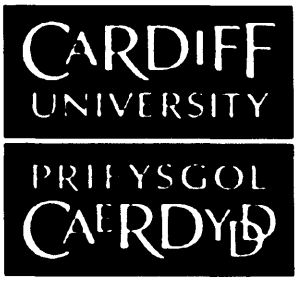

Asymmetric α-Oxygenation of Carbonyl Compounds.

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A Thesis Submitted for the Degree of Doctor of Philosophy

at

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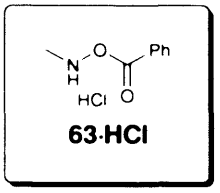
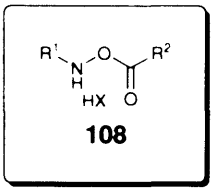
Abstract.

The α-hydroxy carbonyl group represents a significant building block in organic synthesis, which is reflected by the extensive synthetic efforts directed towards introduction of this group in a chemo- regio-, stereo-, and enantioselective manner. Traditional methods for the α-oxygenation of carbonyl compounds involve the formation and reaction of air-sensitive intermediates. This thesis describes an alternative metal-free approach to the formation of C–O bonds α- to a carbonyl group, in an asymmetric manner.



63·HCl



108

Chapter 1 provides an overview of the literature methods for the α-oxygenation of carbonyl compounds, incorporating recent advances in this field achieved previously within the group, following discovery of **63·HCl** to affect a one-pot α-oxygenation transformation. Chapter 2 outlines our objectives and describes methods for the preparation of chiral hydroxylamine reagents based on the generic structure **108**. The focus of this chapter is on establishing asymmetric transformations and their optimisation. Chapter 3 examines varying the size and nature of the *O*-acyl group (R^2) in order to determine its effect on the asymmetric reaction. Chapter 4 studies the influence of relative electronic effects on the asymmetric reaction, by varying the electronic properties of R^1 and R^2. Chapter 5 explores the role of the *N*-substituent (R^1) on an asymmetric α-oxyacylation transformation. Application of our methodology to other carbonyl substrates is also examined. Chapter 6 investigates an alternative method for the synthesis of chiral α-oxygenated carbonyl compounds, involving formation and reaction of chiral nitrones.

In recent years methods have been developed within the group for the α-oxycarbonoylation, oxycarbamoylation and oxytosylation of carbonyl compounds. Chapter 7 investigates application of the methodology developed within this thesis to each of these transformations.

Following an interesting observation, a novel procedure for the conversion of primary amines into ketones was developed, which is discussed in Chapter 8.

Acknowledgements.

I would like to begin by thanking Dr. Nick Tomkinson for giving me the opportunity to study for a PhD under his supervision and as a part of the Tomkinson group. Nick has provided excellent support and guidance and I could not have wished for a better environment to learn and develop, both scientifically and personally. I would also like to thank my industrial collaborator at Syngenta, Dr. Chris Mathews, for discussions and his interest in the project, along with his insightful suggestions. I am also grateful to Syngenta and the EPSRC for financial contributions.

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I thank my fiancé Matthew Smithen for his unconditional love, as well as his encouragement and understanding. His support has been invaluable and I look forward to reciprocating in the near future.

I would finally like to extend my heartfelt thanks to my family for their love and support. To my parents, Anne-Marie and John, my sisters and brother, my grandparents, and my soon-to-be in-laws, I love you all very much and am forever grateful.

Table of Contents.

Detailed Table of Contents.

Abbreviations.

Å – Angstrom

Ac – Acyl

AD – Asymmetric Dihydroxylation

Ad – Adamantyl

aq – Apparent Quartet

aq. – Aqueous

Ar – Aromatic

at – Apparent Triplet

Bn – Benzyl

Boc – Butoxycarbonyl

BPO – Benzoyl Peroxide

^{t}Bu – *Tertiary* Butyl

Bz – Benzoyl

cat. – Catalyst

CBz – Carbobenzyloxy

CDI – Carbonyl Diimidazole

CSA – Camphor Sulfonic Acid

d – Doublet

dd – Doubled Doublet

DBU – 1,8-Diazabicyclo[5.4.0]undec-7-ene

d.e. – Diastereomeric Excess

DFT – Density Functional Theory

$(DHQ)_2$-PHAL – 1,4-Bis(dihydroquininyl) Phthalazine

$(DHQD)_2$-PHAL – 1,4-Bis(dihydroquinidinyl) Phthalazine

DMAP – Dimethylaminopyridine

DMF – Dimethylformamide

DMP – Dess-Martin Periodinane

DMPU - 1,3-Dimethyl-3,4,5,6-Tetrahydro-2(1H)-Pyrimidinone

DMSO – Dimethyl Sulfoxide

2,4-DNPH – 2,4-Dinitrophenylhydrazine

DPP – Diphenyl Phosphate

EDG – Electron Donating Group

e.e. – Enantiomeric Excess

Eq. – Equivalents

Et – Ethyl

Ether – Diethyl Ether

$Eu(hfc)_3$ – Europium Tris[3-(Heptafluoropropylhydroxymethylene)-(+)-Camphorate]

EWG – Electron Withdrawing Group

g – Gramme (s)

(g) – Gas

HCl – Hydrogen Chloride

HMPA - Hexamethylphosphoramide

HPLC – High Performance Liquid Chromatography

HRMS – High Resolution Mass Spectrometry

hrs – Hours

Hz – Hertz

IBA – 2-Iodosobenzoic Acid

IBX – 2-Iodoxybenzoic Acid

IPA – Isopropan-2-ol

IR – Infra Red

J – Coupling Constant

KOH – Potassium Hydroxide

LA – Lewis Acid

Lit – Literature

LRMS – Low Resolution Mass Spectrometry

m – Multiplet

m- – Meta

M – Molar

Me – Methyl

Mesic – Methane Sulphonic

min(s) – Minutes

mL – Millilitre (s)

mmol – Millimole(s)

mol – Mole(s)

MoOPD – MoO_5·Py·DMPU

MoOPH – MoO_5·Py·HMPA

m.p. – Melting Point

Ms – Methane sulphonyl

MS – Mass Spectrometry

MsOH – Methane sulphonic Acid

NaOCl – Sodium Hypochlorite

p-NBSP – *p*-Nitrobenzenesulphonyl Peroxide

NMO – *N*-Methylmorpholine-*N*-Oxide

NMR – Nuclear Magnetic Resonance

o- – Ortho

p- – Para

P.E. – Petroleum Ether

PG – Protecting Group

Ph – Phenyl

pKa – Acid Dissociation Constant

PPNO – 4-Phenylpyridine-*N*-Oxide

^{i}Pr - Isopropyl

Py – Pyridine

reagent – *N*-Substituted-*O*-Acyl Hydroxylamine

Red. – Reduction

r.t. – Room Temperature

s – Singlet

SET – Single Electron Transfer

S.M. – Starting Material

t – Triplet

t – Tertiary

Temp. – Temperature

tert – Tertiary

TCA – Trichloroacetic Acid

TFA – Trifluoroacetic Acid

THF – Tetrahydrofuran

TLC – Thin Layer Chromatography

Tosic – Toluene sulphonic

Tosyl – Toluene sulfonyl

p-Ts – 4-Toluene sulphonyl

UV – Ultra Violet

σ – Hammett Constant

* – Chiral

Chapter 1.

Introduction: Existing Methods Available for the α-Oxygenation of Carbonyl Compounds.

1. Introduction.

In the field of synthetic chemistry, much effort has been afforded to the development of novel selective transformations that are both cleaner and more efficient.[1] As a result of this, the use of metal-free processes for the manipulation and transformation of functional groups has, in recent years, seen a surge of interest, owing to the potential for academic, industrial, economic and environmental gain.

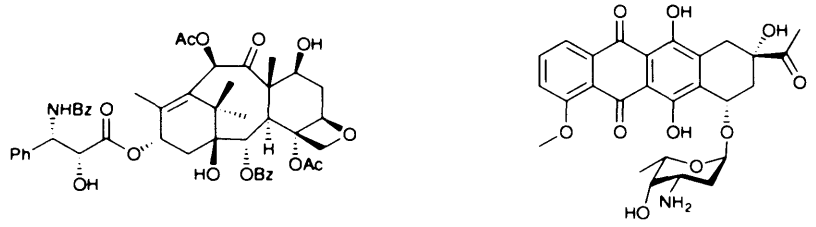
In the past decade, the advancement in new synthetic methods based on organic molecules has been remarkable.[2] Metals have, in many instances, notable advantages over organic compounds, for example, molecular and structural variations, and diverse reactivity patterns adjustable through varying the ligands. Despite this, interest in developing novel metal-free processes has come about due to the inherent disadvantages of metal-mediated reactions, which include expense, toxicity, pollution, product contamination and waste treatment.[3] The application of small, enantiomerically pure organic molecules represents an alternative synthetic concept and many metal-free and organocatalytic reactions meet the standards of established organic reactions.[4,5] In many instances, high enantioselectivities result from these small compounds, and preparative advantages have also been noted, in that the reactions can usually be performed in the presence of moisture and air. Organic molecules are also inexpensive and relatively stable, and through anchoring to a solid support can be reused more easily than analogous organometallic/bioorganic materials.[2]

1.1. α-Oxygenation of Carbonyl Compounds.

The carbonyl group is one of the most fundamental functional groups in organic synthesis. The importance of this group lies with its ability to act as both an electrophile and a nucleophile. For example, by deprotonation at the α-position it can act as a nucleophile and undergo reactions to give a variety of α-functionalised carbonyl compounds.

This introduction will focus on the formation of α-oxygenated carbonyl compounds, which involves forming a new C–O bond α- to a carbonyl group. The target molecules in these reactions are α-hydroxy carbonyl compounds, which represent

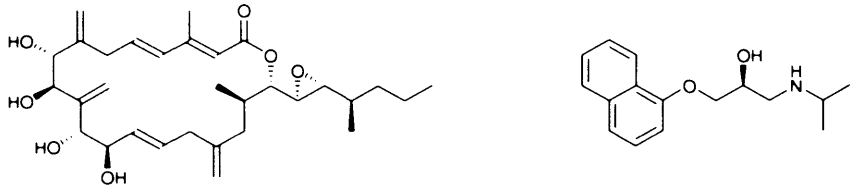
significant building blocks in organic synthesis. This functionality is present in both naturally occurring and synthetic biologically significant compounds including carbohydrates, antibiotics, alkaloids, and terpenes.[6] Two examples of their occurrence in drug molecules are Taxol[7] **1** and Daunomycin[8] **2** (Figure 1.1), both of which are used in the treatment of cancer.



1 **2**

Figure 1.1: Examples of the α-hydroxy carbonyl group in drug molecules.

The α-hydroxy carbonyl group is also a useful precursor to other synthetically useful compounds; for example, through reduction to the diol using sodium borohydride, as seen in (+)-amphidinolide A[9] **3** (Figure 1.2), which is also a potent anti-cancer drug; or reductive amination to give the amino alcohol, as can be found in (*S*)-Propranolol[10] **4**, which is used in the treatment of hypertension.



3 **4**

Figure 1.2: Example of diol (3) and amino alcohol (4) functionalities embedded in drug molecules.

The synthetic importance of the α-hydroxy moiety is reflected in the extensive synthetic effort that has been directed toward introducing this group in a chemo-, regio- and stereoselective manner. As a result, many methods have been developed for the synthesis of the α-hydroxy carbonyl functional group. These fall into two main categories, which are the traditional metal-catalysed or metal-mediated processes,[11] and the more recent metal-free organocatalytic processes.[5,6] Each of these will be examined in more detail.

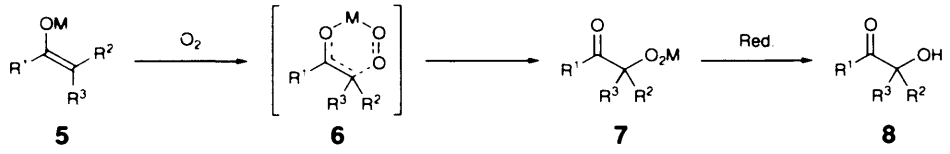
1.2. Traditional Methods for α-Oxygenation using Metals.

1.2.1. Use of Enolates.

The oxidation of metal enolates is the most widely used procedure for the preparation of α-hydroxy carbonyl compounds.[6] Many oxidising reagents have been investigated for this transformation and of these, the use of molecular oxygen[12] and molybdenum complexes[13,14] have proved to be very effective.

1.2.1.1. Molecular Oxygen.

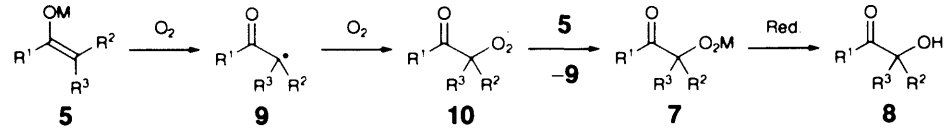
Molecular oxygen reacts with an enolate **5** to give the α-hydroxy carbonyl product **8** following reduction of an α-hydroperoxycarbonyl intermediate **7**.[11] There are two mechanistic rationales that have been proposed for this transformation, the first involving direct oxygenation, by electrophilic addition of oxygen to the enolate **5** *via* a six-membered transition state **6**, as shown in Reaction scheme 1.1.



5 **6** **7** **8**

Reaction scheme 1.1: α-Oxygenation using molecular oxygen *via* a concerted process.[11]

Alternatively, oxidation may follow a radical-chain mechanism, whereby single electron transfer is involved from the enolate **5** to the oxygen, thus generating an α-keto radical **9**, Reaction scheme 1.2. This then reacts with oxygen to give an α-hydroperoxy radical **10**, which in turn reacts with the enolate **5** giving the metallated α-hydroperoxide **7** and simultaneously regenerating the α-keto radical **9**. The desired α-hydroxy carbonyl product **8** is then obtained *via* reduction.

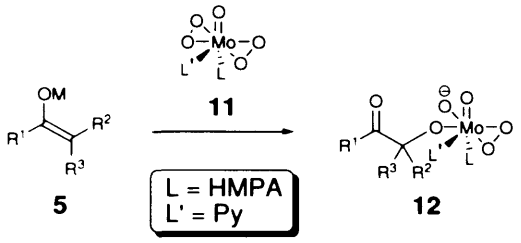


5 **9** **10** **7** **8**

Reaction scheme 1.2: α-Oxygenation using molecular oxygen *via* a radical process.[11]

1.2.1.2. Molybdenum Complexes.

The direct α-hydroxylation of enolates with the highly crystalline and reasonably air-stable molybdenum peroxide reagent MoO_5·Py·HMPA (MoOPH) **11**, was first reported in 1978, where it was used as a more convenient alternative to the hygroscopic epoxidising agent MoO_5·HMPA.[13] Two possible reaction pathways for this transformation were proposed, taking into account the tendency of MoO_5 chelates to transfer one of the peroxidic oxygens rather than the oxo oxygen to potential nucleophiles. The first mechanism involved formation of complex **12** through cleavage of the O–O bond, as show in Reaction scheme 1.3.



Reaction scheme 1.3: α-Oxygenation using MoOPH 11 involving transfer of a peroxidic oxygen.

A second perceivable pathway involves cleavage of an O–Mo bond. This was deemed less likely to be the case, since no α-hydroperoxycarbonyl compounds or their α-carbon cleavage products were isolated, which would be expected if this mechanism was in operation.

MoOPH **11** has since become a well known oxidant for enolates, however; despite its popularity, the toxicity of the complexed HMPA has been cause for much concern.[14] As a result of this, DMPU was examined in 1990 as a harmless, non-carcinogenic alternative, the result being the formation of the stable crystalline complex MoO_5·Py·DMPU (MoOPD). This can also be used as an efficient oxidant of a variety of enolates to the corresponding α-hydroxy carbonyl compounds and is thought to react in the same manner as shown in Reaction scheme 1.3 above.

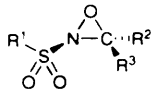
On comparison of the two reagents it has been found that α-hydroxylation reactions with MoOPD are generally cleaner as well as being safer.[11] MoOPD is, however,

somewhat less reactive, with yields in most cases being slightly lower than those obtained with MoOPH **11**.

1.2.1.3. Davis Oxaziridine.

Oxaziridines are three-membered heterocyclic compounds containing oxygen, nitrogen and carbon that were first synthesised by Emmons in 1956.[15] Preparation of these compounds was found to be quite straightforward and was achieved through reaction of an imine (that did not readily undergo acid hydrolysis), with anhydrous peracetic acid. The oxaziridine products were generally obtained in 50–80% yield and the reaction was found to be tolerant of a wide variety of functional groups (including those that would normally react with peracids), with the nature of the substituent groups determining the stability of the product. Many of the products, however, were found to be unstable which was thought to be due to the presence of an inherently weak N–O bond in a strained ring system.

In 1977, Davis and co-workers reported the synthesis of *N*-sulphonyl oxaziridines **13** (Figure 1.3), a new class of oxaziridine prepared by oxidation of the corresponding sulphonimine.[16] These were the first stable examples of this three-membered ring system to have an atom other than carbon attached to the nitrogen, and were characterised by a highly electrophilic oxaziridine oxygen atom.



13

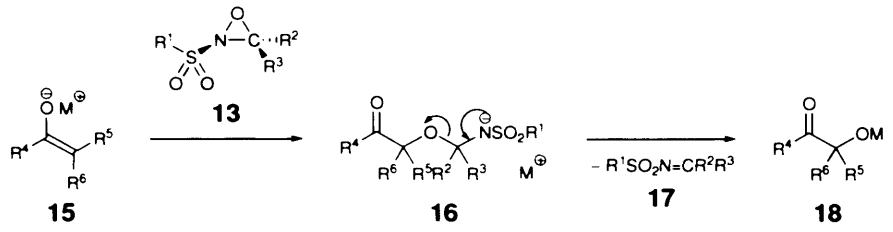
Figure 1.3: *N*-Sulphonyloxaziridine.

The synthesis of diastereo- and enantiomerically pure *N*-sulphonyl oxaziridines (**13**) allowed for the subsequent development of several asymmetric oxidation reactions,[17] including the first example of the asymmetric oxidation of prochiral enolates to enantiomerically enriched α-hydroxy carbonyl compounds, using chiral oxidising reagents.[18] The reagents of choice for these asymmetric enolate oxidation reactions were (camphorylsulphonyl) oxaziridines (+)-**14** and (−)-**14**, Figure 1.4, which were found to give good levels of asymmetric induction (60–95%) along with high chemical yields in their reactions with enolates.[19]

(+)–14 (–)–14

Figure 1.4: Structures of (+)- and (–)-(camphorylsulphonyl)oxaziridine.

A general mechanism for this oxidation reaction was proposed and is shown in Reaction scheme 1.4.[19] This involved initial attack of the nucleophilic enolate **15** on the electrophilic oxygen atom of oxaziridine **13**, with simultaneous N–O bond cleavage. Breakdown of the resulting hemiaminol anion **16** then afforded the α-oxygenated product **18** and an imine by-product **17**. The overall reaction was thought to proceed *via* an initial S_N2 attack.

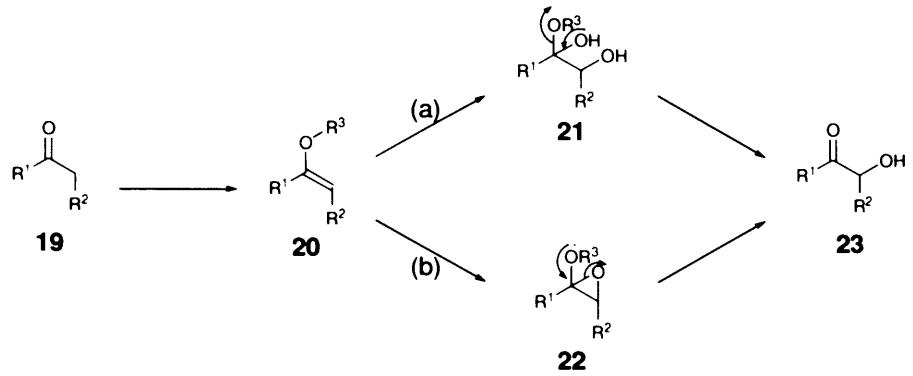


Reaction scheme 1.4: α-Oxygenation using *N*-Sulphonyloxaziridine 13.[19]

The use of enantiomerically pure *N*-sulphonyl oxaziridines (**13**) has proved to be an effective method for hydroxylation α- to a carbonyl group and has several advantages over other reagents including ease of preparation and higher product yields. The reaction was shown to work well for several trisubstituted enolates, giving e.e.'s in the range of 60–95%, with generally good yields. A significantly lower level of asymmetric induction was observed for tetrasubstituted enolates (20–30% e.e.), though good yields of the products were still obtained.

1.2.2. Use of Enol Ethers.

A number of catalytic asymmetric methods have also been developed for the α-oxygenation of carbonyl compounds. These are predominately indirect methods that involve the formation of isolable enol derivatives preceding the oxidation process, and include the asymmetric dihydroxylation (AD) of enol ethers (**20**) developed by Sharpless (a);[20,21] and the asymmetric epoxidation of enol ethers (**20**) with a chiral Mn-salen catalyst (b),[22,23] Reaction scheme 1.5.

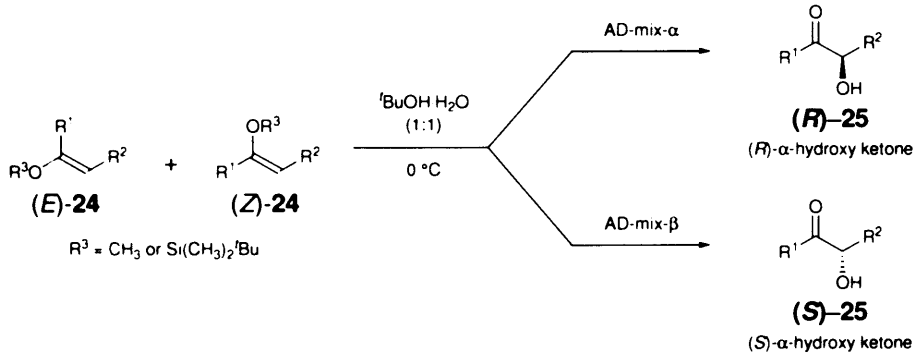


Reaction scheme 1.5: The dihydroxylation (a) and epoxidation (b) of preformed enol ethers 20.

1.2.2.1. Sharpless Asymmetric Dihydroxylation (AD).

In their efforts to extend the asymmetric dihydroxylation work carried out within the group,[24] Sharpless *et al* found that enol ethers (**20**) were excellent substrates for the synthesis of α-hydroxy ketones with the products being obtained in high yields (70–95%) and good to excellent enantiomeric purity (80–99% e.e.).[20]

As illustrated in Reaction scheme 1.6, reactions were carried out using a pre-formed, crude mixture of *E*/*Z* enol ethers (**24**) and either AD-mix-α (containing $(DHQ)_2$-PHAL), which was found to lead to the (*R*)-α-hydroxy ketone product **(*R*)-25**; or AD-mix-β (containing $(DHQD)_2$-PHAL), which gave the (*S*)-α-hydroxy ketone product **(S)-25**. Reactions were carried out under relatively mild conditions and in the presence of water (Reaction scheme 1.6).



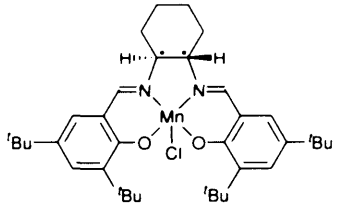
Reaction scheme 1.6: Application of the AD of enol ethers (24) to the synthesis of chiral α-hydroxy ketones (25).[20]

Comparable yields and levels of asymmetric induction were observed for each enantiomer of the product **25**, and interestingly, it was observed that in most cases the enantioselectivity in the reaction was not dependent upon the *E/Z* ratio of the starting enol ether (**24**). Indeed, in the instances where a poor ratio of *E/Z* isomers was examined, high e.e.'s were obtained for each enantiomer of the product **25** (from each reaction), albeit slightly lower than when using a high ratio of *E/Z* isomers.

This method was subsequently extended to the reaction of tetrasubstituted olefins, with varying degrees of success in terms of e.e. and yield of the product, making this procedure applicable to all six classes of olefin.[21]

1.2.2.2. Asymmetric Epoxidation.

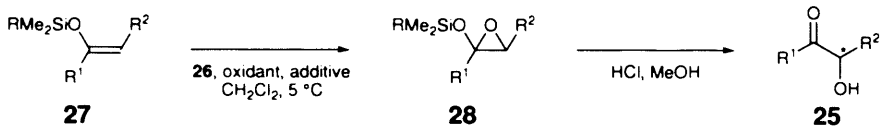
The epoxidation of prochiral, unfunctionalised alkenes was a major advance in catalytic asymmetric oxidations.[25] It was for this purpose that the enantiomerically enriched (salen)manganese(III) complexes (Mn-salen complexes) **26**, which are easily accessible from commercially available precursors, were developed. These are highly enantioselective catalysts, which arose through the modulation of steric and electronic properties as well as the substitution pattern of the catalyst (Figure 1.5).



26

Figure 1.5: Mn-salen complex.

The catalyst **26** was later found to be successful in the catalytic asymmetric α-hydroxylation of prochiral silyl enol ethers **27** and ketene acetals, the products being enantiomerically enriched α-hydroxy carbonyl compounds **25**, Reaction scheme 1.7.[22] These oxidation reactions were carried out in dichloromethane at 5 °C using either (***R,R***)-**26** or (***S,S***)-**26** as the catalyst, which led to opposite enantiomers of the product **25**, along with an excess of an oxidant, and an additive. After 20 hours, the reaction mixture was treated with HCl in methanol, in order to release the desired product **25** from the resulting epoxide intermediate **28**.



27 28 25

Reaction scheme 1.7: Catalytic asymmetric α-hydroxylation of prochiral silyl enol ethers 27 using Mn-salen catalyst 26.[22]

Several silyl enol ethers **27** were examined in this asymmetric oxidation reaction (Reaction scheme 1.7), though limited substitution patterns were examined, with the results being extremely varied. The outcome of the reactions showed that the conversion and enantioselectivity depended strongly on the choice of oxidant and additive. Of the oxygen sources examined, sodium hypochlorite (NaOCl) was found to give the optimum result for both conversion and e.e. Use of an additive, usually PPNO (4-phenylpyridine-*N*-oxide) or NMO (*N*-methylmorpholine-*N*-oxide) was found to be essential for optimum conversions and e.e.'s in the product **25**.

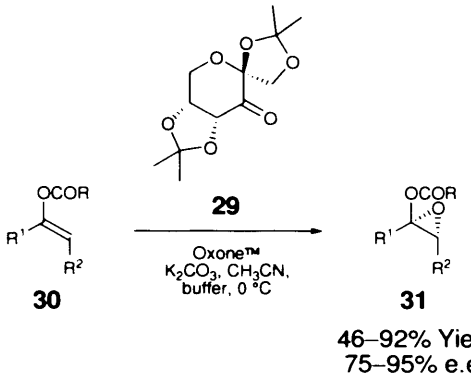
Under these conditions, good to excellent yields of the product **25** were obtained (59–96%); however, the level of asymmetric induction varied greatly (12–87%) depending on the substitution pattern in **26**. The steric demand of the silyl group was also found to be an important factor in the asymmetric oxidation reaction, with a more bulky silyl group leading to higher levels of asymmetric induction in each case.

1.3. Metal-Free Methods.

All methods mentioned thus far for the synthesis of α-hydroxy carbonyl compounds involve the use of metals. These do have a number of advantages being reliable, efficient and providing high enantiomeric excesses in many cases; however, they also have a number of inherent disadvantages. There has been a lot of interest, therefore, in the use of organocatalysts to carry out these transformations, which are cheaper, cleaner and more efficient and are frequently moisture- and air-stable. In many cases, the use of these small, metal-free organic molecules also gives rise to extremely high enantioselectivities.[2]

1.3.1. Metal-Free Epoxidation.

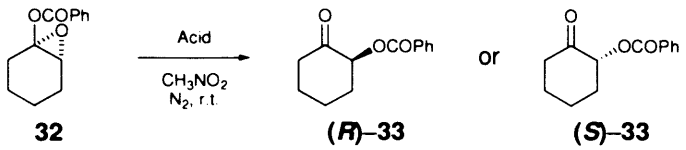
In 1996, Shi developed a highly enantioselective metal-free method for the asymmetric epoxidation of *trans*-disubstituted and trisubstituted olefins, using a fructose-derived ketone (**29**) as a catalyst and Oxone™ as the oxidant.[26] This method was subsequently extended to prochiral enol esters (**30**), providing facile access to chiral enol ester epoxides (**31**), which were obtained in good yields (46–92%) and generally high e.e.'s (75–95%), Reaction scheme 1.8.[27,28]



Reaction scheme 1.8: Asymmetric epoxidation of enol esters (30).

Enol ester epoxides **31** are synthetically useful intermediates that can readily rearrange under acidic or thermal conditions to give α-acyloxy aldehydes or ketones (**37**).[29] Having developed a method for obtaining enantiomerically enriched enol ester epoxides **31** (Reaction scheme 1.8), the possibility of developing a route to chiral α-acyloxy ketones (**37**) was then explored.[28]

Starting with the enol epoxide of cyclohexanone benzoate (**32**), initial efforts focused on developing an acid-catalysed rearrangement process, Reaction scheme 1.9. Reactions were carried out in nitromethane, which was found to be the optimum solvent of those examined, at room temperature under anhydrous conditions, with 10 mol% of an acid catalyst. A variety of acid catalysts were examined in this series of reactions, including protic and Lewis acids (LA).

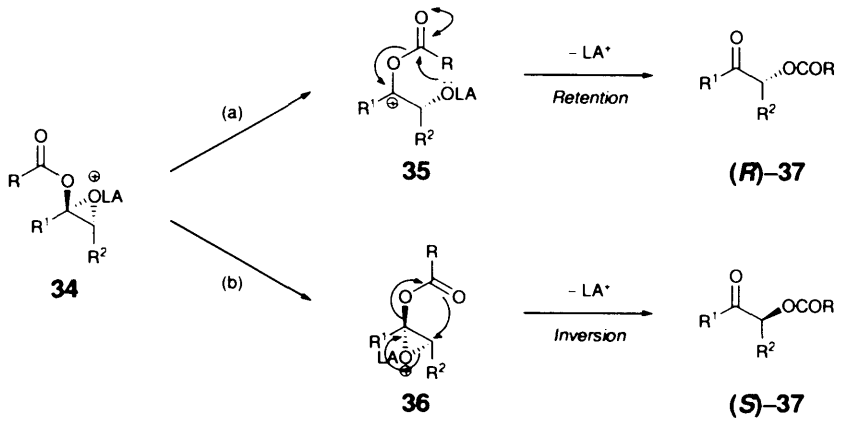


32 **(*R*)–33** **(*S*)–33**

Reaction scheme 1.9: Development of an acid-catalysed rearrangement of chiral enol ester epoxides (32) to α-acyloxy ketones (33).

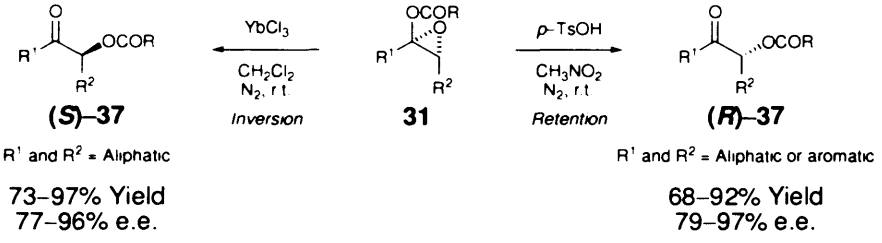
Treatment with a protic acid, such as *p*-toluene sulphonic acid, led to a facile rearrangement, usually complete within 10 minutes, with retention of stereochemistry, the level of which being comparable to that of the starting epoxide (**32**). The results obtained when investigating the effect of a Lewis acid showed that the e.e. of the product (**33**) varied dramatically depending on the Lewis acid used and, in some instances, inversion of the stereochemistry was observed. This suggested that there were two competing pathways by which the acid-catalysed rearrangement was taking place, leading to the two enantiomers of the product (**33**). The factors controlling this competition were not fully understood, however it was believed that the acidity of the catalyst played an important role in determining the outcome of the reaction.

The mechanisms that were proposed for each of the competing pathways are shown below in Reaction scheme 1.10. When using a strong Lewis acid (e.g. $Yb(OTf)_3$), the reaction was thought to follow pathway (a), which involved cleavage of the epoxide C_1–O bond following complexation of the Lewis acid, to give intermediate **35**. Acyloxy migration was then thought to proceed, with retention of stereochemistry, to give the α-acyloxy ketone (***R*)-37**. When using a weaker Lewis acid on the other hand (e.g. $YbCl_3$), the reaction was thought to follow pathway (b), in which complexation of the Lewis acid weakened both epoxide bonds, thus facilitating acyloxy migration with inversion of stereochemistry, giving α-acyloxy ketone (***S*)-37**.



Reaction scheme 1.10: Proposed mechanisms for competing reaction pathways, leading to opposite enantiomers of the product 37.[28]

The discovery of these two reaction pathways ((a) and (b), Reaction scheme 1.10) prompted the investigation of other chiral enol ester epoxide substrates (**31**) to test the generality of these competing reactions, Reaction scheme 1.11. This was to determine if it was possible to selectively generate either enantiomer of an α-acyloxy ketone (**37**) in high e.e., from a single enantiomer of a chiral enol ester epoxide (**31**), under mild conditions.



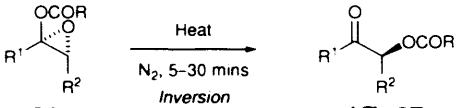
Reaction scheme 1.11: Rearrangement of chiral enol ester epoxides 31 to α-acyloxy ketones 37.

Selective rearrangement *via* pathway (a) (Reaction scheme 1.10) was examined initially using the protic acid *p*-toluene sulfonic acid as the catalyst, which had consistently brought about rearrangement with retention of stereochemistry in earlier studies. This was again found to be the case for the range of chiral epoxides (**31**) examined, leading to the corresponding α-acyloxy products ((***R***)-**37**) in good yields (68–92%) and high e.e. (79–97%).

The same range of chiral epoxide substrates (**31**) were then examined with the weak Lewis acid catalyst $YbCl_3$. In most cases this resulted in inversion of stereochemistry

as hoped, giving the products ((*S*)-**37**) in high yields (73–97%) and excellent e.e.'s (77–96%). The only exceptions noted were in the case of aromatic epoxides, where retention of stereochemistry was observed. This preference for pathway (a) (Reaction scheme 1.10), even with a weak Lewis acid catalyst, was though to be due to a stabilised carbocation intermediate (**35**).

Although use of a weak Lewis acid had brought about inversion of configuration in most of the substrates (**31**) examined, the fact that this method could not be extended to aromatic epoxides (**31**) prompted investigation of thermal rearrangements, which had previously been shown to bring about inversion of stereochemistry in steroid enol ester epoxides.[30]



31 (*S*)-**37**
84–100% Yield
75–99% e.e.

Reaction scheme 1.12: Thermal rearrangement of chiral enol ester epoxides 31.[28]

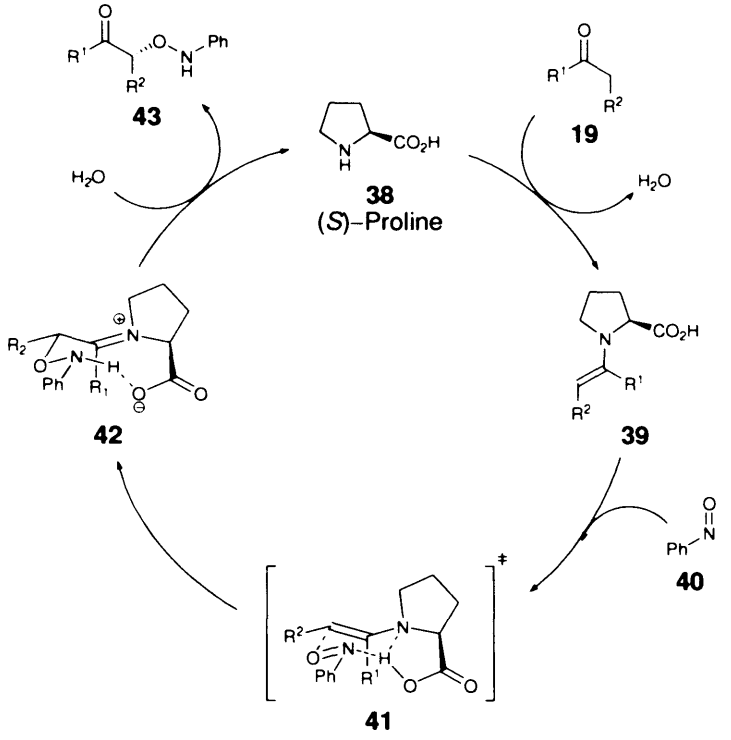
When applied to a range of chiral enol ester epoxides **31**, rearrangement was found to proceed with inversion of stereochemistry in all cases, including aromatic substrates (**31**) giving the product ((*S*)-**37**) in high yields (84–100%) and generally high e.e.'s (75–99%), Reaction scheme 1.12.[28]

These thermal rearrangements, along with the protic acid-catalysed rearrangements, allowed for the enantioselective metal-free synthesis of either enantiomer of an α-acyloxy ketone (**37**), from a single enantiomer of an enol ester epoxide (**31**).

1.3.2. Proline Organocatalysis.

More recently, a direct method for the asymmetric α-oxyamination of aldehydes was simultaneously reported by the groups of MacMillan,[31] Hayashi[32] and Zhong.[33] This method employed a proline-catalysed process and firstly involved condensation of the proline catalyst **38** with an excess of the carbonyl substrate **19**, to give an enamine species **39** (Reaction scheme 1.13).[34] This then reacted with nitrosobenzene

40, which was used as the electrophilic oxidant, in a slightly unusual manner, in that it was the oxygen atom of the nitroso compound **40** that was attacked by the enamine **39**. This resulted in intermediate **42**, *via* a proposed transition state (**41**) that contained a bicyclo-oxazolidinone motif. The product **43** was obtained by hydrolysis of the intermediate iminium ion **42**, which also regenerated the proline catalyst **38**.



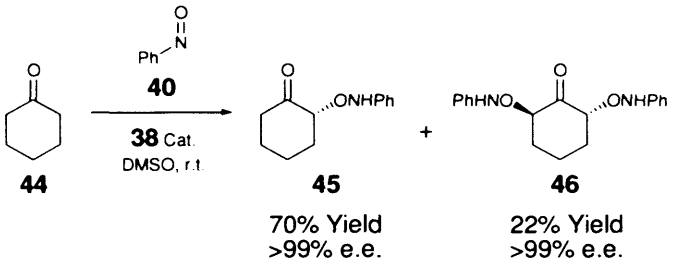
Reaction scheme 1.13: Catalytic cycle of (*S*)-Proline (38)-catalysed α-oxyamination.[34]

This organocatalysed transformation (Reactions scheme 1.13) was a direct method for the synthesis of α-hydroxy carbonyl compounds without the need to preform enolates or their equivalents.[33] The reaction of enamine **39** with nitrosobenzene **40** was both regio- and enantioselective and the product **43** was obtained in generally high yields (60–95%).[34] The reaction was shown to be applicable to both aliphatic and aromatic carbonyl substrates (**19**) and was tolerant of the various functional groups examined.

There were certain drawbacks with this method, with the major problems being the need to use up to 10 equivalents of the carbonyl compound **19** (in effect 90% was wasted); the frequent need for relatively high catalyst loading (usually around 20 mol%) in order to effect the reaction within a reasonable timescale; and the difficulty

in suppressing bis-functionalisation in the reaction of ketones, making this synthesis only really effective for aldehydes. Syringe pump techniques were also required for addition of the nitroso compound **40** and deprotection of the α-aminoxy group in the product **43** was necessary in order to obtain the desired α-hydroxy group.

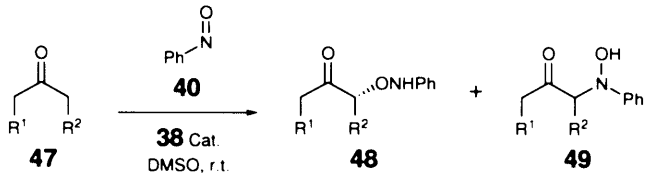
Further development of the reaction has since been achieved, with the extension to cyclic ketones.[35,36] Initial studies were carried out using cyclohexanone **44**, whereby excellent enantioselectivites were again observed; however, along with the desired product **45**, a considerable amount of the α,α'-bis(aminoxylated) product **46** was also found to result, Reaction scheme 1.14.



Reaction scheme 1.14: Extension of proline-catalysed process to cyclic ketones.

Synthetically useful chemical yields, along with the exclusive formation of the desired product **45,** was found to be possible through optimisation of the reaction medium to chloroform and by very slow addition of the nitroso compound **40** by means of a syringe pump. Subsequent extension to other cyclic substrates was found to be quite successful, giving excellent e.e.'s in all cases and good to excellent isolated yields (44–96%).[36]

Further extension of the reaction to acyclic ketones **47** was found to be more complicated.[35] In this instance, excellent regioselectivities were observed for the α-aminoxylation of acyclic ketones, and no α,α'-diaminoxylated ketones were observed to form, however; the reaction was observed to result in mixtures of *O*- and *N*-alkylated products **48** and **49**, Reaction scheme 1.15. Analysis of the reaction mixture revealed that the desired α-aminoxy product **48** was in most cases the major product and was generated with excellent enantioselectivity. The unwanted α-aminated ketone **49** was found to have the same regioselectivity as the *O*-addition, but showed low levels of asymmetric induction.



Reaction scheme 1.15: Extension of proline-catalysed process to acyclic ketones.

Advances are continually being made with regards to this process,[37] and subsequent methods, for example those using a tetrazole catalyst, have been shown to overcome some of the problems often encountered when using a proline catalyst **38**.[38]

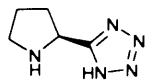
1.3.3. Proline Tetrazole Organocatalysis.

Proline **38** has proven to be an efficient catalyst for many enamine-catalysed processes, giving high yields and excellent enantioselectivites for various substrates, and is ideal in terms of price and availability. There are, however, certain problems that have been encountered with this catalyst **38**, largely relating to low reactivity and low solubility. [39]

On consideration of the structure of the proline catalyst **38**, the carboxylic acid functionality was deemed to be very important to the transformation, with two main functions being identified. Firstly, it directs the incoming nitroso compound **40**, by means of a hydrogen bond, to ensure that reaction takes place on only one face of the pyrrolidine ring. Secondly, the carboxylic acid group is able to lower the activation barrier of the reaction by charge stabilisation following formation of the new C–O bond.

It was proposed that a stronger hydrogen bond donor should lower the energy of the transition state further, thus increasing the reactivity of the catalyst for the desired reaction. It was for this reason that investigations were carried out into replacing the carboxylic acid group with a tetrazole group, which was chosen for several reasons. Firstly due to similarities in structure (both groups are planar) and associated pKa's (both about 5). It was also expected that a tetrazole side chain would be able to stabilise the forming negative charge in the transition state (**42**) better than proline, by being able to delocalise the charge over the whole tetrazole ring. Another rationale for the carboxylic acid group to be replaced by a tetrazole group was that

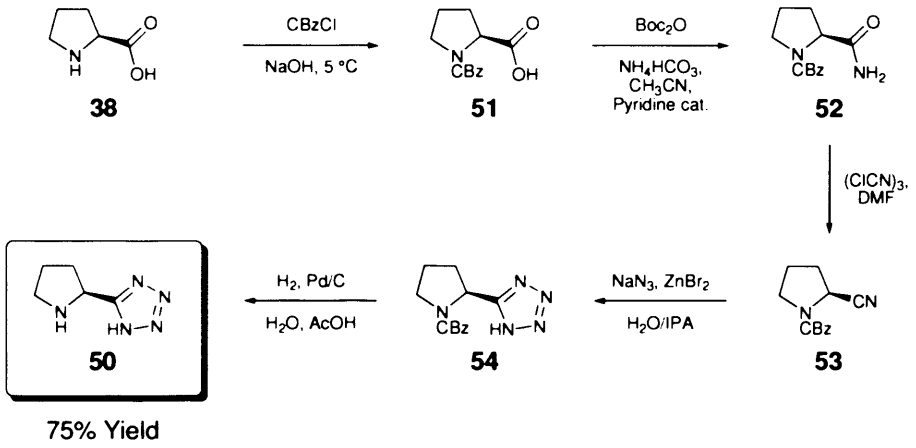
the tetrazole group has increased lipophilicity, and was expected to have a wider solvent scope.



50

Figure 1.6: Proline tetrazole 50.

5-[(2*S*)-Pyrrolidine-2-yl]-1*H*-tetrazole **50** (Figure 1.6), the tetrazolic acid analogue of proline **38**, was discovered independently by Ley,[40] Yamamoto[41] and Arvidsson[39] in 2004. This new catalyst **50** was synthesised from the commercially available L-proline **38**, with the synthesis starting with a CBz protection to give **51**, before being converted into amide **52**, Reaction scheme 1.16.[38] Following dehydration to get the nitrile **53**, the protected tetrazole **54** was obtained through implementation of the 'click-chemistry' protocol developed by Sharpless.[42] The desired product **50** was then obtained by catalytic hydrogenolysis in a 75% overall yield.

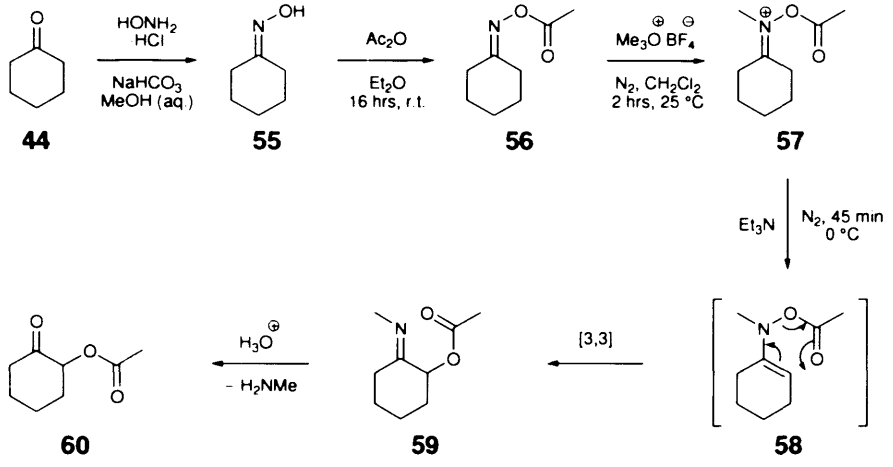


Reaction scheme 1.16: Synthesis of tetrazole catalyst 50.[38]

This proline-derived tetrazole catalyst **50** has since been implemented in a variety of asymmetric transformations including the α-oxyamination[43] and α-amination[44] of aldehydes, as well as in Mannich, Michael and aldol type transformations.[45] In all transformations examined, the tetrazole catalyst gave equivalent or better results than proline in terms of both enantioselectivity and yield. It also showed greater versatility, being effective at much lower catalyst loadings (e.g. 1 mol%) and with shorter reaction times, as well as proving useful in a wider range of reaction media.

1.4. Precedent for Previous Group Work.

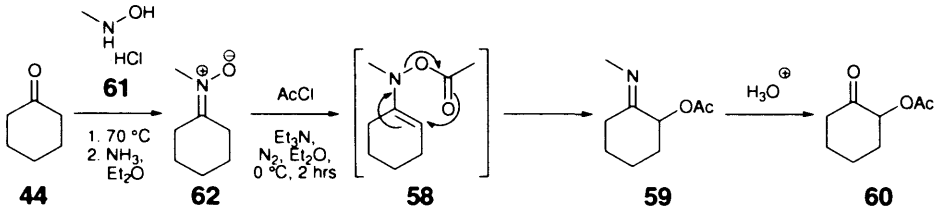
The origins of the work carried out by the group over the past few years, lie within a synthesis developed by House in 1969 for the α-oxygenation of cyclohexanone (Reaction scheme 1.17).[46] This consisted of a 5-step metal-free synthesis of 2-acetoxycyclohexanone **60** from cyclohexanone **44**, firstly involving condensation of the ketone **44** with a hydroxylamine to give oxime **55**. This then underwent *O*-acylation followed by *N*-methylation, giving the iminium ion **57**, which on treatment with triethylamine was converted to the corresponding enamine **58**. This was then thought to undergo a concerted pericyclic rearrangement, giving imine **59**. The final product **60** was then obtained following hydrolysis under aqueous acidic conditions.



Reaction scheme 1.17: House synthesis of 2-acetoxycyclohexanone 60.[46]

This was a very nice synthesis, giving the product **60** in an overall 51% yield; however, the large number of synthetic steps involved made it quite impractical and as a result, this procedure has never been implemented in synthesis.

The process was subsequently shortened to three-steps in 1983 by Coates, Reaction scheme 1.18, who prepared a nitrone species **62** directly from the carbonyl substrate **44**.[47] This was then *O*-acylated under basic conditions, which formed the enamine **58** *in situ*, before undergoing the same rearrangement as shown by House,[46] forming a new C–O bond in the α-position. This gave imine **59** directly, which could then be hydrolysed under aqueous acidic conditions to give the α-oxygenated carbonyl compound **60** (Coates' work is discussed further in Chapter 6.2.1).



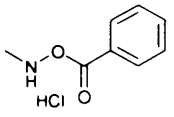
Reaction scheme 1.18: Coates' synthesis of 2-acetoxycyclohexanone 60.[47]

In reducing the number of steps to a three-step synthesis, this method became slightly more synthetically versatile, despite the overall yield being lower (26%). However, there has still only been one synthetic application of this Coates method, which was in the total synthesis of fumagillol in 2003 by Sorensen and co-workers (see Chapter 6.2.1).[48]

Evidently, there was still room for improvement, whereby it was anticipated that a further reduction in the number of steps involved, along with improving chemical yields, would make this overall procedure extremely synthetically useful. Achieving this objective thus became a major focus of the group.

1.5. Previous Group Work.

Previous efforts by the group in this area began with the hypothesis that condensation of a hydroxylamine possessing both *N*- and *O*-substituents with a carbonyl compound, would lead directly to an iminium ion, which had the potential for development of a novel one-pot procedure.



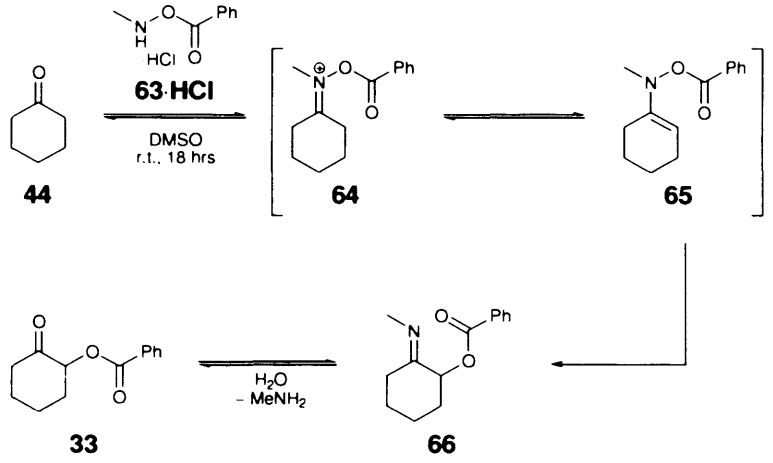
63·HCl

Figure 1.7: Novel reagent for the α-oxybenzoylation of carbonyl compounds.

Subsequent investigation led to the discovery of a new class of reagent to effect these transformations.[49] This reagent was *N*-methyl-*O*-benzoylhydroxylamine hydrochloride **63·HCl**, Figure 1.7, which was found to react with aldehydes and both cyclic and acyclic ketones to generate α-functionalised products in generally high yields (65–90%). Further investigation revealed that this reaction was also applicable

to substrates bearing a wide variety of functional groups, including ethers, sulphides and amides, as well as hydrolytically sensitive groups such as acetals and esters.

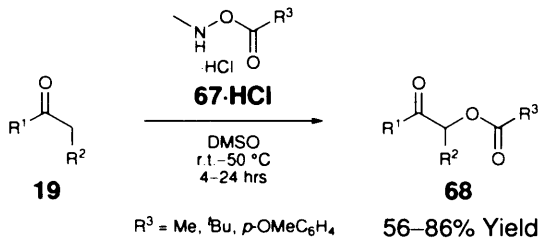
The proposed mechanism for this one-pot α-oxygenation reaction is shown in Reaction scheme 1.19, and firstly involved reaction of the hydroxylamine reagent **63·HCl** with a carbonyl substrate, in this case cyclohexanone **44**, to give an initial iminium ion **64**. Under the acidic reaction conditions, this was converted to the corresponding enamine **65**, which underwent a concerted [3,3]-sigmatropic rearrangement. Hydrolysis of the resulting imine **66** *in situ*, gave the product **33**.



Reaction scheme 1.19: One-pot synthesis of α-oxybenzoyl carbonyl compounds.[49]

These reactions were shown to proceed in one practical step, in the presence of moisture and air, without the need for specialised equipment or techniques. Optimisation of the reaction conditions led to DMSO being adopted as the solvent of choice, as it gave the product in high yields and was observed to provide the cleanest transformations.

On carrying out the reaction on various carbonyl substrates, it was observed that the reaction proceeded at ambient temperatures for aldehydes and cyclic ketones. Higher temperatures of 50 °C, however, were required for acyclic ketones, presumably due to the increase in steric hindrance, retarding initial iminium ion formation. The reaction times also varied, with ketones requiring 18–24 hours, whereas the aldehyde reactions were observed to go to completion after just 4 hours.



Reaction scheme 1.20: General reaction for the α-oxyacylation of carbonyl compounds 19.

Following optimisation of the α-oxybenzoylation transformation, the structure of the reagent (**67·HCl**) was modified in order to investigate the possibility of transferring different *O*-acyl groups, Reaction scheme 1.20. Several different *O*-acyl groups (R^3) were examined in combination with different carbonyl substrates (**19**), where it was found that the products (**68**) were obtained in yields comparable to the analogous α-oxybenzoylation reactions, which increased the synthetic applicability of this procedure. Further work carried out on this novel one-pot α-oxyacylation transformation included examination of the chemospecificity and regioselectivity of the reaction.

1.5.1. Chemospecificity in the One-Pot α-Oxyacylation Reaction.

A further reagent developed **69·HCl**, Figure 1.8, was found to be chemospecific for the reaction of aldehydes.[50] Stirring **69·HCl** in the presence of a ketone resulted in no reaction being observed. This was thought to be the result of the increase in steric bulk surrounding the nucleophilic nitrogen atom, preventing initial iminium ion formation with ketones, which are more sterically encumbered than aldehydes.

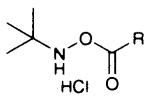
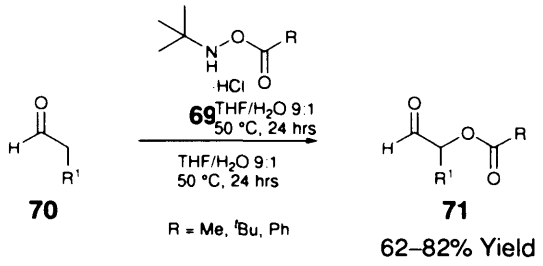


Figure 1.8: Chemospecific reagent for the α-oxyacylation of aldehydes.

This reagent (**69·HCl**) was reacted with a variety of aldehydes **70**, including aliphatic, aromatic and branched aldehydes **70**, all of which proved to be viable substrates for this reaction, Reaction scheme 1.21. Variation of the *O*-acyl group was also examined, leading to a wide range of α-oxygenated aldehyde products (**71**), in

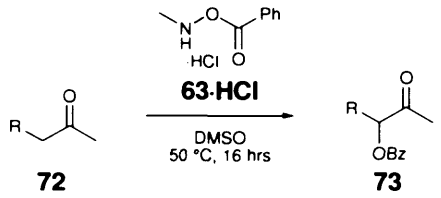
yields comparable to those obtained when using reagent **67·HCl** (Reaction scheme 1.20).



Reaction scheme 1.21: Chemospecific α-oxygenation reaction of aldehydes 70.

1.5.2. Regioselectivity in the One-Pot α-Oxyacylation Reaction.

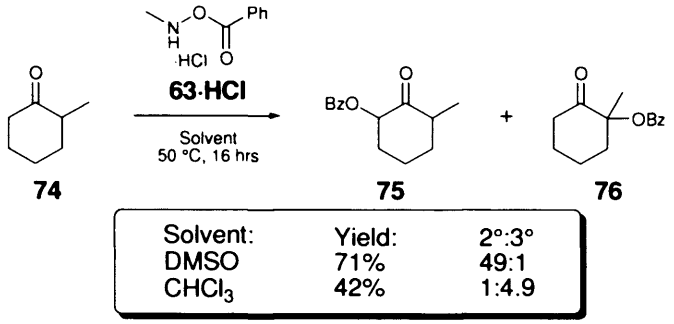
The question of regioselectivity in the novel α-oxyacylation reaction was investigated next, by examining the reaction of non-symmetrical ketone substrates with reagent **63·HCl**. To begin with, ketones of the type **72** were examined, that possessed primary and secondary centres α- to the carbonyl group, Reaction scheme 1.22.



Reaction scheme 1.22: Regioselectivity for secondary centres over primary.

As illustrated above (Reaction scheme 1.22), these reactions were observed to proceed with complete regioselectivity, undergoing α-oxygenation exclusively at the secondary centre, giving the product (**73**) in high yields (73–83%). Whilst such regioselectivity was extremely synthetically useful, this also highlighted a limitation of the procedure, which was that reaction did not proceed at primary centres.

With regard to the regioselectivity in the reaction of ketones of the type (**74**), that possessed secondary and tertiary centres α- to the carbonyl group, the situation was slightly more complex. As illustrated for ketone **74**, Reaction scheme 1.23, in this instance a mixture of products (**75** and **76**) was observed.

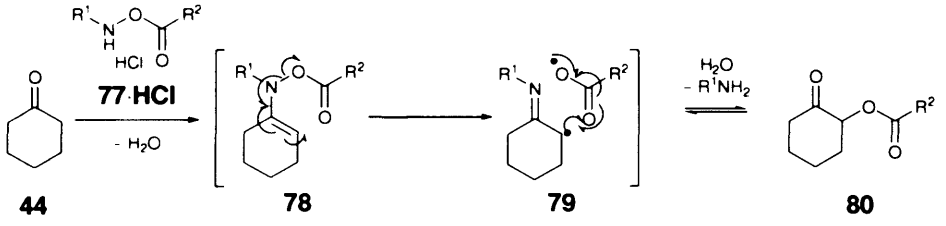


Reaction scheme 1.23: Regioselectivity in the reaction of secondary *vs.* tertiary centres.

The regioselectivity for reaction at the secondary *versus* tertiary centre was found to vary according to the medium used to carry out the reaction. As such, it was possible to assert some level of control over the outcome of the reaction. The optimum solvent found to promote reaction at the secondary centre was DMSO, which gave the products **75** and **76** in the ratio 49:1 respectively and a combined yield of 71%. When the reaction was carried out in chloroform, on the other hand, it was found that reaction at the tertiary centre was favoured, though unfortunately not to the same extent. This instead resulted in products **75** and **76** in a 1:4.9 ratio, and in a lower combined yield of 42%.

1.5.3. Mechanistic Studies.

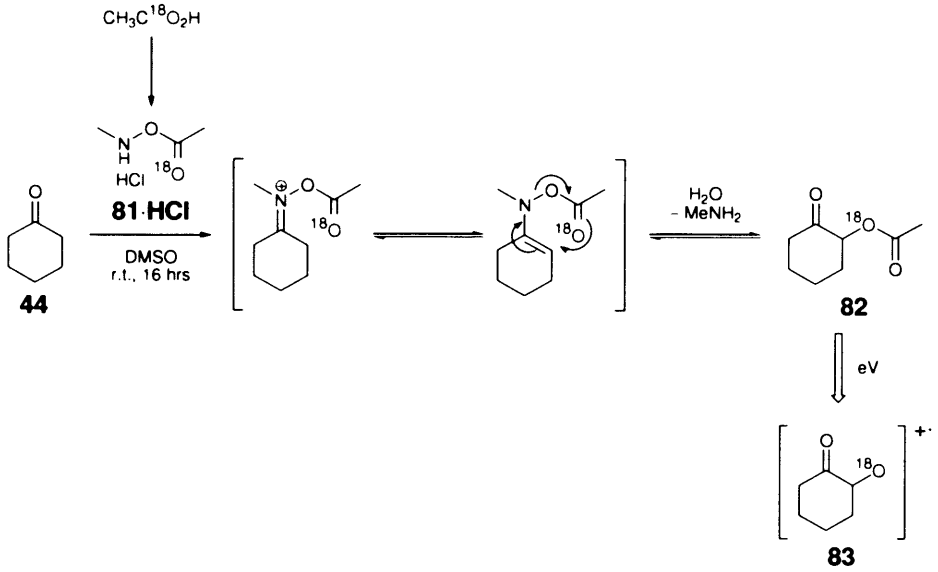
In previous studies (Chapter 1.4) it had been assumed that the rearrangement proceeded *via* a concerted [3,3]-sigmatropic process. An alternative step-wise mechanism is also possible, which would involve the formation and reaction of a radical species (e.g. **79**), as shown in Reaction scheme 1.24.



Reaction scheme 1.24: Alternative possible mechanism involving radicals.

In order to gain further insight and understanding of the reaction, a mechanistic study was carried out. Some ^{18}O labelled acetic acid was used to synthesise the labelled *N*-methyl-*O*-acetylhydroxylamine hydrochloride reagent **81·HCl**. This was

subsequently reacted with cyclohexanone **44** to give the corresponding α-oxyacylated product **82**, which was then analysed by mass spectrometry.

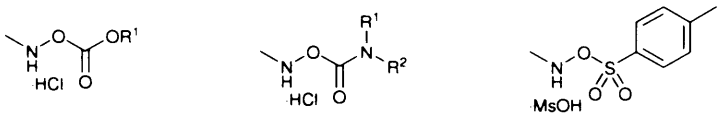


Reaction scheme 1.25: Mechanistic study using ^{18}O labelled reagent 81·HCl.

Results from this analysis revealed that the α-oxygen atom was exclusively the ^{18}O labelled oxygen, following identification of key peaks at *m/z* 158 (corresponding to **82**) and *m/z* 115 (corresponding to **83**). This provided strong evidence to support a concerted pericyclic rearrangement mechanism. Further mechanistic studies carried out with this reaction are discussed in Chapter 4.6.

1.6. Synthesis of Alternative α-Oxygenation Reagents.

A series of reagents based around the generic hydroxylamine scaffold were subsequently prepared, Figure 1.9, providing a new family of reagents for simple and effective bond construction processes. These analogous reagents (Figure 1.9) have now been successfully used in the synthesis of α-oxycarbonoyl (**84·HCl**),[51] oxycarbamoyl (**85·HCl**)[52] and oxytosyl (**86**)[53] carbonyl compounds, thus increasing the synthetic potential of this transformation further.



84·HCl **85·HCl** **86**

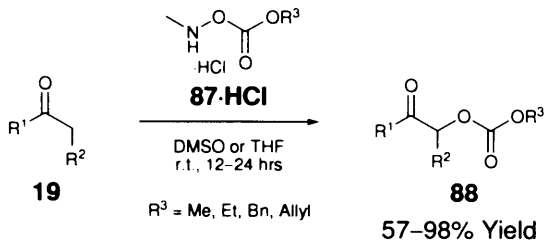
Figure 1.9: Reagents for the α-oxycarbonoylation (84·HCl),[51] oxycarbamoylation (85·HCl)[52] and oxytosylation (86)[53] of carbonyl compounds.

With these reagents (Figure 1.9) bearing such structural similarity to the *N*-methyl-*O*-benzoyl reagent (**63·HCl**), it was thought that each of these alternate transformations proceeded *via* a common mechanism, to give the corresponding α-functionalised product. Each of these further reactions was carried out under the same mild conditions and in the presence of moisture and air, and all showed the same tolerance of various functional groups as the α-oxyacylation reaction. Each of these further transformations established will now be looked at in more detail, and are examined again in Chapter 7.

1.6.1. α-Oxycarbonoylation of Carbonyl Compounds.

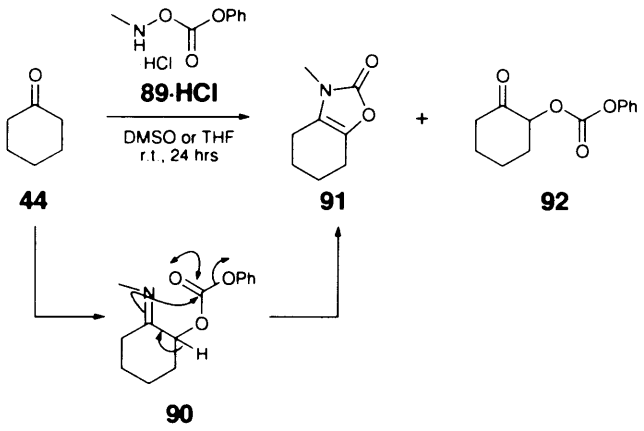
The first alternative transformation examined in detail was the α-oxycarbonylation of carbonyl compounds. This reaction provided a further method for easy access of the much desired α-hydroxy carbonyl functionality, with the carbonate protecting group being stable to a variety of reaction conditions, though easily removed through hydrolysis or reduction.

Several *O*-carbonate reagents (**87·HCl**) were prepared and their reaction with a variety of different carbonyl compounds (**19**) was examined, Reaction scheme 1.26. This gave the desired α-oxycarbonoyl product (**88**) in good to excellent yield (57–98%) in each case and proved to be tolerant of various functional groups, including acid-sensitive groups such as acetals and esters.



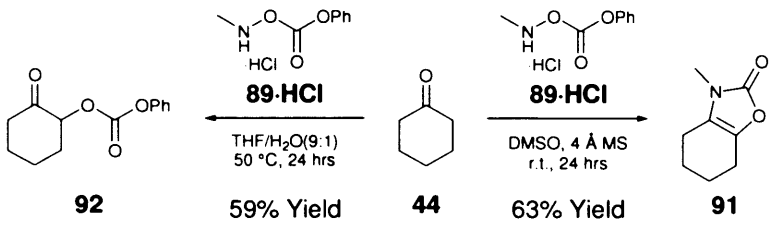
Reaction scheme 1.26: General reaction for the α-oxycarbonoylation of carbonyl compounds 19.

A further reagent synthesised (**89·HCl**), containing a phenyl carbonate group, was also examined in this series of reactions, where it was observed to give very interesting results. As exemplified for cyclohexanone **44** (Reaction scheme 1.27), this reaction gave heterocycle **91** as the major product, instead of the expected α-functionalised product **92**. Formation of this heterocycle (**91**) was thought to proceed following formation of the α-functionalised imine **90**, and was thought possible due to the increased leaving group ability of phenol compared to an aliphatic alcohol.



Reaction scheme 1.27: Outcome of reaction between cyclohexanone 44 and reagent 89·HCl.

Further investigation into this intriguing observation led to the discovery that the outcome of the reaction could be controlled by varying the reaction medium. As such, by increasing the amount of water present by using THF/H_2O (9:1) as the solvent, the originally anticipated α-oxyphenylcarbonoyl product **92** was obtained in a 59% yield. Conversely, use of dry DMSO as the reaction medium, in the presence of 4 Å molecular sieves to prevent hydrolysis of the imine intermediate (**90**), led to heterocycle **91** in a 63% yield.



Reaction scheme 1.28: Alternate reaction products available through modification of reaction conditions.

This ability to control the outcome of the reaction through modification of the reaction conditions proved to be general for alternative carbonyl substrates, providing direct access to various α-oxycarbonoyl carbonyl compounds and heterocyclic motifs, under mild reaction conditions.

1.6.2. α-Oxycarbamoylation of Carbonyl Compounds.

Investigation into whether the α-oxyacylation procedure could be modified for the synthesis of α-oxycarbamoyl carbonyl compounds began with the synthesis of various *O*-carbamoyl hydroxylamine reagents (Figure 1.10). These were based on general structure **85·HCl** and contained both aliphatic (**93·HCl** and **95·HCl**) and aromatic (**94·HCl–96·HCl**) *N*-substituents.

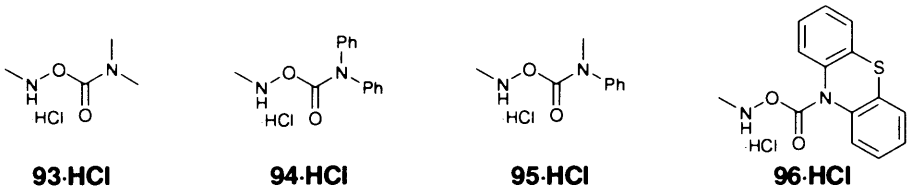
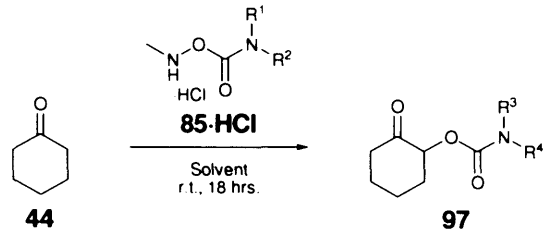


Figure 1.10: *O*-Carbamoyl hydroxylamine reagents prepared.

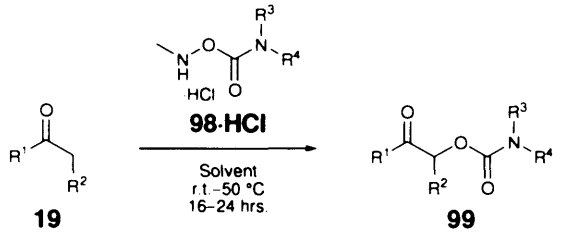
In order to determine their efficacy for the desired transformation, each of these reagents (**93·HCl–96·HCl**) was reacted in turn with cyclohexanone **44** to begin with, Reaction scheme 1.29. This series of reactions produced encouraging results, giving the corresponding α-oxycarbamoyl cyclohexanone products (**97**) as hoped, in good yields of 59–79%.



Reaction scheme 1.29: Initial α-oxycarbamoylation of cyclohexanone 44.

Optimisation of the reaction showed that when using a reagent with aromatic *N*-substituents (**94·HCl** and **96·HCl**), DMSO gave optimal results in terms of yield. When the reagent contained an aliphatic *N*-substituent (**93·HCl** and **95·HCl**), however, THF gave better conversions when used as the reaction medium.

Following this, a series of carbonyl substrates (**19**) were examined for their ability to react with reagents **93·HCl–96·HCl** (Figure 1.10), in order to determine the generality of the procedure, Reaction scheme 1.30. This showed the reaction to work well for a wide variety of carbonyl compounds (**19**), including aldehydes and both cyclic and acyclic ketones, and gave the corresponding α-oxycarbamoyl products (**99**) in good to excellent yields (50–88%).

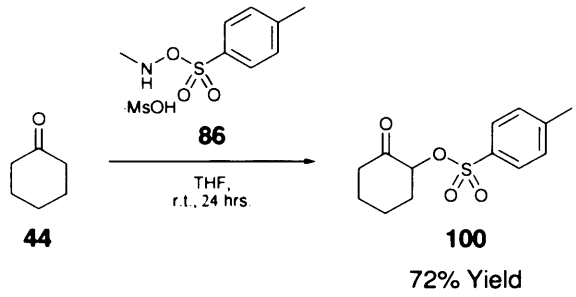


Reaction scheme 1.30: General reaction for the α-oxycarbamoylation of carbonyl compounds 19.

1.6.3. α-Oxytosylation of Carbonyl Compounds.

One further reagent examined in this investigation into alternative transformations was *N*-methyl-*O*-tosyl hydroxylamine **86**, which was prepared in the hope of being able to transfer an oxytosyl group α- to a carbonyl group, in a manner similar to that in operation in previous transformations. This would constitute a novel method for

the synthesis of α-oxytosyl carbonyl compounds, a class of compound with significant synthetic importance.[54]

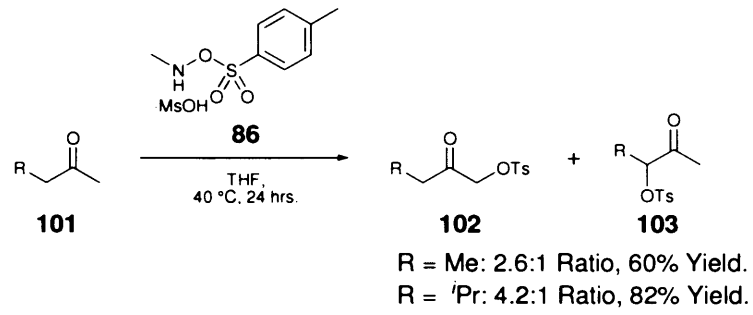


Reaction scheme 1.31: Synthesis of 2-oxytosyl cyclohexanone 100.

As in previous studies, initial reactions were carried out using cyclohexanone **44** as the substrate, and, following optimisation of the reaction, the desired product **100** was obtained in a 72% yield, Reaction scheme 1.31. These optimisation efforts revealed that the standard HCl co-acid used in previous transformations was not effective, resulting in no product (**100**) being isolated. Instead, it was found that a less acidic co-acid was necessary, with the optimal conversions obtained through use of a stoichiometric amount of methane sulphonic acid (MsOH). It was also observed that high polarity solvents were detrimental to the reaction, with DMSO, though optimal in the α-oxyacylation reaction, proving ineffective in this instance.

