NEW CHEMISTRY OF HYDROXYLAMINES

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Declaration

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

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Dedicated to my Mother and Father.

All my achievements are thanks to their constant love, support and encouragement.

A fact is a simple statement that everyone believes. It is innocent, unless found guilty. A hypothesis is a novel suggestion that no one wants to believe. It is guilty, until found effective.

--- Edward Teller

Science is always wrong. It never solves a problem without creating ten more.

--- George Bernard Shaw

Abstract

This thesis consists of the exploration of a novel oxygenation procedure and its applicability in the preparation of synthetically useful compounds.

Chapter **1** provides a review of methods for the preparation of *N*-aryl hydroxylamines.

Chapter **2** focuses on the development of a novel α-oxygenation procedure. It describes work previously carried out within the group and continues with exploration of the scope of the transformation. It describes the development of a novel family of reagents which are synthesised by one of three methods.

Chapter **3** describes the first method for the direct introduction of a carbamate and carbonate functionality α- to a carbonyl group by modification of our generic reagent. Additionally, it explores how by simple variation of the reaction medium oxazolidinone heterocycles can be accessed.

Chapter **4** examines the use of the α-oxygenation procedure followed by reduction and reductive amination protocols to synthesis 1,2-mono protected diols and 1,2-amino alcohols.

Chapter **5** discusses an investigation into the design and synthesis of a number of precursors to hydroxylamine reagents with the potential to introduce a phosphonate group α- to a carbonyl functionality.

Finally, *Chapter* **6** concentrates on the development of conditions for coupling hydroxylamines to aryliodides. It describes the preparation of a family of hydroxylamine reagents withdifferent protecting groups on both the nitrogen (Boc) and oxygen (methyl, benzyl, tetrahydropyran), to couple into the aryliodide using copper iodide. It examines the scope of the reaction by showing the use of substrates with varying functionalities (electron-withdrawing, electron donating, aldehydes, esters, ketones, halides) in the *para*, *meta* and *ortho* positions of the aryliodide. \a brief in vestigation using the rearrangement strategy to access *ortho* hydroxyl anilines whilst utilising this coupling methodology is also examined.

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Abbreviations

Ac	acetyl
APCI	atmospheric pressure chemical ionisation
app.	apparent
Ar	aromatic
atm.	atmosphere(s)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BPO	benzoyl peroxide
b.pt.	boiling point
br	broad
Bu	butyl
cat.	catalyst
Cbz	benzyloxycarbonyl
CDI	*N,N*-carbonyldiimidazole
column chromatography	flash column chromatography
Cy	cyclohexane
d	day(s)
d	doublet
dba	dibenzylideneacetone
DCA	dichloroacetic acid
DCE	dichloroethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
Dppp	1,3-Bis(diphenylphosphino)propane
E^+	electrophile
Et	ethyl
ES	electrospray
ether	diethyl ether
EWG	electron withdrawing group
e.e.	enantiomeric excess

equiv. (eq.)	equivalent(s)
GC	gas chromatography
GLC	gas-liquid chromatography
hr.	hour(s)
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IR	infra red
k	kilo
LA	Lewis acid
LDA	lithium diisopropylamide
light petrol	petroleum ether 40–60 °C
Lit.	literature
LUMO	lowest unoccupied molecular orbital
M	molar
m	mass
m	multiplet
Me	methyl
min.	minute(s)
mmol	millimole(s)
NMR	nuclear magnetic resonance
MO	molecular orbital
mol	mole(s)
mp	melting point
MHz	megahertz
MS	mass spectrometry
Ms	mesyl
NCS	*N*-chlorosuccinimide
n	*normal*
n.d.	not determined
NOESY	nuclear Overhauser enhancement spectroscopy
p	*para*
p	pentet

PEPPSi	**P**yridine **E**nhanced **P**recatalyst **P**reparation **S**tabilization and **I**nitiation
Ph	phenyl
PPTS	pyridinium *para*-toluene sulfonate
PMP	*p*-methoxyphenyl
Pr	propyl
q	quartet
quant.	quantitative
RDS	rate determining step
rt	room temperature
s	singlet
sept.	septet
sol^{n}.	solution
t	tertiary
t	triplet
TBAB	tetrabutyl ammonium bromide
tert	tertiary
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
Ts	tosyl
*p*TSA	*para*-toluene sulfonic acid
vol.	volume(s)
vs.	Versus
w/w	weight to weigt
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
z	charge
Å	Angstroms
Δ	heat
σ	sigma
*	chiral

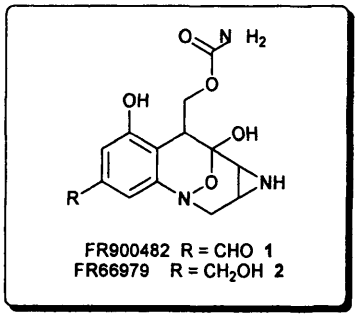
Chapter 1

N-Aryl Hydroxylamines

1.1 Introduction

Organic chemistry is central to everyday existence.[1] One of the most fundamental contributions that can be made is through the pharmaceutical industry. The organic chemist's role is to aid the development of novel methods for synthesis with efficiency, mild conditions, clean and selective procedures,[2] especially those that eliminate problems associated with anhydrous, anaerobic conditions and toxic reagents. This can be applied to the synthesis of candidate drug molecules.

Aryl hydroxylamines are an extremely significant class of compounds that are key building blocks in natural product synthesis and within preparation of biologically active compounds such as *N*-aryl–*N*–hydroxyformamides (Scheme 1).[3]



FR900482 R = CHO 1
FR66979 R = CH_2OH 2

Scheme 1

Additionally, they are used as intermediates in the production of fine chemicals[4] and nitrogen containing heterocycles.[5] There is also particular interest in the construction of *N*-aryl hydroxylamine derivatives due to pharmaceutical applications.[6] Many *N*-aryl hydroxylamines are explosive over 90 °C and decompose rapidly upon storage. Following this, particular care must be taken in the work-up stage due to their instability. Often *N*-aryl hydroxylamines are not isolated prior to reaction.

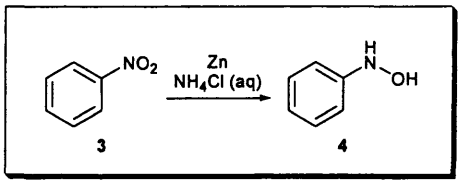
This is a general review of all the different methods currently available to prepare this important class of compound and some of their advantages and limitations.

1.2 Reduction of nitro compounds

Historically, the nitro group was one of the primary functional groups to be reduced due to the simplicity of nitro reduction. This reaction can be facilitated by several reagents and various conditions. The conventional methods for the formation of aryl hydroxylamines from aryl nitro derivatives are essentially:

1) Zinc metal aqueous ammonium chloride.[7]
2) Electrolytic reduction.[8]
3) Raney nickel and hydrazine at 0–10 °C.[9]

In general, reduction of nitro aromatic compounds is possible using zinc metal together with ammonium chloride in an aqueous suspension (Scheme 2). Kamm first discussed this frequently used method of preparing *N*-aryl hydroxylamines although often yields are not reported.[7,10] This is because of the high reactivity of the hydroxylamine derivatives produced which are frequently entered into the next step without isolation or further purification. Optimum results are often obtained when the reaction temperature is 65–70 °C.



Scheme 2

Although traditional methods for synthesising *N*-aryl hydroxylamines stem from careful reduction of nitroarenes tedious work-ups are often involved and strict conditions are required for control.[7]

Other reduction techniques for the preparation of these compounds have included using the corresponding nitro aromatic compounds in conjunction with both catalytic transfer hydrogenation and metal mediated reduction.[9,11] These procedures often involve using catalytic amounts of precious metals (palladium, rhodium, iridium or Raney nickel) together with hazardous reagents (metallic selenium or tellurium with sodium borohydride or bismuth chloride with potassium borohydride).[12] SmI_2, N_2H_4–Rh–C and $KBH_4/BiCl_7$ are just a few

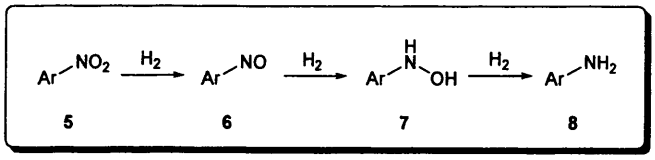
examples of reagents by which aromatic nitro compounds are reduced to their hydroxylamine analogues.

Problems associated with these approaches are often due to the aromatic nitro compounds over-reducing to the aniline. This can subsequently lead to unwanted hydrazines and azoarene byproducts forming. Selective access to the hydroxylamine by reduction of nitro groups is extremely difficult to control. These methods offer the additional limitations with requirements of high pressure conditions and flammable hydrogen gas presenting a need for alternative preparations for the *N*-aryl hydroxylamines.

The different methods for reducing nitroarene compounds to their *N*-aryl hydroxylamine derivatives are discussed below.

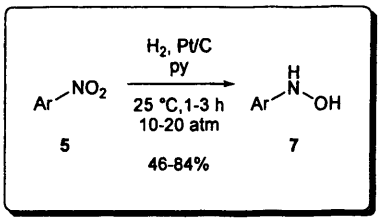
1.2.1 Catalytic Reduction

N-aryl hydroxylamines can be successfully prepared by the catalytic reduction of nitroarenes **5** via the nitrosobenzene intermediate **6** (Scheme 3). Adopting suitable reaction conditions prevent over-reduction to the aryl amine **8** such that the reaction stops at the *N*-aryl hydroxylamine **7** stage.



Scheme 3

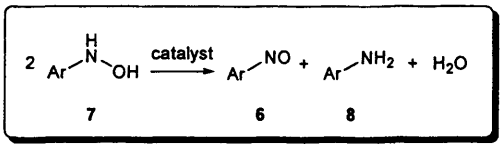
Nitroarenes are reduced effectively with catalytic amounts of platinum with addition of either an organic nitrogen base (piperidine, pyrrolidine, pyridine) or an organic phosphorous (tri or penta valent) compound to produce the *N*-aryl hydroxylamine **7** with good yields (Scheme 4).[13]



Scheme 4

Benefits of this method over electrochemical reduction are the avoidance of waste disposal and cost efficiency. Additionally, the problems associated with over-reduction can be controlled by selectively monitoring the catalyst and solvents.

N-aryl hydroxylamines can be explosive due to their disproportionation into aryl amines, water and nitrosobenzene[14] (Scheme 5) which occurs on the catalyst surface when no hydrogen is present.[15]



Scheme 5

Using dimethylsulfoxide,[16] divalent sulfur compounds,[17] organic bases[18] or phosphorous compounds[19] reduces the rate of disproportionation but results in prolonged reaction times. When there is addition of acetic acid or its derivatives along with one of these compounds it leads to high rates and high selectivity.[20]

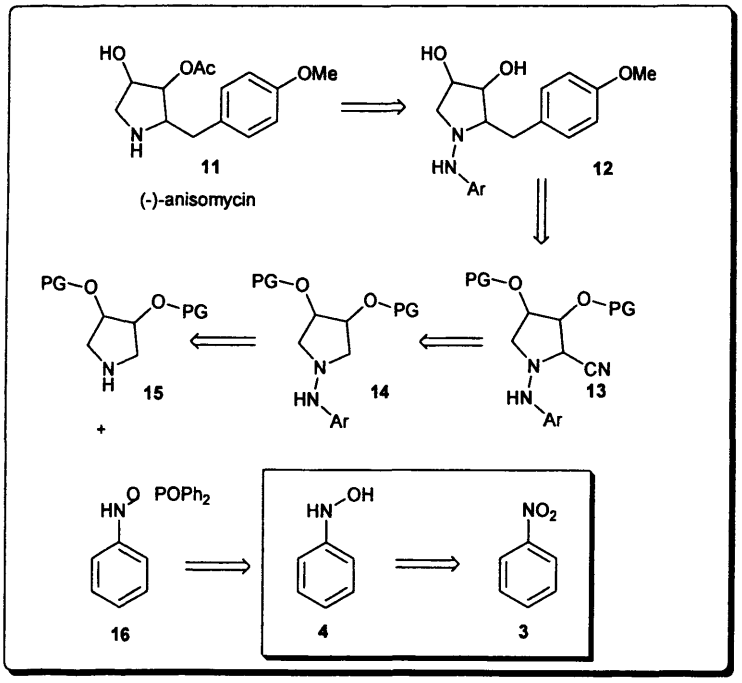
1.2.2 Using Hydrazine

Under the particularly milder conditions of hydrazine hydrate, nitroarenes can be selectively reduced to the corresponding *N*-aryl hydroxylamine **10** in the presence of a catalyst (palladium, iridium, rhodium).[9] The reaction will proceed with a variety of substituents on the aromatic ring e.g. R^1 = Me, Cl, CF_3, OMe and R^2 = H, Me, Cl, and R^3 = H, Cl, OMe. Optimum results are achieved in tetrahydrofuran in either water or ethanol mixtures.

1.2.4 Ultrasound

Ultrasound can create, expand and crack bubbles in ultrasonic irradiated liquid.[23] There is a lot of literature precedent for the use of ultrasound irradiation to enhance various reactions by electron transfer mechanism or radical routes.[24] Advantages of ultrasound technology include energy efficiency, enhanced rates, improve yields, replacement of phase-transfer catalysts and at times they can display positive results for reactions that usually are practically impossible.

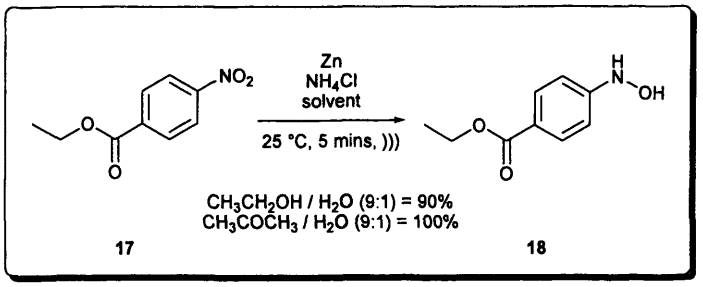
The Ferroud group embarked on forming *N*-aryl hydroxylamines as precursors in the synthesis of the anti tumour substance (–)–anisomycin (Scheme 8) and its selective preparation is a key step within the procedure.



Scheme 8

They reported an efficient, selective process to reduce nitro aromatics to their corresponding hydroxylamines at room temperature with the aid of ultrasound technology.[25]

Optimum conditions developed using 4–hydroxyamino–benzoic acid ethyl ester **17**, as the substrate under investigation, were found to be 2.1M equivalents of zinc in an ethanol/water (9:1) solvent mixture in the presence of ammonium chloride (Scheme 9).



Scheme 9

Total conversion was observed within a few minutes with ultrasound activation to give the *N*-aryl hydroxylamine **18** in high yield of 90% and 99% purity.

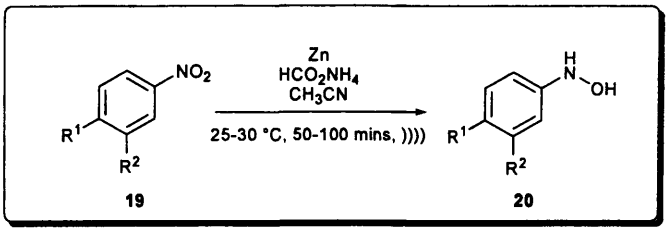
Due to solubility problems in later research the solvent ethanol was substituted by acetone, which improved the process to give a quantitative yield of **18** without loss of purity,

The functional group tolerance was wide, including esters, chlorides and trifluoromethyl functionalities on the nitro aromatics, all producing good to excellent yields with >95% purity of the crude product.

Substrates bearing electron-withdrawing substituents gave almost quantitative yields with excellent purity. Additionally, these conditions worked well for electron-donating substituted nitro aromatics, *p*–methyl and *p*–methoxy. However, the *N*-aryl hydroxylamines formed from these substrates were particularly unstable and transformed into a mixture of over-reduced products.

This report displays how ultrasound irradiation can be used as a viable, high yielding alternative technique for the selective preparation of *N*-aryl hydroxylamines from nitro aromatics with reduced reaction times. Additionally, this method is attractive due to the economical and environmental benefits by use of the inexpensive, non-toxic zinc reagent. Problems associated with this method reside in the fact that the zinc dust must be added slowly in portions.

Subsequently, the Lu group presented a simple $Zn/HCOONH_4/CH_3CN$/ultrasonic system to prepare *N*-aryl hydroxylamines **19** from aromatic nitro compounds (Scheme 10).[26] These conditions were a surprise as previously the $Zn/HCOONH_4$ combination had been found to rapidly and efficiently reduce nitro aromatics directly to the corresponding aniline.



Scheme 10

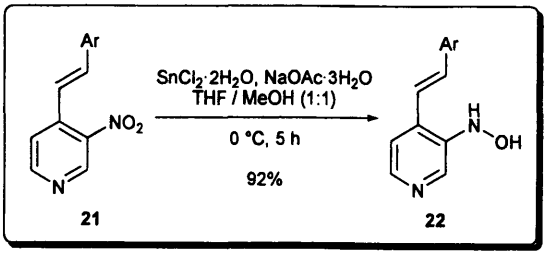
To explore the applicability of this transformation a wide scope of substrates were examined. The reaction was found to tolerate a number of sensitive functionalities on the aromatic nitro compounds such as ketones, nitriles, esters and chlorides with excellent yields and high chemoselectivity. Over-reduction to the aryl amine was again prevented by careful addition tion of the zinc dust. In some cases the aryl amine was observed, but the purity of the crude reaction product was still above 90%.

To examine the exact effect of the ultrasound on the transformation 4–nitrotoluene was reacted under the same conditions without the ultrasound irradiation. The reaction proceeded much slower with the reaction time extended from 1 hour up to 12 hours with evidence of the starting material remaining.

This provides a mild, efficient, chemoselective, simple manner in which to prepare *N*-aryl hydroxylamines with excellent yield from nitro aromatics.

1.2.5 Using Tin(II) Chloride

Using tin(II) chloride as a reagent is a less exploited method for this transformation and only a few specific examples of where it is used to reduce nitroarenes are reported.[27]

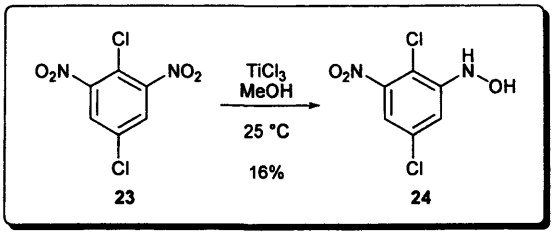


Scheme 11

One of these uses tin(II) chloride and sodium acetate to reduce the 3-nitro-4-styrylipyridine **21** to the *N*-pyridylhydroxylamine **22** (Scheme 11).[28]

1.2.6 Titanium(III) Chloride

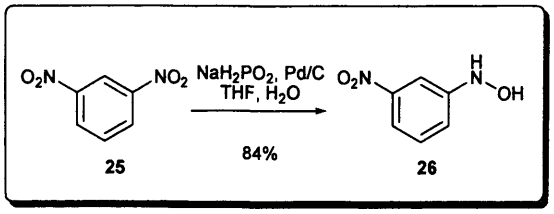
There is very little literature precedent for using titanium(III) chloride to generate *N*-aryl hydroxylamines from nitroarenes. The reaction has been shown to be effective in methanol, although yields of hydroxylamine product are low (Scheme 12).[29]



Scheme 12

1.2.7 Using Hypophosphites

Treating nitroarenes with hypophosphoric acid or its derivatives is another mild route for the synthesis of the aryl hydroxylamines in tetrahydrofuran and water with palladium on charcoal (Scheme 13).[30] This method is tolerant of a number of different functional groups including hydroxylamine, halo, carbamoyl and alkenyl to name just a few.[11b] It is important to note that even when two nitro groups are present on the substrate only one is reduced under these reaction conditions.

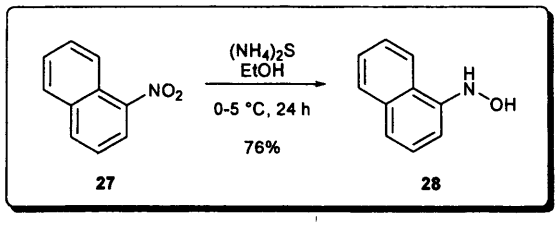


Scheme 13

1.2.8 Using Ammonium Sulfide

These conditions are effective to reduce nitro substituted fused ring systems such as nitronaphthalenes **27** to their corresponding hydroxylamine analogues **28**.[22] A general

procedure includes reacting the substrate with ammonium sulfide in ethanol at a temperature of 0–5 °C (Scheme 14).



Scheme 14

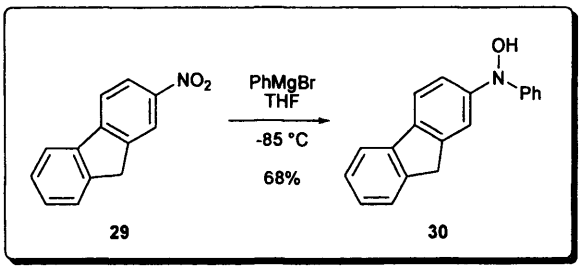
1.2.9 Using Borohydrides

The use of alkali metal borohydrides as reducing agents in organic chemistry is well documented and has been widely used as an economical and mild reducing agent in the reduction of carbonyl groups as well as other unsaturated compounds.[31] Sodium borohydride is found to be highly desirable in comparison with other reducing agents as it is mild and a more selective reagent which can effectively reduce nitroarenes to the hydroxylamine derivatives when reacted in methanol with 50 mol% antimony powder.[32] Additionally, for the reduction of nitro functional groups the reducing power of sodium borohydride can be varied over a wide range. It can be achieved by mixing the sodium borohydride with metal salts such as LiCl, $AlCl_3$, $CoCl_2$, $MgCl_2$, $TiCl_4$, BF_3, I_2, thiols such as ethanethiol, carboxylic acids such as acetic acid, trifluoroacetic acid and quaternary ammonium salts.

It has also been shown that *N*-aryl hydroxylamines can be similarly prepared in excellent yields using potassium borohydride with antimony(III) chloride in aqueous ethanol.[33]

1.2.10 With Grignard Reagents

It has been shown that phenyl magnesium bromide can convert nitroarenes, nitrobiphenyls and nitroterphenyls to their corresponding *N*-aryl-*N*-phenyl hydroxylamines using diethyl ether and tetrahydrofuran as the solvent mixture at –85 °C (Scheme 15).[34] *N*-Alkyl-*N*-phenyl hydroxylamines can be prepared under similar conditions with the addition of dry cerium(III) chloride and quenching the reaction with acetic acid at the slightly elevated temperature of –40 °C.[35]

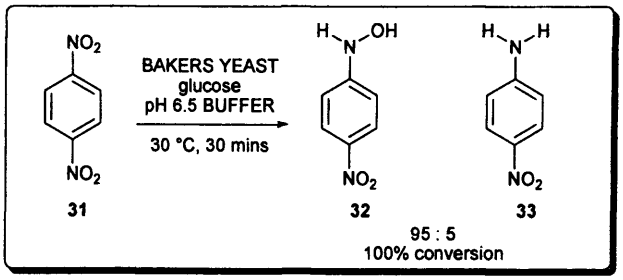


Scheme 15

1.2.11 Using the Biocatalyst Baker's Yeast

A lot of interest has been focused upon using the whole-cell biocatalyst baker's yeast to reduce carbonyl compounds asymmetrically.[36] A variety of novel applications of baker's yeast have also been reported. More recently, research has been focused upon using it to transform aromatic nitro compounds to amines. It had been noted that by using this method the hydroxylamine intermediate was never obtained. However, Cui and co-workers have reported a novel method for the chemoselective reduction of an aromatic nitro compound to the hydroxylamine counter-part enzymatically using baker's yeast. This provides a mild, simple, efficient and environmentally sound method of preparation for this extremely important class of compound.

It was discovered that the chemoselectivity of the reduction relied heavily on the amount of baker's yeast used within the reaction. The optimum conditions were found to be 5% w/w of the baker's yeast to substrate (Scheme 16).[37]

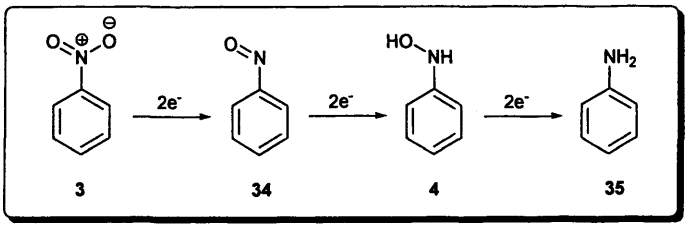


Scheme 16

The scope of this reaction was investigated by successfully reducing several electron withdrawing substituted nitroarenes such as acetyl, methyl sulfonyl and cyano groups to produce the hydroxylamines. Additionally, halide substituent's also delivered the corresponding hydroxylamine with good selectivity under the standard conditions. In general,

it was observed that increasing the number of electron withdrawing groups on the aromatic substrate increased the rate of hydroxylamine formation. Unfortunately, reduction of nitroarenes bearing electron donating groups was unsuccessful using this method.

The proposed mechanism for this transformation is outlined in Scheme 17. It is thought that the aromatic nitro group **3** is first reduced by 2 electrons to form the nitroso intermediate **34** which accepts another 2 electrons to form the aryl hydroxylamine **4**. The N–O bond of the hydroxylamine is thought to be strengthened by electron withdrawing substituents on the substrate disfavouring further reduction.



Scheme 17

Additionally, the nitroso intermediate **34** was not detected. This wasn't entirely unexpected due to the highly reactive and unstable nature of these compounds.

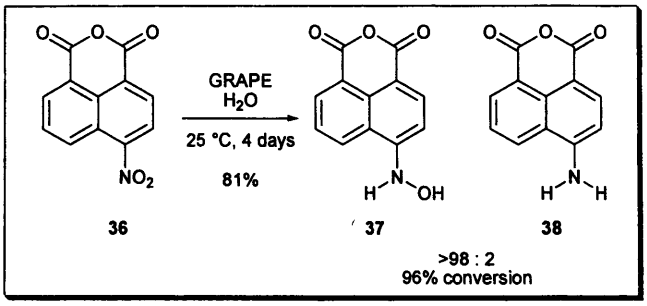
This was the first method reported for the biological preparation of *N*-aryl hydroxylamines.

1.2.12 Using Grape Extracts

As part of their continuing development of biocatalytic methods to reduce the nitro functionality the same group later reported the highly chemoselective reduction of aromatic nitro compounds using plant cells of a grape to generate the *N*-aryl hydroxylamines (Scheme 18).[37] Previously, there had been no reports of using plant cells despite the precedent of their use within many organic reactions including hydroxylation, hydrolysis, oxidation of alcohols and reduction of ketones amongst others.[38]

Initial studies were completed on 4-nitro-1,8-naphthalic anhydride **36** as the substrate using a variety of plant cells under conventional conditions. It was observed that all tests apart from garlic and cactus were successful at the reduction although the ratio of hydroxylamine **37** and amine **38** produced by each plant species varied significantly. The

grape cells appeared to exhibit the optimum results with high reactivity and selectivity towards the desired hydroxylamine product.

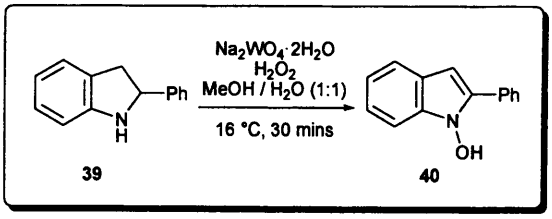


Scheme 18

It was observed that using grape extracts offered a unique advantage as it eliminates the need for strict reaction times and the amount of enzyme was irrelevant, which usually varies for most enzyme catalysed reactions.

1.3 Oxidation of *N*-Aryl Amines

There appears to be only one method for the oxidation of an aryl amine to an *N*-aryl hydroxylamine which uses the dihydroindole **39** as the substrate to give the *N*-hydroxyindole **40** (Scheme 19).[39] This transformation is carried out by use of sodium tungstate as the oxidising agent. It is surprising that this method of formation of *N*-aryl hydroxylamines has not been exploited further.

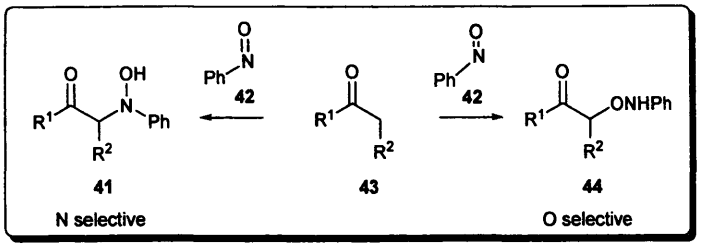


Scheme 19

1.4 Synthesis from Nitrosobenzene

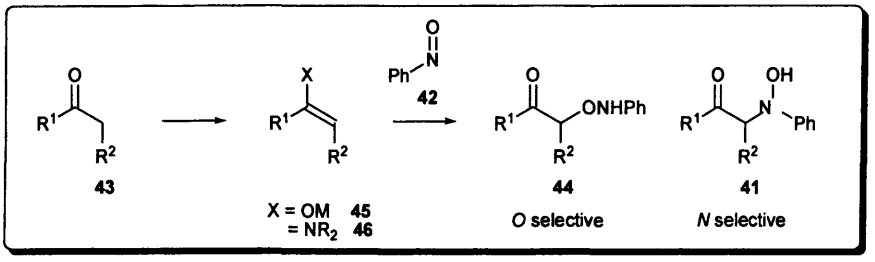
'Nitroso aldol' type reactions in the preparation of *N*-aryl hydroxylamines

One viable method for the preparation of *N*-aryl hydroxylamines is by means of commercially available nitroso reagents in an *N* or *O* selective 'nitroso aldol' manner depending on the conditions adopted (Scheme 20). In these reactions the functionalit y incorporated into the final compound is determined by the nitroso starting reagent and the reaction conditions.



Scheme 20

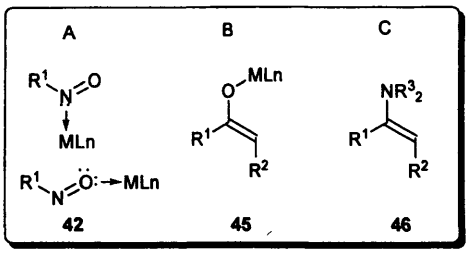
The transformation consists of reacting an enolate **45** (or enamine **46**) with an electrophilic nitroso compound **42** (Scheme 21). The enolate can either be generated *in situ* by using a Lewis acid and a base to perform 'soft' enolization or using preformed silyl enol ethers.



Scheme 21

Both Lewis acids and Lewis bases can catalyse the reaction. Chiral Lewis acids can influence stereochemistry in the product and encourage the reaction by two methods (Scheme 22). Firstly, by activation of the nitroso benzene by co-ordination to the nitrogen or oxygen that then generates the electrophilic species (A) or alternatively a chiral metal enolate can be formed from the chiral Lewis acid metal complex (B). It is also possible that both scenarios can occur. Chiral Lewis bases catalyse the reaction by reversibly forming a chiral enamine (C). In this case, the stereochemical induction is imported by the chiral enamine reacting with

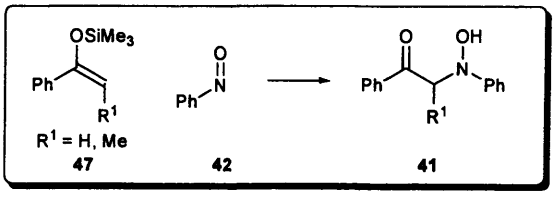
the electrophile. Simple hydrolysis of the iminium product provides the carbonyl and releases the catalyst.



Scheme 22

We are particularly interested in this class of nitroso transformation as not only are *N*-aryl hydroxylamines, formed but the reaction type can also regarded as either an amination or oxygenation of carbonyl compounds.[40] The oxygenated product **44** has also generated interest due to the simple conversion of the product to hydroxyl carbonyl products to useful synthetic intermediates. This topic overlaps nicely with the other section of my research, developing a novel α–oxygenation procedure of carbonyl compounds which will be discussed in detail in the Chapter 2.

Sasaki presented an effective condensation of nirosobenzene and silyl enol ethers at room temperature to form the *N*-aryl hydroxylamine derivative **41** (Scheme 23).[41] However, this procedure has significant limitations due to the fact that very few aromatic ketone enolate substrates gave the required product.

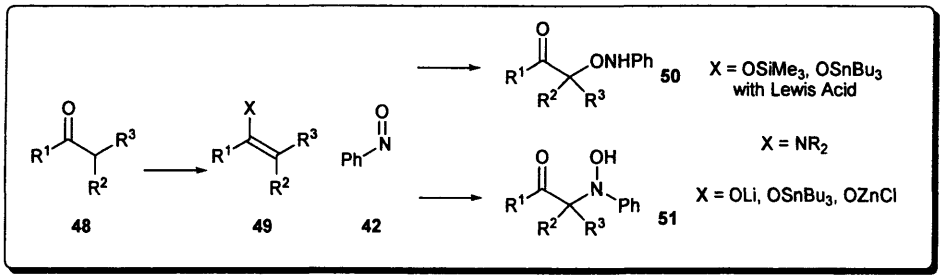


Scheme 23

Although this appears to be a simple and important technique for preparation of this class of compound previous to this work there was limited research into this method.

1.4.1 Chiral Lewis Acids

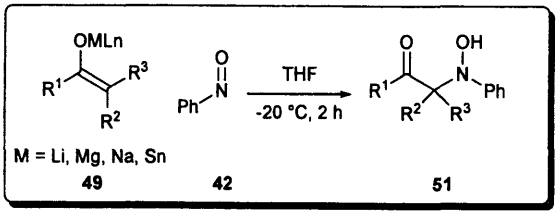
Nitroso benzene has shown success in a number of reports as a versatile electrophile in nucleophilic additions. Similarities in reactivity of nitroso benzene with aldehydes have shown it to be a good comparative nitrogen equivalent. Significantly, it can be observed that the nitroso benzene can either be attacked at the nitrogen or the oxygen to α-aminate or α-oxygenate the carbonyl depending on the conditions (Scheme 24). Specifically as to whether the reaction is carried out in the presence of a catalyst or the origin of the enolate.[42]



Scheme 24

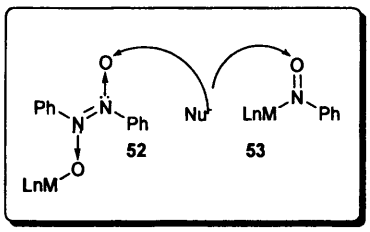
A simple synthesis of synthetically important α-hydroxyamino carbonyl compounds was reported by Momiyama and Yamamoto which expanded the concept of reacting nitroso substrates with enolates to generate the *N*-aryl hydroxylamine derivatives. The drive behind this paper was to utilise the 'nitroso aldol reaction' to introduce a nitrogen atom α– to a carbonyl group.

Furthermore, Hisashi, Yamamoto and co-workers explored the *N*-selective 'nitroso aldol' reaction in the absence of a chiral Lewis acid by using tin(IV), lithium and zinc(II) enolates (Scheme 25).[43]



Scheme 25

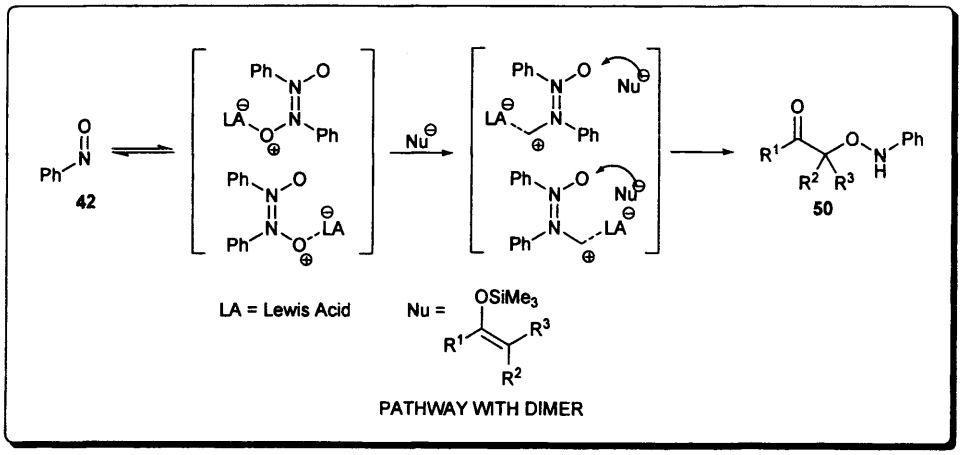
By using a chiral Lewis acid within the reaction selectivity alternates to give primarily the oxygenated product from silyl enol ethers and tin(IV) enolates. The differing selectivity can be associated with the rapid formation of a nitroso benzene dimer when the Lewis acid is added to the reaction. By co-ordination of the metal at one of the oxygen atoms it activates the other oxygen atom to nucleophilic attack therefore encouraging the formation of the oxygenated product.



Scheme 26

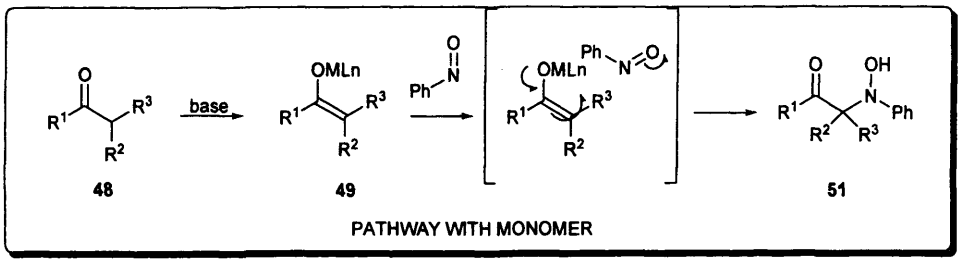
Investigations indicated the formation of the dimer (**52**) but did not completely eliminate the possibility of the monomer (**53**) being the active species although ancillary evidence suggest the dimer. This can be rationalised by the idea that co-ordination of the Lewis acidic metal at one of the oxygen atoms results in increasing the susceptibility of the other oxygen for nucleophilic attack resulting in the *O*-adduct being produced.

These two viable mechanistic routes are displayed in detail below. Firstly, is the suggested pathway involving the formation of the dimer (Scheme 27).



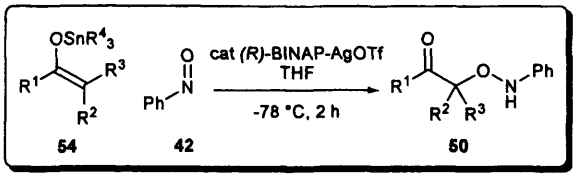
Scheme 27

Whereas the monomer route is thought proceed as shown below (Scheme 28);



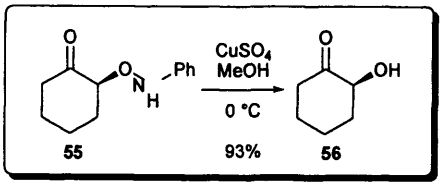
Scheme 28

This group subsequently developed the first Lewis acid catalysed asymmetric nitroso aldol process. They reacted a tin(IV) enolate of a ketone **54** with nitrosobenzene **42** with excellent regioselectivity with a catalytic amount of BINAP-AgOTf complex to generate the oxygenated product **50** >92% yield and 82–99% e.e. (Scheme 29).[44]



Scheme 29

The α–hydoxy ketones **50** prepared contain the fundamental *N*-aryl hydroxylamine that we were interested in. These type of *N*-aryl ketone compound are usually precursors of chiral hydroxy ketones. Yamamoto and co-workers reported using catalytic amounts of copper(II) sulphate (30 mol%) as an extremely effective method to cleave the N-O bond without any racemisation (Scheme 30).[46]



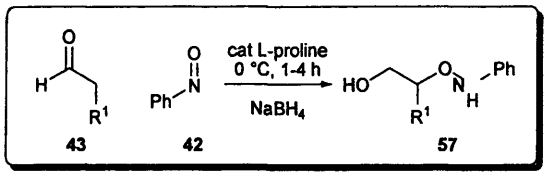
Scheme 30

1.4.2 Chiral Lewis Bases

Previous 'nitroso aldol' reactions to α-oxygenate carbonyl compounds with chiral Lewis acids have required stable metal enolates as substrates. Alternatively, enamines can react with nitroso benzene. There is a large amount of literature reporting the use of chiral Lewis bases as catalysts within aldol reactions by reversible formation of enamines. It was

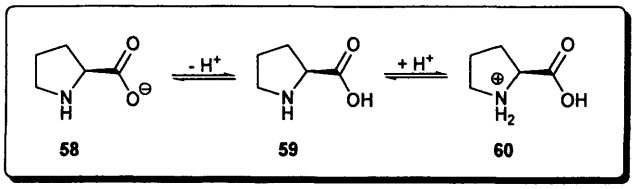
therefore not surprising there was considertable interest in the use of chiral Lewis bases within the 'nitroso aldol' reaction.

Hayashi and co-workers developed a direct L-proline catalysed enantioselective method for the α–aminooxylation of ketones and aldehydes[45] with nitroso compounds to afford the key *N*-aryl hydroxylamine functionality (Scheme 31).



Scheme 31

Proline[46] has been of significant interest due to its large applicability as an excellent asymmetric catalyst in a wide variety of organic reactions over recent years such as the aldol,[47] Mannich[48] and α–amination of carbonyls.[49] Its bifunctional properties allow it to act as either an acid or a base due to the acid and amine fragments within the molecule (Scheme 32).



