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α-Functionalisation of Carbonyl Compounds.

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A Thesis Submitted for the Degree of Doctor of Philosophy

at

Cardiff University

2007

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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)

Acknowledgements

First and foremost I would like to give a massive " go raibh mile maith agat " to Dr. Nick Tomkinson for his constant support and direction along with more second chances then I care to mention. A huge thank you has also to be given to my lab mates and post-docs past and present Ian (Little Gay), Claire, Rach (The Parrymonster), Kerri (Keggers), Tim (Goth), Nonney (Fanny), Anto, Debs, Paul (Never Getting Married), Rob (My Balding Bro), Jackie (Jackie Chan), Huw (Grumpy not Hefner), for making the lab a more enjoyable place to work, not forgetting Bagley's Bitchs for making the lab definitely a more beautiful and attractive place. Of course how could I not thank Evie B for enough coffee and booze to float a battleship and the occasional boob to cry on.

I would also like to thank the technical staff at Cardiff Rob, Robin and Dave for their help with numerous spectroscopic problems, thanks also to the lads in stores Gaz, Jamie, Alan, Mal and JC.

Finally I would like to thank my friends and housemates over the years for more hangovers, embarrassing stories and black outs then I care to remember.

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	Allyloxycarbonyl
APcI	Atomspheric Pressure Chemical Ionisation
Ar	Aromatic
Bn	Benzyl
Boc	*tert* butoxycarbonyl
BOI	2-(benzotriazol-1-yl)-oxy-1,3-dimethyl imidazolium
BPO	Benzoylperoxide
Bz	Benzoyl
CAP	*N*-cyano-4-(dimethylamino)pyridinium bromide
CBMIT	carbonyl bismethylimidazolium triflate
Cbz	Benzyloxycarbonyl
CDI	Carbonyldiimidizole
CI	Chemical Ionisation
Cy	Cyclohexyl
d	doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DEAD	Diethylazodicarboxylate
DBU	Diaza(1,3)bicyclo[5.4.1]undecane
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
dd	double doublet
de	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 di*iso*propylamide
m	multiplet
*m*CPBA	-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 sulfonylperoxide
Pr	Propyl
q	quartet
s	singlet
SAR	Structral Activity Relationship
TADDOL	α,α,α',α'-tetraaryl-4,5-dimethoxy-1,3-dioxolane
TBDMS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TES	Triethlysilyl

TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatrography
TMS	Trimethylsilyl
TMSOTF	Trimethylsilyl
Ts	Tosyl
β-ICD	β-isocupreidine

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 *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]

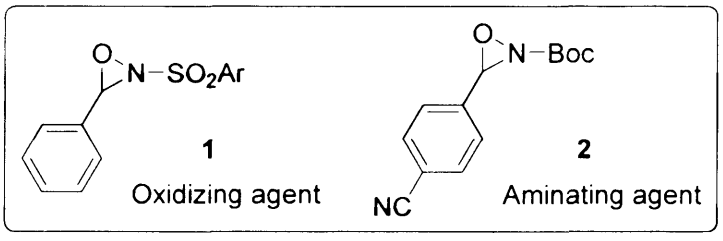


Fig. 1

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).

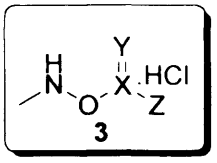


Fig. 3

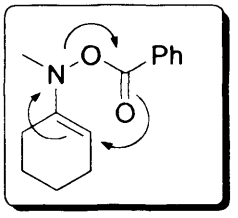


Fig. 4

Since its discovery by Ludwig Claisen in 1912[3] the Claisen rearrangement 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[4] and electronic[5] interactions. Through this transition state it is the relative geometry of the double bonds that determines the stereochemistry of the product.

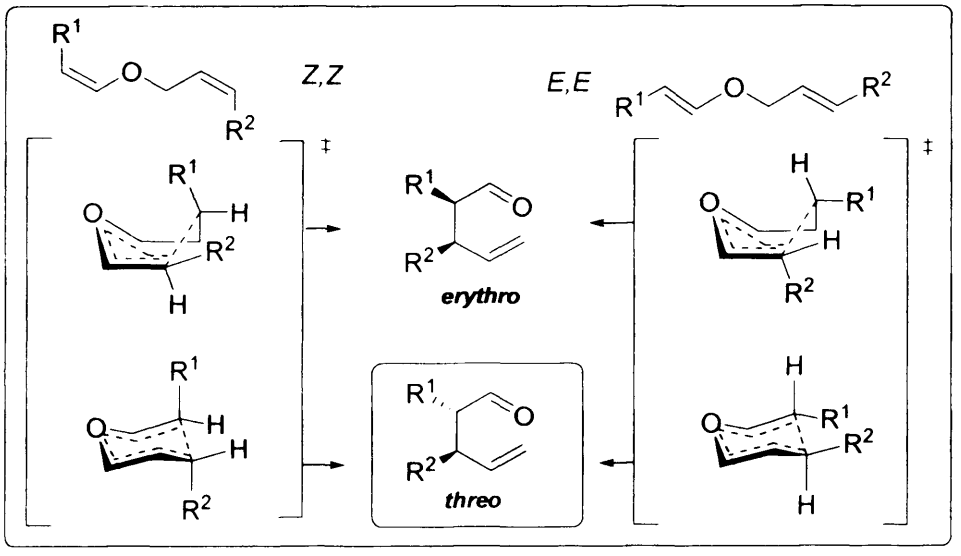


Fig. 5

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]

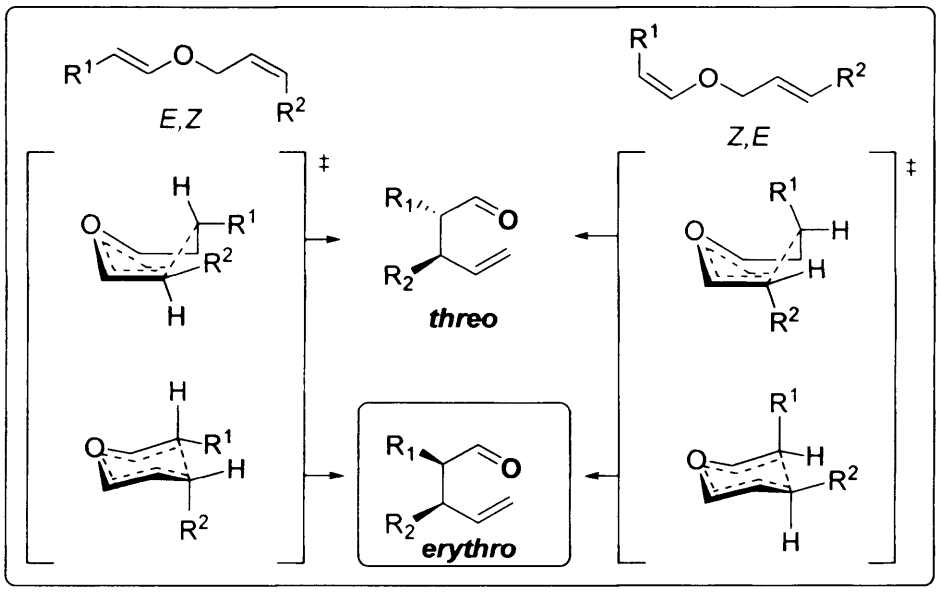


Fig. 6

Based on this *E,Z* and *Z,E* substrates afford the *erythro* product by again adopting the lower energy chair conformation and maximising the separation between subsitutents (Fig. 6). These findings also hold true when additional heteroatoms are introduced into the substrate, therefore it is not suprising 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).

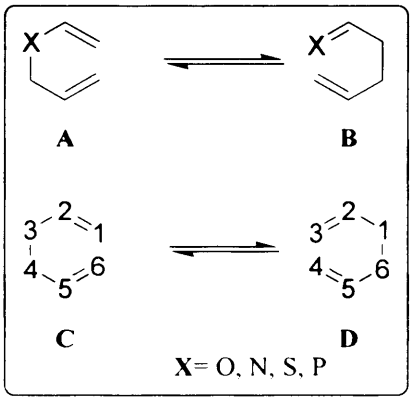


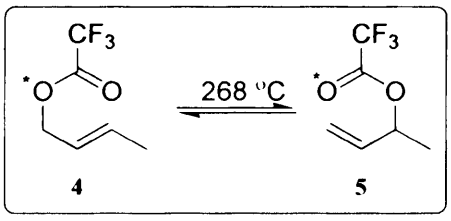
Fig. 7

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 hereroatoms involved and their position in the starting substrate (Fig. 7).

1.2.1 1-*O*,3-*O* Systems:

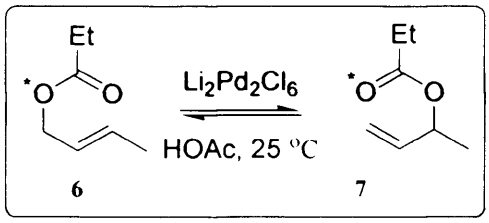
1.2.1.1 Allyl Esters (Carboxylates)

^{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).[7]



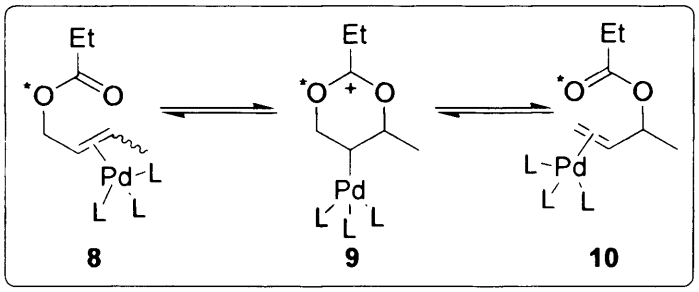
Scheme 1

A similar strategy employing labelled crotyl propionate **6** (Scheme 2) showed that Pd^{II} catalysis of allylic ester isomerizaton using $Li_2Pd_2Cl_6$ also represented a [3,3] process **6** ⇌ **7**.[8]



Scheme 2

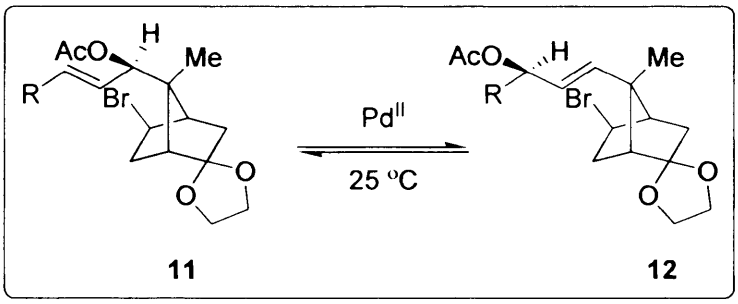
The suggested mechanism involved the action of Pd^{II} as a Lewis Acid to promote cyclization of complex **8** *via* a formal [3,3]-sigmatropic rearrangement. This proceeds through a 1,3-acetoxonium intermediate **9**, followed by ring opening to give **10** (Scheme 3).



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.[9]

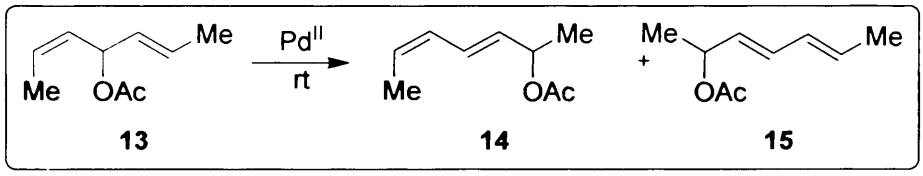
Consistent with a [3,3] process, complete suprafacial chirality transfer was observed under comparable reaction conditions (0.04 eq of $PdCl_2(MeCN)_2$, THF, 25 °C, 1.5h) in the rearrangement of acetate **11** to **12** (Scheme 4).[10]



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_2Ph.[11]

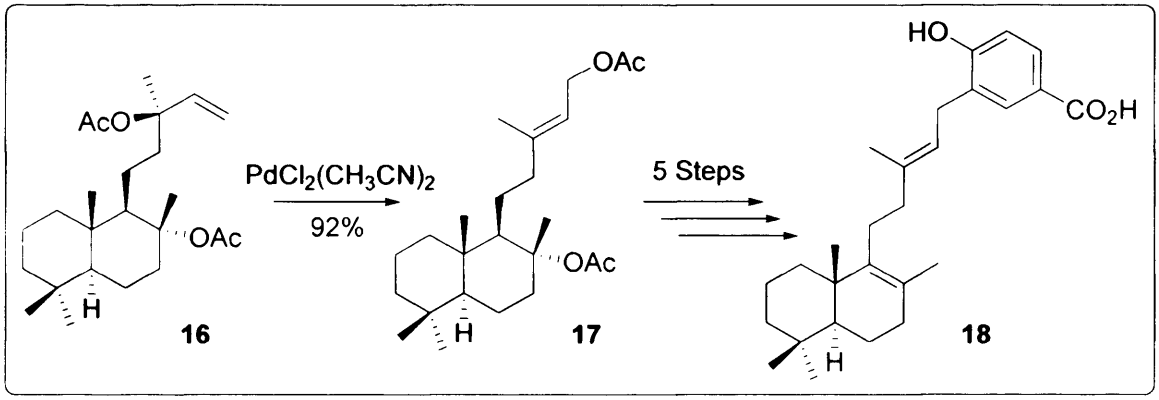
Pd^{II} catalysed allylic ester rearrangement occurs preferentially at *E*- disubstituted double bonds rather than *Z*-disubstituted, as seen in the rearrangement of (*E,Z*)-4-acetoxyhepta-2,5-diene **13** (0.05 eq $PdCl_2(MeCN)_2$, THF, rt, 5mins) to a mixture of **14** (74%) and **15** (18%) (Scheme 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.



Scheme 5

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]

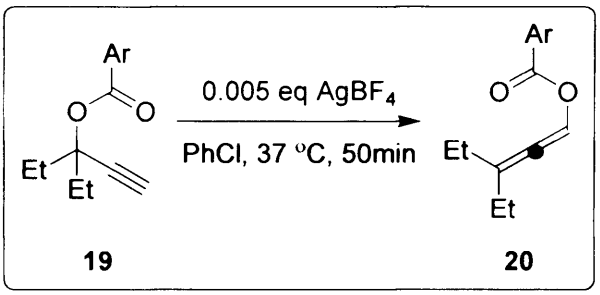
Basabe recently employed this rearrangement in a short effective synthesis of (+)-subersic acid **18**.[14] Sclareol was acetylated in quantitative yield with acetyl chloride and *N,N*-dimethylaminopyridine, affording the diacetyl derivative **16** whose rearrangement with bis-(acetonitrile)palladium^{II}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



Scheme 6

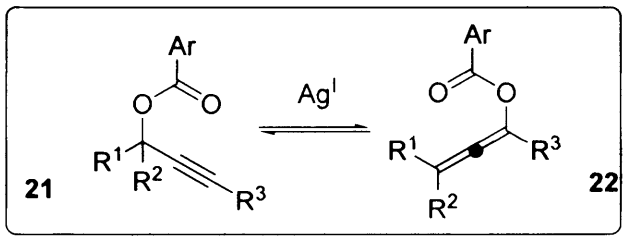
1.2.1.2 Propargyl and Allenyl Esters

Catalysed rearrangements of propargyl esters using silver salts was first reported by Saucy *et al.*,[15] then systematically studied and characterised as [3,3] processes by Schmid.[16] 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).



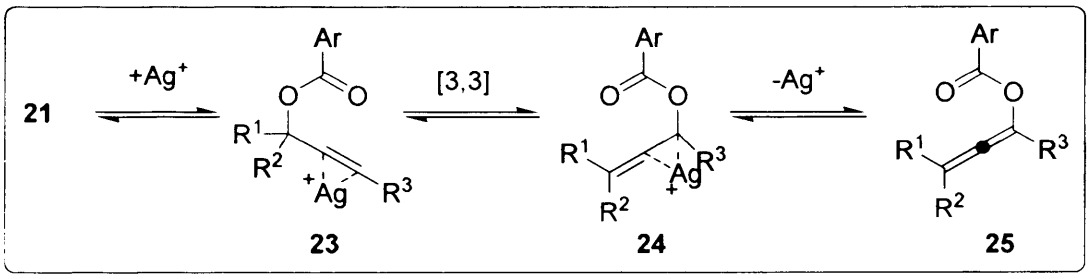
Scheme 7

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).



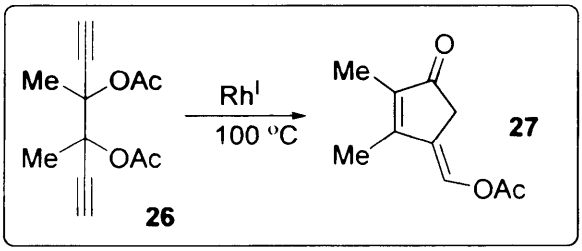
Scheme 8

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 Ag^{I} catalysed allyl ester rearrangement could be observed when α,α-dimethylallyl *p*-benzoate was examined as a substrate ($AgBF_4$, PhCl, 130 °C, 6h). [16]



Scheme 9

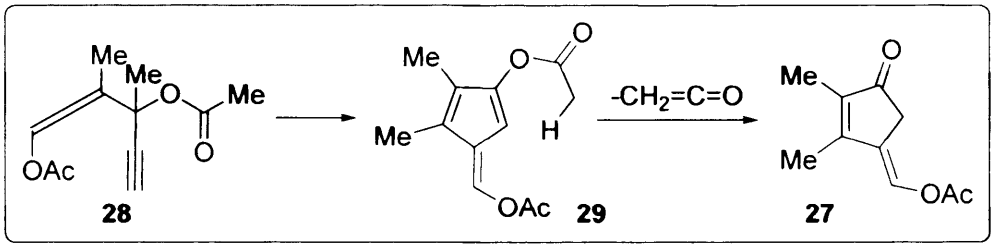
Attempts to catalyse the rearrangements of simple propargyl esters with Rh^{I} were unsuccessful, with α,α-dimethylpropargyl acetate giving a very complex reaction mixture on the introduction of $[Rh(CO)_2Cl]_2$ in chloroform.[17] However, treatment of 3,4-diacetoxyhexa-1,5-diyne **26** with the same catalyst gave a 35% yield of **27** (Scheme 10).



Scheme 10

A possible mechanism to account for the overall transformation was proposed, on the basis of product structure only, to involve Rh^{I} catalysed [3,3]-rearrangement of **26** to

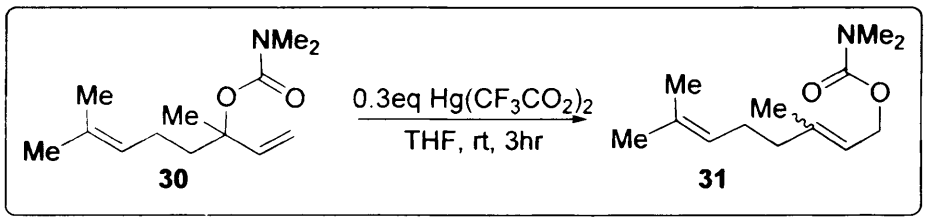
give **28** subsequent rearrangement to **29**, followed by a retro ene reaction to give the observed product **27** (Scheme 11).



Scheme 11

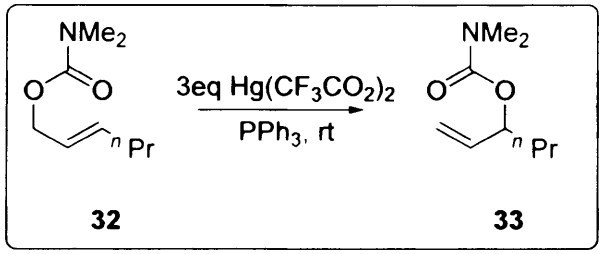
1.2.1.3 Allyl *N,N*-Dialkylcarbamates:

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 $Hg(CF_3CO_2)_2$ in THF at room temperature for 24h in 75% isolated yield (Scheme 13).

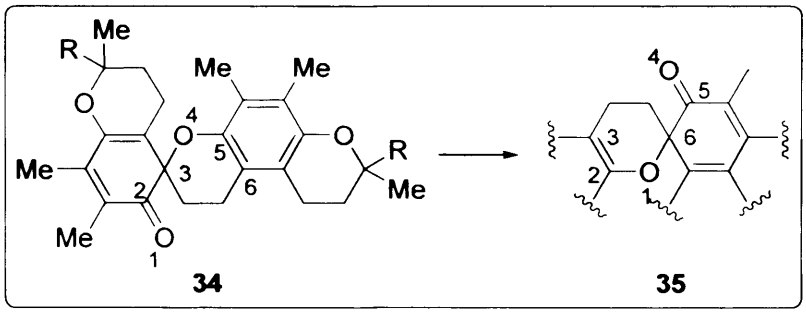


Scheme 13

1.2.2 1-*O*,4-*O* Systems:

1.2.2.1 α-Tocopherol Spiro Dimer

The title compound **34** (Scheme 14) where R = $C_{16}H_{33}$ undergoes a degenerative rearrangement to **35** that is detected by NMR, with coalescence of signals at 70 °C (chloroform, benzene).[19]



Scheme 14

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.

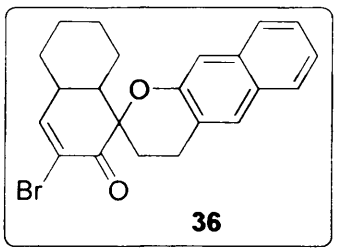


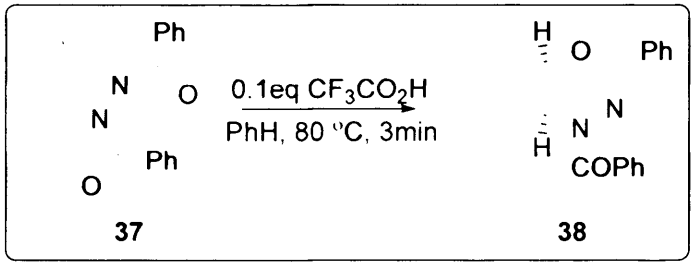
Fig. 8

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 Brønsted and Lewis acids.[20] For example, compound **37** was rapidly converted to the *cis*-oxadiazine **38** by catalytic amounts of CF_3CO_2H (Scheme 15).

Both $BF_3 \cdot Et_2O$ (0.1eq) and $SnCl_4$ (1.0eq) were also very effective catalysts. A low level of asymmetric induction was also observed in this transformation when catalysed by (+)-camphor-10-sulfonic acid.[21]

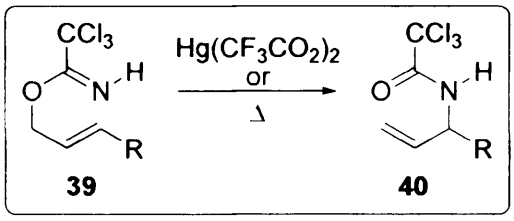


Scheme 15

1.2.4 1-*N*,3-*O* Systems:

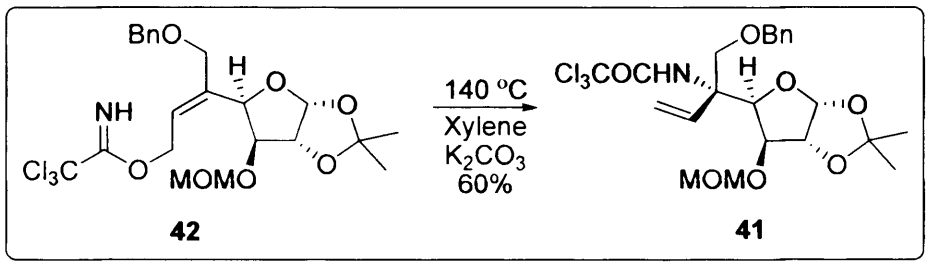
1.2.4.1 Allyl Trichloroacetimidates

Perhaps the most investigated polyheteroatom sigmatropic rearrangement with regard to synthesis is the trichloroacetimidate Overmann rearrangement.[22] This involves the irreversible rearrangement of allylic tricholoracetimidate **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.[23]



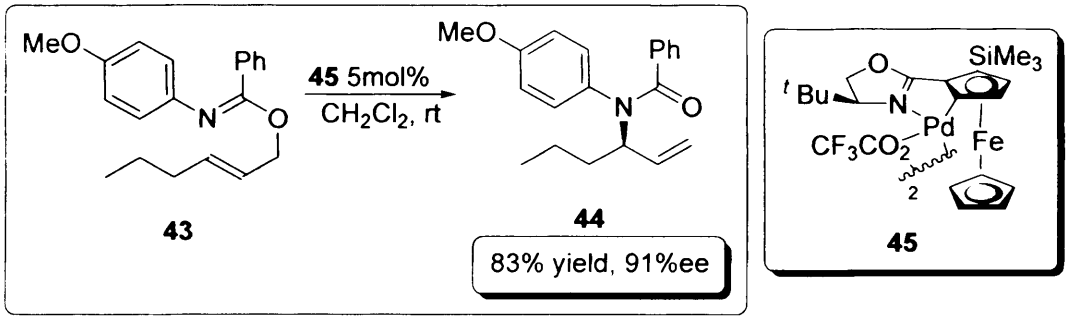
Scheme 16

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.[24] Refluxing compound **42** in xylene with K_2CO_3 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.



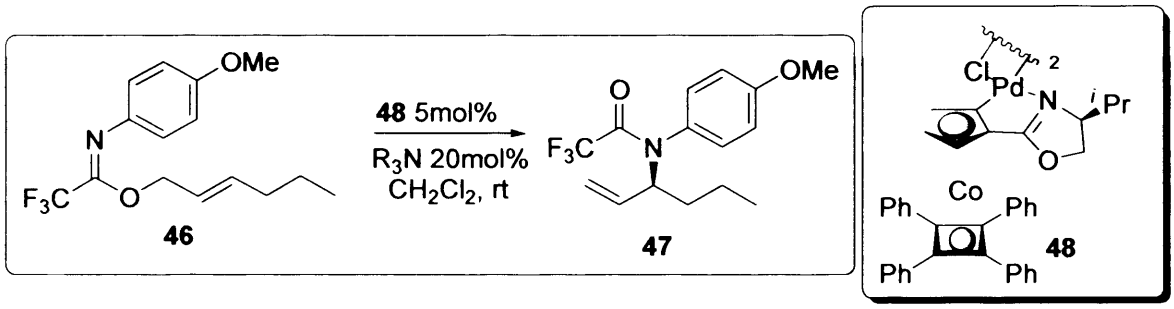
Scheme 17

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.[25] These can be attributed to competitive complexation of the basic trichloroacetimidate nitrogen to the hard palladium centre.[26] This problem was alleviated through the use of less strongly coordinating *N*-arylimidates.[27]



Scheme 18

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.[28]

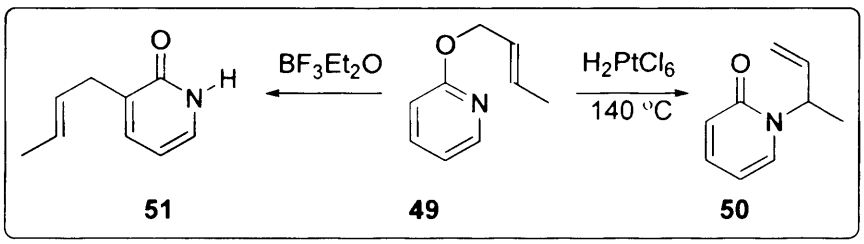


Scheme 19

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 completive complexation 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_2PtCl_6 at 140 °C, yielded >85% of *N*-allyl-α-pyridone **50** (Scheme 20).[30]

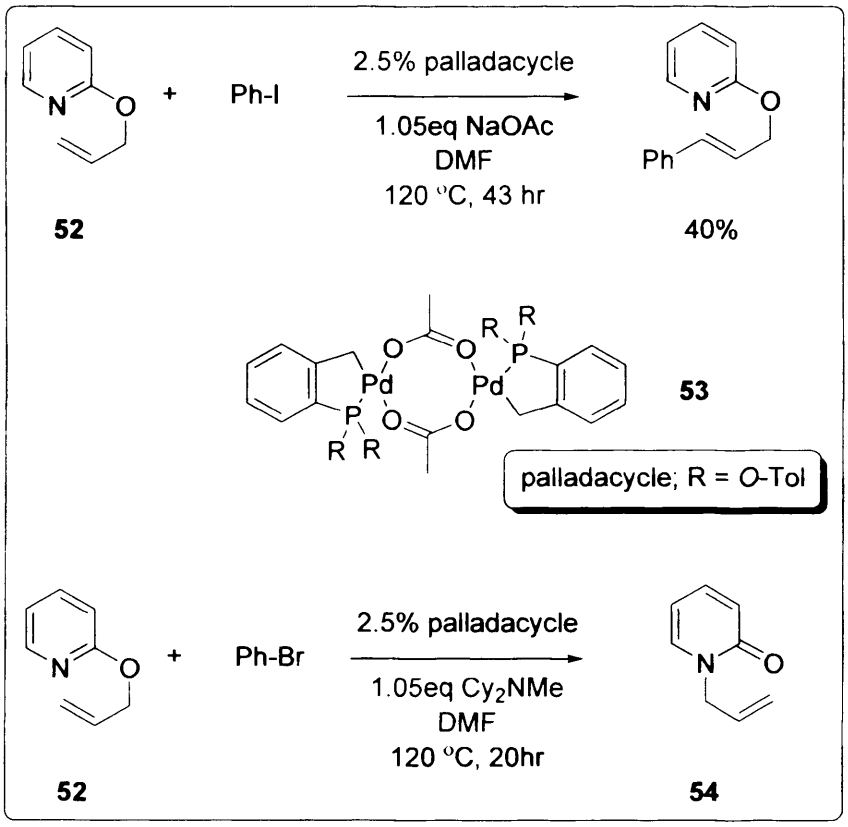


Scheme 20

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 Cy_2-NMe, quantitative conversion of **52** to *N*-allyl-2-pyridone **54** was observed.



Scheme 21

This led Itami to further investigate the different mechanisms through which both Pd^0 ($Pd(PPh_3)_4$, $Pd[P(t\text{-}Bu)_3]_2$) and Pd^{II} ($PdCl_2$, $PdCl_2(PhCN)_2$) may catalyze the rearrangement of 2-allyloxy pyridines.[32] In the Pd^{II} catalyzed rearrangement, an electrophilic Pd^{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 **55** (Fig. 9), which rearranges as a formal [3,3]-rearrangement to the observed product. This is in contrast to the Pd^0 catalyzed rearrangement in which an (π-allyl) palladium complex **56** is thought an intermediary (Fig. 9).

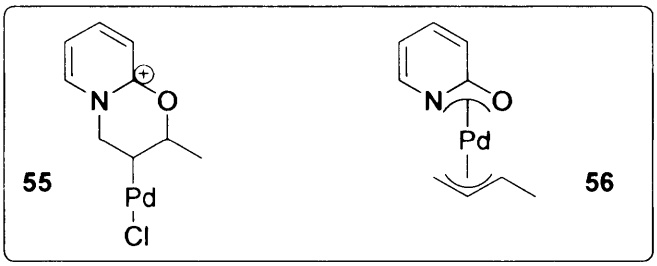
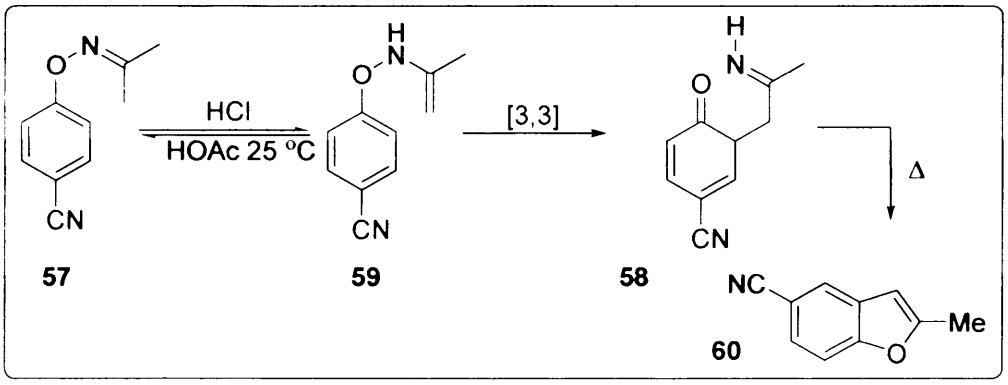


Fig. 9

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]

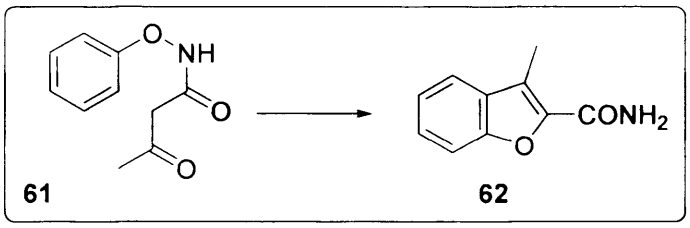


Scheme 22

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. $BF_3{\cdot}Et_2O$ was also found to catalyse the transformation.

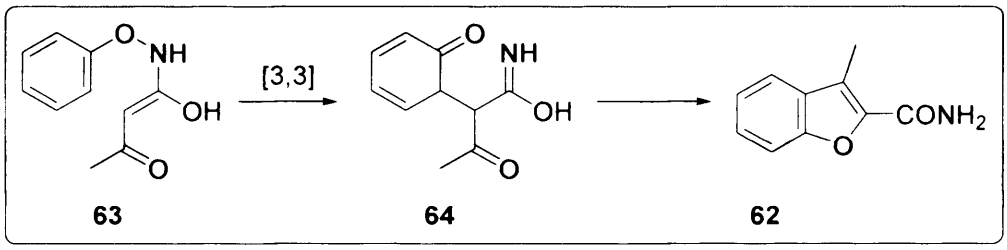
1.2.5.2 *O*-Phenyl-*N*-acetoacetylhydroxylamines:

The reaction of *O*-phenylhydroxylamine with a diketene in THF resultes 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).



Scheme 23

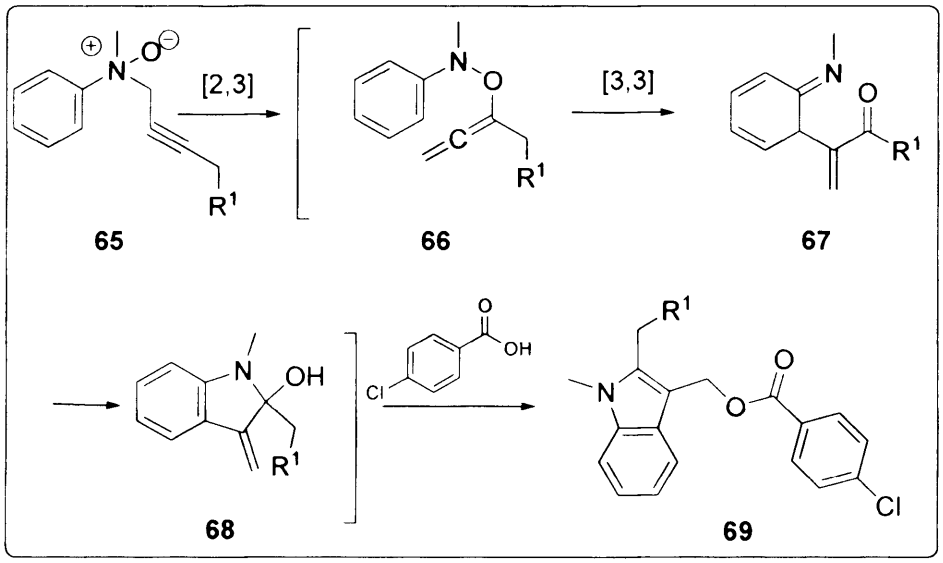
The rearrangement is again consistent with a [3,3]-sigmatropic process, with rearrangement of enol species **63**, prototropic aromatization, cyclization of the resulting 2-(2-actetoacetamido)phenol intermediate **64** and dehydration to give **62** (Scheme 24).