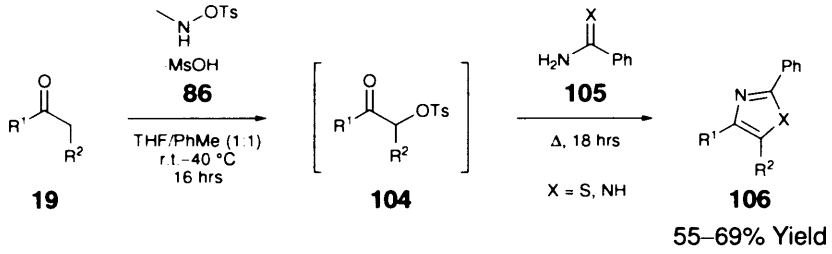
The optimised reaction conditions were then applied to a variety of other carbonyl compounds, where it was observed that not only was the reaction general to all classes of carbonyl substrate, giving the products in generally high yield (38–82%); it was also effective in the α-functionalisation of primary centres, thus increasing the applicability of this reagent (**86**) in synthesis.

Following this discovery, certain trends in regioselectivity were identified. Firstly, when distinguishing between primary and tertiary centres, α-functionalisation occurred exclusively at the primary centre. In the case of primary *versus* secondary centres, primary centres were again favoured, though the extent of the selectivity relied on the steric congestion surrounding the secondary centre. With hindered secondary centres, α-functionalisation took place exclusively at the primary centre; whereas with less hindered secondary centres (e.g **101**), the reaction led to a mixture of products (**102** and **103**), Reaction scheme 1.32.



Reaction scheme 1.32: Illustration of the effect of sterics on regioselectivity.

Following reports that α-oxysulfonyl ketones (**104**) could be used for the synthesis of a variety of biologically significant heterocycles,[54] the possibility of using this reagent **86** to develop a one-pot synthesis of heterocycles **106** from ketones **19** was explored.[53] This was found to be possible by means of addition of a bis-nucleophile (e.g. **105**) directly to the reaction mixture, following formation of the α-oxytosyl carbonyl compound **104** and then heating to promote the cyclo-condensation process, Reaction scheme 1.33.



Reaction scheme 1.33: One pot synthesis of heterocycles.

Results from this final study proved to be positive, with all reactions examined giving the anticipated heterocycle product (**106**) in good overall yield (55–69%). It was also possible to directly obtain a variety of different heterocycle motifs through variation of the structure of the nucleophile (**105**).

1.7. Conclusion.

The carbonyl group is one of the most fundamental functional groups in organic synthesis with its asymmetric α-oxygenation being of extreme synthetic importance. For this reason, many methods have been developed for the enantioselective synthesis of α-hydroxy carbonyl compounds.

Traditional methods for their construction employed the use of metal-catalysed or metal-mediated processes. These methods, despite the many advantages, have in recent years come under scrutiny owing to the numerous disadvantages associated with the use of metals. It is for this reason that much effort has gone towards developing organocatalytic processes that meet the standards of established organic reactions, whilst at the same time being cleaner and more efficient.

Within the past five years, advances in organocatalytic methods towards the synthesis of α-hydroxy carbonyl compounds have seen the development of a proline-catalysed α-oxyamination of aldehydes that was subsequently extended to cyclic and acyclic ketones. This method gave the desired products with excellent enantioselectivity and in generally high yield; however, there were many disadvantages that needed to be addressed. Some of these drawbacks were overcome by modification of the catalyst structure to a proline tetrazole catalyst (**50**), though there still remains room for improvement.

Previous efforts within the group drew precedent from a 5-step synthesis of 2-acetoxycyclohexanone (**60**) developed by House in 1969. It was thought that this method could be modified to a one-pot procedure, which would increase the synthetic potential. This goal was achieved following the discovery of a new class of reagent (**63·HCl**) for the α-oxygenation of carbonyl compounds. This reagent (**63·HCl**) was synthesised from commercially available starting materials and is now itself commercially available.

Reagent **63·HCl** was used to develop a novel one-pot, metal-free process for the α-oxyacylation of carbonyl compounds. This transformation was shown to proceed in the presence of both moisture and air, without the need for specialised equipment or techniques, giving the α-oxygenated products in good to excellent yield. This process was applicable to both aldehydes and ketones, and was tolerant of a wide variety of functional groups, making it highly synthetically useful.

Subsequent efforts resulted in the development of a chemospecific reagent (**69·HCl**) for the reaction of aldehydes. This chemospecificity was thought to be due to the increase in steric bulk surrounding the reactive nitrogen, which prevented reaction

with more sterically encumbered ketone substrates even under conditions of increased temperature and reaction time.

Further studies were carried out to address the question of regioselectivity in the case of non-symmetrical ketone substrates. Results from these studies firstly revealed that α-functionalisation did not proceed at primary centres. This, however, allowed for complete regioselectivity in ketone substrates that possessed a single primary centre α- to the carbonyl group. In the case of secondary *versus* tertiary centres, it was found that the regioselectivity could be controlled, through modulation of the reaction medium.

Several alternative reagents have since been synthesised for the α-oxytosylation (**86**), oxycarbonoylation (**84·HCl**) and oxycarbamoylation (**85·HCl**) of carbonyl compounds. This again has increased the synthetic potential of this transformation, with α-oxytosyl compounds (**104**) in particular being useful synthetic precursors to a variety of different functionalities, including biologically significant heterocycles.

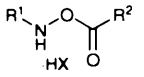
One area that needed to be examined was the possibility of rendering the transformation asymmetric. If this could be achieved, whilst maintaining the high yields observed to date, the synthetic potential of this novel transformation would be increased significantly. This challenge became the focus of my efforts.

Chapter 2.

Our Aim to Develop an Asymmetric Variant of a Novel One-Pot α-Oxygenation Reaction.

2.1. Approach.

Our approach to developing an asymmetric variant of the established α-oxyacylation of carbonyl compounds (Reaction scheme 1.20),[49] was to make the reagents used in the transformation chiral. After consideration of the generic structure of the reagents used **108**, Figure 2.1, there were three possible options of where we could incorporate chirality. We could put it in the *N*-substituent (R^1), the *O*-acyl group (R^2) or use a chiral co-acid (HX).

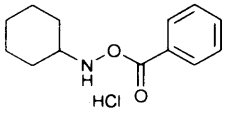


108

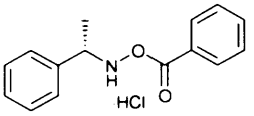
Figure 2.1: Generic structure of reagent used to carry out α-oxyacylation.

After examination of each of these it was decided that the best place to begin our investigations would be to use a chiral *N*-substituent. This was decided upon as this portion of the reagent was not incorporated into the product. Therefore, if we were able to recycle the amine by-product, the possibility remained of developing a catalytic asymmetric transformation at a later stage.

With this decision made, our initial aim was to prepare the achiral and chiral reagents **109·HCl** and **110·HCl**, Figure 2.2. It was necessary to synthesise an achiral reagent alongside a chiral reagent in order to produce racemic α-oxygenated products to be used as standards, in order to ascertain the level of asymmetric induction, if any, through use of a chiral reagent. The structure of the achiral reagent **109·HCl** was chosen as we thought the steric bulk surrounding the nitrogen atom was similar to that of the chiral reagent **110·HCl**. We hoped that this would give us an idea of the level of reactivity to expect from the chiral reagent **110·HCl**.



109·HCl

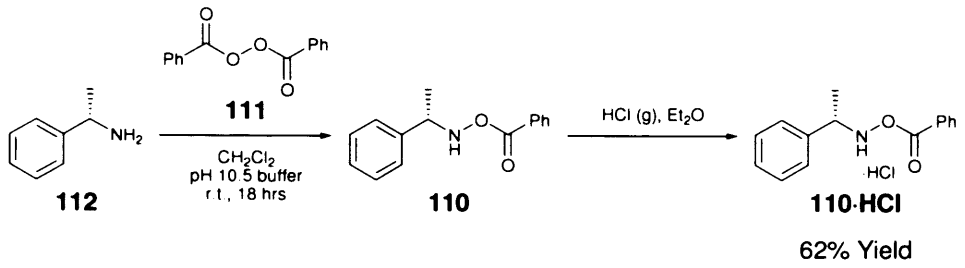


110·HCl

Figure 2.2: Initial reagents prepared.

We went about preparing these reagents **109·HCl** and **110·HCl**, using the Phanstiel method of reacting an amine with benzoyl peroxide (BPO) **111**, in a biphasic solution of dichloromethane and a pH 10.5 buffer, Reaction scheme 2.1.[55] Basic

reaction conditions were necessary in order to avoid attack of the amine on the carbonyl group of the BPO **111**, which would lead to an unwanted amide product.



Reaction scheme 2.1: Synthesis of chiral reagent 110·HCl.[55]

In the case of the chiral reagent **110·HCl**, the starting amine was (*S*)-α-methyl benzylamine **112**, which was chosen for its commercial availability and relative inexpense. The reaction proceeded by attack of the amine **112** on the peroxide oxygen of the BPO **111**, forming the *O*-benzoyl hydroxylamine **110**, accompanied by the loss of benzoic acid (Reaction scheme 2.1). This was then converted to the corresponding hydrochloride salt **110·HCl** by bubbling HCl gas (generated by reaction of ammonium chloride with concentrated sulphuric acid) through a solution of the crude hydroxylamine (**110**) in ether. The product **110·HCl** was a crystalline solid that was collected by filtration, without the need for purification, in an overall 62% yield. The achiral reagent **109·HCl** was prepared in an analogous manner from cyclohexylamine, in a 74% overall yield.

The next step was to carry out reactions between these reagents (**109·HCl** and **110·HCl**) and a variety of carbonyl substrates, Figure 2.3, in order to gauge an idea of their scope and reactivity within the transformation. Substrates chosen comprised both cyclic and acyclic ketones **44** and **113**, as well as aldehydes **114** and **115**, one of which (**115**) would involve the formation of a quaternary centre.

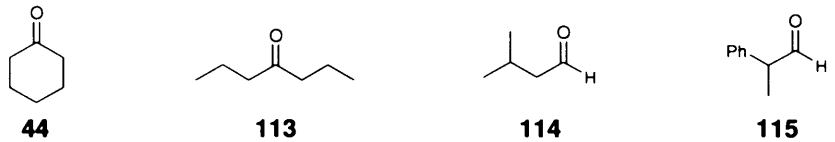
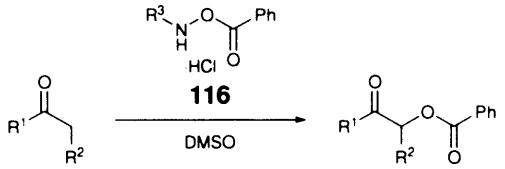
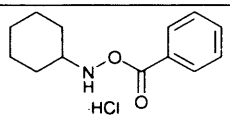
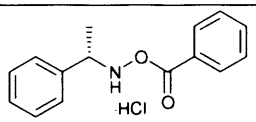
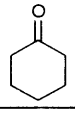
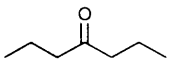
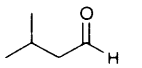
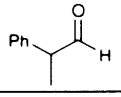


Figure 2.3: Carbonyl substrates chosen for initial screening.

All initial reactions were carried out under standard reaction conditions previously developed for this transformation.[49] This constituted using 1 equivalent of reagent and 1 equivalent of carbonyl substrate, with DMSO as the reaction medium, which

had been found to give the cleanest transformations. For both the aldehydes **114** and **115**, and the cyclic ketone substrate **44**, reactions were performed at 25 °C. The acyclic ketone **113**, being more sterically encumbered, required a higher temperature of 50 °C to enable it to react with the reagent. These reactions gave the corresponding α-oxygenated products (**33**, **118–120**) in varying yields, as shown in Table 2.1.



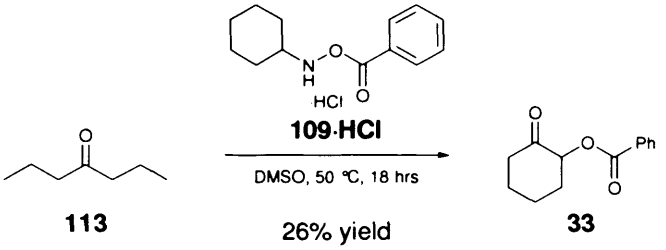
Entry	Substrate				
		Temp. (°C)	Yield (%)[c]	Temp. (°C)	Yield (%)[c]
1		25	59	25	53
2		50	5	50	7
3		25	40	25[b]	70
4		25	22	25	38

[a]All reactions were performed at 0.5M concentration for 18 hrs unless otherwise stated.
[b]Reaction was carried out for 5 hrs.
[c]Isolated yield.

Table 2.1: Results obtained from initial reactions.[a]

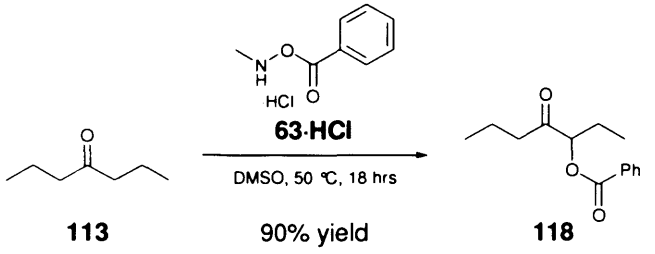
As can be seen in the above table, Table 2.1, the structural similarity of the reagents **109·HCl** and **110·HCl** resulted in the products in most cases being isolated in comparable yields. For cyclohexanone **44**, entry 1, yields were relatively good in both cases. Isovaleraldehyde **114**, entry 3, gave considerably different yields in each case. This could be a result of the reaction time being too long with the achiral reagent **109·HCl**. When monitored by TLC it was found that the reaction in fact only required 5 hours to go to completion, which when implemented with the chiral reagent gave a much higher yield of 70%.

Problems were encountered in the reaction of the reagents **109·HCl** and **110·HCl** with 4-heptanone **113** (Table 2.1, entry 2), both of which gave extremely low yields of <10%. On examination of the ^{1}H NMR spectrum of the crude reaction mixture with the achiral reagent **109·HCl**, it was observed that an unexpected side reaction was in operation that was leading to the α-functionalised cyclohexanone product **33**, Reaction scheme 2.2. Repeat reactions confirmed this result. This observation along with its implications is explored in detail in Chapter 8.



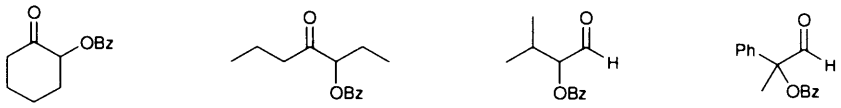
Reaction scheme 2.2: Unexpected side reaction.

In order to obtain a sample of the racemic 4-heptanone product **118** for analysis, an alternative achiral reagent was used, namely *N*-methyl-*O*-benzoyl hydroxylamine hydrochloride **63·HCl**, Reaction scheme 2.3. This was the standard reagent used to carry out this type of transformation and gave the desired α-functionalised product **118** in a 90% yield after purification by column chromatography.



Reaction scheme 2.3: Synthesis of racemic α-oxybenzoyl 4-heptanone 118.

This completed our initial efforts to synthesise each of the α-oxygenated products **33**, **118–120**, Figure 2.4. We were then able to turn our attention to optimising conditions for enantiomer separation and e.e. determination. This was done by means of HPLC on a chiral stationary phase, which proved to be the most convenient method available.



33 **118** **119** **120**

Figure 2.4: α-Functionalised products.

The first attempts at enantiomer separation were made on the cyclohexanone product **33** and were found to be successful, giving an optimal resolution on a Chiracel OD column under the conditions of a 5% IPA in hexane solvent system and a flow rate of 1 mL/min. A typical HPLC trace for this compound **33** is shown in Figure 2.5.

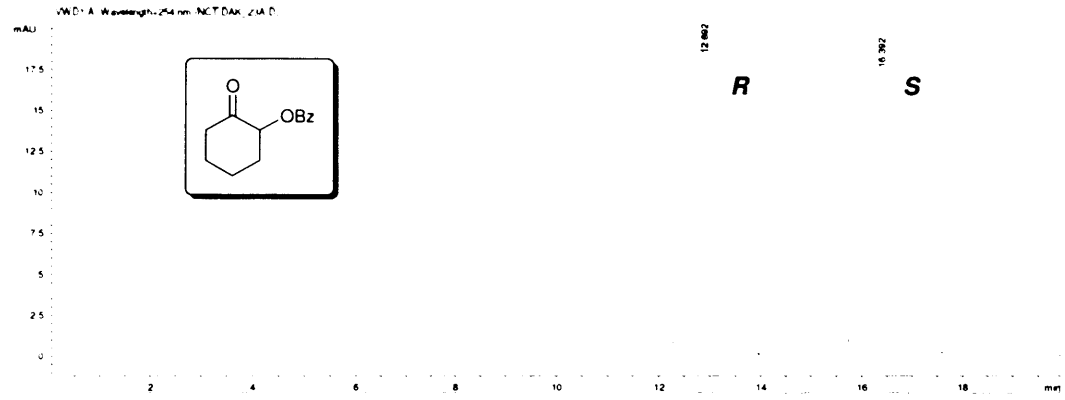
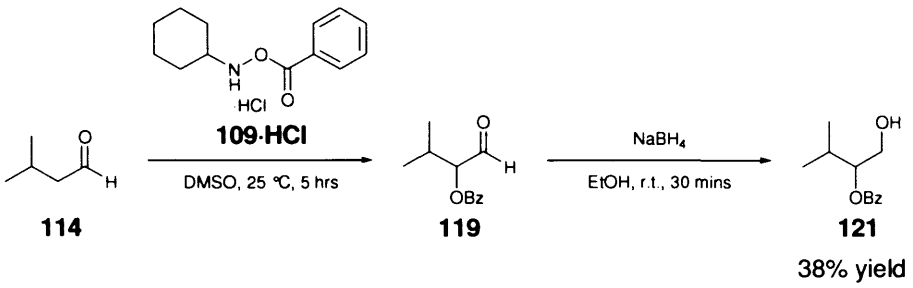


Figure 2.5: Typical HPLC trace obtained for 2-benzoyloxycyclohexanone 33.

As can be seen in the above trace, Figure 2.5, the enantiomers are well separated and defined, and by comparison to literature HPLC results we were able to assign absolute stereochemistry to the peaks.[28]

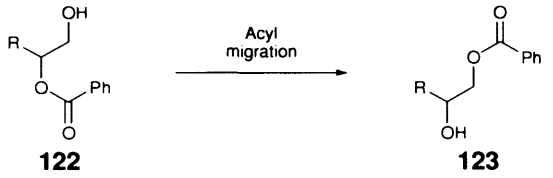
We had similar success in separating the enantiomers of the 4-heptanone product **118**, though they required more effort to separate. This was achieved on the OJ Chiracel column under the conditions of a 1% IPA in hexane solvent system and a flow rate of 0.5 mL/min.

Separating the enantiomers of the aldehyde products **119** and **120** was not quite as straightforward. After much time spent looking at different columns and conditions we realised that the products were not stable to HPLC methods, resulting in numerous peaks being observed in the HPLC trace. In order to circumvent this problem, we devised an alternative strategy for aldehydes which involved reduction of the crude α-functionalised product **119** to the more stable alcohol **121**, as illustrated below for the reaction of isovaleraldehyde **114**, Reaction scheme 2.4.



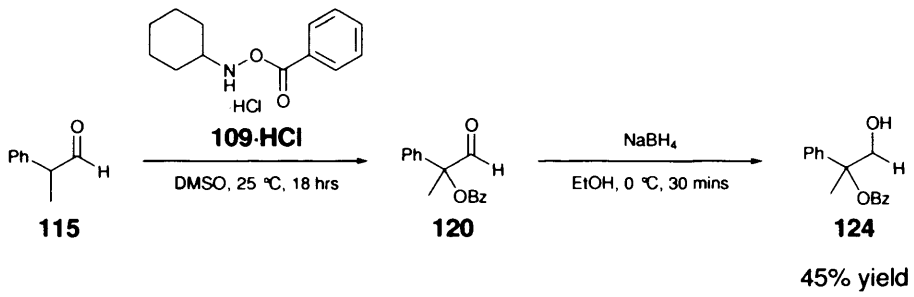
Reaction scheme 2.4: Alternative strategy devised for aldehydes.

Following reduction of the aldehyde product **119**, the possibility existed for an acyl migration, which would result in a mixture of alcohol products (**122** and **123**), as illustrated in Reaction scheme 2.5. This migration can occur as the secondary hydroxyl group is more sterically encumbered than the primary alcohol. Migration therefore reduces the steric strain on the molecule. These compounds (**122** and **123**) were distinguishable by NMR spectroscopy and in the above reaction (Reaction scheme 2.4) only the desired alcohol product **121** was observed.



Reaction scheme 2.5: Possibility of acyl migration following reduction of α-functionalised aldehydes to ease steric strain.

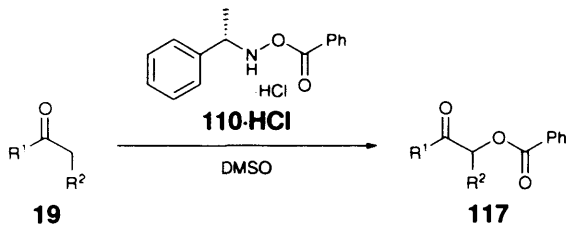
With the even more hindered alcohol **124**, this migration was more facile and led to both possible alcohol products (**122** and **123**) being observed in the ^{1}H NMR spectrum of the crude reaction mixture following reduction. By reducing the temperature of the reduction reaction to 0 °C, however, Reaction scheme 2.6, only the desired alcohol **124** was produced, in a respectable 45% yield.

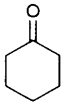
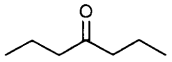
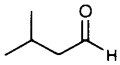
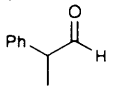


Reaction scheme 2.6: α-Oxybenzoylation of 2-phenyl propionaldehyde 115, followed by reduction to alcohol 124.

Attempts to separate the enantiomers of both of these alcohol products **121** and **124** were successful using the OJ chiracel HPLC column. This allowed us to move on to analysing the products from the reactions using the chiral reagent **110·HCl**.

Each of the products (**33**, **118–120**) obtained from reaction of the chiral reagent **110·HCl** was subsequently analysed by HPLC, using the conditions optimised for each of the racemic compounds. The results obtained from this set of analysis are shown in Table 2.2.



Entry	Substrate	Temp. (°C)	Yield (%)[c]	e.e. (%)
1		25	53	0
2		50	7	8
3[b]		25	40[d]	0
4		25	43[d]	0

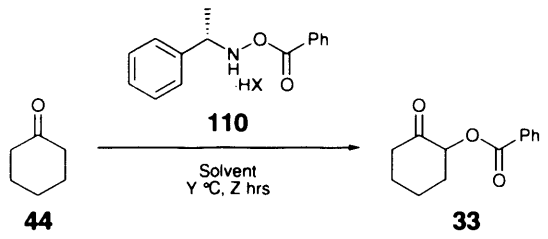
[a]All reactions were performed at 0.5M concentration for 18 hrs unless otherwise stated.
[b]Reaction was carried out for 5 hrs.
[c]Isolated yield.
[d]Product isolated as alcohol.

Table 2.2: Results obtained from analysis of products from chiral reactions.[a]

As can be seen in the above table (Table 2.2), initial results were very disappointing. Most of the products proved to be racemic (entries 1, 3 and 4), with the only exception being the product from the reaction of 4-heptanone **113**, entry 2, which was found to have an e.e. of 8%.

2.2. Optimisation.

From here we decided, for the time being, to concentrate solely on the reaction of cyclohexanone **44**, in the hope that we could achieve some level of asymmetric induction through optimisation of the variables in the reaction. Of the substrates examined to date **44** and **113–115**, we chose to continue with cyclohexanone **44** as it had given fairly good yields and the product **33** could be analysed directly, without the need for further reaction. Furthermore, of all the α-oxygenated products (**33**, **118–120**) synthesised, 2-benzoyloxycyclohexanone **33** was the only one in which the absolute stereochemistry of the enantiomers was known. It was felt that this knowledge could help impart a better understanding of the results and hence the reaction process.



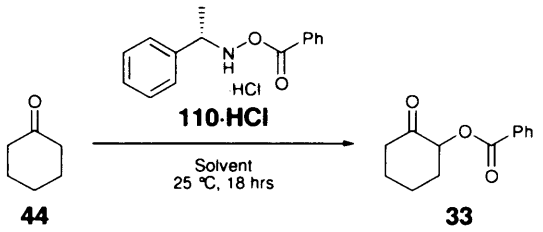
Reactions Scheme 2.7: Reaction of cyclohexanone 44 with chiral reagent 110, illustrating variables.

If we consider the general reaction of cyclohexanone **44** with the chiral reagent **110**, Reaction scheme 2.7, it is apparent that there are four main variables in the reaction which could be varied. These are the solvent, the co-acid, the temperature and the time. Each of these was subsequently examined.

2.2.1. Optimisation of the Solvent.

We began our efforts by examining the effect of the solvent. A wide variety of solvents were chosen, all with varying polarity indices, to determine their effect on

the level of asymmetric induction. The results of this solvent screen are shown in Table 2.3.



44 33

Entry	Solvent	Polarity Index	Yield (%)[a]	e.e. (%)
1	H_2O	10.2	95	1
2	DMSO	7.2	53	0
3	CH_3CN	5.8	38	3
4	Acetone	5.1	37	3
5	$CHCl_3$	4.1	29	0
6	THF/H_2O (9:1)		35	2
7	THF	4.0	32	0
8	CH_2Cl_2	3.1	38	2
9	PhMe	2.4	51	5[b]

[a]Isolated yield.
[b](*S*)-enantiomer of the product **33** produced in excess.

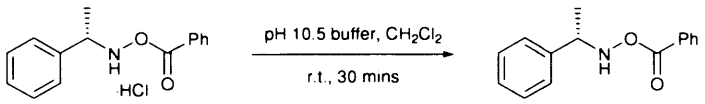
Table 2.3: Results obtained through variation of the solvent.

The results shown in the table above, Table 2.3, suggest that the solvent does affect the reaction and efficiency of the level of asymmetry induced in the product. Ignoring all e.e.'s of or below 2% (entries 1, 2, 5–8), as they were within error boundaries, it was observed that acetonitrile (entry 3), acetone (entry 4) and toluene (entry 9) all produced measurable e.e.'s, with toluene definitely showing some level of asymmetric induction (5% e.e.) of the (*S*)-enantiomer. There did not seem to be any distinguishable pattern emerging from these results. The only conclusion we were able to draw was that asymmetric induction seemed to be promoted by a non-polar, aromatic solvent.

2.2.2. Variation of the Co-Acid.

The next variable examined was the effect of the co-acid. In order to do this, it was necessary to obtain the free base of the reagent (**110**) that could be used in conjunction with a variety of other co-acids. This was obtained through vigorous stirring of the hydrochloride salt **110·HCl** in a biphasic solution of a pH 10.5 buffer

and dichloromethane, Reaction scheme 2.8. Alternatively, reagent **110** could be synthesised (Reaction scheme 2.1) and then purified by column chromatography.

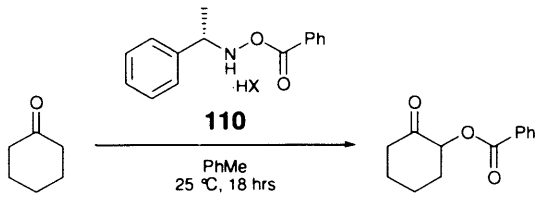


110·HCl **110**

92% Yield

Reaction scheme 2.8: Obtaining the free-base of chiral reagent 110·HCl.

Once obtained, separate reactions were carried out between this reagent **110** and cyclohexanone **44**, adding a stoichiometric amount of the co-acid. A variety of co-acids were chosen, ranging in pKa, in order to determine if the relative acidity of the co-acid or the counter-ion were affecting the reaction. Having established that the optimum solvent for the reaction was toluene, this was implemented as the solvent of choice. The results from this set of experiments are shown in Table 2.4.



44 **33**

Entry	Acid	pKa[a]	Yield (%)[b]	e.e. (%)[c]
1	HCl	−8.5	51	5
2	$MeSO_3H$	−2.6	53	5
3	TFA	−0.25	51	35
4	TCA	0.65	53	38
5	DPP	2.0	51	10
6	$PhCO_2H$	4.2	2	0

[a]pKa values in water.
[b]Isolated yield.
[c](*S*)-enantiomer of the product **33** produced in excess.

Table 2.4: Results obtained through variation of the co-acid.

The results from this set of experiments (Table 2.4) were much more encouraging. One of the first things noted was the need for a relatively strong acid in order to get good levels of reagent activity. By using a very weak acid, like benzoic acid, which has a pKa of about 4.2 (in water), we found that the reagent had very limited reactivity, giving the product **33** in a mere 2% yield (entry 6). It is believed that a

relatively strong acid is needed in order to initiate the crucial first step of the reaction, which is iminium ion formation.

When analysing the product **33** from each of these reactions by HPLC, another trend was observed. We found that the asymmetric reaction was very much dependent on the nature of the co-acid and that by reducing the acidity of the co-acid (relative to HCl) to that of TFA and TCA, we were able to obtain considerably higher levels of asymmetric induction (Table 2.4, entries 3 and 4). Overall, a pKa of about 0 was found to be optimal for the reaction, both in terms of yield and level of asymmetric induction, with notably stronger or weaker acids resulting in significantly lower e.e.'s (entries 1, 2, 5 and 6). Having an abundance of TFA to hand, this became our co-acid of choice.

2.2.3. Effect of a Chiral Co-Acid.

Having investigated the effect of varying the nature of the co-acid, we thought it would be timely to examine the use of a chiral co-acid for its potential to affect an asymmetric transformation. Although not a structural part of the reagent, we had already shown that the co-acid plays an important part in the asymmetric α-oxyacylation reaction (Chapter 2.2.2) and therefore its stereochemistry may well affect the outcome of the reaction. If successful this would constitute another way of incorporating chirality into the product of the α-oxygenation transformation.

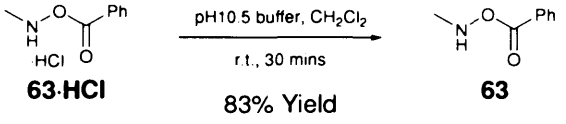
2.2.3.1. Approach.

After consideration, we decided to examine the use of both (*R*)- and (*S*)-camphor-10-sulfonic acid (CSA) **125** as chiral co-acids for the transformation, Figure 2.6, chosen due to the commercial availability of both enantiomers. We then set out to determine their effect as both the sole source of chirality in the reaction, and as a contributing factor, in conjunction with chiral reagent **110**.

(*R*)-125 (*S*)-125

Figure 2.6: Structures of (*R*)- and (*S*)-Camphor Sulphonic Acid (CSA) 125.

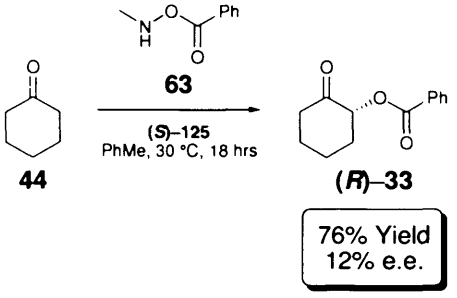
To begin with, we decided to examine the effect of these chiral co-acids (**125**) as the sole source of chirality in the reaction. This was accomplished by carrying out the reactions using an achiral reagent, namely *N*-methyl-*O*-benzoyl hydroxylamine **63**, obtained through free-basing the reagent **63·HCl**, Reaction scheme 2.9 (83%).



63·HCl 83% Yield **63**

Reaction scheme 2.9: Obtaining the free-base of achiral reagent 63·HCl.

Once obtained, this reagent **63** was then reacted with cyclohexanone **44**, in the presence of a stoichiometric amount of (*S*)-CSA (***S*)-125**, Reaction scheme 2.10. This reaction was found to be successful, giving the product **33** in a good yield of 76%, and analysis by HPLC revealed an e.e. of 12% ((*R*)-enantiomer).

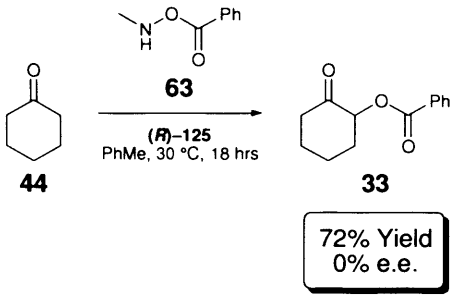


44 (*R*)-33

76% Yield
12% e.e.

Reaction scheme 2.10: Reaction of achiral reagent 63 with (*S*)-CSA (*S*)-125.

Excited by this initial result we turned to examine the effect of using (*R*)-CSA (***R*)-125** in the same reaction, in order to confirm that it brought about a similar enrichment of the opposite enantiomer. Surprisingly, this reaction, Reaction scheme 2.11, was found to give a racemic product **33**.



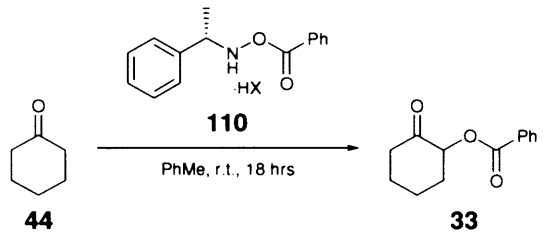
Reaction scheme 2.11: Reaction of achiral reagent 63 with (*R*)-CSA (*R*)-125.

Perplexed by this inexplicable difference in the results obtained, we decided to re-examine the effect of (*S*)-CSA **(*S*)-125** as the co-acid. After repeating this reaction (Reaction scheme 2.10) we obtained a slightly lower (but real) e.e. of 8% of the (*R*)-enantiomer of the product **33**, which still suggested that (*S*)-CSA **(*S*)-125** has some ability to affect an asymmetric transformation. This second value of 8%, however, did not completely agree with the first result (Reaction scheme 2.10), even taking into account the margin for error. We therefore decided that it would be wise to repeat the reaction (Reaction scheme 2.10) one final time, in order to ensure the results were consistent. In the end we carried out 3 further repeat reactions, all of which generated a racemic product **33**. This was very disappointing after the extremely interesting initial result (Reaction scheme 2.10).

We have been unable to explain how e.e.'s were generated in the product **33** of the initial reactions (Reaction scheme 2.10), if (*S*)-CSA **(*S*)-125** is not able to affect an asymmetric transformation; or why, if some other factor was involved, the result could not be repeated, given that all repeat reactions were carried out using the same batch of achiral reagent **63** and chiral co-acid **(*S*)-125**, and were all carried out under identical reaction conditions.

Overall, we had to conclude that chiral co-acid **125** is not able to render the α-oxybenzoylation of cyclohexanone **44** asymmetric when used as the sole source of chirality in the reaction. We did still wonder whether use of this chiral co-acid **125** in conjunction with chiral reagent **110** could augment the effect of chiral reagent **110** and thus improve the existing e.e. of the product **33**.

Separate reactions were therefore carried out between chiral reagent **110** and cyclohexanone **44**, using both (*S*)- and (*R*)-CSA **125** as the co-acid. The results of these reactions are shown in Table 2.5.



44 **33**

Entry	Co-acid	pKa[c]	Yield (%)[a]	e.e. (%)
1	TFA	−0.25	51	37[b]
2	(*S*)-CSA	−2.1	48	0
3	(*R*)-CSA	−2.1	49	0

[a]Isolated yield.
[b](*S*)-enantiomer of the product **33** produced in excess.
[c]pKa values in water.

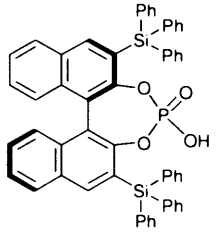
Table 2.5: Results from using chiral co-acid 125 in combination with chiral reagent 110.

As can be seen in the above table, Table 2.5, despite giving the product **33** in yields comparable to that provided by TFA (entry 1), we observed no asymmetric induction in the product **33** when using (*S*)- or (*R*)-CSA **125** (entries 2 and 3). After looking back at the results obtained following variation of the co-acid (Table 2.4), this observation fits with previous results, where it was found that a pKa of around 0 was optimal for the asymmetric transformation and that stronger co-acids gave significantly lower e.e.'s (Table 2.4, entries 1 and 2). These results (Table 2.5) therefore support the previous conclusion that the nature of the co-acid affects the outcome of the reaction, but show no sign that the stereochemistry of the co-acid has an effect.

This concluded our examination of the use of CSA **125** as a chiral co-acid, which we found was unable to transfer any reliable sense of asymmetry to the product **33**. Before making a general conclusion on the effect of a chiral co-acid on the α-oxyacylation reaction, however, we felt that we should investigate at least one more chiral co-acid.

2.2.3.2. Use of a Bulky Chiral Co-Acid.

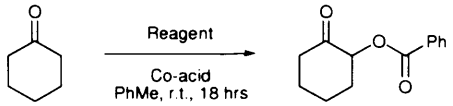
The further chiral acid chosen was (*R*)-(−)-3,3'-bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate **126**, Figure 2.7, which is a very large bulky chiral phosphoric acid, with a molecular weight of 865 g/mol. This acid was chosen as we hoped the steric bulk would perhaps restrict movement in the transition state and thus favour formation of one enantiomer over another. This is commercially available, though very expensive at a cost of approximately £145 per 100 mg, and was very kindly provided by our collaborator at Syngenta. Due to the high cost however, we decided only to examine one enantiomer of the acid.



126

Figure 2.7: Large chiral co-acid examined.

This acid **126** was reacted firstly with the achiral *N*-methyl reagent **63** and then secondly with the chiral (*S*)-α-methyl benzyl reagent **110**. It was hoped that this would answer both questions of whether it could induce asymmetry in the reaction as the sole source of chirality or in combination with another chiral moiety. In the second case it was hoped that when used with reagent **110**, the product **33** would show a change in the level of asymmetry, compared to the result obtained from using a TFA co-acid (Table 2.4, entry 3), indicating a combined effect. The results for these experiments are shown in Table 2.6.



44 33

Entry	Reagent	Co-acid	Yield (%)[a]	e.e. (%)
1	**63**	**126**	61	0
2	**110**	TFA	51	37[b]
3	**110**	**126**	32	0

[a]Isolated yield.
[b](*S*)-enantiomer of the product **33** produced in excess.

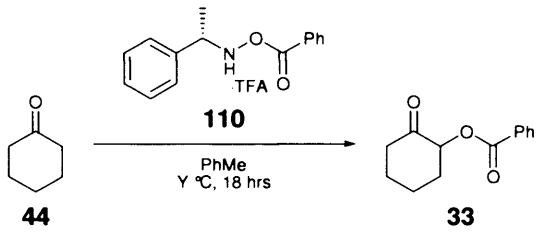
Table 2.6: Results obtained from using bulky chiral acid 126.

As can be seen in the results shown above (Table 2.6), chiral acid **126** was not able to induce asymmetry in the product **33** of this transformation. When looked at as the sole source of chirality it was shown to produce a racemic product **33** (entry 1). It was therefore not surprising that when used together with chiral reagent **33** (entry 3), the product **33** was again racemic.

Overall, our results from these studies suggest that the effect of a chiral co-acid, if any, was complex and we elected to examine alternative variables within our transformation.

2.2.4. Further Optimisation Efforts.

The effect of temperature on the reaction was examined next, with reactions being carried out at several different temperatures using the now optimised conditions of toluene as the solvent with TFA as the co-acid. This study gave the anticipated result that lower temperatures are favourable with respect to the level of asymmetry in the product, Table 2.7, however; lower temperatures also resulted in a decrease in the yield of the reaction, entries 4 and 5. From these results it was decided to conduct future reactions at room temperature. This was shown to give the optimum balance between yield and level of asymmetric induction (entry 3), whilst at the same time being the most convenient.

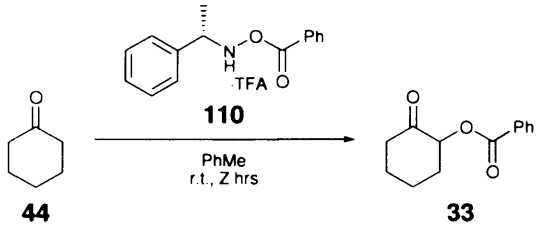


Entry	Temp. (°C)	Yield (%)[a]	e.e. (%)[b]
1	30	54	7
2	25	51	35
3	20[c]	51	37
4	10[d]	41	41
5	0	27	43

[a]Isolated yield.
[b](*S*)-enantiomer of the product **33** produced in excess.
[c]Reaction carried out at r.t., with temp. range of 20–22 °C.
[d]Reaction carried out in fridge, with temp. range of 7–10 °C.

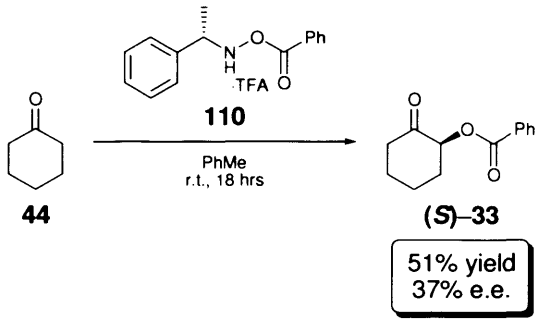
Table 2.7: Results obtained from variation of the reaction temperature.

The final variable to be examined was the effect of time on the reaction. This was looked at briefly with results suggesting that time affects only the yield of the reaction; the e.e. of the product **33** remained about the same. This told us that the product **33** of this reaction, Reaction scheme 2.12, was stable under the reaction conditions and that the e.e.'s being observed are a genuine reflection of the C–O bond forming process.



Reaction scheme 2.12: Exploring the effect of time on the reaction.

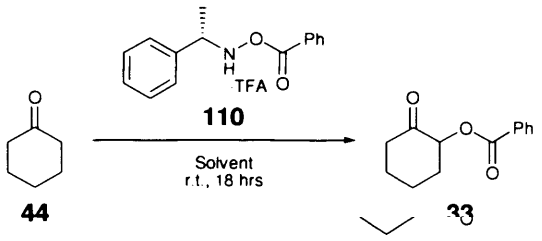
Overall, this gave us the optimised conditions of a TFA co-acid, with the reactions being carried out in toluene, at room temperature for 18 hours, Reaction scheme 2.13. This gave us the α-functionalised product **33** in a 51% yield and a 37% e.e. It was also observed that by using a chiral reagent with (*S*)-stereochemistry **110**, we enriched the (*S*)-enantiomer of the product **(*S*)-33**.



Reaction scheme 2.13: Optimised reaction of cyclohexanone 44 with chiral reagent 110.

Before moving on to our next line of investigation we decided to re-examine the effect of solvent on our reaction system. This was due to the fact that when the effect of solvent was first examined, all e.e.'s measured were ≤ 5%. Looking back this did not seem like a strong case on which to base our decision that toluene was the optimum solvent owing to the percentage error margins involved in each result. We also wanted to answer the question posed earlier on whether the result obtained previously, that showed toluene to be the best solvent, was due to it being a non-polar solvent or an aromatic solvent.

A second set of reactions was carried out, again in solvents varying in their relative polarities, this time including hexane which has a lower polarity index than toluene. If the previous result (Table 2.3, entry 9) was due to the polarity of the solvent, hexane should in theory give a better e.e. than toluene.



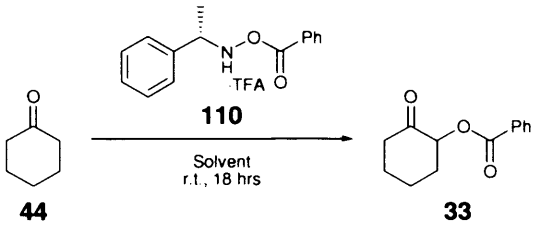
Entry	Solvent	Polarity Index	Yield (%)[a]	e.e. (%)[b]
1	DMSO	7.2	72	0
2	Acetone	5.1	41	0
3	EtOH	4.3	65	0
4	CH_2Cl_2	3.1	45	13
5	Ether	2.8	49	9
6	Toluene	2.4	51	37
7	Hexane	0.1	53	17

[a]Isolated yield.
[b]Where e.e. was measured, (*S*)-enantiomer of the product **33** produced in excess.

Table 2.8: Re-examining the effect of solvent.

As can be seen in the above table (Table 2.8), toluene remained the optimum solvent for the transformation in terms of ability to provide the enantiomerically enriched product **33**, entry 6. These results also suggested that although a less-polar solvent is more favourable, the transformation required an aromatic solvent.

In order to ascertain whether toluene was the best aromatic solvent available, a series of aromatic solvents was examined, Table 2.9. These solvents comprised both electron-poor (entries 5, 6 and 7) and electron-rich (entries 2, 3 and 4) aromatic solvents.



44 33

Entry	Solvent	Yield (%)[a]	e.e. (%)[b]
1	Benzene	49	42
2	Toluene	51	37
3	Xylene	48	33
4	Anisole	38	32
5	Hexafluorobenzene	48	23
6	2-Nitro toluene	35	15
7	Nitro benzene	41	14

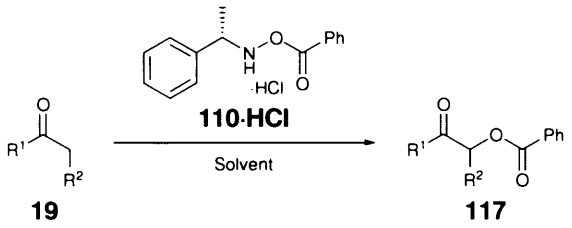
[a]Isolated yield.
[b](*S*)-enantiomer of the product **33** produced in excess.

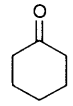
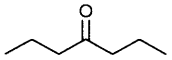
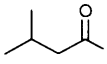
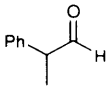
Table 2.9: Results obtained from using aromatic solvents.

The results obtained from this set of experiments told us that a more electron-rich solvent was beneficial. We found benzene to be the optimum solvent however, which gave the product **33** in good yield and a marginally higher e.e. of 42% (Table 2.9, entry 1) compared to that provided by toluene (entry 2). Owing to the hazards associated with benzene, and the fact that it gave only slightly better results, we continued with the use of toluene as our solvent of choice.

2.3. Optimisation of Acyclic ketone (113) and Aldehyde (114 and 115) Reactions.

Going back to the reactions of our original set of carbonyl compounds (**44**, **113–115**), we thought we'd try and implement some of the optimised conditions to see the effect, if any, they had on the reactions of acyclic ketones and aldehydes. To begin with, all reactions were carried out using toluene as the solvent (under the appropriate conditions shown earlier in Table 2.2). This showed an increase in the e.e. in all cases when compared to the results obtained using DMSO, as shown in Table 2.10.



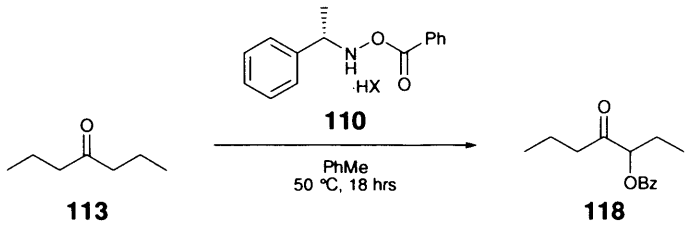
		DMSO		Toluene	
Entry	**Substrate**	**Yield (%)[b]**	**e.e. (%)**	**Yield (%)[b]**	**e.e. (%)**
1		53	0	57	5[f]
2[c]		7	8	15	21
3[d,e]		40	0	29	5
4[e]		43	0	31	6

[a]All reactions were performed at 0.5 M concentration at r.t. for 18 hrs unless otherwise stated.
[b]Isolated yield.
[c]Reactions were carried out at 50 °C
[d]Reactions were carried out for 5 hrs.
[e]Products were isolated as the alcohol.
[f](*S*)-enantiomer of the product **33** produced in excess.

Table 2.10: Results obtained for all substrates in DMSO and toluene.[a]

From these results, we can see a comparative increase in the e.e.'s for aldehydes **114** and **115** when carried out in toluene, entries 3 and 4, as was seen originally for cyclohexanone **44** (entry 1). Yields for these reactions (entries 3 and 4), however, had decreased considerably, making the transformation less appealing for aldehydes.

We did get a very encouraging result from the acyclic ketone **113** however, which generated the product **118** in a 21% e.e. when carried out in toluene (entry 2). This also gave a notably higher yield of 15%. Being such a promising result we thought we'd follow up on the reaction of 4-heptanone **113** by examining the effect of different co-acids to see if they demonstrated the same trend as seen previously. Separate reactions were therefore carried out at 50 °C in toluene, using a stoichiometric amount of different acids. The results for this set of reactions are shown in Table 2.11.



113 118

Entry	Acid	pKa[c]	Yield (%)[a]	e.e. (%)
1	HCl	-8.5	15	21
2	$MeSO_3H$	-2.6	16	2
3	TFA	-0.25	11	15[b]
4	$PhCO_2H$	4.2	No Reaction	

[a]Isolated yield.
[b]Opposite enantiomer produced in excess, compared to other table entries.
[c]pKa values in water.

Table 2.11: Effect of co-acid on the reaction of 4-heptanone 113.

As can be seen above (Table 2.11), the effect of the co-acid was not quite as straightforward as in the reaction of cyclohexanone **44**. In this case it would appear that HCl was the optimal co-acid for inducing asymmetry in the product, entry 1, indicating the need for a strong acid in the reaction. Interestingly, it was noted that reducing the acidity of the co-acid resulted in a decrease in the enantiomeric excess of the product, resulting in an effectively racemic compound with methane sulfonic acid, entry 2. Continued reduction of the acidity of the co-acid, to TFA, was then observed to enrich the other enantiomer of the product **118**, entry 3. This tells us that the co-acid has an integral role in the asymmetric transformation, but at present that role had yet to be defined. Use of a very weak acid severely limited the reactivity, consistent with previous observations, entry 4.

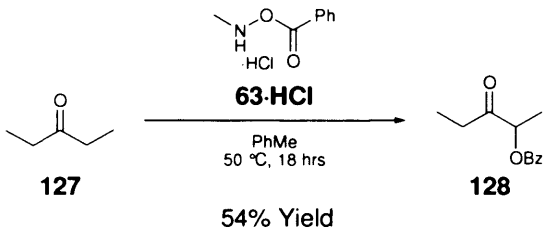
Whilst attempting to optimise the asymmetric α-oxygenation of 4-heptanone **113** we also looked briefly at the effects of temperature and time on the reaction. Results in these instances supported previous findings that firstly the reaction was affected by temperature, with higher temperatures resulting in lower e.e.'s. They also confirmed that time did not affect the level of asymmetric induction, merely the yield of the reaction. This supported previous conclusions that the α-oxygenated products were not racemising under the reaction conditions.

It was becoming increasingly apparent that the transformation was more applicable to cyclic ketones, having obtained good yields and promising e.e.'s for cyclohexanone **44**. We had obtained interesting e.e.'s from acyclic ketone **113** (Table 2.10, entry 2); however, the associated yields were below an acceptable or usable level. We therefore thought that it would be wise to try and address this issue, which would increase the synthetic applications of this transformation.

2.4. Overcoming Low Yields.

We believed the problem of low yields in the reactions of acyclic ketone **113** to be the result of unfavourable steric effects. The steric bulk surrounding the nitrogen atom of the chiral reagent **110·HCl**, combined with the increased sterics of using an acyclic ketone, made initial iminium ion formation extremely difficult at modest temperatures. The most obvious solution was to carry out the reaction at a higher temperature; however, we had seen that this resulted in a decrease in the level of asymmetric induction, along with reagent decomposition (Chapter 8).

To begin with we decided to look at using the less sterically encumbered acyclic ketone 3-pentanone **127**, to see if the reduced sterics helped promote the reaction. Another advantage to using this alternative acyclic substrate **127**, was that the product **128** was a known compound, with optical rotation of $[\alpha]^{23}_{D}$ +20.7 (1 g/100 mL, $CHCl_3$) reported for the (*S*)-enantiomer.[56] This compound **127** was reacted with the achiral *N*-methyl-*O*-benzoyl reagent **63·HCl** (due to previous problems with the *N*-cyclohexyl reagent **109·HCl** under these reaction conditions, Reaction scheme 2.2), in order to generate a reference racemic product **128**, Reaction scheme 2.14.

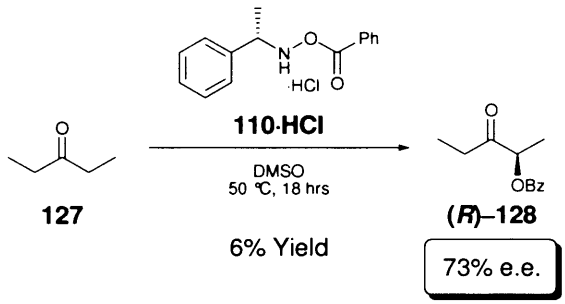


Reaction scheme 2.14: α-Functionalisation of 3-pentanone 127.

The enantiomers of this compound **128** were successfully separated by HPLC, using similar conditions to those used for 3-benzoyloxy-4-heptanone **118**. This allowed us

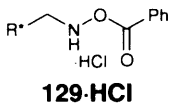
to continue and attempt to generate an enantiomerically enriched product **128** using the chiral reagent **110·HCl**. This reaction was carried out under the conditions of a HCl co-acid and toluene as the solvent as optimised for 4-heptanone **113**. Unfortunately though, this did not prove to be a very clean or efficient reaction and as a result, a pure sample of the product could not be isolated for analysis.

In the hope of being able to isolate some product **128**, this reaction was repeated in DMSO, which generally gave a much cleaner transformation, Reaction scheme 2.15. This gave the product in a similarly low yield of 6%, which this time we were able to isolate. When analysed, we found the product **128** to have a reproducible e.e. of 73% of the (*R*)-enantiomer. The absolute stereochemistry of the product **(*R*)-128** was determined by measuring the optical rotation, which was found to be $[\alpha]^{23}_{D}$ −15.1 (1 g/100 mL, $CHCl_3$).



Reaction scheme 2.15: Reaction of 3-pentanone 127 with chiral reagent 110·HCl.

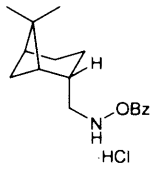
This was the highest e.e. obtained to date and was very exciting; however the problem of low yields had not been overcome. An alternative solution was to try to ease the steric congestion caused by the bulky chiral *N*-substituent of the reagent **110·HCl**, by further removing the stereogenic centre from the reactive nitrogen atom, as illustrated by the general structure **129·HCl** shown below, Figure 2.8.



129·HCl

Figure 2.8: Alternative strategy for increased yields.

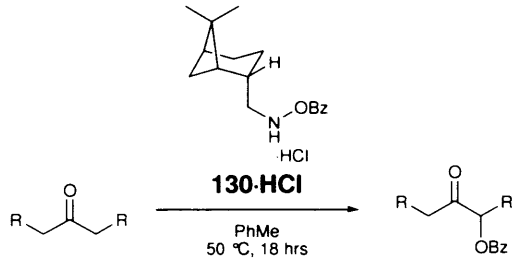
A new reagent **130·HCl**, Figure 2.9, was prepared based on this principle. It was hoped that this would reduce the undesirable steric effects, facilitating iminium ion formation, leading to increased product yields whilst still promoting asymmetric induction.



130·HCl

Figure 2.9: New chiral reagent 130·HCl with further removed stereogenic centre.

This reagent (**130·HCl**) was reacted with both acyclic substrates **113** and **127** in the hope of obtaining the products (**118** and **128**) in higher yields. The results obtained through use of this reagent are shown in Table 2.12.



Entry	R	Yield (%)[a]	e.e. (%)
1	Me	59	6
2	Et	40	3

[a]Isolated yield.

Table 2.12: Results from alternative reagent strategy.

As hoped, we obtained both α-oxygenated products **118** and **128** in significantly greater yields of 59 and 40% respectively (Table 2.12). Unfortunately, when we came to measure the e.e.'s we were very disappointed to discover there was no real sense of asymmetric induction provided by this reagent **130·HCl**. This brought us to the conclusion that a stereogenic centre in close proximity to the reactive nitrogen atom was essential. We therefore did not pursue this line of investigation further.

2.5. Conclusion.

At this stage we had developed a method for the general preparation of chiral hydroxylamine reagents in good yield from commercially available precursors, without the need for chromatography. We subsequently developed successful screens

for the determination of the asymmetric α-oxybenzoylation of cyclic (**44**) and acyclic (**113** and **127**) ketones, and aldehydes (**114** and **115**).

Optimisation of a number of variables revealed e.e.'s of up to 37% of the (*S*)-enantiomer of the product (***S*)-33** from cyclohexanone **44**, and 73% of the (*R*)-enantiomer of the product (***R*)-128** from 3-pentanone **127** using the chiral reagent **110·HCl** derived from (*S*)-α-methyl benzylamine **112**.

The effect of a chiral co-acid was investigated, and was examined as both the sole source of chirality in the α-oxybenzoylation reaction and as a contributing factor in conjunction with chiral reagent **110**. Several chiral co-acids were examined and the results from this set of experiments suggested that a chiral co-acid was not able to effect an asymmetric transformation.

Observed yields for acyclic ketones (**113** and **127**) have not been adequate (frequently <10%). In an effort to overcome this, an alternative reagent **130·HCl** was synthesised from a less sterically encumbered primary amine. This increased the yields, as hoped, unfortunately at the expense of the e.e.

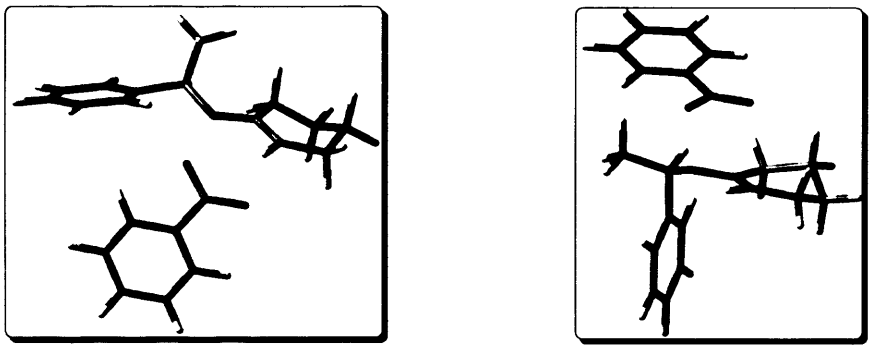
Results suggested that this asymmetric transformation may be most applicable to cyclic ketones, having obtained good yields from cyclohexanone **44** with promising e.e.'s. The product **33** from this reaction could also be analysed directly and had previously defined stereochemistry. Our subsequent work therefore focused on this class of substrate.

Chapter 3.

Variation of the *O*-Acyl Group.

3.1. Introduction.

In order to aid our investigations, we embarked upon developing a transition state model through the use of DFT (density functional theory), in collaboration with Dr. J. A. Platts. To begin with, this theoretical computer modeling study found a low-energy transition state that supported our proposed [3,3]-sigmatropic rearrangement process. The study then progressed to examining the effect of our chiral hydroxylamine reagent **110** on the reaction, in the hope that it would provide us with information that could guide our synthetic studies.

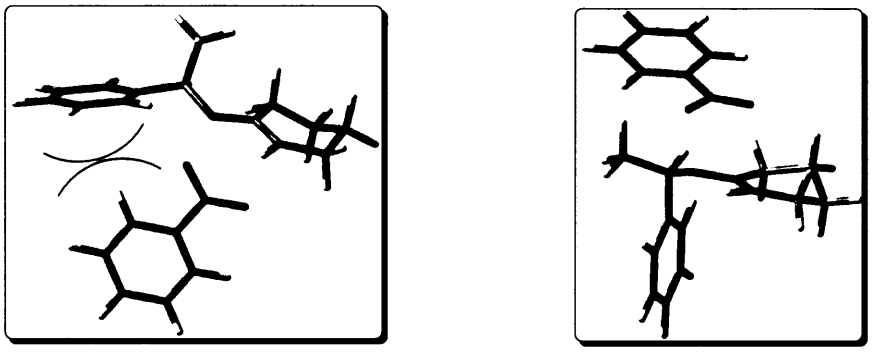


132 **133**

Figure 3.1: Possible transition states for asymmetric transformation generated using computer modeling.

Results from these studies were quite promising and provided us with two possible transition states, **132** and **133** (Figure 3.1), for the reaction between cyclohexanone **44** and the chiral reagent **110**. These transition states (**132** and **133**) result in different enantiomers of the product **33**, with **132** leading to the minor (*R*)-enantiomer and **133**, being lower in energy, leading to the major (*S*)-enantiomer of α-oxybenzoyl cyclohexanone **33**.

Results from previous experiments with cyclohexanone **44**, showed us that using the (*S*)-enantiomer of the reagent **110** preferentially leads to the (*S*)-enantiomer of the product (***S*)-33**. If the above transition states were correct, this means that the reaction favours transition state **133**. In order to increase the level of asymmetric induction in the reaction therefore, we needed to focus on trying to find a way to encourage the reaction through this particular transition state **133**, by disfavouring the alternative transition state **132**.



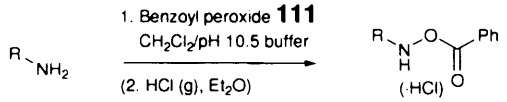
132 133

Figure 3.2: Possible steric interaction in transition state 132.

By examining the proposed transition states (Figure 3.1), it appeared that one way of achieving this could be to increase the size of the *O*-acyl group. This would increase undesirable steric effects in transition state **132**, Figure 3.2, making transition state **133** much more favouable. We decided to test this hypothesis by examining the effect of varying the *O*-acyl group.

3.2. New Approach to Reagent Synthesis.

Hydroxylamine reagents synthesised to date (**109·HCl**, **110(·HCl)** and **130·HCl**) had been generated using the same method, which involved reaction of a primary amine **134** with benzoyl peroxide **111** in a biphasic solution of dichloromethane and a pH 10.5 buffer, Reaction scheme 3.1.[55] These react to form the desired hydroxylamine reagent **135** which can either be converted into the HCl salt, with no need for further purification, or purified by column chromatography to be used in conjunction with a variety of other co-acids.

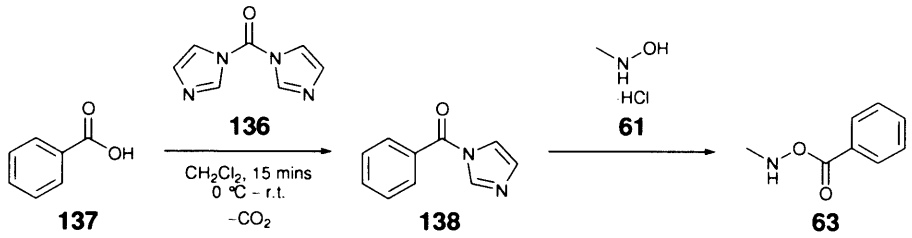


134 135

Reaction scheme 3.1: Traditional method used for reagent synthesis.[55]

Owing to the lack of commercially available acyl peroxides however, this process can not be used to construct reagents with anything other than an *O*-benzoyl group. Another method was therefore needed to synthesise reagents with different *O*-acyl groups and a suitable alternative was the Geffken method, which was previously

employed by the group in the synthesis of the achiral *N*-methyl *O*-benzoyl reagent **63**, Reaction scheme 3.2.[57]



Reaction scheme 3.2: New approach to reagent synthesis.[57]

As exemplified for the synthesis of the general achiral reagent **63**, Reaction scheme 3.2, this method involved reaction of a carboxylic acid **137** with carbonyl diimidazole (CDI) **136**, to form an activated imidazole intermediate **138**. The desired hydroxylamine hydrochloride **61** is then added, which attacks this intermediate **138**, to give the desired product **63**.

Having identified a suitable alternative method for reagent synthesis, a series of carboxylic acids **139–145** was then chosen to examine their effect on the α-oxyacylation transformation, Figure 3.3. The carboxylic acids chosen (**139–145**) all possessed increased steric bulk compared to that of benzoic acid to evaluate our hypothesis. We also thought it would be interesting to use both aliphatic (**139** and **140**) and aromatic (**141–145**) carboxylic acids, in order to determine if this was a relevant factor in the transformation.

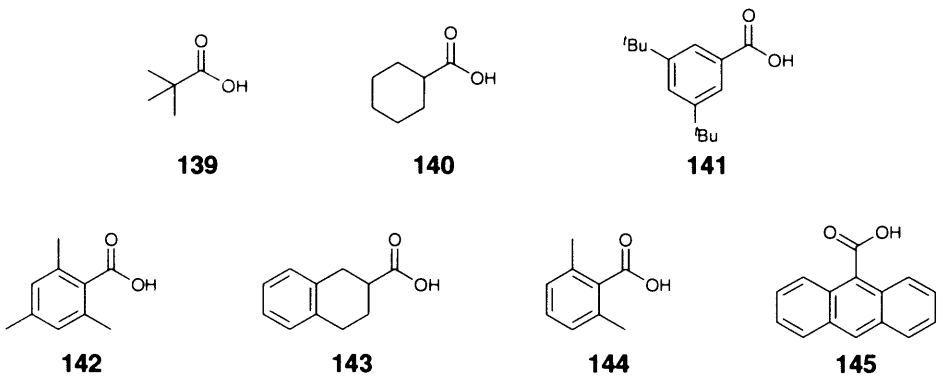
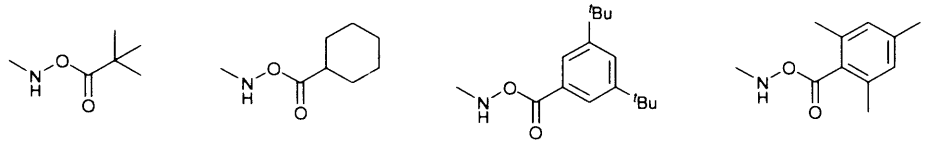


Figure 3.3: Initial set of carboxylic acids to be examined.

Each of these acids **139–140** was reacted with *N*-methyl hydroxylamine hydrochloride **61** in the alternative manner described (Reaction scheme 3.2), in order to firstly determine which would react in the desired manner. The resulting

N-methyl-*O*-acyl hydroxylamine reagents would then be used to generate the corresponding racemic α-oxygenated products to be used as references.

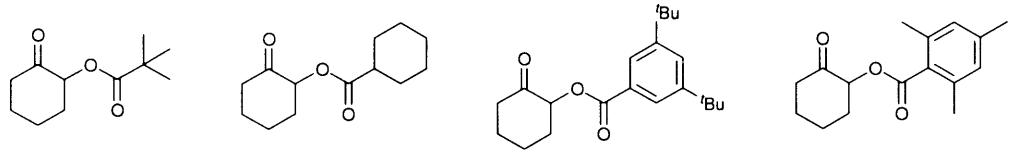
Of those examined, only acids **139–141** were found to give the analogous achiral reagents **146–148** in reasonable yields, Figure 3.4. The remaining acids (**142–145**) were thought to be too bulky to undergo the initial reaction with CDI **136**. A second attempt at reacting acid **142** with CDI **136** was carried out at a slightly higher temperature of 25 °C, using a new bottle of CDI **136**. This was found to produce the desired reagent **149** in a very low yield of 4% following purification by column chromatography. Although low, this provided us with enough material to establish the effect of an *O*-2,4,6-trimethylbenzoyl group on the reaction.



146 **147** **148** **149**

Figure 3.4: Initial achiral reagents generated using Geffken method.[57]

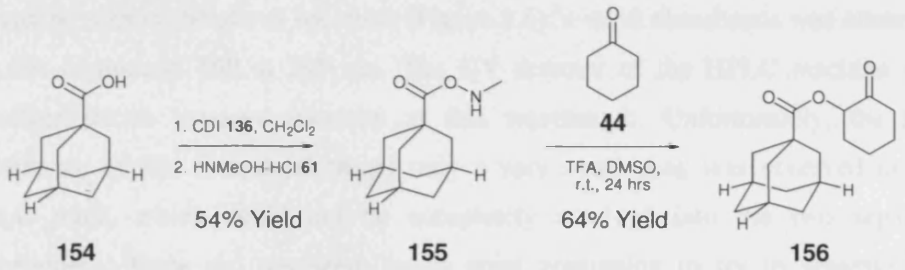
The new achiral reagents formed, **146–149**, were then reacted in turn with cyclohexanone **44** in DMSO to form the corresponding racemic α-oxygenated carbonyl compounds **150–153** in generally good yields, Figure 3.5.



150	**151**	**152**	**153**
71%	84%	64%	31%

Figure 3.5: Products from reaction of new achiral reagents 146–149 with cyclohexanone 44.

At this point a further bulky aliphatic carboxylic acid was identified, namely adamantane carboxylic acid **154**. This was also examined for its potential to give the desired achiral *N*-methyl hydroxylamine reagent **155**. This reaction was successful, along with the subsequent α-oxygenation of cyclohexanone **44**, Reaction scheme 3.3.



Reaction scheme 3.3: Reaction of new bulky aliphatic carboxylic acid 154 and the corresponding achiral reagent 155.

3.3. Separation of Enantiomers.

Having produced a range of new α-oxygenated products (**150–153**, and **156**), the next step was to separate the enantiomers of each of the new compounds. HPLC was the first choice, as this technique had proved to be consistently good at separating the enantiomers of this class of compound, and in cases of enantiomerically enriched products, gave an accurate measure of the e.e. obtained.

We began our efforts looking at compound **150**. Since this product does not contain any aromatic groups or conjugation, a UV spectrum was needed in order to ascertain the wavelength of light this compound absorbs, Figure 3.6. This was necessary as the HPLC technique uses UV as the form of detection.

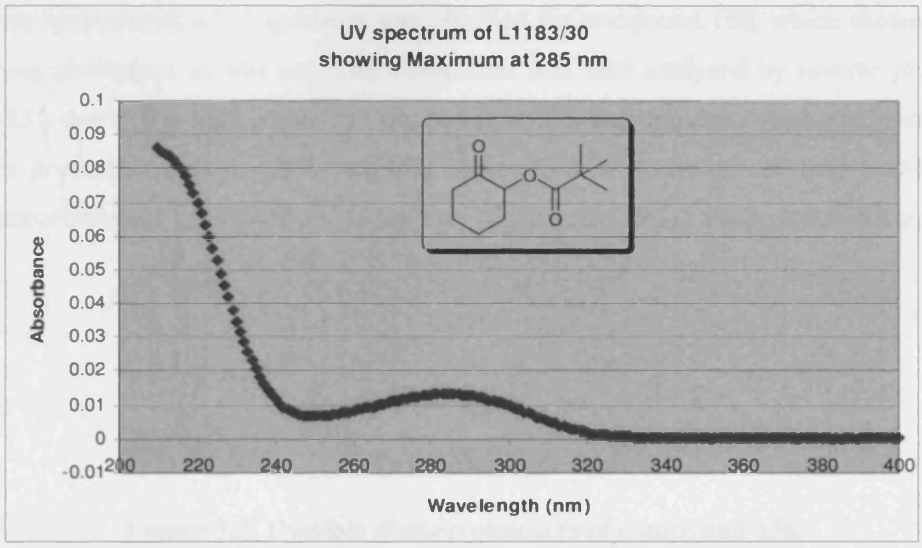
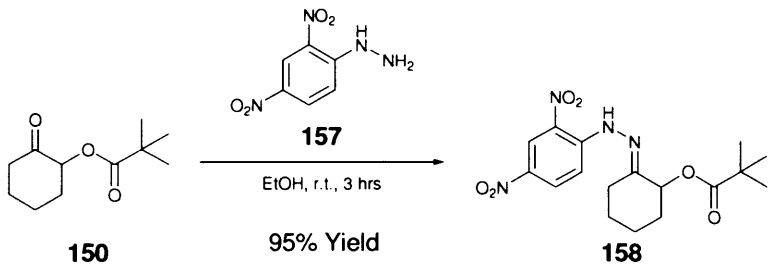


Figure 3.6: UV spectrum obtained for compound 150.

As can be seen in the above spectrum (Figure 3.6), a weak absorbance was observed for this compound **150** at 285 nm. The UV detector of the HPLC machine was therefore set to measure intensity at this wavelength. Unfortunately, the low absorbance of this compound meant only a very small peak was observed in the HPLC trace, which could not be completely resolved into the two separate enantiomers. There did not seem much point continuing to try to separate the enantiomers in this way, since the noise level on the HPLC spectrum would make e.e. determination in the chiral systems unreliable.

With HPLC still being the method of choice, another idea was to form a derivative of compound **150** that would be more UV active and thus give more intense peaks. A suitable derivative was a hydrazone, and so compound **150** was reacted with 2,4-dinitrophenylhydrazine (2,4-DNPH) **157** to give compound **158** in an excellent yield of 95%, Reaction scheme 3.4.



Reaction scheme 3.4: Forming hydrazone derivative of 150 using 2,4-DNPH 157.

Once synthesised, a UV spectrum was obtained for compound **158**, which showed a strong absorption at 340 nm. This compound was then analysed by reverse phase HPLC, due to the high polarity of the compound. Since this compound can exist as two geometric isomers **159** and **160**, Figure 3.7, a maximum of four possible diastereoisomers can result, and hence four peaks in the HPLC trace were expected.

