α-Functionalisation of Carbonyl Compounds.

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A Thesis Submitted for the Degree of Doctor of Philosophy at Cardiff University

2007
Declaration

This work has not previously been accepted in substance for any degree and is not being concurrently submitted for candidature for any degree.

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Dedicated to my parents Helen & Michael

for their loving support throughout my studies.
"the pre-eminence of the profit motive in conducting scientific research ultimately means that science is deprived of its epistemological character, according to which its primary goal is discovery of the truth. The risk is that when research takes a utilitarian turn, its speculative dimension, which is the inner dynamic of man's intellectual journey, will be diminished or stifled"

LETTER OF JOHN PAUL II
"CONFLICT OF INTEREST AND ITS SIGNIFICANCE IN SCIENCE AND MEDICINE" (WARSAW 5-6 APRIL 2002)
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Abstract

Chapter 1
Intrinsic to the methodology developed within this thesis is the exploitation of a polyheteroatom [3,3]-sigmatropic rearrangement. This chapter explores the chemistry of a selection of these rearrangements in order to highlight their utility in the creation of new carbon-carbon and carbon-heteroatom bonds.

Chapter 2
In this chapter the most recent advances in the α-functionalisation of carbonyl compounds are discussed. This review focuses mainly on organocatalyzed methodologies as these represent the forefront of current research in the field.

Chapter 3
In chapter 3 the principle underlying our methodology is further described along with our results for the α-oxybenzoylation of cyclic, heterocyclic and acyclic ketones. Our findings for the α-oxybenzoylation of acetals is also described.

Chapter 4
Elaboration of our family of reagents to introduce α-oxycarbonate and carbamate functionalities is next described with our results for a variety of reactions with cyclic and acyclic ketones.

Chapter 5
Continuing expansion of our reagent family is described in chapter 5. Within this chapter our results for the α-oxytosylation of cyclic, acyclic and di-carbonyl compounds are presented.

Chapter 6
Chapter 6 describes our attempts at synthesising a thio analogue of our reagent for the creation of a C-S bond.
Abbreviations

Ac  Acetal
ADS  Asymmetric Desymmetrization
Alloc  Allyloxy carbonyl
APCI  Atmospheric Pressure Chemical Ionisation
Ar  Aromatic
Bn  Benzyl
Boc  tert butoxycarbonyl
BOI  2-(benzotriazol-1-yl)-oxy-1,3-dimethyl imidazolium
BPO  Benzoyl peroxide
Bz  Benzoyl
CAP  N'-cyano-4-(dimethylamino)pyridinium bromide
CBMIT  carbonyl bismethylimidazolium triflate
Cbz  Benzyloxy carbonyl
CDI  Carboxyldiimidizole
Cl  Chemical Ionisation
Cy  Cyclohexyl
d  doublet
DABCO  1,4-Diazabicyclo[2.2.2]octane
DEAD  Diethyl azodicarboxylate
DBU  Diaza[1,3]bicyclo[5.4.1]undecane
DCC  Dicyclohexylcarbodiimide
DCM  Dichloromethane
dd  double doublet
dc  Diasteromeric excess
DMAP  4-Dimethylaminopyridine
DMC  Dimethyl carbonate
DMF  N,N'-Dimethylformamide
DMSO  Dimethyl sulfoxide
DPDC  Dimethyl peroxydicarbonate
DPPA  Diphenylphosphoryl azide
ee  Enantiomeric excess
eq Equivalent
ES Electrospray
Et Ethyl
HCl Hydrochloride acid
HMDO Hexamethyldisiloxane
HMIB Hydroxymesyl iodobenzene
h Hour
HTIB Hydroxytosyl iodobenzene
Hz Hertz
I. R. Infrared
J Coupling constant
KHMDS Potassium hexamethyldisilazane
LDA Lithium diisopropylamide
m multiplet
mCPBA -chloroperoxybenzoic acid
Me Methyl
min minute
mL millilitres
MOM Methoxymethyl
MSA Methanesulfonic Acid
NMR Nuclear Magnetic Resonance
Ns Nosyl
Ph Phenyl
p-NPSP para-nitrophenyl sulfonyleperoxide
Pr Propyl
q quartet
s singlet
SAR Structural Activity Relationship
TADDOL \(\alpha,\alpha,\alpha',\alpha'\text{-tetraaryl}-4,5\text{-dimethoxy-1,3-dioxolane}\)
TBDMS \(\text{tert}-\text{butyldimethylsilyl}\)
\(t\)-Bu \(\text{tert}-\text{butyl}\)
TES Triethlysilyl
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>TFA</td>
<td>Trifluoroacetic Acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TMSOTF</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl</td>
</tr>
<tr>
<td>β-ICD</td>
<td>β-isocupreidine</td>
</tr>
</tbody>
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Chapter 1: Introduction
1.1 Background:

Chemistry has long stood as a corner stone of science, whose rules, laws and philosophies govern numerous spheres of scientific endeavor. While its principles lie at the heart of many biological sciences its guidance is no less influential in the physical and earth sciences. Even with its position at the core of scientific understanding, one unique facet of chemistry causes it to stand alone, its prominence as the only truly creative science. Curiosity and fascination propel the quest for scientific understanding and comprehension, two motivations felt by all scientists but few ever experience the wonder of creation. To direct the conception of something, which to the best of human knowledge has never existed before, is a truly humbling and awe inspiring experience. It is this unique and fundamental drive that inspires synthetic chemists to express their chemical art through the selection of reactions, processes and procedures, much as an artist would select canvas, paint and brush.

The subjects selected by synthetic chemists be they distinctive analogs of natural products or unique structures derived for a specific need, routinely present two fundamental chemical challenges, the construction of a molecular backbone and the introduction of suitable functionality necessary for activity. Further complications and distractions from the goal with issues of regio- and stereochemical control only add to the unique complexity of the final target. A common link between these two challenges is the formation of carbon-heteroatom bonds either within the core molecular framework of the target or as functional groups attached to its periphery. Numerous approaches have been employed to address these obstacles. The uses of oxaziridines as electrophilic oxidizing agents are well known and in particular \( \text{N-sulfonyl oxaziridines} \) \( 1 \) (Fig. 1) have been widely exploited for the oxidation of a variety of nucleophiles.\(^1\) Interestingly, by altering the nitrogen substituent to one of a less electron withdrawing nature results in an electrophilic aminating reagent \( 2 \) (Fig. 1).\(^2\)

![Fig. 1](image-url)
The subject matter presented within this thesis is centred on the creation of a carbon oxygen bond. Specifically, it is concerned with the α-oxidation of carbonyl compounds through the creation of a carbon-heteroatom bond. This is achieved through the utilisation of suitably substituted O-acylhydroxylamines 3 (Fig. 3), a more thorough introduction to which is presented in Chapter 3. Fundamental to the bond construction presented herein and a characteristic that differentiates this chemistry from its counterparts is the exploitation of a polyheteroatom [3,3]-sigmatropic rearrangement (Fig. 4).

Since its discovery by Ludwig Claisen in 1912 it has been utilised by synthetic chemists for carbon-carbon bond forming processes. Its appeal lies in the ability to introduce two substituted stereogenic centres with high levels of predictability. This stereospecific and predictable nature stems from an ordered chair-like six-membered transition state that adopts a configuration to minimise steric and electronic interactions. Through this transition state it is the relative geometry of the double bonds that determines the stereochemistry of the product.
Taking the example of propenylbut-2'-enyl ether both the $Z,Z$ and $E,E$ isomers give the *threo* product (Fig. 5). For the $Z,Z$ isomer in the chair configuration both methyl groups adopt axial positions minimizing their interactions giving the *threo* product. While for the $E,E$ isomer positioning the methyl groups equatorially minimizes their interaction (Fig. 5).\(^6\)

Based on this $E,Z$ and $Z,E$ substrates afford the *erythro* product by again adopting the lower energy chair conformation and maximizing the separation between substituents (Fig. 6). These findings also hold true when additional heteroatoms are introduced into the substrate, therefore it is not surprising that polyheteroatom sigmatropic rearrangements have attracted much attention. Given the pivotal role these polyheteroatom sigmatropic rearrangements play in the chemistry described in this thesis a more in depth exploration of their chemistry is warranted in order to highlight their utility in the creation of new carbon-heteroatom bonds.
1.2 Polyhetero Claisen Rearrangements:

Traditionally, the Claisen rearrangement involves the concerted sigmatropic rearrangement of an allyl vinyl ether $A$ into a homoallylic carbonyl compound $B$ (Fig. 7).

\[
\begin{array}{c}
\text{A} \\
\text{X} \\
\text{3-2\_1} \\
\text{4-5\_6} \\
\text{C} \\
\text{D} \\
\text{X=O, N, S, P}
\end{array}
\]

Fig. 7

In this section the term Claisen rearrangement is elaborated upon to include concerted rearrangements that are not at first glance commonly identified as such. Examples are restricted to systems containing two or more heteroatoms and so aza-, oxa- and thio-Claisen rearrangements will not be presented. Those rearrangements highlighted are grouped according to the kind of heteroatoms involved and their position in the starting substrate (Fig. 7).

1.2.1 1-0,3-0 Systems:

1.2.1.1 Allyl Esters (Carboxylates)

$^{18}$O labelling and product studies have demonstrated that simple allylic esters $4$ undergo a [3,3]-rearrangement to $5$ in the gas phase at approximately 268 °C (Scheme 1).
A similar strategy employing labelled crotyl propionate 6 (Scheme 2) showed that Pd$^{II}$ catalysis of allylic ester isomerization using Li$_2$Pd$_2$Cl$_6$ also represented a [3,3] process

\[ 6 \quad \rightleftharpoons \quad 7. \]  

The suggested mechanism involved the action of Pd$^{II}$ as a Lewis Acid to promote cyclization of complex 8 via a formal [3,3]-sigmatropic rearrangement. This proceeds through a 1,3-acetoxonium intermediate 9, followed by ring opening to give 10 (Scheme 3).

\[ \begin{align*} 
\text{Et} & \quad \text{Et} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{Pd} & \quad \text{L} \\
\text{L} & \quad \text{L} \\
8 & \quad \text{L} & \quad \text{L} & \quad \text{L} \\
8 & \quad \text{L} & \quad \text{L} & \quad \text{L} \\
9 & \quad \text{L} & \quad \text{L} & \quad \text{L} \\
9 & \quad \text{L} & \quad \text{L} & \quad \text{L} \\
10 & \quad \text{L} & \quad \text{L} & \quad \text{L} \\
10 & \quad \text{L} & \quad \text{L} & \quad \text{L} \\
\end{align*} \]

Scheme 3

A 500-fold rate decrease when Et was replaced by CF$_3$ is consistent with this proposal. A series of preparative runs using acetate esters and PdCl$_2$(MeCN)$_2$ in THF also gave high yields of rearrangement products.

Consistent with a [3,3] process, complete suprafacial chirality transfer was observed under comparable reaction conditions (0.04 eq of PdCl$_2$(MeCN)$_2$, THF, 25 °C, 1.5h) in the rearrangement of acetate 11 to 12 (Scheme 4).
The corresponding cis-isomer and a related compound exhibited similar chirality transfer, as did compounds analogous to 11 where the Me group was replaced by OCH$_2$Ph.$^{11}$

Pd$^{II}$ catalysed allylic ester rearrangement occurs preferentially at $E$- disubstituted double bonds rather than $Z$-disubstituted, as seen in the rearrangement of (E,Z)-4-acetoxyhepta-2,5-diene 13 (0.05 eq PdCl$_2$(MeCN)$_2$, THF, rt, 5mins) to a mixture of 14 (74%) and 15 (18%) (Scheme 5).$^{12}$ The new double bond in this and related acetoxy dienes was exclusively $E$. High yields of a single isomer were obtained under similar conditions with (E,E) and (Z,Z) substrates.

Control of the stereochemical course of the above rearrangement was quite different when employing a Pd$^0$ complex, Pd(PPh$_3$)$_4$ (0.05 eq, PhH, rt). All three stereoisomers of 13 gave only the $E,E$ product 15. It is unclear if [3,3] processes are involved with the Pd$^0$ complex however, it is known that antarafacial allylic ester rearrangement can occur with Pd(PPh$_3$)$_4$.$^{13}$

Basabe recently employed this rearrangement in a short effective synthesis of (+)-subersic acid 18.$^{14}$ Sclareol was acetylated in quantitative yield with acetyl chloride and $N,N$-dimethylaminopyridine, affording the diacetyl derivative 16 whose rearrangement with bis-(acetonitrile)palladium$^{II}$ chloride led to diacetate 17 (92%) (Scheme 6).
1.2.1.2 Propargyl and Allenyl Esters

Catalysed rearrangements of propargyl esters using silver salts was first reported by Saucy et al., then systematically studied and characterised as [3,3] processes by Schmid. One of the more successful rearrangements from a preparative point of view was the conversion of 19 to 20 in 68% yield using AgBF$_4$ as catalyst (Ar = p-nitrophenyl) (Scheme 7).

The position of the propargyl allenyl equilibrium, underlying the success of the rearrangement, could be roughly correlated with the substitution pattern, assuming steric congestion involving the benzoate group and the substituents on the carbon atom to which it was attached. When R$^1$ = R$^2$ = alkyl, R$^3$ = H 21, the reaction was essentially irreversible. For R$^1$ = Me, R$^2$ = R$^3$ = H 22, the reaction mixture contained 60% allenyl ester 22 at equilibrium (Scheme 8).
The silver ion was assumed to complex with the \( p \)-orbitals not involved in the [3,3] transition-state (Scheme 9). This is consistent with the fact that no \( \text{Ag}^+ \) catalysed allyl ester rearrangement could be observed when \( \alpha,\alpha \)-dimethylallyl \( p \)-benzoate was examined as a substrate (\( \text{AgBF}_4, \text{PhCl}, 130 \, ^\circ\text{C}, 6\, \text{h} \)).\(^{16}\)

Attempts to catalyse the rearrangements of simple propargyl esters with \( \text{Rh}^+ \) were unsuccessful, with \( \alpha,\alpha \)-dimethylpropargyl acetate giving a very complex reaction mixture on the introduction of \( [\text{Rh(CO)}_2\text{Cl}]_2 \) in chloroform.\(^{17}\) However, treatment of 3,4-diacetoxyhexa-1,5-diyne 26 with the same catalyst gave a 35% yield of 27 (Scheme 10).

A possible mechanism to account for the overall transformation was proposed, on the basis of product structure only, to involve \( \text{Rh}^+ \) catalysed [3,3]-rearrangement of 26 to...
give 28 subsequent rearrangement to 29, followed by a retro ene reaction to give the observed product 27 (Scheme 11).

![Scheme 11]

1.2.1.3 Allyl N,N-Dialkylcarbamates:
Mercuric trifluoroacetate catalysed the rearrangement of allylic N,N-dimethylcarbamates, including the conversion of 30 to 31 (Scheme 12).\(^{18}\) The rearrangement of 30 to 31 occurred in a thermodynamically favoured sense, in that terminal double bonds were converted to the more stable internal double bond.

![Scheme 12]

However, a contradictory outcome could be achieved in some systems by employing an excess of mercuric trifluoroacetate followed by quenching with PPh\(_3\). For example, carbamate 32 was converted to 33 with 3eq Hg(CF\(_3\)CO\(_2\))\(_2\) in THF at room temperature for 24h in 75% isolated yield (Scheme 13).

![Scheme 13]
1.2.2 1-O,4-O Systems:

1.2.2.1 α-Tocopherol Spiro Dimer

The title compound 34 (Scheme 14) where \( R = \text{C}_{16}\text{H}_{33} \) undergoes a degenerative rearrangement to 35 that is detected by NMR, with coalescence of signals at 70 °C (chloroform, benzene). \(^{19}\)

![Scheme 14](image)

The rearrangement is intramolecular on the basis of cross reactions and acid catalysed with coalescence of signals occurring at constant temperature in 0.2M trichloroacetic acid in benzene. Acid catalysis was accounted for by a heterolytic process involving a univalent oxygen cation (phenoxylium ion). This explanation was somewhat complicated by the fact that the [3,3]-rearrangement of spiro dienone 36 (Fig. 8), whose rate was measured at 50 °C was not accelerated by the presence of 0.2M trichloroacetic acid.

![Fig. 8](image)

1.2.3 1-O,3-N Systems:

1.2.3.1 N-Allyl Amides

The Diels-Alder products from the reaction of cyclopentadiene and azodiacyls undergo a high yielding [3,3]-sigmatropic rearrangement catalysed by both Bronsted and Lewis acids. \(^{20}\) For example, compound 37 was rapidly converted to the cis-oxadiazine 38 by catalytic amounts of CF\(_3\)CO\(_2\)H (Scheme 15).
Both BF₃·Et₂O (0.1 eq) and SnCl₄ (1.0 eq) were also very effective catalysts. A low level of asymmetric induction was also observed in this transformation when catalysed by (+)-camphor-10-sulfonic acid.

1.2.4 1-N,3-O Systems:

1.2.4.1 Allyl Trichloroacetimidates

Perhaps the most investigated polyheteroatom sigmatropic rearrangement with regard to synthesis is the trichloroacetimidate Overmann rearrangement. This involves the irreversible rearrangement of allylic trichloroacetimidate 39 to allylic trichloroacetamide 40 (Scheme 16) and can be conducted under either thermal or metal catalyzed conditions. The attractiveness of this rearrangement is in the preparation of protected allylic amines that in turn allows entry to a wide variety of nitrogen containing compounds such as amino acids, peptides and amino sugars.

Despite the elevated reaction temperatures generally needed to promote the reaction it has of late seen application by Chida et al. in the synthesis of 41 (Scheme 17) on route to the total synthesis of sphingofungin E from D-glucose. Refluxing compound 42 in xylene with K₂CO₃ at 140 °C for 140h is indicative of the harsh conditions required to promote this reaction (Scheme 17). This elegant use of the Overman rearrangement however, demonstrates yet another useful feature of the reaction, namely, for the construction of a quaternary centre containing a C-N bond.
A wide variety of Pd$^{II}$ complexes have been shown to catalyze allylic rearrangements of imidates 43 to 44. Early studies focused on the cationic ferrocenyl oxazoline palladacyclic complex 45 (Scheme 18) but were fraught with complications such as poor yields, low reaction rates, and low enantioselectivities. These can be attributed to competitive complexation of the basic trichloroacetimidate nitrogen to the hard palladium centre. This problem was alleviated through the use of less strongly coordinating N-arylimidates.

Despite the excellent results recorded, the transformation of the amide products to the corresponding allylic amines is not high yielding, which greatly limits the usefulness of this process. Further variation of this process to incorporate N-anisyltrifluoroacetimidates 46 and a modified palladium catalyst 48 (Scheme 19) gave comparable yields of 92% with an ee of 92%, however, subsequent deprotection of the N-anisyltrifluoroacetamide could be accomplished in 73% yield making it a much more efficient procedure.
Catalyst 48 has recently been used by Overman et al. in transforming prochiral \((E)\)-allylic trichloroacetimidates into allylic trichloroacetamides of high enantiopurity up to 98\% ee.\(^{29}\) This is a marked improvement from initial attempts as it reduces the problem of competitive complexion by employing a neutral Pd centre in the catalyst, which is less attractive to an imidate nitrogen than a cationic Pd\(^{II}\) complex.

### 1.2.4.2 2-(Allyloxy)pyridines

Treatment of neat 2-(allyloxy)pyridines 49 with 1\% H\(_2\)PtCl\(_6\) at 140 °C, yielded >85\% of \(N\)-allyl-\(\alpha\)-pyridone 50 (Scheme 20).\(^{30}\)

It was established that different reaction products could be obtained from the reaction, depending on the nature of the catalyst used. Reactions catalyzed by chloroplatinic acid provided essentially quantitative conversion to 50. Reactions catalyzed by boron trifluoridetherate proceed by an entirely different pathway to give the pyridine 51. A possible explanation for the formation of these different products is that the boron trifluoride coordinates with the ether oxygen of 49, providing a pathway for a 1,3-allyl shift to carbon, instead of to nitrogen.

In the course of screening for catalysts and reaction conditions for Mizoroki-Heck reaction of 52, Itami encountered a somewhat surprising result. Under the influence of Herrmann’s palladacycle catalyst,\(^{31}\) 52 underwent the expected Mizoroki-Heck
arylation with iodobenzene (Scheme 21). However, when the arylating agent was switched from iodobenzene to bromobenzene and the base from NaOAc to Cy₂-NMe, quantitative conversion of 52 to \( \text{N-allyl-2-pyridone 54} \) was observed.

![Scheme 21](image)

This led Itami to further investigate the different mechanisms through which both \( \text{Pd}^0 \) (Pd(PPh₃)₄, Pd[P(t-Bu)₃]₂) and \( \text{Pd}^{\text{II}} \) (PdCl₂, PdCl₂(PhCN)₂) may catalyze the rearrangement of 2-allyloxy pyridines. \(^{32}\) In the \( \text{Pd}^{\text{II}} \) catalyzed rearrangement, an electrophilic \( \text{Pd}^{\text{II}} \) coordinates to the C=C bond and activates it toward nucleophilic attack. Thereafter, the intramolecular nucleophilic attack of the lone pair of nitrogen to C=C bond occurs and produces a palladium-bound carbenium ion intermediate \( \text{55} \) (Fig. 9), which rearranges as a formal [3,3]-rearrangement to the observed product. This is in contrast to the \( \text{Pd}^0 \) catalyzed rearrangement in which an (\( \pi \)-allyl) palladium complex \( \text{56} \) is thought an intermediary (Fig. 9).
1.2.5 3-N,4-O Systems:

1.2.5.1 N-(Aryloxy) Enamines

Rearrangement of the O-aryl oxime 57, in the presence of 2equivalent of HCl in acetic acid at 25 °C gave the imine 58, by equilibration of 57 with the less stable tautomeric N-(aryloxy) enamine 59 and subsequent [3,3]-rearrangement (Scheme 22).\(^{33}\)

![Scheme 22](image)

Treatment of 58 with HCl/HOAc at 90-95 °C gave benzofuran 60, which was also formed when 57 was subjected to the latter conditions. The intermediate imine 58 species is generally not isolated. BF\(_3\)-Et\(_2\)O was also found to catalyse the transformation.

1.2.5.2 O-Phenyl-N-acetoacetylhydroxylamines:

The reaction of O-phenylhydroxylamine with a diketene in THF results in O-phenyl-N-acetoacetylhydroxylamine 61, which when treated with a mixture of trifluoromethansulfonic and trifluoroacetic acid (1:20), at 0 °C for 0.5h produced 2-methylbenzofuran-3-carboxamide 62 in 79% yield (Scheme 23).
The rearrangement is again consistent with a [3,3]-sigmatropic process, with rearrangement of enol species 63, prototropic aromatization, cyclization of the resulting 2-(2-actetoacetamido)phenol intermediate 64 and dehydration to give 62 (Scheme 24).

1.2.5.3 \textit{N-arylpynylamine oxide}

Rearrangement of 65, accessed via oxidation with mCPBA, provides an interesting route to substituted indoles \textit{via sequential} [2,3] (65 to 66), then [3,3]-sigmatropic rearrangements (66 to 67).\textsuperscript{34}
1.2.5.4 N-(Allyloxy) enamines

Michael addition of oxime 70 to dimethyl acetylenedicarboxylate 71 results in an N-(allyloxy) enamine 72 (Scheme 26). This intermediate can then undergo a [3,3]-sigmatropic rearrangement to 73 followed by condensation and aromatisation to give the 2,3,5 trisubstituted pyrrole 74.35

![Scheme 26](image)

1.2.6 4-N,3-O Systems:

1.2.6.1 N-Aryl-N,O-diacetylhydroxylamine

Decarboxylative 1-aza-1'-oxa-[3,3]-sigmatropic rearrangements of enolizable N-aryl-N,O-diacetylhydroxylamines 75 to O-(N-acylamino)aryl ketones, esters, and amides provides novel access to ortho alkylation of anilines incorporating differing functionalities (Scheme 27).36 N-Aryl-N-hydroxyamides 76 readily available by partial reduction of nitroarenes to N-arylohydroxylamines37 and selective N-acylation.38 These then are transformed into O-acetoacetyl derivatives 75 by reaction with diketene in the presence of a catalytic amount of triethylamine (1.1 eq of diketene, 1:1 chloroform-ether, 0 °C, overnight).
According to the analogy with the Carroll reaction one plausible mechanism for this reaction consists of a [3,3]-sigmatropic rearrangement of the ketene hemiacetal tautomer 78, prototropic rearomatization, and decarboxylation of the resulting β-keto acid intermediate 79 (Scheme 28).

Variation upon this rearrangement serves to demonstrate further the synthetic value of the reaction. Mixed malonates 80 are readily prepared in 60-86% yield by acylation of the N-aryl-N-hydroxyamides with ethylmalonyl chloride (Scheme 29). Thermolysis of these esters in toluene containing approximately 1 eq of pyridine at reflux gave rise to 55-80% yield of the O-(N-acylamino)aryl acetates 81.
It was also found that N-aryl-N-hydroxyamides react spontaneously with the ynamine, N,N-diethyl-1-amino-1-propyne, at 0 °C to form (N-acyl-amino)arylpropionamides in yields ranging from 42 to 67%, presumably by way of adduct 83.

\[ \text{Scheme 30} \]

1.2.7 3-N,4-N Systems:

1.2.7.1 N-Aryl-N-enylhydrazines

Both the aromatic and aliphatic versions of the 3,4-diaza-[3,3]-sigmatropic rearrangement are known, with the Fischer synthesis of indoles from enylhydrazines being the best documented (Scheme 31). 39

\[ \text{Scheme 31} \]

1.2.7.2 N,N'-Diacylhydrazines

N,N'-Diacylhydrazines rearrange under basic conditions to afford 1,2-disubstituted succinamides. The rearrangement can be explained in terms of an anionic [3,3]-sigmatropic shift of biscarboxamide enolates (Scheme 32). 40 Treatment of N,N'-dimethyl-N,N'-diphenacetylhydrazine 87 with 2.5eq of LDA at 0 °C for 1 h and then at 20 °C for 1.5 h in THF gave two C-C products 88 and 89 in 49% combined yields (threo: erythro 4:1), and a C-O product 90 in a 19% yield.
The yields of C-C products are enhanced by the stabilization ability of substituents α- to the carbonyl group. A similar conclusion can also be drawn for the C-O products, which indicate that the oxygen atoms of acyl groups forming a less stable carbanion rearrange to the other enolates. This methodology has also been expanded to the conversion of cyclic hydrazine diaclyte to medium membered lactams.41

1.2.7.3 N,N'-Diarylhydrazines (Hydrazoarenes)
The thermal and acid catalysed rearrangement of N-2-naphthyl-N'-phenylhydrazine 91 to compound 92 represents another example of 3,4-diaza-[3,3]-sigmatropic rearrangement (Scheme 33).42 Cyclic compounds 93 can also occur in significant amounts. These are not formed from the aromatised [3,3] product but are most likely generated from the initial [3,3] rearranged intermediate, followed by cyclisation through a process analogous to the Fischer indole synthesis.

Other hydrazonaphthalenes and N-naphthyl-N'-phenylhydrazines rearrange in a similar fashion under both thermal and acid catalysed processes.43 In most cases, products of
[5,5] sigmatropic rearrangements were observed. These reactions are related to the ortho- and para- benzidine rearrangements, which formally involve [3,3]- and [5,5]-sigmatropic processes.\textsuperscript{44}

1.2.7.4 \textit{N,N}-Bis(eny1)hydrazines

The bis(eny1)hydrazine 94, derived from 2-tetralone and \textit{N,N}'-dimethylhydrazine, rearranges at room temperature under acidic conditions to give the pyrrole 96 \textit{via} a diimine 95 (Scheme 34).

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {\textbf{94}};
  \node at (2,0) {\textbf{95}};
  \node at (4,0) {\textbf{96}};
  \draw[->] (0.5,0) -- (2.5,0) node[midway,above] {CHCl\textsubscript{3}};
  \draw[->] (2.5,0) -- (4.5,0) node[midway,above] {rt};
\end{tikzpicture}
\end{center}

\textit{N,N}'-Bis(eny1)hydrazines are thought to be intermediates in the Piloty-Robinson synthesis of pyrroles from azines, in a process again similar to the Fischer indole synthesis and is catalysed by both Bronsted and Lewis acids.\textsuperscript{45}

1.2.8 \textit{2-N,5-N} Systems:

1.2.8.1 2,5-Diaza-1,5-dienes

Vögtle \textit{et al.} described a number of 2,5-diaza Cope rearrangements of 1,3,4,6-tetraaryl double Schiff bases 97 to 98 (Scheme 35).\textsuperscript{46} The reversibility of the reactions depended on the substituents, and \textit{meso} substrates generally rearranged \textit{via} a boat transition state to give \textit{meso} products.
The \( dl \) distereoisomers rearranged via a chair like topology to the \( dl \) products. A charge-enhanced rearrangement involving intramolecular catalysis by phenolic protons is believed responsible for the observed facile nature of this specific reaction.\(^{47}\)

### 1.2.9 1-\( \text{N,N,3-S} \) Systems:

#### 1.2.9.1 \( S \)-Thioallylimidates

The rearrangement of \( S \)-thioallylimidates to \( N \)-thioallylamides showed a pronounced propensity for the catalytic effect of \( \text{Pd}^{II} \) salts (Scheme 36). Rearrangement of 99 with 0.01 eq of \( \text{PdCl}_2(\text{PhCN})_2 \) in refluxing THF gave 100 in 98% yield.

Substrates 101 to 103 also rearranged in accordance with this procedure. These examples expanded the applicability of this process to include cyclic thioimidates, amide functionalities and aromatic imidates (Fig. 10).
A cyclization-induced mechanism involving 104 is proposed (Fig. 10), analogous to other Pd\textsuperscript{II} catalysed rearrangements. Pd(Ph\textsubscript{3})\textsubscript{4}, NiCl\textsubscript{2}, CuCl\textsubscript{2} or HgCl\textsubscript{2} did not show any catalytic ability within this transformation.

No catalysed reaction was observed in substrates with a substituent in the β-position (Me, Ph or Cl) of the allyl group, which would require a tertiary Pd-C bond in the cyclized intermediate 104 (Fig. 10). A related series of Pd\textsuperscript{II} catalysed reactions under similar reaction conditions gave N-allyl thioamides 106 from 105 (Scheme 37).\textsuperscript{49} The thermal reaction proceeded through a different pathway, giving C-allyl products 108 (Scheme 37).

Initial isomerization of 105 led to the ketene S,N-acetal 107, followed by [3,3]-rearrangement (Scheme 37). No N-allyl product was observed in the thermal reactions, and only 0-15\% of the C-allyl was isolated in the catalysed rearrangements, such that
S→N or S→C allylic rearrangement could be selectively carried out by choice of reaction conditions.

1.2.9.2 O-Alkyl S-Allyl Iminothiocarbonates

Pd$^{II}$ catalysed S→N [3,3]-rearrangements were reported in the conversion of O-alkyl S-allyl iminothiocarbonates $109$ to O-alkyl-N-allylthiocarbamates $110$, using PdCl$_2$(MeCN)$_2$ in THF (Scheme 38).

![Scheme 38](image)

Yields were lowered if the allyl group was unsubstituted ($R^2 = H$, 24%), or if the allyl group was in the Z-configuration ($R^2 = Z-\text{CH}_2\text{Ph}$, 12%).

1.2.10 1-S,3-O Systems:

1.2.10.1 Allylthionocarbamates

Allylthionocarbamates make excellent substrates for [3,3]-sigmatropic rearrangement processes. It was shown that allyl thionocarbamate $111$ can be converted to the thiocarbamate $112$, with the use of 0.3eq of Hg(CF$_3$CO$_2$)$_2$ in THF (Scheme 39).

![Scheme 39](image)

Allylic thionocarbamates undergo the same rearrangement and have been employed en route during the preparation of α,β-unsaturated aldehydes $117$ (Scheme 41). An allylic alcohol $113$, prepared from the addition of a vinyl Grignard reagent to a ketone, was
treated with \(N,N\)-dimethylthiocarbamoyl chloride under basic conditions, to give the thionocarbamate 114 in 73% yield (Scheme 40).

Thermal rearrangement of 114 then gives the desired allylic thionocarbamate 115 (Scheme 41). Further treatment of 115 with lithium diisopropylamide and dimethyl disulfide gives the \(\alpha\)-sulfenated product 116. Finally, the hydrolysis of 116 with mercuric chloride in the presence of calcium carbonate in aqueous THF afforded the \(\alpha,\beta\)-unsaturated aldehydes 117 in good yield.

1.2.11 1-N,3-O,4-N Systems:

1.2.11.1 N-Acylhydroxylamine-O-carbamates

\(N\)-Acylhydroxylamine-O-carbamates 118 rearrange under basic conditions giving access to \(\alpha\)-amino acid amide derivatives 121 (Scheme 42). This rearrangement, which can be described in terms of an anionic [3,3]-sigmatropic rearrangement, is relevant to the \(\alpha\)-amination of carboxylic acids.
The reaction can be rationalised in terms of a 1,4-diaza-3-oxa [3,3]-sigmatropic shift. Deprotonation of 118 with 2.5eq of base results in the ester isocarbamate dianion 119. [3,3]-Sigmatropic rearrangement of this dianion to 120, followed by decarboxylation leads to the aminated product 121. Variation of substituents on the nitrogen atom of the carbamate group had little effect on the yields recorded for the transformation. Optimum results were achieved where \( R^1 = R^2 = \text{CH}_2\text{Ph} \) and KHMDS was used as base to give a yield of 76%. Overall, the nature of the substituents on the enolate groups with regard to stabilization or steric factors had little influence on the progress of the reaction.