Scheme 32

Along with the Hayashi report two other groups simultaneously published their findings within the proline catalysed addition of nitroso benzene to aldehydes. MacMillan[50] and Zong[51] reported similar findings with the subtle difference of solvent choice and substrate selection.

The advantage of using proline Lewis base catalysis is that it negates the need to preform metal enolates. Furthermore, due to the mild reaction conditions these methods are even more attractive.

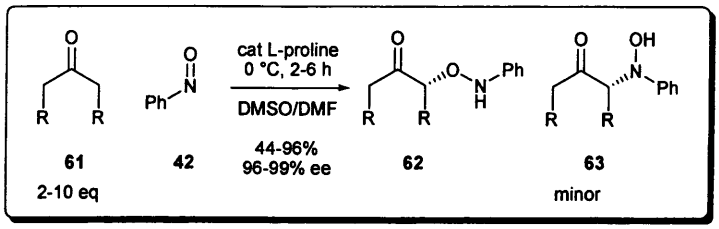
Catalytic amounts of proline can therefore successfully promote the reaction of nitroso benzene with several enolisable aldehydes with varying functionality to produce the α–oxy aldehyde in >80% yields and >95% ee. Subsequently, the diol is formed by addition of

$NaBH_4$ to the product. This is necessary due to the oligomeric nature of the α–oxyamino aldehydes.

A variety of aldehyde substrates were used with varying functional groups. MacMillan reported chloroform as the optimum solvent choice with a catalyst loading as low as 1 mol% with negligible difference in reactivity.

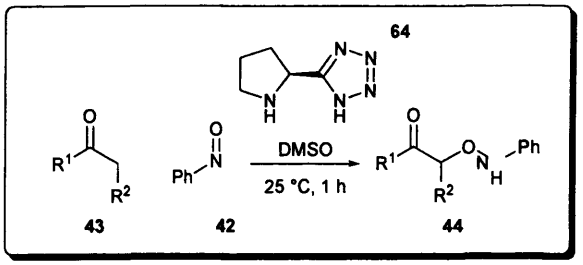
Ketones proved to be more difficult substrates to undergo this 'nitroso aldol' reaction which sparked a lot of interest within the Hayashi and Córdova groups.[52] Prevention of di-functionalisation using substrates with two enolisable positions proved challenging.

It did prove possible to prevent C_2 symmetric products of ketones forming, however, it meant prolonged reaction times of up to 3 days (Scheme 33). This involved slow addition of nitroso benzene by syringe pump with an excess of ketone (up to 5 equivalents). Applying these conditions to symmetrical ketones proved extremely effective giving the products with complete regio and stereo-selectivity. Altering the substrate to incorporate non-symmetrical ketones resulted in preferential selectivity at the more substituted carbon. This is presumably due to the stability of the enamine intermediate.



Scheme 33

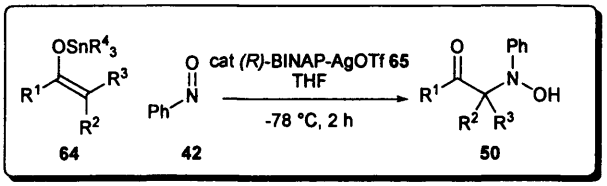
Yamamoto subsequently reported an elegant and efficient proline tetrazole based catalyst **64** for this transformation that gave excellent yields (66–97%) and enantioselectivity for both aldehyde and ketone substrates (Scheme 34). This catalyst also eliminates the problems previously associated with ketones.



Scheme 34

This catalyst reduces reaction times required and catalyst loading can be reduced to as low as 5 mol% without significant loss in activity.

1.4.3 Amination by Chiral Lewis Acids



Scheme 35

Interestingly, Yamamoto has shown chemioselectivity in the 'nitroso aldol' reactions can be reversed by using a combination of Ag(I) triflate and *(R)*-BINAP as the catalyst **65** (Scheme 35). Almost exclusive formation of the α–aminated product **50** can be achieved by reacting nitroso benzene **42** with a range of tin(II) enolates **64**. Highest levels of asymmetric induction were achieved using ethylene glycol diethyl ether as the reaction solvent. Suprisingly, THF provide the adduct with little enantioselectivity.

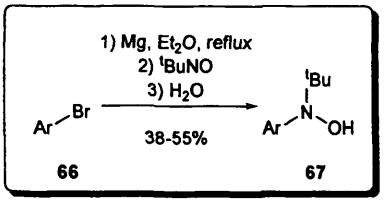
Although no explanation was provided for this change in reactivity, the overall transformation provides a useful complementary synthetic strategy.

1.4.4 Amination Catalysed by Chiral Lewis Bases

In the previously reported examples of L-proline catalysed 'nitroso aldol' reactions with nitroso benzene a high chemoselctivity for attack at the oxygen is observed. The oxygen is thought to be more electrophilic as the nitrogen has a greater basicity and is therefore

protonated under the reaction conditions. Using nitroso benzene in a 'nitroso aldol' manner to generate α-aminated carbonyls via attack at the nitrogen position was incompatible with these conditions.

1.4.5 Reactions with Grignard and Organolithium Reagents



Scheme 36

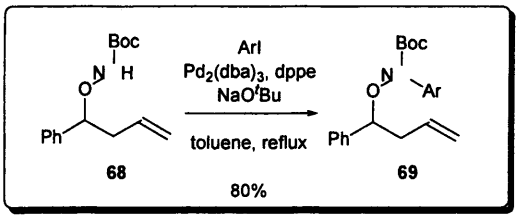
It has been reported that *N*-aryl hydroxylamines can be prepared by reacting aliphattic nitroso substrates with Grignard reagents or organolithium compounds to form 1,2 adducts which are subsequently hydrolysed to generate *N*-aryl hydroxylamine products **67** (Scheme 36).[53]

1.5 C–N Coupling

Palladium plays a central role in the formation of complex organic molecules through metal-catalysed cross coupling reactions, providing powerful methods to generate C–C, C–N, C–O and C–S bonds in excellent yields providing important building blocks for synthesis.

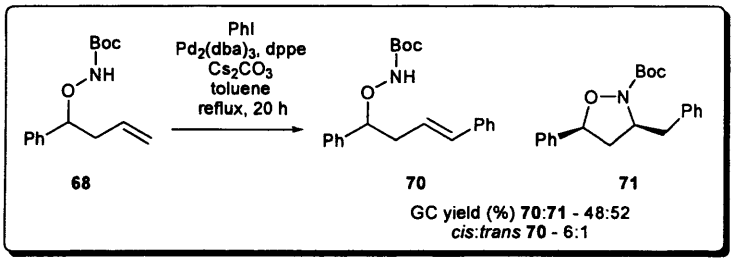
1.5.1Buchwald-Hartwig Coupling of Hydroxylamines

In 2006 the Dongol group reported the coupling of a Boc protected hydroxylamine **68** derivative with an aryl halide with a palladium source and dppe as the ligand (Scheme 37).[54] However, the conditions were not detailed in the literature due to this being an undesired byproduct.



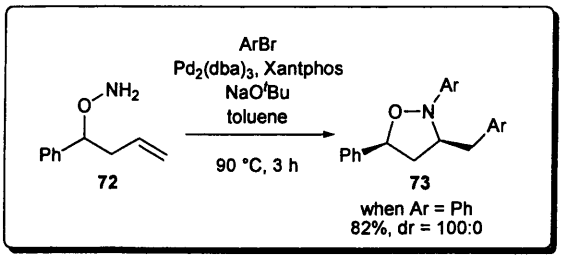
Scheme 37

Within this work the authors were developing a diastereoselective cascade reaction for the synthesis of isoxazolidine derivatives, by coupling the nitrogen to the alkene double bond in an intramolecular process, however, due to the strong base used it formed the *N*-arylated product **69**. They were able to obtain the desired product **70** by using a weaker base, caesium carbonate (Scheme 38).



Scheme 38

Subsequently, Peng reported similar chemistry to achyieve a palladium catalysed tandem arylation of *O*-homoallylic hydroxylamines **72** with 2 equivalents of aryl bromide to generate isoxazolidines **73** *via* sequential *N*-arylation/cyclisation/*C*-arylation (Scheme 39).[55]



Scheme 39

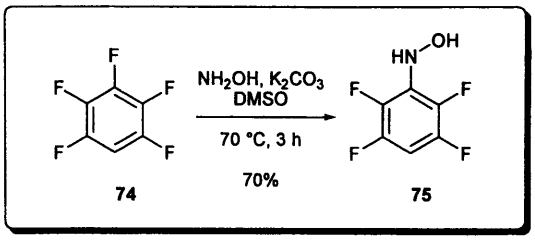
They proposed a catalytic cycle for the transformation that involved initial formation of the *N*-arylated product before subsequent steps. In this sequence they used Xantphos as the ligand choice at a slightly lower temperature of 90 °C.

1.6 Aryl Substitution of Hydrogen at the N–H of the Hydroxylamine

Within substitution reactions the nitrogen of a hydroxylamine is more nucleophilic than the oxygen so generates the *N*-adduct of the aryl hydroxylamine.

1.6.1 From Aryl and Hetaryl Halides

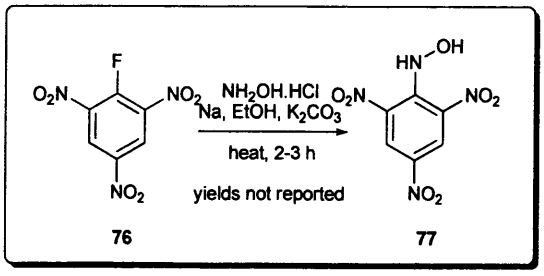
Aromatic halides bearing activated electron withdrawing groups can successfully undergo substitution reactions with hydroxylamines to produce the *N*-aryl hydroxylamines analogues, e.g. **75**.[56]



Scheme 40

1.6.2 From Hydroxy or Alkoxy Substituted Arenes

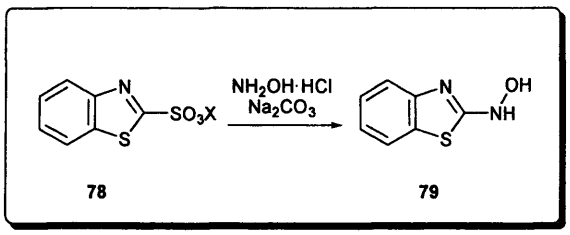
It is also possible for hydroxylamines to undergo displacement reactions when there are activated alkoxy substituents, which are g enerally poor leaving groups.[57] This is an efficient route to synthesising *N*-aryl hydroxylamines **77** and holds several advantages over using aryl halides as substrates.[58]



Scheme 41

1.6.3 From Arenesulfonate

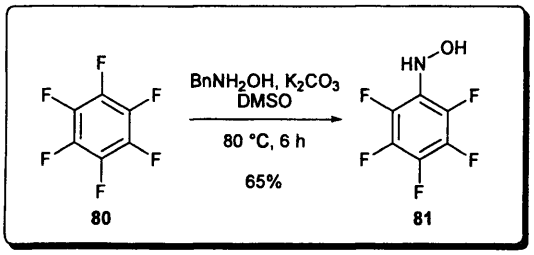
A hydroxylamine group can successfully substitute sulfonate derived heteroaromatic compounds by using hydroxylamine hydrochloride with sodium carbonate to give the *N*-aryl hydroxylamine **79** (Scheme 42).[59]



Scheme 42

1.7 Substitution reaction between *N*-benzyl hydroxylamine and hexaflurobenzene

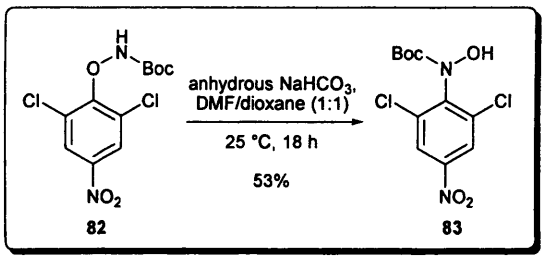
It has been reported that hexafluoroarenes and pentafluorohetarenes are suitable substrates for substitution reactions with *N*-benzyl hydroxylamine in DMSO with potassium carbonate to form the *N*-aryl hydroxylamine **81** with loss of the benzyl group (Scheme 43).[60]



Scheme 43

1.8 Rearrangement Reactions

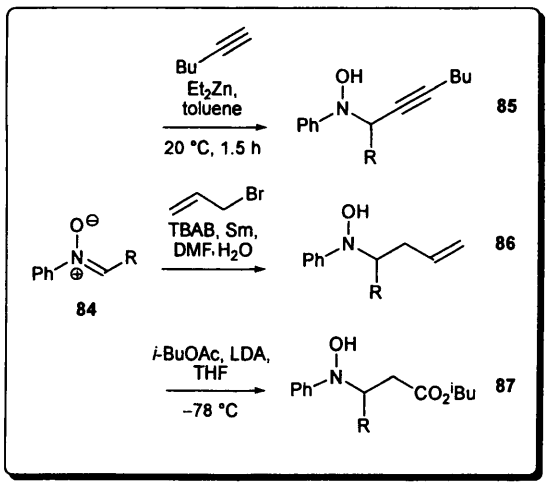
N-Aryl hydroxylamines can also be the product of base promoted rearrangement reactions. *N*-(Alkoxycarbonyl)-*O*-(nitrophenyl) hydroxylamine **82** undergoes rearrangement with anhydrous $NaHCO_3$ in a mixture of DMF and dioxane as the solvent. It results in the aryl ring migrating from the oxygen to the nitrogen to form the *N*-aryl hydroxylamine **83**.[61]



Scheme 44

1.9 Nucleophilic Additions to Nitrones

There has been extensive research into using *N*-aryl nitrones as starting materials to generate *N*-aryl hydroxylamines by nucleophilic addition (Scheme 45).[62] Variation of the reagents reacted with the nitrone provides a way to incorporate different functionalities in the *N*-aryl hydroxylamine products however, it is the starting nitrone that governs the aryl substituent of the hydroxylamine in the final product.



Scheme 45

It has been reported that reacting nitrones **84** with terminal alkynes in the presence of diethylzinc(II) in toluene gives the *N*-alk-2-ynylhydroxylamines **85** in good yields.[63] Using an allyl bromide in the presence of samarium and tetrabutylammonium bromide in an aqueous solvent provides the corresponding allylated *N*-aryl hydroxylamine **86** within just a couple of hours.[64] Similarly, use of an ester enolate as the nucleophile gives the analogous ester derived *N*-aryl hydroxylamine **87**.[65]

1.10 Summary

There has been a vast amount of research into preparing *N*-aryl hydroxylamines and many successful methods have been developed using a range of reagents and conditions. However, there are limited reports of using Buchwald-Hartwig methodology and no literature precedent for Ullmann type chemistry to synthesise these compounds. Particularly, within current research, palladium and copper have sparked great interest in catalysing coupling reactions. Using this technology to prepare *N*-aryl hydroxylamines would be an extremely useful addition to current technology.

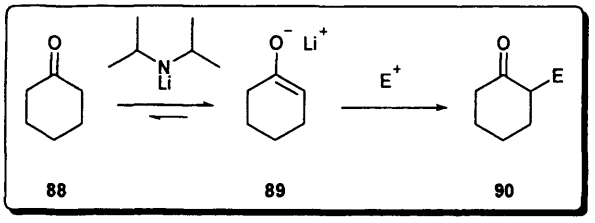
Chapter 2

A novel metal-free α–oxygenation procedure for carbonyl compounds

2.1 Introduction

Organic synthesis is at the forefront of scientific research being one of the largest chemical industries in the world. There has been a lot of recent interest in the use of metal-free procedures for functional group transformations. Although the use of metals provides us with reliable, entrenched reactions, there are certain problems associated with the use of metals in these procedures. This includes toxicity problems within drug preparation; other issues connected are economic and environmental factors.

An essential fundamental chemist's tool is the carbonyl group.[66] Within any organic synthesis journal we find constant use of the carbonyl group. A large amount of the literature depends upon the controlled manipulation of the carbonyl group and its many transformations are used continuously in organic synthesis, as it supplies us with a vast variety of reliable synthetic reactions such as Michael, aldol, Claisen ester and Diels-Alder reactions. The reaction scheme below is an example of the use of a lithium amide in an enolate α-functionalisation of the carbonyl group.



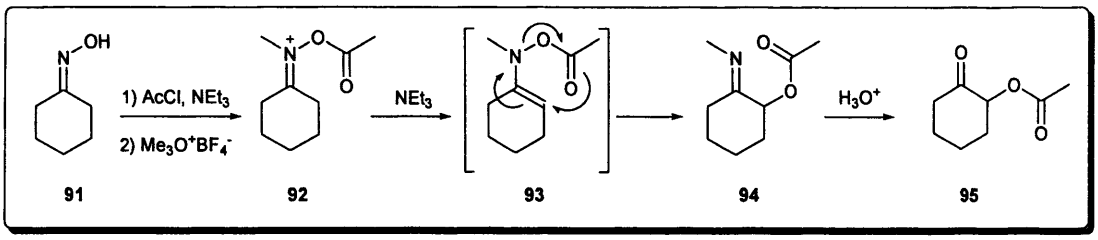
Scheme 46

The enolate is useful for forming carbon-carbon, carbon-oxygen, carbon-nitrogen, and carbon–sulfur bonds, amongst others. This reaction, although viable, often requires low temperatures and anhydrous reaction conditions that can prove to be expensive and difficult to carry out.

Therefore, an alternative method, which requires simpler reaction conditions for the α-oxygenation of a carbonyl in a selective manner at room temperature in the presence of both air and water,[67] would be of benefit to the synthetic community.

2.1.1 Literature Review

The origin of our method for the metal-free α-oxygenation of carbonyl compounds is based on work reported in 1969 by House[68] who showed that cyclohexanone **88** could be converted to 2-acetoxycyclohexanone **95** by a 5-step procedure (Scheme 47).



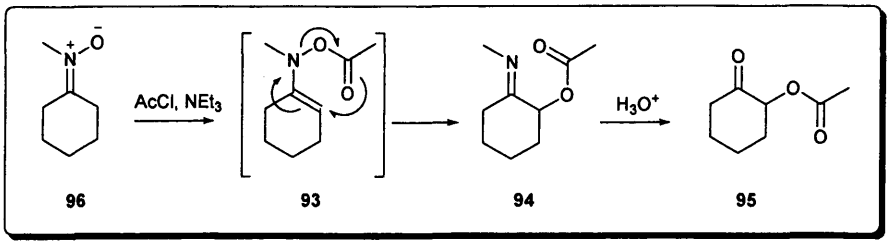
Scheme 47

House condensed cyclohexanone **88** with the hydroxylamine to generate the oxime **91**. Treatment of the oxime **91** with acetyl xhloride gave the acetylated species, which in turn was methylated to produce the iminium salt **92**. Addition of triethylamine, which acts as a base to remove the α-proton, generates the enamine **93**. This is then in a position to undergo a concerted pericyclic rearrangement to give the α-acetoxy imine **94**. By hydrolysis, the required α-oxygenated species **95** was obtained in an overall yield of 45%.

The proposed rearrangement shows a marked resemblance to the Claisen rearrangement and was deduced by the fact that the enamine has a half-life of 30 seconds in chloroform at 0 °C. Additionally, House showed that *N*-methyl-*O*-acetyl hydroxylamine hydrochloride **101** reacts with cyclohexanone with dry dichloromethane to produce the iminium intermediate **92**.

The disadvantage to this method is that it is a 5-step process with a low overall yield. Reducing the number of steps to achieve this overall transformation would be of benefit.

Coates developed this method further in 1983. [69] The Coates variation is shown in Scheme 48 below:



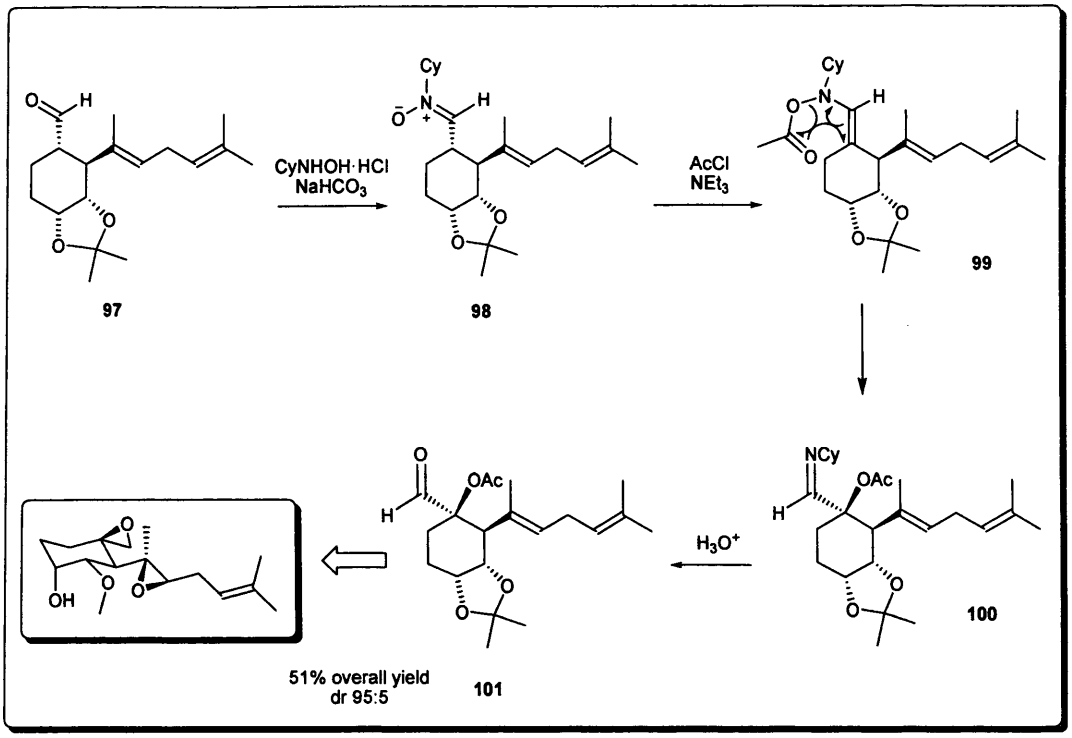
Scheme 48

This involves the reaction of the carbonyl with a *N*-alkylated h ydroxylamine, to generate the nitrone species **96**. By further reaction with acetyl chloride under basic conditions, followed by acid hydrolysis the α-oxygenated carbonyl **95** was obtained in a 26% overall yield.

This method works extremely well for aldehydes, but unfortunately not particularly well for cyclic ketone carbonyl compounds. Although this is a lower yield than that obtained by the House rearrangement (Scheme 47) it must be remembered that 2 steps are being eliminated from the experimental procedure, which makes the overall synthetic sequence more attractive.

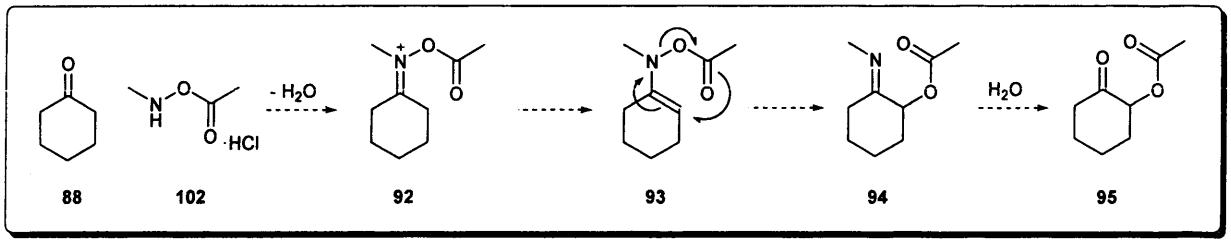
These discoveries by House and the development by Coates have provided the synthetic community with a broadly useful application for inserting an oxygen atom at the α-carbon of a carbonyl group in a simple reliable manner.

This concerted cyclic rearrangement was an integral step in the synthesis of (+/-)-fumagillol.[70] Use of this [3,3]-sigmatropic rearrangement allowed an efficient formation of the α-acetoxyaldehyde **101**, without use of an enolate, in 51% (3-steps). The percentage of unwanted diasteroisomer produced was less than 5%. The scheme below shows the application of the House concept within this synthesis of (+/-) fumagillol.



Scheme 49

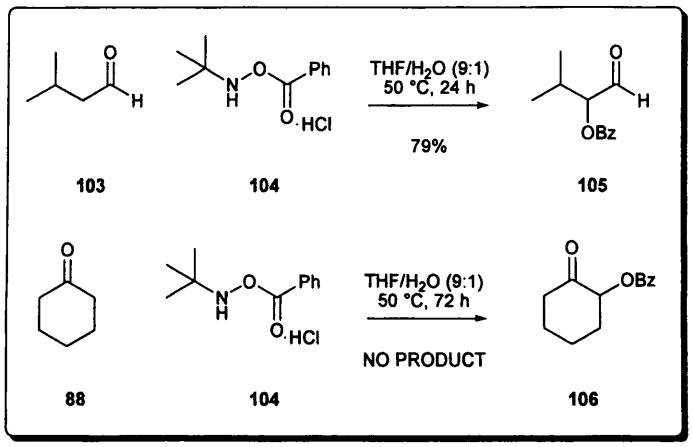
2.1.2 The proposal



Scheme 50

The above reaction scheme is a one-pot process that involves the condensation of a carbonyl compound **88** and a hydroxylamine salt, *N*-methyl-*O*-acetyl hydroxylamine hydrochloride **102**, to give us the enamine **93** that undergoes a concerted rearrangement to generate the α-acetoxy imine **94**. Reintroduction of the water molecule then produces the desired oxygenated species **95**.

Previous work done within the group found two main transformations that provide wide scope for elaboration of this proposed novel synthetic method (Scheme 51).[71]

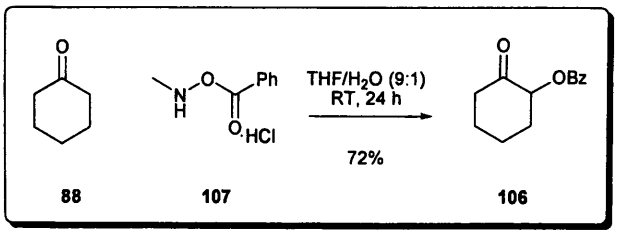


Scheme 51

By using the *N-tert*-butyl-*O*-benzoyl hydroxylamine hydrochloride **104** in the above reaction scheme it was shown that complete chemoselectivity for aldehydes over ketones can be achieved. Upon reaction, the aldehyde **103** reacted with the hydroxylamine salt **104** to produce the α-oxygenated species **105** in a 79% yield. However, the cyclohexanone **88** remained completely unreacted, only starting materials being evident even after heating for extended periods of time. This observation can be rationalised by the steric bulk of the tertiary butyl group attached to the nitrogen preventing iminium ion formation.

The steric hindrance of the butyl group prevents the lone pair of electrons on the nitrogen from being accessible for iminium ion formation with more sterically demanding ketone substrates.

By reducing the steric congestion at the nitrogen of the reagent it was observed that for both aldehydes and ketones the reactions proceeded with good yields at room temperature in the presence of an aqueous and aerobic environment (Scheme 52). [72]

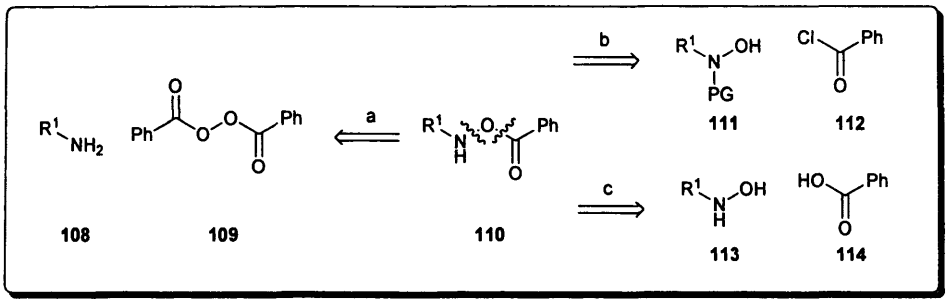


Scheme 52

This observation can again be rationalised with the idea that a smaller nitrogen substituent allows iminium ion formation even on more hindered ketones.

2.2 The Reagent

Within our reaction it is the reagent that contains the oxygenating source. There have been three synthetic pathways developed to generate this class of reagent for the transformation (Scheme 53). Either by disconnecting across the *N-O* bond (a) to provide the primary amine **108** and benzoyl peroxide, or alternatively disconnecting across the *C-O* bond (b or c) provides the hydroxylamine **113** as the starting component.



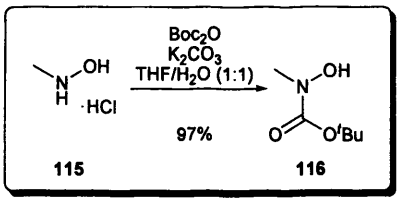
Scheme 53

Within the first disconnection (a) to the primary amine **108**, a synthesis was developed using the amine and benzoyl peroxide **109** which were developed from a report by Phanstiel.[73] This method proves to be a highly economical preparation with excellent yields of reagent and is discussed in detail within Chapter 4. However, there are problems associated with over oxidation of the amine, which can be a limiting factor with this methodology. Additionally, the method is limited to comerically available peroxides.

The original procedure developed to access the reagent **110** was a 3-step method based on disconnection b *via* cleavage of the *O-C* bond. In particular, for the preparation of the *N*-methyl hydroxylamine derived reagents it is the commercial availability of the *N*-methyl hydroxylamine that makes this an attractive route. The initial reagent prepared to investigate the α–oxygenation step was *N*-methyl-*O*-benzoyl hydroxylamine hydrochloride **107**. This salt had been used in previous studies within the group and appeared to be a good starting point for my research.

Firstly, before functionalizing the *O*-position of the *N*-methyl hydroxylamine, protecting group strategies needed to be applied to the nitrogen. By protecting the more nucleophilic nitrogen problems associated with *N*-functionalisation a re avoided. Using a standard Boc protection protocol the hydroxylamine **115** was reacted with Boc anhydride in

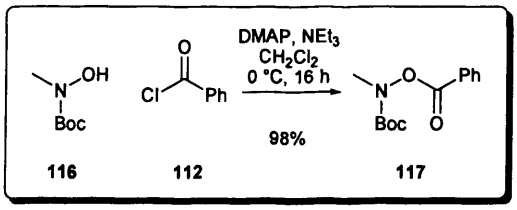
THF/H_2O (1:1) at 0 °C with potassium carbonate for 16 hours allowing the reaction mixture to warm to room temperature (Scheme 54).



Scheme 54

Upon aqueous work-up the *N*-Boc protected hydroxylamine **116** was produced in 97% yield. Upon inspection of the ^1H NMR spectrum of the crude reaction mixture there was evidence of less than 5% of the *O*-Boc protected hydroxylamine present. This problem was overcome by simple distillation to yield the purified product. This reaction proved to be very reliable and was amendable to scale up to produce multiple grams of product **116** at a time.

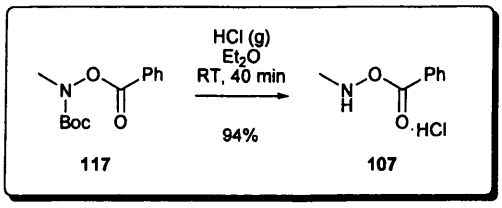
Subsequently, the *N*-Boc-*N*-methyl hydroxylamine **116** was *O*-functionalized by reacting in dichloromethane with catalytic DMAP and triethylamine with benzoyl chloride **112** at 0 °C to room temperature for 16 hours.



Scheme 55

After column chromatography on silica the Boc protected reagent **117** was produced in a pleasing 98% yield.

The final stage was then to generate the hydrochloride salt by simultaneous deprotection and salt formation by bubbling HCl gas through a *N*-Boc-*N*-methyl-*O*-benzoyl hydroxylamine solution in diethyl ether.

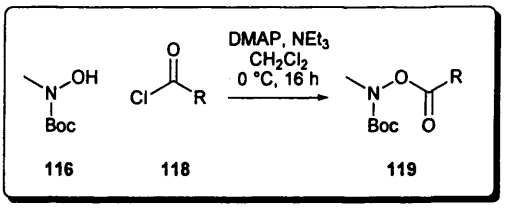


Scheme 56

The salt **107** precipitated rapidly out of solution within 30 minutes. However, it was left for a further 10 minutes to ensure completion of the crystallisation. The salt was collected by filtration and washed with cold diethyl ether to give the *N*-methyl-*O*-benzoyl hydroxylamine hydrochloride **107** in 94% yield. Similar results were obtained for this step by using 3 equivalents of 4M HCl in 1,4-dioxane, although complete removal of the solvent proved to be tricky leading to problems with crystallisation. Additionally, there were economical advantages of generating the HCl gas that showed it to be a more attractive route. The reagent was prepared in a good overall yield of 89% for the 3-steps.

Due to the success of the preparation of the reagent the next stage was to generate a family of the salts with slight modifications. Firstly, we altered the nature of the reagent such that the group migrating could be varied. The particular reagents generated were specifically designed to incorporate factors that could possibly effect the oxygenation of the α-carbon. This included the use of different steric sizes and differing electronic properties of the migrating group.

Taking the previously prepared *N*-Boc-*N*-methyl hydroxylamine **116** and reacting with a series of acid chlorides a number of hydroxylamine analogues **120–123** were prepared and are displayed in the table below:



116 118 119

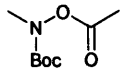
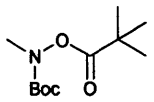
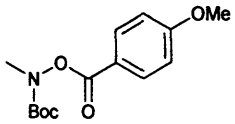
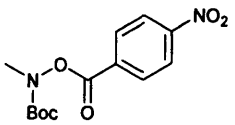
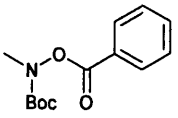
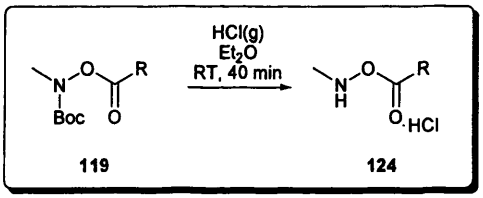
Entry	R	Product	Yield (%)
1	Me	 120	85
2	^{t}Bu	 121	90
3	*p*-$MeOC_6H_4$	 122	95
4	*p*-$NO_2C_6H_4$	 123	87
5	C_6H_5	 117	98

Table 1

All the Boc derivatives **117** and **120–123** were purified by column chromatography and were isolated in good yield (85–98%).

Subsequently, each of the analogues **117** and **120–123** were exposed to HCl gas in diethyl ether, as described previously, to deprotect and crystallise the salt in one-step. Again, it was possible to form the reagent with a dioxane HCl solution with comparative results but similar problems reoccurred with solvent removal, which were more evident with the acetyl and pivaloyl derivatives **102** and **125**. With these particular analogues, crystallization of the salt did not occur as readily in 1,4-dioxane and yielded viscous oils in both cases, however, a bit more attention to these reagents coaxed them into a solid form.



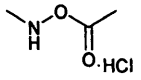
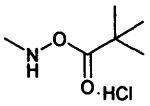
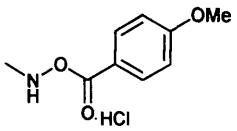
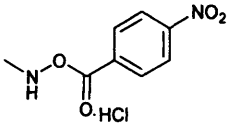
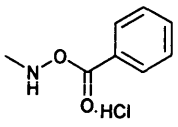
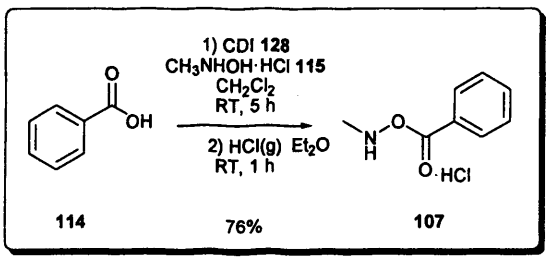
Entry	R	Product	Yield (%)
1	Me	 102	95
2	^{t}Bu	 125	78
3	*p*-$MeOC_6H_4$	 126	79
4	*p*-$NO_2C_6H_4$	 127	78
5	C_6H_5	 107	95

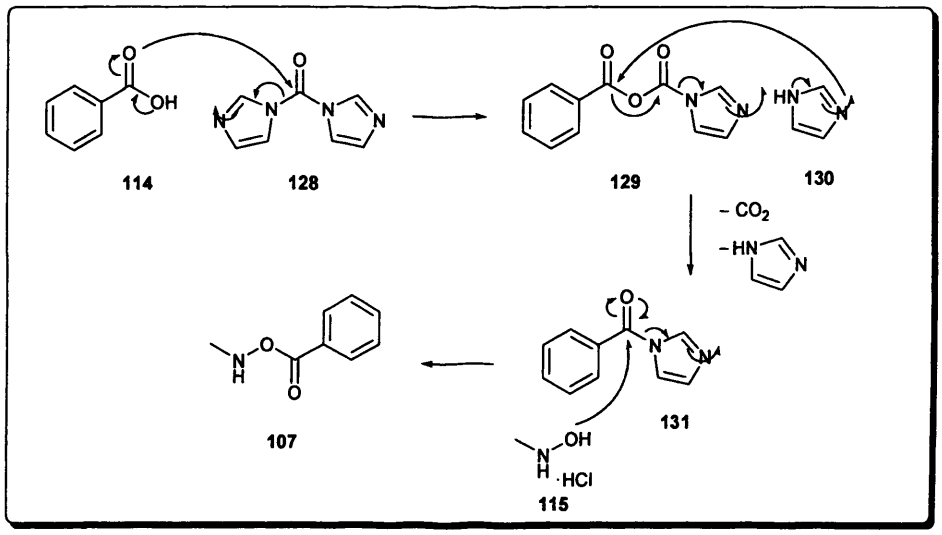
Table 2

A one-pot 2-step synthesis to access our reagents was also developed that used CDI. For *N*-methyl-*O*-benzoyl hydroxylamine hydrochloride salt **107**, benzoic acid **114** was reacted with the CDI **128** in dichloromethane followed by addition of *N*-methyl hydroxylamine hydrochloride **115** which generated the reagent **107** directly. The required hydrochloride salt was formed by dissolving the crude reaction mixture in dry diethyl ether and passing HCl gas through the solution (Scheme 57).[74]



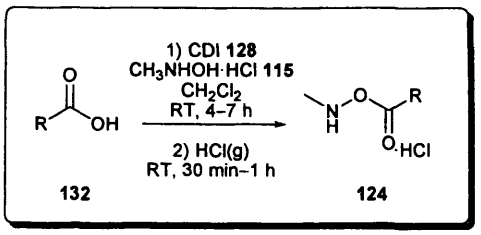
Scheme 57

The proposed mechanism for this reaction is shown below (Scheme 58). Firstly, benzoic acid **114** reacts with CDI to form a carbamate derivative **129** with a loss of a mole of imidazole. The imidazole is re-introduced by attacking on the benzoyl carbonyl group which leads to loss of carbon dioxide gas and imidazole to give the highly electrophilic imidazole benzoyl species **131**. This is more electrophilic than benzoic acid and readily reacts with the hydroxylamine to form the *O*-functionalised hydroxylamine **107**.



Scheme 58

This viable and reproducible method to access the *N*-methyl-*O*-benzoyl hydroxylamine hydrochloride reagent allowed us to embark on synthesizing additional *N*-methyl-*O*-acyl hydroxylamine analogues that were previously prepared using the 3-step method with this more efficient 1-step protocol. The results are presented in the Table below:



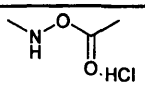
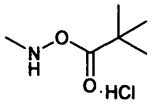
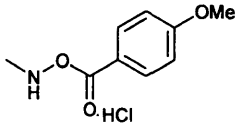
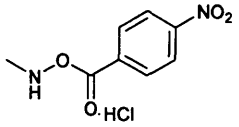
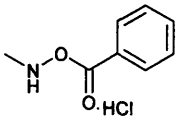
Entry	R	Product	Yield (%)
1	Me	 102	-
2	^{t}Bu	 125	67
3	*p*-$MeOC_6H_4$	 126	74
4	*p*-$NO_2C_6H_4$	 127	72
5	C_6H_5	 107	76

Table 3

A limiting factor with this reaction become evident when using acetic acid as the substrate to form the *N*-methyl-*O*-acetyl hydroxylamine hydrochloride **102**. Several attempts at varying the method gave little success and the salt was not isolated. This alternative synthetic method for preparation of the salts gave good yields (67–76%) with a significant overall decrease in time required.

In the Table below is a direct comparison of two of the alternative approaches to generate the reagents. It can be seen that similar results can be obtained for each procedure,

however, the economic and time benefits of the direct method provide a significant advantage of the previous 3-step method.