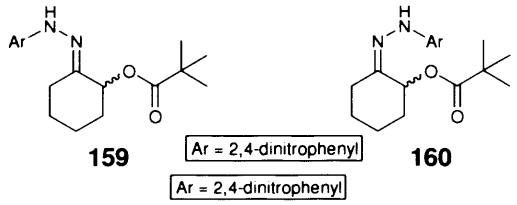
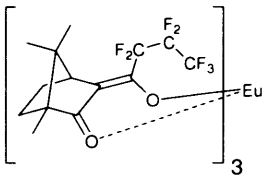


Figure 3.7: Possible diastereoisomers of compound 158.

Under the conditions of a 20% H_2O/CH_3CN solvent system and a flow rate of 1 mL/min, two main peaks were observed, one of which was poorly defined, possibly

showing evidence of further splitting. Attempts to separate the peaks further, into four distinct peaks, were made by reducing the polarity of the solvent system and slowing the flow rate. This led to three of the four peaks being resolved but efforts to separate out the fourth isomer were unsuccessful.

Moving away from HPLC, another option to separate the enantiomers of **150** was through the use a chiral NMR shift reagent. A suitable such reagent was europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] or $Eu(hfc)_3$, **161**, the structure of which is shown in Figure 3.8.



161

Figure 3.8: Structure of NMR shift reagent $Eu(hfc)_3$ 161.

A known amount of racemic **150** was dissolved in deuterated chloroform in an NMR tube and 0.02 equivalents of the shift reagent **161** was added. A ^1H NMR spectrum was then obtained, which showed a slight broadening of the key α-H signal. Addition of the shift reagent **161** was continued in 0.02 equivalent increments, with a ^1H NMR spectrum being obtained after each addition. The results of this experiment are shown in Appendix 1, in which it is clear that by addition of a total of 0.1 equivalents of the shift reagent **161**, the α-H signal was resolved into two separate peaks of equal intensity that can be integrated for e.e. determination in the chiral systems.

Compound **151** was examined next and, as with compound **150**, a UV spectrum was obtained, Figure 3.9. This showed an equally weak absorption at 276 nm, which told us that HPLC would not be of much use with this compound **151**. We therefore went directly to the use of the NMR shift reagent **161**, which unfortunately, in this instance, was unable to clearly resolve the enantiomers.

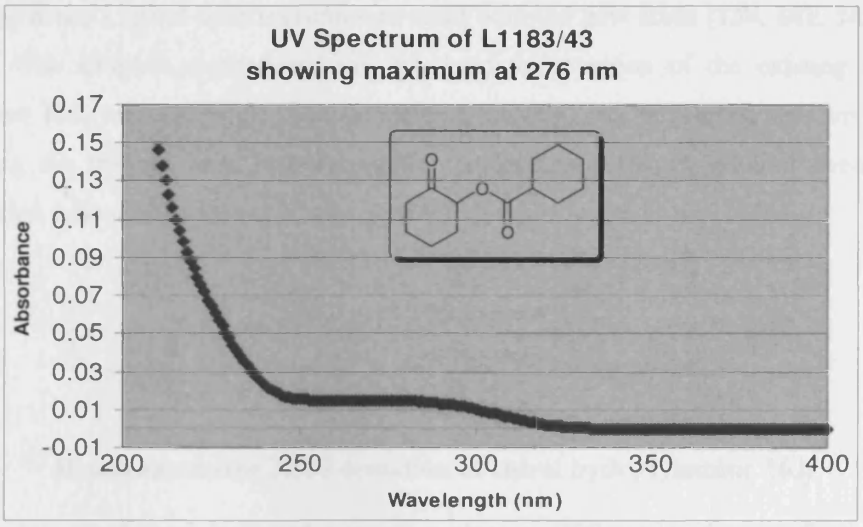


Figure 3.9: UV spectrum obtained for compound 151.

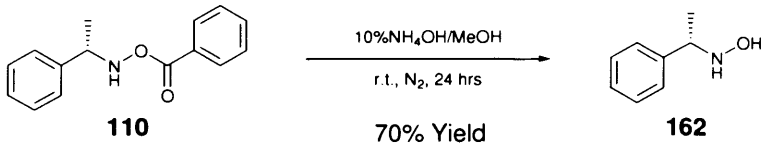
The same problem of weak absorption was encountered again with **156** on obtaining UV spectra. Going straight to using NMR spectroscopy as a technique for resolving enantiomers, we managed to separate the enantiomers, where it was found that 0.3 equivalents of **161** were needed, Appendix 2.

Moving on to compounds **152** and **153**, both of these contained an aromatic group, making them more likely candidates for HPLC analysis. Using the standard wavelength of 254 nm, we attempted to separate the enantiomers for each compound. Compound **153** separated nicely on the normal phase column, under conditions of 5% IPA/hexane and a flow rate of 1 ml/min. These conditions had no effect on compound **152**, however, which showed no sign of splitting even under conditions of decreased solvent polarity and flow rate. The retention time was noted to be very short, therefore this compound was also run on a reverse phase column. Sadly this did not separate the enantiomers either. We returned to NMR spectroscopy as a technique, which was more successful, resolving the enantiomers after addition of 1.3 equivalents of shift reagent **161**, Appendix 3.

3.4. Synthesis and Effect of Chiral Analogues.

Having produced a range of new achiral reagents **146–149** and **155**, and having now separated the enantiomers of most of the new α-oxygenated products **150**, **152, 153** and **156**, the next step was to prepare the chiral analogues. In order to do this we had

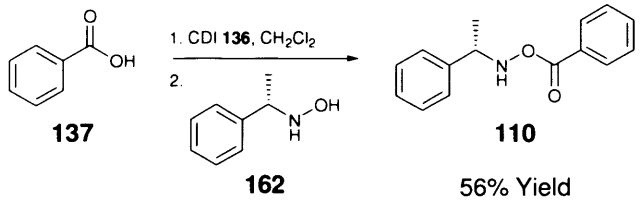
to first make a chiral hydroxylamine to react with the new acids (**139**, **141**, **142** and **154**). The simplest method for this involved deprotection of the existing chiral reagent **110**, and a straightforward method for this was developed that involved stirring the reagent in a 10% ammonium hydroxide/methanol solution overnight, Reaction scheme 3.5.[58]



Reaction scheme 3.5: Formation of chiral hydroxylamine 162.

This gave the desired hydroxylamine in a pleasing 70% yield after purification by column chromatography. Attempts were then made to convert this hydroxylamine **162** into the ·HCl salt. Ordinarily, this is needed to decrease the reactivity and thus protect the nitrogen atom from reacting during the Geffken procedure,[57] as this would lead to the unwanted amide product. This proved to be difficult as the salts did not crash out of solution in the usual manner, instead, appearing to be extremely hygroscopic and remaining in a viscous liquid state.

It was thought that salt formation may perhaps be unnecessary, with the hydroxylamine **162** having a bulky *N*-substituent that would perhaps hinder reaction of the nitrogen with CDI **136**. Therefore, we attempted to synthesise our standard chiral reagent **110** (as we already had an authentic sample to be used as a comparison), using the free base of the chiral hydroxylamine **162**, Reaction scheme 3.6.

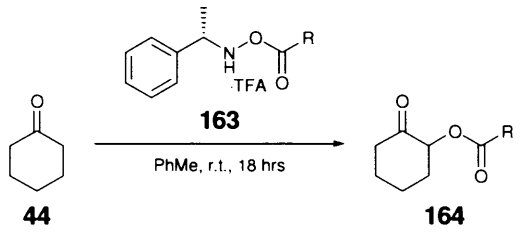


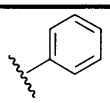
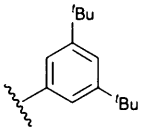
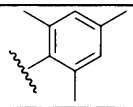
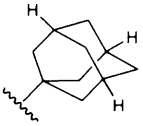
Reaction scheme 3.6: Formation of standard chiral reagent 110 using chiral hydroxylamine 162.

This was found to work well, giving the desired product in an 56% yield (which was slightly lower when compared to the Phanstiel method,[55] Reaction scheme 2.1), with no evidence of the unwanted amide product. This suggested that the steric bulk

surrounding the nitrogen atom was sufficient to prevent reaction. Conversion to the HCl salt was therefore deemed unnecessary and future reactions to form other chiral reagents using this method were performed using the free base **162**.

The chiral reagents formed through reaction of the chiral hydroxylamine **162** with various carboxylic acids (**139**, **141**, **142** and **154**) were then in turn reacted with cyclohexanone **44** under the optimised reaction conditions (Reaction scheme 2.13). The cyclohexane carboxylic acid (**140**) derivative was not examined in this series as we were unable to analyse the corresponding α-oxycyclohexoylcyclohexanone product **151**. The results from this series of experiments are shown in Table 3.1, along with the original results from the parent hydroxylamine reagent **110** (entry 1), for comparison.



Entry	R	Yield (%)[a]	e.e. (%)
1		51	37[b]
2		28	35
3		37	25
4		40	9
5		38	40

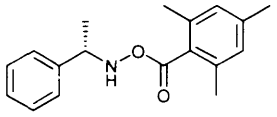
[a]Isolated yield.
[b](*S*)-enantiomer of the product **33** produced in excess.

Table 3.1: Results obtained using chiral reagents with varying *O*-acyl groups.

As can be seen from these results (Table 3.1), increasing the steric bulk of the *O*-acyl group did not appear to improve the level of asymmetric induction in the reaction,

with results showing the products (**150**, **152**, **153** and **156**) to have either similar e.e.'s (entries 2 and 5) or considerably lower e.e.'s (entries 3 and 4) compared to those obtained from reagent **110** (entry 1). This was very disappointing as it suggested that our steric theory derived from the transition state models **132** and **133**, was not effective.

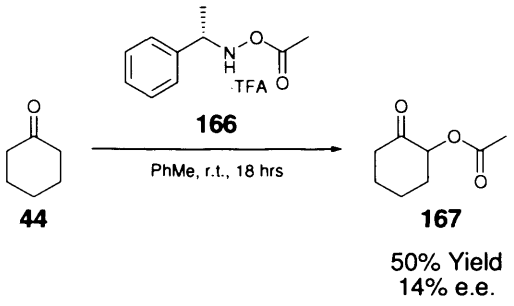
Of the results shown in Table 3.1, we became very interested in the effect of an *O*-2,4,6-trimethylbenzoyl group (entry 4), which had provided an extremely low level of asymmetric induction. This reaction was repeated and the result confirmed. Although not the positive result we had hoped for, this result did provide us with some information about the reaction system, the challenge now was to interpret that information.



165

Figure 3.10: Chiral reagent formed using 2,4,6-trimethylbenzoic acid 142.

Remaining with steric effects, our first thought was that the increased bulk surrounding the carbonyl group of reagent **165** (Figure 3.10), was having a negative effect on the asymmetric transformation. In an attempt to overcome this, we synthesised the chiral reagent **166**, which had a significantly smaller *O*-acyl group. This was reacted with cyclohexanone **44**, Reaction scheme 3.7, to give the corresponding α-functionalised product **167**.



Reaction scheme 3.7: Effect of a small *O*-acyl group on the asymmetric reaction.

We also attempted to synthesise the analogous achiral *N*-methyl reagent using acetic acid, but our efforts did not prove to be successful. Enantiomer separation was therefore carried out on the product **167** from the asymmetric reaction (Reaction

scheme 3.7) and was achieved by NMR spectroscopy using 0.3 equivalents of chiral shift reagent **161**, Appendix 4. This showed the product to have an e.e. of 14%, allowing us to conclude that reducing the sterics of the *O*-acyl group did not have a positive effect on the level of asymmetric induction in these transformations.

A further possibility for how reagent **165** induced such a low level of asymmetric induction (Table 3.1, entry 4) could be the result of electronic effects. This notion is explored further in Chapter 4.

3.5. Examination of the Effect of a Chiral *O*-Acyl Group.

Another question that had yet to be considered was the effect of a chiral *O*-acyl group on the asymmetric reaction, both as the sole source of chirality and in conjunction with a chiral *N*-substituent.

In order to address this question, various chiral carboxylic acids (**168–173**) were chosen, to be examined for their potential to induce asymmetry in α-oxygenated products, Figure 3.11. These acids (**168–173**) were all reacted in turn with *N*-methyl hydroxylamine hydrochloride **61**.

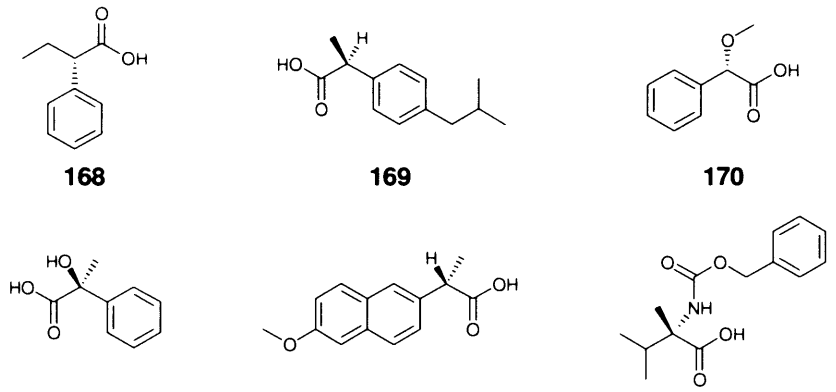
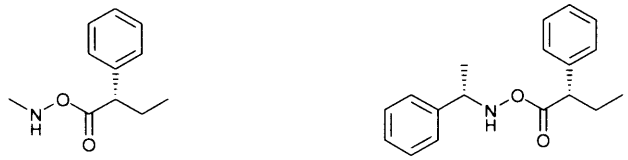


Figure 3.11: Chiral carboxylic acids examined.

Of all the acids examined (Figure 3.11), only acid **168** produced the desired reagent **174**, Figure 3.12, in a 61% yield. This acid **168** was subsequently reacted with *N*-(*S*)-α-methylbenzylhydroxylamine **162** to produce the corresponding diastereomeric reagent **175** that also possessed a chiral *N*-substituent.



174 175

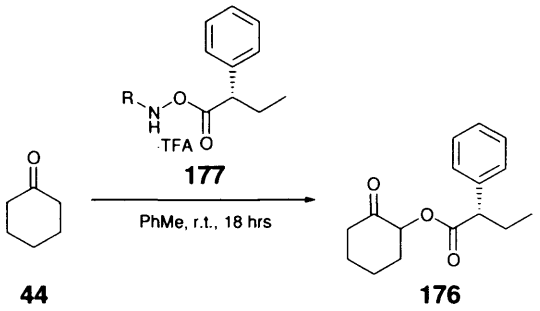
Figure 3.12: Reagents synthesised with chiral *O*-acyl groups.

Beginning with reagent **174**, this was reacted with cyclohexanone **44**, using the optimised conditions of a TFA co-acid and toluene as the reaction medium, to determine the effect of a chiral *O*-acyl group as the sole source of chirality. The resulting product, now possessing two stereogenic centres, can exist as two possible diastereoisomers **176a** and **176b**, Figure 3.13.

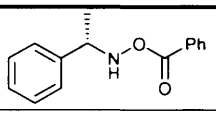
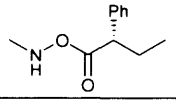
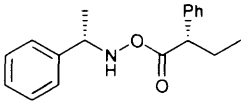
176a **176b**

Figure 3.13: Possible diastereomeric products resulting from α-functionalisation of cyclohexanone 44 with reagents 174 and 175.

With the product being a mix of diastereoisomers (**176a** and **176b**), instead of enantiomers, it was hoped that ^{1}H NMR spectroscopy would be sufficient in determining the ratio of the two isomers (**176a** and **176b**) formed. Unfortunately, there was not a clear separation of key peaks in the ^{1}H NMR spectrum obtained, making integration impractical. HPLC was therefore implemented and was found to readily separate the two isomers **176a** and **176b**.



44 176

Entry	Reagent	Yield (%)[a]	e.e. (%)
1		51	37[b]
2		69	10[c]
3		48	35[c]

[a]Isolated yield.
[b](*S*)-enantiomer of the product **33** produced in excess.
[c]Value is d.e.

Table 3.2: Results from use of a chiral *O*-acyl group.

When analysed, the product **176** from reaction of reagent **174** was found to give a d.e. of 10%, Table 3.2, entry 2. This was very exciting and confirmed that the *O*-acyl group did have a part to play in the asymmetric transformation. We followed up on this result with reaction of reagent **175** and cyclohexanone **44**. It was hoped that the effect of a chiral *O*-acyl group would work together with the effect of a chiral *N*-substituent, thus either enhancing or reducing the level of asymmetric induction, depending on the isomer favoured by each chiral group. When analysed however, it was found that the product **176** from this reaction (entry 3) had a similar level of asymmetric induction compared to that produced by the parent hydroxylamine reagent **110** (entry 1).

Overall, we believe this tells us that the *O*-acyl group is involved in the asymmetric reaction, however, not to the same extent as the *N*-substituent. As a result, when examined as the sole source of chirality, the chiral *O*-acyl group produced a measurable d.e. in the product. In conjunction with a chiral *N*-substituent, however, the effect is shadowed by that of the *N*-substituent and is not sufficient to effect a

significant change in the overall level of asymmetry being induced. Reagent **177** bearing a chiral *N*-substituent with (*R*)-stereochemistry is examined in Chapter 5.3.2.

3.6. Conclusion.

We successfully replaced the *O*-benzoyl group of the hydroxylamine reagents used, with a variety of other *O*-acyl groups. These new reagents were all reacted with cyclohexanone and, where possible, conditions for enantiomer separation were found for the products.

The results obtained from this series of experiments showed that an increase in the size of the *O*-acyl group did not afford an increase in the yield or the e.e. of the α-functionalised products, and hence did not support the computer generated transition state models (**132** and **133**). The effect of a decrease in the size of the *O*-acyl group was also examined and found to have a negative effect on the level of asymmetric induction.

The effect of a chiral *O*-acyl group was also investigated, whereby it was found that as the sole source of chirality in the reagent, this induced a small level of asymmetry in the α-oxygenated product. As a contributing factor, in conjunction with a chiral *N*-substituent, however, no further enhancement of the level of asymmetry was observed.

In conclusion, it is believed that the nature of the *O*-acyl group is an important factor in the transformation, though its exact role had yet to be elucidated. Results obtained showed an *O*-benzoyl group to provide the best results, therefore it was considered to be the optimal group and was maintained in subsequent studies.

Chapter 4.

Variation of the Electronics.

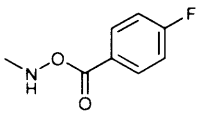
4.1. A New Direction.

In previous studies in which the *O*-acyl group of the hydroxylamine reagent was varied, (Chapter 3) an interesting result was obtained when using an *O*-2,4,6-trimethylbenzoyl group (Table 3.1, entry 4). This group was observed to produce a significantly reduced level of asymmetric induction that was at first attributed to steric effects. Further investigation into the effect of varying the size and bulk of the *O*-acyl group however, failed to identify a pattern linking structure with effect on asymmetric induction.

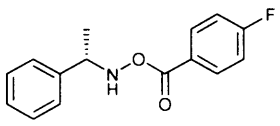
Another possible explanation for this interesting observation could be the result of electronic effects, with the inductive nature of the three methyl groups of reagent **165** having a negative effect on the transformation. We decided to explore this possibility by generating reagents with varying electronic properties, through the incorporation of electron-donating and electron-withdrawing substituents into the acyl substituent, in order to see if there was an appreciable pattern.

4.2. Varying the Electronics of the *O*-Acyl Group.

To begin with, we decided to examine the effect of an electron-withdrawing group (EWG) on the reaction. It was hoped that this would have the opposite effect to that of the electron-rich *O*-2,4,6-trimethylbenzoyl group and thus have a positive effect on the asymmetric induction. To test this theory, achiral reagent **178** and chiral reagent **179** (Figure 4.1) were prepared from 4-fluorobenzoic acid using the Geffken procedure (Reaction scheme 3.2).[57]



178

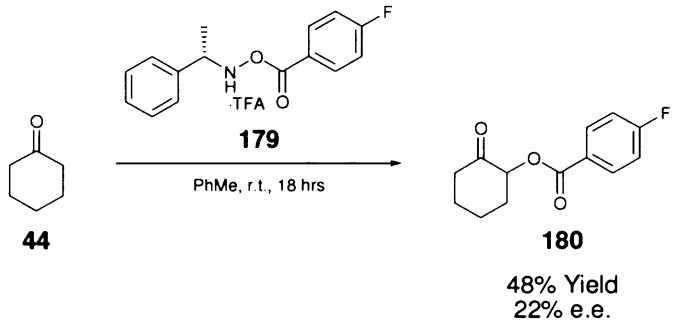


179

Figure 4.1: Reagents synthesised using 4-fluorobenzoic acid.

After using the former of these (**178**) to develop conditions for enantiomer separation in the racemic α-functionalised product (**180**), the latter (**179**) was used to carry out the asymmetric reaction, Reaction scheme 4.1. Unfortunately, this proved to have a

negative effect on the asymmetric reaction, going from 37% e.e. in the model system (Reaction scheme 2.13) down to 22% e.e. The yield appeared to be unaffected.

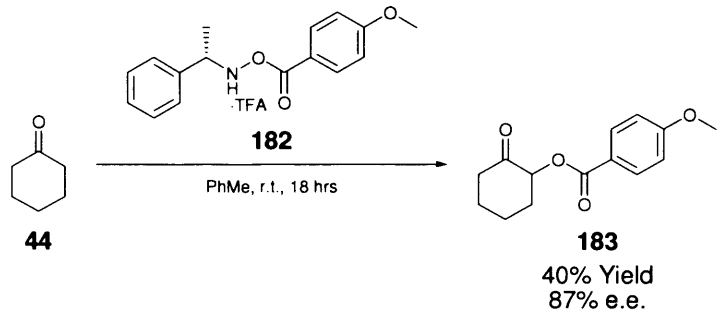


Reaction scheme 4.1: Effect of an electron-withdrawing substituent.

Having identified a definite electronic effect, we thought that perhaps a reagent with an electron-rich *O*-acyl substituent would have a positive effect on the e.e. If found to be the case, this would render the earlier observation, resulting from use of an *O*-2,4,6-trimethylbenzoyl group, an anomalous result, possibly due to a combination of steric and electronic effects. To test this hypothesis we decided to use *p*-anisic acid, which has an electron-donating *p*-methoxy group, to synthesise achiral and chiral reagents **181** and **182** respectively, Figure 4.2.

Figure 4.2: Reagents synthesised from *p*-anisic acid.

Reagent **181** was reacted with cyclohexanone **44** to generate a racemic sample of product **183** (76% yield). Once the enantiomers of this compound (**183**) had been successfully separated, chiral reagent **182** was then examined in the hope of generating an enantiomerically enriched cyclohexanone product (**183**), Reaction scheme 4.2.



Reaction scheme 4.2: Result obtained from using an electron-donating *p*-methoxy substituent in the *O*-acyl group.

The product **183** of this reaction (Reaction scheme 4.2) was subsequently analysed, whereby a seemingly excellent e.e. of 87% was measured. This was extremely exciting and prompted us to examine other carboxylic acids with electron-donating substituents. Several such acids (**184–186**) were selected, Figure 4.3, including an acid **185** with no *p*-substituent, in order to see if this relationship was important. Each of these was initially reacted with *N*-methylhydroxylamine hydrochloride **61** in order to generate the corresponding achiral reagents.

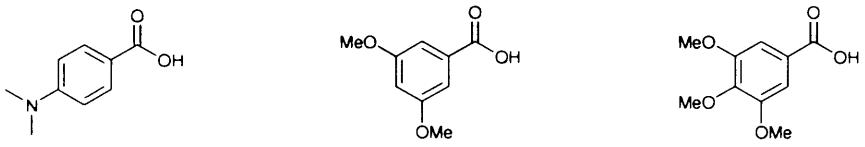
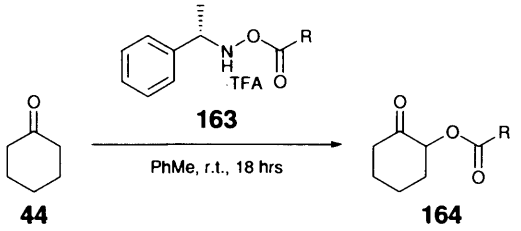
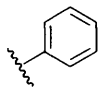
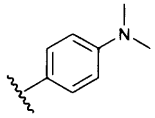
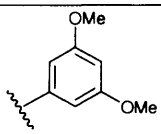
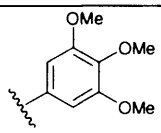


Figure 4.3: Further carboxylic acids examined with electron-donating substituents.

These reactions worked well, along with the subsequent α-oxygenation and enantiomer separation steps. The corresponding chiral reagents were then synthesised from each of these acids (**184–186**) and chiral hydroxylamine **162**, and the effects of the various electron-donating substituents on the asymmetric transformation were then examined in turn, Table 4.1.



Entry	R	Yield (%)[a]	e.e. (%)
1		51	37[b]
2		44	32
3		44	35
4		39	17

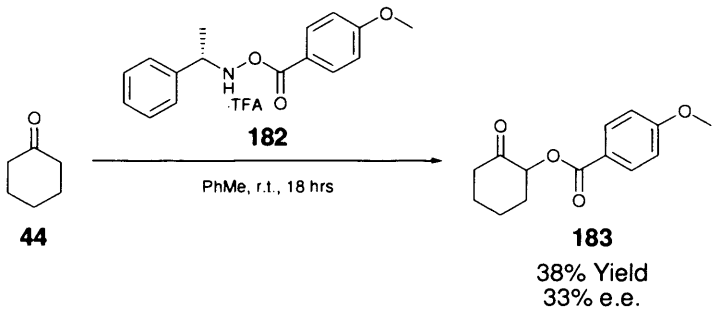
[a]Isolated yield.
[b](*S*)-enantiomer of the product **33** produced in excess.

Table 4.1: Results obtained from reagents with various electron-rich *O*-acyl groups.

Surprisingly, after the apparently fantastic e.e. obtained from incorporation of a *p*-methoxy substituent in the *O*-acyl group (Reaction scheme 4.2), these acids (**184–186**) had no discernible effect on the asymmetric reaction. As can be seen in Table 4.1, use of a *p*-(dimethylamino) group (entry 2), despite being much more electron-donating than a *p*-methoxy group, gave a similar e.e. to that of the standard reagent **110** (entry 1). Use of a 3,5-dimethoxy benzoyl group (entry 3) also had no apparent effect on the e.e. Use of a 3,4,5-trimethoxy benzoyl group (entry 4), however, caused a notable decrease in the e.e., reducing it to 17%, which we believe must be due to a combination of steric and electronic effects, as seen in the case of the *O*-2,4,6-trimethylbenzoyl group (Table 3.1, entry 4).

Puzzled by these results we went back and repeated the earlier reaction (Reaction scheme 4.2) between reagent **182**, and cyclohexanone **44**. When analysing the product **183** of this repeated reaction, Reaction scheme 4.3, we initially obtained a similarly high e.e. to that obtained previously, however; this time it was noticed that

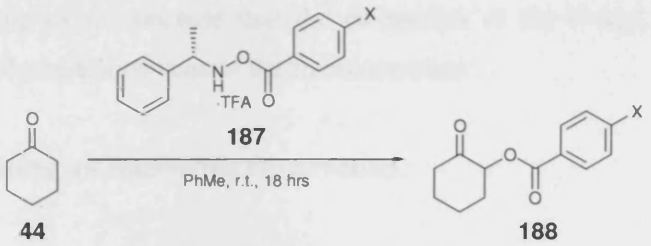
only a partial amount of compound **183** had dissolved in the sample being analysed. This was rectified by adding more IPA to the HPLC analysis sample and shaking vigorously. Once homogeneous, the HPLC analysis was repeated.



Reaction scheme 4.3: Actual effect of a *p*-methoxy substituent.

The results from this second analysis revealed an e.e. of only 33% in the product **183**, which was disappointing, though in keeping with the results from other reagents with electron-rich *O*-acyl groups (Table 4.1). This confirmed that use of an electron-rich *O*-acyl group did not increase the level of asymmetry induced in the α-oxygenated product.

In order to positively determine whether there was an overall connection between electronics of the *O*-acyl group and asymmetric induction, the Hammett constant (σ) for several of the substituents tried was obtained. The σ-values are constants that sum up the total electronic effects (resonance plus field) of a group when attached to a benzene ring. The σ-values, along with the results for several of the reactions carried out in this study are shown in Table 4.2.

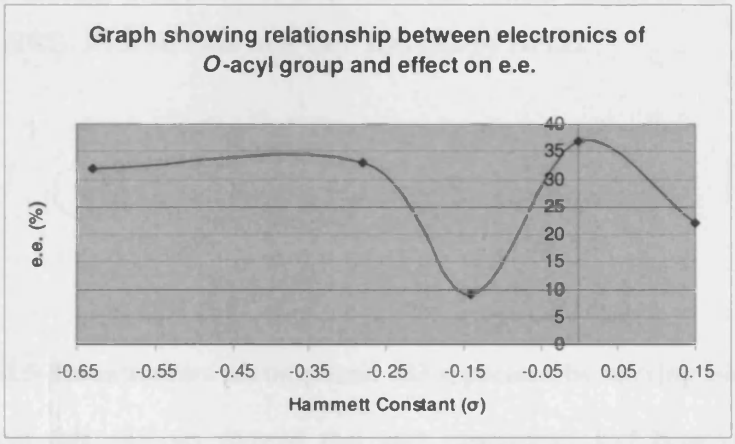


Entry	X	σ-Value	Yield (%)[a]	e.e. (%)
1	F	0.15	48	22
2	H	0	51	37[b]
3	Me[c]	–0.14	40	9
4	OMe	–0.28	38	33
5	NMe_2	–0.63	44	32

[a]Isolated yield.
[b](*S*)-enantiomer of the product **33** produced in excess.
[c]Results obtained using *O*-2,4,6-trimethylbenzoyl group.

Table 4.2: Results obtained from using various *p*-substituents in *O*-acyl group with different Hammet constants (σ).

As can be seen in the table above (Table 4.2), substituents with a range of σ-constants were examined, with a positive σ-value indicating an EWG and a negative value an EDG. In the case of the *O*-2,4,6-trimethyl benzoyl group (entry 3), only the effect of the *p*-methyl group is considered since the Hammett constant principle usually fails for the *ortho*-position.



For a more accurate plot, separate results are needed for an *O*-4-methylbenzoyl group.

Figure 4.4: Graph displaying relationship between σ-value and e.e. obtained.

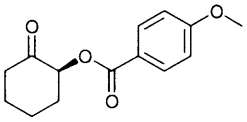
The relationship between the σ-value and the e.e. obtained in the reaction was then plotted, Figure 4.4. A straight line plot would indicate a direct relationship between the two values, however; as can be seen in the graph above, no such relationship is

evident allowing us to conclude that the electronics of the *O*-acyl group do not directly affect the transition state of the transformation.

4.3. Re-Examining an Interesting Observation.

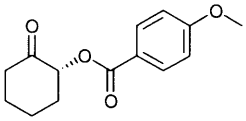
Going back to the earlier observation, we were intrigued by the initial false result of 87% e.e. measured for the product **183** of the reaction between reagent **182** and cyclohexanone **44** (Reaction scheme 4.2). This had been the result of a partial amount of compound **183** dissolving in the 10% IPA/hexane solvent system being used for analysis. Although enantiomers should in theory have the same physical properties, and therefore dissolve equally in a given solvent (as seen in all other cases to date), in this instance it was thought that some sort of crystalline stacking process was in effect. We believed that the enantiomer present in excess had been able to form crystal structures that were less soluble in the solvent system.

We thought that it might be possible to exploit this effect. We therefore took a sample of enantiomerically enriched compound **183** and dissolved as much of it as possible in a 5% IPA/hexane solution, which was a less polar solvent system than used previously. The solvent, containing a partial amount of compound **183**, was then removed using a pipette and the remaining compound was dissolved in a much more polar solvent system of 50% IPA/hexane, which dissolved the remaining compound (**183**). Both samples were then analysed by HPLC.



(*S*)–183

95% e.e.



(*R*)–183

95% e.e.

Figure 4.5: Enantiomers of compound 183 separated by varying solubility.

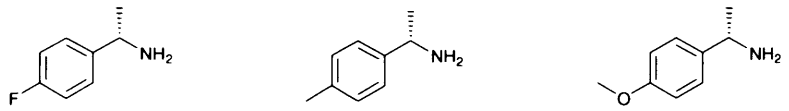
Results from this analysis showed that each enantiomer had been obtained in approximately 95% enantiomeric purity, Figure 4.5. This was an excellent result; however, this unusual behaviour appears to be limited to this compound **183** only.

We also thought that it would be worth examining this reaction (Reaction scheme 4.2) on a larger scale, in order to see if the same effect was still in operation. We

therefore increased the scale of this reaction (Reaction scheme 4.2) from 100 mg to 750 mg (of reagent **182**), and then again attempted to separate the enantiomers of the product **183** according to their relative solubilities. HPLC analysis was then carried out on the separated fractions of the product **183**, whereby it was observed that the same effect was in operation, though e.e.'s were not as high as those obtained previously (Figure 4.5). This may well have been due to any number of a variety of factors, including time, temperature, solvent volume and crystal morphology amongst others. In addition, this would undoubtedly be substrate-specific. For these reasons, we did not pursue this interesting phenomenon further, however; this may well be of some use to those working in the area.

4.4. Varying the Electronics of the *N*-Substituent.

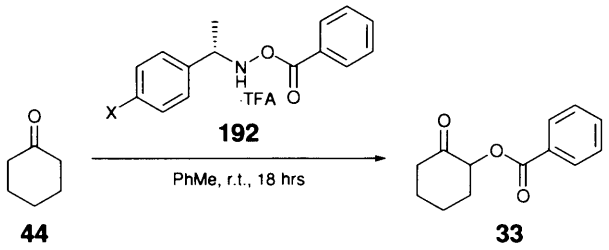
After examining the effect of varying the electronics of the *O*-acyl group of the reagent on the asymmetric reaction, we thought it would be interesting to explore the effect, if any, of varying the electronics of the *N*-group of the reagent. In order to do this, several new chiral amines were sought based on the (*S*)-α-methyl benzylamine skeleton, in order to provide a direct comparison to existing results. Amines chosen comprised both those with an electron-withdrawing substituent (**189**) and electron-donating substituents (**190** and **191**), Figure 4.6.



189 **190** **191**

Figure 4.6: New chiral amines chosen with various electronic potentials.

Using the Phanstiel method for reagent synthesis (Reaction scheme 2.1),[55] the corresponding *O*-benzoyl hydroxylamine reagents were synthesised. Each of these was subsequently reacted with cyclohexanone **44**, under the optimised reaction conditions, and the product **33** from each reaction was analysed by HPLC. The results from this set of experiments are shown in Table 4.3.



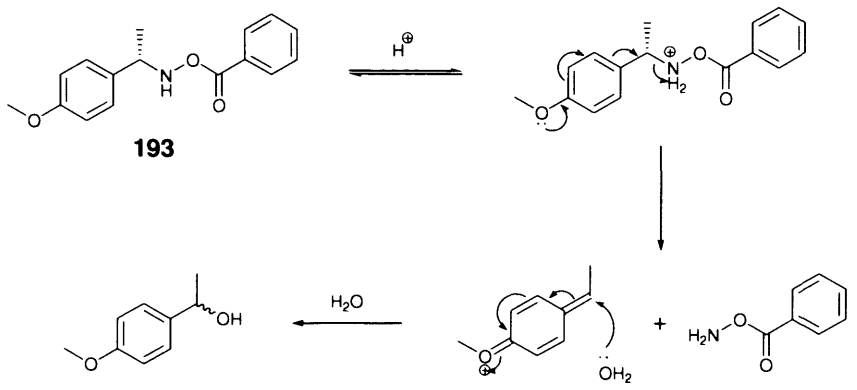
Entry	X	Yield (%)[a]	e.e. (%)[b]
1	H	51	37
2	F	43	22
3	Me	42	56
4	OMe	Reagent Decomposed	

[a]Isolated yield.
[b](*S*)-enantiomer of the product **33** produced in excess.

Table 4.3: Initial results obtained from varying the electronics of the *N*-substituent of the reagent 192.

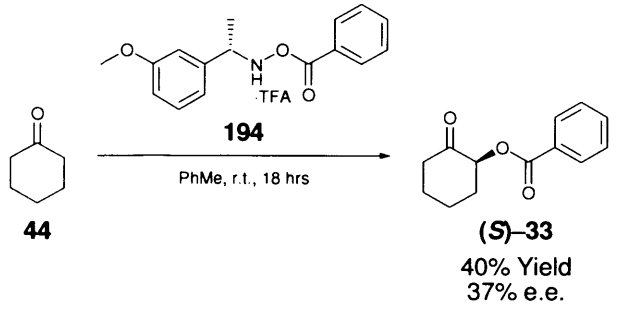
As can be seen by the results in the above table (Table 4.3), varying the electronics of the *N*-group seemed to have a much more profound effect on the asymmetric transformation than observed with the *O*-acyl group. From these results it can be seen that an electron-withdrawing substituent on the benzene ring (entry 2) caused a significant decrease in the e.e. of the product; whereas an electron-donating group (entry 3) was observed to have the opposite effect, causing a significant increase in the e.e., compared to the parent reagent **110** (entry 1).

Following these initial results it was hoped that by increasing the electron-donating ability of the X group further, by using a *p*-methoxy group, an even greater increase in the level of asymmetric induction would be observed. Unfortunately, when carrying out the reaction it was found that the reagent **193** decomposed on addition of the TFA acid (entry 4). A possible mechanism for this acid-initiated decomposition is shown in Reaction scheme 4.4.



Reaction scheme 4.4: Possible acid decomposition of reagent 193.

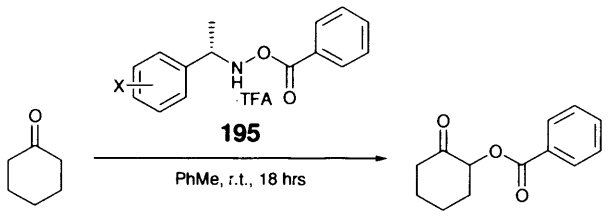
The undesirable decomposition of reagent **193** was thought to be due to the presence of a lone pair of electrons in the methoxy group and also to the direct relationship between the *p*-position of the benzene ring and the nitrogen atom. As we were still interested in the effect of a methoxy substituent on the asymmetric reaction, we synthesised reagent **194**, an isomer of reagent **193**, which has the methoxy group in the *m*-position.



Reaction scheme 4.5: Results obtained from reaction of reagent 194 with cyclohexanone 44.

Reaction of **194** with cyclohexanone **44** worked well, as expected, giving the product **33** in a 40% yield, Reaction scheme 4.5. Analysis of the product **33**, however, revealed no further improvement in the e.e., instead producing an identical e.e. (37% of the (*S*)-enantiomer) to that of the parent reagent **110**. This suggested that a direct *para*-relationship is required between the EDG of the *N*-substituent and the reactive nitrogen in order to increase the level of asymmetric induction in the reaction. Unfortunately, in not being able to use a *p*-substituent possessing a lone pair of electrons, due to the associated reagent decomposition, we were unable to investigate this effect further.

With the results obtained from this study on electronic effects, we wanted to determine if there was a definitive relationship between the relative electronics of the amine portion of the reagent and the effect on the e.e. of the product **33**. We therefore decided again to compare the σ-values for the different substituents with the e.e.'s measured in the product **33** of each reaction, Table 4.4. When looking up σ-values it was found that a *m*-methoxy group on a benzene ring, instead of being strongly electron-donating like a *p*-methoxy group (σ = −0.28), was in fact an electron-withdrawing substituent with a σ-value of 0.10 (entry 2). This may explain the surprisingly low e.e. obtained from using a *m*-methoxy substituent (Reaction scheme 4.5).



44 **33**

Entry	Substituent	σ-Value	Yield (%)[a]	e.e. (%)[b]
1	*p*-F	0.15	43	20
2	*m*-OMe	0.10	40	37
3	H	0	51	37
4	*p*-Me	-0.14	42	52

[a]Isolated yield.
[b](*S*)-enantiomer of the product **33** produced in excess.

Table 4.4: Amine substituent σ-values and effects.

A graph was then plotted comparing the relative σ-value with the e.e. of the product obtained, Figure 4.7. Again we were looking for a straight-line plot that would suggest a definite relationship between the figures.

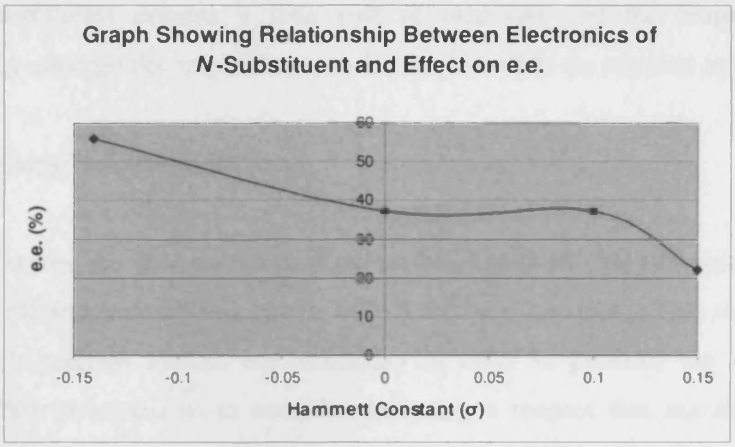


Figure 4.7: Graph displaying relationship between σ-value and e.e. obtained.

As can be seen in the graph shown above, Figure 4.7, this time we observed a much more definite trend, although the plot did not completely form a straight line as hoped. If we were to remove the results from the *m*-methoxy reagent **194** however, since it is the *p*-position that seems to have the most influence, we get a very straight line, Figure 4.8, confirming a direct relationship between the relative electronics of the *p*-substituent of the *N*-group and the level of asymmetric induction in the reaction.

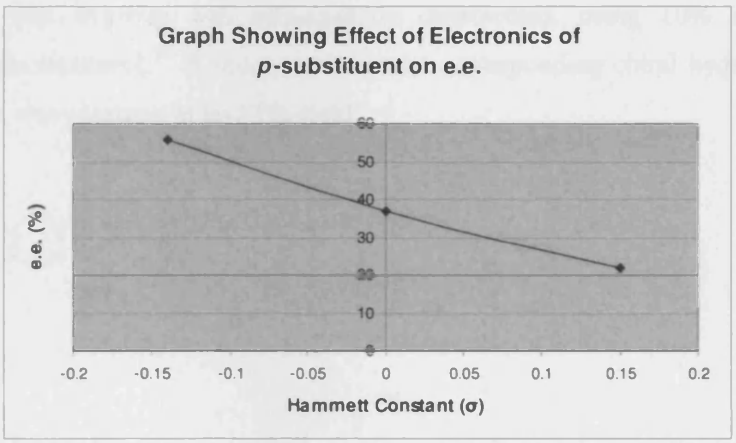


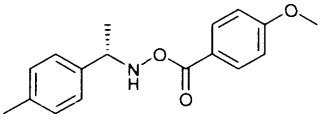
Figure 4.8: Graph showing effect of electronic of *N*-group on e.e. corrected for *p*-substituent only.

This trend (Figure 4.8) suggests that if we were to use a *p*-EDG with σ-value ≥-0.50 in the *N*-group of the reagent (**192**), for example a *p*-NH_2 or a *p*-NMe_2 group, an e.e. of ≥90% would be obtained. Unfortunately, we were unable to test this theory as

these *p*-substituents possess a lone pair of electrons and the reagents would undoubtedly undergo decomposition on addition of acid to the reaction mixture.

4.5. Optimising Electronic Effects.

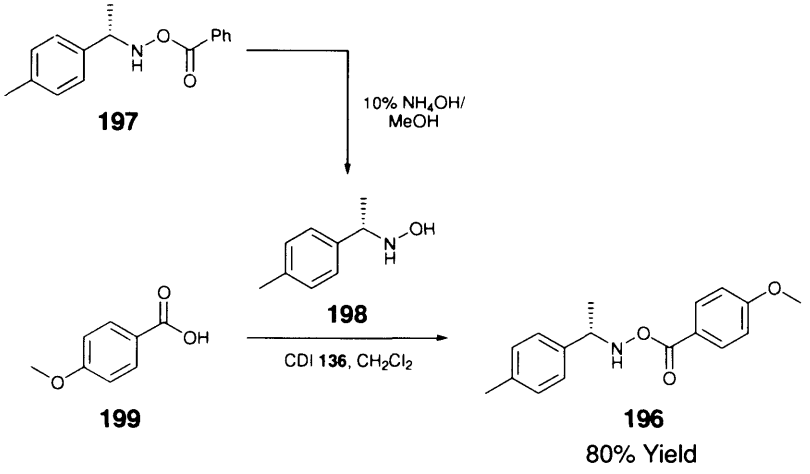
As a brief recap, the best results in these studies had been obtained using reagents with more electron-rich *O*-acyl groups or *N*-benzylic substituents. This suggested an electron-rich reaction system was necessary in order to promote the asymmetric reaction. This prompted us to consider designing a reagent that maximised these electronic effects. We therefore attempted to synthesise reagent **196**, Figure 4.9, which possessed both an electron-rich *N*-group and *O*-acyl group.



196

Figure 4.9: Electron-rich chiral reagent designed to maximize electronic effects.

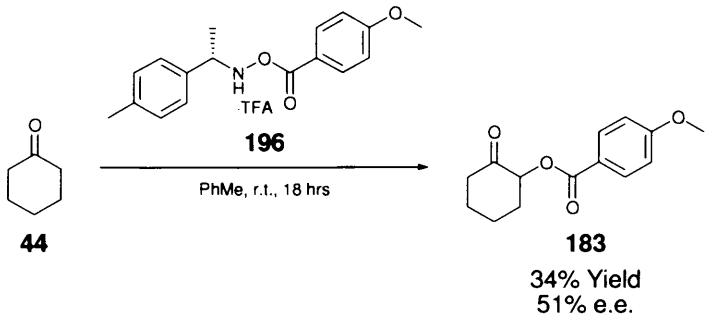
When varying the amine portion of the reagent, use of a *p*-methyl group (reagent **197**) had provided us with the best results (Table 4.3, entry 3). The reagent **197** that possessed that *N*-group was subsequently deprotected, using 10% ammonium hydroxide in methanol,[58] in order to obtain the corresponding chiral hydroxylamine **198**, which was obtained in an 83% yield.



Reaction scheme 4.6: Synthesis of electron-rich reagent 196.

This hydroxylamine **198** was then reacted with *p*-anisic acid **199** in order to form reagent **196**, which possessed both an electron-rich *N*-group and *O*-acyl group,

Reaction scheme 4.6. This reagent **196** was then reacted with cyclohexanone **44** in the hope that the electronic effects of both groups would act together to give a high e.e. in the product **183**, Reaction scheme 4.7.



Reaction scheme 4.7: Reaction of reagent 196 with cyclohexanone 44.

The same problem of partial insolubility of this compound **183** was observed again during analysis, but was overcome by increasing the polarity of the solvent system. Subsequent analysis of the product **183** of this reaction (Reaction scheme 4.7), unfortunately showed no further increase in the level of asymmetry in the reaction, instead giving an e.e. of 51% that was attributed to the sole effect of the *p*-methyl group in the amine portion of the reagent **196**.

Overall, this tells us that the effect of the *N*-group on the asymmetric reaction is greater than that of the *O*-acyl group. This is the same conclusion that was drawn when investigating the use of a chiral *O*-acyl group (Chapter 3.4).

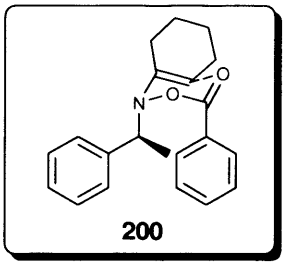
4.6. Development of a Transition State Model.

Following discovery and development of the metal-free α-oxyacylation transformation (Reaction scheme 1.20), mechanistic studies were carried out within the group in the hope of better understanding the reaction process. These studies were carried out using the achiral *N*-methyl-*O*-benzoylhydroxylamine hydrochloride reagent **63·HCl** and consisted of isotope labelling experiments, to support a concerted rearrangement process (Chapter 1.5.3); and NMR experiments, from which many of the key intermediate species were identified.

Results from these studies supported the belief that the reaction proceeded *via* a [3,3]-sigmatropic rearrangement process and thus involved a six-membered

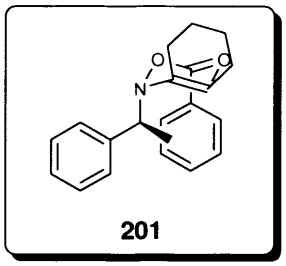
transition state, which would most likely adopt a chair or boat conformation. We also learned from these NMR experiments that the nitrogen atom was protonated in the transition state, following identification of key peaks in the ^{13}C NMR, corresponding to post-rearrangement *cis*- and *trans*-iminium ions. After consideration, this seemed logical, as the pKa of the HCl co-acid present was lower than that of both the proposed enamine precursor and the forming imine, making protonation of the imine to give the corresponding iminium ion inevitable. This could also lead to further stabilisation of the transition state, by allowing the formation of hydrogen bonds to nearby oxygen atoms.

This information, along with the results obtained from our investigations to date, have enabled us to propose a possible transition state model for our asymmetric α-oxygenation of cyclohexanone **44** using chiral reagent **110**, Figure 4.10. This model (Figure 4.10) comprises transition states **200–203**, which allows for the formation of both the (*R*)- and (*S*)-enantiomers of the product **33** respectively.



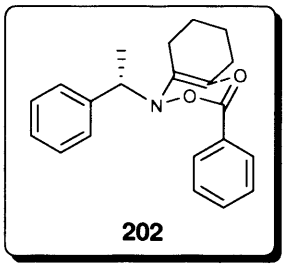
200

Gives (*R*)-product (**33**)



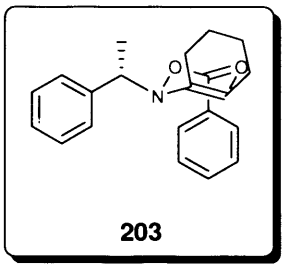
201

Gives (*S*)-product (**33**)



202

Gives (*R*)-product (**33**)



203

Gives (*S*)-product (**33**)

Figure 4.10: Possible transition state models for asymmetric transformation.

As can be seen above (Figure 4.10), we have proposed that the reaction proceeds through a low energy, 6-membered chair-like transition state, which follows previous literature findings that analogous Claisen and Cope rearrangements also adopt a chair-like transition state.[59]

After consideration of the transition states (Figure 4.10), we came to the conclusion that it was most likely that the *N*-substituent would adopt an axial position (**200** and **201**). This was thought to be the case, as we believed that it was necessary for the chiral auxiliary to be in close proximity to the site of the forming C–O bond, in order to be able to influence the stereochemistry of the bond. In transition states **202** and **203**, the chiral auxiliary is further removed from the site of the forming C–O bond, and was therefore not expected to have the same level of influence on the stereochemical outcome of the reaction.

Results to date have demonstrated that in this reaction (Reaction scheme 2.13), the (*S*)-enantiomer of the product **(*S*)-33** is formed preferentially over the (*R*)-enantiomer. This fits with the transition state models shown (Figure 4.10), as the unfavourable steric interaction between the methyl group of the chiral auxiliary and the benzoyl group in **200**, directs the carbonyl oxygen to attack the *Si*-face of the enamine. This leads to transition state **201** and hence the (*S*)-enantiomer of the product **(*S*)-33** being favoured.

Similarly, in the case of an equatorial *N*-group, transition state **202** would be disfavoured, owing to the steric interactions between the chiral auxiliary and the cyclohexane ring. This would again lead to the (*S*)-enantiomer of the product **(*S*)-33** being favoured, this time *via* transition state **203**. This also fits with the observation that higher temperatures result in a lower e.e. in the product **33**, as an increase in energy in the reaction system would overcome the unfavourable steric interactions in **200** and **202**.

The proposed transition state model (Figure 4.10) can also be used to explain the need for an electron-rich aromatic solvent and electron-donating substituents in order to obtain good levels of asymmetric induction. Within transition states **200** and **201**, both aromatic groups adopt an axial position. In the case of transition state **201**, the aromatic groups are stacked above each other, which allows for possible stabilising face-face π–π interactions. An increase in the electron density of the aromatic groups, arising from the incorporation of EDG's, would improve these interactions.[60] Insertion of electron-rich aromatic solvent molecules between these aromatic groups could also act as a further stabilising effect, making transition state **201**, and thus formation of the (*S*)-enantiomer of the product **(*S*)-33**, more favourable.

In contrast to previous findings, we believe that the transition states (**200–203**) in this reaction (Reaction scheme 2.13) are not protonated. This conclusion was reached after consideration of the results obtained through variation of the co-acid (Table 2.4), which showed that reducing the acidity of the co-acid had a significant effect on the asymmetric transformation. It seems reasonable to assume that when using a strong acid, for example HCl, as the co-acid, the nitrogen atom is protonated in the transition state, as was seen in NMR studies carried out using reagent **63·HCl**. However, when using a weaker acid, for example TFA, we believe that the nitrogen atom is not protonated in the transition state. We have not been able to carry out NMR experiments to support this theory due to the complex nature of the NMR spectrum obtained of the reaction mixture, from which we would be unlikely to observe any reaction intermediates. Neither have we been able to ascertain why the nitrogen being protonated in the transition state would affect the level of asymmetry in the reaction.

At this stage, this solely provides a reasonable working transition state model. Further work in the area should focus on rigorously examining these hypotheses, to further improve reagent design.

4.7. Conclusion.

The effect of the electronics of the chiral reagent on the asymmetric reaction was explored, with electron-donating and electron-withdrawing substituents examined in both the *N*-substituent and the *O*-acyl group.

These studies told us that the asymmetric reaction is promoted by an electron-rich *N*-substituent, with a definite relationship being observed between the relative electronics of the *p*-substituent of the *N*-group and the subsequent e.e. obtained in the product **33**. We also observed that a more electron-rich *O*-acyl group is favoured in the asymmetric reaction, though a similar linear relationship was not observed.

Overall this told us that electronics have an integral role in this transformation and that the asymmetric reaction is augmented by an electron-rich reaction system. This is supported by the fact that a more electron-rich aromatic solvent proved to be optimal for the reaction (Chapter 2.2). In an attempt to maximise electronic effects, a

chiral reagent (**196**) was synthesised that contained both an electron-rich *N*-substituent and *O*-acyl group. Unfortunately this did not provide any further increase in the level of asymmetric induction in the reaction, instead showing that the *N*-group had a dominant effect.

Our results to date have enabled us to propose a possible transition state model for our asymmetric α-oxygenation reaction. The model produced (Figure 4.10) is consistent with the sense of asymmetric induction observed in the product **33** of these reactions, and allows rationalisation of the subtle electronic effects described within this Chapter, along with previous trends observed following our efforts to optimise the asymmetric transformation (Chapter 2).

Chapter 5.

Variation of the *N*-Substituent.

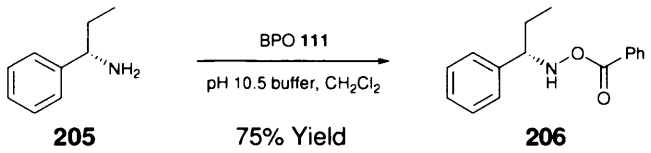
5.1. Introduction.

In our efforts to optimise the structure of the chiral hydroxylamine reagents, in order to impart the greatest level of asymmetric induction in the α-oxyacylation transformation, we had examined the structure of the *O*-acyl group, as well as varying the electronics of both the *O*-acyl group and the *N*-substituent.

The greatest success obtained during these investigations arose from variation of the electronics of the *N*-substituent of the reagent, whereby it was found that incorporation of a *p*-EDG significantly improved the e.e. of the product **33**. From here we decided to vary both the structure and nature of the *N*-substituent of the reagent, as this had not yet been examined in depth and observations to date had led us to believe that it was this portion of the reagent that had the most influence in the asymmetric transformation.

5.2. Variation of Chiral Amine.

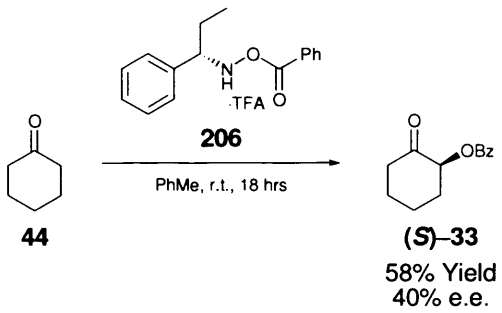
We began our investigation into the effect of varying the *N*-substituent of the reagent, by taking (*S*)-α-ethyl benzylamine **205** and making the corresponding *O*-benzoyl hydroxylamine reagent **206**, Reaction scheme 5.1.[55] This chiral amine **205** was chosen as we thought it would be interesting to see the effect of increasing the steric bulk of the amine (compared to amine **112**), whilst keeping the nature of the group the same.



205 75% Yield **206**

Reaction scheme 5.1: Synthesis of chiral reagent 206.

This new chiral reagent **206** was then reacted with cyclohexanone **44** under our optimised reaction conditions where it was observed to generate the desired product **33** in a slightly higher yield of 58% (compared to reagent **110**, which gave a 51% yield), Reaction scheme 5.2. This was surprising as the increased steric bulk surrounding the reactive nitrogen atom was anticipated to hinder initial iminium ion formation.



Reaction scheme 5.2: Reaction of new chiral reagent 206 with cyclohexanone 44.

As the amine portion of the reagent is not incorporated into the product, variation of this group alone did not vary the product of the reaction. This made analysis straightforward, as the synthesis of racemic products and developing conditions for enantiomer separation were not necessary in this study. HPLC analysis of the product **33** from the above reaction (Reaction scheme 5.2), suggested that a slight increase in the steric bulk surrounding the nitrogen atom was responsible for a slight increase in the e.e. to 40% of the (*S*)-enantiomer **(S)-33** (compared with 37% obtained from reagent **110**, Reaction scheme 2.13). Taking into account the margin for error in these measurements however, the improvement in the e.e. is minimal at best.

This result was quite disappointing; however, results from other studies to date had given us the firm belief that it was the amine portion of the reagent that had the most control over the asymmetric reaction. We therefore decided to pursue this investigation. A slight increase in the steric bulk of the *N*-group had obviously not been sufficient to significantly effect the asymmetric transformation (Reaction scheme 5.2). We therefore decided to further increase the size and nature of the chiral amine used.

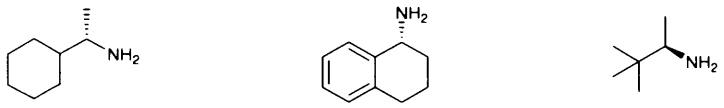
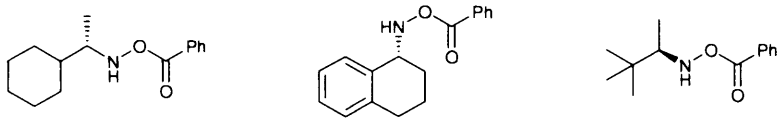


Figure 5.1: New chiral amines to be investigated.

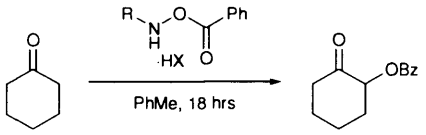
After much searching, we came across several chiral amines (Figure 5.1) that were commercially available and relatively inexpensive. These were converted to the corresponding reagents **207–209** (Figure 5.2), which comprised both aliphatic (**207** and **209**) and benzylic (**208**) *N*-groups and all had increased steric requirements compared to that of the parent reagent **110**.



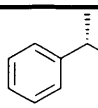
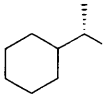
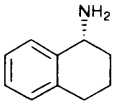
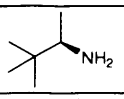
207 208 209

Figure 5.2: Corresponding chiral reagents prepared from new chiral amines.

These reagents (**207–209**) were initially prepared as their HCl salts, for ease of purification. It therefore seemed logical to carry out separate reactions between each of these reagents (**207–209**) and cyclohexanone **44**, using both HCl and TFA as the stoichiometric co-acid. This was done in order to gauge an idea of the reactivity of these new reagents (Figure 5.2) compared to our standard reagent **110** and to determine if the same trends were apparent.



44 33

Entry	Co-acid →	HCl[a]		TFA[b]	
	Amine	Yield (%)[c]	e.e. (%)	Yield (%)[c]	e.e. (%)
1		51	5[d]	51	37[d]
2		59	0	46	28[d]
3		29	3[e]	38	55[e]
4		12	12[e]	35	77[e]

[a]Reactions carried out with HCl co-acid at 25 °C.
[b]Reactions carried out with TFA co-acid at r.t.
[c]Isolated yield.
[d](*S*)-enantiomer of product **33** produced in excess.
[e](*R*)-enantiomer of product **33** produced in excess.

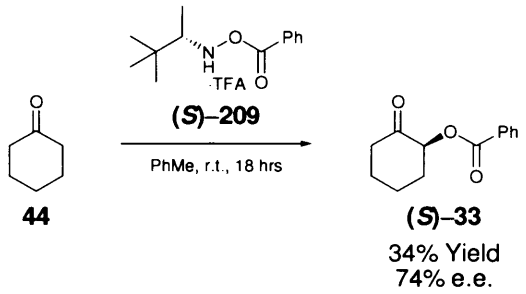
Table 5.1: Results obtained from new chiral amines with HCl and TFA co-acids.

Initially we investigated reactions carried out using a HCl co-acid, which were all carried out at 25 °C, to provide a direct comparison to the results obtained using the parent reagent **110·HCl**. The results obtained from this set of reactions (Table 5.1[a]) were quite poor on the most part (entries 2[a] and 3[a]) with regards to the level of asymmetric induction, which was disappointing though in keeping with the results obtained from reagent **110·HCl** (entry 1[a]). There was one exception however, which

was the reaction of reagent **209·HCl** (entry 4[a]). This gave a notably increased e.e. of 12% of the (*R*)-enantiomer of the product **33**, which was encouraging, however; due to the increased steric bulk surrounding the reactive nitrogen atom of this reagent **209·HCl**, the product **33** was obtained in a very low yield of 12% (entry 4[a]).

We then moved on to examining the effect of a TFA co-acid in conjunction with each of these reagents (**207–209**). In previous studies, variation of the co-acid to TFA had significantly improved the e.e. of the product **33** as illustrated by the comparative results shown in entry 1 (Table 5.1). The same trend was observed in the results from this set of reactions, whereby a significant increase in the e.e. of the product **33** was observed in all cases (entries 2[b]–4[b]). It was also noted that in each instance where an e.e. was measured in the product **33**, it was found that the absolute stereochemistry of the reagent was the same as the absolute stereochemistry of the enantiomer in excess, suggesting a consistent transition state regardless of reagent structure. The best result obtained was again from the reagent (**209**) derived from (*R*)-3,3-dimethyl-2-butylamine (entry 4[b]), which gave a fantastic e.e. of 77% of the (*R*)-enantiomer (***R*)-33**. Much to our delight we also observed a notable improvement in the yield of this reaction (entry 4[b]), when compared to the use of **209·HCl** (entry 4[a]), up to a much more practical 35% yield.

In having found a reagent **209** that significantly enriched the (*R*)-enantiomer of the α-oxygenated cyclohexanone product (***R*)-33**, we thought it would be worthwhile to synthesise the opposite enantiomer of this reagent ((***S*)-209**), in order to see if it provided a similar excess of the opposite enantiomer of the product (***S*)-33**. We therefore prepared reagent (***S*)-209** and reacted this with cyclohexanone **44**, Reaction scheme 5.3. We were pleased to find that the opposite enantiomer of the reagent ((***S*)-209**) gave the product **33** in a similar yield of 34% and provided us with a similar excess of the (*S*)-enantiomer of 74%, Appendix 5 (both of which can be considered to be within experimental error).



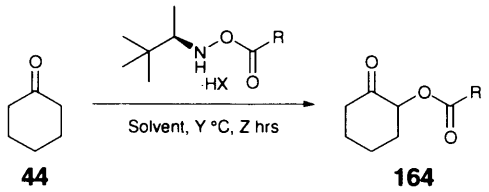
Reaction scheme 5.3: Reaction of reagent (*S*)-209 with cyclohexanone 44.

Results obtained from these series of experiments confirmed that the *N*-substituent of the chiral reagent had a strong influence on the asymmetric transformation and that increasing the steric bulk around the *N*-substituent had a positive effect on the level of asymmetric induction. We also observed that it was not necessary to use an aromatic *N*-substituent as previously thought, with the best results being obtained from reagent **209**, derived from a bulky aliphatic amine.

Further optimisation of the structure of the *N*-group was unfortunately not possible, due to the lack of commercially available chiral amines. Although *de-novo* synthesis of alternative amines was a distinct possibility, we considered convenient access to the reagent an important consideration within our design. We therefore elected to further examine the properties of the easily prepared reagent **209**.

5.3. Optimisation of Reaction.

In having optimised the *N*-substituent of the chiral hydroxylamine reagent, we decided it was worthwhile to re-examine all variables in the asymmetric α-oxygenation reaction of cyclohexanone **44**, as illustrated in Reaction scheme 5.4.

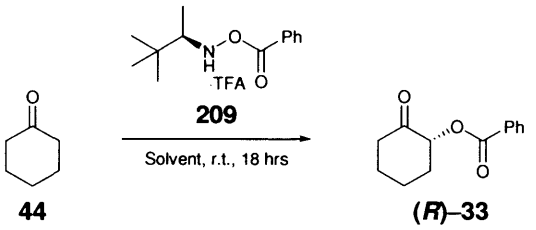


Reactions scheme 5.4: Final optimisation of the asymmetric α-oxygenation of cyclohexanone 44.

We decided to examine these variables one final time in order to determine if the pre-established conditions remained optimal for the transformation when using a reagent derived from an aliphatic amine.

5.3.1. Optimisation of Reaction Conditions.

To begin with we decided to re-examine the reaction conditions of solvent, co-acid, temperature and time. Beginning with solvent, the reaction was carried out in several different media, all varying in their relative polarity index. The results from this set of experiments are shown in Table 5.2.



44 **(*R*)-33**

Entry	Solvent	Polarity	Yield (%)[a]	e.e. (%)[b]
1	Acetone	5.1	11	77
2	CH_2Cl_2	3.1	27	81
3	Ether	2.8	14	74
4	Toluene	2.4	35	77
5	Hexane	0.1	16	79

[a]Isolated yield.
[b](*R*)-enantiomer of product **33** produced in excess.

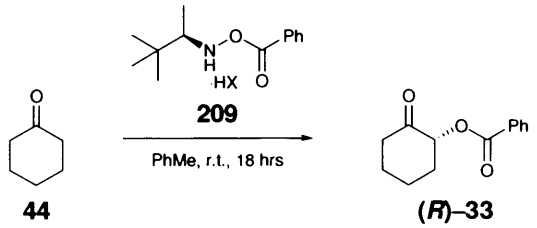
Table 5.2: Results obtained through variation of the solvent.

Surprisingly, all of the solvents examined (entries 1–3 and 5) gave equally good if not better results in terms of e.e. of the product **33**, compared to the results obtained from toluene (entry 4), despite the relative nature of the solvent. This was unexpected as earlier studies suggested a non-polar aromatic solvent was essential for good levels of asymmetric induction (Table 2.8). It is possible, however, that this could be related to the loss of an aromatic group in the *N*-substituent of the reagent.

Following this set of experiments, we decided to continue with toluene as the solvent of choice for carrying out our transformations, as it gave the product in a comparably high e.e. and a much higher yield (Table 5.2, entry 4), compared to the other solvents that had generated high e.e.'s (entries 1–3 and 5) but lower overall yields. The fact that other more polar solvents had generated high e.e.'s was thought to be due to the

dominant effect of the now optimised *N*-substituent overcoming some of the other minor solvent effects.

Moving on to variation of the co-acid, this had already been looked at briefly by carrying out initial reactions using both HCl and TFA as the co-acid (Table 5.1). We decided to try a few more co-acids however, in order to give us a range of results from which we could identify any possible trends, Table 5.3.



44 **(*R*)-33**

Entry	Co-Acid	pKa[c]	Yield (%)[a]	e.e. (%)[b]
1	HCl	-8.5	12	12
2	$MeSO_3H$	-2.6	10	70
3	TFA	-0.25	35	77
4	TCA	0.65	25	70
5	DPP	2.0	18	73
6	$PhCO_2H$	4.2	No reaction	

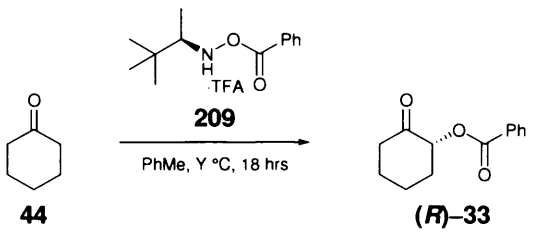
[a]Isolated yield.
[b](*R*)-enantiomer of product **33** produced in excess.
[c]pKa values in water.

Table 5.3: Results obtained through variation of the co-acid.

By carrying out the reaction using co-acids ranging in their associated pKa, we were able to determine that the same trend in reactivity was in operation, as was seen in earlier studies. These results (Table 5.3) showed that a very strong acid, for example HCl (entry 1) gave a low level of asymmetric induction, whereas use of a weaker acid (entries 2–5) gave significantly improved results in terms of e.e. Of these reactions, TFA was identified as the optimum co-acid (entry 3) as it provided the best e.e. in the product and a significantly better yield than other co-acids in this series. Use of a very weak acid, such as benzoic acid (entry 6) was not sufficient to promote the reaction, resulting in no product being observed in this case.

Following this we looked at varying the temperature of the reaction. Previous efforts had told us that increasing the temperature had a negative effect on the e.e. whilst decreasing the temperature had a positive effect on the e.e. We were interested in this latter effect and wanted to see if we could significantly increase the level of

asymmetric induction without affecting the reagent activity and thus yield for the reaction.



44 (*R*)-33

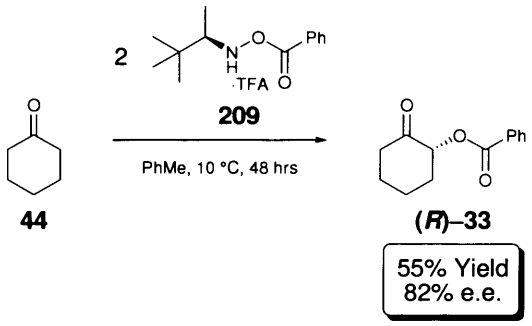
Entry	Temp. (°C)	Yield (%)[a]	e.e. (%)[b]
1	35	51	67
2	25	43	74
3	20[c]	35	77
4	10[d]	28	82
5	0[e]	20	83

[a]Isolated yield.
[b](*R*)-enantiomer of product **33** produced in excess.
[c]Reaction carried out at r.t. with temperature range of 20–23 °C.
[d]Reaction carried out in fridge with temperature range of 7–10 °C.
[e]Reaction carried out in an ice bath.

Table 5.4: Effect of temperature on the reaction.

As anticipated, the expected trends were evident in the results (Table 5.4), with an increase in temperature producing a relative decrease in e.e. (entries 1 and 2) compared to the result previously obtained from conducting the reaction at room temperature (entry 3). Reducing the temperature had the desired positive effect on the e.e. observed and we found that reducing the temperature of the reaction to 10 °C (entry 4) gave a higher e.e. of 82%, without being too detrimental to the yield. Further lowering of the reaction temperature to 0 °C (entry 5) did not appear to provide any further enhancement of the e.e. of the product **33**, but did lower reagent activity.

We were pleased to obtain an e.e. of greater than 80% for the transformation, (Table 5.4, entry 4), though the associated yield of 28% was not very useful synthetically. We were aware from earlier studies that time had no effect on the asymmetric induction, however; we recalled that it did have a slightly beneficial effect on the yield. The reaction at 10 °C was therefore repeated, this time for a duration of 48 hours. We also used 2 equivalents of the chiral hydroxylamine reagent **209** to promote the reaction, Reaction scheme 5.5.

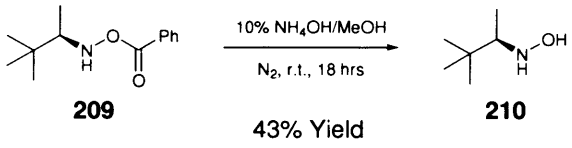


Reaction scheme 5.5: Optimised reaction of reagent 209 with cyclohexanone 44.

This reaction (Reaction scheme 5.5) was observed to work better than hoped, maintaining the high e.e. of 82%, Appendix 6, whilst significantly improving the yield up to a much more practical 55%.

5.3.2. Variation of *O*-Acyl Group.

The second stage of our efforts to optimise the reaction around the new *N*-substituent was to re-examine the effect of varying the *O*-acyl group. In order to do this we first of all needed to obtain the novel chiral hydroxylamine **210** that could be reacted with a variety of carboxylic acids (as explored in Chapter 3).



Reaction scheme 5.6: Formation of chiral hydroxylamine 210 from reagent 209.

This was achieved by deprotecting reagent **209**, using our previously developed methodology. This consisted of stirring the reagent **209** in a 10% ammonium hydroxide/methanol solution overnight, which gave the desired chiral hydroxylamine **210** in a 43% yield, Reaction scheme 5.6.

This new hydroxylamine **210** was then reacted with a range of carboxylic acids (**139**, **141**, **142**, **154** and **168**) that had previously been found to react with hydroxylamines to give the desired hydroxylamine based products. This generated a new set of chiral reagents, Figure 5.3.