1.2.11.2 \( N \)-(Oxyisocyanate) enamines:
An effective synthesis of \( N \)-monosubstituted imidazolones 124 was achieved by introducing a cyano group using either BrCN or \( N \)-cyano-4-(dimethylamino)pyridinium bromide (CAP), onto the \( N \)-hydroxy group of an enehydroxylamine 122 (Scheme 43).\(^{53}\) This then facilitates [3,3]-rearrangement to 123, upon which cyclization to the \( N \)-monosubsituted imidazolones occurs.

A yield of 81% was recorded when DABCO was used as base. Other enehydroxylamines with bulky alkyl groups on the nitrogen such as isopropyl or cyclohexyl, were found to give poorer yields or no reaction.
1.2.12 3-N,4-O,6-O Systems:

1.2.12.1 N-Methyl-O-Acyl hydroxylamines:

In the late 1960's investigations conducted by House, showed intriguing results with regard to the use of ketoxime derivatives in the preparation of $\alpha$-acetoxy ketones 129. House observed that the successive treatment of ketone oxime acetates 125 with trimethylloxonium fluoroborate then triethylamine yielded $\alpha$-acetoxy ketones, upon hydrolysis of the imine 128 (Scheme 44).$^{54}$

Methylation of oxime acetate 125 produces an iminium ion 126, which after conversion to the enamine 127, under basic conditions, underwent the proposed $[3,3]$-rearrangement.

A similar procedure employing the same intermediate O-acyl hydroxylamine, but starting from nitrones was later developed by Coates (Scheme 45).$^{55}$ It was observed that the reaction of $N$-tert-butynitrones of aldehydes 130 and $N$-methyl-nitrones of cyclic ketones with acid chlorides under basic conditions afforded $\alpha$-acyloxy imines 131 by rearrangement of $N$-vinyl-O-acylhydroxylamine intermediates 132.
Sorensen et al. employed this rearrangement to great effect in the synthesis of (±)-fumagillol 136, where contemporary oxidation procedures via an aldehyde enolate proved ineffective. The prerequisite nitrone 133 (Scheme 46) could be simply introduced through condensation of N-cyclohexylhydroxylamine with the corresponding aldehyde.

Acylation of 133 with acylchloride and triethylamine then gave direct access to the rearrangement substrate N-vinyl-O-acetylhydroxylamine 134 (Scheme 46), which underwent rearrangement at room temperature to the α-acetoxy-N-cyclohexylimine 135 (Scheme 47).
Sorensen’s application of this rearrangement is an excellent example of the potential offered by these polyheteroatom rearrangements. The introduction of an oxygen atom to form a quaternary carbon centre in a diastereocontrolled manner is no minor achievement, a point that is highlighted by Sorensen, regarding this under utilised rearrangement.

1.2.12.2 N-(Oxymethylcarbonate) enehydroxylamine:
The reaction of ketone oximes with dimethyl carbonate (DMC) carried out in an autoclave at 180-190 °C in the presence of K$_2$CO$_3$ gave 3-methyl-4,5-disubstituted-4-oxazolin-2-ones 141 (Scheme 49). The reaction can be applied to both aliphatic and aromatic ketone oximes, provided that a methylene group is present at the C=N bond. Non-optimized yields ranged from 22 to 48 %. The reaction proceeded through a [3,3]-sigmatropic rearrangement where DMC plays a key role in the initial N-methylation of the oximes 137 (Scheme 48).

\[
\begin{align*}
\text{Scheme 48}
\end{align*}
\]

O-carbonylation followed by N-methylation of the O-carbonate derivative of the oxime 137 to give 138 that, in turn, produced the enamine intermediate 139, followed by sigmatropic rearrangement to 140 (Scheme 49).

\[
\begin{align*}
\text{Scheme 49}
\end{align*}
\]
Further cyclization was encouraged by the elimination of one equivalent of methanol following intramolecular nucleophilic attack of the imine nitrogen to give the observed product 141 (Scheme 49).

1.2.13 1-N,2-P,3-O Systems:
1.2.13.1 Allylic Phosphorimidates:
The use of allylic phosphorimidates has recently been shown to provide an alternate route into protected allylic amines by utilising an Overman type rearrangement.\(^{58}\) Allylic alcohols were readily converted into phosphorimidates 143 by reaction with a chlorophosphine to give 142, followed by a Staudinger reaction\(^{59}\) with benzyl azide giving 143 (Scheme 50).

\[
\begin{align*}
\text{Allylic alcohol} & \rightarrow \text{chlorophosphine} \rightarrow \text{phosphorimidate} \\
\text{142} & \rightarrow \text{Staudinger reaction} \rightarrow \text{phosphorimidate} \\
\text{143}
\end{align*}
\]

Scheme 50

Thermal [3,3]-sigmatropic 3-aza-2-phospha-1-oxa-Claisen rearrangement of 143 then generates a phosphoramidate 144, with retention of stereochemical integrity (Scheme 51).

\[
\begin{align*}
\text{143} & \rightarrow \text{thermal rearrangement} \rightarrow \text{phosphoramidate} \\
\text{144} & \rightarrow \text{phosphoramidate} \rightarrow \text{allylic amine} \\
\text{145}
\end{align*}
\]

Scheme 51

The phosphoramidate group also acts as a protecting group that confers stability under a wide range of reaction conditions to the masked allylic amine 145. This group can
readily be removed, however, either by treatment with TMS-I or by the addition of a nucleophilic thiol followed by addition of HCl/MeOH.

1.2.13.2 (Allyloxy) Iminodiazaphospholidines

A similar enantioselective variant of this reaction was demonstrated by Batey et al. for the rearrangement of cis-(allyloxy) iminodiazaphospholidines 149 with cobalt oxazoline palladacycle (COP-X) catalysts 48 (5mol%) in high yield and enantioselectivities (up to 96% ee) (Scheme 53). These compounds were cleanly prepared in a one-pot process by the sequential treatment of allylic alcohols with phospholidine 146, as described by Alexakis to give 147 followed by reaction with either tosyl azide or diphenylphosphoryl azide (DPPA), respectively to give 148.

There was a dramatic dependence of the catalyst counterion and olefin geometry for the COP-X catalyst system on the selectivities observed, with a chlorine counterion giving the best results. With reasonably low catalyst loading (5mol%) at 45 °C, cis-substrates of 149 underwent rearrangement in high yields (up to 97%) and enantioselectivities (up to 96% ee) for 151. These results demonstrate the synthetic utility of the COP-X family of catalysts for enantioselective [3,3]-sigmatropic rearrangements other than the Overman rearrangement.
1.3 Conclusion:

As can be seen there is a rich and diverse array of chemical processes possible through the use of [3,3]-sigmatropic rearrangements. The potential of this heteroatom bond forming rearrangement is vast but somewhat currently under utilized. Its aptitude for C-O, C-S and C-N bond formation presents numerous possibilities and permutations for its exploitation. These have slowly seen heteroatom [3,3]-sigmatropic rearrangements become more established as a synthetic tool since the discovery over nine decades ago of the classical Claisen rearrangement. Ongoing research into the asymmetric catalysis of heteroatom [3,3]-sigmatropic rearrangements is a continually evolving area, indicative of the latent potential of these heteroatom rearrangements, and will most likely offer the greatest advancements in scope and utility. The future may seem bright for these rearrangements, however, there are some limitations, which must be addressed before it can truly become a versatile addition to the synthetic chemists toolbox. Prominent amongst these is the need to construct a suitable rearrangement substrate prior to the bond-forming step, although not overly complicated this can add two to three additional steps to a synthesis, detracting away from its application. The current reliance on metal catalysis is also somewhat of an Achilles heel given the current move towards more green chemistry.
Chapter 2: Literature Review
2.1.0 Introduction:

An ever-continuing fundamental drive in synthetic organic chemistry is the movement towards more efficient bond forming processes. This is evident in the multitude of catalytic systems presented in current literature for an exhausting catalogue of organic transformations. Within this sphere there is an under-current of movement away from the reliance on transition-metal catalysts. In spite of the enormous catalytic power of transition-metal catalysts in terms of both asymmetric control and kinetic acceleration their stringent reaction conditions, laborious removal and significant environmental footprint mean they have been used somewhat reluctantly by synthetic chemists. As a result this has energised an ever-increasing interest in organo-catalytic systems (Lewis Bases/Lewis Acids) to answer these deficiencies. As with the rest of the synthetic world the area of α-functionalisation of carbonyl compounds is no different with new catalytic methodologies continually improving the process. Therefore, it is thought prudent to confine a literature review to the area of catalytic α-functionalisation of carbonyl compounds as this resides at the forefront of the field.

2.2.0 Chiral Lewis bases:

The area of organocatalysis has received increasing attention of late, in accordance with the drive toward more environmentally friendly catalysts to augment contemporary metal systems. The majority of organo-catalysts are N-, C-, O-, P- or S-containing, Lewis base systems. They derive their catalytic ability from the formation of a wide variety of reactive intermediates. Examples of the variety of some of the different methods in organo-catalytic methodology are shown (Fig. 11).
One remarkable molecule, the amino acid proline 152, has become a crucial component in numerous catalytic strategies. The first example of asymmetric enamine catalysis was the Hajos–Parrish–Eder–Sauer–Wiechert reaction, an intramolecular aldol reaction catalyzed by proline.\textsuperscript{64} The astonishing catalytic activity of proline can be attributed to various chemical reasons. Proline is bifunctional, with both an amino and carboxylic acid portion. These two functional groups can both act as acid or base. In addition, proline is a chiral bidentate ligand that can form catalytically active metal complexes. These characteristics apply to all amino acids, however, proline is a secondary, cyclic, pyrrolidine based amino acid. The most important difference is prolines ability to carry out amino-catalytic transformations due to its ability to function as a Lewis base, that facilitates iminium ion and enamine based transformations. Chiral Lewis bases catalyse these reactions by the reversible formation of a chiral enamine 153 (Fig 12). Chiral induction imparts asymmetry upon reaction between this enamine and the
electrophile, followed by hydrolysis of the resulting iminium ion 154 and release of the product 155, which allows for catalyst turnover.\textsuperscript{65}

Prolines unique nucleophilicity is primarily a consequence of the pyrrolidine portion, which forms iminium ions and enamines with carbonyl compounds more readily than most other amines, including cyclic ones such as piperidine.\textsuperscript{66} The carboxylate further enhances the aminocatalytic ability of proline by acting as a general Bronsted cocatalyst.

2.3.0 $\alpha$-Functionalisation of Carbonyl Compounds:

$\alpha$-Hydroxy carbonyl compounds are versatile synthetic intermediates that are useful for the preparation of 1,2-aminoalcohols,\textsuperscript{67} $\alpha$-aminocarbonyl compounds,\textsuperscript{68} and 1,2-diols.\textsuperscript{69} In addition to their utility as synthetic precursors, $\alpha$-hydroxy carbonyl compounds are also important substructures present in a wide variety of natural products and pharmaceutically important compounds.\textsuperscript{70} Accordingly, this functionality has generated considerable attention from the synthetic community. The traditional method for their
preparation from the parent carbonyl involves the hydroxylation of preformed enolates or enol ethers with a variety of oxidizing agents, including peroxyacids,\textsuperscript{71} OsO\textsubscript{4},\textsuperscript{72} MoO\textsubscript{4}Ph,\textsuperscript{73} oxaziridines,\textsuperscript{74} and DMDO.\textsuperscript{75} More recent trends have also expanded to incorporate Sharpless dihydroxylation of enol ethers,\textsuperscript{76} manganese-salen epoxidation of enol ethers\textsuperscript{77} and Shi epoxidation of enol esters.\textsuperscript{78}

As with \(\alpha\)-oxidation reagents there has been paralleled interest into stoichiometric \(\alpha\)-aminating reagents with azodicarboxylates proving effective coupling partners with enol ethers and enolates.\textsuperscript{79} This interest has been spurred on by the utility of \(\alpha\)-amino carbonyl compounds in synthetic chemistry. An alternative approach receiving some attention is the direct amination of carbanions using a variety of hydroxylamines as electrophilic \(\text{NH}_2^+\) equivalents.\textsuperscript{80} Included in these hydroxylamine derivatives \(O\)-diarylphosphinyl,\textsuperscript{81} \(O\)-acyl,\textsuperscript{82} \(O\)-sulfonyl,\textsuperscript{83} and \(O\)-dinitrophenyl derivatives,\textsuperscript{84} and a variety of \(O\)-alkyl hydroxylamines have been examined with varying degrees of success.\textsuperscript{85} The diphenylphosphinyl reagent has the most extensive track record for aminations and works moderately well with a range of Grignard reagents and somewhat better with increasingly stabilized enolates.\textsuperscript{86,87} However, in relation to Grignard reagents this has been some what superseded of late by work conducted by Johnson \textit{et al.} into copper catalysed electrophilic aminations of organo-zinc nucleophiles using \(O\)-benzoylhydroxylamines as \(R_2N^+\) and \(RNH^-\) synthons.\textsuperscript{88} Despite their effectiveness, the prerequisite enolate or anion remains a significant limiting factor in the propagation of hydroxylamines as aminating reagents. However, recent advances in Lewis base catalysed amination techniques have shown azodicarboxylates to be versatile electrophilic reagents, as will be highlighted later in this chapter.

2.3.1 \(\alpha\)-Oxygenation Catalyzed by Chiral Lewis Bases:

\(\alpha\)-Hydroxy carbonyl compounds have proven to be versatile synthetic intermediates in modern synthetic procedures. Their versatility has generated significant interest into their catalytic asymmetric synthesis of late, providing a more efficient route to their synthesis. Yamamoto reported the first catalytic enantioselective synthesis of \(\alpha\)-
hydroxy carbonyl synthesis catalyzed by a Lewis acid.89 Results for a variety of cyclic ketones showed that Ag\textsuperscript{I}-binap complexes effectively catalyze the enantioselective reaction between Sn\textsuperscript{IV} enolates and nitrosobenzene giving the α-oxygenated carbonyl compound in >95% yield and ee.

Despite the efficient processes available through Lewis acid catalytic methodologies, the ever-burgeoning area of organocatalysis has somewhat over shadowed them. Given the ever-increasing volume of literature regarding Lewis base catalysis it is perhaps not surprising to note the almost simultaneous publications from Zhong,\textsuperscript{90} MacMillan,\textsuperscript{91} and Hayashi,\textsuperscript{92} on the use of proline to catalyze the addition of simple aldehydes and ketones to nitrosobenzene. These publications will inevitably form a benchmark in organocatalysis, although they differ only in the choice of solvent and selection of suitable substrates. By employing chiral Lewis bases, initially proline, it over comes one of the major disadvantages associated with previous methods, namely, the need to first form a metal-enolate. In conjunction with this, the tolerance of more benign reaction condition is an additional advantage.

\[
\begin{array}{c}
\text{HO}^{-} + \text{NPh} \rightarrow \text{HO}^{-} \text{NPh} \\
\text{1. L-proline (cat)} \\
0 \degree \text{C-rt, <1-4hr} \\
\text{2. NaBH}_4 \\
\text{156} \rightarrow \text{157}
\end{array}
\]

Scheme 54

The overall conclusions from these investigations showed that enolizable aldehydes with varying degrees of branching and functionality react quite well with nitrosobenzene \textbf{156} in the presence of catalytic amounts of L-proline to give \textbf{157} in >80% yield and 98% ee (Scheme 54). Since the initial α-alkoxy aldehydes produced are oligomeric, subsequent reduction with NaBH\textsubscript{4} is necessary to give the diol.

The α-oxygenation of ketones using chiral Lewis bases has proven a more challenging reaction than that of aldehydes and has received particular attention from the labs of both Hayashi\textsuperscript{93} and Cordova.\textsuperscript{94} Combined with their diminished ability to reversibly form enamines with proline, they have two enolizable carbon atoms, which compromises chemoselectivity in the oxygenation reaction, leading to a mixture of
mono-and di-oxygenated species. To avoid this complication, a large excess (2–10 eq.) of ketone is often used and nitrosobenzene is added slowly using a syringe pump. This procedure prevents the formation of any \( C_2 \)-symmetric di-oxygenated products but requires addition times of up to 60 hr. Under these conditions however, cyclic ketones were excellent substrates with complete regio- and stereoselectivity. Interestingly, nonsymmetric ketones exhibited a propensity to react at the more substituted carbon, this observation is most likely due to the initial formation of the more stable, substituted enamine.

To overcome the obstacles presented by ketone \( \alpha \)-oxygenation Yamamoto et al. described a more efficient proline–tetrazole based catalyst 158, which mediates the oxygenation of both aldehydes and ketones in high yields (65–97\%) and enantioselectivities (Scheme 55).\(^9\)

\[
\begin{align*}
156 & : R^1\text{riger}_{2} + \text{O}^2\text{N}\text{-Ph} \\
158 & : \text{NHPh} \\
\text{DMSO, rt, 1 hr} & : \text{R}^1\text{O}^2\text{NHPh} \\
\end{align*}
\]

Scheme 55

In conjunction with this, Sunden et al. have shown that proline derived \( N \)-sulfonylcarboxamides 159 are active catalysts for the asymmetric \( \alpha \)-oxidations.\(^9\) Unlike the related investigation with \( N \)-sulfonyl-2-aminomethylpyrrolidines,\(^9\) which required a five step synthesis to reach the desired catalyst, this modified carboxamide approach allowed a two-step synthesis form commercially (S)-benzyl-4-nitrophenyl pyrroldine-1,2-dicarboxylate 160 (Scheme 56).

\[
\begin{align*}
160 & : \text{C}bz \\
\text{1. RSO}_2\text{NH}_2, \text{DMF} & : \text{159} \\
\text{2. Pd(C), H}_2, \text{MeOH} & : \text{O}^2\text{S}_R \\
\end{align*}
\]

Scheme 56
The reaction catalysed by 159 proceeds smoothly, furnishing the corresponding α-aminoxylated compounds in good yields. Interestingly, the direct asymmetric α-oxidation of cyclohexanone with 10mol% of the N-sulfonylcarboxamide proline derivative 159 as catalyst showed a marked selectivity for the mono-oxygenated product 161 over the di-oxygenated ketone 162 (Scheme 57).

![Scheme 57](image)

An overall yield of 80% with an ee of >99% was recorded for the mono-oxygenated ketone 161 with only trace amounts of di-oxygenated ketone observed.

Further modification of this general proline methodology has led to the examination of various oxidants. An examination of several synthetically common oxidants revealed that iodosobenzene and N-sulfonyloxaziridines act as electrophiles in the direct organocatalytic asymmetric α-hydroxylation of ketones. The direct proline-catalyzed asymmetric α-oxidation of ketones with iodosobenzene yielded the corresponding α-hydroxylated ketones 163 with up to 77% ee but with a poor yield of only 29% (Scheme 58).

![Scheme 58](image)

Furthermore, several amino acid derivatives catalyze the stereoselective α-oxidation of ketones with N-sulfonyloxaziridines. For example, the direct diamine-catalyzed enantioselective α-hydroxylation of ketones with N-sulfonyloxaziridines furnished the
corresponding α-hydroxylated products in moderate yield with up to 63% ee (Scheme 58).

Proline catalysis has also been applied to the asymmetric desymmetrization (ADS) of carbonyl compounds, which represents a potent method for the synthesis of two or more contiguous stereogenic centers in a single procedure. The ADS of meso-compounds by enzymatic\textsuperscript{99} and nonenzymatic\textsuperscript{100} methods has already proven to be a versatile and powerful strategy. The degree of catalyst control observed is very high as both cis- and trans-ketones are produced in high ee.\textsuperscript{101} In examples where R = 'Bu, yields of 31% were recorded for both products 164 and 165, with ee of 99 and 94% respectively (Scheme 59). Substitution of a 'Bu group for a OSi('Bu)Ph\textsubscript{2} resulted in yields of 46 and 23% respectively, with ee's of 99 and 96%.

```
O
\text{\textsuperscript{10}mol\% L-proline}
\text{Ph} \text{ONHPh} \text{\textsuperscript{156}} \text{164, 165}
```

Scheme 59

Barbas et al. have also demonstrated methods for the ADS and O-N bond reduction of highly substituted prochiral spirotrione 166 with nitrosobenzene (3eq.) 156 under amino acid catalysis.\textsuperscript{102} The tandem reaction proceeds in good yield with >99% ee and >99% de recorded for 167 using L-proline as the catalyst (Scheme 60).
It was also demonstrated that the \textit{in situ}-generated \textit{R}-aminoxyketones 161 undergo further O-N bond reduction with nitrosobenzene 156 to yield hydroxyketones 169 (Scheme 61).

![Scheme 61](image)

From these observations nitrosobenzene 156 plays a dual role: it facilitates synthesis of chiral \textit{R}-hydroxyketones 161 through enantioselective oxidation of prochiral ketones and reduces O-N bonds to result in \textit{R}-oxy generated products 169 under amine or amino acid catalysis.

\section*{2.3.2 \(\alpha\)-Amination Catalyzed by Chiral Lewis Bases:}

Although somewhat superseded by advancements in chiral Lewis base techniques, Lewis acid catalyzed amination reactions have generated valuable results. Yamamoto has shown that the \textit{O}-selectivity of reactions with nitrosobenzene can be completely reversed, when conducted in the presence of a 10 mol\% preformed catalyst composed of a 2:1 mixture of Ag\(^+\) triflate and (\textit{R})-binap\(^{103}\). Evans has employed azodicarboxylates as ready electrophiles in conjunction with \(C_2\)-symmetric Mg\(^{1+}\) complexes\(^{104}\) and Cu\(^{1+}\) bis(oxazoline) complexes\(^{105,106,107,108}\).

Until recently there have been no reported organocatalytic reactions of nitrosobenzene that give the aminated product resulting from attack at nitrogen as the major product. In the L-proline-catalyzed \(\alpha\)-aminoxylations of aldehydes and ketones with nitrosobenzene the high chemoselectivity is possibly due to the higher basicity of nitrogen compared to that of oxygen, which leads to preferential protonation of the nitrogen, making the oxygen more electrophilic. There are however, limited examples of stoichiometric morpholine enamines giving the \(N\)-adduct\(^{109}\). Morpholine-derived
enamines give predominantly N-adduct, whereas pyrrolidine enamines give mainly O-adduct.\textsuperscript{95} Although no explanation for this selectivity has been formulated, it is known that enamines derived from pyrrolidine are orders of magnitude more nucleophilic than those from morpholine.\textsuperscript{110} Yamamoto has demonstrated that stoichiometric amounts of enamine reacted with nitrosobenzene in the presence of chiral carboxylic acids to preferentially perform an amination reaction, while in the presence of chiral alcohol the oxygenated product was generated.\textsuperscript{111} A recent development in this area has been the exploitation of prolinamide derivatives 170 (Fig. 13) in the nitroso-aldol reaction. The catalytic ability of 170 is grounded on the assumption that it is difficult to protonate the nitrogen with the proton of either the alcohol or the acylamide, and a hydrogen bond between the oxygen of the nitroso group and the proton of either the amide or hydroxy group (or both) preferentially forms to make the nitrogen more electrophilic than oxygen.\textsuperscript{112}

Therefore, it was proposed that prolinamide derivative 170 would be able to catalyze the reaction of unmodified aldehydes and nitrosobenzene via a presumed transition state 171, chemoselectively giving N'-nitroso aldol adducts (Scheme 62).

The ee's reported were, however, moderate at best with 64% for 173 and a reaction time measured in days that was also less than encouraging (Scheme 62). Instead,
Jørgensen et al. as well as List have reported the amination of aldehydes and ketones with azodicarboxylates under proline-mediated catalysis giving \( \text{174} \) in 97% yield and 95% ee (Scheme 63).\(^{113,114}\)

![Scheme 63](image)

The mechanism of this amination shows some unexpected kinetics.\(^{115}\) An exploration of this transformation using calorimetry indicates both a non-linear effect and an accelerating rate of reaction. Both of these indicate an autocatalytic reaction whereby the product or a reaction intermediate also functions as a catalyst. Also, premixing proline and the product resulted in a precatalyst, characterized as oxazolidinone \( \text{175} \), which led to improved rates of reaction.

![Fig. 15](image)

The exact role and mode of action of this precatalyst is not yet understood, but it is believed to serve as a more soluble proline species that can immediately enter the catalytic cycle. In addition, Jørgensen also demonstrated that the \( \alpha \)-amination of \( \alpha \)-cyanoacetates and \( \beta \)-dicarbonyl compounds was catalyzed by the quinidine-derived alkaloid (\( \beta \)-isocupreidine, \( \beta \)-ICD) \( \text{176} \) (Scheme 64).\(^{116}\)
With a catalyst loading of 5mol%, the products 178 were recovered in high yield with an ee of 91 to 99% for a variety of aryl-substituted α-cyanoacetates 177 and β-dicarbonyl compounds. As of yet, no mechanistic rationale has been proposed for this process. Although, given the high acidity of the substrates and the basic nature of the catalyst, an enolate with a chiral ammonium (β-ICD-H⁺) counterion is a likely intermediate.

2.3.3 α-Sulfenylation Catalyzed by Chiral Lewis Bases:

To date, all practical methods for the preparation of chiral α-sulfenylated aldehydes have been multistep procedures that involve chiral auxiliaries. The catalytic abilities of Ti(TADDOLato) complexes have been known for several decades and recent studies into the use of [TiCl₂(R,R)-1-Np-TADDOLato)(MeCN)₂] in relation to the Lewis acid catalytic enantioselective halogenation of β-ketoesters has led to their use as efficient asymmetric catalysts in carbon-sulfur bond forming processes. One of the major obstacles to overcome was the initial selection of a suitable electrophile. This was remedied in the first catalytic α-sulfenylation, which employed a triazole containing sulfenylating reagent 179 and a modified proline catalyst 180 (Scheme 65).
Substrates having a small (R = Me) or bulky (R = t-Bu) substituent were efficiently converted into functionalized products with high yields and 95-98% ee. To avoid racemization, the newly functionalized aldehyde products were isolated after in situ reduction with NaBH₄ to the corresponding optically active alcohol 181. Very recently, several attempts were carried out to perform direct organocatalytic enantioselective α-sulfenylation and selenenylation reactions of aldehydes. For the direct α-sulfenylation, a large number of organocatalysts, such as L-proline, L-proline amide, and pyrrolidine trifluoromethanesulfonamide, as well as other chiral amines, were screened using N-(phenylthio)phthalimide 182 as the sulfenylating reagent. Excellent yields were observed with a combination of N-(phenylthio)phthalimide as the sulfenylating reagent and pyrrolidine trifluoromethanesulfonamide 183 as organocatalyst (Scheme 66).

However, no enantiomeric excess was reported (which presumably means there was none). The related α-selenenylation of both aldehydes and ketones was also studied with L-proline amide and pyrrolidine trifluoromethanesulfonamide as the catalysts and N-(phenylseleno)phthalimide as the selenenylation reagent. Low enantioselectivity was reported for this transformation.
2.4.0 Conclusion:
The catalytic, asymmetric $\alpha$-amination and $\alpha$-oxygenation of carbonyl compounds represents a valuable advance in synthetic methodology. Although great strides have been made in developing this chemistry, the field is still in its adolescence with many challenges and questions still remaining. A deeper understanding of the mechanism and the factors that govern $O$-versus $N$-selectivity with nitroso compounds is crucial. A deeper understanding of this will allow for innovation in catalyst design and make this methodology a more robust and efficient way to access valuable, enantiopure molecules. In addition, more convenient electrophilic sources of nitrogen and oxygen along with a more wide ranging substrate compatibility would be a tremendous advance. The increasing volume of literature regarding this field is representative that this area is developing at a rapid pace and surely further progress in both catalyst design and mechanistic determination will be forthcoming in the near future.
Chapter 3: $\alpha$-Oxyacylation
3.1.0 Introduction:

Modern synthetic chemistry, whether motivated by economic, industrial, environmental or academic reasons, has followed an inexorable path toward novel, cleaner, more efficient transformations. To this end there has been a concerted movement towards the development and application of metal-free methodologies to undertake synthetic transformations. The explosion of recent interest in metal-free enamine catalysis using proline perhaps best exemplifies this progression. MacMillan and List, amongst others, have demonstrated proline to be an effective agent for asymmetric Diels-Alder, conjugate addition, aldol, Mannich, amination and aminohydroxylation reactions.

The carbonyl group plays a central and fundamental role in synthetic chemistry. Its use as an in-road into numerous synthetic manipulations and transformations has secured it a place in the synthetic chemists' arsenal. For example, the treatment of a carbonyl compound with one equivalent of strong base such as lithium diisopropylamide (LDA) generates the corresponding enolate, which can in turn react with a variety of electrophiles to introduce carbon or heteroatom functionalities (Fig 16).

![Fig. 16](image_url)

Despite the effectiveness of this procedure it requires low temperatures and anhydrous conditions, which are difficult to ensure on a lab-scale and is expensive in the industrial environment. With this in mind we set out to develop a one-pot transformation, which could facilitate this same transformation, but under more benign reaction conditions, with a tolerance of both moisture and air.

The origin of our one-pot transformation lay in a report by House, who showed that cyclohexanone could be converted into 2-acetoxy cyclohexanone through a five-step procedure (Scheme 67). This involved conversion of a ketone to the oxime, O-acylation...
followed by N-methylation to give the iminium species \textbf{126}. Under basic conditions \textbf{126} was converted to the enamine \textbf{127}. The enamine rapidly underwent a proposed concerted Claisen like pericyclic \([3,3]\)-rearrangement to give the imine \textbf{128}. Hydrolysis of this imine under aqueous acidic conditions gave the \(\alpha\)-functionalised ketone \textbf{129} in 45\% yield over five steps (Scheme 67).

![Scheme 67](image)

Closer consideration of iminium ion species \textbf{126} provides a perfect point to consolidate the underlying principles of the oxidation methodology presented within this thesis. Disconnection X crucial with respect to the construction of the rearrangement substrate is also fundamental with regard to the design of any possible reagent 193 (Fig. 17). The major limiting factor with regard the application of polyheteroatom rearrangements is that several steps are generally required to introduce the rearrangement substrate prior to the actual rearrangement step. By exploiting this disconnection this could be overcome through the one-step condensation of a substituted \(N\)-alkyl-\(O\)-acyl hydroxylamine 192 with a carbonyl compound under acidic conditions (Fig 17).
The acidic conditions required for this condensation are brought about by the use of the hydrochloride salt of the hydroxylamine starting material. It is at this point that our methodology would diverge significantly from those previously reported. The acyloxylation processes developed by House and the modified three-step process by Coates (Scheme 67) in which an enehydroxylamine 188 is used to access the rearrangement substrate, both possess a [3,3]-sigmatropic rearrangement in the key bond-forming sequence but under basic reaction conditions. More recently, Lobo has described the α-oxyacylation of enehydroxylamines by a proposed sigmatropic rearrangement, once again under basic reaction conditions. Within our proposed reaction sequence, following condensation the resulting iminium ion 194 should exist in equilibrium with the enamine 195, which in turn would undergo a polyheteroatom Claisen rearrangement (Scheme 68). The cleavage of the weaker of N-O bond, with a bond strength of c.a. 63 kCal/mol, provides a thermodynamic driving force for this rearrangement with a stronger C-O bond being formed.
In situ acid hydrolysis of the functionalized imine \( \text{196} \) would provide the desired product \( \text{197} \), delivering a procedure with not only a tolerance for, but also a prerequisite for at least one equivalent of water in the reaction medium. From this initial disconnection \( \text{X} \) that provided the concept of a general reagent of the type \( \text{3} \), a \( O,N \)-substituted hydroxylamine which could condense with a carbonyl compound under acidic reaction conditions to directly furnish the required iminium ion. Within this simple reagent scaffold there are also numerous possible permutations, offering the possibility for the introduction of several different functionalities, which will be described in the following chapters.

3.2.0 Reagent Preparation:

3.2.1 \( N \)-Methyl-\( O \)-benzoyl hydroxylamine hydrochloride:

As with \( N \)-sulfonyloxaziridine oxidising reagents our oxygen source is contained within the reagent itself, but exclusive to the chemistry presented in this chapter, it is transferred via an \( O \)-benzoyl group. At this point disconnection \( \text{Z} \) and \( \text{Y} \) (Fig. 17) offer two possible pathways to the desired \( N \)-methyl-\( O \)-benzoyl hydroxylamine. Disconnection \( \text{Z} \) via a \( N-O \) bond formation or \( \text{Y} \) via a \( C-O \) bond formation. In this case, synthesis via an \( N-O \) bond formation process was discounted, as the oxidation of primary amines is inherently troublesome with over oxidation a common drawback. More importantly \( N \)-methylhydroxylamine hydrochloride \( \text{198} \) was commercially available and served as a suitable starting material, removing the need for this oxidation step. In order to exploit disconnection \( \text{Y} \) \( N \)-methylhydroxylamine hydrochloride \( \text{198} \) was first protected on the nitrogen to allow attack by the less nucleophilic oxygen. This could be achieved using (Boc\(_2\)O in a bi-phasic THF/H\(_2\)O system (Scheme 69). \( N \)-Boc-\( N \)-methylhydroxylamine \( \text{199} \) could be purified by simple short-path distillation under reduced pressure with an excellent overall yield of 97\%. Trace amounts of oxygen-protected hydroxylamine were evident by \(^1\)H NMR, however, these could be easily removed via distillation. Conducting the reaction at a reduced temperature may alleviate this side-product, although this was deemed unnecessary as the side-product could be easily removed via distillation.
Once protected, the important C-O bond could be constructed by reacting \( N\text{-Boc-}N\text{-methylhydroxylamine 199} \) with benzoyl chloride under basic conditions with a catalytic amount of DMAP to ensure a reasonable rate of reaction (Scheme 70). The desired \( N\text{-Boc-}N\text{-methyl-}O\text{-benzoylhydroxylamine 200} \) could be accessed by a simple acidic wash with 2M aqueous HCl removing any residual triethylamine along with DMAP and subsequently purified by short-path distillation under reduced pressure to give 200 in 98%.