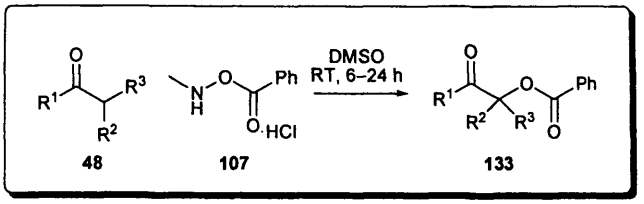
Entry	R	CDI method		3-step method
		Reaction Time (Hours)	Yield (%)	Yield (%)
1	CH_3	6	-	90
2	^tBu	5	67	71
3	*p*-$MeOC_6H_4$	5	74	73
4	*p*-$NO_2C_6H_4$	5	72	65
5	C_6H_5	4	76	87

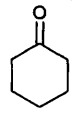
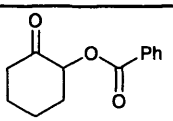
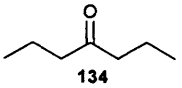
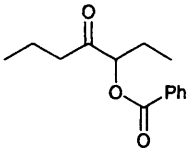
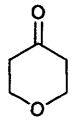
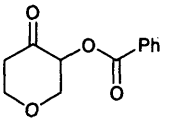
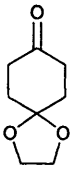
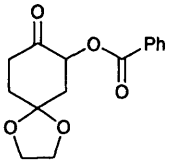
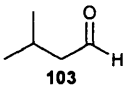
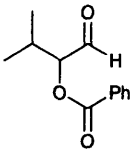
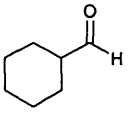
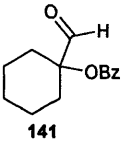
Table 4

2.3 The α-Oxygenation Procedure

The next stage was to react the reagents **102**, **107** and **125–127** with a number of carbonyl substrates to explore the scope of this novel reaction and discover some of the scope and limitations of the transformation.

Firstly, *N*-methyl-*O*-benzoyl hydroxylamine hydrochloride **107** was examined as the reagent using aldehydes and both cyclic and acyclic ketones as substrates under the optimum solvent of DMSO (Table 5) developed previously within the group.



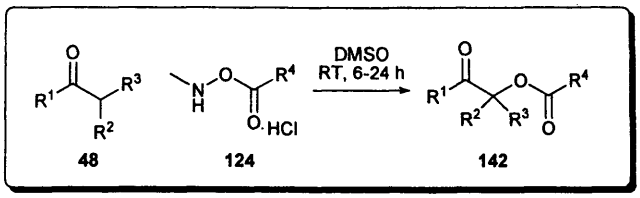
Entry	Substrate	Product	Yield (%)
1	 88	 106	80
2*	 134	 135	90
3	 136	 137	79
4	 138	 139	70
5	 103	 105	80
6	 140	 141	74

*Reaction performed at 50 °C.

Table 5

The reagent worked well for all substrates with good to excellent yields. The reaction was performed at room temperature except for acylic ketones (Entry 2) which required a slightly higher temperature of 50 °C. Additionally, aldehydes (Entry 5 and 6) required less time to react due to the high reactivity of the aldehydes in comparison to ketones. This lowered the reaction time from typically 16 hours to 5 hours.

Subsequently, the alterative reagents were reacted with a range of carbonyl substrates to observe whether the α-oxygenation reaction could sustain modification of the acyl group (Table 6).



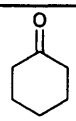
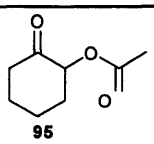
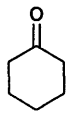
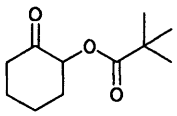
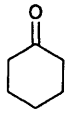
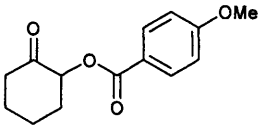
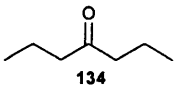
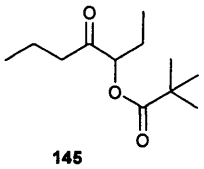
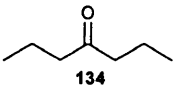
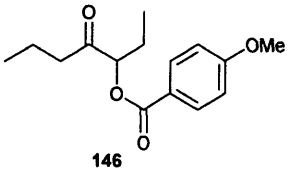
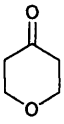
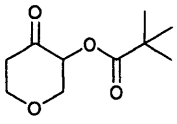
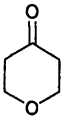
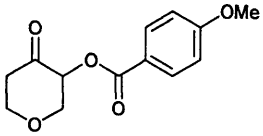
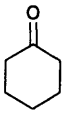
Entry	R^4	Substrate	Product	Yield (%)
1	C_6H_5	 88	 95	67
2	*t*-Bu	 88	 143	69
3	*p*-$MeOC_6H_4$	 88	 144	70
4	*t*-Bu	 134	 145	58
5	*p*-$MeOC_6H_4$	 134	 146	76
6	*t*-Bu	 136	 147	56
7	*p*-$MeOC_6H_4$	 136	 148	86
8	*p*-$NO_2C_6H_4$	 88	NO PRODUCT	-

Table 6

It was found that both the methoxybenzoyl- (Entries 3, 5 and 7) and pivaloyl- (Entries 2, 4 and 6) reagents **126** and **125** underwent the one-pot α-oxygenation procedure, in good yields with each of the carbonyl substrates examined. Although the methoxy substituted aromatic reagent gave the desired product there was no evidence that suggested the rate of reaction was facilitated by the methoxy group in the para position.

In general, the acyclic ketones required a higher temperature as found in previous cases (Entries 4 and 5).

The 4-nitro benzoyl substituted reagent **127** failed to oxygenate at the α-carbon of the carbonyl substrates, even at elevated temperature and prolonged reaction times. However, the reagent slowly decomposed over time. A possible explanation for this may be that the electron withdrawing nature of the *O*-substituent could reduce the nucleophilicity of the hydroxylamine nitrogen as well as weaken the N–O bond.

2.4 Conclusion

We have developed a novel family of reagents that can be prepared by one of three methods depending upon the substitution pattern required. All the reagents are easily accessible in good yield and are bench stable.

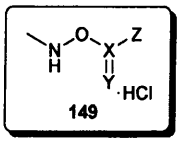
It can be concluded the α-oxygenation reaction is not influenced by sterics on the oxygen substituent. The reaction is unsuccessful for the electron deficient *O*-acyl groups. However, the reaction works well for a number of alkyl and aryl groups.

Chapter 3

Preparation of carbonates and carbamates

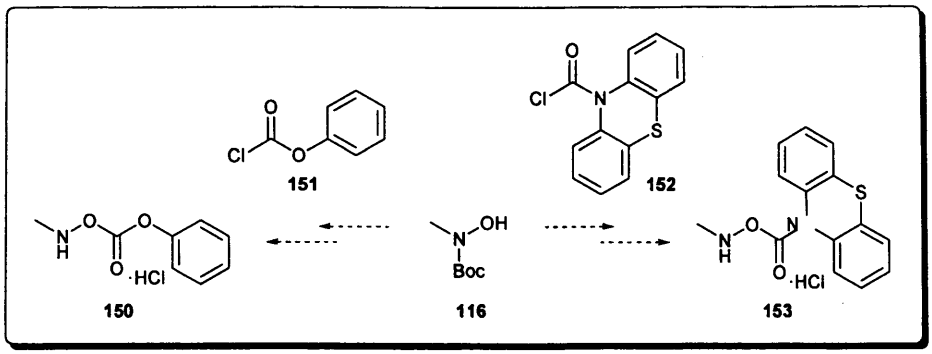
3.1 Introduction

Following the success of the novel oxygenation procedure this chapter will report further research into widening the scope of our transformation. There is currently no literature precedent for the direct introduction of hydroxyl groups bearing different protecting groups due to the limited availability of oxidants for the α-oxidation of carbonyl groups. Our attention therefore became focused on the development of reagents for the incorporation of carbonate and carbamate functionalities α- to a carbonyl group by simply modifying the scaffold of the generic reagent **149** (Scheme 59).



Scheme 59

Broadening our family of reagents, *N*-Boc-*N*-methyl hydroxylamine **116** was reacted with 10H-phenothiazine-10-carbonyl chloride **152** and phenyl chloroformate **151** to generate the carbamate and carbonate derivativess **153** and **150** respectively after removal of the Boc protecting groups (Scheme 60). This provided a *N* and *O* atom in the Z position of **149** (Scheme 59) whereas previous research focused on a *C* atom at this position. Overall, the addition of carbamate and carbonate functionalities into a molecule are relatively simple strategies although there has yet to be a method reported for their direct introduction α- to the carbonyl group.

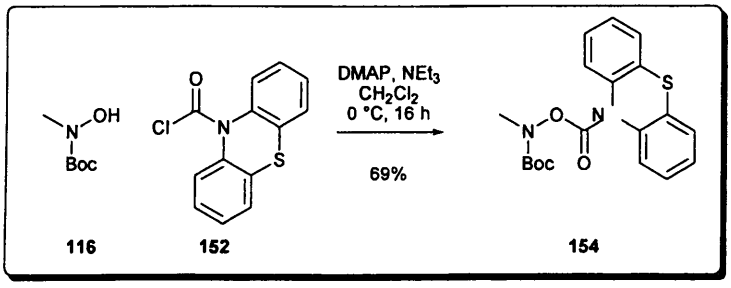


Scheme 60

3.2 Reagent Preparation

3.2.1 Preparing the *N*-methyl-*O*-(10H-phenothiazine-10-carbonyl) hydroxylamine hydrochloride reagent 153

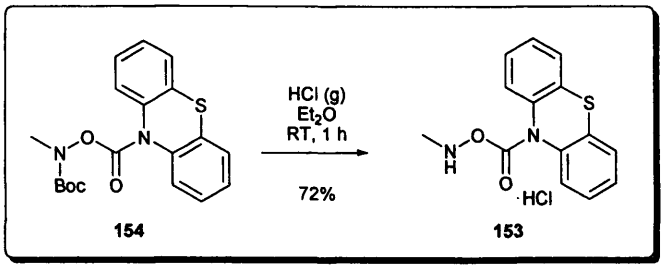
The carbamate reagent **153** was prepared in an analogous fashion to that adopted in Chapter 2 from Boc protected *N*-methyl hydroxylamine **116**. Reaction with commercially available 10H-phenothiazone-10-carbonyl chloride **152** under basic conditions using catalytic DMAP produced the Boc protected reagent **154** in 69% after purification by column chromatography.



Scheme 61

The hydrochloride salt **153** was generated by deprotection and *in situ* salt formation under strictly anhydrous reaction conditions (Scheme 62). The Boc protected precursor **154** was dissolved in diethyl ether and HCl gas was bubbled through the N_2 flushed reaction mixture. The desired salt **153** precipitated directly from the reaction mixture and could be isolated in a reproducible 72% yield. Similar results were obtained when using 1,4 dioxane as

the reaction solvent. In this case, complete removal of all traces of the solvent after the reaction lead to difficulties in isolating the product by crystallisation.

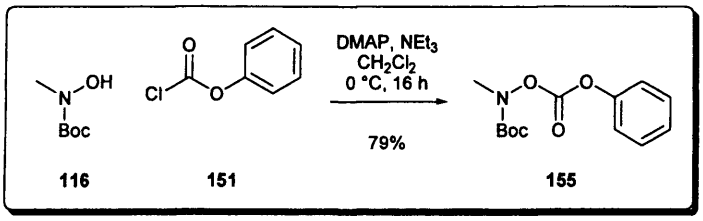


Scheme 62

This reliable 2-step procedure provided access to gram quantities of the desired salt **153** in an overall yield of 49%.

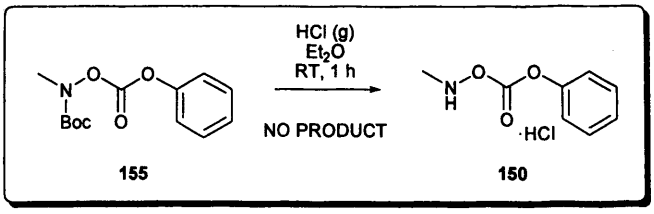
3.2.2 Preparing the *N*-methyl-*O*-(phenoxycarbonyl) hydroxylamine hydrochloride reagent 150

A similar protocol was developed for the synthesis of the salt **150** starting with reaction of *N*-Boc-*N*-methyl hydroxylamine **116** with phenyl chloroformate **151** in the presence of triethylamine, 2 mol% DMAP in CH_2Cl_2 to give the Boc protected reagent **155** in 79% yield after purification by column chromatography (Scheme 63).



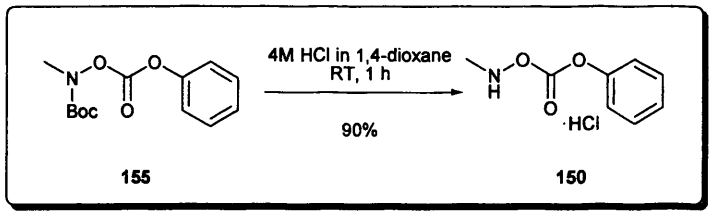
Scheme 63

Interestingly, attempted deprotection of the precursor **155** by our standard method of passing freshly prepared HCl gas through an ethereal solution were unsuccessful. It appeared that a salt was initially precipitating from solution, however, this precipitate redissolved as the reaction progressed. This was the first indication that the target reagent **150** was going to prove to be sensitive and needed to be treated with care.



Scheme 64

This problem was overcome by using 3 equivalents of the 4M HCl in 1,4-dioxane. This produced the target salt **150** in 90% yield (Scheme 65). We reasoned this success was due to the fact we had controlled the amount of HCl added to the system whereas we were unable to monitor the quantity of HCl gas added by generating the acid and bubbling it directly through the reaction mixture.

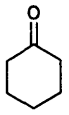
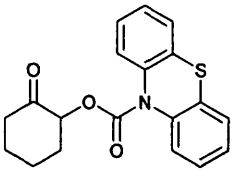
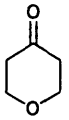
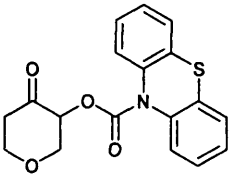
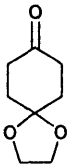
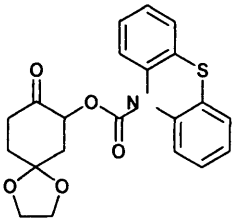
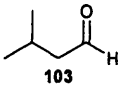
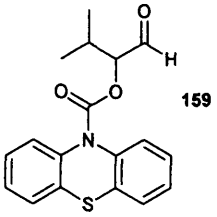
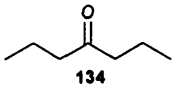
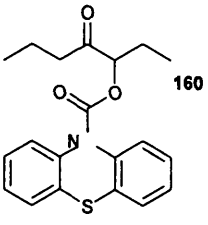


Scheme 65

The reagent **150** was prepared with an overall yield of 72%.

3.3 Reaction of *N*-methyl-*O*-(10H-phenothiazine-10-carbonyl) hydroxylamine hydrochloride 153

Following the preparation of the carbamate reagent *N*-methyl-*O*-(10H-phenothiazine-10-carbonyl) hydroxylamine hydrochloride **153** it was reacted with a variety of carbonyl substrates to examine the potential of this modified reagent (Table 7).[75] Standard conditions developed in Chapter 2 were adopted. The results are displayed in the Table below:

Entry	Carbonyl Substrates	Product	Temperature (°C)	Time (hours)	Yield (%)
1	 88	 156	25	16	74
2	 136	 157	25	16	80
3	 138	 158	25	16	82
4	 103	 159	25	4	88
5	 134	 160	50	16	73

*All reactions were performed at 0.5M concentration in DMSO with 1 eq. of **153** and 1 eq. of carbonyl substrate

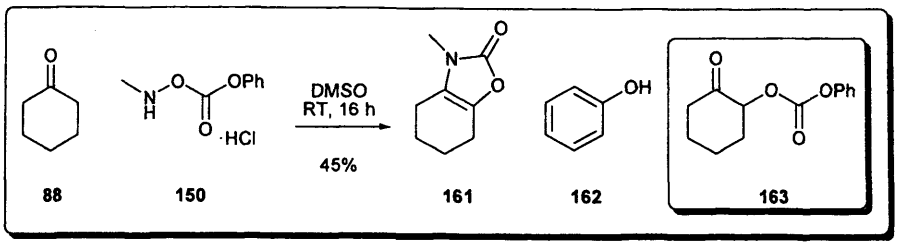
Table 7

Initially, cyclohexanone **88** was reacted with the salt to determine whether the expected [3,3]-sigmatropic rearrangement occurred. Upon reacting **88** and **153** at room temperature in dimethyl sulfoxide for a 16 hour period the organic product was isolated by an aqueous work-up. Inspection of the ^{1}H NMR spectrum of the crude reaction mixture suggested that the transformation had occurred due to the presence of a characteristic double doublet at 5.12 ppm indicative of the CH proton α to the carbonyl group. Further analysis showed a large axial-axial proton coupling constant, indicative of the new substituent adopting an equatorial position. The carbamoylated product **156** (Entry 1) was isolated in 74% yield after purification by column chromatography.

The tetrahydropyran-4-one substrate **136** gave excellent result with an 80% yield of the α-functionalised product **157** (Entry 2), indicating tolerance of heteroatom substitution within the transformation. The reaction proved tolerant of acid sensitive moieties by successfully functionalising the ketal substrate **138** in a 82% yield (Entry 3). This is of particular interest due to the acidic nature of the reaction conditions. When using acyclic compound **134** (Entry 5) we noted a higher temperature of 50 °C was required to encourage the reaction to provide the product **160** in a good yield o f 73%. This need for higher temperatures can be accounted for by the 'flexibility' of the substrate when compared to cyclic substrates. Reactions at room temperature proved to be extremely sluggish for acyclic substrates. With the aldehyde substrate **103** only 4 hours were required for the reaction to have reached completion in a yield of 88% (Entry 4). This is as expected due to the higher reactivity of aldehydes towards nucleophiles. Careful monitoring of this reaction was needed, however, with longer reaction times resulting in significantly lower yields due to decomposition of the product **159**.

3.4 Reacting the *N*-methyl-*O*-(phenoxycarbonyl) hydroxylamine hydrochloride reagent 150 - an unexpected result

Investigations into the use of the *N*-methyl-*O*-(phenoxycarbonyl) hydroxylamine hydrochloride reagent **150** began by reaction with cyclohexanone **88** under the now familiar standard one-pot manner. Using DMSO as the solvent at room temperature a serendipitous reaction occurred with the unexpected product **161** being isolated in 45% yield (Scheme 66).

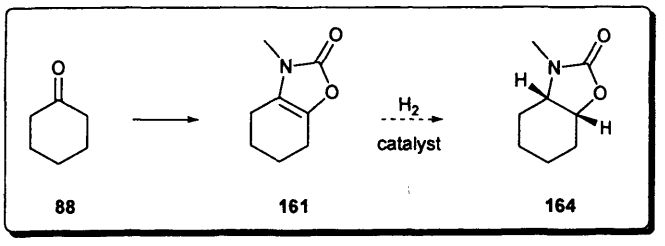


Scheme 66

There was evidence in the ^{1}H NMR spectrum of the crude reaction mixture of a very small amount of the expected α–oxygenated product **163**, with the characteristic double doublet of the proton on the chiral carbon at 5.04 ppm. Upon purification the major products from the reaction were phenol **162** and the curious heterocycle **161** (45%).

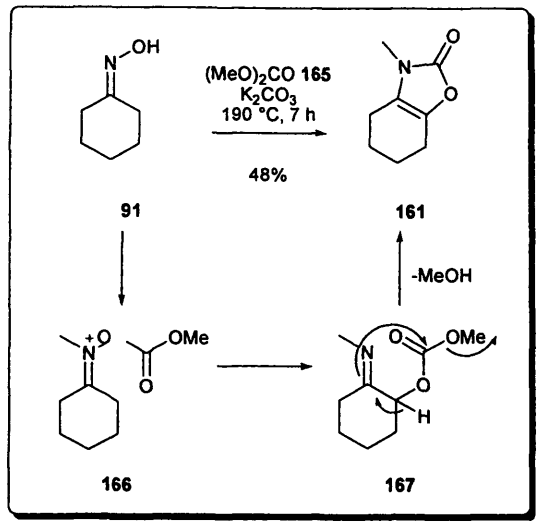
This heterocycle **161** is a class of compound known as oxazolidinone. Upon literature research it was found that derivatives of this type of compound exhibit anti-cancer activity as a vascular tumour targeting agent and there is an interest for developing the production of these *cis*-restricted systems due to their prevalence within natural products.[76]

It could be envisaged that the alkene within the oxazolidinone heterocycle can be reduced to provide the *cis*-substituted cyclohexanone derivative **164**. This new method, therefore, has the potential to be applied to prepare protected 1,2-amino alcohols from carbonyl compounds sterospecifically in 2-steps (Scheme 67).



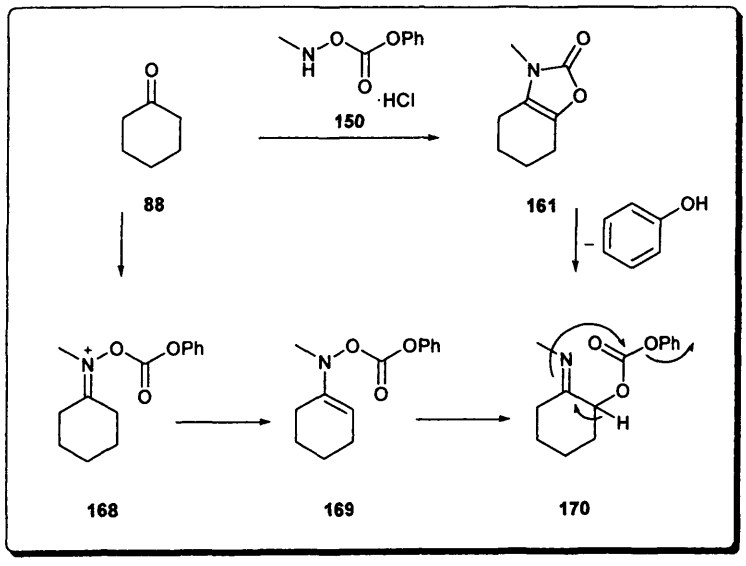
Scheme 67

It has been reported that heating cyclohexanone oxime **91** with 20 equivalents of dimethyl carbonate **165** at 190 °C in an autoclave under basic conditions gives the same product that we had isolated **161**.[77] The reaction was proposed to proceed by a mechanism involving a [3,3]-sigmatropic rearrangement followed by intramolecular cyclisation eliminating a molecule of methanol (Scheme 68). These harsh reaction conditions provide the product in similar yields to those we had obtained under ambient conditions.



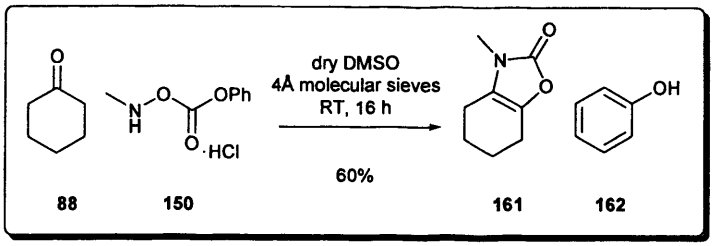
Scheme 68

In our one-pot α-oxygenation procedure the mole of water lost in the condensation step is reintroduced in the final imine hydrolysis to give the α–functionalised carbonyl **163**. However, what appeared to be happening was before the imine hydrolysis the lone pair of electrons on the nitrogen intramolecularly attacked the electrophilic carbonate carbonyl, with a subsequent loss of phenol. The fact that phenol is an extremely good leaving group explains why this intramolecular cyclisation producing this class of heterocycle had not been observed in similar investigations within the group using alternative reagents.



Scheme 69

In an attempt to improve the yield of this transformation, anhydrous conditions were adopted to encourage intramolecular cyclisation by reducing the rate of imine hydrolysis. This was achieved by using dry solvent to prevent additional water being present within the system and addition of a desiccant to remove water generated during the reaction. Using dry DMSO and 4Å molecular sieves we were able to increase the yield of **161** to a pleasing 60%.

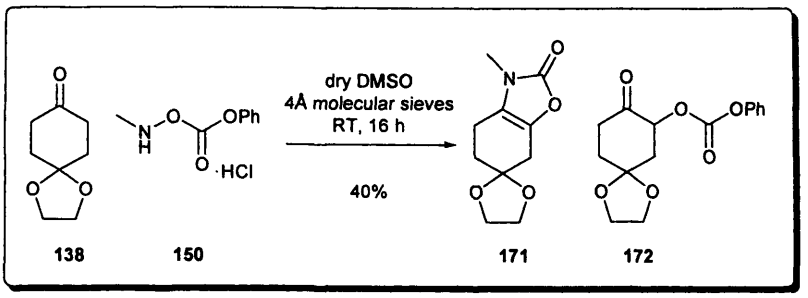


Scheme 70

Both factors were found to contribute to the overall improvement in the yield with separate reactions using dry DMSO and 4Å molecular sieves individually resulting in yields of 54% and 51% respectively. It is also important to note that in dry DMSO there was absolutely no evidence of the α-functionalised carbonyl compound 163 and the sole discrete product being the heterocycle 161. Increasing the temperature of the reaction to 50 °C had no significant benefit to the transformation and gave similar results (61%) to that observed at room temperature.

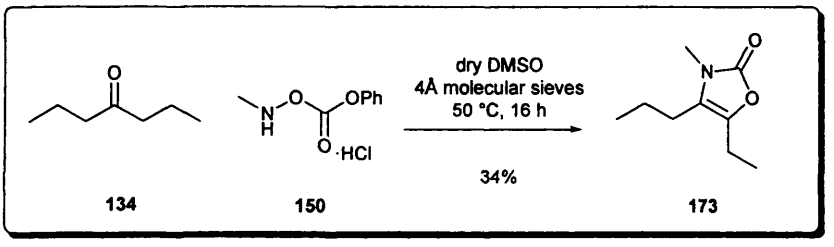
3.4.1 Using the *N*-methyl-*O*-(phenoxycarbonyl) hydroxylamine hydrochloride reagent 150 to prepare oxazolidinone derived heterocycles

Exploring this new transformation, we applied the conditions to alternative carbonyl substrates. Firstly, we used the ketal substrate **138** with the carbonate salt **150** under the optimised conditions (dry DMSO, 4Å molecular sieves at room temperature). The corresponding heterocycle **171** was prepared in a 40% yield. There was an indication within the ^{1}H NMR spectra of the crude reaction mixture of the functionalised carbonyl compound **172** forming, however, this was not isolated due to it being a very minor component.



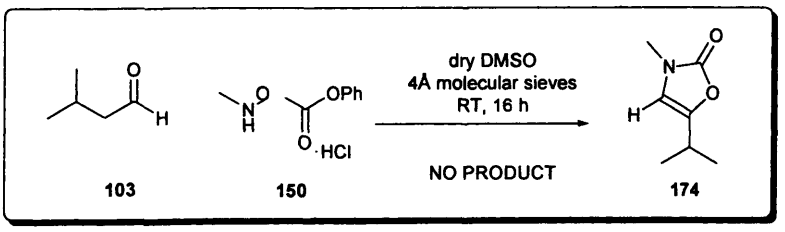
Scheme 71

Subsequently, acyclic substrates were examined under the optimised conditions to observe how general the intramolecular cyclisation proved to be. By using heptan-4-one **134** it was found that the now expected product **173** was formed in a poor 23% yield. By raising the reaction temperature to 50 °C the yield of this product could be increased to a slightly improved 34% (Scheme 72).



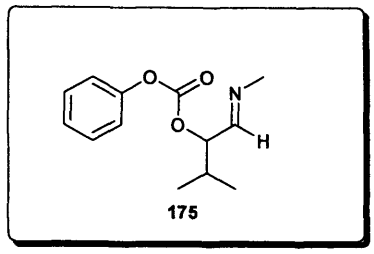
Scheme 72

A limitation to this cyclisation was encountered when attention became focused on aldehydes as substrates. Using isovaleraldehyde **103** as the carbonyl component, standard conditions provided no indication of the desired heterocycle **174**. Increasing the reaction temperature to 50 °C and altering the reaction solvent to anhydrous THF were unsuccessful (Scheme 73).



Scheme 73

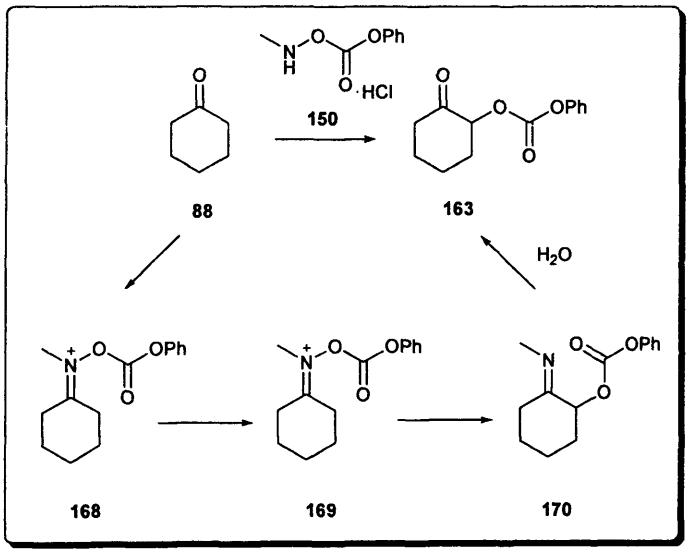
It is possible that hydrolysis of the intermediate imine **175** was too rapid to suppress under the conditions adopted (Scheme 74).



Scheme 74

3.4.2 Altering the conditions to α-oxygenate with the *N*-methyl-*O*-(phenoxycarbonyl) hydroxylamine hydrochloride reagent 150

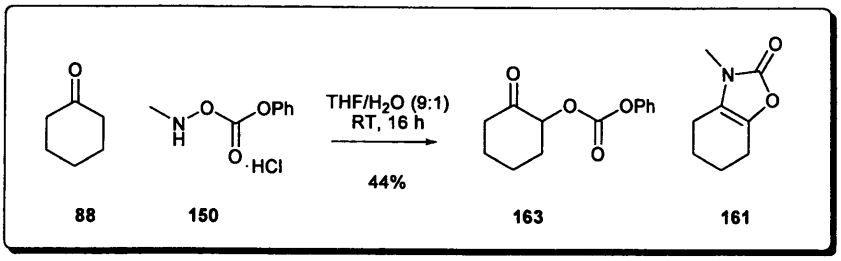
Striving to achieve our original goal of introducing the carbonate functionality α- to the carbonyl group it was reasoned that adding excess water into the reaction would competitively hydrolyse the intermediate imine **170** to favour the oxygenated product **163** over the previously observed heterocycle **161**. Intrigued by using simple modification of the reaction medium to generate alternative compounds we began to develop conditions for bringing about this transformation.



Scheme 75

Due to prior success with THF and water mixtures we took our lead from here.[72] Using THF/H_2O (9:1) combination we performed the reaction with cyclohexanone **88** and our carbonate reagent **150** at room temperature until all the starting material has been consumed by TLC.

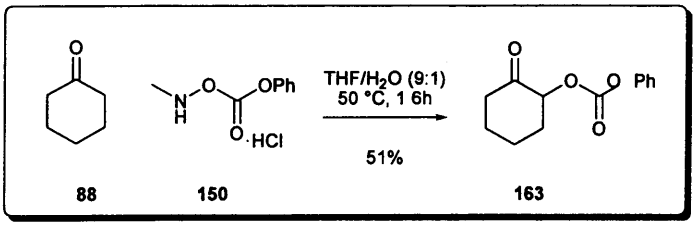
From the ^{1}H NMR spectrum of the crude reaction mixture it was observed that a prominent signal at 5.04 ppm indicative of the proton α- to the carbonyl group within the oxygenated product **163** was present. Additionally, the heterocycle **161** was also present but now as the minor component of the mixture. The α-oxygenated product **163** was isolated in 44% yield by flash chromatography on silica (Scheme (Scheme 76).



Scheme 76

Subsequently, we increased the amount of water within the system by altering the solvent ratio to THF/H_2O (1:1) to see whether this would increase the yield of desired compound **163**. However, the reaction was a lot 'messier' on analysis of the ^{1}H NMR spectrum of the crude reaction mixture and by TLC, with the α-oxygenated product **163** being isolated in a slightly lower 41% yield. This infers that extra water appears to have no beneficial effect on the reaction.

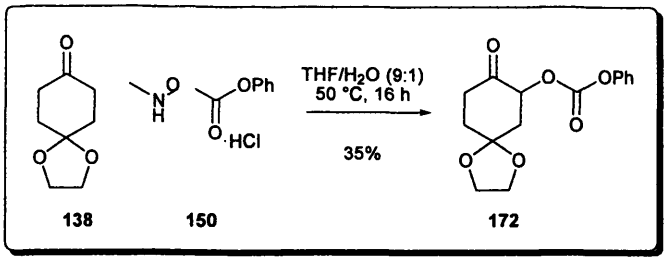
In an attempt to increase the yield of the transformation and reduce the amount of heterocycle formed we raised the reaction temperature to 50 °C using the THF/H_2O (9:1) solvent mixture to see whether the reaction temperature had any significant influence (Scheme 77).



Scheme 77

This did aid the formation of the α-oxygenated compound with the isolated yield of the α-carbonate **163** increasing to 51% (Scheme 77).

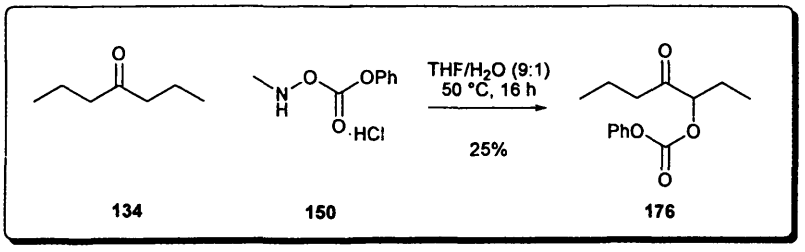
Next we turned our attention to the acid sensitive substrate cyclohexanedione mono ethylene ketal **138** by reacting it under the optimised conditions of THF/H_2O (9:1) at 50 °C with the reagent **150** (Scheme 78).



Scheme 78

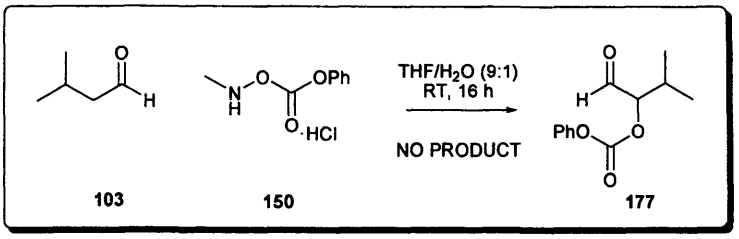
The corresponding α-functionalised product **172** was isolated in a 35% yield. This is of interest due to the aqueous acidic nature of the reaction not leading to hydrolysis of the acetal.

Examination of heptan-4-one **134** as the substrate under standard conditions lead to the expected product **176** in a disappointing yield of 25%.



Scheme 79

Attempting to use aldehydes as substrates to generate the α-functionalised product **176** was unsuccessful. Using isovaleraldehyde **103** and the carbonate reagent **150** in THF/H_2O (9:1) at room temperature gave a gross intractable mixture of compounds. Inspection of the ^1H NMR spectrum of the crude reaction mixture showed no significant evidence of the desired product **177**. Unfortunately, no discrete compound was isolated by flash chromatography from this reaction.



Scheme 80

3.5 Conclusion

In summary, we have developed the first method for the direct introduction of a carbamate and carbonate functionality α- to a carbonyl group by modification of our generic reagent **149**. Both transformations proceed without metals under aerobic and aqueous reaction conditions. Depending upon the reaction conditions adopted by simple variation of the reaction medium, the major product obtained from the carbonate reagent **150** can be modified allowing access to both an α-functionalized carbonyl compound or the interesting oxazolidinone heterocycle.[78]

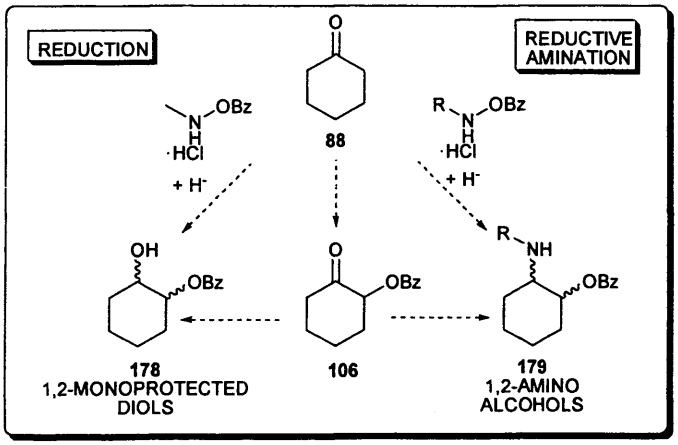
Chapter 4

Preparation of other synthetically useful compounds

1,2-mono protected diols and 1,2-amino alcohols

4.1 Introduction

On the quest to widen the scope of our novel α-oxygenation methodology work focused on the preparation of other synthetically useful compounds. This chapter will concentrate on the exploitation of this reaction in conjunction with reduction and reductive amination, to generate 1,2-mono protected diols **178** and 1,2-amino alcohols **179** respectively.

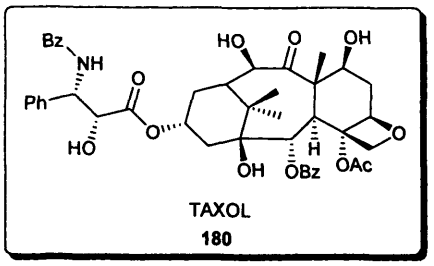


Scheme 81

The 1,2-diol and 1,2-amino alcohol functionalities are frequently found within the literature, indicating development of simple routes to incorporate these motifs into carbon skeletons would be extremely beneficial, within both pharmaceutical and natural product research.

A prime example of the importance of compounds containing the diol functionality is observed within Paclitaxel.[79] Taxol **180** is the more commonly used brand name of the molecule, was originally found in extracts from the bark of Pacific yew trees, Taxus

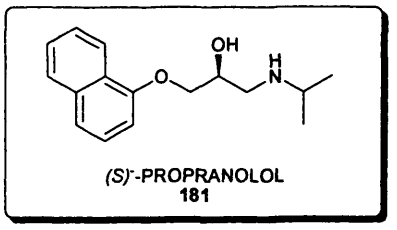
brevifolia. It can be seen that it has the 1,2-mono protected diol in a *trans* geometry present within the molecule.



Scheme 82

Taxol is a drug used to treat ovarian, breast and non-single cell lung cancer.[80] The relatively non-toxic properties of Taxol have made it a leading light in the treatment of cancer since the 1990's, providing a non-intrusive alternative to the more radical techniques of radiotherapy and surgery. Its ability to inhibit cancer cell growth has resulted in intensive synthetic investigation making it a desirable synthetic target for research. However, the cost of producing sufficient quantities of this wonder drug is a severely limiting factor.

Another important compound that contains the 1,2-amino alcohol functionality is *(S)*-Propranolol **181**.[81] Propranolol is a non-selective beta blocker mainly used in the treatment of hypertension. It was the first successful beta blocker developed. It is the only effective drug for the prophylaxis of migraines in children. Propranolol is available in generic form as propranolol hydrochloride, as well as an AstraZeneca product under the trade name Inderal. It contains the important structural 1,2-amino alcohol motif.



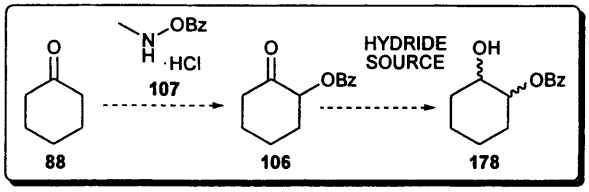
Scheme 83

Both Taxol **180** and *(S)*-Propranolol **181** represent enormous challenges to the ingenuity and creativity of the synthetic organic chemist. Within this part of our investigation we sought to extend our methodology to prepare the 1,2-diol and 1,2-amino alcohol functionality embedded in these structures.

4.2 The Reduction

Interest in mono protected 1,2-diols arises from problems associated with predominant ease of primary alcohol protection over secondary. Preparation of this functionality often involves additional protection and deprotection steps within synthesis. Therefore a synthetic sequence to generate 1,2-diols protected at the secondary hydroxyl group would be extremely useful methodology to add to the chemists toolbox.

Reaction of the reagent **107** with a carbonyl compound **88** would give the α-functionalised product **106**. Subsequent *in situ* reduction with a hydride source should form the 1,2-protected diol **178** by reduction of the carbonyl group. This stategy could provide a convenient one-pot two-step method to generate this important class of compound.

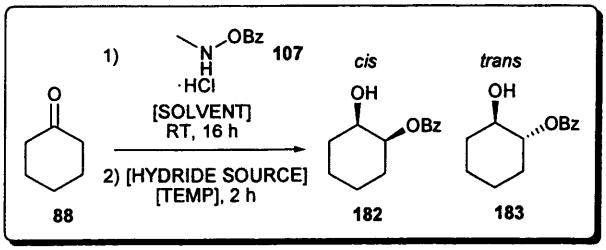


Scheme 84

4.2.1 Reaction optimisation

The first substrate we examined in this sequence was cyclohexanone **88**, due to the reliability of this molecule to undergo α-functionalisation in our previous investigations.

As previously described (Chapter 2), for the initial α-oxygenation step, cyclohexanone **88** and the reagent **107** were allowed to stir at room temperature for a period of 16 hours (all starting material consumed by TLC). The hydride source was then added and allowed to react for a further 2 hours.



Scheme 85

The solvents examined were THF and THF/H_2O (9:1) as these solvents were compatible within both individual steps. It was found that by altering the solvent and hydride source the yield and the ratio of isomers (**182** and **183**) formed altered. The results are displayed in Table 8.

