)H-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, 50.21, 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\(_2\)O\(_8\)SiNa ([M+Na]\(^+\)) 393.1458, found 393.1452.

**Methyl (2S*,3R*)-2-hydroxy-3-phenyl-3-((2-(trimethylsilyl) ethoxy)carbonylamino)propanoate**\(^{172}\)

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

The reaction was conducted according to the general procedure 4.3 using \textit{trans}-methyl cinnamate \(122\) (56.0 mg, 0.35 mmol), potassium osmate dihydrate (5.00 mg, 14.0 \(\mu\)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 \(\mu\)m, 2% isopropanol/\(n\)-hexane, 10 mL/min) afforded methyl (2S*,3R*)-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, ...)
A second fraction (t R 19.87 min.) afforded methyl (2S*,3R*)-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, CDCl₃) 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, CH₂), 3.76 (3H, s, CH₃) 2.76 (1H, s, OH), 0.91 (2H, t, J 7.6 Hz, CH₂), 0.00 (9H, s, 3xCH₃). ¹³C-NMR (100 MHz, CDCl₃) 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 ([M+Na]⁺, 100%), 118 (60), 73 (16). HRMS (ESI⁺) calcd. for C₁₆H₂₅NO₃SiNa ([M+Na]⁺) 362.1400, found 362.1400; calcd. for C₁₆H₂₆NO₅Si ([M+H]⁺) 340.1580, found 362.1580.

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

![Structure 222](image)

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 °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, CDCl₃) 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

![But-3-en-2-ol](image)

To a stirred solution of methylimagnesium 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

![But-3-en-2-yl acetate](image)
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%). Rf 0.51 (20% ethyl acetate/n-hexane). IR (thin film, cm⁻¹) 3090, 2985, 2935 (C-H), 1737 (C=O). ¹H-NMR (400 MHz, CDCl₃) 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, CH₃), 1.31 (3H, d, J 6.4 Hz, H1). ¹³C-NMR (100 MHz, CDCl₃) 170.29, 137.66, 115.71, 70.96, 21.30, 19.88.

Pent-1-en-3-ol¹⁷⁴

![293](image)

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). ¹H-NMR (400 MHz, CDCl₃) 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, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 140.90, 114.70, 74.50, 29.80, 9.50.

Pent-1-en-3-yl acetate¹⁴²

![305](image)
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%). Rf 0.48 (20% ethyl acetate/n-hexane). IR (thin film, cm⁻¹) 3086, 2972, 2939, 2881 (C-H), 1739 (C=O), 1647 (C=C). ¹H-NMR (400 MHz, CDCl₃) 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, CH₃), 1.64 (2H, m, H4), 0.90 (3H, t, J 8.0 Hz, H5). ¹³C-NMR (100 MHz, CDCl₃) 170.42, 136.27, 116.67, 75.99, 27.14, 21.22, 9.35.

4-Methylpent-1-en-3-ol[^1]

![Chemical Structure](image)

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[^2] 134-137 °C, 760 mmHg). IR (cm⁻¹) 3368 (O-H), 3080, 2957, 2927, 2870 (C-H), 1648 (C=C). ¹H-NMR (300 MHz, CDCl₃) 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, CH₃), 0.90 (3H, d, J 6.9 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 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 acetate\textsuperscript{143}

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306
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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%), \textit{Rf} 0.55 (20% ethyl acetate/\textit{n}-
hexane). $^1$H-NMR (400 MHz, CDCl\textsubscript{3}) 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, CH\textsubscript{3}), 1.86 (1H, m, H4),
0.89-0.92 (6H, m, 2xCH\textsubscript{3}). $^{13}$C-NMR (100 MHz, CDCl\textsubscript{3}) 170.38, 134.75, 117.46, 79.37,
31.76, 21.16, 17.96, 17.93.

3-Methylbut-3-en-2-ol\textsuperscript{177}

\begin{center}
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295
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\end{center}
\end{center}
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=O). ¹H-NMR (300 MHz, CDCl₃) 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, CH₃), 1.51 (1H, s, broad, OH), 1.28 (3H, d, J 6.9 Hz, H1). ¹³C-NMR (100 MHz, CDCl₃) 148.95, 109.52, 71.57, 21.73, 17.84.

3-Methylbut-3-en-2-yl acetate

\[ \text{O} \quad \text{O} \]  
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=O), 1598. ¹H-NMR (300 MHz, CDCl₃) 5.27 (1H, q, J 7.2 Hz, H2), 4.95 (1H, m, H4A), 4.85 (1H, m, H4B), 2.06 (3H, s, CH₃), 1.74 (3H, s, CH₃), 1.31 (3H, d, J 6.6 Hz, H1). ¹³C-NMR (100 MHz, CDCl₃) 170.30, 144.52, 111.46, 73.32, 21.28, 19.06, 18.30
((3-Methylbut-3-en-2-yloxy)methyl)benzene$^{179}$

\[
\begin{align*}
&\text{308} \\
&\text{O} \\
&\text{CH}_3
\end{align*}
\]

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). $^1$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, CH$_2$Ph), 4.27 (1H, d, J 12.4 Hz, CH$_2$H$_2$Ph), 3.91 (1H, q, J 6.4 Hz, CH$_2$), 1.72 (3H, s, CH$_3$), 1.27 (3H, d, J 6.8 Hz, CH$_3$). $^{13}$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)benzene$^{180}$

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\begin{align*}
&\text{MeO} \\
&\text{O} \\
&\text{CH}_3
\end{align*}
\]

To a stirred suspension of hexane-washed of 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, CDCl₃) 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, CH₃H₂Ar), 4.20 (1H, d, J 11.2 Hz, CH₃H₂Ar), 3.90 (1H, q, J 6.4 Hz, H2), 3.78 (3H, s, CH₃), 1.71 (3H, s, CH₃), 1.25 (3H, d, J 6.4 Hz, H1). ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₁H₁₈O₂ (M⁺⁺) 206.1307, found 206.1312.

tert-Butyldimethyl(3-methylbut-3-en-2-yloxy)silane⁸¹

![310]

To a stirred solution of 3-methylbut-3-en-2-ol 295 (100 mg, 1.16 mmol) in dimethylformamide (2 mL) was added 1H-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, CDCl₃) 4.89 (1H, s, H4A), 4.71 (1H, s, H4B), 4.20 (1H, q, J 6.0 Hz, H2), 1.69 (3H, s, CH₃), 1.21 (3H, d, J 6.3 Hz, CH₃), 0.89 (9H, s, 3°CH₃), 0.05 (3H, s, CH₃), 0.03 (3H, s, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 149.20, 108.90, 72.19, 25.82, 23.17, 18.26, 17.65, -4.93, -5.02. HRMS (ESI⁺) calcd. for C₁₁H₂₄ONaSi ([M+Na⁺]⁺) 223.1494, found 223.1493.
2-Methylpent-1-en-3-ol\textsuperscript{182}