Scheme 24

1.2.5.3 *N*-arylpropynylamine oxide

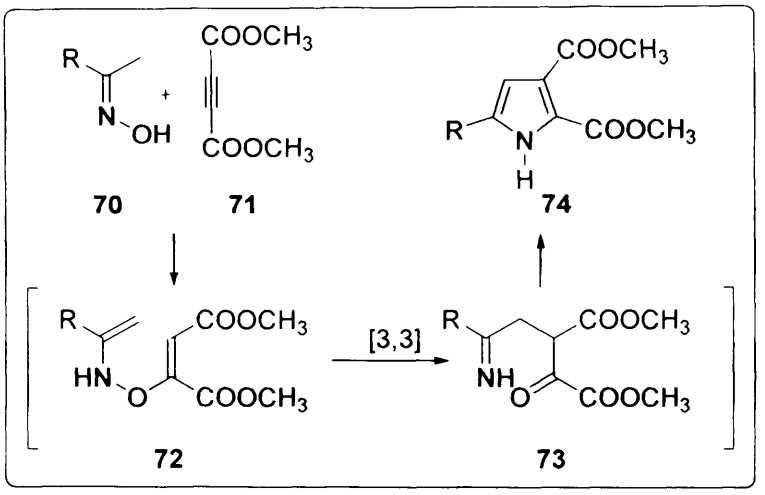
Rearrangement of **65**, accessed via oxidation with *m*CPBA, provides an interesting route to substituted indoles *via* sequential [2,3] (**65** to **66**), then [3,3]-sigmatropic rearrangements (**66** to **67**).[34]



Scheme 25

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]

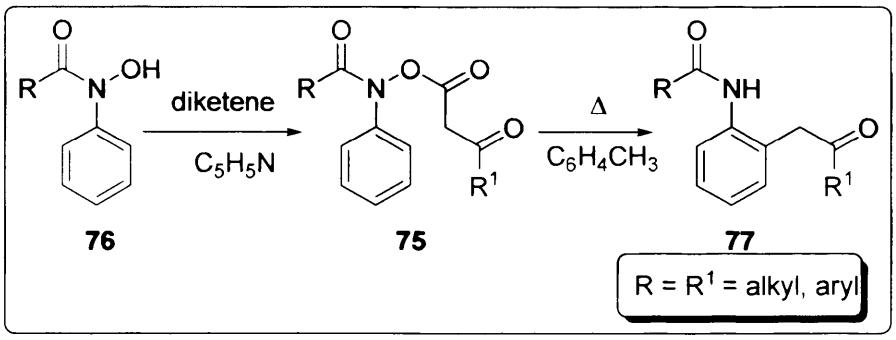


Scheme 26

1.2.6 4-*N*,3-*O* Systems:

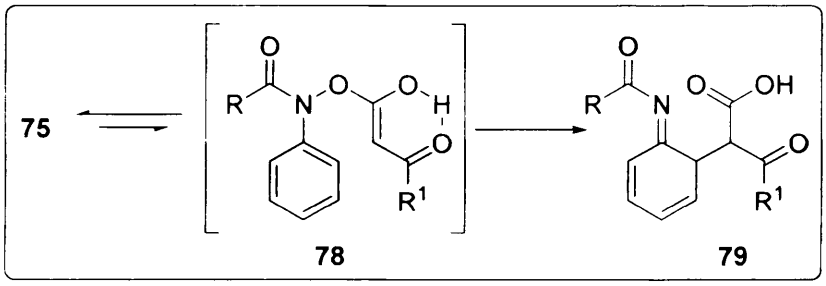
1.2.6.1 *N*-Aryl-*N*,*O*-diacylhydroxylamine

Decarboxylative 1-aza-1'-oxa-[3,3]-sigmatropic rearrangements of enolizable *N*-aryl-*N*,*O*-diacylhydroxylamines **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*-arylhydroxylamines[37] 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).



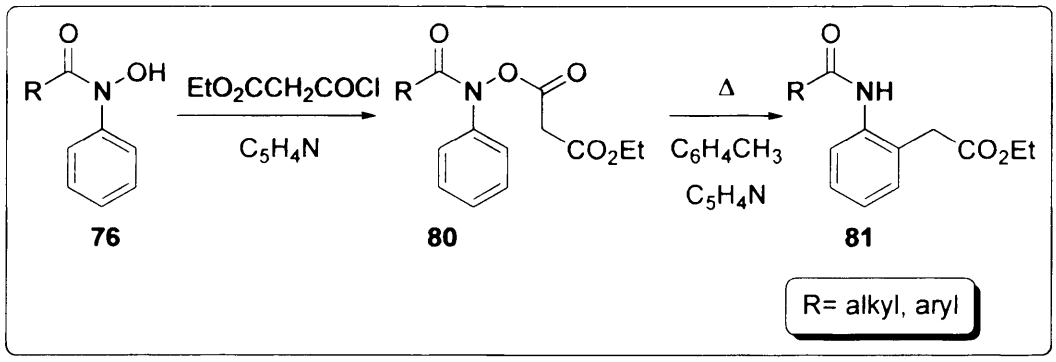
Scheme 27

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).



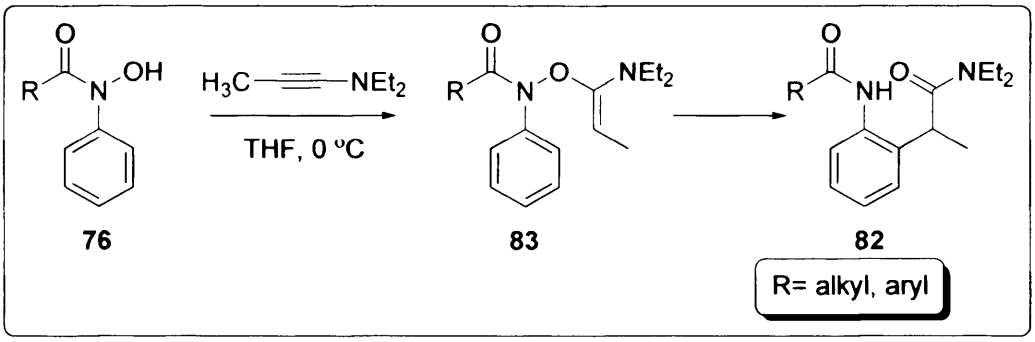
Scheme 28

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.**



Scheme 29

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 **82** in yields ranging from 42 to 67%, presumably by way of adduct **83.**

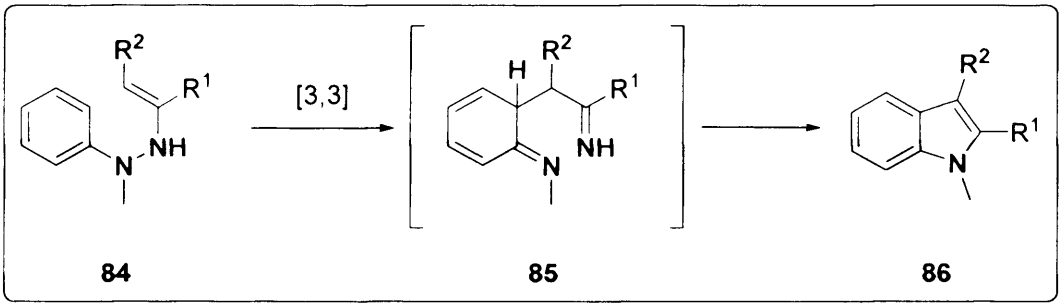


Scheme 30

1.2.7 3-*N*,4-*N* Systems:

1.2.7.1 *N*-Aryl-*N*-enylhydrazines

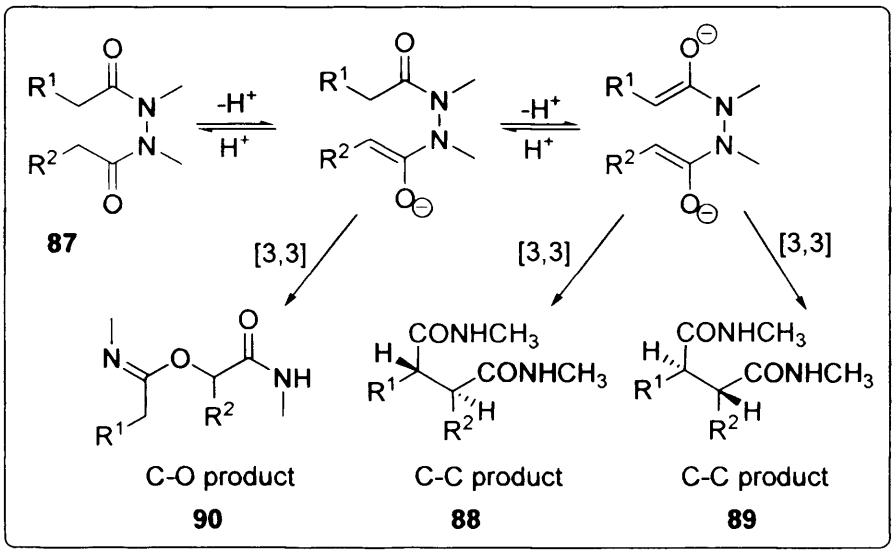
Both the aromatic and aliphatic versions of the 3,4-diaza-[3,3]-sigmatropic rearrangement are known, with the Fischer synthesis of indoles from enylhydrazines being the best documented (Scheme 31).[39]



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.

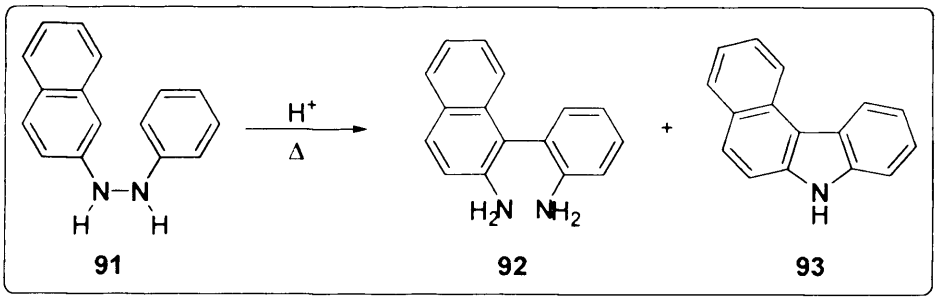


Scheme 32

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 diacylate 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.



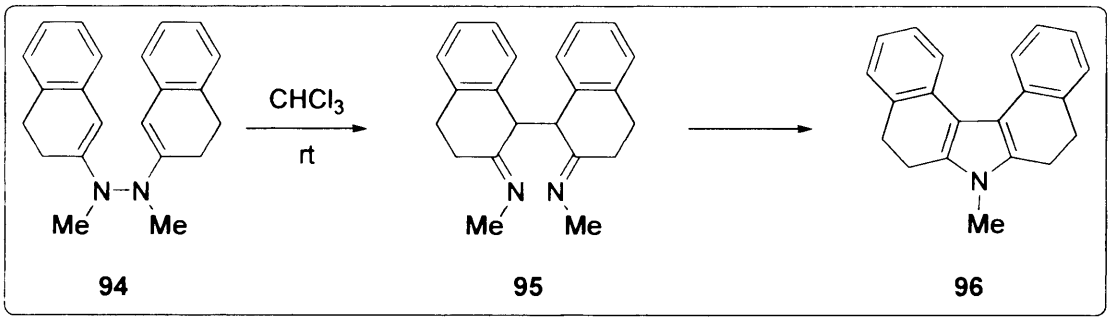
Scheme 33

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.[44]

1.2.7.4 *N,N*-Bis(enyl)hydrazines

The bis(enyl)hydrazine **94**, derived from 2-tetralone and *N,N'*-dimethylhydrazine, rearranges at room temperature under acidic conditions to give the pyrrole **96** *via* a di-imine **95** (Scheme 34).



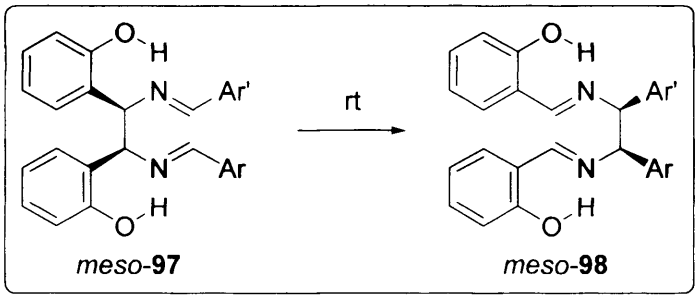
Scheme 34

N,N'-Bis(enyl)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 Brønsted and Lewis acids.[45]

1.2.8 2-*N*,5-*N* Systems:

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

Vögtle *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).[46] The reversibility of the reactions depended on the substituents, and *meso* substrates generally rearranged *via* a boat transition state to give *meso* products.



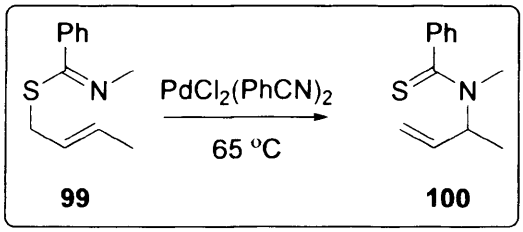
Scheme 35

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-*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 Pd^{II} salts (Scheme 36). Rearrangement of **99** with 0.01eq of $PdCl_2(PhCN)_2$ in refluxing THF gave **100** in 98% yield.



Scheme 36

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).

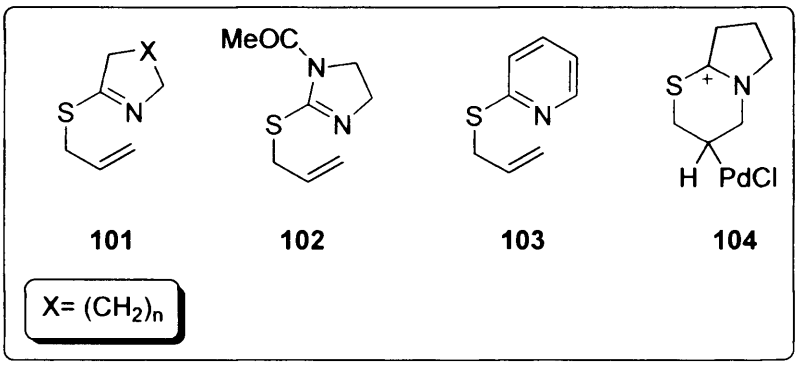
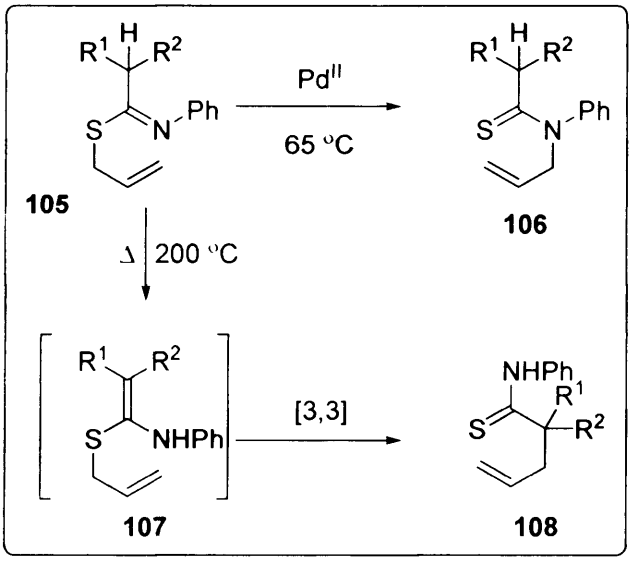


Fig. 10

A cyclization-induced mechanism involving **104** is proposed (Fig. 10),[48] analogous to other Pd^{II} catalysed rearrangements. $Pd(Ph_3)_4$, $NiCl_2$, $CuCl_2$ or $HgCl_2$ 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^{II} catalysed reactions under similar reaction conditions gave *N*-allyl thioamides **106** from **105** (Scheme 37).[49] The thermal reaction proceeded through a different pathway, giving *C*-allyl products **108** (Scheme 37).



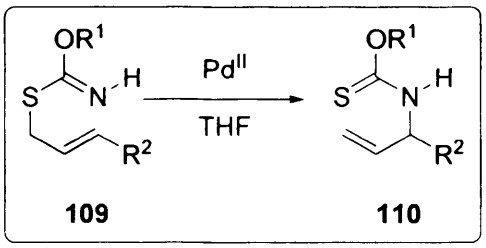
Scheme 37

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).



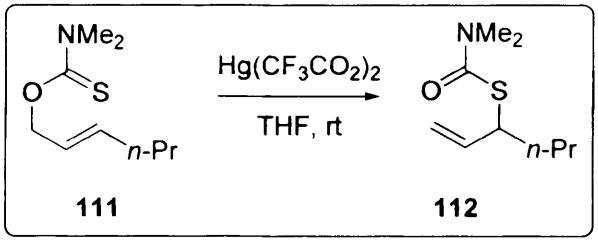
Scheme 38

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*-CH_2Ph, 12%).

1.2.10 1-*S*,3-*O* Systems:

1.2.10.1 Allylthionocarbamates

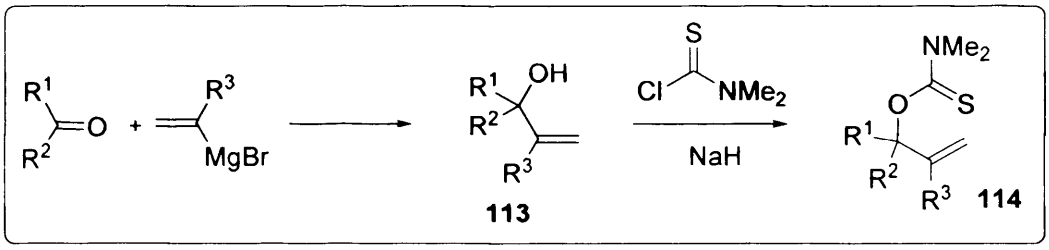
Allylthionocarbamates make excellent substrates for [3,3]-sigmatropic rearrangement processes. It was shown that allyl thionocarbamate **111** can be converted to the thiocarbamate **112**, with the use of 0.3eq of $Hg(CF_3CO_2)_2$ in THF (Scheme 39).[50]



Scheme 39

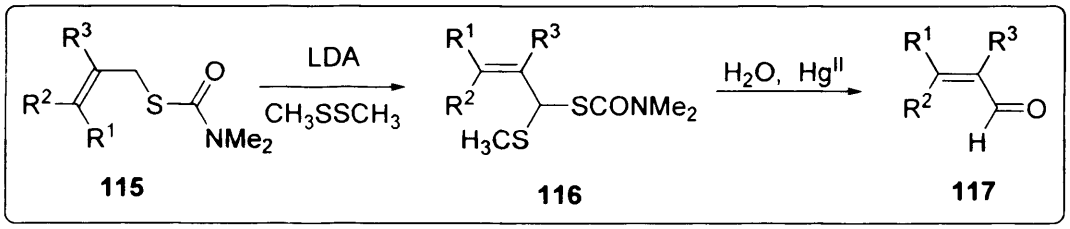
Allylic thionocarbamates undergo the same rearrangement and have been employed en route during the preparation of α,β-unsaturated aldehydes **117** (Scheme 41). An allylic alcohol **113**, prepared from the addition of a vinyl Grignard reagent to a ketone, was

treated with *N,N*-dimethylthiocarbamoyl chloride under basic conditions, to give the thionocarbamate **114** in 73% yield (Scheme 40).[51]



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 α-sulfenated product **116**. Finally, the hydrolysis of **116** with mercuric chloride in the presence of calcium carbonate in aqueous THF afforded the α,β-unsaturated aldehydes **117** in good yield.

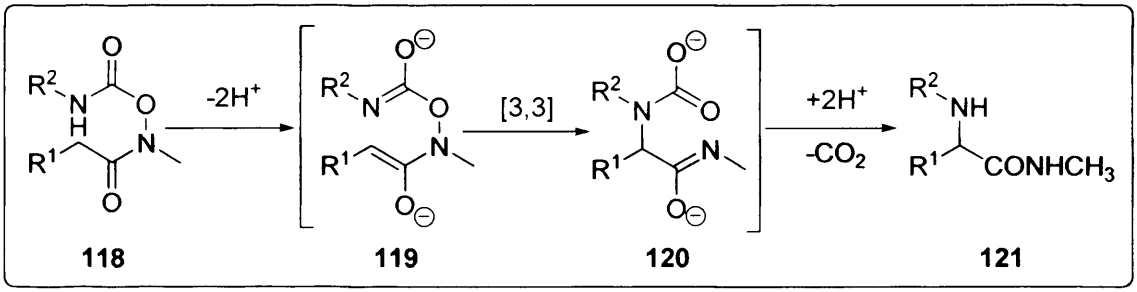


Scheme 41

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 α-amino acid amide derivatives **121** (Scheme 42).[52] This rearrangement, which can be described in terms of an anionic [3,3]-sigmatropic rearrangement, is relevant to the α-amination of carboxylic acids.

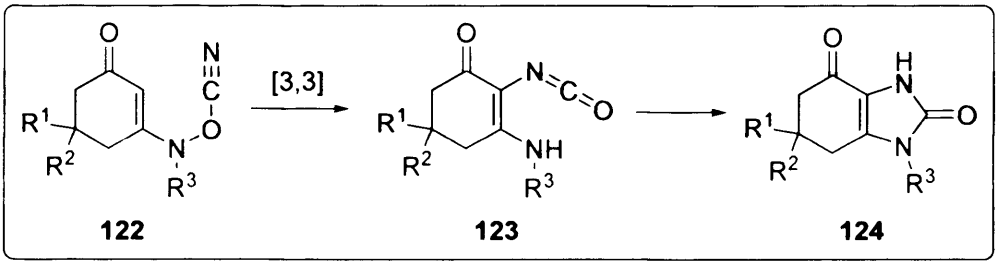


Scheme 42

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 where achieved where R^1=R^2= CH_2Ph 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*-monosubsituted 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.



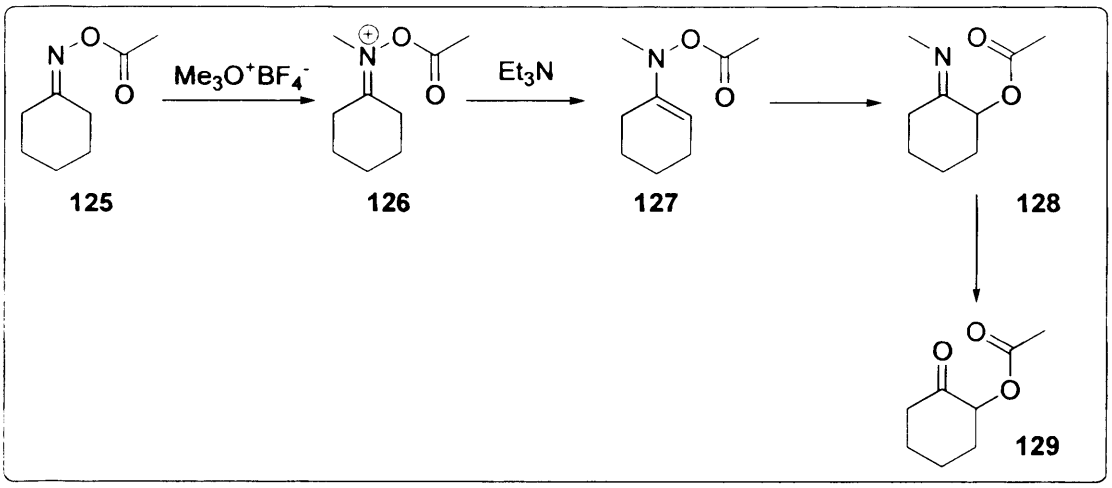
Scheme 43

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 hydroxlyamines:

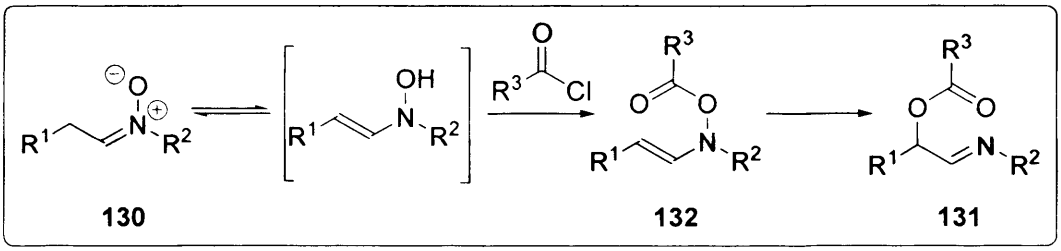
In the late 1960's investigations conducted by House, showed intriguing results with regard to the use of ketoxime derivatives in the preparation of α-acetoxy ketones **129**. House observed that the successive treatment of ketone oxime acetates **125** with trimethyloxonium fluoroborate then triethylamine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



Scheme 44

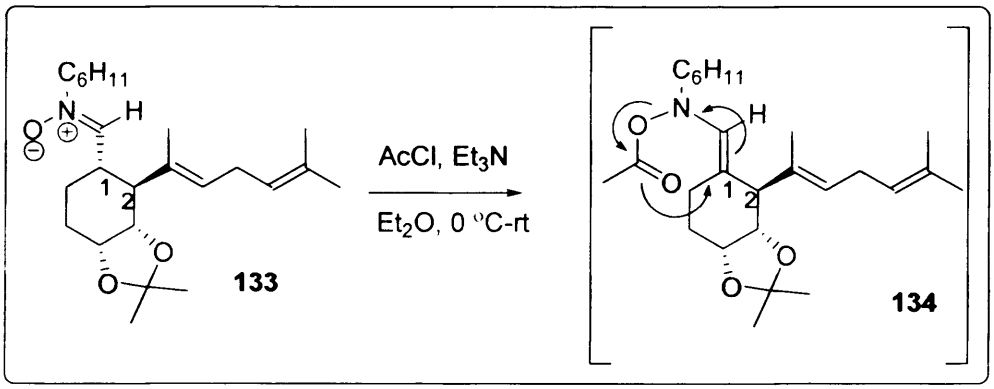
Methylation of oxime acetate **125** produces an iminium ion **126**, which after conversion to the enamine **127**, under basic conditions, underwent the proposed [3,3]-rearrangement.

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*-butylnitrones of aldehydes **130** and *N*-methyl-nitrones of cyclic ketones with acid chlorides under basic conditions afforded α-acyloxy imines **131** by rearrangement of *N*-vinyl-*O*-acylhydroxlyamine intermediates **132**.



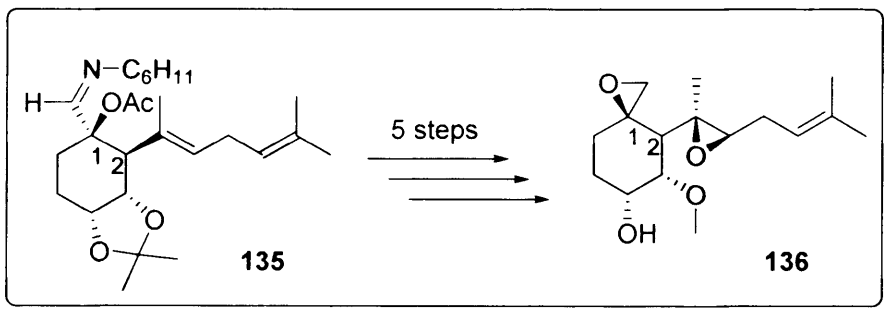
Scheme 45

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.[56] The prerequisite nitrone **133** (Scheme 46) could be simply introduced through condensation of *N*-cyclohexylhydroxylamine with the corresponding aldehyde.



Scheme 46

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).

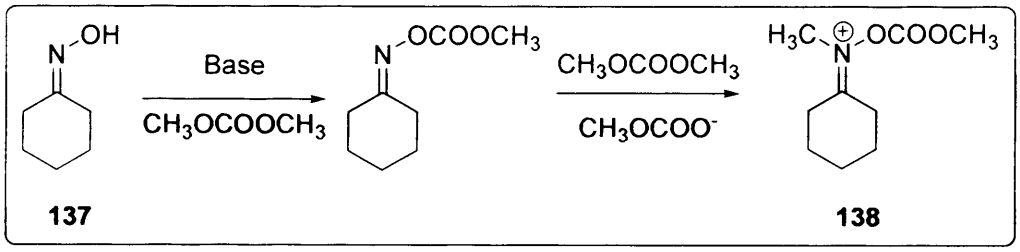


Scheme 47

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.

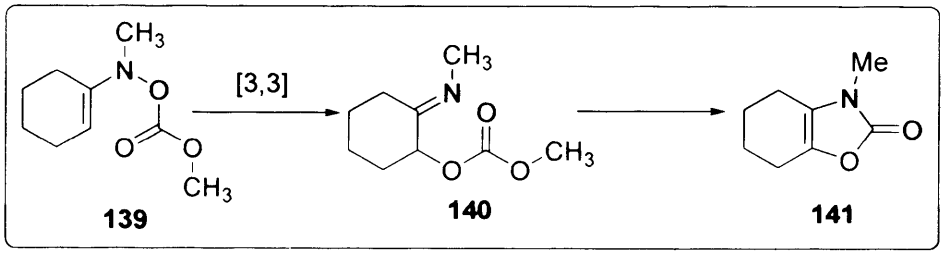
1.2.12.2 *N*-(Oxymethylcarbonate) enehydroxylamine:

The reaction of ketone oximes with dimethyl carbonate (DMC) carried out in an autoclave at 180-190 °C in the presence of K_2CO_3 gave 3-methyl-4,5-disubstituted-4-oxazolin-2-ones **141** (Scheme 49).[57] The reaction can be applied to both aliphatic and aromatic ketone oximes, provided that a methylene group is present α 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).



Scheme 48

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).



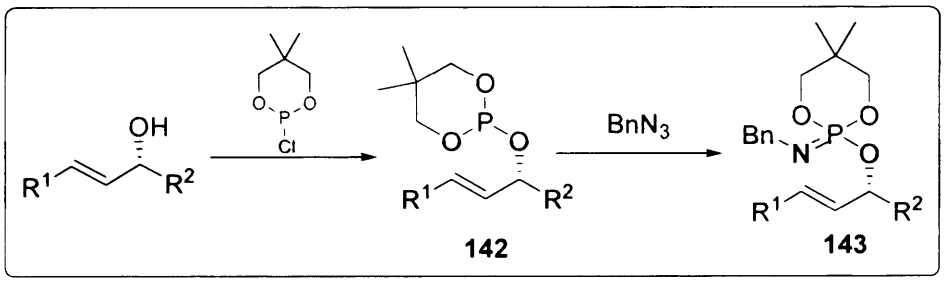
Scheme 49

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:

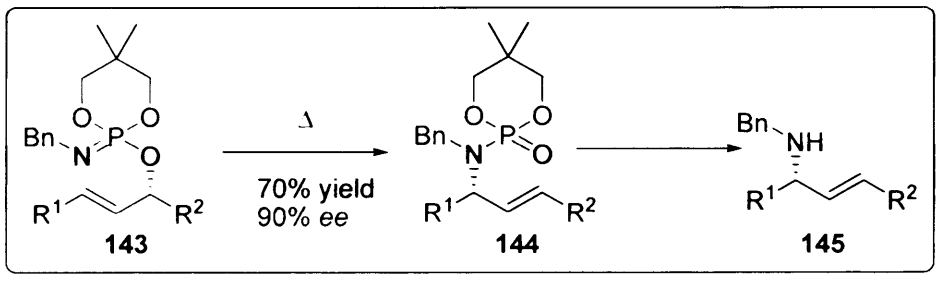
1.2.13.1 Allylic Phosphorimidates:

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).



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).



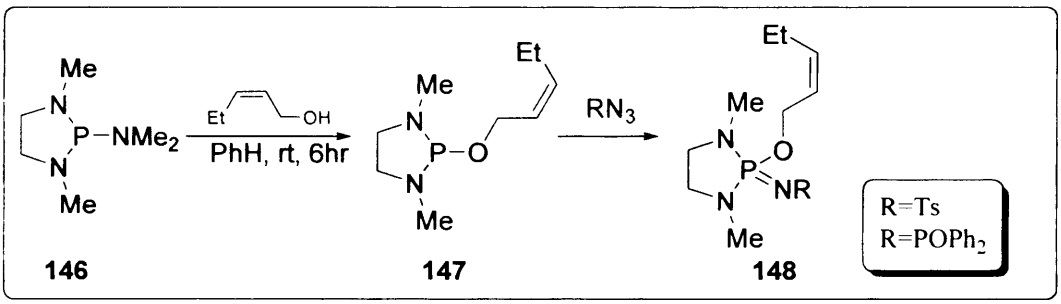
Scheme 51

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.

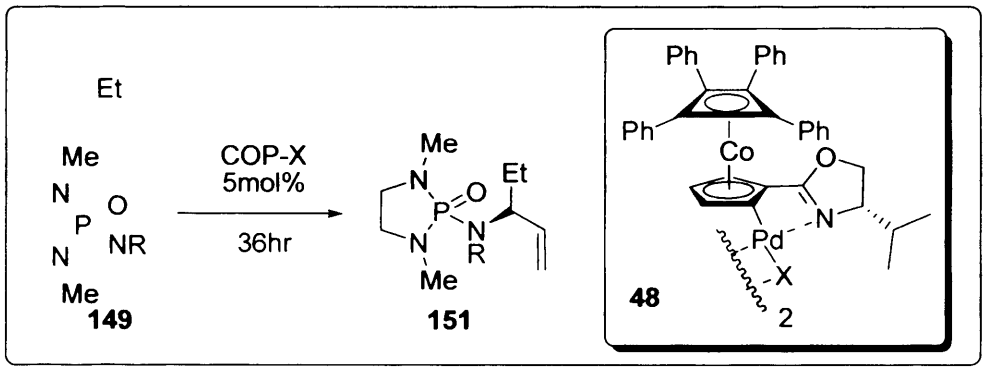
1.2.13.2 (Allyloxy) Iminodiazaphospholidines

A similar enantioselective variant of this reaction was demonstrated by Batey *et al.* [60] for the rearrangement of *cis*-(allyloxy) iminodiazaphospholidines **149** with cobalt oxazoline palladacycle (COP-X) catalysts **48** (5mol%) in high yield and enantioselectivites (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**,[61] followed by reaction with either tosyl azide or diphenylphosphoryl azide (DPPA), respectively to give **148**.



Scheme 52

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.



Scheme 53

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.[62] 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.[63] Examples of the variety of some of the different methods in organo-catalytic methodology are shown (Fig. 11).