The effect on yield and ratio of reaction by altering the hydride source and solvent.

Entry	Solvent	Hydride Source	Ratio[a] (*cis:trans*)	Yield[b] (%)
1	THF/H_2O (9:1)	$NaBH_4$	1:1.1	69
2	THF/H_2O (9:1)	$NaBH_4$ (0 °C)	1:1.1	80
3	THF/H_2O (9:1)	$NaCNBH_3$ (0 °C)	1:2.8	70
4	DRY THF	$NaCNBH_3$ (0 °C)	1:3.0	56

a) Ratio determined by ^{1}H NMR spectroscopy of crude reaction mixture.
b) Combined isolated yield.

Table 8

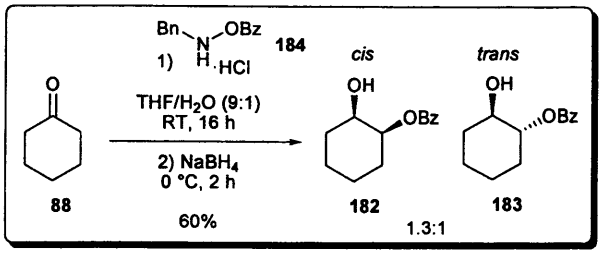
From these preliminary investigations a series of important trends were observed. In the presence of water the overall transformation was more efficient (Entries 1–3). Using sodium borohydride as the reducing agent provided a poor ratio of *cis:trans* product (1:1.1) (Entries 1 and 2) even when performing the reduction at lower temperatures (Entry 2). Altering the reducing agent to sodium cyano borohydride and conducting the reduction at 0 °C in the presence of water provided the optimal balance of reactivity and selectivity (Entry 3). It should be noted that no isolation of a reductive amination product was detected using sodium cyanoborohydride as the reducing agent.

Each product was isolated by flash column chromatography on silica and reported yields are of inseparable isomers produced. The ratios were determined from the ^{1}H NMR spectra of the crude reaction mixture. The configurations were assigned by analysis of the coupling constants within the ^{1}H NMR spectrum of each isomer with the large axial-axial value of the CH protons of the *trans*-isomer being extremely distinct within the spectra.

We then changed the reagent from the *N*–methyl–*O*–benzoyl hydroxylamine hydrochloride **107** to *N*–benzyl–*O*–benzoyl hydroxylamine hydrochloride **184** to see whether

the alteration would alter the stereochemical course of the reaction. This is additionally a cheaper reagent to prepare (discussed later) and displays similar chemical reactivity in the α-oxygenation procedure.

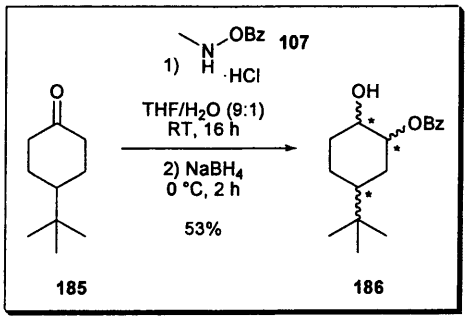
This alternative reagent **184** was reacted with cyclohexanone **88** in THF/H_2O (9:1) until all the starting materials were consumed and then cooled to 0 °C followed by addition of $NaBH_4$ as the reducing agent. It was observed upon inspection that the stereoselectivity was reversed towards the *cis* isomer **182**. It can be deduced that although the reagent is more economical to prepare the yield of the transformation was lower.



Scheme 86

In another attempt to alter the stereoselectivity of the reaction we changed the substrate to 4-*t*-butyl cyclohexanone **185**. Due to the bulkiness of the *t*-butyl group it should lock the conformation of the cyclohexanone ring.

Upon reacting the 4-*t*-butyl cyclohexanone **185** with the reagent **107** in THF/H_2O (9:1) followed by reduction with $NaBH_4$ it was observed that a number of isomers were formed. This indicated a lack of control that was hoped to be induced by the large *t*-butyl group. None of the individual isomers were isolated and the yield is of the isomers combined. The three stereogenic centres within the final product results in the possibility of nine isomers of the product, therefore explaining the gross mixture of compounds.

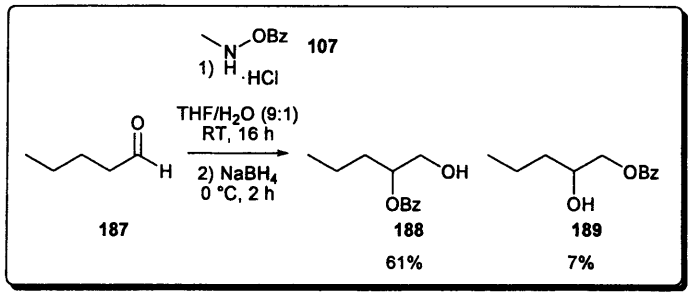


Scheme 87

This substrate was then abandoned due to the lack of stereoselectivity observed within the products formed and the increased number of isomers produced. Our focus therefore turned to using aldehydes as substrates to eliminate the possibility of forming diastereoisomeric products.

4.2.2 Altering the substrates - using aldehydes

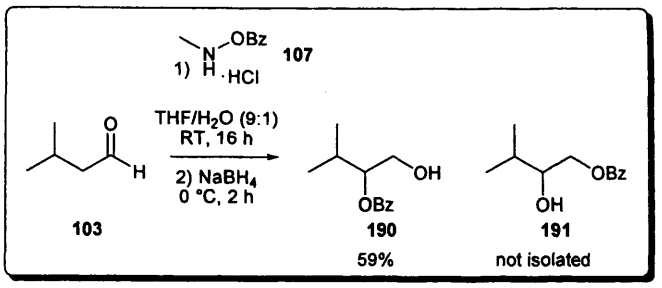
The aldehyde substrate investigated was valeraldehyde **187**, which was reacted with *N*-methyl-*O*-benzoyl hydroxylamine hydrochloride **107** in THF/H_2O (9:1) until the reaction was complete by TLC. Addition of the reducing agent $NaBH_4$ at 0 °C for two hours generated the expected secondary alcohol **188** in a respectable yield of 61% for this one-pot two-step process. Also isolated was the primary protected alcohol **189** as a minor product in 7%, where the benzoyl group had migrated to the less sterically encumbered primary alcohol (Scheme 88).



Scheme 88

These compounds were purified by SP4 chromatography using an ethyl acetate/hexane gradient. The ratio of isomers was calculated from the ^1H NMR spectra of the crude reaction mixture which was in good agreement with isolated yields.

Similarly, isovaleraldehyde **103** was examined within this transformation (Scheme 89). The major product was isolated as the protected secondary alcohol **190** in a yield of 59%. Although the primary protected isomer **191** was evident in the crude reaction mixture it was not isolated and only the major product **190** was obtained.

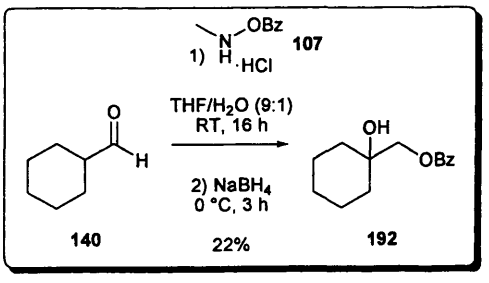


Scheme 89

The next substrate used in this reaction was cyclohexanecarboxaldehyde **140**. This transformation involves the preparation of a quaternary centre so could prove to be a more difficult aldehyde to react.

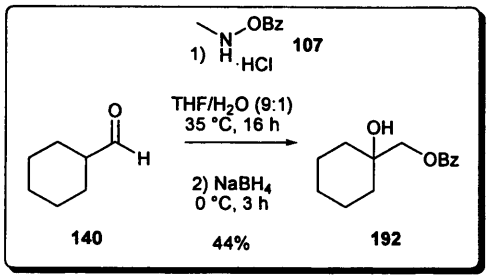
Using our now standard conditions of THF/H_2O (9:1) at room temperature with the *N*-methyl derived reagent **107** for 16 hours. The α-oxygenated product formation was monitored by LCMS. There was still evidence of starting material by TLC after 16 hours but the mixture was subjected to the next stage despite this observation. The crude mixture was cooled to 0 °C and then sodium borohydride was added and the reaction was allowed to proceed for a further 3 hours (monitoring by LCMS) followed by a basic work-up. The crude reaction mixture was purified by SP4 chromatography using a solvent gradient of ethyl acetate/hexane to yield the mono protected diol **192** in a 22% yield.

Upon spectroscopic analysis of the compound it was evident we had in fact isolated the compound where the benzoyl group had migrated to the primary oxygen (Scheme 90). This was determined by use of 2D and nOe studies which indicated the free hydroxyl group to be on the quarternary carbon. This can be rationalised by using a steric explanation, the benzoyl group is more stable on the less hindered alcohol.



Scheme 90

In attempt to increase the yield, the first step was performed at a slight higher temperature of 35 °C. The reduction step again was carried ot at 0 °C. The reaction this time produced the same product **192** in an improved 44% yield (Scheme 91). The reaction appears to be optimal at this temperature due to the fact that at higher temperatures (50 °C) the isolated yield falls and the reaction begins to generate additional by-products within the α-oxygenation step.

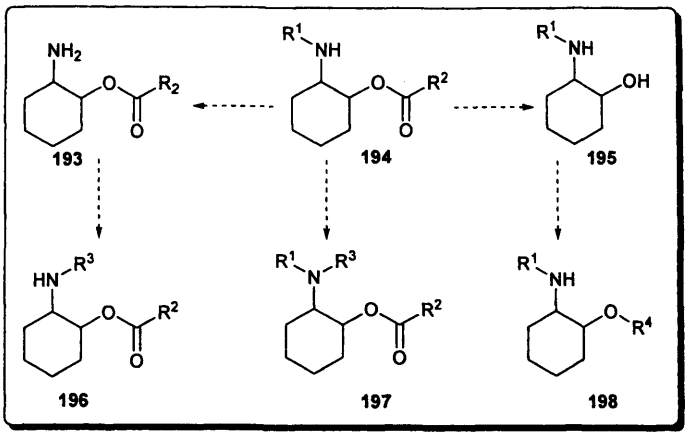


Scheme 91

In summary, our brief investigations suggest that this methodology can be used to generate the synthetically challenging mono-protected 1,2-diols selectively, however, initial attempts to apply the methodology to prepare 1,2-diols with the ester located on a tertiary alcohol were unsuccessful with the benzoyl group migrating to the less sterically encumbered primary centre.

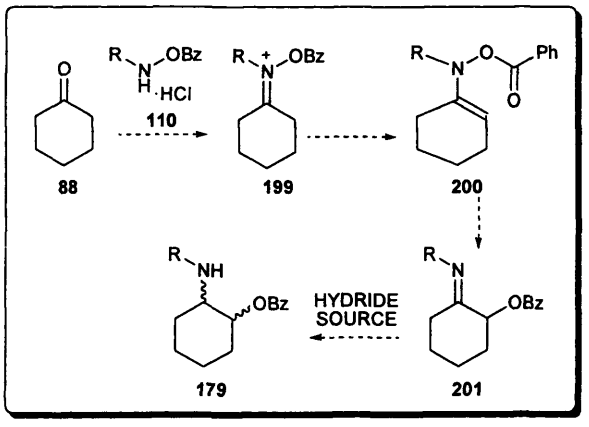
4.3 Reductive Amination

To use our α-oxygenation reaction further it was questioned whether using the reaction in conjunction with a reductive amination in a one-pot two-step method, the formation of 1,2-amino alcohols could be developed. By preparing this class of compound we could use it as a scaffold to target many other complex molecules by functionalising the products. Possible selective transformations of the desired 1,2-amino alcohol produced **194** are summarised in Scheme 92.



Scheme 92

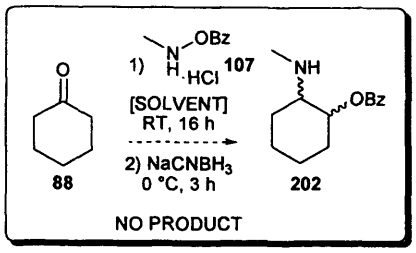
It was envisaged this class of compound could be accessed by initially reacting carbonyl **88** with our reagent **110** in the usual manner followed by *in-situ* reduction of the imine, providing an extremely atom efficient procedure in which all the reagent **110** is incorporated into the final compound **179**.



Scheme 93

4.3.1 Preliminary studies

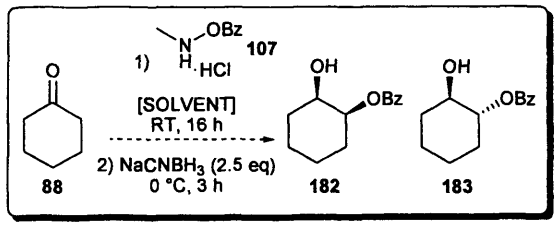
Preliminary studies were completed using cyclohexanone **88** and *N*-methyl-*O*-benzoyl hydroxylamine hydrochloride **107** within a variety of solvents, using sodium cyanoborohydride as the reducing agent. The carbonyl substrate and reagent were allowed to react at room temperature for 16 hours (all starting material consumed by TLC) then the reaction mixture was cooled to 0 °C and sodium cyanoborohydride was added in portions.



Scheme 94

Within each different solvent system there was no evidence of the expected 1,2-amino alcohol **202** by ^{1}H NMR spectrum of the crude reaction mixture. In each case the α-oxygenated carbonyl **106** was predominantly present along with minor amounts of the diol isomers **182** and **183**. It can be speculated that the hydrolysis of the imine to the carbonyl was occurring too rapidly, so the hydride source was not able to reduce the imine to the amine.

In an attempt to encourage the 1,2-amino alcohol formation increasing equivalents of the hydride source was examined. The only alternative product isolated was the corresponding 1,2-diol isomers **182** and **183**. This was an unexpected result as sodium cyanoborohydride is usually thought of as a selective reducing agent for imines and should leave carbonyls untouched.

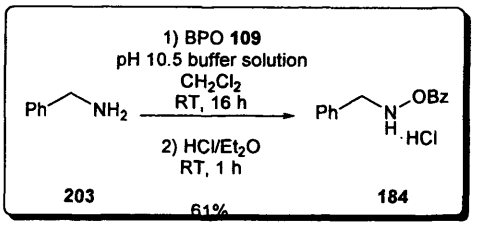


Scheme 95

To overcome this problem, the reducing agent was changed to an alternative imine specific hydride source, sodium triacetoxyborohydride. Within the literature a particular paper by Abdel-Magid and co-workers referred to using this compound when reductively aminating carbonyl compounds with various amines.[82] Taking my lead from here I opted to use modified reagents, corresponding to the amines successfully used in this report.

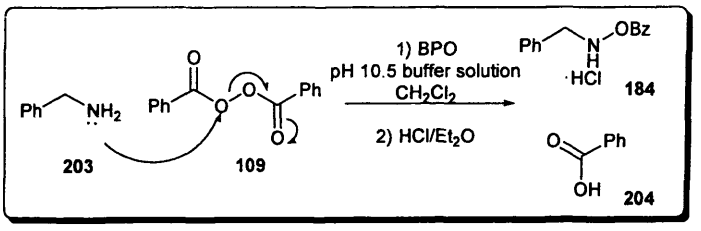
4.3.2 Alternative Reagents

Preparation of *N*-benzyl-*O*-benzoyl hydroxylamine hydrochloride salt **184** could also increase the attractiveness of this transformation by being a more cost effective and accessible reagent. The compound is synthesised with the use of relatively cheap starting materials as shown in the reaction scheme below (Scheme 96).



Scheme 96

Benzylamine **203** was allowed to stir vigorously in a pH 10.5 buffer solution for 16 hours at room temperature in the presence of benzoyl peroxide **109** in dichloromethane. These conditions were adopted from a report by Phanstiel[73] who developed this biphasic basic reaction which makes the oxygen of the peroxide bond more susceptible to the attack of the nitrogen nucleophile rather than at the carbonyl oxygen (Scheme 97).

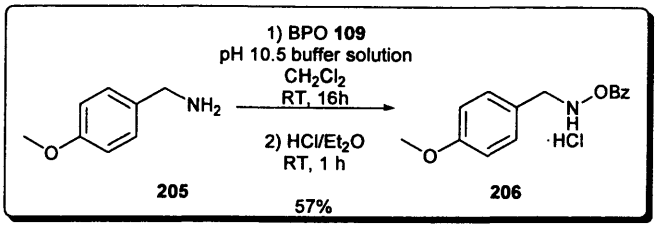


Scheme 97

On completion of the reaction the organic layer was separated and concentrated under reduced pressure to produce the free base of the reagent. The crude product was immediately dissolved in diethyl ether and treated with freshly generated HCl gas. This protonated the amine and the salt **184** crashed out of solution within 30 minutes.

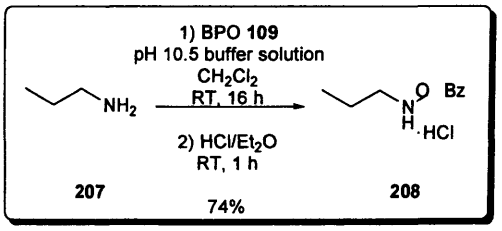
The method is a two-step process that gives a reproducible yield of 61% of the salt **184** whilst avoiding the need for purification by chromatography. The method therefore represents a significant improvement over the previous 3-step synthesis (Chapter 2).

In addition to the *N*-benzyl reagent **184** three other substituted reagents were synthesised for the purpose of developing a method for preparing 1,2-amino alcohols and provide diversity in the compounds generated. We prepared reagents with 4-methoxybenzyl **206** and propyl **208** amine functionalities. These amines were all present in the reductive amination paper by Abdel-Magid and co-workers suggesting a good choice for our investigations.[83]



Scheme 98

The 4-methoxybenzyl reagent **206** required the same conditions and reaction times as described above. The 4-methoxybenzyl amine **205** in the pH 10.5 buffer solution was rapidly stirred with the benzoyl peroxide in dichloromethane at room temperature for 16 hours to produce the free base. Again, the hydrochloride salt **206** crashed out of solution to give pale yellow crystals of the product in a 57% yield when HCl gas was bubbled through the crude reaction mixture (Scheme 98).

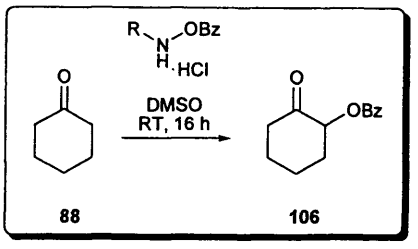


Scheme 99

The conditions were applied to propyl amine **207**. This salt **208** was generated in a good yield of 74% and required less time for salt formation. No purification was required as the pure salt precipitated directly from the reaction solvent.

4.3.3 Reaction

The first stage was to assess whether our new modified salts **184**, **206** and **208** had a similar reaction profile to that of our original reagent **107**. Each of the new reagents was reacted under standard conditions with cyclohexanone in the optimum α-oxygenation solvent, dimethyl sulfoxide, at room temperature for 16 hours. The results are displayed below in Table 9.

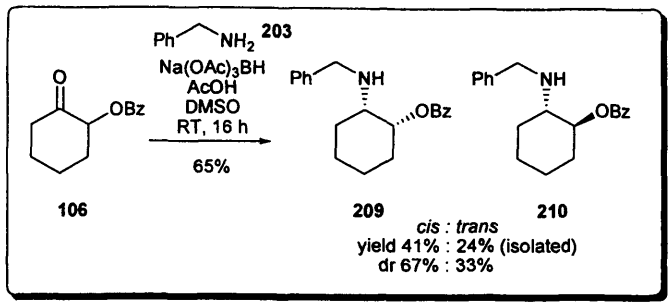


Reagent	R	Yield (%)
184	Benzyl	84
206	4-Methoxybenzyl	77
208	Propyl	68

Table 9

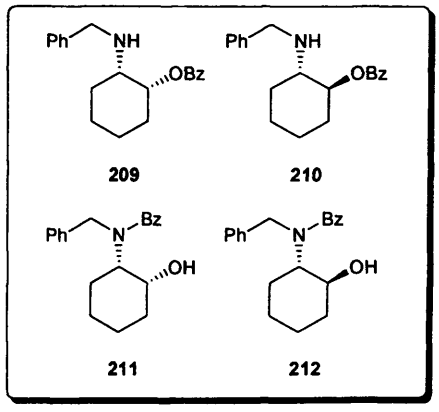
Analysis of the results show that each of the reagents **184**, **206** and **208** were successful in undergoing the reaction, suggesting the α-oxygenation procedure is tolerant of a variety of nitrogen substitution.

The next logical step was to take some of the 2-oxybenzoyl cyclohexanone **106** and to perform a reductive amination in dimethyl sulfoxide to see whether this stage of the proposed reaction sequence would be compatible. By using benzyl amine **203** as the amine the results shown below were obtained (Scheme 100).



Scheme 100

By the analysis of the ^{1}H NMR spectrum of the crude reaction mixture the reaction had reached 90% conversion after 5 hours but required 16 hours to go to completion. The overall yield was 65% (isolated) with the *cis* isomer **209** as the major diastereoisomer. Upon separation a number of studies were carried out on each isomer to determine connectivity and conjugation of each (Scheme 101). There were 4 possible products (**209–212**) shown below.



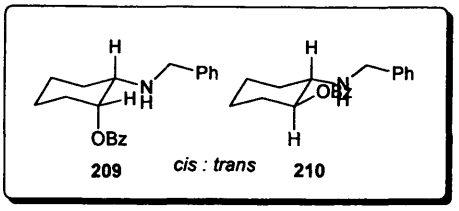
Scheme 101

Although it is ultimately the amino alcohol synthesis that was our goal, it was expected that the amides **211** or **212** would be the major compounds isolated. This is due to the nucleophilicity of the nitrogen lone pair which would facilitate migration of the benzoyl group.

IR spectroscopy was an important tool for assessing the nature of the compounds produced. Taking a spectrum of each of the two products, each showed characteristic peaks of esters at 1714 cm^{-1} present in both cases and failed to show any evidence of an amide carbonyl stretch.

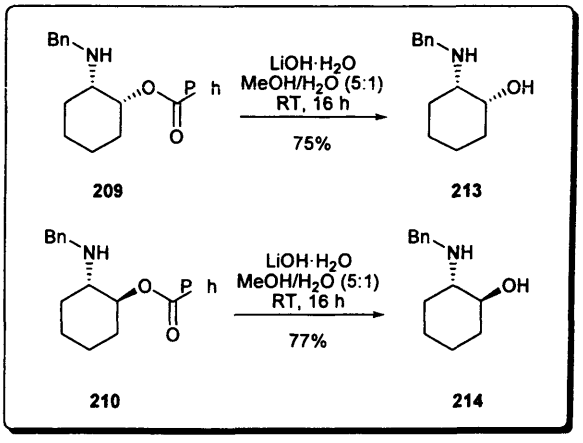
An alternative method to analyse the compounds was by performing an acidic wash where an amide would remain in an organic phase whereas an amine would generate a water soluble salt. Unfortunately our tests were inconclusive.

NMR studies and analysis of the ^{1}H, ^{13}C and dept spectra inferred the ester compounds **209** and **210** due to the chemical shifts of the CH protons. COSY, NOESY and nOe studies helped us assign the stereochemistry of the products and conclude the structures observed were the esters.



Scheme 102

The conformation of the connectivity came from ester hydrolysis which was key in assisting the structural assignment (Scheme 103).



Scheme 103

In both cases the free alcohol **213** or **214** was generated in good yield. This result reiterates the fact that we had the ester products from the reductive amination step and not the corresponding amides.

In an attempt to encourage migration of the benzoyl group in the 1,2-amino alcohol to give the corresponding amide both thermal and microwave heating was employed. These tests were completed to gain greater knowledge of the reactivity and stability of our products.

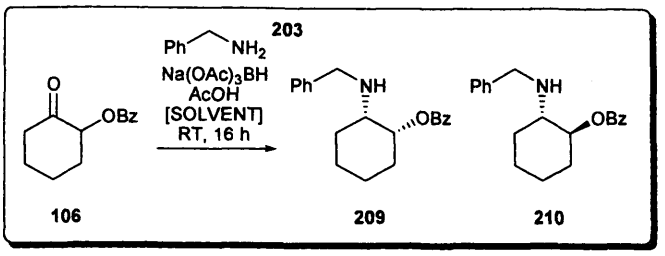
Using conventional methods both diastereoisomers were heated at varying temperatures (40 °C–100 °C) and a ^{1}H NMR spectrum was taken of the reaction mixture at 20 minute intervals. The only evidence of any migration occurred when the *trans* isomer was heated at 100 °C for a one hour period

Both compounds were additionally subjected to microwave heating at a temperate of 75 °C, at 100W for 15 minutes reaction time (5 minutes hold time). Again, there was no evidence of migration of the benzoyl group.

We can conclude from this that both amino alcohols are stable under our reaction conditions and problems previously anticipated with migration were not as significant as originally thought. The observation that only the *trans* isomer shows conversion to the amide can be rationalised by the fact that in the *trans*-conformation the amine and the carbonyl group are closer to each other in space.

4.3.4 Reaction optimisation

A solvent screen was completed to see the effects of different solvents on the reductive amination procedure. The results are displayed in the Table below:

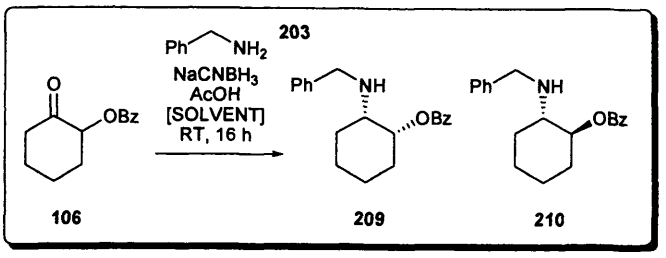


Solvent	*cis* Isomer 209	*trans* Isomer 210	Starting Material **106**
DMSO	1.00	0.53	0
CH_2ClCH_2Cl	1.00	0.21	0.04
MeOH	1.00	0.28	0.47
THF	1.00	0.37	0.09
DMSO/H_2O (9:1)	1.00	0.97	0.29
THF/H_2O (9:1)	1.00	1.24	0.27

Table 10

This data showed that polar aprotic solvents DMSO, THF and 1,2-DCE provide the best results. This can perhaps be rationalised by the fact that aprotic solvents do not act as hydrogen bond donors such that these solvent molecules solvate anionic nucleophiles relatively weakly. The result is that the reactivity of the nucleophile is raised. Protic solvents tended to return a lot of starting material **106**.

A solvent screen was also conducted repeating the reaction using sodium cyanoborohydride as the reducing agent. It was envisaged this would help us identify the importance of the hydride source and whether this altered selectivity. The results are presented below:



Solvent	*cis* Isomer	*trans* Isomer	Substrate	Diol
	209	**210**	**106**	**182/183**
DMSO	1.00	2.45	0	0
CH_2ClCH_2Cl	1.00	1.03	0	0.07
MeOH	1.00	0.76	0	0.07
THF	1.00	1.50	0.11	0.31
DMSO/H_2O (9:1)	1.00	1.15	0	0.45
THF/H_2O (9:1)	1.00	4.27	0.13	1.06

Table 11

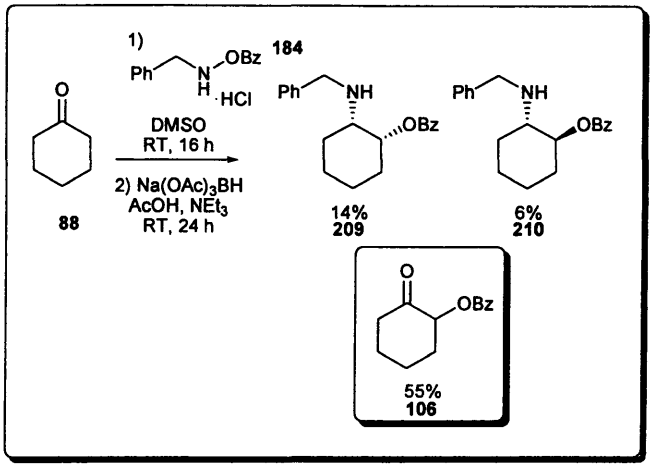
It can be seen that a general increase of the *trans* to *cis* ratio occurs on changing the hydride source, so altering the selectivity of this transformation. Additionally, the amount of starting material returned decreased but was replaced by significant presence of the diol isomers. This observation was not entirely unexpected when considering our earlier investigations into the reduction. However, from this study it was confirmed that the diol compounds **182** and **183** were formed in all solvents using sodium cyanoborohydride as the reducing agent. The presence of the 1,2-diol in the crude reaction mixture can create problems when attempting to isolate and purify the 1,2-amino alcohols **209** and **210**.

It was concluded that the best solvent for the overall one-pot process would be DMSO due to the apparent compatibility of the α-functionalisation and reductive amination steps using sodium triacetoxy borohydride as the reducing agent.

Attempting to combine the two steps in a one-pot reaction, cyclohexanone **88** was reacted with *N*-benzyl-*O*-benzoyl hydroxylamine hydrochloride **184** in DMSO for 16 hours (all starting material consumed by TLC) at room temperature. The reaction mixture was then

cooled to 0 °C and triethylamine, acetic acid and sodium triacetoxyborohydride were added. After a 16 hour period there was still α-functionalised intermediate **106** present so the reaction was left for an additional 8 hours. At this stage there was still evidence of the α-functionalised carbonyl by TLC, however, we decided to work-up the reaction. Inspection of the ^{1}H NMR spectrum of the crude mixture showed the 1,2 amino alcohol diastereoisomers **210** and **209** present in a 1:2 ratio.

Upon purification of the mixture, the compounds were isolated in a 14% and 6% yield for the *cis* **209** and *trans* **210** compounds respectively. Additionally, a significant amount of the 2-oxybenzoylated cyclohexanone **106** was recovered 55%.



Scheme 104

In an attempt to help the formation of the product the use of prolonged reaction times for the second step and additional amounts of sodium triacetoxyborohydride failed to improve conversion to the 1,2-amino alcohols **209** and **210**. The intermediate 2-oxybenzoylated cyclohexanone **106** still remained unreacted in significant quantities.

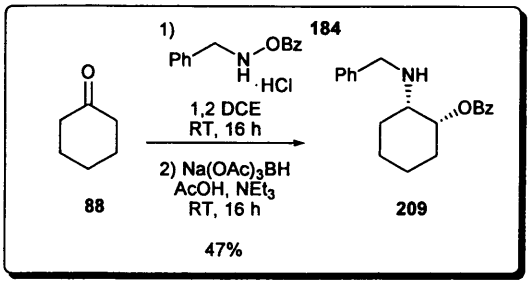
Desiccants were used to try to aid the transformation. By removing water after the α-oxygenation step we hoped to inhibit hydrolysis to the ketone, encouraging formation of the imine intermediate that can then be reduced to the amine products.

The desiccants examined were sodium sulphate, magnesium sulphate, triethyl orthoformate and 4Å molecular sieves. Each of these are well established techniques for removing water from a reaction mixture.

On analysis of the ^{1}H NMR spectrum of the crude reaction mixture it was concluded that the molecular sieves had a slight effect leading to a 20% yield with respect to the *cis* isomer **209** and 10% for the *trans* isomer **210**. However, the other techniques did not prove to be beneficial to the reaction.

In an attempt to produce the product in a greater yield in the one-pot process we altered the solvent to 1,2-DCE due to the observations in our solvent screen in the reductive amination process.

Cyclohexanone **88** and reagent **184** were reacted in the presence of 4Å molecular sieves for 16 hours (monitored by TLC) then the reducing agent was added at 0 °C along with acetic acid and triethylamine and stirring was continued for a further 16 hours.



Scheme 105

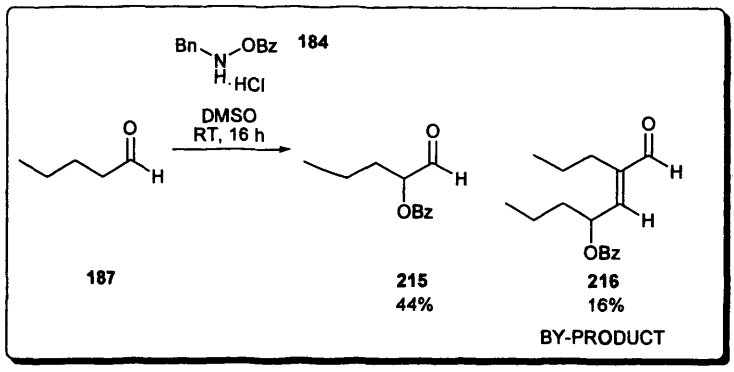
On inspection of the ^{1}H NMR spectrum of the crude reaction mixture we only observed the *cis* isomer **209** forming. Additionally, the spectra looked a lot cleaner compared to previous investigations. The purified compound was obtained in a much improved 47% yield.

To eliminate the problems associated with forming diastereoisomers our attention turned to using aldehydes as the substrates instead of ketones although we continued to use the benzylamine derived reagent **184** for the reactions and returned to using DMSO as the solvent of choice.

4.3.5 Using aldehydes

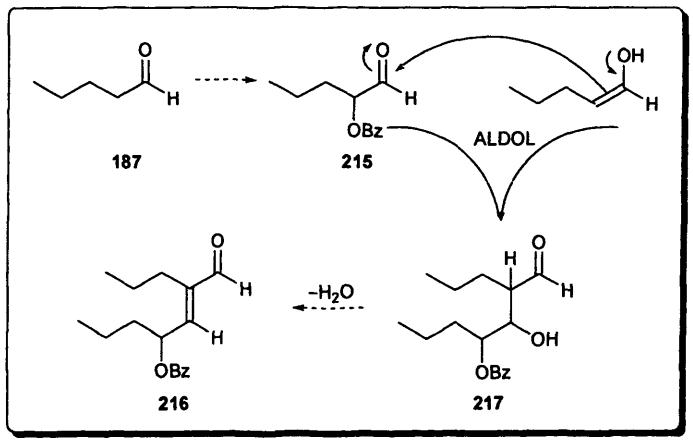
The first aldehyde examined was valeraldehyde **187**, which under standard conditions was reacted in DMSO at room temperature until all starting material was consumed by LCMS. The mixture was subjected to an aqueous work-up and purified by SP4 automated

column chromatography with an ethyl acetate/hexane solvent gradient to yield the α-oxybenzoylated valeraldehyde **215** in a moderate 44% yield.



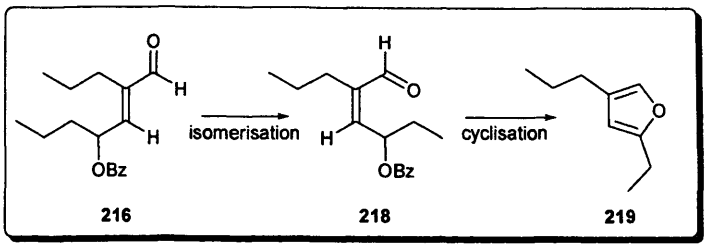
Scheme 106

From this reaction an unexpected by-product **216** was isolated during purification. It is believed that this product arises through initial formation of the α-functionalised product **106** followed by an intermolecular aldol condensation between the product **106** and another molecule of unreacted starting material **187** (Scheme 107).



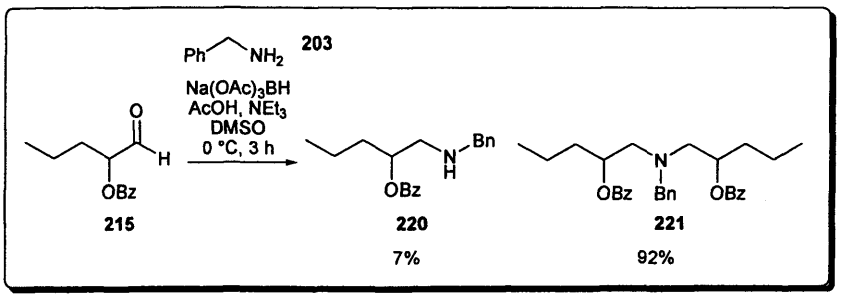
Scheme 107

This class of compound are useful precursors for the preparation of heterocyclic systems, and this method could be exploited in the preparation of furans (Scheme 108).



Scheme 108

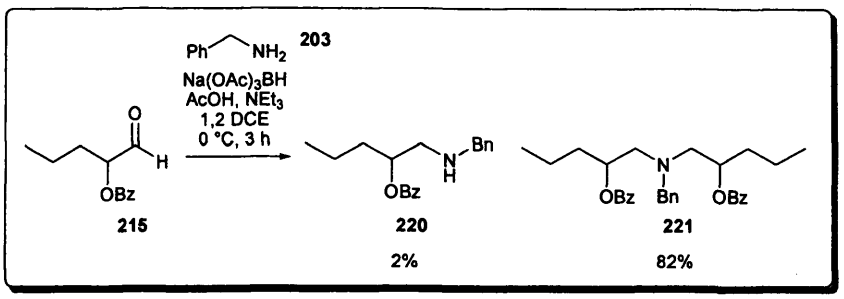
The isolated and purified 2-oxybenzoylated valeraldehyde **215** was then used for the reductive amination step by adding benzylamine, acetic acid and 4Å molecular sieves in DMSO. The mixture was cooled to 0 °C before the slow addition of the sodium triacetoxyborohydride. After the starting material was consumed (indicated by TLC and LCMS) a basic work-up was performed to generate another unexpected product **221**.



Scheme 109

The 1,2-amino alcohol **220** was the minor product formed in the reaction (7%). The major product appeared to be a doubly benzoylated compound. It suggested that the amine reductively aminates one molecule of the 2-oxybenzoylated aldehyde to generate the intermediate **220** which subsequently undergoes reductive amination with a second molecule of the starting material to produce the final compound **221** in a 92% yield. The product obtained was a mixture of diastereoisomers in 1:1 ratio, calculated by LCMS.

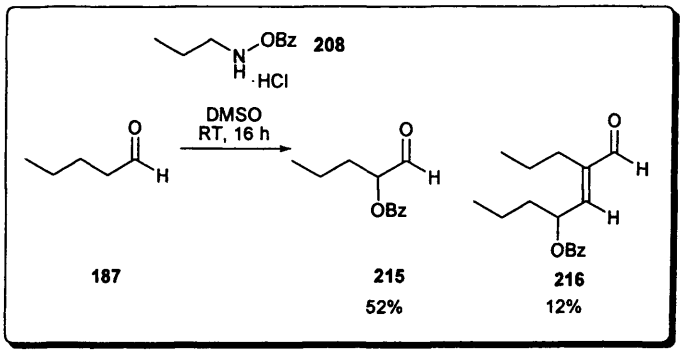
A change in the solvent to 1,2-DCE was considered in case it altered the selectivity and ratio of products formed. Once again, we obtained the tertiary amine **221** as the major product (Scheme 110).



Scheme 110

Removing the acetic acid (which is thought to catalyse the reaction) did not alter the selectivity of the reaction in both solvents. We therefore did not add acetic acid to any of our subsequent reactions.

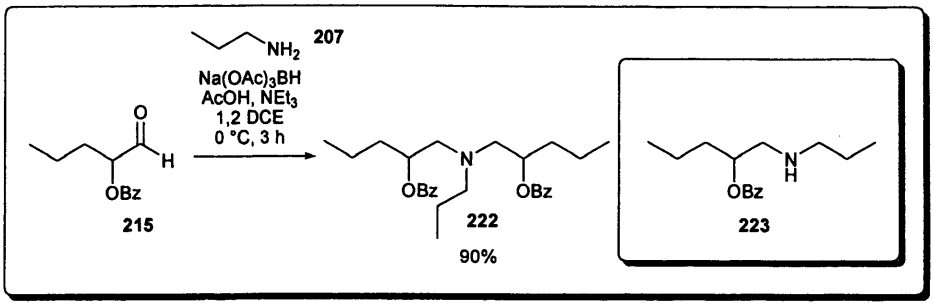
Due to the unexpected observations we became focused on the alternative reagent **208** in the hope that changing the electronics may alter the outcome of the reaction. Initially, valeraldehyde **187** was reacted with the salt **208** in DMSO to observe whether our first step was plausible. It was reacted as previously described and yielded the expected α-oxygenated product **215** in 52% after SP4 column purification using an ethyl acetate/hexane gradient (Scheme 111). The reaction also led to the aldol by-product **216** being isolated in 12% yield.



Scheme 111

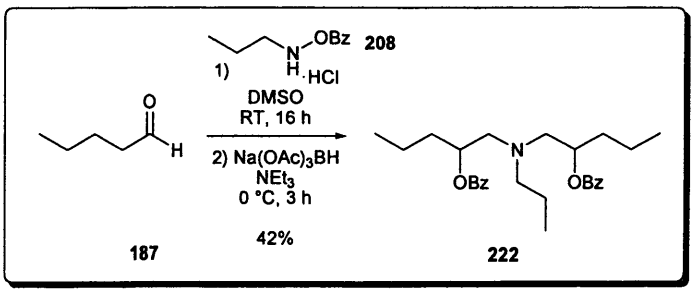
The 2-oxybenzoylated valeraldehyde **215** was then subjected to the reductive amination step with propyl amine **207** in the presence of 4Å molecular sieves in DMSO (Scheme 112). Upon cooling to 0 °C sodium triacetoxyborohydride was slowly added to the mixture. After the reaction was completed, a basic work-up was performed followed by SP4 purification. Unlike the benzylamine case only the doubly benzoylated derivative **222** was isolated in a 90% yield as a 1:1 mixture of diasteroisomers. There was no indication of the

1,2-amino alcohol **2 23** forming from inspection of the ^1H NMR spectrum of the crude reaction mixture.