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\text{OH}
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\text{296}
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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 \textbf{296} as a yellowish oil (6.91 g, 100%), R\textsubscript{f} 0.5 (40% ethyl acetate/n-hexane). IR (thin film, cm\textsuperscript{-1}) 3369 (O-H), 3074, 2963, 2935, 2876 (C-H), 1651 (C=C). \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) 4.93 (1H, m, H1A), 4.84 (1H, m, H1B), 3.99 (1H, t, \textit{J} 6.4 Hz, H3), 1.71 (3H, m, CH\textsubscript{3}), 1.49-1.64 (3H, m, H4 and OH), 0.89 (3H, t, \textit{J} 7.6 Hz, H5). \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}) 147.25, 111.08, 77.18, 27.68, 17.43, 9.74. LRMS (EI+) 100 (M\textsuperscript{+*}, 15%), 83 (70), 71 (100), 58 (28), 55 (58). HRMS (EI+) calcd. for C\textsubscript{8}H\textsubscript{12}O (M\textsuperscript{+*}) 100.0888, found 100.0888.

2-Methylpent-1-en-3-yl acetate\textsuperscript{183}

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\text{O}
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\text{311}
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To a stirred solution of 2-methylpent-1-en-3-ol \textbf{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 \textbf{311} as a
colourless oil (278 mg, 41%). R<sub>f</sub> 0.5 (20%) ethyl acetate/n-hexane. IR (thin film, cm<sup>-1</sup>) 3079, 2963, 2935, 2876 (C-H), 1742 (C=O), 1653 (C=C). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 5.10 (1H, t, J 6.4 Hz, H3), 4.94 (1H, m, H1A), 4.89 (1H, m, H1B), 2.06 (3H, s, CH<sub>3</sub>), 1.71 (3H, s, CH<sub>3</sub>), 1.65 (2H, m, H4), 0.87 (3H, t, J 7.6 Hz, H5). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) 170.39, 142.88, 112.71, 78.53, 25.49, 21.17, 18.05, 9.59. LRMS (EI+) 142 (M<sup>+</sup>, 10%), 135 (48), 124 (12), 111 (30), 100 (100), 95 (20), 83 (70), 77 (12), 69 (45), 55 (64). HRMS (EI+) calcd. for C<sub>8</sub>H<sub>14</sub>O<sub>2</sub> for (M<sup>+</sup>) 142.0994, found 142.0996.

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

![Diagram](image)

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<sub>f</sub> 0.27 (5% ethyl acetate/n-hexane). IR (thin film, cm<sup>-1</sup>) 3071, 3034, 2963, 2936, 2874, 2836 (C-H), 1649, 1613 (C=C), 1586, 1513. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 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, CH<sub>2</sub>H<sub>2</sub>Ar), 4.18 (1H, d, J 11.6 Hz, CH<sub>2</sub>H<sub>2</sub>Ar), 3.79 (3H, s, CH<sub>3</sub>), 3.59 (1H, t, J 6.8 Hz, H3), 1.42-1.68 (5H, m, H4 and CH<sub>3</sub>), 0.89 (3H, t, J 7.6 Hz, H5). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) 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<sup>++</sup>, 5%), 137 (62), 121 (100), 109 (8), 91 (6), 84 (20), 77 (15), 69 (19), 65 (4), 55 (10). HRMS (EI+) calcd. for C<sub>14</sub>H<sub>20</sub>O<sub>2</sub> (M<sup>++</sup>) 220.1463, found 220.1466.
2,4-Dimethylpent-1-en-3-ol<sup>184</sup>

![Chemical Structure](image)

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<sup>-1</sup>) 3406 (O-H), 3070, 2969, 2959, 2923, 2873 (C-H), 1650 (C=C). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 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<sub>3</sub>), 0.95 (3H, d, J 6.8 Hz, CH<sub>3</sub>), 0.86 (3H, d, J 7.2 Hz, CH<sub>3</sub>). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) 146.69, 112.04, 81.69, 30.84, 19.37, 17.62, 17.52.

2,4-Dimethylpent-1-en-3-yl acetate<sup>185</sup>

![Chemical Structure](image)

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<sub>f</sub> 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, CDCl₃) 4.89-4.92 (3H, m, H1 and H3), 2.07 (3H, s, CH₃), 1.90 (1H, m, H4), 1.70 (3H, m, CH₃), 0.90 (3H, d, J 6.8 Hz, CH₃), 0.87 (3H, d, J 6.8 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 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 C₉H₁₆O₂ (M⁺) 156.1150, found 156.1151.

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

![Chemical Structure](image)

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%), R₁ 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, CDCl₃) 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, CH₃HBRAr), 4.13 (1H, d, J 11.6 Hz, CH₃HBRAr), 3.79 (3H, s, CH₃), 3.20 (1H, d, J 8.8 Hz, H3), 1.76 (1H, m, H4), 1.66 (3H, s, CH₃), 0.99 (3H, d, J 6.4 Hz, CH₃), 0.74 (3H, d, J 6.8 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₅H₂₂O₂ (M⁺) 234.1620, found 234.1619.
4-Methylpent-3-en-2-ol\textsuperscript{186}

![Chemical Structure](image)

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.\textsuperscript{186} 71 °C, 44 mmHg). IR (thin film, cm\textsuperscript{-1}) 3344 (O-H), 2970, 2928, 2874 (C-H), 1676 (C=C). \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) 5.21 (1H, m, H2), 4.56 (1H, m, H3), 1.71 (3H, s, CH\textsubscript{3}), 1.68 (3H, s, CH\textsubscript{3}), 1.32 (1H, s, broad, OH), 1.23 (3H, d, J 6.4 Hz, H1). \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}) 134.21, 129.31, 64.79, 25.64, 23.59, 17.99.