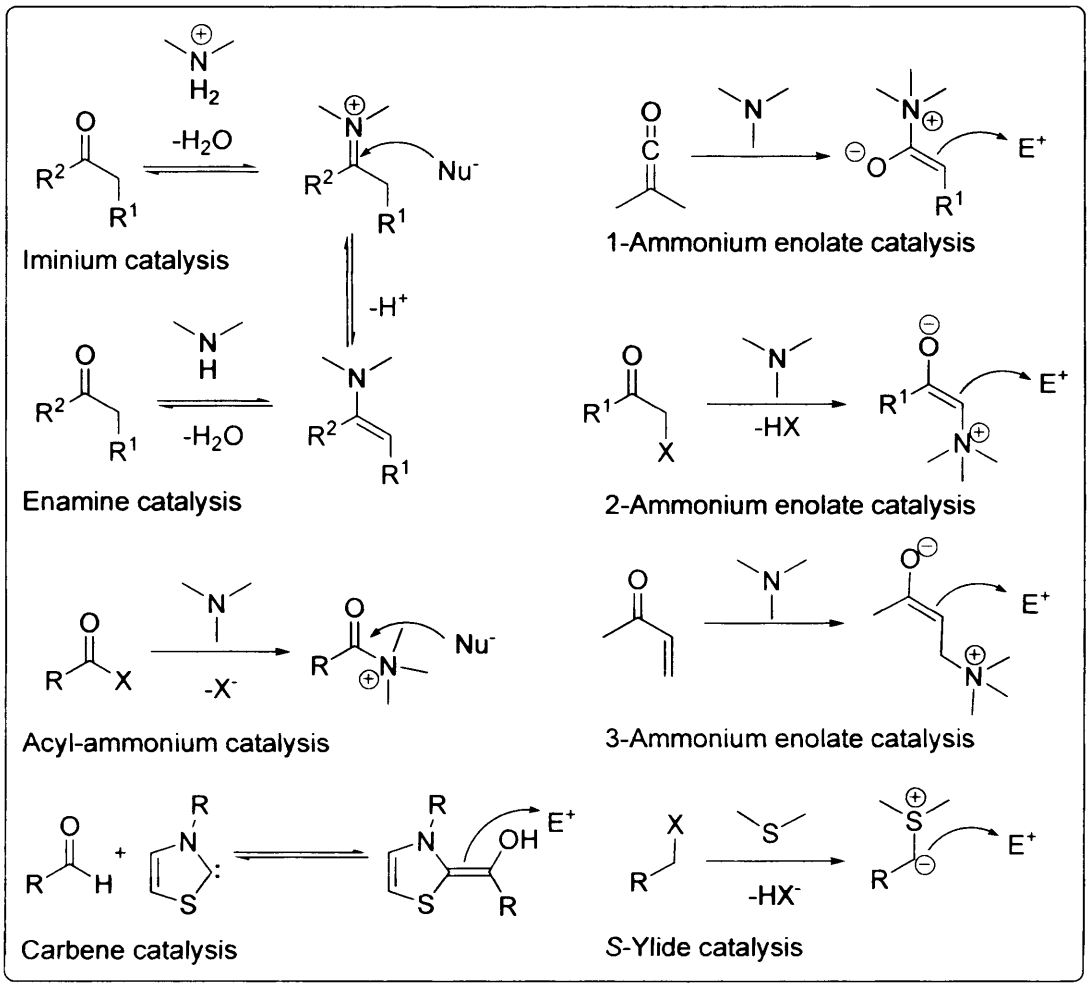


Fig. 11

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.[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.[65]

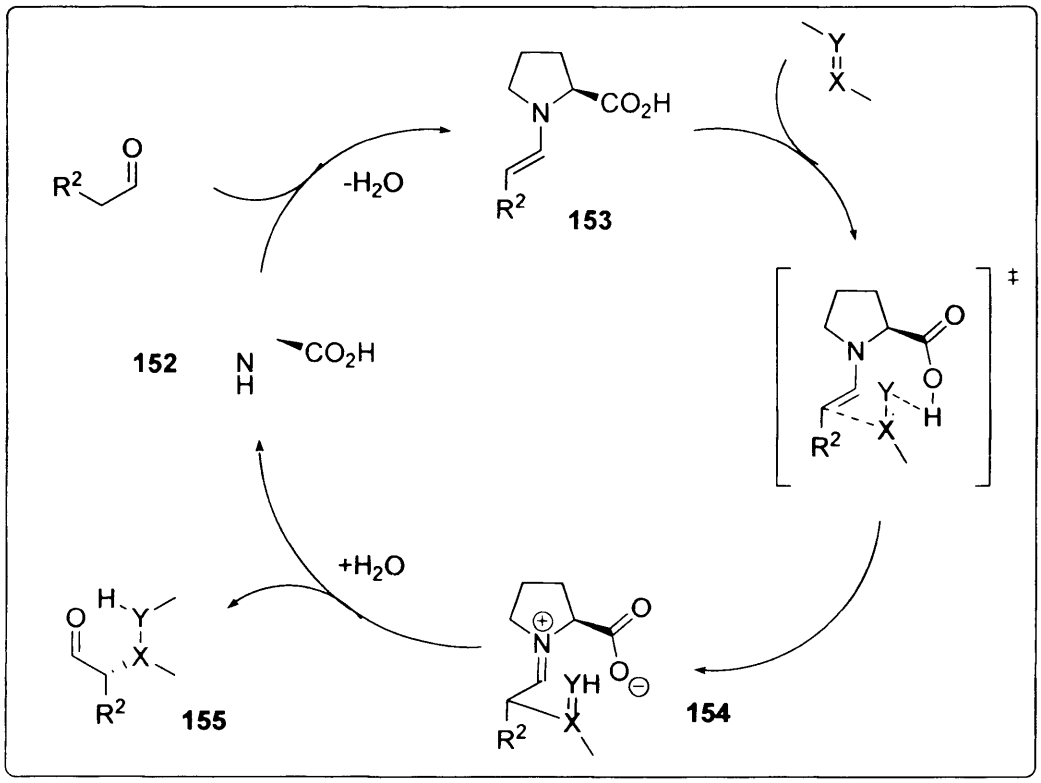


Fig. 12

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.[66] The carboxylate further enhances the aminocatalytic ability of proline by acting as a general Bronsted cocatalyst.

2.3.0 α-Functionalisation of Carbonyl Compounds:

α-Hydroxy carbonyl compounds are versatile synthetic intermediates that are useful for the preparation of 1,2-aminoalcohols,[67] α-aminocarbonyl compounds,[68] and 1,2-diols.[69] In addition to their utility as synthetic precursors, α-hydroxy carbonyl compounds are also important substructures present in a wide variety of natural products and pharmaceutically important compounds.[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,[71] OsO_4,[72] MoOPh,[73] oxaziridines,[74] and DMDO.[75] More recent trends have also expanded to incorporate Sharpless dihydroxylation of enol ethers,[76] manganese-salen epoxidation of enol ethers [77] and Shi epoxidation of enol esters.[78]

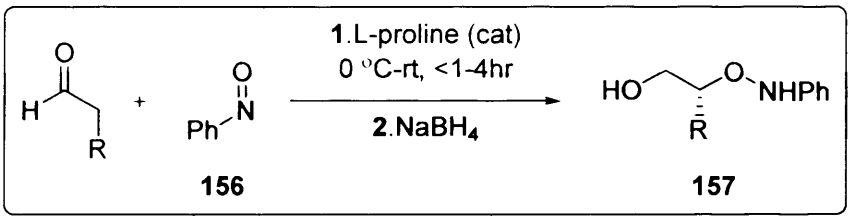
As with α-oxidation reagents there has been paralleled interest into stoichiometric α-aminating reagents with azodicarboxylates proving effective coupling partners with enol ethers and enolates.[79] This interest has been spurred on by the utility of α-amino carbonyl compounds in synthetic chemistry. An alternative approach receiving some attention is the direct amination of carbanions using a variety of hydroxylamines as electrophilic NH_2^+ equivalents.[80] Included in these hydroxylamine deritives *O*-diarylphosphinyl,[81] *O*-acyl,[82] *O*-sulfonyl,[83] and *O*-dinitrophenyl derivatives,[84] and a variety of *O*-alkyl hydroxylamines have been examined with varying degrees of success.[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.[86,87] However, in relation to Grignard reagents this has been some what superseded of late by work conducted by Johnson *et al.* into copper catalysed electrophilic aminations of organo-zinc nucleophiles using *O*-benzoylhydroxylamines as R_2N^+ and RNH^+ synthons.[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 α-Oxygenation Catalyzed by Chiral Lewis Bases:

α-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 α-

hydroxy carbonyl synthesis catalyzed by a Lewis acid.[89] Results for a variety of cyclic ketones showed that Ag^{I}–binap complexes effectively catalyze the enantioselective reaction between Sn^{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,[90] MacMillan,[91] and Hayashi,[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.



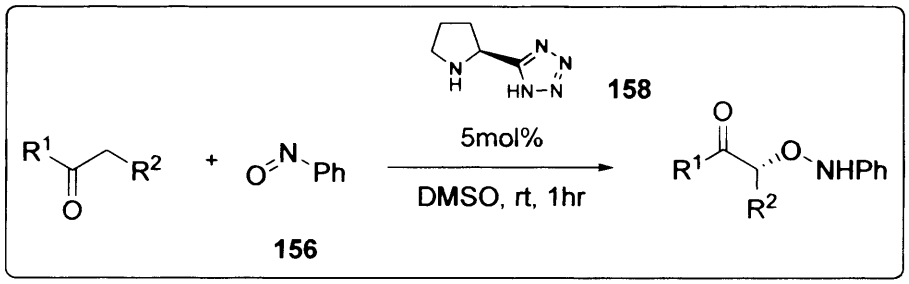
Scheme 54

The overall conclusions from these investigations showed that enolizable aldehydes with varying degrees of branching and functionality react quite well with nitrosobenzene **156** in the presence of catalytic amounts of L-proline to give **157** in >80% yield and 98% *ee* (Scheme 54). Since the initial α-alkoxy aldehydes produced are oligomeric, subsequent reduction with $NaBH_4$ 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[93] and Cordova.[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

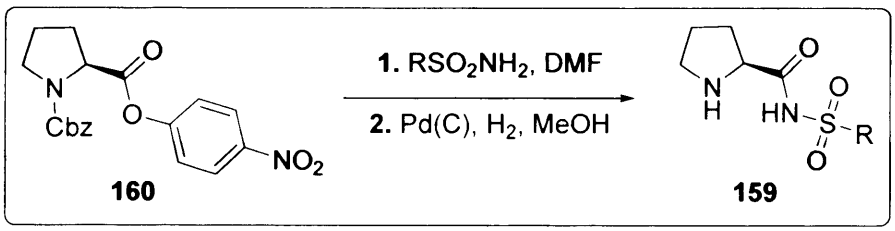
mono-and di-oxygenated species. To avoid this complication, a large excess (2–10 eq.) of ketone is often used and nitrosobenzene is added slowly using a syringe pump. This procedure prevents the formation of any C_2-symmetric di-oxygenated products but requires addition times of up to 60hr. Under these 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 α-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).[95]



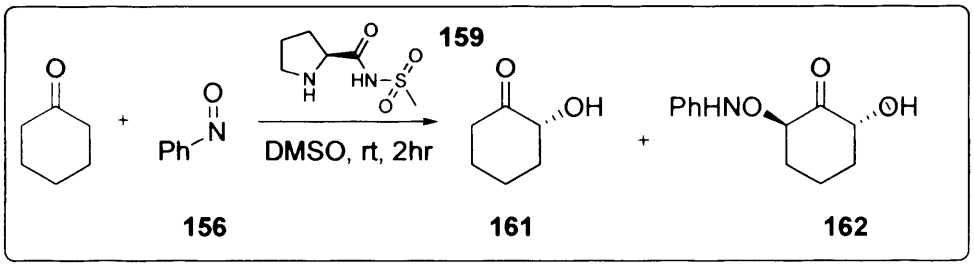
Scheme 55

In conjunction with this, Sunden *et al.* have shown that proline derived *N*-sulfonylcarboxamides **159** are active catalysts for the asymmetric α-oxidations.[96] Unlike the related investigation with *N*-sulfonyl-2-aminomethylpyrrolidines,[97] 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 pyrrolidine-1,2-dicarboxylate **160** (Scheme 56).



Scheme 56

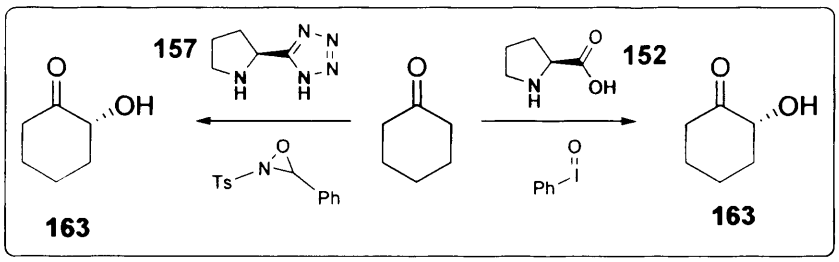
The reaction catalysed by **159** proceeds smoothly, furnishing the corresponding α-aminoxylated compounds in good yields. Interestingly, the direct asymmetric α-oxidation of cyclohexanone with 10mol% of the *N*-sulfonylcarboxamide proline derivative **159** as catalyst showed a marked selectivity for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



Scheme 57

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[98] 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).

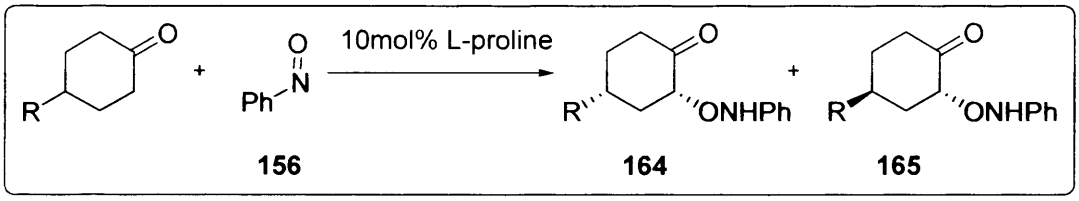


Scheme 58

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

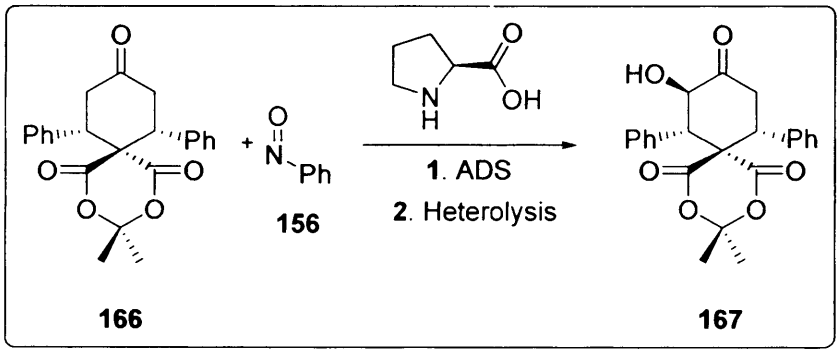
corresponding α-hydroxylated products in moderate yield with up to 63% *ee* (Scheme 58).

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[99] and nonenzymatic[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*.[101] In examples where R = ^{t}Bu, yields of 31% were recorded for both products **164** and **165**, with *ee* of 99 and 94% respectively (Scheme 59). Substitution of a ^{t}Bu group for a OSi(^{t}Bu)Ph$_2$ resulted in yields of 46 and 23% respectively, with *ee's* of 99 and 96%.



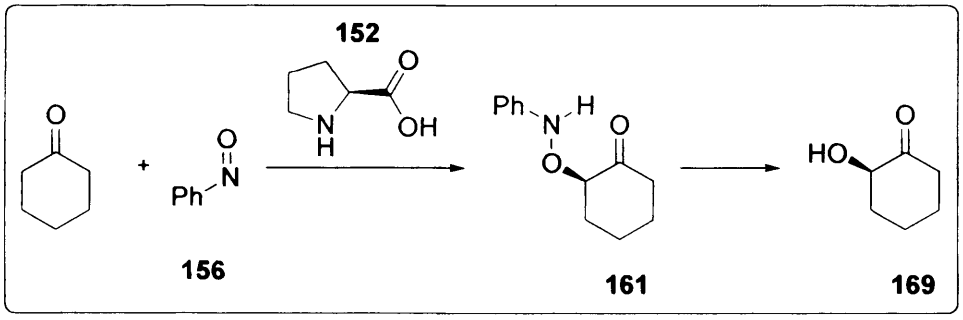
Scheme 59

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.[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).



Scheme 60

It was also demonstrated that the *in situ*-generated *R*-aminoxyketones **161** undergo further O-N bond reduction with nitrosobenzene **156** to yield hydroxyketones **169** (Scheme 61).



Scheme 61

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

2.3.2 α-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 *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^{I} triflate and (*R*)-binap.[103] Evans has employed azodicarboxylates as ready electrophiles in conjunction with C_2-symmetric Mg^{II} complexes[104] and Cu^{II} 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 α-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.[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.[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.[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.[112]

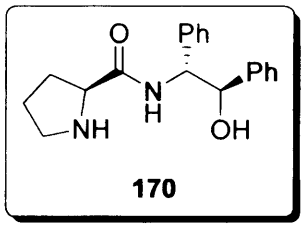


Fig. 13

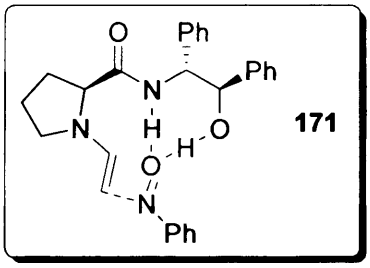
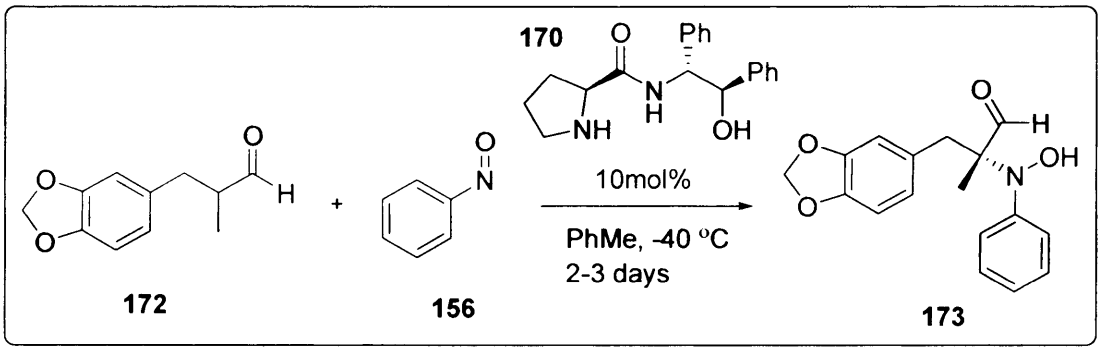


Fig. 14

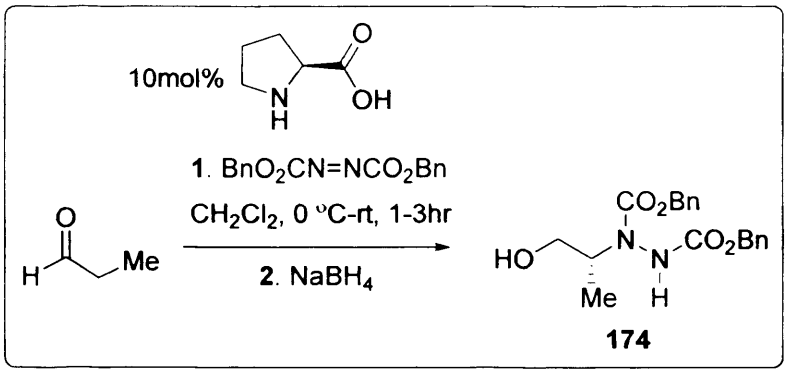
Therefore, it was proposed that prolinamide derivative **170** would be able to catalyze the reaction of unmodified aldehydes and nitrosobenzene *via* a presumed transition state **171**, chemoselectively giving *N*-nitroso aldol adducts (Scheme 62).



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 **174** in 97% yield and 95% *ee* (Scheme 63).[113, 114]



Scheme 63

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 **175**, which led to improved rates of reaction.

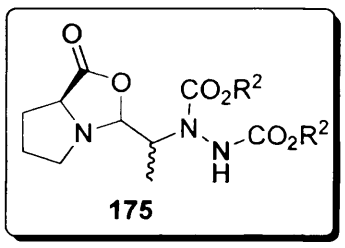
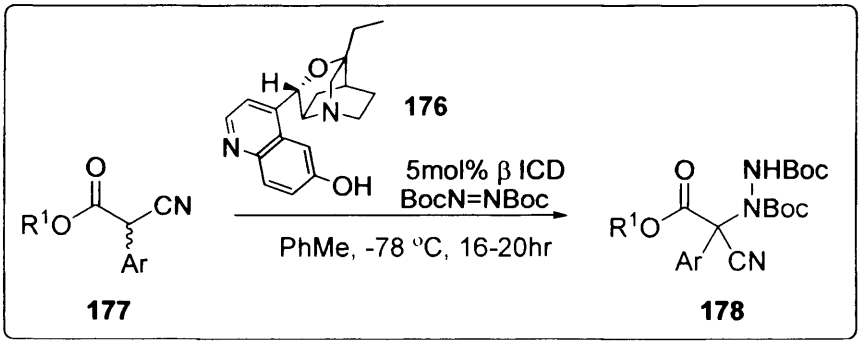


Fig. 15

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 α-amination of α-cyanoacetates and β-dicarbonyl compounds was catalyzed by the quinidine-derived alkaloid (β-isocupreidine, β-ICD) **176** (Scheme 64).[116]

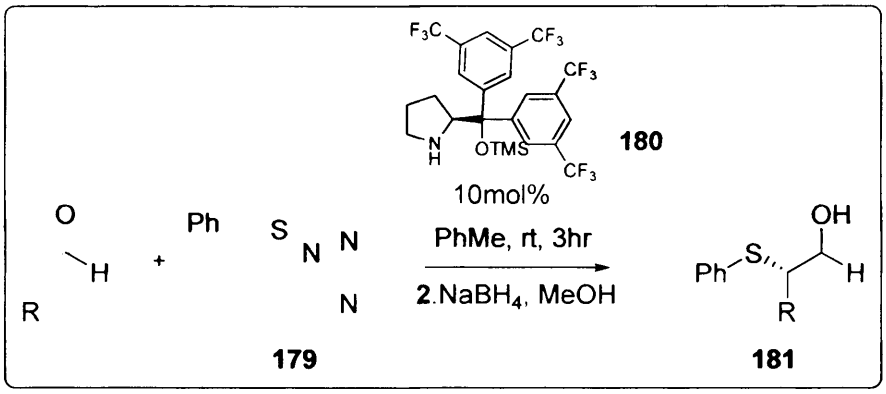


Scheme 64

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.

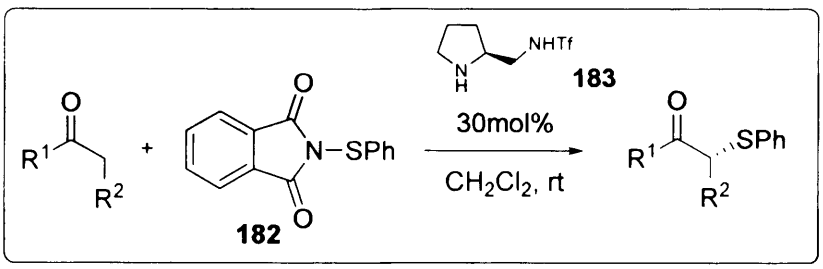
2.3.3 α-Sulfenylation Catalyzed by Chiral Lewis Bases:

To date, all practical methods for the preparation of chiral α-sulfenylated aldehydes have been multistep procedures that involve chiral auxiliaries.[117] The catalytic abilities of Ti(TADDOLato) complexes have been known for several decades[118] and recent studies into the use of [$TiCl_2$(*R*,*R*)-1-Np-TADDOLato)($MeCN)_2$] in relation to the Lewis acid catalytic enantioselective halogenation of β-ketoesters,[119,120] 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).[121]



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 $NaBH_4$ 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.[122] 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).[123]



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 α-amination and α-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: α-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,[124] conjugate addition,[125] aldol,[126] Mannich,[127] amination[128] and aminohydroxylation reactions.[129]

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 **184** with one equivalent of strong base such as lithium di*iso*propylamide (LDA) generates the corresponding enolate **185**, which can in turn react with a variety of electrophiles to introduce carbon or heteroatom functionalities **186** (Fig 16).

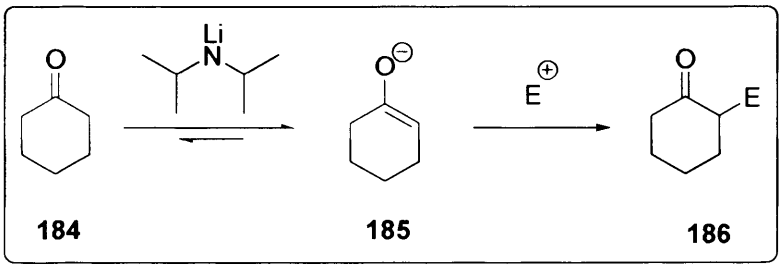
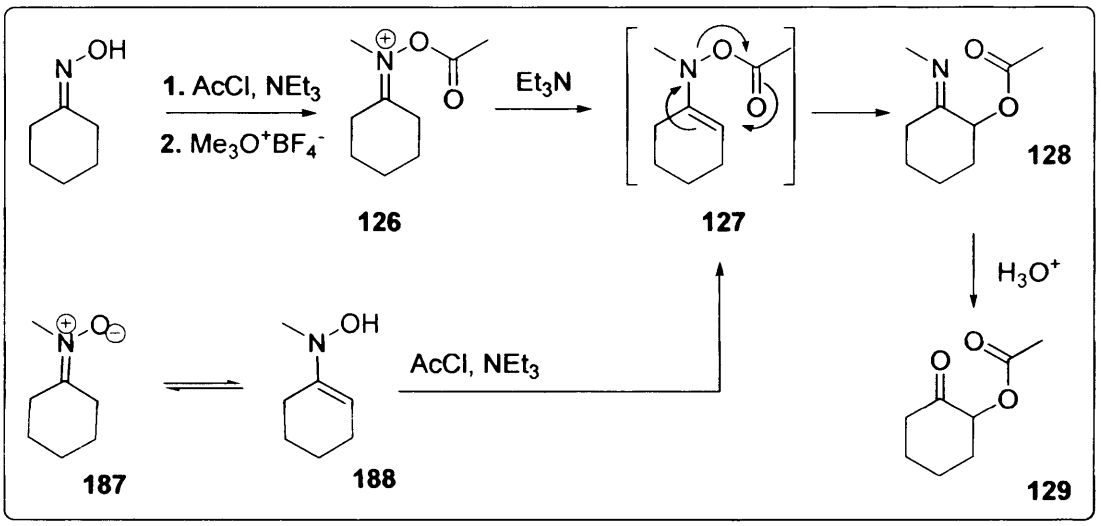


Fig. 16

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,[130] who showed that cyclohexanone could be converted into 2-acetoxycyclohexanone **129** 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 **126**. Under basic conditions **126** was converted to the enamine **127**. The enamine rapidly underwent a proposed concerted Claisen like pericyclic [3,3]-rearrangement to give the imine **128**. Hydrolysis of this imine under aqueous acidic conditions gave the α-functionalised ketone **129** in 45% yield over five steps (Scheme 67).



Scheme 67

Closer consideration of iminium ion species **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).

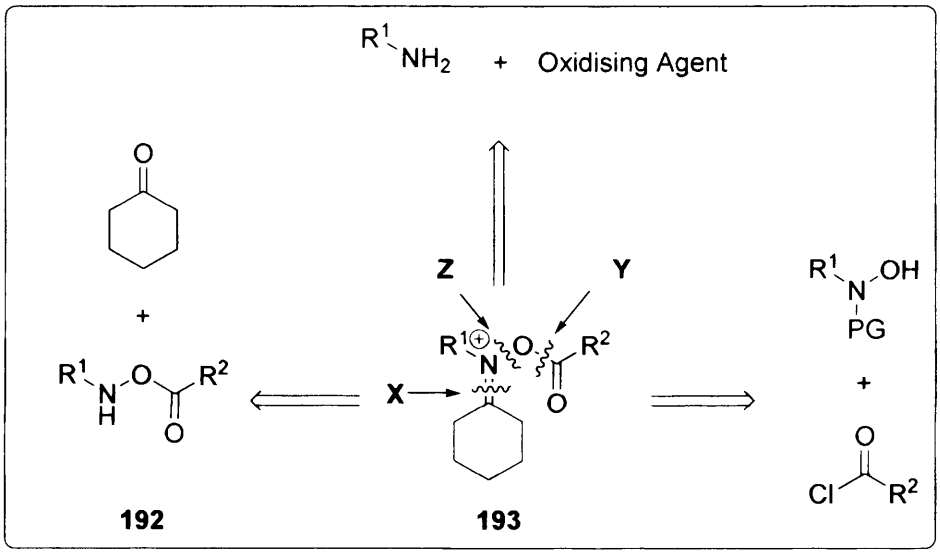
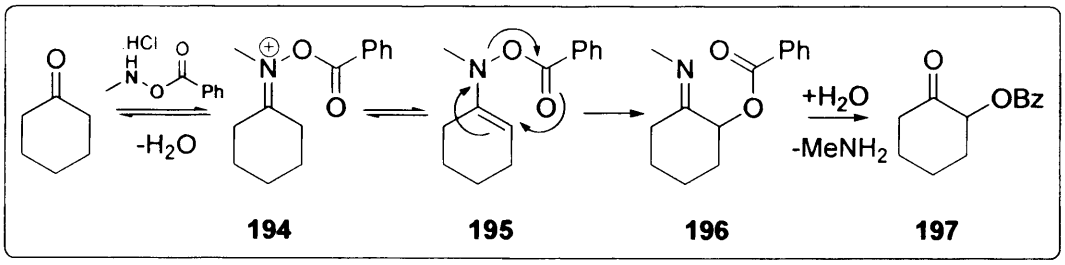


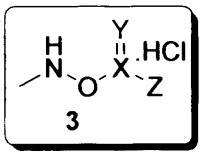
Fig. 17

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,[131] 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.[132] 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^{-1},[133] provides a thermodynamic driving force for this rearrangement with a stronger *C-O* bond being formed.



Scheme 68

In situ acid hydrolysis of the functionalized imine **196** would provide the desired product **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 **X** that provided the concept of a general reagent of the type **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.

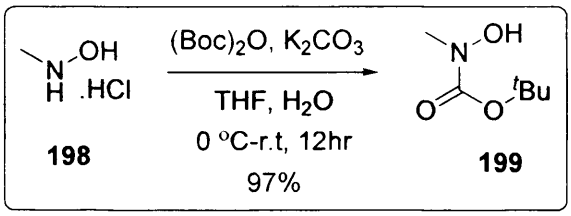


3

3.2.0 Reagent Preparation:

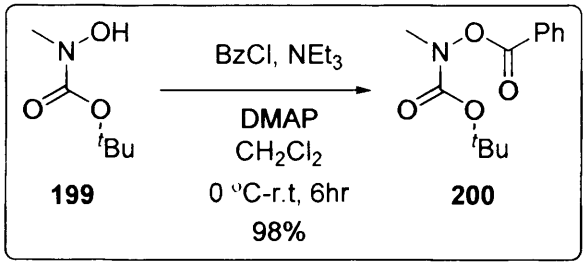
3.2.1 *N*-Methyl-*O*-benzoyl hydroxylamine hydrochloride:

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 **Z** and **Y** (Fig. 17) offer two possible pathways to the desired *N*-methyl-*O*-benzoyl hydroxylamine. Disconnection **Z** *via* a *N-O* bond formation or **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 **198** was commercially available and served as a suitable starting material, removing the need for this oxidation step. In order to exploit disconnection **Y** *N*-methylhydroxylamine hydrochloride **198** was first protected on the nitrogen to allow attack by the less nucleophilic oxygen. This could be achieved using $(Boc)_2O$ in a bi-phasic THF/H_2O system (Scheme 69). *N*-Boc-*N*-methylhydroxylamine **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 ^1H 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.



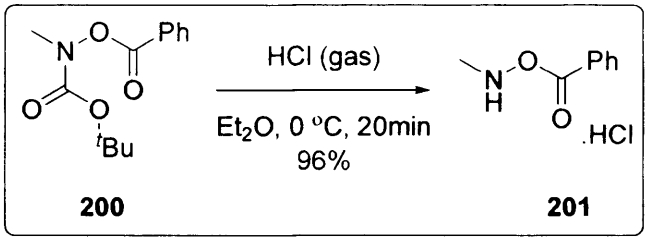
Scheme 69

Once protected, the important *C*-*O* bond could be constructed by reacting *N*-Boc-*N*-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*-Boc-*N*-methyl-*O*-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%.



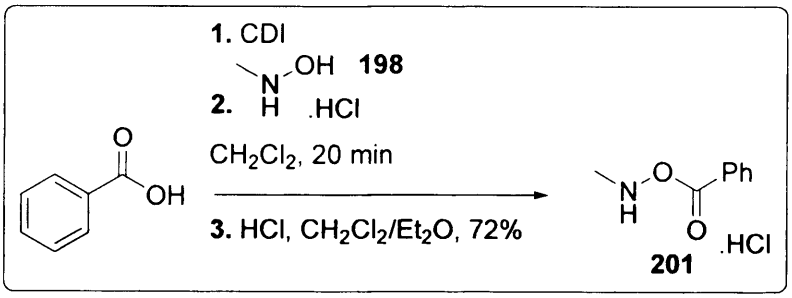
Scheme 70

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*-methyl-*O*-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_2Cl_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*-methyl-*O*-benzoylhydroxylamine, which was fortuitous in accessing what would become our primary reagent.



Scheme 71

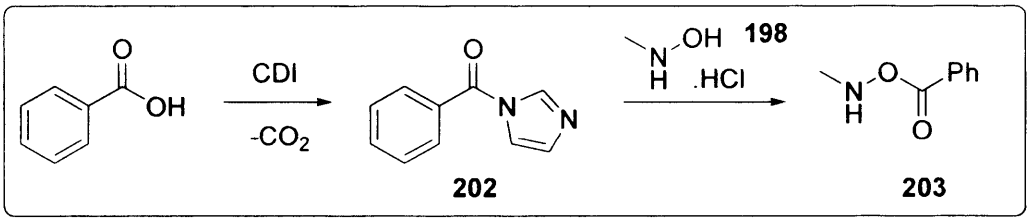
Although the initial route was very successful, with excellent yields recorded over three steps, the synthesis suffered from two prominent restrictions. Firstly, although effective, a three-step procedure to access our desired reagent was deemed too lengthy and indirect. The need to purify both *N*-Boc-*N*-methylhydroxylamine **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]



Scheme 72

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 $NaHCO_3$ 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.

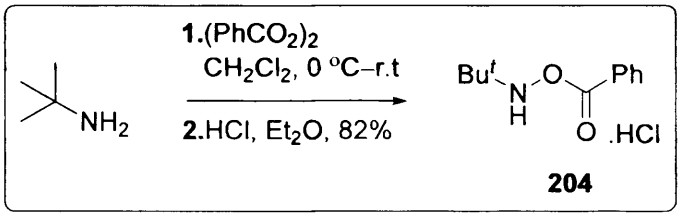


Scheme 73

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-tert*-Butyl-*O*-benzoylhydroxylamine hydrochloride:

The preparation of *N-tert*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-tert*butyl-*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-tert*butyl-*O*-benzoylhydroxylamine **205** with aqueous sodium hydroxide if the debenzoylated hydroxylamine is required.[137]



Scheme 74

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).

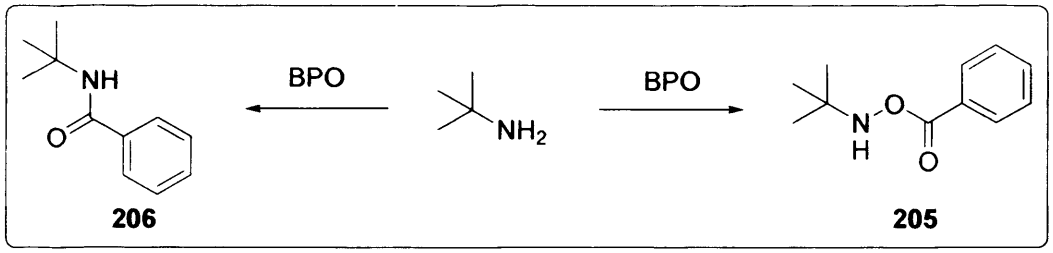
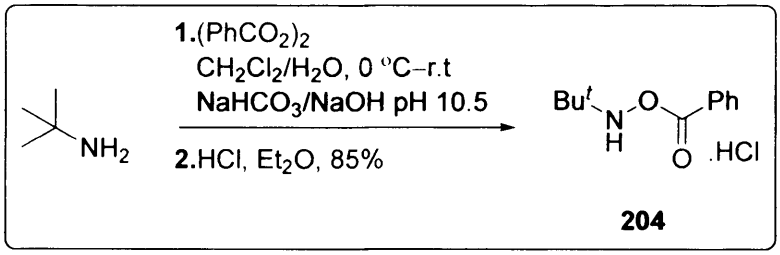


Fig. 18

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 counter act this loss. Together with this, several re-crystillation 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]



Scheme 75

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).

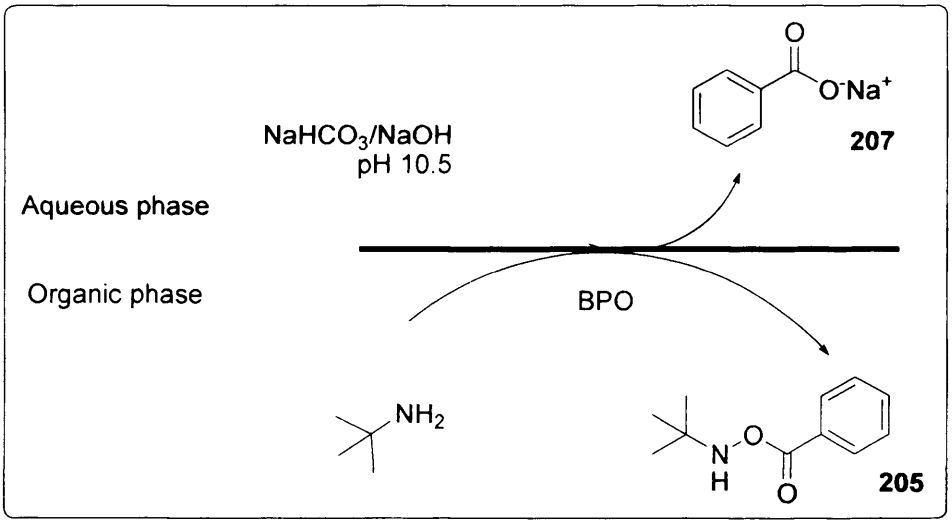


Fig. 19

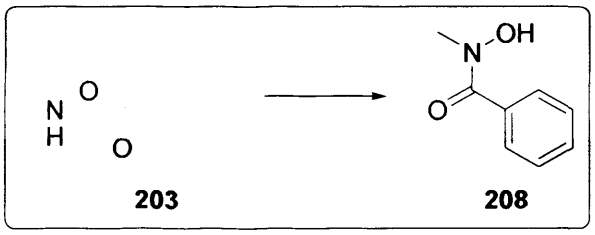
From the results obtained, both the CDI coupling approach for the preparation of *N*-methyl-*O*-benzoylhydroxylamine hydrochloride **201** (Scheme 72) and the buffered bi-phasic reaction for *N*-*tert*butyl-*O*-benzoylhydroxylamine hydrochloride **204** (Scheme 75) proved extremely robust procedures, 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.