Scheme 112

Reacting the salt **208** and aldehyde **187** in DMSO in the usual manner for 16 hours, followed by addition of the sodium triacetoxyborohydride and triethylamine at 0 °C we obtained the tertiary amine **222** in a yield of 42% as a 1:1 mixture of diastereoisomers.



Scheme 113

4.4 Conclusion

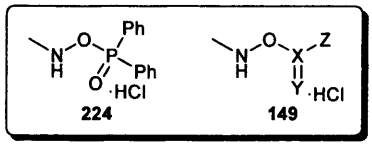
Despite the simplicity of our proposed transformations poor selectivity, low yields and formation of unexpected by-products were continually frustrating our investigations. We therefore elected to abandon this phase of our research.

Chapter 5

Modification of the Reagent

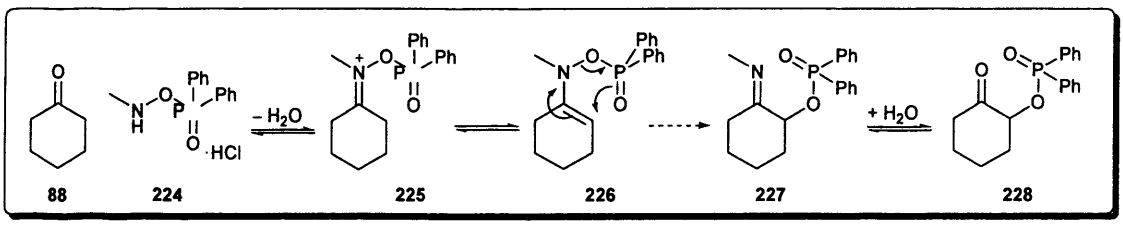
5.1 Introduction

Continuing the development and exploitation of the rearrangement we embarked on preparing a reagent to α-phosphonylate carbonyl compounds. It was envisaged this could be achieved by modifying the generic reagent **124** to incorporate the phosphate functionality **224** (Scheme 114).



Scheme 114

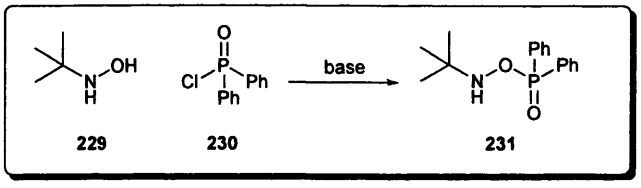
Previous work had been direct towards using carbon as the Z component within our reagent, consequently forming a new C-O-C bond within the oxygenation step. Our next goal was to form a new C-O-P bond, therefore, effectively altering the functionality on the α-hydroxy carbonyl compound formed. By extending our reagent family to encompass the phosphate group we were striving to improve the applicability and increase the scope of our methodology. It was believed that reaction of target reagent **224** with a carbonyl compound would proceed *via* a similar mechanistic pathway to provide accessto the α-functionalised product **228** (Scheme 115).



Scheme 115

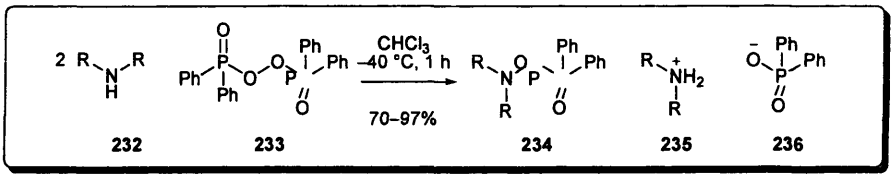
5.1.1 Literature Review

From an examination of the literature, it was apparent that *N*-unsubstituted-*O*-(diphenylphosphinyl) hydroxylamines are useful reagents.[83] However, reports on the *N*-mono substituted analogues were rare. One example within the literature was the preparation of the *N*-^{t}butyl analogue **231** which is the precursor for a heteroatom centred stable radical. It was prepared using diphenylphosphinyl chloride **230** and the hydroxylamine **229** under basic conditions (Scheme 116).[84]



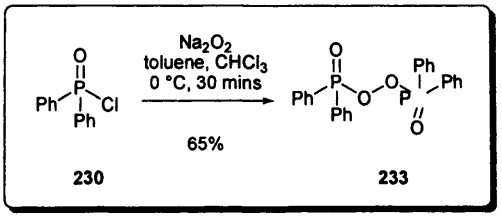
Scheme 116

The Sturtz group developed a method for the preparation of *N*-mono substituted diphenylphosphinyl hydroxylamines.[85] Concurrently, the Boche group also reported a similar method for the preparation of these phosphinyl hydroxylamine derivatives (Scheme 117).[86] Both required the formation of the bisdiphenylphoshinic peroxide **232**.



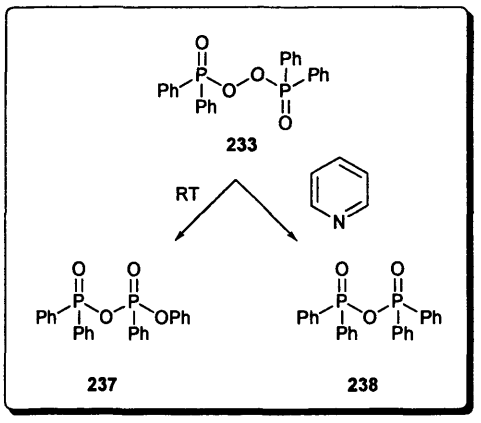
Scheme 117

Bis(diphenylphosphinic) peroxide **233** was first reported in 1965.[87] The peroxide is extremely challenging to prepare due to its susceptibility to decomposition. The method involves treatment of the phosphonyl chloride **230** with sodium peroxide at 0 °C to give the peroxide **233** in 65% isolated yield (Scheme 118).



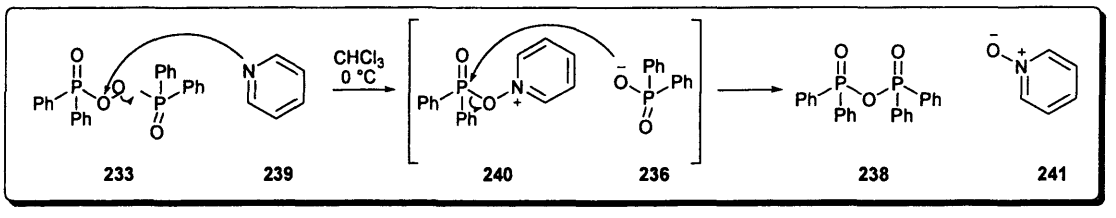
Scheme 118

Sturtz and co-workers described the mechanistic deterioration of the peroxide compound **233**.[88] It was reported to be stable at –80 °C but at room temperature they showed how the bis(diphenylphosphinyl) peroxide **233** in most solvents rearranged to give the unsymmetrical anhydride **237**. When the reaction is conducted in the presence of a base the peroxide can oxidise an amine.



Scheme 119

The phosphinic peroxides decomposition is also catalysed by acid conditions. Acid catalysis is complex due to parallel catalysis with the conjugate base. Furthermore, decomposition of the peroxide arising from a photochemical reaction produces an unsymmetrical anhydride **237**. The symmetrical anhydride **238** can be formed by eliminating a peroxo oxygen atom with stoichiometric amounts of pyridine or quinoline (Scheme 120). The pyridine was recovered unchanged which infers that the solvent is subsequently oxidised by the pyridine-*N*-oxide.

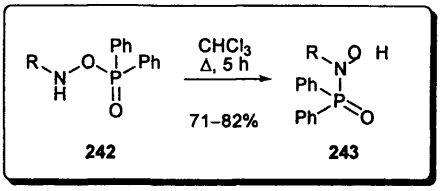


Scheme 120

The peroxide **233** was thought to be an effective oxidising agent as well as being able to dissociate homolytically to fragments with a radical site on oxygen. From these observations the high reactivity and instability of **233** is evident. Along with the potentially explosive nature of the peroxide this methodology has significant drawbacks. It can be

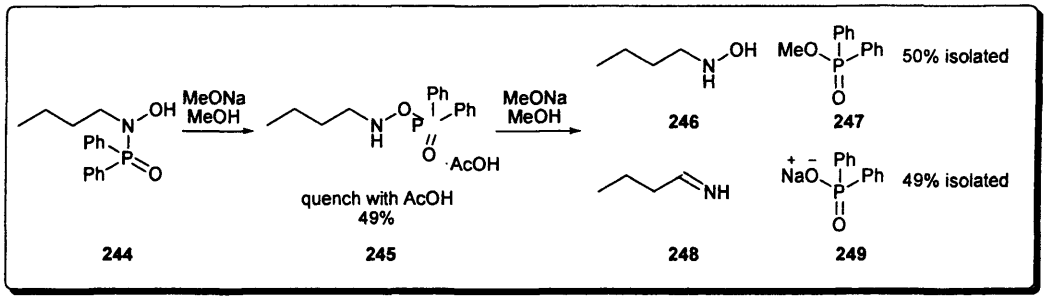
speculated that these limiting factors provide reasons why there is little reference to **233** being used in the literature.

The *N*–alkyl–*O*–diphenylphosphinyl hydroxylamine **242** has also been shown to be thermally unstable. It is found to rearrange when warmed slightly to generate the *N,N* disubstituted hydroxylamine **243** (Scheme 121).[85]



Scheme 121

It has also been reported that the *N*-alkyl-*N*-diphenylphosphinyl hydroxylamine **244** can rearrange to give the *N*-alkyl-*O*-diphenylphosphinyl hydroxylamine **245** by reacting it with sodium methoxide in methanol at room temperature.[89] The reaction must be quenched with acetic acid after one minute to isolate the *O* functionalised hydroxylamine **245** otherwise it decomposes. Decomposition proceeds via two pathways to give a mixture of products in equal amounts. By either undergoing attack at the phosphorus by the methoxide to give the phosphonate ester **247** together with the parent hydroxylamine **246** or through elimination to give the imine **248**.

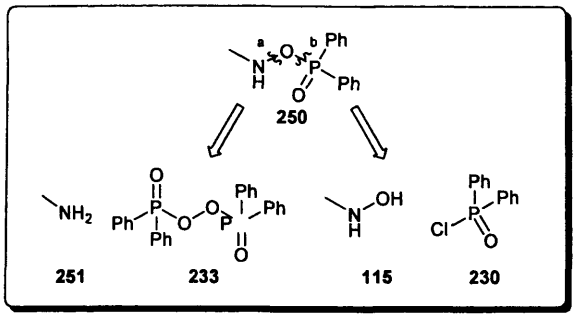


Scheme 122

5.2 Preparing the reagent

Embarking on tackling the synthesis of the *N*-methyl-*O*-diphenylphosphinyl hydroxylamine **250** we speculated there were two main disconnections we could apply. Firstly, by disconnecting across the N-O bond (a) to give the amine **251** and the diphenylphosphinyl peroxide **233** precursor. Alternatively, disconnecting across the O-P

bond (b) gave the hydroxylamine **115** and the diphenylphosphonyl chloride **230** as starting materials (Scheme 123).

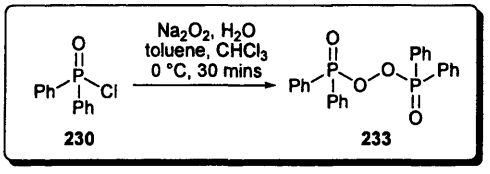


Scheme 123

This chapter describes our effects in preparing **224** by these two alternative routes.

5.2.1 Peroxide Route

Firstly, we attempted preparing the reagent **224** by replicating the peroxide protocol as the only reported synthesis of the *N*-methyl-*O*-diphenylphosphinyl hydroxylamine **250** was through reaction of the peroxide **233**. The method involved using sodium peroxide in water and adding diphenylphosphonyl chloride **230** in toluene slowly whilst keeping the reaction below 0 °C throughout.



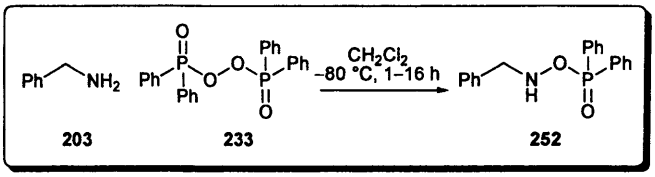
Scheme 124

Unfortunately, the peroxide proved extremely difficult to handle with it being essential to complete the purification of the product below 10 °C with alcohol free chloroform. Analysis also proved difficult due to the peroxides tendency to decompose in solution. The only characterisation data available was the melting point. However, due to the explosive nature of peroxides we wanted to avoid preparing and heating the dry compound until we had a better feeling for its reactivity.

When following the procedure exactly as reported a number of times in each case the reaction didn't go as expected. The peroxide **233** was reported to dissolve in alcohol-free chloroform. However, the compound prepared in our tests was insoluble. The only compound identified was the diphenylphosphonic acid.

Scouring the literature for other reports of research groups preparing the peroxide **233** to gain additional information. The only mention of the peroxide synthesis within the three reports simply referenced a paper by the Dannley group which was the method we had adapted.[85,86,88] It can be speculated that the problems are due to strict reaction conditions required which were not fully described within the literature.

Despite the lack of evidence inferring whether the peroxide was actually being formed the attempt to prepare the hydroxylamine analogue **252** was continued by repeating the proceedure in the literature. Taking the 'peroxide' compound prepared without purification it was reacted with benzyl amine **203** in dichloromethane at –80 °C .



Scheme 125

The crude product obtained was examined by ^{1}H NMR spectrum. Unfortunately, there was no evidence of the desired hydroxylamine **252** within the mixture of compounds formed.

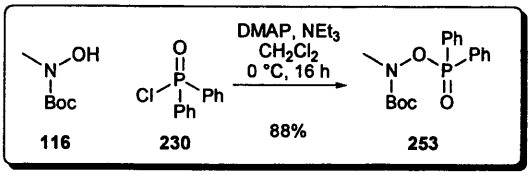
Various alterations were made to this second step. Including varying the temperature, prolonged and shortened reaction times, and increasing the equivalents of amine. The amine was also altered. However, none of the changes were successful in preparing the reagent.

It was the initial formation of the peroxide which appeared to be the problem with this methodology due to the peroxides high instability. Frustrated by the disappointing findings an alternative synthetic route to the *N*-substututed-*O*-(diphenylphosphinyl) hydroxylamine reagent was investigated.

5.2.2 *N*-Boc-*N*-methyl hydroxylamine

A 3-step protocol was devised similar to that used for previous reagent synthesis (Chapter 2 and 3). Using disconnection (a) across the O-P bond of the target reagent we can envisage preparing the reagent from the parent hydroxylamine **116** and diphenyl phosphinyl chloride **230**. Speculating that by protecting the hydroxylamine we could selectively *O*-functionalise the hydroxylamine we began our proposed synthesis.

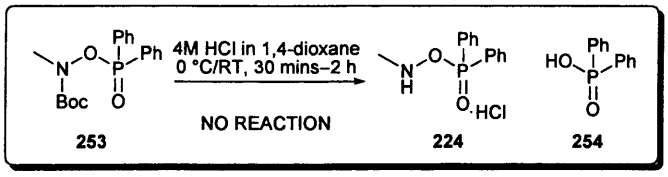
The known *N*-Boc-*N*-methyl hydroxylamine **116** was reacted with diphenyl phosphonyl chloride **230** under standard conditions (Scheme 126).



Scheme 126

Upon purification by column chromatography the *O*-functionalised hydroxylamine **253** was isolated in an excellent 88%.

Problems arose when trying to remove the Boc protecting group to generate the target hydroxylamine **224**. Under our standard acidic conditions that had proven so effective previously we were unable to isolate the target reagent **224**. Attempts initially focused on using 4M HCl in dioxane to remove the protecting group (Scheme 127).



Scheme 127

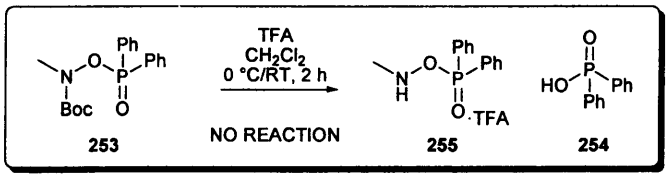
This gave diphenyl phosphonic acid **254** as the only stable phosphorus containing product. When monitoring the reaction by TLC it was observed that the substrate transforms straight to the acid. The acid was identified by comparison of the melting point, ^{1}H NMR spectrum and ^{13}C NMR spectrum to the literature reference. Clearly these conditions were too harsh.

The next logical step was to modify these conditions. Firstly, the reaction temperature was lowered to 0 °C but there was still no success and a similar result was obtained. Subsequently, the equivalents of acid used were lowered to both 1 and 2 equivalents. This still generated the acid **25 4**. Finally, the concentration of the reaction was altered. Not surprisingly, these runs gave the same result.

Altering the solvent was the next stage. The substrate **253** was dissolved in diethyl ether and 2M HCl in diethyl ether was added. Once again, no indication of the desired product **224** was obtained.

Additionally, saturated HCl in ethyl acetate was prepared (~7M) and used as the acid source. It was evident that the reagent was decomposing under these conditions. Lower temperatures, lower concentrations and less equivalents of HCl produced the same result.

Abandoning HCl as the acid source our attention focused on using trifluroacetic acid as a well-established alternative for Boc deprotection. By dissolving the substrate **253** in dichloromethane and adding 20 equivalents of the TFA at 0 °C the reaction was closely monitored by TLC and kept cold throughout. These conditions were successfully developed previously within the group for the removal of a Boc group from *N*-Boc-*N*-methyl-*O*-tosyl hydroxylamine.[90]



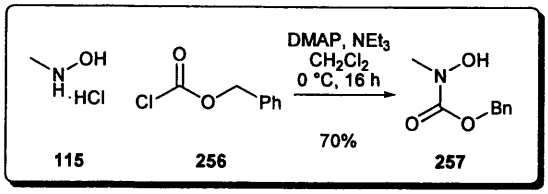
Scheme 128

Unfortunately, as before, the target reagent **255** was not produced but the diphenyl phosphonic acid generated instead. Decreasing the equivalents of TFA and lowering the reaction temperature did not result in the formation of the target compound **255** required.

At this point this route was discarded and our attentions turned towards using an alternative protecting group.

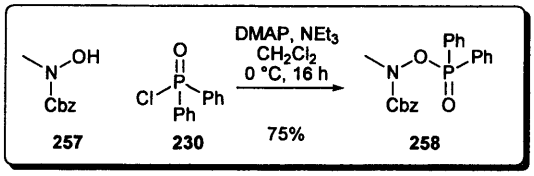
5.2.3 *N*-Cbz-*N*-methyl hydroxylamine

A 3-step procedure was devised similar to that used previously (Scheme 129). The initial step was to prepare the Cbz protected hydroxylamine **257**. Reaction of *N*-methyl hydroxylamine hydrochloride **115** with benzyl chloroformate **256** with triethylamine and a catalytic amount of DMAP in dichloromethane gave the *N*-protected hydroxylamine **257** in a respectable 70% yield.



Scheme 129

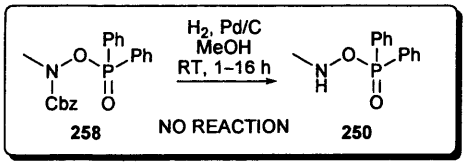
This compound was then reacted with diphenylphosphonyl chloride **230** under standard conditions to give the *O*-functionalised hydroxylamine **258** (Scheme 130).



Scheme 130

The required Cbz protected analogue **258** was generated in 75% yield after purification by flash chromatography. Having prepared a suitable precursor, we focused on removing the protecting group to produce the free hydroxylamine.

Our initial approach involved stirring the protected hydroxylamine **258** in the presence of Pd/C under an atmosphere of hydrogen (Scheme 131).

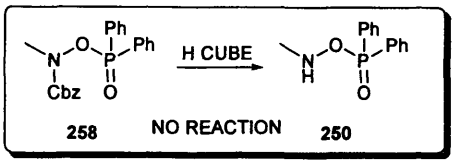


Scheme 131

Upon reacting *N*-Cbz-*N*-methyl-*O*-diphenylphosphinyl hydroxylamine **258** in methanol it was observed that diphenylphosphonic acid was forming rapidly. This was not entirely surprising with respect to our previous observations when trying to deprotect the Boc

analogue **250**. It can be inferred that the N-O bond of the hydroxylamine was too weak to sustain standard hydrogenation methods.

Due to the availability of a H-Cube hydrogenation apparatus within the laboratory the *N*-Cbz-*N*-methyl-*O*-diphenylphosphinyl hydroxylamine **258** was was subjected to alternative reduction conditions (Scheme 132).

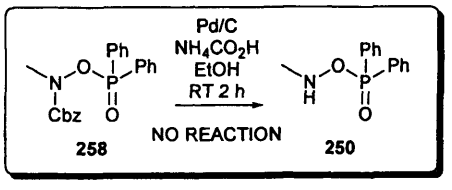


Scheme 132

The conditions adopted were standard for hydrogenation using this equipment. The catalyst used was palladium on carbon with HPLC 1 ml/min, 4–5 bar, 20 °C and H_2 (full mode/running 6 bar/pressure regulator 0 bar). However, it was observed that the diphenylphosphonic acid was once again isolated in 98% yield. Increasing the flow rate (2 ml/min) such that the starting material had less contact with the catalyst gave the same result suggesting this method of deprotection was not appropriate.

Finally, we moved our attention towards hydrogen transfer. Initially, the conditions attempted used ammonium formate as the hydrogen source. These were adopted from previous successful work within a different area of my research (Chapter 6). This is considered a mild form of hydrogenation.

Using the hydrogen transfer source with palladium on carbon in ethanol we again observed the formation of the diphenylphosphonic acid in 93% which was fast becoming expected. By carefully monitoring the reaction by TLC it was evident yet again the phosphonic acid derivative was forming directly without any indication of the desired hydroxylamine reagent **250** being formed as an intermediate.



Scheme 133

Due to the number of limitations and problems associated with synthesising this reagent it was concluded that this reagent was not a suitable addition to our family. The main objective was to gain diversity, but also through efficient, easily accessible reagents. This reagent proved to be extremely tricky to handle and prepare so decreasing its potential as a candidate for gaining diversity in our one-pot α-functionalisation reactions.

5.3 Conclusion

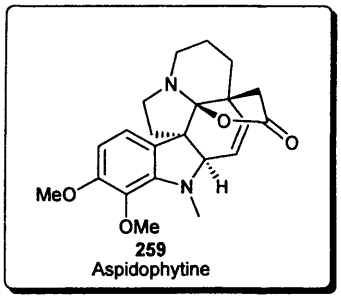
Within this part of the investigation we prepared a number of precursors to a hydroxylamine reagent with the potential to introduce a phosphonate group α- to a carbonyl functionality. We were unable to isolate any of the desired reagent **224** *via* a series of methods and concluded that the hydroxylamine bond, the source of the thermodynamic driving force for each of our transformations was too weak to allow for a simple and effective method for the preparation of our desired material. At this stage, our focus turned to the preparation of *N*-aryl hydroxylamines for exploitation within our rearrangement chemistry.

Chapter 6

New Chemistry of Hydroxylamine Derivatives

6.1 Introduction

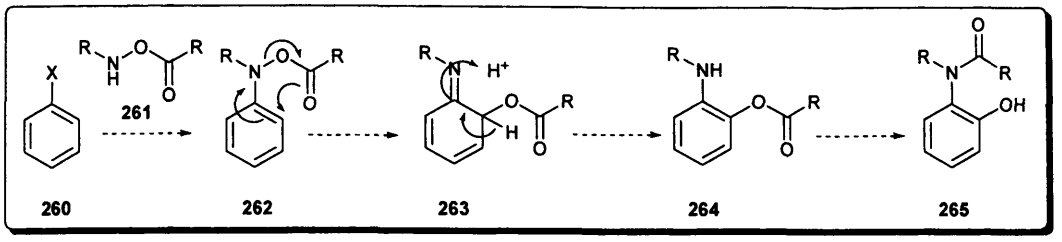
To extend our methodology in the one-pot α-functionalisation procedure our attention turned to using the [3,3] sigmatropic rearrangement strategy to form 1,2 difunctionalised aromatics in one-pot. These classes of compounds are important building blocks to more complex molecules, such as Aspidophytine **259** (Scheme 134). This intriguing structure has made its total synthesis of great interest for several research groups, including a cascade type mechanism by Nicholaou.[91] Hence, new methodology to introduce 1,2 difunctionalisation on an aromatic system would be a beneficial addition to the chemists tool box.



259
Aspidophytine

Scheme 134

The proposal was to couple our class of reagent **261**, for example *N*-methyl-*O*-benzoyl hydroxylamine hydrochloride salt **224**, with an aryl halide **260** (Scheme 135) in a Buchwald-Hartwig (B-H) manner forming the new nitrogen aromatic carbon bond. Then, by rearrangement the oxybenzoyl group could be introduced to the ortho position **263**. Rearomatisation would then led to the 1,2 difunctionalised aromatic **264**. It was expected that the benzoyl group would actually migrate to the more nucleophilic nitrogen rather than remaining as the oxybenzoylated group ultimately providing **265**.



Scheme 135

At the outset of this work there was little literature precedent for the coupling of hydroxylamines through B-H (palladium catalysis) or Ullmann (copper catalysis) chemistry but a vast range of conditions for coupling amines, amides and hydrazine derivatives were known within the literature.[92]

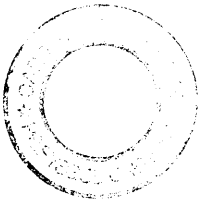
6.1.1 Literature Review

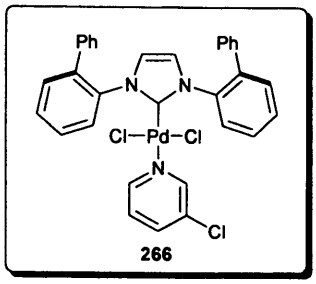
Palladium had played a central role in the formation of complex organic molecules through metal-catalysed cross coupling reactions, providing a powerful series of transformation to generate C–C, C–N, C–O, C–S bonds in excellent yields.[93]

Within the introduction of this thesis the known methods for the coupling of hydroxylamines in a Buchwald-Hartwig manner were discussed in detail. Both the Dongol[54] and Peng[55] used palladium with phosphine derived ligands to bring about the transformation (see P. 22).

There are problems associated with using tertiary phosphine ligands such as high cost, sensitivity and commercial availability. Few of these catalysts provide good activity for a wide range of reactions. From the literature it was evident that carbene based ligands have been reported as a good alternative that undergo similar reactions under milder conditions.[94]

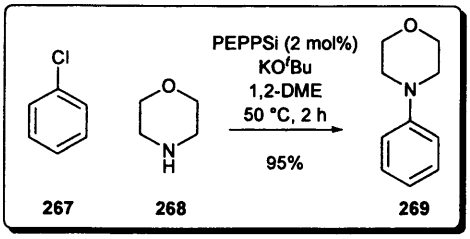
PEPPSi **266** (Scheme 136) is a recently available pre-catalyst for many of the traditional palladium catalysed cross-coupling reactions (Suzuki, Sonogashira, Heck, Buchwald-Hartwig and Negishi coupling) with its robust stability, air and moisture tolerance, and competitive cost make it a very desirable catalyst.[95] The palladium is a Pd(II) source and requires reducing to Pd(0) to generate the active catalyst which is usually accomplished under the reaction conditions. The carbene ligand binds to the metal more tightly than traditional phosphines and prevents metal dissociation.





Scheme 136

PEPPSi **266** has been shown to work very effectively in Buchwald-Hartwig type transformations for coupling aryl chlorides and bromides with an amine at temperatures ranging from room temperature to 50 °C in 1,2 dimethoxyethane using potassium *tert*-butoxide as the base (which also reduces the precatalyst to its active form). One example is shown below and gives excellent yields with only 2 mol% of catalyst (Scheme 137).

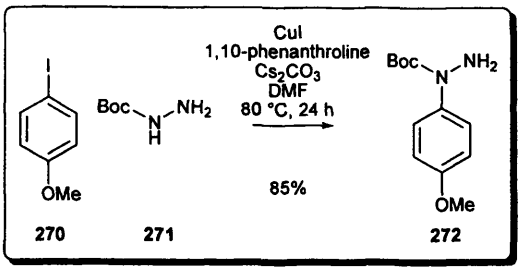


Scheme 137

With increasing high demand of alternative technology for the synthesis of diaryl ethers, alkylaryl ethers, diaryl amines, alkylaryl amines, diaryl thioethers, alkylaryl thioethers considerable research has also been directed towards development of Ullmann reactions. Despite the robust and reliable nature of Pd catalysed processes the use of Cu as an alternative and considerably cheaper source of catalyst has generated significant interest.[96]

In 2001 the Buchwald group reported a copper catalysed cross coupling of Boc protected hydrazines **271** with aryl iodides.[97] These conditions provided good yields for the *N*-arylation of the hydrazine derivatives with both electron donating and electron withdrawing substituents in both the *meta* and *para* positions. They also demonstrated the coupling of *ortho* substituted iodide substrates. This method exhibits significant advantages over other procedures due to the substrate generality, inexpensive catalyst and use of air sable copper iodide under experimentally simple, mild conditions. The original paper reported the use of copper iodide, 1,10-phenanthroline and caesium carbonate in 1,4 dioxane at 110 °C.

Buchwald has subsequently reduced the temperature to 80 °C in dimethylformaldehyde with just 1 mol% of the catalyst and 10 mol% of the bidentate diamine ligand (Scheme 138).[55]

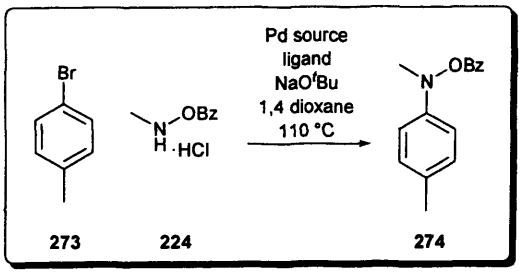


Scheme 138

Our aim in this work was to develop effective transition-metal catalysed couplings of hydroxylamines with aryl halides that could be exploited in our rearrangement technology for the functionalisation of aryl halides.

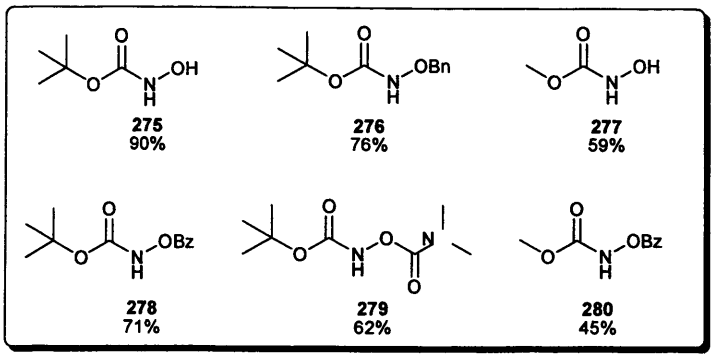
6.2 Developing conditions

Initially, we screened a range of palladium sources (palladium acetate and dipalladium dba) and phosphine ligands (BINAP, Xantphos and dppp) with sodium *tert*-butoxide in 1,4 dioxane and toluene at 110 °C (both conventional heating and in a microwave) (Scheme 139). The experiments were conducted using 4-bromotoluene **273** and the reagent *N*-methyl-*O*-benzoyl hydroxylamine hydrochloride **224**. In each experiment there was no evidence of the expected product by LCMS or ^{1}H NMR spectrum. Other than starting material, the only observation was the decomposition of the reagent to generate benzoic acid. These experiments inferred that these conditions were not suitable and perhaps less harsh conditions were required.



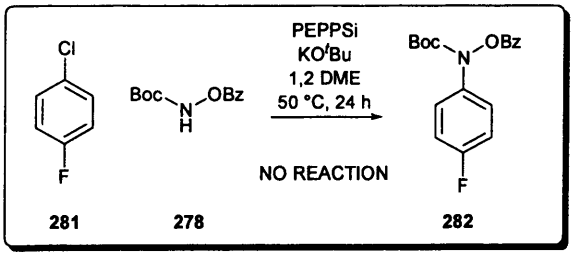
Scheme 139

Despite these frustrating initial investigations it was deemed appropriate to prepare a series of alternative hydroxylamine coupling partners with a view to altering the stability and electronic properties of the coupling partner. The reagents shown below **275–280** (Scheme 140) were all prepared in good yield using well established standard transformations.



Scheme 140

After examination of the literature we decided to investigate the coupling of **278** and **281** using PEPPSi as the palladium source due to the mild conditions and apparent versatility of the catalyst. Using the conditions reported for the B-H reaction for an amine with an aryl halide (PEPPSi (2 mol%), sodium *tert*-butoxide in 1,2 dimethoxyethane at 50 °C) we examined the coupling of our hydroxylamine derivatives. It was found that for each of the analogues **275–280** no apparent coupling was observed. An extensive screening involving increase in catalyst loading (up to 20 mol%), elevated temperatures (up to 80 °C), altering the base (NaO^{t}Bu and KO^{t}Bu) prolonged reaction times (up to 72 hours) or use of microwave technology were unsuccessful at promoting the desired reaction.



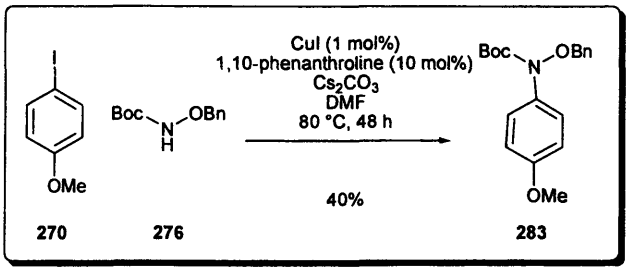
Scheme 141

Additionally, a significant amount of time was dedicated to the coupling of *N*-methyl-*O*-benzoyl hydroxylamine **278** and **224** (free base and hydrochloride salt) to 1-chloro-4-flurobenzene **281** with no apparent success, we therefore decided to examine copper as an alternative method to promote our desired transformation.

6.2.1 Using Ullmann conditions

Using copper iodide as an alternative catalyst we adapted the conditions developed by Buchwald for the coupling of hydrazine derivatives (copper iodide (1 mol%), 1,10-phenanthroline (10 mol%) and caesium carbonate (1.4 eq) in *N,N*-dimethylformamide at 80 °C) to each of our analogues **275–280**. It was observed that with one exception none of the results were very encouraging. All reactions returned starting material with no product formation and eventual decomposition of the reagents.

Our first break-through was with *N*-Boc-*O*-benzyl hydroxylamine **276** which gave an isolated yield of 40% of the desired product after 48 hours. Upon purification by flash chromatography it was evident that we had successfully coupled in the hydroxylamine **276** to give **283** (Scheme 142). This was achieved by using 1 mol% of copper iodide and 10 mol% of the 1,10-phenanthroline over 48 hours with 1 equivalent of aryl halide **270** with a slight excess of the hydroxylamine **276** (1.2 equivalents).



Scheme 142

From this result we began to optimize this new copper catalysed Ullmann coupling of hydroxylamines. Rationalizing that if we could optimize the conditions on this notoriously challenging electron rich substrate we stood ourselves in good stead for a generally applicable procedure. All conversions were calculated from the ^{1}H NMR spectrum of the crude reaction mixture (integration and comparison of the amount of aryl iodide starting material remaining compared to the product formed), and where stated, isolated yields were obtained by flash chromatography.

Altering the ratio of the aryl iodide to hydroxylamine

All reactions were conducted at 80 °C with 1 mol% of copper iodide and 10 mol% of 1,10-phenanthroline for 48 hours in DMF (1M).

Entry	Ratio aryl iodide 270 : hydroxylamine 276	% Conversion	Isolated yield (%)
1	1:1.2	41	40
2	1:3	60	57
3	3:1	65	62

Table 12

The best result was found to be with 3 equivalents of 4 -iodoanisole **270** and 1 equivalent of hydroxylamine reagent **276** (Entry 3) which gave a conversion of 65% (62% isolated yield).

Altering catalyst to ligand ratio and catalyst loading

All reactions were conducted at 80 °C with 3 equivalents of 4-iodoanisole ***270*** *and 1 equivalent of the N-Boc-O-benzyl hydroxylamine* ***276*** *in DMF at 1M concentration for 24 hours.*

Entry	Copper(I) iodide		1,10-phenanthroline		Conversion (%)
	Ratio	Mol% (%)	Ratio	Mol% (%)	Product **283**
1	1	1	10	10	19
2	1	2	10	20	22
3	1	2.5	10	25	30
4	1	5	2	10	36
5	1	5	5	25	63
6	1	5	10	50	84
7	1	5	20	100	70
8	1	10	10	100	80
9	1	20	2	40	63

Table 13

It was observed that the best combination was 5 mol% copper iodide and 50 mol% ligand (1:10 ratio), which appeared to be the superior combination in general (Entry 6). Catalyst loading below 5 mol% had low conversions (Entries 1–3) whereas loading above this did not increase the conversion (Entry 8 and Entry 9). From these experiments we adopted 5 mol% catalyst in combination with 50 mol% of the ligand 1,10-phenanthroline in our standard protocol.

Altering the reaction temperature

*All reactions were conducted with 5 mol% of copper iodide and 50 mol% of 1,10-phenanthroline and 3 equivalents of 4-iodoanisole **270** and 1 equivalent of the N-Boc-O-benzyl hydroxylamine **276** in DMF at 1M concentration for 48 hours.*

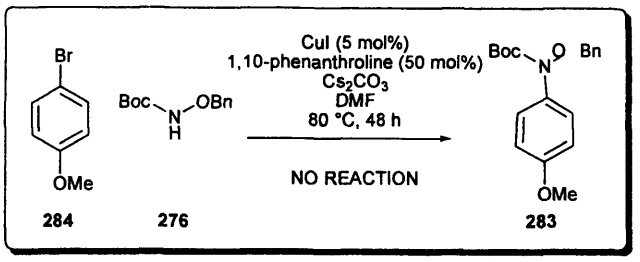
Entry	Temperature (°C)	% Conversion	Isolated yield (%)
1	RT	0	0
2	50	0	0
3	80	84	69
4	100	69	49

Table 14

It was found that the optimum temperature for the reaction was 80 °C (Entry 3). At lower temperatures (Entry 1 and 2) the reaction did not proceed within the 48 hours. At an elevated temperature (Entries 4) the conversion to the product was reduced due to formation of an A-B coupled aromatic byproduct. This altered the conversion percentage of the expected product significantly. Additionally, the byproduct had a very similar RF value to the product which created problems when attempting purify the desired product. The byproduct was not identified due to purification difficulties when isolating.

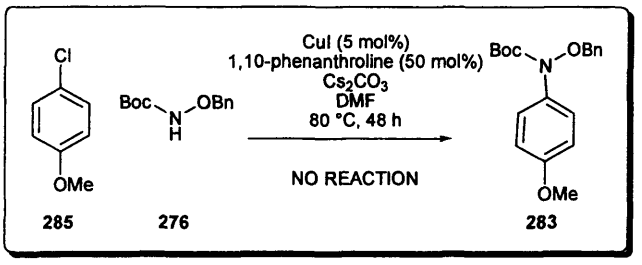
6.2.2 Altering the substrate

To identify the applicability of these conditions we attempted to alter the parent halide in the substrate from iodoaryl to bromoaryl derivatives. With our optimised reaction conditions only starting material was isolated from the reaction mixture with no indication of the desired product (Scheme 143).



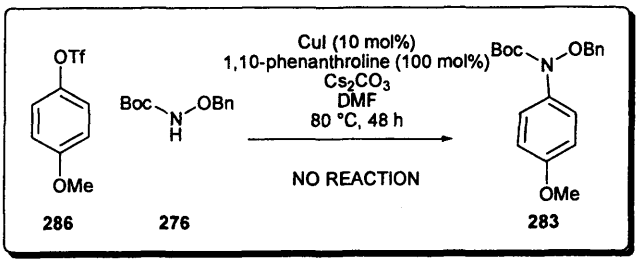
Scheme 143

A similar observation was made using 4-chloroanisole **285** as the substrate under the optimum reaction conditions where starting material was recovered (Scheme 144). Increasing the loading of copper iodide to 10 mol% and 1,10 phenanthroline to 100 mol% resulted in similar frustrations.



Scheme 144

Finally, a triflate was examined as the substrate to determine the scope of our reaction. We reacted phenol triflate **286** with the *N*-Boc-*N*-benzyl hydroxylamine **276** in DMF with 10 mol% of copper iodide, 100 mol% of 1,10-phenanthroline and caesium carbonate under nitrogen at 80 °C. Even after a prolonged reaction time of 48 hours there was no indication of the coupled product **283**.