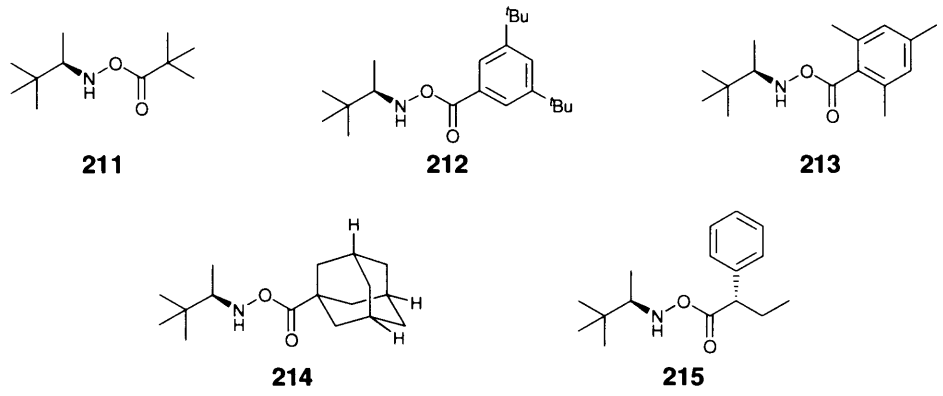
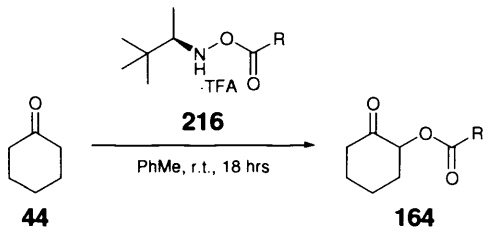
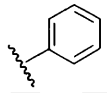
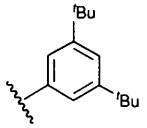
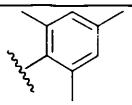
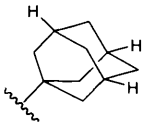
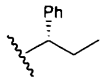


Figure 5.3: New chiral reagents synthesised using *N*-(*R*)-3,3-dimethyl-2-butyl hydroxylamine 210.

These new reagents (Figure 5.3) comprised both aliphatic (**211** and **214**) and aromatic (**212**, **213** and **215**) *O*-acyl groups in combination with the optimised aliphatic *N*-substituent, and the use of a chiral *O*-acyl group (**215**) was also re-examined. These reagents (Figure 5.3) were subsequently reacted with cyclohexanone **44** to give the corresponding α-functionalised products (**150**, **152**, **153**, **156** and **176**). Conditions for enantiomer separation of these products (**150**, **152**, **153**, **156** and **176**) had already been established, allowing for their immediate analysis following isolation. The results from this set of experiments are shown in Table 5.5.



Entry	R	Yield (%)[a]	e.e. (%)
1		35	77[b,c]
2		8	56[d]
3		26	53[d]
4		30	76[c]
5		10	68[d]
6		44	76[c]

[a]Isolated yield.
[b](*R*)-enantiomer of product **33** produced in excess.
[c]e.e. determined using HPLC.
[d]e.e. determined using NMR shift reagent **161**.

Table 5.5: Results obtained using chiral reagents 216, varying *O*-acyl group.

These results (Table 5.5) were obtained from reactions carried out overnight at room temperature and therefore were compared to the results obtained from reagent **209** under the same conditions (entry 1). As can be seen in Table 5.5 above, no further improvement of the e.e. was observed as a result of varying the *O*-acyl group. There also did not appear to be a definitive pattern linking the nature of the *O*-acyl group with its effect on asymmetric induction.

In earlier efforts to optimise the *O*-acyl group, an interesting result was obtained when using an *O*-2,4,6-trimethylbenzoyl group (Table 3.1, entry 4). This group was observed to give the product **153** in a comparable yield to that provided by reagent **110**, but with an extremely low level of asymmetric induction. We were unfortunately not able to explain this observation, instead having to resign ourselves

to regarding it as anomalous. In the above set of results (Table 5.5), however, no such anomalous effect was observed (entry 4). The *O*-acyl group in question instead was observed to give the product **153** in both a comparable e.e. and yield to that of reagent **209** (entry 1).

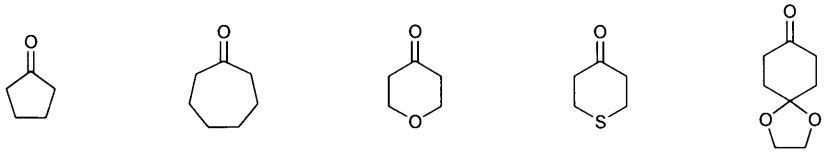
The use of a chiral *O*-acyl group in conjunction with our new optimised *N*-group was also examined (entry 6). This was found to have no apparent impact on the level of asymmetric induction, providing further evidence that the structure and nature of the *O*-acyl group does not determine or significantly affect the outcome of the reaction.

The electronics of the reaction system were not re-examined as we were unable to vary the electronics of the *N*-substituent and we did not feel that varying the electronics of the *O*-acyl group would provide any useful information (as found in Chapter 4).

5.4. Application to Other Cyclic Ketone Substrates.

Having produced a structurally optimised chiral hydroxylamine reagent **209**, and having confirmed that the reaction conditions were optimised for cyclohexanone **44**, we decided to apply our asymmetric α-oxyacylation procedure to a variety of other cyclic ketone substrates, to see if we could obtain a range of enantiomerically enriched α-oxygenated products.

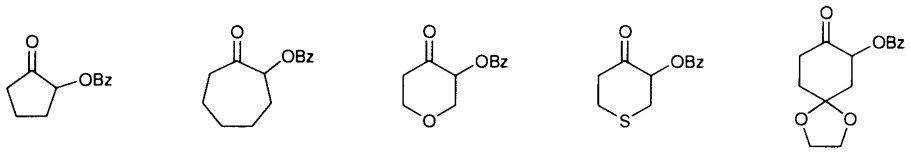
To begin with we looked at a range of readily available cyclic ketone substrates, Figure 5.4. These were comprised of substrates that examined the question of the effect of varying the size of the ring (**217** and **218**); substrates that looked at the effect of the presence of other heteroatoms (**219** and **220**); and a substrate that possessed an acid-labile acetal group (**221**).



217 **218** **219** **220** **221**

Figure 5.4: Readily available cyclic ketone substrates examined.

As these substrates (Figure 5.4) had not been examined previously, it was necessary to carry out reactions between each of the substrates (**217–221**) and the achiral *N*-methyl reagent **63·HCl** initially, in order to generate the corresponding racemic reference products **222–226** (Figure 5.5). These reactions were successful, giving the desired compounds **222–226** in high yield as shown in Figure 5.5.

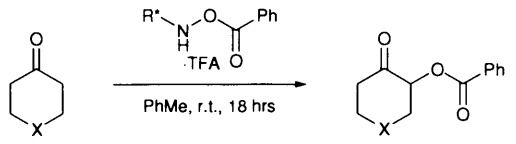


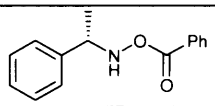
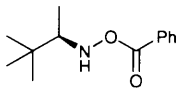
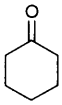
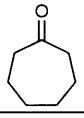
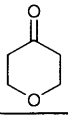
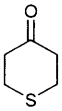
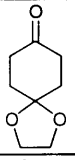
222	**223**	**224**	**225**	**226**
72%	72%	84%	66%	75%

Figure 5.5: Corresponding α-oxybenzoyl products with racemic yields.

Having obtained samples of the racemic products **222–226**, we set about developing conditions for enantiomer separation. We found that this was relatively straightforward and was achieved by HPLC, using the OD chiral column in each case.

Following this, we investigated the potential to prepare each of these α-oxygenated products (Figure 5.5), by carrying out the analogous asymmetric reactions. Separate reactions were carried out between the new substrates (Figure 5.4) and reagents **110** and **209**. This was done in order to establish whether the same trends in reagent activity were in operation across a range of ketone substrates and also to determine if a change in the stereochemistry of the reagent brought about a change in the absolute configuration of the product, as seen for cyclohexanone **44**. The results from these series of experiments are shown below in Table 5.6 and represent the best results obtained for each substrate (**217–221**) to date. They have therefore been compared to the best result obtained for cyclohexanone **44** (entry 1).



Entry	Substrate				
		Yield (%)[b]	e.e. (%)	Yield (%)[b]	e.e. (%)
1		51	37[c]	55[e]	82[d,e]
2		28	24	Not Isolated	
3		35	25[c]	9	55[d]
4		24	22	15	49
5		8	23	Not Isolated	
6		51	39	35[f]	89[f]

[a]All reactions were performed in toluene at r.t. for 18 hours unless stated otherwise.
[b]Isolated yield.
[c](*S*)-enantiomer of the product produced in excess.
[d](*R*)-enantiomer of the product produced in excess.
[e]Reaction performed at 10 °C for 48 hours with 2 equivalents of reagent **209**.
[f]Reaction performed at r.t., for 48 hours with 2 equivalents of reagent **209**.

Table 5.6: Results obtained from various cyclic ketone substrates.[a]

As can be seen from the results shown in Table 5.6, reagent **209** was observed to induce a much higher level of asymmetry in the product (where isolated) of each reaction, in comparison to the level of asymmetry induced by reagent **110** (entries 1, 3, 4 and 6). This increase in e.e. was also noted to be proportional in each case, increasing by a factor of approximately 2.2 when going from reagent **110** to reagent **209**, suggesting a degree of confidence in the results obtained.

We were interested in this proportional increase in e.e. by a relatively constant factor of 2.2 and, as the only variable in these reactions was the *N*-substituent of the chiral reagent, we suspected that this trend might be the result of relative steric effects. If

this trend was indeed due solely to steric effects, then we can consider A-values (which are the free-energy differences between equatorial and axial substituents on a cyclohexane ring) as a possible means for explanation. We felt that this was appropriate owing to the 6-membered ring structure present in our proposed transition state model (Figure 4.10). The A-value for a phenyl substituent is approximately 11 kJ mol^{-1}; whereas that of a *tert*-butyl group is approximately 21 kJ mol^{-1}.[61] The increase in A-value between these groups is by an approximate factor of 2, which we felt supported the theory that there may be a link between the A-value of the *N*-substituent of the reagent and the observed e.e. of the product in our chiral reactions. A more definitive conclusion, however, would require further examination. Due to the lack of commercially available bulky chiral amines, we did not prepare a reagent with a higher anticipated A-value in order to test this theory, however; this provides opportunity for further research in the area.

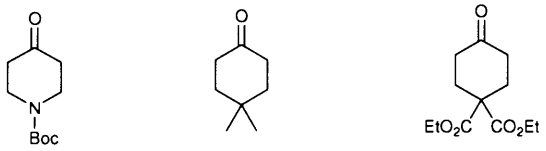
Going back to the results obtained in this series of reactions, (Table 5.6), we also observed in each instance that a change in the stereochemistry of the reagent brought about a change in the absolute configuration of the product (**222–226**) as expected. In the case of cycloheptanone **218** (entry 3), the absolute configuration of the product **223** had been reported in the literature and by comparison to these results we were able to determine that a reagent with (*S*)-stereochemistry (**110**) enriches the (*S*)-enantiomer of the product **223** and that a reagent with (*R*)-stereochemistry (**209**) enriches the (*R*)-enantiomer of the product **223**.[28] This was the same trend as was seen for cyclohexanone **44** and we believe this to be the case for all other substrates examined; however, without having a reference chiral sample or literature results, this cannot be confirmed for the other substrates (**217**, **219–221**).

We did have some concerns about the low yields obtained for most of the reactions carried out in these sets of experiments (Table 5.6). It would appear that changing the size of the ring (entries 2 and 3), or replacing one of the carbon atoms with a heteroatom (entries 4 and 5), is unfavourable with regards to the yield and e.e. when using chiral reagents **110** and **209**. Altering the nature of the substrate will change both the steric and electronic environment of the carbonyl group. This could have an effect on iminium ion/enamine formation and the rearrangement steps in the proposed mechanism. It is possible that the reaction could be optimised for each of these substrates (**217–221**), in an analogous manner to that described for

cyclohexanone **44**; however, this would take significant chemical resource to achieve.

Reaction of substrate **221**, however, was observed to give an extremely positive result in terms of yield and e.e. (Table 5.6, entry 6). This substrate **221**, which has a structure based on the cyclohexanone (**44**) skeleton, was initially reacted with reagent **110** and gave the product **226** in the same yield as obtained with cyclohexanone **44** (entry 1) and a marginally better e.e. This substrate **221** was then reacted with reagent **209**, which was found to give the opposite enantiomer of the product **226** in a fantastic 89% e.e., Appendix 7, which constituted our highest e.e. to date. This second reaction was carried out at room temperature; therefore, by reducing the temperature, it is possible that we could improve upon this e.e. further.

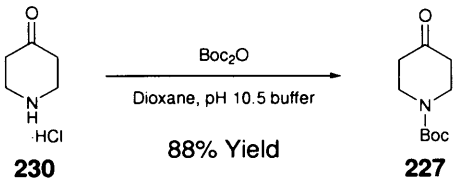
The results obtained following the examination of a range of substrates (Figure 5.4) suggested that the α-oxybenzoylation transformation was most applicable to substrates based on the cyclohexanone **44** skeleton. We therefore decided to examine several substrates based on this premise and decided upon substrates **228** and **229** (Figure 5.6). A further substrate **227** was also included in this second screen, which we felt was worth examining, despite the presence of a heteroatom in the ring, owing to the fact that it had potential to undergo further chemical transformations and, if successful, could prove to be extremely synthetically useful.



227 **228** **229**

Figure 5.6: Further substrates examined.

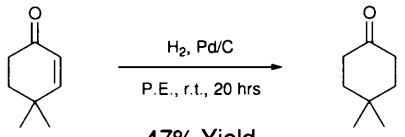
All of the further substrates (**227–229**) to be examined (Figure 5.6) were synthesised, owing to their lack of commercial availability. Beginning with substrate **227**, this was obtained quite simply by reacting 4-piperidinone hydrochloride **230** with Boc-anhydride, which gave the desired product **227** in an 88% yield, Reaction scheme 5.7.[62]



230 227

Reaction scheme 5.7: Synthesis of substrate 227.[62]

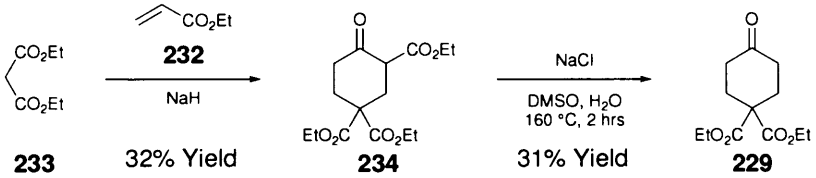
Moving on to 4,4-dimethyl cyclohexanone **228**, this was readily synthesised by hydrogenation of the corresponding alkene **231**, Reaction scheme 5.8.[63] This reaction gave the product **228** in a 47% isolated yield, which was obtained by filtration and concentration of the reaction mixture, without the need for purification. This yield was considerably lower than the reported 92% yield and was thought to be due to volatility of the compound.



231 228

Reaction scheme 5.8: Synthesis of substrate 228.[63]

Synthesis of the final substrate **229** proved to be more challenging and involved a two-step synthesis, the first step involving reaction of diethyl malonate **233** with an excess of ethyl acrylate **232**, in the presence of sodium hydride, Reaction scheme 5.9.[64] This step effects two transformations, namely a 1,4-addition and a Dieckmann cyclisation, giving the tricarbethoxy compound **234**. After purification by distillation, **234** was then heated in wet DMSO, containing a three-fold excess of sodium chloride, at 160 °C for 2 hours. After purification by column chromatography, the desired dicarbethoxy substrate **229** was obtained in a 31% yield.

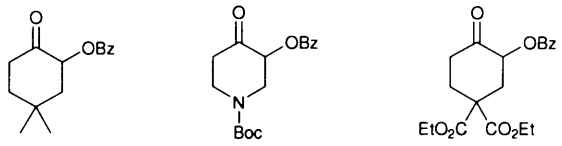


233 234 229

Reaction scheme 5.9: Synthesis of substrate 229.[64]

Following the synthesis of substrates **227–229**, the subsequent α-oxybenzoylation reactions were carried out using the achiral *N*-methyl reagent **63·HCl**. In the case of substrate **229**, use of achiral reagent **109·HCl** was employed to synthesise the

racemic product **237**, following problems with isolation when using achiral reagent **63·HCl**. This provided us with the corresponding α-oxygenated products **235–237**, in good yields as shown in Figure 5.7.



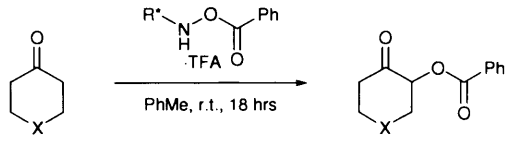
235 65%

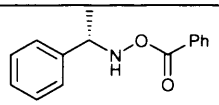
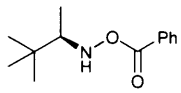
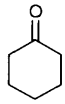
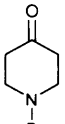
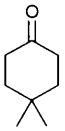
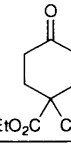
236 73%

237 73%

Figure 5.7: Further α-oxybenzoyl products and corresponding racemic yields.

The enantiomers of each of these products **235–237** were subsequently separated by HPLC, allowing all substrates **227–229** to be examined in the asymmetric reactions. Separate reactions were carried out between the substrates **227–229** and reagents **110** and **209**, under the previously optimised reaction conditions. The results from this second screen are shown in Table 5.7.



Entry	Substrate				
		Yield (%)[b]	e.e. (%)	Yield (%)[b]	e.e. (%)
1	 **44**	51	37[c]	55[e]	82[d,e]
2	 **227**	34	26	4	45
3	 **228**	49	28	44	62
4	 **229**	51	30	28	67

[a]All reactions were performed in toluene at r.t. for 18 hours unless stated otherwise.
[b]Isolated yield.
[c](*S*)-enantiomer of the product **33** produced in excess.
[d](*R*)-enantiomer of the product **33** produced in excess.
[e]Reaction performed at 10 °C for 48 hours with 2 equivalents of reagent **209**.

Table 5.7: Results obtained from further substrates examined.[a]

As hoped, when using substrates **228** and **229**, which have structures based on the cyclohexanone (**44**) skeleton, the corresponding products (**235** and **237**) were obtained in reasonable yields (Table 5.7, entries 3 and 4). As seen in the first screen (Table 5.6), when using a substrate containing a heteroatom in the ring (**227**), the yields obtained in both reactions were considerably lower (entry 2) when compared to the results obtained from cyclohexanone **44** (entry 1).

With regard to the e.e.'s obtained in this second set of reactions (Table 5.7), we again observed a significant increase in the e.e. when going from reagent **110** to **209**. In the latter cases (entries 3 and 4), this was again proportional, increasing by an approximate factor of 2.2. In changing from reagent **110** to **209**, these increases in e.e. were also accompanied by a change in the absolute stereochemistry of the product, as anticipated.

The results obtained from carrying out our asymmetric α-oxygenation reaction on a variety of carbonyl substrates led us to the conclusion that this transformation is most applicable to six-membered cyclic ketones based on the cyclohexanone **44** skeleton. Incorporation of various substituents on the ring structure being reasonably well tolerated.

It was following this conclusion that we thought that it would be worth examining carbonyl substrates that possessed substituents that would direct the stereochemistry of the forming α-C–O bond. Several substrates were chosen to examine this possibility, Figure 5.8, comprising two in which the conformation of the ring structure was restricted (**239** and **240**) and two that contained a stereogenic centre (**238** and **241**), in the hope that the restrictions on conformation, along with the directing effects of a chiral substrate, would provide high levels of asymmetric induction.

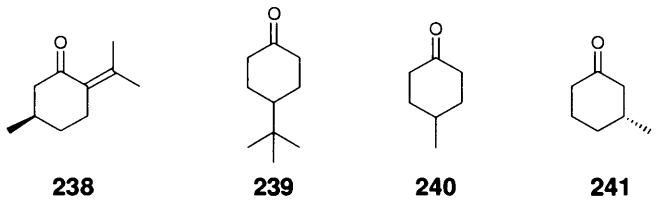
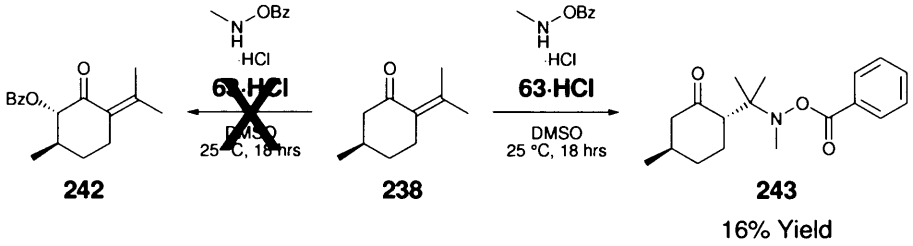


Figure 5.8: Sterically confined cyclic ketone substrates examined.

Beginning with (*R*)-pulegone **238**, this presented as a very good substrate since there was only one α-position that could react in the desired manner and the stereogenic centre at the β-position should direct stereoselectivity toward forming the (*S*)-α-*O*-benzoyl diastereoisomer **242** in excess, Reaction scheme 5.10.

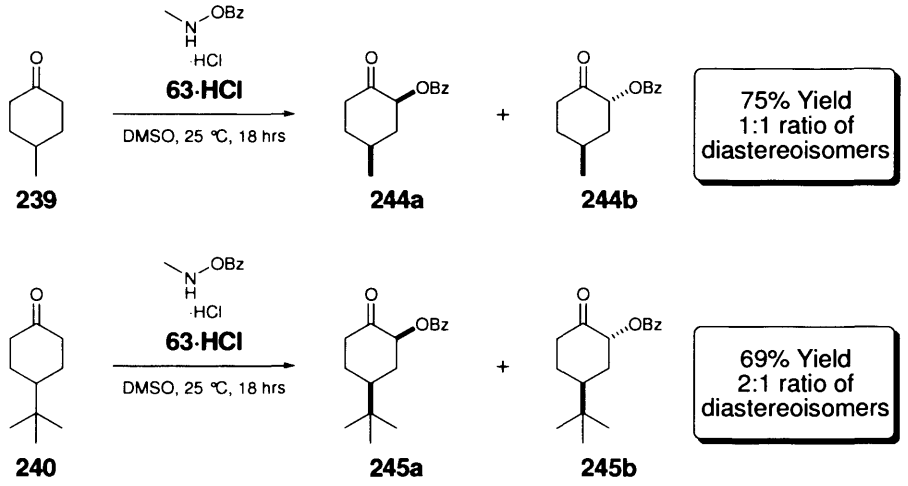


Reaction scheme 5.10: Results following reaction of 238 with achiral reagent 63·HCl.

Reaction of this substrate **238** with the achiral *N*-methyl reagent **63·HCl** (Reaction scheme 5.10), however, proved to be disappointing, with the only identifiable

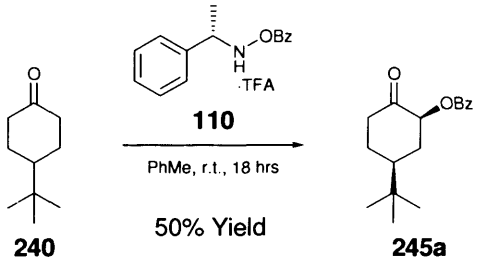
product being the addition product **243**, which was obtained in a 16% isolated yield as a single diastereoisomer. Formation of this product **243** was confirmed by mass spectrometry.

Following this we turned our attention to substrates **239** and **240**, which are both *meso* compounds, possessing a single substituent in the 4-position. Separate reactions were carried out between these substrates (**239** and **240**) and achiral reagent **63·HCl**, Reaction scheme 5.11. As can be seen below, both substrates (**239** and **240**) underwent the transformation well, giving the products (**244** and **245**) in good yield, as a mixture of diastereoisomers in each case.



Reaction scheme 5.11: Results obtained following reaction of substrates 239 and 240 with achiral reagent 63·HCl.

Selectivity in these transformations was not optimal. In the first instance, substrate **239** was observed to give no selectivity at all, forming the two diastereoisomers (**244a** and **244b**) in a 1:1 ratio. In the second reaction, the selectivity was observed to be slightly better, giving the two diastereoisomers (**245a** and **245b**) in a 2:1 ratio. Due to the fact substrate **240** gave more encouraging results, it was this substrate alone that we examined with our chiral reagent **110**.



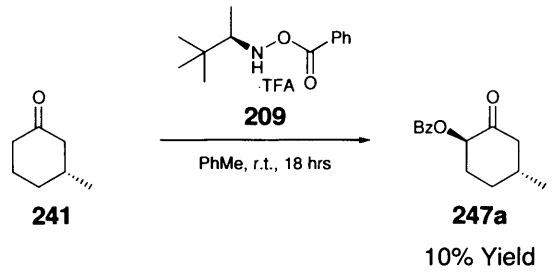
Reaction scheme 5.12: Reaction of 240 with chiral reagent 110.

The outcome of this reaction, Reaction scheme 5.12, was the formation of exclusively diastereoisomer **245a** in a 50% yield. This was very exciting and supported the theory that substituents that restrict conformation can direct the stereochemistry of the forming α-C–O bond.

The final carbonyl substrate examined was (*R*)-3-methyl cyclohexanone **241**, which, as with substrate **238**, had a stereogenic centre in the 3-position that we hoped would direct the stereochemistry of the forming α-C–O bond. In this instance however, as the substrate is not symmetrical, there were four possible diastereomeric products that could result from reaction of this substrate **241**, Figure 5.9.

Figure 5.9: Possible diastereomeric products resulting from α-oxybenzoylation of substrate 241, with relative stereochemistry given at α- and β- positions.

Of these compounds (Figure 5.9), **246a** and **247a** could be expected to be favoured by sterics, and when reacted with the achiral *N*-Me reagent **63·HCl** these were found to be the predominant products. Furthermore, when attempting to purify the reaction mixture by column chromatography, we found that we were only able to isolate isomer **247a**, in a 14% yield; the remaining isomers (**246a**, **246b** and **247b**) were found to co-elute in a combined 23% yield. As the isomer (**247a**) that we were able to isolate had (*R*)-stereochemistry at the α-position, we decided to react substrate **241** with chiral reagent **209**, Reaction scheme 5.13. This chiral reagent **209**, also having (*R*)-stereochemistry, was hoped to favour formation of this isomer (**247a**) alone.



Reaction scheme 5.13: Showing major product resulting from reaction of 241 with chiral reagent 209.

Indeed, this was found to be the case, giving isomer **247a** in a 10% isolated yield. The remaining isomers (**246a**, **246b** and **247b**) were obtained in a 2% combined yield. This concluded the investigation into the effect of using substituents as a means to direct the stereochemistry of the α-oxygenated product.

5.5. Conclusion.

The variation of the structure and nature of the *N*-substituent of the chiral reagent was investigated. This led us to identify reagent **209**, derived from (*R*)-3,3-dimethyl-2-butylamine, as the best reagent synthesised to date for carrying out the asymmetric α-oxygenation of cyclohexanone. Under standard reaction conditions this provided us with a 35% yield and a 77% e.e. of the (*R*)-enantiomer of the product (***R*)-33**. We were subsequently able to synthesise the opposite enantiomer of this reagent ((***S*)-209**) and produced the (*S*)-enantiomer of the product (***S*)-33** in a similar 74% excess and 34% yield. The ability to obtain the product **33** in high e.e. of both enantiomers and in reasonable yield will increase the synthetic potential of this reagent and transformation.

Following this, we set about re-examining the reaction conditions for the transformation in order to confirm that the reaction remained fully optimised. This led us to our best result to date for cyclohexanone **44**, which was an 82% e.e. of the (*R*)-enantiomer of the product (***R*)-33** and a 55% yield, which was obtained following reduction of the temperature to 10 °C and increase of reaction time to 48 hours.

This reagent **209**, along with our original chiral reagent **110**, was then applied to the asymmetric α-functionalisation of various cyclic substrates, in order to get an idea of

the scope and limitations of this transformation. In all cases, the chiral reagent **209** proved to be more effective in inducing asymmetry than the original reagent **110**, and generated good to excellent e.e's in the products. Yields in some cases were much lower than expected, and led us to the conclusion that the transformation was most applicable to six-membered cyclic substrates that do not contain heteroatoms in the ring. The presence of various substituents on the other hand appeared to be well tolerated.

As a final thought we examined a variety of carbonyl substrates that possessed substituents that were expected to have a directing effect with respect to the stereochemistry of the forming α-C–O bond. Results from these experiments suggested the stereochemistry of the product could be controlled in certain instances; however, this would appear to be substrate-specific.

Chapter 6.

Investigation into the use of Nitrones in the Asymmetric α-Functionalisation of Carbonyl Compounds.

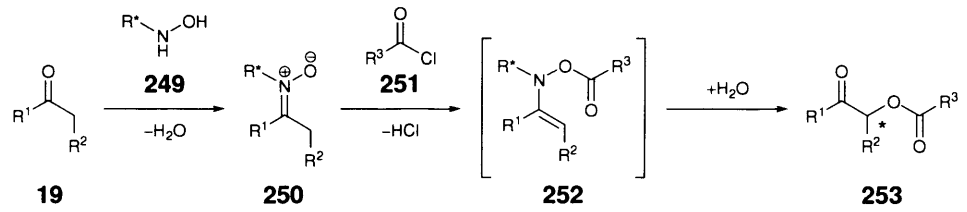
6.1. An Alternative Approach.

At this stage we had thoroughly investigated our initial objective to establish an asymmetric variant of the α-oxyacylation of carbonyl compounds, previously developed within the group.[49] These asymmetric transformations lead to high levels of enantiomeric excess in many cases; however, a constant battle had been obtaining acceptable yields for the transformation.

Our results had shown us that it is possible to induce high levels of asymmetry in the products by incorporating a bulky chiral *N*-substituent in the structure of a hydroxylamine reagent. It was this steric bulk, however, that we believed was responsible for the low yields frequently observed for the transformation, by hindering condensation of the nitrogen atom of the reagent with the carbonyl group of the substrate.

Previous attempts to overcome low yields included raising the temperature of the reaction, in an attempt to overcome undesirable steric effects; and moving the stereogenic centre and steric bulk of the *N*-substituent further from the reactive nitrogen, in an attempt to make the chiral reagent less sterically encumbered. In both instances this resulted in increased yields as anticipated; unfortunately though, this was accompanied by lower e.e.'s.

After much consideration, we decided to implement an alternative strategy for carrying out the α-oxyacylation transformation that we believed could also maintain comparable levels of asymmetric induction to those observed to date. This alternative method comprised a two-step procedure, Reaction scheme 6.1, firstly involving reaction of a carbonyl compound **19** with a chiral hydroxylamine **249** to form a nitrone **250**. We hoped to be able to isolate this species (**250**), as it was expected to be relatively stable due to the intramolecular charge stabilisation. The second step would then involve reaction of the nitrone **250** with an acyl chloride **251**, to from an *O*-acyl enamine intermediate **252** that would rearrange under the reaction conditions to give the desired α-oxyacylated product **253**.



Reaction Scheme 6.1: General reaction for the α-oxygenation of carbonyl compounds, employing the use of nitrones.

This alternative method, though slightly longer, was anticipated to deliver the products **253** in much higher yields, as the steric bulk surrounding the nitrogen atom of the chiral hydroxylamine **249** was reduced compared to that of a chiral hydroxylamine reagent (e.g. **110**), which had both *N*- and *O*-substituents. We hoped that this would facilitate approach and thus attack of the nitrogen atom on the carbonyl group of the substrate **19**. At the same time, we believed that this method would generate α-oxygenated products **253** with a similar level of enantiomeric excess compared to those obtained from the standard one-pot reaction (Reaction scheme 2.13). We envisaged that the second step of the reaction, involving the [3,3]-sigmatropic rearrangement, would go through the same transition state as previously described.

6.2. Precedent for Alternative Approach.

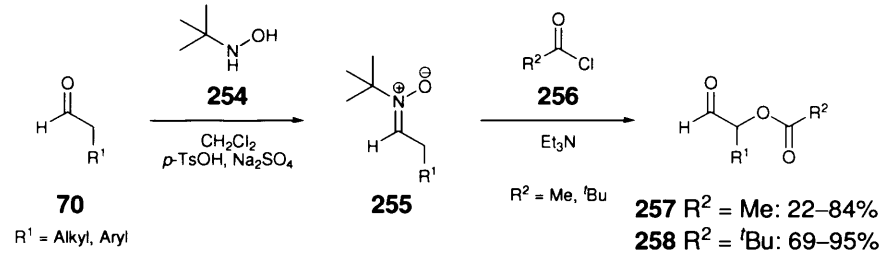
6.2.1. Coates Work.

Precedent for this new approach can firstly be found in work carried out by Cummins and Coates in 1983, which was briefly discussed in Chapter 1.4.[47] This involved formation of nitrones, from both aldehydes and cyclic ketones, which were then reacted with acid chlorides, in the presence of triethylamine, affording *N*-vinyl-*O*-acyl hydroxylamine intermediates. It was then shown that these intermediates underwent rapid rearrangement to form the corresponding α-acyloxy imines, which, due to their unstable, hygroscopic nature, were in most cases hydrolysed immediately to the desired α-acyloxy carbonyl product.

The mild reaction conditions required for this transformation, along with interest in developing new synthetic methods for the α-oxygenation of carbonyl compounds,

prompted investigation of the scope and limitations of this novel nitrone acylation-rearrangement reaction.

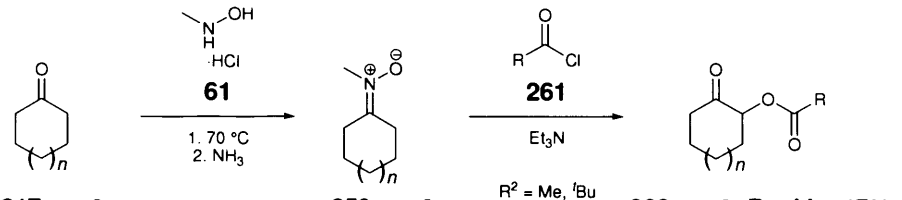
A series of five aldehydes (**70**) was examined initially, each of which was reacted in turn with *N-tert*-butyl hydroxylamine **254**, according to the procedure of Torssell and Zeuthen,[65] to afford the corresponding nitrone **255**, Reaction scheme 6.2.



Reaction scheme 6.2: Synthesis of α-acetoxy aldehydes.[47]

These nitrone products (**255**) were subsequently isolated (in good to excellent yield of 59–93%), before further reaction with both pivaloyl and acetyl chloride (**256**). These reactions were carried out under mild conditions and afforded the corresponding α-pivaloyloxy and α-acyloxy aldehydes **257** and **258** in generally high yield (22–84% and 69–95% respectively, Reaction scheme 6.2).

Application of this procedure to cyclic ketones was then investigated briefly, using cyclopentanone **217** and cyclohexanone **44** as substrates, Reaction scheme 6.3. These were condensed with *N*-methylhydroxylamine hydrochloride **61** at 70 °C, according to the procedure of Exner,[66] which gave the corresponding *N*-methyl nitrones **259** and **260**, in 35 and 37% yields respectively, after treatment with ammonia.



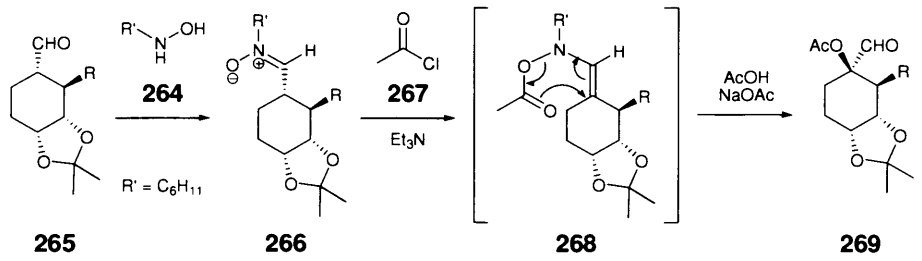
Reaction scheme 6.3: Synthesis of *N*-methyl nitrones from cyclic ketones.[47]

Following this, the nitrone products, **259** and **260**, were again reacted with both pivaloyl and acetyl chloride (**261**). This led to the corresponding α-acyloxy

cyclopentanones (**262** and **263**) and cyclohexanones (**167** and **150**), this time however, in much lower yields of 26–59%.

Overall, the acylation-rearrangement reaction of *N-tert*-butyl nitrones (**255**) was shown to be an effective method for the α-oxygenation of aldehydes, giving the products in good to excellent yields under mild reaction conditions. Application of the method to cyclic ketones was somewhat less successful, requiring harsher conditions and providing the products of both steps of the reaction in significantly lower yields.

Stereoselectivity in these transformations was not considered in these studies. A later application of this method, however, did address this question. This later application was in 1999, in the total synthesis of fumagillol, which was carried out by Sorenson and co-workers.[48] The nitrone method developed by Coates[47] was used in this instance to overcome the non-trivial problem of introducing an oxygen atom α- to an aldehyde group in a diastereocontrolled manner.



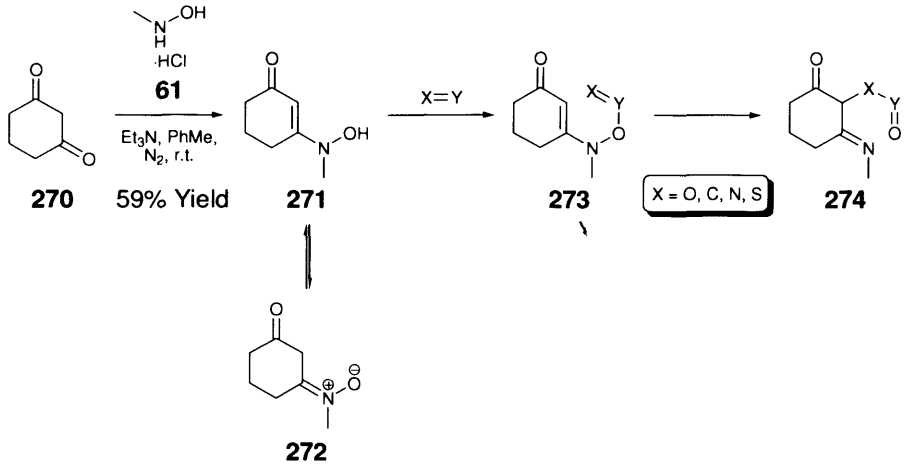
265 **266** **268** **269**

Reaction scheme 6.4: Introduction of an α-acetoxy group in a diastereocontrolled fashion.[48]

This was achieved in a two-step reaction, Reaction scheme 6.4, firstly involving reaction of the aldehyde **265** with *N*-cyclohexyl hydroxylamine **264** to give a nitrone **266**. This was followed by reaction of **266** with acetyl chloride **267** in the presence of triethylamine, which gave the desired α-acetoxy aldehyde **269**, following hydrolysis of the resulting imine, in a 51% overall yield and a 90% diastereomeric excess. The high diastereoselectivity obtained was attributed to the presence of other substituents on the bicyclic ring structure.

6.2.2. Lobo Work.

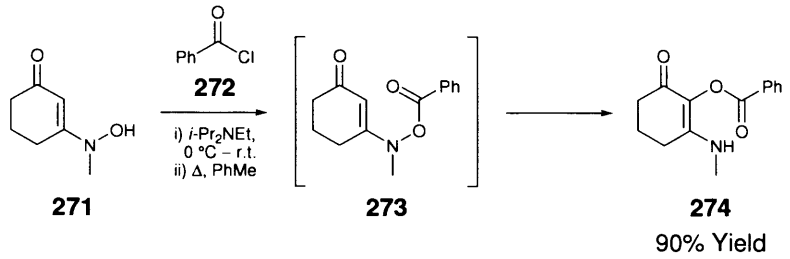
Further precedent for our alternative approach, this time focusing on the reaction of cyclic ketones, can be found in the work carried out by Lobo *et al*, who extended the idea of using nitrones for the α-oxygenation of carbonyl compounds to the introduction of a variety of different functional groups at the α-position, Reaction scheme 6.5.[67]



Reaction scheme 6.5: General reaction scheme for the selective introduction of oxygen, nitrogen or sulphur at the α-position.[67]

As can be seen in the general reaction scheme above (Reaction scheme 6.5), this work was centred around a single cyclic ketone substrate, namely 1,3-cyclohexanedione **270**, which was reacted with *N*-methyl hydroxylamine hydrochloride **61**, in order to obtain the desired enehydroxylamine **271** starting material, which is a tautomer of the nitrone **272**. This reaction was carried out under milder reaction conditions compared to those used by Coates for cyclic ketones (Reaction scheme 6.3),[47] and gave the product **271** in a higher yield of 59%.

They then proceeded to show that this enehydroxylamine **271** could be used to introduce a carbon, nitrogen, oxygen or sulphur atom at the α-position, following reaction with the appropriate reagents followed by a subsequent [3,3]-sigmatropic rearrangement.



271 273 274

90% Yield

Reaction scheme 6.6: α-Oxybenzoylation of a cyclic diketone.[67]

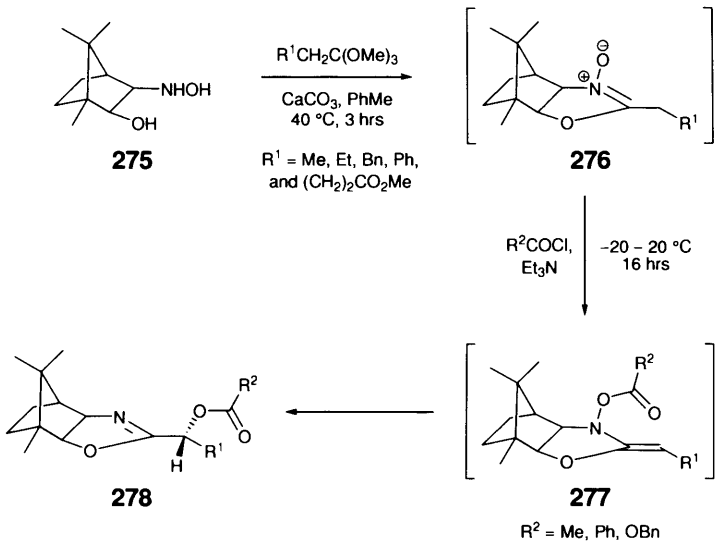
For example, transfer of an *O*-benzoyl group was achieved by reaction of the enehydroxylamine **271** with benzoyl chloride **272** in the presence of *N*,*N*-di*iso*propyl ethylamine, Reaction scheme 6.6, to give the product **274** in an excellent 90% yield.

Overall, this method appeared to be extremely encouraging, being based on a cyclic ketone substrate and giving the α-oxygenated product **274** in high yield. However, the cyclic 1,3-diketone **270** was the only substrate examined, which was chosen for the presence of a conjugated EWG. It was therefore not clear how widely applicable this method would be to other cyclic substrates that did not possess such EWG's, for example our substrate of choice cyclohexanone **44**.

6.2.3. Dalko and Langlois Work.

A final study worth noting was that conducted by Dalko and Langlois in 1998,[68] which involved formation of a C–O bond *via* a stereoselective hetero Claisen rearrangement, using oxazoline-*N*-oxides as the starting material. This constituted the first asymmetric version of these rearrangements, forming α-acyloxy-substituted oxazolines in a stereocontrolled manner and provided some insight into the mechanism and transition state of these reactions.

The mechanism proposed for this reaction involved initial condensation of hydroxylamino *iso*borneol **275** with an orthoester to give an oxazoline-*N*-oxide **276**, Reaction scheme 6.7. This nitrone species **276** was not isolated, due to its hygroscopic nature; instead, an acid chloride was added directly into the reaction mixture, along with triethylamine, whereby, upon standing at room temperature for 16 hours, the desired α-acyloxy oxazoline **278** was isolated.



Reaction scheme 6.7: Proposed mechanism for formation of enantiomerically enriched α-acyloxy substituted oxazolines 278.

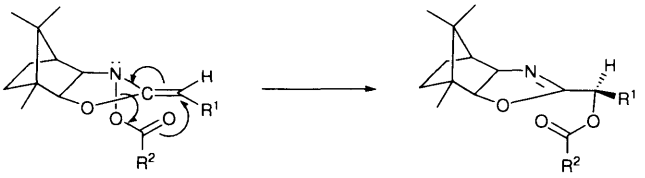
This reaction was carried out on nitrones (**276**) with a variety of substitution patterns in the side chain (R^1) and with a variety of acylating agents (R^2). The overall yields obtained for the 3-step nitrone formation, acylation and rearrangement were generally good (in the range 38–67%), but not excellent, which was attributed to the instability of the intermediate species (**276** and **277**). It was also observed that the products **278** were unstable, and hydrolysed on standing.

An interesting observation was made when R^1 was made a phenyl group, in that no product was obtained. This was thought to be the result of conjugation of the double bond with the phenyl group in intermediate **277**, which provided increased stability thus preventing rearrangement.

The diastereoselectivity in these reactions was found to be very good, with d.e.'s generally in the range 92–95%. The only exception was when using benzyl chloroformate as the acylating agent, which provided the product in the lowest yield of 38% and a d.e. of only 32%.

A final study undertaken was a chemical correlation to confirm the sense of induction in the newly formed acyloxy group. The results from this study enabled a transition state model for the transformation to be proposed, Reaction scheme 6.8,

whereby it was thought that the *Z*-keteneaminoketal **279** was the precursor to the [3,3]-sigmatropic rearrangement.



279 **280**

Reaction scheme 6.8: Proposed transition state for asymmetric rearrangement.

The proposed transition state **279** shows the *O*-acyl group adopting an axial position. The high diastereoselectivities obtained support the argument that a concerted process is in operation.

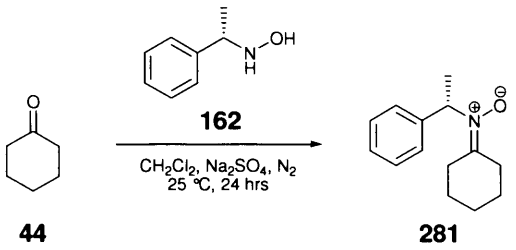
6.2.4. Summary.

There are several established methods for the use of nitrones in the α-oxygenation of carbonyl compounds. These studies show that it is possible to achieve high yields of the α-acyloxy product using this method, which is encouraging, though in most cases, this appears to be dependent on the substrate.

There was not, however, precedent for the use of nitrones with chiral *N*-substituents in the synthesis of chiral α-acyloxy carbonyl compounds. In the instances where the question of asymmetry was examined, the high d.e.'s observed in the products was the result of other chiral directing groups. We therefore felt it would be interesting to see if we could produce asymmetric α-oxyacylated products using our proposed two-step procedure (Reaction scheme 6.1).

6.3. Our Efforts.

Our efforts to examine this alternative method began by looking at the reaction between *N*-(*S*)-α-methyl benzyl hydroxylamine **162** and cyclohexanone **44**, Reaction scheme 6.9.

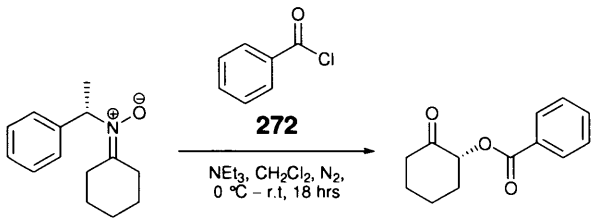


Reaction Scheme 6.9: Formation of nitrone 281 using *N*-(*S*)-α-methyl benzyl hydroxylamine 162.

The reaction conditions used were those developed by Torssell and Zeuthen for the reaction of aldehydes.[65] Although Coates had been seen to use different, harsher conditions for the reaction of cyclic ketones (Reaction scheme 6.3),[47] we saw no reason why the milder conditions could not be used.

The reaction was therefore carried out in dry dichloromethane at 25 °C, in the presence of sodium sulphate in order to prevent hydrolysis of the nitrone **281**. We followed the reaction by TLC for the first 8 hours, after which starting material **162** was still present so stirring was continued overnight. After 24 hours, the starting material **162** was barely visible by TLC, at which point, the reaction mixture was filtered, and concentrated. A ^{1}H NMR spectrum obtained of the crude reaction mixture showed there to be starting hydroxylamine **162** still present in the reaction mixture as a minor component, in an approximate 7:1 ratio (of **281**:**162**), along with a considerable amount of cyclohexanone **44** which was used in excess in the reaction. We found we were able to remove the cyclohexanone **44** by placing the concentrated reaction mixture under reduced pressure with the use of a high vacuum pump.

Attempts were made to remove the remaining hydroxylamine **162** contaminant by column chromatography. Half of the reaction mixture was placed on a silica column, the remainder was reserved, and eluted with 20% ethyl acetate in petroleum ether, increasing to 50%. Once the starting hydroxylamine **162** had been identified in the fractions collected, the product **281**, which had remained on the base line, was eluted using methanol. The ^{1}H NMR spectrum of the resulting product, however, now showed an approximate 1:1 ratio of nitrone **281** to starting material **162**, suggesting that the silica and/or methanol was responsible for hydrolysing the nitrone **281**.



Reaction Scheme 6.10: Reaction of nitrone 281 with benzoyl chloride 272.

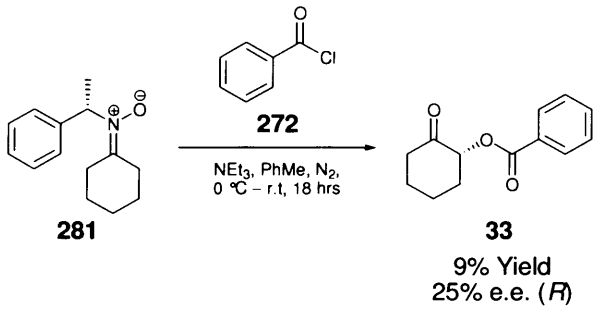
Further attempts at purification were abandoned and using the reserved portion of the nitrone **281**, we turned our attention to examining the second step of the reaction, Reaction scheme 6.10. This involved reaction of the nitrone **281** with benzoyl chloride **272**, which gave the product **33** in a 53% isolated yield. The reaction was carried out under basic conditions, in the presence of triethylamine, which ensured that the product isolated was entirely the result of the intended reaction. We were certain of this as although any free hydroxylamine **162** was able to react with benzoyl chloride **272** and form the hydroxylamine reagent **110**, this would then be unable to react with any cyclohexanone **44** that may be present, as basic reaction conditions would not promote iminium ion formation.

Once isolated, the product **33** was analysed by HPLC, which showed it to have an e.e. of 14% of the (*R*)-enantiomer. Repeat reactions confirmed this result. This was quite surprising, as all previous reactions carried out using an (*S*)-*N*-substituent had led to enrichment of the (*S*)-enantiomer of the product **33**.

In our previous studies, toluene has been shown to be the optimum solvent, significantly enhancing the level of asymmetric induction (Table 2.8, entry 6). We therefore also carried out this second step of the reaction (Reaction scheme 6.10) using toluene as the reaction medium. This gave a similar result of 9% e.e. of the (*R*)-enantiomer of the product **33** (12% yield), supporting the earlier result but showing no enhancement. The yield for this reaction was unfortunately very low, due to difficulties in isolation.

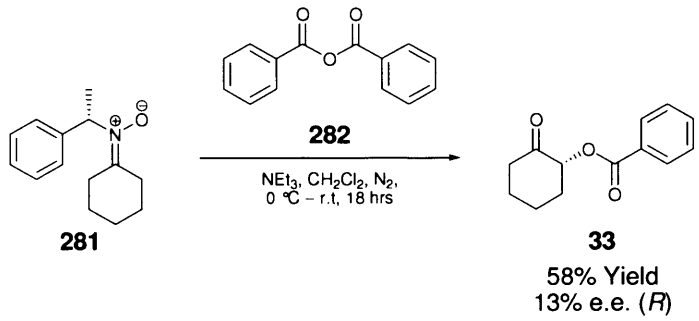
At this point a second batch of the nitrone **281** was made. By extending the time of the reaction slightly to 30 hours, we were able to increase the yield of **281** to 88%, and thus reduce the amount of starting material **162** contaminant present (^{1}H NMR

spectrum showed an approximate 11:1 ratio). The second step of the reaction was then repeated in toluene, using the purer nitrone **281**, which again resulted in a low yield (9%) of the product **33** due to difficulties in isolation, but showed an increased e.e. of 25% of the (*R*)-enantiomer, Reaction scheme 6.11.



Reaction scheme 6.11: Reaction of nitrone 281 with benzoyl chloride 272 in toluene.

Along with the effect of solvent, another variable observed in the past to have a significant affect on the reaction was the co-acid. In early studies it was shown that the presence of HCl had a negative effect on the level of asymmetric induction (Table 2.4, entry 1). In the second step of the nitrone reaction, HCl is formed as a by-product when using benzoyl chloride. This is removed by the triethylamine present, but in order to see if it was affecting the outcome in any way, the reaction was carried out using benzoic anhydride **282** instead of benzoyl chloride **272**, Reaction scheme 6.12. The by-product of this reaction is benzoic acid **137**. Instead, it was found that this change in acylating agent did not impart a change in the results (compared to those shown in Reaction scheme 6.10), giving the product **33** in a 58% yield and a 13% e.e of the (*R*)-enantiomer.

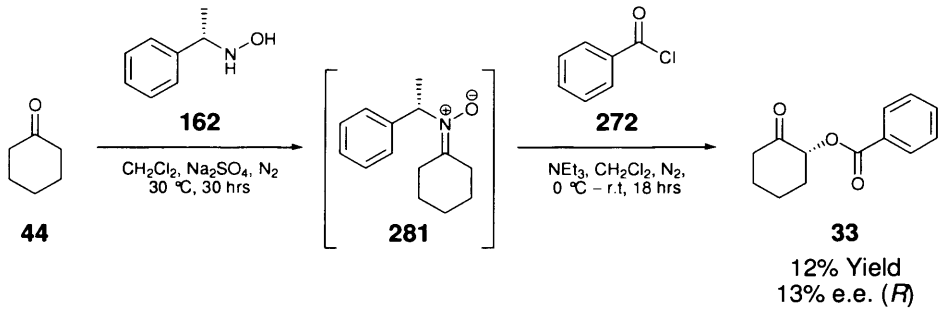


Reaction scheme 6.12: Reaction of nitrone 281 with benzoic anhydride 282.

The above reaction (Reaction scheme 6.12) was also carried out in DMSO, which in previous studies has consistently provided cleaner transformations and better yields.

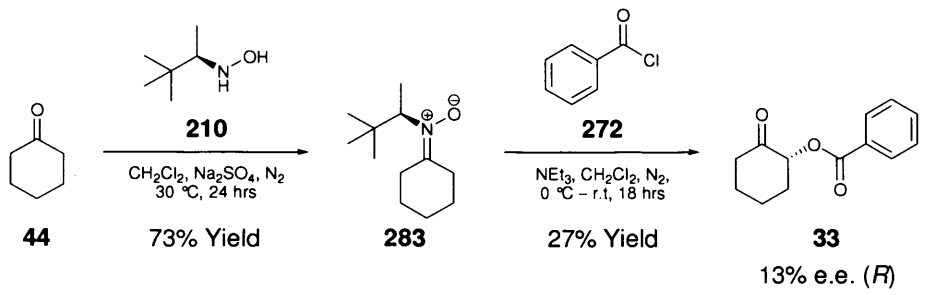
In this instance, however, the product **33** was obtained in roughly the same yield of 59%. Use of DMSO as the solvent had also been shown to result in the poorest levels of asymmetric induction. It was therefore not surprising that HPLC analysis revealed the product (**33**) of this reaction to be racemic. This again confirmed the importance of the effect of solvent in these transformations.

This alternative, two-step, nitrone method was subsequently simplified to a one-pot method, Reaction scheme 6.13. This was found to be quite straightforward, as both steps of the reaction could be carried out using dichloromethane as the solvent. In this case, instead of isolating the nitrone **281** after 30 hours, the temperature of the reaction was reduced to 0 °C and triethylamine and benzoyl chloride **272** were added to the reaction mixture. This was then left overnight, warming to room temperature, giving the product **33** in an overall 12% yield. HPLC analysis showed an e.e. of 13% of the (*R*)-enantiomer in the product **33** using this one-pot method, comparable to the e.e. obtained using the two-step method (Reaction scheme 6.10).



Reaction scheme 6.13: One-pot α-oxygenation of cyclohexanone 44 using nitrone method.

As increasing the steric bulk surrounding the nitrogen atom had proved to have the greatest effect on the level of asymmetric induction in earlier studies (Chapter 5.2), this nitrone method was also attempted using *N*-(*R*)-3,3-dimethyl-2-butyl hydroxylamine **210**. Using the original two-step method to ensure that there were no problems with nitrone formation, we began by reacting hydroxylamine **210** with cyclohexanone **44**, Reaction scheme 6.14.



Reaction scheme 6.14: Two-step nitrone method using alternative chiral hydroxylamine 210.

This was found to be very successful, giving the product **283** in a 73% isolated yield, with the ^{1}H NMR spectrum of the crude reaction mixture showing only the expected nitrone product **283**, with no trace of the starting hydroxylamine **210**. This was then reacted with benzoyl chloride **272**, in the presence of triethylamine, which afforded the α-functionalised cyclohexanone product **33** in a 27% yield and a 13% e.e. of the (*R*)-enantiomer.

We decided not to pursue this nitrone method any further at this point, due to time considerations and the fact that we had been unable to improve upon previous results in any significant way. Results to date had shown that we could obtain good yields for the first step of the reaction, nitrone formation; the second step of the reaction, however, frequently furnished us with low yields of the product **33**. This was not anticipated as it was thought that the problems concerning low yields lay with the first step of iminium ion formation.

HPLC analysis of the product (**33**) from these reactions also caused some confusion. When using nitrone **281**, results showed enrichment of the opposite enantiomer of the product **33** to that expected, compared to previous results obtained using an *N*-(*S*)-α-methylbenzyl substituent. When using nitrone **283**, however, we also observed enrichment of the *R*-enantiomer of the product **33**, but to a much lesser extent than that expected. These results do not appear to follow the same trends as the results obtained in previous studies using the traditional method (Reaction scheme 2.13), and have caused us to speculate that an alternative transition state or mechanism might be in operation under these basic reaction conditions. Further study of this reaction would be necessary in order to reach a definitive conclusion.

6.4. Conclusion.

We set about examining an alternative method for the α-oxygenation of carbonyl compounds, employing the use of nitrones. This was achieved through development of a two-step method, which was subsequently condensed to a one-pot method, involving formation of a nitrone species, which could undergo *O*-acylation followed by rearrangement to give the desired α-benzoyloxy cyclohexanone product **33**.

Using this two-step method, nitrones **281** and **283** were formed in good yields of 88% and 73% respectively, and could be isolated and stored in a freezer for up to a month without showing signs of decomposition. The subsequent *O*-acylation and rearrangement steps, however, did not provide the product **33** in the high yields anticipated.

The induction of asymmetry in the product **33** of these transformations did not prove trivial. Instead of mirroring the results obtained in previous studies, HPLC analysis revealed a comparable enrichment of the (*R*)-enantiomer of the product **33** from both (*S*)- and (*R*)- chiral nitrones (**281** and **283**). This could suggest that an alternative transition state, or even mechanism, may be in operation under these basic reaction conditions, compared to the established transformation (Reaction scheme 2.13), which is carried out under acidic conditions. Further investigation is needed to provide insight into these results.

The effect of solvent on the reaction of nitrone **281** was examined briefly, whereby the same trends were observed to be in operation as seen in earlier studies. Use of toluene as a solvent provided an increase in the e.e. of **33**, up to 25% of the (*R*)-enantiomer; DMSO on the other hand gave a racemic product **33**. Variation of the acylating agent to benzoic anhydride **282**, in order to avoid the formation of HCl, was also examined, but afforded no change in the results.

Development of a one-pot method for this two-step transformation was established. This was found to give the product **33** in a very low yield of 12%, which was attributed to the second step of the reaction following previous results. Analysis of the product **33** of this one-pot method revealed an e.e. of 13% of the (*R*)-enantiomer,

which was the same as that seen in the two-step reaction using dichloromethane as the solvent.

Although brief, this investigation certainly revealed ample opportunity for further development of this transformation as a method for the asymmetric α-functionalisation of carbonyl compounds.

Chapter 7.

Efforts Towards the α-Oxytosylation, Oxycarbonoylation and Oxycarbamoylation of Carbonyl Compounds.

7.1. Introduction.

Following the development of a novel one-pot α-oxyacylation reaction for carbonyl compounds within the group,[49] it was thought that analogous reagents could be developed for the transfer of various functional groups α- to a carbonyl group. To this end, reagents **86**,[53] **84·HCl**[51] and **85·HCl**[52] (Figure 7.1) were established for the synthesis of several synthetically useful functionalities, namely α-oxytosyl, α-oxycarbonoyl and α-oxycarbamoyl carbonyl compounds respectively (see Chapter 1.6 also).

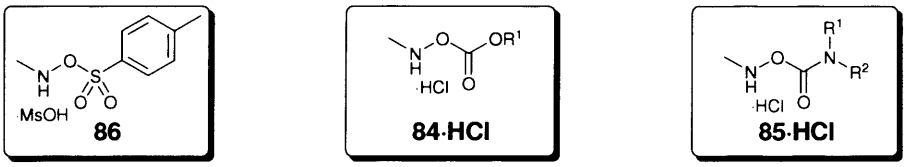
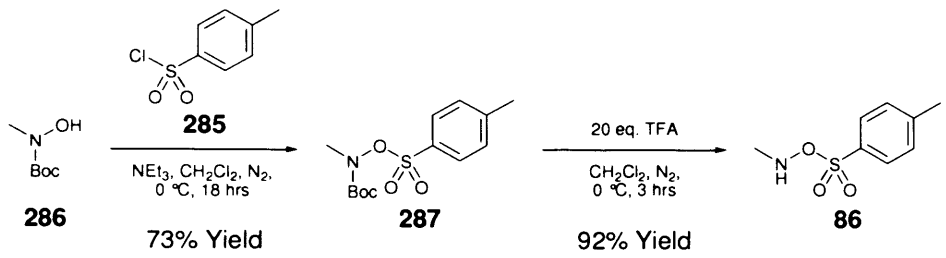


Figure 7.1: General reagents for the α-oxytosylation 86,[53] oxycarbonoylation 84·HCl[51] and oxycarbamoylation 85·HCl[52] of carbonyl compounds.

The main focus of our efforts to this point had been the development of an asymmetric variant of the α-oxyacylation reaction. This was achieved with varying degrees of success, dependent on the substrate examined, so at this point we decided to turn our attention to these alternative transformations, namely the α-oxytosylation, α-oxycarbonoylation, and α-oxycarbamoylation reactions. Each of these reactions was believed to go through the same pericyclic rearrangement process as the α-oxyacylation, so it was hoped that these transformations could in turn be rendered asymmetric.

7.2. Efforts Towards the Asymmetric α-Oxytosylation of Carbonyl Compounds.

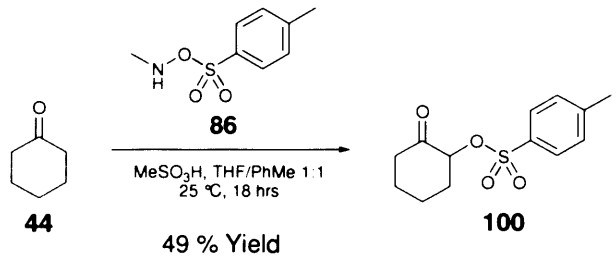
The first of the transformations examined was the α-oxytosylation reaction. We began by synthesising the achiral *N*-methyl-*O*-tosyl hydroxylamine reagent **86**, which was needed in order to synthesise racemic α-functionalised products to be used as references.



Reaction scheme 7.1: Synthesis of achiral tosyl reagent 86.[53]

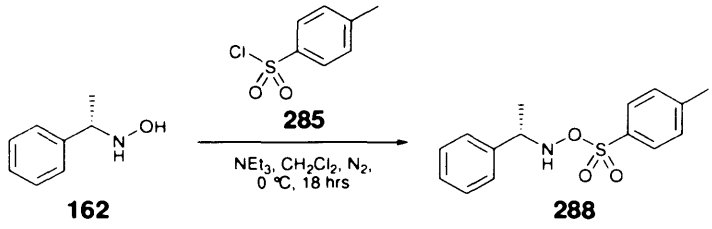
This was done by reacting Boc-protected *N*-methyl hydroxylamine **286** with tosyl chloride **285** in the presence of triethylamine, which gave us the Boc-protected form of the reagent **287**, Reaction scheme 7.1.[53] It was then necessary to remove the Boc group, which was carried out using 20 eq. of TFA. During the initial development of the transformation, many conditions were examined for the removal of the Boc-group, including more common conditions such as 4M HCl/dioxane in varying amounts, and 1–10 eq. of TFA. None of these proved to be successful however, resulting in partial removal of the protecting group only, or decomposition of the product. By looking in the literature, however, we found a reference for the use of 20 eq. of TFA, which was found to be successful in removing a Boc-group.[69] This was tried and found to be extremely successful, giving the product **86** in a 92% yield without the need for purification.

Having synthesised the achiral tosyl reagent **86**, we were then able to use this to carry out the α-oxytosylation of cyclohexanone **44**, Reaction scheme 7.2. Having had the most success in the past with cyclohexanone **44** as a substrate it was logical to continue with its use in this study. This reaction (Reaction scheme 7.2) was carried out using previously established conditions of a THF/Toluene solvent (in a 1:1 ratio), with methane sulphonic acid as the co-acid.[53] This afforded the desired product **100** in a reasonable yield of 49% after purification.



Reaction scheme 7.2: Synthesis of racemic α-oxytosyl cyclohexanone 100.

After establishing conditions for enantiomer separation, we set about synthesising a chiral analogue of the reagent **86**, using *N*-(*S*)-α-methyl benzyl hydroxylamine **162**, Reaction scheme 7.3. Previous experiments using this chiral hydroxylamine **162** had shown reaction only at the oxygen atom, suggesting that the steric bulk surrounding the nitrogen atom was sufficient to prevent the nitrogen from reacting. We therefore felt it unnecessary to use a protecting group strategy.

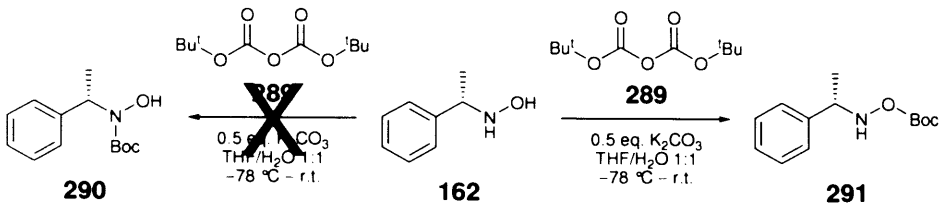


Reaction scheme 7.3: First attempt at synthesising chiral tosyl reagent 288.

Analysis of the ^{1}H NMR spectrum of the crude reaction mixture for this reaction (Reaction scheme 7.3), showed starting materials **162** and **285** were still present after 18 hours, along with numerous by-products. We were able to identify that a small amount of product **288** was also present, which we were able to isolate by column chromatography in a 4% yield. This was very disappointing; however, we weren't worried about the yield at this point. Instead we simply wanted to obtain enough of the chiral reagent **288** in order to carry out the next step and to determine if we could induce asymmetry in the product **100**.

One consideration was the quality of the tosyl chloride **285** used. Therefore, to ensure this wasn't affecting the yield, a new bottle was sourced. Unfortunately, the result was the same, giving the product in a very low yield which we were unable to isolate.

It was thought at this point that use of a protecting group on the nitrogen atom of the hydroxylamine **162** could perhaps be beneficial, if only by limiting the number of possible by-products. Our chiral hydroxylamine **162** was therefore reacted with Boc-anhydride **289**, under standard conditions used previously on *N*-methyl hydroxylamine hydrochloride **61** (Reaction scheme 7.4),[49] which was unsuccessful. Instead, reaction was observed to proceed solely at the oxygen atom of **162**, giving the *O*-carbonate product **291** in a 24% isolated yield.



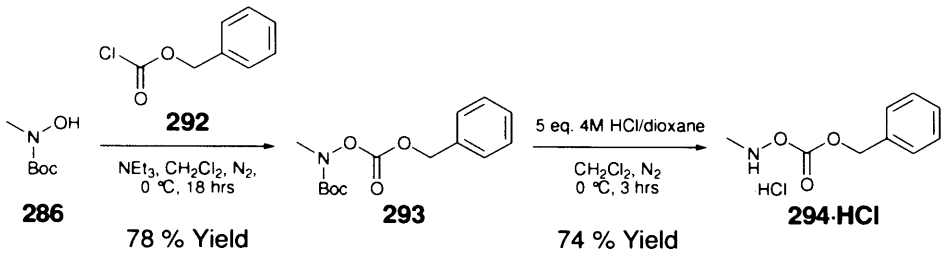
Reaction scheme 7.4: Attempted Boc-protection of chiral hydroxylamine 162.

In a further attempt to protect the nitrogen, we reacted reagent **110** with Boc-anhydride **289**, in the same manner as that described above (Reaction scheme 7.4). It was hoped that this would result in the nitrogen atom being protected, as reaction would be unable to take place at the oxygen atom due to the presence of the *O*-benzoyl group. If the reaction was then found to be successful, we could then remove this *O*-acyl group, in order to proceed with synthesising chiral tosyl reagent **288**. Unfortunately, this reaction was also found to be unsuccessful, with the ^{1}H NMR spectrum of the crude reaction mixture showing only starting materials **110** and **289**. It was thought that the steric bulk surrounding the nitrogen atom prevented the reaction from taking place.

Due to time considerations, we did not pursue this aspect of the work any further. Instead, we moved on to looking at the next transformation, which was the α-oxycarbonoylation reaction. Following the results from the α-oxytosylation efforts, however, we did not have high expectations.

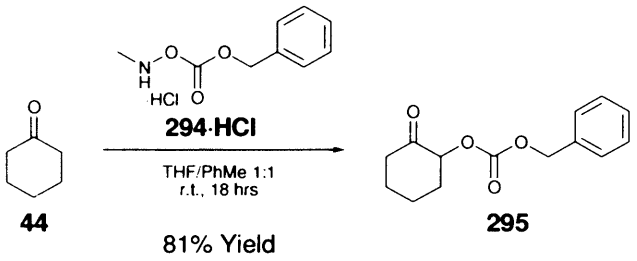
7.3. The Asymmetric α-Oxycarbonoylation of Carbonyl Compounds.

Starting again with Boc-protected *N*-methyl hydroxylamine **286**, we reacted it with benzyl chloroformate **292** using established reaction conditions, and were able to obtain the Boc-protected carbonate reagent **293** in a reasonable yield of 78%, Reaction scheme 7.5.[51] Once obtained, the Boc-group was then removed, this time using the regular conditions of 4M HCl in dioxane, which worked well and gave the product as the HCl salt **294·HCl** in a 74% yield.



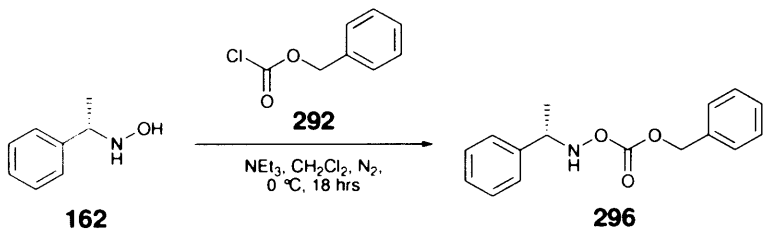
Reaction scheme 7.5: Synthesis of achiral carbonate reagent 294·HCl.[51]

This was reacted with cyclohexanone **44**, again using established conditions, this time consisting of a HCl co-acid, and THF/toluene (1:1) as the solvent, Reaction scheme 7.6. Purification using column chromatography afforded the desired α-carbonate product **295** in an 81% yield. The enantiomers of this achiral α-carbonate product were subsequently separated by HPLC.



Reaction scheme 7.6: Synthesis of racemic α-carbonate product 295.[51]

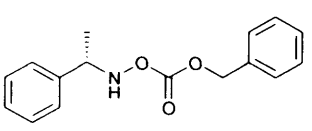
Following this, we began our efforts to synthesise the analogous chiral carbonate reagent **296**, Reaction scheme 7.7. Using the same approach as before, we attempted to carry out the reaction using the unprotected *N*-(*S*)-α-methyl benzyl hydroxylamine **162**, as previous efforts to protect the nitrogen had failed (Reaction scheme 7.4). This was reacted with benzyl chloroformate **292** under the conditions used previously to synthesise the achiral reagent **293** (Reaction scheme 7.5).



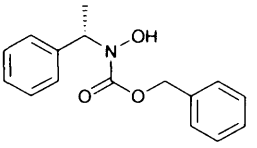
Reaction scheme 7.7: Attempt at formation of chiral carbonate reagent 296.

When analyzing the ^{1}H NMR spectrum of the crude reaction mixture, we were able to determine that the reaction had gone to completion, however; there appeared to be

two main products resulting from the reaction, both giving very similar peaks in the NMR spectrum. These products were isolated and characterised, and were determined to be compounds **296** and **297** (Figure 7.2), in yields of 48% and 35% respectively. This was encouraging as although the selectivity was not great, the reaction had worked better than hoped following work on the oxytosylate system (Chapter 7.2), and as such we had enough compound (**296**) to investigate the possibility of inducing asymmetry in the product **295**.