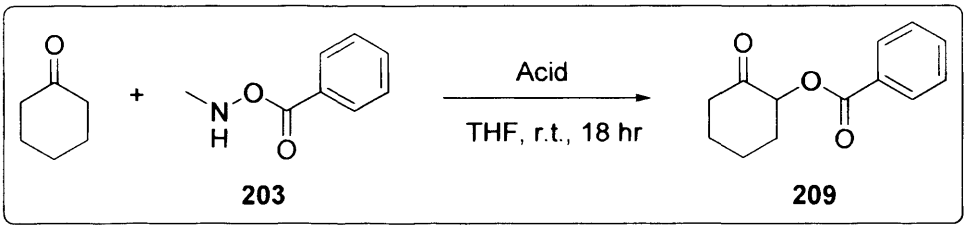
3.3.1 Acid Source:

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

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

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%.

Acid	Yield %
Benzoic Acid	0
Trifluoroacetic Acid	Trace
Methansulfonic Acid	21
Hydrochloric Acid	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.[139] It was shown that homolytic N-O bond cleavage of acylhydroxylamines generates both a benzoyloxy radical (PhCOO$^{\cdot}$) and a primary aminyl radical (RHN$^{\cdot}$). 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,

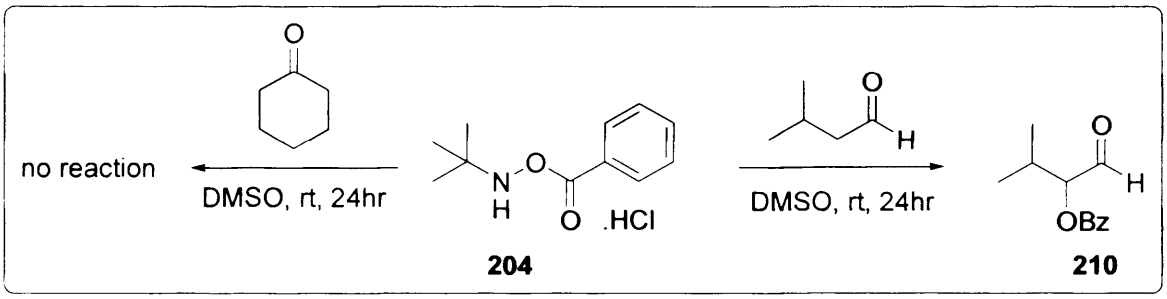
Solvent	Yield %
Ether	64
Tetrahydrofuran	62
Chloroform	Trace
Dichloromethane	Trace
Dimethyl Sulfoxide	72

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 18hr 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 *iso*valeraldehyde in one pot gave exclusively the aldehyde-functionalized product **210** in 68% yield (Scheme 78).



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-*O*-benzoylhydroxylamine hydrochloride **201** or *N-tert*-butyl-*O*-benzoylhydroxylamine hydrochloride **204**.

The product from the reaction was distinguished by the observation of a characteristic doublet of doublets splitting pattern for H_a (Fig. 20). This splitting pattern arises from the coupling observed between H_a and diastereotopic protons H_b and H_c (Fig. 20). In keeping with the Karplus relationship[140] the magnitude of the coupling interactions is determined by the dihedral angle α between H_a and distereotopic protons H_b and H_c. The coupling constant between two axial protons is normally 10-14Hz (α = 180°), whereas the magnitude of coupling between an axial and an equatorial proton is generally 4 to 5Hz (α = 60°).

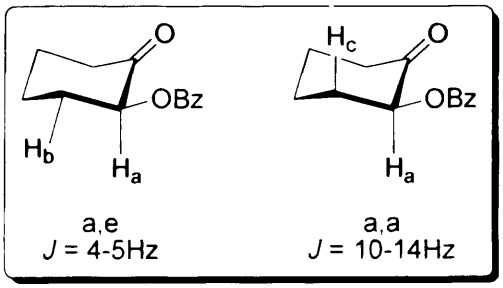
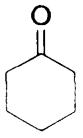
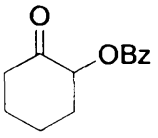
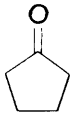
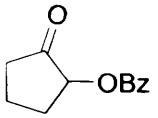
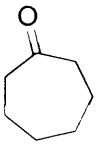
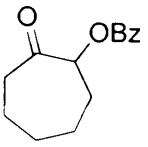
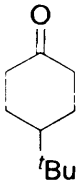
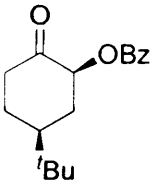


Fig. 20

The observed coupling constants of 6.7Hz and 10.5Hz for **209** (Table 1, Entry 1) are in keeping with this trend indicating the presence of the expected thermodynamically stable equatorially positioned confomer. 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 1. Reaction of 201 with Cyclic Ketones

Entry	Starting Ketone	Oxygenated Product	Reaction Temperature (°C)	Yield
1		 **209**	r.t.	72%
2		 **211**	r.t.	73%
3		 **212**	r.t.	79%
4		 **213**	r.t.	75%

[a]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 maybe 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).

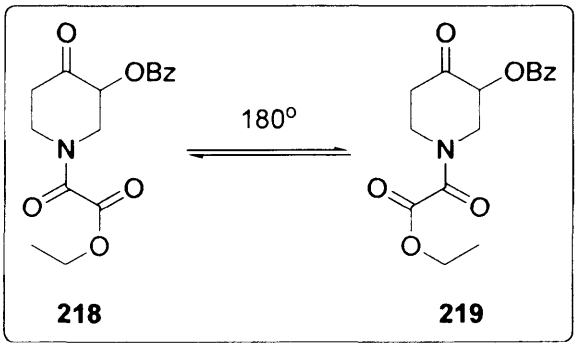
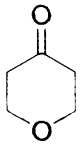
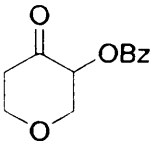
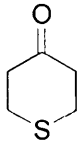
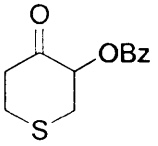
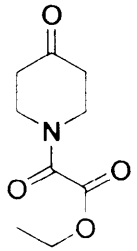
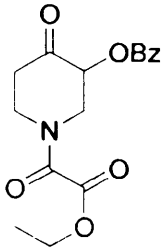
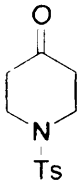
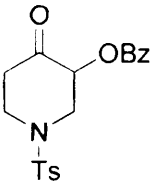


Fig. 21

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).

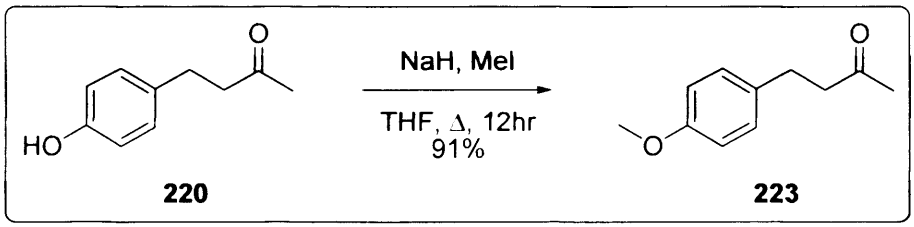
Table 2. Reaction of 201 with Heterocyclic Ketones[a]

Entry	Starting Ketone	Oxygenated Product	Reaction Temperature (°C)	Yield
1		 **214**	r.t.	74%
2		 **215**	r.t.	72%
3		 **216**	r.t.	71%
4	 **217a**[141]	 **217**	r.t.	75%

[a] All reactions were preformed 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:

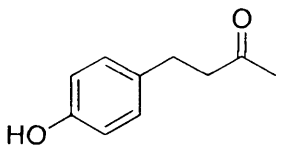
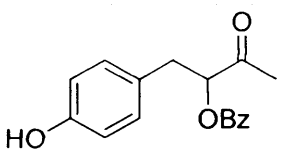
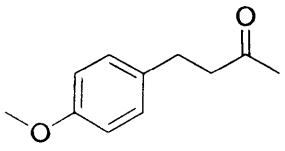
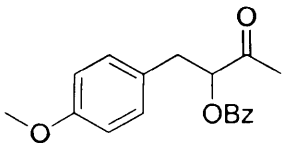
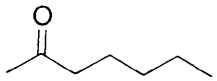
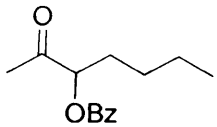
Our success with cyclic ketones led us to explore the applicability of **201** to functionalise acyclic ketones. Investigations focused on two commercially available generic acyclic ketones 4-(4-hydroxyphenyl) butan-2-one **220** and heptan-2-one **221**. 4-(4-Hydroxyphenyl) butan-2-one was also converted 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 MeI in THF under reflux for 12 hr, to give **223** in 91% yield (Scheme 79).



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 3 Reaction of 201 with Acylic Ketones[a]

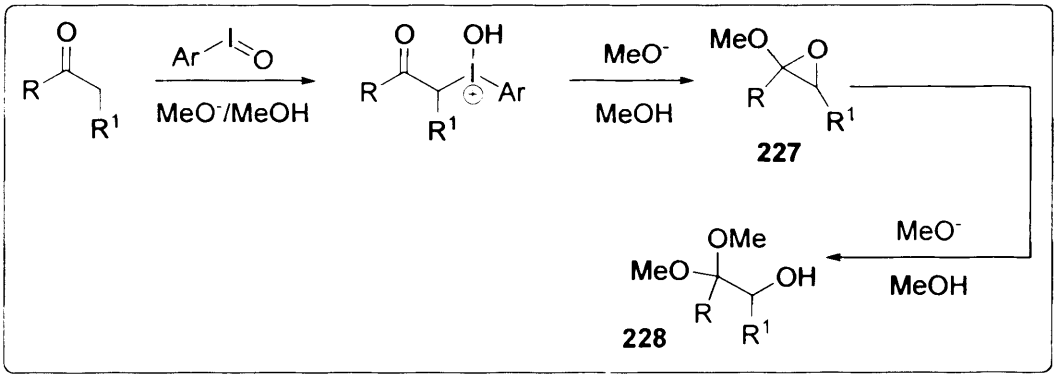
Entry	Starting Ketone	Oxygenated Product	Reaction Temperature (°C)	Yield
1		 **224**	50	83%
2		 **225**	50	83%
3		 **226**	50	81%

[a]All reactions were preformed for 18hr at 0.5M concentration in DMSO with 1 eq. **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.

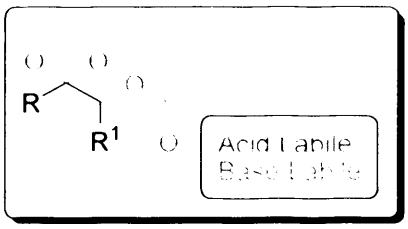
3.7.0 Ketals as Substrates:

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.[142] 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).

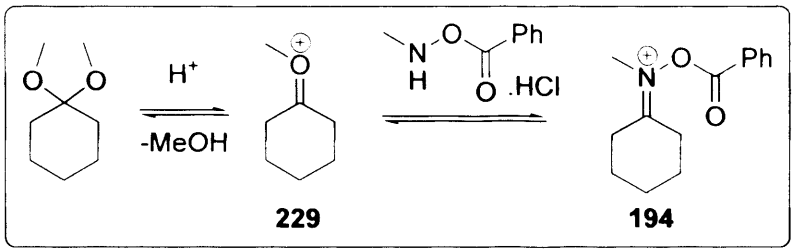


Scheme 80

The utilization of elemental iodine as a reagent for this reaction has been shown to be a reasonably effective alternative.[143] 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

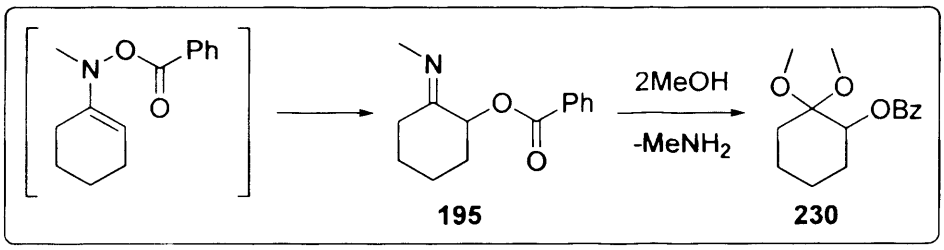


protected 1,2-system. By utilizing the opposing deprotection procedures needed for these groups it would therefore be possible to differentiate one position in favour of the other. The protection and deprotection of acetals under acidic conditions complements the acidic conditions of our transformation in that both progress through an oxinium ion intermediate **229** (Scheme 81).



Scheme 81

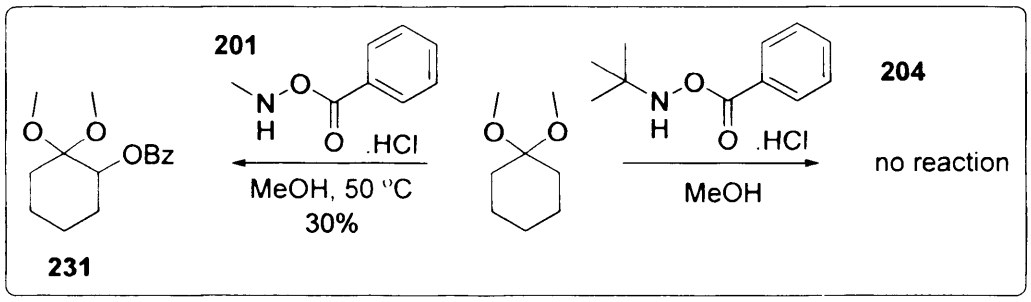
While attack on **229** with methanol allows for reversion to the protected carbonyl compound, attack by *N*-methyl-*O*-benzoylhydroxylamine hydrochloride would facilitate iminium ion formation **194** (Scheme 81). The reaction would then proceed as normal to give the functionalized imine **194** at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



Scheme 82

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 α-oxygenation of cyclohexanone dimethyl ketal with both *N*-*tert*-butyl-*O*-benzoyl hydroxylamine hydrochloride **204** and *N*-methyl-*O*-benzoyl hydroxylamine

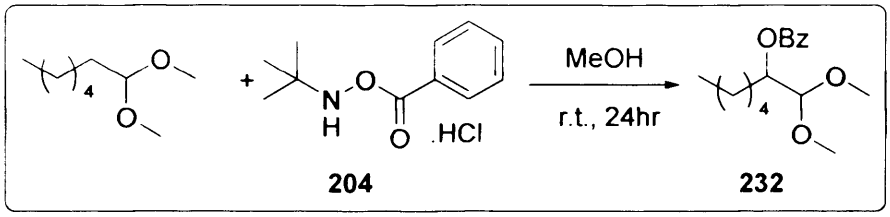
hydrochloride **201** were as expected with the sterically encumbered *N-tert*-butyl-*O*-benzoyl hydroxylamine hydrochloride showing no reaction.



Scheme 83

In comparison to the *N-tert*-butyl-*O*-benzoyl hydroxylamine hydrochloride reactions, functionalisation using the *N*-methyl-*O*-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-tert*-butyl-*O*-benzoyl hydroxylamine hydrochloride **204** under identical reaction conditions (Scheme 84).



Scheme 84

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 α-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 α-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.

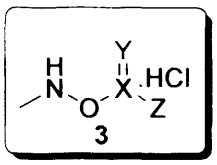


Fig. 22

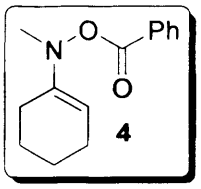
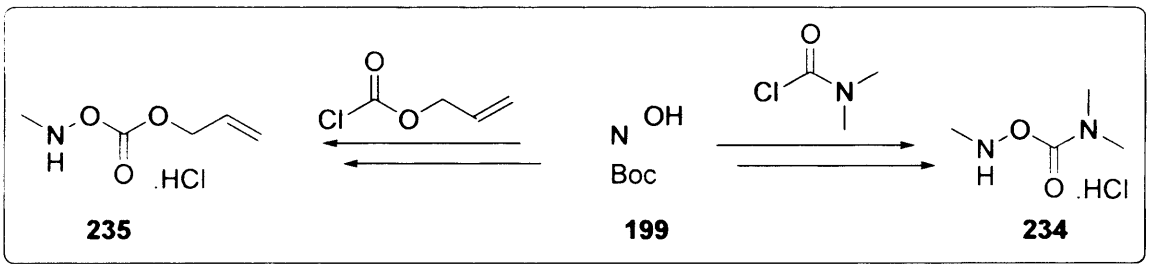


Fig. 23

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).

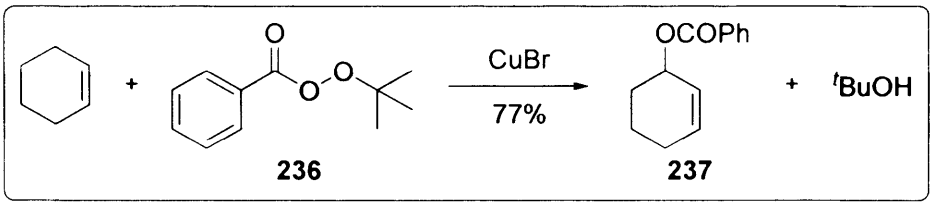


Scheme 85

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.

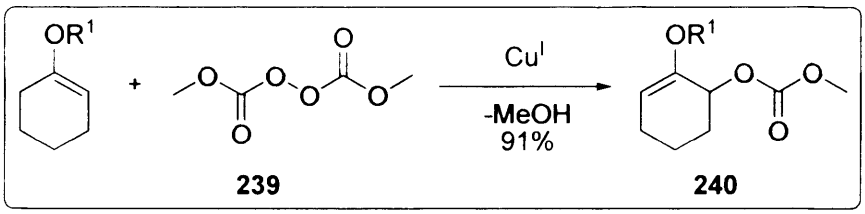
Contemporary strategies to access these functional groups generally depend on the reaction between a preformed α-hydroxy carbonyl compound and a suitable electrophile. Schank *et al.* has reported interesting, if somewhat limited, success with

the use of dimethyl peroxydicarbonate (DPDC) for the acyloxylation of enol ethers based on the allylic oxidation of alkenes.[144] Inspiration for this was taken from the Kharasch-Sosnovsky reaction in which replacement of an allylic hydrogen by acyloxy groups occurs with *tert*-butyl peroxycarboxylates **236** in the presence of $Cu^{(I)}$ salts as electron transfer catalysts (Scheme 86).[145]



Scheme 86

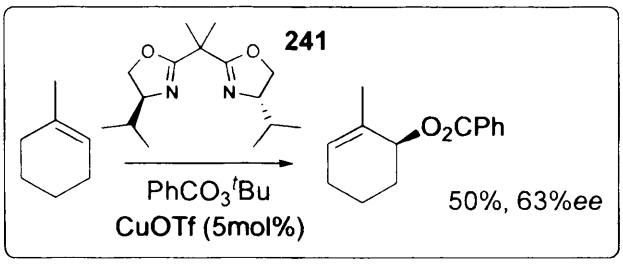
Attempts by Schank to mimic this reaction in the oxyacylation of 1-methoxycyclohex-1-ene with *tert*-butyl peracetate and *tert*-butyl perbenzoate in turn, incorporating CuBr, were unsuccessful with the corresponding carboxylic acid being the main product isolated. The reaction was further modified to include DPDC **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 **240** where R^1 was Me (Scheme 89).



Scheme 89

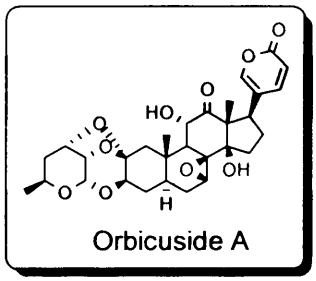
Acid hydrolysis of **240** gave the desired ketone product in 72% yield. The higher reactivity of **239** compared to that of *tert*-butyl peracetate or *tert*-butyl perbenzoate could be attributed to the particularly low *O-O* bond dissociation energy (30kcal/mol). In view of the potential utility of peroxycarboxylates 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,[146] Andrus,[147] and Katsuki.[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^I triflate with cyclic olefinic substrates (Scheme 90).

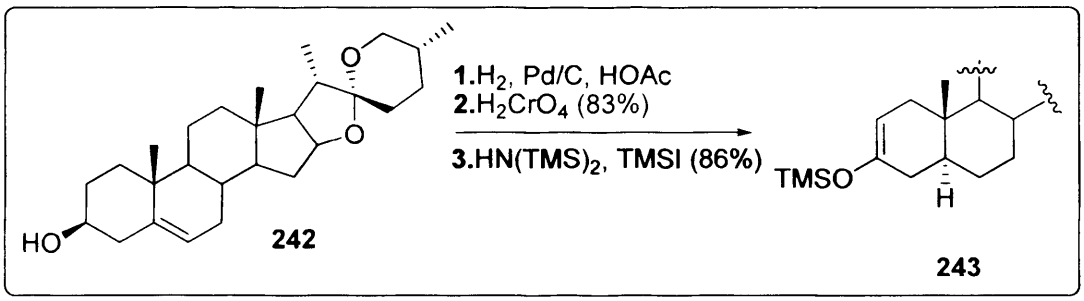


Scheme 90

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.[149] In addition the use of peroxycarboxylates is plagued by poor substrate compatibility and inconsistent yields.



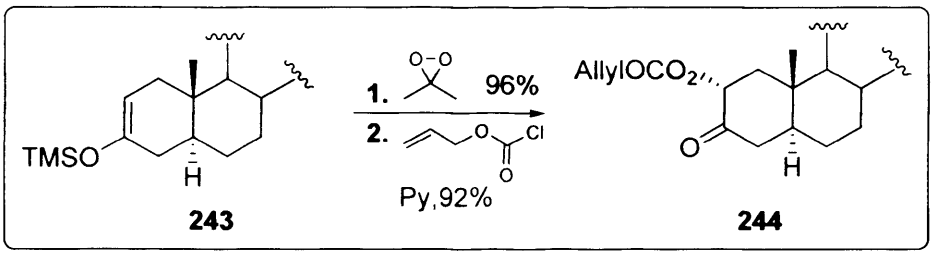
The potential complexity of introducing a carbonate group alpha to a ketone is exemplified by Dixon *et al.* in the preparation of an analogue of orbicuside A.[150] Diosgenin **242** was used as the starting material, since the D/E/F ring system of this steroid can be transformed into a 16-dehydropregnane 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



Scheme 91

and a Pd/C catalyst. This was then followed by oxidation of the hydroxyl group to the corresponding ketone using H_2CrO_4 (Scheme 91).

The oxygen functionality was then introduced at C-2 by formation of the TMS enol ether. Huffman and Balke[151] 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).

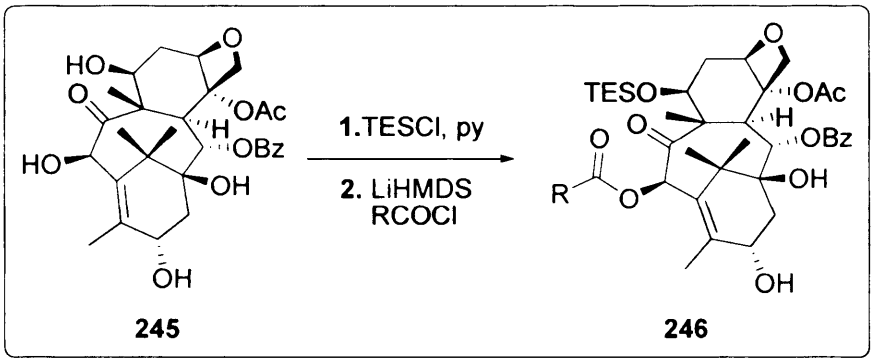


Scheme 92

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).

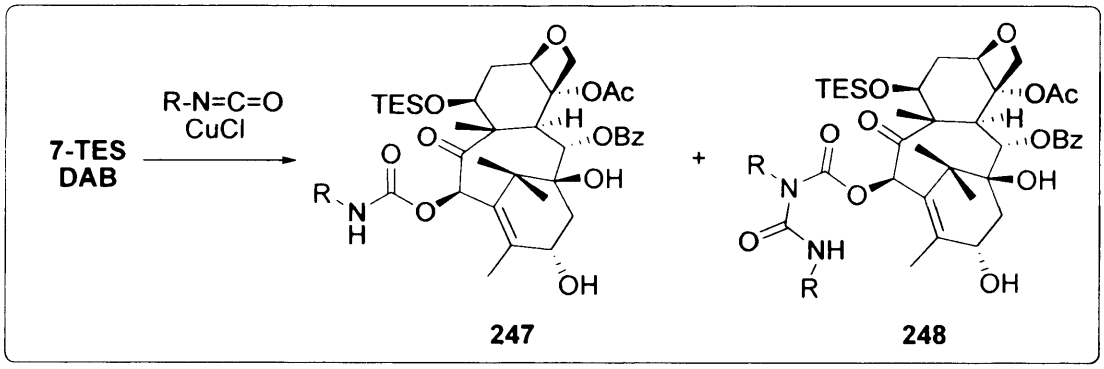
Investigation into the structural activity relationship (SAR) of α-carbonate ketones in second generation Taxoids has recently been reported and again exemplifies the potential difficulties that can be encountered.[152] In this work, two standard methods were employed in order to introduce derivatives 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).



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.[153] Subsequent modification at the C-10 position with acyl, alkoxycarbonyl, *N,N*-dialkylcarbamoyl, and alkyl halides in turn using LiHMDS as the base proceeded in good yields. The C-10 modification with *N*-alkyl and *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 *et al.* through the reaction with isocyanates was also reported to have similar difficulties with low yields and mixture of products.[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.[155]



Scheme 94

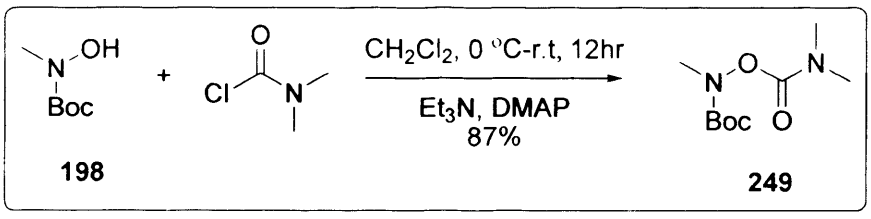
This turned out to be a judicious choice, giving the desired 10-carbamoyl-DABs **247** (Scheme 94). However, this procedure yields a side product, an allophanate **248**, arising from the addition of a second molecule of isocyanate to the carbamate nitrogen. In order to minimize this side reaction, a 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 α-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 α-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 α-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:

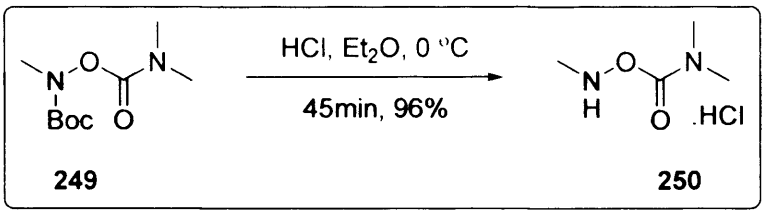
Access to *N*-methyl-*O*-(*N*,*N*-dimethylcarbamoyl) hydroxylamine hydrochloride **250** was once again reasonably straight forward starting from the Boc protected *N*-methyl hydroxylamine **198**. Condensation of **198** with *N*,*N*-dimethylcarbamoyl chloride under basic conditions gave the protected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



Scheme 95

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_2O, in a system pre-flushed with N_2, to give the deprotected HCl salt **250** in an excellent yield of 96% (Scheme 96).

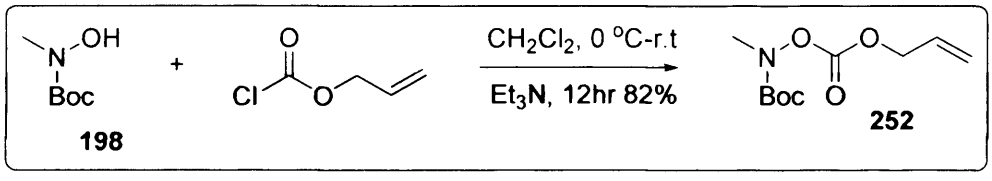


Scheme 96

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:

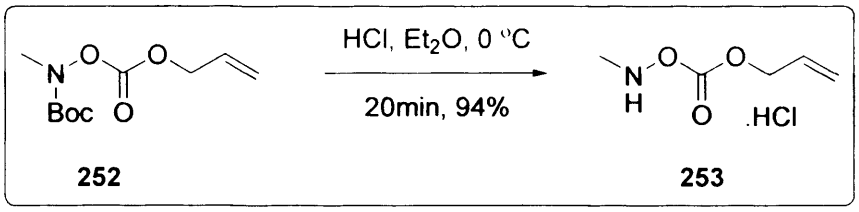
A similar synthetic pathway was again employed in the preparation of *N*-methyl-*O*-allylcarbonate hydroxylamine hydrochloride **251**. Condensation of Boc protected *N*-methylhydroxylamine **198** with allyl chloroformate gave the corresponding *N*- protected allylcarbonate **252** in an excellent yield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



Scheme 97

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).



252 253

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*-allylcarbonate 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:

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

ACID	YIELD %
Benzoic Acid	0
Trifluoroacetic Acid	0
Methanesulfonic Acid	28
Hydrochloric Acid	45

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 by detected with either dichloromethane or chloroform.

SOLVENT	YIELD %
Ether	40
Tetrahydrofuran	45
Chloroform	Trace
Dichloromethane	Trace
Dimethyl Sulfoxide	0

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

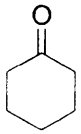
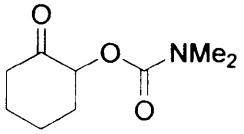
also applied to the reactions of *N*-methyl-*O*-allylcarbonate hydroxylamine hydrochloride **253**.

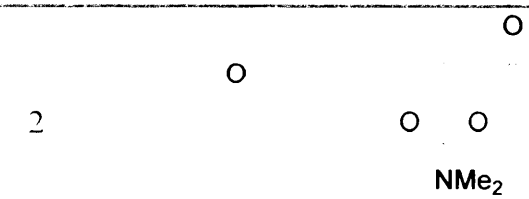
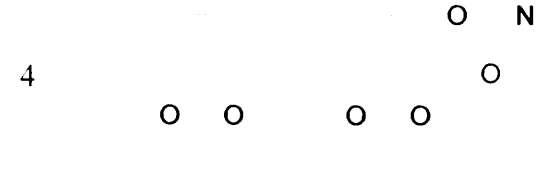
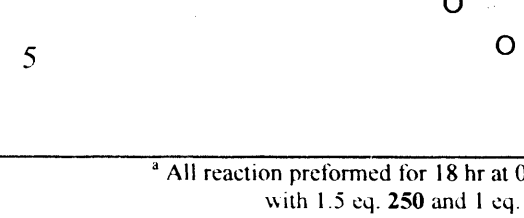
4.4.0 Introduction of Carbamates:

N-methyl-*O*-(*N*,*N*-dimethylcarbamoyl) hydroxylamine hydrochloride **250** was successfully employed in the elaboration of our α-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 4. Introduction of α-Carbamate Group[a]

Entry	Starting Ketone	Oxygenated Product	Reaction Temperature (°C)	Yield (%)
1		 **254**	50	60

2		50	64
3		50	50
4		50	57
5		50	55

255 **256** **257** **258**

[a] All reaction preformed for 18 hr at 0.5M concentration in THF with 1.5 eq. **250** and 1 eq. starting ketone

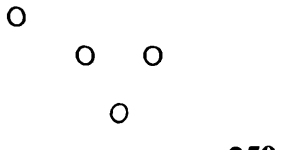
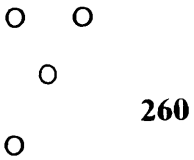
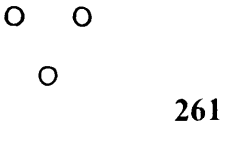
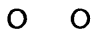
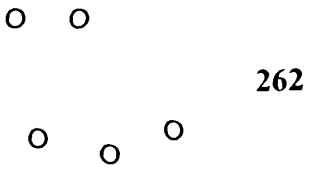
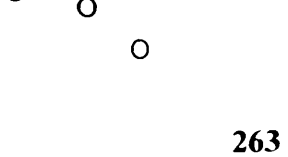
Interestingly, the reaction between **250** and 1,4-cyclohexanone dimethyl ketal (Table 4, entry 4) showed a tolerance for ketal protecting groups with a yield of 57% for **257**, which is a particular point of note given the strongly acidic reaction conditions used in this transformation. This observation 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[a]

Entry	Starting Ketone	Oxygenated Product	Reaction Temperature (°C)	Yield (%)
1		 **259**	50	62
2		 **260**	50	53
3		 **261**	50	50
4		 **262**	50	41
5		 **263**	50	55

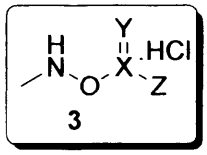
[a] All reaction preformed for 18 hr at 0.5M concentration in THF with 1.5 eq. **253** and 1 eq. starting ketone

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 group to 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.



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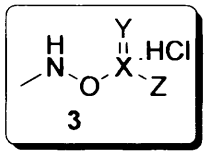
Chapter 5: α-Oxytosylation

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.[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.

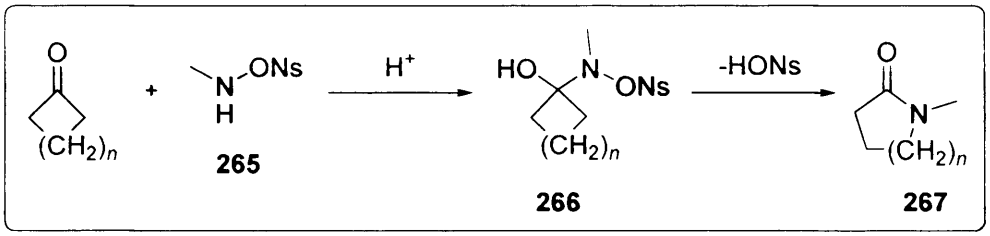


3

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:

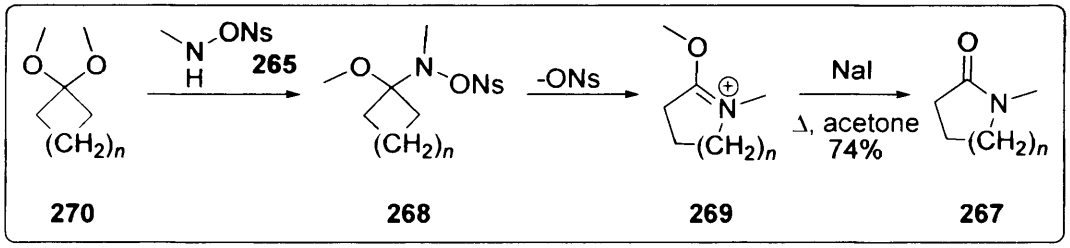
Previous to our work Hoffman *et al.* investigated the reactions of *N*-methyl-*O*-nosylhydroxylamines **265** with various carbonyl compounds and reported the direct preparation of *N*-substituted lactams **267** from cycloalkanones[159] (Scheme 99). Carbon-to-nitrogen rearrangement led to the lactam products, reminiscent of the β-lactam synthesis of Wasserman[160] without the need for stable carbinolamine intermediates, and analogous to Barton's[161] 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**.



Scheme 99

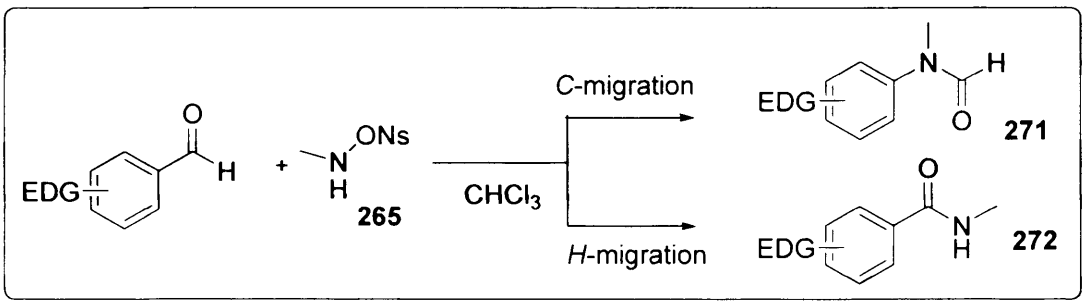
This intermediate then rearranges to give the ring-expanded amide by carbon to nitrogen migration of a ring bond, a basic work-up then gives the amide product.