5-Methylhex-4-en-3-ol\textsuperscript{137}

![Chemical Structure](image)

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.\textsuperscript{137} 60 °C, 12 mmHg). IR (thin film, cm\textsuperscript{-1}) 3349 (O-H), 2968, 2930, 2877 (C-H), 1678 (C=C). \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) 5.15 (1H, m, H4), 4.26 (1H, ddd, J 10.8, 6.4, 3.2 Hz, H3), 1.73 (3H, s, CH\textsubscript{3}), 1.69 (3H, s, CH\textsubscript{3}), 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

![Structural formula of 2,5-Dimethylhex-4-en-3-ol](image)

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

![Structural formula of ((2,5-Dimethylhex-4-en-3-yloxy)methyl)benzene](image)

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%), Rf 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). ¹H-NMR (400 MHz, CDCl₃) 7.30-7.23 (5H, m, ArH), 5.10 (1H, m, H3), 4.60 (1H, d, J 12.0 Hz, CH₃Ar), 4.30 (1H, d, J 12.0 Hz, CH₂Ar), 3.70 (1H, dd, J 9.1, 7.2 Hz, H4), 1.73-1.81 (4H, m, CH₃ and H2), 1.62 (3H, m, H6), 0.96 (3H, d, J 6.8 Hz, H1), 0.84 (3H, d, J 6.4 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 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 ([M+Na]⁺, 5%), 145 (5), 105 (10), 91 (45), 69 (100). HRMS (ESI⁺) calcd. for C₁₅H₂₂O₆Na ([M+Na]⁺) 241.1568, found 241.1569.

**(E)-3-Methylpent-3-en-2-ol**¹⁴⁰

![Image](298)

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). ¹H-NMR (300 MHz, CDCl₃) 5.48 (1H, q, J 6.6 Hz, H4), 4.21 (1H, q, J 6.3 Hz, H2), 1.59-1.62 (6H, m, CH₃ and H5), 1.41 (1H, s, OH), 1.24 (3H, d, J 6.3 Hz, H1). ¹³C-NMR (75 MHz, CDCl₃) 139.20, 119.28, 73.45, 21.51, 13.01, 11.08.
(E)-4-Methylhex-4-en-3-ol\textsuperscript{38}

![Chemical structure](image)

299

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\textsuperscript{-1}) 3350 (O-H), 2963, 2934, 2876 (C-H), 1671 (C=C). \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}) 5.46 (1H, m, H5), 3.90 (1H, t, J 6.6 Hz, H3), 1.50-1.62 (8H, m, H6, CH\textsubscript{3} and H2), 1.42 (1H, s, OH), 0.84 (3H, t, J 7.8 Hz, H1). \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}) 137.60, 121.00, 79.54, 27.63, 13.02, 10.73, 10.15.

(E)-((4-Methylhex-4-en-3-yl oxy)-methyl)-benzene

![Chemical structure](image)

315

To a stirred solution of (E)-4-4methylhex-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%), \textit{Rf} 0.12 (100% n-hexane). IR (thin film, cm\textsuperscript{-1}) 3088, 3064, 3030, 2963, 2934, 2874, 2860 (C-H), 1669, 1606 (C=C), 1586. \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) 7.29-7.36 (5H, m, ArH), 5.41 (1H, m, H5), 4.44 (1H, d, J 11.6 Hz,
CH₄H₂BAr), 4.21 (1H, d, J 11.6 Hz, CH₄H₂BAr), 3.52 (1H, t, J 6.8 Hz, H3), 1.60-1.71 (4H, m, CH₃ and H2A), 1.42-1.57 (4H, m, H6 and H2B), 0.82 (3H, t, J 6.9 Hz, H1). ¹³C-NMR (100 MHz, CDCl₃) 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 ([M+H]^+), 10%, 204 (M^+, 5), 181 (10), 175 ([M-C₂H₅]^+), 100), 163 (10). HRMS (EI+) calcd. for C₁₄H₂₀O ([M]^+) 204.1514, found 204.1519.

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

![Chemical structure](image)

To a stirred solution of [(E)-4-methylhex-4-en-3-ol] 299 (100 mg, 0.88 mmol) and 1H-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%), Rₚ 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, CDCl₃) 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 CH₃), 0.87 (9H, s, 3xCH₃), 0.79 (3H, t, J 6.2 Hz, CH₃), -0.01 (3H, s, CH₃), -0.03 (3H, s, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 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 ([M+H]^+), 25%, 217 (18), 214 (100), 201 (25), 193 (10). HRMS (ESI+) calcd. for C₁₃H₂₀OSi ([M+H]^+) 229.1988, found 229.1986.
(E)-2,4-Dimethylhex-4-en-3-ol\textsuperscript{139}

\[
\begin{align*}
\text{OH} \\
\text{300}
\end{align*}
\]

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\textsuperscript{-1}) 3368 (O-H), 2956, 2922, 2871 (C-H), 1670 (C=C). \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}) 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, 2xCH\textsubscript{3}), 1.44 (1H, s, broad, OH), 0.98 (3H, d, J 6.6 Hz, CH\textsubscript{3}), 0.76 (3H, d, J 7.2 Hz, H1). \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}) 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.

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

![Chemical structure](image)

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 **(2R*,3S*)-4-(benzyloxycarbonylamino)-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, H4A), 3.11 (1H, m, H4B), 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 C₁₄H₂₀N₂O₅ ([M+Na]⁺) 282.1341, found 282.1339; calcd. for C₁₄H₁₉NO₃Na ([M+Na]⁺) 304.1161, found 304.1159.

A second fraction afforded **(2R*,3R*)-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, H4A), 3.28 (1H, m, H4B).
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 C₁₄H₁₉NO₄Na ([M+Na]⁺) 304.1161, found 304.1161.

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

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

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

![Chemical structures](image)

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-toluencesulfonyloxy)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%), Rf 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 (2S*,3R*)-2,3-dihydroxybutylcarbamate 319 and benzyl (2R*,3R*)-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. ( Asterisk indicates signals for the minor diastereomer).
Procedure 2:
To a solution of \((2R^*,3S^*)\)-4-(benzyloxy carbonylamino)-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 \((2S^*,3R^*)\)-2,3-dihydroxybutylcarbamate 319 as a colorless oil (17.0 mg, 100%), Rf 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. \(^1\)H-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). \(^13\)C-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 acetone derivatives.

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

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

![Diagram 335](image)

![Diagram 336](image)

The reaction was conducted according to the General Procedure 5.2 with mixture of benzyl \((2S^*,3R^*)\)-2,3-dihydroxybutylcarbamate 319 and benzyl \((2R^*,3R^*)\)-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 ((4S*,5R*)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methylcarbamate 335 and benzyl ((4R*,5R*)-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, CDCl₃) 7.30-7.37 (5H, m, ArH), 5.08-5.12 (3H, m, NH and CH₂Ar), 3.82 (1H, m, H5), 3.64 (1H, m, H4), 3.48 (1H, m, CH₃H₂NH), 3.30 (3H, s, CH₃), 1.39 (3H, s, CH₃), 1.37 (3H, s, CH₃), 1.29 (3H, d, J 6.4 Hz, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 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 ([M+Na]+, 100%), 91 (30). HRMS (ESI+) calcd. for C₁₅H₂₁NO₄Na ([M+Na]+) 302.1368, found 302.1366.