296

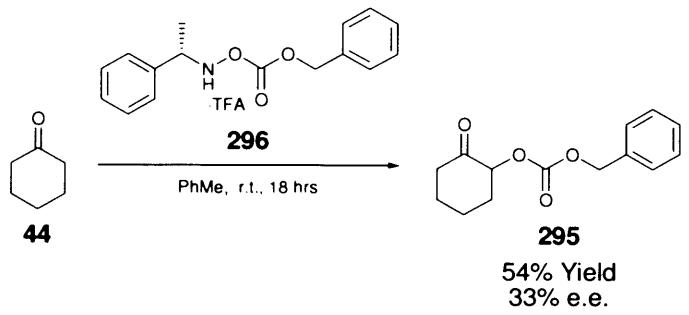


297

Figure 7.2: Products resulting from reaction of *N*-(*S*)-α-methyl benzyl hydroxylamine 162 and benzyl chloroformate 292.

Owing to the structural similarity of these compounds **296** and **297**, it was difficult to distinguish between them without using destructive chemical means. The only differences noted during characterisation, appeared to be the chemical shift of two peaks in the ^{1}H NMR spectrum, for the proton and methyl group α- to the nitrogen. As a crude means to distinguish between the compounds **296** and **297**, both structures were fed into ChemDraw, and the predicted NMR spectra, both ^{1}H and ^{13}C, were obtained for each, appendices 8 and 9. When compared to the actual spectra, the predictions were found to be remarkably accurate and we were able to confidently assign the structure of each product. IR spectroscopy was also found to be very useful in distinguishing between the structures, with notable differences in the carbonyl stretching frequency being observed for compounds **296** (1747 cm^{-1}) and **297** (1698 cm^{-1}).

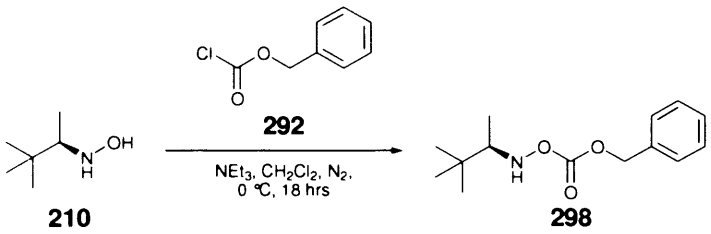
The compound determined to be the chiral carbonate reagent **296** was then taken forward to the next step, which was reaction with cyclohexanone **44**, Reaction scheme 7.8. This was carried out using the standard conditions of the optimised α-oxyacylation reaction, of a TFA co-acid, with the reaction being carried out in toluene at room temperature overnight, and gave the desired α-functionalised product **295** in a 54% yield. The fact that this reaction was successful was solid evidence supporting the previous assignment of structures for compounds **296** and **297**.



Reaction scheme 7.8: Reaction of cyclohexanone 44 with chiral (*S*)-α-methyl benzyl carbonate reagent 296.

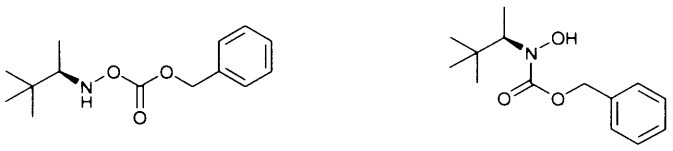
Once obtained, the e.e. of the product **295** from this reaction, Reaction scheme 7.8, was measured and found to be 33%. This is comparable to the level of asymmetric induction observed in the α-oxybenzoylation reaction of cyclohexanone **44**, using *N*-(*S*)-α-methyl benzyl-*O*-benzoyl hydroxylamine **110**, which gave an e.e. of 37% (Reaction scheme 2.13).

In order to find further evidence to suggest that the same mechanism was in operation in the α-oxycarbonoylation reaction as in the α-oxyacylation reaction, and also to improve the level of asymmetric induction in the product **295**, we set about the synthesis of a second chiral carbonate reagent, based on (*R*)-3,3-dimethyl-2-butyl hydroxylamine **210**, Reaction scheme 7.9. Use of this *N*-substituent has been shown to impart the greatest level of asymmetry in all cases to date.



Reaction scheme 7.9: Formation of second chiral carbonate reagent 298.

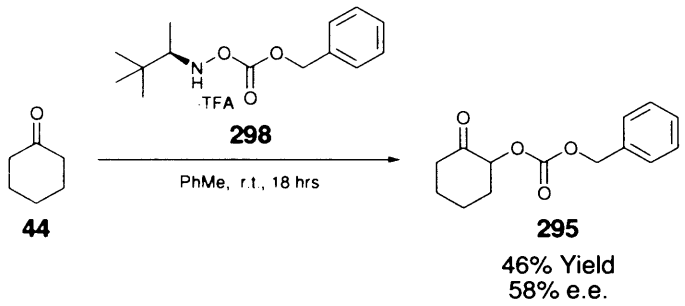
As with the synthesis of the chiral carbonate reagent **296**, we observed reaction of both the nitrogen and oxygen atoms of the hydroxylamine **210** with benzyl chloroformate **292**, giving rise to both compound **298** and **299**, in yields of 47 and 42% respectively, Figure 7.3.



298 299

Figure 7.3: Products from reaction of chiral ^{t}butyl hydroxylamine 210 with benzyl chloroformate 292.

The structures of these compounds (**298** and **299**) were once again assigned after comparative analysis between the NMR spectra obtained for each compound and the predicted NMR spectra generated using ChemDraw, appendices 10 and 11. Owing to the apparent accuracy of the predicted NMR spectra we were once again confident in our assignment of structure, and continued on with reaction of the new chiral carbonate reagent **298** with cyclohexanone **44**, Reaction scheme 7.10.



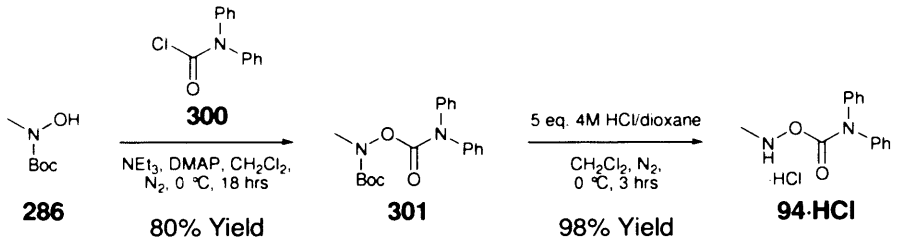
Reaction scheme 7.10: Reaction of cyclohexanone 44 with chiral ^{t}butyl carbonate reagent 298.

Following isolation, the product **295** from this reaction, Reaction scheme 7.10, was analysed by HPLC and found to have an increased e.e. of 58%, Appendix 12. The level of asymmetric induction was noted to be lower than that observed in the α-oxybenzoylation reaction, which gave a 77% e.e. in the product **33** under the same reaction conditions (Table 5.1[b], entry 4). As with each of the transformations described within this thesis, variations in the level of asymmetric induction in a particular reaction was thought to be the result of changes in the relative activation energy barriers leading to each of the enantiomers of a particular product. In this instance, it was believed that the relative activation energy barriers were closer in energy level, which unfortunately reduces the ability of the reaction (Reaction scheme 7.10) to favour one particular enantiomer of the product **295**.

Interestingly, it was observed that in using the (*R*)-enantiomer of the carbonate reagent **298**, we obtained an excess of the opposite enantiomer of the product **295** compared to when using the (*S*)-carbonate reagent **296**. This was the same trend as that observed previously in the α-oxyacylation reactions and is further evidence to suggest that the mechanism of the α-oxycarbonoylation transformation is the same as that of the α-oxyacylation transformation.

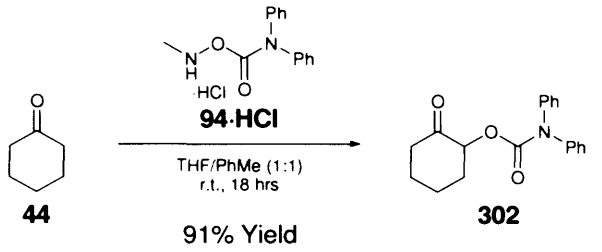
7.4. The Asymmetric α-Oxycarbamoylation of Carbonyl Compounds.

The final reaction examined in this series was the α-oxycarbamoylation reaction. As with the previous transformations, synthesis of the achiral *N*-methyl carbamate reagent **94·HCl** proved to be straightforward, using the pre-existing procedure of reacting *N*-methyl-*N*-Boc hydroxylamine **286** with diphenyl carbamoyl chloride **300**, Reaction scheme 7.11. The reaction conditions differed slightly in this reaction than with previous transformations discussed, in that a stoichiometric amount of DMAP, a nucleophilic catalyst, was used in order to activate the carbamoyl chloride **300**. This reaction generated the Boc-protected form of the reagent **301** which, as with the achiral carbonate reagent **293**, was deprotected quite easily using 5 equivalents of 4M HCl in dioxane. This generated the desired achiral reagent as the hydrochloride salt **94·HCl** in a 98% yield.



Reaction scheme 7.11: Synthesis of achiral carbamate reagent 94·HCl.

We then proceeded to react this achiral carbamate reagent **94·HCl** with our substrate of choice, cyclohexanone **44**, which underwent the anticipated α-oxycarbamoylation transformation, generating the racemic α-functionalised product **302** in an excellent 91% yield, Reaction scheme 7.12. The enantiomers of this product were subsequently separated successfully using HPLC.

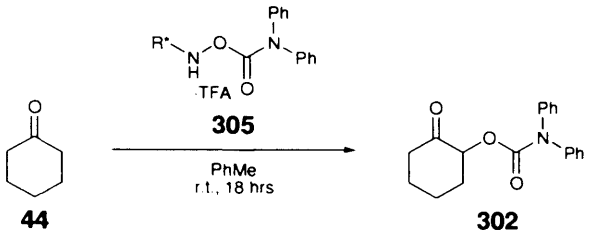


Reaction scheme 7.12: Synthesis of racemic α-oxydiphenylcarbamoyl cyclohexanone 302.

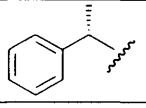
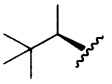
Using the same reaction conditions as with the synthesis of the achiral carbamate reagent **301** (Reaction scheme 7.11), chiral reagents **303** and **304** were synthesised from the respective chiral hydroxylamines **162** and **210**, Figure 7.4. Unlike in the synthesis of the chiral carbonate reagents **296** and **298**, in this instance the desired products **303** and **304** were the only compounds isolated from the reactions, in 77% and 90% yields respectively, with no sign of the nitrogen reacting in either case to give the unwanted *N*-carbamoyl compounds. This would suggest that when carrying out a reaction with these chiral hydroxylamines **162** and **210**, it is the steric bulk of both the hydroxylamine and the reacting acid chloride that determines the selectivity in the reaction.

Figure 7.4: Chiral variants 303 and 304 of the carbamate reagent 94·HCl.

Our new chiral carbamate reagents **303** and **304** were then in turn reacted with cyclohexanone **44**, under the optimised α-oxyacylation conditions. Both reactions resulted in the desired product **302** in reasonable yields and, as expected, the different reagents induced different (and opposite) levels of asymmetry as can be seen in Table 7.1.



44 302

Entry	R*	Yield (%)	e.e. (%)
1		51	39 ('*S*')[a]
2		44	63 ('*R*')[a]

[a]Absolute stereochemistry assignment based on previous results and is unconfirmed.

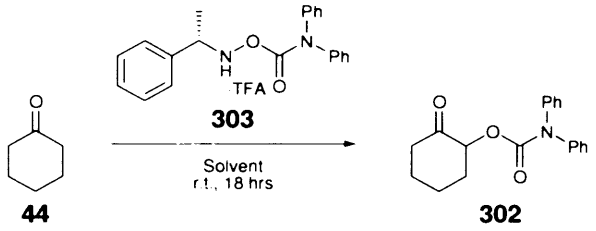
Table 7.1: Results from chiral α-oxycarbamoylation transformation.

In the first case, entry 1, an e.e. of 39% was found in the product **302**, which is again comparable with the analogous *O*-benzoyl reagent **110** (Reaction scheme 2.13). On varying the structure of the reagent to the more bulky chiral carbamate reagent **304**, entry 2, an increase in the e.e. to 63% was obtained, Appendix 13, which is not quite as high as in the analogous α-oxybenzoylation reaction (77% e.e., Table 5.1[b], entry 4), but nevertheless shows the same trend. A similar inversion of stereochemistry was also observed when using a reagent with (*S*)- or (*R*)-stereochemistry.

We were interested at this point in whether these transformations, particularly the α-oxycarbonoylation and oxycarbamoylation reactions which had now been rendered asymmetric, were fully optimised considering we were using conditions that were optimised for another reaction system. We were also interested in whether these transformations were as dependent on the variables in the reaction, as was observed in the α-oxyacylation reactions.

In order to answer these questions, we began by looking at the α-oxycarbamoylation reaction, as we had plenty of the chiral carbamate reagents **303** and **304** already prepared. As most of the optimisation work done in the past had been with *N*-(*S*)-α-methylbenzyl-based reagents, we decided to carry out our investigations using reagent **303**.

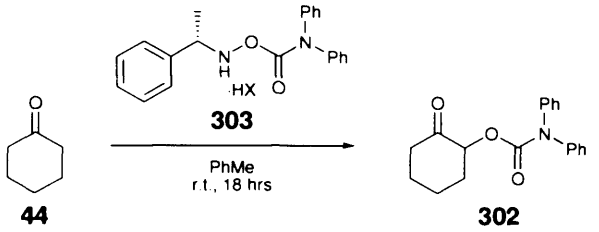
The first variable examined was the solvent. Several solvents were chosen, with different polarity indexes, and the effect of each of these on the reaction was examined. As can be seen in the results shown in Table 7.2, the choice of solvent does affect the level of asymmetric induction in the product **302**, as found in previous studies. As with the α-oxybenzoylation studies, DMSO gave the cleanest reaction and best yield of 77%, entry 1, however, it also gave the poorest e.e. of 24%. The results obtained from the use of acetone as a solvent were quite surprising, entry 2. This was found to give comparable results to toluene in terms of both yield and e.e., unlike in previous screens where it did not promote the induction of asymmetry at all (Table 2.8, entry 2).



Entry	Solvent	Polarity Index	Yield (%)	e.e. (%)
1	DMSO	7.2	77	24
2	Acetone	5.1	49	40
3	Toluene	2.4	51	39
4	Hexane	0.1	54	27

Table 7.2: Results obtained from variation of solvent in α-oxycarbamoylation reaction.

Following this, the effect of the co-acid was examined, whereby several co-acids were selected with different pKa's. Separate reactions were carried out with a stoichiometric amount of each of the chosen co-acids in conjunction with the chiral reagent **303**. Reactions were carried out in toluene, which we believe remains the optimum solvent. The results from this set of experiments are shown in Table 7.3.

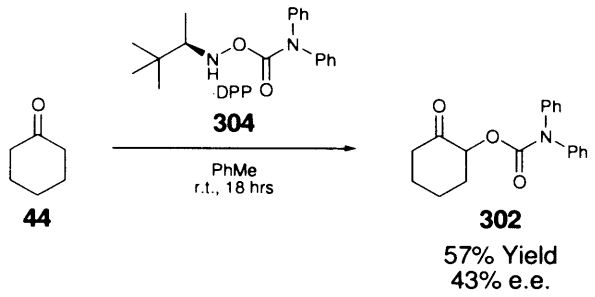


Entry	Co-acid	pKa	Yield (%)	e.e. (%)
1	HCl	-8.5	82	21
2	$MeSO_3H$	-2.6	11	22
3	TFA	-0.25	51	39
4	DPP	2.0	55	57

Table 7.3: Results obtained from variation of co-acid in α-oxycarbamoylation reaction.

On the whole, the results backed up previous findings, showing that use of a very strong co-acid, like HCl, whilst beneficial to the yield was detrimental to the e.e. (Table 7.3, entry 1). Use of a less acidic co-acid, like TFA, was shown to provide a more optimal balance between yield and level of asymmetric induction (entry 3). We did however, get an unexpected result in this series, which arose from the use of a diphenyl phosphate (DPP) as a co-acid (entry 4). In previous studies, use of such a weak acid moved away from the optimum results, giving a comparative level of asymmetric induction but a poor yield for the transformation (Table 5.3, entry 5). In this case, we observed a significant increase in the e.e. of the product **302** resulting from the use of DPP, whilst at the same time maintaining a good yield.

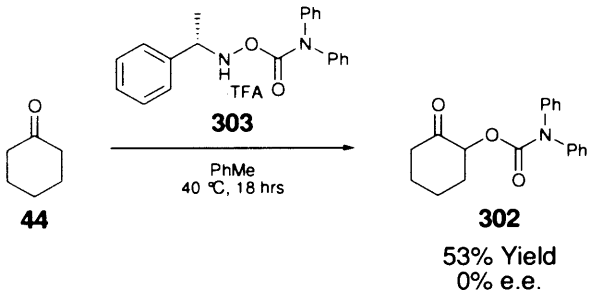
Encouraged by this result, we thought it might be possible to obtain a similar increase in e.e. for the reaction between the more bulky chiral carbamate reagent **304** and cyclohexanone **44**, by using DPP as the co-acid. If found to be the case, this would constitute the best result obtained to date, for the asymmetric α-functionalisation of carbonyl compounds using our novel method.



Reaction scheme 7.13: Use of DPP co-acid with the more bulky (*R*)-carbamate reagent 304.

Sadly, the results from this reaction, Reaction scheme 7.13, did not prove to be as exciting, giving an increased yield of 57%, but a much lower e.e. of 43% (compared to the result obtained for TFA of 63% e.e., Table 7.1, entry 2). The results from this reaction allowed us to conclude that TFA remained the optimal co-acid for these types of transformations, with the interesting DPP result (Table 7.3, entry 4) simply being an anomaly that at present we have no explanation for.

A final variable looked at in this series was the effect of temperature. Results to date had shown that the level of asymmetric induction was strongly dependent on the temperature, with an increase in temperature above room temperature, causing a decrease in the e.e. of the product. To see if a similar effect was in operation in the α-oxycarbamoylation transformation, a single reaction was carried out between our parent carbamate reagent **303** and cyclohexanone **44**, at a higher temperature of 40 °C, Reaction scheme 7.14. All other variables were maintained as previously established.



Reaction scheme 7.14: Examination of the effect of temperature on the α-oxycarbamoylation reaction.

As anticipated, an increase in the temperature caused a significant decrease in the e.e., resulting in a racemic product **302**, whilst having a slightly favourable effect on the yield. This fits with previous findings and concluded our investigations into the effects of variables on the α-oxycarbamoylation transformation. Overall, our findings concur with the results obtained from looking at variables in the α-oxyacylation reaction and as such, support the belief that this transformation goes through the same transition state as the α-oxyacylation. We have also assumed that the α-oxycarbonoylation transformation would act comparably, and therefore feel it unnecessary to re-examine the variables in this reaction as well.

7.5 Conclusion.

We successfully extended the asymmetric protocol previously developed for the α-oxyacylation transformation, to the synthesis of α-oxycarbonoyl and oxycarbamoyl carbonyl compounds. Use of carbonate and carbamate reagents **298** and **304**, derived from (*R*)-3,3-dimethyl-2-butyl hydroxylamine **210**, have revealed e.e.'s of up to 58% for the α-oxycarbonoylation and 63% for the α-oxycarbamoylation of cyclohexanone **44**.

Results obtained for these transformations suggest that they proceed through a transition state similar to that of the α-oxyacylation reaction. Similar trends in results were observed in terms of both degree and sense of asymmetric induction, as was seen with analogous reagents during the α-oxyacylation studies. Optimisation of variables in the α-oxycarbamoylation also gave the same results for optimum solvent, co-acid and temperature as was seen previously, providing further evidence for a similar rearrangement process.

It is apparent from the investigations conducted that although some success was achieved during these studies, the development of a general hydroxylamine reagent of broad substrate scope under standard reaction conditions would not be possible; however, several important trends provide great insight into optimal reaction conditions for each specific transformation. Altering the nature of the reagent on the whole provided similar reactivity trends and opened several new areas for further investigation.

Chapter 8.

A Novel Method for the Oxidation of Primary Amines to Ketones.

8.1. Introduction.

The carbonyl group, with its capacity for manipulation in a chemo-, diastereo-, and enantioselective manner, is one of the most fundamental functional groups in organic synthesis.[70] Owing to the importance of this functionality, new methods for its preparation from readily available precursors, are of great use synthetically and are constantly being sought.

Amines represent another extremely useful class of compound and have long been used as building blocks in organic synthesis as a result of their availability and versatility. They are also regarded as fundamental synthetic intermediates that are readily available. The oxidation of amines is a subject to which much time and research has been devoted over the years, with the result being an array of methods for the oxidation of amines to a wide variety of different functional groups including imines, amides, nitriles, aldehydes and ketones. Of these, we have developed an interest in the latter transformations: The generation of carbonyl compounds from amines.

8.1.1. Metal-Based Methods.

Early methods developed to carry out this transformation, saw the use of stoichiometric amounts of transition metal reagents including nickel-,[71] mercury-,[72] lead-,[73] manganese-,[74] iron-,[75] and zinc-derived[76] species. More recently, methods using sub-stoichiometric amounts of metals have been described, using palladium,[77] as well as tungsten,[78] rhodium,[79] ruthenium,[80] and manganese[81] salts.

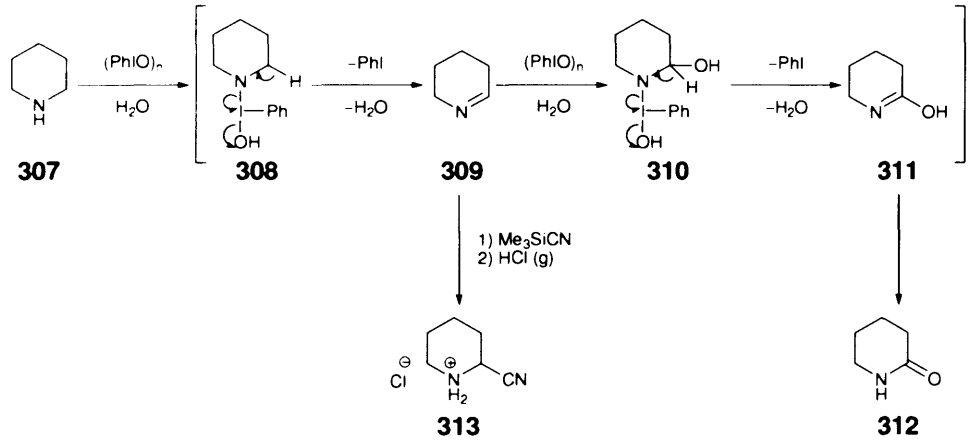
8.1.2. Metal-Free Methods.

Several stoichiometric methods that avoid the use of transition metals have also been developed using iodosobenzene,[82] 2-iodoxybenzoic acid (IBX),[83] sulphonyl peroxides,[84] and benzoquinones.[85] These methods provide important alternatives for carrying out the overall oxidation of primary and secondary amines to carbonyl compounds, with varied levels of scope and limitations in substrate tolerance and reaction conditions. Each of these methods will be examined in more detail.

8.1.2.1. Use of Iodosobenzene.

In 1988, as an extension of their work on the oxidative decarboxylation of cyclic amino acids,[86] Moriarty *et al.* reported the oxidation of amines using iodosobenzene.[82] It was observed that under the reaction conditions, primary aliphatic amines were converted to the corresponding nitriles, whilst primary cycloalkylamines gave the corresponding ketones and cyclic amines gave lactams.

A probable mechanism for the α-oxidation of cyclic amines to lactams was proposed, involving the formation of an initial nitrogen-iodine type intermediate **308**, from the cyclic amine **307**, Reaction scheme 8.1. The nitrogen-iodine bond of this intermediate **308** was then thought to dissociate, giving an imine **309** with the loss of iodobenzene and water. The imine **309** then reacts with a second molecule of iodosobenzene and water, giving intermediate **310**, which again loses iodobenzene by reductive elimination, forming **311**. This then tautomerises, giving the observed lactam product **312**. As evidence for their proposed mechanism they were able to trap the imine intermediate **309** using trimethylsilyl cyanide, isolating the α-aminonitrile product as the hydrochloride salt **313**.



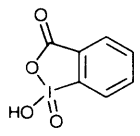
Reaction scheme 8.1: Conversion of cyclic amines to lactams using iodosobenzene.

This oxidation method has been shown to work on a variety of alkyl amines; however, it would seem that in order to generate a carbonyl-containing product, the reaction is limited to cyclic amines. Reactions are generally carried out under ambient, (though anhydrous) conditions, making this a fairly practical method,

though the time and temperature appear to be substrate-dependent, requiring optimisation in each case. There is also no indication as to the scope of the reaction for substituted cyclic amines and whether different functional groups would affect the reaction. Isolated yields on the whole were only average, ranging from 45–58% leaving definite room for improvement.

8.1.2.2. Use of *o*-Iodoxybenzoic Acid (IBX).

o-Iodoxybenzoic acid (IBX) **314**, Figure 8.1, is the precursor to the renowned oxidant Dess-Martin periodinane (DMP), and is a highly versatile hypervalent iodine(V) reagent. In work carried out by Nicolaou *et al* in 2004, it was found that IBX **314** can be used, amongst other things, to mediate the oxidation of amines *via* dehydrogenation.[83]



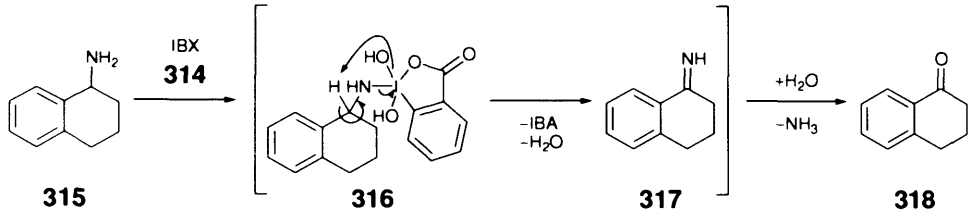
314

Figure 8.1: Structure of IBX

Through the development of IBX-based procedures, it was found that many useful synthetic intermediates are readily accessible from primary and secondary amines, under relatively mild reaction conditions, including imines, oximes and ketones. The focus of their efforts was the synthesis of imines from primary and secondary amines, which in the latter case was achieved readily. The products were obtained in good to excellent yields, often without the need for purification, and the transformations were tolerant of a wide variety of functional groups.

In the case of primary amines, the isolation of pure imine proved to be difficult, with subsequent hydrolysis proceeding readily to give the corresponding ketones. The proposed mechanism for this reaction involves reaction of the amine **315** with IBX **314** to form the iodine-intermediate **316**, Reaction scheme 8.2. This then undergoes dehydrogenation to give an imine **317**, with the loss of *o*-iodosobenzoic acid (IBA) as a by-product, along with a molecule of water. Hydrolysis of the intermediate imine **317** gives the ketone product **318**. This mechanism is believed to be the most

likely, however, a single electron transfer (SET) mechanism for the breakdown of the iodine intermediate **316** could not be ruled out.



Reaction scheme 8.2: IBX-mediated formation of ketone 318 from primary amine 315.

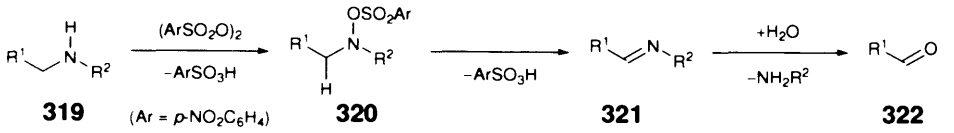
This IBX method for the oxidation of primary amines to ketones was shown to work well, giving the products in good to excellent yields of 79–99%. Although only a few examples were provided, the reaction is anticipated to be tolerant of a range of functional groups as was shown to be the case with secondary amines. There do appear to be a few limitations with this method. Firstly, it seems only to be applicable to benzylic amines. Another drawback is that the transformation is limited to the synthesis of ketones, with problems arising in the attempted synthesis of aldehydes. When a second α-amino hydrogen atom is available in the starting amine, the intermediate imine undergoes a second dehydrogenation forming a nitrile as the major product.

8.1.2.3. Use of Sulphonyl Peroxides.

The use of sulphonyl peroxides for the oxidation of amines was first reported by Hoffman in 1976 and constituted the first report of sulphonyl peroxides reacting with compounds other than π-electron donors.[84] From the work undertaken it was found that *p*-nitrobenzenesulphonyl peroxide (*p*-NBSP) could be used to oxidise both primary and secondary amines to the corresponding imines. The oxidative deamination was completed by hydrolysis, leading to the corresponding carbonyl compound, whereby it was observed that this method is applicable to the synthesis of both aldehydes and ketones.

The oxidation most likely proceeds as shown below in Reaction scheme 8.3, whereby initial attack of the amine **319** on the peroxide bond of the *p*-NBSP gives the *O*-sulphonate hydroxylamine adduct **320**. This then loses

p-nitrobenzenesulphonic acid by elimination to give the imine **321**, hydrolysis of which gives the corresponding carbonyl compound **322**.



Reaction scheme 8.3: Use of sulphonyl peroxides for the oxidation of amines.

Since 2 equivalents of *p*-nitrobenzenesulphonic acid are produced during the oxidation reaction, it was found that at least 3 equivalents of amine are needed, making the peroxide the limiting factor. This is due to protonation of the amine by the sulphonic acid by-product, which renders it non-nucleophilic towards the peroxide. Addition of an excess of a heterogeneous base (powdered KOH) to remove the sulphonic acid formed in the reaction allowed for the use of just 1 equivalent of amine. However, this significantly increased reaction times and led to overall lower yields of the carbonyl product due to partial decomposition of the imine intermediate.

The yields for these transformations ranged from 37–96%, depending on the amine starting material, with higher yields generally obtained from benzylic amines. In the case of primary amines, the yield of the carbonyl product was increased by using 4 equivalents of amine, which undergoes transamination, to give more stable *N*-substituted imines. The question of functional group tolerance was not addressed in this study.

The conditions used for these oxidation reactions are not as mild as in previous methods discussed and require a temperature of −78 °C and an inert atmosphere for the initial addition of the amine to the *p*-NBSP. The hydrolysis step is also carried out under harsh conditions of an excess of 2M HCl with heating at 150 °C to remove aqueous solvent.

8.1.2.4. Use of Benzoquinones.

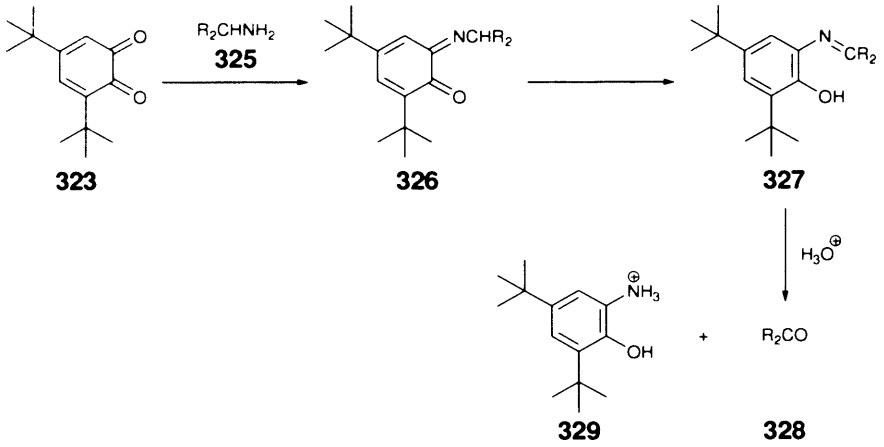
In 1968 a study was carried out by Corey, with the aim of developing new procedures for the conversion of primary amines to carbonyl compounds.[85] This was prompted by the need to carry out this transformation under mild conditions, whereby the few existing methods at the time were found to be inadequate.

The result of the work carried out was the successful development of two types of reagents **323** and **324**, Figure 8.2, for the selective oxidation of primary amines *via* a transamination pathway.

323 **324**

Figure 8.2: Reagents for the oxidation of amines

Beginning with benzoquinone **323**, this was readily prepared by oxidation of 3,5-di-*tert*-butylcatechol and was found to be a very effective reagent for the conversion of primary amines to ketones under very mild conditions, though an inert atmosphere was required. Ordinarily, amines react with quinones to give, amongst other things, amino hydroquinones. The substitution pattern in 3,5-di-*tert*-butyl-1,2-benzoquinone **323**, however, favours formation of the Schiff base **326** by preventing nucleophilic attack of the amine **325** on all but C(1) of the aromatic ring, Reaction scheme 8.4. The reaction then proceeds by deprotonation of **326**, forming a stable anion intermediate that rearranges to give the desired isomeric Schiff base **327**. Hydrolysis under aqueous acidic conditions affords the final ketone product **328**.

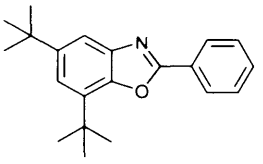


323 **326** **327** **329** **328**

Reaction scheme 8.4: Use of a benzoquinone reagent 323 for the oxidation of primary amines.

This reaction was shown to work well for both aliphatic and benzylic primary amines, forming a range of ketone products, though the effect of different functional group substituents was not addressed. Extension to the synthesis of aldehydes was

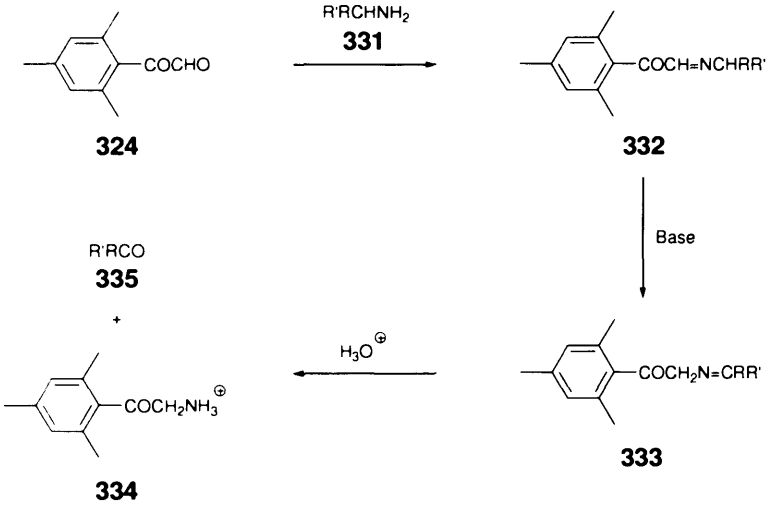
not possible since benzoxazoles and benzoxazolines were formed by further transformations of the Schiff base intermediates. In the case of benzylamine, instead of the desired benzaldehyde product, the benzoxazole **330** (Figure 8.3) was found to be the major product.



330

Figure 8.3: Benzoxazole product resulting from reaction of benzaldehyde.

The second type of reagent developed was mesitylglyoxal **324** (and its 3-nitro and 3,5-dinitro derivatives), which is characterised by the presence of an α-keto aldehyde system. As with the benzoquinone reagent **323**, internal steric shielding was used to control the site of reactivity, allowing for nucleophilic attack of the primary amine **331** on the formyl group alone, Reaction scheme 8.5. This forms the expected Schiff base **332** which, under basic conditions, undergoes a rapid prototropic rearrangement to the isomeric Schiff base **333**, though not quite as readily as the quinine-derived intermediate **326**. As before, hydrolysis under aqueous acidic conditions gives the final carbonyl product **335**.



Reaction scheme 8.5: Synthesis of carbonyl compounds using mesitylglyoxal 324.

As with reactions involving the quinone reagent **323**, the reactions proceed under mild conditions of temperature (in most cases r.t.) and time, though an inert

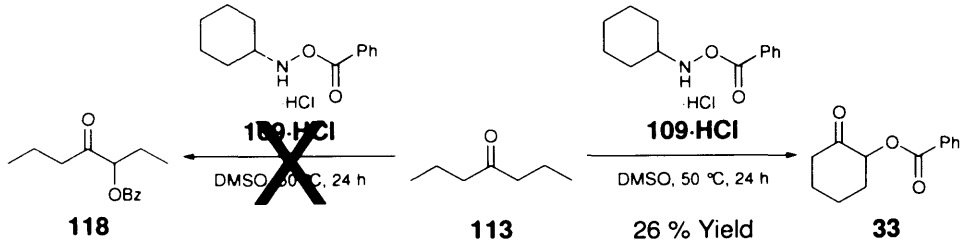
atmosphere is again required, and gives the product in varying yields of 38–90%. Unlike the previous method, this reagent **324** has been shown to be applicable to the synthesis of aldehydes as well as ketones, though these reactions may require further optimisation. The question of functional group tolerance was again not considered.

8.1.3. Summary.

Of the transition metal-free methods described, there are varying degrees of scope and limitations in substrate tolerance in each case, making no one method suitable for the effective oxidation of all amines to their respective carbonyl compounds. Furthermore, many of the optimised methods require anhydrous reaction conditions and use of an inert atmosphere, thus limiting their practicality and applicability. The development of a general metal-free method that circumvents these practical considerations would represent an advance in the methods available for the overall transformation.

8.2. Novel Metal-Free Method for the Oxidation of Primary Amines.

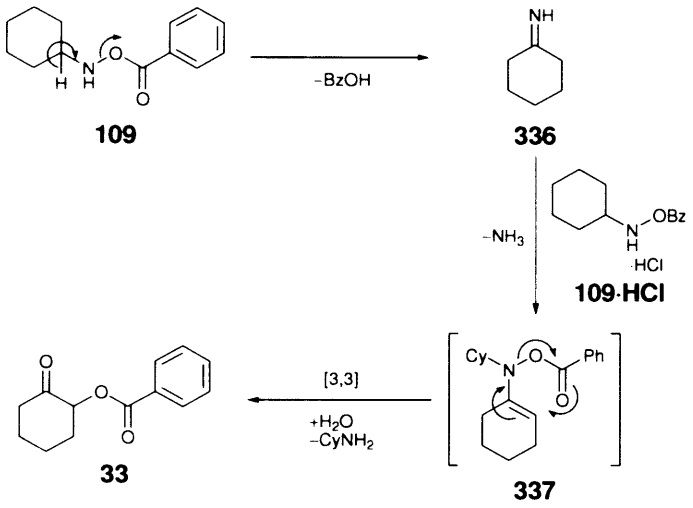
As part of our efforts to develop an asymmetric method for the α-oxybenzoylation of carbonyl compounds, we attempted to react 4-heptanone **113** with a stoichiometric amount of *N*-cyclohexyl-*O*-benzoyl hydroxylamine hydrochloride **109·HCl**, and obtained an interesting result, Reaction scheme 8.6 (Chapter 2.1). Instead of producing the expected α-oxygenated compound **118**, we found the reaction, carried out in DMSO at 50 °C, resulted in the α-functionalised cyclohexanone compound **33** as the major product, in a 26% isolated yield. Repeat reactions confirmed this result.



Reaction scheme 8.6: Unexpected side reaction.

A possible mechanism for this unexpected transformation was rationalised, whereby deprotonation of the reagent **109** gives the imine **336** with loss of benzoic acid (**137**), Reaction scheme 8.7. This imine **336** is then free to react with a second molecule of

reagent **109·HCl** to give the intermediate enamine **337**. Subsequent [3,3]-sigmatropic rearrangement, followed by hydrolysis of the resulting imine then leads to the observed product **33**. The reaction of **336** with the reagent **109·HCl** is much more favourable than the competing reaction of 4-heptanone **113**, owing to the increased steric effects involved in reaction of an acyclic ketone. As a result of this, none of the originally anticipated α-functionalised 4-heptanone product **118** was observed.

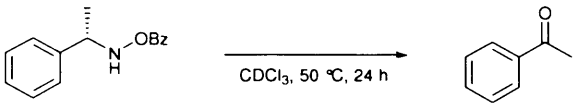


Reaction scheme 8.7: Possible mechanism for observed side reaction.

On consideration of this mechanism, we became interested in the initial conversion of the hydroxylamine reagent **109** to an imine **336**. It was thought that if we were able to stop this process at the intermediate imine **336**, the transformation would constitute a new method for amine oxidation. Our aim, therefore, was to firstly try to find conditions to favour this transformation and secondly to apply those conditions to a range of systems, both benzylic and alkyl, in order to generate a wide range of carbonyl compounds.

We began by looking at the conversion of (*S*)-α-methylbenzyl-*O*-benzoyl hydroxylamine **110**, the corresponding ketone being acetophenone **338**, Reaction scheme 8.8. This was chosen for several reasons, namely that we had an abundance of the chiral hydroxylamine reagent **110** already prepared, and the ketone product **338** was ideal, being easy to spot by TLC and stable to column chromatography; it also has a relatively high boiling point and is not too volatile making isolation practical. Separate reactions were carried out in deuterated chloroform at 50 °C with the reagent present as the free base, under acidic conditions as the hydrochloride salt,

and under basic conditions with a stoichiometric amount of DBU. These reactions were then monitored by ^{1}H NMR spectroscopy.

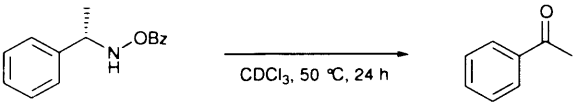


i) 110
ii) 110·HCl
iii)110·DBU

338

Reaction scheme 8.8: Initial oxidation reactions.

Preliminary results indicated that acidic or basic conditions were necessary in order to promote the reaction; the reagent itself was not reactive enough, Table 8.1 entry 1. Of these, acidic conditions proved to be very inefficient (<10%, entry 2) and resulted in a number of unidentified by-products. Basic conditions on the other hand, significantly accelerated the reaction and afforded a much cleaner transformation, giving the product **338** in a more encouraging 30% yield, entry 3.



110 **338**

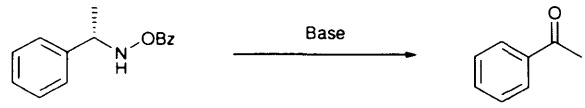
Entry	Conditions	Conversion (%)
1	Free Base	No Reaction
2	Acidic	<10[a]
3	Basic	30[b]

[a]Estimated yield by ^{1}H NMR.
[b]Isolated yield.

Table 8.1: Initial results obtained.

The polarity of the solvent was investigated next and after examining a range of solvents, it was identified that a more polar solvent was beneficial, Table 8.2. Of those tried, DMF gave the optimal result, giving the product **338** in a 66% yield, entry 4. Variation of the base to cesium carbonate, which is often used as a base in conjunction with DMF, gave a further increase in yield up to an excellent 84%, entry 10. Use of an excess of base did not appear to significantly improve the yield, entries 2, 3, 5, 6, 7, 11, however; use of sub-stoichiometric amounts of the base was not detrimental to the yield. We found that catalytic quantities of cesium carbonate could be used to effect the amine oxidation, with 0.5 and 0.1 equivalents of base giving the product **338** in isolated yields of 76 and 71% respectively, entries 8 and 9. The

reaction times required for the reaction to go to completion were increased slightly when using sub-stoichiometric amounts of base.



110 **338**

Entry	Solvent	Base	Eq. base	Temp (°C)	Yield (%)[b]
1	$CHCl_3$	DBU	1	50	30
2	$CHCl_3$	DBU	2	50	36
3	PhMe	DBU	2	50	34
4	DMF	DBU	1	50	66
5	DMF	DBU	2	50	64
6	DMF	DBU	3	50	64
7	DMF	DBU	2	70	70
8	DMF	Cs_2CO_3	0.1	50[c]	71
9	DMF	Cs_2CO_3	0.5	50	76
10	DMF	Cs_2CO_3	1	50	84
11	DMF	Cs_2CO_3	2	50	78

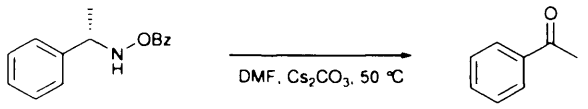
[a]All reactions carried out for 18 hours unless otherwise stated.
[b]Isolated yield
[c]Reaction carried out for 48 hours.

Table 8.2: Optimisation of reaction conditions.[a]

After establishing the optimum solvent and base for this reaction, the effect of other variables, such as time and temperature, were also investigated. The effect of temperature on this reaction system was looked at briefly, with results indicating that this factor affects only the rate of reaction, the overall isolated yield remained about the same, Table 8.2, entry 7.

Information gained from looking at the effect of time on the reaction told us that the reaction at 50 °C takes between 9 and 16 hours to go to completion, Table 8.3, entries 3 and 4. This was based on ^1H NMR spectra of the reaction mixture obtained at different reaction times. By using 1,4-dimethoxybenzene as a standard, we were able to calculate the amount of starting material (S.M.) remaining in the reaction mixture, and thus approximate the stage of the reaction in terms of percentage of S.M. converted. Isolated yields, however, at reaction times less than 9 hours, were almost as high as those after completion despite the presence of starting material in

the reaction mixture, entries 1 and 2. There are a few possible explanations for this observation, the most likely of which, however, is decomposition of the starting material **110** over time. Leaving the reaction for longer periods of time was observed to be slightly detrimental to the yield, entry 7, which fits with the previous conclusion, but also suggests a possible decomposition of the product **338** over time.



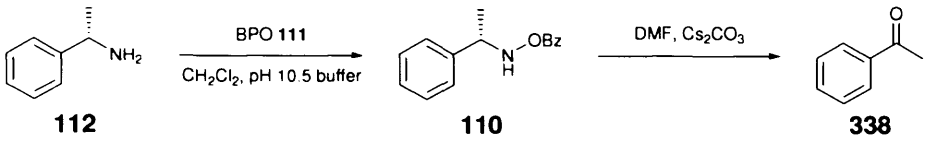
110 **338**

Entry	Solvent	Base[a]	Time (hrs)	Conversion (%)	Yield (%)[b]
1	DMF	Cs_2CO_3	3	73	82
2	DMF	Cs_2CO_3	6	87	80
3	DMF	Cs_2CO_3	9	97	86
4	DMF	Cs_2CO_3	16	100	84
5	DMF	Cs_2CO_3	20	100	68
6	DMF	Cs_2CO_3	24	100	76
7	DMF	Cs_2CO_3	48	100	68

[a]One equivalent of base used
[b]Isolated Yield

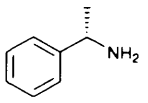
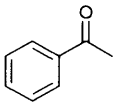
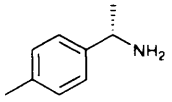
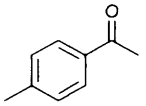
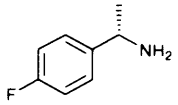
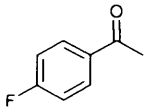
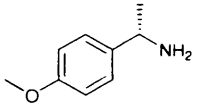
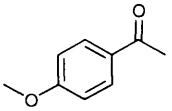
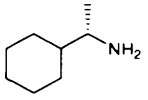
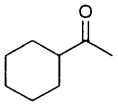
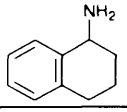
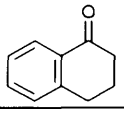
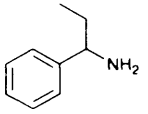
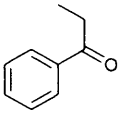
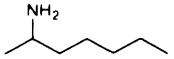
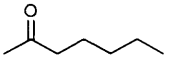
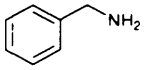
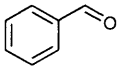
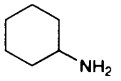
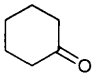
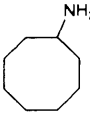
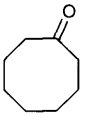
Table 8.3: Examining the effect of time on the reaction.

Having optimised the reaction for the synthesis of acetophenone, the optimal conditions found were applied to various other reaction systems. *O*-Benzoyl hydroxylamine reagents were formed from a variety of primary amines, using the robust and convenient method reported by Phanstiel that is currently employed in our asymmetric investigations. These reagents were then used in attempts to form the corresponding carbonyl compounds in order to determine some of the scope and limitations of this transformation. The overall reaction is exemplified in Reaction scheme 8.9 for the synthesis of acetophenone **338** from 1-phenylethylamine **112**. Unfortunately, initial results were not nearly as good as hoped, with many yields being below 20%. It was found, however, that these could be vastly improved by subtle optimisation of temperature and time in each case, Table 8.4.



112 **110** **338**

Reaction scheme 8.9: Two-step conversion of primary amine to ketone.

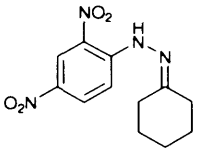
Entry	Amine	Product	Yield (%)[b]
1			84
2			72
3			90
4			90
5[c]			63
6[c,d]			75
7			70
8[c]			68
9[e,d]			41
10[c,f]			53
11[g]			29

[a]All reactions carried out at 50 °C for 18 hours, unless otherwise stated.
[b]Isolated yield.
[c]Reaction carried out at 70 °C.
[d]Reaction carried out for 72 hours.
[e]Reaction carried out at 25 °C.
[f]Product isolated as 2,4-DNPH derivative.
[g]Reaction carried out for 48 hours

Table 8.4: Results obtained from oxidation of various amines.[a]

From the results shown in the above table (Table 8.4) it can be seen that the majority of reagents undergo this oxidation reaction in good yield under optimised conditions, entries 1–8. The reaction was found to work efficiently for both benzylic and aliphatic amines. The effect of the presence of different functional groups was also examined, whereby it was found that both electron-donating (entries 2 and 4) and electron-withdrawing (entry 3) substituents were tolerated on the aromatic ring, as well as increased steric crowding around the nitrogen atom (entries 6 and 7).

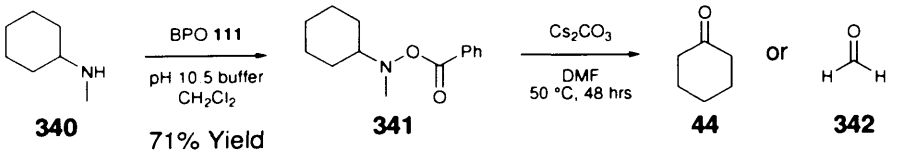
A few reagents did not undergo the transformation quite as efficiently as hoped. For example, in the reaction forming benzaldehyde (**371**), Table 8.4, entry 9, the best yield obtained was 41%. After consideration, it was concluded that enolisable aldehydes would be inherently unstable to the basic reaction conditions required for this transformation. These substrates were therefore not examined further, though a definitive conclusion will require further investigation. Formation of cyclic ketones also proved to be slightly problematic with low yields obtained in several instances, most probably the result of the products being too volatile. This was overcome in the formation of cyclohexanone **44**, entry 10, by isolating the product as the 2,4-DNPH derivative **339**, Figure 8.4.



339

Figure 8.4: Structure of 2,4-DNPH derivative of cyclohexanone.

One further area of investigation worth considering is whether this reaction is applicable to secondary amines and, if so, what sort of selectivity is observed. We hoped to begin to answer this question with the secondary amine **340**, which was firstly converted to the corresponding *O*-benzoyl hydroxylamine **341**, shown below in Reaction scheme 8.10.



340 **341** **44** **342**

Reaction scheme 8.10: Use of a secondary amine in our amine oxidation reaction.

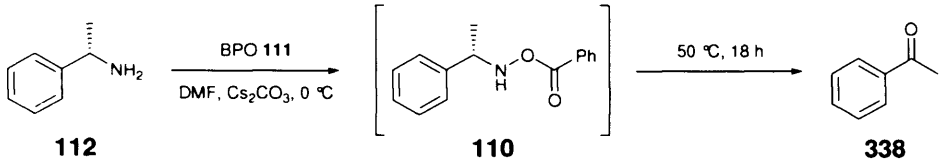
This hydroxylamine-based reagent **341** was then subjected to our amine oxidation conditions of a stoichiometric amount of cesium carbonate and DMF as the solvent. The reaction mixture was heated to 50 °C and monitored by TLC. Unfortunately initial results were unsuccessful, with the reaction mixture containing mostly starting hydroxylamine **341** after 48 hours. Further investigation is required to address this question; however, in light of the results obtained from cyclic ketones to date, the choice of secondary amine may have to be refined.

8.3. Development of a One-Pot Procedure.

The current procedure for carrying out this oxidation is a two-step method involving the conversion of a primary amine, for example 1-phenylethylamine **112**, to the corresponding hydroxylamine reagent **110**; followed by conversion of the reagent **110** into the corresponding carbonyl compound, in this case acetophenone **338** (Reaction scheme 8.9). In order to improve this reaction, we sought to discover if a one-pot method for the direct conversion of amines to ketones could be established.

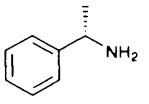
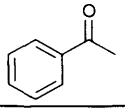
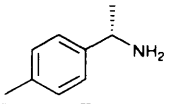
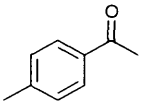
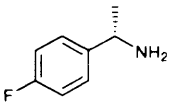
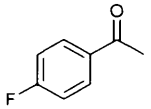
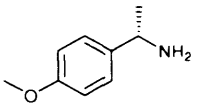
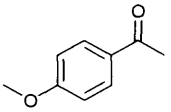
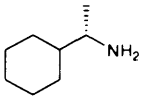
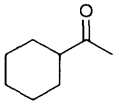
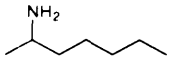
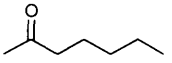
The synthesis of *O*-benzoyl hydroxylamines from primary amines has been shown to require basic conditions in order to suppress the formation of unwanted amide products. Bases that have been used for this transformation include sodium carbonate,[55] sodium hydroxide,[87] *tert*-butylamine,[88] and disodium hydrogen phosphate.[89] We were pleased to discover that cesium carbonate was also an effective base for this transformation, allowing for the direct conversion of primary amines to ketones.

This was done by reaction of the amine **112** with BPO **111**, using DMF as the solvent and in the presence of Cs_2CO_3 as the base, with the reaction carried out at 0 °C warming to room temperature. This forms the desired hydroxylamine intermediate **110** *in situ* and after a few hours there was not any BPO **111** remaining by TLC. At this point the reaction mixture was heated to the required temperature, dependent on the reaction system, and for the required time, which resulted in the desired product **338** in a one-pot procedure, Reaction scheme 8.11.



112 110 338

Reaction Scheme 8.11: One-pot oxidation of 1-phenyl ethylamine 112 to acetophenone 338.

Entry	Amine	Product	Yield (%)[a]
1			59
2			66
3			57
4			69
5			59
6[b]			32

[a]Isolated Yield.
[b]Reaction unoptimised.

Table 8.5: Results for the one-pot conversion of amines to ketones.

This novel, convenient, one-pot amine oxidation reaction has been shown to be successful in a number of cases, Table 8.5, in both benzylic (entries 1–4) and aliphatic (entries 5 and 6) reaction systems, giving the product in good yields. As can be seen in all cases, the yields obtained using the one-pot method were not quite as high as those obtained when using the two-step method. It is thought that this could be due to problems in forming the hydroxylamine reagent in the initial, unoptimised, reaction of the amine with BPO **111**. Ordinarily, this process requires more basic conditions in order to prevent amide formation, and even then gives good, but not excellent yields of around 60–90%.

8.4. Conclusion.

A novel procedure for the conversion of primary amines into ketones has been developed. The protocol is applicable to both aliphatic and benzylic amines, with a variety of functional groups tolerated, leading to the products in good to excellent yield. The reactions are simple to perform, and can be carried out in the presence of both moisture and air. A direct method for the conversion was also shown to be possible, with formation of the required hydroxylamine *in situ* under basic conditions.

There still remains scope for improving this procedure. Future investigations could be carried out into establishing conditions for the synthesis of aldehydes. The question of selectivity in this type of reaction also remains to be looked at, along with optimising the reaction between amines and BPO **111**, which gives the hydroxylamine intermediates *in situ*.

Chapter 9.

Experimental.

Reagents were obtained from Aldrich, Lancaster and Fluka chemical suppliers. Solvents and reagents were purified according to the procedures of Perrin, Armarego and Perrin.[i] Dichloromethane was dried by refluxing over, and distilling from calcium hydride. Ethanol was dried by refluxing over magnesium, followed by distillation. Toluene was dried over sodium wire for twenty-four hours prior to use. Petroleum ether refers to petroleum ether fraction 40–60 °C.

All reactions using air/moisture sensitive reagents were performed in oven-dried or flame-dried apparatus, under a nitrogen atmosphere. Catalytic runs were performed using a Radley's carousel, which consists of twelve test tubes with suba-seals and nitrogen inlets, a stirrer plate and a bath for heating. All reactions were followed and monitored by TLC, ^{1}H NMR, ^{13}C NMR and mass spectrometry as appropriate.

TLC analysis refers to analytical thin layer chromatography, using aluminium-backed plates coated with Merck Kieselgel 60 GF_{254}. Product spots were viewed either by the quenching of UV fluorescence, or by staining with a solution of 2% aqueous potassium permanganate. Chromatography refers to flash column chromatography using head pressure by means of compressed air according to the procedure of Still,[ii] using Merck Kieselgel 60 H silica or Matrix silica 60.

Melting points were recorded using a Kofler Heated Stage Micro Melting Point Apparatus and are uncorrected.

Infra-red spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1600 series FTIR instrument either as a thin film, a nujol mull or dissolved in dichloromethane between sodium chloride plates. All absorptions are quoted in wave numbers (cm^{-1}).

^{1}H NMR spectra (δ_H) were recorded using an Avance Bruker DPX 400 instrument (400 MHz) or an Avance Bruker DPX 500 (500MHz), with ^{13}C NMR spectra (δ_C) recorded at 100 MHz or 125 MHz respectively. Chemical shifts (δ_H and δ_C) were recorded in parts per million (ppm) from tetramethylsilane (or chloroform) and are corrected to 0.00 (TMS) and 7.27 ($CHCl_3$) for ^{1}H NMR and 77.30 ($CHCl_3$), centre line, for ^{13}C NMR. The abbreviations s, d, t, q, m, and br, denote singlet, doublet,

triplet, quartet, multiplet and broadened resonances, respectively; all coupling constants were recorded in hertz (Hz).

Low resolution mass spectrometric data was determined using a Fisons VG Platform II Quadrapole instrument using atmospheric pressure chemical ionisation (APcI) unless otherwise stated. APcI refers to atmospheric pressure chemical ionisation, EI refers to electron ionisation and ES refers to electrospray. High resolution mass-spectrometric data was obtained courtesy of the EPSRC Mass Spectrometry Service at the University of Wales, Swansea, UK, using the ionisation methods specified. Calculated accurate masses are of the parent ion (exclusive of an electron, mass = 0.00055 Da).

---

[i] D. D. Perrin, W. L. F. Armarego, D. R. Perrin, In *Purification of Laboratory Chemicals*, 2nd Ed; Pergamon Press, Oxford. **1980**.

[ii] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.*, **1978**, *43*, 2923.

Chapter 9.1. Reagent Experimentals.

9.1.1 General Procedure 1. Hydroxylamine Reagent Synthesis using Phanstiel Method.[55]

A solution of benzoyl peroxide **111** (75% solution in water, 6.66 g, 0.021 mol) in CH_2Cl_2 (103 mL) was added quickly to a mixture of an amine (0.021 mol) and pH 10.5 buffer solution (103 mL). Vigorous stirring was continued at r.t. overnight. The reaction mixture was then extracted with CH_2Cl_2 (3 x 50 mL), washed with brine (50 mL), dried (Na_2SO_4) and concentrated to give the crude product.

9.1.1.1. Synthesis of pH 10.5 Buffer.[55]

pH 10.5 buffer was made by mixing aqueous $NaHCO_3$ (222 mL, [0.75M]) with aqueous sodium hydroxide (78 mL, [1.5M]).

9.1.1.2. Conversion of hydroxylamine reagents to the corresponding HCl Salt.

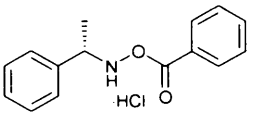
HCl gas was bubbled through a solution of the crude hydroxylamine reagent product (6 mmol) in diethyl ether (150 mL). After 20 min, the desired hydrochloride salt had precipitated and was collected by filtration under reduced pressure, washing with ether, and then dried under reduced pressure.

9.1.2. General Procedure 2. Hydroxylamine Reagent Synthesis using Geffken Method.[57]

CDI **136** (1.04 g, 6.40 mmol) was added slowly (over 5 min) to a solution of a carboxylic acid (6.40 mmol) in CH_2Cl_2 (20 mL) with stirring for 15 min. The appropriate hydroxylamine (1.2 eq., 7.68 mmol) was then added quickly, and stirring was continued for 1 hour. The reaction mixture was then diluted with CH_2Cl_2 (10 mL), washed with ice-cold 1M HCl (13 mL), saturated $NaHCO_3$ solution (13 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated to give the crude product, which was purified by column chromatography.

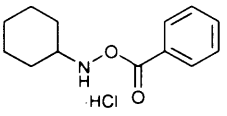
9.1.3. Reagent Experimental Data.

N-(*S*)-α-Methylbenzyl-*O*-benzoyl hydroxylamine hydrochloride 110·HCl.



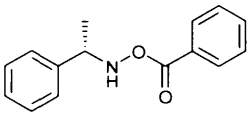
Compound **110·HCl** was synthesised from *N*-(*S*)-α-methylbenzylamine **112** using general procedure 1. Conversion to the HCl (Chapter 9.1.1.2) salt gave *N-(S)-α-methylbenzyl-(O)-benzoyl hydroxylamine hydrochloride* **110·HCl** (3.52 g, 62%) as a white crystalline solid which was collected by filtration. M.p. 92–96 °C. IR (nujol)/ cm^{-1}: 2925, 2293, 1765, 1458, 1378, 1263, 1052; ^1H NMR (400 MHz, DMSO) δ 9.00–9.20 (br, 2H, NH_2^+), 7.75 (d, 2H, *J* 7.1 Hz, ArH), 7.60 (t, 1H, *J* 7.4 Hz, ArH), 7.4–7.5 (m, 4H), 7.30 (m, 2H), 7.20 (m, 1H), 4.35 (q, 1H, *J* 6.7 Hz, CHN), 1.35 (d, 3H, *J* 6.7 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO), δ 165.6, 142.8, 133.9, 129.3, 129.1, 128.9, 128.7, 127.8, 127.4, 59.9, 19.9 ppm; MS (ES): *m/z* 242 $[M+H]^+$. HRMS calculated for $C_{15}H_{16}NO_2$ $[M+H]^+$ 242.1176, found 242.1177.

N-Cyclohexyl-*O*-benzoyl hydroxylamine hydrochloride 109·HCl.



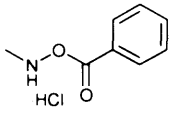
Compound **109·HCl** was synthesised from cyclohexylamine (2.5 g, 0.025 mol) using general procedure 1. Conversion to the HCl salt (Chapter 9.1.1.2) gave *N-cyclohexyl-O-benzoyl hydroxylamine hydrochloride* **109·HCl**. as a white solid (74%), which was collected by filtration. M.p. 135–140 °C. Lit. ref. m.p. 155 °C.[90] IR (thin film)/cm^{-1}: 2932, 2855, 1757, 1718, 1450, 1265, 1055, 704; ^1H NMR (400 MHz, DMSO) δ 9.20–9.40 (br, 2H, NH_2^+), 7.95 (d, 2H, *J* 7.1 Hz, ArH), 7.65 (t, 1H, *J* 7.4 Hz, ArH), 7.50 (at, 2H, *J* 7.7 Hz, ArH), 3.05–3.15 (m, 1H, CHN), 1.85–1.95 (m, 2H), 1.50–1.80 (m, 2H), 1.50–1.60 (m, 1H), 1.05–1.30 (m, 5H); ^{13}C NMR (100 MHz, DMSO), δ 165.3, 134.3, 129.5, 129.5, 128.2, 59.2, 29.4, 25.8, 24.4 ppm; MS (APcI): *m/z* 220 $[M+H]^+$. HRMS calculated for $C_{13}H_{18}NO_2$ $[M+H]^+$ 220.1332, found 220.1331.

N-(S)-α-Methyl benzyl-O-benzoyl hydroxylamine 110.



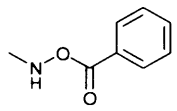
pH 10.5 buffer (250 mL) was added quickly to a solution of *N*-(*S*)-α-methylbenzyl-*O*-benzoyl hydroxylamine hydrochloride **110·HCl** (500 mg, 1.8 mmol) in dichloromethane (250 mL), with vigorous stirring at r.t. for one hour. The reaction mixture was then separated and the aqueous layer was extracted with dichloromethane (3 x 100 mL). The organic extracts were then combined with the organic layer and washed with brine (250 mL), dried (Na_2SO_4) and concentrated to give *N-(S)-α-methylbenzyl-O-benzoyl hydroxylamine* **110** (92%) as a clear colourless oil. IR (nujol)/ cm^{-1}: 3233, 3063, 3031, 2977, 1719, 1601, 1584, 1493, 1451, 1373, 1316, 1268, 1177, 1090, 1066, 1025, 979, 762, 701; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 2H, *J* 7.1 Hz, ArH), 7.55 (t, 1H, *J* 7.5 Hz, ArH), 7.30–7.50 (m, 7H, ArH), 4.25 (q, 1H, *J* 6.7 Hz, CHN), 1.45 (d, 3H, *J* 6.7 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.9, 141.3, 133.4, 129.4, 128.7, 128.5, 128.4, 127.9, 127.2, 61.0, 19.8 ppm; MS (APcI): *m/z* 242 $[M+H]^+$. $[\alpha]^{23}_D$ −80 (1 g/100 mL, $CHCl_3$).

N-Methyl-O-benzoyl hydroxylamine hydrochloride 63·HCl.[49]



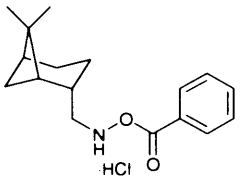
Compound **63·HCl** was synthesised from benzoic acid **137** (5.0 g, 0.041 mmol) and *N*-methyl hydroxylamine hydrochloride **61** using general procedure 2. Conversion to the HCl salt (Chapter 9.1.1.2) gave *N-methyl-O-benzoyl hydroxylamine hydrochloride* **63·HCl** (54%) as a white solid, which was collected by filtration. M.p. 121–126 °C. Lit. ref. m.p. 129–129.5 °C.[49] IR (nujol)/cm^{-1}: 3458, 3056, 1712, 1600, 1550, 1422, 1264; ^1H NMR (400 MHz, DMSO) δ 11.95 (br, 2H, NH_2^+), 7.95 (d, 2H, *J* 7.0 Hz, ArH), 7.73 (t, 1H, *J* 7.5 Hz, ArH), 7.57 (dd, 2H, *J* 7.0, 7.5 Hz, ArH), 2.93 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO), δ 164.3, 134.9, 129.7, 129.6, 127.2, 37.5 ppm; MS (APcI): *m/z* 152 $[M+H]^+$. HRMS calculated for $C_8H_{10}NO_2$ $[M+H]^+$ 152.0711, found 152.0712.

N-Methyl-O-benzoyl hydroxylamine 63.



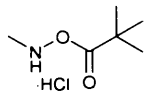
pH 10.5 buffer (250 mL) was added quickly to a solution of *N*-methyl-*O*-benzoyl hydroxylamine hydrochloride **63·HCl** (500 mg, 2.7 mmol) in dichloromethane (250 mL), with vigorous stirring at r.t. for one hour. The reaction mixture was then separated and the aqueous layer was extracted with dichloromethane (3 x 100 mL). The organic extracts were then combined with the organic layer and washed with brine (250 mL), dried (Na_2SO_4) and concentrated to give *N-methyl-O-benzoyl hydroxylamine* **63** (334 mg, 83%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3189, 2923, 1725, 1609, 1570, 1447, 1385, 1268, 1214, 1067; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, 2H, *J* 7.1 Hz, ArH), 7.50 (t, 1H, *J* 7.5 Hz, ArH), 7.35 (at, 2H, *J* 7.7 Hz, ArH), 2.90 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.9, 133.4, 129.4, 128.6, 128.3, 39.8 ppm.

N-(−)-cis-myrtanyl-O-benzoyl hydroxylamine hydrochloride 130·HCl.



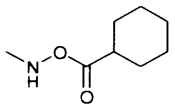
Compound **130·HCl** was synthesised from (−)-cis-myrtanylamine (0.5 g, 3.26 mmol) using general procedure 1. Conversion to the HCl salt (Chapter 9.1.1.2) gave *N-(−)-cis-myrtanyl-O-benzoyl hydroxylamine hydrochloride* **130·HCl** (58%) as a white solid which was collected by filtration. M.p. 116–121 °C. IR (thin film)/cm^{-1}: 3136, 2914, 1718, 1446, 1270, 1064, 1020, 767, 705; ^1H NMR (400 MHz, DMSO) δ 9.95–10.20 (br, 2H, NH_2^+), 7.95 (d, 2H, *J* 7.4 Hz, ArH), 7.65 (t, 1H, *J* 7.5 Hz, ArH), 7.50 (at, 2H, *J* 7.8 Hz, ArH), 3.05–3.15 (m, 2H, CH_2CN), 2.30–2.40 (m, 2H), 2.00–2.05 (m, 2H), 1.75–1.95 (m, 3H), 1.50–1.60 (m, 1H) 1.15 (s, 3H, CH_3), 0.95 (s, 3H CH_3), 0.90 (d, 1H, *J* 9.5 Hz); ^{13}C NMR (100 MHz, DMSO), δ 165.6, 134.1, 129.4, 129.3, 128.7, 57.9, 44.2, 41.1, 39.3, 38.8, 33.0, 28.2, 26.2, 23.5, 20.2 ppm; MS (ES): *m/z* 274 $[M+H]^+$. HRMS calculated for $C_{17}H_{24}NO_2$ $[M+H]^+$. 274.1802, found 274.1802.

N-Methyl-O-pivaloyl hydroxylamine hydrochloride 146·HCl.[49]



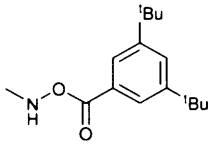
Compound **146·HCl** was synthesised from pivalic acid **139** (2.0 g, 19.6 mmol) and *N*-methyl hydroxylamine hydrochloride **61** using general procedure 2. Conversion to the HCl salt (Chapter 9.1.1.2) gave *N-methyl-O-pivaloyl hydroxylamine hydrochloride* **146·HCl** (37%) as a white solid which was collected by filtration. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90–10.00 (br, 2H, NH_2^+), 2.80 (s, 3H, CH_3), 1.25 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 178.5, 39.5, 38.2, 27.1 ppm.

N-Methyl-O-cyclohexanoyl hydroxylamine 147.



Compound **147** was synthesised from cyclohexanoic acid **140** (2.0 g, 15.6 mmol) and *N*-methyl hydroxylamine hydrochloride **61** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (7:3), gave *N-methyl-O-cyclohexoyl hydroxylamine* **147** (43%) as a white solid. M.p. 83–88 °C. IR (thin film)/cm^{-1}: 3175, 2930, 2855, 1613, 1450, 1391, 1197, 955, 894; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.70 (br, 1H, NH), 2.75 (s, 3H, CH_3), 2.25–2.40 (m, 1H, CHCO), 1.80–1.90 (m, 2H), 1.70–1.80 (m, 2H), 1.60–1.70 (m, 1H), 1.35–1.50 (m, 2H), 1.15–1.35 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 176.0, 41.8, 39.6, 28.6, 25.6, 25.2 ppm; MS (ES): *m/z* 158 $[M+H]^+$. HRMS calculated for $C_8H_{16}NO_2$ $[M+H]^+$ 158.1181, found 158.1179.

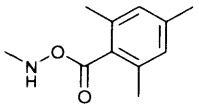
N-Methyl-O-3,5-di-*tert*-butylbenzoyl hydroxylamine 148.



Compound **148** was synthesised from 3,5-di-*tert*-butylbenzoic acid **141** (2.0 g, 8.5 mmol) and *N*-methyl hydroxylamine hydrochloride **61** using general procedure 2.

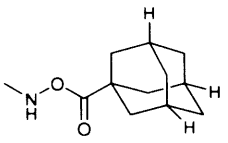
Purification by column chromatography, eluting with petroleum ether-ethyl acetate (3:1), gave *N-methyl-O-3,5-di-tert-butylbenzoyl hydroxylamine* **148** (68%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3250, 2963, 2871, 1720, 1600, 1476, 1364, 1312, 1238, 1106; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 2H, ArH), 7.65 (s, 1H, ArH), 6.90–7.05 (br, 1H, NH), 3.00 (s, 3H, CH_3), 1.40 (s, 18H, *m*-^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 167.7, 151.3, 127.7, 127.6, 123.6, 40.0, 35.0, 31.4 ppm; MS (ES): *m/z* 264 $[M+H]^+$. HRMS calculated for $C_{16}H_{26}NO_2$ $[M+H]^{+}$ 264.1964, found 264.1969.

N-Methyl-O-2,4,6-trimethylbenzoyl hydroxylamine 149.



Compound **149** was synthesised from 2,4,6-trimethylbenzoic acid **142** (2.0 g, 12.2 mmol) and *N*-methyl hydroxylamine hydrochloride **61** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (7:3), gave *N-methyl-O-2,4,6-trimethylbenzoyl hydroxylamine* **149** (6%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3252, 2922, 1724, 1611, 1467, 1438, 1258, 1168, 1061, 847; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.80 (br, 1H, NH), 6.75 (s, 2H, ArH), 2.90 (s, 3H, CH_3), 2.25 (s, 6H, *o*-CH_3), 2.00 (s, 3H, *p*-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 170.2, 140.1, 135.6, 128.53, 128.49, 39.8, 21.2, 19.6 ppm; MS (ES): *m/z* 194 $[M+H]^+$. HRMS calculated for $C_{11}H_{16}NO_2$ $[M+H]^{+}$ 194.1181, found 194.1190.