The required oxonium ion intermediate can also be generated from protonation of either enol ethers,[162] or by acid catalyzed elimination of acetals.[163] The latter showed an interesting observation in the appearance of the imidate salt **269** 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).



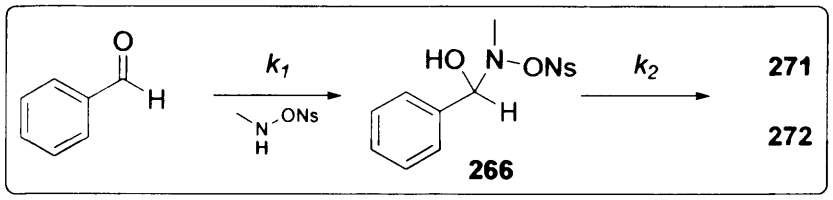
Scheme 100

Further to this, a series of aromatic and aliphatic aldehydes were shown to react with *N*-methyl-*O*-nosylhydroxylamine **265** to give products from both carbon migration and hydride migration to nitrogen (Scheme 101).[164] A series of substituted benzaldehydes were reacted with **265** to give a mixture of *N*-methyl-*N*-arylformamide **271** (carbon migration) and *N*-methylbenzamide **272** (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.



Scheme 101

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.

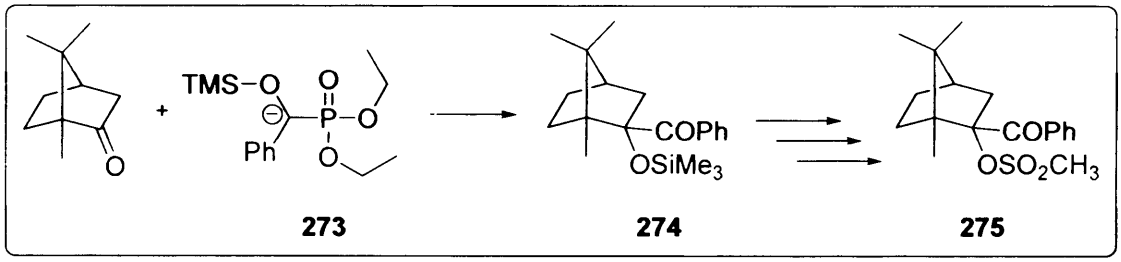


Scheme 102

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

Deprotection of the trimethylsilyl group could be accomplished under either acidic or basic conditions. Conversion to the mesylate then involved treatment with CH_3SOCl 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 $ArIL_1L_2$ possess identical heteroatom ligands **276** and **277**, (i.e., L_1=L_2=RCO_2, Cl, F). Later Neiland and Karele reported the synthesis of non-symmetrical iodinane, [hydroxy(tosyloxy)iodo] benzenes **279-281** (Fig. 24).

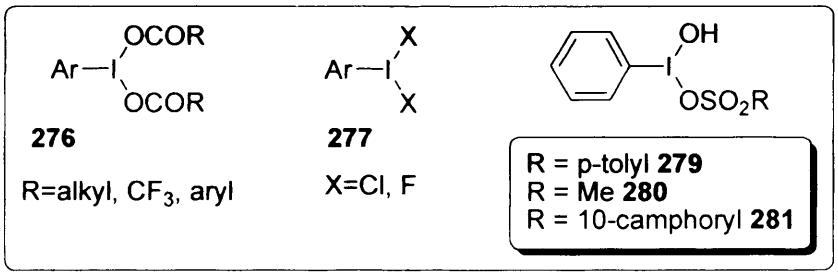
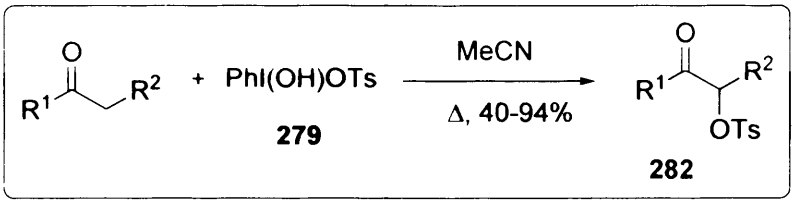


Fig. 24

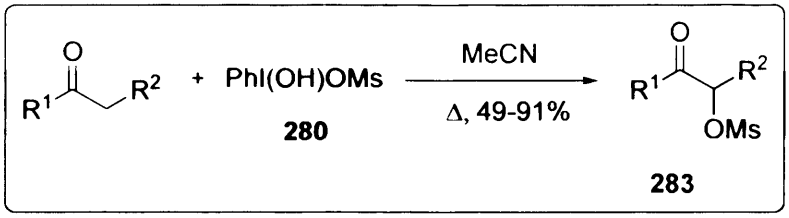
The preparation of these reagents is reasonably direct, adding to their popularity and applicability. [Hydroxy(tosyloxy)iodo] benzene (HTIB) **279** can be prepared from the treatment of (diacetoxyiodo)benzene with *p*-toluenesulfonic acid monohydrate in acetonitrile.[168] [Hydroxy(mesyloxy)iodo] benzene[169] (HMIB) **280** and the chiral analog [hydroxy[((+)-10-camphorsulfonyl)-oxy]iodo] benzene[170] **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]



Scheme 104

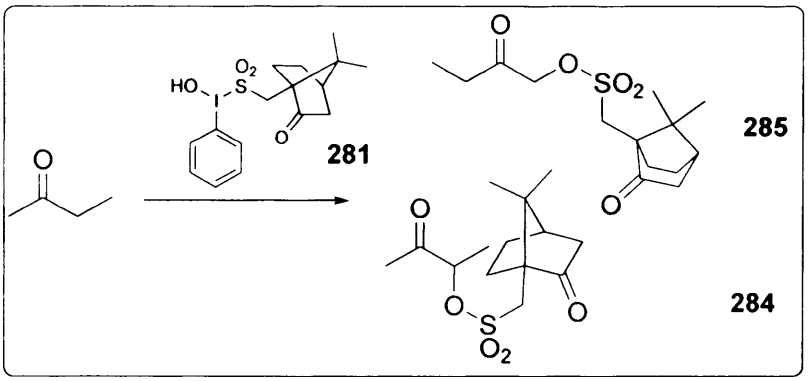
[Hydroxy(mesyloxy)iodo] benzene **280** has been employed in the analogous synthesis of α-mesyloxyketones **283** (Scheme 105).[173]



Scheme 105

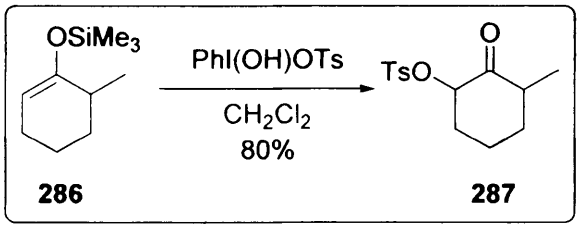
These transformations, like α-halogenation of ketones, require ketones with an enolizable proton. An acidic α-proton therefore opens the use of hypervalent reagents to numerous substrates especially β-diketones[171] and β-ketoesters.[172] α-Mesyloxy β-dicarbonyl compounds and may also be prepared from β-diketones and β-ketoesters with iodobenzene and methanesulfonic acid in chloroform, employing *in situ* generation of HMIB.[174]

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



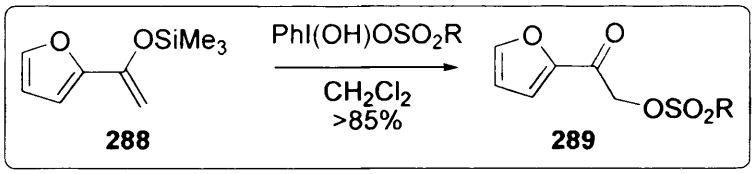
Scheme 106

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.[176] 2-Methyl-6-tosyloxycyclohexanone **287** can be prepared regioselectively from 1-trimethylsilyloxy-6-methylcyclohexanone **286** with HTIB in dichloromethane (Scheme 107).



Scheme 107

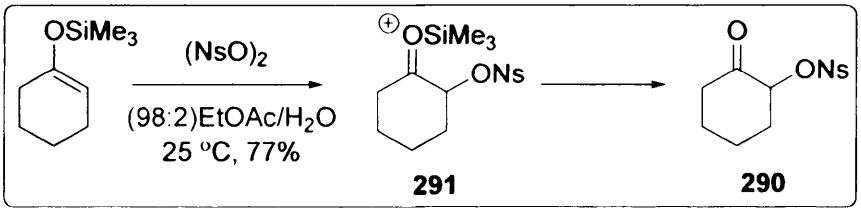
The silyl enol ether approach also permits the preparation of α-oxysulfonyl ketones with acid sensitive or oxidizable ring systems. For example, the (oxysulfonyl)-methyl-2-furyl ketones **289** have been obtained in high yields of >85% from the appropriate silyl enol ether **288** with either HTIB or HMIB (Scheme 108).[176]



Scheme 108

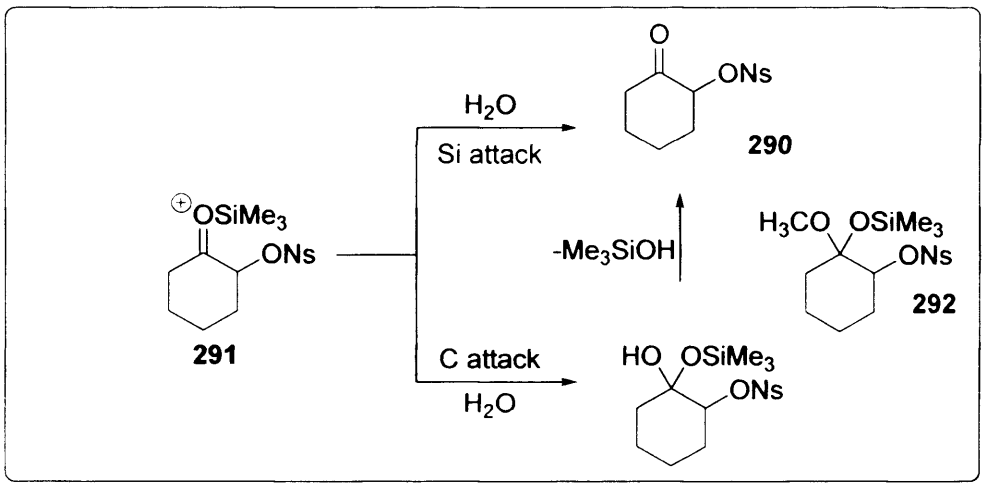
5.3.2 Arylsulfonyl peroxides:

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 regioselectivley 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)sulfonoxy ketone **290** in 77% yield (Scheme 109).



Scheme 109

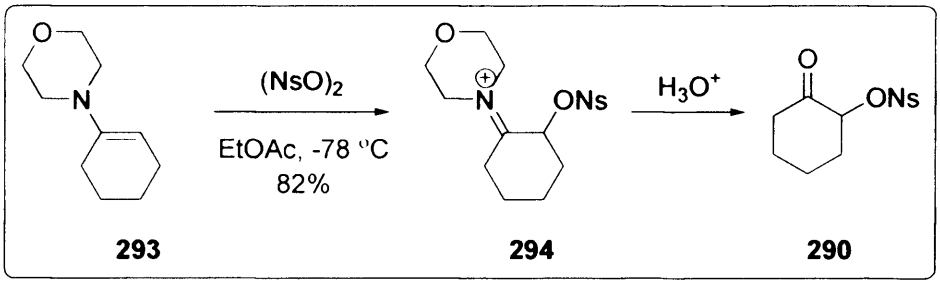
These undesirable by-products were thought to originate from the *O*-(trimethylsilyl)oxonium ion **291**, produced from electrophilic addition. Nucleophiles were therefore added in order to trap out the oxonium ion **291** by transfer of the trimethylsilyl group. By carrying out the reaction in the presence of methanol only two products were observed, namely, the desired α-sulfonoxy ketone **290** and a mixed ketal **292** (Scheme 110).



Scheme 110

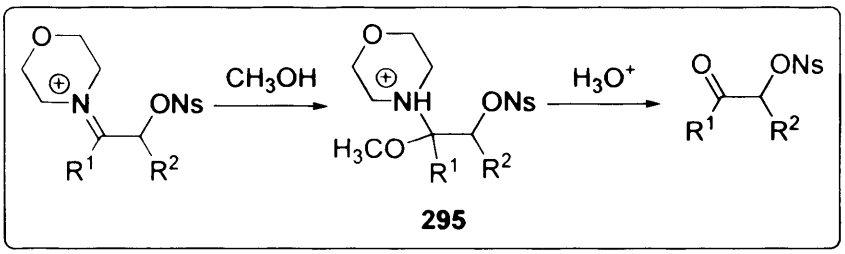
This mix of products could be explained by attack of methanol on the oxonium ion **291** at either silicon to give **290** or carbon to give **292**. These two modes of attack could be made equivalent if water were the attacking nucloephile, as was ultimately applied giving a yield of 77% (Scheme 109)

Enamines have also been shown to be useful carbonyl derivatives that provide access to α-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.



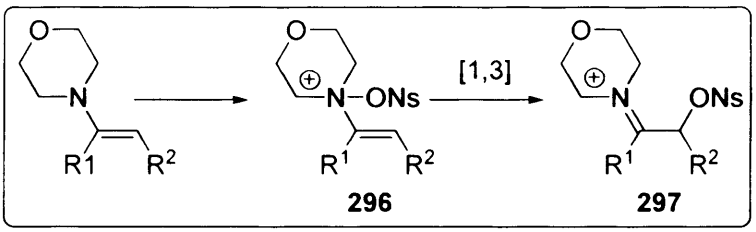
Scheme111

Minor byproducts were recovered, by analogy to the halogenation of enamines,[180] these products possibly arose from side reactions of the iminium ion. The addition of 2% methanol gave the desired α-arylsulfonoxy ketones in quantitive yields by nucleophilic trapping of the iminium ion to give the more stable tetrahedral intermediate **295** (Scheme 112).



Scheme 112

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 π-bond and thus exhibit reactivities comparable to other reactive olefins.[181] Whereas, enamines react at nitrogen, giving an *N*-arylsulfonoxy (Scheme 113) intermediate **296** that undergoes a 1,3-rearrangement to the α-aryloxysulfonyl iminium product **297**.



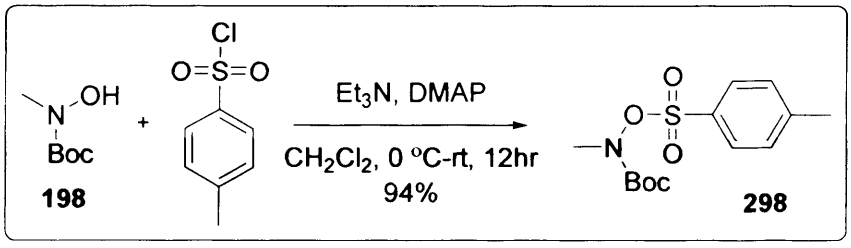
Scheme 113

The reactivity exhibited by enamines is similar to that found for the oxidation of amines by *p*-NPSP,[182] also [1,3]-rearrangements of both oxyacyl and aryloxysulfonyl groups from nitrogen to carbon are known to be facile.[183]

Since the discovery of Koser's reagent almost a century ago, hypervalent iodine reagents have proven an effective route to α-sulfyloxyl 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 α-oxytosylation of ketones,[184] which marks a significant step forward in the chemistry.[185] These advancements will undoughtably lead to an increase in the application of reactions mediated by hypervalent iodine reagents.

5.4.0 Reagent Preparation:

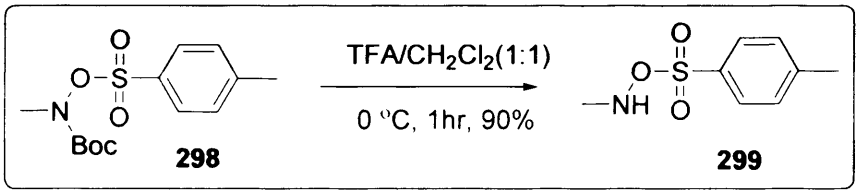
Access to the desired reagent relied on similar chemistry to that developed previously. The initial tosylation reaction at first, however, proved slightly problematic with low yields and difficulties in separating *p*-toluenesulfonic acid from our desired product. Initially it was thought that excessive 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 Et_3N and the slow addition of a 0.7M solution of **198** in dichloromethane.



Scheme 114

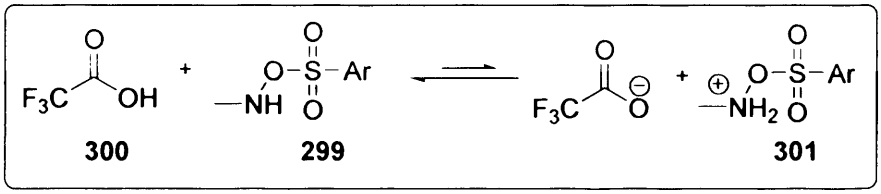
As with our previous oxy-benzoylation, oxy-carbonylation and oxy-carbamoylation we sought to employ our simultaneous deprotection, hydrochloride salt formation procedure for the conversion of *N*-Boc-*N*-methyl-*O*-*p*-tosylhydroxylamine **298** to the corresponding *N*-methyl-*O*-*p*-tosylhydroxylamine 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 20-25min, 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 to proved ineffective with 20eq. and 10eq. of HCl giving only decomposition of **298** to a complex reaction mixture when analysed by ^{1}H NMR, while 5eq. and 2eq. gave no reaction after 1hr. 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 alterative deprotection procedure that employed the weaker trifluoroacetic acid (20 eq.) in a 1:1 ratio with CH_2Cl_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 1hr.



Scheme 115

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

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.

Acid	Yield %
Benzoic Acid	0
Trifluoroacetic Acid	Trace
Methanesulfonic Acid	55
Hydrochloric Acid	0

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**.

SOLVENT	YIELD %
Ether	52
Tetrahydrofuran	55
Dichloromethane	Trace
Acetonitrile	Trace
Dimethyl Sulfoxide	Trace
Toluene/THF	69

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

5.6.0 Reactions with Cyclic Ketones:

The α-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 α-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.

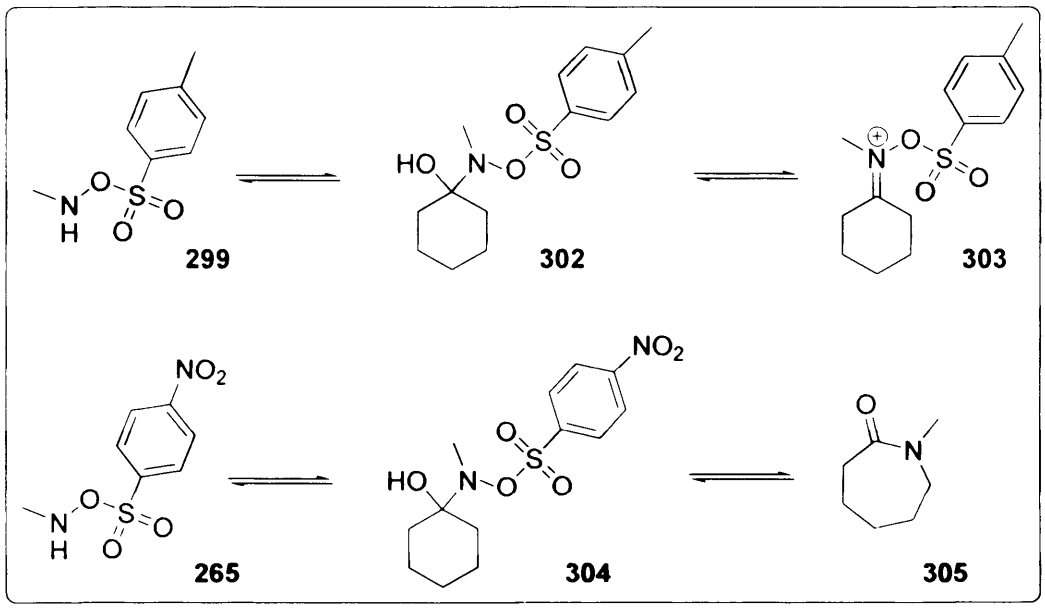
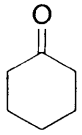
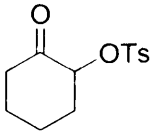


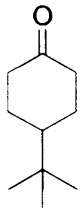
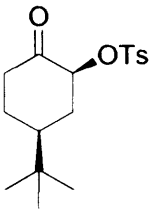
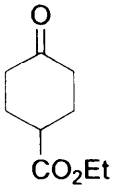
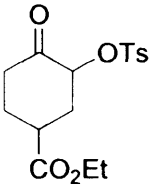
Fig. 25

These contrasting reactivity's 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*-butylcyclohexanone 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[a]

Entry	Starting Ketone	Tosylated Product	Reaction Temperature (°C)	Yield (%)
1		 **306**	50 °C	69

2		 **307**	50 °C	70
3		 **308**	50 °C	64

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

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 α-proton or protons (Fig. 26).

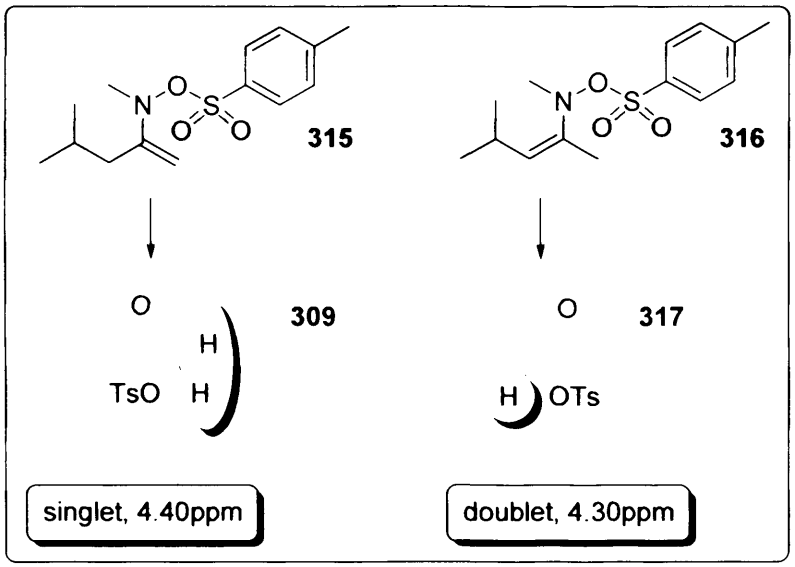


Fig. 26

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 7 Ratio Vs. Temp

Temperature (°C)	Ratio **309/317**	Yield[a] (%)
-20	0	0
0	6:1	21
r.t.	4:1	52
50	4:1	65

[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[a]

Entry	Starting Ketone	Tosylated Product	Reaction Temperature (°C)	Ratio[b]	Yield[c] (%)
1		  **309**	50 °C	4:1	65
2		  **310**	50 °C	4:1	71
3		  **311**	50 °C	4:1	69
4		  **312**	50 °C	4:1	61
5		 **313**	50 °C	N/A	72
6		  **314**	50 °C	N/A	81

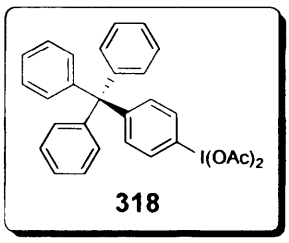
[a] All reactions were preformed for 18 hr at 0.5M concentration in 1:1 THF/PhMe with 1.5 eq. **299** and MSA and 1 eq. starting ketone

[b] Ratio of primary : secondary functionalisation products

[c] Combined yield for both regio-isomers

Leading on from these results we sough 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.[186] 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**.

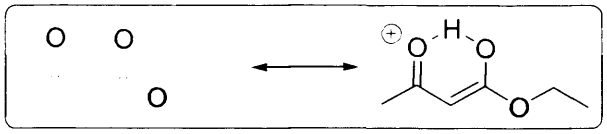


318

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 acetophone to give **314** in a very good 81% (Table 8, Entry 6).

5.8.0 Reaction with Dicarbonyls:

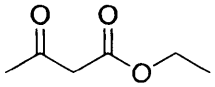
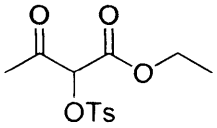
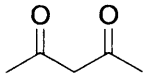
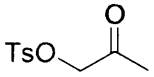
Using the reagents developed in previous chapters we were unable to α-functionalise di-carbonyl compounds such as ethyl acetoacetate and 2,4-pentanedione. This was perplexing given the acidity of the alpha position that should favour rearrangement. Given the acidic conditions of the reaction it was expected 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.



Scheme 117

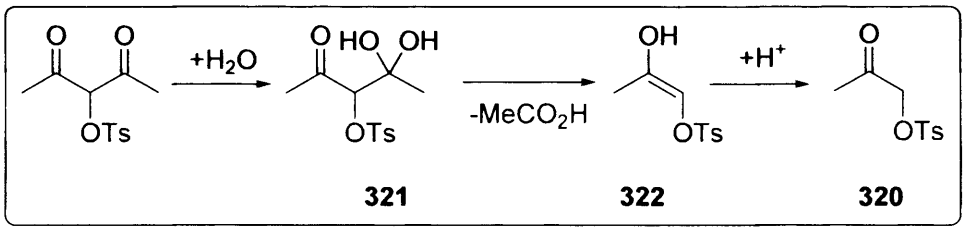
Ethyl acetoacetate was first reacted with **299** under standard conditions with 1.5eq of **299** and MSA in 1:1 THF/PhMe for 18 hr at 50 °C. We were delighted to discover that the application of our reagent gave the expected product **319** (Table 9, Entry 1) in a good yield of 69%. The stability of 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 9. Reaction of 299 with Dicarbonyls[a]

Entry	Starting Ketone	Tosylated Product	Reaction Temperature (°C)	Yield (%)
1		 **319**	50 °C	69
2		 **320**	50 °C	52

[a] All reactions were preformed 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).

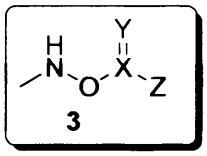


Scheme 118

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 tautimerises 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*-tosylhydroxylamine **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*-tosylhydroxylamine **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.



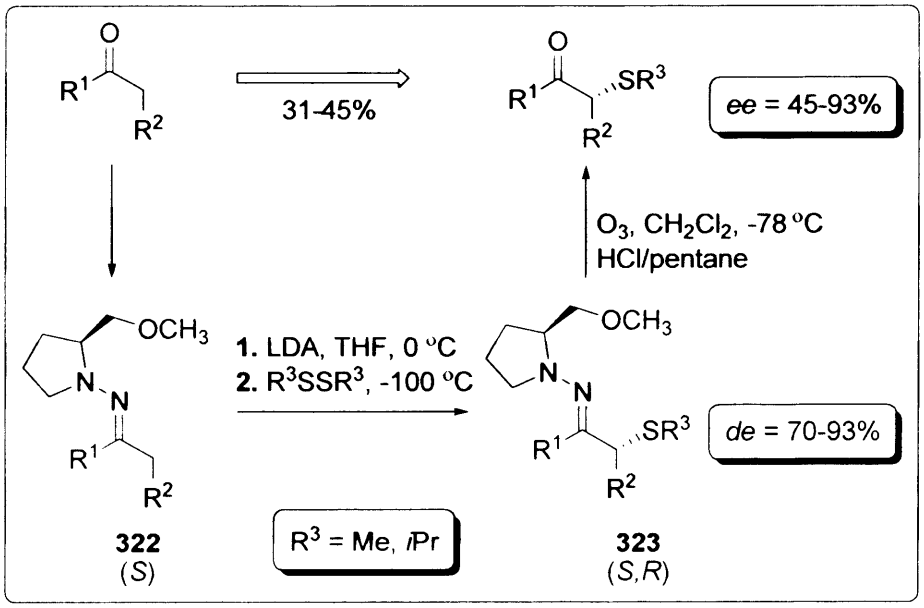
3

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.[187] 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).[188] 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.

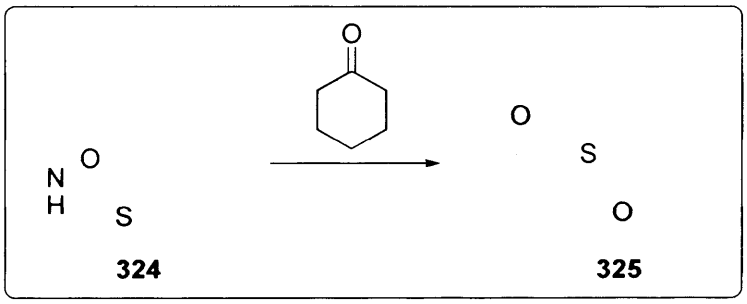


Scheme 119

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 α to the carbonyl **325** (Scheme 120).



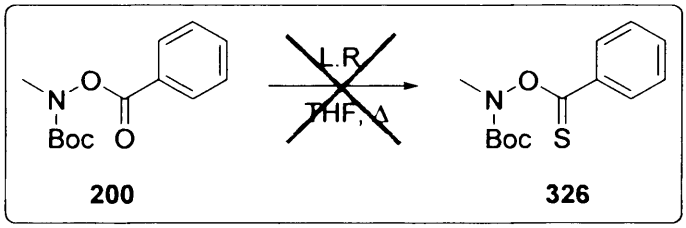
Scheme 120

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

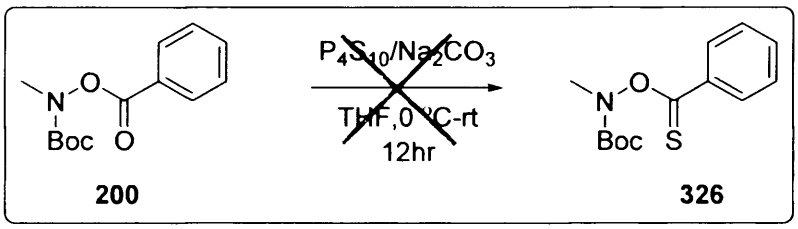
reagent (L.R).[189] Our first attempt at this conversion used the classical method of using Lawesson's reagent as the thionation reagent in refluxing THF (Scheme 121). The crude reaction material was obtained by filtration through a short pad of silica gel to give a brown material which when analysed 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.[190] 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.

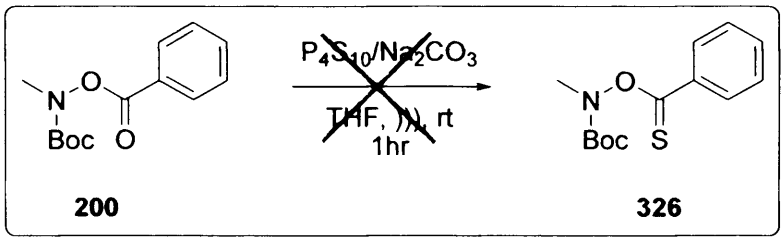
Despite this negative result the direct thionation of *N*-Boc-*N*-methyl-*O*-benzoylhydroxylamine **200** was again attempted using a mixture of P_4S_{10} and anhydrous Na_2CO_3 in THF (Scheme 122) based on work by Soheeren on milder thionation reactions.[191]



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}.



Scheme 123

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 out 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**.

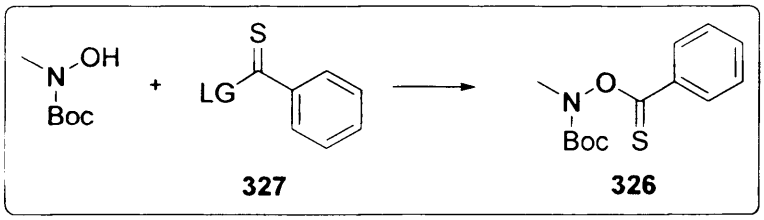
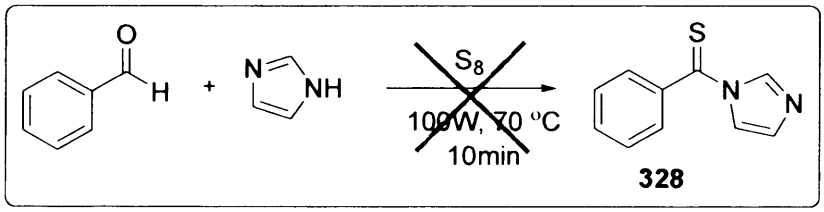


Fig. 27

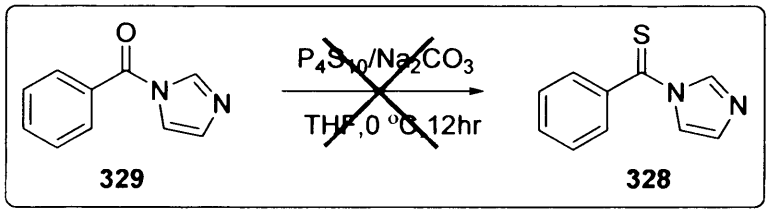
Thioacyl halides were not pursued due to their sensitive nature regarding both synthesis and use.[193] A modification of the Willgerodt-Kindler reaction was thought of as a possible route to install a leaving group and thiocarbonyl group in one step.[194] In the original reaction, ketones and aldehydes 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

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).

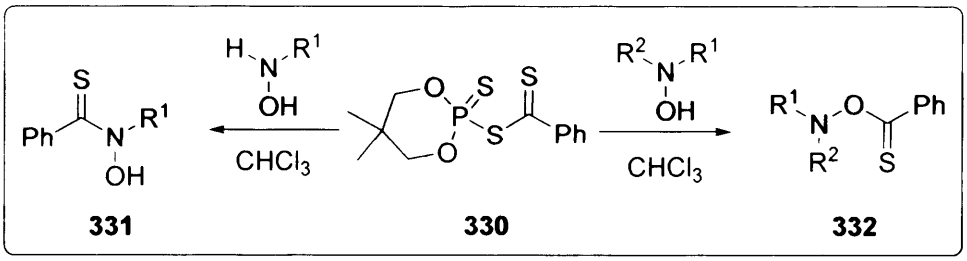


Scheme 125

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:

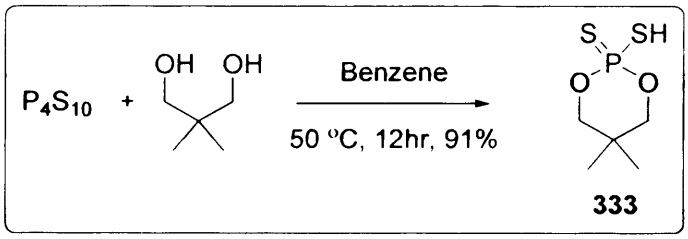
S-Thioacyldithiophosphates **330**, accessible from carboxylic acid derivatives have been proven to be excellent thioacylating agents by Rachon *et al.*[195] They show a low reactivity towards oxygen nucleophiles and are highly reactivity to nitrogen ones, lending themselves to thiohydroxamic acid **331** 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).



Scheme 126

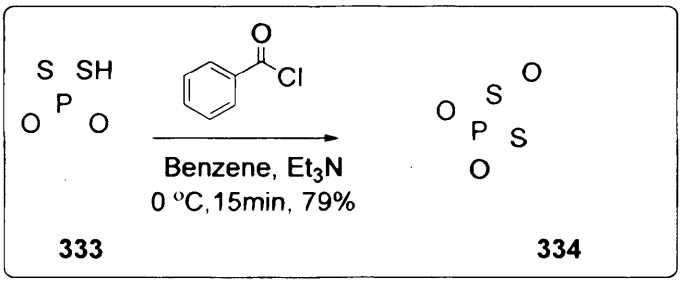
This reversed reactivity can be explained by the supernucleophilic properties of oxygen in hydroxylamines when compared to common alcohols. The lower thermodynamic stability of the *N*-thioacylated products due to steric hindrance when compared to the *O*-thioacylated products is also a factor.[196] 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*-thioacyldithiophosphate **330** was prepared in three-steps according to literature procedures.[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 P_4S_{10} by heating in benzene at 50 °C for 12 hr (Scheme 127).



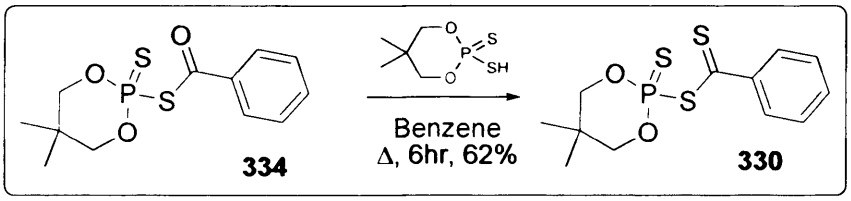
Scheme 127

Upon distillation of the crude thioacid, a colourless crystalline solid that conformed to the literature data was isolated.[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.