Removal of the Boc protecting group was carried out using acidic deprotection conditions. This method of deprotection involved bubbling HCl gas through a solution of 200 in dry ether. A constant stream of HCl gas was generated by the dropwise addition of concentrated sulfuric acid onto ammonium chloride. Passing this stream of gas through a solution of 200 in dry ether at 0 °C gave an extremely efficient method of deprotection with the corresponding \( N\text{-methyl-}O\text{-benzoylhydroxylamine hydrochloride 201} \) crystallising directly from the reaction mixture and being recovered by filtration in 96% yield (Scheme 71). Unlike standard methods of Boc deprotection such as TFA/CH\(_2\)Cl\(_2\) systems, the use of Lewis acids or thermolysis, using this HCl method proved extremely advantageous. This approach let us simultaneously deprotect and access the desired hydrochloride salt of \( N\text{-methyl-}O\text{-benzoylhydroxylamine} \), which was fortuitous in accessing what would become our primary reagent.
Although the initial route was very successful, with excellent yields recorded over three steps, the synthesis suffered from two prominent restrictions. Firstly, although effective, a three-step procedure to access our desired reagent was deemed too lengthy and indirect. The need to purify both $N$-Boc-$N$-methylhydroxylamine 199 and $N$-Boc-$N$-methyl-$O$-benzoylhydroxylamine 200 by distillation before subsequent reaction led to a rather time consuming, laborious process. Secondly, a method by which the protection of $N$-methylhydroxylamine hydrochloride 198 could be circumvented would present a much more efficient, economical procedure. To this end, the reaction scheme was conceptually simplified. The hydroxylamine was envisaged as a simple primary alcohol, which led to a simple ester product, which opens the possibility of employing standard coupling reactions. It was this concept of simplification, which led to the extremely successful implementation of a coupling reaction using carbonyl-diimidizole (CDI), between $N$-methylhydroxylamine hydrochloride 198 and benzoic acid (Scheme 72).^{134}

Imidazolium coupling agents such as CDI or the newer generation CBMIT (carbonyl bismethylimidazolium triflate) and BOI (2-(benzotriazol-1-yl)-oxy-1,3-dimethyl imidazolium) have proven extremely effective in peptide coupling reaction,^{135} although for our purposes CDI proved extremely effective. The addition of 1eq. CDI to benzoic acid gave the intermediate 202 after effervesce of CO$_2$, at which point 1eq. of 198 was added with stirring to give 203. Washing the reaction solution after the addition of 198...
with 1M cold aqueous HCl to remove excess imidizole then aqueous NaHCO₃ to remove any residual benzoic acid purified the N-methyl-O-benzoylhydroxylamine free base 203 sufficiently to continue without directly isolating 203 (Scheme 73). Isolation of the final hydrochloride salt was achieved by passing a stream of HCl gas through the reaction solution that had been initially reduced in volume by half then replaced with anhydrous ether.

This procedure circumvented the need for a protection step because the reaction was conducted under acidic conditions that provided a pseudo-protecting group effect on the hydroxylamine nitrogen. The hydroxylamine nitrogen, which is more basic than that of imidazole, remains protonated throughout the reaction, thereby reducing its nucleophilicity and allowing oxygen to react preferentially.

3.2.2 *N*-ter/-Butyl-O-benzoylhydroxylamine hydrochloride:

The preparation of *N*-ter/butyl-O-benzoylhydroxylamine hydrochloride 204 was first achieved by exploiting disconnection Z (Fig. 17). The oxidation of *tert*-butylamine was carried out using a widely employed process developed by Gambarjan in which benzoyl peroxide (BPO) is the oxidant (Scheme 74).¹³⁶ This two-step procedure involved nucleophilic displacement along the peroxide O-O linkage followed by hydrochloride salt formation. The *N*-tert-butyl-O-benzoylhydroxylamine hydrochloride salt 204 was again isolated by bubbling a stream of HCl gas through a solution of *N*-tertbutyl-O-benzoylhydroxylamine 205 in ether followed by simple filtration. This methodology was taken further by Denny in that liberation of the hydroxylamine could be achieved by treating *N*-tertbutyl-O-benzoylhydroxylamine 205 with aqueous sodium hydroxide if the debenzoylated hydroxylamine is required.¹³⁷
tert-Butlyamine is sterically hindered enough to minimise nucleophilic attack at the benzoylperoxide carbonyl group, limiting the formation of unwanted $N$-tert-butylbenzamide 206 (Fig. 18).

Distillation of the crude reaction product provided a simple method of purification of the $N$-tert-butyl-$O$-benzoylhydroxylamine free base 205, which on exposure to HCl gas in dry ether gave 204 as a crystalline solid (Scheme 74). While initial results gave a yield of 82% for 204 there was one major drawback to the reaction. Under the reaction conditions the progress of the reaction produces one equivalent of the benzoic acid salt of tert-butylamine, therefore two equivalents of amine were required to counteract this loss. Together with this, several re-crystallization steps prior to distillation were required to remove this salt making for an unnecessarily laborious procedure. These limitations were, however, overcome by the use of a bi-phasic buffered system (Scheme 75). 138
Once the reaction medium was buffered to a pH of 10.5 (5ml aqueous buffer solution/mmol amine) the resulting benzoic acid anion could be removed from the reaction as its sodium salt 207 (Fig. 19) minimising any unwanted benzoic acid salt formation, giving a much more efficient reaction albeit with a lower yield of 72% (Scheme 75).

From the results obtained, both the CDI coupling approach for the preparation of N-methyl-O-benzoylhydroxylamine hydrochloride 201 (Scheme 72) and the buffered biphasic reaction for N-tertbutyl-O-benzoylhydroxylamine hydrochloride 204 (Scheme 75) proved extremely robust procedures, allowing access to multi-gram quantities of both products. Satisfied we had a direct route for the preparation of our reagents we next turned our attention to refining our reaction conditions and exploring the scope of the possible transformation.

**3.3.0 Reaction Optimisation:**

Having found efficient routes to our desired reagents, general optimisation of conditions for the α-functionalisation of generic ketones using N-methyl-O-benzoylhydroxylamine 203 focused on three distinct variables, namely, the acid source, reaction temperature and reaction solvent.
3.3.1 Acid Source:

Our choice of acid source proved crucial in that it had to fulfil two requirements. Firstly, the reaction conditions had to be acidic enough to promote condensation of our reagent with a selected carbonyl compound, accelerate iminium ion formation and hydrolysis after rearrangement. The second selection criteria related to storage of N-methyl-O-benzoylhydroxylamine. There were some concerns that the N-methyl-O-benzoylhydroxylamine free base 203 could degrade to the corresponding hydroxamic acid 208, through either an inter- or intra-molecular rearrangement (Scheme 76). A method of storage, which would avoid this possible problem, was therefore required. Also, simple degenerative cleavage of the N-O bond to yield benzoic acid could not be ruled out.

![Scheme 76](image)

This examination was approached in a systematic manner using the reaction between cyclohexanone and 1eq. of 203 as a basis from which the effects of varying the acid source could be compared. These comparison reactions were all conducted in THF over 18hr and at room temperature with a reaction concentration of 0.5M (Scheme 77).

![Scheme 77](image)

By serendipity, the N-methyl-O-benzoylhydroxylamine hydrochloride salt initially prepared fulfilled both these requirements. The hydrochloride salt could be stored for several months without significant degradation and gave an excellent level of reactivity. It was pertinent however, to examine other N-methyl-O-benzoylhydroxylamine salts, which were formed in situ from stoichiometric amounts of benzoic acid, trifluoroacetic
acid and methansulfonic acid. The reduced acidity of these acids proved less effective for the transformation with benzoic acid giving no oxygenated product. Trifluoroacetic acid showed a trace amount of product visible by $^1$H NMR but could not be recovered while methansulfonic acid showed a small amount of oxygenated product 21%. Neither was as effective as the hydrochloride salt that gave the best non-optimized yield of 62%.

**3.3.2 Temperature:**

Our concerns over the thermal stability of our reagents arose from the studies conducted by Phanstiel et al. into the thermal decomposition of various N-(benzoyloxy)amines.\textsuperscript{130} It was shown that homolytic N-O bond cleavage of acylhydroxylamines generates both a benzoyloxy radical (PhCOO\textsuperscript{•}) and a primary aminyl radical (RHN\textsuperscript{•}). This degradation resulted in benzoic acid being formed as the major degradation product, via a hydrogen atom abstraction by the benzoyloxy radical. By stirring our N-methyl-O-benzoylhydroxylamine hydrochloride reagent 201 in THF at a concentration of 0.5M, at 30 °C, 50 °C and 70 °C over 18hr we were able to examine its thermal sensitivity. Exposure of 201 to 70 °C resulted in considerable degradation to a complex mixture as determined by $^1$H NMR. Negligible degradation was observed at room temperature. Conducting the experiment at 50 °C offered an acceptable compromise with reduced decomposition and the possibility of introducing a significant amount of energy to the system if required.

**3.3.3 Reaction Solvent:**

We next examined the reaction of N-methyl-O-benzoylhydroxylamine hydrochloride 201 and cyclohexanone (Scheme 77) in a range of solvents. This sequence of reactions were carried out at room temperature over 18hr and again with a reaction concentration of 0.5M. While similar yields were observed for tetrahydrofuran and ether, both were accompanied by-products,
needlessly complicating isolation and purification. Dimethyl sulfoxide was determined to be the optimal solvent with this polar, aprotic solvent serving as an excellent medium for the reaction allowing complete dissolution of the hydrochloride salt, a feature not observed with less polar solvents. Dimethyl sulfoxide also allowed for an extremely efficient reaction with no major by-products observed by $^1$H NMR. The highly polarised nature of dimethyl sulfoxide may also allow for some stabilisation of the iminium ion intermediate intrinsic to the transformation.

Based on the observations made it was concluded that hydrochloric acid was most successful. It proved effective in providing a sufficiently acidic reaction medium to promote the transformation, with the hydrochloric acid being provided through the use of the hydrochloride salts of our hydroxylamine reagent 201. Together with this, DMSO proved to be the most effective solvent in which to carry out the reaction. Although ether and THF gave respectable yields, neither provided a reaction as clean as that carried out in DMSO.

**3.4.0 Reaction with Cyclic Ketones:**

The general reaction procedure involved the addition of one equivalent of a carbonyl compound to a solution of the reagent in DMSO. After stirring the reaction for 18 hr at room temperature it was added to ethyl acetate and washed with water to remove the bulk of DMSO. The residual DMSO and any minor impurities were then removed by column chromatography. Paradoxically DMSO is both the sinner and saint of this process. Although its use as a solvent provides astonishingly clean, its removal is tedious and a major drawback. A method by which DMSO could be effectively removed during workup would greatly add to the overall procedure. Our primary reagent $N$-methyl-$O$-benzoylhydroxylamine hydrochloride 201 showed a good reactivity under optimized reaction conditions for a variety of cyclic ketones (Table 1), while $N$-tert-butyl-$O$-benzoylhydroxylamine hydrochloride 204 showed no reactivity for ketones. Indeed, reaction of $N$-tert-butyl-$O$-benzoylhydroxylamine hydrochloride 204 with a mixture of one eq. of both cyclohexanone and isovaleraldehyde in one pot gave exclusively the aldehyde-functionalized product 210 in 68% yield (Scheme 78).
A simple explanation for this lies in the added steric bulk of the N-tert-butyl group, which hinders the attacking nitrogen lone-pair preventing iminium ion formation. This result is interesting, in that it opened the possibility of a chemoselective process, whereby aldehydes could be functionalised over ketones, through the judicious choice of either N-methyl-\(\text{O-}\)benzoylhydroxylamine hydrochloride 201 or N-tert-butyl-\(\text{O-}\)benzoylhydroxylamine hydrochloride 204.

The product from the reaction was distinguished by the observation of a characteristic doublet of doublets splitting pattern for \(\text{H}_a\) (Fig. 20). This splitting pattern arises from the coupling observed between \(\text{H}_a\) and diastereotopic protons \(\text{H}_b\) and \(\text{H}_c\) (Fig. 20). In keeping with the Karplus relationship\(^{140}\) the magnitude of the coupling interactions is determined by the dihedral angle \(\alpha\) between \(\text{H}_a\) and diastereotopic protons \(\text{H}_b\) and \(\text{H}_c\). The coupling constant between two axial protons is normally \(10-14\text{Hz}\) \((\alpha = 180^\circ)\), whereas the magnitude of coupling between an axial and an equatorial proton is generally \(4\) to \(5\text{Hz}\) \((\alpha = 60^\circ)\).

The observed coupling constants of \(6.7\text{Hz}\) and \(10.5\text{Hz}\) for 209 (Table 1, Entry 1) are in keeping with this trend indicating the presence of the expected thermodynamically stable equatorially positioned conformer. Expanding the range of the procedure to
encompass both 5-membered and 7-membered cyclic ketones was also successful. Both cyclopentanone (Table 1, Entry 2) and cycloheptanone (Table 1, Entry 3) were functionalised in good yields of 73 and 79% for 211 and 212 respectively.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Ketone</th>
<th>Oxygenated Product</th>
<th>Reaction Temperature (°C)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Cyclopentanone" /></td>
<td><img src="image2" alt="Cyclopentanone with oxygen" /></td>
<td>r.t.</td>
<td>72%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Cycloheptanone" /></td>
<td><img src="image4" alt="Cycloheptanone with oxygen" /></td>
<td>r.t.</td>
<td>73%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="4-tButyl cyclohexanone" /></td>
<td><img src="image6" alt="4-tButyl cyclohexanone with oxygen" /></td>
<td>r.t.</td>
<td>79%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image5" alt="4-tButyl cyclohexanone" /></td>
<td><img src="image6" alt="4-tButyl cyclohexanone with oxygen" /></td>
<td>r.t.</td>
<td>75%</td>
</tr>
</tbody>
</table>

*All reactions were preformed for 18hr at 0.5M concentration in DMSO with 1eq. 201 and 1eq. starting ketone*

Incorporation of the 4-tert-butyl cyclohexanone (Table 1, Entry 4) resulted in the cis-isomer 213 being isolated in 75% yield, suggesting that the reaction favours the thermodynamically more favourable product.

### 3.5.0 Reaction with Heterocyclic Ketones:

With a firm foothold established for the functionalisation of ketones we turned our attention to examining the functional group tolerance of our process. This aspect was vital to establish with regard to the practicality and applicability of our methodology. The selection of functional groups examined was driven by one chief concern. Unlike previous applications of this rearrangement by House, Coates and Lobo who employed
basic reaction conditions, the defining characteristic of our methodology is the use of a strongly acidic reaction medium. Given that the reaction proceeds at an acidic pH it is entirely plausible that hydrolysis of sensitive functional groups would occur with our methodology and therefore, these needed to be investigated. The first substrate chosen was tetrahydropyran-4-one as it may be susceptible to elimination under the acidic reaction conditions. Much to our delight, the corresponding functionalised tetrahydropyran-4-one 214 (Table 2, Entry 1) was obtained in 74% yield with no evidence of any elimination by-product. Elaboration of this substrate to the thio analogue also gave a positive result with the functionalised product 215 being recovered in 72% yield (Table 2, Entry 2). The success of the thio ether oxidation is especially encouraging given the inherent problems with oxidative processes in the presence of these easily oxidised functionalities. (Table 2, Entry 3) offers additional information regarding the compatibility of functional groups. As with the previous examples no elimination was observed, as well as the reaction being tolerant to both amide and hydrolytically sensitive ester functionalities. Interestingly, the functionalised product was observed as a rotomers (Appendix Fig. A & B). Restricted rotation about the amide bond caused the chemical shift of three neighbouring protons to separate in the $^1$H NMR. Each split chemical shift gave an integration of half a proton indicating there is a one to one mixture of each rotomer 218 and 219 at equilibrium (Fig. 21).

Despite this minor anomaly the functionalised product 216 was still recovered in a good yield of 71% (Table 2, Entry 3). Further expansion to include the sulphonamide functional group was also successful with N-tosylamide product 217 being isolated in 75% (Table 2, entry 4).
Table 2. Reaction of 201 with Heterocyclic Ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Ketone</th>
<th>Oxygenated Product</th>
<th>Reaction Temperature (°C)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>r.t.</td>
<td>74%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>r.t.</td>
<td>72%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>r.t.</td>
<td>71%</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>r.t.</td>
<td>75%</td>
</tr>
</tbody>
</table>

All reactions were performed for 18 hr at 0.5M concentration in DMSO with 1 eq. 201 and 1 eq. starting ketone.

3.6.0 Reactions with Acyclic Ketones:

Our success with cyclic ketones led us to explore the applicability of 201 to functionalise acyclic ketones. Investigations focused on two commercially available generic acyclic ketones 4-(4-hydroxyphenyl) butan-2-one 220 and heptan-2-one 221. 4-(4-Hydroxyphenyl) butan-2-one was also converted to 4-(4-methoxyphenyl) butan-2-one 222 to provide an additional substrate. This was achieved by treating 4-(4-hydroxyphenyl) butan-2-one 220 with one eq. of NaH and Mel in THF under reflux for 12 hr. to give 223 in 91% yield (Scheme 79).
Preliminary investigations indicated a need to increase the reaction temperature to 50 °C, in order to achieve a reasonable rate of reaction. This is not surprising given the more hindered nature of the acyclic carbonyl compounds, which required more energy for initial iminium ion formation. The non-symmetrical ketones selected could possibly have given rise to two possible products resulting from functionalisation at either the primary or secondary centre. The selectivity between these centres is dependent on the stability of the corresponding enamine. Oxidation at the secondary centre could, however, be expected with the more thermodynamically stable enamine dictating the regiochemical outcome of the reaction. With each of the substrates used within this transformation (Table 3) exclusive reaction was observed at the secondary centre with no indication of functionalisation at the primary centre being apparent by examination of the \(^1\)H NMR of the crude reaction mixture.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Ketone</th>
<th>Oxygenated Product</th>
<th>Reaction Temperature (°C)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{220})</td>
<td>(\text{224})</td>
<td>50</td>
<td>83%</td>
</tr>
<tr>
<td>2</td>
<td>(\text{226})</td>
<td>(\text{225})</td>
<td>50</td>
<td>83%</td>
</tr>
<tr>
<td>3</td>
<td>(\text{OBz})</td>
<td>(\text{OBz})</td>
<td>50</td>
<td>81%</td>
</tr>
</tbody>
</table>

*All reactions were performed for 18hr at 0.5M concentration in DMSO with 1 eq \(\text{201}\) and 1 eq starting ketone*
Each of the products were isolated analytically pure in an excellent 81-83% yield. The progression of the reaction in the presence of both, a free phenol (Table 3, Entry 1) and methoxy (Table 3, Entry 2) functionality further adds to the functional group tolerance of the transformation. The selectivity for secondary over primary adds an important regiochemical aspect to this transformation.

### 3.7.0 Ketals as Substrates:

An alternative approach to the synthesis of α-hydroxy ketones involves the one step formation of α-hydroxyketals 228 from the corresponding carbonyl via the hydroxylation of enolates (Scheme 80). This strategy largely involves the use of hypervalent iodine reagents such as iodosobenzene, (diacetoxy)iodobenzene, and iodosylbenzoic acid. These reactions proceed via an intermediate epoxide 227, and bear mechanistic similarity to the traditional method of treating preformed α-halo ketones with alkoxides (Scheme 80).

![Scheme 80](image)

The utilization of elemental iodine as a reagent for this reaction has been shown to be a reasonably effective alternative. One advantage of such a process would be the prevention of iodobenzene formation as a by-product, which can be difficult to remove from a non-crystalline product without resorting to column chromatography. With this transformation in mind we were intrigued to discover if our methodology could be applied to protected carbonyl compounds, thereby allowing for the introduction of an orthogonally...
protected 1,2-system. By utilizing the opposing deprotection procedures needed for these groups it would therefore be possible to differentiate one position in favour of the other. The protection and deprotection of acetals under acidic conditions complements the acidic conditions of our transformation in that both progress through an oxinium ion intermediate 229 (Scheme 81).

![Scheme 81](image)

While attack on 229 with methanol allows for reversion to the protected carbonyl compound, attack by \(N\)-methyl-\(O\)-benzoylhydroxylamine hydrochloride would facilitate iminium ion formation 194 (Scheme 81). The reaction would then proceed as normal to give the functionalized imine 194 at which point reversion to the acetal 230 could be achieved under the acidic conditions in the presence of methanol (Scheme 82).

![Scheme 82](image)

For simplicity, it was decided to use cyclohexanone dimethyl ketal and 1,1-dimethoxyheptane as test substrates as they were both commercially available. As with the previous oxidations, the investigation began with the comparison of which hydroxyacylation reagent was more effective. Our selected protected carbonyl compounds were reacted in turn with 1 eq. of both reagents 201 and 204 for 24 and 48 hours at room temperature and 50 °C in methanol (Scheme 83). The results for the \(\alpha\)-oxygenation of cyclohexanone dimethyl ketal with both \(N\)-tert-butyl-\(O\)-benzoyl hydroxylamine hydrochloride 204 and \(N\)-methyl-\(O\)-benzoyl hydroxylamine
hydrochloride 201 were as expected with the sterically encumbered \( N\text{-}tert\text{-}butyl\text{-}O\text{-}benzoyl \) hydroxylamine hydrochloride showing no reaction.

![Scheme 83](image)

In comparison to the \( N\text{-}tert\text{-}butyl\text{-}O\text{-}benzoyl \) hydroxylamine hydrochloride reactions, functionalisation using the \( N\text{-}methyl\text{-}O\text{-}benzoyl \) hydroxylamine hydrochloride 201 showed a moderately promising result, in which a yield of 27% was observed for 2,2-dimethoxycyclohexyl benzoate 231 when conducted at room temperature. Elevating the reaction temperature to 50 °C showed only a negligible increase in yield to 30%.

A comparable yield of 24% for 232 was recovered for the reaction of 1,1-dimethoxyheptane and \( N\text{-}tert\text{-}butyl\text{-}O\text{-}benzoyl \) hydroxylamine hydrochloride 204 under identical reaction conditions (Scheme 84).

![Scheme 84](image)

Although isolated examples, these two transformations provide a good indication that this methodology may be extended to include acetals and ketals and certainly warrants further investigation.
3.8.0 Conclusion:

In conclusion, a novel approach to the \( \alpha \)-functionalisation of carbonyl compounds has been developed. Through the utilization of the hydrochloride salts of \( N \)-substituted \( O \)-benzoylhydroxylamines, a novel reagent has been developed to facilitate this rearrangement, incorporating a distinctive [3,3]-sigmatropic process. Application of this methodology has allowed for the \( \alpha \)-functionalisation of cyclic and heterocyclic ketones in good overall yields. This approach was then expanded to the inclusion of acyclic ketones along with ketals, although with moderate success for the latter. Consideration of the general structure of 3 and the proposed intermediate 4 suggested that alterations could be made to the structure of our reagent for the introduction of alternative functional groups.
Chapter 4: α-Oxycarbonates and Carbamates
4.1.0 Introduction:
The introduction of an α-hydroxy group is of significant importance in synthetic chemistry. It allows access to numerous 1,2 functionalities, which are important in both the pharmaceutical industry and natural product synthesis. The limited number of oxidants currently available for the α-oxidation of carbonyl compounds presents very little scope for the direct introduction of α-hydroxy moieties with variable protecting groups, or simply the introduction of different molecular motifs. Based on the success of our oxy-benzoylation reagent we were interested to discover if it would be possible to incorporate other functional groups into our reagent, thereby broadening the possible family of reagents. By altering our generic reagent 3 we saw an opportunity that would allow us to form the same C-O bond but through the transfer of alternative functional groups. Referring back to the generic reagent scaffold 3, we first examined the possibility of introducing variation at position Z. This modification was achieved by reacting N-Boc-N-methylhydroxylamine with allyl chloroformate and N,N-dimethylcarbamoyl chloride (Scheme 85).

![Scheme 85](image)

This allowed the incorporation of an N and O atom in the Z position. The introduction of a carbonate or carbamate group in itself is not overly complicated with several strategies providing reasonable access to these groups. To date however, the introduction of a carbonate or carbamate group alpha to a carbonyl compound in a single step has not been reported.

Contemporary strategies to access these functional groups generally depend on the reaction between a preformed α-hydroxy carbonyl compound and a suitable electrophile. Schank et al. has reported interesting, if somewhat limited, success with
the use of dimethyl peroxydicarbonate (DPDC) for the acyloxylation of enol ethers based on the allylic oxidation of alkenes.\textsuperscript{144} Inspiration for this was taken from the Kharasch-Sosnovsky reaction in which replacement of an allylic hydrogen by acyloxy groups occurs with \textit{tert}-butyl peroxyxcarbonates \textsuperscript{236} in the presence of Cu\textsuperscript{I} salts as electron transfer catalysts (Scheme 86).\textsuperscript{145}

\[ \text{Scheme 86} \]

Attempts by Schank to mimic this reaction in the oxyacylation of 1-methoxycyclohex-1-ene with \textit{tert}-butyl peracetate and \textit{tert}-butyl perbenzoate in turn, incorporating CuBr, were unsuccessful with the corresponding carboxylic acid being the main product isolated. The reaction was further modified to include DPDC \textsuperscript{239} because elimination of methyl monocarbonate instead of carboxylic acid would lead subsequently to carbon dioxide and methanol adding a further thermodynamic favourability; this modification gave a yield of 91\% for \textsuperscript{240} where R\textsuperscript{1} was Me (Scheme 89).

\[ \text{Scheme 89} \]

Acid hydrolysis of \textsuperscript{240} gave the desired ketone product in 72\% yield. The higher reactivity of \textsuperscript{239} compared to that of \textit{tert}-butyl peracetate or \textit{tert}-butyl perbenzoate could be attributed to the particularly low O-O bond dissociation energy (30kcal/mol). In view of the potential utility of peroxyxcarboxylates for oxidative processes, it does seem remarkable that the first synthetically useful asymmetric variant was only reported in the mid 1990’s, independently by the groups of Pfaltz,\textsuperscript{146} Andrus,\textsuperscript{147} and Katsuki.\textsuperscript{148} Pfaltz and Andrus and their co-workers both employed the same series of
enantiomerically pure $C_2$-symmetric bis(oxazoline) ligand 241 groups as the ligand in the presence of Cu triflate with cyclic olefinic substrates (Scheme 90).

The enantio control was generally good, although yields were somewhat more variable. In all cases the facial preference of the newly formed C-O bond was the same, giving an S-configuration at the newly formed allylic stereocentre. Currently, the use of peresters for allylic oxidation has not found widespread acceptance, primarily because of the infancy of this asymmetric reaction. In view of the potential utility and versatility of this transformation within organic synthesis, it seems likely that further applications will soon appear. Central to its progression will most likely be the development of a generic catalytic system. In addition, some general problems need addressing, such as the requirement for high alkene concentrations, the long reaction times and apparent substrate restrictions before the potential of this reaction can be truly realized. In addition the use of peroxycarboxylates is plagued by poor substrate compatibility and inconsistent yields.

The potential complexity of introducing a carbonate group alpha to a ketone is exemplified by Dixon et al. in the preparation of an analogue of orbicuside A. Diosgenin 242 was used as the starting material, since the D/E/F ring system of this steroid can be transformed into a 16-dehydropregnane derivative that can serve as a precursor to a 14β-hydroxy cardenolide. Steroid 242 was transformed into the 3-oxo-5,6-dihydro-5α-analogue 243 by hydrogenation of the B-ring double bond in 242 using hydrogen
and a Pd/C catalyst. This was then followed by oxidation of the hydroxyl group to the corresponding ketone using H₂CrO₄ (Scheme 91).

The oxygen functionality was then introduced at C-2 by formation of the TMS enol ether. Huffman and Balke¹⁵¹ observed that, under thermodynamic control, the 2,3-enol ether was formed from a 3-keto-5α-steroid, whereas kinetically controlled conditions gave the 3,4-enol ether. By using TMSI in the presence of hexamethyldisilazane, enol ether 243 was obtained in a good yield and none of the 3,4-isomer was detected (Scheme 91). Subsequent epoxidation of the double bond was carried out with dimethyldioxirane in an excellent yield of 96% (Scheme 92).

Under the experimental conditions used for the epoxidation of 243, an in situ rearrangement of the epoxide occurred and only the required 2α-hydroxy ketone was isolated (Scheme 92). Subsequent reaction of the α-hydroxy ketone with allylchloroformate yielded the protected α-hydroxy group 244 in 92% (Scheme 92).

Investigation into the structural activity relationship (SAR) of α-carbonate ketones in second generation Taxoids has recently been reported and again exemplifies the potential difficulties that can be encountered.¹⁵² In this work, two standard methods were employed in order to introduce derivatives in the C-10 position. Both of these
methods required initial protection at the C-7 position of 10-deacetylbaccatin III (DAB) 245 with a triethylsilyl (TES) group (Scheme 93).

Interestingly, in view of NMR studies carried out by Chen the C-13 hydroxyl group was deemed sterically congested due to its location inside the skeletal concavity of 245 and not protected.\textsuperscript{153} Subsequent modification at the C-10 position with acyl, alkoxy carbonyl, N,N-dialkyl carbamoyl, and alkyl halides in turn using LiHMDS as the base proceeded in good yields. The C-10 modification with \textit{N}-alkyl and \textit{N}-allyl isocyanates under the same conditions resulted in the formation of a mixture of C-10 (minor) and C-13 (major) carbamoyl-DABs. Previous attempts at the introduction of a carbamoyl group at C-7 by Chen \textit{et al.} through the reaction with isocyanates was also reported to have similar difficulties with low yields and mixture of products.\textsuperscript{154} However, this provided a direction in using cuprous chloride as the activator based on a general procedure for the reactions of isocyanates and alcohols reported by Duggan and Imagire.\textsuperscript{155}
This turned out to be a judicious choice, giving the desired 10-carbamoyl-DABs 247 (Scheme 94). However, this procedure yields a side product, an allophanate 248, arising from the addition of a second molecule of isocyanate to the carbamate nitrogen. In order to minimize this side reaction, a slow addition of isocyanate to 7-TEs-DAB was employed in the presence of CuCl (1.0 eq) in dry dichloromethane.

Although the elaboration of \( \alpha \)-hydroxy carbonyl compounds is entirely possible, the selected examples shown above highlight the potential complication and synthetic manipulations that are encountered in their introduction. In each case, the \( \alpha \)-hydroxy group was preformed, which can be a non-trivial procedure, and competing functional groups must also be considered. To this end, a method by which a \( \alpha \)-hydroxy group that could be delivered pre-functionalized would offer considerable advantages.

### 4.2.0 Reagent Preparation:

#### 4.2.1 \( N \)-methyl-\( O \)-(\( N \),\( N \)-dimethylcarbamoyl) hydroxylamine hydrochloride:

Access to \( N \)-methyl-\( O \)-(\( N \),\( N \)-dimethylcarbamoyl) hydroxylamine hydrochloride 250 was once again reasonably straightforward starting from the Boc protected \( N \)-methyl hydroxylamine 198. Condensation of 198 with \( N \),\( N \)-dimethylcarbamoyl chloride under basic conditions gave the protected \( N \)-Boc-\( N \)-methyl-\( O \)-(\( N \),\( N \)-dimethylcarbamoyl) hydroxylamine 249 in 87% yield after purification by short-path distillation (Scheme 95).

\[
\begin{align*}
\text{N-OH} & \quad \text{Cl-N} \\
\text{Boc} & \quad \text{CH}_2\text{Cl}_2, 0 \ ^\circ\text{C} - \text{r.t.}, 12\text{hr} \\
198 & \quad \text{Et}_3\text{N}, \text{DMAP} \\
& \quad 87\% \\
\text{N-O} & \quad \text{N} \\
\text{Boc} & \quad 249
\end{align*}
\]

Simultaneous deprotection and in situ salt formation proved slightly problematic with the final hydrochloride salt being hydroscopic and difficult to crystallize. Therefore, it was necessary to conduct the deprotection under stringent anhydrous conditions. Deprotection was achieved as with the previous \( N \)-methyl-\( O \)-benzoylhydroxylamine
hydrochloride 201, in which case HCl gas was generated from dropping concentrated sulfuric acid onto ammonium chloride. To ensure the gas generated was dry it was first passed through concentrated sulfuric acid before being bubbled through the reaction mixture. The dry HCl gas generated was then bubbled through a solution of 249 in dry Et$_2$O, in a system pre-flushed with N$_2$, to give the deprotected HCl salt 250 in an excellent yield of 96% (Scheme 96).