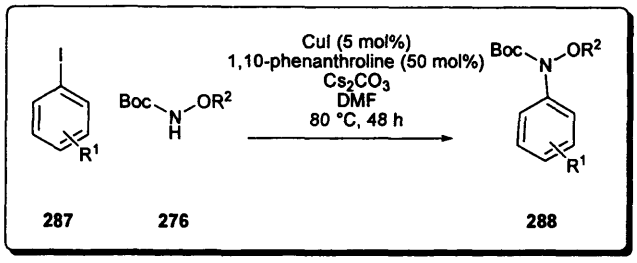
Scheme 145

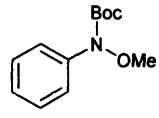
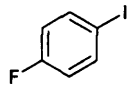
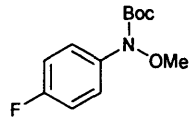
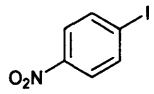
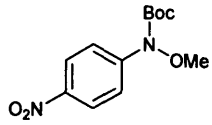
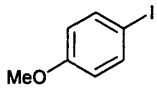
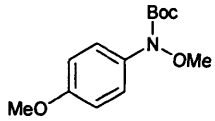
From these observations we were beginning to learn more about our reaction. In particular, that it required reactive aryl iodides for the transformation to occur. This can be

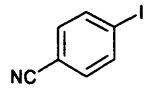
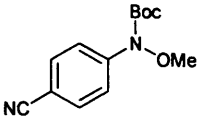
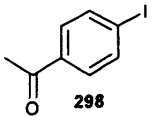
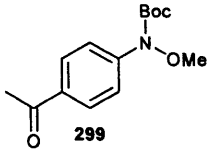
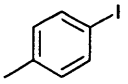
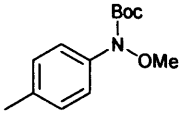
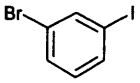
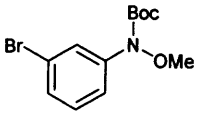
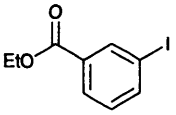
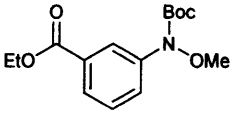
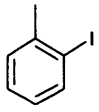
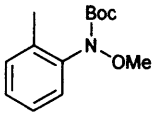
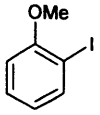
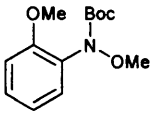
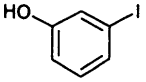
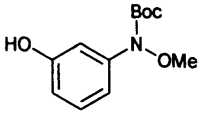
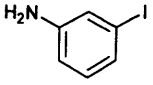
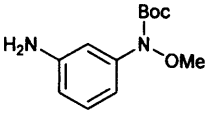
explained by the fact that in iodoaryl compounds the iodine–carbon bond is more polarisable and hence reactive.

6.2.3 Using the conditions

Using the optimised reaction conditions developed (5 mol% of CuI, 50 mol% 1,10-phenanthroline, 1.4 equivalents of Cs_2CO_3, 3 equivalents ArI, 1 equivalent of hydroxylamine **276** in DMF (1M concentration) at 80 °C). We examined the scope of the aryl iodide and hydroxylamine coupling partner (Table 14).



Entry	Aryl Iodide	R^2	Product	Yield (%)
1	 **289**	Me	 **290**	89
2	 **291**	Me	 **292**	72
3	 **293**	Me	 **294**	77
4	 **270**	Me	 **295**	69

5	 296	Me	 297	86
6	 298	Me	 299	73
7	 300	Me	 301	70
8	 302	Me	 303	74
9	 304	Me	 305	84
10	 306	Me	 307	0
11	 308	Me	 309	0
12	 310	Me	 311	0
13	 311	Me	 312	0

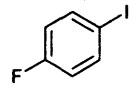
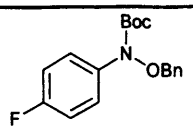
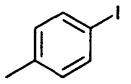
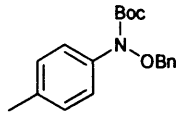
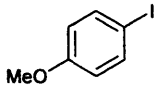
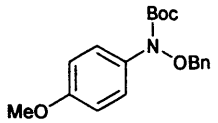
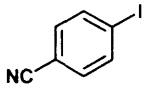
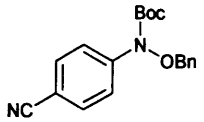
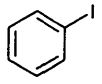
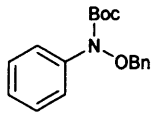
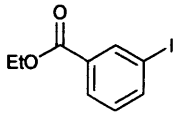
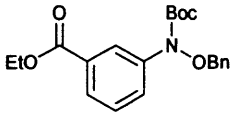
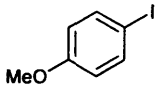
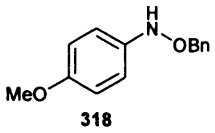
14	 291	Bn	 313	70
15	 300	Bn	 314	74
16	 270	Bn	 283	69
17	 296	Bn	 315	65
18	 289	Bn	 316	83
19	 304	Bn	 317	70
20	 270	Bn	 318	0

Table 14

It can be seen that the coupling works well for electron withdrawing (Entries 2, 3, 5, 6, 8, 9, 14 and 17), electron donating (Entries 4, 7, 15 and 16), halides (Entry 2, 6 and 14), aldehyde (Entry 6), esters (Entries 9 and 19), nitro (Entry 3) substituents to give the products in good yields (65–89%). Problems arise when using free alcohol (Entry 12) and amine (Entry 13) groups. Both these reactions gave a mixure of products. This could be due to the possibility of the hydroxyl and amine functionalities on the substrate undergoing coupling with the aryl iodide substrates.

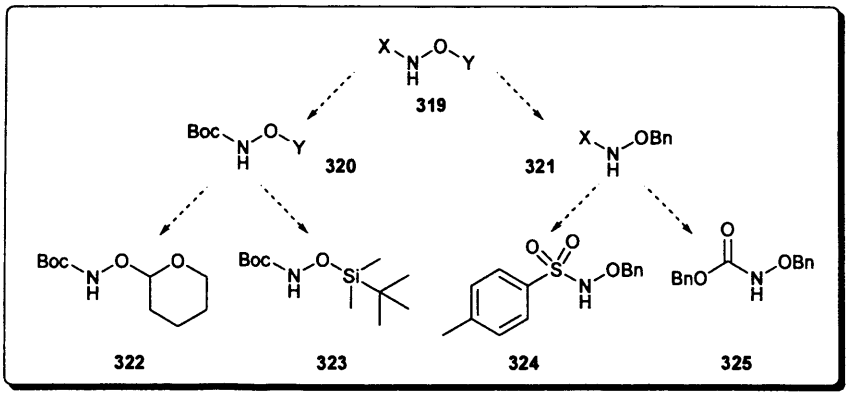
Additionally, it can be observed that the reaction occurs when the substituents are in the *para* (Entries 2–7 and Entries 14–17) and *meta* position (Entries 8 and 9) but not in the *ortho* position (Entries 10 and 11). This is possibly due to the steric hindrance associated with a substituent in this position. Considering methyl and methoxy groups are relatively small, this implies no other group would be tolerated in this position.

Additionally, *O*-benzyl hydroxylamine (Entry 20) failed to give the coupled product under the conditions developed. An increase in catalytic loading (10 mol% CuI) had no bearing on the reaction with the starting material remaining unconverted. It appears for the reaction to occur the nitrogen needs to be electron deficient.

In summary, we developed copper catalysed conditions for the coupling of hydroxylamine analogues into a variety of aryl iodide substrates in good yield and have started to explore the scope of the methodology and its versatility.

6.3 Altering the reagent

We decided to use the *N*-Boc-*O*-benzyl hydroxylamine reagent **276** as a scaffold to generate greater diversity within the reaction by placing different protecting groups at *N* and *O* position of the hydroxylamine.



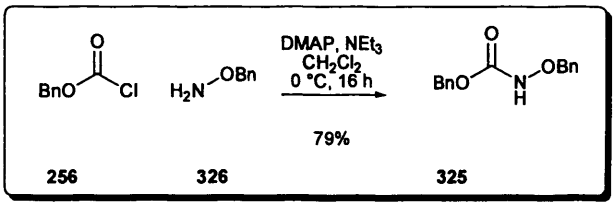
Scheme 146

By choosing the groups carefully we should hopefully be able to selectively remove each protecting group in the coupled product to functionalise the molecule further at either the nitrogen or oxygen substituent (Scheme 146).

6.3.1 Varying the *N*-substituent

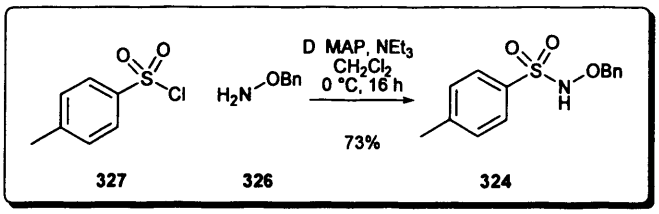
Following the success of the coupling conditions we began to look at altering the nature of the protecting group on the nitrogen to incorporate functionalities such as benzyl carbamate and tosyl into the reagent.

The *N*-Cbz-*O*-benzyl hydroxylamine reagent **325** was prepared using standard conditions. Reaction of benzyl chloroformate **256** and *O*-benzyl hydroxylamine **326** in CH_2Cl_2 with triethylamine and 2 mol% DMAP at 0 °C gave the product **325** in 79% yield.



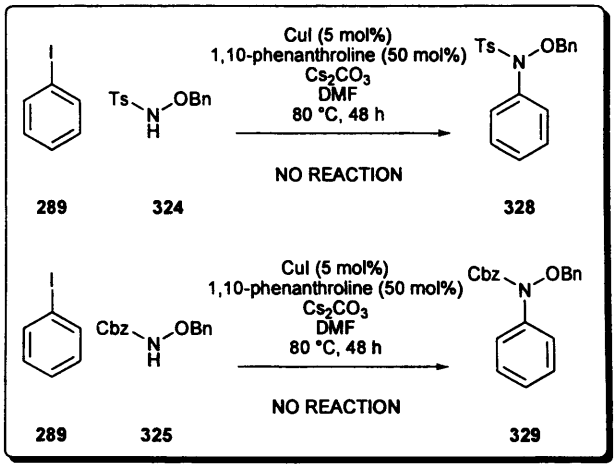
Scheme 147

Similarly, the corresponding *N*-tosyl-*O*-benzyl hydroxylamine reagent **324** was prepared from *para*-toluene sulfonyl chloride **327** and *O*-benzyl hydroxylamine **326** in the presence of triethylamine and a catalytic amount of DMAP in CH_2Cl_2 at 0 °C to generate the *N*-tosyl protected reagent **324** in 73% yield.



Scheme 148

Subsequently, both of these new reagents were reacted under the optimised protocol with iodobenzene **289** with 5 mol% copper iodide and 50 mol% of 1,10-phenanthroline. Surprisingly, neither of these reactions resulted in the desired products **328** or **329** (Scheme 149).

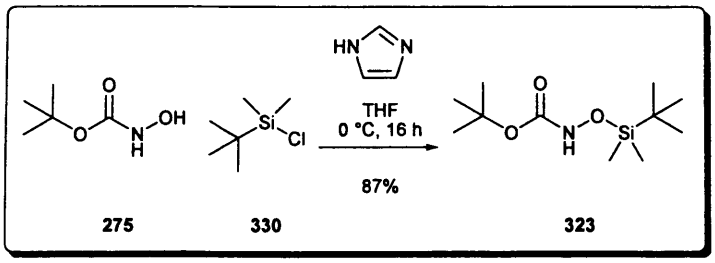


Scheme 149

Prolonged reaction times (up to 72 hours) and increasing the catalyst loading (10 mol%) gave no indication of product forming in either case. It appears from these results that these conditions are quite specific for *N*-Boc protected hydroxylamine substrates.

6.3.2 Varying the *O*-substituent

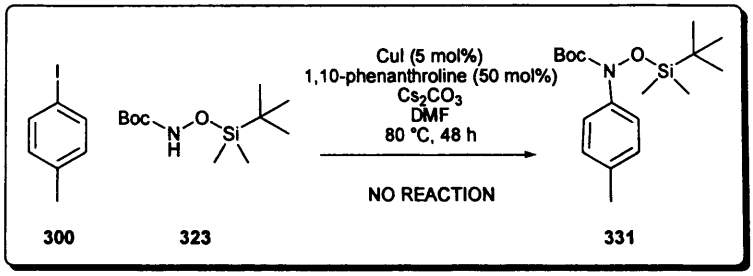
Next we varied the *O*-substituent incorporating a *tert*-butyldimethylsilyl group. We prepared the reagent by reacting the *tert*-butyl hydroxycarbamate **275** with *tert*-butyldimethylchlorosilane **330** in THF with imidazole as a catalyst. The reaction was monitored by TLC and the product was purified by flash chromatography to generate a viscous colourless oil **323** in 87% yield.



Scheme 150

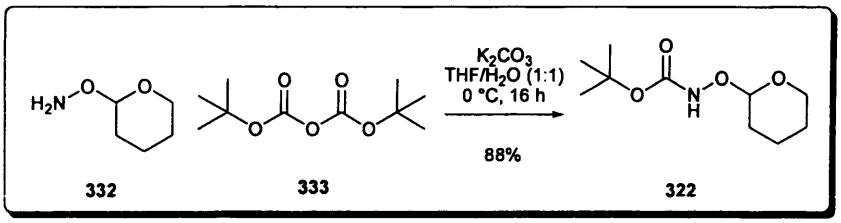
Upon isolation, the reagent was reacted with 4-iodotoluene **300** with 5 mol% copper iodide and 50 mol% of the diamine ligand. However, even after 72 hours there was no evidence of the coupled product **323** forming on inspection of the ^{1}H NMR spectrum of the

crude reaction mixture. Doubling the loading of catalyst and ligand did not encourage the coupling procedure.



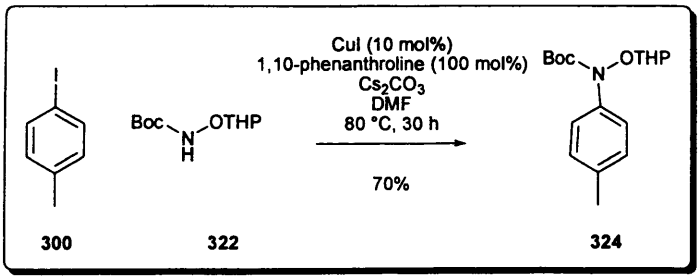
Scheme 151

Additionally, a *N*-Boc-*O*-tetrahydropyran hydroxylamine analogue **322** was prepared. The reagent was synthesized from *O*-tetrahydropyranyl hydroxylamine **332** by simple protection of the nitrogen by using Boc anhydride **333** with potassium carbonate in a THF/H_2O mixture (1:1) in 88% yield.



Scheme 152

Upon reacting **322** under the standard conditions with 4-iodotoluene **300** we were pleased to observe the coupled product **334** forming. However, the reaction was very sluggish with low conversion after 48 hours. Increasing the catalyst loading to 10 mol% and 1,10-phenanthroline to 100 mol% increased the isolated yield to a very respectable 70% after 30 hours reaction time.



Scheme 153

Using the 10 mol% of copper iodide and 100 mol% of 1,10-phenanthroline with 1.4 equivalents of caesium carbonate in DMF for 30 hours at 80 °C as our standard protocol for the reagent **322** we were able to successfully couple a range of aryl iodides (Table 15).

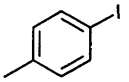
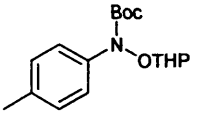
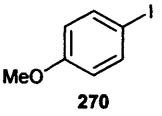
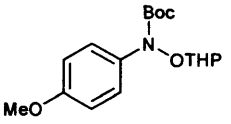
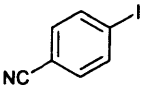
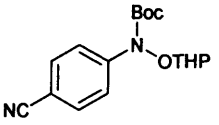
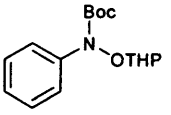
Entry	Aryl Iodide	Product	Yield (%)
1	 **300**	 **324**	70
2	 **270**	 **325**	52
3	 **296**	 **326**	76
4	 **289**	 **327**	80

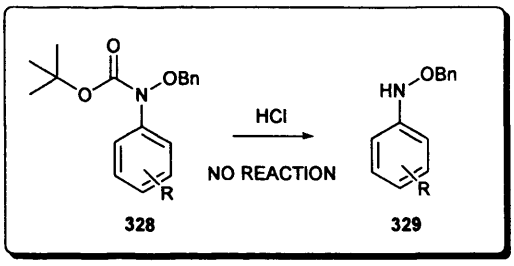
Table 15

6.4 Deprotection

Having developed a simple method for coupling a series of protected hydroxylamine substrates with aryl iodides we turned our attention to removal of the nitrogen and oxygen porotecting groups to allow further manipulation of the product.

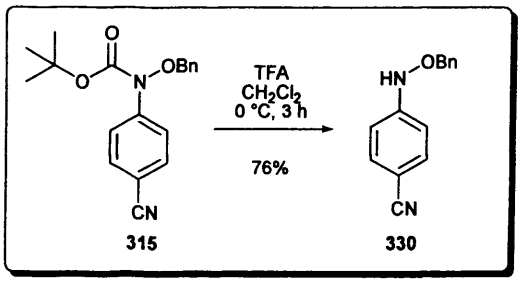
6.4.1 Removal of the Boc protecting group

Initial attempts to remove the Boc group with hydrochloric acid solutions (4M HCl in 1,4 dioxane, HCl in ethyl acetate, HCl gas, 2M HCl in diethyl ether) on several substrates were unsuccessful. Each gave multiple spots by TLC that proved difficult to purify.



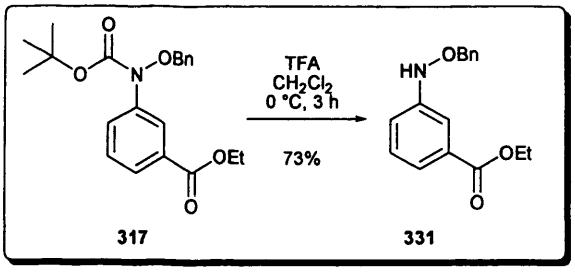
Scheme 154

Altering the acid to 20 equivalents of TFA in CH_2Cl_2 with the *N*-Boc-*N*-(4-benzonitrile)-*O*-benzyl hydroxylamine **315** at 0 °C for 3 hours (starting materials consumed) gave the deprotected compound **330** in an excellent yield of 76%. It was noted that the reaction mixture must remain at 0 °C or additional products began to form.



Scheme 155

Subsequently, we applied these conditions to *N*-Boc-*N*-(3-ethylbenzoate)-*O*-benzyl hydroxylamine **317** to give the product **331** in a good yield of 73% which was isolated by flash chromatography.

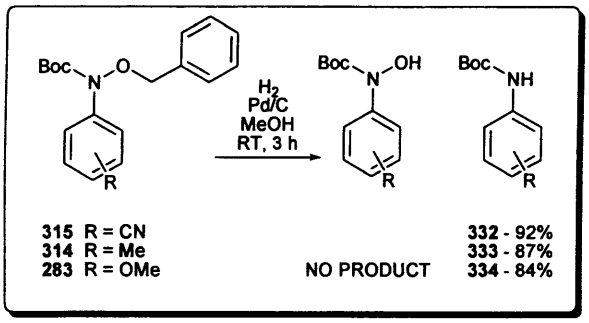


Scheme 156

6.4.2 Removal of the *O*-benzyl group

As our ultimate aim was to examine rearrangements of *N*-aryl hydroxylamines we put considerable effort into removing the oxygen protecting group. Our initial efforts were directed towards removal of the *O*-benzyl group. Firstly, we examined conventional methods of a hydrogen balloon with palladium on carbon in methanol. We reacted *N*-Boc-*N*-anisyl-*O*-benzyl hydroxylamine **283** with 10 mol% of the catalyst (monitored closely by TLC) and the product was isolated as a white solid by flash column chromatography.

On inspection of the melting point and chemical shifts in the ^{13}C NMR of the product it was realized we had produced the aniline **334** (84%), rather than the desired hydroxylamine. There was evidence in the ^{1}H NMR spectrum of the crude reaction mixture of the hydroxylamine product but it was less than 5% and was not isolated.

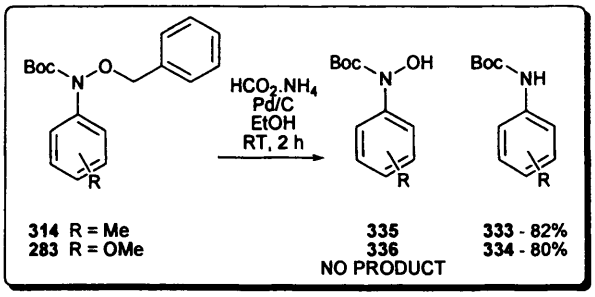


Scheme 157

Lowering the catalyst loading had no bearings on the resulting product. It was evident from the TLC that the free hydroxylamine did not appear first then reduce down to the aniline, the substrate **283** reducing directly to the aniline **334**.

Using the *N*-Boc-*N*-toluene and the *N*-Boc-*N*-4-cyanophenyl analogues **314** and **315** as substrates with differing electronics gave the same result, the anilines **333** and **332** being isolated in 87% and 92% respectively.

Further attempts to remove the benzyl group involved the use of a hydrogen transfer catalyst. Within the literature a report suggested that using ammonium formate a *O*-benzyl hydroxylamine could be deprotected.[98] Under these conditions we reacted *N*-Boc-*N*-anisoyl-*O*-benzyl hydroxylamine **283** with 6 equivalents of ammonium formate over palladium on carbon in ethanol for 3 hours (monitored by TLC).

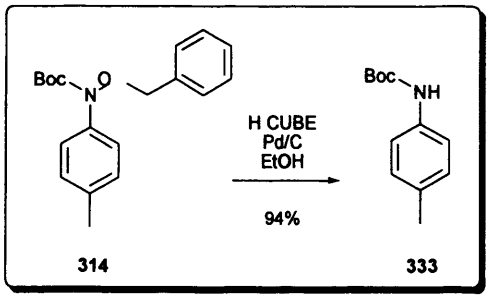


Scheme 158

Again we produced the aniline **334** in 80% yield with no evidence of the desired hydroxylamine **336** within this reaction.

Altering the substrate to *N*-Boc-*N*-tolyl-*O*-benzyl hydroxylamine **314** didn't provide the desired product and gave similar results to those obtained previously (82%).

Finally, we tried to use a H-Cube™ to remove the benzyl group. Using a 5 mol% palladium on carbon cartridge we passed through our coupled product, *N*-Boc-*N*-(4-tolyl)-*O*-benzyl hydroxylamine **314**, in ethyl acetate at 1 ml min^{-1}, 4–5 bar at a 20 °C in full hydrogen mode. It was observed yet again that the analine **333** was formed in an excellent yield of 94%. Increasing the flow rate up to 3 ml min^{-1} was also unsuccessful (Scheme 159).

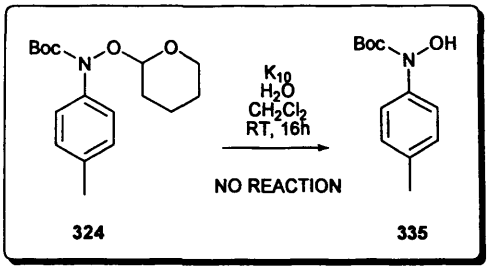


Scheme 159

We resigned to the fact that the N-O bond was too weak to survive hydrogenation conditions and abandoned our attempts to remove this oxygen protecting group.

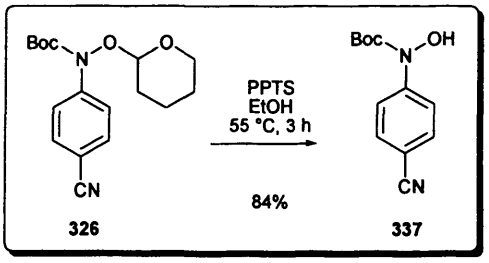
6.4.3 Removal of the THP group

Initial attempts at removing the THP group from our substate with montmorillonite K_{10} failed. Reacting *N*-Boc-*N*-anisole-*O*-THP hydroxylamine **324** in CH_2Cl_2 with a drop of water the presence of K_{10} gave no indication of the product **335**.[99]



Scheme 160

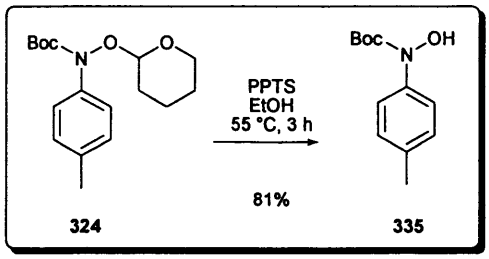
Due to the problems that arose when trying to remove the benzyl group we wanted extremely mild conditions to prevent the reaction of the compound to the aniline product. Our next attempt at removing the THP group involved reacting our *N*-Boc-*N*-tolyl-*O*-THP hydroxylamine **326** with 10 mol% of pyridinium *para*-toluene sulfonate (PPTS) in ethanol for 3 hours (starting material consumed by TLC) at 55 °C (Scheme 161).



Scheme 161

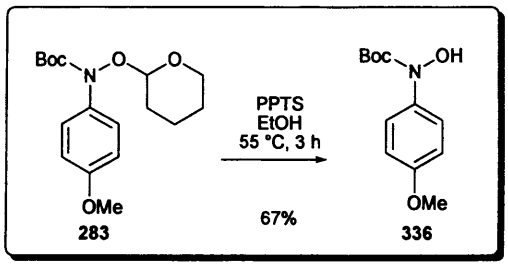
The product was isolated in 84% yield. On analysis of the melting point and ^1H NMR spectra it was evident we had the desired hydroxylamine product **337**.

We also applied these conditions to hydroxylamine analogue **324** to generate the corresponding deprotected product **335** in good yield of 81% (Scheme 162). This suggested the conditions would be generally applicable to different substrates providing access to the required hydroxylamine.



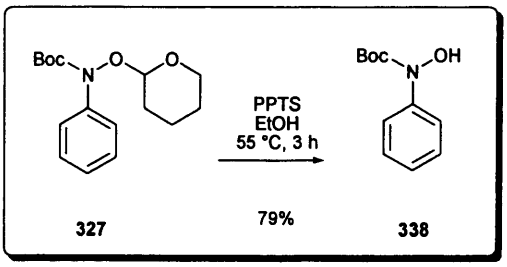
Scheme 162

Additionally, the *N*-Boc-*N*-anisoyl-*O*-THP hydroxylamine **283** was subjected to these reaction conditions to give the free hydroxylamine **336** in a 67% yield.



Scheme 163

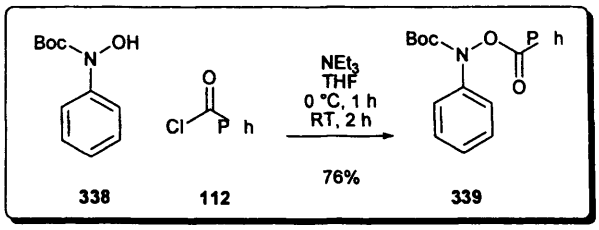
The deprotection was also performed on *N*-Boc-*N*-phenyl-*O*-THP hydroxylamine **327** to produce the free hydroxylamine **338** in a good 79% yield.



Scheme 164

6.5 Working towards the rearrangement

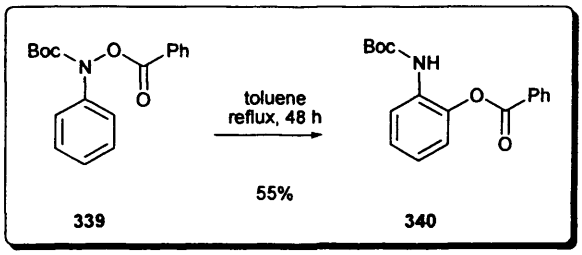
We progressed within the project by striving towards attempting the rearrangement step by reacting *N*-Boc-*N*-phenyl hydroxylamine **338** with benzoyl chloride in THF under basic reaction conditions for 1 hour at 0 °C and 2 hours at room temperature (Scheme 165).



Scheme 165

The functionalized product **339** was isolated by flash column chromatography in 76% yield.

With the resulting *N*-Boc-*N*-phenyl-*O*-benzoyl hydroxylamine **339** in hand it was found that by heating under reflux in toluene for 48 hours in fact gave the rearranged product **340** in a 55 % yield (Scheme 166).



Scheme 166

6.6 Conclusions

We have effectively developed conditions for coupling hydroxylamine analogues to a variety of aryl iodides. We have prepared a number of hydroxylamine reagents to incorporate different protecting groups on both the nitrogen (Boc) and oxygen (methyl, benzyl, tetrahydropyran), to couple into the aryl iodide. The scope of the reaction was examined by using substrates with varying functionalities (electron-withdrawing, electron-donating, aldehydes, esters, ketones, halides) in the *para* and *meta* positions of the aryl iodides. We have also found limitations when trying to use *ortho* substituted aryliodides, using a free alcohol or amine on the aryl iodides and the inability to vary the nitrogen protecting group from Boc on the reagent.

At this stage our investigations were terminated. Subsequent work within the group has optimised conditions for the rearrangement process,[100] allowed for the development for conditions for the Pd catalysed coupling of aryl iodides, bromides and chlorides[101] and developed alternative methods to prepare hydroxylamine substrates from nitroarenes.[102] This has allowed for further exploitation of the rearrangement strategy as a method to access *ortho* hydroxy anilines.

Experimental

Reagents were obtained from Aldrich, Lancaster and Fluka chemical suppliers. Solvents and reagents were purified according to the procedures of Perrin, Armarego and Perrin.[103] Dichloromethane was dried by refluxing over, and distilling from calcium hydride. Ethanol was dried by refluxing over magnesium, followed by distillation. Toluene was dried over sodium wire for twenty-four hours prior to use. Anhydrous diethyl ether was obtained by distillation from sodium benzophenone ketyl. Light petrol refers to petroleum ether 40–60 °C.

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

TLC analysis refers to analytical thin layer chromatography, using aluminium-backed plates coated with Merck Kieselgel 60 GF_{254}. Product spots were viewed either by the quenching of UV fluorescence, or by staining with a solution of 2 % aqueous potassium permanganate. Chromatography refers to flash column chromatography using head pressure by means of compressed air according to the procedure of Still,[104] using Merck Kieselgel 60 H silica or Matrix silica 60.

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

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

^{1}H NMR spectra (δ_H) were recorded using an Avance Bruker DPX 400 instrument (400 MHz) or an Avance Bruker DPX 500 (500 MHz), with ^{13}C NMR spectra (δ_C) recorded at 100

MHz or 125 MHz respectively. Chemical shifts (δ_H and δ_C) were recorded in parts per million (ppm) from tetramethylsilane (or chloroform) and are corrected to 0.00 (TMS) and 7.27 ($CHCl_3$) for ^1H NMR and 77.3 ($CHCl_3$), centre line, for ^{13}C NMR. The abbreviations s, d, t, q, sept., m, and br, denote singlet, doublet, triplet, quartet, septet, multiplet and broadened resonances, respectively; all coupling constants were recorded in hertz (Hz).

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

General experimental procedure for the α-oxyacylation of carbonyl compounds:

The carbonyl compound (1.02 mmol) and hydroxylamine hydrochloride (1.02 mmol) were dissolved in dimethyl sulfoxide (3.6 mL) and the resultant mixture stirred at room temperature or 50 °C until TLC analysis showed the reaction to be complete. The solution was subsequently diluted with ethyl acetate (50 mL) and washed repeatedly with saturated brine (5 × 50 mL). The organic fraction was dried (magnesium sulfate), concentrated *in vacuo*, and the crude product purified by flash column chromatography (4:1 light petroleum/ethyl acetate) to yield the product.

General methods for the preparation of hydroxylamine reagents:

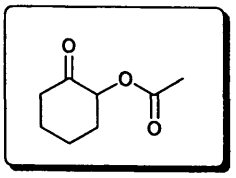
Method 1: A solution of *N*-Boc-*N*-methyl hydroxylamine (2.03 g, 15 mmol), 4-dimethyl amino pyridine (184 mg, 10 mol%) and triethylamine (2.08 mL, 15 mmol) in dichloromethane (35 mL) was cooled to 0 °C prior to slow addition of the acyl chloride (15 mmol). The reaction was allowed to warm to room temperature and stirred for 16 hours. Evaporation under reduced pressure gave a crude product, which was dissolved in CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ (2 x 20 mL), water (30 mL) and brine (30 mL). The organic layers were combined, dried over Na_2SO4 and concentrated and the product purified by flash column chromatography ((1:5) ethyl acetate/petroleum ether) to yield the *N*-protected-*O*-acyl hydroxylamine.

The *N*-Boc protected hydroxylamine (39.8 mmol) was dissolved in anhydrous diethyl ether at 0 °C. Gaseous hydrogen chloride (generated from reacting concentrated sulfuric acid (50 mL) and ammonium chloride (50 g)) was bubbled through the cooled solution for a period of 2 hours whilst stirring. The precipitate was collected under filtration to yield the hydoxylaminereagent.

Method 2: The carboxylic acid (40 mmol) was added portion wise to a solution of *N,N* carbonyl diimidazole (6.5 g, 40 mmol) in CH_2Cl_2 (60 mL). Once effervescence has finished *N*-methyl hydroxylamine hydrochloride (3.3 g, 50 mmol) was added and the resultant mixture stirred for 30 minutes at room temperature. CH_2Cl_2 (150 mL) was added and the organic phase was washed with cold 1M HCl (30 mL), aqueous $NaHCO_3$ (30mL) and dried over Na_2SO_4. Under reduced pressure approximately half the solvent volume was removed and replaced by dry diethyl ether (80 mL). HCl gas (generated from reacting concentrated sulfuric

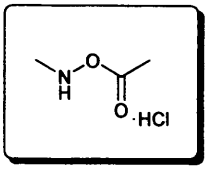
acid (50 mL) and ammonium chloride (50 g)) was bubbled through the reaction mixture at 0 °C for ten minutes and the resultant precipitate was collected by filtration to yield the reagent.

2-Acyloxy cyclohexanone 95[105]



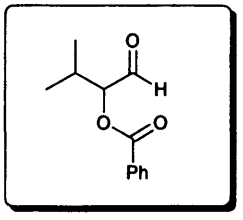
Following the general α-oxygenation procedure the title compound was isolated as a colourless oil (107 mg, 67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15–5.08 (m, 1H), 2.44–2.23 (m, 3H), 2.09 (s, 3H), 2.01–1.54 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7 (s), 170.1 (s), 76.6 (d), 40.7 (t), 33.1 (t), 27.2 (t), 23.8 (t), 20.8 (q).

***N*-Methyl-*O*-acyl hydroxylamine hydrochloride 102**[106]



Following general method 1 the title compound was prepared as a colourless solid (2.7 g, 95%); Mpt 87–89 °C (Mpt Lit 96–98 °C); IR (nujol) 3437, 1796 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d^6) δ 9.55 (bs, 2H), 2.97 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d^6) δ 166.7 (s), 35.6 (q),18.1 (q); MS (APCI) 91 *m/z* $[M+H]^{+}$.

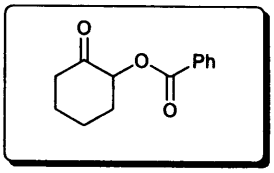
2-Formyl-2-methylpropyl benzoate 105[71]



Following the general procedure the title compound was isolated as a colourless oil (180 mg, 80%); IR (thin film) 1720, 1602 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (d, J = 0.7 Hz, 1H), 8.03 (d, J = 8.2 Hz, 2H), 7.53 (t, J = 8.2 Hz, 1H), 7.40 (*app.* t, J = 8.2 Hz, 2H), 5.00 (dd, J = 4.5 Hz, 0.7 Hz, 1H), 2.45–2.30 (m, 1H), 1.06 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9 (s), 166.2 (s), 133.5 (d), 129.8 (s), 129.2 (d), 128.4

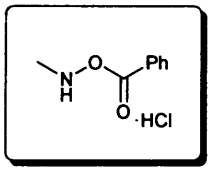
(d), 82.7 (d), 29.3 (d), 18.9 (q), 17.3 (q); MS (APCI) 207 *m/z* $[M+H]^+$; HRMS found 207.1016 $C_{12}H_{14}O_3$ requires 207.1016 $[M+H]^+$.

2-Benzoyloxy cyclohexanone 106[107]



Following the general procedure cyclohexanone (100 mg, 1.09 mmol) and *N*-methyl-*O*-benzoyl hydroxylamine hydrochloride (187 mg, 1.09 mmol) gave the title compound as a colourless solid (168 mg, 80%); Mpt 86–88 °C (Mpt Lit 85–86 °C); IR (nujol) 1731, 1709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.4 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.35 (*app.* t, *J* = 7.4 Hz, 2H), 5.38 (dd, *J* = 11.2 Hz, 6.4 Hz, 1H), 2.59–2.32 (m, 3H), 2.09–1.51 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3 (s), 165.5 (s), 133.1 (d), 130.1 (s), 129.8 (d), 128.4 (d), 76.7 (d), 40.7 (t), 33.2 (t), 27.2 (t), 23.8 (t); MS (APCI) 219 *m/z* $[M+H]^{\cdot+}$; HRMS (ES+) calculated for $C_{13}H_{14}O_3$ 219.0976 $[M+H]^{\cdot+}$, found 219.0974.

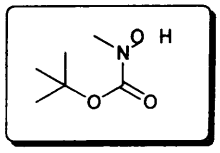
***N*-Methyl-*O*-benzoyl hydroxylamine hydrochloride 107**[108]



Following general method 1 the title compound **107** was prepared as a colourless solid (3.53 g, 94%); Mpt 130–132 °C (Mpt Lit 135–136 °C); IR (thin film) 3458, 1712 cm^{-1}; ^1H NMR (400 MHz, DMSO-d^6) δ 11.95 (bs, 2H), 7.95 (d, *J* = 7.0 Hz, 2H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.57 (dd, *J* = 7.5 Hz, 7.0 Hz, 2H), 2.93 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d^6) δ 164.3 (s), 134.9 (d), 129.7 (d), 129.6 (d), 127.2 (s), 37.5 (q); MS (APCI) 152 *m/z* $[M+H]^{\cdot+}$; HRMS calculated for $C_8H_9NO_2$ 152.0711 $[M+H]^{\cdot+}$, found 152.0712.

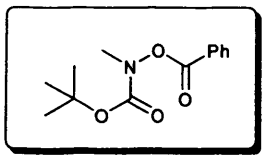
Following general method 2 the title compound **107** was also prepared (5.69 g, 76%).

***N*-Boc-*N*-Methyl hydroxylamine 116**[109]



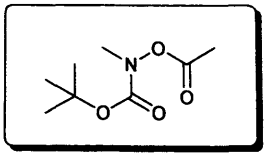
A solution of *N*-methyl hydroxylamine hydrochloride (20 g, 240 mmol) in THF/H_2O (1:1) (480 mL) was cooled to 0 °C and potassium carbonate (16.5 g, 120 mmol) was added. Careful addition of the di-*tert* butyl dicarbonate (52.3 g, 240 mL) to the reaction followed. The reaction was left to stir over 6 hours and allowed to warm to room temperature. Subsequently the THF was removed under reduced pressure. The remaining aqueous solution was added to CH_2Cl_2 (300 mL), washed with water (3 x 100 mL) and brine (100 mL). The solution was then dried over Na_2SO_4 then the solvent was removed under pressure. The crude product was purified under reduced pressure by distillation (< 1mbar, 85–87 °C) to yield compound **116** (34.2 g, 97%) as a colourless oil; IR (neat) 3257, 1699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.05 (1H, bs), 3.31 (3H, s), 1.63 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4 (s), 80.6 (s), 37.5 (q), 27.5 (q); MS (ES) 148.2 *m/z* $[M+H]^+$; HRMS calculated for $C_6H_{13}NO_3$ 148.0973 $[M+H]^+$ found 148.0974.

_N_-Boc-_N_-Methyl-_O_-benzoyl hydroxylamine 117



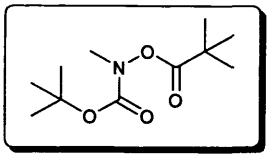
To a solution of *N*-Boc-*N*-methyl hydroxylamine (4.05 g, 30 mmol) in CH_2Cl_2 (70 mL), dimethyl amino pyridine (74 mg, 2 mol%) and triethylamine (4.16 mL, 30 mmol) was added. The solution was then cooled to 0 °C and stirred, followed by slow addition of benzoyl chloride (3.5 mL, 30 mmol). The reaction was left to proceed for 16 hours and allowed to rise to room temperature. Evaporation under reduced pressure followed to produce yellow oil which was then dissolved in CH_2Cl_2 (100 mL). The solution was then washed with sodium hydrogen carbonate (2 x 50 mL), water (50 mL) and brine (50 mL) then dried over Na_2SO_4. The crude reaction mixture was purified by flash chromatography (1:5) ethyl acetate/petroleum ether to give the product (7.2 g, 98%) as a colourless solid; Mpt 79–81 °C; IR (thin film) 1763, 1709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.5 Hz, 2H), 7.61 (t, J = 7.1 Hz, 1H), 7.46 (dd, J = 8.5 Hz, 7.1 Hz, 2H), 3.34 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7 (s), 155.4 (s), 133.9 (d), 129.9 (d), 128.6 (d), 127.6 (s), 82.4 (s) 38.0 (q), 28.1 (q); MS (APCI) 252 *m/z* $[M+H]^{+}$; HRMS calculated for $C_{13}H_{17}NO_4$ 252.1236 $[M+H]^{+}$ found 252.1236.