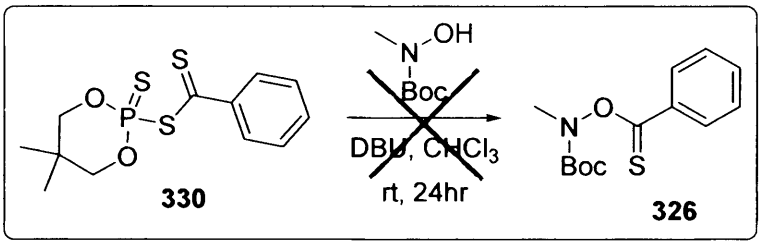
Scheme 128

After crystallisation a white solid was obtained which again corresponded to the literature data.[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

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).

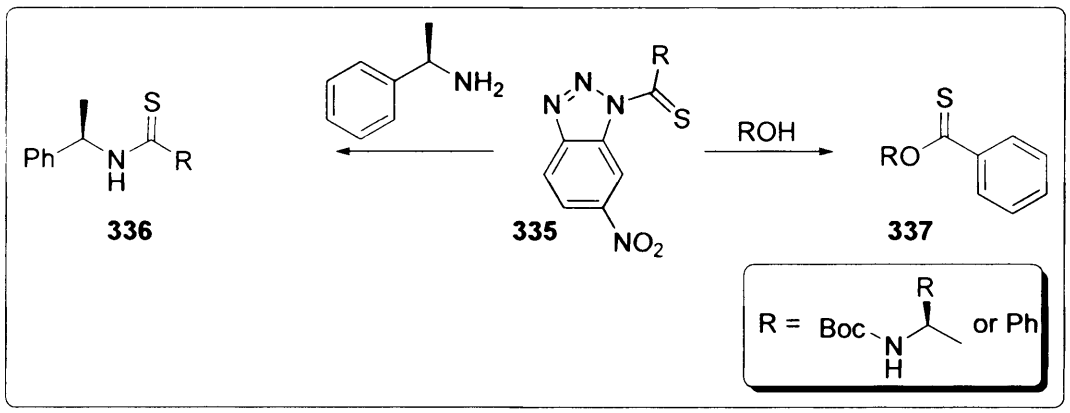


Scheme 130

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.

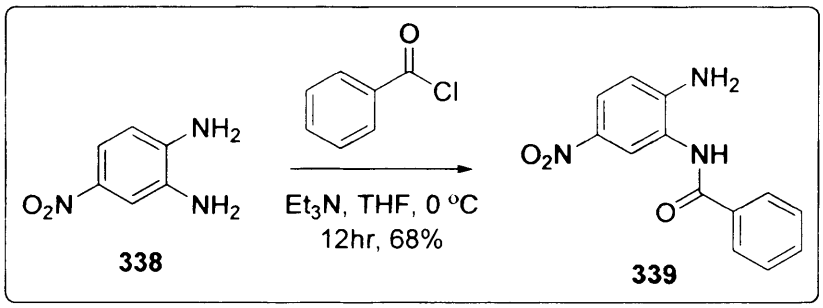
6.2.4 Synthesis via Thionoacyl Nitrobenzotriazoles:

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).[199] Soon after it was shown that nitrobenzotriazole could also be utilized as a leaving group in thionoester **337**synthesis.[200] 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.



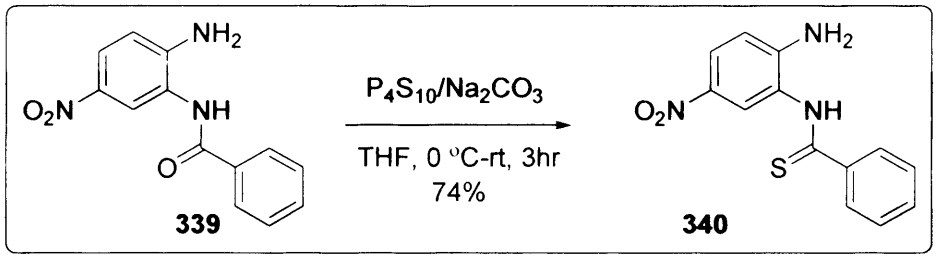
Scheme 131

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.



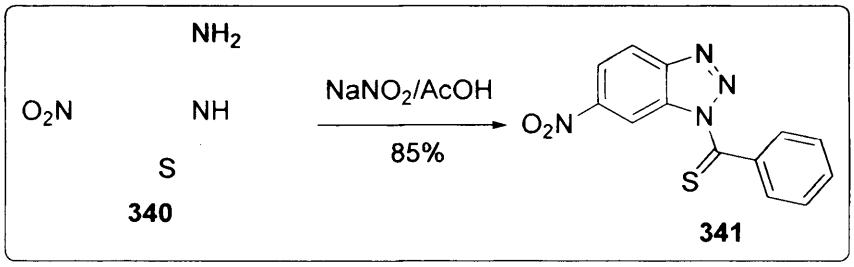
Scheme 132

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 P_4S_{10} and anhydrous Na_2CO_3 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

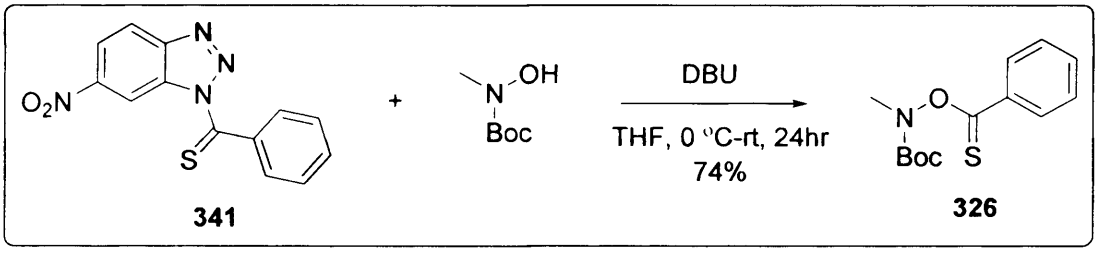
Intramolecular diazonium cyclization of **340** using nitrous acid, generated *in situ* from $NaNO_2$ and AcOH gave benzotriazole **341** as a red solid in an excellent yield of 85% (Scheme 134).



Scheme 134

In spite of the increasing interest in benzotriazole-mediated thioacylations, as exemplified in a recent article by Katritzky[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 thioacylating reagent **341** (Scheme 135).



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

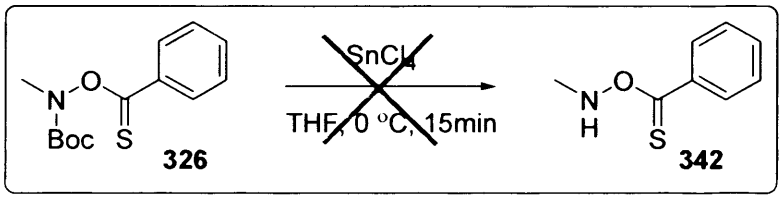
purification proved unworkable. TLC analysis of the impure *N*-Boc-*N*-methyl-*O*-thiobenzoylhydroxylamine **326** showed two spots when viewed under UV. Subjecting the crude **326** to chromatography on both silica and alumina proved ineffective, as it was not possible to separate these spots and so 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 ^{1}H 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/CH_2Cl_2 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 ^{1}H 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.[202] Beside dethioxylation, thiolated products often under went a side reaction similar to the Edman degradation.[203]

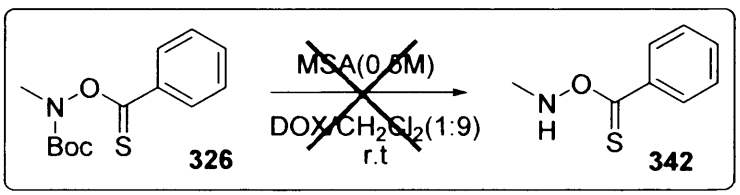
Numerous methods have been reported for Boc deprotection, although most involve the use of strong acids such as CF_3COOH, HCl, H_2SO_4, TsOH and MsOH. Lewis acids such as $BF_3 \cdot OEt_2$ TMSI, TMSOTf, $TiCl_4$, $SnCl_4$, $AlCl_3$, $Sn(OTf)_2$, $ZnBr_2$ have also been proven successful,[204] less acidic conditions using Montmorillonite K10 clay,[205]

and silica gel have also been used.[206] In order to achieve Boc removal under relatively mild conditions four possible methods were attempted. The $SnCl_4$ 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.[207] It was proposed that Boc removal is facilitated by the initial formation of a chelate between the Lewis acid $SnCl_4$ and the *tert*-butyl *N*-alkylcarbamate leading to solvolytic loss of isobutene and CO_2 formation leading to the deprotected compound. The literature procedure called for the use of 5 equivalents of $SnCl_4$, 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

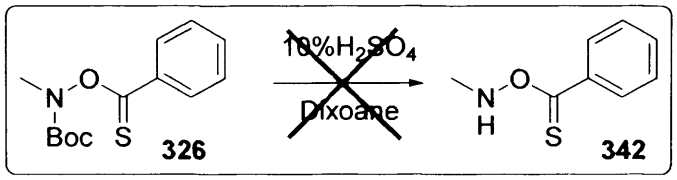
Variation of the number of equivalents of $SnCl_4$, time and temperature proved unproductive. The next attempted deprotection employed an alternative to the conventional TFA/CH_2Cl_2 approach, in which decreasing the acid concentration was shown to be effective in the selective removal of Boc and Z(OMe) groups in peptide chemistry.[208] 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 CH_2Cl_2required the addition of 10% dioxane to aid dissolution. In addition dixoane was reported to play an important role for the selective deprotection by the buffer capacity resulting from its weak basicity.[209]



Scheme 137

Once again this procedure was unsuccessful with no discernible product being recovered. Altering the MSA concentration and equivalents along with reaction time

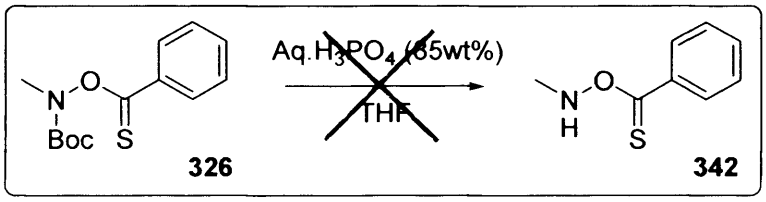
and temperature were futile. Despite this negative result we switched our attention to a similar dixoane base deprotection method using 10% H_2SO_4 which was reported to offer a milder alternative to the conventional TFA/ CH_2Cl_2method (Scheme 138).[210]



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_3COOH (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.

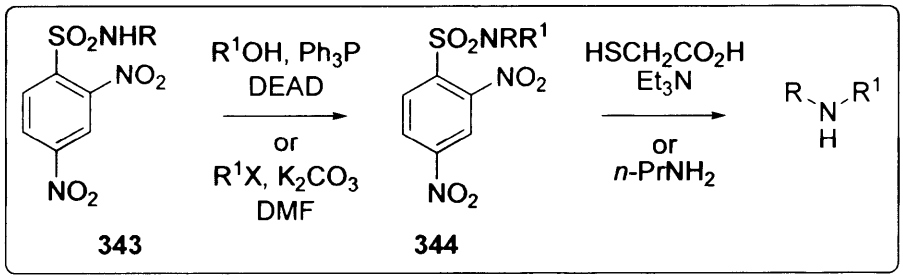


Scheme 139

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.

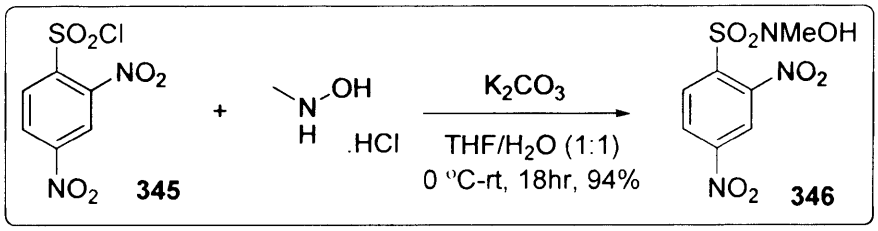
With an effective entry to our protected *N*-methyl-*O*-thiobenzoylhydroxylamine **326** secured by the use of thionoacyl nitrobenzotriazoles we were hesitant to alter our strategy in an attempt to allow variation of protection groups. Therefore base labile groups were disregarded as possible nitrogen 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.[212] In this, *N*-monosubsituted 2,4-dinitrobenzenesulfonamide **343** was prepared from the corresponding amine and 2,4-dinitrobenzenesulfonyl chloride. Alkylation of this amine to **344** was then efficiently carried out under Mitsunobu conditions (ROH, DEAD, PPh_3, benzene, 23 °C) or under more conventional conditions (RX, K_2CO_3, DMF, 23 °C) (Scheme 140).



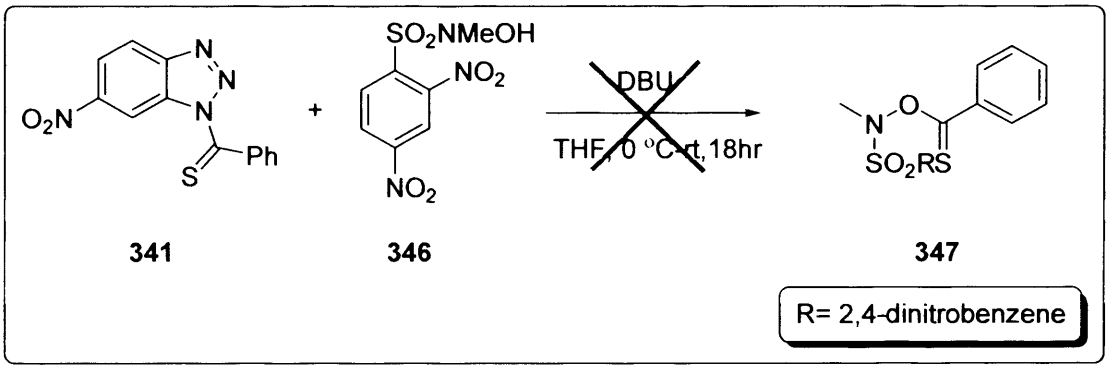
Scheme 140

Facile deprotection could be achieved by treatment with excess *n*-isopropylamine. Alternatively **344** can be deprotected by treatment with $HSCH_2CO_2H$ and Et_3N. The latter procedure was found to be more convenient in that the by-product 2,4-dinitrophenylthioacetic 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 **346** was achieved by reacting 2,4-dinitrobenzenesulfonyl chloride and *N*-methylhydroxylamine hydrochloride under basic conditions (Scheme 141).



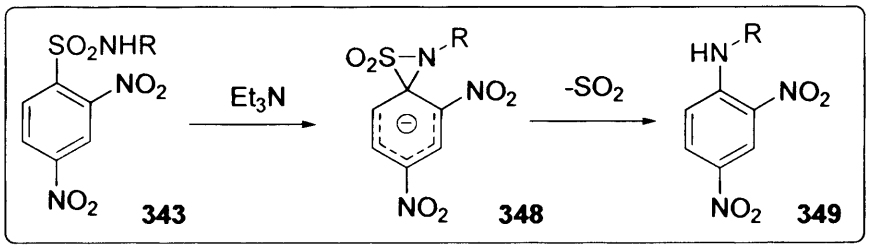
Scheme 141

Extraction of the reaction mixture with dichloromethane followed by recrystillization 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 ^{1}H 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

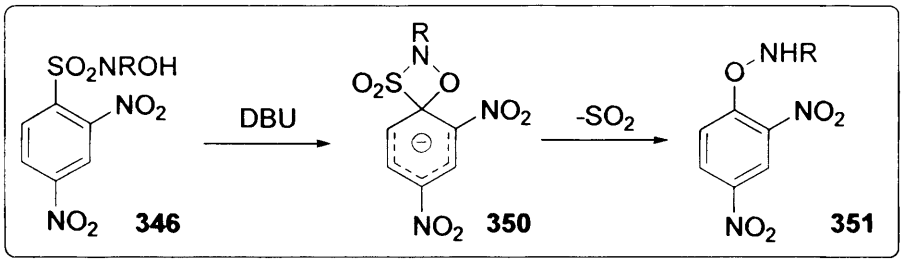
Initial observations were encouraging, in that monitoring the reaction by TLC showed the consumption of thioacylating reagent **341**. However, ^{1}H NMR analysis of the crude reaction mixture showed no evidence of the desired *N*-2,4-dinitrophenylsulfonyl-*N*-methyl-*O*-thioacyl hydroxylamine **347**. 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). [212]



Scheme 143

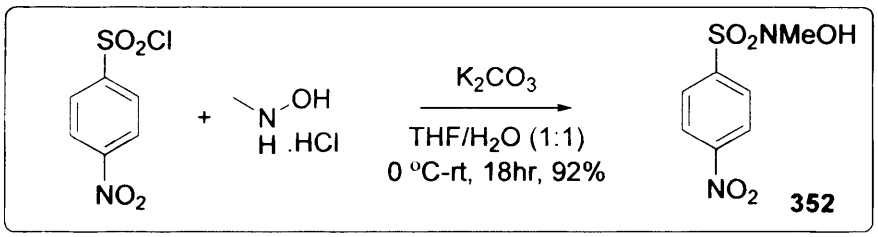
A similar decomposition based on the intramolecular Meisenhiemer complex **350** (or intermolecular attack) can be envisaged for a hydroxylamine-based sulfonamide in the

presence of a strong base to give **351** (Scheme 144). This could in part explain the poor results observed.



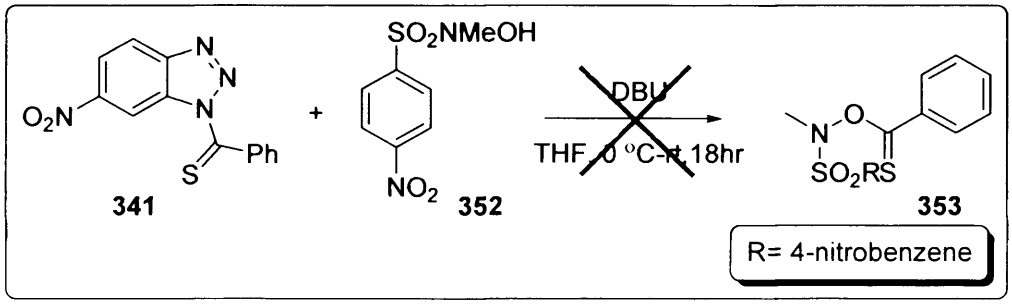
Scheme 144

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).



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).

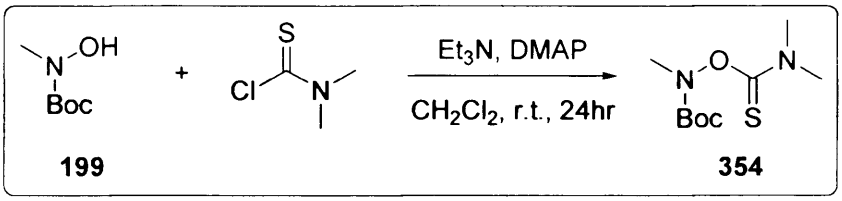


Scheme 146

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.

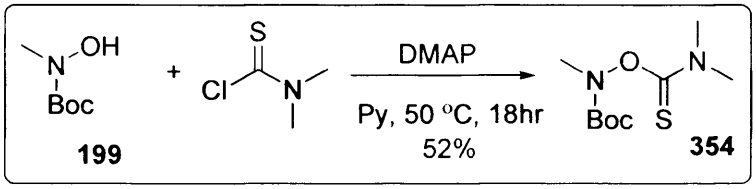
6.3.0 Synthesis of *N*-methyl-*O*-*N*,*N*-dimethylthiocarbamate hydroxylamine:

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).



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**.



Scheme 148

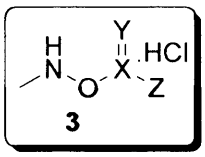
With an alternative protected reagent in hand, removing the protecting group again proved impossible under both Lewis and Brønsted acid conditions. All efforts to deprotect **354** using HCl, $SnCl_4$, MSA, TFA, H_2SO_4 and H_3PO_4 procedures again were in vain. The results obtained mirrored those of 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 P_2S_5. 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 Brønstead 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

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 a 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.



3

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 acylic 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.

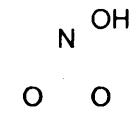
Further modification of our generic reagent allowed the synthesis of α-oxytosyl ketones in very good yields of (64-81%) for a variety of cyclic, acyclic and previously inaccessible di-carbonyl substrates. This reagent also proved extremely effective for functionalising primary centres, with a regioselectivity 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*-dimethylthiocarbamoylhydroxylamine **354** were isolated, deprotection proved impossible.

Experimental

Commercially available solvents and reagents were used without further purification unless other wise 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 ^1H NMR and melting point analysis.

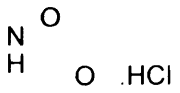
_N_-Methyl-_N_-Boc hydroxylamine 199:[214]



N-Methylhydroxylamine hydrochloride (20 g, 240 mmole) was dissolved in (1:1) THF/H_2O (480 mL) at 0 °C. Potassium carbonate (16.5 g, 120 mmole) was then added in one portion. Di-*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_2SO_4. 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

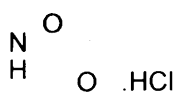
compound **199** as a colourless oil (34.2 g, 97%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.16 (3H, s), 1.50 (9H, s)

N-Methyl-*O*-benzoylhydroxylamine hydrochloride 201:[134]



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_2O (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)[134]; IR (ν, cm^{-1}, Nujol) 3458, 3056, 1712, 1600, 1550, 1422, 1264; ^{1}H NMR (400 MHz, DMSO-d^6) δ 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) δ 164.3 (C), 134.8 (C), 129.6 (CH), 129.6 (CH), 127.1 (CH), 37.4 (CH_3); *m/z* (APcI) 152 $[M+H]^+$-HCl; HRMS (ES) found 152.0711 $C_8H_9NO_2$ requires 151.0713 $[M+H]^+$-HCl

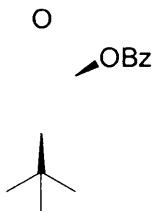
N-tert-Butyl-*O*-benzoylhydroxylamine hydrochloride 204:[215]



A solution of benzoyl 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

$NaHCO_3$/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 Na_2SO_4 and the solvent removed under reduced pressure. The crude *N-tert*-butyl-*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 Et_2O to HCl gas. Filtration of this yielded the title compound **204** as a colourless solid (6.8g, 85%); mp 119-121 °C; IR (ν, cm^{-1}, Nujol) 3458, 3056, 1713, 1612, 1543, 1422, 1268; ^1H NMR (400 MHz, DMSO-d^6) δ 8.00 (2H, d, J = 8.1Hz, Ar-H), 7.73 (1H, t, J = 7.5Hz, Ar-H), 7.53 (2H, t, J = 7.7Hz, Ar-H), 1.19 (9H, s, CCH_3); ^{13}C NMR (100 MHz, DMSO-d^6) δ 164.6 (C), 134.7 (C), 129.7 (CH), 129.6 (CH), 127.4 (CH), 57.9 (C), 25.5 (CH_3); *m/z* (APcI) $[M+H]^+$-HCl 194 (100 %); HRMS found 194.1175 $C_{11}H_{16}O_2N$ requires 194.1176 $[M+H]^+$-HCl

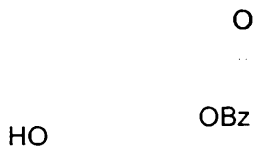
(±)-(1*R*,5*R*)-5-*tert*-butyl-2-oxocyclohexyl benzoate 213:



4-*tert*-Butylcyclohexanone (100 mg, 0.64 mmole) was added to dimethyl sulfoxide (1.5 mL). *N*-Methyl-*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 H_2O (20 mL) and extracted with ethyl acetate (4 x 25mL), 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 **213** as a white solid (105 mg, 75 % yield); mp 154-156 °C; IR (ν, cm^{-1}, $CHCl_3$) 2966, 1716, 1453, 1273, 1112; ^1H NMR (400MHz, $CDCl_3$) δ 8.02 (2H, d, J = 7.4Hz, Ar-H), 7.50 (1H, t, J = 7.4Hz, Ar-H), 7.37 (2H, t, J = 7.4Hz, Ar-H), 5.38-5.45 (1H, dd, $J_{H\text{-}He}$ = 6.4Hz, $J_{H\text{-}Ha}$ = 11.9Hz, 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, $CHC(CH_3)_3$); ^{13}C NMR (100MHz, $CDCl_3$), δ 204.7 (C), 165.6 (C), 133.1 (CH), 129.8

(CH), 129.6 (C), 128.3 (CH), 76.5 (CH), 45.8 (CH), 39.6 (CH_2), 34.3 (CH_2), 32.5 (C), 28.0 (CH_2), 27.3 (CH_3); *m/z* (APcI) $[M+H]^+$ 275 (100%), 153 (20%); HRMS (ES) found 275.1641 $C_{17}H_{23}O_3$ requires 275.1642 $[M+H]^+$

1-(4-Hydroxyphenyl)-3-oxobutan-2-yl benzoate 224:



4-(4-Hydroxyphenyl)butan-2-one (100 mg, 0.61 mmole) was added to dimethyl sulfoxide (1.5 mL). *N*-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_2O (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 **224** as a white solid (147 mg, 83 % yield); mp 184-185 °C; IR (ν, cm^{-1}, $CHCl_3$) 3397, 1716, 1614, 1451, 1271, 1110, 711; ^1H NMR (500MHz, $CDCl_3$) δ 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, $J_{H\text{-}Hcis}$ = 5.1Hz, $J_{H\text{-}Htrans}$ = 7.6Hz COCH), 4.85 (1H, bs, OH), 3.07-3.18 (2H, m, $COCHCH_2$), 2.00 (3H, s, $COCH_3$); ^{13}C NMR(100MHz,$CDCl_3$), δ 206.0 (C), 166.0 (C), 154.7 (C), 133.5 (CH), 130.6 (CH), 129.8 (CH), 129.2 (C), 128.5 (CH), 127.8 (C), 115.5 (CH), 79.7 (CH), 36.1 (CH_2), 27.0 (CH_3); *m/z* (APcI) $[M+H]^+$ 285 (100%); HRMS (ES) found 285.1121 $C_{17}H_{17}O_4$ requires 285.1121 $[M+H]^+$

4-(4-Methoxyphenyl)butan-2-one 223:

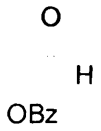
4-(4-Hydroxyphenyl)butan-2-one (500 mg, 3.05 mmole) was added to anhydrous THF (7.5 mL) under an atmosphere of nitrogen at room temperature. NaH (80.4 mg, 3.35mmole) was then added in two portions. MeI (43.3 mg, 3.05 mmole) was added dropwise over 5 min. The reaction mixture was then heated to reflux 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_2Cl_2 (15 mL), which was then washed with H_2O (2 x 5 ml), brine (10 mL) and dried over Na_2SO_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 (ν, cm^{-1}, $CHCl_3$) 2934, 1718, 1512, 1248, 1036, 711; ^1H NMR (400MHz, $CDCl_3$) δ 7.15 (2H, d, J = 8.5Hz, Ar-*H*), 6.80 (2H, d, J = 8.5Hz, Ar-H), 3.81 (3H, s, OCH_3), 2.85 (2H, t, J = 7.5Hz, $COCH_2CH_2$), 2.75 (2H, t, J = 7.5Hz, $COCH_2CH_2$), 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 $C_{11}H_{15}O_2$ requires 179.1027 $[M+H]^+$

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

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_2O (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 (ν, cm^{-1}, $CHCl_3$) 2934, 1718, 1612, 1452, 1249, 1110, 711; ^1H NMR (400MHz, $CDCl_3$) δ 7.95 (2H, d, J = 7.4Hz, Ar-H), 7.52 (1H, t, J = 7.4Hz, Ar-H),

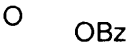
7.45 (2H, t, J = 7.4Hz, Ar-H),), 7.10 (2H, d, J = 8.5Hz, Ar-H), 6.75 (2H, d, J = 8.5Hz, Ar-H), 5.33-5.41 (1H, dd, $J_{H\text{-}Hcis}$ = 5.1Hz, $J_{H\text{-}Htrans}$ = 7.6Hz,COCH), 3.69 (3H, s, OCH_3), 3.08-3.15 (2H, m, $COCHCH_2$), 2.05 (3H, s, $COCH_3$); ^{13}C NMR(100MHz,$CDCl_3$), δ 205.7 (C), 165.9 (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_3), 36.1 (CH_2), 27.0 (CH_3); *m/z* (APcI) $[M+H]^+$ 299 (100%), 285 (10%); HRMS (ES) found 299.1279 $C_{18}H_{19}O_4$ requires 299.1278 $[M+H]^+$

1-formyl-2-methylpropyl benzoate 209:[216]



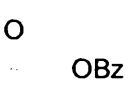
Isovaleraldehyde (100 mg, 1.1 mmole) was added to dimethyl sulfoxide (1.5 mL). *N*-Methyl-*O*-benzoyl hydroxylamine hydrochloride (217 mg, 1.1 mmole) was then added, the reaction was then stirred at room temperature for 24 h. After this the reaction mixture was added to H_2O (20 mL) and extracted with ethyl acetate (4 x 25mL), 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 **209** as a colourless oil (185 mg, 82 % yield) IR (ν, cm^{-1}, $CHCl_3$) 2357, 1749, 1689, 1111; ^1H NMR (500MHz, $CDCl_3$); 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, COHCHCH), 1.01-1.19 (6H, m, $CH(CH_3)_2$); ^{13}C NMR (100MHz, $CDCl_3$); 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_3), 17.3 (CH_3); *m/z* (APcI) $[M+H]^+$ 207 (70%); HRMS (ES) found 207.7381 $C_{12}H_{15}O_3$ 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-*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_2O (20 mL) and washed 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 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 (ν, cm^{-1}, $CHCl_3$) 2926, 1717, 1271, 1113, 902; ^1H 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), 5.34-5.40 (1H, dd, $J_{H\text{-}Ha}$ = 9.5Hz, $J_{H\text{-}He}$ = 3.3Hz, COCH), 2.57-2.65 (1H, m, COCH), 2.37-2.45 (1H, m, COCH), 1.99-2.07 (1H, m, $COCH_2CH_2$), 1.57-1.88 (7H, m), 1.28-1.39 (1H, m, $COCH2CH_2CH_2$); ^{13}C NMR (100MHz, $CDCl_3$); δ 207.4 (C), 165.7 (C), 133.2 (CH), 129.8 (C), 129.6 (C), 128.0 (CH), 79.0 (CH), 40.7 (CH_2), 30.3 (CH_2), 28.3 (CH_2), 26.4 (CH_2), 23.0 (CH_2); *m/z* (APcI) $[M+H]^+$ 233 (100 %), 157 (60 %), 139 (40 %), 175 (20 %); HRMS (ES) found 233.1172 $C_{14}H_{17}O_3$ requires 233.1172 $[M+H]^+$

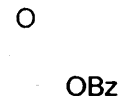
2-Oxocyclohexyl benzoate 210:[218]



Cyclohexanone (100 mg, 1.0 mmole) was added to dimethyl sulfoxide (1.5 mL). *N*-Methyl-*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_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 25 % ether/petroleum ether 40-60

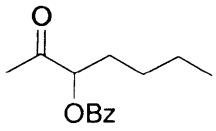
°C, to give the title compound **210** as a white solid (150 mg, 72 %); mp 102-104 °C (lit. mp 105-106.5 °C)[218]; IR (ν, cm^{-1}, $CHCl_3$) 2926, 1717, 1271, 1113, 902; ^1H NMR (400MHz, $CDCl_3$); δ 8.00 (2H, d, J = 7.4Hz, Ar-H), 7.48 (1H, t, J = 7.4, Ar-H), 7.35 (2H, t, J = 7.4Hz, Ar-H), 5.35-5.42 (1H, dd, $J_{H\text{-}Ha}$ = 11.6Hz, $J_{H\text{-}He}$ = 6.5Hz, COCH), 2.32-2.59 (3H, m), 1.51-2.09 (5H, m), ^{13}C NMR (100MHz, $CDCl_3$); δ 204.3 (C), 165.5 (C), 133.1 (CH), 130.1 (C), 129.8 (CH), 128.4 (CH), 76.7 (CH), 40.7 (CH_2), 33.2 (CH_2), 27.2 (CH_2), 23.8 (CH_2); *m/z* (APcI) $[M+H]^+$ 219 (100%); HRMS (ES) found 219.0974 $C_{13}H_{15}O_3$ requires 219.0976 $[M+H]^+$

2-Oxocyclopentyl benzoate 211:



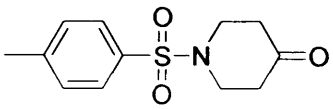
Cyclopentanone (100 mg, 1.2 mmole) was added to dimethyl sulfoxide (1.5 mL). *N*-Methyl-*O*-benzoyl hydroxylamine hydrochloride (224 mg, 1.2 mmole) was then added, the reaction was then stirred at room temperature for 18h. After this the reaction mixture was added to H_2O (20 mL) and extracted with ethyl 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 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 (ν, cm^{-1}, $CHCl_3$) 2926, 1717, 1271, 1113, 902; ^1H NMR (400MHz, $CDCl_3$); δ 8.00 (2H, d, J = 7.5Hz, Ar-H), 7.48 (1H, t, J = 7.5, Ar-H), 7.35 (2H, t, J = 7.5Hz, Ar-H), 5.35-5.41 (1H,m, COCH), 1.80-2.35 (6H, m), ^{13}C NMR (100MHz, $CDCl_3$); δ 204.3 (C), 165.5 (C), 133.1 (CH), 130.1 (C), 129.8 (CH), 128.4 (CH), 76.7 (CH), 40.7 (CH_2), 33.2 (CH_2), 27.2 (CH_2); *m/z* (APcI) $[M+H]^+$ 205 (65%); HRMS (ES) found 205.0819 $C_{12}H_{13}O_3$ requires 205.0820 $[M+H]^+$

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_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 25% ether/petroleum ether 40-60 °C, to yield the title compound **226** as a colourless oil (151 mg, 81%); IR (ν, cm^{-1}, $CHCl_3$) 2964, 1716 1270, 1112, 713; ^1H 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_2CH_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 $[M+H]^+$

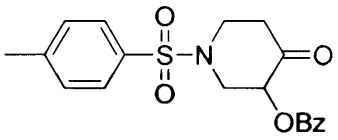
1-(Toluene-4-sulfonyl)-4-piperidone 217a:[141]



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_3N (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 recrystillisation 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)[141];

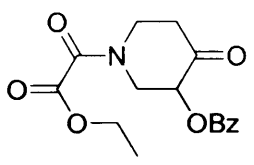
^{1}H NMR (400MHz, $CDCl_3$), δ 7.68 (2H, d, J = 8.0Hz,), 7.34 (2H , d, J = 7.4 Hz), 3.39 (4H, t, J = 5.9 Hz), 2.53 (4H, t, J = 5.9 Hz), 2.34 (3H, s)

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



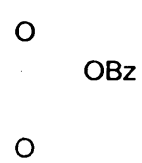
1-tosylpiperidin-4-one (100 mg, 0.40 mmole) was added to dimethyl sulfoxide (1.5 mL). *N*-Methyl-*O*-benzoyl hydroxylamine hydrochloride (73 mg, 0.40 mmole) was then added, the reaction was then stirred at room temperature for 18h. After this the reaction mixture was added to H_2O (20 mL) and extracted 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 recrystalisation 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, ArH), 7.31 (2H, d, J = 8.0Hz, ArH), 5.45-5.57 (1H, dd, $J_{H\text{-}He}$ = 6.7Hz, $J_{H\text{-}Ha}$ = 10.5Hz, COCH), 4.25-4.35 (1H, m, COCHCH), 4.01-4.10 (1H, m, COCHCH), 2.80-2.91 (1H, m, $COCH_2CH$), 2.68-2.75 (2H, m, $COCH_2$), 2.38-2.57 (1H, m, $COCH_2CH$), 2.34 (3H, s, CH_3); ^{13}C 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 $C_{19}H_{19}NO_5S$ requires 374.0942 $[M+H]^+$