![Scheme 96](image)

Reaction times greater then 45mins led to significant decomposition of the salt and so the reaction was closely followed by TLC. Attempts to use 4M HCl in dixoane as an alternative to this procedure gave similar results, however, additional complications with the removal of dioxane made this an unreliable procedure and were not followed up.

4.2.2 N-methyl-O-allylcarbonate hydroxylamine hydrochloride:

A similar synthetic pathway was again employed in the preparation of N-methyl-O-allylcarbonate hydroxylamine hydrochloride 251. Condensation of Boc protected N-methylhydroxylamine 198 with allyl chloroformate gave the corresponding N-protected allylcarbonate 252 in an excellent yield of 82% (Scheme 97).

![Scheme 97](image)

Unlike previous procedures, DMAP was excluded from the reaction as its inclusion led to decomposition of allyl chloroformate starting material. This was observed as
excessive effervescence of the reaction solution, possibly due to the production of CO$_2$ from the Michael addition of DMAP to the allyl group, along with the recovery of predominately Boc protected hydroxylamine starting material. The careful addition of triethylamine was also necessary and was carried out dropwise over several minutes. Deprotection and *in situ* salt formation were carried out under the same stringent anhydrous conditions as previously described (Scheme 98).

Unfortunately the hydroscopic nature of the compound meant that even under strict anhydrous reaction conditions it was necessary to repeatedly azeotrope the product with toluene in order to obtain a crystalline material. Despite this complication *N*-methyl-*$O$-allylcarbamate hydroxylamine hydrochloride 253 was obtained in an excellent yield of 94%.

**4.3.0 Reaction Optimisation for *N*-methyl-*O*-(*N*,*N*-dimethylcarbamoyl) hydroxylamine hydrochloride:**

This examination was approached in a systematic manner using the reaction between cyclohexanone and 1.5eq of 250 as a basis from which the effects of varying the acid source could be compared. These comparison reactions were all conducted in THF over 18 hr and at 50 °C with a reaction concentration of 0.5M.

**4.3.1 Acid Source:**

<table>
<thead>
<tr>
<th>ACID</th>
<th>YIELD %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoic Acid</td>
<td>0</td>
</tr>
<tr>
<td>Trifluoroacetic Acid</td>
<td>0</td>
</tr>
<tr>
<td>Methanesulfonic Acid</td>
<td>28</td>
</tr>
<tr>
<td>Hydrochloric Acid</td>
<td>45</td>
</tr>
</tbody>
</table>

As with our previous investigations the choice of acid source proved crucial in that strongly acidic reaction conditions were intrinsic to the success of the reaction. Again the acid source had a duel role, with firstly acidifying the reaction conditions enough to promote condensation of our reagent with a selected carbonyl compound, accelerate iminium ion formation and
hydrolysis after rearrangement. The second selection criteria again related to storage of the reagents. The hydrochloride salt once again proved to be the most effective acid source. The \(N\)-methyl-\(O\)-(\(N\)-,\(N\)-dimethylcarbamoyl) hydroxylamine hydrochloride 250 proved to be slightly more sensitive then the previous \(N\)-methyl-\(O\)-benzoylhydroxylamine salt 201. However, the hydrochloride salt could be stored for several months at < 0 °C without significant degradation and gave an excellent level of reactivity. It was pertinent however, to examine other acid sources that were, formed in situ from stoichiometric amounts of benzoic acid, methanesulfonic acid and trifluoroacetic acid. The reduced acidity of these acids proved ineffective for the transformation with benzoic acid giving no oxygenated product. Trifluoroacetic acid also showed no amount of product visible by \(^1\)H NMR while methanesulfonic acid showed a small amount of oxygenated product 28% under the reaction conditions examined. Neither was as effective as the hydrochloride salt that gave the best non-optimized yield of 45%.

4.3.2 Reaction Solvent:

By analysing the reaction of 250 and with cyclohexanone in a range of solvents, tetrahydrofuran was determined to be optimal solvent. This aprotic, electron donating solvent served as an excellent medium for the reaction allowing complete dissolution of the hydrochloride salt at 50 °C. Although THF gave the best yield 45 %, unfortunately the reaction was not as efficient as that previously observed for the oxy-benzoylation reactions in DMSO. While similar yields were observed for ether as the reaction medium and no discernable products could be detected with either dichloromethane or chloroform.

<table>
<thead>
<tr>
<th>SOLVENT</th>
<th>YIELD %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ether</td>
<td>40</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>45</td>
</tr>
<tr>
<td>Chloroform</td>
<td>Trace</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>Trace</td>
</tr>
<tr>
<td>Dimethyl Sulfoxide</td>
<td>0</td>
</tr>
</tbody>
</table>

Early in our investigations it was noted that in general, 1.5 eq. of 250 was required to give a reasonable yield, along with this, an elevated reaction temperature of 50 °C was necessary to give a reasonable rate of reaction. Together with these findings, conducting the reaction in THF gave the best results. These optimised reaction conditions were then
also applied to the reactions of \(N\)-methyl-\(O\)-allylcarbonate hydroxylamine hydrochloride 253.

### 4.4.0 Introduction of Carbamates:

\(N\)-methyl-\(O\)-(\(N\),\(N\)-dimethylcarbamoyl) hydroxylamine hydrochloride 250 was successfully employed in the elaboration of our \(\alpha\)-oxybenzoylation methodology for the one step introduction of a carbamate group. In general, a lower activity was observed for \(N\)-methyl-\(O\)-(\(N\),\(N\)-dimethylcarbamoyl) hydroxylamine hydrochloride 250 when compared to \(N\)-methyl-\(O\)-benzoylhydroxylamine hydrochloride 201. Although this lower reactivity could not be directly attributed to any structural feature of the reagent, the more sensitive nature of this reagent in general may be a likely cause. However, increasing the reaction temperature to 50 °C along with using 1.5eq. of reagent, while maintaining a reaction concentration of 0.5M with respect to 250, gave an acceptable level of reactivity.

As with the previous observations, the reaction between cyclohexanone (Table 4, Entry 1) and cycloheptanone (Table 4, Entry 5) with \(N\)-methyl-\(O\)-(\(N\),\(N\)-dimethylcarbamoyl) hydroxylamine hydrochloride 250 proceeded smoothly with a good yield of 60 % for 254 and 55 % for 258. The functionalisation of cyclic ketones was heralded by the appearance of the now characteristic doublet of doublets of chemical shift around 4-5 ppm. Analysis of the coupling constants again indicated the product adopted an equatorially substituted conformation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Ketone</th>
<th>Oxygenated Product</th>
<th>Reaction Temperature (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{Cyclic Ketone})</td>
<td>(\text{Oxygenated Product})</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>254</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Introduction of \(\alpha\)-Carbamate Group*
Interestingly, the reaction between \(250\) and 1,4-cyclohexanone dimethyl ketal (Table 4, entry 4) showed a tolerance for ketal protecting groups with a yield of 57% for \(257\), which is a particular point of note given the strongly acidic reaction conditions used in this transformation. This observation is significant in that it opens the possibility of selecting one carbonyl group over another, providing that these groups can be selectively protected.

The regiospecific functionalisation of secondary over primary centres was again observed for \(225\) and \(226\) (Table 4, Entries 2 & 3) indicating a preference for the more stable enamine. Having successfully developed a method for the direct installation of a carbamate group we turned our attention to the carbonate reagent \(253\).
4.5.0 Introduction of Carbonates:

The introduction of carbonate groups in the α-position proceeded in a similar fashion to the introduction of carbamates. \( N \)-methyl-\( O \)-allylcarbonatehydroxylamine hydrochloride 253 was reacted under identical conditions to those developed for the carbonate reagent 250 (1.5eq reagent. 50 °C. THF. 18hr).

### Table 5. Introduction of α-Carbonate Group

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Ketone</th>
<th>Oxygenated Product</th>
<th>Reaction Temperature (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O</td>
<td>O</td>
<td>50</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>259</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>O</td>
<td>O</td>
<td>50</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td></td>
<td>260</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>O</td>
<td>O</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>261</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>O</td>
<td>O</td>
<td>50</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>262</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>O</td>
<td>O</td>
<td>50</td>
<td>55</td>
</tr>
</tbody>
</table>

*All reaction performed for 18 hr at 0.5M concentration in THF with 1.5 eq. 253 and 1 eq. starting ketone

The reaction between cyclohexanone (Table 5, Entry 1) and \( N \)-methyl-\( O \)-allylcarbonatehydroxylamine hydrochloride 253 proceeded without complication with a good yield of 62% for 259. The use of \( N \)-methyl-\( O \)-allylcarbonatehydroxylamine
hydrochloride 253 again showed a remarkable tolerance for the presence of the acid labile ketal-protecting group (Table 5, Entry 4), with the introduction of the carbonate functionality 262. Despite the lower yield this observation is still significant in that it allows for the introduction of an alternative protected hydroxyl group different from those described previously. The proclivity for secondary over primary centres was again observed with products 260 and 261 (Table 5, Entries 2 & 3) being isolated in a yield of 53 and 50% respectively.

4.6.0 Conclusion:

From the results obtained here the elaboration of our generic reagent to facilitate the introduction of the carbamate and carbonate group was effective. Despite the lower yields observed, the manipulation of Z to incorporate oxygen and nitrogen atoms is shown to further expand the scope of the transformation detailed herein. This modification represents a unique one-step route for the instillation of a carbamate or carbonate group α to a carbonyl functionality. Based on the success of this modification our attention turned to the further manipulation of position X in our generic reagent. It is the results from this modification which are described in the following chapter.
Chapter 5: $\alpha$-Oxytosylation
5.1.0 Introduction:

Within this chapter, we sought to expand our family of reagents to encompass N-methyl-O-tosyl hydroxylamines 264, which we thought would mark a significant step forward in the evolution of our methodology. α-Oxysulfonyl carbonyl compounds, like α-halo ketones are relatively common in synthetic chemistry, since their main utility has been as reactive intermediates. A-Oxysulfonyl carbonyl compounds, like α-halo ketones are relatively common in synthetic chemistry, since their main utility has been as reactive intermediates.156 We therefore thought it interesting to see if this useful functional group could be introduced using our methodology. The introduction of this useful group also coincided with the further elaboration of our generic reagent structure, in that it allowed us to vary position X of 3 by the introduction of a sulfur atom.

Prior to our work N-methyl-O-nosylhydroxylamines 265 have been prepared and their reactions with various carbonyl compounds examined.157 This work is briefly highlighted in the following section as it represents a noteworthy investigation into the chemistry of O-sulfonylhydroxylamines with carbonyl compounds under acidic reaction conditions. N-methyl-O-tosylhydroxylamines 264 have also been reported and used as electrophilic aminating reagents,158 but have to date, not been reacted directly with carbonyl compounds.

5.2.0 N-Methyl-O-nosylhydroxylamines:

Previous to our work Hoffman et al. investigated the reactions of N-methyl-O-nosylhydroxylamines 265 with various carbonyl compounds and reported the direct preparation of N-substituted lactams 267 from cycloalkanones159 (Scheme 99). Carbon-to-nitrogen rearrangement led to the lactam products, reminiscent of the β-lactam synthesis of Wasserman160 without the need for stable carbinolamine intermediates, and analogous to Barton’s161 procedure without the need for preparation of nitrone intermediates. The mechanism of the reaction presumably involves the acid catalyzed nucleophilic addition of 265 to the carbonyl group to give a carbinolamine type intermediate 266.
This intermediate then rearranges to give the ring-expanded amide by carbon to nitrogen migration of a ring bond, a basic work-up then gives the amide product.

The required oxonium ion intermediate can also be generated from protonation of either enol ethers, or by acid catalyzed elimination of acetals. The latter showed an interesting observation in the appearance of the imidate salt arising from the nitrogen atoms lone pair of electrons prompting rearrangement instead of oxygen. The lactam was later obtained by refluxing the product mixture with NaI in acetone overnight to give 267 in 74% yield (Scheme 100).

Further to this, a series of aromatic and aliphatic aldehydes were shown to react with \( N \)-methyl-\( O \)-nosylhydroxylamine to give products from both carbon migration and hydride migration to nitrogen (Scheme 101). A series of substituted benzaldehydes were reacted with 265 to give a mixture of \( N \)-methyl-\( N \)-arylformamide (carbon migration) and \( N \)-methylbenzamide (hydride migration) with a total yield of 96% and a ratio of 23:1 for 271 and 272, where a methoxy group was present on the aromatic ring.
Hoffman observed that electron donating groups on the aromatic ring increased the rate of reaction. In general, alkyl-group migration was not favored over hydride migration to the extent seen for aromatic groups. Within the aliphatic series, however, migratory aptitudes were seen to decrease in the order tert-butyl > cyclohexyl > isopropyl > ethyl. These observations were used to elucidate the mechanistic process involved in the reaction between aldehydes and N-(nosyloxy)amines. It was reported that the overall process involved two steps (Scheme 102). The first was nucleophilic addition of 265 to the aldehyde to give a tetrahedral intermediate 266. The second was rearrangement of the intermediate to give the observed products. The fact that methoxy-substituted aldehyde derivatives reacted appreciably faster than bromo compounds strongly suggested that the carbon to nitrogen rearrangement of the tetrahedral intermediate was the rate-determining step.

If nucleophilic addition were rate determining, an electron-withdrawing bromo substituent should render the carbonyl group more electrophilic and thus increase the rate of addition of 265 relative to an electron-donating methoxy substituent. The stability of the migratory intermediate therefore determined the product ratio.
5.3.0 Contemporary Synthesis:

Given the unique nature by which we proposed the introduction of this useful α-oxysulfonyl group it is prudent to highlight the predominant methods by which they are synthesised. One of the more common routes for the synthesis of α-oxysulfonyl ketones involves the condensation of α-hydroxy ketones with a sulfonyl chloride in the presence of base.\(^{165}\) This method, although successful, can be lengthy, as Creary reported in his investigation into α-keto cations (Scheme 103).\(^{166}\) Mesylate 275 was prepared by the treatment of camphor with 273, an acyl anion equivalent developed by Zimmer,\(^{167}\) to give the protected hydroxy ketone 274.

![Scheme 103](image)

Deprotection of the trimethylsilyl group could be accomplished under either acidic or basic conditions. Conversion to the mesylate then involved treatment with \(\text{CH}_3\text{SOCl}\) and triethylamine, which upon oxidation with \(m\)-chloroperoxybenzoic acid gave the mesylate 275. In general however, two distinct strategies are widely utilized for the synthesis of α-oxysulfonyl ketones, firstly, treatment of ketones and enol ethers with hypervalent iodine reagents and secondly, oxidation of enol esters, enol ethers, and enamines with arylsulfonyl peroxides.

5.3.1 Hypervalent Iodine Reagents:

Most known tricoordinate iodine compounds of general structure \(\text{Ar} \equiv \text{L}_1 \equiv \text{L}_2\) possess identical heteroatom ligands 276 and 277, (i.e., \(\text{L}_1 = \text{L}_2 = \text{RCO}_2, \text{Cl}, \text{F}\)). Later Neiland and Karele reported the synthesis of non-symmetrical iodonane, \([\text{hydroxy(tosyloxy)iodo}]\) benzenes 279-281 (Fig. 24).
The preparation of these reagents is reasonably direct, adding to their popularity and applicability. [Hydroxy(tosyloxy)iodo] benzene (HTIB) 279 can be prepared from the treatment of (diacetoxyiodo)benzene with p-toluenesulfonic acid monohydrate in acetonitrile.168 [Hydroxy(mesyloxy)iodo] benzene169 (HMIB) 280 and the chiral analog [hydroxy[((+)-10-camphorsulfonyl)-oxy]iodo] benzene170 281 can both be prepared under similar procedures using the appropriate sulfonic acid.

[Hydroxy(tosyloxy)iodo] benzene 279 has proven to be a useful reagent for the direct conversion of ketones to α-tosyloxy ketones 282 in non-hydrolytic solvents (Scheme 104).171,172

[Hydroxy(mesyloxy)iodo] benzene 280 has been employed in the analogous synthesis of α-mesyloxyketones 283 (Scheme 105).173
These transformations, like α-halogenation of ketones, require ketones with an enolizable proton. An acidic α-proton therefore opens the use of hypervalent reagents to numerous substrates especially β-diketones\textsuperscript{171} and β-ketoesters.\textsuperscript{172} α-Mesyloxy β-dicarbonyl compounds and may also be prepared from β-diketones and β-ketoesters with iodobenzene and methanesulfonic acid in chloroform, employing \textit{in situ} generation of HMIB.\textsuperscript{174}

Although successful the oxysulfonylation of non-symmetrical ketones with HTIB \textsuperscript{279} and HMIB \textsuperscript{280} proceeds with little regioselectivity. 2-Butanone reacts with HTIB \textsuperscript{279} in refluxing acetonitrile to give a 1.57:1.00 mixture of 3-tosyloxy and 1-tosyloxy-2-butanonones. The direct functionalisation of ketones with [hydroxy\textit{[(+)-10-camphorsulfonyl]-oxy]iodo} benzene \textsuperscript{281} however, exhibits an interesting feature in that it's steric bulk exerts an influence over the regiochemistry of the product.\textsuperscript{175} The oxytosylation and oxymesylation of 2-butanone with HTIB and HMIB occurs with low selectivity for C-1, whereas the oxycamphorsulfonylation of 2-butanone with \textsuperscript{281} proceeds preferentially at C-1 to give a 2.3:1.0 mixture in favour of the 3-camphorsulfonates \textsuperscript{284} (Scheme 106).

\centerline{Scheme 106}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme106.png}
\end{figure}

Silyl enol ethers are readily transformed into α-oxysulfonyl ketones with HTIB and HMIB and have been demonstrated to impart a high level of regiochemical control. The reaction is general for any carbonyl compound from which the trimethylsilyl ether can be obtained.\textsuperscript{176} 2-Methyl-6-tosyloxycyclohexanone \textsuperscript{287} can be prepared regioselectively from 1-trimethylsilyloxy-6-methylycyclohexanone \textsuperscript{286} with HTIB in dichloromethane (Scheme 107).
The silyl enol ether approach also permits the preparation of α-oxysulfonyl ketones with acid sensitive or oxidizable ring systems. For example, the (oxysulfonyl)-methyl-2-furyl ketones 289 have been obtained in high yields of >85% from the appropriate silyl enol ether 288 with either HTIB or HMIB (Scheme 108).176

5.3.2 Arylsulfonyl peroxides:
Enol acetates, in the presence of methanol, react with arylsulfonyl peroxides to give α-aryloxysulfonyl ketones in high yield.177 Enol acetates are most commonly prepared from ketones by one of several methods.178 Enamines and silyl enol ethers are also open to oxidation using arylsulfonyl peroxides. They possess an electron rich double bond that can react with the electrophilic peroxides and are prepared regioselectively from unsymmetrical ketones.179 When an ethyl acetate solution of 1-(trimethylsiloxy)cyclohexene was reacted with bis[(p-nitrophenyl)sulfonyl] peroxide multiple products were recovered in addition to the desired α-(p-nitrophenyl)sulfoxony ketone 290 in 77% yield (Scheme 109).
These undesirable by-products were thought to originate from the $O$-(trimethylsilyl)oxonium ion 291, produced from electrophilic addition. Nucleophiles were therefore added in order to trap out the oxonium ion 291 by transfer of the trimethylsilyl group. By carrying out the reaction in the presence of methanol only two products were observed, namely, the desired $\alpha$-sulfonyl ketone 290 and a mixed ketal 292 (Scheme 110).

This mix of products could be explained by attack of methanol on the oxonium ion 291 at either silicon to give 290 or carbon to give 292. These two modes of attack could be made equivalent if water were the attacking nucleophile, as was ultimately applied giving a yield of 77% (Scheme 109).

Enamines have also been shown to be useful carbonyl derivatives that provide access to $\alpha$-oxysulfonyl ketones by reaction with sulfonyl peroxides (Scheme 111). 179 Initially, it was felt that electrophilic addition would provide an iminium ion 294 stable enough to preclude the need for added nucleophiles.
Minor byproducts were recovered, by analogy to the halogenation of enamines,\textsuperscript{180} these products possibly arose from side reactions of the iminium ion. The addition of 2\% methanol gave the desired $\alpha$-arylsulfonoxy ketones in quantitative yields by nucleophilic trapping of the iminium ion to give the more stable tetrahedral intermediate \textbf{295} (Scheme 112).

![Scheme 112](image)

Interestingly, the reactivity of enamines toward $p$-NPSP relative to enol derivatives showed a marked difference. The latter required temperatures of 0 °C or above, whereas enamines react smoothly at -78 °C. It is likely that this difference in reactivity lies in the site of electrophilic attack. Enol derivatives favor reaction at the electron-rich carbon-carbon $\pi$-bond and thus exhibit reactivities comparable to other reactive olefins.\textsuperscript{181} Whereas, enamines react at nitrogen, giving an $N$-arylsulfonoxy (Scheme 113) intermediate \textbf{296} that undergoes a 1,3-rearrangement to the $\alpha$-aryloxysulfonyl iminium product \textbf{297}.

![Scheme 113](image)

The reactivity exhibited by enamines is similar to that found for the oxidation of amines by $p$-NPSP,\textsuperscript{182} also [1,3]-rearrangements of both oxyacyl and aryloxysulfonyl groups from nitrogen to carbon are known to be facile.\textsuperscript{183}
Since the discovery of Koser’s reagent almost a century ago, hypervalent iodine reagents have proven an effective route to \( \alpha \)-sulfoxy carbonyl compounds. The utility of hypervalent iodine reagents for oxidative processes has generated ongoing interest into their chemistry. This has recently culminated in the publication of a number of catalytic hypervalent iodine methodologies including the catalytic \( \alpha \)-oxytosylation of ketones\(^{184} \), which marks a significant step forward in the chemistry\(^{185} \). These advancements will undoubtedly lead to an increase in the application of reactions mediated by hypervalent iodine reagents.

### 5.4.0 Reagent Preparation:

Access to the desired reagent relied on similar chemistry to that developed previously. The initial tosylation reaction at first, however, proved slightly problematic with low yields and difficulties in separating \( p \)-toluenesulfonic acid from our desired product. Initially it was thought that excessive water in the reaction medium might be responsible by forming unwanted \( p \)-toluenesulfonic acid from \( p \)-toluenesulfonyl chloride. However, conducting the reaction under anhydrous reaction conditions gave only a moderate increase in yield for 298, indicating this was not the problem. A simple solution to this problem was found in the use of 1.5eq. of \( \text{Et}_3\text{N} \) and the slow addition of a 0.7M solution of 198 in dichloromethane.

![Scheme 114](image)

As with our previous oxy-benzoylation, oxy-carbonylation and oxy-carbamoylation we sought to employ our simultaneous deprotection, hydrochloride salt formation procedure for the conversion of \( N \)-Boc-\( N \)-methyl-\( O \)-\( p \)-tosylhydroxylamine 298 to the corresponding \( N \)-methyl-\( O \)-\( p \)-tosylhydroxylamine hydrochloride 299. As with the previous uses of this technique, TLC was used to monitor the reaction, in that the immobile HCl salt would remain on the base line while the Boc protected reagent would
migrate up the plate. In this way once the spot corresponding to the Boc reagent had disappeared this would indicate the completion of the reaction. Monitoring the reaction in this way indicated the reaction was complete within 20-25 min, by the disappearance of the \( N \)-Boc-\( N \)-methyl-\( O \)-\( p \)-tosylhydroxylamine spot. Removal of the reaction solvent under reduced pressure gave a solid material which when analysed indicated a complex mixture by \(^1\)H NMR with no discernable product present. An alternative deprotection method was then tried using 4M HCl in dixoane, this allowed a more precise amount of acid to be used, therefore making the reaction more controllable overall. Unfortunately, this proved ineffective with 20 eq. and 10 eq. of HCl giving only decomposition of 298 to a complex reaction mixture when analysed by \(^1\)H NMR, while 5 eq. and 2 eq. gave no reaction after 1 hr. These results led us to believe that HCl was simply too strong an acid to be used in sufficient concentration to facilitate deprotection. We therefore looked at an alternative deprotection procedure that employed the weaker trifluoroacetic acid (20 eq.) in a 1:1 ratio with \( \text{CH}_2\text{Cl}_2 \) (Scheme 115). Using this approach we were delighted to discover the deprotection was successful with \( N \)-methyl-\( O \)-\( p \)-tosylhydroxylamine 299 isolated in an excellent 90\% yield after only 1 hr.

![Scheme 115](image)

Interestingly, upon quenching the reaction in ice-cold water the tosyl hydroxylamine free base 299 could be directly extracted into organic solvent. Initially this is counter intuitive as the TFA salt would be expected to be water soluble (Scheme 116).

![Scheme 116](image)

Predictive pKa analysis of the protonated tosyl hydroxylamine 301 showed it had a projected pKa of \(-2.1\) which makes it more acidic than TFA therefore, favoring the left-hand side of the equilibrium, which explained the solubility in the organic phase.
5.5.0 Reaction Optimization:

5.5.1 Acid Source:

With the reagent 299 in hand we then went on to explore its reactivity with carbonyl substrates. The selection of acid source for our oxytosylation protocol proved even more pivotal than in previous procedures. This was investigated by reacting 1eq. of cyclohexanone with 1.5eq. of N-methyl-O-p-tosylhydroxylamine 299 for 18 hr at 50 °C in THF. The complications encountered during the deprotection of N-Boc-N-methyl-O-p-tosylhydroxylamine 298 gave us an insight that N-methyl-O-p-tosylhydroxylamine 299 was unstable to strongly acid conditions. As it was not possible to use the N-methyl-O-p-tosylhydroxylamine hydrochloride salt as acid source, other sources of acid were examined by the addition of stoichiometric amounts of benzoic acid, trifluoroacetic acid and methanesulfonic acid. In each case 1.5eq. of the corresponding acid was added to 1eq. of the ketone. The weakest of the acids chosen, benzoic acid, was ineffective in promoting the reaction with no product visible by $^1$H NMR. Trifluoroacetic acid showed a trace amount of product by $^1$H NMR, however, this could not be isolated by flash chromatography. The stronger methanesulfonic acid gave the best conversion to 306 of 39% under these reaction conditions.

<table>
<thead>
<tr>
<th>Acid</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoic Acid</td>
<td>0</td>
</tr>
<tr>
<td>Trifluoroacetic Acid</td>
<td>Trace</td>
</tr>
<tr>
<td>Methanesulfonic Acid</td>
<td>55</td>
</tr>
<tr>
<td>Hydrochloric Acid</td>
<td>0</td>
</tr>
</tbody>
</table>

5.5.2 Reaction Solvent:

As with our previous investigations, a solvent scan was necessary to determine the most effective solvent in which to conduct the reaction. This was done by reacting 1eq. of cyclohexanone with 1.5eq. N-methyl-O-p-tosylhydroxylamine 299 and 1.5eq. MSA for 18 hr at 50 °C. Looking at the results obtained it was again evident that there was no discernible preference for one specific solvent throughout our methodology. DMSO, which proved extremely effective in our α-oxybenzoylation procedure, was ineffective here with only trace amounts of product visible by $^1$H NMR. THF gave the best results for our
oxycarbonates and carbamates, and here both ether and THF gave similar results (52 and 55\% respectively). Unlike the previous procedures a co-solvent was found to give the best yield with 69\% recorded for the reaction between cyclohexanone and \(N\)-methyl-\(O\)-\(p\)-tosylhydroxylamine 299. This (1:1) solvent mixture served as an excellent medium for the reaction allowing a more efficient dissolution of the \(N\)-methyl-\(O\)-tosylhydroxylamine 299.

Although DMSO gave the best results for the oxycarbonylations, there is a general preference for less polar electron donating solvents with this reagent.

### 5.6.0 Reactions with Cyclic Ketones:

The \(\alpha\)-oxytosylation of cyclic ketones was carried out following a similar procedure to previous chapters. Our tosylating reagent 299 1.5eq. was mixed with 1eq. of our selected ketone in a 1:1 mixture of THF/PhMe, to which 1.5eq MSA was finally added and the reaction heated to 50 °C. The \(\alpha\)-oxytosylation of cyclohexanone proceeded smoothly to give the functionalised product in a good yield of 306 (Table 6, Entry 1) after purification. This first result was significant because it deviates dramatically from those reported by Hoffman for his exploration of the reactivity of nosyl hydroxylamines with cyclic ketones. Both our chemistry and Hoffman’s observations share a similar proposed reaction intermediate. Under the acidic reaction conditions both hydroxylamines react with a ketone to produce a \(O,N\) acetal 302 or 304 (Fig. 25). It is from this point on that our chemistries diverge. While our methodology is purposed to progress to an iminium ion 303 via the elimination of water from 302, Hoffman reported the creation of ring expanded lactams 305. This observation was explained by the \(C\-N\) migration of a ring carbon bond to nitrogen followed by elimination of a \(p\)-nitrosulfonic acid.
These contrasting reactivities could be explained by the difference in leaving group ability between the tosyl and nosyl groups. The presence of a para nitro group in 304 may polarise the N-O bond sufficiently to promote the ring expansion via cleavage of the hydroxylamine N-O bond.

Under our reaction conditions, cyclohexanone was functionalised smoothly in 69% yield 306 (Table 6, Entry 1). The functionalisation of 4-tert-butylocyclohexanone proceeded in good order to give only one diastereoisomer in 70% yield 307 (Table 6, Entry 2), while 308 gave two diastereoisomers. This observation is most likely explained by 307 epimerising to give the more thermodynamically stable cis isomer.

Table 6. Reactions of 299 with Cyclic Ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Ketone</th>
<th>Tosylated Product</th>
<th>Reaction Temperature (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{C} )</td>
<td>( \text{C} \text{OTs} )</td>
<td>50 °C</td>
<td>69</td>
</tr>
</tbody>
</table>

306
5.7.0 Reaction with Acyclic Ketones:

Building on the success of our reactions with cyclic ketones we next turned our attention to acyclic ketones and the reaction of 4-methyl-2-pentanone with 299 (Table 8, Entry 1). This reaction was carried out under the same reaction conditions as for cyclic ketones, however, it presented us with an unexpected result. Analysis of the crude reaction mixture revealed there were two major and distinct products from the reaction. Further analysis of the $^1$H NMR showed these to be 4-methyl-2-oxopentyl 4-methyl-$p$-toluenesulfonate 309 and 4-methyl-3-oxopentyl 4-methyl-$p$-toluenesulfonate 317, having arisen from functionalisation occurring at both the primary and secondary centres. These products were distinguished by the characteristic chemical shift of the relevant $\alpha$-proton or protons (Fig. 26).
By comparing the integration of these chemical shifts it became apparent there was a ratio of 4:1 for the product arising from primary functionalisation 309 over that of secondary 317. This selectivity was rationalised on the basis that 299 favours reaction with the kinetic enamine 315 instead of the thermodynamic 316, which is contrary to what had been previously observed. This observation marks a significant advance in our methodology in that we had been previously unable to functionalise primary positions.

This intriguing result led us to further examine the regioselectivity of our α-tosylation reaction by observing the product ratio against increasing temperature, the results of which are summarised in Table 7.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Ratio 309/317</th>
<th>Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>6:1</td>
<td>21</td>
</tr>
<tr>
<td>r.t.</td>
<td>4:1</td>
<td>52</td>
</tr>
<tr>
<td>50</td>
<td>4:1</td>
<td>65</td>
</tr>
</tbody>
</table>

\(^a\) Mixture of both regio-isomers

While conducting the reaction at -20 °C gave no reaction, increasing the reaction temperature to 0 °C resulted in an improved selectivity of 6:1, however, with a reduced yield of 21%. Further increasing the reaction temperature to r.t. improved the yield but reduced the selectivity to 4:1. This selectivity remained consistent with a further increase to 50 °C, which gave the best yield of 65%. These results indicated that while
a reduction in reaction temperature improved the regio-selectivity it also seriously reduced the overall yield of the reaction.

### Table 8. Reactions of 299 with Ayclic Ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Ketone</th>
<th>Tosylated Product</th>
<th>Reaction Temperature (°C)</th>
<th>Ratio</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>OTs 309</td>
<td>50 °C</td>
<td>4:1</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>OTs 310</td>
<td>50 °C</td>
<td>4:1</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>OTs 311</td>
<td>50 °C</td>
<td>4:1</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>HO</td>
<td>HO OTs 312</td>
<td>50 °C</td>
<td>4:1</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>OTs 313</td>
<td>50 °C</td>
<td>N/A</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>OTs 314</td>
<td>50 °C</td>
<td>N/A</td>
<td>81</td>
</tr>
</tbody>
</table>

All reactions were performed for 18 hr at 0.5M concentration in 1:1 THF/PhMe with 1.5 eq 299 and MSA and 1 eq starting ketone. Ratio of primary : secondary functionalisation products. Combined yield for both regio-isomers.