***N*-Boc-*N*-Methyl-*O*-acyl hydroxylamine 120**



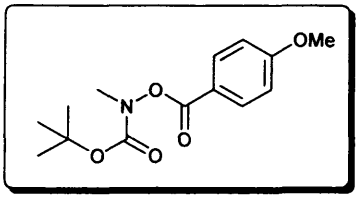
Following general method 1 the product **120** was prepared (4.5 g, 85%) as a colourless oil; IR (nujol) 1792, 1718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.19 (s, 3H), 2.10 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6 (s), 155.2 (s), 82.4 (s), 37.8 (q), 28.1 (q), 18.5 (q); MS (APCI) 192.2 *m/z* $[M+H]^+$.

***N*-Boc-*N*-Methyl-*O*-pivaloyl hydroxylamine 121**



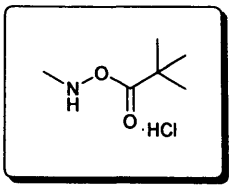
Following general method 1 the compound **121** was produced (2.8 g, 90%) as a colourless oil; IR (nujol) 1776, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.08 (s, 3H), 1.40 (s, 9H), 1.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8 (s), 155.2 (s), 81.9 (s), 38.0 (s), 37.4 (q), 28.0 (q), 26.9 (q); MS (APCI) 232.3 *m/z* $[M+H]^+$.

***N*-Boc-*N*-Methyl-*O*-(4-methoxybenzoyl) hydroxylamine 122**



Following general method 1 the compound **122** was produced (10.07 g, 95%) as a colourless solid; Mpt 52–54 °C IR (nujol) 1755, 1707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H), 3.34 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4 (s), 164.1 (s), 155.5 (s), 132.3 (d), 132.1 (d), 119.8 (s), 113.9 (d), 113.7 (d), 82.2 (s), 55.5 (q), 38.0 (q), 28.1 (q); MS (APCI) 282.4 *m/z* $[M+H]^+$.

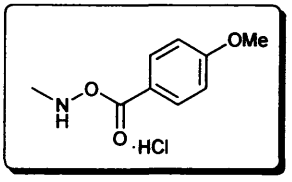
_N_-Methyl-_O_-pivaloyl hydroxylamine hydrochloride 125[74]



Following general method 1 the title compound **125** was produced (1 .44 g, 78%) as a colourless oil; IR (nujol) 3412, 1780 cm^{-1}; ^1H NMR (400 MHz, DMSO-d^6) δ 10.50 (bs, 2H), 3.09 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d^6) δ 174.2 (s), 38.4 (s), 35.7 (q), 27.1 (q), 26.8 (q); MS (APCI) 132 *m/z* $[M+H]^+$.

Following general method 2 the title compound **125** was also prepared (4.49 g, 67%).

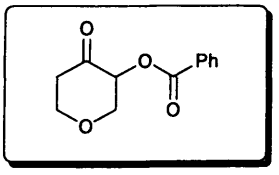
_N_-Methyl-_O_-(4-methoxybenzoyl) hydroxylamine hydrochloride 126



Following general method 1 the title compound **126** was produced (1.01 g, 79%) as a colourless solid; Mpt 129–131 °C; IR (nujol) 2929, 1740 cm^{-1}; ^1H NMR (400 MHz, DMSO-d^6) δ 10.90 (bs, 2H) 7.89 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 3.82 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d^6) δ 165.2 (s), 162.6 (s), 132.6 (d), 116.5 (s), 114.4 (d), 55.7 (q), 36.3 (q); MS (APCI) 182 *m/z* $[M+H]^+$.

Following general method 2 the title compound **126** was also prepared (6.44 g, 74%).

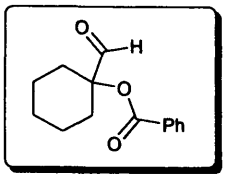
2-Acetoxy tetrahydropyranone 137



Following the general α-oxygenation procedure the title compound **137** was isolated as a colourless oil (181 mg, 79%); IR (nujol) 1720, 1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 7.4 Hz, 2H), 7.52 (t, J = 7.4 Hz, 1H), 7.38 (*app.* t, J = 7.4 Hz, 2H), 5.45 (dd, J = 10.5 Hz, 7.0 Hz, 1H), 4.51–4.40 (m, 1H), 4.32–4.25 (m, 1H), 3.75–3.60 (m, 2H), 2.83–2.70

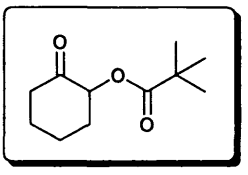
(m, 1H), 2.55–2.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5 (s), 165.0 (s), 133.5 (d), 130.1 (s), 129.9 (d), 128.4 (d), 74.0 (d), 70.5 (t), 68.5 (t), 42.2 (t); MS (APCI) 221 *m/z* $[M+H]^{\cdot+}$; HRMS (ES+) calculated for $C_{12}H_{12}O_4$ 221.0808 $[M+H]^{\cdot+}$, found 221.0808.

1-Formylcyclohexyl benzoate 141[69(a)]



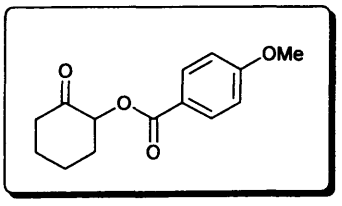
Following the general α-oxygenation procedure the title compound 141 was isolated (100 mg, 74%) as a colourless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 8.09 (d, J = 7.4 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.50 (*app.* t, J = 7.4 Hz, 2H), 2.16–2.13 (m, 2H), 1.76–1.64 (m, 7H) 1.55–1.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9 (d), 165.7 (s), 133.6 (d), 129.9 (d), 129.5 (s), 128.6 (d), 84.5 (s), 29.4 (t), 25.0 (t), 21.1 (t); LCMS 233.1 *m/z* $[M+H]^+$.

2-Pivaloyloxy cyclohexanone 143[110]



Following the general α-oxygenation protocol to yield the title product **143** (0.13 g, 69%) as a colourless oil: IR (nujol) 1755, 1729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.35 (dd, J = 11.1, 6.3 Hz, 1H), 2.51–1.52 (m, 8H), 1.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 204.0 (s), 178.0 (s), 77.0 (d), 41.0 (t), 38.0 (s), 33.5 (t), 27.0 (t), 26.5 (q), 24.0 (t); MS (APCI) 199.3 *m/z* $[M+H]^+$; HRMS calculated for $C_{11}H_{18}O_5$ 199.1334 $[M+H]^{\cdot+}$, found 199.1339.

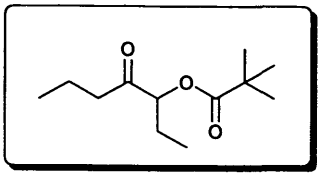
2-(4-Methoxybenzoyl)oxy cyclohexanone 144[110]



Following the general α-oxygenation procedure to yield the product **144** (0.18 g, 70%) as a colourless solid; Mpt 122–125 °C; IR (nujol) 1720, 1705, 1604 cm^{-1}; ^1H NMR (400 MHz,

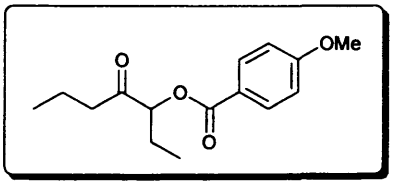
$CDCl_3$) δ 7.98 (dd, J = 9.5 Hz, 2.4 Hz, 2H), 6.85 (dd, J = 9.5 Hz, 2.4 Hz, 2H), 5.32 (dd, J = 11.7 Hz, 6.4 Hz, 1H), 3.80 (s, 3H), 1.62–1.55 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.8, 165.3 (s), 163.6 (s), 132.0 (d), 122.1 (s), 113.6 (d), 76.8 (d), 55.5 (q), 40.8 (t), 33.3 (t), 27.3 (t), 23.8 (t); MS (APCI) 249 *m/z* $[M+H]^{\cdot+}$; HRMS calculated for $C_{14}H_{16}O_4$ 249.1121 $[M+H]^{\cdot+}$, found 249.1122.

2-Pivaloyloxy heptan-4-one 145



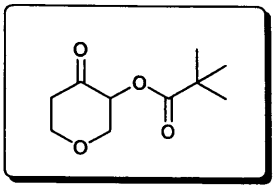
Following the general α-oxygenation procedure (at 50 °C) to yield the title compound **145** (0.11 g, 58%) as a colourless oil; IR (nujol) 1755, 1639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 4.85 (dd, J = 8.0 Hz, 4.4 Hz, 1H), 2.45–2.44 (m, 1H), 2.31–2.30 (m, 1H), 1.90–1.65 (m, 2H), 1.55 (sex, J = 7.4 Hz, 2H), 1.15 (s, 9H), 0.95 (t, J = 7.4 Hz, 3H), 0.85 (t, J =7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 207.0 (s), 178.0 (s), 79.0 (d), 41.0 (t), 38.2 (s), 27.0 (q), 24.0 (t), 16.0 (t), 14.0 (q), 10.0 (q); MS (APCI) 215.3 *m/z* $[M+H]^+$.

2-(4-Methoxybenzoyl)oxy heptan-4-one 146



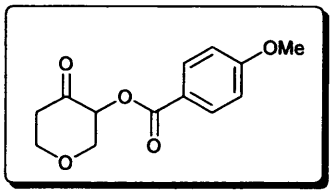
Following the general α-oxygenation procedure (at 50 °C) to yield the title compound **146** as a colourless oil (0.19 g, 76%); IR (nujol) 1713, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, J = 9.4 Hz, 2.4 Hz, 2H), 6.88 (dd, J = 9.4 Hz, 2.4 Hz, 2H), 5.10 (dd, J = 7.9 Hz, 4.6 Hz, 1H), 3.81 (s, 3H), 2.54–2.32 (m, 1H), 1.93–1.78 (m, 1H), 1.62–1.53 (m, 2H), 1.62–1.53 (m, 2H), 0.98 (t, J = 9.4 Hz, 3H), 0.85 (t, J = 9.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.3 (s), 165. 9 (s), 163.7 (s), 131.9 (d), 121.9 (s), 113.8 (d), 79.7 (d), 55.5 (q), 40.6 (t), 24.2 (t), 16.6 (t), 13.7 (q), 9.8 (q); MS (APCI) 265.1 *m/z* $[M+H]^{\cdot+}$; HRMS calculated for $C_{15}H_{20}O_4$ 265.1440 $[M+H]^{\cdot+}$, found 265.1451.

2-Pivaloyloxy tetrahydropyranone 147



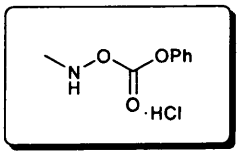
Following the general α-oxygenation procedure to yield the title compound **147** as a colourless oil (0.15 mg, 56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (dd, J = 10.8 Hz, 7.1 Hz, 1H), 4.42–4.18 (m, 2H), 3.63–3.49 (m, 2H), 2.72–2.69 (m, 1H), 2.45–2.44 (m, 1H), 1.19 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6 (s), 177.1 (s), 73.4 (d), 70.4 (t), 68.5 (t), 42.2 (t), 38.9 (s), 27.2 (q); MS (APCI) 203 *m/z* $[M+H]^{+}$.

2-(4-Methoxybenzoyl)oxy tetrahydropyran-4-one 148



Following the general α-oxygenation procedure to yield the title compound **148** as a colourless solid (0.21 g, 86%); Mpt 94–97 °C; IR (nujol) 1714, 1603 cm^{-1}; ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.96 (d, J = 9.7 Hz, 2H), 6.87 (d, J = 9.7 Hz, 2H), 5.44 (dd, J = 10.7 Hz, 7.3 Hz, 1H), 4.38 (dd, J = 10.7 Hz, 7.0 Hz, 1H), 4.26–4.23 (m, 1H), 3.80 (s, 3H) 3.69–3.62 (m, 2H), 2.79–2.76 (m, 1H), 2.54–2.53 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8 (s), 164.8 (s), 163.8 (s), 132.1 (d), 121.4 (s), 113.7 (d), 73.9 (d), 70.7 (t), 68.5 (t), 55.5 (q), 42.3 (t); MS (APCI) 251 *m/z* $[M+H]^{+}$; HRMS calculated for $C_{13}H_{14}O_5$ 251.0914 $[M+H]^{+}$, found 251.0916.

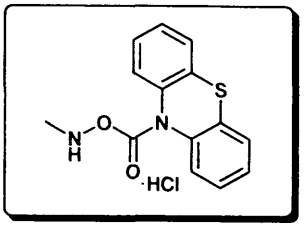
***N*-Methyl-*O*-(phenoxycarbonyl) hydroxylamine hydrochloride 150**



Hydrochloride gas was generated by slow addition of sulphuric acid (c.a. 50 mL) to ammonium chloride (ca. 50 g) and bubbled over a solution of *N*-Boc-*N*-methyl-*O*-(phenoxycarbonyl) hydroxylamine **155** (2 g, 9.1 mmol) in 1, 4 dioxane for 2 hours. The

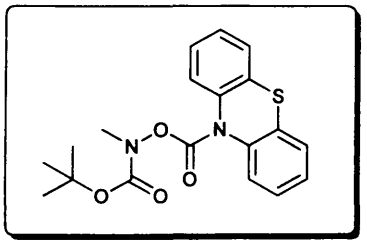
precipitate was filtered, washed with cold diethyl ether and dried on high vacuum to give the product (1.69 g, 90%) as a colourless solid; Mpt 66–69 °C; IR (thin film) 2924, 1631, 1254 cm^{-1}; ^1H NMR (400 MHz, DMSO-d^6) δ 7.45 (*app.* t, J = 7.6 Hz, 2H), 7.31 (td, J = 7.6 Hz, 1.1 Hz, 1H), 7.24 (dd, J = 7.6 Hz, 1.1 Hz, 2H), 4.99 (bs, 2H), 2.77 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d^6) δ 153.6 (s), 151.1 (s), 130.2 (d), 126.8 (d), 121.7 (d), 24.6 (q);

_N_-Methyl-_O_-(10H-phenothiazine-10-carbonyl) hydroxylamine 153



Hydrochloride gas was generated by slow addition of sulphuric acid (c.a. 50 mL) to ammonium chloride (ca. 50 g) and bubbled over a solution of *N*-Boc-*N*-methyl-*O*-(10H-phenothiazine-10-carbonyl) hydroxylamine hydroxylamine **154** (1.5 g, 4 mmol) in 1, 4 dioxane for 2 hours. The precipitate was filtered, washed with cold diethyl ether and dried on high vacuum to generate the title product (0.89 g, 72%) as a colourless solid; Mpt 121–124 °C; IR (thin film) 2922, 1759 cm^{-1}; ^1H NMR (400 MHz, DMSO-d^6) δ 7.76–7.73 (m, 2H), 7.66–7.64 (m, 2H), 7.56–7.51 (m, 2H), 7.45–7.41 (m, 2H), 2.83 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d^6) δ 152.7 (s), 138.1 (s), 137.7 (s), 131.8 (s), 131.7 (s), 128.2 (d), 128.0 (d), 127.9 (d), 127.7 (d), 127.6 (d), 127.4 (d), 127.3 (d), 127.2 (d), 38.6 (q);

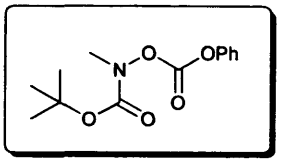
N-Boc-*N*-Methyl-*O*-(10H-phenothiazine-10-carbonyl) hydroxylamine 154



To a solution of *N*-Boc-*N*–methyl hydroxylamine **116** (4.0 g, 27.2 mmol) in CH_2Cl_2 (110 mL), dimethyl amino pyridine (67 mg, 2 mol%) and triethylamine (3.8 mL, 27.2 mmol) was added. The solution was then cooled to 0 °C and stirred followed by slow addition of 10H-phenothiazine-1,10-carbonyl chloride (7.12 g, 27.2 mmol). The reaction was left to proceed for 16 hours and allowed to rise to room temperature. Evaporation under reduced pressure produced a yellow oil which was then dissolved in CH_2Cl_2 (200 mL). The solution was then

washed with sodium hydrogen carbonate (2 x 100 mL), water (100 mL) and brine (100 mL) then dried over Na_2SO_4. The crude reaction mixture was purified by flash chromatography to give the product (6.68 g, 69%) as a colourless oil; IR (thin film) 1755, 1718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.9 Hz, 2H), 7.31–7.30 (m, 2H), 7.24–7.23 (m, 2H), 7.14–7.13 (m, 2H), 3.18 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2 (s), 152.4 (s), 137.5 (s), 132.1 (s), 127.7 (d), 127.1 (d), 126.9 (d), 126.8 (d), 82.5 (s), 38.1 (q), 28.3 (q); MS (ES) 373.1 *m/z* $[M+H]^+$; HRMS calculated for $C_{19}H_{21}N_2SO_4$ 373.1225 $[M+H]^+$ found 373.1222.

N-Boc-*N*-Methyl-*O*-(phenoxycarbonyl) hydroxylamine 155



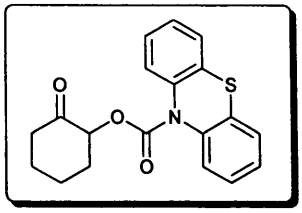
To a solution of *N*-Boc-*N*–methyl hydroxylamine **116** (5.0 g, 34.0 mmol) in CH_2Cl_2 (67 mL), dimethyl amino pyridine (10 mg, 2 mol%) and triethylamine (4.74 mL, 34 mmol) was added. The solution was then cooled to 0 °C and stirred followed by slow addition of phenyl chloroformate (5.3 g, 34 mmol). The reaction was left to proceed for 16 hours and allowed to rise to room temperature. Evaporation under reduced pressure followed to produce a colourless oil which was then dissolved in CH_2Cl_2 (100 mL). The solution was then washed with 1M HCl (2 x 50 mL), water (50 mL) and brine (50 mL) then dried over Na_2SO_4. The crude reaction mixture was purified by flash chromatography to generate the title product (7.17 g, 79%) as a colourless viscous oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (*app.* t, J =7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 1H), 7.24 (d, J = 7.5 Hz, 2H), 3.32 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d^6) δ 155.2 (s), 152.8 (s), 150.9 (s), 129.7 (d), 126.5 (d), 120.6 (d), 82.89 (s), 37.72 (q), 28.03 (q).

General experimental procedure for the α-carbamoylation of carbonyl compounds:

The carbonyl compound (1.09 mmol) and *N*-methyl-*O*-(10H-phenothiazine-10-carbonyl) hydroxylamine hydrochloride **153** (1.09 mmol) were dissolved in dimethyl sulfoxide (2.1 mL) and the resultant mixture stirred at room temperature or 50 °C until TLC analysis showed the reaction to be complete. The solution was subsequently diluted with ethyl acetate (40 mL) and washed repeatedly with saturated brine (3 × 40 mL). The organic fraction was

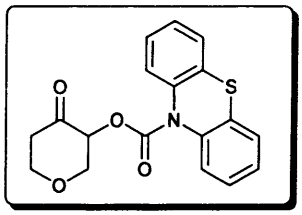
dried ($MgSO_4$), concentrated *in vacuo*, and the crude product purified by flash column chromatography (4:1 light petroleum/ethyl acetate) to yield the product.

2-Oxocyclohexyl 10H-phenothiazine-10-carboxylate 156



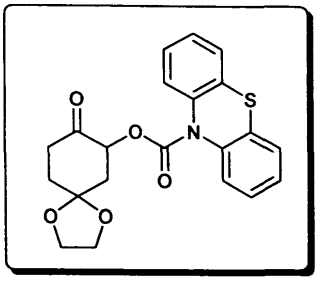
Following the general α-carbamoylation procedure to yield the title compound **156** as a colourless solid (256 mg, 74%); Mpt 136–138 °C; IR (thin film) 1734, 1702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 7.8 Hz, 2H), 7.29 (dd, J = 7.8 Hz, 1.3Hz, 2H), 7.19–7.16 (m, 2H), 7.10 (*app.* t, J = 7.8 Hz, 2H), 5.12 (dd, J = 12.2 Hz, 6.3 Hz, 1H), 2.57–1.51 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2 (s), 152.6 (s), 138.3 (s), 132.0 (s), 127.5 (d), 127.2 (d), 126.8 (d), 126.3 (d), 78.5 (d), 40.7 (t), 33.0 (t), 27.1 (t), 23.7 (t); MS (ES) 340.1 *m.z* $[M+H]^+$. HRMS calculated for $C_{19}H_{18}NSO_3$ 340.1002 $[M+H]^{\cdot+}$, found 340.1002.

4-Oxotetrahydro-2H-pyran-3-yl 10H-phenothiazine-10-carboxylate 157



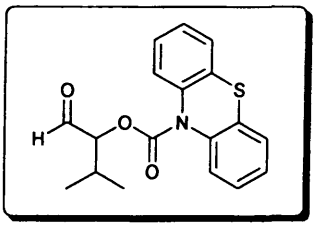
Following the general α-carbamoylation procedure to yield the title compound **157** as a colourless solid (204 mg, 80%); Mpt (186–188 °C); IR (thin film) 1732, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61–7.59 (m, 2H), 7.29 (d, J = 7.7 Hz, 2H), 7.21 (*app.* t, J = 7.7 Hz, 2H), 7.10 (*app.* t, J = 7.7 Hz, 2H), 5.27 (dd, J = 10.5 Hz, 7.2 Hz, 1H), 4.25–4.17 (m, 2H), 3.60–3.54 (m, 1H), 3.41–3.36 (m, 1H), 2.79–2.70 (m, 1H), 2.51–2.47 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.4 (s), 152.5 (s), 138.0 (s), 132.1 (s), 127.6 (d), 127.1 (d), 126.9 (d), 126.6 (d), 75.3 (d), 70.4 (t), 68.4 (t), 42.2 (t); MS (APCI) 342.3 *m/z* $[M+H]^+$; HRMS calculated for $C_{18}H_{16}NSO_4$ 342.0795 $[M+H]^{\cdot+}$ found 342.0797.

8-Oxo-1,4-dioxaspiro[4.5]decan-7-yl 10H-phenothiazine-10-carboxylate 158



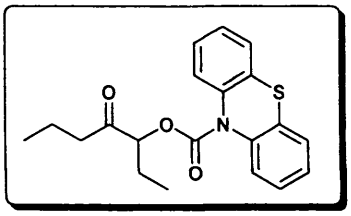
Following the general α-carbamoylation procedure to yield the title compound **158** as a white solid (203 mg, 82%); Mpt 165–167 °C; IR (thin film) 1736, 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63–7.61 (m, 2H), 7.27 (dd, *J* = 7.7 Hz, 1.2 Hz, 2H), 7.19 (*app.* td, *J* = 7.7 Hz, 1.2 Hz, 2H), 7.08 (*app.* td, *J* = 7.7 Hz, 1.2 Hz, 2H), 5.41 (dd, *J* = 13.2 Hz, 6.7 Hz, 1H), 3.91–3.86 (m, 4H), 2.73–2.64 (m, 1H), 2.43–2.38 (m, 1H), 2.27–2.21 (m, 1H), 1.99–1.87 (m, 3H); ^{13}C NMR (125 Mz, $CDCl_3$) δ 138.2 (s), 132.0 (s), 127.5 (d), 127.1 (d), 126.9 (d), 126.4 (d), 107.2 (s), 75.2 (d), 64.9 (t), 64.8 (t), 40.1 (t), 35.7 (t), 34.6 (t) (2 X carbonyl peaks missing); MS (APCI) 398.2 *m/z* $[M+H]^+$; HRMS calculated for $C_{21}H_{19}NSO_5$ 398.1062 $[M+H]^+$, found 398.1057.

3-Methyl-1-oxobutan-2-yl 10H-phenothiazine-10-carboxylate 159



Following the general α-carbamoylation procedure to yield the title compound **159** as a colourless oil (335 mg, 88%); IR (thin film) 2254, 1714, 1592 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (*app.* s, 1H), 7.56–7.54 (m, 2H), 7.30 (dd, *J* = 7.7 Hz, 1.2 Hz, 2H), 7.21 (*app.* td, *J* = 7.7 Hz, 1.2 Hz, 2H), 7.11 (*app.* td, *J* = 7.7 Hz, 1.2 Hz 2H), 4.85 (*app.* d, *J* = 4.0 Hz, 1H), 2.19–2.14 (m, 1H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6 (d), 153.3 (s), 138.0 (s), 132.2 (s), 127.6 (d), 127.1 (d), 126.9 (d), 126.7 (d), 84.2 (d), 28.9 (d), 18.9 (q), 17.0 (q); MS (APCI) 328 *m/z* $[M+H]^+$; HRMS calculated for $C_{18}H_{17}NSO_3$ 328.1007 $[M+H]^+$, found 328.1010.

4-Oxoheptan-3-yl 10H-phenothiazine-10-carboxylate 160



Following the general α-carbamoylation procedure to yield the title compound **160** as a colourless solid (183 mg, 73%); Mpt 74–76 °C; IR (thin film)_1730, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60–7.58 (m, 2H), 7.30 (dd, *J* = 7.7 Hz, 1.2 Hz, 2H), 7.13 (*app.* td, *J* = 7.7 Hz, 1.2 Hz, 2H), 7.12 (*app.* td, *J* = 7.7 Hz, 1.2 Hz, 2H), 4.99 (dd, *J* = 6.9 Hz, 4.6 Hz, 1H), 2.36–2.31 (m, 2H), 1.78–1.66 (m, 2H), 1.58–1.52 (m, 2H), 0.84 (t, *J* = 7.4 Hz, 3H), 0.78 (t, *J* = 7.4 Hz, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 207.6 (s), 153.2 (s), 138.2 (s), 132.2 (s), 127.5 (d), 127.1 (d), 126.8 (d), 126.5 (d), 81.1 (d), 40.7 (t), 23.8 (t), 16.6 (t), 13.7 (q), 9.3 (q); MS (APCI) 356.3 *m/z* $[M+H]^+$. HRMS calculated for $C_{20}H_{22}NSO_3$ 356.13 15 $[M+H]^+$ found 356.1311.

General experimental procedure for the preparation of heterocyclic compounds:

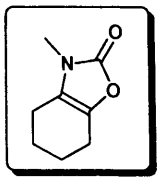
The carbonyl compound (0.5 mmol) and *N*-methyl-*O*-(phenoxycarbonyl) hydroxylamine hydrochloride **150** (100 mg, 0.5 mmol) were dissolved in dry dimethyl sulfoxide (5 mL) the resultant mixture with 4Å molecular sieves were allowed to stir at room temperature for 16 hours. The solution was subsequently diluted with ethyl acetate (40 mL) and water (40 mL). The aqueous layer was then extracted with ethyl acetate (2 x 30 mL) The organic fractions were combined and washed repeatedly with brine (2 x 40 mL) and dried over $MgSO_4$ then concentrated under reduced pressure. The crude product was purified by flash column chromatography (3:1) light petroleum/diethyl ether on silica to yield the product.

General experimental procedure for the α-carbonoylation of carbonyl compounds:

The carbonyl compound (0.5 mmol) and *N*-methyl-*O*-(phenoxycarbonyl) hydroxylamine hydrochloride **150** (100 mg, 0.5 mmol) were dissolved in THF/H_2O (9:1) (5 mL) and the resultant mixture allowed to stir at 50 °C for 16 hours. The solution was subsequently diluted with ethyl acetate (40 mL) and water (40 mL). The aqueous layer was then extracted with ethyl acetate (2 x 30 mL) The organic fractions were combined and washed repeatedly with brine (2 x 40 mL) and dried over $MgSO_4$ then concentrated under reduced pressure. The

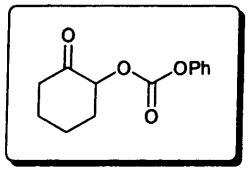
crude product was purified by flash column chromatography (3:1) light petroleum ether/diethyl ether on silica to yield the product.

3-Methyl-4,5,6,7-tetrahydrobenzo[d]oxazol-2(3H)-one 161



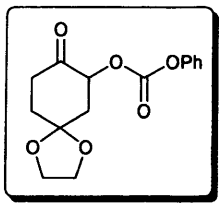
Following the general heterocyclic formation procedure to yield the product **161** as a colourless oil (46 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.04 (s, 3H), 2.30–2.29 (m, 2H), 2.25–2.24 (m, 2H), 1.75–1.71 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1 (s), 134.5 (s), 120.8 (s), 27.8 (q), 22.3 (t), 21.9 (t), 20.9 (t), 19.3 (t); MS (APCI) 154.1 *m/z* $[M+H]^{\cdot+}$; HRMS (ES) calculated for $C_8H_{11}NO_2$ 153.0790 $[M+H]^{\cdot+}$, found 153.0794.

2-Oxocyclohexyl phenyl carbonate 163



Following the general α-oxycarbonation procedure to yield the product as a colourless solid (59 mg, 51%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (*app.* t, J = 8.0 Hz 2H), 7.19–7.15 (m, 3H), 5.04 (dd, J = 12.1 Hz, 5.8 Hz, 1H), 2.50–1.16 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.8 (s), 152.9 (s), 151.1 (s), 129.5 (d), 126.1 (d), 121.0 (d), 80.1 (d), 40.6 (t), 32.9 (t), 27.0 (t), 23.6 (t); MS (APCI) 235.1 *m/z* $[M+H]^{\cdot+}$; HRMS (APCI) calculated for $C_{13}H_{14}O_4$ 235.0970 $[M+H]^{\cdot+}$, found 235.0965.

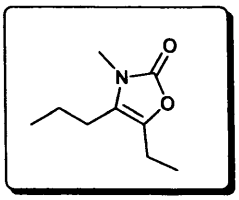
8-Oxo-1,4-dioxaspiro[4.5]decan-7-yl phenyl carbonate 172



Following the general α-oxycarbonation procedure to yield the product **172** as a colourless oil (51 mg, 35%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (*app.* t, J = 7.0 Hz, 2H), 7.18–7.14 (m,

3H), 5.30 (dd, J = 13.2 Hz, 6.8 Hz, 1H), 4.04–3.96 (m, 4H), 2.68–2.67 (m, 1H), 2.46–2.40 (m, 2H), 2.14–2.13 (m, 1H), 2.00–1.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7 (s), 152.7 (s), 151.1 (s), 129.5 (d), 126.2 (d), 121.0 (d), 107.1 (s), 76.8 (d), 65.1 (t), 64.9 (t), 40.1 (t), 35.6 (t), 34.5 (t).

5-Ethyl-3-methyl-4-propyloxazol-2(3H)-one 173

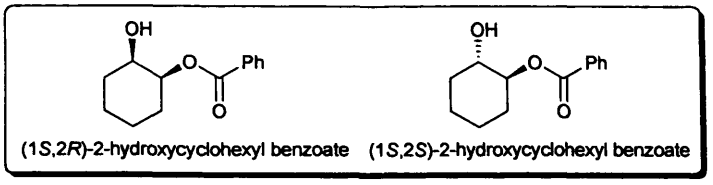


Following the general heterocyclic formation procedure to yield the product **173** as a colourless solid (20 mg, 23%);_^{1}H NMR (400 MHz, $CDCl_3$) δ 3.06 (s, 3H), 2.32 (q, J = 7.5 Hz, 2H), 2.22 (t, J = 7.4 Hz, 2H), 1.44 (sex, J = 7.4 Hz, 2H), 1.08 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1 (s), 136.9 (s), 120.4 (s), 28.0 (q), 24.4 (t), 21.9 (t), 18.0 (t), 13.4 (q), 12.7 (q).

General experimental procedure for the preparation of 1,2-mono protected diols by reduction:

The carbonyl compound (0.54 mmol) and hydroxylamine hydrochloride reagent (100 mg, 0.54 mmol) were dissolved in THF/H_2O (9:1) (1.1 mL) and the resultant mixture stirred at room temperature until TLC analysis showed the complete reaction of starting material. The solution was then cooled to 0 °C and $NaBH_4$ (24 mg, 0.64 mmol) was added in portions. The reaction was left to proceed until completed by TLC. The solution was then reduced under pressure and subsequently diluted with ethyl acetate (40 mL) and washed with $NaHCO_3$ (2 x 30 mL) and repeatedly with saturated brine (5 × 50 mL). The organic fraction was dried (magnesium sulfate), concentrated *in vacuo*, and the crude product purified by SP4 column chromatography using a hexane/ethyl acetate gradient to yield the product.

(1S,2R)-2-Hydroxycyclohexyl benzoate and (1S,2S)-2-hydroxycyclohexyl benzoate 182/183[111]



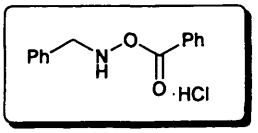
(1S,2*R*)-2-hydroxycyclohexyl benzoate (1S,2*S*)-2-hydroxycyclohexyl benzoate

Following the general reduction reaction procedure for to give the product as a mixture of diastereoisomers as a colourless oil (92 mg, 80%); IR (neat) 3428, 1716, 1270 cm^{-1}; **182**:**183** in a (1:1.1) ratio; **182** ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.6 Hz, 2H), 7.50 (t, J = 7.6 Hz, 1H), 7.48 (*app.* t, J = 7.6 Hz, 2H), 5.16–5.14 (m, 1H), 3.91–3.89 (m, 1H), 2.27–1.31 (m, 8H); **183** ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.6 Hz, 2H), 7.50 (t, J = 7.6 Hz, 1H), 7.48 (*app.* t, J = 7.6 Hz, 2H), 4.81–4.76 (m, 1H), 3.70–3.64 (m, 1H), 2.27–1.31 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8 (s), 133.1 (d), 130.3 (s), 129.7 (d), 129.6 (d), 128.4 (d), 128.4 (d), 78.7 (d), 72.8 (d), 33.0 (t), 30.0 (t), 23.9 (t), 23.7 (t); MS (APCI) 219 *m/z* $[M+H]^+$.

General experimental procedure for the preparation of *N*-sustituted reagents:

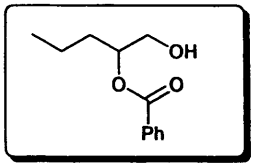
A solution of the amine (18.7 mmol) in the pH 10.5 buffer solution (94 mL) was placed in a round bottomed flask. Rapidly the solution of 70% benzoyl peroxide (9.08 g, 18.7 mmol) in CH_2Cl_2 (94 mL) was added. A solution was left to react at room temperature with vigorous stirring for 8 hours. An aqueous work up was then completed by separation of the organic CH_2Cl_2 layer, then extraction of the aqueous layer with CH_2Cl_2 (3 x 50 mL). The organic layers were then combined and washed with brine (100 mL), then dried over anhydrous Na_2SO_4 and reduced *in vacuo*. This yielded the free base of the reagent. Subsequently hydrochloric acid was bubbled over the free base solution in diethyl ether (20 mL) and after 30 minutes the white crystals of the salt crashed out in the solution. A further 15 minutes was ensured completion of the hydrochloric salt formation. The crystals were then collected under nitrogen by filtration and washed with cold diethyl ether to yield the salt.

***O*-Benzoyl-*N*-benzylhydroxylamine hydrochloride 184**[112]



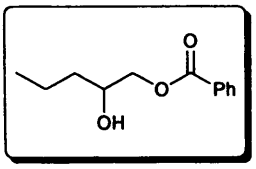
Following the general reaction procedure for reagent preparation to yield the salt **184** (3.1 g, 62%) as a white solid; Mpt 121–124 °C (Mpt Lit 141 °C); IR (nujol) 3283, 1636 cm^{-1}; ^1H NMR (400 MHz, DMSO-d^6) δ 7.84 (d, *J* = 7.7 Hz, 2H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.51 (*app.* t, *J* = 7.7 Hz, 7.5 Hz, 2H). 7.44 (d, *J* = 7.2 Hz, 2H), 7.34 (*app.* t, *J* = 7.2 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 4.25 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d^6) δ 165.4 (s), 136.8 (s), 134.1 (d), 129.7 (d), 129.5 (d), 129.4 (d), 129.2 (d), 129.2 (d), 129.0 (d), 128.9 (d), 128.7 (d), 128.5 (s), 128.0 (d), 55.3 (t); MS (APCI) 228 *m/z* $[M+H(-HCl)]^+$.

(1-Hydroxypentan-2-yl benzoate 188[113]



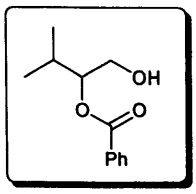
Following the general reduction reaction procedure to give the product **188** as a colourless oil (67 mg, 61%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.4 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.45 (*app.* t, *J* = 7.4 Hz, 2H), 5.21–5.14 (m, 1H), 3.87–3.34 (m, 2H), 2.05–2.04 (m, 1H), 1.80–1.63 (m, 2H), 1.50–1.43 (m, 2H), 0.96 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8 (s), 132.9 (d), 129.7 (s), 129.4 (d), 128.2 (d), 69.6 (d), 69.2 (t), 25.6 (t), 18.6 (t), 14.5 (q); LCMS (ES+) 231.1 *m/z* $[M+H+Na]^+$; HRMS (ES) calculated 226.1438 $[M+H+NH_4]^+$ for $C_{12}H_{20}O_3N$ found 226.1438.

2-Hydroxypentyl benzoate 189



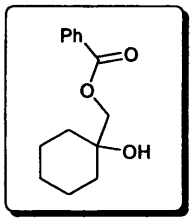
Following the general reduction reaction procedure to give the product **189** as a colourless oil As a colourless oil (8 mg, 7%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.4 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.45 (*app.* t, *J* = 7.4 Hz, 2H), 4.40–4.39 (m, 1H), 4.23–4.22 (m, 1H), 4.00–3.99 (m, 1H), 2.11–2.10 (m, 1H), 1.61–1.25 (m, 4H), 0.97 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8 (s), 132.9 (d), 129.7 (s), 129.4 (d), 128.2 (d), 69.6 (d), 69.2 (t), 25.6 (t), 18.6 (t), 14.5 (q); LCMS (ES+) 231.1 *m/z* $[M+H+Na]^+$. HRMS (ES) calculated 226.1438 $[M+H+NH_4]^+$ for $C_{12}H_{20}O_3N$ found 226.1437.

1-Hydroxy-3-methylbutan-2-yl benzoate 190[114]



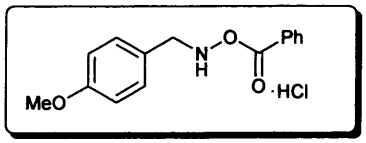
Following the general reduction reaction procedure to yield the α-mono protected diol **190** as a colourless oil (66 mg, 59%); IR (neat) 3456, 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.5 Hz, 2H), 7.53 (t, J = 7.5 Hz, 1H), 7.40 (*app.* t, J = 7.5 Hz, 2H), 4.94–4.90 (m, 1H), 3.83–3.74 (m, 2H), 2.06 (oct, J = 6.8 Hz, 1H), 0.95 (d, J = 6.8 Hz, 6H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2 (s), 133.1 (d), 130.2 (s), 129.7 (d), 128.4 (d), 81.0 (d), 67.1 (t), 29.4 (d), 18.9 (q), 18.0 (q); MS 209 *m/z* $[M+H]^+$.

(1-Hydroxycyclohexyl)methyl benzoate 192



Following the general reduction reaction procedure (raising α-oxygenation step to 35 °C) to yield the product **192** as a colourless oil (56 mg, 44%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, J = 7.4 Hz, 1.5 Hz, 2H), 7.58 (td, J = 7.4 Hz, 1.5 Hz, 1H), 7.46 (*app.* t, J = 7.4 Hz, 2H), 4.24 (s, 2H), 1.73–1.53 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7 (s), 133.2 (d), 130.0 (s), 129.6 (d), 128.4 (d), 72.0 (t), 70.9 (s), 34.4 (t), 25.7 (t), 21.6 (t); MS 234.0 *m/z* $[M+H+H_2O]^+$.

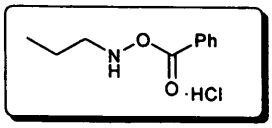
***O*-Benzoyl-*N*-(4-methoxybenzyl)hydroxylamine hydrochloride 206**



Following the general procedure for reagent preparation to yield the salt **206** (3.2 g , 59%) as a white solid; Mpt 71–73 °C; IR (nujol) 3408, 1613 cm^{-1}; ^1H NMR (400 MHz, DMSO-d^6) δ 7.89 (d, J = 7.7 Hz, 2H), 7.47 (t, J = 7.7 Hz, 1H). 7.34 (*app.* t, J = 7.7 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 4.17 (s, 2H), 3.69 (s, 3H); ^{13}C NMR (125 MHz,

DMSO-d^6) δ 166.9 (s), 159.4 (s), 133.4 (d), 130.4 (d), 129.4 (d), 128.5 (d), 128.4 (s), 127.8 (s), 114.1 (d), 56.2 (t), 55.3 (q); MS (APCI) 256 *m/z* [M+H(-HCl)]$^+$.

O-Benzoyl-N-propylhydroxylamine hydrochloride 208[74]



Following the general procedure for reagent preparation to yield the salt **208** to yield the salt (4.3 g, 74%) as a white solid; Mpt 121–123 °C (Mpt Lit 129 °C); IR (nujol) 3373, 1757 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d^6) δ 7.97 (d, *J* = 7.4 Hz, 2H), 7.73 (t, *J* = 7.4 Hz, 1H), 7.58 (*app.* t, *J* = 7.4 Hz, 2H), 3.19 (t, *J* = 7.5 Hz, 2H), 1.68 (sex, *J* = 7.5 Hz, 2H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d^6) δ 167.7 (s), 164.6 (s), 134.7 (d),129.7 (d), 129.6 (d), 129.1 (d), 129.0 (d), 52.4 (t), 19.1 (t), 11.7 (q); MS (APCI) 180.1 *m/z* [M+H(-HCl)]$^+$; HRMS calculated 180.1019 for $C_{10}H_{13}NO_2$, found 180.1019.