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

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

![Chemical structure of 335](image)

The reaction was conducted according to the General Procedure 5.2 with benzyl (2S*,3R*)-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-toluensulfonic acid (0.500 mg, 0.003 mmol). Purification by flash chromatography (20% ethyl acetate/n-hexane) afforded benzyl ((4S*,5R*)-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, CDCl₃) 7.30-7.37 (5H, m, ArH), 5.11 (2H, s, CH₂Ar), 5.07 (1H, s, NH), 4.33 (1H, m, H5), 4.11 (1H, m, H4), 3.48 (1H, m, CH₃H₂NH), 3.05 (1H, m, CH₃H₂NH), 1.44 (3H, s, CH₃), 1.33 (3H, s, CH₃), 1.23 (3H, d, J 6.4 Hz, CH₃). ¹³C-
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 ((4S*,5R*)-2,2,5-trimethyl-1,3-dioxolan-4-yl) methylcarbamate 335 were determined by NOESY 1D.

(2S*,3R*)-1-(Benzylxoycarbonylamino)-2-hydroxypentan-3-yl acetate
(2R*,3R*)-1-(Benzylxoycarbonylamino)-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 (2S*,3R*)-1-(benzylxoycarbonylamino)-2-hydroxypentan-3-yl acetate 326 as a colourless oil (53.1 mg, 43%) in the first fraction, Rₜ 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 (2R*,3R*)-1-(benzylxoycarbonylamino)-2-hydroxypentan-3-yl acetate 327 as a colourless oil (34.8 mg, 28%), Rₜ 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, CDCl₃) 7.29-7.38 (5H, m, ArH), 5.33 (1H, s, NH), 5.09-5.10 (2H, m, CH₂Ar), 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, CH₃), 1.62-1.72 (2H, m, H4), 0.90 (3H, t, J 6.8 Hz, H5). ¹³C-NMR (100 MHz, CDCl₃) 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 ([M+Na⁺], 90%), 91 (100). HRMS (ESI⁺) calcd. for C₁₅H₂₁N₅O₇Na ([M+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 (2S*,3R*)-2,3-dihydroxypentylcarbamate**

**Benzyl (2R*,3R*)-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 mixture of two diastereomers as a white solid (58.9 mg, 65%), Rf 0.19 (60% ethyl acetate/n-hexane). Integration of the NH signals in the 400 MHz ¹H-NMR spectrum provided a 2:1 ratio of benzyl (2S*,3R*)-2,3-dihydroxypentylcarbamate 320 and benzyl (2R*,3R*)-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, CDCl₃) 7.30-7.37 (5H, m, ArH), 5.32 (1H, s, NH) and 5.25* (1H, s, NH⁺), 5.11 (2H, m, CH₂Ar), 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⁺). ¹³C-NMR (100 MHz, CDCl₃) 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 C_{13}H_{19}NO_{4}Na ([M+Na]⁺) 276.1212, found 276.1213. (° indicates peaks for the minor product)

Procedure 2:
To a solution of (2S*,3R*)-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 (2S*,3R*)-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 C_{13}H_{19}NO_{4}Na ([M+Na]⁺) 276.1212, found 276.1212.

Benzyl ((4S*,5R*)-5-ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)methylcarbamate
Benzyl ((4R*,5R*)-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 (2S*,3R*)-2,3-dihydroxypentylcarbamate 320 and benzyl (2R*,3R*)-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 [(4S*,5R*)-5-ethy1-2,2-dimethyl-1,3-dioxolan-4-yl]-methylcarbamate 337 and benzyl [(4R*,5R*)-5-ethy1-2,2-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+) calcld. for C16H23NO4Na ([M+Na]+) 316.1525, found 316.1530. (*denotes peaks of the minor product).

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

\[
\begin{align*}
\text{OAc} & \quad \text{N} & \quad \text{O} & \quad \text{OH} \\
\text{328} & \quad \text{OH} & \quad \text{N} & \quad \text{O} & \quad \text{OAc} \\
\text{329}
\end{align*}
\]

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-toluenesulfonyl oxy)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%), Rf 0.55 (65% ethyl acetate/n-hexane). Further purification by
HPLC (SunFire Prep Silica OBD 5 μm, 3% isopropanol 97% n-hexane, flow rate 1.0 mL/min) provided (2S*,3R*)-1-(benzoxycarbonylamino)-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, CDCl₃) 7.29-7.36 (5H, m, ArH), 5.35 (1H, s, NH), 5.06-5.15 (2H, m, CH₂Ar), 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 CH₃), 1.66 (1H, s, OH), 0.93-0.94 (6H, m, 2xCH₃). ¹³C-NMR (100 MHz, CDCl₃) 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 ([M+Na]⁺, 99%), 293 (10), 266 (5), 250 (6), 232 (7), 188 (8), 120 (11), 91 (100), 81 (8). HRMS (ESI⁺) calcd. for C₁₆H₂₄NO₅ ([M+H]⁺) 310.1654, found 310.1654; HRMS (ESI⁺) calcd. for C₁₆H₂₃NO₅Na ([M+Na]⁺) 332.1474, found 332.1474.

A second fraction afforded (2R*,3R*)-1-(benzoxycarbonylamino)-2-hydroxy-4-methylpentan-3-yl acetate 329 as a colourless oil (26.1 mg, 20%), t_R 0.29 (65% ethyl acetate/n-hexane). Further purification by HPLC (column SunFire Preparative Silica 5 μm, 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, CDCl₃) 7.30-7.36 (5H, m, ArH), 5.26 (1H, s, NH), 5.10 (2H, s, CH₂Ar), 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 CH₃), 0.95 (3H, d, J 6.8 Hz, CH₃), 0.91 (3H, d, J 7.2 Hz, H5). ¹³C-NMR (100 MHz, CDCl₃) 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 ([M+Na]⁺, 100%), 246 (5), 91 (21). HRMS (ESI⁺) calcd. for C₁₆H₂₃NO₅Na ([M+Na]⁺) 332.1474, found 332.1473.