Leading on from these results we sought to investigate a more general substrate in order to compare our regio-selective results with those previously reported. We therefore selected 2-butanone and reacted it for 18hr at 0.5M concentration in 1:1 THF/PhMe with 1.5 eq 299 and MSA. This reaction again progressed with an excellent 71% yield with a regio-selectivity of 4:1 310 (Table 8, Entry 2). The significance of these results becomes clear when compared to similar attempts to α-oxytosylate 2-butanone.
Moriarty had previously attempted to α-oxytosylate 2-butanone with HTIB but reported a poor regio-selectivity of 1.5:1 for secondary centre functionalisation over primary. This result was later improved upon by using a camphor sulfonic acid derived hypervalent iodine reagent, which gave a regio-selectivity of 2.3:1 for primary functionalisation over secondary. Yasuyuki et al. has recently published work using a tetraphenylmethane based iodine reagent 318 but with a poor selectivity of 1.9:1 for secondary over primary in 58% yield. These mixed results contrast to our own in which functionalisation occurs predominantly at the primary centre complementary to Moriarty and Yasuyukis results and with a greater selectivity. This trend for selectivity is again evident in two further substrates; 2-heptanone gave the corresponding functionalized product 311 (Table 8, Entry 3) in a good yield of 69% and a 4:1 ratio. The reaction of 4-(4-hydroxyphenyl)butan-2-one (Table 8, Entry 4) also proceeded smoothly to give a good yield of 61% for 312.

The remarkable ability of 299 to functionalize primary centres was best exemplified by its reaction with acetone (Table 8, Entry 5) to give 313 in an excellent 72% yield, this ability was also expanded to include the α-oxytosylation of acetophene to give 314 in a very good 81% (Table 8, Entry 6).

5.8.0 Reaction with Dicarbonyls:

Using the reagents developed in previous chapters we were unable to α-functionalise di-carbonyl compounds such as ethyl acetoacetate and 2,4-pentanedione. This was perplexing given the acidity of the alpha position that should favour rearrangement. Given the acidic conditions of the reaction it was expected that tautomerisation of the substrate to its enol form may encourage iminium ion formation by amplifying the electron deficient nature of the carbonyl (Scheme 117), however, previous attempts had proven unsuccessful. Given our oxytosylating reagents ability to functionalise previously inaccessible primary centres we were interested to see if its unique reactivity could access di-carbonyl derivatives.
Ethyl acetoacetate was first reacted with 299 under standard conditions with 1.5 eq of 299 and MSA in 1:1 THF/PhMe for 18 hr at 50 °C. We were delighted to discover that the application of our reagent gave the expected product 319 (Table 9, Entry 1) in a good yield of 69%. The stability of this acid sensitive substrate is additional evidence for the compatibility of our methodology with hydrolysis sensitive groups. With this promising result we next turned our attention to 2,4-pentanedione.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Ketone</th>
<th>Tosylated Product</th>
<th>Reaction Temperature (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
</table>
| 1     | \[\begin{array}{c}
|     |                 | \end{array}\] \[\begin{array}{c}
|     |                 | \end{array}\] | 50 °C | 69 |
| 2     | \[\begin{array}{c}
|     |                 | \end{array}\] \[\begin{array}{c}
|     |                 | \end{array}\] | 50 °C | 52 |

Table 9. Reaction of 299 with Dicarbonyls

All reactions were performed for 18 hr at 0.5M concentration in 1:1 THF/PhMe with 1.5 eq 299 and MSA and 1 eq starting ketone.

Extension of this methodology to include 2,4-pentanedione (Table 9, Entry 2) gave an unexpected result in the recovery of only functionalised acetone. Analysis of what was thought to be the functionalised 2,4-pentanedione product was initially confusing with the isolated product not having a sufficient number of protons however, given the inherently acidic reaction conditions one plausible explanation for this may involve the elimination of acetic acid (Scheme 118).
The α-oxytosyl group may sufficiently increase the electron deficient nature of either of the carbonyls to render it susceptible to attack by water. This unstable acetal 321 can then eliminate an equivalent of acetic acid giving the corresponding enol 322, which then tautomerises to the ketone 320 under the reaction conditions.

5.9.0 Conclusion:

From the results detailed here, it has been shown that it is possible to further modify our generic reagent to incorporate a heteroatom in the X position through the use of N-methyl-O-p-tosyloxyhydroxylamine 299. Unlike the previous methods described it was necessary to form the reactive salt in situ using methanesulfonic acid. By using this approach it presented a novel route for the introduction of a tosyl group in the α-position. Exploration of the scope of this transformation showed it to be applicable to the functionalisation of cyclic ketones giving a good conversion in all cases. Previously inaccessible primary centres could also be functionalised using 299 as was demonstrated in the functionalisation of both acetone and acetophenone. The contrasting nature of this reagent is again evident in its predilection to favour reaction with the kinetic rather than the thermodynamic enamine. Consequently this characteristic manifested itself where there was competition between primary or secondary positions, with primary being favoured with a regioselectivity of 4:1. Additionally, the use of N-methyl-O-p-tosyloxyhydroxylamine 299 allowed the functionalisation of a α,β-ketoester, which was not possible using 201. The functionalisation of 2,4-pentandione proved unsuccessful due to the elimination of acetic acid, which resulted in the isolation of 320 in good yield.

The final alteration of our generic reagent we wished to investigate was the substitution of an alternative heteroatom for Y. This is perhaps the most intriguing modification, as it would allow the construction of additional carbon heteroatom bonds. It is this final alteration, which is discussed, in the following chapter.
Chapter 6: α-Sulfenylation
6.1.0 Introduction:

The importance of α-sulfenylated carbonyl compounds in synthetic chemistry has been well known for many years. They have been used as precursors for a large number of synthetically valuable target molecules. Organocatalysed additions of simple carbonyl compounds to diazacarboxylates and nitrobenzene allow the incorporation of nitrogen and oxygen containing α-substituted aldehydes and ketones. In contrast, the related introduction of sulfur-based substituents have not been extensively reported. Traditionally, practical methods for the preparation of chiral α-sulfenylated carbonyl compounds have been multi-step procedures that involve chiral auxiliaries. Procedures such as the asymmetric α-sulfenylation of lithiated SAMP ketone and aldehyde hydrozones 322 with disulfides affords the α-thiorated hydrazones 323 in good yields and high diasteromeric excesses (Scheme 119). The chiral auxiliary can be removed by ozonolysis without racemisation to afford the α-thiorated carbonyl. The competing oxidation of the thioether moiety to the corresponding sulfoxides, however, limited the overall yields. Better yields were observed for ketones when the hydrazones were vigorously stirred in a two-phase system of 2M hydrochloric acid/pentane with the ozonolysis step, but some racemisation was observed under these harsh conditions.

Recently this auxiliary approach has been superseded by the first enantioselective organocatalysed α-sulfenylation of aldehydes, which represents the first enantioselective organocatalysed synthesis of α-sulfenylated of aldehydes.
6.2.0 Synthesis of \(N\)-methyl-\(O\)-thiobenzoylhydroxylamine

Despite the effectiveness of these procedures, both introduce a sulfide moiety, which is susceptible to oxidation. We saw that this shortcoming could be addressed through the possibility of preparing a protected thiol by using our methodology. We purposed that a thio analogue \(324\) of our \(N\)-methyl-\(O\)-benzoylhydroxylamine reagent could rearrange in a similar manner to introduce a benzothioate group \(\alpha\) to the carbonyl \(325\) (Scheme 120).

![Scheme 120](image)

This would allow for the introduction of a much more synthetically useful group in that it would be stable to oxidative processes while the thiol could be unmasked by hydrolysis of the thio ester.

6.2.1 Conversion of \(N\)-Boc-\(N\)-methyl-\(O\)-benzoylhydroxylamine to \(N\)-Boc-\(N\)-methyl-\(O\)-thiobenzoylhydroxylamine:

Firstly, it was believed both logical and economical to attempt the direct conversion of our \(N\)-Boc-\(N\)-methyl-\(O\)-benzoylhydroxylamine \(200\) to \(N\)-Boc-\(N\)-methyl-\(O\)-thiobenzoylhydroxylamine \(326\). Given the thermal sensitivity of \(O\)-acylhydroxylamines \(200\) their conversion to the corresponding \(O\)-thioacylhydroxylamines \(324\) using contemporary techniques was thought challenging. Nevertheless this was deemed a reasonable starting place. We were unable to locate any precedent for the direct conversion of \(O\)-acylhydroxylamines to \(O\)-thioacylhydroxylamines, therefore, we were limited to attempting to adapt other methods to fit our system. We based our initial investigations on a publication by Curphey on a comparable thionation of esters with phosphorus pentasulfide/hexamethyldisiloxane (HMDO) (Scheme 121) and Lawesson's

107
Our first attempt at this conversion used the classical method of using Lawesson's reagent as the thionation reagent in refluxing THF (Scheme 121). The crude reaction material was obtained by filtration through a short pad of silica gel to give a brown material which when analysed by $^1$H NMR indicated a very complex mixture of compounds. Unfortunately, no thionated product or starting material could be recovered by further chromatography.

![Scheme 121]

Although this attempt was unsuccessful it is perhaps not surprising. The conversion of esters to thioesters is amongst the most difficult of thionations because of the generally low reactivity of the ester carbonyl group toward usual thionation reagents. It is believed that $O$-acylhydroxylamine carbonyl groups are prone to the same low reactivity toward thionating reagents, and are unable to withstand the more harsh conditions necessary for reaction.

Despite this negative result the direct thionation of $N$-Boc-$N$-methyl-$O$-benzoylhydroxylamine 200 was again attempted using a mixture of $P_4S_{10}$ and anhydrous $Na_2CO_3$ in THF (Scheme 122) based on work by Soheeren on milder thionation reactions.

![Scheme 122]

Unfortunately, despite the milder reaction conditions this procedure proved unsuccessful. As with the previous attempt, the crude material obtained after filtration through a short pad of silica gel gave a complex $^1$H NMR when analyzed.
As the reaction was heterogeneous an attempt to encourage this transformation using ultrasonic irradiation was thought plausible (Scheme 123). Raucher had shown this technique useful in the synthesis of thioamides using $P_4S_{10}$.

It was hoped that sonocation of a solution of $P_4S_{10}$ and $Na_2CO_3$ would aid in dissolution of the less soluble reagents thereby promoting activity.\(^{192}\) This procedure again proved ineffective and it was at this point that the strategy to directly convert $N$-Boc-$N$-methyl-$O$-benzoylhydroxylamine 200 to the $N$-Boc-$N$-methyl-$O$-thiobenzoylhydroxylamine 326 was abandoned.

### 6.2.2 Willgerodt-Kindler Reaction:

As our traditional approach to introducing a thiocarbonyl group using thionation reagents had failed, we switched our attention to the thioacyl group instead. Using this approach our intention was to employ a suitable thioacyl reagent 327 (Fig. 27), which would facilitate displacement of an appropriate leaving group (L.G.) by nucleophilic attack of hydroxylamine to give 326.

Thioacyl halides were not pursued due to their sensitive nature regarding both synthesis and use.\(^{193}\) A modification of the Willgerodt-Kindler reaction was thought of as a possible route to install a leaving group and thiocarbonyl group in one step.\(^{194}\) In the original reaction, ketones and aldehydes were found to react with sulfur and secondary
amines to give terminal thioamides as a result of consecutive oxidations and rearrangements. Darabi et al. recently accessed thiomorpholides via a one-step solvent free procedure under microwave irradiation. By utilizing this approach but substituting imidazole for morpholine our intention was to access the corresponding thioacyl imidazole 328 (Scheme 124), from which it may be possible to displace imidazole with the relevant hydroxylamine.

![Scheme 124](image)

It was not possible to exactly follow the conditions outlined by Darabi as they had employed a domestic microwave oven. Variation of power, temperature and duration failed to give any satisfactory results. In each case an extremely insoluble crystalline solid was recovered which did not allow for meaningful analysis. The thioacyl imidazole, if formed, was thought too unstable under the high-energy conditions of microwave irradiation leading to the observed decomposition. At this point the strategy was simplified to a sequential imidazole adduct formation, followed by a thionation procedure (Scheme 125).

![Scheme 125](image)

By reacting benzoic acid and 1eq of CDI in ether the resulting imidazole adduct 329 was easily isolated after the addition of a small amount of hexane to precipitate the eliminated imidazole that was then removed by filtration. The isolated imidazole adduct 329 was reacted without further purification using the milder $P_4S_{10}/Na_2CO_3$ reaction conditions. Unfortunately, this too was unsuccessful with only a small amount of benzoic acid and imidazole recovered.
6.2.3 Synthesis via S-Thioacyldithiophosphates:

S-Thioacyldithiophosphates 330, accessible from carboxylic acid derivatives have been proven to be excellent thioacrylating agents by Rachon et al.\textsuperscript{195} They show a low reactivity towards oxygen nucleophiles and are highly reactive to nitrogen ones, lending themselves to thiohydroxamic acid 331 synthesis directly from hydroxylamines without the need for protection of the hydroxyl group. However, in the case of hydroxylamines with bulky substituents O-thioacylhydroxylamines 332 are formed (Scheme 126).

\[
\begin{align*}
\text{Ph} & \text{N} \quad \text{OH} & \text{H} \quad \text{N} \quad \text{OH} & \text{Ph} \\
& \text{R}^1 & & \text{R}^1 \\
\text{Ph} & \text{CHCl}_3 & \text{Cl} & \text{Ph} \quad \text{CHCl}_3 & \text{R}^1 \\
\end{align*}
\]

Scheme 126

This reversed reactivity can be explained by the supernucleophilic properties of oxygen in hydroxylamines when compared to common alcohols. The lower thermodynamic stability of the N-thioacrylated products due to steric hindrance when compared to the O-thioacrylated products is also a factor.\textsuperscript{196} Utilising this procedure we were confident in our intention to react N-Boc-N-methylhydroxylamine 199 with 330, followed by deprotection of the Boc group to facilitate access to N-methyl-O-thiobenzoylhydroxylamine.

The S-thioacryldithiophosphate 330 was prepared in three-steps according to literature procedures.\textsuperscript{197} The phosphoric thioacid 5,5-dimethyl-2-thiolo-2-thiono-1,3,2-dioxaphosphorinane 333 was prepared in 91% yield from 2,2-dimethylpropane-1,3-diol and \( \text{P}_4\text{S}_{10} \) by heating in benzene at 50 °C for 12 hr (Scheme 127).

\[
\begin{align*}
\text{P}_4\text{S}_{10} & \quad \text{OH} \quad \text{OH} & \quad \text{OH} \quad \text{OH} & \quad \text{SH} \quad \text{SH} \\
& \quad \text{50 °C, 12hr, 91%} & \quad \text{91%} \\
\end{align*}
\]

Scheme 127
Upon distillation of the crude thioacid, a colourless crystalline solid that conformed to the literature data was isolated.\textsuperscript{198} Acyl 2-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) sulfide was then prepared by reacting benzoyl chloride and 333 (Scheme 128). Triethylamine hydrochloride precipitated out of the reaction immediately and the desired product 334 could be obtained by filtration through a short pad of silica gel in 79\% yield.

![Scheme 128](image)

After crystallisation a white solid was obtained which again corresponded to the literature data.\textsuperscript{197} The final conversion to the thioacyl dithiophosphate 330 was attempted through the reuse of 5,5-dimethyl-2-thiolo-2-thiono-1,3,2-dioxaphosphorinane 333 as the thionating reagent (Scheme 129).

![Scheme 129](image)

It was at this point that complications regarding the isolation and purification of 330 were encountered. Using the method outlined in the literature a pure sample could not be obtained. However, this complication was noted by the authors, for which they make an exemption by using a 25\% excess of impure 330. With this in mind we set about reacting N-Boc-N-methylhydroxylamine 199 with thioacyl 2-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) sulfide 330 under the reaction conditions specified (Scheme 130).
With the report by Doszczak a similar reaction using N-benzoyl-N-isopropylhydroxylamine was carried out in darkness due to the reported photochemical instability of the product. The presence of a Boc group within our substrate with comparable electron withdrawing ability caused us to believe there was potential for similar photochemical instability. Unfortunately, conducting the reaction in the dark proved ineffective. Variation of reaction time and temperature proved futile and no discernable product could be recovered. At this point our efforts were redirected to an analogous approach.

6.2.4 Synthesis via Thionoacyl Nitrobenzotriazoles:

Further inspiration came from work published by Rapoport et al. in which it was demonstrated that α-amino thionoacid derivatives of nitrobenzotriazole 335 were effective thioacylating agents for site-specific incorporation of thioamide linkages into a growing peptide 336 (Scheme 131). Soon after it was shown that nitrobenzotriazole could also be utilized as a leaving group in thionoester 337 synthesis. The effectiveness of this procedure arises from the introduction of a masked leaving group in the form of an anilide, which can be thionated to install the thio-carbonyl after which diazonium cyclization reveals the necessary nitrobenzotriazole.
The procedure for the preparation of benzotriazole thioacylating agents was quite straightforward. Condensation between 4-nitro-1,2-phenylenediamine 338 and benzoyl chloride in THF at 0 °C, under basic conditions gave adequate access to the crystalline anilide 339 in 68% yield (Scheme 132). This approach differed from the literature method in which, coupling was effected between 4-nitro-1,2-phenylenediamine 338 and the necessary carboxylic acids in THF at 0 °C using mixed anhydride methodology for amide synthesis.

![Scheme 132](image)

Although the yield was lower than that reported by Rapoport, after recrystallization with ethyl acetate sufficient quantities of the anilide was recovered to continue. Direct thionation of 339 was achieved with a mixture of purified P₄S₁₀ and anhydrous Na₂CO₃ in THF. The reaction proceeded smoothly over 3hr at 0 °C to room temperature to afford thioanilide 340 in a very good yield of 74% (Scheme 133).

![Scheme 133](image)

Intramolecular diazonium cyclization of 340 using nitrous acid, generated in situ from NaNO₂ and AcOH gave benzotriazole 341 as a red solid in an excellent yield of 85% (Scheme 134).

![Scheme 134](image)
In spite of the increasing interest in benzotriazole-mediated thioacylations, as exemplified in a recent article by Katritzky\textsuperscript{201} regarding their use in thioacylations, thiocarbamoylation, aryl/alkoxy-thioacylations and aryl/alkylthioacylations, we were unable to locate any precedent for their reaction with hydroxylamines. Despite this it was thought that the best course of action would be to take into account the complications and observations made in our previously described \( S \)-thioacyldithiophosphates approach.

Fortuitously, these conditions partly agreed with the recommendations made by Rapoport in the choice of solvent and the strong non-nucleophilic base diaza(1,3)bicyclo[5.4.0]undecane (DBU). By combining these conditions with a longer reaction time and the possible photosensitivity of our product we arrived at a set of conditions by which we set about reacting \( N \)-Boc-\( N \)-methylhydroxylamine with our benzotriazole thioacetylating reagent 341 (Scheme 135).

We were delighted to discover that after the dropwise addition of DBU over 20min the reaction proceeded smoothly over 24hr to give the \( N \)-Boc-\( N \)-methyl-\( O \)-thiobenzoylhydroxylamine 326, which was identified by \( ^1 \)H and \( ^{13} \)C NMR (Appendix, Fig. B & C) however, it was not possible to obtain a mass spectral analysis via either APcI or ES ionization. Trituration of the crude reaction mixture allowed the desired product to be recovered from the crude reaction in reasonable purity but further
purification proved unworkable. TLC analysis of the impure N-Boc-N-methyl-O-thiobenzoylhydroxylamine 326 showed two spots when viewed under UV. Subjecting the crude 326 to chromatography on both silica and alumina proved ineffective, as it was not possible to separate these spots and so the deprotection was attempted without any further purification.

With our desired reagent now within reach our attention turned to its deprotection. Given the complications we had encountered with the acid deprotection of our oxy-carbonate, oxy-carbamate and oxy-tosylation reagents we were cautious in our approach to the deprotection of N-Boc-N-methyl-O-thiobenzoylhydroxylamine 326. This deprotection was first attempted using 4M HCl in dixoane, as this would allow for a precise amount of acid to be used. We first carried out the deprotection with 2eq. of HCl at room temperature. TLC analysis of the reaction after 5min showed both spots as was seen for the chromatography in 326, along with some material on the base line. Repeated TLC analysis of the reaction after 15min showed the disappearance of both spots indicating the reaction was complete, at which point the solvent was removed under reduced pressure to give a solid residue. However, analysis of this by 1H NMR revealed a very complex mixture of compounds, indicating the decomposition of 326.

We were however, not too perturbed as similar complications were encountered in the deprotection of our oxy-tosylation reagent and so we next tried our previously successful (1:1) TFA/CH2Cl2 deprotection system. This reaction was carried out with 20eq. of TFA at 0 °C. Unfortunately this system too proved unsuccessful with only the decomposition of 326 observed by 1H NMR after 30min.

The difficulties we have thus far encountered are however, not isolated. Complications seen in the use of the Boc group for the protection of amino functionalities in the presence of acid sensitive moieties such as thioamides, in which acidolytic deprotection of thioxo containing peptides is employed, have led in most cases to unsatisfactory yields. Beside dethioxylation, thiolated products often under went a side reaction similar to the Edman degradation.

Numerous methods have been reported for Boc deprotection, although most involve the use of strong acids such as CF3COOH, HCl, H2SO4, TsOH and MsOH. Lewis acids such as BF3·OEt2, TMSI, TMSOTf, TiCl4, SnCl4, AlCl3, Sn(OTf)2, ZnBr2 have also been proven successful, less acidic conditions using Montmorillonite K10 clay.
and silica gel have also been used. In order to achieve Boc removal under relatively mild conditions four possible methods were attempted. The SnCl₄ mediated Boc deprotection of amino groups under extremely mild conditions in the presence of acid labile thioamide moieties has been shown to be very effective. It was proposed that Boc removal is facilitated by the initial formation of a chelate between the Lewis acid SnCl₄ and the tert-butyl N-alkylcarbamate leading to solvolytic loss of isobutene and CO₂ formation leading to the deprotected compound. The literature procedure called for the use of 5 equivalents of SnCl₄, however, initially this was seen as slightly excessive in that only one equivalent is theoretically required. Application of this procedure under anhydrous conditions using one equivalent, proved unsuccessful with thio benzoic acid being the only recoverable product (Scheme 136).

![Scheme 136](image)

Variation of the number of equivalents of SnCl₄, time and temperature proved unproductive. The next attempted deprotection employed an alternative to the conventional TFA/CH₂Cl₂ approach, in which decreasing the acid concentration was shown to be effective in the selective removal of Boc and Z(OMe) groups in peptide chemistry. This literature procedure used dilute methanesulfonic acid (0.5M) in a solution of dioxane, dichloromethane (1:9) (Scheme 137). The insolubility of organosulfonic acids in CH₂Cl₂ required the addition of 10% dioxane to aid dissolution. In addition dioxane was reported to play an important role for the selective deprotection by the buffer capacity resulting from its weak basicity.

![Scheme 137](image)

Once again this procedure was unsuccessful with no discernible product being recovered. Altering the MSA concentration and equivalents along with reaction time...
and temperature were futile. Despite this negative result we switched our attention to a similar dioxane base deprotection method using 10% H$_2$SO$_4$ which was reported to offer a milder alternative to the conventional TFA/CH$_2$Cl$_2$ method (Scheme 138).$^{210}$

Scheme 138

Unfortunately, applying this method to our substrate was again unproductive. Similar variation of time, temperature and duration showed no improvement in the reaction.

Further to the methods already employed to facilitate Boc deprotection, aqueous phosphoric acid (85wt%) is an effective reagent for the deprotection of N-Boc groups (Scheme 139), in which acid sensitive functionalities including benzyl and methyl esters, TBDMS ether, Cbz and isopropylidene groups are compatible with reaction conditions.$^{211}$ Phosphoric acid is a much weaker acid ($pK_a$ 2.15) than CF$_3$COOH ($pK_a$ 0.13), MsOH ($pK_a$ -0.6), TsOH ($pK_a$ -1.3) and other mineral acids, therefore it offers advantages for substrates with acid sensitive functionalities.

Scheme 139

Once again, this approach proved ineffective and at this point our only remaining logical alternative was to substitute the Boc protecting group for one with a more compatible deprotection procedure.

With an effective entry to our protected $N$-methyl-$O$-thiobenzoxyhydroxylamine 326 secured by the use of thionoacyl nitrobenzotriazoles we were hesitant to alter our strategy in an attempt to allow variation of protection groups. Therefore base labile groups were disregarded as possible nitrogen protecting groups. Hydrogenation labile
groups were also considered impractical given the susceptibility for cleavage of the \( N-O \) bond under hydrogenation conditions. Our attention was therefore drawn to the possible use of sulfonamides as protecting groups suitable for our needs. Fukuyama et al. has employed sulfonamides effectively in the preparation of a variety of secondary amines and diamines from alcohols.\textsuperscript{212} In this, \( N \)-monosubstituted 2,4-dinitrobenzenesulfonamide \textbf{343} was prepared from the corresponding amine and 2,4-dinitrobenzenesulfonyl chloride. Alkylation of this amine to \textbf{344} was then efficiently carried out under Mitsunobu conditions (ROH, DEAD, PPh\(_3\), benzene, 23 °C) or under more conventional conditions (RX, K\(_2\)CO\(_3\), DMF, 23 °C) (Scheme 140).

![Scheme 140](image)

Facile deprotection could be achieved by treatment with excess \( n \)-isopropylamine. Alternatively \textbf{344} can be deprotected by treatment with HSCH\(_2\)CO\(_2\)H and Et\(_3\)N. The latter procedure was found to be more convenient in that the by-product 2,4-dinitrophenvlthioacetic acid can easily be removed by washing the organic layer with an aqueous NaHCO\(_3\) solution. It is this nucleophilic removal of the sulfonylamide that was hoped would be advantageous to our goal. It is also noteworthy that oxygen nucleophiles are ineffective at removing these protecting groups. Preparation of \( N \)-2,4-dinitrophenylsulfonyl-N-methyl hydroxylamine \textbf{346} was achieved by reacting 2,4-dinitrobenzenesulfonyl chloride and \( N \)-methylhydroxylamine hydrochloride under basic conditions (Scheme 141).

![Scheme 141](image)
Extraction of the reaction mixture with dichloromethane followed by recrystallization gave the desired \( N\-2,4\-dinitrophenylsulfonyl\-N\-methyl hydroxylamine \( 346 \) in sufficient purity to continue. Mass spectral analysis of \( 346 \) proved inconclusive as no molecular ion could be observed, therefore identification was based on both \( ^1H \) and \( ^{13}C \) Dept NMR (Appendix, Fig. D & E). It was envisaged that further reaction with our thionoacyl nitrobenzotriazole reagent \( 341 \) would progress under similar conditions to those developed previously (Scheme 142).

![Scheme 142](image)

Initial observations were encouraging, in that monitoring the reaction by TLC showed the consumption of thioacylating reagent \( 341 \). However, \( ^1H \) NMR analysis of the crude reaction mixture showed no evidence of the desired \( N\-2,4\-dinitrophenylsulfonyl\-N\-methyl-O-thioacyl hydroxylamine \( 347 \). Two possible complications contributing to the failure of this procedure were considered. Fukuyama made reference to the decomposition of sulfonamide \( 343 \) via the intramolecular Meisenhiemer complex \( 348 \) (Scheme 143).

![Scheme 143](image)

A similar decomposition based on the intramolecular Meisenhiemer complex \( 350 \) (or intermolecular attack) can be envisaged for a hydroxylamine-based sulfonamide in the
presence of a strong base to give 351 (Scheme 144). This could in part explain the poor results observed.

Together with this, the nucleophilic ability of the benzotriazole anion was an unknown variable. It is unclear whether or not the benzotriazole anion is nucleophilic enough to facilitate ipso attack on N-2,4-dinitrophenylsulfonyl-N-methyl hydroxylamine 346. These proposals are however conjecture and could not be directly confirmed. An analogous approach was decided upon, again in keeping with work outlined by Fukuyama.213 In this instance a slightly less labile sulfonamide was used to form N-4-nitrophenylsulfonyl-N-methyl hydroxylamine 352 (Scheme 145).

Our intention was to reduce the susceptibility by which the sulfonamide underwent ipso attack, but to still maintain the viable removal of this group by using nucleophiles. As with the di-nitro analog 346 no molecular ion could be observed via either APcI or ES ionization and effective characterization was limited to $^1$H and $^{13}$C Dept NMR (Appendix, Fig. F & G).
The reaction was repeated under identical conditions as with Scheme 142. Unfortunately, the reaction was unsuccessful with a complex crude reaction mixture recovered (Scheme 146). It was at this point that further investigations into the N-methyl-O-thiobenzoylhydroxylamine reagent were ceased.

6.3.0 Synthesis of N-methyl-O-N,N-dimethylthiocarbamate hydroxylamine:

Initially, running in parallel with our investigations into possible N-methyl-O-thiobenzoylhydroxylamine reagents was our interest in the thio analogue of N-methyl-O-N,N-dimethylcarbamatehydroxylamine developed in chapter 4. Although this is less synthetically attractive, its synthesis could be attempted from commercially available starting materials and would be sufficient to prove the concept of our transformation (Scheme 147).

Annoyingly, however, under our standard conditions the reaction between protected hydroxylamine 199 and N,N-dimethylthiocarbamoyl chloride was ineffective with only starting material being visible by $^1$H NMR of the crude reaction mixture. Modifying the procedure by carrying out the reaction in excess pyridine along with 10mol% 4-dimethylaminopyridine DMAP at 50 °C proved more effective (Scheme 148) with a yield of 52% recorded for 354.
With an alternative protected reagent in hand, removing the protecting group again proved impossible under both Lewis and Brønsted acid conditions. All efforts to deprotect 354 using HCl, SnCl₄, MSA, TFA, H₂SO₄ and H₃PO₄ procedures again were in vain. The results obtained mirrored those of the previous N-Boc-N-methyl-O-thiobenzoylhydroxylamine deprotection strategies, with complicated reaction mixtures being recovered in each case.

6.4.0 Conclusion:

The remaining manipulation of X allowing the possible creation of a new reagent for the formation of carbon sulfur bonds proved somewhat elusive within the timelines of this work as accessing a suitable reagent proved challenging. Direct conversion of N-methyl-O-benzoylhydroxylamine proved unsuccessful using both Lawesson’s Reagent and P₂S₅. Using a modification of the Willgerodt-Kindler reaction, synthesis of suitable thioamides, from which nucleophilic displacement could be achieved, was also unsuccessful. Elaboration of this leaving group approach using S-thioacyldithiophosphates once again proved fruitless. Initial results employing thionoacyl nitrobenzotriazole strategies were promising with the protected N-Boc-N-methyl-O-thiobenzoylhydroxylamine 326 being isolated in good yield. However, subsequent Boc deprotection under both Lewis and Brønsted acid conditions proved ineffective. It was hoped that substituting the Boc protecting group for a sulfonamide, which could be removed under nucleophilic conditions, would alleviate this deprotection problem, unfortunately this again failed. An alternative reagent precursor N-Boc-N-methyl-O,N,N-dimethylthiocarbamatehydroxylamine 354 was prepared from the corresponding thiocarbamoyl chloride in reasonable yield, however, similar frustrations were encountered in attempting to remove the protecting group under both Lewis and Brønsted acid conditions.
Summary
Summary

Within this thesis we have examined the preparation and reactivity of a new family of hydroxylamine reagents based upon the generic scaffold 3. We have successfully introduced an α-hydroxy group in the form of an O-benzoyl group for cyclic, heterocyclic and acyclic ketones in excellent yields (72-83%). Extension of the process to include acetals was less successful but warrants further investigation. A chemoselective aspect of our chemistry was also examined with N-tert-butyl-O-benzoylhydroxylamine hydrochloride 204 reacting preferentially with aldehydes over ketones.

We modified our generic reagent to facilitate the introduction of carbonate and carbamate groups in the alpha position. This functionalisation proceeded smoothly for both cyclic and acyclic ketones in good yield (41-64%). These transformations represent the first one-step introduction of either a carbonate or carbamate group in the α position of a carbonyl compound.

Further modification of our generic reagent allowed the synthesis of α-oxytosyl ketones in very good yields of (64-81%) for a variety of cyclic, acyclic and previously inaccessible di-carbonyl substrates. This reagent also proved extremely effective for functionalising primary centres, with a regioselectivity of 4:1 primary/secondary in the case of non-symmetrical substrates.

Unfortunately, the final modification of our generic reagent proved elusive. Although two reagent precursors N-Boc-N-methyl-O-thiobenzoylhydroxylamine 326 and N-Boc-N-methyl-O-N,N-dimethylthiocarboxamoylhydroxylamine 354 were isolated, deprotection proved impossible.
Experimental
Commercially available solvents and reagents were used without further purification unless otherwise stated. Light petroleum refers to the fraction with bp 40-60 °C and ether refers to diethyl ether. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF254 that were visualised under UV light (at 254 and/or 360 nm). Infra-red (IR) spectra were recorded in the range 4000-600 cm\(^{-1}\) using KBr disks for solid samples and thin films between NaCl plates for liquid samples and are reported in cm\(^{-1}\). Melting points were recorded on a Reichert apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded in CDCl\(_3\) at 18 °C unless stated otherwise and were reported in ppm, \(J\) values were recorded in Hz and multiplicities were expressed by the usual conventions. Low-resolution mass spectra (MS) were determined using atmospheric pressure chemical ionization (APCI) unless otherwise stated. ES refers to electrospray ionization, CI refers to chemical ionization (ammonia) and EI refers to electron ionization. High-resolution mass spectra were obtained courtesy of the EPSRC Mass Spectrometry Service at University College of Wales, Swansea, UK using the ionization methods specified. Compounds prepared by literature procedures were characterised by \(^1\)H NMR and melting point analysis.