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



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 H_2O (20 mL) and extracted with ethyl acetate (4 x 25 mL), dried over $MgSO_4$ and reduced. The resulting crude product was purified by recrystalisation in ethanol, to yield the title compound **216** as a white solid (110 mg, 69%), mp 245-247 °C; IR (ν, cm^{-1}, $CHCl_3$) 1727, 1665, 1451, 1267, 1187, 711; ^1H NMR (400MHz, $CDCl_3$) 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, $COCH_2CH_3$), 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, $COCH_2$), 1.22-1.32 (3H, m, $COCH_2CH_3$) ^{13}C NMR (100MHz, $CDCl_3$); 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 (CH_2), 46.2 (CH_2), 45.8 (CH_2), 39.8 (CH_2), 21.5 (CH_3); *m/z* (APcI) $[M+H]^+$ 320 (75 %); HRMS (ES) found 320.1089 $C_{16}H_{18}NO_6$ requires 320.1090 $[M+H]^+$

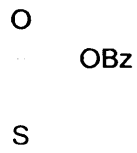
Tetrahydro-4-oxo-2H-pyran-3-yl benzoate 214:



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 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 25% ether/petroleum ether 40-60 °C, to yield the title compound **214** as a colourless oil (172 mg, 75%); IR (ν, cm^{-1}, $CHCl_3$) 2863, 1721, 1602, 1451, 1278, 1123, 710; ^1H NMR (400MHz, $CDCl_3$) 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, $J_{H\text{-}Ha}$ = 10.5Hz, $J_{H\text{-}He}$ = 7.0Hz, COCH), 4.40-4.51 (1H, m, COCHCH), 4.25-4.32 (1H, m, COCHCH), 3.60-3.75 (2H, m,

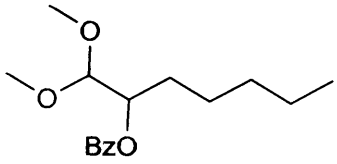
COC$\underline{H}_2$), 2.70-2.83 (1H, m, $COCH_2C\underline{H}$), 2.41-2.55 (1H, m, $COCH_2C\underline{H}$) ^{13}C NMR (100MHz, $CDCl_3$), δ 200.5 (C), 165.0 (C), 133.5 (CH), 130.1 (C), 129.9 (CH), 128.4 (CH), 74.0 (CH), 70.5 (CH_2), 68.5 (CH_2), 42.2 (CH_2); *m/z* (APcI) $[M+H]^+$ 221 (100 %), 153 (24 %), 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:



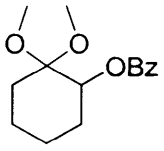
Tetrahydrothiopyran-4-one (100 mg, 0.86 mmole) was added to dimethyl sulfoxide (1.5 mL). *N*-Methyl-*O*-benzoyl hydroxylamine hydrochloride (160 mg, 0.86 mmole) was then added, the reaction was then stirred at room temperature for 18h. After this the reaction mixture was added to H_2O (20 mL) and extracted with ethyl acetate (4 x2 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, $CDCl_3$); δ 8.00 (2H, d, *J* = 7.4Hz, Ar-$\underline{H}$), 7.52 (1H, t, *J* = 7.4Hz, Ar-$\underline{H}$), 7.38 (2H, t, *J* = 7.4Hz, Ar-$\underline{H}$), 5.49-5.61 (1H, dd, $J_{H\text{-}Ha}$ = 11.2Hz, $J_{H\text{-}He}$ = 6.1Hz $COC\underline{H}$), 3.05-3.19 (2H, m, $COC\underline{H}_2$), 2.85-2.95 (4H, m): ^{13}C NMR (100MHz,$CDCl_3$), δ 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 $C_{12}H_{12}O_3S$ requires 237.0580 $[M+H]^+$

1,1-Dimethoxy-2-benzoyloxyheptane 232:



To a flame dried Radley tube, anhydrous methanol (1.5 mL) was added under an atmosphere of N_2. 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}, $CHCl_3$) 2937, 1780, 1190, 1050; ^1H NMR (400MHz, $CDCl_3$) 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, $ArCO_2CH$), 4.35 (1H, d, J = 5.4Hz, CH_3OCH), 3.41 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 1.75-1.92 (2H, m, $CHCH_2$), 1.25-1.40 (6H, m, $CHCH_2(CH_2)_3$), 0.75-0.91 (3H, m, $CHCH_3$); ^{13}C NMR (100MHz,$CDCl_3$) δ 166.1 (C), 132.9 (CH), 130.2 (C), 129.7 (CH), 128.3 (CH), 104.6 (CH), 73.2 (CH), 55.4 (CH_3), 54.4(CH_3), 31.3 (CH_2), 29.7 (CH_2), 24.8 (CH_2), 22.6 (CH_2), 14.0 (CH_3); *m/z* (ES) $[M+NH_4]^+$ 298 (2 %), 250 (10 %), 249 (100 %), 208 (25 %), 159 (21 %), 142 (35 %); HRMS found 298.2012 $C_{16}H_{28}O_4N$ requires 298.2013 $[M+NH_4]^+$

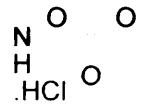
1,1-Dimethoxy-2-benzoyloxycyclohexanone 230:



To a flame dried Radley tube, anhydrous methanol (1.5 mL) was added under an atmosphere of N_2. 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

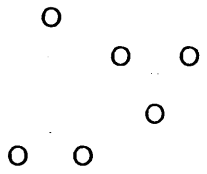
colourless oil (55 mg, 30 %), IR (ν, cm^{-1}, $CHCl_3$) 2937, 1721, 1210, 1069; ^1H NMR (400MHz, $CDCl_3$) δ 7.99 (2H, d, J = 7.4Hz, Ar-H), 7.48 (1H, t, J = 7.4Hz, Ar-H), 7.37 (2H, t, J = 7.4Hz, Ar-H), 5.24 (1H, m, CCH), 3.11 (3H, s, OCH_3), 3.09 (3H, s, OCH_3), 1.25-1.90 (8H, m, $(CH_2)_4$); ^{13}C NMR (100MHz, $CDCl_3$) δ 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 $C_{15}H_{24}O_4N$ requires 282.1700 $[M+NH_4]^+$

_N_-Methyl-_O_-allylcarbonatehydroxylamine hydrochloride 253:



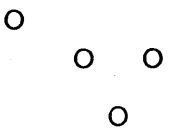
_N_-Methyl-_N_-Boc hydroxylamine (5 g, 33.9 mmole) was added to a solution of allyl chloroformate (4.1 g, 34 mmole) in DCM (70 mL) at 0 °C under an atmosphere of N_2. Et_3N (3.4 g, 33.9 mmole) was then added dropwise over several minutes. The reaction was stirred for 18h gradually warming to room temp. 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_2SO_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_2O 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 (ν, cm^{-1}, $CHCl_3$) 2937, 1721, 1210, 1069; ^1H NMR (400MHz, $CDCl_3$) δ 5.82-5.94 (1H, m, CH_2CHCH_2), 5.34 (1H, d, J = 17.1Hz, CH_2CHCHH), 5.25 (1H, d, J = 10.4Hz, CH_2CHCHH), 4.66 (2H, d, J = 5.8 Hz, CH_2CHCH_2), 3.19 (3H, s, NCH_3); ^{13}C NMR (100MHz, $CDCl_3$) δ 151.6 (C), 129.5 (CH), 121.2 (CH_2), 71.9 (CH_2), 35.9 (CH_3); HRMS (ES) found 132.0616 $C_5H_9NO_3$ 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, $CH_2C\underline{H}CH_2$), 5.29-5.36 (1H, d, J = 17.2Hz, $CH_2CHCH\underline{H}$), 5.18-5.25(2H, m), 4.59 (2H, d, J = 5.8Hz, $C\underline{H_2}CHCH_2$), 3.89-4.15 (4H, m, $OC\underline{H_2}C\underline{H_2}O$), 2.55-2.70 (1H, m, $CH\underline{H}$), 2.25-2.45 (2H, m, $C\underline{H_2}$), 2.07 (1H, t, J = 12.9Hz, $C\underline{H_2}$), 1.75-2.00 (2H, m, $C\underline{H_2}$): ^{13}C 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 $[M+H]^+$

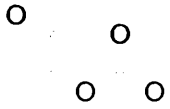
2-Oxocyclohexyl allylcarbonate 259:



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 x25 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

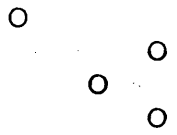
40-60°C, to yield the title compound **259** as a colourless oil (113 mg, 61%); IR (ν, cm^{-1}, $CHCl_3$) 3453, 1734, 1442, 1363; ^1H NMR (400MHz, $CDCl_3$), δ 5.88-6.00 (1H, m, $CH_2C\underline{H}CH_2$), 5.33 (1H, d, J = 15.9Hz, $CH_2CHC\underline{H}H$), 5.23 (1H, d, J = 11.7Hz, $CH_2CHCH\underline{H}$), 4.91-5.05 (1H, dd, $J_{H\text{-}Ha}$ = 6.5Hz, $J_{H\text{-}He}$ = 11.9Hz, $COC\underline{H}$), 4.50-4.65 (2H, m, $C\underline{H_2}CHCH_2$), 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); ^{13}C NMR (100MHz, $CDCl_3$), δ 204.1 (C), 154.1 (C), 131.3 (CH), 118.9 (CH_2), 79.4 (CH), 68.7 (CH), 40.5 (CH_2), 32.9 (CH_2), 27.0 (CH_2), 23.6 (CH_2);); *m/z* (APcI) $[M+H]^+$ 199 (100 %), 137 (45 %); HRMS (ES) found 199.0965 $C_{10}H_{15}O_4$ requires 199.0965 $[M+H]^+$

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



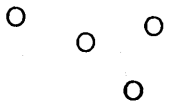
4-Methylpentan-2-one (100 mg, 0.99 mmole) was added to tetrahydrofuran (1.5 mL). *N*-Methyl-*O*-allyl carbonate hydroxylamine hydrochloride (247 mg, 1.49 mmole) was then added, the reaction was then stirred at 50 °C for 18h. After this the reaction mixture was added to H_2O (20 mL) and extracted with 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 40-60 °C, to yield the title compound **260** as a colourless oil (97 mg, 53%); IR (ν, cm^{-1}, $CHCl_3$) 3453,1733, 1442, 1362, 1122, 709; ^1H NMR (400MHz, $CDCl_3$), δ 5.90-6.01 (1H, m, $CH_2C\underline{H}CH_2$), 5.33 (1H, d, J = 17.2Hz, $CH_2CHC\underline{H}H$), 5.23 (1H, d, J = 10.4Hz, $CH_2CHCH\underline{H}$), 4.70 (1H, d, J = 4.2Hz, $COC\underline{H}$), 4.59 (2H, d, J = 5.7Hz, $COC\underline{H_2}$), 2.10-2.20 (1H, m, $COCHC\underline{H}$), 2.05 (3H, s, $COC\underline{H_3}$), 0.95 (3H, d, J = 6.8Hz $CHC\underline{H_3}$), 0.87 (3H, d, J = 6.8Hz, $CHC\underline{H_3}$); ^{13}C NMR (100MHz, $CDCl_3$), δ 205.2 (C), 154.9 (C), 131.2 (CH), 119.2 (CH_2), 85.9 (CH), 68.9 (CH_2), 29.7 (CH), 26.8 (CH_3), 19.0 (CH_3), 16.5 (CH_3); *m/z* (APcI) $[M+H]^+$ 201 (100 %); HRMS (ES) found 201.1120 $C_{10}H_{17}O_4$ requires 201.1121 $[M+H]^+$

2-Oxoheptan-3-yl allylcarbonate 261:



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 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 40-60 °C, to yield the title compound **261** as a colourless oil (93 mg, 50%); IR (ν, cm^{-1}, $CHCl_3$) 3453, 1733, 1442, 1362, 1122, 709; ^1H NMR (400MHz, $CDCl_3$), δ 5.85-6.00 (1H, m, $CH_2C\underline{H}CH_2$), 5.34 (1H, d, J = 17.8Hz, $CH_2CHC\underline{H}H$), 5.23 (1H, d, J = 10.5Hz, $CH_2CHCH\underline{H}$), 4.82 (1H, dd, $J_{H\text{-}Hcis}$ = 4.5Hz, $J_{H\text{-}Htrans}$ = 8.0Hz, $COC\underline{H}$), 4.57-4.58 (2H, d, J = 4.2Hz, $C\underline{H}_2CHCH_2$), 2.10 (3H, s, $COC\underline{H}_3$), 1.60-1.80 (2H, m, $COCHC\underline{H}_2$), 1.25-1.40 (4H, m, $CH_2(C\underline{H}_2)_2CH_3$), 0.85 (3H, t, J = 7.3Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (100MHz,$CDCl_3$), δ 205.2 (C), 154.6 (C), 131.2 (CH), 119.2 (CH_2), 81.8 (CH), 68.8 (CH_2), 30.1 (CH_2), 27.0 (CH_2), 25.9 (CH_3), 22.3 (CH_2), 13.7 (CH_3); *m/z* (APcI) $[M+H]^+$ 215 (100 %); HRMS (ES) found 215.1278 $C_{11}H_{19}O_4$ requires 215.1278. $[M+H]^+$

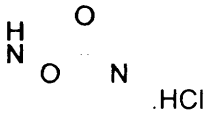
2-Oxocycloheptyl allylcarbonate 263:



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 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 40-60 °C, to yield the title compound **263** as a colourless oil (103 mg, 55%); IR (ν, cm^{-1}, $CHCl_3$) 3452, 1732, 1442, 1362, 1122; ^1H NMR (400MHz, $CDCl_3$), δ 5.85-6.05 (1H, m, $CH_2C\underline{H}CH_2$), 5.34 (1H, d, J = 17.8Hz, $CH_2CHC\underline{H}H$), 5.21 (1H, d, J = 10.3Hz,

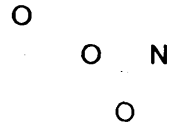
$CH_2CHCH\underline{H}$), 5.08 (1H, dd, $J_{H\text{-}Ha}$ = 9.5Hz, $J_{H\text{-}He}$ = 3.5Hz, $COC\underline{H}$), 4.57 (2H, d, J = 5.6Hz, $C\underline{H_2}CHCH_2$), 2.59-2.72 (1H, m), 2.35-2.44 (1H, m), 1.85-2.00 (1H, m), 1.62-1.91 (6H, m), 1.27-1.35 (1H, m); ^{13}C NMR (100MHz,$CDCl_3$), δ 207.0 ($\underline{C}$), 154.2 ($\underline{C}$), 131.3 ($\underline{C}H$), 119.0 ($\underline{C}H_2$), 81.3 ($\underline{C}H$), 68.7 ($\underline{C}H_2$), 40.5 (CH_2), 30.2 ($\underline{C}H_2$), 28.5 ($\underline{C}H_2$), 26.2 ($\underline{C}H_2$), 23.0 ($\underline{C}H_2$); *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:



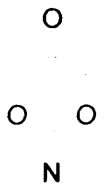
_N_-Methyl-_N_-Boc hydroxylamine (5g, 33.9mmole) was added to a solution of _N,N_ dimethylcarbanamol chloride (3.6g, 34mmole) and Et_3N (3.4g, 33.9mmole) in DCM (70 mL) at 0 °C under an atmosphere of N_2, including 10mol% DMAP. The reaction was stirred for 18h gradually warming to room temp. Upon completion the reaction mixture was quickly washed with 1M cold aqueous HCl (20mL) followed by water (50mL), brine (50mL) and dried with Na_2SO_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_2O 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 (ν, cm^{-1}, $CHCl_3$) 3427, 2937, 1731; ^1H NMR (400MHz, $CDCl_3$), δ 2.95 (3H, s, $NC\underline{H_3}$), 2.97 (3H, s, $CONC\underline{H_3}$), 2.85 (3H, s, $CONC\underline{H_3}$); ^{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 $C_4H_{11}N_2O_2$ requires 119.0776 $[M+H]^+$-HCl

2-Oxocyclohexyl dimethylcarbamate 254:



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 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 40-60 °C, to yield the title compound **254** as a colourless oil (112 mg, 60 %); IR (ν, cm^{-1}, $CHCl_3$) 2937, 1789, 1651, 1149; ^1H NMR (400MHz, $CDCl_3$), δ 5.05 (1H, dd, $J_{H\text{-}Ha}$ = 12.0Hz, $J_{H\text{-}He}$ = 7.1Hz, COC<u>H</u>), 2.95 (3H, s, NC<u>H</u>$_3$), 2.90 (3H, s, NC<u>H</u>$_3$), 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); ^{13}C NMR (100MHz, $CDCl_3$), δ 206.0 (C), 155.5 (C), 77.4 (CH), 40.7 (CH_2), 36.5 (CH_3), 35.9 (CH_3), 33.4 (CH_2), 27.2 (CH_2), 23.8 (CH_2); *m/z* (APcI) $[M+H]^+$ 186 (100 %); HRMS (ES) found 186.1123 $C_9H_{16}NO_3$ requires 186.1125 $[M+H]^+$

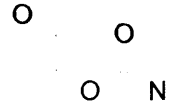
2-Oxoheptan-3-yl dimethylcarbamate 256:



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 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 40-60 °C, to yield the title compound **256** as colourless oil (87 mg, 50%); IR (ν, cm^{-1}, $CHCl_3$) 2937, 1789, 1651, 1149; ^1H NMR (400MHz, $CDCl_3$), δ 4.91 (1H, dd, J = 4.7Hz, J = 8.6Hz, COC<u>H</u>),

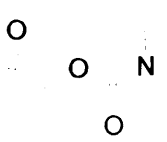
2.95 (3H, s, NCH_3), 2.90 (3H, s, NCH_3), 2.17 (3H, s, $COCH_3$), 1.70-1.90 (2H, m), 1.26-1.40 (4H, m), 0.55 (3H, t, J = 7.1Hz, CH_2CH_3); ^{13}C NMR (100MHz, $CDCl_3$), δ 207.0 (C), 155.9 (C), 79.4 (CH), 36.5 (CH_3), 36.0 (CH_3), 30.2 (CH_2), 27.4 (CH_2), 26.1 (CH_3), 22.3 (CH_2), 13.8 (CH_3); *m/z* (APcI) $[M+H]^+$ 202 (100 %); HRMS (ES) found 202.1440 $C_{10}H_{19}NO_3$ requires 202.1438 $[M+H]^+$

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



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 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 40-60 °C, to yield the title compound **255** as a colourless oil (119 mg, 64%); IR (*v*, cm^{-1}, $CHCl_3$) 2937, 1789, 1651, 1147; ^1H NMR (400MHz, $CDCl_3$), δ 4.70 (1H, d, J = 4.3Hz, $COCH$), 2.95 (3H, s, NCH_3), 2.87 (3H, s, NCH_3), 2.05-2.15 (1H, m, $COCHCH$), 2.00 (3H, s, $COCH_3$), 0.95 (3H, d, J = 6.8Hz, $CHCH_3$), 0.85 (3H, d, J = 6.8Hz, $CHCH_3$); ^{13}C NMR (100MHz, $CDCl_3$), δ 206.9 (C), 156.0 (C), 83.5 (CH), 36.5 (CH_3), 35.9 (CH_3), 29.7 (CH), 27.0 (CH_3), 19.3 (CH_3), 17.0 (CH_3); *m/z* (APcI) $[M+H]^+$ 188 (100 %); HRMS (ES) found 188.1283 $C_9H_{18}NO_3$ requires 188.1281 $[M+H]^+$

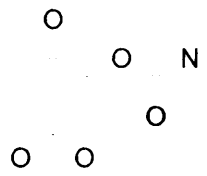
2-Oxocycloheptyl dimethylcarbamate 258:



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

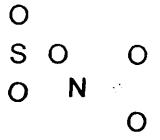
was added to H_2O (20 mL) and extracted with ethyl acetate (4 x 25 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. The resulting crude product was purified by column chromatography eluting with 50% ethyl acetate /petroleum ether 40-60 °C, to yield the title compound **258** as a colourless oil (97 mg, 55 %); IR (ν, cm^{-1}, $CHCl_3$) 2941, 1789, 1651, 1147; ^1H NMR (400MHz, $CDCl_3$), δ 5.09 (1H, dd, $J_{H\text{-}He}$ = 3.1Hz, $J_{H\text{-}Ha}$ = 9.6Hz, 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, $CDCl_3$), δ 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:



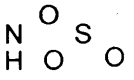
Cyclohexanone-1,4 monoketal (100 mg, 0.64 mmole) was added to tetrahydrofuran (1.5 mL). *N*-Methyl-*O*-dimethyl carbamate hydroxylamine hydrochloride (148 mg, 0.96 mmole) was then added and stirred at 50 °C for 18h. After this the reaction mixture was added to H_2O (20 mL) and extracted with ethyl acetate (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 40-60 °C, to yield the title compound **257** as a colourless oil (88 mg, 57 %); IR (ν, cm^{-1}, $CHCl_3$) 2937, 1789, 1735, 1651, 1457, 1369, 1149; ^1H NMR (400MHz, $CDCl_3$), δ 5.33 (1H, dd, $J_{H\text{-}He}$ = 6.5Hz, $J_{H\text{-}Ha}$ = 12.8Hz, COCH), 3.85-4.00 (4H, m, OCH_2CH_2O), 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,$CDCl_3$), δ 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 $C_{11}H_{18}NO_5$ requires 244.1140 $[M+H]^+$

_N_-Boc-_N_-methyl-_O_-_p_-tosylhydroxylamine 298:[219]



_p_-Toluenesulfonyl chloride (2.6 g,13.6 mmole) was added to DCM (20 mL) at 0 °C under N_2. Et_3N (2.1 g, 20.4 mmole) was then added in one portion followed by DMAP (10mol%). 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 18h gradually rising to room temperature. Once complete the reaction mixture was washed with 1M aqueous HCl (20 mL), water (20 mL) and brine (20 mL). Solvent was then removed under reduced pressure. The crude product was purified by recrystillation using hexane to afford the title compound **298** as a colourless solid (3.8 g, 94%), mp 69-72 °C; IR (ν, cm^{-1}, $CHCl_3$) 1727, 1455, 1371, 1179, 1090, 846, 757; ^1H NMR (400MHz, $CDCl_3$), δ 7.85 (2H, d, J = 8.2Hz, Ar<u>H</u>), 7.35 (2H, d, J = 8.2Hz, Ar<u>H</u>), 3.25 (3H, s, NC<u>H</u>$_3$), 2.45 (3H, s, Ar-C<u>H</u>$_3$), 1.20(9H, s, $(CH_3)_3$); ^{13}C NMR (100MHz,$CDCl_3$), δ 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) $[M+H]^+$-Me 287 (5 %), 201 (25 %), 156 (75 %), 92 (65 %), 60 (80 %), 58 (100%); HRMS (ES) found 287.0758 $C_{12}H_{18}NO_5S$ requires 287.0749. $[M+H]^+$-Me

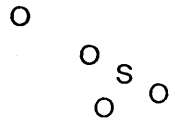
_N_-Methyl-_O_-_p_-tosylhydroxylamine 299:[219]



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 N_2 at 0 °C. The reaction mixture was stirred for 1h 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 Na_2SO_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 (ν, cm^{-1}, $CHCl_3$) 3447, 1769,

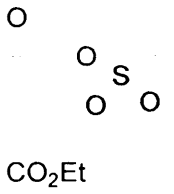
1598, 1360, 1177, 1010, 814, 660; ^{1}H NMR (400MHz, $CDCl_3$), δ 7.85 (2H, d, J = 8.2Hz, ArH), 7.35 (2H, d, J = 8.2Hz, ArH), 2.65 (3H, s, NCH_3), 2.45 (3H, s, Ar-CH_3); ^{13}C NMR (100MHz, $CDCl_3$), δ 145.0 (C), 131.9 (C), 129.5 (CH), 129.1 (CH), 40.2 (CH_3), 21.7 (CH_3); *m/z* (ES) $[M+H]^+$ 202 (15 %), 187 (55 %), 156 (100 %), 60 (45 %); HRMS (ES) found 202.0546 $C_8H_{12}NO_3S$ requires 202.0493. $[M+H]^+$

2-Oxocyclohexyl 4-methylbenzenesulfonate 306:



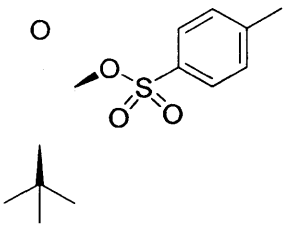
N-Methyl-*O*-*p*-tosylhydroxylamine (50 mg, 0.24 mmole) was added to a (1:1) mixture of toluene/THF (0.5 mL). Cyclohexanone (16 mg, 0.16 mmole) was then added, followed by methane sulfonic acid (15 μl, 0.24 mmole). The reaction mixture was then stirred at 50 °C for 18h. Upon completion the reaction solvent 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, $J_{H\text{-}He}$ = 8.1Hz, $J_{H\text{-}Ha}$ = 13.5Hz, COCH), 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 $C_{13}H_{18}O_4S$ requires 269.0803 $[M+H]^+$

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



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; ^1H NMR (400MHz, $CDCl_3$), δ 7.75 (2H, d, J = 8.2Hz, Ar-H), 7.27 (2H, d, J = 8.2Hz, Ar-H), 4.85-4.95 (1H, m, COCH), 4.00-4.20 (2H, m, $CO_2CH_2CH_3$), 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, $CO_2CH_2CH_3$); ^{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_2), 28.8 (CH_2), 21.7 (CH_3), 14.1(CH_3); *m/z* (APcI) $[M+NH_4]^+$ 359 (45%); HRMS (ES) found 359.1358 $C_{16}H_{24}NO_6S$ requires 359.1358 $[M+NH_4]^+$

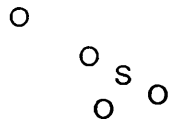
5-*tert*-Butyl-2-oxocyclohexyl 4-methylbenzenesulfonate 307:



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*-butylcyclohexanone (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

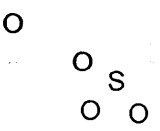
under reduced pressure and the crude product adsorbed onto silica. Purification was achieved by column chromatography eluting with 20 % ethyl acetate /petroleum ether 40-60 °C, to yield the title compound **307** as a colourless oil (33 mg, 64%); IR (ν, cm^{-1}, $CHCl_3$) 2930, 1735, 1651, 1452, 1358, 1177, 1096; ^1H NMR (400MHz, $CDCl_3$), δ 7.75 (2H, d, J = 8.2Hz, Ar-H), 7.28 (2H, d, J = 8.2Hz, Ar-H), 4.95 (1H, dd, $J_{H\text{-}He}$ = 6.4Hz, $J_{H\text{-}Ha}$ = 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, $(CH_3)_3$); ^{13}C NMR (100MHz, $CDCl_3$), δ 202.5 (C), 144.8 (C), 133.9 (C), 129.6 (CH), 127.9 (CH), 81.5 (CH), 45.9 (C), 39.6 (CH_2), 35.9 (CH_2), 32.5 (CH_2), 27.5 (CH_3), 21.6 (CH_3); *m/z* (APcI) $[M+NH_4]^+$ 343 (80%); HRMS (ES) found 343.1768 $C_{17}H_{28}NO_4S$ requires 343.1770 $[M+NH_4]^+$

2-Oxopropyl 4-methylbenzenesulfonate 313:[220]



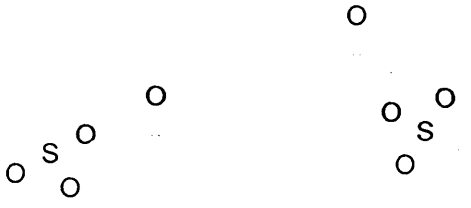
N-Methyl-*O*-*p*-tosylhydroxylamine (50 mg, 0.24 mmole) was added to a (1:1) mixture of toluene/THF (0.5 mL). Acetone (9 mg, 0.16 mmole) was then added, followed by methane sulfonic acid (15 µl, 0.24 mmole). The reaction mixture was then stirred at 50 °C for 18h. Upon completion the reaction solvent 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}, $CHCl_3$) 1736, 1651, 1457, 1358, 1177; ^1H NMR (400MHz, $CDCl_3$), δ 7.75 (2H, d, J = 8.2Hz, Ar-H), 7.27 (2H, d, J = 8.2Hz, Ar-H), 4.38 (2H, s, $COCH_2$), 2.39 (3H, s, Ar-CH_3), 2.07 (3H, s, $COCH_3$); ^{13}C NMR (100MHz,$CDCl_3$), δ 201.3 (C), 145.6 (C), 132.2 (C), 130.1 (CH), 128.1 (CH), 72.0 (CH_2), 26.7 (CH_3), 21.8 (CH_3); *m/z* (APcI) $[M+NH_4]^+$ 246 (100 %), 141 (12 %); HRMS (ES) found 246.0799 $C_{10}H_{16}O_4SN$ requires 246.0800 $[M+NH_4]^+$

2-Oxo-2-phenyl 4-methylbenzenesulfonate 314:[221]



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 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 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)[221]; IR (ν, cm^{-1}, $CHCl_3$) 2927, 1713, 1651, 1558, 1455, 1369, 1157, 903, 730; ^{1}H NMR (400MHz, $CDCl_3$), δ 7.75-7.81 (4H, m), 7.54 (1H, t, J = 7.4Hz, Ar-H), 7.40 (2H, t, J = 7.4Hz, Ar-H), 7.28 (2H, d, J = 8.2Hz, Ar-H), 5.19 (2H, s, CH_2), 2.35 (3H, s, Ar-CH_3); ^{13}C NMR (100MHz, $CDCl_3$), δ 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 $C_{15}H_{18}O_4NS$ 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 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 **310** as a colourless oil in a 1:4 mixture of isomers (28 mg,

71%); IR (ν, cm^{-1}, $CHCl_3$) 2926, 1721, 1651, 1558, 1369, 1178, 907; ^1H NMR (400MHz, $CDCl_3$), 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, COCH $_{\text{minor isomer}}$), 4.41 (2H, s, CH_2), 2.45 (2H, q, J = 7.3Hz, $COCH_2$), 2.39 (3H, s, Ar-CH_3), 2.11 (3H, s, $COCH_3$ $_{\text{minor isomer}}$), 1.19 (3H, d, J = 7.3Hz, $CHCH_3$ $_{\text{minor isomer}}$), 0.95 (3H, t, = 7.3Hz, CH_2CH_3); ^{13}C NMR (100MHz, $CDCl_3$), 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 (CH_2), 32.4 (CH_2), 25.6 (CH_3), 21.7 (CH_3), 17.7 (CH_3), 6.8 (CH_3); m/z (APcI) $[M+H]^+$ 243 (30 %), 155 (45 %), 127 (62 %), 125 (100 %); HRMS (ES) found 265.0508 $C_{11}H_{14}O_4SNa$ requires 265.0505 $[M+Na]^+$

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

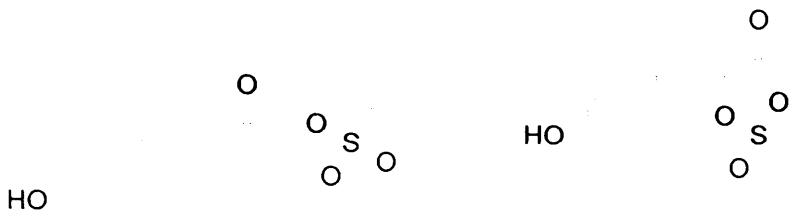
N-Methyl-*O*-*p*-tosylhydroxylamine (50 mg, 0.24 mmole) was added to a (1:1) mixture of toluene/THF (0.5 mL). 4-Methylpentan-2-one (16 mg, 0.16 mmole) was then added, followed by methane sulfonic acid (15 µl, 0.24 mmole). The reaction mixture was then stirred at 50 °C for 18h. Upon completion the reaction 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}, $CHCl_3$) 2988, 1736, 1651, 1558, 1457, 1370, 1178, 908; ^1H NMR (400MHz, $CDCl_3$), δ 7.75 (2H, d, J = 8.2Hz, Ar-H), 7.28 (2H, d, J = 8.2Hz, Ar-H), 4.40 (2H, s, CH_2), 4.32 (2H, d, J = 5.1Hz, $COCH_2$ $_{\text{minor isomer}}$), 2.39 (3H, s, Ar-CH_3), 2.27 (2H, d, J = 7.0Hz, $COCH_2$), 2.11 (3H, s, $COCH_3$ $_{\text{minor isomer}}$), 1.95-2.10 (1H, m, CH3CH), 0.85 (6H, d, J = 6.7Hz, $CH(CH_3)_2$), 0.78 (3H, d, J = 6.8Hz, $CHCH_3$ $_{\text{minor isomer}}$), 0.72 (3H, d, J = 6.8Hz, $CHCH_3$ $_{\text{minor isomer}}$); ^{13}C NMR (100MHz, $CDCl_3$), 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 (CH_2), 47.6 (CH_2), 30.7 (CH_3), 26.9 (CH_2), 22.4 (CH), 21.7

(CH_3), 18.4 (CH_3), 16.9 (CH_3); *m/z* (APcI) $[M+H]^+$ 271 (100 %); HRMS (ES) found 293.0823 $C_{13}H_{18}NaO_4S$ requires 293.0823 $[M+Na]^+$

2-Oxoheptyl 4-methylbenzenesulfonate 311 and 311a:

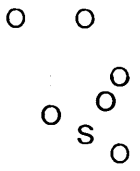
N-Methyl-*O*-*p*-tosylhydroxylamine (50 mg, 0.24 mmole) was added to a (1:1) mixture of toluene/THF (0.5 mL). 2-Heptanone (18 mg, 0.16 mmole) was then added, followed by methane sulfonic acid (15 µl, 0.24 mmole). The reaction mixture was then stirred at 50 °C for 18h. Upon completion the reaction solvent 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 **311** as a colourless oil in a 1:4 mixture of isomers (32 mg, 69%); IR (ν, cm^{-1}, $CHCl_3$) 2930, 1735, 1651, 1452, 1358, 1177, 1096, 911; ^1H NMR (400MHz, $CDCl_3$), δ 7.75 (2H, d, J = 8.2Hz, Ar-H), 7.30 (2H, d, J = 8.2Hz, Ar-H), 4.50 (1H, dd, $J_{H\text{-}Hcis}$ = 4.5Hz, $J_{H\text{-}Htrans}$ = 8.2Hz, COCH minor isomer), 4.41 (2H, s, $COCH_2$), 2.40 (3H, s, Ar-CH_3), 2.15 (3H, s, $COCH_3$ minor isomer), 1.45 (2H, t, J = 7.4Hz, $COCH_2$), 1.05-1.30 (6H, m), 0.85 (3H, t, J = 6.8Hz, CH_3), 0.75 (3H, t, J = 6.8Hz, CH_3 minor isomer); ^{13}C NMR (100MHz, $CDCl_3$), δ 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 (CH_2), 38.9 (CH_2), 31.2 (CH_2), 31.1 (CH_2), 26.4 (CH_2), 25.9 (CH_3), 21.9 (CH_3), 21.7 (CH_2), 13.8 (CH3); *m/z* (APcI) $[M+NH_4]^+$ 302 (50 %), 285 (20 %), 155 (25 %), 141 (100 %); HRMS (ES) found 302.1420 $C_{14}H_{24}O_4SN$ requires 302.1421 $[M+NH_4]^+$

4-(4-Hydroxyphenyl)-2-oxobutyl 4-methylbenzenesulfonate 312 and 312a:



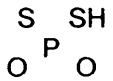
N-Methyl-*O*-*p*-tosylhydroxylamine (50 mg, 0.24 mmole) was added to a (1:1) mixture of toluene/THF (0.5 mL). 4-(4-Hydroxyphenyl)butan-2-one (26 mg, 0.16 mmole) was then added, followed by methane sulfonic acid (15 µl, 0.24 mmole). The reaction mixture was then stirred at 50 °C for 18h. Upon completion 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}, $CHCl_3$) 3452, 2930, 1735, 1651, 1452, 1358, 1177, 1096, 911; ^1H NMR (400MHz, $CDCl_3$), 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, $J_{H\text{-}Hcis}$ = 4.3Hz, $J_{H\text{-}Htrans}$ = 8.3Hz, COCH $_{minor\ isomer}$), 4.45 (2H, s, $COCH_2$), 3.00-3.50 (1H, brs, OH) 2.60-2.75 (2H, m, Ar-CH_2), 2.35 (3H, s, Ar-CH_3), 2.31 (3H, s, Ar-$CH_{3\ minor\ isomer}$), 2.11 (2H, s, $COCH_2$), ^{13}C NMR (100MHz, $CDCl_3$), 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 (CH_2), 30.1 (CH_3), 28.9 (CH_2), 28.0 (CH_2), 21.7 (CH_3); *m/z* (APcI) $[M+NH_4]^+$ 352 (100 %); HRMS (ES) found 352.1210 $C_{17}H_{22}O_5SN$ requires 352.1213 $[M+NH_4]^+$