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

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

![Chemical Structures](image-url)
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 μmol) and benzyl N-(4-toluensulfonyloxy)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 $^1$H-NMR spectrum showed a 3.1:1 ratio of benzyl (2$R^*$,3$S^*$)-2,3-dihydroxy-4-methylpenty carbamate 322 and benzyl (2$R^*$,3$R^*$)-2,3-dihydroxy-4-methylpentyl carbamate 323. IR (thin film, cm$^{-1}$) 3405 (O-H, N-H), 3067, 3034, 2960, 2930, 2875 (C-H), 1695 (C=O), 1532. $^1$H-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$_2$Ar), 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, m, 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 ([M+Na]$^+$, 100%), 91 (38). HRMS (ESI+) calcd. for C$_{14}$H$_{21}$NO$_4$Na ([M+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**

![Chemical structure](image-url)

The reaction was conducted according to the General Procedure 5.2 with a mixture of benzyl (2$R^*$,3$S^*$)-2,3-dihydroxy-4-methylpentyl carbamate 322 and benzyl (2$R^*$,3$R^*$)-2,3-dihydroxy-4-methylpentyl carbamate 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-toluen 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 \(^1\)H-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. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 7.30-7.36 (5H, m, ArH), 5.11-5.15 (3H, m, NH and CH\(_2\)Ar), 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 ([M+Na]*, 100%). HRMS (ESI+) calcd. for C\(_{17}\)H\(_{25}\)NO\(_4\)Na ([M+Na]*) 330.1681, found 330.1680. (*Indicates peaks of the minor product).

\((2R^*,3S^*)\)-4-(Benzylxoycarbonylamino)-3-hydroxy-3-methylbutan-2-yl acetate
\((2R^*,3R^*)\)-4-(Benzylxoycarbonylamino)-3-hydroxy-3-methylbutan-2-yl acetate

![Image of structures 347 and 348]

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 \((2R^*,3S^*)\)-4-(benzylxoycarbonylamino)-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. \(^1\)H-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\(_2\)Ar), 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 (2R*,3R*)-4-(benzylxycarbonylamino)-3-hydroxy-3-
methylbutan-2-yl acetate 348 as a colourless oil (12.1 mg, 19%), Rf 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 (2S*,3R*)-2,3-dihydroxy-2-methylbutylcarbamate
Benzyl (2R*,3R*)-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 $^1$H-NMR spectrum showed a 2.4:1 ratio of benzyl (2S*,3R*)-2,3-di-hydroxy-2-methylbutylcarbamate 341 and benzyl (2R*,3R*)-2,3-di-hydroxy-2-methylbutylcarbamate 342. IR (thin film, cm$^{-1}$) 3401 (O-H, N-H), 3066, 3033, 2976, 2924, 2853 (C-H), 1697 (C=O), 1534. $^1$H-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$_2$Ar), 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 ([M+Na]$^+$, 100%), 91 (5). HRMS (ESI+) calcd. for C$_{13}$H$_{19}$NO$_4$Na ([M+Na]$^+$) 276.1212, found 276.1213; calcd. for C$_{13}$H$_{20}$NO$_4$ ([M+H]$^+$) 254.1392, found 254.1392; calcd. for C$_{13}$H$_{19}$NO$_4$K ([M+K]$^+$) 292.0951, found 292.0954 (*indicates peaks of the minor product).

Procedure 2:

To a solution of (2R*,3S*)-4-(benzyloxy carbonylamino)-3-hydroxy-3-methyl-butanol-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 (2S*,3R*)-2,3-di-hydroxy-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. $^1$H-NMR (400 MHz, CDCl$_3$) 7.30-7.38 (5H, m, ArH), 5.28 (1H, s, NH), 5.12 (2H, s, CH$_2$Ar), 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 ([M+Na]$^+$, 100%), 190 (4), 91 (23), 74 (4). HRMS (ESI+) calcd. for C$_{13}$H$_{19}$NO$_4$Na ([M+Na]$^+$) 276.1212, found 276.1213.
Procedure 3:
To a solution of (2R*,3R*)-4-(benzyloxy carbonylamino)-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 benzy (2R*,3R*)-2,3-dihydroxy-2-methyl-butyl-carbamate 342 as a colourless liquid (10.1 mg, 59%), Rf 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 ((4S*,5R*)-2,2,4,5-tetramethyl-1,3-dioxolan-4-yl)methylcarbamate

![Chemical Structure](image)

The reaction was conducted according to the General Procedure 5.2 with benzyl (2S*,3R*)-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%), Rf 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 ((4R*,5R*)-2,2,4,5-tetramethyl-1,3-dioxolan-4-yl)methylcarbamate

The reaction was conducted according to the General Procedure 5.2 with benzyl (2R*,3R*)-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 (2R*,3S*)-2-hydroxy-3-(4-methoxybenzoyloxy)-2-methylbutyl carbamate
Benzyl (2R*,3R*)-2-hydroxy-3-(4-methoxybenzoyloxy)-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%), Rf 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 (2R*,3S*)-2-hydroxy-3-(4-methoxybenzoyloxy)-2-methylbutyl carbamate 353 and benzyl (2R*,3R*)-2-hydroxy-3-(4-methoxybenzoyloxy)-2-methylbutyl carbamate 354. Further separation by preparative HPLC (column µPorasil silica 10 µm, 3.9 x 300 mm, solvent 1% isopropanol/n-hexane, flow rate 0.7 mL/min) afforded benzyl (2R*,3R*)-2-hydroxy-3-(4-methoxybenzyl-oxy)-2-methylbutylcarbamate 354 at tR 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, CH3HAr), 4.31 (1H, d, J 11.2 Hz, CH3H2Ar), 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 (2R*,3S*)-2-hydroxy-3-(4-methoxybenzyl-oxy)-2-methylbutylcarbamate 353 at tR 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. $^1$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$_2$Ar), 4.60 (1H, d, J 10.8 Hz, CH$_2$Ar), 4.30 (1H, d, J 11.6 Hz, CH$_2$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$_3$). $^{13}$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 ([M+Na]$^+$, 75%), 121 (100). HRMS (ESI+) calcd. for C$_{21}$H$_{27}$NO$_3$Na ([M+Na]$^+$) 396.1787, found 396.1788.