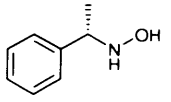
N-Methyl-O-adamantoyl hydroxylamine 155.



Compound **155** was synthesised from adamantane carboxylic acid **154** (2.0 g, 11.1 mmol) and *N*-methyl hydroxylamine hydrochloride **61** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (7:3), gave *N-methyl-O-adamantoyl hydroxylamine* **155** (53%) as a white solid. M.p. 33–38 °C. IR (thin film)/cm^{-1}: 3244, 2906, 2852, 1724, 1453, 1268, 1230, 1182, 1062; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.75 (br, 1H, NH), 2.80 (s, 3H, CH_3),

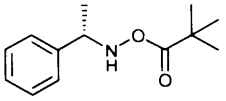
2.00–2.10 (m, 3H), 1.90–1.95 (m, 6H), 1.65–1.80 (m, 6H). MS (ES): *m/z* 210 $[M+H]^+$.

N-(S)-α-Methylbenzyl hydroxylamine 162.[91]



Ammonium hydroxide (33%, 3.5 mL) was added dropwise (over 5 min) to a solution of *N*-(*S*)-α-methylbenzyl-*O*-benzoyl hydroxylamine **110** (3.28 g, 13.59 mmol) in methanol (7 mL) under nitrogen, with stirring at r.t. overnight. The methanol was then removed under reduced pressure and the residue dissolved in ethyl acetate (50 mL), washed with brine (30 mL), dried ($MgSO_4$) and concentrated to give the crude product, which was purified on silica, eluting with petroleum ether-ethyl acetate (1:1) to give *N-(S)-α-methylbenzyl hydroxylamine* **162** (1.29 g, 70%) as a white solid. M.p. 89–93 °C. IR (thin film)/cm^{-1}: 3254, 3130, 2966, 2871, 1495, 1453, 1422, 1366, 1207, 1069, 1006; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15–7.30 (m, 5H, ArH), 5.90–6.05 (br, 2H, NH and OH), 4.00 (q, 1H, *J* 6.7 Hz, CHN), 1.30 (d, 3H, *J* 6.7 Hz, CH_3CN); ^{13}C NMR (100 MHz, $CDCl_3$), δ 142.0, 128.6, 127.7, 127.2, 61.8, 19.3 ppm; MS (ES): *m/z* 137 $[M+H]^+$. $[\alpha]^{23}_D$ −30.8 (1 g/100 mL, $CHCl_3$).

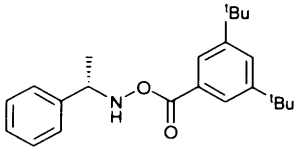
N-(S)-α-Methylbenzyl-O-pivaloyl hydroxylamine 344.



Compound **344** was synthesised from pivalic acid **139** (1.0 g, 9.8 mmol) and *N*-(*S*)-α-methylbenzyl hydroxylamine **162** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *N-(S)-α-methylbenzyl-O-pivaloyl hydroxylamine* **344** (51%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3233, 2975, 2867, 1727, 1480, 1455, 1368, 1280, 1146, 1025, 978, 760, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.75 (br, 1H, NH), 7.30–7.35 (m, 4H, ArH), 7.25–7.30 (m, 1H, ArH), 4.20 (q, 1H, *J* 6.7 Hz, CHN), 1.45 (d, 3H, *J* 6.7 Hz, CH_3CN), 1.10 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 178.3, 141.2, 128.5, 127.8, 127.1, 60.8, 38.3, 27.0, 19.4 ppm; MS (ES): *m/z* 222 $[M+H]^+$. HRMS

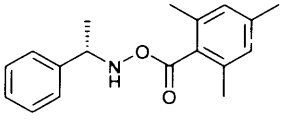
calculated for $C_{13}H_{20}NO_2$ $[M+H]^+$ 222.1494, found 222.1499. $[\alpha]^{23}_D$ −14.2 (1 g/100 mL, $CHCl_3$).

N-(S)-α-Methylbenzyl-O-3,5-di-tert-butylbenzoyl hydroxylamine 345.



Compound **345** was synthesised from 3,5-di-*tert*-butylbenzoic acid **141** (1.0 g, 4.3 mmol) and *N*-(*S*)-α-methyl benzyl hydroxylamine **162** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *N-(S)-α-methylbenzyl-O-3,5-di-tert-butyl benzoyl hydroxylamine* **345** (63%) as a white solid. M.p. 32–34 °C. IR (thin film)/cm^{-1}: 3236, 2959, 2872, 1713, 1601, 1475, 1454, 1363, 1311, 1233, 1112, 895; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 2H, ArH), 7.65 (s, 1H, ArH), 7.45–7.50 (m, 2H, ArH), 7.30–7.40 (m, 3H, ArH), 4.35 (q, 1H, *J* 6.6 Hz, CHN), 1.60 (d, 3H, *J* 6.6 Hz, CH_3CN), 1.30 (s, 18H, *m*-^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 167.6, 151.2, 141.0, 128.6, 128.0, 127.7, 127.6, 127.3, 123.6, 61.0, 35.0, 31.3, 19.5 ppm; MS (ES): *m/z* 354 $[M+H]^+$. HRMS calculated for $C_{23}H_{32}NO_2$ $[M+H]^+$ 354.2428, found 354.2430. $[\alpha]^{23}_D$ −44 (1 g/100 mL, $CHCl_3$).

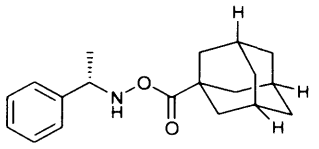
N-(S)-α-Methylbenzyl-O-2,4,6-trimethylbenzoyl hydroxylamine 165.



Compound **165** was synthesised from 2,4,6-trimethylbenzoic acid **142** (1.4 g, 8.5 mmol) and *N*-(*S*)-α-methyl benzyl hydroxylamine **162** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *N-(S)-α-methylbenzyl-O-2,4,6-trimethylbenzoyl hydroxylamine* **165** (5%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3234, 2976, 2925, 1722, 1611, 1453, 1374, 1260, 1166, 1066, 852, 762, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20–7.35 (m, 5H, ArH), 6.70 (s, 2H, ArH), 4.25 (q, 1H, *J* 6.7 Hz, CHN), 2.15 (s, 3H, *p*-CH_3), 2.00 (s, 6H, *o*-CH_3), 1.40 (d, 3H, *J* 6.7 Hz, CH_3CN); ^{13}C NMR (100 MHz, $CDCl_3$), δ

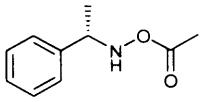
170.1, 141.6, 139.9, 135.7, 128.6, 128.5, 128.4, 127.9, 127.0, 60.8, 21.2, 20.1, 19.5 ppm; MS (ES): *m/z* 284 $[M+H]^+$. HRMS calculated for $C_{18}H_{22}NO_2$ $[M+H]^+$ 284.1645, found 284.1648.

N-(S)-α-Methylbenzyl-O-adamantoyl hydroxylamine 346.



Compound **346** was synthesised from adamantane carboxylic acid **154** (1.5 g, 8.3 mmol) and *N*-(*S*)-α-methylbenzyl hydroxylamine **162** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *N-(S)-α-methylbenzyl-O-adamantoyl hydroxylamine* **346** (41%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3229, 2975, 2906, 2852, 1723, 1494, 1453, 1372, 1323, 1267, 1225, 1182, 1102, 1064, 977; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15–7.30 (m, 5H, ArH), 4.05 (q, 1H, *J* 6.7 Hz, CHN), 2.90–2.95 (m, 3H), 1.75 (d, 6H, *J* 2.7 Hz), 1.55–1.70 (m, 6H), 1.35 (d, 3H, *J* 6.7 Hz, CH_3CN); ^{13}C NMR (100 MHz, $CDCl_3$), δ 177.4, 141.2, 128.5, 127.8, 127.1, 60.8, 40.3, 38.6, 36.4, 27.8, 19.4 ppm; MS (ES): *m/z* 300 $[M+H]^+$. HRMS calculated for $C_{19}H_{26}NO_2$ $[M+H]^+$ 300.1964, found 300.1959. $[\alpha]^{23}_D$ −24.6 (1 g/100 mL, $CHCl_3$).

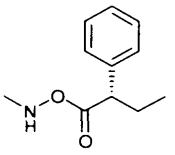
N-(S)-α-Methylbenzyl-O-acetoyl hydroxylamine 166.



Compound **166** was synthesised from glacial acetic acid (0.4 g, 6.7 mmol) and *N*-(*S*)-α-methylbenzyl hydroxylamine **162** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (7:3), gave *N-(S)-α-methylbenzyl-O-acetoyl hydroxylamine* **166** (49%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3236, 3030, 2978, 2933, 2876, 1742, 1604, 1496, 1454, 1369, 1232, 1054, 946; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20–7.30 (m, 5H, ArH), 4.10 (q, 1H, *J* 6.7 Hz, CHN), 1.95 (s, 3H, CH_3), 1.35 (d, 3H, *J* 6.7 Hz, CH_3CN); ^{13}C NMR (100 MHz, $CDCl_3$), δ 171.0, 141.3, 128.6, 127.8, 127.0, 60.7, 19.7, 19.2 ppm; MS

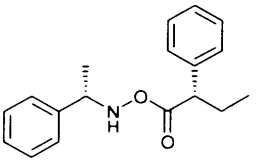
(EI): *m/z* 179 $[M+H]^+$. HRMS calculated for $C_{10}H_{14}NO_2$ $[M+H]^+$ 179.0941, found 179.0942. $[\alpha]^{23}_D$ −56.8 (1 g/100 mL, $CHCl_3$).

_N_-Methyl-_O_-(_S_)-2-phenylbutanoyl hydroxylamine 174.



Compound **174** was synthesised from (*S*)-2-phenylbutyric acid **168** (1.0 g, 6.1 mmol) and *N*-methyl hydroxylamine hydrochloride **61** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (7:3), gave *N-methyl-O-(S)-2-phenylbutanoyl hydroxylamine* **174** (61%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3249, 3030, 2966, 2934, 2876, 1734, 1602, 1492, 1455, 1438, 1354, 1265, 1221, 1197, 1162, 1131, 961; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15–7.30 (m, 5H, ArH), 6.95–7.10 (br, 1H, NH), 3.40 (t, 1H, *J* 7.7 Hz, CHCO), 2.65 (s, 3H, CH_3), 2.00–2.10 (m, 1H, CH_2), 1.70–1.80 (m, 1H, CH_2), 0.80 (t, 3H, *J* 7.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 174.2, 138.2, 128.7, 127.9, 127.5, 51.9, 39.6, 26.7, 12.1 ppm; MS (EI): *m/z* 193 $[M+H]^+$. HRMS calculated for $C_{11}H_{16}NO_2$ $[M+H]^+$ 193.1097, found 193.1096. $[\alpha]^{23}_D$ +58.6 (1 g/100 mL, $CHCl_3$).

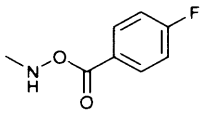
_N_-(_S_)-α-Methylbenzyl-_O_-(_S_)-2-phenylbutanoyl hydroxylamine 175.



Compound **175** was synthesised from (*S*)-2-phenylbutyric acid **168** (0.75 g, 4.6 mmol) and *N*-(*S*)-α-methylbenzyl hydroxylamine **162** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *N-(S)-α-methylbenzyl-O-(S)-2-phenylbutanoyl hydroxylamine* **175** (63%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3236, 3029, 2968, 2933, 2875, 1732, 1602, 1495, 1454, 1362, 1264, 1196, 1150; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10–7.25 (m, 10H, ArH), 4.00 (q, 1H, *J* 6.7 Hz, CHN), 3.30 (t, 1H, *J* 7.7 Hz, CHCO), 1.90–2.00 (m, 1H, CH_2), 1.60–1.70 (m, 1H, CH_2), 1.30 (d, 3H, *J* 6.7 Hz, CH_3CN), 0.70 (t, 3H, *J* 7.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 174.1, 141.3, 138.2, 128.7,

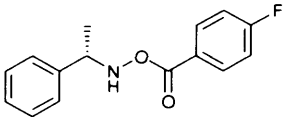
128.5, 128.0, 127.8, 127.4, 127.1, 60.7, 51.9, 26.5, 19.4, 12.0 ppm; MS (EI): *m/z* 283 $[M+H]^+$. HRMS calculated for $C_{18}H_{22}NO_2$ $[M+H]^+$ 283.1567, found 283.1569. $[\alpha]^{23}_D$ −13.2 (1 g/100 mL, $CHCl_3$).

_N_-Methyl-_O_-4-fluorobenzoyl hydroxylamine 178.



Compound **178** was synthesised from 4-fluorobenzoic acid (0.75 g, 5.35 mmol) and *N*-methyl hydroxylamine hydrochloride **61** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (3:2), gave *N-methyl-O-4-fluorobenzoyl hydroxylamine* **178** (42%) as a white solid. M.p. 26–28 °C. IR (thin film)/cm^{-1}: 3246, 2969, 1724, 1603, 1508, 1474, 1436, 1414, 1272, 1239, 1156, 1080, 1014, 853, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, 2H, *J* 9.0, 5.4 Hz, ArH), 7.05 (t, 2H, *J* 8.7 Hz, ArH), 6.95–7.05 (br, 1H, NH), 2.90 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.0, 165.9, 132.0, 124.62, 115.8, 39.9 ppm; MS (ES): *m/z* 170 $[M+H]^+$. HRMS calculated for $C_8H_9NO_2F$ $[M+H]^+$ 170.0612, found 170.0612.

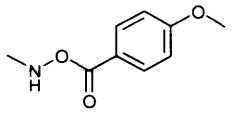
_N_-(*S*)-α-Methylbenzyl-_O_-4-fluorobenzoyl hydroxylamine 179.



Compound **179** was synthesised from 4-fluorobenzoic acid (0.5 g, 3.6 mmol) and *N*-(*S*)-α-methylbenzyl hydroxylamine **162** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *N-(S)-α-methylbenzyl-O-4-fluorobenzoyl hydroxylamine* **179** (59%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3233, 2977, 1724, 1604, 1507, 1454, 1412, 1373, 1306, 1269, 1239, 1155, 1084, 1014, 852, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.90 (m, 2H, ArH), 7.30–7.35 (m, 2H, ArH), 7.25–7.30 (m, 2H, ArH), 7.20–7.25 (m, 1H, ArH), 7.00 (at, 2H, *J* 8.7 Hz, ArH), 4.25 (q, 1H, *J* 6.7 Hz, CHN), 1.45 (d, 3H, *J* 6.7 Hz, CH_3CN); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.0, 165.9, 141.2, 132.0, 128.7, 128.0, 127.1, 124.6, 115.8, 61.0, 19.7 ppm; MS (ES): *m/z* 260 $[M+H]^+$. HRMS

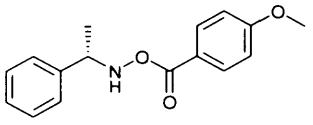
calculated for $C_{15}H_{15}NO_2F$ $[M+H]^+$ 260.1081, found 260.1084. $[\alpha]^{23}_D$ −71.6 (1 g/100 mL, $CHCl_3$).

N-Methyl-O-4-methoxybenzoyl hydroxylamine 181.



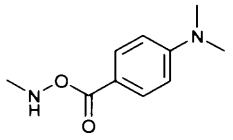
Compound **181** was synthesised from 4-methoxybenzoic acid **199** (5.0 g, 33 mmol) and *N*-methyl hydroxylamine hydrochloride **61** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (1:1), gave *N-methyl-O-4-methoxybenzoyl hydroxylamine* **181** (72%) as a white solid. M.p. 38–43 °C. IR (thin film)/cm^{-1}: 3246, 2932, 1718, 1606, 1511, 1465, 1421, 1318, 1257, 1170, 1080, 1027, 846, 763; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 2H, *J* 9.0 Hz, ArH), 6.85 (d, 2H, *J* 9.0 Hz, ArH), 3.80 (s, 3H, OMe), 2.85 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.7, 163.7, 131.4, 120.6, 113.8, 55.5, 39.9 ppm; MS (ES): *m/z* 182 $[M+H]^+$.

N-(S)-α-Methylbenzyl-O-4-methoxybenzoyl hydroxylamine 182.



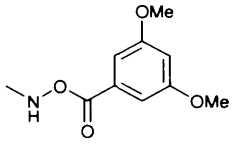
Compound **182** was synthesised from 4-methoxybenzoic acid **199** (0.6 g, 3.9 mmol) and *N*-(*S*)-α-methylbenzyl hydroxylamine **162** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (3:1), gave *N-(S)-α-methylbenzyl-O-4-methoxybenzoyl hydroxylamine* **182** (81%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3232, 2975, 1714, 1606, 1581, 1510, 1455, 1421, 1317, 1258, 1169, 1089, 1027, 845, 762; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, 2H, *J* 9.0 Hz, ArH), 7.30–7.35 (m, 2H, ArH), 7.25 (t, 2H, *J* 7.3 Hz, ArH), 7.20–7.25 (m, 1H, ArH), 6.80 (d, 2H, *J* 9.0 Hz, ArH), 4.20 (q, 1H, *J* 6.7 Hz, CHN), 3.75 (s, 3H, OMe), 1.45 (d, 3H, *J* 6.7 Hz, CH_3CN); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.7, 163.7, 141.3, 131.4, 128.6, 127.9, 127.2, 120.6, 113.8, 60.9, 55.5, 19.8 ppm; MS (APcI): *m/z* 272 $[M+H]^+$. HRMS calculated for $C_{16}H_{18}NO_3$ $[M+H]^+$ 272.1281, found 272.1278. $[\alpha]^{23}_D$ −76 (1 g/100 mL, $CHCl_3$).

N-Methyl-O-4-dimethylaminobenzoyl hydroxylamine 347.



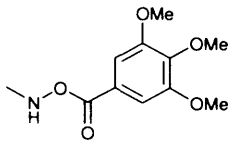
Compound **347** was synthesised from 4-dimethylaminobenzoic acid **184** (1.0 g, 6.1 mmol) and *N*-methyl hydroxylamine hydrochloride **61** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (1:1), gave *N-methyl-O-4-dimethylaminobenzoyl hydroxylamine* **347** (41%) as a white solid. M.p. 103–108 °C. IR (thin film)/cm^{-1}: 3253, 2906, 1702, 1620, 1461, 1377, 1320, 1289, 1236, 1190, 1098, 971, 826, 764; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, 2H, *J* 9.0 Hz, ArH), 6.60 (d, 2H, *J* 9.0 Hz, ArH), 3.00 (s, 6H, NMe_2), 2.80 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 167.4, 153.5, 131.1, 114.7, 110.7, 40.1, 40.0 ppm; MS (APcI): *m/z* 195 $[M+H]^+$. HRMS calculated for $C_{10}H_{15}N_2O_2$ $[M+H]^{+}$ 195.1134, found 195.1142.

N-Methyl-O-3,5-dimethoxybenzoyl hydroxylamine 348.



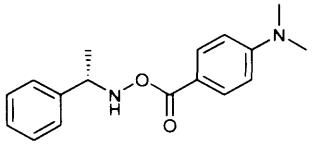
Compound **348** was synthesised from 3,5-dimethoxybenzoic acid **185** (1.0 g, 5.5 mmol) and *N*-methyl hydroxylamine hydrochloride **61** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (1:1), gave *N-methyl-O-3,5-dimethoxy benzoylhydroxylamine* **348** (25%) as a white solid. M.p. 39–44 °C. IR (thin film)/cm^{-1}: 3246, 2941, 1720, 1596, 1461, 1428, 1351, 1326, 1304, 1225, 1206, 1158, 1096, 1064, 1045, 933, 846, 757; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.80 (br, 1H, NH), 7.10 (s, 2H, ArH), 6.60 (s, 1H, ArH), 3.75 (s, 6H, OMe), 2.90 (s, 3H, NMe); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.7, 160.7, 130.1, 106.9, 106.1, 55.6, 39.8 ppm; MS (EI): *m/z* 211 $[M+H]^+$. HRMS calculated for $C_{10}H_{14}NO_4$ $[M+H]^{+}$ 211.0845, found 211.0854.

N-Methyl-O-3,4,5-trimethoxybenzoyl hydroxylamine 349.



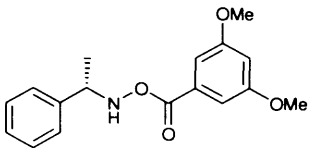
Compound **349** was synthesised from 3,4,5-trimethoxybenzoic acid **186** (1.0 g, 4.7 mmol) and *N*-methyl hydroxylamine hydrochloride **61** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (2:3), gave *N-methyl-O-3,4,5-trimethoxybenzoyl hydroxylamine* **349** (42%) as a white solid. M.p. 71–74 °C. IR (thin film)/cm^{-1}: 3246, 2942, 1713, 1588, 1504, 1463, 1415, 1336, 1230, 1185, 1130, 993, 862, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.80 (br, 1H, NH), 7.20 (s, 2H, ArH), 3.85 (s, 9H, OMe), 2.90 (s, 3H, NMe); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.6, 153.0, 142.5, 123.2, 106.5, 61.0, 56.3, 40.0 ppm; MS (EI): *m/z* 241 $[M+H]^+$. HRMS calculated for $C_{11}H_{16}NO_5$ $[M+H]^+$ 241.0950, found 241.0950.

N-(S)-α-Methylbenzyl-O-4-methoxybenzoyl hydroxylamine 350.



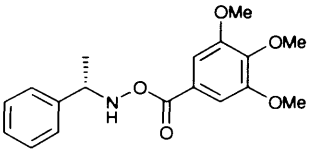
Compound **350** was synthesised from 4-dimethylaminobenzoic acid **184** (0.6 g, 3.6 mmol) and *N*-(*S*)-α-methylbenzyl hydroxylamine **162** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (65:35), gave *N-(S)-α-methylbenzyl-O-4-dimethylaminobenzoyl hydroxylamine* **350** (84%) as a white solid. M.p. 54–58 °C. IR (thin film)/cm^{-1}: 3230, 2928, 1701, 1607, 1529, 1445, 1370, 1275, 1184, 1068, 825, 762, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, 2H, *J* 9.1 Hz, ArH), 7.45 (d, 2H, *J* 7.0 Hz, ArH), 7.35 (t, 2H, *J* 7.3 Hz, ArH), 7.30–7.35 (m, 1H, ArH), 6.65 (d, 2H, *J* 9.1 Hz, ArH), 4.30 (q, 1H, *J* 6.7 Hz, CHN), 3.05 (s, 6H, NMe_2), 1.50 (d, 3H, *J* 6.7 Hz, CH_3CN); ^{13}C NMR (100 MHz, $CDCl_3$), δ 167.4, 153.5, 141.5, 131.1, 128.5, 127.8, 127.2, 114.8, 110.8, 60.9, 40.1, 19.8 ppm; MS (ES): *m/z* 285 $[M+H]^+$. HRMS calculated for $C_{17}H_{21}N_2O_2$ $[M+H]^+$ 285.1598, found 285.1601. $[\alpha]^{23}_D$ −98 (1 g/100 mL, $CHCl_3$).

N-(S)-α-Methylbenzyl-O-4-methoxybenzoyl hydroxylamine 351.



Compound **351** was synthesised from 3,5-dimethoxybenzoic acid **185** (0.6 g, 3.3 mmol) and *N*-(*S*)-α-methylbenzyl hydroxylamine **162** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *N-(S)-α-methylbenzyl-O-3,5-dimethoxybenzoyl hydroxylamine* **351** (66%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3230, 2969, 2932, 1720, 1595, 1458, 1428, 1351, 1326, 1305, 1206, 1157, 1045, 845, 757, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.90 (br, 1H, NH), 7.45 (d, 2H, *J* 6.9 Hz, ArH), 7.40 (t, 2H, *J* 7.3 Hz, ArH), 7.30–7.35 (m, 1H, ArH), 7.10 (d, 2H, *J* 2.4 Hz, ArH), 6.65 (t, 1H, *J* 2.4 Hz, ArH), 4.35 (q, 1H, *J* 6.6 Hz, CHN), 3.80 (s, 6H, OMe), 1.55 (d, 3H, *J* 6.6 Hz, CH_3CN); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.7, 160.7, 141.1, 130.1, 128.6, 127.9, 127.2, 106.9, 106.0, 60.9, 55.6, 19.6 ppm; MS (EI): *m/z* 301 $[M+H]^+$. HRMS calculated for $C_{17}H_{20}NO_4$ $[M+H]^+$ 302.1387, found 302.1389.

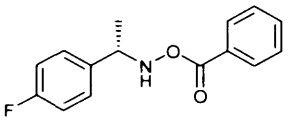
N-(S)-α-Methylbenzyl-O-4-methoxybenzoyl hydroxylamine 352.



Compound **352** was synthesised from 3,4,5-trimethoxybenzoic acid **186** (0.6 g, 2.8 mmol) and *N*-(*S*)-α-methylbenzyl hydroxylamine **162** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (3:1), gave *N-(S)-α-methylbenzyl-O-3,4,5-trimethoxybenzoyl hydroxylamine* **352** (88%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3239, 2935, 1715, 1588, 1504, 1457, 1416, 1337, 1218, 1174, 1128, 1002, 754, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.90 (br, 1H, NH), 7.45 (d, 2H, *J* 6.8 Hz, ArH), 7.40 (t, 2H, *J* 7.4 Hz, ArH), 7.30–7.35 (m, 1H, ArH), 7.20 (s, 2H, ArH), 4.30 (q, 1H, *J* 6.4 Hz, CHN), 3.90 (s, 3H, *p*-OMe), 3.85 (s, 6H, *m*-OMe), 1.55 (d, 3H, *J* 6.4 Hz, CH_3CN); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.6, 153.0, 142.4, 141.1, 128.6, 128.0, 127.2, 123.2, 106.5, 61.2,

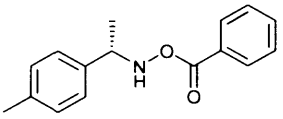
61.0, 56.2, 19.6 ppm; MS (EI): *m/z* 331 $[M+H]^+$. HRMS calculated for $C_{18}H_{22}NO_5$ $[M+H]^+$ 332.1492, found 332.1494.

N-(S)-α-Methyl-4-fluorobenzyl-O-benzoyl hydroxylamine 353.



Compound **353** was synthesised from (*S*)-α-methyl-4-fluorobenzylamine **189** using general procedure 1. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1) gave *N-(S)-α-methyl-4-fluorobenzyl-O-benzoyl hydroxylamine* **353** (2.41 g, 63%) as a white solid. M.p. 41–46 °C. IR (thin film)/cm^{-1}: 3226, 2976, 1720, 1602, 1510, 1452, 1316, 1268, 1225, 1178, 1159, 1091, 1066, 1025, 997, 836; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, 2H, *J* 7.1 Hz, ArH), 7.50 (t, 1H, *J* 7.5 Hz, ArH), 7.30–7.40 (m, 4H, ArH), 6.95 (t, 2H, *J* 8.7 Hz, ArH), 4.20 (q, 1H, *J* 6.7 Hz, CHN), 1.45 (d, 3H, *J* 6.7 Hz, CH_3CN); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.8, 162.4, 137.0, 133.4, 129.3, 128.8, 128.6, 128.2, 115.5, 60.2, 19.8 ppm; MS (APcI): *m/z* 260 $[M+H]^+$. HRMS calculated for $C_{15}H_{15}NO_2F$ $[M+H]^+$ 260.1081, found 260.1081. $[\alpha]^{23}_D$ –69.2 (1 g/100 mL, $CHCl_3$).

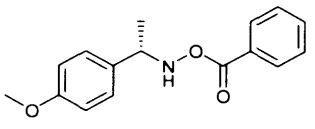
N-(S)-α-Methyl-4-methylbenzyl-O-benzoyl hydroxylamine 354.



Compound **354** was synthesised from (*S*)-α-methyl-4-methylbenzylamine **190** using general procedure 1. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1) gave *N-(S)-α-methyl-4-methylbenzyl-O-benzoyl hydroxylamine* **354** (2.61 g, 75%) as a white solid. M.p. 33–35 °C. IR (thin film)/cm^{-1}: 3226, 2964, 1718, 1600, 1514, 1451, 1313, 1268, 1174, 1088, 1066, 1022, 816; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, 2H, *J* 7.1 Hz, ArH), 7.45 (t, 1H, *J* 7.5 Hz, ArH), 7.30 (at, 2H, *J* 7.7 Hz, ArH), 7.20 (d, 2H, *J* 8.0 Hz, ArH), 7.10 (d, 2H, *J* 8.0 Hz, ArH), 4.20 (q, 1H, *J* 6.6 Hz, CHN), 2.25 (s, 3H, *p*-Me), 1.45 (d, 3H, *J* 6.6 Hz, CH_3CN); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.9, 138.1, 137.6, 133.3, 129.4, 129.3, 128.5, 128.4, 127.1, 60.7, 21.2, 19.7 ppm; MS (ES): *m/z* 256 $[M+H]^+$. HRMS

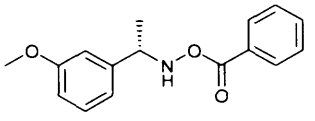
calculated for $C_{16}H_{18}NO_2$ $[M+H]^+$ 256.1332, found 256.1331. $[\alpha]^{23}_D$ −78 (1 g/100 mL, $CHCl_3$).

N-(S)-α-Methyl-4-methoxybenzyl-O-benzoyl hydroxylamine 193.



Compound **193** was synthesised from (*S*)-α-methyl-4-methoxybenzylamine **191** using general procedure 1. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1) gave *N-(S)-α-methyl-4-methoxybenzyl-O-benzoyl hydroxylamine* **193** (2.7 g, 74%) as a white solid. M.p. 34–37 °C. IR (thin film)/cm^{-1}: 3235, 2973, 1719, 1611, 1514, 1451, 1264, 1248, 1177, 1088, 1059, 1025, 829; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 2H, *J* 7.1 Hz, ArH), 7.45 (t, 1H, *J* 7.5 Hz, ArH), 7.35 (at, 2H, *J* 7.7 Hz, ArH), 7.25 (d, 2H, *J* 8.7 Hz, ArH), 6.80 (d, 2H, *J* 8.7 Hz, ArH), 4.20 (q, 1H, *J* 6.6 Hz, CHN), 3.70 (s, 3H, OMe), 1.45 (d, 3H, *J* 6.6 Hz, CH_3CN); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.9, 159.3, 133.3, 133.0, 129.3, 128.5, 128.38, 128.36, 114.0, 60.3, 55.3, 19.7 ppm; MS (ES): *m/z* 272 $[M+H]^+$. HRMS calculated for $C_{16}H_{18}NO_3$ $[M+H]^+$ 272.1281, found 272.1280. $[\alpha]^{23}_D$ −82.2 (1 g/100 mL, $CHCl_3$).

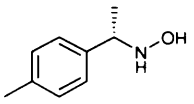
N-(S)-α-Methyl-3-methoxybenzyl-O-benzoyl hydroxylamine 194.



Compound **194** was synthesised from (*S*)-α-methyl-3-methoxybenzylamine using general procedure 1. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (3:1) gave *N-(S)-α-methyl-3-methoxybenzyl-O-benzoyl hydroxylamine* **194** (2.95 g, 80%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3232, 2975, 2835, 1720, 1601, 1586, 1489, 1452, 1436, 1372, 1316, 1267, 1177, 1091, 1066, 1025, 983, 876, 829, 784; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, 2H, *J* 7.1 Hz, ArH), 7.40–7.45 (m, 1H, ArH), 7.30 (t, 2H, *J* 7.7 Hz, ArH), 7.15 (t, 1H, *J* 8.2 Hz, ArH), 6.85–6.90 (m, 2H, ArH), 6.70–6.75 (m, 1H, ArH), 4.20 (q, 1H, *J* 6.7 Hz, CHN), 3.65 (s, 3H, OMe), 1.40 (d, 3H, *J* 6.7 Hz, CH_3CN); ^{13}C NMR (100 MHz,

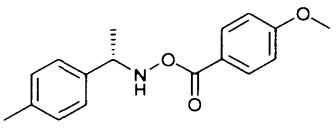
$CDCl_3$), δ 166.8, 159.8, 142.9, 133.4, 129.6, 129.4, 128.5, 128.3, 119.4, 113.4, 112.5, 60.9, 55.2, 19.8 ppm; MS (ES): *m/z* 272 $[M+H]^+$. HRMS calculated for $C_{16}H_{18}NO_3$ $[M+H]^+$ 272.1281, found 272.1280. $[\alpha]^{23}_D$ −73 (1 g/100 mL, $CHCl_3$).

N-(S)-α-Methyl-4-methylbenzyl hydroxylamine 198.



Ammonium hydroxide (33%, 1 mL) was added dropwise (over 5 min) to a solution of *N*-(*S*)-α-methyl-4-methylbenzyl-*O*-benzoyl hydroxylamine **354** (1.0 g, 3.92 mmol) in methanol (2 mL) under nitrogen, with stirring at r.t. overnight. The methanol was then removed under reduced pressure and the residue dissolved in ethyl acetate (20 mL), washed with brine (20 mL), dried ($MgSO_4$) and concentrated to give the crude product, which was purified on silica, eluting with petroleum ether-ethyl acetate (1:1) to give *N-(S)-α-methyl-4-methylbenzyl hydroxylamine* **198** (592 mg, 83%) as a white solid. M.p. 70–75 °C. IR (thin film)/cm^{-1}: 3255, 3166, 2972, 2875, 1682, 1654, 1634, 1560, 1508, 1458, 1077, 992; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, 2H, *J* 8.0 Hz, ArH), 7.10 (d, 2H, *J* 8.0 Hz, ArH), 4.20–4.70 (br, 2H, NH and OH), 4.00 (q, 1H, *J* 6.6 Hz, CHN), 2.25 (s, 3H, *p*-Me), 1.30 (d, 3H, *J* 6.6 Hz, CH_3CN); ^{13}C NMR (100 MHz, $CDCl_3$), δ 139.1, 137.3, 129.3, 127.1, 61.5, 21.1, 19.4 ppm.

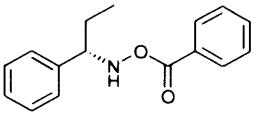
N-(S)-α-Methyl-4-methylbenzyl-O-4-methoxy benzoyl hydroxylamine 196.



Compound **196** was synthesised from 4-methoxybenzoic acid **199** and *N*-(*S*)-α-methyl-4-methylbenzyl hydroxylamine **162** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *N-(S)-α-methyl-4-methylbenzyl-O-4-methoxy benzoyl hydroxylamine* **196** (0.50 g, 80%) as a white solid. M.p. 54–58 °C. IR (thin film)/cm^{-1}: 2972, 1718, 1660, 1606, 1509, 1458, 1416, 1258, 1168, 1028; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, 2H, *J* 8.8 Hz, ArH), 7.20 (d, 2H, *J* 7.9 Hz, ArH), 7.10 (d, 2H, *J* 7.9 Hz, ArH), 6.80 (d, 2H, *J* 8.8 Hz, ArH), 4.20 (q, 1H, *J* 6.6 Hz, CHN), 3.75 (s, 3H, OMe), 2.25 (s,

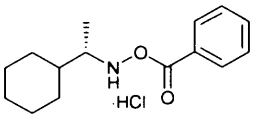
3H, *p*-Me), 1.45 (d, 3H, *J* 6.6 Hz, CH_3CN); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.7, 163.6, 138.2, 137.5, 131.4, 129.3, 127.1, 120.7, 113.8, 60.7, 55.5, 21.1, 19.7 ppm; MS (ES): *m/z* 286 $[M+H]^+$. HRMS calculated for $C_{17}H_{20}NO_3$ $[M+H]^+$ 286.1438, found 286.1441. $[\alpha]^{23}_D$ –90.6 (1 g/100 mL, $CHCl_3$).

N-(S)-α-Ethylbenzyl-O-benzoyl hydroxylamine 206.



Compound **206** was synthesised from (*S*)-α-ethylbenzylamine **205** (1.0 g, 7.4 mmol) using general procedure 1. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1) gave *N-(S)-α-ethylbenzyl-O-benzoyl hydroxylamine* **206** (75%) as a white solid. M.p. 28–33 °C. IR (thin film)/cm^{-1}: 3229, 2963, 2931, 2876, 1720, 1452, 1268, 1089, 1065; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–8.00 (br, 1H, NH), 7.80 (d, 2H, *J* 7.1 Hz, ArH), 7.45 (t, 1H, *J* 7.5 Hz, ArH), 7.20–7.35 (m, 7H, ArH), 3.95 (dd, 1H, *J* 8.3, 5.8 Hz, CHN), 1.90–2.00 (m, 1H, CH_2), 1.70–1.80 (m, 1H, CH_2), 0.80 (t, 3H, *J* 7.5 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.9, 140.0, 133.3, 129.3, 128.53, 128.49, 128.4, 127.9, 127.7, 67.7, 26.8, 10.6 ppm; MS (ES): *m/z* 256 $[M+H]^+$. HRMS calculated for $C_{16}H_{18}NO_2$ $[M+H]^+$ 256.1338, found 256.1341. $[\alpha]^{23}_D$ +64 (1 g/100 mL, $CHCl_3$).

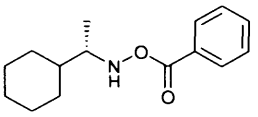
N-(S)-α-Methylcyclohexyl-O-benzoyl hydroxylamine hydrochloride 207·HCl.



Compound **207·HCl** was synthesised from *N*-(*S*)-α-methylcyclohexylamine (1.0 g, 7.9 mmol) using general procedure 1. Conversion to the HCl salt (Chapter 9.1.1.2) gave *N-(S)-α-methylcyclohexyl-O-benzoyl hydroxylamine hydrochloride* **207·HCl** (76%) as a white solid, which was collected by filtration. M.p. 105–109 °C. IR (thin film)/cm^{-1}: 2925, 2843, 1718, 1446, 1270, 1064, 1020, 767, 707; ^1H NMR (400 MHz, $CDCl_3$) δ 9.40–9.70 (br, 2H, NH_2^+), 7.95 (d, 2H, *J* 7.1 Hz, ArH), 7.65 (t, 1H, *J* 7.5 Hz, ArH), 7.55 (at, 2H, *J* 7.7 Hz, ArH), 3.00–3.10 (m, 1H, CHN), 1.65–1.80 (m, 4H), 1.55–1.65 (m, 1H), 1.44–1.55 (m, 1H), 1.10–1.25 (m, 4H), 1.05 (d, 3H, *J* 6.6

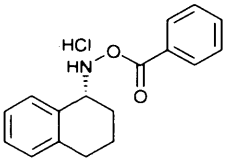
Hz, CH_3CN), 1.00–1.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.8, 134.1, 129.5, 129.3, 128.7, 60.5, 40.1, 29.8, 28.1, 26.6, 26.5, 26.3, 14.6 ppm; MS (APcI): *m/z* 248 $[M+H]^+$. HRMS calculated for $C_{15}H_{22}NO_2$ $[M+H]^+$ 248.1645, found 248.1645.

_N_-(_S_)-α-Methylcyclohexyl-_O_-benzoyl hydroxylamine 207.



pH 10.5 buffer (250 mL) was added quickly to a solution of _N_-(_S_)-α-methylcyclohexyl-_O_-benzoyl hydroxylamine hydrochloride **207·HCl** (500 mg) in dichloromethane (250 mL), with vigorous stirring at r.t. for one hour. The reaction mixture was then separated and the aqueous layer was extracted with dichloromethane (3 x 100 mL). The organic extracts were then combined with the organic layer and washed with brine (250 mL), dried (Na_2SO_4) and concentrated to give *N-(S)-α-methylcyclohexyl-O-benzoyl hydroxylamine* **207** (371 mg, 85%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3235, 2925, 2852, 1719, 1602, 1584, 1450, 1377, 1315, 1271, 1177, 1092, 1066, 1025, 708; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, 2H, *J* 7.0 Hz, ArH), 7.70–7.85 (br, 1H, NH), 7.50 (t, 1H, *J* 7.5 Hz, ArH), 7.40 (at, 2H, *J* 7.7 Hz, ArH), 2.90–3.00 (m, 1H, CHN), 1.65–1.80 (m, 4H), 1.55–1.65 (m, 1H), 1.40–1.50 (m, 1H), 1.10–1.25 (m, 3H), 1.05 (d, 3H, *J* 6.5 Hz, CH_3CN), 1.00–1.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 167.0, 133.3, 129.3, 128.6, 128.5, 61.3, 40.8, 29.7, 28.4, 26.5, 26.4, 26.3, 15.0 ppm; MS (ES): *m/z* 248 $[M+H]^+$. $[\alpha]^{23}_D$ +2 (1 g/100 mL, $CHCl_3$).

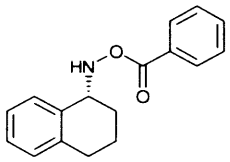
_N_-(_S_)-1,2,3,4-Tetrahydronaphthyl-_O_-benzoyl hydroxylamine hydrochloride 208·HCl.



Compound **208·HCl** was synthesised from _N_-(_S_)-1,2,3,4-tetrahydronaphthylamine (0.5 mL, 3.5 mmol) using general procedure 1. Conversion to the HCl salt (Chapter

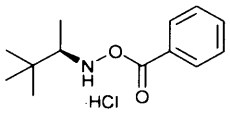
9.1.1.2) gave *N-(S)-1,2,3,4-tetrahydronaphthyl-O-benzoyl hydroxylamine hydrochloride* **208·HCl** (11%) as a white crystalline solid, which was collected by filtration. M.p. 90–93 °C. IR (thin film)/cm^{-1}: 2939, 1717, 1450, 1315, 1268, 1089, 1065, 1025, 707; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 2H, *J* 7.0 Hz, ArH), 7.65 (m, 1H, ArH), 7.55 (t, 2H, *J* 7.8 Hz, ArH), 7.50 (d, 1H, *J* 6.9 Hz, ArH), 7.15–7.25 (m, 2H, ArH), 7.10–7.15 (m, 1H. ArH), 6.10–6.50 (br, 2H, NH_2^+), 4.30 (t, 1H, *J* 4.5 Hz, CHN), 2.65–2.85 (m, 2H), 1.90–2.10 (m, 2H), 1.80–1.90 (m, 1H), 1.65–1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.0, 138.7, 134.1, 134.0, 130.1, 129.44, 129.41, 129.3, 128.9, 127.9, 126.1, 57.9, 29.2, 26.7, 18.7 ppm; MS (ES): *m/z* 268 $[M+H]^+$. HRMS calculated for $C_{17}H_{18}NO_2$ $[M+H]^{\cdot+}$ 268.1332, found 268.1330.

N-(S)-1,2,3,4-Tetrahydronaphthyl-O-benzoyl hydroxylamine 208.



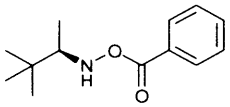
Compound **208** was synthesised from (*S*)-1,2,3,4-tetrahydronaphthylamine (2.5 g, 17.0 mmol) using general procedure 1. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1) gave *N-(S)-1,2,3,4-tetrahydronaphthyl-O-benzoyl hydroxylamine* **208** (45%) as a pale brown solid. M.p. 30–34 °C. IR (thin film)/cm^{-1}: 3224, 2937, 1717, 1449, 1314, 1286, 1088, 1064, 1022; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 2H, *J* 7.6 Hz, ArH), 7.80–7.85 (br, 1H, NH), 7.50 (t, 1H, *J* 7.4 Hz, ArH), 7.35–7.45 (m, 3H, ArH), 7.10–7.20 (m, 2H, ArH), 7.00–7.10 (m, 1H, ArH), 4.20–4.30 (m, 1H, CHN), 2.75–2.85 (m, 1H), 2.60–2.70 (m, 1H), 2.10–2.20 (m, 1H), 2.00–2.10 (m, 1H),1.60–1.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 167.2, 138.8, 133.4, 132.9, 130.1, 129.4, 128.6, 128.5, 128.0, 126.1, 126.1, 58.7, 29.3, 26.5, 18.1 ppm. $[\alpha]^{23}_D$ −1.2 (1 g/100 mL, $CHCl_3$).

N-(R)-3,3-Dimethyl-2-butyl-O-benzoyl hydroxylamine hydrochloride 209·HCl.



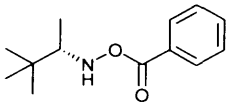
Compound **209·HCl** was synthesised from *N*-(*R*)-3,3-dimethyl-2-butylamine (2.0 g, 19.8 mmol) using general procedure 1. Conversion to the HCl salt (Chapter 9.1.1.2) gave *N-(R)-3,3-dimethyl-2-butyl-O-benzoyl hydroxylamine hydrochloride* **209·HCl** (81%) as a white crystalline solid, which was collected by filtration. M.p. 95–99 °C. IR (thin film)/cm^{-1}: 2962, 1719, 1602, 1451, 1364, 1315, 1271, 1177, 1089, 1066, 1026, 707; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90–10.20 (br, 2H, NH_2^+), 7.95 (d, 2H, *J* 7.2 Hz, ArH), 7.70 (t, 1H, *J* 7.5 Hz, ArH), 7.55 (at, 2H, *J* 7.7 Hz, ArH), 2.90 (q, 1H, *J* 7.0 Hz, CHN), 1.10 (d, 3H, *J* 7.0 Hz, CH_3CN), 0.95 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.2, 134.0, 129.4, 129.2, 128.8, 64.4, 34.0, 27.2, 13.7 ppm; MS (APcI): *m/z* 222 $[M+H]^+$. HRMS calculated for $C_{13}H_{20}NO_2$ $[M+H]^{+}$ 222.1489, found 222.1489.

N-(R)-3,3-Dimethyl-2-butyl-O-benzoyl hydroxylamine 209.



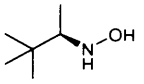
Compound **209** was synthesised from (*R*)-3,3-dimethyl-2-butylamine (2.0 g, 19.8 mmol) using general procedure 1. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1) gave *N-(R)-3,3-dimethyl-2-butyl-O-benzoyl hydroxylamine* **209** (81%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3247, 2963, 2860, 1720, 1602, 1452, 1365, 1316, 1272, 1178, 1089, 1067, 1026, 707; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 2H, *J* 7.1 Hz, ArH), 7.60 (t, 1H, *J* 7.5 Hz, ArH), 7.45 (at, 2H, *J* 7.7 Hz, ArH), 2.85 (q, 1H, *J* 6.5 Hz, CHN), 1.10 (d, 3H, *J* 6.5 Hz, CH_3CN), 0.95 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 167.1, 133.3, 129.3, 129.1, 128.5, 65.1, 33.7, 26.8, 13.7 ppm; MS (APcI): *m/z* 222 $[M+H]^+$. $[\alpha]^{23}_D$ –44.2 (1 g/100 mL, $CHCl_3$).

N-(S)-3,3-Dimethyl-2-butyl-O-benzoyl hydroxylamine (S)-209.



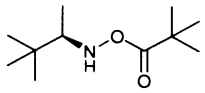
Compound **(S)-209** was synthesised from (*S*)-3,3-dimethyl-2-butylamine (2.5 g, 24.7 mmol) using general procedure 1. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1) gave *N-(S)-3,3-dimethyl-2-butyl-O-benzoyl hydroxylamine* **(S)-209** (85%) as a clear colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, 2H, *J* 6.8 Hz, ArH), 7.95–8.00 (br, 1H, NH), 7.55 (t, 1H, *J* 7.3 Hz, ArH), 7.45 (at, 2H, *J* 8.0 Hz, ArH), 2.90 (q, 1H, *J* 6.6 Hz, CHN), 1.20 (d, 3H, *J* 6.6 Hz, CH_3CN), 1.05 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 167.1, 133.3, 129.3, 129.3, 128.5, 65.0, 33.7, 26.8, 13.7 ppm. $[\alpha]^{23}_D$ +39.6 (1 g/100 mL, $CHCl_3$).

N-(R)-3,3-Dimethyl-2-butyl hydroxylamine 210.



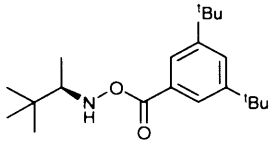
Ammonium hydroxide (33%, 6 mL) was added dropwise (over 5 min) to a solution of *N*-(*R*)-3,3-dimethyl-2-butyl-*O*-benzoyl hydroxylamine **209** (5.79 g, 26.16 mmol) in methanol (12 mL) under nitrogen, with stirring at r.t. overnight. The methanol was then removed under reduced pressure and the residue dissolved in ethyl acetate (20 mL), washed with brine (20 mL), dried ($MgSO_4$) and concentrated to give the crude product, which was purified on silica, eluting with petroleum ether-ethyl acetate (3:2) to give *N-(R)-3,3-dimethyl-2-butyl hydroxylamine* **210** (1.32 g, 43%) as a clear, pale yellow oil. IR (thin film)/cm^{-1}: 3281, 2961, 2871, 1464, 1396, 1372, 1340, 997, 880; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60–5.90 (br, 2H, NH and OH), 2.65 (q, 1H, *J* 6.4 Hz, CHN), 1.05 (d, 3H, *J* 6.4 Hz, CH_3CN), 0.85 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 65.7, 33.1, 26.7, 13.1 ppm.

N-(*R*)-3,3-Dimethyl-2-butyl-*O*-pivaloyl hydroxylamine 211.



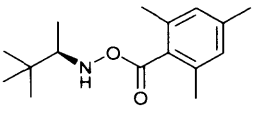
Compound **211** was synthesised from pivalic acid **139** (0.58 g, 5.7 mmol) and *N*-(*R*)-3,3-dimethyl-2-butyl hydroxylamine **210** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (85:15), gave *N-(R)-3,3-dimethyl- 2-butyl-O-pivaloyl hydroxylamine* **211** (59%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3258, 2968, 2872, 1727, 1480, 1461, 1396, 1365, 1279, 1146, 1105, 985; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.75 (br, 1H, NH), 2.70 (q, 1H, *J* 6.5 Hz, CHN), 1.20 (s, 9H, ^{t}Bu), 1.05 (d, 3H, *J* 6.5 Hz, CH_3CN), 0.95 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 178.8, 64.9, 38.3, 33.6, 27.1, 26.7, 13.4 ppm; MS (EI): *m/z* 201 $[M+H]^+$. HRMS calculated for $C_{11}H_{24}NO_2$ $[M+H]^{+}$ 201.1729, found 201.1728.

N-(*R*)-3,3-Dimethyl-2-butyl-*O*-3,5-di-*tert*-butylbenzoyl hydroxylamine 212.



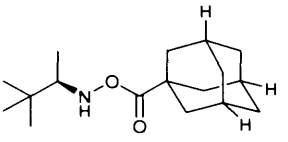
Compound **212** was synthesised from 3,5-di-*tert*-butyl benzoic acid **141** (1.5 g, 6.4 mmol) and *N*-(*R*)-3,3-dimethyl-2-butyl hydroxylamine **210** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *N-(R)-3,3-dimethyl-2-butyl-O-3,5-di-tert-butylbenzoyl hydroxylamine* **212** (53%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3257, 2963, 2869, 1719, 1601, 1477, 1395, 1364, 1312, 1235, 1114, 896; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 2H, ArH), 7.65 (s, 1H, ArH), 2.90 (q, 1H, *J* 6.5 Hz, CHN), 1.35 (s, 18H, *m*-^{t}Bu), 1.15 (d, 3H, *J* 6.5 Hz, CH_3CN), 1.05 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 168.0, 151.2, 127.8, 127.5, 123.6, 65.1, 35.0, 33.8, 31.4, 26.8, 13.7 ppm; MS (ES): *m/z* 334 $[M+H]^+$. HRMS calculated for $C_{21}H_{36}NO_2$ $[M+H]^{+}$ 334.2741, found 334.2744.

N-(*R*)-3,3-Dimethyl-2-butyl-*O*-2,4,6-trimethylbenzoyl hydroxylamine 213.



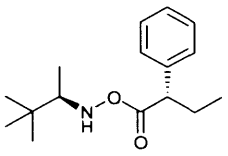
Compound **213** was synthesised from 2,4,6-trimethyl benzoic acid **142** (1.2 g, 7.3 mmol) and *N*-(*R*)-3,3-dimethyl-2-butyl hydroxylamine **210** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (85:15), gave *N-(R)-3,3-dimethyl-2-butyl-O-2,4,6-trimethylbenzoyl hydroxylamine* **213** (6%) as a clear colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 2H, ArH), 2.80 (q, 1H, *J* 6.5 Hz, CHN), 2.25 (s, 6H, *o*-CH_3), 2.00 (s, 3H, *p*-CH_3), 1.10 (d, 3H, *J* 6.5 Hz, CH_3CN), 0.95 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 170.5, 139.9, 135.7, 128.9, 128.5, 65.0, 33.7, 26.7, 21.2, 19.7, 14.0 ppm; MS (ES): *m/z* 264 $[M+H]^+$.

N-(*R*)-3,3-Dimethyl-2-butyl-*O*-adamantoyl hydroxylamine 214.



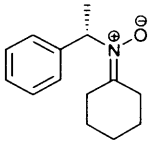
Compound **214** was synthesised from adamantane carboxylic acid **154** (1.4 g, 7.8 mmol) and *N*-(*R*)-3,3-dimethyl-2-butyl hydroxylamine **210** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *N-(R)-3,3-dimethyl-2-butyl-O-adamantoyl hydroxylamine* **214** (48%) as a white solid. M.p. 123–127 °C. IR (thin film)/cm^{-1}: 3255, 2907, 2852, 1721, 1452, 1364, 1266, 1221, 1182, 1102, 1060, 977; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (q, 1H, *J* 6.6 Hz, CHN), 1.95–2.00 (m, 3H), 1.85 (d, 6H, *J* 2.6 Hz), 1.60–1.70 (m, 6H), 1.00 (d, 3H, *J* 6.6 Hz, CH_3CN), 0.90 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 177.9, 65.0, 40.4, 38.7, 36.4, 33.6, 27.9, 26.7, 13.4 ppm; MS (ES): *m/z* 280 $[M+H]^+$. HRMS calculated for $C_{17}H_{30}NO_2$ $[M+H]^+$ 280.2277, found 280.2274.

N-(*R*)-3,3-Dimethyl-2-butyl-*O*-(*S*)-2-phenylbutanoyl hydroxylamine 215.



Compound **215** was synthesised from (*S*)-2-phenylbutyric acid **168** (0.58 g, 3.6 mmol) and *N*-(*R*)-3,3-dimethyl-2-butyl hydroxylamine **210** using general procedure 2. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (85:15), gave *N-(R)-3,3-dimethyl-2-butanoyl-O-(S)-2-phenylbutanoyl hydroxylamine* **215** (70%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3257, 2966, 2874, 1732, 1601, 1455, 1364, 1265, 1196, 1150, 1069, 984, 728, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20–7.25 (m, 4H, ArH), 7.15–7.20 (m, 1H, ArH), 3.40 (t, 1H, *J* 7.3 Hz, CHCO), 2.60 (q, 1H, *J* 6.5 Hz, CHN), 2.00–2.10 (m, 1H, CH_2), 1.70–1.80 (m, 1H, CH_2), 0.90 (d, 3H, *J* 6.5 Hz, CH_3CN), 0.80–0.85 (m, 12H, ^tBu and CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 174.5, 138.3, 128.6, 128.0, 127.4, 64.7, 52.1, 33.6, 26.6, 26.5, 13.4, 12.2 ppm; MS (APcI): *m/z* 264 $[M+H]^+$. HRMS calculated for $C_{16}H_{26}NO_2$ $[M+H]^+$ 264.1958, found 264.1962.

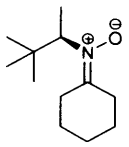
N-(*S*)-α-Methylbenzyl cyclohexyl nitrone 281.



Cyclohexanone **44** (1.13 mL, 10.9 mmol) was added dropwise (over 5 min) to a mixture of *N*-(*S*)-α-methylbenzyl hydroxylamine **162** (1.0 g, 7.29 mmol) and sodium sulphate (1.55 g, 10.9 mmol) in dry dichloromethane (6.0 mL), with stirring at 25 °C under nitrogen for 30 hours. The reaction mixture was was then diluted with dichloromethane (6.0 mL) and filtered, before concentrating *in vacuo*, to give *N-(S)-α-methylbenzyl cyclohexyl nitrone* **281** (1.48 g, 88%), as a pale yellow solid. M.p. 23–28 °C. IR (thin film)/cm^{-1}: 3242 (v. br), 2933, 2859, 1574, 1495, 1450, 1359, 1283, 1161, 1056, 996; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.40 (m, 2H, ArH), 7.15–7.30 (m, 3H, ArH), 5.40 (q, 1H, *J* 6.7 Hz, CHN), 2.60–2.80 (m, 2H), 2.50–2.60 (m, 1H), 2.40–2.50 (m, 1H), 1.70 (d, 3H, *J* 6.7 Hz, CH_3CN), 1.50–1.70 (m, 3H), 1.35–1.50 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 149.1, 139.8, 128.7,

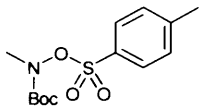
127.9, 126.8, 64.9, 29.5, 27.4, 25.7, 24.74, 24.67, 19.7 ppm; MS (ES): *m/z* 218 $[M+H]^+$. HRMS calculated for $C_{14}H_{20}NO$ $[M+H]^{\cdot+}$ 218.1545, found 218.1549.

N-(R)-3,3-Dimethyl-2-butylcyclohexyl nitrone 283.



Cyclohexanone **44** (0.18 mL, 1.73 mmol) was added dropwise (over 5 min) to a mixture of *N*-(*R*)-3,3-dimethyl-2-butyl hydroxylamine **210** (135 mg, 1.15 mmol) and sodium sulphate (245 mg, 1.73 mmol) in dry dichloromethane (1.0 mL), with stirring at 30 °C under nitrogen for 18 hours. The reaction mixture was then diluted with dichloromethane and filtered, before concentrating *in vacuo*, to give *N-(R)-3,3-dimethyl-2-butylcyclohexyl nitrone* **283** (165 mg, 73%), as a pale yellow solid. IR (thin film)/cm^{-1}: 3207 (v. br), 2938, 2861, 1452, 1367, 1163; ^1H NMR (400 MHz, $CDCl_3$) δ 4.10 (q, 1H, *J* 6.6 Hz, CHN), 2.65–2.80 (m, 2H), 2.50 (t, 2H, *J* 6.4 Hz), 1.55–1.65 (m, 4H), 1.50–1.55 (m, 2H), 1.30 (d, 3H, *J* 6.6 Hz, CH_3CN), 0.95 (s, 9H, ^{t}Bu).

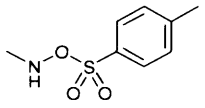
N-Methyl-N-Boc-O-toluene sulphonyl hydroxylamine 287.[53]



N-Methyl-*N*-Boc hydroxylamine **286** (1.0 g) was dissolved in dry dichloromethane (13.6 mL, [0.5M]) under nitrogen, and cooled to 0 °C. Triethylamine (1.14 mL, 8.15 mmol) and toluene sulphonyl chloride **285** (1.55 g, 8.15 mmol) were then added slowly (over 5 min) with stirring overnight warming to r.t. The reaction mixture was diluted with 1M HCl (15 mL) and extracted with ethyl acetate (3 x 30 mL). The combined extracts were washed with brine (90 mL), dried ($MgSO_4$) and concentrated to give the crude product, which was purified on silica, eluting with petroleum ether-ethyl acetate (4:1), to give *N-methyl-N-Boc-O-toluene sulphonyl hydroxylamine* **287** (73%), as a white solid. M.p. 59–64 °C. Lit. ref. m.p. 51–52 °C.[53] IR (thin film)/cm^{-1}: 2982, 1725, 1599, 1453, 1371, 1331, 1191, 1179, 1155, 1084, 846, 816, 758; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, 2H, *J* 8.2 Hz, ArH), 7.30 (d, 2H, *J* 8.2 Hz, ArH), 3.20 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 1.15 (s, 9H, ^{t}Bu); ^{13}C NMR (100

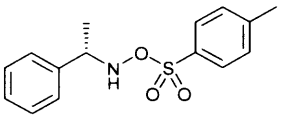
MHz, $CDCl_3$), δ 156.1, 145.8, 131.1, 129.7, 129.6, 83.3, 40.2, 27.6, 21.7 ppm; MS (ES): *m/z* 340 $[M+K]^+$. HRMS calculated for $C_{13}H_{19}NSO_5K$ $[M+K]^{\cdot+}$ 340.0621, found 340.0605.

N-Methyl-O-toluene sulphonyl hydroxylamine 86.[53]



N-Methyl-*N*-Boc-*O*-toluene sulphonyl hydroxylamine **287** (750 mg, 2.49 mmol) was dissolved in dry dichloromethane (2.5 mL, [1M]) under nitrogen, and cooled to 0 °C. Trifluoroacetic acid (3.8 mL, 49.77 mmol, 20 eq.) was then added dropwise (over 5 min) with stirring at 0 °C for 3 hours. The reaction mixture was then poured into ice-water (25 mL) and extracted with dichloromethane (3 x 30 mL). The organic extracts were then combined and washed with ice-cold water (50 mL), dried (Na_2SO_4) and concentrated at low temperature to give *N-methyl-O-toluene sulphonyl hydroxylamine* **86** (461 mg, 92%), as a pale orange solid. M.p. 41–46 °C. Lit. ref. m.p. 49–52 °C.[53] IR (thin film)/cm^{-1}: 3288, 2916, 1598, 1359, 1190, 1177, 1094, 1010, 808, 776; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, 2H, *J* 8.2 Hz, ArH), 7.25 (d, 2H, *J* 8.2 Hz, ArH), 5.60–5.70 (br, 1H, NH), 2.65 (s, 3H, CH_3), 2.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 145.1, 132.2, 129.6, 129.0, 40.1, 21.7 ppm; MS (APcI): *m/z* 202 $[M+H]^+$. HRMS calculated for $C_8H_{12}NSO_3$ $[M+H]^{\cdot+}$ 202.0538, found 202.0530.

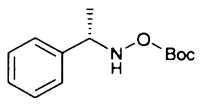
N-(S)-α-Methylbenzyl-O-toluene sulphonyl hydroxylamine 288.



N-(*S*)-α-Methylbenzyl hydroxylamine **162** (200 mg, 1.46 mmol) was dissolved in dry dichloromethane (2.9 mL, [0.5M]) under nitrogen, and cooled to 0 °C. Triethylamine (0.244 mL, 1.75 mmol) and toluene sulphonyl chloride **285** (334 mg, 1.75 mmol) were then added slowly (over 5 min) with stirring overnight warming to r.t. The reaction mixture was diluted with 1M HCl (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined extracts were washed with brine (60 mL), dried ($MgSO_4$) and concentrated to give the crude product, which was purified on silica, eluting with

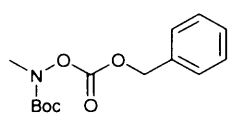
petroleum ether-ethyl acetate (4:1), to give *N-(S)-α-methylbenzyl-O-toluene sulphonyl hydroxylamine* **288** (12 mg, 4%), as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 2H, *J* 8.3 Hz, ArH), 7.20–7.25 (m, 2H, ArH), 7.10–7.15 (m, 5H, ArH), 4.90 (q, 1H, *J* 7.1 Hz, CHN), 2.30 (s, 3H, CH_3), 1.25 (d, 3H, *J* 7.1 Hz, CH_3CN) ppm.

N-(S)-α-Methylbenzyl-O-Boc hydroxylamine 291.



Potassium carbonate (1.23 g, 9.0 mmol) was added to a cooled (-78 °C) solution of *N*-(*S*)-α-methylbenzyl hydroxylamine **162** (2.5 g, 18.0 mmol) in a 1:1 mixture of THF and water (14 mL). A cooled (-78 °C) solution of di-*tert*-butyl dicarbonate **289** (4.37 g, 20.0 mmol) in THF (11 mL) was then added dropwise (over 5 min) to the reaction mixture and stirring was continued at -78 °C for 2 hours, then 0 °C for 2 hours, and finally at room temperature for a further hour. After this period, the solution was concentrated *in vacuo* and the residue was dissolved in dichloromethane (30 mL) before washing with water (2 x 20 mL) and brine (30 mL). The organic fraction was collected and dried (Na_2SO_4) and concentrated to give the crude product, which was purified on silica, eluting with petroleum ether-ethyl acetate (4:1), to give *N-(S)-α-methylbenzyl-O-Boc hydroxylamine* **291** (1.04 g, 24%), as a white solid. M.p. 26–30 °C. IR (thin film)/cm^{-1}: 3245, 2981, 2934, 1734, 1455, 1395, 1371, 1285, 1256, 1156, 1065, 833, 763; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.35 (m, 5H, ArH), 6.80–6.85 (br, 1H, NH), 4.15 (q, 1H, *J* 6.6 Hz, CHN), 1.35 (d, 3H, *J* 6.6 Hz, CH_3CN), 1.35 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 154.6, 141.1, 128.5, 127.8, 127.2, 83.7, 60.8, 27.7, 19.6 ppm; MS (ES): *m/z* 237 $[M+H]^+$. HRMS calculated for $C_8H_{12}NSO_3$ $[M+H]^+$ 237.1365, found 237.1362.

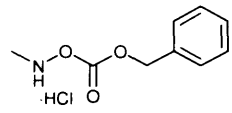
N-Methyl-N-Boc-O-benzylcarbonate hydroxylamine 293.



N-Methyl-*N*-Boc hydroxylamine **286** (1.0 g, 6.8 mmol) was dissolved in dry dichloromethane (13.6 mL, [0.5M]) under nitrogen, and cooled to 0 °C.

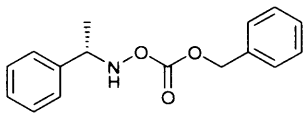
Triethylamine (1.14 mL, 8.15 mmol) and benzyl chloroformate **292** (1.16 mL, 8.15 mmol) were then added dropwise (over 5 min) with stirring overnight warming to r.t. The reaction mixture was diluted with 1M HCl (15 mL) and extracted with ethyl acetate (3 x 30 mL). The combined extracts were washed with brine (90 mL), dried ($MgSO_4$) and concentrated to give the crude product, which was purified on silica, eluting with petroleum ether-ethyl acetate (4:1), to give *N-methyl-N-Boc-O-benzylcarbonate hydroxylamine* **293** (1.5 g, 78%) as a white solid. M.p. 57–61 °C. IR (thin film)/cm^{-1}: 2980, 1786, 1718, 1456, 1411, 1369, 1238, 1149, 965, 854, 754, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.45 (m, 5H, ArH), 5.25 (s, 2H, CH_2), 3.25 (s, 3H, NMe), 1.45 (s, 9H, ^tBu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 155.3, 154.3, 134.4, 128.9, 128.7, 128.6, 82.8, 71.0, 37.7, 28.0 ppm; MS (ES): *m/z* 304 $[M+Na]^+$. HRMS calculated for $C_{14}H_{19}NO_5Na$ $[M+Na]^+$ 304.1161, found 304.1160.

N-Methyl-O-benzylcarbonate hydroxylamine hydrochloride 294·HCl.



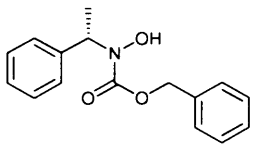
N-Methyl-*N*-Boc-*O*-benzylcarbonate hydroxylamine **293** (750 mg, 2.67 mmol) was dissolved in dry dichloromethane (2.67 mL) under nitrogen and cooled to 0 °C. 4M HCl/dioxane (3.33 mL, 13.33 mmol) was added dropwise (over 5 min) with stirring for 3 hours, by which time a precipitate had formed. The reaction mixture was then filtered under reduced pressure, washing with ether (10 mL), to give *N-methyl-O-benzylcarbonate hydroxylamine hydrochloride* **294·HCl** (428 mg, 74%) as a white solid. M.p. 93–98 °C. IR (thin film)/cm^{-1}: 3260, 2970, 1759, 1452, 1377, 1245, 1139, 959, 840, 748, 696; ^1H NMR (400 MHz, DMSO) δ 8.35–8.50 (br, 2H, NH_2^+), 7.30–7.40 (m, 5H, ArH), 5.15 (s, 2H, CH_2), 2.70 (s, 3H, NMe); ^{13}C NMR (100 MHz, DMSO), δ 154.8, 135.7, 129.0, 128.98, 128.8, 69.9, 39.0 ppm; MS (ES): *m/z* 182 $[M+H]^+$.

N-(S)-α-Methylbenzyl-O-benzylcarbonate hydroxylamine 296.



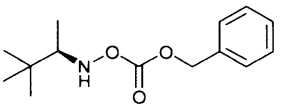
N-(*S*)-α-Methylbenzyl hydroxylamine **162** (1.0 g, 7.3 mmol) was dissolved in dry dichloromethane (14.6 mL) under nitrogen, and cooled to 0 °C. Triethylamine (1.22 mL, 8.75 mmol) and benzyl chloroformate **292** (1.25 mL, 8.75 mmol) were then added dropwise (over 5 min) with stirring overnight warming to r.t. The reaction mixture was diluted with 1M HCl (15 mL) and extracted with ethyl acetate (3 x 30 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated to give the crude product, which was purified on silica, eluting with petroleum ether-ethyl acetate (3:1), to give *N-(S)-α-methylbenzyl-O-benzylcarbonate hydroxylamine* **296** (955 mg, 48%) as a white solid. M.p. 27–31 °C. IR (thin film)/cm^{-1}: 3205 (small, sharp), 2963, 1747, 1493, 1455, 1378, 1259, 1225; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.30 (m, 10H, ArH), 6.30–6.40 (br, 1H, NH), 5.05 (s, 2H, CH_2), 4.20 (q, 1H, *J* 6.7 Hz, CHN), 1.35 (d, 3H, *J* 6.7 Hz, CH_3CN); ^{13}C NMR (100 MHz, $CDCl_3$), δ 156.1, 140.6, 134.7, 128.7, 128.64, 128.62, 128.4, 128.0, 127.2, 70.4, 60.9, 19.5 ppm; MS (ES): *m/z* 272 $[M+H]^+$. HRMS calculated for $C_{16}H_{18}NO_3$ $[M+H]^+$ 272.1287, found 272.1284. $[\alpha]^{23}_D$ –40.8 (1 g/100 mL, $CHCl_3$).

N-(S)-α-Methylbenzyl-N-benzylcarbonate hydroxylamine 297.



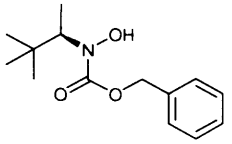
Compound **297** was synthesised in the same manner as that described for compound **296** above. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (3:1) gave *N-(S)-α-methylbenzyl-N-benzylcarbonate hydroxylamine* **297** (0.7 g, 35%) as a white solid. M.p. 63–68 °C. IR (thin film)/cm^{-1}: 3252 (v. br), 2934, 1698, 1455, 1410, 1305, 1210, 1123; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.30 (m, 10H, ArH), 6.20–6.30 (br, 1H, OH), 5.25 (q, 1H, *J* 7.0 Hz, CHN), 5.10 (s, 2H, CH_2), 1.50 (d, 3H, *J* 7.0 Hz, CH_3CN); ^{13}C NMR (100 MHz, $CDCl_3$), δ 157.1, 140.3, 135.9, 128.6, 128.4, 128.3, 128.1, 127.6, 127.3, 68.1, 57.6, 17.1 ppm; MS (ES): *m/z* 272 $[M+H]^+$. HRMS calculated for $C_{16}H_{18}NO_3$ $[M+H]^+$ 272.1287, found 272.1275.

N-(*R*)-3,3-Dimethyl-2-butyl-*O*-benzylcarbonate hydroxylamine 298.



N-(*R*)-3,3-Dimethyl-2-butyl hydroxylamine **210** (500 mg, 4.3 mmol) was dissolved in dry dichloromethane (8.5 mL) under nitrogen, and cooled to 0 °C. Triethylamine (0.71 mL, 5.12 mmol) and benzyl chloroformate **292** (0.73 mL, 5.12 mmol) were then added dropwise (over 5 min) with stirring overnight warming to r.t. The reaction mixture was diluted with 1M HCl (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated to give the crude product, which was purified on silica, eluting with petroleum ether-ethyl acetate (4:1), to give *N-(R)-3,3-dimethyl-2-butyl-O-benzylcarbonate hydroxylamine* **298** (502 mg, 47%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3267 (small, sharp), 2962, 1748, 1456, 1378, 1268, 1243; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.35 (m, 5H, ArH), 6.10–6.30 (br, 1H, NH), 5.10 (s, 2H, CH_2), 2.80 (q, 1H, *J* 6.5 Hz, CHN), 1.00 (d, 3H, *J* 6.5 Hz, CH_3CN), 0.85 (s, 9H, ^tBu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 156.4, 134.9, 128.7, 128.66, 128.4, 70.3, 65.0, 33.5, 26.7, 13.5 ppm; MS (ES): *m/z* 252 $[M+H]^+$. HRMS calculated for $C_{14}H_{22}NO_3$ $[M+H]^+$ 252.1600, found 252.1611. $[\alpha]^{23}_D$ –42 (1 g/100 mL, $CHCl_3$).

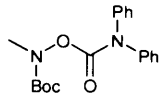
N-(*R*)-3,3-Dimethyl-2-butyl-*N*-benzylcarbonate hydroxylamine 299.