\textbf{N-Methyl-N-Boc hydroxylamine 199:}\(^\text{214}\)

\[
\begin{align*}
\text{N-Methylhydroxylamine hydrochloride (20 g, 240 mmole) was dissolved in (1:1) THF/H}_2\text{O (480 mL) at 0 °C. Potassium carbonate (16.5 g, 120 mmole) was then added in one portion. Di-}\text{-}\text{tert-butyl dicarbonate (52.3 g, 240 mmole) was dissolved in THF (60 mL) and added to the reaction mixture in three (20 mL) portions at 0 °C. The reaction was stirred for 18h gradually warming to room temperature. After this the THF was removed under reduced pressure and the remaining aqueous solution was added to DCM (300 mL) and washed with water (3 x 100 mL), brine (50 mL) and dried with Na}_2\text{SO}_4. \text{Solvent was then removed under reduced pressure. The resulting crude product was purified by distillation under reduced pressure (85-87 °C) to yield the title}
\end{align*}
\]
compound 199 as a colourless oil (34.2 g, 97%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.16 (3H, s), 1.50 (9H, s)

*N-Methyl-O-benzoylhydroxylamine hydrochloride 201:*\(^{134}\)

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{H} \\
\text{O} \\
\text{.HCl}
\end{array}
\]

Prepared in accordance with literature procedure as follows, benzoic acid (2.4 g, 20 mmole) was added portion wise to a solution of carbonyl diimidazole (3.2 g, 20 mmole) in DCM (30 mL). Once effervescence had stopped N-methylhydroxylamine hydrochloride (2.1 g, 25 mmole) was added and stirred for 20 min at room temperature. DCM (100 mL) was then added to the reaction mixture and this was washed with cold 1M HCl (20 mL), then aqueous NaHCO\(_3\) (20 mL) and dried over NaSO\(_4\). Approximately half the reaction solution was removed under reduced pressure and replaced with dry Et\(_2\)O (75 mL). HCl gas was bubbled through the reaction mixture at 0 °C for ten minutes and collected the resulting participates by filtration to yield the title compound 201 as a colourless solid (2.7g, 72%), mp 129-129.5 °C (lit. mp 123-124 °C); IR (\(\nu\), cm\(^{-1}\), Nujol) 3458, 3056, 1712, 1600, 1550, 1422, 1264; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 11.95 (2H, brs), 7.95 (2H, d, \(J = 7.0\) Hz, Ar-H), 7.73(1H, t, \(J = 7.5\) Hz, Ar-H), 7.57 (2H, dd, \(J = 7.0\) 7.5 Hz, Ar-H), 2.93 (3H, s); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 164.3 (C), 134.8 (C), 129.6 (CH), 129.6 (CH), 127.1 (CH), 37.4 (CH\(_3\)); \(m/\zeta\) (APcl) 152 [M+H]\(^+\)-HCl; HRMS (ES) found 152.0711 C\(_8\)H\(_9\)NO\(_2\) requires 151.0713 [M+H]\(^+\)-HCl

*N-tert-Butyl-O-benzoylhydroxylamine hydrochloride 204:*\(^{215}\)

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{H} \\
\text{O} \\
\text{.HCl}
\end{array}
\]

A solution of benzyol peroxide (10 g, 41 mmole) in DCM (200 mL) was added quickly in one portion to a solution of tert-butylamine (2.9 g, 41 mmole) in a pH 10.5 aqueous
NaHCO₃/NaOH buffer (200 mL) at room temperature. The reaction mixture was stirred vigorously for 18 h. Once complete by TLC the aqueous layer was extracted with DCM (3 x 50 mL). The organic layers were combined, dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude \textit{N}-tert-butyl-\textit{O}-benzoylhydroxylamine was purified by column chromatography eluting with 20% ethyl acetate/petroleum ether 40-60 °C. Conversion to the hydrochloride salt was carried out immediately by exposure of a solution of the compound in Et₂O to HCl gas. Filtration of this yielded the title compound 204 as a colourless solid (6.8 g, 85%); mp 119-121 °C; IR (\nu, \text{cm}^{-1}, \text{Nujol}) 3458, 3056, 1713, 1612, 1543, 1422, 1268; \textit{¹}H NMR (400 MHz, DMSO-\textit{d}⁶) \delta 8.00 (2H, d, \text{J} = 8.1 \text{Hz}, \text{Ar-H}), 7.73 (1H, t, \text{J} = 7.5 \text{Hz}, \text{Ar-H}), 7.53 (2H, t, \text{J} = 7.7 \text{Hz}, \text{Ar-H}), 1.19 (9H, s, \text{CCH}_3); \textit{¹}C NMR (100 MHz, DMSO-\textit{d}⁶) \delta 164.6 (C), 134.7 (C), 129.7 (CH), 129.6 (CH), 127.4 (CH), 57.9 (C), 25.5 (CH₃); \textit{m/z} (APCI) [M+H]+ -HCl 194 (100 %); HRMS found 194.1175  

\textit{C}_{11}\text{H}_{16}\text{O}_2\text{N} \text{ requires 194.1176 [M+H]+ -HCl}

(\pm)-(1\text{R},5\text{R})-5-tert-butyl-2-oxocyclohexyl benzoate 213:

\[
\begin{align*}
\text{O} & \\
\text{OBz}
\end{align*}
\]

4-tert-Butylcyclohexanone (100 mg, 0.64 mmole) was added to dimethyl sulfoxide (1.5 mL). \textit{N}-Methyl-\textit{O}-benzoyl hydroxylamine hydrochloride (119 mg, 0.64 mmole) was then added, the reaction was then stirred at room temperature for 12 h. After this the reaction mixture was add to H₂O (20 mL) and extracted with ethyl acetate (4 x 25mL), dried over MgSO₄ and the solvent was removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 25% ether/petroleum ether 40-60 °C, to yield the title compound 213 as a white solid (105 mg, 75 % yield); mp 154-156 °C; IR (\nu, \text{cm}^{-1}, \text{CHCl₃}) 2966, 1716, 1453, 1273, 1112; \textit{¹}H NMR (400MHz, CDCl₃) \delta 8.02 (2H, d, \text{J} = 7.4 \text{Hz}, \text{Ar-H}), 7.50 (1H, t, \text{J} = 7.4 \text{Hz}, \text{Ar-H}), 7.37 (2H, t, \text{J} = 7.4 \text{Hz}, \text{Ar-H}), 5.38-5.45 (1H, dd, \text{J}_{\text{H₁H₁a}} = 6.4 \text{Hz}, \text{J}_{\text{H₁H₁a}} = 11.9 \text{Hz}, \text{COCH}), 2.40-2.47 (3H, m), 2.05-2.16 (1H, m), 1.69-1.75 (2H, m), 1.45-1.51 (1H, m), 0.87 (9H, s, \text{CH(C(CH₃))₃}); \textit{¹}C NMR (100MHz, CDCl₃), \delta 204.7 (C), 165.6 (C), 133.1 (CH), 129.8
Experimental

(\text{CH}), 129.6 (\text{C}), 128.3 (\text{CH}), 76.5 (\text{CH}), 45.8 (\text{CH}), 39.6 (\text{CH}_2), 34.3 (\text{CH}_2), 32.5 (\text{C}), 28.0 (\text{CH}_2), 27.3 (\text{CH}_3); m/z (\text{APCI}) [\text{M+H}]^+ 275 (100\%), 153 (20\%); HRMS (ES) found 275.1641 \text{C}_{17}\text{H}_{23}\text{O}_3 \text{requires 275.1642 [M+H]^+}

\begin{align*}
\text{1-(4-Hydroxyphenyl)-3-oxobutan-2-yl benzoate 224:} & \\
\begin{array}{c}
\text{O} \\
\text{HO} \\
\text{OBz}
\end{array}
\end{align*}

4-(4-Hydroxyphenyl)butan-2-one (100 mg, 0.61 mmole) was added to dimethyl sulfoxide (1.5 mL). \text{A-Methyl-O-benzoyl hydroxylamine hydrochloride (113 mg, 0.61 mmole) was then added, the reaction was then stirred at 50 °C for 18 h. After this the reaction mixture was add to H}_2\text{O (20 mL) and extracted with ethyl acetate (4 x 25 mL). dried over MgSO}_4 \text{ and the solvent was removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 25% ether/petroleum ether 40-60 °C. to yield the title compound 224 as a white solid (147 mg, 83 % yield); mp 184-185 °C; IR (v, cm}^{-1}, \text{CHCl}_3) 3397, 1716, 1614, 1451, 1271, 1110. 711; ^1\text{H NMR (500MHz, CDCl}_3) \delta 7.95 (2H, d, J = 7.4Hz, Ar-H), 7.52 (1H, t, J = 7.4Hz, Ar-H), 7.39 (2H, t, J = 7.4Hz, Ar-H), 7.07 (2H, d, J = 8.5Hz, Ar-H), 6.69 (2H, d, J = 8.5Hz, Ar-H), 5.32-5.40 (1H, dd, J_{\text{H-cis}} = 5.1Hz, J_{\text{H-trans}} = 7.6Hz COCH), 4.85 (1H, bs, OH), 3.07-3.18 (2H, m, COCHCH}_2), 2.00 (3H, s, COCH}_3); ^{13}\text{C NMR(100MHz,CDCl}_3) \delta 206.0 (\text{C}), 166.0 (\text{C}), 154.7 (\text{C}), 133.5 (\text{CH}), 130.6 (\text{CH}), 129.8 (\text{CH}), 129.2 (\text{C}), 128.5 (\text{CH}), 127.8 (\text{C}), 115.5 (\text{CH}), 79.7 (\text{CH}), 36.1 (\text{CH}_2), 27.0 (\text{CH}_3); m/z (\text{APCI}) [\text{M+H}]^+ 285 (100\%); HRMS (ES) found 285.1121 \text{C}_{17}\text{H}_{17}\text{O}_4 \text{requires 285.1121 [M+H]^+}

\begin{align*}
\text{4-(4-Methoxyphenyl)butan-2-one 223:} & \\
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\end{align*}
4-(4-Hydroxyphenyl)butan-2-one (500 mg, 3.05 mmole) was added to anhydrous THF (7.5 mL) under an atmosphere of nitrogen at room temperature. NaH (80.4 mg, 3.35 mmole) was then added in two portions. Mel (43.3 mg, 3.05 mmole) was added dropwise over 5 min. The reaction mixture was then heated to reflux for 18 h. After this the reaction was cooled to room temperature and EtOH (0.5 mL) was added to neutralise any residual NaH, at which point the solvent was removed under reduced pressure and the residue re-dissolved in CH$_2$Cl$_2$ (15 mL), which was then washed with H$_2$O (2 x 5 mL), brine (10 mL) and dried over Na$_2$SO$_4$. The solvent was then removed under reduced pressure and the resulting crude product was purified by column chromatography eluting with 25% ether/petroleum ether 40-60 °C, to yield the title compound 223 as a colourless oil (494 mg, 91%); IR (v, cm$^{-1}$, CHCl$_3$) 2934, 1718, 1512, 1248, 1036, 711; $^1$H NMR (400MHz, CDCl$_3$) δ 7.15 (2H, d, $J = 8.5$Hz, Ar-H), 6.80 (2H, d, $J = 8.5$Hz, Ar-H), 3.81 (3H, s, OCH$_3$), 2.85 (2H, t, $J = 7.5$Hz, COCH$_2$CH$_2$), 2.75 (2H, t, $J = 7.5$Hz, COCH$_2$CH$_2$), 2.11 (3H, s, COCH$_3$); $^{13}$C NMR (100MHz,CDCl$_3$), δ 208.2 (C), 157.9 (C), 133.0 (C), 129.2 (CH), 113.8 (CH), 55.2 (CH$_3$), 45.4 (CH$_2$), 30.1 (CH$_3$). 28.8 (CH$_2$); $m/z$ (APCI) [M+H]$^+$ 179 (100 %), 146 (22 %), 139 (94 %), 134 (51 %), 126 (55 %), 121 (78 %); HRMS (ES) found 179.1024 C$_{11}$H$_{13}$O$_2$ requires 179.1027 [M+H]$^+$

1-(4-Methoxyphenyl)-3-oxobutan-2-yl benzoate 225:

$$\begin{align*}
\text{O} & \\
\text{O} & \text{OBz}
\end{align*}$$

4-(4-methoxyphenyl)butan-2-one (100 mg, 0.56 mmole) was added to dimethyl sulfoxide (1.5 mL). N-Methyl-O-benzoyl hydroxylamine hydrochloride (104 mg, 0.56 mmole) was then added, the reaction was then stirred at 50 °C for 18 h. After this the reaction mixture was add to H$_2$O (20 mL) and extracted with ethyl acetate (4 x 25 mL), dried over MgSO$_4$ and the solvent was removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 25% ether/petroleum ether 40-60 °C, to yield the title compound 225 as a colourless oil (142 mg, 83 % yield). IR (v, cm$^{-1}$, CHCl$_3$) 2934, 1718, 1612, 1452, 1249, 1110, 711; $^1$H NMR (400MHz, CDCl$_3$) δ 7.95 (2H, d, $J = 7.4$Hz, Ar-H), 7.52 (1H, t, $J = 7.4$Hz, Ar-H),
Experimental

7.45 (2H, t, J = 7.4Hz, Ar-H), 7.10 (2H, d, J = 8.5Hz, Ar-H), 6.75 (2H, d, J = 8.5Hz, Ar-H), 5.33-5.41 (1H, dd, J_{H-Hcis} = 5.1Hz, J_{H-Htrans} = 7.6Hz, COCH), 3.69 (3H, s, OCH\textsubscript{3}), 3.08-3.15 (2H, m, COCH\textsubscript{2}), 2.05 (3H, s, COCH\textsubscript{3}); \textsuperscript{13}C NMR(100MHz,CDCl\textsubscript{3}), δ 205.7 (C), 165.9 (C), 158.6 (C) 133.4 (CH), 130.4 (CH), 129.8 (CH), 129.3 (C), 128.5 (CH), 127.7 (C), 114.0 (CH), 79.7 (CH), 55.2 (CH\textsubscript{3}), 36.1 (CH\textsubscript{2}), 27.0 (CH\textsubscript{3}); m/z (APcI) [M+H]+ 299 (100%), 285 (10%); HRMS (ES) found 299.1279 C\textsubscript{18}H\textsubscript{19}O\textsubscript{4} requires 299.1278 [M+H]+

1-formyl-2-methylpropyl benzoate 209:

\[
\begin{array}{c}
\text{O} \\
\text{H} \\
\text{OBz}
\end{array}
\]

Isovaleraldehyde (100 mg, 1.1 mmole) was added to dimethyl sulfoxide (1.5 mL). N-Methyl-O-benzoyl hydroxylamine hydrochloride (217 mg, 1.1 mmole) was then added, the reaction was then stirred at room temperature for 24 h. After this the reaction mixture was added to H\textsubscript{2}O (20 mL) and extracted with ethyl acetate (4 x 25mL), dried over MgSO\textsubscript{4} and the solvent was removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 25% ether/petroleum ether 40-60 °C, to yield the title compound 209 as a colourless oil (185 mg, 82 % yield) IR (ν, cm\textsuperscript{-1}, CHCl\textsubscript{3}) 2357, 1749, 1689, 1111; \textsuperscript{1}H NMR (500MHz, CDCl\textsubscript{3}); δ 9.60 (1H, s, COH), 8.02 (2H, d, J = 7.4Hz, Ar-H), 7.57 (1H, t, J = 7.4Hz, Ar-H), 7.43 (2H, t, J = 7.4Hz, Ar-H), 5.00-5.09 (1H, m, COHCH), 2.36-2.49 (1H, m, COCH\textsubscript{2}CHCH\textsubscript{2}), 1.01-1.19 (6H, m, CH\textsubscript{2}(CH\textsubscript{3})\textsubscript{2}); \textsuperscript{13}C NMR (100MHz, CDCl\textsubscript{3}); δ 198.8 (C), 166.2 (C), 133.5(CH), 129.8(C), 129.3 (CH), 128.5(CH), 82.6 (CH), 29.3 (CH), 18.9 (CH\textsubscript{3}), 17.3 (CH\textsubscript{3}); m/z (APcI) [M+H]+ 207 ( 70% ); HRMS (ES) found 207.7381 C\textsubscript{12}H\textsubscript{15}O\textsubscript{3} requires 207.7381 [M+H]+
2-Oxocycloheptyl benzoate 212: 217

Cycloheptanone (0.105 mL, 0.89 mmole) was added to dimethyl sulfoxide (1.5 mL). N-Methyl-\textit{O}-benzoyl hydroxylamine hydrochloride (166 mg, 0.89 mmole) was then added, the reaction was then stirred at room temperature for 18h. After this the reaction mixture was added to H\textsubscript{2}O (20 mL) and washed with ethyl acetate (4 x 25 mL), dried over MgSO\textsubscript{4} and the solvent was removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 30% ether/petroleum ether 40-60 °C, to yield the title compound 212 as a white solid (161 mg, 79 %), mp 114-115 °C (lit. mp 57-57.5 °C) 217; IR (\textit{v}, cm\textsuperscript{-1}, CHCl\textsubscript{3}) 2926, 1717, 1271, 1113, 902; \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}); \delta 8.00 (2H, d, \textit{J} = 7.4Hz, Ar-H), 7.48 (1H, t, \textit{J} = 7.4, Ar-H), 7.35 (2H, t, \textit{J} = 7.4Hz, Ar-H), 5.34-5.40 (1H, dd, \textit{J}_{H-Ha} = 9.5Hz, \textit{J}_{H-Hc} = 3.3Hz, COCH), 2.57-2.65 (1H, m, COCH), 2.37-2.45 (1H, m, COCH), 1.99-2.07 (1H, m, COCH\textsubscript{2}CH\textsubscript{2}), 1.57-1.88 (7H, m), 1.28-1.39 (1H, m, COCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}); \textsuperscript{13}C NMR (100MHz, CDCl\textsubscript{3}); \delta 207.4 (C), 165.7 (C), 133.2 (CH), 129.8 (C), 129.6 (C), 128.0 (CH), 79.0 (CH), 40.7 (CH\textsubscript{2}), 30.3 (CH\textsubscript{2}), 28.3 (CH\textsubscript{2}), 26.4 (CH\textsubscript{2}), 23.0 (CH\textsubscript{2}); \textit{m/z} (APcI) [M+H]\textsuperscript{+} 233 (100 %), 157 (60 %), 139 (40 %), 175 (20 %); HRMS (ES) found 233.1172 C\textsubscript{14}H\textsubscript{17}O\textsubscript{3} requires 233.1172 [M+H]\textsuperscript{+}

2-Oxocyclohexyl benzoate 210: 218

Cyclohexanone (100 mg, 1.0 mmole) was added to dimethyl sulfoxide (1.5 mL). N-Methyl-\textit{O}-benzoyl hydroxylamine hydrochloride (187 mg, 1.0 mmole) was then added, the reaction was then stirred at room temperature for 18h. After this the reaction mixture was added to H\textsubscript{2}O (20 mL) and extracted with ethyl acetate (4 x 25 mL), dried over MgSO\textsubscript{4} and the solvent removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 25 % ether/petroleum ether 40-60
Experimental

°C. to give the title compound 210 as a white solid (150 mg, 72 %); mp 102-104 °C (lit. mp 105-106.5 °C)\textsuperscript{18}; IR (\nu, \text{cm}^{-1}, \text{CHCl}_3) 2926, 1717, 1271, 1113, 902; \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}); \delta 8.00 (2H, d, \textit{J} = 7.4Hz, Ar-H), 7.48 (1H, t, \textit{J} = 7.4, Ar-H), 7.35 (2H, t, \textit{J} = 7.4Hz, Ar-H), 5.35-5.42 (1H, dd, \textit{J}_{1,11a} = 11.6Hz, \textit{J}_{11a,11c} = 6.5Hz, COCH), 2.32-2.59 (3H, m), 1.51-2.09 (5H, m), \textsuperscript{13}C NMR (100MHz, CDCl\textsubscript{3}); \delta 204.3 (C), 165.5 (C), 133.1 (CH), 130.1 (C), 129.8 (CH), 128.4 (CH), 76.7 (CH), 40.7 (CH\textsubscript{2}), 33.2 (CH\textsubscript{2}), 27.2 (CH\textsubscript{2}), 23.8 (CH\textsubscript{2}); m/z (APCI) [M+H]\textsuperscript{+} 219 (100% ); HRMS (ES) found 219.0974 C\textsubscript{13}H\textsubscript{15}O\textsubscript{3} requires 219.0976 [M+H]\textsuperscript{+}

2-Oxocyclopentyl benzoate 211:

Cyclopentanone (100 mg, 1.2 mmole) was added to dimethyl sulfoxide (1.5 mL). N-Methyl-O-benzoyl hydroxylamine hydrochloride (224 mg, 1.2 mmole) was then added, the reaction was then stirred at room temperature for 18h. After this the reaction mixture was added to H\textsubscript{2}O (20 mL) and extracted with ethyl acetate (4 x 25 mL), dried over MgSO\textsubscript{4} and the solvent removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 25% ether/petroleum ether 40-60 °C, to yield the title compound 211 as a colourless oil (177 mg, 73%) (lit. mp 88-91 °C); IR (\nu, \text{cm}^{-1}, \text{CHCl}_3) 2926, 1717, 1271, 1113, 902; \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}); \delta 8.00 (2H, d, \textit{J} = 7.5Hz, Ar-H), 7.48 (1H, t, \textit{J} = 7.5, Ar-H), 7.35 (2H, t, \textit{J} = 7.5Hz, Ar-H), 5.35-5.41 (1H,m, COCH), 1.80-2.35 (6H, m), \textsuperscript{13}C NMR (100MHz, CDCl\textsubscript{3}); \delta 204.3 (C), 165.5 (C), 133.1 (CH), 130.1 (C), 129.8 (CH), 128.4 (CH), 76.7 (CH), 40.7 (CH\textsubscript{2}), 33.2 (CH\textsubscript{2}), 27.2 (CH\textsubscript{2}), 23.8 (CH\textsubscript{2}); m/z (APCI) [M+H]\textsuperscript{+} 205 (65% ); HRMS (ES) found 205.0819 C\textsubscript{12}H\textsubscript{13}O\textsubscript{3} requires 205.0820 [M+H]\textsuperscript{+}
2-Oxoheptan-3-yl benzoate 226:

2-Heptanone (100 mg, 0.8 mmole) was added to dimethyl sulfoxide (1.5 mL). N-Methyl-O-benzoyl hydroxylamine hydrochloride (163 mg, 0.8 mmole) was then added, the reaction was then stirred at 50 °C for 18h. After this the reaction mixture was added to H$_2$O (20 mL) and extracted with ethyl acetate (4 x 25 mL), dried over MgSO$_4$ and the solvent removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 25% ether/petroleum ether 40-60 °C, to yield the title compound 226 as a colourless oil (151 mg, 81%); IR (v, cm$^{-1}$, CHCl$_3$) 2964, 1716, 1270, 1112, 713; $^1$H NMR (400MHz, CDCl$_3$); δ 8.00 (2H, d, $J$ = 7.4Hz, Ar-H), 7.48 (1H, t, $J$ = 7.4, Ar-H), 7.35 (2H, t, $J$ = 7.4Hz, Ar-H), 5.15-5.24 (1H, m, COCH), 2.13 (3H, s, COCH$_3$), 1.75-1.90 (2H, m, COCH$_2$), 1.31-1.57 (4H, m), 0.74 (3H, t, $J$ = 7.1Hz, CH$_2$CH$_3$), $^{13}$C NMR (100MHz,CDCl$_3$); δ 205.7 (C), 166.6 (C), 133.4 (CH), 129.8 (C), 129.4 (CH), 128.5 (CH), 79.2 (CH), 30.2 (CH$_2$), 27.4 (CH$_2$), 26.2 (CH$_3$), 22.4 (CH$_2$), 13.8 (CH$_3$); m/z (APCI) [M+H]$^+$ 235 (100 %); HRMS (ES) found 235.1328 C$_{14}$H$_{18}$O$_3$ requires 235.1329 [M+H]$^+$

1-(Toluene-4-sulfonyl)-4-piperidone 217a:

$p$-Toluenesulphonyl chloride (1.0 g, 5.24mmole) was added in one portion to a solution to 4-piperidinone monohydrate (709 mg, 5.24 mmole), Et$_3$N (0.65 mL) and DMAP (10 mole%) in acetonitrile (12 mL). The reaction was stirred over night at room temperature after which the reaction solvent was removed under reduced pressure and the crude solid re-digested with DCM (50 mL). This was washed with 1M HCl (2 x 20 mL), water (2 x 20 mL) and brine (20 mL). The reaction solvent was removed under reduced pressure and the crude product purified by recrystallisation with ethanol to give the title compound 217a as a white solid (1.13 g, 85 %); mp 120-124 °C (lit. mp 129-132 °C).
Experimental

$^1$H NMR (400MHz, CDCl$_3$), δ 7.68 (2H, d, $J$ = 8.0Hz), 7.34 (2H, d, $J$ = 7.4 Hz), 3.39 (4H, t, $J$ = 5.9 Hz), 2.53 (4H, t, $J$ = 5.9 Hz), 2.34 (3H, s)

4-Oxo-1-tosylpiperidin-3-yl benzoate 217:

\[
\begin{align*}
\text{\(SO\)} & \quad \text{\(NO\)} \\
\text{\(OBz\)} & \quad \text{\(OBz\)}
\end{align*}
\]

1-tosylpiperidin-4-one (100 mg, 0.40 mmole) was added to dimethyl sulfoxide (1.5 mL). N-Methyl-O-benzoyl hydroxylamine hydrochloride (73 mg, 0.40 mmole) was then added, the reaction was then stirred at room temperature for 18h. After this the reaction mixture was added to H$_2$O (20 mL) and extracted with ethyl acetate (4 x 25 mL), dried over MgSO$_4$ and the solvent removed under reduced pressure. The resulting crude product was purified by recrystallisation in ethanol, to yield the title compound 217 as a white solid (101 mg, 72%); mp 235-237 °C. IR (v, cm$^{-1}$, CHCl$_3$) 1726, 1599, 1451, 1347, 1264, 1167, 1112, 731; $^1$H NMR (400MHz, CDCl$_3$); δ 7.95 (2H, d, $J$ = 8.0Hz, Ar-H), 7.66 (2H, d, $J$ = 8.0Hz, Ar-H), 7.54 (1H, t, $J$ = 7.4Hz, Ar-H), 7.38 (2H, t, $J$ = 7.4Hz, Ar-H), 7.31 (2H, d, $J$ = 8.0Hz, Ar-H), 5.45-5.57 (1H, dd, $J_{H-He}$ = 6.7Hz, $J_{H-Ha}$ = 10.5Hz, COCH), 4.25-4.35 (1H, m, COCHCH), 4.01-4.10 (1H, m, COCHCH), 2.80-2.91 (1H, m, COCH$_2$CH), 2.68-2.75 (2H, m, COCH$_2$), 2.38-2.57 (1H, m, COCH$_2$CH), 2.34 (3H, s, CH$_3$); $^1$3C NMR (100MHz, CDCl$_3$) δ 199.8 (C), 165.8 (C), 144.4 (C), 133.7(C), 133.5(CH), 130.1(CH) 129.9(CH), 128.8(C), 128.4(CH), 127.5(CH), 73.2 (CH), 49.7 (CH$_2$), 46.2 (CH$_2$), 39.8 (CH$_2$), 21.5 (CH$_3$); m/z (APci) [M+H]$^+$ 374 (100 %), 252 (80 %); HRMS (ES) found 374.0942 C$_{19}$H$_{19}$NO$_5$S requires 374.0942 [M+H]$^+$

4-Oxo-1-(ethyl carbamoylformate)piperidin-3-yl benzoate 216:

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{OBz} & \quad \text{OBz}
\end{align*}
\]
Experimental

Ethyl 2-oxo-2-(4-oxopiperidin-1-yl)acetate (100 mg, 0.50 mmole) was added to dimethyl sulfoxide (1.5 mL). N-methyl-O-benzoyl hydroxylamine hydrochloride (93 mg, 0.50 mmole) was then added, the reaction was then stirred at room temperature for 18h. After this the reaction mixture was added to H₂O (20 mL) and extracted with ethyl acetate (4 x 25 mL), dried over MgSO₄ and reduced. The resulting crude product was purified by recrystallisation in ethanol, to yield the title compound 216 as a white solid (110 mg, 69%), mp 245-247 °C; IR (ν, cm⁻¹, CHCl₃) 1727, 1665, 1451, 1267, 1187, 711; ¹H NMR (400MHz, CDCl₃) δ 8.02 (2H, d, J = 7.4Hz, Ar-H), 7.53 (1H, t, J = 7.4Hz, Ar-H), 7.34 (2H, t, J = 7.4Hz, Ar-H), 5.31-5.51 (1H, m, COCH), 4.85-4.92 (m), 4.50-4.60 (m), 4.25-4.31 (2H, m, COCH₂CH₃), 4.15-4.21 (m), 3.95-4.05 (m), 3.59-3.70 (m), 3.40-3.49 (m), 3.25-3.37 (m), 2.60-2.85 (2H, m, COCH₂), 1.22-1.32 (3H, m, COCH₂CH₃) ¹³C NMR (100MHz, CDCl₃); δ 205.6 (C), 199.9 (C), 164.8 (C), 144.5 (C), 133.5 (CH), 129.2 (C), 128.4 (CH), 127.4 (CH), 73.2 (CH), 49.7 (CH₂), 46.2 (CH₂), 45.8 (CH₂), 39.8 (CH₂), 21.5 (CH₃); m/z (APci) [M+H]+ 320 (75 %); HRMS (ES) found 320.1089 C₁₆H₁₈NO₆ Requires 320.1090 [M+H]+

Tetrahydro-4-oxo-2H-pyran-3-yl benzoate 214:

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OBz

O

Tetrahydropyran-4-one (100 mg, 0.99 mmole) was added to dimethyl sulfoxide (1.5 mL). N-Methyl-O-benzoyl hydroxylamine hydrochloride (186 mg, 0.99 mmole) was then added, the reaction was then stirred at room temperature for 18h. After this the reaction mixture was added to H₂O (20 mL) and extracted with ethyl acetate (4 x 25 mL), dried over MgSO₄ and the solvent removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 25% ether/petroleum ether 40-60 °C, to yield the title compound 214 as a colourless oil (172 mg, 75%); IR (ν, cm⁻¹, CHCl₃) 2863, 1721, 1602, 1451, 1278, 1123, 710; ¹H NMR (400MHz, CDCl₃) δ 8.00 (2H, d, J = 7.4Hz, Ar-H), 7.52 (1H, t, J = 7.4Hz, Ar-H), 7.38 (2H, t, J = 7.4Hz, Ar-H), 5.40-5.50 (1H, dd, J₉,₁₁₈a = 10.5Hz, J₁₁₈,₁₁₆c = 7.0Hz, COCH), 4.40-4.51 (1H, m, COCHCH), 4.25-4.32 (1H, m, COCHCH), 3.60-3.75 (2H, m,
Experimental

COCH$_2$, 2.70-2.83 (1H, m, COCH$_2$CH), 2.41-2.55 (1H, m, COCH$_2$CH) $^{13}$C NMR (100MHz, CDCl$_3$), $\delta$ 200.5 (C), 165.0 (C), 133.5 (CH), 130.1 (C), 129.9 (CH), 128.4 (CH), 74.0 (CH), 70.5 (CH$_2$), 68.5 (CH$_2$), 42.2 (CH$_2$); $m/z$ (APci) [M+H]$^+$ 221 (100 %), 153 (24 %), 139 (21 %); HRMS (ES) found 221.0808 C$_{12}$H$_{12}$O$_4$ requires 221.0808 [M+H]$^+$

Tetrahydro-4-oxo-2H-thiopyran-3-yl benzoate 215:

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\begin{align*}
\text{O} & \quad \text{OBz} \\
S
\end{align*}
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Tetrahydrothiopyran-4-one (100 mg, 0.86 mmole) was added to dimethyl sulfoxide (1.5 mL). N-Methyl-O-benzoyl hydroxylamine hydrochloride (160 mg, 0.86 mmole) was then added, the reaction was then stirred at room temperature for 18h. After this the reaction mixture was added to H$_2$O (20 mL) and extracted with ethyl acetate (4 x 5mL), dried over MgSO$_4$ and the solvent was removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 25% ether/petroleum ether 40-60 °C, to yield the title compound 215 as a colourless oil (152 mg, 75%). IR (v, cm$^{-1}$, CHCl$_3$) 1718, 1266, 1111, 709; $^1$H NMR (400MHz, CDCl$_3$); $\delta$ 8.00 (2H, d, $J = 7.4$Hz, Ar-H), 7.52 (1H, t, $J = 7.4$Hz, Ar-H), 7.38 (2H, t, $J = 7.4$Hz, Ar-H), 5.49-5.61 (1H, dd, $J_{H-Ha} = 11.2$Hz, $J_{H-He} = 6.1$Hz COCH), 3.05-3.19 (2H, m, COCH$_2$), 2.85-2.95 (4H, m); $^{13}$C NMR (100MHz,CDCl$_3$), $\delta$ 206.2(C), 166.0 (CO), 133.6 (CH), 130.1 (CH), 129.2 (C), 128.4 (CH), 76.7 (CH), 44.1 (CH$_2$), 34.6 (CH$_2$), 30.42 (CH$_2$); $m/z$ (APci) [M+H]$^+$ 237 (100 %), 153 (55 %), 139 (60 %), 123 (29 %); HRMS (ES) found 237.0578 C$_{12}$H$_{12}$O$_3$S requires 237.0580 [M+H]$^+$

1,1-Dimethoxy-2-benzoyloxyheptane 232:

138
To a flame dried Radley tube, anhydrous methanol (1.5 mL) was added under an atmosphere of N₂. To this 1,1-dimethoxyheptane (0.12 mL, 0.62 mmole) was added. N-Methyl-O-benzoyl hydroxylamine hydrochloride (115 mg, 0.62 mmole) was finally added. The reaction was then heated to 50 °C for 24h. The reaction solution was then removed under reduced pressure and the crude residue purified by column chromatography eluting with 30% ether/petroleum ether 40-60°C, to yield the title compound 232 as a colourless oil (43 mg, 24 %); IR (ν, cm⁻¹, CHCl₃) 2937, 1780, 1190, 1050; ¹H NMR (400MHz, CDCl₃) δ 8.00 (2H, d, J = 7.4Hz, Ar-H), 7.40 (1H, t, J = 7.4Hz, Ar-H), 7.35 (2H, t, J = 7.4Hz, Ar-H), 5.16-5.29 (1H, m, ArCO₂CH), 4.35 (1H, d, J = 5.4Hz, CH₃OCH), 3.41 (3H, s, OCH₃), 3.35 (3H, s, OCH₃), 1.75-1.92 (2H, m, CHCH₂), 1.25-1.40 (6H, m, CHCH₂(CH₃)₂), 0.75-0.91 (3H, m, CHCH₃); ¹³C NMR (100MHz,CDCl₃) δ 166.1 (C), 132.9 (CH), 130.2 (C), 129.7 (CH₃), 128.3 (CH), 104.6 (CH₂), 73.2 (CH), 55.4 (CH₃), 54.4(CH₃), 31.3 (CH₂), 29.7 (CH₂), 24.8 (CH₂), 22.6 (CH₂), 14.0 (CH₃); m/z (ES) [M+NH₄]+ 298 (2 %), 250 (10 %), 249 (100 %), 208 (25 %), 159 (21 %), 142 (35 %); HRMS found 298.2012 C₁₆H₂₈O₄N requires 298.2013 [M+NH₄]⁺

1,1-Dimethoxy-2-benzoylloxycyclohexanone 230:

To a flame dried Radley tube, anhydrous methanol (1.5 mL) was added under an atmosphere of N₂. To this cyclohexanone dimethyl ketal (0.10 mL, 0.70 mmole) was added. N-Methyl-O-benzoyl hydroxylamine hydrochloride (104 mg, 0.70 mmole) was finally added. The reaction was then heated to 50 °C for 24h. The reaction solution was then under reduced pressure and the crude residue purified by column chromatography eluting with 25% ether/petroleum ether 40-60°C, to yield the title compound 230 as a
colourless oil (55 mg, 30 %), IR (v, cm\(^{-1}\), CHCl\(_3\)) 2937, 1721, 1210, 1069; \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\) 7.99 (2H, d, \(J = 7.4\)Hz, Ar-H), 7.48 (1H, t, \(J = 7.4\)Hz, Ar-H), 7.37 (2H, t, \(J = 7.4\)Hz, Ar-H), 5.24 (1H, m, CCH), 3.11 (3H, s, OCH\(_3\)), 3.09 (3H, s, OCH\(_3\)), 1.25-1.90 (8H, m, (CH\(_2\))\(_4\)); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 165.5 (C), 132.9 (CH), 130.5 (C), 129.7 (CH), 128.3 (CH), 99.3 (C), 70.0 (CH), 47.8 (CH\(_3\)), 47.5 (CH\(_3\)), 28.6 (CH\(_2\)), 27.8 (CH\(_2\)), 21.8 (CH\(_2\)), 20.1 (CH\(_2\)); m/z (ES) [M+NH\(_4\)]\(^+\) 282 (3 %), 233 (64 %), 146 (10 %), 142 (100 %); HRMS found 282.1700 C\(_{15}\)H\(_{24}\)O\(_4\)N requires 282.1700 [M+NH\(_4\)]\(^+\)

\(N\)-Methyl-\(O\)-allylcarbonatehydroxylamine hydrochloride 253:

\[\text{N-Methyl-N-Boc hydroxylamine (5 g, 33.9 mmole)} \rightarrow \text{A-Methyl-A-Boc hydroxylamine (5 g, 33.9 mmole)} \]

\(\text{in DCM (70 mL) at 0 °C under an atmosphere of N}_2\).