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

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

![Structure](image)

The reaction was conducted according to the General Procedure 5.1 with ((3-methylbut-3-en-2-yl)oxy)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 (2R*,3S*)-3-(benzyloxy)-2-hydroxy-2-methylbutylcarbamate 345 and benzyl (2R*,3R*)-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 $^1$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. $^1$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$_2$Ar), 4.67 (1H, d, J 11.6 Hz, CH$_2$Ar), 4.38 (1H, d, J 11.2 Hz, CH$_2$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$$^*$). $^{13}$C-NMR (100 MHz, CDCl$_3$) 157.36, 138.09,
(2S*,3R*)-1-(Benzyloxycarbonylamino)-2-hydroxy-2-methylpentan-3-yl acetate

(2R*,3R*)-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 (2S*,3R*)-1-(benzyloxycarbonylamino)-2-hydroxy-2-methylpentan-3-yl acetate 349 in the first fraction as a colourless oil (67.0 mg, 55%). Rf 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, CDCl₃) 7.29-7.36 (5H, m, ArH), 5.44 (1H, s, NH), 5.07-5.16 (2H, m, CH₂Ar), 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, CH₃), 1.80 (1H, m, H4A), 1.54 (1H, m, H4B), 1.15 (3H, s, CH₃), 0.90 (3H, t, J 7.6 Hz, H5). ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₆H₂₃NO₄Na ([M+Na]⁺) 332.1474, found 332.1487; calcd. for C₁₆H₂₄NO₅ ([M+H]⁺) 310.1654, found 310.1654.

A second fraction afforded (2R*,3R*)-1-(benzyloxycarbonylamino)-2-hydroxy-2-methylpentan-3-yl acetate 350 as a colourless oil (23.8 mg, 20%), Rf 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, CDCl₃) 7.30-7.36 (5H, m, ArH), 5.23 (1H, s, NH), 5.11 (2H, s, CH₂Ar), 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 C₁₆H₂₂NO₅K ([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 acetoniide derivatives.

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

**Benzyl (2R*,3R*)-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 (2S*,3R*)-2,3-dihydroxy-2-methyl-pentylcarbamate 343 and benzyl (2R*,3R*)-2,3-dihydroxy-2-methylpentylcarbamate 344 as a colourless oil (67.2 mg, 40%), Rf 0.36 (70% ethyl acetate/n-hexane). Integration of C₂-H₃ 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_{4}Na ([M+Na]^+) 290.1368, found 290.1368; calcd. for C_{14}H_{21}NO_{4}K (M+K)^+ 306.1108, found 306.1108 (*Indicates signal of the minor product).

Procedure 2:^{187}

To (2S*,3R*)-1-(benzoxycarbonylamino)-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 (2S*,3R*)-2,3-dihydroxy-2-methylpentyl carbamate 343 as a colourless oil (21.6 mg, 100%), R_B 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, CDCl3) 7.30-7.37 (5H, m, ArH), 5.28 (1H, s, NH), 5.09-5.16 (2H, m, CH₂Ar), 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, CH₃), 1.03 (3H, t, J 8.0 Hz, H5). ^13C-NMR (100 MHz, CDCl₃) 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_{4}Na ([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 (2R*,3R*)-1-(benzoxycarbonylamino)-2-hydroxy-2-methylpentan-3-yl acetate 350 (20.0 mg, 0.065 mmol) was added a freshly prepared 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 (2R*,3R*)-2,3-dihydroxy-2-methylpentyl carbamate 344 as a colourless oil (16.7 mg, 97%), R_B 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, CDCl₃) 7.30-7.38 (5H, m, ArH), 5.22 (1H, s, NH), 5.11 (2H, s, CH₂Ar), 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, CH₃), 1.00 (3H, t, J 7.2 Hz, H5). ¹³C-NMR (100 MHz, CDCl₃) 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 ([M+Na⁺], 100%), 204 (4), 91 (5). HRMS (ESI⁺) calcd. for C₁₄H₂₂NO₄ ([M+H⁺]⁺) 268.1549, found 268.1541; calcd. for C₁₄H₂₁NO₄Na ([M+Na⁺]⁺) 290.1368, found 290.1364.

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

![Structural formula of benzyl ((4S*,5R*)-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 (2S*,3R*)-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%), Rf 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, CDCl₃) 7.30-7.37 (5H, m, ArH), 5.11 (2H, s, CH₂Ar), 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, CH₃), 1.35 (3H, s, CH₃), 1.23 (3H, s, CH₃), 1.05 (3H, t, J 7.2 Hz, H10). ¹³C-NMR (100 MHz, CDCl₃) 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 ([M+Na⁺]⁺, 100%), 91 (9). HRMS (ESI⁺) calcd. for C₁₇H₂₆NO₄ ([M+H⁺]⁺) 308.1862, found 308.1865; calcd. for C₁₇H₂₅NO₄Na ([M+Na⁺]⁺) 330.1681, found 330.1678.
The NOE interactions for product benzyl ((4S*,5R*)-5-ethyl-2,2,4-trimethyl-1,3-dioxolan-4-yl)methylcarbamate 337 were determined by NOESY_1D.

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

![Chemical Structure](image)

The reaction was conducted according to the General Procedure 5.2 with benzyl (2R*,3R*)-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-toluene sulfonic acid (0.500 mg, 0.003 mmol). The title compound 338 was afforded as a yellowish oil (19.2 mg, 100%), Rf 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, CDCl₃) 7.30-7.37 (5H, m, ArH), 5.11 (3H, s, broad, NH and CH₂Ar), 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, CH₃), 1.31 (3H, s, CH₃), 1.07 (3H, s, CH₃), 1.01 (3H, t, J 7.2 Hz, H10). 

¹³C-NMR (100 MHz, CDCl₃) 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 ([M+Na]⁺, 100%), 91 (52). HRMS (ESI⁺) calcd. for C₁₇H₂₃NO₄ ([M+Na]⁺) 308.1862, found 308.1861; calcd. for C₁₇H₂₃NO₄Na ([M+Na]⁺) 330.1681, found 330.1681; calcd. for C₁₇H₂₃NO₄K ([M+K]⁺) 346.1421, found 346.1420.

The NOE interactions for product benzyl ((4R*,5R*)-5-ethyl-2,2,4-trimethyl-1,3-dioxolan-4-yl)methylcarbamate 338 were determined by NOESY_1D.
Benzyl (2S*,3R*)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylpentylcarbamate
Benzyl (2R*,3R*)-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-(toluenesulfonyloxy)carbamate 202 (114 mg, 0.35 mmol). Purification by flash chromatography (20% ethyl acetate/n-hexane) afforded an inseparable mixture of benzyl (2S*,3R*)-2-hydroxy-3-(4-methoxybenzyloxy)-2-methylpentylcarbamate 355 and benzyl (2R*,3R*)-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-CH$_3$ signal of the 400 MHz $^1$H-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. $^1$H-NMR (400 MHz, CDCl$_3$) 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, ArCH$_2$), 4.65 (1H, d, $J$ 10.4 Hz, CH$_2$ArB), 4.50 (1H, d, $J$ 11.2 Hz, CH$_2$ArB), 3.78 (3H, s, OCH$_3$), 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, CH$_3$) and 1.11 (3H, s, CH$_3^*$), 1.07 (3H, t, $J$ 7.6 Hz, H5) and 1.04 (3H, t, $J$ 7.6 Hz, H5$^*$). $^{13}$C-NMR (100 MHz, CDCl$_3$) 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 C$_{22}$H$_{29}$NO$_3$Na ([M+Na]$^+$) 410.1943, found 410.1938. (*Indicates signals of the minor product)
(2S*,3R*)-1-(Benzyloxycarbonylamino)-2-hydroxy-2,4-dimethylpentan-3-yl acetate