Compound **299** was synthesised in the same manner as that described for compound **298** above. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1) gave *N-(R)-3,3-dimethyl-2-butyl-N-benzylcarbonate hydroxylamine* **299** (0.45 g, 42%) as a pale pink solid. M.p. 44–46 °C. IR (thin film)/cm^{-1}: 3240 (v. br), 2957, 1692, 1450, 1418, 1330, 1306, 1204, 1116, 1086; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20–7.30 (m, 5H, ArH), 5.10 (s, 2H, CH_2), 3.80–3.90 (br, 1H, CHN), 1.10 (d, 3H, *J* 6.9 Hz, CH_3CN), 0.85 (s, 9H, ^tBu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 157.1, 136.2, 128.5, 128.2, 128.0, 67.9, 61.9, 35.2, 27.2, 12.0 ppm;

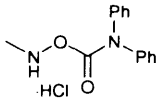
MS (ES): *m/z* 252 $[M+H]^+$. HRMS calculated for $C_{14}H_{22}NO_3$ $[M+H]^{\cdot+}$ 252.1600, found 252.1604.

N-Methyl-*N*-Boc-*O*-diphenylcarbamoyl hydroxylamine 301.[52]



N-Methyl-*N*-Boc hydroxylamine **286** (1.01 g, 6.86 mmol) was dissolved in dry dichloromethane (13.7 mL) under nitrogen, and cooled to 0 °C. DMAP (838 mg, 6.86 mmol), triethylamine (1.15 mL, 8.23 mmol) and diphenyl carbamoyl chloride **300** (1.91 g, 8.23 mmol) were then added with stirring overnight warming to r.t. The reaction mixture was diluted with 1M HCl (15 mL) and extracted with ethyl acetate (3 x 30 mL). The combined extracts were washed with brine (90 mL), dried ($MgSO_4$) and concentrated to give the crude product, which was purified on silica, eluting with petroleum ether-ethyl acetate (4:1), to give *N-methyl-N-Boc-O-diphenylcarbamoyl hydroxylamine* **301** (1.87 g, 80%) as a white solid. M.p. 99–103 °C. IR (thin film)/cm^{-1}: 2977, 1754, 1722, 1592, 1492, 1363, 1340, 1304, 1149; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15–7.30 (m, 10H, ArH), 3.20 (s, 3H, NMe), 1.45 (s, 9H, ^tBu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 155.1, 153.3, 141.7, 129.1 (8 x ArCH), 126.7 (2 x ArCH), 82.2, 37.9, 28.3 ppm; MS (ES): *m/z* 343 $[M+H]^+$. HRMS calculated for $C_{19}H_{23}N_2O_4$ $[M+H]^{\cdot+}$ 343.1658, found 343.1653.

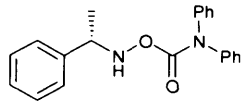
N-Methyl-*O*-diphenylcarbamoyl hydroxylamine hydrochloride 94·HCl.[52]



N-Methyl-*N*-Boc-*O*-diphenyl carbamoyl hydroxylamine **301** (500 mg, 1.46 mmol) was dissolved in dry CH_2Cl_2 (1.5 mL) under nitrogen and cooled to 0 °C. 4M HCl/dioxane (1.8 mL, 7.3 mmol) was added dropwise (over 5 min) with stirring for 3 hours, by which time a precipitate had formed. The reaction mixture was then filtered under reduced pressure, washing with ether (7.5 mL), to give *N-methyl-O-diphenylcarbamoyl hydroxylamine hydrochloride* **94·HCl** (400 mg, 98%) as a white solid. M.p. 125–130 °C (decomposed). IR (thin film)/cm^{-1}: 3238, 2924, 1719, 1592, 1490, 1341, 1307, 1023; ^1H NMR (400 MHz, DMSO) δ 8.20–8.40

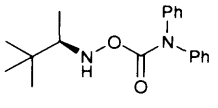
(br, 2H, NH_2^+), 7.40–7.50 (m, 4H, ArH), 7.30–7.40 (m, 6H, ArH), 2.75 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO), δ 153.4, 141.9, 129.7, 127.49, 127.46, 38.2 ppm; MS (ES): *m/z* 243 $[M+H]^+$. HRMS calculated for $C_{14}H_{14}N_2O_2$ $[M+H]^+$ 243.1134, found 243.1131.

N-(S)-α-Methylbenzyl-O-diphenylcarbamoyl hydroxylamine 303.



N-(*S*)-α-Methylbenzyl hydroxylamine **162** (1.0 g, 7.29 mmol) was dissolved in dry dichloromethane (14.6 mL) under nitrogen, and cooled to 0 °C. DMAP (890 mg, 7.29 mmol), triethylamine (1.22 mL, 8.75 mmol) and diphenylcarbamoyl chloride **300** (2.03 g, 8.75 mmol) were then added with stirring overnight warming to r.t. The reaction mixture was diluted with 1M HCl (15 mL) and extracted with ethyl acetate (3 x 30 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated to give the crude product, which was purified on silica, eluting with petroleum ether-ethyl acetate (4:1), to give *N-(S)-α-methylbenzyl-O-diphenylcarbamoyl hydroxylamine* **303** (1.85 g, 77%) as a white solid. M.p. 62–65 °C. IR (thin film)/cm^{-1}: 3227, 2975, 1716, 1591, 1491, 1454, 1340, 1300, 1198, 1010, 757, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15–7.30 (m, 10H, ArH+NH), 7.10–7.15 (m, 2H, ArH), 7.00–7.10 (m, 4H, ArH), 4.15 (q, 1H, *J* 6.7 Hz, CHN), 1.30 (d, 3H, *J* 6.7 Hz, CH_3CN); ^{13}C NMR (100 MHz, $CDCl_3$), δ 155.6, 141.6, 141.2, 129.0, 128.5, 127.8, 127.3, 126.7, 126.5, 60.9, 19.4 ppm; MS (ES): *m/z* 333 $[M+H]^+$. HRMS calculated for $C_{21}H_{21}N_2O_2$ $[M+H]^+$ 333.1603, found 333.1607. $[\alpha]^{23}_D$ −28 (1 g/100 mL, $CHCl_3$).

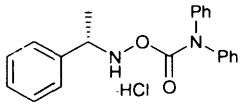
N-(R)-3,3-Dimethyl-2-butyl-O-diphenylcarbamoyl hydroxylamine 304.



N-(*R*)-3,3-Dimethyl-2-butyl hydroxylamine **210** (500 mg, 4.27 mmol) was dissolved in dry dichloromethane (8.5 mL) under nitrogen, and cooled to 0 °C. DMAP (521 mg, 4.27 mmol), triethylamine (0.71 mL, 5.12 mmol) and diphenylcarbamoyl chloride **300** (1.186 g, 5.12 mmol) were then added with stirring overnight warming

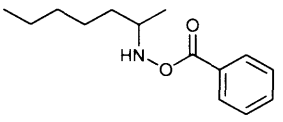
to r.t. The reaction mixture was diluted with 1M HCl (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated to give the crude product, which was purified on silica, eluting with petroleum ether-ethyl acetate (4:1), to give *N-(R)-3,3-dimethyl-2-butyl-O-diphenylcarbamoyl hydroxylamine* **304** (1.201 g, 90%) as a white solid. M.p. 60–65 °C. IR (thin film)/cm^{-1}: 3233, 2957, 2867, 1716, 1592, 1492, 1450, 1340, 1299, 1201, 1014, 756, 694; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, 4H, *J* 7.8, ArH), 7.10–7.20 (m, 6H, ArH), 2.70 (q, 1H, *J* 6.5 Hz, CHN), 0.90 (d, 3H, *J* 6.5 Hz, CH_3CN), 0.80 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 156.1, 141.7, 129.1, 126.8, 126.6, 65.1, 33.5, 26.6, 13.5 ppm; MS (ES): *m/z* 313 $[M+H]^+$. HRMS calculated for $C_{19}H_{25}N_2O_2$ $[M+H]^{\cdot+}$ 313.1916, found 313.1923. $[\alpha]^{23}_D$ −15.2 (1 g/100 mL, $CHCl_3$).

N-(S)-α-Methylbenzyl-O-diphenylcarbamoyl hydroxylamine hydrochloride 303·HCl.



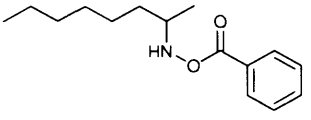
Conversion of *N*-(*S*)-α-methylbenzyl-*O*-diphenyl carbamoyl hydroxylamine **303** to the HCl salt (Chapter 9.1.1.2) gave *N-(S)-α-methylbenzyl-O-diphenylcarbamoyl hydroxylamine hydrochloride* **303·HCl** (0.3 g, 66%) as a white solid, which was collected by filtration. M.p. 98–103 °C. IR (thin film)/cm^{-1}: 3229, 2920, 1712, 1584 1491, 1337, 1301, 1195, 1009; ^1H NMR (400 MHz, DMSO) δ 9.10–9.30 (br, 2H, NH_2^+), 7.25–7.35 (m, 9H, ArH), 7.20 (t, 2H, *J* 7.3 Hz, ArH), 7.05 (d, 4H, *J* 8.0 Hz, ArH), 4.15 (q, 1H, *J* 6.7 Hz, CHN), 1.25 (d, 3H, *J* 6.7 Hz, CH_3CN); ^{13}C NMR (100 MHz, DMSO), δ 154.6, 142.3, 142.2, 129.5, 128.7, 127.9, 127.7, 127.3, 126.9, 60.1, 19.6 ppm; MS (ES): *m/z* 333 $[M+H]^+$. HRMS calculated for $C_{21}H_{21}N_2O_2$ $[M+H]^{\cdot+}$ 333.1603, found 333.1611.

N-2-Heptyl-O-benzoyl hydroxylamine 355.



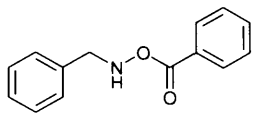
Compound **355** was synthesised from 2-heptylamine (3.45 g, 29.9 mmol) using general procedure 1. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1) gave *N-2-heptyl-O-benzoyl hydroxylamine* **355** (80%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3238, 2957, 2931, 2859, 1719, 1602, 1452, 1378, 1316, 1270, 1177, 1092, 1067, 1026, 708; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, 2H, *J* 7.1 Hz, ArH), 7.50 (t, 1H, *J* 7.5 Hz, ArH), 7.40 (at, 2H, *J* 7.7 Hz, ArH), 3.10–3.15 (m, 1H, CHN), 1.50–1.60 (m, 1H), 1.30–1.40 (m, 3H), 1.20–1.30 (m, 4H), 1.10 (d, 3H, *J* 6.4 Hz, CH_3CN), 0.80 (t, 3H, *J* 6.9 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.9, 133.3, 129.3, 129.1, 128.5, 56.8, 33.9, 31.9, 25.6, 22.6, 18.1, 14.0 ppm; MS (ES): *m/z* 236 $[M+H]^+$. HRMS calculated for $C_{14}H_{22}NO_2$ $[M+H]^{+}$ 236.1645, found 236.1644.

N-2-Octyl-O-benzoyl hydroxylamine 356.



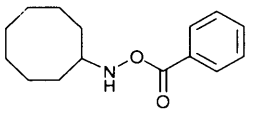
Compound **356** was synthesised from 2-octylamine (1.54 g, 12 mmol) using general procedure 1. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1) gave *N-2-octyl-O-benzoyl hydroxylamine* **356** (79%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3238, 2929, 2857, 1719, 1601, 1452, 1378, 1316, 1270, 1177, 1091, 1066, 1026; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, 2H, *J* 7.1 Hz, ArH), 7.60 (t, 1H, *J* 7.4 Hz, ArH), 7.45 (at, 2H, *J* 7.6 Hz, ArH), 3.15–3.25 (m, 1H, CHN), 1.55–1.70 (m, 1H), 1.35–1.45 (m, 3H), 1.25–1.35 (m, 6H), 1.20 (d, 3H, *J* 6.3 Hz, CH_3CN), 0.90 (t, 3H, *J* 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.9, 133.3, 129.3, 129.1, 128.5, 56.8, 34.0, 31.8, 29.4, 25.9, 22.6, 18.1, 14.1 ppm; MS (EI): *m/z* 249 $[M+H]^+$. HRMS calculated for $C_{15}H_{24}NO_2$ $[M+H]^{+}$ 249.1729, found 249.1728.

N-Benzyl-O-benzoyl hydroxylamine 357.[92]



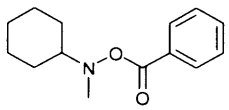
Compound **357** was synthesised from benzylamine (4.0 g, 37 mmol) using general procedure 1. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1) gave *N-benzyl-O-benzoyl hydroxylamine* **357** (68%) as a white solid. M.p. 25–28 °C. IR (thin film)/cm^{-1}: 3230, 3030, 1721, 1601, 1452, 1310, 1270, 1171, 1086, 1066, 1026, 750, 707; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 2H, *J* 7.1 Hz, ArH), 7.45 (t, 1H, *J* 7.5 Hz, ArH), 7.35 (t, 2H, *J* 7.7 Hz, ArH), 7.20–7.30 (m, 5H, ArH), 4.20 (s, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.9, 135.9, 133.4, 129.4, 129.1, 128.7, 128.6, 128.3, 128.0, 56.8 ppm; MS (ES): *m/z* 228 $[M+H]^+$. HRMS calculated for $C_{14}H_{14}NO_2$ $[M+H]^{+}$ 228.1019, found 228.1022.

N-Cyclooctyl-O-benzoyl hydroxylamine 358.



Compound **358** was synthesised from cyclooctylamine (2.26 g, 17.7 mmol) using general procedure 1. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1) gave *N-cyclooctyl-O-benzoyl hydroxylamine* **358** (84%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3231, 2923, 2853, 1718, 1601, 1466, 1450, 1315, 1270, 1177, 1091, 1067, 1026, 708; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, 2H, *J* 7.2 Hz, ArH), 7.40 (t, 1H, *J* 7.4 Hz, ArH), 7.25 (at, 2H, *J* 7.7 Hz, ArH), 3.00–3.10 (m, 1H, CHN), 1.65–1.75 (m, 2H), 1.50–1.65 (m, 2H), 1.20–1.50 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.9, 133.3, 129.3, 128.6, 128.5, 61.2, 29.8, 27.0, 25.8, 24.0 ppm; MS (ES): *m/z* 248 $[M+H]^+$. HRMS calculated for $C_{15}H_{22}NO_2$ $[M+H]^{+}$ 248.1645, found 248.1641.

N-Cyclohexyl-N-methyl-O-benzoyl hydroxylamine 341.



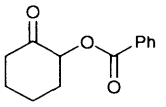
Compound **341** was synthesised from *N*-methyl cyclohexylamine **340** (3.0 g, 26.8 mmol) using general procedure 1. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (3:1) gave *N-cyclohexyl-N-methyl-O-benzoyl hydroxylamine* **341** (71%) as a clear colourless oil. IR (thin film)/cm^{-1}: 3062, 2934, 2856, 1742, 1601, 1450, 1370, 1314, 1262, 1176, 1081, 1059, 1024, 895, 866, 820, 784, 709; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, 2H, *J* 7.1 Hz, ArH), 7.50 (t, 1H, *J* 7.4 Hz, ArH), 7.35 (at, 2H, *J* 7.7 Hz, ArH), 2.80 (s, 3H, NMe), 2.70–2.75 (m, 1H, CHN), 1.90–2.00 (m, 2H), 1.70–1.80 (m, 2H), 1.50–1.60 (m, 1H), 1.00–1.35 (m, 5H). MS (ES): *m/z* 234 $[M+H]^+$. HRMS calculated for $C_{14}H_{20}NO_2$ $[M+H]^+$ 234.1494, found 234.1496.

9.2. α-Oxygenated Product Experimentals.

9.2.1. General Procedure 3.

The racemic α-functionalised carbonyl compounds were synthesised by condensation of the appropriate carbonyl compound with *N*-methyl-*O*-benzoyl hydroxylamine hydrochloride **63·HCl**, unless otherwise stated, in the manner described as follows:

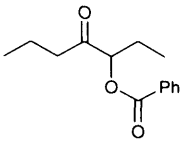
2-Benzoyloxy cyclohexanone 33.[49]



Cyclohexanone **44** (3.3 mL, 32 mmol) was added dropwise (over 5 min) to a stirred solution of *N*-methyl-*O*-benzoyl hydroxylamine hydrochloride **63·HCl** (6.00 g, 32 mmol) in DMSO (45 mL). Stirring was continued at 25 °C overnight. The reaction mixture was diluted with brine (50 mL) and extracted with ethyl acetate (4 x 50 mL). The combined extracts were washed with brine (150 mL), dried ($MgSO_4$) and concentrated to give the crude product which was purified on silica, eluting with petroleum ether-ethyl acetate (3:1) to give *2-benzoyloxy cyclohexanone* **33** (4.74 g, 68%) as a white crystalline solid. M.p. 81–85 °C. Lit. ref. m.p. 81–83 °C.[93] IR (thin film)/ cm^{-1}: 2945, 2867, 1743, 1719 1603, 1451, 1316, 1271, 1177, 1112, 1071, 1034; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, 2H, *J* 8.3 Hz, ArH), 7.50 (t, 1H, *J* 7.4 Hz, ArH), 7.35 (at, 2H, *J* 7.7 Hz, ArH), 5.35 (dd, 1H, *J* 12.0, 9.5 Hz, CHCO), 2.45–2.55 (m, 1H), 2.30–2.45 (m, 2H), 2.00–2.10 (m, 1H), 1.90–2.00 (m, 1H), 1.70–1.90 (m, 2H), 1.55–1.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 204.4, 165.6, 133.2, 129.9, 129.7, 128.4, 77.0, 40.8, 33.2, 27.2, 23.8 ppm; MS (ES): *m/z* 219 $[M+H]^+$. HRMS calculated for $C_{13}H_{15}O_3$ $[M+H]^+$ 219.1016, found 219.1015. Enantiomers separated on OD chiral column, 5% IPA/Hexane, 1.0 mL/min (t_1 = 12.2 min; t_2 = 16.5 min).

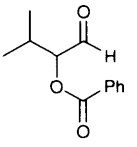
9.2.2. Experimental Data.

3-Benzoyloxy-4-heptanone 118.[49]



Compound **118** was synthesised from 4-heptanone **113** using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (9:1), gave *3-benzoyloxy-4-heptanone* **118** (180 mg, 72%) as a clear colourless oil. IR (thin film)/ cm^{-1}: 2978, 2935, 2848, 1741, 1717, 1592, 1576, 1457, 1380, 1315, 1272, 1250, 1174, 1109, 1065, 1022, 957; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 2H, *J* 8.2 Hz, ArH), 7.50 (t, 1H, *J* 7.5 Hz, ArH), 7.35 (at, 2H, *J* 7.7 Hz, ArH), 5.10 (dd, 1H, *J* 7.9, 4.6 Hz, CHCO), 2.40–2.50 (m, 1H), 2.30–2.40 (m, 1H), 1.75–1.95 (m, 2H), 1.50–1.60 (m, 2H), 0.95 (t, 3H, *J* 7.5 Hz, CH_3), 0.85 (t, 3H, *J* 7.5 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 207.5, 166.1, 133.4, 129.8, 129.5, 128.5, 80.0, 40.6, 24.1, 16.6, 13.7, 9.8 ppm; MS (ES): *m/z* 235 $[M+H]^+$. HRMS calculated for $C_{14}H_{19}O_3$ $[M+H]^+$ 235.1334, found 235.1332. Enantiomers separated on OJ chiral column, 1.5% IPA/Hexane, 0.75 mL/min (t_1 = 16.8 min; t_2 = 18.7 min).

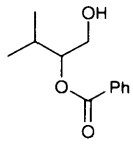
2-Benzoyloxy isovaleraldehyde 119.[49]



Compound **119** was synthesised from isovaleraldehyde **114** using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *2-benzoyloxy isovaleraldehyde* **119** (52 mg, 70%) as a clear colourless oil. IR (thin film)/ cm^{-1}: 2968, 1742, 1721, 1602, 1452, 1315, 1276, 1112, 1070, 1026, 711; ^1H NMR (400 MHz, $CDCl_3$) δ 9.55 (s, 1H, CHO), 8.05 (d, 2H, *J* 7.2 Hz, ArH), 7.50 (t, 1H, *J* 7.5 Hz, ArH), 7.40 (at, 2H, *J* 7.7 Hz, ArH), 5.00 (d, 1H, *J* 4.4 Hz, CHCO), 2.25–2.35 (m, 1H, CH), 1.05 (d, 3H, *J* 7.0 Hz, CH_3), 1.00 (d, 3H, *J* 6.9 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 198.9, 166.2, 133.6, 129.8, 129.3, 128.6,

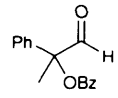
82.7, 29.3, 18.9, 17.3 ppm; MS (ES): *m/z* 207 $[M+H]^+$. HRMS calculated for $C_{12}H_{15}O_3$ $[M+H]^{+}$ 207.1016, found 207.1016.

2-Benzoyloxy-3-methylbutan-1-ol 121.



Sodium borohydride (25.3 mg, 0.669 mmol), was added slowly (over 5 min) to a solution of 2-benzoyloxy isovaleraldehyde **119** (115 mg, 0.558 mmol) in ethanol (1.12 mL, [0.5M]), with stirring at room temperature for 2 hours. The reaction was then quenched with water (5 mL), before removing the ethanol under reduced pressure. The reaction mixture was then diluted with brine (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were then washed with brine (45 mL), dried ($MgSO_4$) and concentrated to give the crude product. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *2-benzoyloxy-3-methylbutan-1-ol* **121** (63 mg, 54%) as a clear colourless oil. IR (thin film)/ cm^{-1}: 3475 (broad), 2962, 1716, 1453, 1277, 1117, 1072; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 2H, *J* 7.1 Hz, ArH), 7.50 (t, 1H, *J* 7.4 Hz, ArH), 7.40 (at, 2H, *J* 7.7 Hz, ArH), 4.40 (dd, 1H, *J* 11.5, 3.0 Hz, CH_2OH), 4.20 (dd, 1H, *J* 11.5, 7.5 Hz, CH_2OH), 3.60–3.70 (m, 1H, CHOCO), 2.10 (ad, 1H, *J* 4.2, OH), 1.70–1.85 (m, 1H, $CH(CH_3)_2$), 0.95 (d, 3H, *J* 6.8 Hz, CH_3), 0.90 (d, 3H, *J* 6.9 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.9, 133.2, 129.9, 129.7, 128.5, 74.9, 67.9, 31.2, 18.8, 17.8 ppm; MS (APcI): *m/z* 209 $[M+H]^+$. HRMS calculated for $C_{12}H_{15}O_3$ $[M+H]^{+}$ 209.1172, found 209.1171. Enantiomers separated on OJ chiral column, 1% IPA/Hexane, 0.5 mL/min (t_1 = 55.2 min; t_2 = 58.1 min).

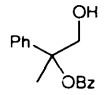
2-Benzoyloxy-2-phenylpropionaldehyde 120.



Compound **120** was synthesised from 2-phenylpropionaldehyde **115** using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (9:1), gave *2-benzoyloxy-2-phenylpropionaldehyde* **120** (188 mg, 28%)

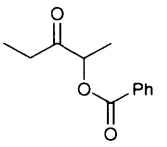
as a clear colourless oil. IR (thin film)/ cm^{-1}: 3063, 2815, 1736, 1713, 1600, 1492, 1451, 1381, 1285, 1230, 1108, 1070, 712; ^1H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H, CHO), 8.10 (d, 2H, *J* 7.1 Hz, ArH), 7.55–7.60 (m, 1H, ArH), 7.40–7.50 (m, 4H, ArH), 7.30–7.40 (m, 2H, ArH), 7.25–7.30 (m, 1H, ArH), 1.90 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 194.5, 165.7, 136.4, 133.9, 130.0, 129.3, 129.1, 128.74, 128.68, 125.7, 86.4, 21.0 ppm; MS (APcI): *m/z* 255 $[M+H]^+$. HRMS calculated for $C_{16}H_{15}O_3$ $[M+H]^+$ 255.1021, found 255.1033.

2-Benzoyloxy-2-phenylpopan-1-ol 124.



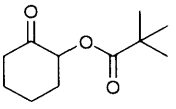
Sodium borohydride (9 mg, 0.236 mmol), was added slowly (over 5 min) to a solution of 2-benzoyloxy-2-phenylpropionaldehyde **120** (50 mg, 0.197 mmol) in ethanol (0.39 mL, [0.5M]), with stirring at 0 °C for 2 hours, warming to room temperature. The reaction was then quenched with water (5 mL), before removing the ethanol under reduced pressure. The reaction mixture was then diluted with brine (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were then washed with brine (30 mL), dried ($MgSO_4$) and concentrated to give the crude product. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (3:1), gave *2-benzoyloxy-2-phenylpropan-1-ol* **124** (35 mg, 69%) as a clear colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 2H, *J* 7.2 Hz, ArH), 7.45–7.50 (m, 3H, ArH), 7.25–7.40 (m, 4H, ArH), 7.20–7.25 (m, 1H, ArH), 4.45 (d, 1H, *J* 11.4, Hz, CH_2OH), 4.40 (d, 1H, *J* 11.4 Hz, CH_2OH), 2.40–2.60 (br, 1H, OH), 1.60 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.6, 144.3, 133.2, 129.8, 129.7, 128.5, 128.4, 127.4, 125.1, 73.9, 72.3, 26.7 ppm; MS (ES): *m/z* 256 $[M]^+$. HRMS calculated for $C_{16}H_{16}O_3NH_4$ $[M+NH_4]^+$ 274.1443, found 274.1439. Enantiomers separated on OJ chiral column, 10% IPA/Hexane, 0.75 mL/min (t_1 = 22.4 min; t_2 = 35.2 min).

2-Benzoyloxy-3-pentanone 128.[49]



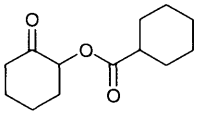
Compound **128** was synthesised from 3-pentanone **127** using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *2-benzoyloxy-3-pentanone* **128** (143 mg, 65%) as a clear colourless oil. IR (thin film)/ cm^{-1}: 3063, 2983, 2940, 1719, 1602, 1584, 1492, 1451, 1411, 1268, 1177, 1109, 1027, 974; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 2H, *J* 7.1 Hz, ArH), 7.50 (t, 1H, *J* 7.5 Hz, ArH), 7.35 (at, 2H, *J* 7.7 Hz, ArH), 5.25 (q, 1H, *J* 7.0 Hz, CHCO), 2.55–2.65 (m, 1H), 2.40–2.50 (m, 1H), 1.45 (d, 3H, *J* 7.0 Hz, CH_3), 1.00 (t, 3H, *J* 7.3 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 208.6, 166.0, 133.4, 129.8, 129.5, 128.5, 75.2, 31.5, 16.5, 7.2 ppm; MS (APcI): *m/z* 207 $[M+H]^+$. HRMS calculated for $C_{12}H_{15}O_3$ $[M+H]^+$ 207.1016, found 207.1017. Enantiomers separated on OJ chiral column, 1% IPA/Hexane, 0.5 mL/min (t_1 = 31.4 min; t_2 = 34.5 min).

2-Pivaloyloxy cyclohexanone 150.[47]



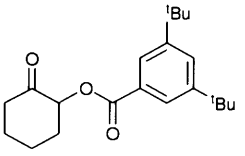
Compound **150** was synthesised through reaction of cyclohexanone **44** and *N*-methyl-*O*-pivaloyl hydroxylamine hydrochloride **146·HCl** (100 mg, 0.6 mmol), using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (3:1), gave *2-pivaloyloxy cyclohexanone* **150** (71%) as a white crystalline solid. M.p. 26–31 °C. IR (thin film)/ cm^{-1}: 2958, 2870, 1737, 1726, 1480, 1458, 1397, 1280, 1158, 1114, 1064; ^1H NMR (400 MHz, $CDCl_3$) δ 5.05 (dd, 1H, *J* 11.1, 6.3 Hz, CHCO), 2.40–2.45 (m, 1H), 2.25–2.40 (m, 1H), 2.15–2.25 (m, 1H), 1.95–2.05 (m, 1H), 1.85–1.95 (m, 1H), 1.65–1.80 (m 2H), 1.50–1.65 (m, 1H), 1.20 (s, 9H, ^tBu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 204.6, 177.7, 76.2, 40.7, 38.7, 32.9, 27.19, 27.18, 23.7 ppm; MS (ES): *m/z* 199 $[M+H]^+$. HRMS calculated for $C_{11}H_{19}O_3$ $[M+H]^+$ 199.1329, found 199.1331. Enantiomers separated by ^1H NMR spectroscopy, using 0.1 equivalents of shift reagent **161**, Appendix 1.

2-Cyclohexoyloxy cyclohexanone 151.



Compound **151** was synthesised through reaction of cyclohexanone **44** and *N*-methyl-*O*-cyclohexyl hydroxylamine **147** (100 mg, 0.64 mmol), using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (3:1), gave *2-cyclohexoyloxy cyclohexanone* **151** (84%) as a white crystalline solid. M.p. 43–47 °C. IR (thin film)/ cm^{-1}: 2934, 2857, 1739, 1726, 1451, 1316, 1246, 1168, 1133, 1113, 1064; ^1H NMR (400 MHz, $CDCl_3$) δ 5.10 (dd, 1H, *J* 11.3, 6.3 Hz, CHCO), 2.40–2.50 (m, 1H), 2.10–2.40 (m, 4H), 1.95–2.05 (m, 1H), 1.80–2.00 (m, 3H), 1.60–1.75 (m, 3H), 1.50–1.60 (m, 2H), 1.35–1.50 (m, 2H), 1.10–1.30 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 204.8, 175.2, 76.1, 42.9, 40.7, 33.1, 29.1, 28.97, 27.2, 25.8, 25.4, 25.4, 23.8 ppm; MS (ES): *m/z* 225 $[M+H]^+$. HRMS calculated for $C_{13}H_{21}O_3$ $[M+H]^{+}$ 225.1485, found 225.1488.

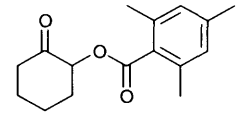
2-(3,5-Di-*tert*-butylbenzoyloxy) cyclohexanone 152.



Compound **152** was synthesised through reaction of cyclohexanone **44** and *N*-methyl-*O*-3,5-di-*tert*-butylbenzoyl hydroxylamine **148**, using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *2-(3,5-di-tert-butylbenzoyloxy) cyclohexanone* **152** (169 mg, 90%) as a white crystalline solid. M.p. 85–89 °C. IR (thin film)/ cm^{-1}: 2962, 2868, 1735, 1718, 1598, 1476, 1459, 1364, 1319, 1241, 1114, 895; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 2H, ArH), 7.55 (s, 1H, ArH), 5.30 (dd, 1H, *J* 12.1, 6.3 Hz, CHCO), 2.45–2.50 (m, 1H), 2.30–2.45 (m, 2H), 2.00–2.10 (m, 1H), 1.80–2.00 (m, 2H), 1.70–1.80 (m, 1H), 1.60–1.70 (m, 1H), 1.25 (s, 18H, *m*-^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 204.6, 166.4, 151.0, 129.0, 127.5, 124.1, 77.4, 40.8, 34.9, 33.2, 31.4, 27.2, 23.8 ppm; MS (ES): *m/z* 331 $[M+H]^+$. HRMS calculated for $C_{21}H_{31}O_3$ $[M+H]^{+}$ 331.2268, found

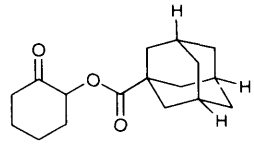
331.2267. Enantiomers separated by ^{1}H NMR spectroscopy, using 1.3 equivalents of shift reagent **161**, Appendix 3.

2-(2,4,6-Trimethylbenzoyloxy) cyclohexanone 153.



Compound **153** was synthesised through reaction of cyclohexanone **44** and *N*-methyl-*O*-2,4,6-trimethylbenzoyl hydroxylamine **149**, using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (3:1), gave *2-(2,4,6-trimethylbenzoyloxy) cyclohexanone* **153** (31 mg, 40%) as a white crystalline solid. M.p. 57–62 °C. IR (thin film)/ cm^{-1}: 2944, 2866, 1736, 1722, 1611, 1451, 1428, 1313, 1263, 1169, 1090, 1034, 852; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 2H, ArH), 5.35 (dd, 1H, *J* 12.1, 6.4 Hz, CHCO), 2.45–2.55 (m, 1H), 2.35–2.45 (m, 1H), 2.30 (s, 6H, *o*-CH_3), 2.20 (s, 3H, *p*-CH_3), 2.00–2.10 (m, 1H), 1.90–2.00 (m, 1H), 1.70–1.85 (m, 2H), 1.50–1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 204.2, 168.9, 139.5, 135.7, 130.1, 128.5, 76.9, 40.9, 33.1, 27.2, 23.9, 21.2, 19.9 ppm; MS (APcI): *m/z* 261 $[M+H]^+$. HRMS calculated for $C_{16}H_{21}O_3$ $[M+H]^{+}$ 261.1491, found 261.1484. Enantiomers separated on OD chiral column, 5% IPA/Hexane, 1.0 mL/min (t_1 = 9.7 min; t_2 = 12.1 min).

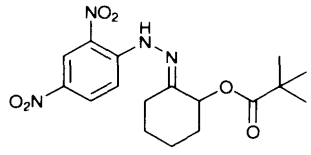
2-Adamantoyloxy cyclohexanone 156.



Compound **156** was synthesised through reaction of cyclohexanone **44** and *N*-methyl-*O*-adamantoyl hydroxylamine **155** (100 mg, 0.48 mmol), using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (85:15), gave *2-adamantoyloxy cyclohexanone* **156** (64%) as a white crystalline solid. M.p. 87–89 °C. IR (thin film)/ cm^{-1}: 2906, 2851, 1734, 1723, 1453, 1228, 1100, 1085; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (dd, 1H, *J* 11.1, 6.3 Hz, CHCO), 2.50–2.55 (m, 1H), 2.35–2.45 (m, 1H), 2.25–2.30 (m, 1H), 2.05–2.15 (m, 1H), 2.00–2.05 (m, 3H, CH), 2.00 (d, 6H, *J* 2.9 Hz, CH_2), 1.75–1.85 (m, 2H), 1.70–

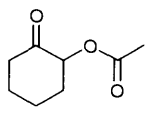
1.75 (m, 6H, CH_2), 1.60–1.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 204.7, 176.8, 76.0, 40.71, 40.66, 38.8, 36.5, 33.0, 27.9, 27.2, 23.7 ppm; MS (ES): *m/z* 277 $[M+H]^+$. HRMS calculated for $C_{17}H_{25}O_3$ $[M+H]^+$ 277.1798, found 277.1800. Enantiomers separated by ^1H NMR spectroscopy, using 0.3 equivalents of shift reagent **161**, Appendix 2.

2-Pivaloyloxy cyclohexanone-2,4-dinitrophenylhydrazone 158.



2,4-Dinitrophenyl hydrazine **157** (240 mg, 1.21 mmol) was added to a solution of 2-pivaloyloxy cyclohexanone **150** (200 mg, 1.01 mmol) in ethanol (0.5M, 2 mL), with stirring at room temperature for 2 hours. The reaction mixture was then concentrated *in vacuo*. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *2-pivaloyloxy cyclohexanone-2,4-dinitrophenylhydrazone* **158** (382 mg, 95%) as a yellow crystalline solid. M.p. 136–140 °C. IR (thin film)/ cm^{-1}: 3306, 2926, 2846, 1729, 1619, 1587, 1512, 1432, 1335, 1282, 1141; ^1H NMR (400 MHz, $CDCl_3$) δ 9.05 (d, 1H, *J* 2.6 Hz, ArH), 8.25 (dd, 1H, *J* 9.6, 2.6 Hz, ArH), 7.90 (d, 1H, *J* 9.6 Hz, ArH), 5.35 (dd, 1H, *J* 6.4, 3.2 Hz, CHCO), 2.50–2.55 (m, 2H), 1.95–2.00 (m, 1H), 1.80–1.90 (m, 3H), 1.60–1.70 (m 2H), 1.20 (s, 9H, ^tBu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 177.2, 156.2, 145.3, 138.1, 130.0, 129.4, 123.4, 116.6, 73.2, 39.0, 32.5, 27.3, 25.7, 25.2, 21.4 ppm; MS (EI): *m/z* 378 $[M+H]^+$. HRMS calculated for $C_{17}H_{23}N_4O_6$ $[M+H]^+$ 378.1539, found 378.1542.

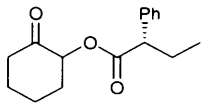
2-Acetoyloxy cyclohexanone 167.[94]



Compound **167** was synthesised through reaction of cyclohexanone **44** and *N*-(*S*)-α-methyl benzyl-*O*-acetyl hydroxylamine **166**, using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (7:3), gave *2-acetoyloxy cyclohexanone* **167** (44 mg, 50%) as a white crystalline

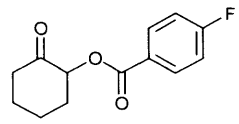
solid. M.p. 25–29 °C. Lit. ref. m.p. 35–36 °C.[94] IR (thin film)/ cm^{-1}: 2940, 2861, 1745, 1725, 1376, 1239, 1070; ^1H NMR (400 MHz, $CDCl_3$) δ 5.10 (dd, 1H, *J* 11.5, 6.4 Hz, CHCO), 2.40–2.50 (m, 1H), 2.25–2.40 (m, 1H), 2.20–2.25 (m, 1H), 2.10 (s, 3H, CH_3), 2.00–2.10 (m, 1H), 1.85–1.95 (m, 1H), 1.65–1.75 (m, 2H), 1.50–1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 204.6, 170.1, 76.6, 40.7, 33.1, 27.2, 23.8, 20.8 ppm; MS (ES): *m/z* 156 $[M+H]^+$. HRMS calculated for $C_8H_{13}O_3$ $[M+H]^+$ 156.0786, found 156.0786. Enantiomers separated by NMR, using 0.3 equivalents of shift reagent **161**, Appendix 4.

2-(2-(*S*)-phenylbutanoyloxy) cyclohexanone 176.



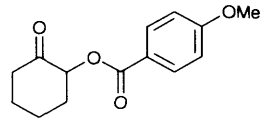
Compound **176** was synthesised through reaction of cyclohexanone **44** and *N*-methyl-*O*-(*S*)-2-phenylbutanoyl hydroxylamine **174**, using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (3:1), gave *2-(2-(S)-phenylbutanoyloxy) cyclohexanone* **176** (140 mg, 69%) as a clear colourless oil, as a 1:1 mixture of diastereoisomers. Data on mixture. IR (thin film)/ cm^{-1}: 2942, 2870, 1742, 1726, 1495, 1454, 1315, 1265, 1198, 1163, 1113; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20–7.30 (m, 4H), 7.15–7.20 (m, 1H), 5.00–5.10 (m, 1H, CHCO), 3.50 (aq, 1H, *J* 7.9 Hz, CHPh), 2.20–2.45 (m, 2H), 2.00–2.20 (m, 2H), 1.90–2.00 (m, 1H), 1.45–1.90 (m, 5H), 0.85 (aq, 3H, *J* 7.6 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$); both diastereoisomers of compound **176** were observed, as illustrated by the second set of values given (in brackets); δ 204.5 (204.2), 173.3 (173.1), 139.1 (138.8), 128.5 (128.4), 128.2 (128.0), 127.2 (127.2), 76.7 (76.6), 53.5 (53.0), 40.7 (40.6), 33.0 (32.9), 27.2 (27.1), 27.0 (26.8), 23.7 (23.7) 12.2 (12.1) ppm; MS (ES): *m/z* 260 $[M+H]^+$. HRMS calculated for $C_{16}H_{21}O_3$ $[M+H]^+$ 260.1407, found 260.1405. Enantiomers separated on OD chiral column, 10% IPA/Hexane, 1.0 mL/min (t_1 = 10.7 min; t_2 = 13.5 min).

2-(4-fluorobenzoyloxy) cyclohexanone 180.



Compound **180** was synthesised through reaction of cyclohexanone **44** and *N*-methyl-*O*-4-fluorobenzoyl hydroxylamine **178**, using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (3:1), gave *2-(4-fluorobenzoyloxy) cyclohexanone* **180** (71 mg, 51%) as a white crystalline solid. M.p. 74–79 °C. IR (thin film)/ cm^{-1}: 2948, 2865, 1731, 1716, 1604, 1507, 1312, 1270, 1241, 1150, 1112, 1091, 766; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00–8.10 (m, 2H, ArH), 7.05 (at, 2H, *J* 8.7 Hz, ArH), 5.30 (dd, 1H, *J* 12.0, 6.4 Hz, CHCO), 2.45–2.55 (m, 1H), 2.30–2.50 (m, 2H), 2.00–2.10 (m, 1H), 1.90–2.00 (m, 1H), 1.70–1.90 (m, 2H), 1.55–1.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 204.2, 167.0, 164.8, 132.5, 126.0, 115.5, 77.1, 40.8, 33.2, 21.2, 23.8 ppm; MS (ES): *m/z* 237 $[M+H]^+$. HRMS calculated for $C_{13}H_{14}O_3F$ $[M+H]^{\cdot+}$ 237.0921, found 237.0919. Enantiomers separated on OD chiral column, 5% IPA/Hexane, 1.0 mL/min (t_1 = 10.5 min; t_2 = 12.6 min).

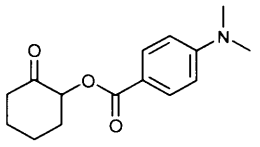
2-(4-methoxybenzoyloxy) cyclohexanone 183.



Compound **183** was synthesised through reaction of cyclohexanone **44** and *N*-methyl-*O*-4-methoxybenzoyl hydroxylamine **181**, using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (65:35), gave *2-(4-methoxybenzoyloxy) cyclohexanone* **183** (104 mg, 76%) as a white crystalline solid. M.p. 114–118 °C. IR (thin film)/ cm^{-1}: 2944, 1727, 1702, 1604, 1511, 1320, 1280, 1260, 1173, 1109, 1038, 770; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 2H, *J* 9.0 Hz, ArH), 6.85 (d, 2H, *J* 9.0 Hz, ArH), 5.30 (dd, 1H, *J* 11.2, 6.3 Hz, CHCO), 3.80 (s, 3H, CH_3), 2.45–2.55 (m, 1H), 2.30–2.45 (m, 2H), 2.00–2.10 (m, 1H), 1.90–2.00 (m, 1H), 1.70–1.90 (m, 2H), 1.55–1.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 204.6, 165.3, 163.6, 132.0, 122.1, 113.6, 76.9, 55.4, 40.8, 33.3, 27.3, 23.8 ppm; MS (APcI): *m/z* 249 $[M+H]^+$. HRMS calculated for $C_{14}H_{17}O_4$

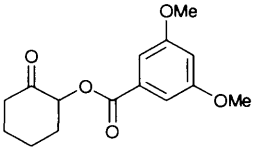
$[M+H]^+$ 249.1121, found 249.1122. Enantiomers separated on OD chiral column, 10% IPA/Hexane, 1.0 mL/min (t_1 = 15.7 min; t_2 = 20.7 min).

2-(4-Dimethylaminobenzoyloxy) cyclohexanone 360.



Compound **360** was synthesised through reaction of cyclohexanone **44** and *N*-methyl-*O*-4-dimethylaminobenzoyl hydroxylamine **347**, using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (7:3), gave *2-(4-dimethylaminobenzoyloxy) cyclohexanone* **360** (64 mg, 48%) as a white crystalline solid. M.p. 107–112 °C. IR (thin film)/ cm^{-1}: 2941, 2867, 1731, 1702, 1607, 1528, 1448, 1368, 1311, 1299, 1273, 1183, 1107; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 2H, *J* 9.0 Hz, ArH), 6.55 (d, 2H, *J* 9.0 Hz, ArH), 5.30 (dd, 1H, *J* 11.2, 6.3 Hz, CHCO), 2.95 (s, 6H, NMe_2), 2.45–2.50 (m, 1H), 2.35–2.45 (m, 1H), 2.30–2.35 (m, 1H), 2.00–2.10 (m, 1H), 1.90–2.00 (m, 1H), 1.70–1.90 (m, 2H), 1.60–1.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 205.2, 165.9, 153.5, 131.7, 116.3, 110.7, 76.3, 40.8, 40.1, 33.4, 27.3, 23.9 ppm; MS (EI): *m/z* 261 $[M+H]^+$. HRMS calculated for $C_{15}H_{20}NO_3$ $[M+H]^+$ 261.1359, found 261.1361. Enantiomers separated on OD chiral column, 20% IPA/Hexane, 1.0 mL/min (t_1 = 22.9 min; t_2 = 28.5 min).

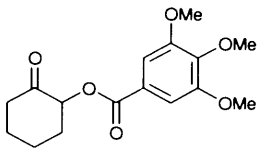
2-(3,5-Dimethoxybenzoyloxy) cyclohexanone 361.



Compound **361** was synthesised through reaction of cyclohexanone **44** and *N*-methyl-*O*-3,5-dimethoxybenzoyl hydroxylamine **348**, using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (3:2), gave *2-(3,5-dimethoxybenzoyloxy) cyclohexanone* **361** (86 mg, 65%) as a white crystalline solid. M.p. 67–72 °C. IR (thin film)/ cm^{-1}: 2942, 2860, 1736, 1718, 1596, 1458, 1429, 1350, 1328, 1229, 1206, 1158, 1107, 1063; ^1H NMR (400 MHz, $CDCl_3$)

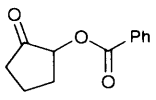
δ 7.15 (s, 2H, ArH), 6.60 (s, 1H, ArH), 5.30 (dd, 1H, *J* 11.4, 6.3 Hz, CHCO), 3.75 (s, 6H, *m*-OMe), 2.45–2.55 (m, 1H), 2.30–2.45 (m, 2H), 2.00–2.10 (m, 1H), 1.90–2.00 (m, 1H), 1.70–1.90 (m, 2H), 1.55–1.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 204.3, 165.4, 160.6, 131.5, 107.5, 106.0, 77.2, 55.6, 40.8, 33.1, 27.2, 23.8 ppm; MS (EI): *m/z* 278 $[M+H]^+$. HRMS calculated for $C_{15}H_{19}O_5$ $[M+H]^{\cdot+}$ 278.1149, found 278.1148. Enantiomers separated on OD chiral column, 5% IPA/Hexane, 1.0 mL/min (t_1 = 18.8 min; t_2 = 21.3 min).

2-(3,4,5-Trimethoxybenzoyloxy) cyclohexanone 362.



Compound **362** was synthesised through reaction of cyclohexanone **44** and *N*-methyl-*O*-3,4,5-trimethoxybenzoyl hydroxylamine **349**, using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (3:2), gave *2-(3,4,5-trimethoxybenzoyloxy) cyclohexanone* **362** (108 mg, 85%) as a white crystalline solid. M.p. 93–98 °C. IR (thin film)/ cm^{-1}: 2941, 1735, 1717, 1589, 1501, 1458, 1415, 1337, 1224, 1127; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 2H, ArH), 5.30 (dd, 1H, *J* 11.3, 6.4 Hz, CHCO), 3.80 (s, 9H, *m,p*-OMe), 2.45–2.55 (m, 1H), 2.35–2.45 (m, 2H), 2.00–2.10 (m, 1H), 1.95–2.00 (m, 1H), 1.70–1.90 (m, 2H), 1.55–1.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 204.4, 165.3, 152.9, 142.6, 124.7, 107.1, 77.2, 61.0, 56.3, 40.8, 33.2, 27.2, 23.9 ppm; MS (EI): *m/z* 308 $[M+H]^+$. HRMS calculated for $C_{16}H_{21}O_6$ $[M+H]^{\cdot+}$ 308.1254, found 308.1253. Enantiomers separated on OD chiral column, 2.5% IPA/Hexane, 0.5 mL/min (t_1 = 48.2 min; t_2 = 55.5 min).

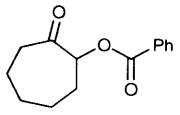
2-Benzoyloxy cyclopentanone 222.[49]



Compound **222** was synthesised from cyclopentanone **217** using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (7:3), gave *2-benzoyloxy cyclopentanone* **222** (79 mg, 72%) as a white crystalline

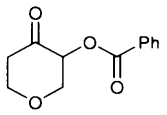
solid. M.p. 82–86 °C. Lit. ref. m.p. 88–91 °C.[95] IR (thin film)/ cm^{-1}: 2915, 2846, 1751, 1716, 1451, 1287, 1269, 1117, 709; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 2H, *J* 7.1 Hz, ArH), 7.50 (t, 1H, *J* 7.4 Hz, ArH), 7.35 (at, 2H, *J* 7.8 Hz, ArH), 5.25 (dd, 1H, *J* 10.1, 8.6 Hz, CHCO), 2.40–2.50 (m, 1H), 2.20–2.40 (m, 2H), 2.05–2.15 (m, 1H), 1.80–2.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 212.4, 165.8, 133.4, 130.0, 129.4, 128.4, 76.1, 35.0, 28.6, 17.2 ppm; MS (APcI): *m/z* 205 $[M+H]^+$. HRMS calculated for $C_{12}H_{13}O_3$ $[M+H]^{+}$ 205.0859, found 205.0861. Enantiomers separated on OD chiral column, 2.5% IPA/Hexane, 0.5 mL/min (retention time approximately 50 min).

2-Benzoyloxy cycloheptanone 223.[49]



Compound **223** was synthesised from cycloheptanone **218** using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *2-benzoyloxy cycloheptanone* **223** (89 mg, 72%) as a white crystalline solid. M.p. 52–56 °C. Lit. ref. m.p. 57–57.5 °C.[95] IR (thin film)/ cm^{-1}: 2932, 2861, 1734, 1714, 1448, 1315, 1272, 1107; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 2H, *J* 7.1 Hz, ArH), 7.50 (t, 1H, *J* 7.5 Hz, ArH), 7.35 (at, 2H, *J* 7.7 Hz, ArH), 5.40 (dd, 1H, *J* 9.6, 3.3 Hz, CHCO), 2.60–2.70 (m, 1H), 2.35–2.50 (m, 1H), 2.00–2.10 (m, 1H), 1.60–1.90 (m, 6H), 1.30–1.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 207.5, 165.8, 133.2, 129.9, 129.6, 128.4, 79.0, 40.8, 30.4, 28.4, 26.5, 23.0 ppm; MS (ES): *m/z* 233 $[M+H]^+$. HRMS calculated for $C_{14}H_{17}O_3$ $[M+H]^{+}$ 233.1172, found 233.1172. Enantiomers separated on OD chiral column, 5% IPA/Hexane, 1.0 mL/min (t_1 = 11.5 min; t_2 = 13.5 min).

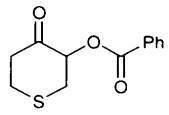
2-Benzoyloxy tetrahydropyran-4-one 224.



Compound **224** was synthesised from tetrahydropyran-4-one **219** using general procedure 3. Purification by column chromatography, eluting with petroleum ether-

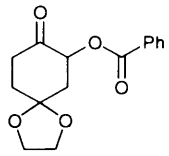
ethyl acetate (1:1), gave *2-benzoyloxy tetrahydropyran-4-one* **224** (99 mg, 84%) as a white crystalline solid. M.p. 76–79 °C. IR (thin film)/ cm^{-1}: 2913, 2856, 1736, 1719, 1597, 1451, 1315, 1275, 1261, 1204, 1121, 1096; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 2H, *J* 7.2 Hz, ArH), 7.50 (t, 1H, *J* 7.5 Hz, ArH), 7.35 (at, 2H, *J* 7.7 Hz, ArH), 5.45 (dd, 1H, *J* 9.9, 7.1 Hz, CHCO), 4.30–4.40 (m, 1H), 4.20–4.30 (m, 1H), 3.60–3.70 (m, 2H), 2.70–2.85 (m, 1H), 2.50–2.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 200.5, 165.1, 133.6, 130.0, 129.0, 128.5, 74.1, 70.6, 68.6, 42.3 ppm; MS (EI): *m/z* 221 $[M+H]^+$. HRMS calculated for $C_{12}H_{13}O_4$ $[M+H]^{+}$ 221.0814, found 221.0809. Enantiomers separated on OD chiral column, 5% IPA/Hexane, 1.0 mL/min (t_1 = 16.2 min; t_2 = 21.8 min).

2-Benzoyloxy tetrahydrothiopyran-4-one 225.[49]



Compound **225** was synthesised from tetrahydrothiopyran-4-one **220** using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (3:2), gave *2-benzoyloxy tetrahydrothiopyran-4-one* **225** (255 mg, 68%) as an off-white coloured solid. M.p. 73–78 °C. IR (thin film)/ cm^{-1}: 2912, 1736, 1721, 1602, 1451, 1300, 1267, 1177, 1112, 1070, 1028, 772, 710; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 2H, *J* 7.1 Hz, ArH), 7.50 (t, 1H, *J* 7.4 Hz, ArH), 7.35 (at, 2H, *J* 7.6 Hz, ArH), 5.50 (dd, 1H, *J* 11.0, 6.3 Hz, CHCO), 3.05–3.15 (m, 2H), 2.85–2.95 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 201.6, 165.2, 133.5, 130.0, 129.2, 128.5, 77.2, 44.8, 34.7, 30.4 ppm; MS (EI): *m/z* 236 $[M+H]^+$. HRMS calculated for $C_{12}H_{13}O_3S$ $[M+H]^{+}$ 237.0580, found 237.0579. Enantiomers separated on OD chiral column, 5% IPA/Hexane, 1.0 mL/min (t_1 = 16.0 min; t_2 = 19.4 min).

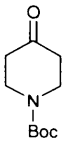
2-Benzoyloxy cyclohexane-1,4-dione monoethylene ketal 226.[49]



Compound **226** was synthesised from cyclohexanedione monoethylene ketal **221** using general procedure 3. Purification by column chromatography, eluting with

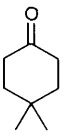
petroleum ether-ethyl acetate (7:3), gave *2-benzoyloxy cyclohexane-1,4-dione monoethylene ketal* **226** (110 mg, 75%) as a white crystalline solid. M.p. 98–103 °C. Lit. ref. m.p. 114–116 °C.[49] IR (thin film)/ cm^{-1}: 2961, 1735, 1719, 1452, 1293, 1274, 1247, 1111, 1043; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 2H, *J* 7.1 Hz, ArH), 7.50 (t, 1H, *J* 7.4 Hz, ArH), 7.35 (at, 2H, *J* 7.7 Hz, ArH), 5.60 (dd, 1H, *J* 13.2, 6.7 Hz, CHCO), 3.90–4.10 (m, 4H), 2.70–2.80 (m, 1H), 2.40–2.50 (m, 2H), 2.15–2.25 (t, 1H, *J* 12.8 Hz), 1.90–2.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 203.4, 165.4, 133.3, 129.9, 129.5, 128.4, 107.3, 73.7, 65.0, 64.9, 40.3, 35.9, 34.6 ppm; MS (EI): *m/z* 276 $[M+H]^+$. HRMS calculated for $C_{15}H_{17}O_5$ $[M+H]^+$ 277.1071, found 277.1069. Enantiomers separated on OD chiral column, 5% IPA/Hexane, 0.3 mL/min (t_1 = 55.8 min; t_2 = 63.0 min).

N-Boc-4-piperidinone 227.[96]



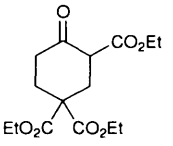
4-Piperidone hydrochloride monohydrate **230** (4.0 g, 26 mmol) was dissolved in dioxane (25 mL) and cooled to 0 °C. pH 10.5 buffer (25 mL, see chapter 9.1.1.1) was then added, followed by di-*tert*-butyl dicarbonate **289** (6.82 g, 31 mmol) with stirring at 0 °C for 30 minutes. During this time the pH of the reaction mixture was monitored and maintained at approximately pH 10 by the addition 2M NaOH when necessary. The reaction mixture was then warmed to room temperature, with stirring for 1 hour, before diluting with brine (50 mL) and extracting with ether (4 x 50 mL). The organic extracts were combined and washed with brine (200 mL), dried ($MgSO_4$) and concentrated to give the crude product, which was purified on silica, eluting with petroleum ether-ethyl acetate (4:1), to give *N-Boc-4-piperidinone* **227** (4.59 g, 88%) as a white crystalline solid. M.p. 68–71 °C. Lit. ref. m.p. 81–83 °C.[97] IR (thin film)/ cm^{-1}: 2870, 1708, 1685, 1420, 1242, 1164; ^1H NMR (400 MHz, $CDCl_3$) δ 3.65 (t, 4H, *J* 6.2 Hz, CH_2), 2.40 (t, 4H, *J* 6.2 Hz, CH_2), 1.40 (s, 9H, ^tBu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 207.9, 154.5, 80.4, 43.0, 41.2, 28.4 ppm; MS (ES): *m/z* 199 $[M+H]^+$. HRMS calculated for $C_{10}H_{18}O_3$ $[M+H]^+$ 199.1208, found 199.1215.

4,4-Dimethylcyclohexanone 228.[98]



Palladium on carbon (10%, 20 mg) was added to a solution of 4,4-dimethylcyclohexen-1-one **231** (1.242 g, 10 mmol) in petroleum ether (6 mL), and the reaction mixture was stirred under an atmosphere of hydrogen for 20 hours. The reaction mixture was then filtered through celite, washing with petrol, and the organics were concentrated to give *4,4-dimethylcyclohexanone* **238** (589 mg, 47%) as a white crystalline solid. M.p. 38–40 °C. Lit. ref. m.p. 44–45 °C.[99] IR (thin film)/ cm^{-1}: 2949, 2926, 2863, 1699, 1457, 1421, 1385, 1339, 1315, 1234, 1143, 1008; ^1H NMR (400 MHz, $CDCl_3$) δ 2.25 (t, 4H, *J* 6.9 Hz, CH_2), 1.55 (t, 4H, *J* 6.9 Hz, CH_2), 1.00 (s, 6H, Me); ^{13}C NMR (100 MHz, $CDCl_3$), δ 212.8, 39.1, 38.0, 29.9, 27.5 ppm; MS (ES): *m/z* 126 $[M+H]^+$. HRMS calculated for $C_8H_{15}O$ $[M+H]^{+}$ 126.1045, found 126.1043.

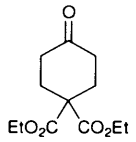
2,4,4-Tricarbethoxycyclohexanone 234.[100]



Freshly distilled diethyl malonate **233** (7.11 mL, 46.9 mmol) in dry THF (15 mL) was added dropwise (over 5 min) over 30 minutes to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 4.68 g, 0.117 mmol) in dry THF (50 mL) at 45 °C. After 15 minutes, a solution of ethyl acrylate **232** (9.86 g, 98.5 mmol) in THF (15 mL) was added slowly over 30 minutes. The resulting mixture was allowed to stir for an additional 15 minutes before pouring into ice-water (75 mL), reducing to pH 3 by means of 1M HCl and extracting with ethyl acetate (1 x 100 mL, 3 x 50 mL). The organic extracts were combined, washed with brine (200 mL), dried ($MgSO_4$) and concentrated to give the crude product, which was purified on silica, eluting with petroleum ether-ethyl acetate (4:1), to give *2,4,4-tricarbethoxycyclohexanone* **234** (4.65 g, 32%) as a clear colourless oil. IR (thin film)/ cm^{-1}: 2982, 2940, 1746, 1733, 1660, 1618, 1446, 1368, 1295, 1228, 1177,

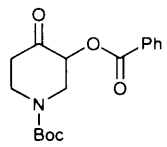
1098, 1040, 827; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10–4.20 (m, 6H, CH_2CH_3), 4.05–4.10 (m, 1H, CHCO), 2.30–2.40 (m, 2H), 2.10–2.20 (m, 2H), 1.25–1.30 (m, 2H), 1.15–1.25 (m, 9H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 171.9, 170.7, 170.1, 168.9, 95.2, 61.5, 61.4, 60.5, 50.8, 27.8, 26.6, 26.0, 14.2, 14.0, 14.0 ppm; MS (ES): *m/z* 314 $[M+H]^+$. HRMS calculated for $C_{15}H_{23}O_7$ $[M+H]^+$ 314.1366, found 314.1361.

4,4-Dicarbethoxycyclohexanone 229.[100]



A suspension of 2,4,4-tricarbethoxycyclohexanone **234** (1.1 g, 3.5 mmol), sodium chloride (0.6 g, 10.25 mmol) and water (0.15 mL, 8.33 mmol) in freshly distilled DMSO (5 mL) was heated to 150–160 °C with stirring under nitrogen for 2 hours. The resulting brown mixture was cooled to room temperature, poured into ice-water (100 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic extracts were then washed with brine (100 mL), dried ($MgSO_4$) and concentrated to give the crude product, which was purified on silica, eluting with petroleum ether-ethyl acetate (9:1), to give *4,4-dicarbethoxycyclohexanone* **229** (265 mg, 31%) as a white crystalline solid. M.p. 34–38 °C. IR (thin film)/ cm^{-1}: 2980, 2907, 1745, 1728, 1465, 1445, 1368, 1338, 1292, 1230, 1183, 1108, 1066, 1023; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (q, 4H, *J* 7.2 Hz, CH_2CH_3), 2.40–2.50 (m, 4H), 2.35–2.40 (m, 4H), 1.25 (t, 6H, *J* 7.2 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 209.4, 170.7, 61.8, 53.5, 37.7, 30.9, 14.1 ppm; MS (EI): *m/z* 242 $[M+H]^+$. HRMS calculated for $C_{12}H_{19}O_5$ $[M+H]^+$ 242.1149, found 242.1147.

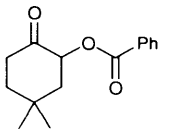
2-Benzoyloxy-*N*-Boc-4-piperidinone 236.



Compound **236** was synthesised from *N*-Boc-4-piperidinone **227** using general procedure 3. Purification by column chromatography, eluting with petroleum ether-

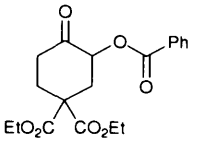
ethyl acetate (4:1), gave *2-benzoyloxy-N-Boc-4-piperidinone* **236** (461 mg, 68%) as a white crystalline solid. M.p. 93–97 °C. IR (thin film)/ cm^{-1}: 2976, 1739, 1724, 1700, 1472, 1452, 1420, 1367, 1297, 1272, 1236, 1164, 1112, 711; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 2H, *J* 7.2 Hz, ArH), 7.50 (t, 1H, *J* 7.4 Hz, ArH), 7.35 (at, 2H, *J* 7.7 Hz, ArH), 5.30 (dd, 1H, *J* 10.4, 6.5 Hz, CHCO), 4.35–4.65 (br, 1H), 4.20–4.30 (br, 1H), 3.20–3.35 (br, 1H), 3.10–3.20 (m, 1H), 2.45–2.65 (m, 2H), 1.40 (s, 9H, ^tBu); ^{13}C NMR (100 MHz, $CDCl_3$), δ 201.5, 165.1, 154.2, 133.5, 130.0, 129.1, 128.5, 81.2, 73.9, 48.0, 43.5, 40.5, 28.3 ppm; MS (ES): *m/z* 320 $[M+H]^+$. HRMS calculated for $C_{17}H_{22}O_5$ $[M+H]^{+}$ 320.1498, found 320.1492. Enantiomers separated on OD chiral column, 5% IPA/Hexane, 1.0 mL/min (t_1 = 24.6 min; t_2 = 28.4 min).

2-Benzoyloxy-4,4-dimethylcyclohexanone 235.



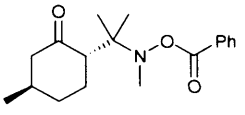
Compound **235** was synthesised from 4,4-dimethylcyclohexanone **228** using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *2-benzoyloxy-4,4-dimethylcyclohexanone* **235** (85 mg, 65%) as a white crystalline solid. M.p. 63–66 °C. IR (thin film)/ cm^{-1}: 2946, 2862, 1739, 1713, 1602, 1585, 1450, 1392, 1365, 1284, 1266, 1172, 1120, 1068, 1023; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 2H, *J* 7.5 Hz, ArH), 7.50 (t, 1H, *J* 7.4 Hz, ArH), 7.35 (at, 2H, *J* 7.7 Hz, ArH), 5.50 (dd, 1H, *J* 13.1, 6.4 Hz, CHCO), 2.55–2.65 (m, 1H), 2.30–2.40 (m, 1H), 2.00–2.10 (m, 1H), 1.85 (t, 1H, *J* 12.9 Hz), 1.80–1.60 (m, 2H), 1.25 (s, 3H, CH_3), 1.05 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 205.0, 165.7, 133.2, 129.9, 129.7, 128.4, 74.2, 45.3, 39.6, 37.0, 32.1, 31.4, 24.7 ppm; MS (ES): *m/z* 247 $[M+H]^+$. Enantiomers separated on OD chiral column, 10% IPA/Hexane, 0.5 mL/min.

2-Benzoyloxy-4,4-dicarbethoxycyclohexanone 237.



Compound **237** was synthesised from 4,4-dicarbethoxycyclohexanone **229** and reagent **109·HCl** using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (3:1), gave *2-benzoyloxy-4,4-dicarbethoxycyclohexanone* **237** (104 mg, 73%) as a clear colourless oil. IR (thin film)/ cm^{-1}: 2981, 2938, 1750, 1732, 1720, 1602, 1452, 1368, 1284, 1236, 1180, 1113, 1027, 861, 712; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 2H, *J* 7.1 Hz, ArH), 7.50 (t, 1H, *J* 7.4 Hz, ArH), 7.40 (at. 2H, *J* 7.7 Hz, ArH), 5.50 (dd, 1H, *J* 12.5, 6.2 Hz, CHCO), 4.30 (q, 2H, *J* 7.1 Hz, CH_2CH_3), 4.10–4.20 (m, 2H, CH_2CH_3), 2.90–3.00 (m, 1H), 2.60–2.70 (m, 2H), 2.45–2.55 (m, 1H), 2.35 (t, 1H, *J* 12.9 Hz), 2.05–2.15 (m, 1H), 1.25 (t, 3H, *J* 7.1 Hz, CH_2CH_3), 1.15 (t, 3H, *J* 7.2 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 202.6, 169.82, 169.75, 165.2, 133.4, 129.9, 129.3, 128.4, 73.3, 62.34, 62.25, 54.5, 36.9, 36.7, 31.6, 14.1, 14.0 ppm; MS (EI): *m/z* 362 $[M+H]^+$. HRMS calculated for $C_{22}H_{20}O_7$ $[M+H]^+$ 362.1360, found 362.1364. Enantiomers separated on OD chiral column, 5% IPA/Hexane, 0.3 mL/min (t_1 = 28.1 min; t_2 = 32.8 min).

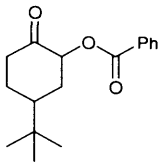
(*S*)-2-(2'-(*N*-benzoyloxy-*N*-methylamino)propan-2'-yl)-(*R*)-5-methylcyclohexanone 243.



Compound **243** was synthesised from (*R*)-pulegone **238** using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *(S)-2-(2'-(N-benzoyloxy-N-methylamino)propan-2'-yl)-(R)-5-methylcyclohexanone* **243** (26 mg, 16%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, 2H, *J* 7.1 Hz, ArH), 7.50 (t, 1H, *J* 7.4 Hz, ArH), 7.40 (at, 2H, *J* 7.7 Hz, ArH), 2.70 (s, 3H, CH_3), 2.55–2.65 (m, 1H), 2.45 (dd, 1H, *J* 13.1, 4.6 Hz, CHCO), 2.15–2.25 (m, 1H), 1.90 (t, 1H, *J* 12.0 Hz), 1.75–1.85 (m, 2H), 1.55–1.70 (m, 1H), 1.35 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.00–1.15 (m, 1H), 0.85 (d, 3H, *J* 6.2

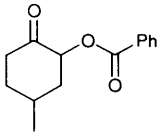
Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 211.1, 164.9, 133.1, 129.4, 128.6, 128.56, 63.1, 56.5, 52.5, 37.5, 36.6, 34.5, 27.9, 22.2, 19.6, 17.5 ppm; MS (ES): *m/z* 304 $[M+H]^+$.

2-Benzoyloxy-4-*tert*-butylcyclohexanone 245.[49]



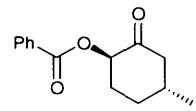
Compound **245** was synthesised from 4-*tert*-butylcyclohexanone **239** using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (7:3), gave *2-benzoyloxy-4-tert-butylcyclohexanone* **245** (101 mg, 69%) as a 2:1 mixture of diastereoisomers. Data on mixture. IR (thin film)/ cm^{-1}: 2959, 2870, 1733, 1719, 1454, 1272, 1120; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00–8.05 (m, 4H, ArH), 7.45–7.55 (m, 2H, ArH), 7.35–7.45 (m, 4H), 5.40 (dd, 1H, *J* 11.8, 6.3 Hz, CHCO, major isomer), 5.20–5.25 (m, 1H, CHCO, minor isomer), 1.35–2.65 (m, 14H), 0.90 (s, 9H, ^{t}Bu), 0.85 (s, 9H, ^{t}Bu) ppm.

2-Benzoyloxy-4-methylcyclohexanone 244.[49]



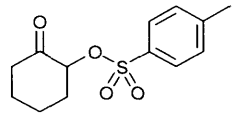
Compound **244** was synthesised from 4-methylcyclohexanone **240** using general procedure 3. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (7:3), gave *2-benzoyloxy-4-methylcyclohexanone* **244** (93 mg, 75%) as a 1:1 mixture of diastereoisomers. Data on mixture. IR (thin film)/ cm^{-1}: 2927, 2862, 1731, 1717, 1454, 1269, 1111; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 4H, *J* 6.8 Hz, ArH), 7.40–7.50 (m, 2H), 7.30–7.40 (m, 4H), 5.30-5.45 (m, 2H), 2.40–2.55 (m, 4H), 2.20–2.40 (m, 2H), 2.05–2.20 (m, 2H), 1.90–2.05 (m, 2H), 1.55–1.75 (m, 2H), 1.30–1.45 (m, 1H), 1.20 (d, 3H, *J* 7.0 Hz, CH_3), 1.00 (d, 3H, *J* 6.5 Hz, CH_3), 1.70–1.85 (m, 1H) ppm.

2-(*R*)-Benzoyloxy-3-(*R*)-methylcyclohexanone 247a.



Compound **247a** was synthesised from (*R*)-3-methylcyclohexanone **241** using general procedure 3. Purification by column chromatography, eluting with petroleum ether-diethyl ether (1:1), gave *(R)-2-benzoyloxy-(R)-3-methylcyclohexanone* **247a** (17 mg, 14%) as a white crystalline solid. M.p. 83–86 °C. IR (thin film)/ cm^{-1}: 2922, 2852, 1733, 1715, 1449, 1270, 1113; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, 2H, *J* 7.1 Hz, ArH), 7.60 (t, 1H, *J* 7.4 Hz, ArH), 7.45 (at, 2H, *J* 7.7 Hz, ArH), 5.40 (dd, 1H, *J* 12.7, 6.5 Hz, CHCO), 2.50–2.60 (m, 1H), 2.35–2.45 (m, 1H), 2.15–2.30 (m, 1H), 1.90–2.10 (m, 3H), 1.55–1.65 (m, 1H), 1.10 (d, 3H, *J* 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 203.8, 165.7, 133.2, 129.8, 129.7, 128.4, 76.6, 48.8, 35.1, 32.3, 31.8, 22.1 ppm; MS (ES): *m/z* 233 $[M+H]^+$. HRMS calculated for $C_{14}H_{17}O_3$ $[M+H]^+$ 233.1178, found 233.1183.

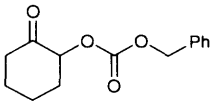
2-Oxytosyl cyclohexanone 100.[53]



Cyclohexanone **44** (0.052 mL, 0.497 mmol) was added dropwise (over 5 min) to a stirred solution of *N*-methyl-*O*-toluene sulphonyl hydroxylamine **86** (150 mg, 0.745 mmol) and methane sulphonic acid (0.048 mL, 0.745 mmol) in THF-toluene (1:1, 1.0 mL). Stirring was continued at 25 °C overnight. The reaction mixture was diluted with brine (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined extracts were washed with brine (45 mL), dried ($MgSO_4$) and concentrated to give the crude product, which was purified on silica, eluting with petroleum ether-ethyl acetate (65:35), to give *2-oxytosyl cyclohexanone* **100** (66 mg, 49%) as a white crystalline solid. M.p. 55–61 °C. Lit. ref. m.p. 72–76 °C.[53] IR (thin film)/ cm^{-1}: 2941, 2867, 1734, 1650, 1594, 1444, 1356, 1185, 1175, 1093, 1018, 920; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, 2H, *J* 8.4 Hz, ArH), 7.35 (d, 2H, *J* 8.4 Hz, ArH), 4.90 (dd, 1H, *J* 10.9, 5.9 Hz, CHCO), 2.55–2.60 (m, 1H), 2.45 (s, 3H, CH_3), 2.25–2.40 (m, 2H), 1.85–2.05 (m, 3H), 1.65–1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 202.8,

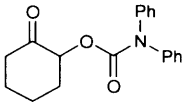
144.9, 133.7, 129.8, 128.0, 81.9, 40.6, 34.6, 27.0, 23.2, 21.7 ppm; MS (EI): *m/z* 268 $[M+H]^+$. HRMS calculated for $C_{13}H_{17}SO_4$ $[M+H]^+$ 268.0769, found 268.0765. Enantiomers separated on OD chiral column, 5% IPA/Hexane, 1.0 mL/min.

2-(Benzylcarbonoyloxy) cyclohexanone 295.