\(\text{Et}_3\text{N (3.4 g, 33.9 mmole)} \rightarrow \text{was added dropwise over several minutes. The reaction was stirred for 18h gradually warming to room temp. Upon completion the reaction mixture was quickly washed with 1M cold aqueous HCl (20 mL) followed by water (50 mL). brine (50 mL) and dried with Na\(_2\)SO\(_4\). Solvent was removed under reduced pressure and the resulting crude product subjected to column chromatography eluting with 20% ethyl acetate/ petroleum ether 40-60 °C. Upon exposure to dry HCl gas bubbled through anhydrous Et\(_2\)O for 20 min at 0 °C, simultaneous deprotection, isolation as the hydrochloride salt was achieved giving the title compound 253 as a pale yellow solid (4.3g, 77%); mp 87-88 °C; IR (v, cm\(^{-1}\), CHCl\(_3\)) 2937, 1721, 1210, 1069; \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\) 5.82-5.94 (1H, m, CH\(_2\)CHCH\(_2\)), 5.34 (1H, d, \(J = 17.1\)Hz, CH\(_2\)CHCH\(_2\)), 5.25 (1H, d, \(J = 10.4\)Hz, CH\(_2\)CHCH\(_2\)), 4.66 (2H, d, \(J = 5.8\) Hz, CH\(_2\)CHCH\(_2\)), 3.19 (3H, s, NCH\(_3\)); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 151.6 (C), 129.5 (CH), 121.2 (CH\(_2\)), 71.9 (CH\(_2\)), 35.9 (CH\(_3\)); HRMS (ES) found 132.0616 C\(_3\)H\(_6\)NO\(_3\) requires 132.0616 [M+H]\(^+\)
**5,5-monoketal 2-oxocyclohexyl allylcarbonate 262:**

Cyclohexanone-1,4 monoketal (100 mg, 0.64 mmole) was added to tetrahydrofuran (1.5 mL). N-Methyl-O-allyl carbonate hydroxylamine hydrochloride (158 mg, 0.96 mmole) was then added, the reaction was then stirred at 50 °C for 18h. After this the reaction mixture was added to H_2O (20 mL) and extracted with ethyl acetate (4 x 25mL), dried over MgSO_4 and the solvent removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 50% ethyl acetate /petroleum ether 40-60 °C, to yield the title compound 262 as a colourless oil (63 mg, 41%); IR (ν, cm^{-1}, CHCl_3) 3452, 1734, 1442, 1363, 1244, 1122, 784; ^1H NMR (400MHz, CDCl_3); δ 5.80-5.95 (1H, m, CH_2CHCH_2), 5.29-5.36 (1H, d, J = 17.2Hz, CH_2CHCHH), 5.18-5.25(2H, m), 4.59 (2H, d, J = 5.8Hz, CH_2CHCH_2), 3.89-4.15 (4H, m, OCH_2CH_2O), 2.55-2.70 (1H, m, CHH), 2.25-2.45 (2H, m, CH_2), 2.07 (1H, t, J = 12.9Hz, CH_2), 1.75-2.00 (2H, m, CH_2); ^13C NMR (100MHz,CDCl_3), δ 203.1 (C), 153.9 (C), 131.2 (CH), 119.0 (CH_2), 107.1 (C), 76.1 (CH), 68.8 (CH_2), 64.9 (CH_2), 64.8 (CH_2), 40.0 (CH_2), 35.5 (CH_2), 34.3 (CH_2); APci [M+H]^+ 257 ( 100% ); HRMS (ES) found 257.0980 C_{12}H_{16}O_6 requires 257.0980 [M+H]^+

**2-Oxocyclohexyl allylcarbonate 259:**

Cyclohexanone (100 mg, 1.01 mmole) was added to tetrahydrofuran (1.5 mL). N-Methyl-O-allyl carbonate hydroxylamine hydrochloride (225 mg, 1.52 mmole) was then added, the reaction was then stirred at 50 °C for 18h. After this the reaction mixture was added to H_2O (20 mL) and extracted with ethyl acetate (4 x 25 mL), dried over MgSO_4 and the solvent removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 50% ethyl acetate /petroleum ether.
Experimental

40-60°C, to yield the title compound 259 as a colourless oil (113 mg, 61%); IR (ν, cm⁻¹, CHCl₃) 3453, 1734, 1442, 1363; ¹H NMR (400MHz, CDCl₃), δ 5.88-6.00 (1H, m, CH₂CH₂CH₂), 5.33 (1H, d, J = 15.9Hz, CH₂CH₂CH₂H), 5.23 (1H, d, J = 11.7Hz, CH₂CH₂CH₂H), 4.91-5.05 (1H, dd, J₁₁₁₂ = 6.5Hz, J₁₂₁₃ = 11.9Hz, COCH), 4.50-4.65 (2H, m, CH₂CH₂CH₂), 2.49-2.65 (1H, m), 2.25-2.30 (2H, m), 1.95-2.10 (1H, m), 1.88-1.93 (1H, m), 1.62-1.84 (2H, m), 1.50-1.83 (1H, m); ¹³C NMR (100MHz, CDCl₃), δ 204.1 (C), 154.1 (C), 131.3 (CH), 118.9 (CH₂), 79.4 (CH), 68.7 (CH), 40.5 (CH₂), 32.9 (CH₂), 27.0 (CH₂), 23.6 (CH₂); m/z (APcl) [M+H]⁺ 199 (100 %), 137 (45 %); HRMS (ES) found 199.0965 C₁₀H₁₅O₄ requires 199.0965 [M+H]⁺

Ethyl 4-methyl-2-oxopentan-3-yl allylcarbonate 260:

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4-Methylpentan-2-one (100 mg, 0.99 mmole) was added to tetrahydrofuran (1.5 mL). N'-Methyl-O-allyl carbonate hydroxylamine hydrochloride (247 mg, 1.49 mmole) was then added, the reaction was then stirred at 50 °C for 18h. After this the reaction mixture was added to H₂O (20 mL) and extracted with ethyl acetate (4 x 25 mL), dried over MgSO₄ and the solvent removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 50% ethyl acetate/petroleum ether 40-60 °C, to yield the title compound 260 as a colourless oil (97 mg, 53%); IR (ν, cm⁻¹, CHCl₃) 3453,1734, 1442, 1362, 1122, 709; ¹H NMR (400MHz, CDCl₃), δ 5.90-6.01 (1H, m, CH₂CH₂CH₂), 5.33 (1H, d, J = 17.2Hz, CH₂CH₂CH₂H), 5.23 (1H, d, J = 10.4Hz, CH₂CH₂CH₂H), 4.70 (1H, d, J = 4.2Hz, COCH), 4.59 (2H, d, J = 5.7Hz, COCH₂), 2.10-2.20 (1H, m, COCH₂H), 2.05 (3H, s, COCH₃), 0.95 (3H, d, J = 6.8Hz CHCH₃), 0.87 (3H, d, J = 6.8Hz, CHCH₃); ¹³C NMR (100MHz, CDCl₃), δ 205.2 (C), 154.9 (C), 131.2 (CH), 119.2 (CH₂), 85.9 (CH), 68.9 (CH₂), 29.7 (CH), 26.8 (CH₃), 19.0 (CH₃), 16.5 (CH₃); m/z (APcl) [M+H]⁺ 201 (100 %); HRMS (ES) found 201.1120 C₁₀H₁₅O₄ requires 201.1121 [M+H]⁺

2-Oxohexan-3-yl allylcarbonate 261:

142
2-Heptanone (100 mg, 0.87 mmole) was added to tetrahydrofuran (1.5 mL). N-Methyl-O-allyl carbonate hydroxylamine hydrochloride (216 mg, 1.31 mmole) was then added, the reaction was then stirred at 50 °C for 18h. After this the reaction mixture was added to H2O (20 mL) and extracted with ethyl acetate (4 x 25 mL), dried over MgSO4 and the solvent removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 50% ethyl acetate /petroleum ether 40-60 °C, to yield the title compound 261 as a colourless oil (93 mg, 50%); IR (v, cm⁻¹, CHCl₃) 3453, 1733, 1442, 1362, 1122, 709; ¹H NMR (400MHz, CDCl₃), δ 5.85-6.00 (1H, m, CH₂CHCH₂), 5.34 (1H, d, J = 17.8Hz, CH₂CHCHH), 5.23 (1H, d, J = 10.5Hz, CH₂CHCHH), 4.82 (1H, dd, JH-Hcis = 4.5Hz, JH-Htrans = 8.0Hz, COCH), 4.57-4.58 (2H, d, J = 4.2Hz, CH₂CHCH₂), 2.10 (3H, s, COCH₃), 1.60-1.80 (2H, m, COCHCH₂), 1.25-1.40 (4H, m, CH₂(CH₂)₂CH₃), 0.85 (3H, t, J = 7.3Hz, CH₂CH₃); ¹³C NMR (100MHz,CDCl₃), δ 205.2 (C), 154.6 (C), 131.2 (CH), 119.2 (CH₂), 81.8 (CH), 68.8 (CH₂), 30.1 (CH₂), 27.0 (CH₂), 25.9 (CH₃), 22.3 (CH₂), 13.7 (CH₃); m/z (APCI) [M+H]+ 215 (100 %); HRMS (ES) found 215.1278 C₁₁H₁₆O₄ requires 215.1278. [M+H]+

2-Oxocycloheptyl allylcarbonate 263:

Cycloheptanone (100 mg, 0.89 mmole) was added to tetrahydrofuran (1.5 mL). N-Methyl-O-allyl carbonate hydroxylamine hydrochloride (220 mg, 1.33 mmole) was then added, the reaction was then stirred at 50 °C for 18h. After this the reaction mixture was added to H₂O (20 mL) and extracted with ethyl acetate (4 x 25 mL), dried over MgSO₄ and the solvent removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 50% ethyl acetate /petroleum ether 40-60 °C, to yield the title compound 263 as a colourless oil (103 mg, 55%); IR (v, cm⁻¹, CHCl₃) 3452, 1732, 1442, 1362, 1122; ¹H NMR (400MHz, CDCl₃), δ 5.85-6.05 (1H, m, CH₂CHCH₂), 5.34 (1H, d, J = 17.8Hz, CH₂CHCHH), 5.21 (1H, d, J = 10.3Hz,
CH$_2$CHCH$_2$H), 5.08 (1H, dd, $J_{H-1a} = 9.5$Hz, $J_{H-1e} = 3.5$Hz, COCH), 4.57 (2H, d, $J = 5.6$Hz, CH$_3$CHCH$_2$), 2.59-2.72 (1H, m), 2.35-2.44 (1H, m), 1.85-2.00 (1H, m), 1.62-1.91 (6H, m), 1.27-1.35 (1H, m); $^{13}$C NMR (100MHz,CDCl$_3$), $\delta$ 207.0 (C), 154.2 (C), 131.3 (CH), 119.0 (CH$_2$), 81.3 (CH), 68.7 (CH$_2$), 40.5 (CH$_2$), 30.2 (CH$_2$), 28.5 (CH$_2$), 26.2 (CH$_2$), 23.0 (CH$_2$); m/z (APcI) [M+H]$^+$ 213 (90 %), 111 (100 %), 83 (82 %) HRMS (ES) found 213.1123 C$_{11}$H$_{18}$O$_4$ requires 213.1121 [M+H]$^+$

$N$-Methyl-$O$-$N$,$N$-dimethylcarbamatehydroxylamine hydrochloride 250:

\[ \text{H} \quad \text{N} \quad \text{O} \quad \text{N} \quad \text{HCl} \]

$N$-Methyl-$N$-Boc hydroxylamine (5g, 33.9mmole) was added to a solution of $N$,$N$ dimethylcarbanamol chloride (3.6g, 34mmole) and Et$_3$N (3.4g, 33.9mmole) in DCM (70 mL) at 0 °C under an atmosphere of N$_2$, including 10mol% DMAP. The reaction was stirred for 18h gradually warming to room temp. Upon completion the reaction mixture was quickly washed with 1M cold aqueous HCl (20mL) followed by water (50mL), brine (50mL) and dried with Na$_2$SO$_4$. Solvent was removed under reduced pressure and the resulting crude product was purified by distillation under reduced pressure. Upon exposure to dry HCl gas bubbled through a solution of anhydrous Et$_2$O for 45min at 0 °C, simultaneous deprotection, isolation as the hydrochloride salt gave the title compound 250 as a colourless solid (4.2g, 81%), mp 102-104 °C; IR (v, cm$^{-1}$, CHCl$_3$) 3427, 2937, 1731; $^1$H NMR (400MHz, CDCl$_3$), $\delta$ 2.95 (3H, s, NCH$_3$), 2.97 (3H, s, CONCH$_3$), 2.85 (3H, s, CONCH$_3$); $^{13}$C NMR(100MHz, CDCl$_3$) 151.9 (C), 37.9 (CH$_3$), 36.5 (CH$_3$), 36.1 (CH$_3$); m/z (APcI) [M+H]$^+$-HCl 119 (62%) HRMS (ES) found 119.0774 C$_4$H$_{11}$N$_2$O$_2$ requires 119.0776 [M+H]$^+$-HCl
2-Oxocyclohexyl dimethylcarbamate 254:

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Cyclohexanone (100 mg, 1.01 mmole) was added to tetrahydrofuran (1.5 mL). N-Methyl-O-dimethyl carbamate hydroxylamine hydrochloride (234 mg, 1.51 mmole) was then added and stirred at 50 °C for 18h. After this the reaction mixture was added to H₂O (20 mL) and extracted with ethyl acetate (4 x 25 mL), dried over MgSO₄ and the solvent removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 50% ethyl acetate /petroleum ether 40-60 °C, to yield the title compound 254 as a colourless oil (112 mg, 60 %); IR (v, cm⁻¹, CHCl₃) 2937, 1789, 1651, 1149; ¹H NMR (400MHz, CDCl₃), δ 5.05 (1H, dd, J₂-H₁ = 12.0Hz, J₃-H₄ = 7.1Hz, COCH), 2.95 (3H, s, NCH₃), 2.90 (3H, s, NCH₃), 2.20-2.45 (3H, m), 1.90-2.00 (1H, m), 1.80-1.90 (1H, m), 1.65-1.80 (2H, m), 1.45-1.55 (1H, m); ¹³C NMR (100MHz, CDCl₃), δ 206.0 (C), 155.5 (C), 77.4 (CH), 40.7 (CH₂), 36.5 (CH₃), 35.9 (CH₃), 33.4 (CH₂), 27.2 (CH₂), 23.8 (CH₂); m/z (APci) [M+H]+ 186 (100 %); HRMS (ES) found 186.1123 C₉H₁₆N₂O₃ requires 186.1125 [M+H]⁺

2-Oxoheptan-3-yl dimethylcarbamate 256:

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2-Heptanone (100 mg, 0.87 mmole) was added to tetrahydrofuran (1.5 mL). N-Methyl-O-dimethyl carbamate hydroxylamine hydrochloride (200 mg, 1.30 mmole) was then added and stirred at 50 °C for 18h. After this the reaction mixture was added to H₂O (20 mL) and extracted with ethyl acetate (4 x 25 mL), dried over MgSO₄ and the solvent removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 50% ethyl acetate /petroleum ether 40-60 °C, to yield the title compound 256 as colourless oil (87 mg, 50%); IR (v, cm⁻¹, CHCl₃) 2937, 1789, 1651, 1149; ¹H NMR (400MHz, CDCl₃), δ 4.91 (1H, dd, J = 4.7Hz, J = 8.6Hz, COCH),
Experimental

2.95 (3H, s, NCH₃), 2.90 (3H, s, NCH₃), 2.17 (3H, s, COCH₃), 1.70-1.90 (2H, m), 1.26-1.40 (4H, m), 0.55 (3H, t, J = 7.1Hz, CH₂CH₃); ¹³C NMR (100MHz, CDCl₃), δ 207.0 (C), 155.9 (C), 79.4 (CH), 36.5 (CH₃), 36.0 (CH₃), 30.2 (CH₂), 27.4 (CH₂), 26.1 (CH₃), 22.3 (CH₂), 13.8 (CH₃); m/z (APcI) [M+H]^+ 202 (100 %); HRMS (ES) found 202.1440 C₁₀H₁₉NO₃ requires 202.1438 [M+H]^+

4-Methyl-2-oxopentan-3-yl dimethylcarbamate 255:

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O \\
O \ N \\
O \\
\end{array}\]

4-Methylpentan-2-one (100 mg, 0.99 mmole) was added to tetrahydrofuran (1.5 mL). N-Methyl-O-dimethyl carbamate hydroxylamine hydrochloride (228 mg, 1.48 mmole) was then added and stirred at 50 °C for 18h. After this the reaction mixture was added to H₂O (20 mL) and extracted with ethyl acetate (4 x 25 mL), dried over MgSO₄ and the solvent removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 50% ethyl acetate /petroleum ether 40-60 °C, to yield the title compound 255 as a colourless oil (119 mg, 64%); IR (v, cm⁻¹, CHCl₃) 2937, 1789, 1651, 1147; ¹H NMR (400MHz, CDCl₃), δ 4.70 (1H, d, J= 4.3Hz, COCH), 2.95 (3H, s, NCH₃), 2.87 (3H, s, NCH₃), 2.05-2.15 (1H, m, COCHCH), 2.00 (3H, s, COCH₃), 0.95 (3H, d, J = 6.8Hz, CH₂CH₃), 0.85 (3H, d, J = 6.8Hz, CH₂CH₃); ¹³C NMR (100MHz, CDCl₃), δ 206.9 (C), 156.0 (C), 83.5 (CH), 36.5 (CH₃), 35.9 (CH₃), 29.7 (CH), 27.0 (CH₃), 19.3 (CH₃), 17.0 (CH₃); m/z (APcI) [M+H]^+ 188 (100 %); HRMS (ES) found 188.1283 C₉H₁₈NO₃ requires 188.1281 [M+H]^+

2-Oxocycloheptyl dimethylcarbamate 258:

\[\begin{array}{c}
O \\
O \\
O \ N \\
O \\
\end{array}\]

Cycloheptanone (100 mg, 0.89 mmole) was added to tetrahydrofuran (1.5 mL). N-Methyl-O-dimethyl carbamate hydroxylamine hydrochloride (205 mg, 1.33 mmole) was then added and the mixture was stirred at 50 °C for 18h. After this the reaction mixture
Experimental

was added to H$_2$O (20 mL) and extracted with ethyl acetate (4 x 25 mL), dried over MgSO$_4$ and the solvent removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 50% ethyl acetate/petroleum ether 40-60 °C, to yield the title compound 258 as a colourless oil (97 mg, 55 %); IR (v, cm$^{-1}$, CHCl$_3$) 2941, 1789, 1651, 1147; $^1$H NMR (400MHz, CDCl$_3$), $\delta$ 5.09 (1H, dd, $J_{HH} = 3.1$Hz, $J_{H-He} = 9.6$Hz, COCH), 2.93 (3H, s, NCH$_3$), 2.83 (3H, s, NCH$_3$), 2.55-2.65 (1H, m), 2.30-2.42 (1H, m), 1.90-2.00 (1H, m), 1.55-1.85 (6H, m), 1.25-1.39 (1H, m) $^{13}$C NMR (100MHz, CDCl$_3$), $\delta$ 208.9 (C), 155.7 (C), 67.9 (CH), 40.6 (CH$_2$), 36.4 (CH$_3$), 36.0 (CH$_3$), 30.5 (CH$_2$), 26.5 (CH$_2$), 25.6 (CH$_2$), 22.8 (CH$_2$); $m/z$ (APCI) [M+H]$^+$ 200 (100 %); HRMS (ES) found 200.1282 C$_{10}$H$_{18}$NO$_3$ requires 200.1281. [M+H]$^+$

5,5-Monoketal 2-oxocyclohexyl dimethylcarbamate 257:

\[
\begin{align*}
&O \\
&\text{N} \\
&\text{O} \\
&O
\end{align*}
\]

Cyclohexanone-1,4 monoketal (100 mg, 0.64 mmole) was added to tetrahydrofuran (1.5 mL). N-Methyl-O-dimethyl carbamate hydroxylamine hydrochloride (148 mg, 0.96 mmole) was then added and stirred at 50 °C for 18h. After this the reaction mixture was added to H$_2$O (20 mL) and extracted with ethyl acetate (4 x 25 mL), dried over MgSO$_4$ and the solvent removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 50% ethyl acetate/petroleum ether 40-60 °C, to yield the title compound 257 as a colourless oil (88 mg, 57 %); IR (v, cm$^{-1}$, CHCl$_3$) 2937, 1789, 1735, 1651, 1457, 1369, 1149; $^1$H NMR (400MHz, CDCl$_3$), $\delta$ 5.33 (1H, dd, $J_{H-He} = 6.5$Hz, $J_{H-He} = 12.8$Hz, COCH), 3.85-4.00 (4H, m, OCH$_2$CH$_2$O), 2.85 (3H, s, CH$_3$), 2.80 (3H, s, CH$_3$), 2.65-2.75 (1H, m), 2.25-2.40 (2H, m), 1.80-2.00 (3H, m); $^{13}$C NMR (100MHz,CDCl$_3$), $\delta$ 205.0 (C), 155.3 (C), 107.3 (C), 73.9 (CH), 64.9 (CH$_2$), 64.5 (CH$_2$), 40.5 (CH$_2$), 36.5 (CH$_3$), 36.0 (CH$_3$), 35.7 (CH$_2$), 34.5 (CH$_2$); $m/z$ (APCI) [M+H]$^+$ 244 (100 %), 59 (60 %); HRMS (ES) found 244.1140 C$_{11}$H$_{18}$NO$_3$ requires 244.1140 [M+H]$^+$

147
Experimental

N-Boc-N-methyl-O-p-tosylhydroxylamine 298:219

\[
\begin{align*}
\text{O} & \quad \text{S} \quad \text{O} \quad \text{O} \\
\text{O} & \quad \text{N} \quad \text{O} \\
\end{align*}
\]

\(p\)-Toluenesulfonyl chloride (2.6 g, 13.6 mmole) was added to DCM (20 mL) at 0 °C under \(\text{N}_2\). \(\text{Et}_3\text{N}\) (2.1 g, 20.4 mmole) was then added in one portion followed by DMAP (10 mol%). A solution of \(N\)-Methyl-N-Boc hydroxylamine (2 g, 13.6 mmole) in DCM (10 mL) was added dropwise over 10 min to the reaction mixture. The reaction was stirred over 18 h gradually rising to room temperature. Once complete the reaction mixture was washed with 1 M aqueous \(\text{HCl}\) (20 mL), water (20 mL) and brine (20 mL). Solvent was then removed under reduced pressure. The crude product was purified by recrystallisation using hexane to afford the title compound 298 as a colourless solid (3.8 g, 94%), mp 69-72 °C; IR (\(v\), cm\(^{-1}\), CHCl\(_3\)) 1727, 1455, 1371, 1179, 1090, 846, 757; \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) 7.85 (2H, d, \(J = 8.2\) Hz, ArH), 7.35 (2H, d, \(J = 8.2\) Hz, ArH), 3.25 (3H, s, \(\text{NCH}_3\)), 2.45 (3H, s, Ar-\(\text{CH}_3\)), 2.00 (9H, s, \(\text{CH}_3\)); \(^13\)C NMR (100 MHz, CDCl\(_3\)), \(\delta\) 156.0 (C), 145.8 (C), 131.1 (C), 129.7 (CH), 129.5 (CH), 83.3 (C), 40.2 (CH\(_3\)), 27.689 (CH\(_3\)), 21.7 (CH\(_3\)); \(m/z\) (ES) \([\text{M+H}]^+\)-Me 287 (5%), 201 (25%), 156 (75%), 92 (65%), 60 (80%), 58 (100%); HRMS (ES) found 287.0758 \(\text{C}_{12}\text{H}_{18}\text{NO}_5\text{S}\) requires 287.0749. \([\text{M+H}]^+\)-Me

N-Methyl-O-p-tosylhydroxylamine 299:219

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{H} & \quad \text{S} \quad \text{O} \\
\end{align*}
\]

Trifluoroacetic acid (15 g, 132.1 mmole) was added dropwise to a solution of \(N\)-Boc-N-Methyl-O-p-tosylhydroxylamine (2 g, 6.6 mmole) in anhydrous DCM (15 mL) under \(\text{N}_2\) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was poured into ice water (100 mL) and extracted with DCM (3 x 30 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL) and dried with \(\text{Na}_2\text{SO}_4\). The solvent was removed under reduced pressure to give the title compound 299 as a pale brown solid (1.25 g, 95%), mp 35-37 °C; IR (\(v\), cm\(^{-1}\), CHCl\(_3\)) 3447, 1769,
Experimental

1598, 1360, 1177, 1010, 814, 660; $^1$H NMR (400MHz, CDCl$_3$), δ 7.85 (2H, d, J = 8.2Hz, ArH), 7.35 (2H, d, J = 8.2Hz, ArH), 2.65 (3H, s, NCH$_3$), 2.45 (3H, s, Ar-CH$_3$);

$^{13}$C NMR (100MHz, CDCl$_3$), δ 145.0 (C), 131.9 (C), 129.5 (CH), 129.1 (CH), 40.2 (CH$_3$), 21.7 (CH$_3$); $m/z$ (ES) [M+H]$^+$ 202 (15%), 187 (55%), 156 (100%), 60 (45%);

HRMS (ES) found 202.0546 C$_8$H$_{12}$NO$_3$S requires 202.0493 [M+H]$^+$

2-Oxocyclohexyl 4-methylbenzenesulfonate 306:

\[ \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \]

$N$-Methyl-$O$-$p$-tosylhydroxylamine (50 mg, 0.24 mmole) was added to a (1:1) mixture of toluene/THF (0.5 mL). Cyclohexanone (16 mg, 0.16 mmole) was then added, followed by methane sulfonic acid (15 μL, 0.24 mmole). The reaction mixture was then stirred at 50 °C for 18h. Upon completion the reaction solvent was removed under reduced pressure and the crude product adsorbed onto silica. Purification by column chromatography, eluting with 20% ethyl acetate/petroleum ether 40-60 °C, gave the title compound 306 as a colourless oil (30 mg, 69%), (lit. mp 105-106.5 °C);

IR (ν, cm$^{-1}$, CHCl$_3$) 2930, 1736, 1651, 1452, 1388, 1169; $^1$H NMR (400MHz, CDCl$_3$), δ 7.75 (2H, d, J = 8.2Hz, ArH), 7.35 (2H, d, J = 8.2Hz, ArH), 4.82 (1H, dd, J$_{H_{141h}}$ = 8.1Hz, J$_{H_{141h}}$ = 13.5Hz, COCH$_3$), 2.40-2.45 (1H, m), 2.30 (3H, s, CH$_3$), 2.10-2.30 (2H, m), 1.75-2.00 (2H, m), 1.45-1.70 (2H, m), 1.44 (1H, s); $^{13}$C NMR (100MHz, CDCl$_3$), δ 202.8 (C), 144.9 (C), 133.6 (CH), 129.7 (C), 127.9 (CH), 81.8 (CH), 40.6 (CH$_2$), 34.6 (CH$_2$), 26.9 (CH$_2$), 23.1 (CH$_2$), 21.7 (CH$_3$); $m/z$ (ES) [M+H]$^+$ 269 (75%); HRMS (ES) found 269.0803 C$_{11}$H$_{18}$O$_4$S requires 269.0803 [M+H]$^+$

149
5-(Ethoxycarbonyl)-2-oxocyclohexyl 4-methylbenzenesulfonate 308:

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{SO} \\
\text{CO}_2\text{Et}
\end{array}
\]