(2R*,3R*)-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 μmol) and benzyl N-(4-toluenesulfonyl)carbamate 202 (148 mg, 0.46 mmol). Purification by flash chromatography (30% ethyl acetate/n-hexane) afforded (2S*,3R*)-1-(benzyloxycarbonylamino)-2-hydroxy-2,4-dimethylpentan-3-yl acetate 351 as a colourless oil (31.0 mg, 25%) in the first fraction, Rf 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, CDCl₃) 7.29-7.37 (5H, m, ArH), 5.36 (1H, s, NH), 5.08-5.16 (2H, m, CH₂Ar), 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, CH₃ and H4), 1.19 (3H, s, CH₃), 1.00 (3H, d, J 6.8 Hz, CH₃), 0.94 (3H, d, J 6.4 Hz, H5). ¹³C-NMR (100 MHz, CDCl₃) 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 ([M+Na]+, 100%), 286 (5), 91 (11). HRMS (ESI+) calcd. for C₁₇H₂₅NO₄Na ([M+Na]+) 346.1630, found 346.1623.

A second fraction afforded (2R*,3R*)-1-(benzyloxycarbonylamino)-2-hydroxy-2,4-dimethylpentan-3-yl acetate 352 as a colourless oil (8.9 mg, 7%), Rf 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, CDCl₃) 7.30-7.36 (5H, m, ArH), 5.24 (1H, s, NH), 5.11 (2H, s, CH₂Ar), 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, CH₃ and H4), 1.21 (3H, s, CH₃), 0.99 (3H, d, J 7.2 Hz, CH₃), 0.94 (3H, d, J 6.4 Hz, H5). ¹³C-NMR (100 MHz, CDCl₃) 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 ([M+Na]+, 100%), 286 (5), 91 (11). HRMS (ESI+) calcd. for C₁₇H₂₅NO₄Na ([M+Na]+) 346.1630, found 346.1623.
286 (7), 260 (5), 91 (8). HRMS (ESI+) calcd. for C_{17}H_{23}NO_{4}Na ([M+Na]^+) 346.1630, found 346.1630.

**Benzyl (2S*,3R*)-2-hydroxy-3-(4-methoxybenzyl)oxy)-2,4-dimethylpentylcarbamate**

**Benzyl (2R*,3R*)-2-hydroxy-3-(4-methoxybenzyl)oxy)-2,4-dimethylpentylcarbamate**

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 diastereomers as a colourless oil (25.2 mg, 17%) with d.r. 12:1:1. Purification with preparative HPLC (column μPorasil silica 10 µm, 3.9x300 mm, 1% isopropanol/n-hexane, flow rate 0.7 mL/min) afforded benzyl (2S*,3R*)-2-hydroxy-3-(4-methoxybenzyl)oxy)-2,4-dimethylpentylcarbamate 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. \(^1\)H-NMR (400 MHz, CDCl₃) 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, CH₂Ar), 4.68 (1H, d, J 10.8 Hz, CH₃Ar), 4.46 (1H, d, J 10.8 Hz, CH₃Ar), 3.78 (3H, s, OCH₃), 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, CH₃), 1.12 (3H, d, J 6.8 Hz, CH₃), 1.03 (3H, d, J 6.8 Hz, H5). \(^1\)C-NMR (100 MHz, CDCl₃) 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_{4}Na ([M+Na]^+) 424.2100, found 424.2102; calcd. for C_{23}H_{32}NO₅ ([M+H]^+) 402.2280, found 424.2290.
A second fraction (t<sub>R</sub> 21.33 min) afforded benzyl (2R*,3R*)-2-hydroxy-3-(4-methoxybenzyl-oxy)-2,4-dimethylpentyl carbamate 358 as a colourless oil (1.8 mg, 7%). IR (thin film, cm<sup>-1</sup>) 3401 (O-H, N-H), 3031, 2958, 2925, 2872, 2852 (C-H), 1705 (C=O), 1612, 1587 (C=C), 1514. LRMS (ESI+) 424 ([M+Na]<sup>+</sup>, 100%), 413 (11), 302 (32), 181 (8), 149 (18), 121 (65), 91 (42). HRMS (ESI+) calcd. for C<sub>23</sub>H<sub>31</sub>NO<sub>5</sub>Na ([M+Na]<sup>+</sup>) 424.2100, found 424.2099.

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

![Chemical structure of 368](image)

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<sub>f</sub> 0.14 (80% diethyl ether/n-hexane). IR (thin film, cm<sup>-1</sup>) 3414 (broad, O-H, N-H), 3067, 3033, 2956, 2923, 2852 (C-H), 1721, 1699 (C=O), 1513. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 7.31-7.37 (5H, m, ArH), 5.56 (1H, d, J 9.6 Hz, NH), 5.14 (2H, s, CH<sub>2</sub>Ar), 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<sub>3</sub>), 1.24 (3H, s, H1), 1.18 (3H, d, J 6.4 Hz, H5). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) 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 ([M+Na]<sup>+</sup>, 85%), 272 (28), 245 (11), 232 (5), 177 (5), 149 (6), 132 (10), 91 (100), 89 (9), 57 (5). HRMS (ESI+) calcd. for C<sub>14</sub>H<sub>21</sub>NO<sub>3</sub>Na ([M+Na]<sup>+</sup>) 290.1368, found 290.1367.

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

![Chemical structure of 369](image)
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%), Rf 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, CDCl₃) 7.29-7.36 (5H, m, ArH), 5.52 (1H, d, J 10.0 Hz, NH), 5.09-5.16 (2H, m, CH₂Ar), 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, CH₃), 1.25 (3H, s, H1), 0.95 (3H, t, J 7.6 Hz, H6). ¹³C-NMR (100 MHz, CDCl₃) 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 ([M+Na]⁺, 100%), 286 (4), 145 (5), 91 (84), 85 (5). HRMS (ESI⁺) calcd. for C₁₅H₂₃NO₃Na ([M+Na]⁺) 304.1525, found 304.1526.