Cyclohexanone **44** (0.048 mL, 0.459 mmol) was added dropwise (over 5 min) to a stirred solution of *N*-methyl-*O*-benzylcarbonate hydroxylamine hydrochloride **294·HCl** (100 mg, 0.459 mmol) in THF-toluene (1:1, 0.66 mL). Stirring was continued at 25 °C overnight. The reaction mixture was diluted with brine (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to give the crude product, which was purified on silica, eluting with petroleum ether-ethyl acetate (7:3), to give *2-(benzylcarbonoyloxy) cyclohexanone* **295** (92 mg, 81%) as a white crystalline solid. M.p. 47–51 °C. IR (thin film)/ cm^{-1}: 2944, 2866, 1752, 1728, 1499, 1455, 1386, 1300, 1262, 1216, 1115, 1017, 902, 889, 784, 744; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20–7.35 (m, 5H, ArH), 5.10 (s, 2H, CH_2), 4.95 (dd, 1H, *J* 11.9, 6.5 Hz, CHCO), 2.40–2.50 (m, 1H), 2.25–2.40 (m, 2H), 1.95–2.05 (m, 1H), 1.85–1.95 (m, 1H), 1.65–1.80 (m, 2H), 1.50–1.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 204.2, 154.3, 135.0, 128.6, 128.5, 128.3, 79.5, 70.0, 40.6, 33.0, 27.0, 23.6 ppm; MS (EI): *m/z* 248 $[M+H]^+$. HRMS calculated for $C_{14}H_{17}O_4$ $[M+H]^+$ 248.1049, found 248.1048. Enantiomers separated on OD chiral column, 20% IPA/Hexane, 1.0 mL/min (t_1 = 11.5 min; t_2 = 14.6 min).

2-(Diphenylcarbamoyloxy) cyclohexanone 302.[52]



Cyclohexanone **44** (0.037 mL, 0.359 mmol) was added dropwise (over 5 min) to a stirred solution of *N*-methyl-*O*-diphenylcarbamoyl hydroxylamine hydrochloride **94·HCl** (100 mg, 0.359 mmol) in THF-toluene (1:1, 0.51 mL). Stirring was continued at 25 °C overnight. The reaction mixture was diluted with brine (5 mL)

and extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to give the crude product which was purified on silica, eluting with petroleum ether-ethyl acetate (7:3), to give *2-(diphenylcarbamoyloxy) cyclohexanone* **302** (101 mg, 91%) as a white crystalline solid. M.p. 138–141 °C. IR (thin film)/ cm^{-1}: 2938, 1729, 1709, 1587, 1492, 1446, 1373, 1341, 1280, 1212, 1091, 760, 694; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20–7.30 (m, 8H, ArH), 7.05–7.15 (m, 2H, ArH), 5.15 (dd, 1H, *J* 12.4, 6.3 Hz, CHCO), 2.35–2.45 (m, 1H), 2.25–2.35 (m, 1H), 2.10–2.20 (m, 1H), 1.90–2.00 (m, 1H), 1.80–1.90 (m, 1H), 1.60–1.75 (m, 1H), 1.45–1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 205.1, 153.9, 142.6, 128.8, 127.1, 126.1, 78.0, 40.6, 32.9, 27.1, 23.7 ppm; MS (ES): *m/z* 310 $[M+H]^+$. HRMS calculated for $C_{19}H_{20}NO_3$ $[M+H]^+$ 310.1443, found 310.1433. Enantiomers separated on OD chiral column, 20% IPA/Hexane, 1.0 mL/min (t_1 = 11.6 min; t_2 = 19.8 min).

9.2.3. Synthesis of 33 from Nitrone 281 (reaction scheme 6.10).

Benzoyl chloride **272** (0.06 mL, 0.519 mmol) and triethylamine (0.07 mL, 0.519 mmol) were added dropwise (over 5 min) to a solution of *N*-(*S*)-α-methyl-benzyl cyclohexyl nitrone **281** (94 mg, 0.433 mmol) in dry dichloromethane (1.08 mL) under nitrogen at 0 °C, with stirring for 18 hours, warming to room temperature. The reaction mixture was then poured into ethyl acetate (10 mL), washed with brine (2 x 5 mL), dried ($MgSO_4$) and concentrated to give the crude product, which was purified on silica, eluting with petroleum ether-ethyl acetate (3:1), to give *2-benzoyloxy cyclohexanone* **33** (55 mg, 58%) as a white crystalline solid (See Chapter 9.2.1 for full experimental data).

9.2.4. One-pot Procedure for the Synthesis of 33 using Nitrone Method (reaction scheme 6.13).

Cyclohexanone **44** (0.40 mL, 3.83 mmol) was added dropwise (over 5 min) to a mixture of *N*-(*S*)-α-methyl benzyl hydroxylamine **162** (350 mg, 2.55 mmol) and sodium sulphate (544 mg, 3.83 mmol) in dry dichloromethane (2.0 mL) under nitrogen, with stirring at 30 °C for 30 hours. The reaction mixture was then cooled to 0 °C and benzoyl chloride **272** (0.38 mL, 3.32 mmol) and triethylamine (0.46 mL, 3.32 mmol) were added dropwise, with stirring for a further 18 hours, warming to

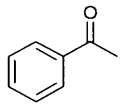
room temperature. The reaction mixture was then poured into ethyl acetate (20 mL), washed with brine (2 x 10 mL), dried ($MgSO_4$) and concentrated to give the crude product, which was purified on silica, eluting with petroleum ether-ethyl acetate (4:1), to give *2-benzoyloxy cyclohexanone* **33** (66 mg, 12%) as a white crystalline solid (See Chapter 9.2.1 for full experimental data).

9.3. Ketone Experimentals.

9.3.1. General Procedure 4. Two-Step Amine Oxidation.

The amine oxidation reactions were carried out using the appropriate hydroxylamine based reagent, at 50 °C for 18 hours, unless otherwise stated, in the manner described as follows:

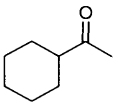
Acetophenone 338.



N-(*S*)-α-Methyl benzyl-*O*-benzoyl hydroxylamine **110** (100 mg, 0.41 mmol) was dissolved in DMF (0.59 mL, [0.7M]) at r.t. Cesium carbonate (135 mg, 0.41 mmol) was added and the resulting reaction mixture was heated to 50 °C with stirring overnight. The resulting reaction mixture was purified directly by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), to give *acetophenone* **338** (42 mg, 84%) as a clear colourless oil. IR (thin film): 1683, 1599, 1582, 1449, 1359, 1266, 1180, 1078, 1025, 955, 760, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, 2H, *J* 7.2 Hz, ArH), 7.45 (t, 1H, *J* 7.3 Hz, ArH), 7.35 (at, 2H, *J* 7.6 Hz, ArH), 2.50 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 137.1, 133.1, 128.6, 128.3, 26.6 ppm; MS (EI): *m/z* 120 $[M+H]^+$. Structure also confirmed by comparison of NMR data to that previously reported.[101]

9.3.2. General Procedure 5. One-Pot Amine Oxidation.

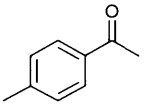
Cyclohexyl methyl ketone 364.



75 % Benzoyl peroxide **111** (326 mg, 1.01 mmol) was dissolved in DMF (2.53 mL, [0.4M]) and cooled to 0 °C. Cesium carbonate (493 mg, 1.51 mmol) was added with stirring followed by (*S*)-1-cyclohexyl ethylamine (0.18 mL, 1.21 mmol). The resulting reaction mixture was stirred at 0 °C for 2 hours before warming to r.t. Thin layer chromatography was used to confirm complete consumption of benzoyl peroxide before heating to 50 °C with stirring overnight. The resulting reaction mixture was purified directly by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), to give *cyclohexyl methyl ketone* **364** (75 mg, 59%) as a clear colourless oil. IR (thin film): 2931, 2854, 1706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.30–2.35 (m, 1H), 2.05 (s, 3H, CH_3), 1.85–1.80 (m, 2H), 1.75–1.70 (m 2H), 1.65–1.55 (m, 1H), 1.30–1.05 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.2, 51.4, 28.4, 27.8, 25.8, 25.6 ppm; MS (EI): *m/z* 126 $[M+H]^+$. Structure also confirmed by comparison of NMR data to that previously reported.[102]

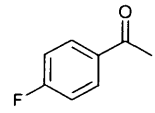
9.3.3. Experimental Data.

4-Methylacetophenone 365.



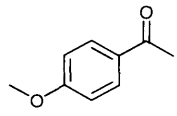
Compound **365** was synthesised from *N*-(*S*)-α-methyl-4-methylbenzyl-*O*-benzoyl hydroxylamine **354** using general procedure 4. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *4-methylacetophenone* **365** (38 mg, 72%) as a clear yellowish oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 2H, *J* 8.3 Hz, ArH), 7.05 (d, 2H, *J* 8.3 Hz, ArH), 2.40 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$); δ 197.9, 143.9, 134.7, 129.3, 128.5, 26.6, 21.7 ppm; MS (ES): *m/z* 134 $[M+H]^+$. Structure also confirmed by comparison of NMR data to that previously reported.[103]

4-Fluoroacetophenone 366.



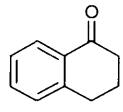
Compound **366** was synthesised from *N*-(*S*)-α-methyl-4-fluorobenzyl-*O*-benzoyl hydroxylamine **353** using general procedure 4. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *4-fluoroacetophenone* **366** (48 mg, 90%) as a clear yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75–7.8 (m, 2H, ArH), 6.90 (at, 2H, *J* 8.6 Hz, ArH), 2.40 (s, 3H, CH_3) ppm; MS (ES): *m/z* 138 $[M+H]^+$. Structure also confirmed by comparison of NMR data to that previously reported.[104]

4-Methoxyacetophenone 367.



Compound **367** was synthesised from *N*-(*S*)-α-methyl-4-methoxybenzyl-*O*-benzoyl hydroxylamine **193** using general procedure 4. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (7:3), gave *4-methoxyacetophenone* **367** (50 mg, 90%) as a white solid. M.p. 18–22 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, 2H, *J* 8.9 Hz, ArH), 6.90 (d, 2H, *J* 8.9 Hz, ArH), 3.85 (s, 3H, *O*-CH_3), 2.55 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$); δ 196.8, 163.5, 130.6, 130.3, 113.7, 55.5, 26.4 ppm; MS (ES): *m/z* 151 $[M+H]^+$.

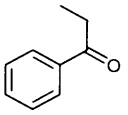
α-Tetralone 318.



Compound **318** was synthesised from *N*-(*S*)-1,2,3,4-tetrahydronaphthyl-*O*-benzoyl hydroxylamine **208**, at 70 °C for 72 hours, using general procedure 4. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *α-tetralone* **318** (41 mg, 75%) as a clear colourless oil. IR (thin film): 2945, 2868, 1682, 1601, 1455, 1435, 1324, 1286, 1225, 1183, 1116, 1025, 906, 764, 735 cm^{-1}; ^{1}H

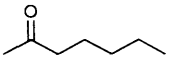
NMR (400 MHz, $CDCl_3$): δ 8.00 (dd, 1H, *J* 7.8, 1.2 Hz, ArH), 7.40 (t, 1H, *J* 7.5 Hz, ArH), 7.20–7.30 (m, 1H, ArH), 7.15–7.20 (d, 1H, *J* 7.7 Hz, ArH), 2.92 (t, 2H, *J* 6.1 Hz, CH_2), 2.90 (t, 2H, *J* 6.6 Hz, CH_2), 2.00–2.10 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 144.5, 133.4, 132.5, 128.8, 127.1, 126.6, 39.1, 29.7, 23.3 ppm; MS (EI): *m/z* 146 $[M+H]^+$.

Propiophenone 368.



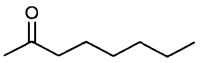
Compound **368** was synthesised from *N*-(*S*)-α-ethylbenzyl-*O*-benzoyl hydroxylamine **206** using general procedure 4. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *propiophenone* **368** (37 mg, 70%) as a clear colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, 2H, *J* 7.6 Hz, ArH), 7.55 (t, 1H, *J* 7.2 Hz, ArH), 7.45 (at, 2H, *J* 7.4 Hz, ArH), 3.00 (q, 2H, *J* 7.2, CH_2), 1.20 (t, 3H, *J* 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8, 136.9, 132.9, 128.6, 128.0, 31.8, 8.2 ppm. Structure also confirmed by comparison of NMR data to that previously reported.[105]

2-Heptanone 369.



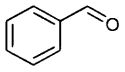
Compound **369** was synthesised from *N*-2-heptyl-*O*-benzoyl hydroxylamine **355**, at 70 °C, using general procedure 4. Purification by column chromatography, eluting with petroleum ether-ether (4:1), gave *2-heptanone* **369** (33 mg, 68%) as a clear colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 2.30 (t, 2H, *J* 7.5 Hz, CH_2CO), 2.10 (s, 3H, CH_3CO), 1.45–1.55 (m, 2H), 1.10–1.30 (m, 4H), 0.80 (t, 3H, *J* 7.0 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.2, 43.7, 31.3, 29.7, 23.5, 22.4, 13.8 ppm. Structure also confirmed by comparison of NMR data to that previously reported.[106]

2-Octanone 370.



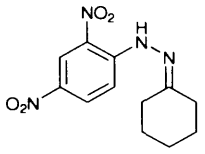
Compound **370** was synthesised from *N*-2-octyl-*O*-benzoyl hydroxylamine **356**, at 70 °C for 48 hours, using general procedure 4. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *2-octanone* **370** (27 mg, 53%) as a clear colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (t, 2H, *J* 7.4 Hz, CH_2CO), 2.05 (s, 3H, CH_3CO), 1.45–1.55 (m, 2H), 1.15–1.30 (m, 6H), 0.80 (t, 3H, *J* 6.6 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.2, 43.7, 31.5, 29.7, 28.8, 23.7, 22.4, 13.9 ppm. Structure also confirmed by comparison of NMR data to that previously reported.[101]

Benzaldehyde 371.



Compound **371** was synthesised from *N*-benzyl-*O*-benzoyl hydroxylamine **357**, at 70 °C for 72 hours, using general procedure 4. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *benzaldehyde* **371** (19 mg, 41%) as a clear colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (s, 1H, CHO), 7.80 (d, 2H, *J* 6.8 Hz, ArH), 7.55 (t, 1H, *J* 7.2 Hz, ArH), 7.45 (at, 2H, *J* 7.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4, 136.3, 134.5, 129.7, 129.0 ppm.

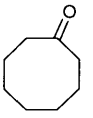
Cyclohexanone-2,4-dinitrophenylhydrazone 339.



N-Cyclohexyl-*O*-benzoyl hydroxylamine **109** (100 mg, 0.456 mmol) was dissolved in DMF (0.91 mL, [0.5M]) at r.t. Cesium carbonate (149 mg, 0.456 mmol) was added and the resulting reaction mixture was heated to 70 °C with stirring overnight. 2,4-DNPH (65%, 348 mg, 1.14 mmol) was then added to the reaction mixture, with stirring at r.t. for 3 hours. The reaction mixture was diluted with brine (10 mL) and extracted with ethyl acetate (4 x 10 mL). The combined extracts were washed with

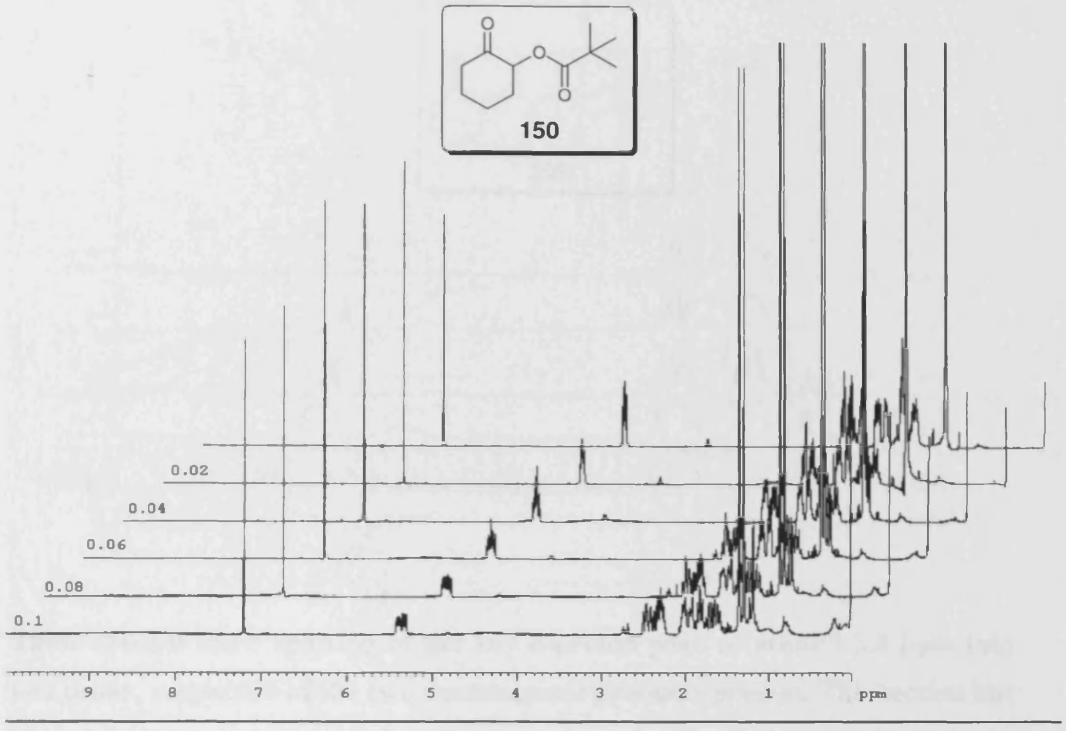
brine (30 mL), dried ($MgSO_4$) and concentrated to give the crude product which was purified on silica, eluting with petroleum ether-ethyl acetate (4:1), to give *cyclohexanone-2,4-dinitrophenylhydrazone* **339** (127 mg, 53%) as a yellow crystalline solid. IR (thin film): 3306, 2917, 2855, 1619, 1587, 1517, 1419, 1335, 1304, 1282, 1256, 1211, 1127, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.10–11.20 (br, 1H, NH), 9.05 (d, 1H, *J* 2.5 Hz, ArH), 8.25 (dd, 1H, *J* 9.6, 2.5, ArH), 7.90 (d, 1H, *J* 9.6 Hz, ArH), 2.35–2.45 (m, 4H), 2.70–2.80 (m, 4H), 2.60–2.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5, 145.3, 137.4, 130.0, 128.8, 123.7, 116.3, 35.6, 27.2, 27.1, 26.0, 25.5 ppm; MS (ES): *m/z* 279 $[M+H]^+$. HRMS calculated for $C_{12}H_{14}N_4O_4$ $[M]^{\cdot+}$ 278.1015, found 278.1016.

Cyclooctanone 372.

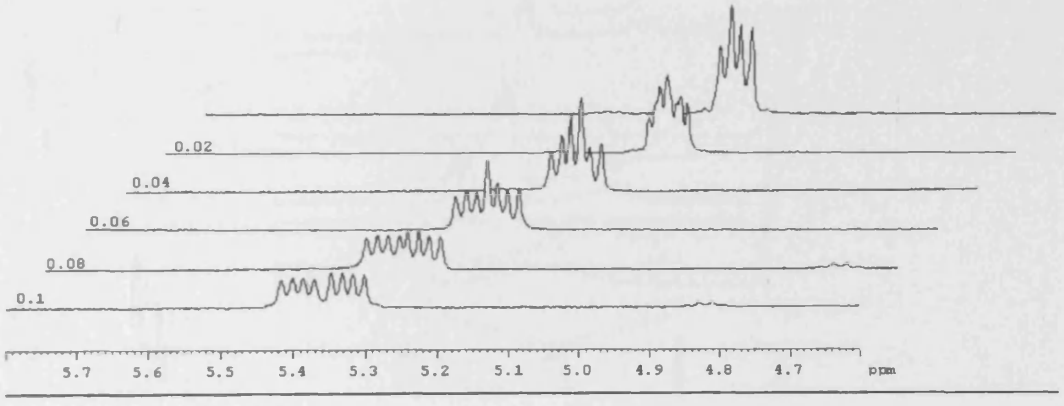


Compound **372** was synthesised from *N*-cyclooctyl-*O*-benzoyl hydroxylamine **358**, at 50 °C for 48 hours, using general procedure 4. Purification by column chromatography, eluting with petroleum ether-ethyl acetate (4:1), gave *cyclooctanone* **372** (15 mg, 29%) as a clear colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 2.20–2.30 (m, 4H), 1.70–1.80 (m, 4H), 1.35–1.45 (m, 4H), 1.20–1.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.4, 41.8, 27.0, 25.5, 24.6 ppm.

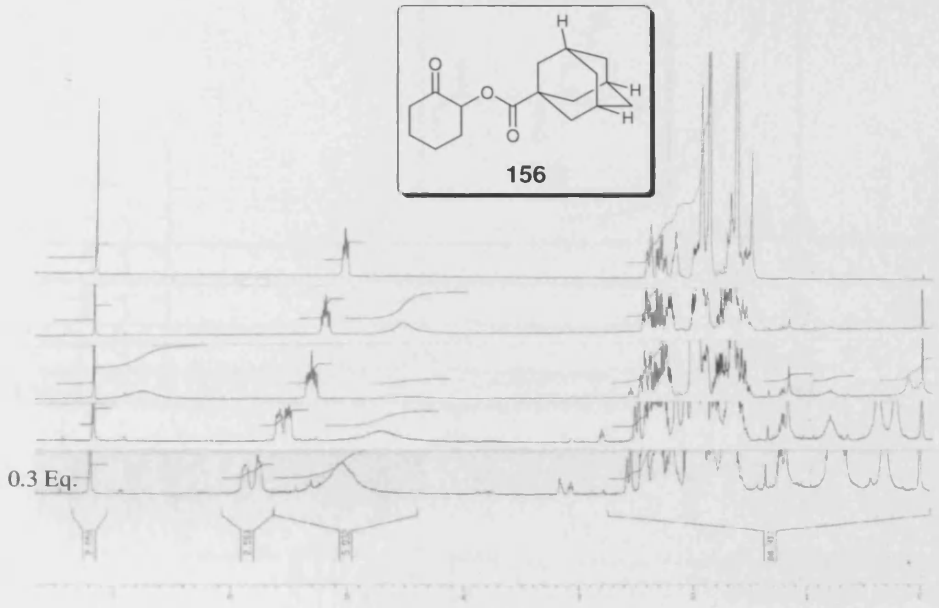
Appendix 1: Separation of enantiomers of compound 150 using NMR shift reagent 161.



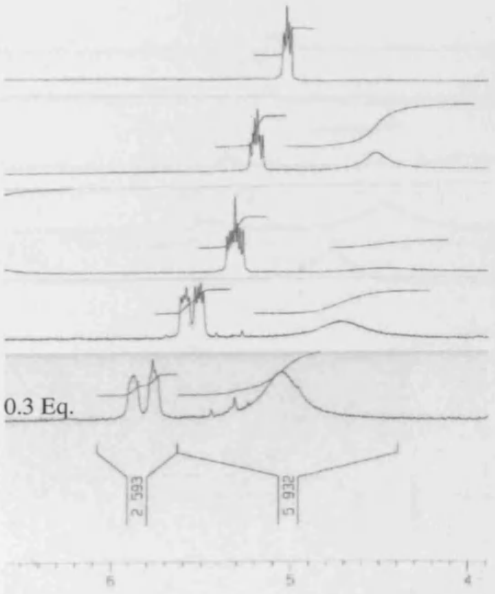
These spectra show splitting of the key α-proton peak at around 5.4 ppm into two peaks, respective of the two enantiomeric products present. This section has been highlighted below so as to see more clearly the separation of the enantiomers.



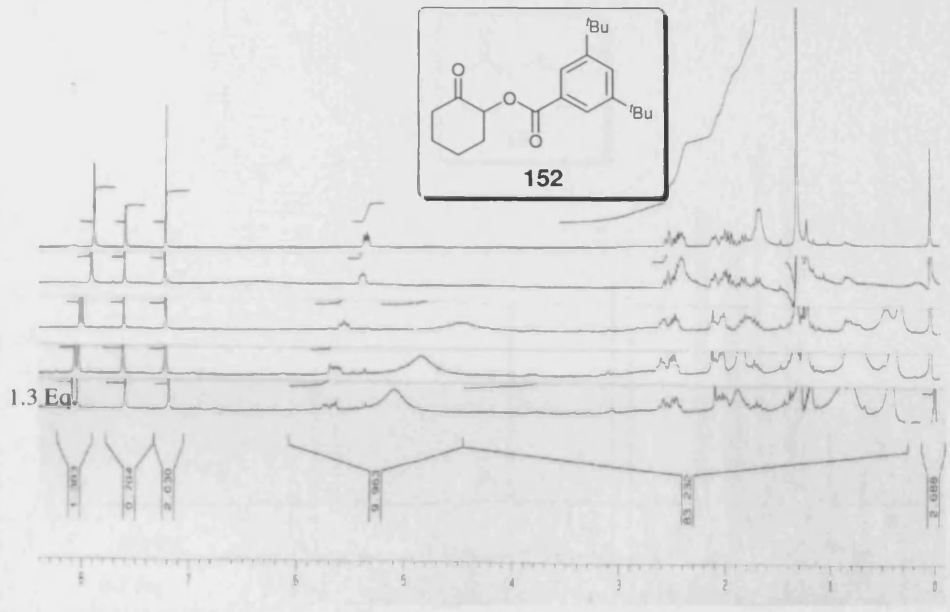
Appendix 2: Separation of enantiomers of compound 156 using NMR shift reagent 161.



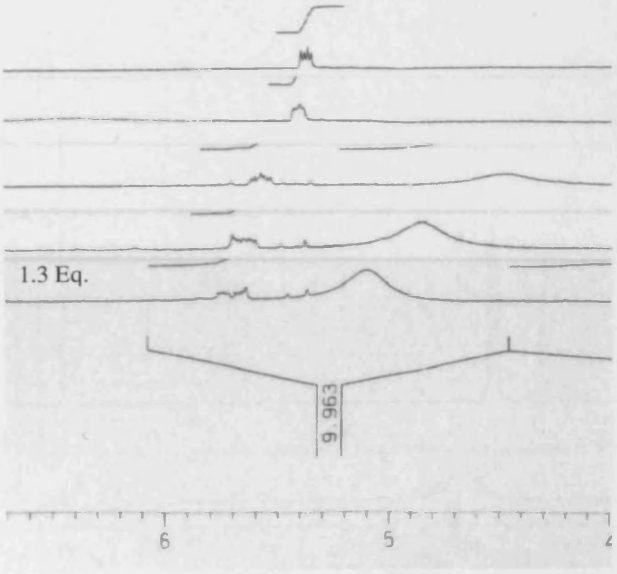
These spectra show splitting of the key α-proton peak at around 5.8 ppm into two peaks, respective of the two enantiomeric products present. This section has been highlighted below so as to see more clearly the separation of the enantiomers.



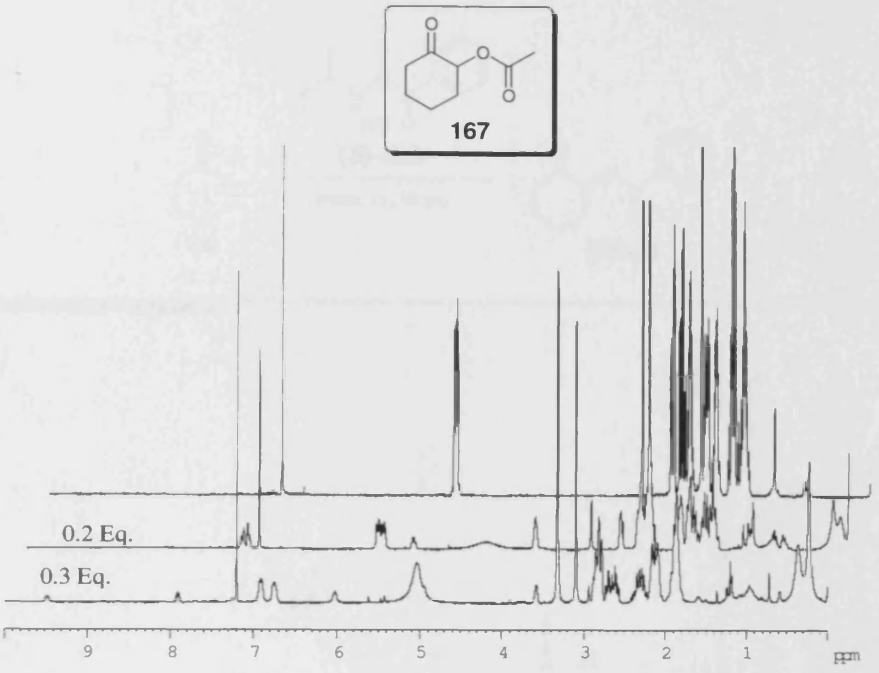
Appendix 3: Separation of enantiomers of compound 152 using NMR shift reagent 161.



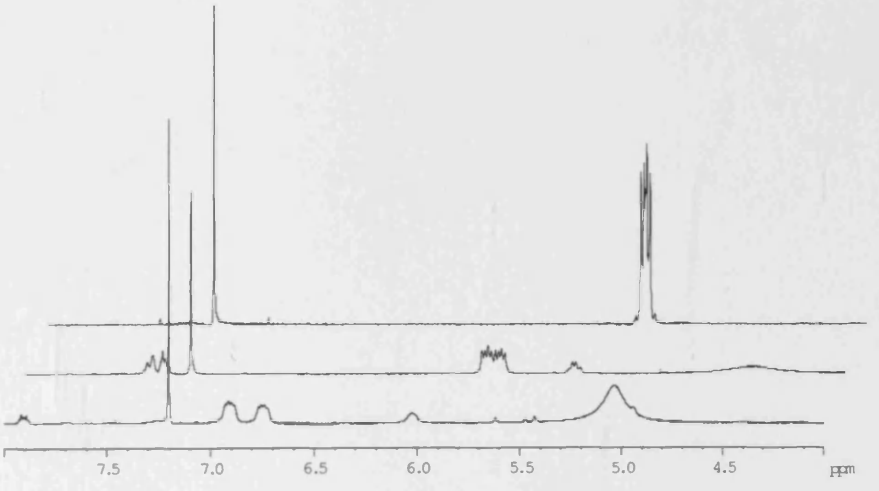
These spectra show splitting of the key α-proton peak at around 5.7 ppm into two peaks, respective of the two enantiomeric products present. This section has been highlighted below so as to see more clearly the separation of the enantiomers.



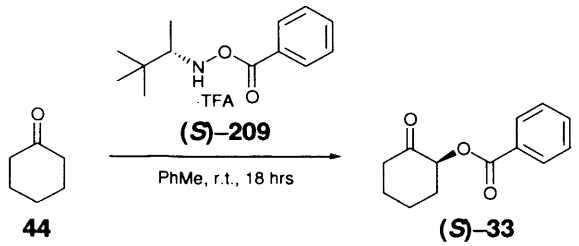
Appendix 4: Separation of enantiomers of compound 167 using NMR shift reagent 161.

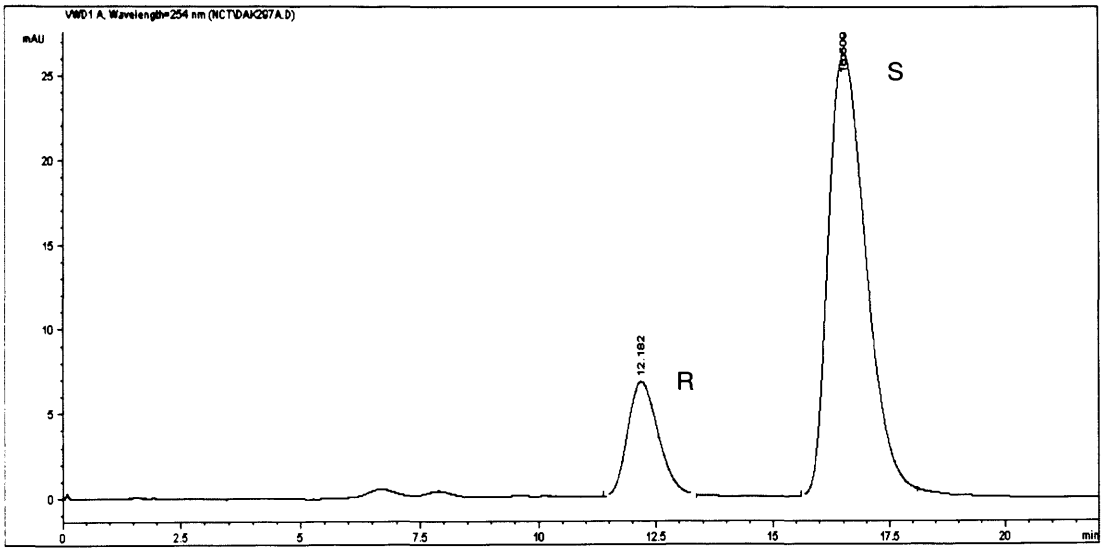


These spectra show splitting of the key α-proton peak at around 6.8 ppm into two peaks, respective of the two enantiomeric products present. This section has been highlighted below so as to see more clearly the separation of the enantiomers.

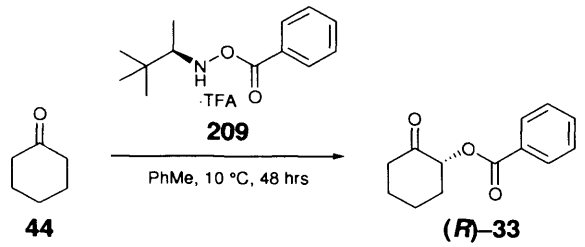


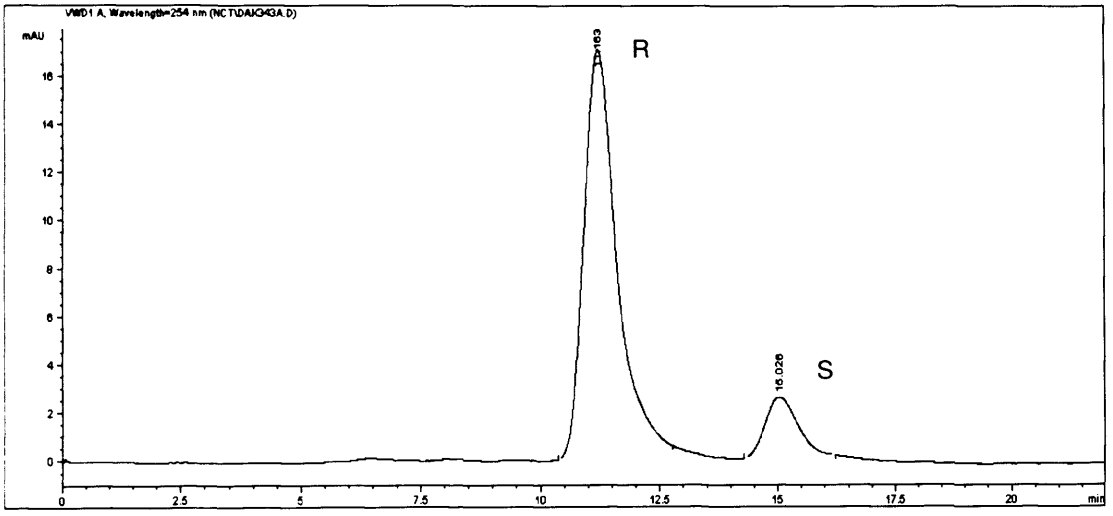
Appendix 5: HPLC spectra obtained from analysis of compound 33 showing a 74% e.e of the (*S*)-enantiomer.



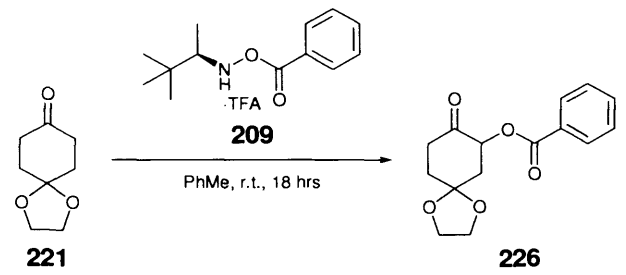


Appendix 6: HPLC spectra obtained from analysis of compound 33 showing an 82% e.e. of the (*R*)-enantiomer.

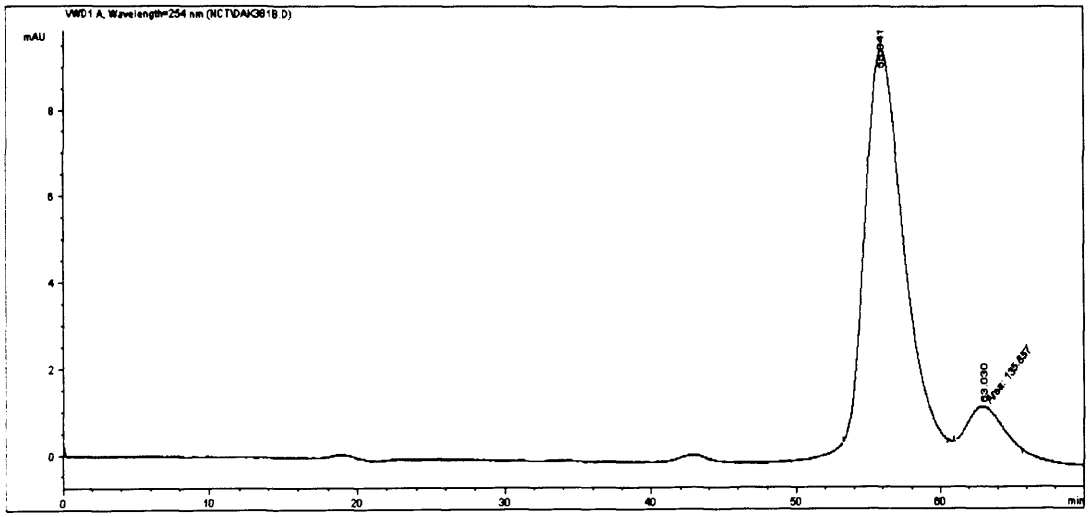




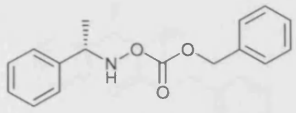
Appendix 7: HPLC spectra obtained from analysis of compound 226 showing an 89% e.e.



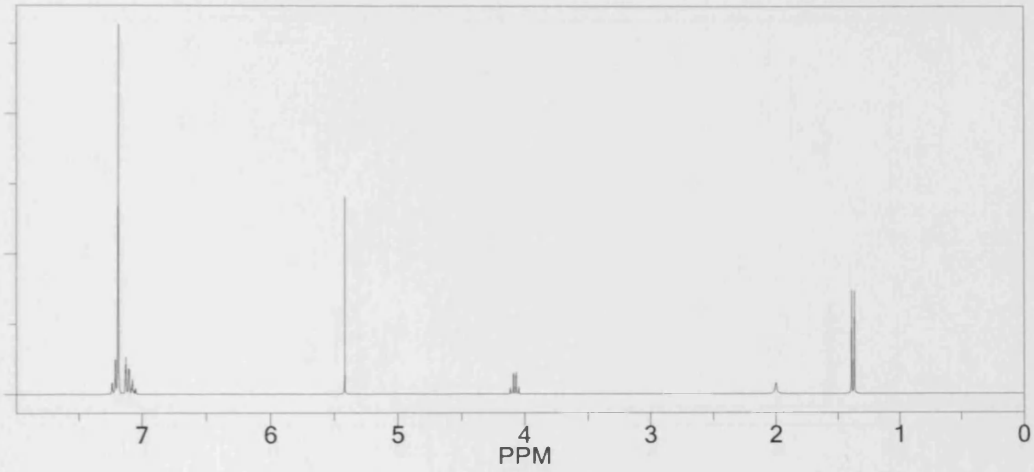
221 226

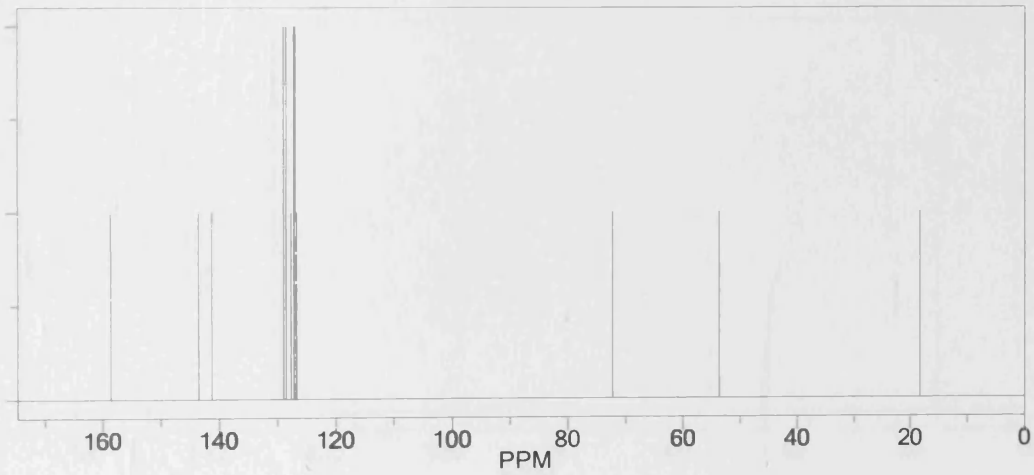


Appendix 8: ^{1}H and ^{13}C NMR predictions for compound 296 generated using ChemDraw.

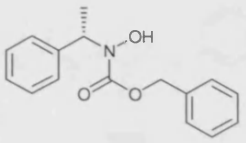


296

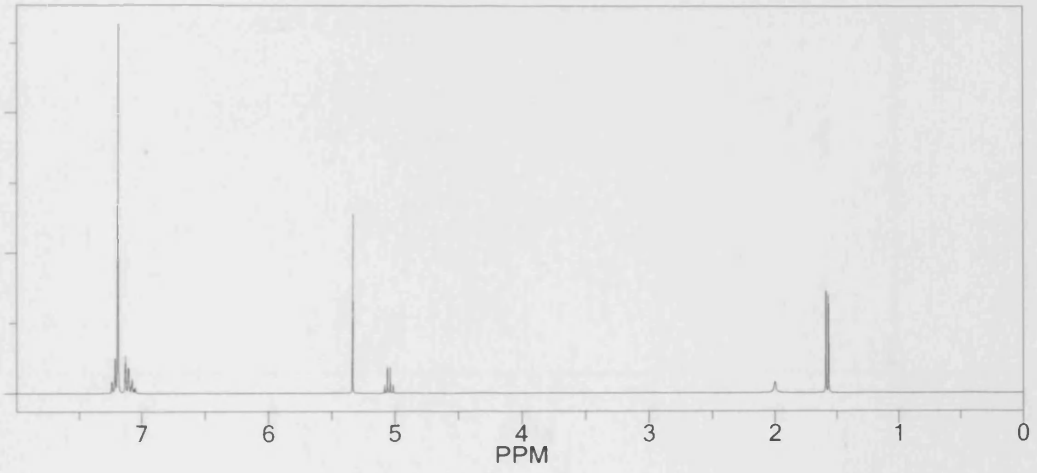


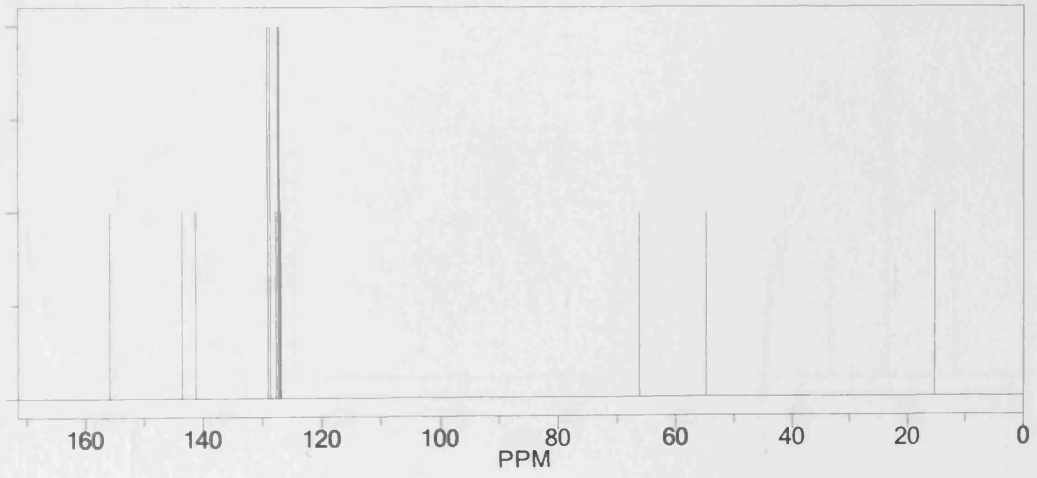


Appendix 9: ^{1}H and ^{13}C NMR predictions for compound 297 generated using ChemDraw.

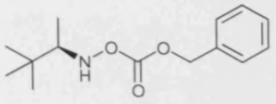


297

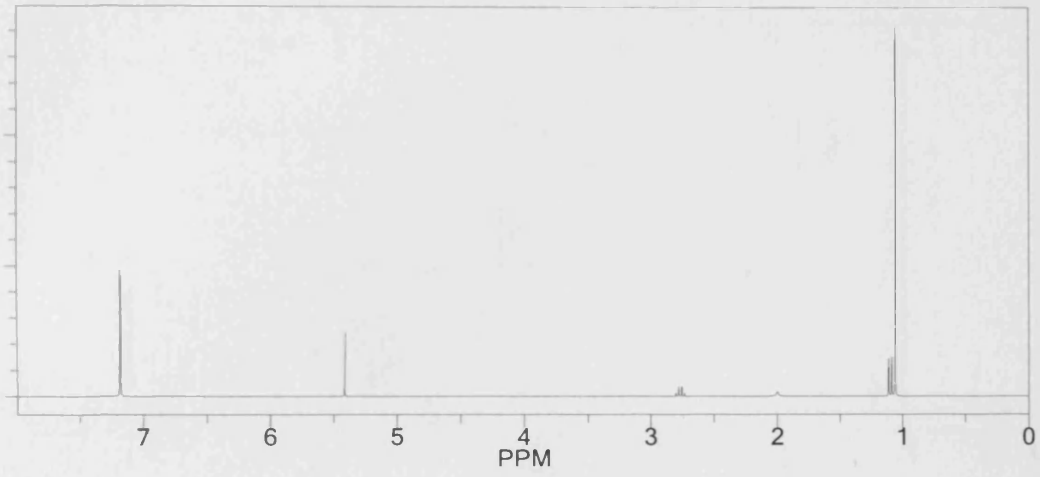


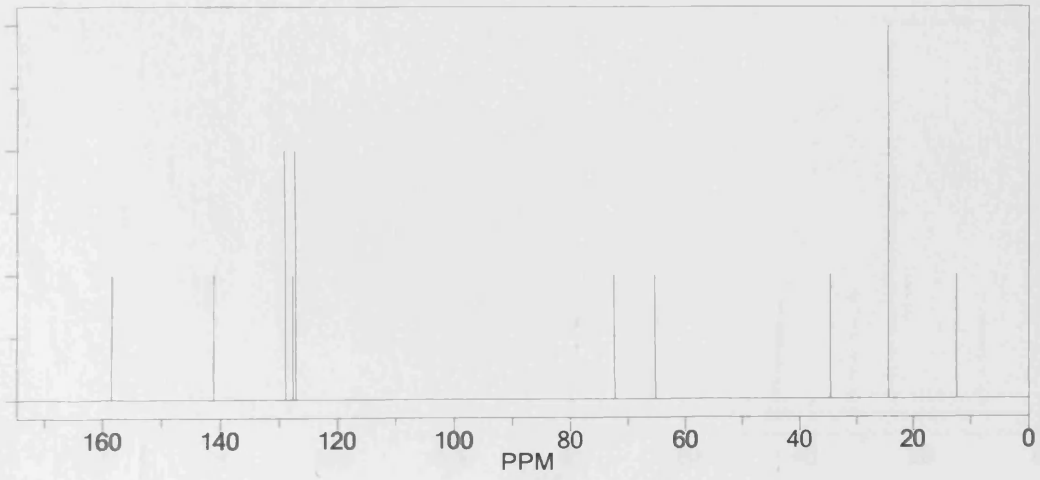


Appendix 10: ^{1}H and ^{13}C NMR predictions for compound 298 generated using ChemDraw.

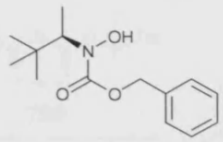


298

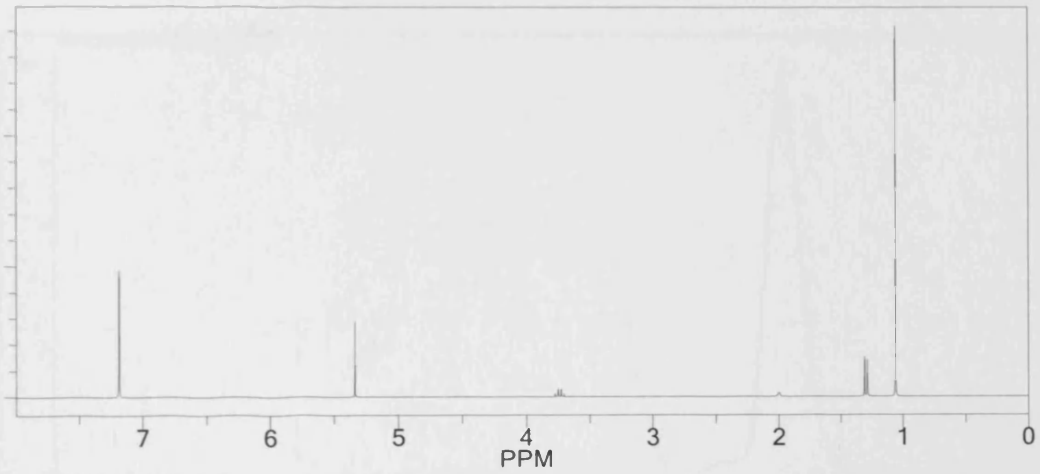


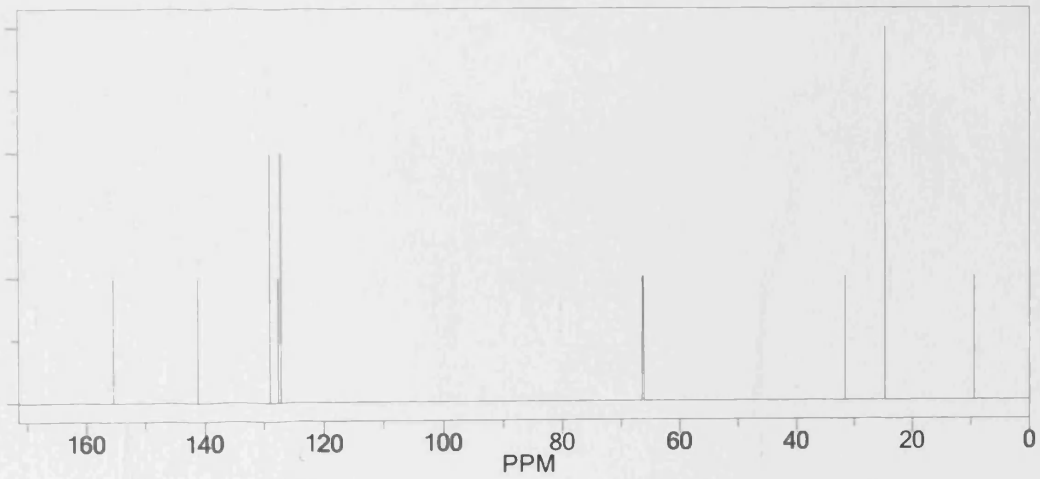


Appendix 11: ^{1}H and ^{13}C NMR predictions for compound 299 generated using ChemDraw.

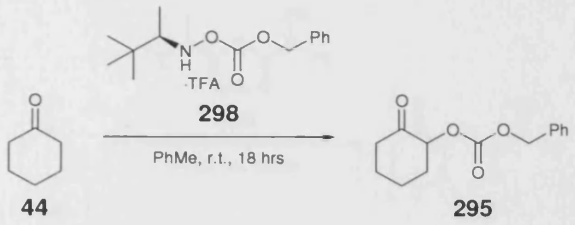


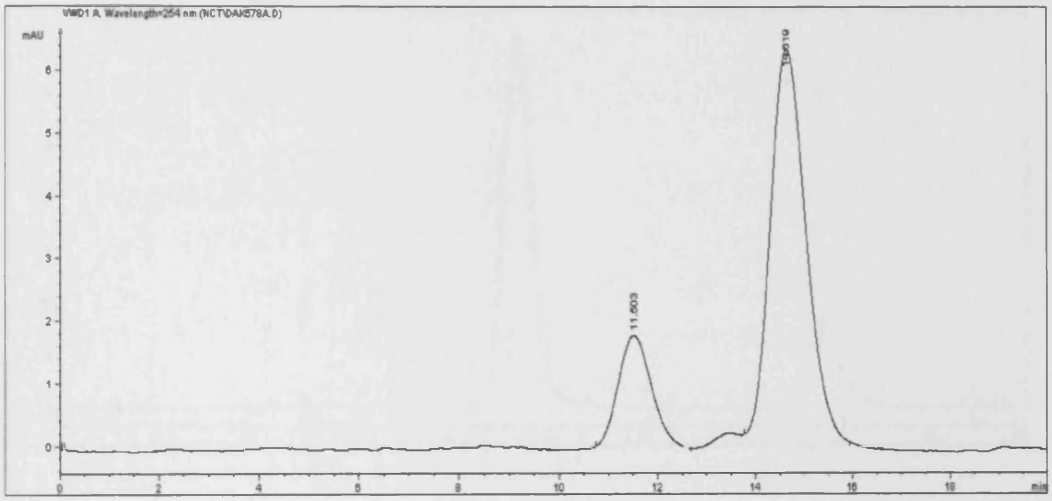
299



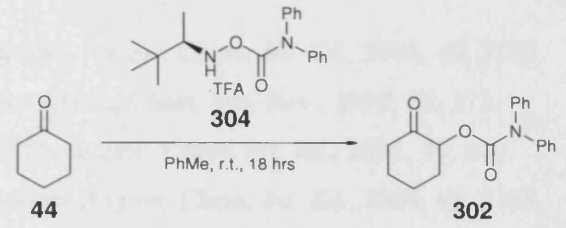


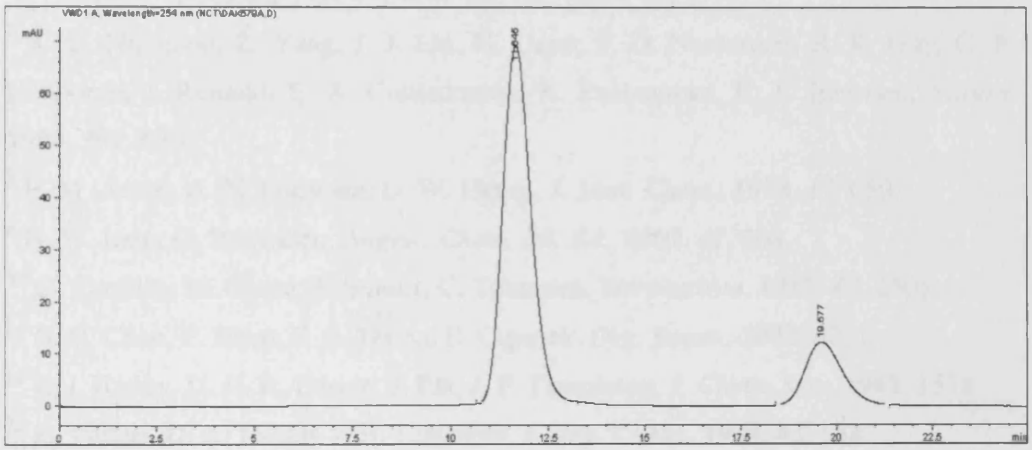
Appendix 12: HPLC spectra obtained from analysis of compound 295 showing a 58% e.e.





Appendix 13: HPLC spectra obtained from analysis of compound 302 showing a 63% e.e.





References.

[1] A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH: Weinheim, **2005**.

[2] P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.*, **2001**, *40*, 3726.

[3] B. Fubini, C. Otero Areán, *Chem. Soc. Rev.*, **1999**, *28*, 373.

[4] H. Gröger, J. Wilken, *Angew. Chem. Int. Ed.*, **2001**, *40*, 529.

[5] P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.*, **2004**, *43*, 5138.

[6] P. Merino, T. Tejero, *Angew. Chem. Int. Ed.*, **2004**, *43*, 2995.

[7] K. C. Nicolaou, Z. Yang, J. J. Liu, H. Ueno, P. G. Nantermet, R. K. Guy, C. F. Claiborne, J. Renaud, E. A. Couladouros, K. Paulvannan, E. J. Sorensen, *Nature*, **1994**, *367*, 630.

[8] E. M. Acton, A. N. Fujiwara, D. W. Henry, *J. Med. Chem.*, **1974**, *17*, 659.

[9] H. W. Lam, G. Pattenden, *Angew. Chem. Int. Ed.*, **2002**, *41*, 508.

[10] G. Cardillo, M. Orena, S. Sandri, C. Tomasini, *Tetrahedron*, **1987**, *43*, 2505.

[11] B. C. Chen, P. Zhou, F. A. Davis, E. Ciganek, *Org. React.*, **2003**, *62*, 1.

[12] E. J. Bailey, D. H. R. Barton, J. Els, J. F. Templeton, *J. Chem. Soc.*, **1962**, 1578.

[13] E. Vedejs, D. A. Engler, J. E. Telschow, *J. Org. Chem.*, **1978**, *43*, 188.

[14] J. C. Anderson, S. C. Smith, *Synlett*, **1990**, 107.

[15] a) W. D. Emmons, *J. Am. Chem. Soc.*, **1956**, *78*, 6208; b) W. D. Emmons, *J. Am. Chem. Soc.*, **1957**, *79*, 5739.

[16] a) F. A. Davis, U. K. Nadir, E. W. Kluger, *J. Chem. Soc., Chem. Commun.*, **1977**, 25; b) F. A. Davis, J. Lamendola, Jr., U. Nadir, E. W. Kluger, T. C. Sedergran, T. W. Panunto, R. Billmers, R. Jenkins, Jr., I. J. Turchi, W. H. Watson, J. S. Chen, M. Kimura, *J. Am. Chem. Soc.*, **1980**, *102*, 2000.

[17] a) F. A. Davis, S. Chattopadhyay, *Tetrahedron Lett.*, **1986**, 27, 5079; F. A. Davis, J. P. McCauley, S. Chattopadhyay, M. E. Harakal, J. C. Towson, W. H. Watson, I. J. Tavanaiepour, *J. Am. Chem. Soc.*, **1987**, *109*, 3370.

[18] F. A. Davis, J. C. Towson, M. C. Weismiller, S. Lal, P. J. Carroll, *J. Am. Chem. Soc.*, **1988**, *110*, 8477.

[19] a) F. A. Davis, A. C. Sheppard, B.-C. Chen, M. S. Haque, *J. Am. Chem. Soc.*, **1990**, *112*, 6679; b) F. A. Davis, B.-C. Chen, *Chem. Rev.*, **1992**, *92*, 919.

[20] T. Hashiyama, K. Morikawa, K. B. Sharpless, *J. Org. Chem.*, **1992**, *57*, 5067.

[21] K. Morikawa, J. Park, P. G. Andersson, T. Hashiyama, K. B. Sharpless, *J. Am. Chem. Soc.*, **1993**, *115*, 8463.

[22] a) W. Adam, R. T. Fell, C. Mock-Knoblauch, C. R. Saha-Möller, *Tetrahedron Lett.*, **1996**, *37*, 6531; b) W. Adam, R. T. Fell, V. R. Stegmann, C. R. Saha-Möller, *J. Am. Chem. Soc.*, **1998**, *120*, 708.

[23] T. Fukuda, T. Katsuki, *Tetrahedron Lett.*, **1996**, *37*, 4389.

[24] K. B. Sharpless, W. Amberg, M. Beller, H. Chen, J. Hartung, Y. Kawanami, D. Lubben, E. Manoury, Y. Ogino, T. Shibata, T. Ukita, *J. Org. Chem.*, **1991**, *56*, 4585; K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.–M. Wang, D. Xu, *J. Org. Chem.*, **1992**, *57*, 2768, and references cited therein.

[25] a) E. N. Jacobsen, *Catalytic Asymmetric Synthesis*, VCH: New York, 1993, Chapter 4.2; b) E. N. Jacobsen, *Comprehensive Organometallic Chemistry*, Pregamon: New York, **1995**, Volume 12, Chapter 11.1; c) T. Katsuki, *J. Mol. Catal. A, Chem.*, **1996**, *113*, 87; d) T. Katsuki, *Coord. Chem. Rev.*, **1995**, *140*, 189; e) T. Linker, *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 2060.

[26] a) Y. Tu, Z. X. Wang, Y. Shi, *J. Am. Chem. Soc.*, **1996**, *118*, 9806; b) Z. X. Wang, Y. Tu, M. Frohn, Y. Shi, *J. Org. Chem.*, **1997**, *62*, 2328; c) Z. X. Wang, Y. Tu, M. Frohn, J. R. Zhang, Y. Shi, *J. Am. Chem. Soc.*, **1997**, *119*, 11224.

[27] Y. Zhu, Y. Tu, H. Yu, Y. Shi, *Tetrahedron Lett.*, **1998**, *39*, 7819.

[28] Y. Zhu, L. Shu, Y. Tu, Y. Shi, *J. Org. Chem.*, **2001**, *66*, 1818.

[29] a) R. N. McDonald, *Mech. Mol. Migr.*, **1971**, *3*, 67; b) J.-J. Riehl, P. Casara, A. Fourgerousse, *C. R. Acad. Sci. Paris, Ser. C*, **1974**, *279*, 79.

[30] a) A. H. Soloway, W. J. Considine, D. K. Fukushima, T. F. Gallagher, *J. Am. Chem. Soc.*, **1954**, *76*, 2941; b) K. L. Williamson, W. S. Johnson, *J. Org. Chem.*, **1961**, *26*, 4563; c) S. C. Smith, C. H. Heathcock, *J. Org. Chem.*, **1992**, *57*, 6379.

[31] S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2003**, *125*, 10808.

[32] Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, *Tetrahedron Lett.*, **2003**, *44*, 8293.

[33] G. Zhong, *Angew. Chem. Int. Ed.*, **2003**, *42*, 4247.

[34] P. Merino, T. Tejero, *Angew. Chem. Int. Ed.*, **2004**, *43*, 2995.

[35] A. Bøgevig, H. Sundén, A. Córdova, *Angew. Chem. Int. Ed.*, **2004**, *43*, 1109.

[36] Y. Hayashi, J. Yamaguchi, T. Sumiya, M. Shoj, *Angew. Chem. Int. Ed.*, **2004**, *43*, 1112.

[37] For a recent application see S. Kumarn, D. M. Shaw, D. A. Longbottom, S. V. Ley, *Org. Lett.*, **2005**, *7*, 4189 and references therein.

[38] A. Hartikka, P. I. Arvidsson, *Eur. J. Org. Chem.*, **2005**, *20*, 4287.

[39] A. Hartikka, P. I. Arvidsson, *Tetrahedron: Asymmetry*, **2004**, *15*, 1831.

[40] A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett*, **2004**, *3*, 558.

[41] H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem. Int. Ed.*, **2004**, *43*, 1983.

[42] Z. P. Demko, K. B. Sharpless, *Org. Lett.*, **2002**, *4*, 2525.

[43] a) S. Kumarn, D. M. Shaw, D. A. Longbottom, S. V. Ley, *Org. Lett.*, **2005**, *7*, 4189; b) S. Kumarn, D. M. Shaw, S. V. Ley, *Chem. Commun.*, **2006**, 3211.

[44] S.-G. Kim, T.-H. Park, *Tetrahedron Lett.*, **2006**, *47*, 9067.

[45] A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.*, **2005**, *3*, 84.

[46] H. O. House, F. A. Richey, *J. Org. Chem.*, **1969**, *34*, 1430.

[47] C. H. Cummins, R. M. Coates, *J. Org. Chem.*, **1983**, *48*, 2070.

[48] D. A. Vosburg, S. Weiler, E. J. Sorensen, *Chirality*, **2003**, *15*, 156.

[49] C. S. Beshara, A. Hall, R. L. Jenkins, K. L. Jones, T. C. Jones, N. M. Killeen, P. H. Taylor, S. P. Thomas, N. C. O. Tomkinson, *Org. Lett.*, **2005**, *7*, 5729.

[50] C. S. Beshara, A. Hall, R. L. Jenkins, T. C. Jones, R. T. Parry, S. P. Thomas, N. C. O. Tomkinson, *Chem. Commun.*, **2005**, 1478.

[51] A. Hall, K. L. Jones, T. C. Jones, N. M. Killeen, R. Pörzig, P. H. Taylor, S. C. Yau, N. C. O. Tomkinson, *Synlett*, **2006**, 3435.

[52] A. Hall, E. P. Huguet, K. L. Jones, T. C. Jones, N. M. Killeen, S. C. Yau, N. C. O. Tomkinson, *Synlett*, **2007**, 293.

[53] O. R. S. John, N. M. Killeen, D. A. Knowles, S. C. Yau, M. C. Bagley, N. C. O. Tomkinson, *Org. Lett.*, **2007**, *9*, 4009.

[54] a) K. C. Nicolaou, T. Montagnon, T. Ulven, P. S. Baran, Y.–L. Zhong, F. Sarabia, *J. Am. Chem. Soc.*, **2002**, *124*, 5718; b) K. C. Nicolaou, P. S. Baran, Y.–L. Zhong, *J. Am. Chem. Soc.*, **2000**, *122*, 10246.

[55] Q. X. Wang, J. King, O. I. Phanstiel V, *J. Org. Chem.*, **1997**, *62*, 8104.

[56] I. Paterson, D. J. Wallace, S. M. Velázquez, *Tetrahedron Lett.*, **1994**, *35*, 9083.

[57] D. Geffken, *Chem. Ber.*, **1986**, *119*, 744.

[58] L. Wang, O. Phanstiel, IV, *J. Org. Chem.*, **2000**, *65*, 1442.

[59] K. J. Shea, G. J. Stoddard, W. P. England, C. D. Haffner, *J. Am. Chem. Soc.*, **1992**, *114*, 2635, and references therein.

[60] G. B. Jones, B. J. Chapman, *Synthesis*, **1995**, *5*, 475.

[61] M. B. Smith, J. March, *March's Advanced Organic Chemistry, 5th Edition*, Wiley-Interscience, **2001**, Chapter 4, 174.

[62] Boc-protection ref, *Tetrahedron Lett.*, **1983**, *24*, 231.

[63] J. A. Murphy, A. G. J. Commeureuc, T. N. Snaddon, T. M. McGuire, T. A. Khan, K. Hisler, M. L Dewis, R. Carling, *Org. Lett.*, **2005**, *7*, 1427, supporting info. (OL050337B).

[64] I. H. Sánchez, A. Ortega, G. Garcia, M. I. Larraza, H. J. Flores, *Synth. Commun.*, **1985**, *15*, 141.

[65] K. Torssell, O. Zeuthen, *Acta Chem. Scand., Ser. B*, **1978**, *B32*, 118.

[66] G. Exner, *Collect. Czech. Chem. Commun.*, **1951**, *16*, 258.

[67] a) L. V. Reis, A. M. Lobo, S. Prabhakar, *Tetrahedron Lett.*, **1994**, *35*, 2747; b) L. V. Reis, A. M. Lobo, S. Prabhakar, M. P. Duarte, *Eur. J. Org. Chem.*, **2003**, 190; c) M. P. Duarte, R. F. Mendonça, S. Prabhakar, A. M. Lobo, *Tetrahedron Lett.*, **2006**, *47*, 1173.

[68] P. I. Dalko, Y. Langlois, *Tetrahedron Lett.*, **1998**, *39*, 2107.

[69] Y. Tamura, H. Ikeda, I. Morita, H. Tsubouchi, M. Ikeda, *Chem. Pharm. Bull.*, **1982**, *30*, 1221.

[70] Modern Carbonyl Chemistry, J. Otera, Ed.; Wiley-VCH: Weinheim, **2000**.

[71] K. Nakagawa, H. Onoue, J. Sugita, *Chem. Pharm. Bull.*, **1964**, *12*, 1135.

[72] K. Orito, T. Hatakeyama, M. Takeo, S. Uchiito, M. Tokuda, H. Suginome, *Tetrahedron*, **1998**, *54*, 8403.

[73] F. F. Stephens, J. D. Bower, *J. Chem. Soc.*, **1949**, 2971.

[74] (a) S. S. Rawalay, H. Shechter, *J. Org. Chem.*, **1967**, *32*, 3129. (b) N. A. Noureldin, J. W. Bellegarde, *Synthesis*, **1999**, 939.

[75] R. J. Audette, J. W. Quail, P. J. Smith, *Tetrahedron Lett.*, **1971**, *12*, 279.

[76] H. G. Chen, P. Knochel, *Tetrahedron Lett.*, **1988**, *29*, 6701.

[77] A. Miyazawa, K. Tanaka, T. Sakakura, M. Tashiro, H. Tashiro, G. K. S. Prakash, G. A. Olah, *Chem. Commun.*, **2005**, 2104.

[78] H. Hamamoto, Y. Suzuki, H. Takahashi, S. Ikegami, *Tetrahedron Lett.*, **2007**, *48*, 4239.

[79] H. Choi, M. P. Doyle, *Chem. Commun.*, **2007**, 745.

[80] S. –I. Murahashi, N. Komiya, In *Modern Oxidation Methods*, J. -E. Backvall, Ed.; Wiley-VCH: Weinheim, **2004**, 175–179.

[81] J. Larsen, K. A. Jørgensen, *J. Chem. Soc., Perkin Trans. 2*, **1992**, 1213.

[82] R. M. Moriarty, R. K. Vaid, M. P. Duncan, *Tetrahedron Lett.*, **1988**, *29*, 6913.

[83] K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *J. Am. Chem. Soc.*, **2004**, *126*, 5192.

[84] R. V. Hoffman, *J. Am. Chem. Soc.*, **1976**, *98*, 6702.

[85] E. J. Corey, K. Achiwa, *J. Am. Chem. Soc.*, **1969**, *91*, 1429.

[86] M. Ochiai, M. Inenauga, Y. Nagao, R. M. Moriarty, R. K. Vaid, M. P. Duncan, *Tetrahedron Lett.*, **1988**, *29*, 6917.

[87] R. B. Roy, G. A. Swan, *J. Chem. Soc. C*, **1968**, 80.

[88] P. F. Alewood, I. C. Calder, R. L. Richardson, *Synthesis*, **1981**, 121.

[89] A. M. Berman, J. S. Johnson, *J. Am. Chem. Soc.*, **2004**, *126*, 5680.

[90] M. Psiorz, G. Zinner, *Synthesis*, **1984**, *3*, 217.

[91] A. M. Beauchemin, J. Moran, M.-E. Lebrun, C. Séguin, E. Dimitrijevic, L. Zhang, S. I. Gorelsky, *Angew. Chem. Int. Ed.*, **2008**, *47*, 1410.

[92] E. H. White, M. Ribi, L. K. Cho, N. Egger, P. M. Dzadzic, M. J. Todd, *J. Org. Chem.*, **1984**, *49*, 4866.

[93] X. Feng, L. Shu, Y. Shi, *J. Am. Chem. Soc.*, **1999**, *121*, 11002.

[94] J. Sheng, X. Li, M. Tang, B. Gao, G. Huang, *Synthesis*, **2007**, *8*, 1165.

[95] G. M. Rubottom, R. C. Mott, H. D. Juve, *J. Org. Chem.*, **1981**, *46*, 2717.

[96] S. S. Diwan, S. Dalvi, H. Mulla, *Synth. Commun.*, **2009**, *39*, 273.

[97] I. M. Labouta, E. Falch, H. Hjeds, P. Krogsaard-Larsen, *Eur. J. Med. Chem.*, **1982**, *17*, 531.

[98] W. L. Meyer, M. J. Brannon, C. da G. Burgos, T. E. Goodwin, R. W. Howard, *J. Org. Chem.*, **1985**, *50*, 438.

[99] J. A. Murphy, A. G. J. Commeureuc, T. N. Snaddon, T. M. Mcguire, T. A. Khan, K. Hisler, M. L. Dewis, R. Carling, *Org. Lett.*, **2005**, *7*, 1427, supplementary data.

[100] I. H. Sánchez, A. Ortega, G. Garcia, M. I. Larraza, H. J. Flores, *Synth. Commun.*, **1985**, *15*, 141.

[101] P. O. Miranda, D. D. Diaz, J. I. Padrón, M. A. Ramirez, V. S. Martin, *J. Org. Chem.*, **2005**, *70*, 57.

[102] M. J. Schultz, S. S. Hamilton, D. R. Jensen, M. S. Sigman, *J. Org. Chem.*, **2005**, *70*, 3343.

[103] S. W. Lee, K. Lee, D. Seomoon, S. Kim, H. Kim, H. Kim, E. Shim, M. Lee, S. Lee, M. Kim, P. H. Lee, *J. Org. Chem.*, **2004**, *69*, 4852.

[104] S. Liu, N. Berry, N. Thomson, A. Pettman, Z. Hyder, J. Mo, J. Xiao, *J. Org. Chem.*, **2006**, *71*, 7467.

[105] B. Zhao, X. Lu, *Tetrahedron Lett.*, **2006**, *47*, 6765.

[106] V. Janout, S. L. Regen, *J. Org. Chem.*, **1982**, *47*, 3331.