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 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 give the title compound **319** as a pale yellow oil (32 mg, 69%); IR (ν, cm^{-1}, $CHCl_3$) 2921, 1735, 1652, 1377, 1179, 907, 743; ^1H NMR (400MHz, $CDCl_3$), δ 7.75 (2H, d, J = 8.2Hz, Ar-H), 7.31 (2H, d, J = 8.2Hz, Ar-H), 5.11 (1H, s, CH), 4.00-4.09 (2H, m, CH_2CH_3), 2.35 (3H, s, Ar-CH_3), 2.19 (3H, s, $COCH_3$), 1.12 (3H, t, J = 7.2Hz, CH_2CH_3); ^{13}C NMR (100MHz, $CDCl_3$), δ 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 $C_{13}H_{19}O_6SN$ requires 318.1011 $[M+NH_4]^+$

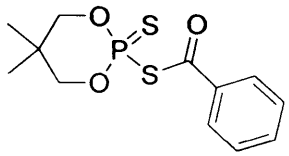
5,5-Dimethyl-2-thiolo-2-thiono-1,3,2-dioxaphosphorinane 333:[198]



Prepared in accordance with literature procedure as follows, to P_2S_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 °C for 12h until there was no further evolution of H_2S gas and almost all the P_2S_5 had dissolved. The mixture was then filtered through Celite to remove any residual P_2S_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

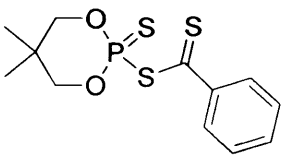
white solid (2.4 g, 91%), mp 79.5-80.0 °C (lit. mp 78 °C)[198]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (2H, s, $C\underline{H}_2$), 3.98 (2H, s, $C\underline{H}_2$), 1.05 (6H, s, $(C\underline{H}_3)_2$)

Benzoyl 2-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) sulphide 334:[197]



Prepared in accordance with literature procedure as follows, benzoyl chloride (420 mg, 3 mmole) was added to a solution of 5,5-dimethyl-2-thiolo-2-thiono-1,3,2-dioxaphosphorinane (600 mg, 3 mmole) in benzene (10 mL). Subsequently, Et_3N (0.31 mL, 3 mmole) was added dropwise to the ice-cold solution, with immediate precipitation of $Et_3N.HCl$. 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)[197]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $J_{H\text{-}H}$ = 10.7 Hz, $J_{P\text{-}H}$ = 3.9 Hz), 4.02 (2H, dd, $J_{H\text{-}H}$ = 10.7 Hz, $J_{P\text{-}H}$ = 25.9 Hz), 1.38 (3H, s), 0.93 (3H, s)

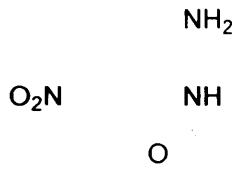
Thiobenzoyl 2-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) sulphide 335:[197]



Prepared in accordance with literature procedure as follows, a solution of Benzoyl 2-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) sulphide (1.51 g, 5 mmole) and 5,5-dimethyl-2-thiolo-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_2CO_3 (2 x 5 mL) and then H_2O (5 mL). The organic layer was separated and dried with $MgSO_4$ and the

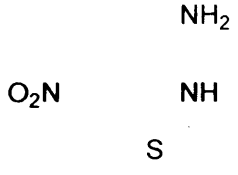
solvent removed under reduced pressure. The crude **335** product was used for thioacylation without further purification with a crude yield of (1.50 g, 94%), mp 96-101 °C (lit. mp 95-97 °C)[197]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (2H, d, J = 8.3 Hz), 7.59 (1H, t, J = 7.8 Hz), 7.4 (2H, t, J = 7.8 Hz), 4.29 (2H, dd, $J_{H\text{-}H}$ = 10.7Hz, $J_{P\text{-}H}$ = 3.4Hz), 3.98 (2H, dd, $J_{H\text{-}H}$ = 10.7Hz, $J_{P\text{-}H}$ = 25.9Hz), 1.37 (3H, s), 0.97 (3H, s)

_N_-Benzoyl-2-amino-5-nitroaniline 339:[200]



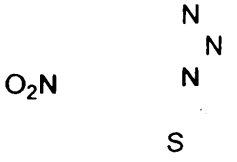
4-Nitro-1,2-phenylenediamine (5 g, 32.6 mmole) was dissolved in anhydrous THF (70 mL) at 0 °C. To this triethylamine (4.2 mL, 32.6 mmole) was then added in one portion and stirred for ten minutes. Benzoyl chloride (4.56 g, 32.6 mmole) was then added dropwise to the reaction mixture under an atmosphere 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), $NaHCO_3$ (30 mL), brine (30 mL), then dried over $NaSO_4$ 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)[200]; ^{1}H NMR (400MHz, $CDCl_3$) 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)

_N_-Thiobenzoyl-2-amino-5-nitroaniline 340:[200]



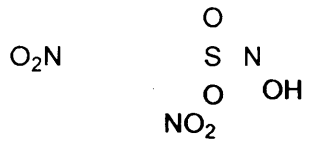
Prepared in accordance with literature procedure as follows, under an atmosphere of nitrogen, P_4S_{10} (1 g, 2.2 mmole) was mixed with Na_2CO_3 (0.27 g, 2.2 mmole) in anhydrous THF (100 mL). The mixture was stirred for 1 h at 25 °C and then cooled to 0 °C. To this clear solution was added *N*-Benzoyl-2-amino-5-nitroaniline (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)[200]; ^{1}H NMR (400MHz, $CDCl_3$) δ 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:[200]



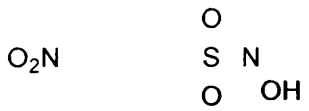
Prepared in accordance with literature procedure as follows, *N*-Thiobenzoyl-2-amino-5-nitroaniline (545 mg, 2.0 mmol) was dissolved by gentle warming at 40 °C in 70 % acetic acid (15 mL). This was then cooled to 0 °C and $NaNO_2$ (0.21 g, 3 mmol) was added in small portions with stirring. After 30 min, ice-water (100 mL) was added, and the precipitate was filtered off, washed with water, and dried *in vacuo* to afford the title compound **341** as a red solid, which was crystallized from CH_2Cl_2 (409 mg, 72%), mp 158 °C (lit. mp 158 °C)[200]; ^{1}H NMR (400MHz, $CDCl_3$) δ 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:**



N-Methylhydroxylamine hydrochloride (5 g, 59.8 mmole) was dissolved in (1:1) THF/H_2O (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 Na_2SO_4. Solvent was then removed under reduced pressure. The resulting crude product was crystallized with hexane to yield the title **346** compound as a yellow solid (11.9 g, 72%), mp 122-124 °C; IR (ν, cm^{-1}, $CHCl_3$) 3565, 1698, 1377, 1251; ^1H NMR (500MHz, C_3D_6O) 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, CH_3); ^{13}C NMR (100MHz, $CDCl_3$), δ 151.2 (C), 149.17 (C), 134.01 (CH), 128.63 (CH), 126.29 (CH), 119.62 (CH), 40.2 (CH_3)

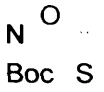
_N_-4-nitrophenylsulfonyl-_N_-methyl hydroxylamine 347:



N-Methylhydroxylamine hydrochloride (5 g, 59.8 mmole) was dissolved in (1:1) THF/H_2O (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 Na_2SO_4. Solvent was then removed under reduced pressure. The resulting crude product was purified by

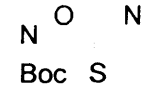
crystillation with hexane to yield the title compound **347** as a yellow solid (8.6 g, 68%), mp 151-153 °C; IR (ν, cm^{-1}, $CHCl_3$) 3265, 1508, 1261, 1090, 1020, 798; ^1H NMR (400MHz, C_3D_6O) δ 8.45 (2H, d, J = 6.7Hz, Ar-H), 8.05 (2H, d, J = 6.7Hz, Ar-H), 2.77 (3H, s, NCH_3); ^{13}C NMR (100MHz, $CDCl_3$), δ 151.0 (C), 137.9 (CH), 131.2 (C), 123.9 (CH), 40.5 (CH_3).

N-Boc-*N*-methyl-*O*-thiobenzoylhydroxylamine 326:



To a cooled solution of benzotriazole **341**(0.5 g, 1.75 mmol) and *N*-Boc-*N*-methyl-*O*-benzoylhydroxylamine **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 (ν, cm^{-1}, $CHCl_3$) 2981, 1699, 1454, 1370, 1150; ^1H NMR (400MHz, $CDCl_3$), 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, NCH_3), 1.35 (9H, s, $(C(CH_3)_3)$); δ ^{13}C NMR (100MHz,$CDCl_3$), δ 209.5 (C), 154.9 (C), 136.8(C), 133.7 (CH), 129.5 (C), 128.7 (CH), 82.9 (C), 37.6 (CH_3), 28.6 (CH_3).

N-Boc-N-methyl-*O-N,N*-dimethylthiocarbamatehydroxylamine 354:



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 Na_2SO_4. 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}, $CHCl_3$) 2979, 1681, 1313, 1149, 917, 731; ^1H NMR (400 MHz, $CDCl_3$) δ 3.30 (3H, s, $CSNC\underline{H}_3$), 3.25 (3H, s, $CSNC\underline{H}_3$), 3.09 (3H, s, $NC\underline{H}_3$), 1.35 (9H, s, $C(C\underline{H}_3)_3$); ^{13}C NMR (100MHz, $CDCl_3$), δ 187.9 (C), 154.5 (C), 82.0 (C), 38.41 (CH_3), 37.7 (CH_3), 28.1 (CH_3); *m/z* (APcI) 235 (100%) $[M+H]^+$ HRMS (ES) found 235.1109 $C_9H_{19}N_2O_3S$ requires 235.1111 $[M+H]^+$

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Appendix

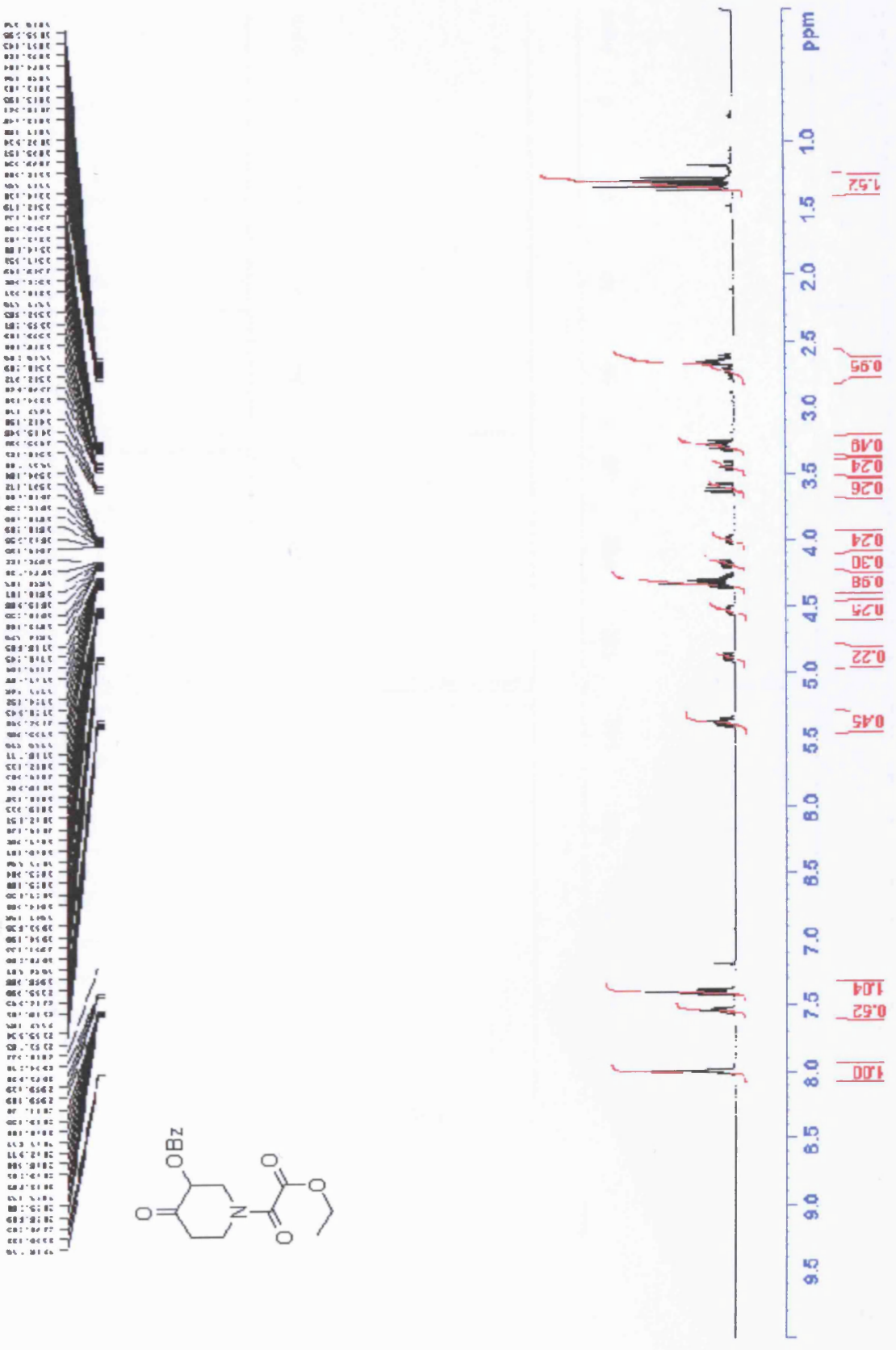

Fig. A ^{1}H NMR of **217** 400MHz, $CDCl_3$

Fig. B ^{13}C DEPT of **216** 100MHz, $CDCl_3$

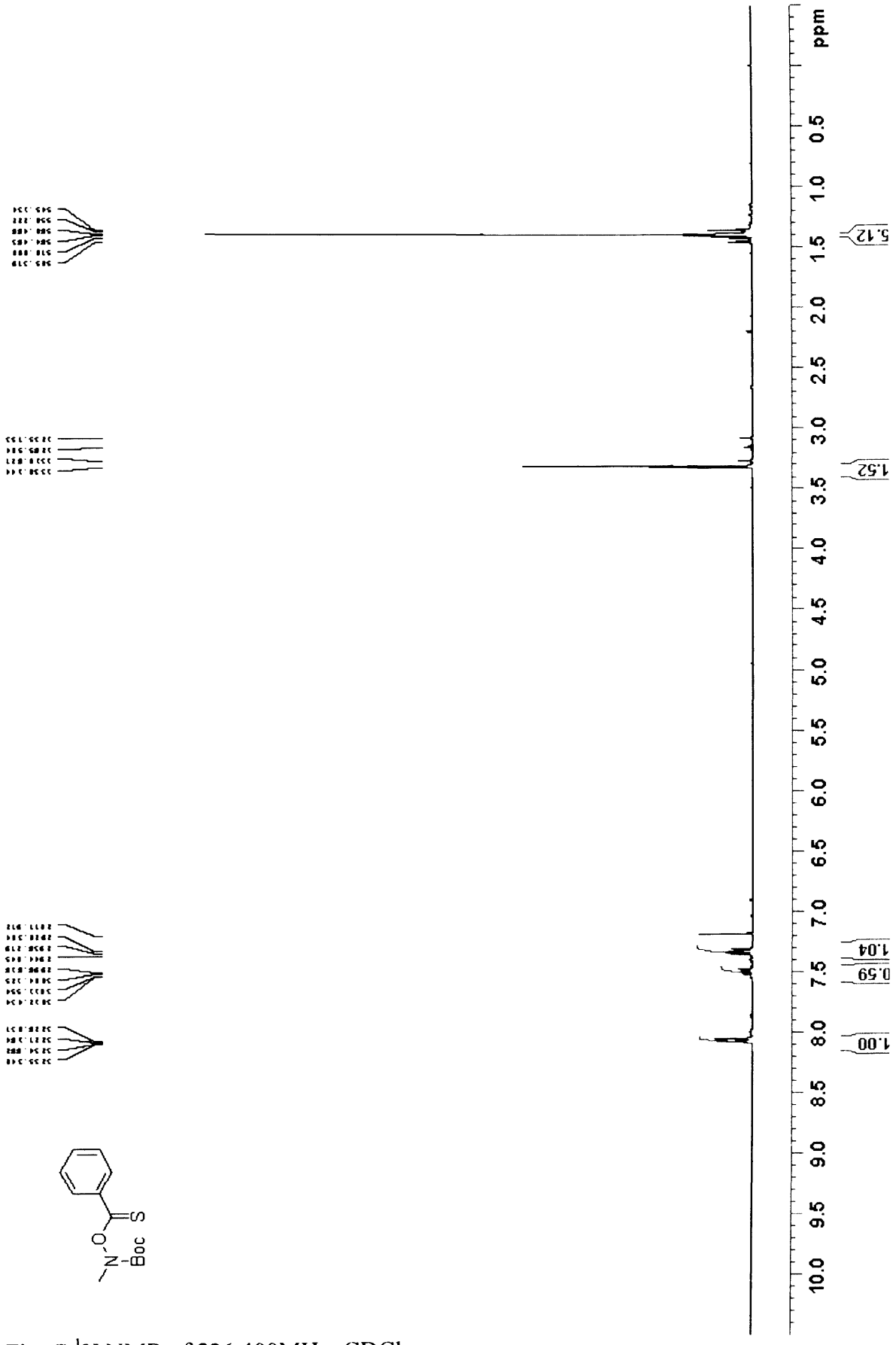

Fig. C ^{1}H NMR of **326** 400MHz, $CDCl_3$

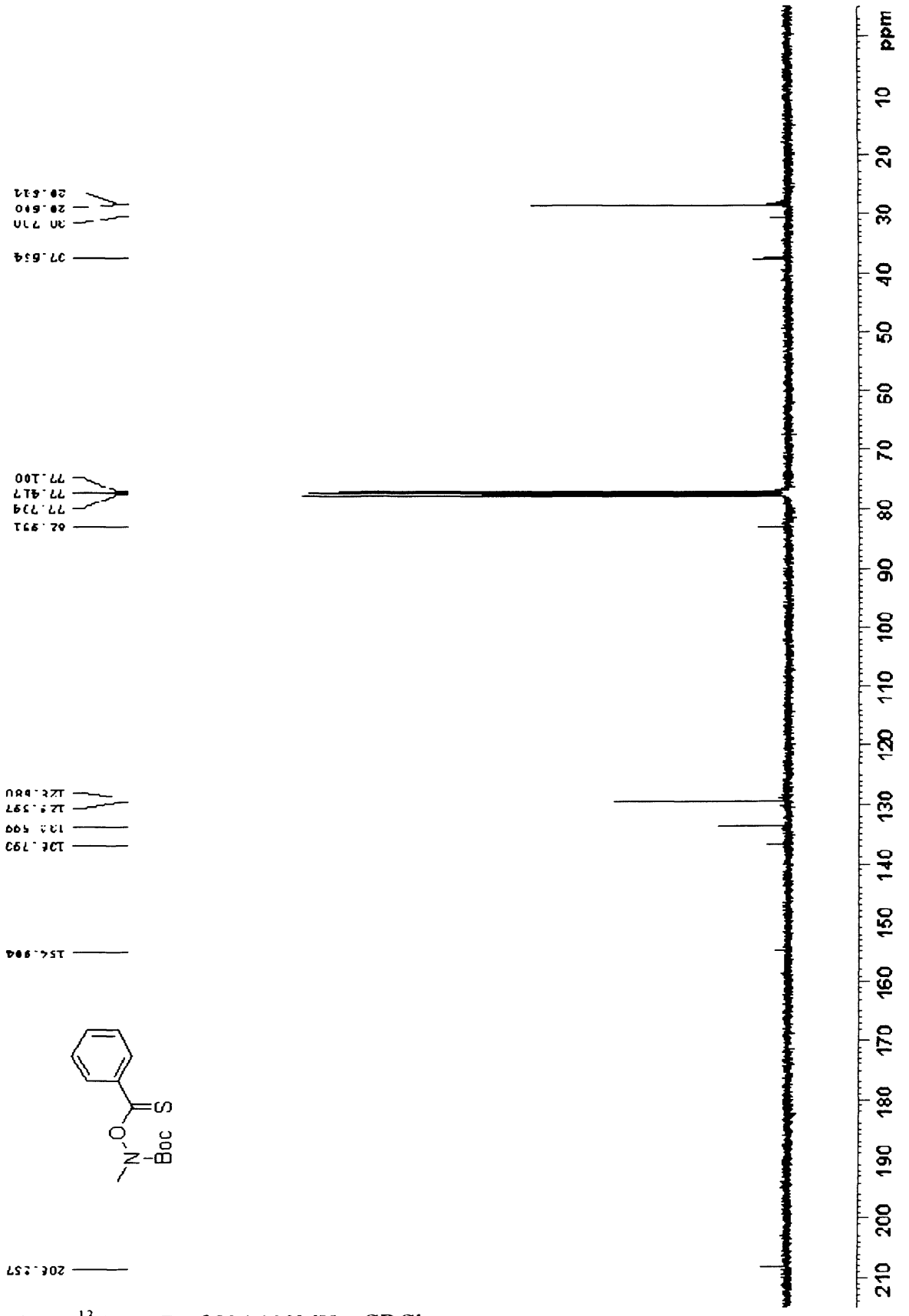

Fig. D ^{13}C NMR of **326** 100MHz, $CDCl_3$

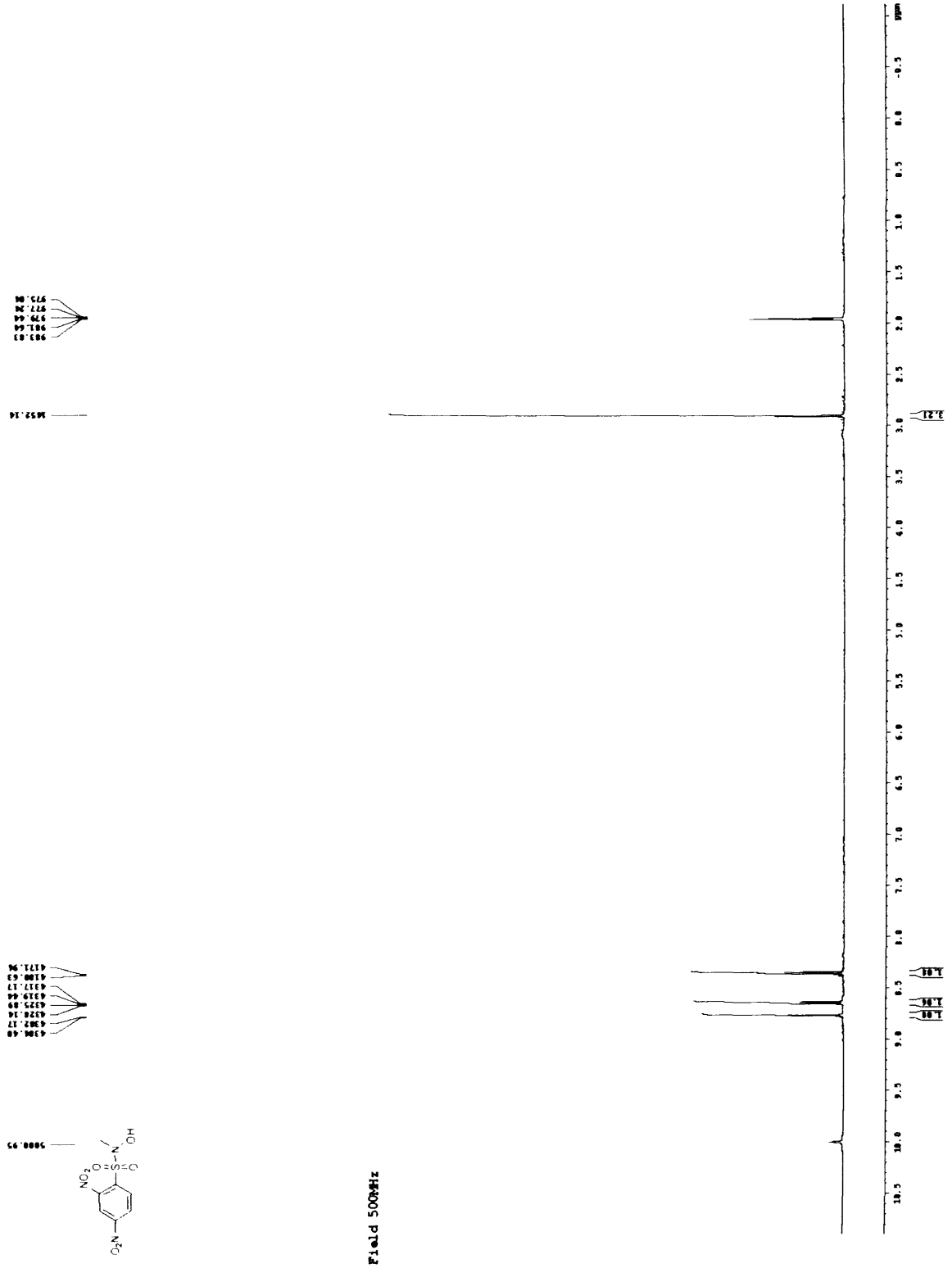

Fig. E ^{1}H NMR of **346** 500MHz, C_3D_6O

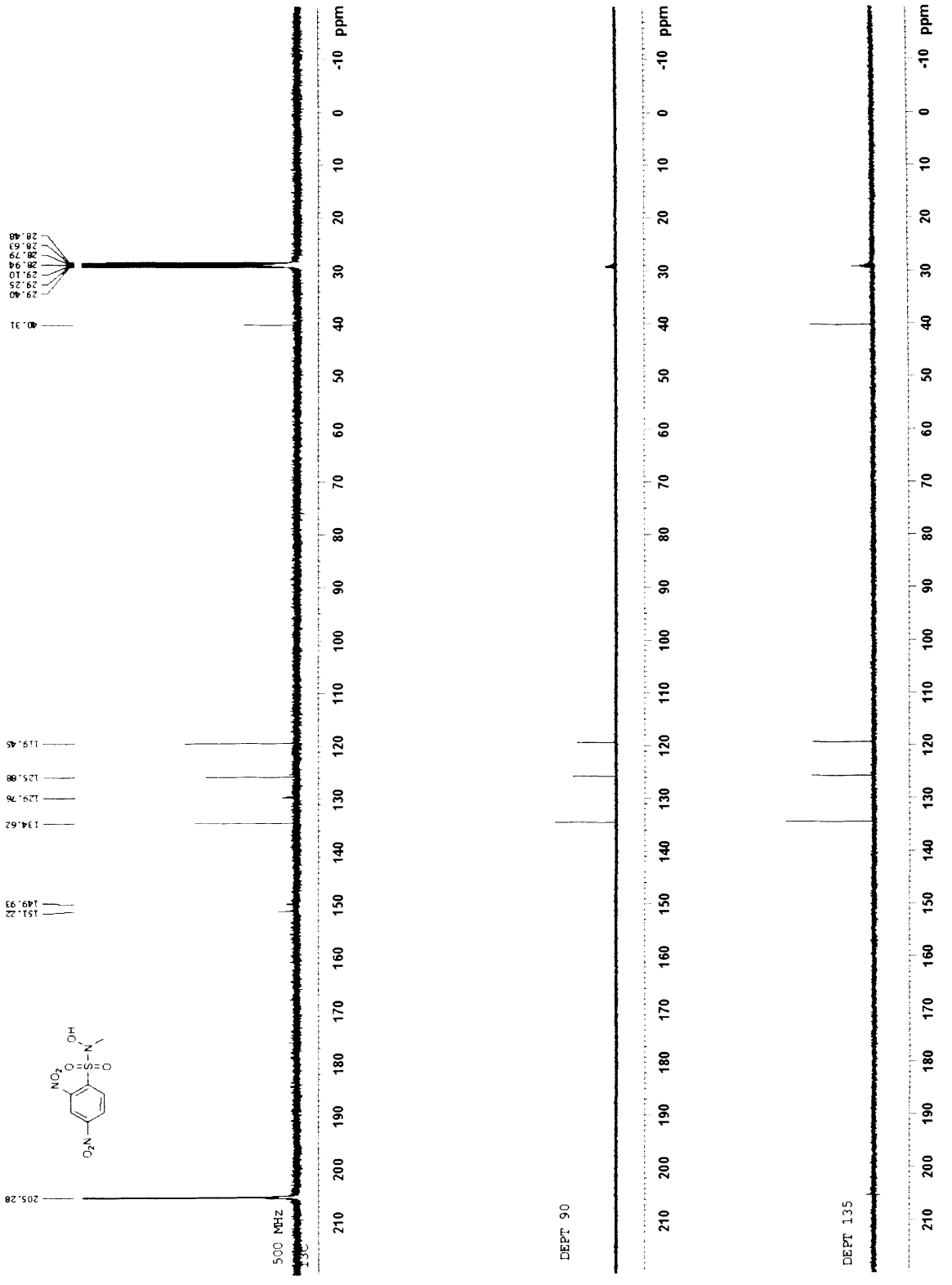

Fig. F ^{13}C Dept of **346** 125MHz, C_3D_6O

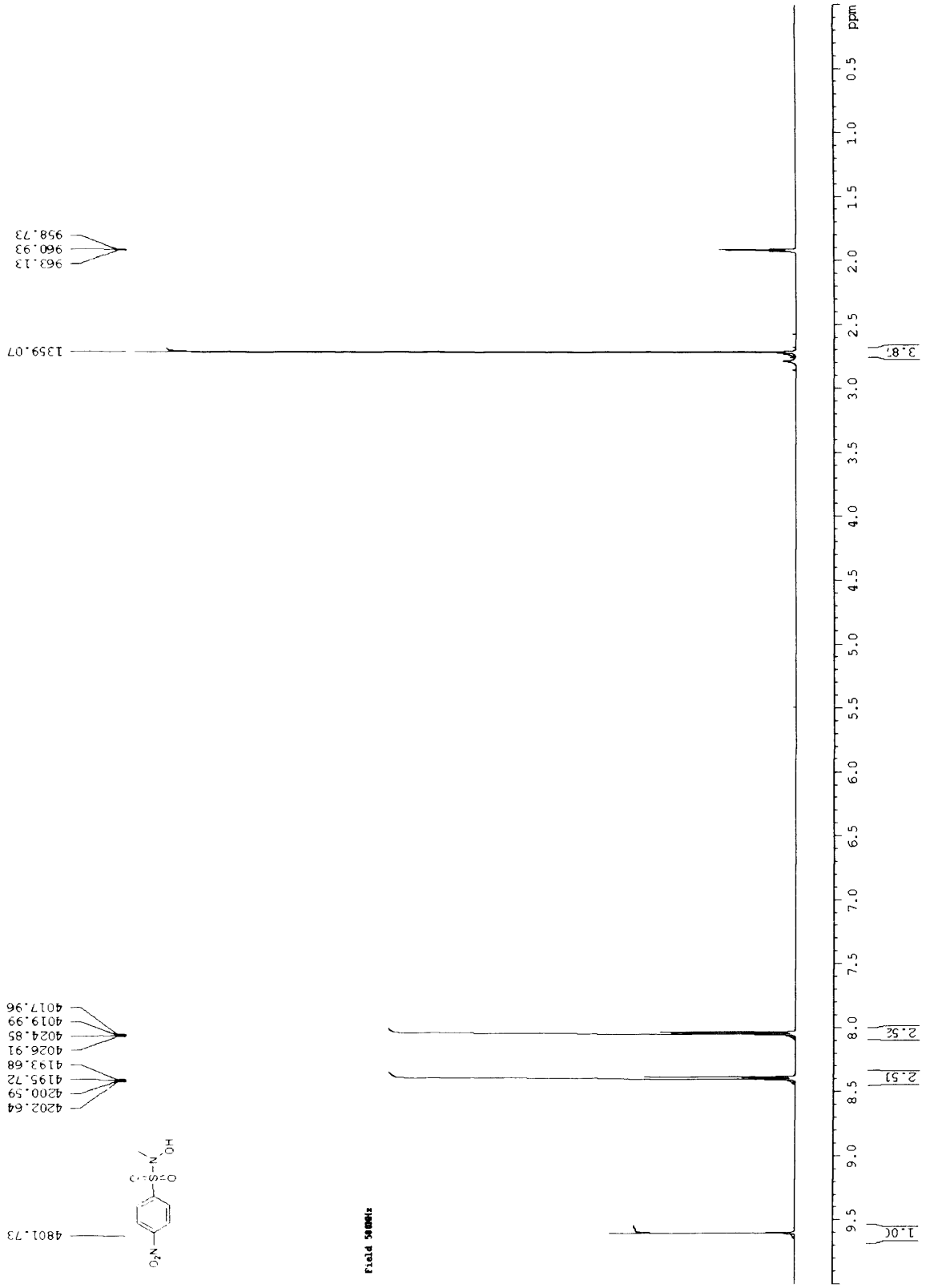

Fig. G ^{1}H NMR of **347** 500MHz, C_3D_6O

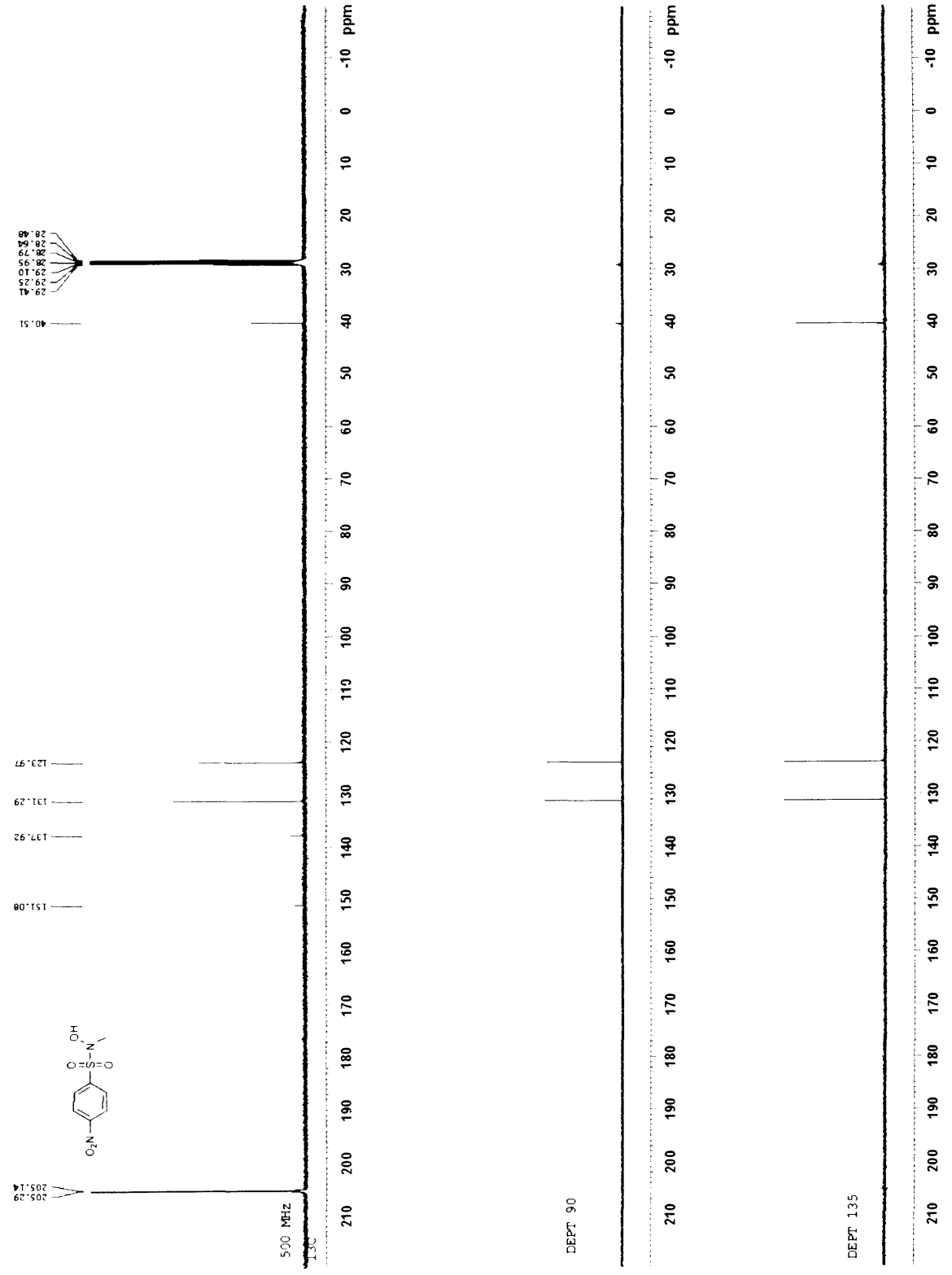

Fig. H ^{13}C Dept of **347** 125 MHz, C_3D_6O