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

![Reaction Scheme]

**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 (2S*,3R*)-2,3-dihydroxy-2-methylpentylcarbamate 343 and benzyl (2R*,3R*)-2,3-dihydroxy-2-methylpentylcarbamate 344 as a colourless oil (30.2 mg, 23%), Rf 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-toluenesulfonyl-oxy)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 (2S*,3R*)-2,3-dihydroxy-2-methylpentylcarbamate 343 and benzyl (2R*,3R*)-2,3-dihydroxy-2-methylpentylcarbamate 344 as a colourless oil (33.7 mg, 25%), Rf 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**

\[ \text{51} + \text{49} \xrightarrow{(i)} \text{214} + \text{144} \]

**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 μmol) and benzyl N-(4-toluenesulfonyloxy)carbamate 202 (125 mg, 0.39 mmol). Purification by flash chromatography (25% ethyl acetate/n-hexane) afforded benzyl (1R*,2R*)-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. \(^1\text{H-NMR (400 MHz, CDCl₃)}\) 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). \(^1\text{C-NMR (100 MHz, CDCl₃)}\) 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. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 7.29-7.37 (10H, m, ArH), 5.12 (3H, m, broad, NH and CH\(_2\)Ar), 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). \(^1^3\)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 \(1H\)-indene and styrene**

![Chemical structure](image)

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

The reaction was conducted according to the General Procedure 5.3 with \(1H\)-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-toluenesulfonyl)carbamate 202 (135.6 mg, 0.42 mmol). Purification by flash chromatography (20% ethyl acetate/n-hexane) afforded inseparable mixture of two regioisomers from \(1H\)-indene and one regioisomer from styrene. Further separation with preparative HPLC (column SunFire prep silica 5 \(\mu\)m, 2% isopropanol/n-hexane, flow rate 0.7 mL/min) afforded benzyl (1\(R^*,2S^*\))-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. \(^1\)H-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\(_2\)Ar), 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). \(^1^3\)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 ([M+Na]+, 85%), 304 (38), 266 (5), 235 (8), 222 (20), 205 (5), 174 (4), 91 (100). HRMS (ESI+) calcd. for C\(_{17}\)H\(_{17}\)NO\(_3\)Na ([M+Na]+) 306.1106, found 306.1105.
A second fraction afforded benzyl (1R*,2S*)-2-hydroxy-2,3-dihydro-1H-inden-1-y1carbamate 370 as an orange oil (20.1 mg, 17%) at tR 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, CDCl₃) 7.23-7.38 (10H, m, ArH), 5.41 (1H, s, NH), 5.09-5.19 (3H, m, H1 and CH₂Ar), 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). ¹³C-NMR (100 MHz, CDCl₃) 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 ([M+Na]⁺), 220 (6), 133 (8), 91 (84). HRMS (ESI⁺) calcd. for C₁₇H₁₇NO₃Na ([M+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 tR 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, CDCl₃) 7.27-7.38 (10H, m, ArH), 5.18 (1H, s, NH), 5.11 (2H, s, CH₂Ar), 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). ¹³C-NMR (100 MHz, CDCl₃) 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**

![Chemical structure](image)

**Conditions:** (i) 3-methylbut-2-en-1-ol 243 (1.0 eq.), styrene 49 (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-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, Rf 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, CDCl₃) 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, H1A), 3.31 (1H, ddd, J 13.6, 7.6, 4.8 Hz, H1B), 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%), Rf 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**

![Chemical structures](image)

**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
(2R*,3S*)-4-(benzylxocarbonylamino)-3-hydroxy-3-methylbutan-2-yl acetate 347 as a colourless liquid (11.2 mg, 11%) at tR 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. ¹H-NMR (400 MHz, CDCl₃) 7.29-7.36 (5H, m, ArH), 5.30 (1H, s, NH), 5.06-5.15 (2H, m, CH₂Ar), 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, CH₃), 1.25 (3H, d, J 6.4 Hz, H1), 1.16 (3H, s, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 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.

(2R*,3R*)-4-(Benzyloxy carbonylamino)-3-hydroxy-3-methylbutan-2-yl acetate 348 was afforded as a colorless oil (4.7 mg, 5%) at tR 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. ¹H-NMR (400 MHz, CDCl₃) 7.30-7.36 (5H, m, ArH), 5.08-5.14 (3H, m, NH and CH₂Ar), 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, CH₃), 1.25 (3H, d, J 6.0 Hz, H1), 1.16 (3H, s, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 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 (2S*,3R*)-2,3-dihydroxy-2-methylbutylcarbamate 341 as a colourless oil (24.4 mg, 28%) at tR 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. ¹H-NMR (400 MHz, CDCl₃) 7.31-7.37 (5H, m, ArH), 5.27 (1H, s, NH), 5.12 (2H, s, CH₂Ar), 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, CH₃). ¹³C-NMR (100 MHz, CDCl₃) 158.09, 136.19, 128.57, 128.27, 128.14, 74.70, 71.36, 67.21, 47.11, 20.69, 16.67.

Benzyl (2R*,3R*)-2,3-dihydroxy-2-methylbutylcarbamate 342 was afforded as a colourless oil (5.4 mg, 6%) at tR 25.69 min. IR (thin film, cm⁻¹) 3401 (O-H, N-H), 3066, 3034, 2975, 2927 (C-H), 1697 (C=O), 1532. ¹H-NMR (400 MHz, CDCl₃) 7.30-7.36 (5H, m, ArH), 5.36 (1H, s, NH), 5.11 (2H, s, CH₂Ar), 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), 215
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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Appendix
Benzyl N-(4-toluenesulfonyloxy)carbamate

$^1$H-NMR (400 MHz, CDCl$_3$)

$^{13}$C-NMR (100 MHz, CDCl$_3$)
tert-Butyl N-(methanesulfonyloxy)carbamate

$^1$H-NMR (300 MHz, CDCl$_3$)

$^{13}$C-NMR (75 MHz, CDCl$_3$)
NOESY1D (400 MHz, CDCl3)
Benzyl ((4S^*,5R^*)-2,2,5-tetramethyl-1,3-dioxolan-4-yl)methylcarbamate

ppm
NOESY 1D (400 MHz, CDCl3)
Benzyl ((4R*,5R*)-2,2,4,5-tetramethyl-1,3-dioxolan-4-yl)methylcarbamate

Appendix A.4
Example of NOESY spectra of actinonide 365
NOESY1D (400 MHz, CDCl3)
Benzyl ((4S*,5R*)-5-ethyl-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl carbamate
NOESY 1D (400 MHz, CDCl3)
Benzyl ((4R*,5R*)-5-ethyl-2,2,4-trimethyl-1,3-dioxolan-4-yl)methyl carbamate

C2-CH₃
C4-CH₂
H5
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).