\(N\)-Methyl-\(O\)-\(p\)-tosylhydroxylamine (50 mg, 0.24 mmole) was added to a (1:1) mixture of toluene/THF (0.5 mL). Ethyl 4-oxocyclohexanecarboxylate (27 mg, 0.16 mmole) was then added, followed by methane sulfonic acid (15 µl, 0.24 mmole). The reaction mixture was then stirred at 50 °C for 18h. Upon completion the reaction solvent was removed under reduced pressure and the crude product adsorbed onto silica. Purification was achieved by column chromatography eluting with 20% ethyl acetate/petroleum ether 40-60 °C, to yield the title compound 308 as a colourless oil, as a mixture of diastereoisomers (38 mg, 70%); IR (ν, cm\(^{-1}\), CHCl\(_3\)) 2976, 1736, 1651, 1452, 1388; \(^1\)H NMR (400MHz, CDCl\(_3\)), δ 7.75 (2H, d, \(J = 8.2\) Hz, Ar-H), 7.27 (2H, d, \(J = 8.2\) Hz, Ar-H), 4.85-4.95 (1H, m, COCH), 4.00-4.20 (2H, m, CH\(_2\)CH(CH\(_3\))\(_2\)), 2.71-3.00 (1H, m), 2.45-2.61 (2H, m), 2.35 (3H, s, Ar-CH\(_3\)), 1.70-2.31 (4H, m), 1.13-1.25 (3H, m, CO\(_2\)CH\(_2\)CH\(_3\)); \(^{13}\)C NMR (100MHz, CDCl\(_3\)), δ 202.6 (C), 173.1 (C), 145.1(C), 133.5 (C), 129.8 (CH), 128.0 (CH), 79.7 (CH), 61.2 (CH\(_2\)), 40.6 (CH), 38.8 (CH\(_2\)), 37.3 (CH\(_3\)), 28.8 (CH\(_2\)), 21.7 (CH\(_3\)), 14.1(CH\(_3\))\(^\dagger\); \(m/z\) (APci) \([M+NH_4]^+\) 359 (45%); HRMS (ES) found 359.1358 C\(_{16}\)H\(_{24}\)N\(_{6}\)O\(_6\)S requires 359.1358 \([M+NH_4]^+\)\(^\dagger\)

5-tert-Butyl-2-oxocyclohexyl 4-methylbenzenesulfonate 307:

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{S} \\
\text{O} \\
\text{SO}
\end{array}
\]

\(N\)-Methyl-\(O\)-\(p\)-tosylhydroxylamine (50 mg, 0.24 mmole) was added to a (1:1) mixture of toluene/THF (0.5 mL). 4-Tert-butylecyclohexanone (24 mg, 0.16 mmole) was then added, followed by methane sulfonic acid (15 µl, 0.24 mmole). The reaction mixture was then stirred at 50 °C for 18h. Upon completion the reaction solvent was removed
under reduced pressure and the crude product adsorbed onto silica. Purification was achieved by column chromatography eluting with 20 % ethyl acetate /petroleum ether 40-60 °C. to yield the title compound 307 as a colourless oil (33 mg, 64%); IR (ν, cm⁻¹, CHCl₃) 2930, 1735, 1651, 1452, 1358, 1177, 1096; ¹H NMR (400MHz, CDCl₃), δ 7.75 (2H, d, J = 8.2Hz, Ar-H), 7.28 (2H, d, J = 8.2Hz, Ar-H), 4.95 (1H, dd, J_H-H_e = 6.4Hz, J_H-H_o = 11.4Hz, COCH), 2.35 (3H, s, CH₃), 1.90-2.00 (2H, m), 1.51-1.60 (2H, m), 1.10-1.42 (3H, m), 0.85 (9H, s, (CH₃)₃); ¹³C NMR (100MHz, CDCl₃), δ 202.5 (C), 144.8 (C), 133.9 (C), 129.6 (CH), 127.9 (CH), 81.5 (CH), 45.9 (C), 39.6 (CH₂), 35.9 (CH₂), 32.5 (CH₂), 27.5 (CH₃), 21.6 (CH₃); m/z (APcl) [M+NH₄]⁺ 343 (80%); HRMS (ES) found 343.1768 C₁₇H₂₈N0₄S requires 343.1770 [M+NH₄]⁺

2-Oxopropyl 4-methylbenzenesulfonate 313:

\[
\begin{align*}
&\text{O} \\
&\text{OS} \\
&\text{O}
\end{align*}
\]

N-Methyl-O-p-tosylhydroxylamine (50 mg, 0.24 mmole) was added to a (1:1) mixture of toluene/THF (0.5 mL). Acetone (9 mg, 0.16 mmole) was then added, followed by methane sulfonic acid (15 µL, 0.24 mmole). The reaction mixture was then stirred at 50 °C for 18h. Upon completion the reaction solvent was removed under reduced pressure and the crude product adsorbed onto silica. Purification was achieved by column chromatography eluting with 20 % ethyl acetate /petroleum ether 40-60 °C, to yield the title compound 313 as a colourless oil (26 mg, 72%); IR (ν, cm⁻¹, CHCl₃) 1736, 1651, 1457, 1358, 1177; ¹H NMR (400MHz, CDCl₃), δ 7.75 (2H, d, J = 8.2Hz, Ar-H), 7.27 (2H, d, J = 8.2Hz, Ar-H), 4.38 (2H, s, COCH₂), 2.39 (3H, s, Ar-CH₃), 2.07 (3H, s, COCH₃); ¹³C NMR (100MHz,CDCl₃), δ 201.3 (C), 145.6 (C), 132.2 (C), 130.1 (CH), 128.1 (CH), 72.0 (CH₂), 26.7 (CH₃), 21.8 (CH₃); m/z (APcl) [M+NH₄]⁺ 246 (100 %), 141 (12 %); HRMS (ES) found 246.0799 C₁₀H₁₆O₄SN requires 246.0800 [M+NH₄]⁺
Experimental

2-Oxo-2-phenyl 4-methylbenzenesulfonate 314:

N-Methyl-O-\(p\)-tosylhydroxylamine (50 mg, 0.24 mmole) was added to a (1:1) mixture of toluene/THF (0.5 mL). Acetophenone (20 mg, 0.16 mmole) was then added, followed by methane sulfonic acid (15 \(\mu\)l, 0.24 mmole). The reaction mixture was then stirred at 50 °C for 18h. Upon completion the reaction solvent was removed under reduced pressure and the crude product adsorbed onto silica. Purification by column chromatography, eluting with 50% ethyl acetate /petroleum ether 40°-60°C, to yield the title compound 314 as a colourless solid (38 mg, 81%), mp 75 -77 °C (lit. mp 90-91 °C); IR (\(v\), cm\(^{-1}\), CHC\(_2\)) 2927, 1713, 1651, 1558, 1455, 1369, 1157, 903, 730; \(^1\)H NMR (400MHz, CDCl\(_3\)), \(\delta\) 7.75-7.81 (4H, m), 7.54 (1H, t, \(J = 7.4\)Hz, Ar-H), 7.40 (2H, t, \(J = 7.4\)Hz, Ar-H), 7.28 (2H, d, \(J = 8.2\)Hz, Ar-H), 5.19 (2H, s, CH\(_2\)), 2.35 (3H, s, Ar-CH\(_3\)); \(^{13}\)C NMR (100MHz, CDCl\(_3\)), \(\delta\) 190.3 (C), 145.3 (C), 134.2 (CH), 133.8 (C), 132.6 (C), 129.9 (CH), 128.9 (CH), 128.1 (CH), 128.0 (CH), 69.9 (CH\(_2\)), 21.7 (CH\(_3\)); \(m/z\) (ES) [M+H]\(^+\) 291 (40 %), 132 (25 %), 115 (100 %); HRMS (ES) found 308.0952 C\(_{15}\)H\(_{18}\)O\(_4\)NS requires 308.0951. [M+NH\(_4\)]\(^+\)

2-Oxobutyl 4-methylbenzenesulfonate 310 and 310a:

N-Methyl-O-\(p\)-tosylhydroxylamine (50 mg, 0.24 mmole) was added to a (1:1) mixture of toluene/THF (0.5 mL). 2-Butanone (11 mg, 0.16 mmole) was then added, followed by methane sulfonic acid (15 \(\mu\)l, 0.24 mmole). The reaction mixture was then stirred at 50 °C for 18h. Upon completion the reaction solvent was removed under reduced pressure and the crude product adsorbed onto silica. Purification was achieved by column chromatography eluting with 20% ethyl acetate /petroleum ether 40-60°C, to yield the title compound 310 as a colourless oil in a 1:4 mixture of isomers (28 mg,
Experimental

71%); IR (ν, cm⁻¹, CHCl₃) 2926, 1721, 1651, 1558, 1369, 1178, 907; ¹H NMR (400MHz, CDCl₃), δ 7.73 (2H, d, J = 8.2Hz, Ar-H), 7.28 (2H, d, J = 8.2Hz, Ar-H), 4.65 (1H, q, J = 6.9Hz, COCH₃ minor isomer), 4.41 (2H, s, CH₂), 2.45 (2H, q, J = 7.3Hz, COCH₂), 2.39 (3H, s, Ar-CH₃), 2.11 (3H, s, COCH₃ minor isomer), 1.19 (3H, d, J = 7.3Hz, CHCH₃ minor isomer), 0.95 (3H, t, J = 7.3Hz, CH₂CH₃); ¹³C NMR (100MHz, CDCl₃), δ 205.3 (C), 204.1 (C), 145.5 (C), 145.4 (C), 133.0 (C), 132.2 (C), 130.0 (CH), 128.1 (CH), 127.9 (CH), 80.8 (CH), 71.7 (CH₂), 32.4 (CH₂), 25.6 (CH₃), 21.7 (CH₃), 17.7 (CH₃), 6.8 (CH₃); m/z (APCI) [M+H]+ 243 (30 %), 155 (45 %), 127 (62 %), 125 (100 %); HRMS (ES) found 265.0508 C₁₁H₁₄O₄Na requires 265.0505 [M+Na]⁺

4-Methyl-2-oxopentyl 4-methylbenzenesulfonate 309 and 309a:

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{OS} \\
\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{OS} \\
\text{O} \\
\end{array}
\]

A'-Methyl-O-p-tosylhydroxylamine (50 mg, 0.24 mmole) was added to a (1:1) mixture of toluene/THF (0.5 mL). 4-Methylpentan-2-one (16 mg, 0.16 mmole) was then added, followed by methane sulfonic acid (15 μl, 0.24 mmole). The reaction mixture was then stirred at 50 °C for 18h. Upon completion the reaction solvent was removed under reduced pressure and the crude product adsorbed onto silica. Purification was achieved by column chromatography eluting with 20% ethyl acetate/petroleum ether 40-60°C, to yield the title compound 309 as a colourless oil in a 1:4 mixture of isomers (29 mg, 65 %); IR (ν, cm⁻¹, CHCl₃) 2988, 1736, 1651, 1558, 1457, 1370, 1178, 908; ¹H NMR (400MHz, CDCl₃), δ 7.75 (2H, d, J = 8.2Hz, Ar-H), 7.28 (2H, d, J = 8.2Hz, Ar-H), 4.40 (2H, s, CH₂), 4.32 (2H, d, J = 5.1Hz, COCH₂ minor isomer), 2.39 (3H, s, Ar-CH₃), 2.27 (2H, d, J = 7.0Hz, COCH₂), 2.11 (3H, s, COCH₃ minor isomer), 1.95-2.10 (1H, m, CH₃CH), 0.85 (6H, d, J = 6.7Hz, CH(CH₃)₂), 0.78 (3H, d, J = 6.8Hz, CHCH₃ minor isomer). 0.72 (3H, d, J = 6.8Hz, CHCH₃ minor isomer); ¹³C NMR (100MHz, CDCl₃), δ 205.7 (C), 202.7 (C), 145.4 (C), 145.3 (C), 133.0 (C), 132.3 (C), 130.0 (C), 129.9 (CH), 128.0 (CH), 88.8 (CH), 72.0 (CH₂), 47.6 (CH₂), 30.7 (CH₃), 26.9 (CH₂), 22.4 (CH), 21.7
Experimental

(CH₃), 18.4 (CH₃), 16.9 (CH₃); \textit{m/z} (APCI) [M+H]^+ 271 (100 %); HRMS (ES) found 293.0823 C₁₃H₁₈NaO₄S requires 293.0823 [M+Na]^+

2-Oxoheptyl 4-methylbenzenesulfonate 311 and 311a:

\[
\begin{align*}
&\text{O} \\
&\text{O} \\
&\text{O} \\
&\text{O} \\
&\text{O} \\
&\text{O} \\
&\text{S} \\
&\text{S} \\
&\text{S} \\
&\text{S} \\
&\text{S}
\end{align*}
\]

\textit{N}-Methyl-\textit{O}-\textit{p}-tosylhydroxylamine (50 mg, 0.24 mmole) was added to a (1:1) mixture of toluene/THF (0.5 mL). 2-Heptanone (18 mg, 0.16 mmole) was then added, followed by methane sulfonic acid (15 \textmu L, 0.24 mmole). The reaction mixture was then stirred at 50 °C for 18 h. Upon completion the reaction solvent was removed under reduced pressure and the crude product adsorbed onto silica. Purification was achieved by column chromatography eluting with 20% ethyl acetate/petroleum ether 40-60 °C, to yield the title compound 311 as a colourless oil in a 1:4 mixture of isomers (32 mg, 69 %); IR (\nu, \text{ cm}^{-1}, \text{ CHCl}_3) 2930, 1735, 1651, 1452, 1358, 1177, 1096, 911; \textit{1}H NMR (400MHz, CDCl₃), \delta 7.75 (2H, d, \textit{J} = 8.2Hz, \textit{Ar-H}), 7.30 (2H, d, \textit{J} = 8.2Hz, \textit{Ar-H}), 4.50 (1H, dd, \textit{J} \textit{H} - \textit{H} = 4.5Hz, \textit{CH} = \textit{CH}_2 \text{ minor isomer}), 4.41 (2H, s, COCH₂), 2.40 (3H, s, Ar-CH₃), 2.15 (3H, s, COCH₃ \text{ minor isomer}), 1.45 (2H, t, \textit{J} = 7.4Hz, COCH₂), 1.05-1.30 (6H, m), 0.85 (3H, t, \textit{J} = 6.8Hz, CH₃), 0.75 (3H, t, \textit{J} = 6.3Hz, CH₃ \text{ minor isomer}); \textit{1}C NMR (100MHz, CDCl₃), \delta 205.6 (C), 203.4 (C), 145.5 (C), 145.4 (C), 132.9 (C), 132.3 (C), 130.0 (CH), 129.9 (CH), 128.1 (CH), 128.0 (CH), 84.5 (CH), 71.8 (CH₂), 38.9 (CH₂), 31.2 (CH₂), 31.1 (CH₂), 26.4 (CH₂), 25.9 (CH₃), 21.9 (CH₃), 21.7 (CH₂), 13.8 (CH₃); \textit{m/z} (APCI) [M+NH₄]^+ 302 (50 %), 285 (20 %), 155 (25 %), 141 (100 %); HRMS (ES) found 302.1420 C₁₄H₂₄O₄SN requires 302.1421 [M+NH₄]^+
4-(4-Hydroxyphenyl)-2-oxobutyl 4-methylbenzenesulfonate 312 and 312a:

N-Methyl-O-p-tosylhydroxylamine (50 mg, 0.24 mmole) was added to a (1:1) mixture of toluene/THF (0.5 mL). 4-(4-Hydroxyphenyl)butan-2-one (26 mg, 0.16 mmole) was then added, followed by methane sulfonic acid (15 μl, 0.24 mmole). The reaction mixture was then stirred at 50 °C for 18h. Upon completion the reaction solvent was removed under reduced pressure and the crude product adsorbed onto silica. Purification was achieved by column chromatography eluting with 20% ethyl acetate/petroleum ether 40-60 °C, to yield the title compound 312 as a colourless oil in a 1:4 mixture of isomers (32 mg, 61%); IR (ν, cm⁻¹, CHCl₃) 3452, 2930, 1735, 1651, 1452, 1358, 1177, 1096, 911; ¹H NMR (400MHz, CDCl₃), δ 7.75 (2H, d, J = 8.2Hz, Ar-H), 7.30 (2H, d, J = 8.2Hz, Ar-H), 7.07 (2H, d, J = 8.5Hz, Ar-H), 6.69 (2H, d, J = 8.5Hz, Ar-H), 4.60 (1H, dd, J₁₁-H₁cis = 4.3Hz, J₁₁-H₁trans = 8.3Hz, COCH₂(minor isomer)), 4.45 (2H, s, COCH₂), 3.00-3.50 (1H, brs, OH) 2.60-2.75 (2H, m, Ar-CH₂), 2.35 (3H, s, Ar-CH₃), 2.31 (3H, s, Ar-CH₃ (minor isomer)), 2.11 (2H, s, COCH₂), ¹³C NMR (100MHz, CDCl₃), δ 202.8 (C), 154.2 (C), 154.1 (C), 145.5 (C), 132.3 (C), 132.2 (C), 130.6 (CH), 130.0 (CH), 129.8 (CH), 129.4 (CH), 128.0 (CH), 127.7 (CH), 115.4 (CH), 85.0 (CH), 71.9 (CH₂), 30.1 (CH₃), 28.9 (CH₂), 28.0 (CH₂), 21.7 (CH₃); m/z (APcI) [M+NH₄]⁺ 352 (100 %); HRMS (ES) found 352.1210 C₁₇H₂₂O₅SN requires 352.1213 [M+NH₄]⁺

1-(Ethoxycarbonyl)-2-oxopropyl 4-methylbenzenesulfonate 319:
N-Methyl-\(O-p\)-tosylhydroxylamine (50 mg, 0.24 mmole) was added to a (1:1) mixture of toluene/THF (0.5 mL). Ethyl acetoacetate (20 mg, 0.16 mmole) was then added, followed by methane sulfonic acid (15 \(\mu\)l, 0.24 mmole). The reaction mixture was then stirred at 50 \(^\circ\)C for 18h. Upon completion the reaction solvent was removed under reduced pressure and the crude product adsorbed onto silica. Purification was achieved by column chromatography eluting with 20 % ethyl acetate /petroleum ether 40 - 60 \(^\circ\)C, to give the title compound 319 as a pale yellow oil (32 mg, 69%); IR (\(\nu\), cm\(^{-1}\), CHCl\(_3\)) 2921, 1735, 1377, 907, 743; \(^1\)H NMR (400MHz, CDCl\(_3\)), \(\delta\) 7.75 (2H, d, \(J = 8.2\)Hz, Ar-H), 7.31 (2H, d, \(J = 8.2\)Hz, Ar-H), 5.11 (1H, s, CH), 4.00-4.09 (2H, m, CH\(_2\)CH\(_3\)), 2.35 (3H, s, Ar-CH\(_3\)), 2.19 (3H, s, COCH\(_3\)), 1.12 (3H, t, \(J = 7.2\)Hz, CH\(_2\)CH\(_3\)); \(^{13}\)C NMR (100MHz, CDCl\(_3\)), \(\delta\) 197.1 (C), 163.4 (C), 145.8 (C), 132.3 (C), 129.8 (CH), 128.4 (CH), 80.5 (CH), 62.8 (CH\(_2\)), 26.5 (CH\(_3\)), 21.5 (CH\(_3\)), 13.7 (CH\(_3\)); \(m/z\) (APcI) [M+NH\(_4\)]\(^+\) 318 (75 %) HRMS (ES) found 318.1011 C\(_{13}\)H\(_{19}\)O\(_5\)SN requires 318.1011 [M+NH\(_4\)]\(^+\)

5,5-Dimethyl-2-thiolo-2-thiono-1,3,2-dioxaphosphorinane 333: \(^{198}\)

\[
\begin{array}{c}
\text{S} \quad \text{SH} \\
\text{O} \quad \text{P} \\
\text{O} \quad \text{O}
\end{array}
\]

Prepared in accordance with literature procedure as follows, to P\(_2\)S\(_5\) (5.0 g, 22.5 mmole) in benzene (50 mL) was added 2,2-dimethylpropane-1,3-diol (4.7 g, 45.0 mmole). The reaction mixture was stirred at 50 \(^\circ\)C for 12h until there was no further evolution of H\(_2\)S gas and almost all the P\(_2\)S\(_5\) had dissolved. The mixture was then filtered through Celite to remove any residual P\(_2\)S\(_5\). Solvent was removed under reduced pressure to give a sticky white solid that was purified by distillation to give the title compound 333 as a
white solid (2.4 g, 91%), mp 79.5-80.0 °C (lit. mp 78 °C)\textsuperscript{198}; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.05 (2H, s, CH$_2$), 3.98 (2H, s, CH$_2$), 1.05 (6H, s, (CH$_3$)$_2$)

**Experimental**

**Benzoyl 2-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) sulphide 334:**\textsuperscript{197}

![Chemical Structure](image)

Prepared in accordance with literature procedure as follows, benzoyl chloride (420 mg, 3 mmole) was added to a solution of 5,5-dimethyl-2-thioolo-2-thiono-1,3,2-dioxaphosphorinane (600 mg, 3 mmole) in benzene (10 mL). Subsequently, Et$_3$N (0.31 mL, 3 mmole) was added dropwise to the ice-cold solution, with immediate precipitation of Et$_3$N.HCl. After 15 min the reaction mixture was filtered through a short pad of silica gel. Solvent was then removed under reduced pressure to give the title compound 334 of sufficient purity (860 mg, 95%), mp 113-115 °C (lit. mp 114-115 °C)\textsuperscript{197}; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.97 (2H, d, $J$ = 7.8 Hz), 7.64 (1H, t, $J$ = 7.3 Hz), 7.49 (2H, t, $J$ = 7.3 Hz), 4.38 (2H, dd, $J_{H,H}$ = 10.7 Hz, $J_{P,H}$ = 3.9 Hz), 4.02 (2H, dd, $J_{H,H}$ = 10.7 Hz, $J_{P,H}$ = 25.9 Hz), 1.38 (3H, s), 0.93 (3H, s)

**Thiobenzoyl 2-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) sulphide 335:**\textsuperscript{197}

![Chemical Structure](image)

Prepared in accordance with literature procedure as follows, a solution of Benzoyl 2-(5,5-dimethyl-2-thioolo-1,3,2-dioxaphosphorinanyl) sulphide (1.51 g, 5 mmole) and 5,5-dimethyl-2-thioolo-2-thiono-1,3,2-dioxaphosphorinane (1.98 g, 10 mmole) in benzene was heated under reflux for 4h. This was then washed with aqueous Na$_2$CO$_3$ (2 x 5 mL) and then H$_2$O (5 mL). The organic layer was separated and dried with MgSO$_4$ and the
Experimental

solvent removed under reduced pressure. The crude 335 product was used for thioacetylation without further purification with a crude yield of (1.50 g, 94%), mp 96-
101 °C (lit. mp 95-97 °C)\textsuperscript{197}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 8.04 (2H, d, J = 8.3 Hz), 7.59 (1H, t, J = 7.8 Hz), 7.4 (2H, t, J = 7.8 Hz), 4.29 (2H, dd, J\textsubscript{H-H} = 10.7Hz, J\textsubscript{P-H} = 3.4Hz), 3.98 (2H, dd, J\textsubscript{H-H} = 10.7Hz, J\textsubscript{P-H} = 25.9Hz), 1.37 (3H, s), 0.97 (3H, s)

\textit{N-Benzyol-2-amino-5-nitroaniline 339:\textsuperscript{200}}

\[
\begin{array}{c}
\text{NH}_2 \\
\text{O}_2\text{N} \quad \text{NH} \\
\text{O}
\end{array}
\]

4-Nitro-1,2-phenylenediamine (5 g, 32.6 mmole) was dissolved in anhydrous THF (70 mL) at 0 °C. To this triethylamine (4.2 mL, 32.6 mmole) was then added in one portion and stirred for ten minutes. Benzoyl chloride (4.56 g, 32.6 mmole) was then added dropwise to the reaction mixture under an atmosphere of nitrogen, warming to room temperature over night. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was redissolved in dichloromethane and washed with 1M HCl (30 mL), water (30 mL), NaHCO\textsubscript{3} (30 mL), brine (30 mL), then dried over NaSO\textsubscript{4} and the solvent was then removed under reduced pressure. Crystallization of the residue from EtOAc/ hexane afforded the title compound 339 as yellow solid in (5.67 g, 68%), mp 215 °C (lit. mp 214 °C)\textsuperscript{200}; \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}) δ 9.74 (1H, s), 8.10 (2H, dd, J = 7.2Hz, 2.2Hz), 7.95 (2H, dd, J = 9.0Hz, 2.5Hz), 7.52 (3H, m), 6.87 (1H, d, J = 9.0Hz), 6.55 (2H, s)

\textit{N-Thiobenzyol-2-amino-5-nitroaniline 340:\textsuperscript{200}}

\[
\begin{array}{c}
\text{NH}_2 \\
\text{O}_2\text{N} \quad \text{NH} \\
\text{S}
\end{array}
\]
Prepared in accordance with literature procedure as follows, under an atmosphere of nitrogen, $P_4S_{10}$ (1 g, 2.2 mmole) was mixed with $Na_2CO_3$ (0.27 g, 2.2 mmole) in anhydrous THF (100 mL). The mixture was stirred for 1 h at 25 °C and then cooled to 0 °C. To this clear solution was added $N$-Benzoyl-2-amino-5-nitroaniline (560 mg, 2.2 mmol), and the reaction was stirred at this temperature for 30 min and then at room temperature overnight. The solution was filtered through Celite, and the filtrate was evaporated to dryness. The residue was dissolved in EtOAc/heptane (2/1, v/v, 75 mL) and washed with 5% NaHCO$_3$ (2 x 30 mL), and the aqueous layers were back extracted with EtOAc/hexane (75 mL). The combined organic layer was washed with brine (2 x 30 mL), dried with MgSO$_4$, and the solvent removed under reduced pressure. The resulting crude solid was crystallized from ethyl acetate/hexane to give the title compound 340 as a yellow solid (468 mg, 78%), mp 211 °C (lit. mp 210 °C)\textsuperscript{200}; $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 10.25 (1H, s), 8.00 (1H, d, $J$ = 2.5Hz), 7.93 (3H, m), 7.53 (1H, s), 7.50 (1H, d, $J$ = 9.0Hz), 7.44 (1H, d, $J$ = 7.7Hz), 6.81 (1H, d, $J$ = 9.12Hz), 6.69 (2H, s)

1-Thiobenzoyl-6-nitrobenzotriazole 341:\textsuperscript{200}

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{O}_2\text{N} \\
\text{N} \\
\text{S}
\end{array}
\]

Prepared in accordance with literature procedure as follows, $N$-Thiobenzoyl-2-amino-5-nitroaniline (545 mg, 2.0 mmol) was dissolved by gentle warming at 40 °C in 70 % acetic acid (15 mL). This was then cooled to 0 °C and NaNO$_2$ (0.21 g, 3 mmol) was added in small portions with stirring. After 30 min, ice-water (100 mL) was added, and the precipitate was filtered off, washed with water, and dried \textit{in vacuo} to afford the title compound 341 as a red solid, which was crystallized from CH$_2$Cl$_2$ (409 mg, 72%), mp 158 °C (lit. mp 158 °C)\textsuperscript{200}; $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 9.42 (1H, s), 8.41 (1H, d, $J$ = 8.9Hz), 8.30 (1H, d, $J$ = 8.9Hz), 7.76 (2H, d, $J$ = 8.2Hz), 7.62 (1H, t, $J$ = 7.0Hz), 7.40 (2H, t, $J$ = 7.5Hz)

$N$-2,4-dinitrophenylsulfonyl-$N$-methyl hydroxylamine 346:
A-Methylhydroxylamine hydrochloride (5 g, 59.8 mmole) was dissolved in (1:1) THF/H₂O (140 mL) at 0 °C. Potassium carbonate (4.1 g, 29.9 mmole) was then added in one portion. 2,4-Dinitrobenzenesulfonyl chloride (16.5 g, 59.8 mmole) was dissolved in THF (15 mL) and added to the reaction mixture at 0 °C. The reaction was stirred for 18h gradually warming to room temperature. After this the THF was removed under reduced pressure and the remaining aqueous solution was added to DCM (200 mL) and washed with water (3 x 100 mL), brine (50 mL) and dried with Na₂SO₄. Solvent was then removed under reduced pressure. The resulting crude product was crystallized with hexane to yield the title compound as a yellow solid (11.9 g, 72%), mp 122-124 °C; IR (ν, cm⁻¹, CHCl₃) 3565, 1698, 1377, 1251;¹H NMR (500MHz, C₃D₆O) δ 8.99 (1H, d, J = 2.2Hz, Ar-H), 8.57 (1H, dd, J = 8.8Hz, 2.2Hz, Ar-H), 8.20 (1H, d, J = 8.8Hz, Ar-H), 3.15 (1H, s, OH), 2.75 (3H, s, CH₃);¹³C NMR (100MHz, CDCl₃) δ 151.2 (C), 149.17 (C), 134.01 (CH), 128.63 (CH), 126.29 (CH), 119.62 (CH), 40.2 (CH₃)

N-4-nitrophenylsulfonyl-N-methyl hydroxylamine 347:

A-Methylhydroxylamine hydrochloride (5 g, 59.8 mmole) was dissolved in (1:1) THF/H₂O (140 mL) at 0 °C. Potassium carbonate (4.1 g, 29.9 mmole) was then added in one portion. 4-nitrobenzenesulfonyl chloride (13.8 g, 59.8 mmole) was dissolved in THF (15 mL) and added to the reaction mixture at 0 °C. The reaction was stirred for 18h gradually warming to room temperature. After this the THF was removed under reduced pressure and the remaining aqueous solution was added to DCM (200 mL) and washed with water (3 x 100 mL), brine (50 mL) and dried with Na₂SO₄. Solvent was then removed under reduced pressure. The resulting crude product was purified by
crystillation with hexane to yield the title compound 347 as a yellow solid (8.6 g, 68%), mp 151-153 °C; IR (v, cm⁻¹, CHCl₃) 3265, 1508, 1261, 1090, 1020, 798; ¹H NMR (400MHz, C₃D₆O) δ 8.45 (2H, d, J = 6.7Hz, Ar-H), 8.05 (2H, d, J = 6.7Hz, Ar-H), 2.77 (3H, s, NCH₃); ¹³C NMR (100MHz, CDCl₃), δ 151.0 (C), 137.9 (CH), 131.2 (C), 123.9 (CH), 40.5 (CH₃).

_N-Boc-N-methyl-O-thiobenzoylhydroxylamine 326:_

\[ \text{Boc} \quad \text{O} \quad \text{N} \]

\[ \text{Boc} \quad \text{S} \]

To a cooled solution of benzotriazole 341 (0.5 g, 1.75 mmol) and _N-Boc-N-methyl-O-thiobenzoylhydroxylamine 199_ (0.38 g, 2.63 mmol) in anhydrous THF (20 mL) at 0 °C DBU was added (0.3 g, 1.75 mmol) in THF (10 mL) dropwise over a period of 20 min, and then stirred for 24h raising to room temperature. The solvent was evaporated under reduced pressure to give a dark tar. The tar was triturated with warmed hexane (3 x 50 mL). Solvent was removed under reduced pressure to yield the title 326 compound as a yellow oil (380 mg, 75%); IR (v, cm⁻¹, CHCl₃) 2981, 1699, 1454, 1370, 1150; ¹H NMR (400MHz, CDCl₃), 8.08 (2H, d, J = 8.4Hz, Ar-H), 7.50 (1H, t, J = 7.7Hz, Ar-H), 7.35 (2H, t, J = 7.7Hz, Ar-H), 3.31 (3H, s, NCH₃), 1.35 (9H, s, (C(CH₃)₃); δ ¹³C NMR (100MHz,CDCl₃), δ 209.5 (C), 154.9 (C), 136.8(C), 133.7 (CH), 129.5 (C), 128.7 (CH), 82.9 (C), 37.6 (CH₃), 28.6 (CH₃).

_N-Boc-N-methyl-O,N,N-dimethylthiocarbamatehydroxylamine 354:_

\[ \text{Boc} \quad \text{O} \quad \text{N} \]

\[ \text{Boc} \quad \text{S} \]

_N-Methyl-N-Boc hydroxylamine (500 mg, 2.3 mmole) was added to a solution of _N,N-Dimethylthiocarbamoyl chloride (309 mg, 2.5 mmole)_ in pyridine (20 mL), with 20 mol% DMAP. The reaction was then heated to 50 °C for 18h. Once complete the pyridine was removed under reduced pressure and the crude material was digested with DCM (150 mL). The organic layer was washed with 2M aqueous HCl (3 x 30 mL),
brine (50 mL), water (50 mL) and dried over Na₂SO₄. Solvent was then removed under reduced pressure. Purification was achieved by column chromatography eluting with 40% ethyl acetate/petroleum ether 40-60 °C, to yield the title compound 354 as a pale yellow oil (540 mg, 52%). IR (ν, cm⁻¹, CHCl₃) 2979, 1681, 1313, 1149, 917, 731; ¹H NMR (400 MHz, CDCl₃) δ 3.30 (3H, s, CSNCH₃), 3.25 (3H, s, CSNCH₃), 3.09 (3H, s, NCH₃), 1.35 (9H, s, C(CH₃)₃); ¹³C NMR (100MHz, CDCl₃), δ 187.9 (C), 154.5 (C), 82.0 (C), 38.41 (CH₃), 37.7 (CH₃), 28.1 (CH₃); m/z (APCI) 235 (100%) [M+H]⁺ HRMS (ES) found 235.1109 C₉H₁₉N₂O₃S requires 235.1111 [M+H]⁺
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Appendix
Fig. A $^1\text{H}$ NMR of 217 400MHz, CDCl$_3$
Fig. B. $^{13}$C DEPT of 216.100MHz, CDCl$_3$
Fig. C $^1$H NMR of 326 400MHz, CDCl$_3$
Fig. D $^{13}$C NMR of 326 100MHz, CDCl$_3$
Fig. E $^1$H NMR of 346 500MHz, $C_3D_6O$
Fig. G $^1$H NMR of 347 500MHz, C$_3$D$_6$O