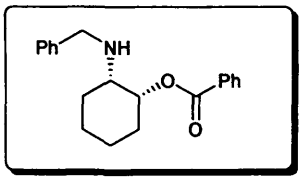
General experimental procedure for the preparation of 1,2-amino alcohols by reductive amination:

Method 1 The carbonyl compound (0.54 mmol) and the *N*-benzyl-*O*-benzoyl hydroxylamine hydrochloride (100 mg, 0.54 mmol) were dissolved in DMSO (or 1,2 DCE) (1.1 mL) and the resultant mixture stirred at room temperature under an atmosphere of nitrogen until TLC analysis showed the complete reaction of starting material. To the solution 4Å molecuar sieves and $Na(OAc)_3BH$ (171 mg, 0.81 mmol) were added in portions, along with triethylamine (55 mg, 0.54mmol) (along with acetic acid for ketone substrates). The reaction was left to proceed until completed by TLC. The solution was then reduced under pressure and subsequently diluted with ethyl acetate (40 mL) and washed with $NaHCO_3$ (2 x 30 mL) and repeatedly with saturated brine (5 × 50 mL). The organic fraction was dried (magnesium sulfate), concentrated *in vacuo*, and the crude product purified by SP4 column chromatography using a hexane/ethyl acetate gradient to yield the product.

Method 2 The α-oxygenated carbonyl compound (0.92 mmol) and the amine (0.92 mmol) were dissolved in DMSO (3.2 mL). To the solution 4Å molecuar sieves and $Na(OAc)_3BH$ (291 mg mg, 1.37 mmol) were added in portions to the solution (along with acetic acid for ketone substrates). The resultant mixture was stirred at room temperature under an atmosphere of nitrogen until TLC analysis showed the complete reaction of starting material.

The reaction was left to proceed until completed by TLC. The solution was then reduced under pressure and subsequently diluted with ethyl acetate (40 mL) and washed with $NaHCO_3$ (2 x 30 mL) and repeatedly with saturated brine (5 × 50 mL). The organic fraction was dried (magnesium sulfate), concentrated *in vacuo*, and the crude product purified by SP4 column chromatography using a hexane/ethyl acetate gradient to yield the product.

(1R,2S)-2-(Benzylamino)cyclohexyl benzoate 209

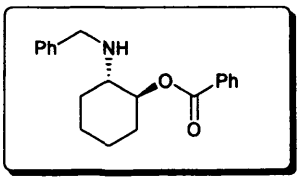


Following the general procedure Method 1 in DMSO to give the title product **209** as a colourless oil (24 mg, 14%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 7.6 Hz, 2H), 7.48 (t, J = 7.6 Hz, 1H), 7.40 (*app.* t, J = 7.6 Hz, 2H), 7.26–7.14 (m, 5H), 5.42–5.41 (m, 1H), 3.81 (d, J = 13.3 Hz, 1H), 3.74 (d, J = 13.3 Hz, 1H), 2.71 (*app.* dt, J = 10.2 Hz, 3.0 Hz, 1H), 2.04–1.18 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1 (s), 140.7 (s), 132.9 (d), 130.8 (s), 129.7 (d), 128.4 (d), 128.4 (d), 12vbbb8.1 (d), 126.8 (d), 71.7 (d), 56.8 (d), 50.5 (t), 29.1 (t), 28.7 (t), 21.9 (t), 21.2 (t); LCMS 310.2 *m/z* $[M+H]^+$.

Following the general Method 1 in 1,2 DCE the title product **209** was prepared again (79 mg, 47%).

Following the general Method 2 in DMSO the title product **209** was prepared again (117 mg, 41%).

(1S,2S)-2-(Benzylamino)cyclohexyl benzoate 210

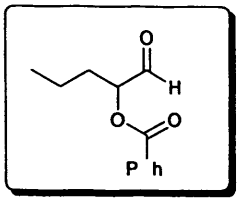


Following the general procedure Method 1 in DMSO to yield the product **210** as a colourless oil (11 mg, 6%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 7.7 Hz, 2H), 7.49 (t, J =7.7 Hz, 1H), 7.38 (*app.* t, J = 7.7 Hz, 2H), 7.21–7.15 (m, 5H), 4.85–4.84 (m, 1H), 3.83 (d, J = 13.4 Hz, 1H), 3.70 (d, J = 13.4 Hz, 1H), 2.73–2.12 (m, 1H), 2.09–0.78 (m, 8H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 166.2 (s), 140.8 (s), 132.9 (d), 130.7 (s), 129.6 (d), 128.4 (d), 128.4 (d), 128.0 (d), 126.8 (d), 77.0 (d), 59.0 (d), 50.9 (t), 30.7 (t), 30.5 (t), 24.0 (t), 24.0 (t); LCMS 310.3 *m/z* $[M+H]^+$.

Following the general Method 2 in DMSO the title product **210** was prepared again (68 mg, 24%).

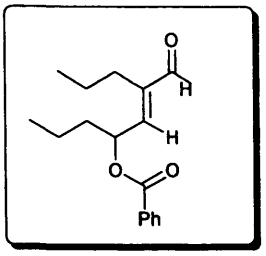
1-Oxypentan-2-yl benzoate 215



Isovaleraldehyde (65 mg, 0.76 mmol) and *N*-benzyl-*O*-benzoyl hydroxylamine hydrochloride (200 mg, 0.76 mmol) were dissolved in DMSO (1.6 mL) and the resultant mixture allowed to stir at room temperature for 16 hours. The solution was subsequently diluted with ethyl acetate (40 mL) and water (2 x 40 mL). The aqueous layer was then extracted with ethyl acetate (2 x 30 mL) The organic fractions were combined and washed repeatedly with brine (2 x 40 mL) and dried over $MgSO_4$ then concentrated under reduced pressure. The crude product was purified by SP4 automated column chromatography with an ethyl acetate and hexane gradient on silica to yield the title compound **215** (69 mg, 44%) as a colourless oil; IR (thin film) 1749, 1689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, J = 0.8 Hz, 1H), 8.11 (d, J = 8.0 Hz, 2H), 7.61 (t, J = 8.0 Hz, 1H), 7.48 (*app.* t, J = 8.0 Hz, 2H), 5.25–5.23 (m, 1H), 2.05–1.85 (m, 2H), 1.61–1.50 (m, 2H), 1.00 (t, J = 7.4Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6 (s), 166.2 (s), 133.5 (d), 129.9 (s), 129.2 (d), 128.5 (d), 78.6 (d), 30.9 (t), 18.4 (t), 13.8 (q); LCMS 207.1 *m/z* $[M+H]^+$.

Following the above reaction procedure using the *N*-propyl-*O*-benzoyl hydroxylamine hydrochloride reagent the product **215** was prepared again (82 mg, 52%).

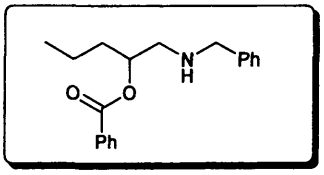
(E)-6-Formylnon-5-en-4-yl benzoate 216



Isovaleraldehyde (65 mg, 0.76 mmol) and *N*-benzyl-*O*-benzoyl hydroxylamine hydrochloride (200 mg, 0.76 mmol) were dissolved in DMSO (1.6 mL) and the resultant mixture allowed to stir at room temperature for 16 hours. The solution was subsequently diluted with ethyl acetate (40 mL) and water (2 x 40 mL). The aqueous layer was then extracted with ethyl acetate (2 x 30 mL) The organic fractions were combined and washed repeatedly with brine (2 x 40 mL) and dried over $MgSO_4$ then concentrated under reduced pressure. The crude product was purified by SP4 automated column chromatography with an ethyl acetate and hexane gradient on silica to yield the product as a colourless oil (21 mg, 16%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.05 (dd, J = 7.4 Hz, 1.3 Hz, 2H), 7.58 (td, J = 7.4 Hz, 1.3 Hz, 1H), 7.46 (*app.* t, J = 7.4 Hz, 2H), 6.38 (d, J = 9.0 Hz, 1H), 5.91–5.93 (m, 1H), 2.44–2.29 (m, 2H), 1.97–1.90 (m, 1H), 1.75–1.68 (m, 1H), 1.54–1.37 (m, 4H), 1.00 (t, J = 7.5 Hz, 3H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 194.9 (d), 165.8 (s), 149.8 (d), 144.4 (s), 133.2 (d), 129.9 (s), 129.6 (d), 128.4 (d), 70.8 (d), 36.4 (t), 26.7 (t), 22.1 (t), 18.4 (t), 14.3 (q), 13.9 (q); LCMS (ES+) 297.2 *m/z* [M+H+Na].

Following the above reaction procedure using the *N*-propyl-*O*-benzoyl hydroxylamine hydrochloride reagent the product **216** was prepared again (25 mg, 12%).

1-(Benzylamino)pentan-2-yl benzoate 220

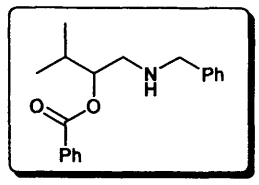


Following the reductive amination procedure Method 2 in DMSO to give the product **220** as a colourless oil (19 mg, 7%); ^{1}H NMR (500 Mz, $CDCl_3$), 7.47 (dd, J = 8.0 Hz, 1.5 Hz, 2H), 7.42–7.29 (m, 6H), 7.18 (d, J = 6.5 Hz, 2H), 4.62–4.60 (m, 1H), 3.88–3.75 (m, 2H), 3.27–3.25 (m, 2H), 1.44 (t, J = 6.8 Hz, 2H), 1.36–1.25 (m, 2H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 174.4 (s), 136.4 (s), 135.7 (s), 130.0 (d), 129.9 (d), 128.6 (d), 127.8 (d), 126.9 (d), 126.8 (d), 71.2 (d), 54.5 (t), 52.8 (t), 37.9 (t), 18.6 (t), 14.0 (q); LCMS (ES) 298.1 *m/z* $[M+H]^+$.

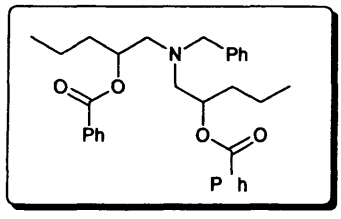
Following the reductive amination procedure Method 2 in 1,2 DCE the product **220** was prepared again (6 mg, 2%).

1-(Benzylamino)-3-methylbutan-2-yl benzoate



Following the reductive amination procedure Method 2 in DMSO to give the product **220** as a colourless oil as a colourless oil (27 mg, 10%); ^1H NMR (500 Mz, $CDCl_3$), 8.00 (d, J = 7.5 Hz, 2H), 7.50 (t, J = 7.5 Hz, 1H), 7.39 (*app.* t, J = 7.5 Hz, 2H), 7.23–7.16 (m, 5H), 5.10–5.06 (m, 1H), 3.81–3.70 (m, 2H), 2.84–2.82 (m, 2H), 2.02–2.00 (m, 1H), 0.94–0.92 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5 (s), 140.1 (s), 133.0 (d), 130.5 (s), 129.7 (d), 128.4 (d), 128.4 (d), 128.1 (d), 127.0 (d), 78.4 (d), 53.5 (t), 49.9 (t), 30.3 (d), 18.9 (q), 17.8 (q); LCMS (ES) 298.2 *m/z* $[M+H]^+$.

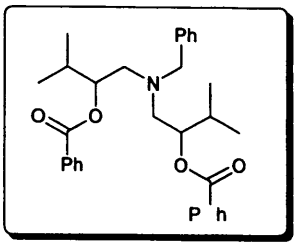
1,1'-(Benzylazanediyl)bis(pentane-2,1-diyl) dibenzoate 221



Following the general reductive amination procedure Method 2 in DMSO to yield the title compound **221** as a colourless oil (207 mg, 92%); ^1H NMR (500 Mz, $CDCl_3$), 8.03 (d, J = 8.0 Hz, 2H), 7.98 (d, J = 8.0 Hz, 2H), 7.56–7.50 (m, 2H), 7.47–7.37 (m, 4H), 7.27–7.21 (m, 5H), 5.31–5.29 (m, 2H), 3.81–3.64 (m, 2H), 2.76–2.74 (m, 4H), 1.63–1.55 (m, 4H), 1.30–1.20 (m, 4H), 0.85 (t, J = 7.4 Hz, 3H), 0.75 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3 (s), 166.2 (s), 139.2 (s), 139.0 (s), 132.8 (d), 132.7 (d), 130.6 (s), 129.6 (d), 129.2 (d), 129.1 (d), 128.3 (d), 128.2 (d), 128.1 (d), 126.9 (d), 72.4 (d), 72.3 (d), 59.7 (t), 59.6 (t), 57.9 (t), 57.8 (t), 34.7 (t), 18.5 (t), 18.5 (t), 13.9 (q), 13.9 (q); LCMS (ES) 488.3 *m/z* $[M+H]^+$.

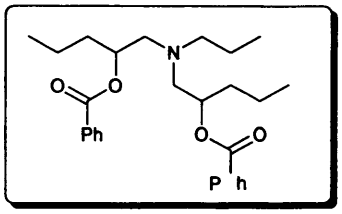
Following the general reductive amination procedure Method 2 in 1,2 DCE the title compound **221** was prepared again (185 mg, 82%)

1-(Benzylamino)-2,3-di(methylbutan-2-yl benzoate)



Following the general reductive amination procedure Method 2 in DMSO to yield the title compound **221** as a colourless oil (178 mg, 79%); ^{1}H NMR (500 Mz, $CDCl_3$), 8.00 (d, J = 8.1 Hz, 2H), 7.91 (d, J = 8.1 Hz, 2H), 7.48–7.46 (m, 2H), 7.38–7.32 (m, 4H), 7.16–7.13 (m, 5H), 5.16–4.95 (m, 2H), 3.74–3.53 (m, 2H), 2.77–2.63 (m, 4H), 1.94–1.80 (m, 2H), 0.82–0.76 (m, 6H), 0.71–0.66 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.30 (s), 166.23 (s), 139.20 (s), 132.79 (d), 132.72 (d), 130.70 (s), 130.59 (s), 129.64 (d), 129.61 (d), 128.26 (d), 128.34 (d), 128.26 (d), 128.09 (d), 126.90 (d), 76.12 (d), 76.04 (d), 59.52 (t), 59.25 (t), 55.28 (t), 30.04 (d), 29.78 (d), 19.21 (q), 19.12 (q), 16.92 (q), 16.41 (q).

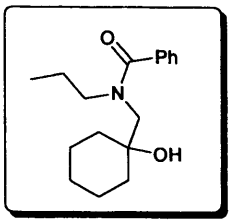
1,1'-(Propylazanediyl)bis(pentane-2,1-diyl) dibenzoate 222



Following the procedure for reductive amination Method 1 to yield the title compound as a colourless oil (50 mg, 42%); ^{1}H NMR (500 Mz, $CDCl_3$), 8.05–8.00 (m, 4H), 7.56–7.51 (m, 2H), 7.44–7.39 (m, 4H), 5.30–5.18 (m, 2H), 2.79–2.47 (m, 6H), 1.74–1.20 (m, 10H), 0.88 (t, J = 7.4 Hz, 3H), 0.83 (t, J = 7.4 Hz, 3H), 0.79 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2 (s), 166.2 (s), 132.7 (d), 132.7 (d) 130.7 (s), 130.7 (s), 129.5 (d), 129.5 (d), 128.3 (d), 128.2 (d), 73.0 (d), 72.9 (d), 58.6 (t), 58.4 (t), 57.3 (t), 57.1 (t), 34.8 (t), 20.5 (t), 18.7 (t), 18.7 (t), 14.0 (q), 14.0 (q), 11.7 (q); LCMS (ES) *m/z* 440.26 $[M+H]^+$.

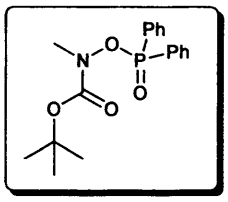
Following the procedure for reductive amination Method 2 the title compound was again prepared (182 mg, 90%).

_N_-((1-Hydroxycyclohexyl)methyl)-_N_-propylbenzamide



Following the general reductive amination procedure Method 2 to yield the title compound as a colourless oil (77 mg, 30%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.37 (m, 5H), 4.24 (s, 1H), 3.56 (s, 2H), 3.29 (t, J = 7.5 Hz, 2H), 1.72–1.25 (m, 12H), 0.72 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6 (s), 136.6 (s), 129.4 (d), 128.5 (d), 126.4 (d), 72.8 (s), 56.3 (t), 53.6 (t), 36.3 (t), 25.9 (t), 22.0 (t), 21.8 (t), 11.0 (q); LCMS (ES) 276.2 *m/z* $[M+H]^+$.

_N_-Boc-_N_-Methyl-_O_-(diphenylphosphoryl) hydroxylamine 253

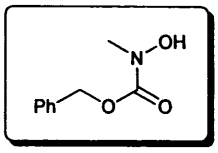


Under an atmosphere of nitrogen, a round-bottomed flask containing dichloromethane (28mL) was charged with _N_-Boc-_N_-methylhydroxylamine (2.0 g. 13.6 mmol) with continuous stirring triethylamine (1.89 mL) was added drop-wise to the solution. The mixture was then cooled to 0 °C for 15 minutes and 2 mol% of DMAP (35 mg) was added. This was followed by subsequent addition of diphenyl phosphinic chloride (3.22 g, 13.6 mmol), which turns the reaction mixture from colourless to deep pink colour. The reaction was left to react 16 hours under nitrogen from 0 °C to room temperature.

The resulting solution was filtered and reduced *in vacuo*. The pink oil produced was dissolved in dichloromethane (60 mL) and partitioned with water (70 mL). The organic layer was extracted and the aqueous re-extracted with CH_2Cl_2 (2 x 50 mL). The organic layers were combined, washed with brine (70 mL) and dried over anhydrous Na_2SO_4. The solution was then reduced in vacuo to yield the crude pink viscous oil, which was purified by flash chromatography (10:1) hexane/ethyl acetate to give _N_-Boc-_N_-methyl-O-phosphinic diphenyl hydroxylamine **253** (4.54 g, 94%) as a white crystalline solid; Mpt 80–82 °C); IR (neat) 1642, 1154 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.91 (m, 4H), 7.54–7.45 (m, 6H), 3.38

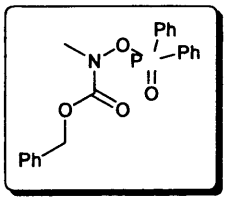
(s, 3H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1 (s), 132.5 (d, J^2CP = 15.0 Hz), 132.2 (d, J^1CP = 40.0 Hz) (d), 129.1 (d), 128.0 (d),, 83.3 (s), 42.0 (q), 27.0 (q); ^{31}P NMR (300 MHz, $CDCl_3$) 37.7 (s); MS (ES) 348.2 *m/z* $[M+H]^+$; HRMS (ES) calculated for $[M+H]^+$, found 348.1365.

_N_-Cbz-_N_-Methyl hydroxylamine 257



A solution of *N*-methyl hydroxylamine (10 g, 0.12 mol) in CH_2Cl_2 (240 mL) was cooled to 0 °C and triethylamine (36.7 mL, 0.26 mol), D-MAP (293 mg, 2.4 mmol) along with benzyl chloroformate (20.5 mL, 0.14 mol) was added to the reaction followed. The reaction was left to stir over 6 hours and allowed to warm to room temperature. Subsequently, evaporation under reduced pressure produced gave an oil which was dissolved in CH_2Cl_2 (100 mL) and exhibited to an aqueous work-up. The organic solution was washed with water (3 x 100 mL) and brine (100 mL). The solution was then dried over Na_2SO_4 then the solvent was removed under pressure. The crude product was purified by flash chromatography (3:1) hexane/ethyl acetate to yield compound **257** (15.2 g, 70%) as a colourless oil; IR (neat) 3397, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.34 (5H, m), 5.22 (2H, s), 3.23 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1 (s), 136.0 (s), 128.6 (d), 128.3 (d), 128.0 (d), 68.0 (t), 38.1 (q).

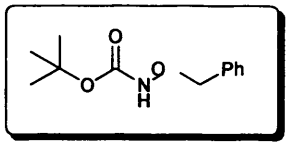
_N_-Cbz-_N_-Methyl-_O_-(diphenylphosphoryl) hydroxylamine 258



A solution of *N*-Cbz-*N*-methyl hydroxylamine (2.0 g, 11 mmol), 4-dimethyl amino pyridine (27 mg, 2 mol%) and triethylamine (1.51 mL, 11 mmol) in dichloromethane (22 mL) was cooled to 0 °C prior to slow addition of the diphenyl phosphinic chloride (2.61 g, 11 mmol). The reaction was allowed to warm to room temperature and stirred for 16 hours. Evaporation under reduced pressure gave a crude product, which was dissolved in CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ (2 x 20 mL), water (30 mL) and brine (30 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated and the product purified by flash column chromatography (3:1) hexane/ethyl acetate to yield the *N*-Cbz protected

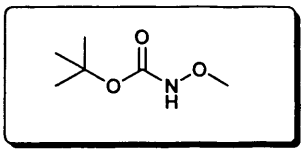
hydroxylamine (3.13 g, 75%) as a viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.72 (m, 4H), 7.48–7.42 (m, 2H), 7.35–7.27 (m, 7H), 7.19–7.18 (m, 2H) 4.98 (s, 2H), 3.36 (s, 3H); ^{31}P NMR (300 MHz, $CDCl_3$) 39.8 (s); MS (EI) 381.1 *m/z* $[M+H]^+$; HRMS (ES) calculated for $C_{21}H_{20}NPO_4Na$ 404.1022 $[M+H]^{+}$ found 404.1021.

_N_-Boc-_O_-Benzyl hydroxylamine 276



A solution of *O*-benzyl hydroxylamine (20 g, 240 mmol) in THF/H_2O (1:1) (480 mL) was cooled to 0 °C and potassium carbonate (16.5 g, 120 mmol) was added. Careful addition of the di-*tert* butyl dicarbonate (52.3 g, 240 mL) to the reaction followed. The reaction was left to stir over 6 hours and allowed to warm to room temperature. Subsequently the THF was removed under reduced pressure. The remaining aqueous solution was added to CH_2Cl_2 (300 mL), washed with water (3 x 100 mL) and brine (100 mL). The solution was then dried over Na_2SO_4 then the solvent was removed under pressure. The crude product was purified by flash chromatography with (3:1) hexane/ethyl acetate to yield compound **276** (40.1 g, 75%) as a white solid; Mpt 50–52 °C; IR (neat) 3320, 1686 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.44 (m, 5H), 4.78 (s, 2H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7 (s), 135.8 (s), 133.1 (d), 129.1 (d), 128.5 (d), 81.7 (s), 78.5 (t), 28.2 (q); MS (EI) 224.0 *m/z* $[M+H]^+$; HRMS calculated for $C_{12}H_{21}O_3N_2$ 241.1547 $[M+NH_4]^+$ found 241.1547.

_N_-Boc-_O_-Methyl hydroxylamine



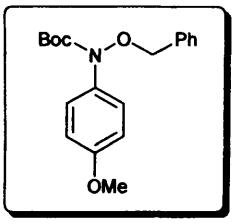
Following the genereal Boc protection procedure gave the reagent (25.1 g, 71%) as a viscous oil; IR (neat) 3299, 1694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5 (s), 81.2 (s), 62.5 (q), 28.3 (q); MS (EI) 148.3 *m/z* $[M+H]^+$.

General experimental procedure for the coupling of hydroxylamines:

To an oven dried Schlenk-tube under an atmosphere of nitrogen copper iodide (9 mg, 0.05 mmol), 1,10-phenanthroline (90 mg, 0.50 mmol), caesium carbonate (456 mg, 1.4 mmol) and 4-iodobenzonitrile (687 mg, 3 mmol) were added. The Schlenk was evacuated and back filled with nitrogen twice before addition of *N*-Boc-*O*-methyl hydroxylamine (147 mg, 1

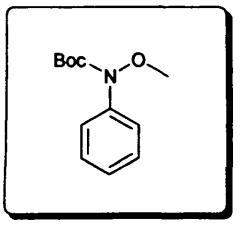
mmol). The Schlenk was evacuated and flushed with nitrogen before addition of dry *N,N*-dimethylformamide (1 mL). The reaction vessel was sealed and stirred at 80 °C for 24 hours. The reaction mixture was diluted with ethyl acetate (5 mL) then filtered through a short silica plug and washed with ethyl acetate (2 x 100 mL). The solvent was then removed *in vacuo* to give a yellow oil. The crude product was purified by flash column chromatography on silica eluting with ethyl acetate:light petroleum (1:9).

_N_-Boc-_N_-(4-Methoxyphenyl)-_O_-benzyl hydroxylamine 283



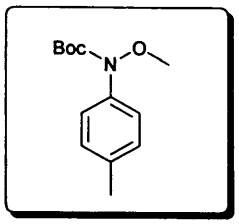
Following the general procedure to give the product **283** (227 mg, 69%) as a white solid; Mpt 52–54 °C; IR (neat) 1711.1 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.31 (m, 7H), 6.88 (d, J = 8.9 Hz, 2H), 4.85 (s, 2H), 3.81 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8 (s), 154.2 (s), 135.2 (s), 133.6 (s), 129.6 (d), 128.6 (d), 128.4 (d), 125.1 (d), 113.9 (d), 81.9 (s), 76.5 (t), 55.5 (q), 28.3 (q); MS (EI) *m/z* 329.2 $[M]^{\cdot+}$; HRMS (EI) found 329.1634 $[M]^{\cdot+}$; calculated for $C_{19}H_{23}NO_4$ 329.1627.

_N_-Boc-_N_-Phenyl-_O_-methyl hydroxylamine[115] 290[116]



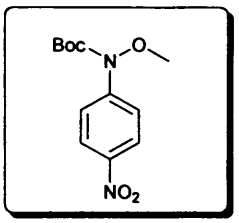
Following the general procedure to give the product **290** (198mg, 89%) as a colourless oil. IR (neat) 1714 cm cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.43 (m, 2H), 7.35–7.31 (m, 2H), 7.14 (t, J = 7.3 Hz, 1H), 3.73 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3 (s), 140.1 (s), 128.5 (d), 125.3 (d), 121.7 (d), 82.2 (s), 62.1 (q), 28.3 (q); MS (EI) *m/z* 223.1 $[M]^{\cdot+}$; HRMS (EI) found 223.1203 $[M]^{\cdot+}$; calculated for $C_{12}H_{17}NO_3$ 223.1208.

***N*-Boc-*N*-(4-Fluorophenyl)-*O*-methyl hydroxylamine 292**



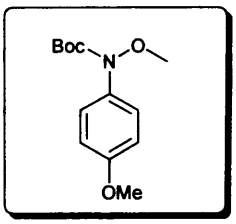
Following the general procedure to give the product **292** (174 mg, 72%) as a pale yellow oil. IR (neat) 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.35 (m, 2H), 7.03–6.98 (m, 2H), 3.71 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.3 (d, J^1CF = 242.5 Hz), 153.5 (s), 136.3 (s), 124.1 (d, J^3CF = 7.5 Hz) (d), 115.2 (d, J^2CF = 22.5 Hz) (d), 82.3 (s), 62.1 (q), 28.2 (q); MS (EI) *m/z* 240.9 $[M]^{\cdot+}$; HRMS (EI) found 241.1122 $[M]^{\cdot+}$; calculated for $C_{12}H_{16}{}^{19}FNO_3$ 241.1114.

***N*-Boc-*N*-(4-Nitrophenyl)-*O*-methyl hydroxylamine 294**



Following the general procedure to give the product **294** (206 mg, 77%) as an orange oil. IR (neat) 1721, 1515, 1317 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 2H), 3.73 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0 (s), 145.6 (s), 143.5 (s), 124.5 (d), 118.7 (d), 83.8 (s), 62.7 (q), 28.2 (q); MS (APCI) *m/z* 269.1 $[M+H]^{\cdot+}$; HRMS (EI) found 268.1052 $[M]^{\cdot+}$; calculated for $C_{12}H_{16}N_2O_5$ 268.1054.

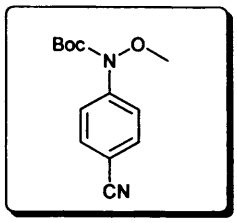
***N*-Boc-*N*-(4-Methoxyphenyl)-*O*-methyl hydroxylamine 295**



Following the general procedure to give the product **295** (175 mg, 69%) as a colourless oil. IR (neat) 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 3.73 (s, 3H), 3.64 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8 (s),

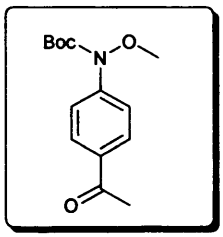
154.0 (s), 133.3 (s), 125.0 (d), 113.8 (d), 81.9 (s), 61.8 (q), 55.5 (q), 28.3 (q); MS (EI) *m/z* 253.1 $[M]^{\cdot+}$; HRMS (EI) found 253.1319 $[M]^{\cdot+}$; calculated for $C_{13}H_{19}NO_4$ 253.1314.

_N_-Boc-_N_-(4-Cyanophenyl)-_O_-methyl hydroxylamine 297



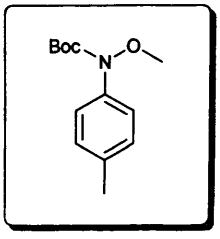
Following the general procedure to give the product **297** (213 mg, 86%) as a colourless oil. IR (neat) 2226, 1718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.59 (m, 4H), 3.76 (s, 3H), 1.56 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1 (s), 143.9 (s), 132.8 (d), 119.3 (d), 118.9 (s), 107.1 (s), 83.5 (s), 62.6 (q), 28.2 (q); MS (ES) *m/z* 249.3 $[M+H]^{\cdot+}$; HRMS (ES) found 249.1236 $[M+H]^{\cdot+}$; calculated for $C_{13}H_{17}N_2O_3$ 249.1234.

_N_-Boc-_N_-(4-Acetylphenyl)-_O_-methyl hydroxylamine 299



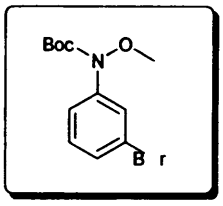
Following the general procedure to give the product **299** (193 mg, 73%)as a pale yellow oil. IR (neat) 1717, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94–7.91 (m, 2H), 7.59–7.56 (m, 2H), 3.75 (s, 3H), 2.56 (s, 3H), 1.55 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.9 (s), 152.3 (s), 144.1 (s), 133.0 (s), 129.1 (d), 119.1 (d), 83.1 (s), 62.4 (q), 28.2 (q), 26.4 (q); MS (APCI) *m/z* 266.1 $[M+H]^{\cdot+}$; HRMS (ES) found 266.1388 $[M+H]^{\cdot+}$; calculated for $C_{14}H_{20}NO_4$ 266.1387.

_N_-Boc-_N_-(4-Methylphenyl)-_O_-methyl hydroxylamine 301



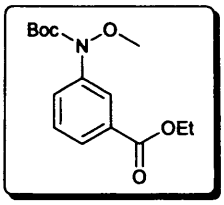
Following the general procedure to give the product **301** (166 mg, 70%) as a yellow oil. IR (neat) 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 3.71 (s, 3H), 2.32 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5 (s), 137.6 (s), 135.3 (s), 129.1 (d), 122.3 (d), 82.0 (s), 62.0 (q), 28.3 (q) 20.9 (q); MS (EI) *m/z* 237.1 $[M]^{+}$; HRMS (EI) found 237.1364 $[M]^{+}$; calculated for $C_{13}H_{19}NO_3$ 237.1365.

_N_-Boc-_N_-(3-Bromophenyl)-methyl hydroxylamine 303



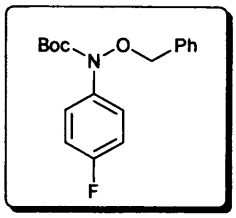
Following the general procedure to give the product **303** (223 mg, 74%) as an orange oil. IR (neat) 1716 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59–7.58 (m, 1H), 7.35–7.32 (m, 1H), 7.20-7.18 (m, 1H), 7.14–7.10 (m, 1H), 3.67 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8 (s), 141.4 (s), 129.8 (d), 127.7 (d), 123.7 (d), 122.2 (s), 119.3 (d), 82.8 (s), 62.4 (q), 28.3 (q); MS (EI) *m/z* 303.1 (50%), 301.1 (50%) $[M]^{+}$; HRMS (EI) found 301.0325 $[M]^{+}$; calculated for $C_{12}H_{16}{}^{79}BrNO_3$ 301.0314.

_N_-Boc-_N_-(3-Carboethoxyphenyl)-_O_-methyl hydroxylamine 305



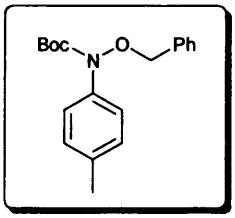
Following the general procedure to give the product **305** (248 mg, 84%) as a colourless oil. IR (neat) 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 1.6 Hz, 1H) 7.71–7.75 (m, 1H), 7.59–7.57 (m, 1H), 7.34 (*app.* t, J = 8.0 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 3.69 (s, 3H), 1.48 (s, 9H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2 (s), 153.0 (s), 140.4 (s), 131.0 (s), 128.5 (d), 126.1 (d), 125.5 (d), 122.3 (d), 82.6 (s), 62.3 (q), 61.1 (t), 28.2 (q), 14.3 (q); MS (APCI) *m/z* 296.1 $[M+H]^{+}$; HRMS (ES) found 313.1757 $[M+NH_4]^{+}$; calculated for $C_{15}H_{25}N_2O_5$ 313.1758.

***N*-Boc-*N*-(4-Fluorophenyl)-*O*-benzyl hydroxylamine 313**



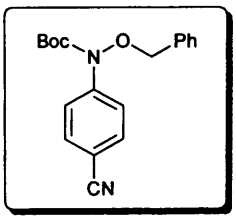
Following the general procedure to give the product **313** (222 mg, 70%) as a yellow oil; IR (neat) 1710.1 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.33 (m, 7H), 7.04–7.00 (m, 2H), 4.85 (s, 2H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4 (d, J^1CF = 243.8 Hz), 153.8 (s), 136.7 (s), 134.8 (s), 129.6 (d), 128.7 (d), 128.5 (d), 124.4 (d, J^3CF = 7.5 Hz) (d), 115.3 (d, J^2CF = 22.5 Hz) (d), 82.3 (s), 76.8 (t), 28.2 (q); MS (EI) *m/z* 317.1 $[M]^{\cdot+}$; HRMS (EI) found 317.1426 $[M]^{\cdot+}$; calculated for $C_{18}H_{20}{}^{19}FNO_3$ 317.1427.

***N*-Boc-*N*-(4-Tolyl)-*O*-benzyl hydroxylamine 314**



Following the general procedure to give the product **314** (232 mg, 74%) as a colourless oil; IR (neat) 1712.8 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.32 (m, 7H), 7.15 (d, *J* = 8.4 Hz, 2H), 4.85 (s, 3H), 2.34 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8 (s), 137.9 (s), 135.3 (s), 135.0 (s), 129.6 (d), 129.2 (d), 128.6 (d), 128.4 (d), 122.5 (d), 82.0 (s), 76.5 (t), 28.3 (q), 20.9 (q); MS (EI) *m/z* 313.2 $[M]^{\cdot+}$; HRMS (EI) found 313.1676 $[M]^{\cdot+}$; calculated for $C_{19}H_{23}NO_3$ 313.1678.

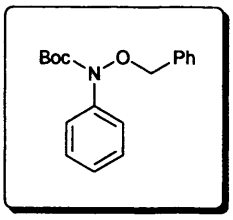
***N*-Boc-*N*-(4-Cyanophenyl)-*O*-benzyl hydroxylamine 315**



Following the general procedure to give the product **315** (211 mg, 65%) as a white solid; Mpt 70 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.59 (m, 4H), 7.40–7.36 (m, 5H), 4.88 (s, 2H),

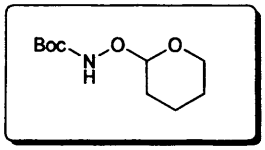
1.56 (s, 9H); ^{13}C NMR (60 MHz, $CDCl_3$) δ 152.5 (s), 144.3 (s), 134.0 (s), 132.7 (d), 129.7 (d), 129.1 (d), 128.7 (d), 119.9 (d), 118.9 (s), 107.3 (s), 83.6 (s), 77.3 (t), 28.2 (q); MS (ES) *m/z* 342.3 $[M+NH_4]^{+}$; HRMS (ES) found 342.1815 $[M+NH_4]^{+}$; calculated for $C_{19}H_{24}N_3O_3$ 342.1812.

_N_-Boc-_N_-Phenyl-_O_-benzyl hydroxylamine 316[101]



Following the general procedure to give the product **316** (248 mg, 83%) as a pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51–7.34 (m, 7H), 7.17 (t, J = 6.0 Hz, 1H), 4.88 (s, 2H), 1.52 (s, 9H); ^{13}C NMR (60 MHz, $CDCl_3$) δ 153.6 (s), 140.5 (s), 134.9 (s), 129.7 (d), 128.7 (d), 128.6 (d), 128.5 (d), 125.3 (d), 122.0 (d), 82.2 (s), 76.7 (t), 28.3 (q); MS (ES) *m/z* 317.3 $[M+NH_4]^{+}$; HRMS (ES) found 317.1862 $[M+NH_4]^{+}$; calculated for $C_{18}H_{25}N_2O_3$ 317.1860.

_N_-Boc-_O_-tetrahydropyranyl hydroxylamine 322



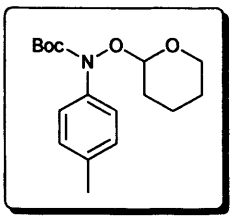
Following the general Boc protection procedure to give (2.1 g, 88%) as a colourless viscous oil; IR (neat) 1708.1 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.13–5.12 (m, 1H), 3.70–1.53 (m, 8H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2 (s), 101.5 (d), 81.9 (s), 62.0 (t), 28.3 (t), 28.2 (q), 25.2 (t), 18.1 (t).

General experimental procedure for the coupling of _N_-Boc-_O_-THP hydroxylamine:

To an oven dried Schlenk-tube under an atmosphere of nitrogen copper iodide (18 mg, 0.1 mmol), 1,10-phenanthroline (180 mg, 1 mmol), caesium carbonate (456 mg, 1.4 mmol) and 4-iodotoluene (655 mg, 3 mmol) were added. The Schlenk was evacuated and back filled with nitrogen twice before addition of *N*-Boc-*O*-THP hydroxylamine (217 mg, 1 mmol). The Schlenk was evacuated and flushed with nitrogen before addition of dry *N,N*-dimethylformamide (1 mL). The reaction vessel was sealed and stirred at 80 °C for 24 hours.

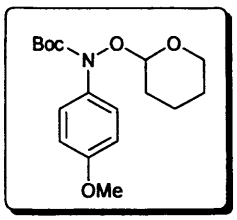
The reaction mixture was diluted with ethyl acetate (5 mL) then filtered through a short silica plug and washed with ethyl acetate (2 x 100 mL). The solvent was then removed *in vacuo* to give a yellow oil. The crude product was purified by flash column chromatography on silica eluting with ethyl acetate:light petroleum (1:5) to give *N*-Boc-*N*-(4-tolyl)-*O*-tetrahydropyranyl hydroxylamine **324**.

***N*-Boc-*N*-(4-Tolyl)-*O*-tetrahydropyranyl hydroxylamine 324**[101]



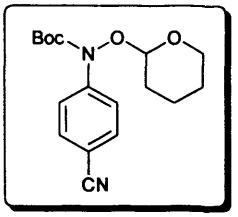
Following the general coupling procedure to give **324** (215 mg, 70%) as a colourless oil; IR (neat) 1724.0 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 8.2 Hz, 2H), 5.12 (*app.* t, J = 2.6 Hz, 1H), 3.72–3.71 (m, 1H), 3.44–3.41 (m, 1H), 2.32 (s, 3H), 1.84.–1.57 (m, 6H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7 (s), 136. 0 (s), 129.0 (d), 124.4 (d), 101.5 (d), 82.0 (s), 62.1 (t), 28.3 (t), 28.3 (q), 25.1 (t), 21.0 (q) 18.3 (t), (1 x C missing); MS (EI) *m/z* 307.2 $[M]^{+}$; HRMS (EI) found 307.1781$[M]^{+}$;calculated for $C_{17}H_{25}NO_4$ 307.1784.

***N*-Boc-*N*-(4-Methoxyphenyl)-*O*-tetrahydropyranyl hydroxylamine 325**[101]



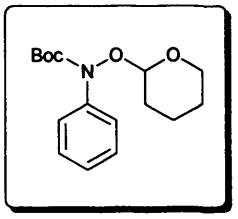
Following the general coupling procedure to give **324** (168 mg, 52%) as a colourless viscous oil; IR (neat) 1717.3 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 9.8 Hz, 2H), 6.85 (d, J = 9.8 Hz, 2H), 5.14–5.13 (m, 1H), 3.80 (s, 3H), 3.70–3.65 (m, 1H), 3.43–3.41 (m, 1H), 1.82–1.58 (m, 6H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1 (s), 155.0 (s), 126.8 (d), 113.7 (d), 101.5 (d), 81.9 (s), 61.9 (t), 55.4 (q), 28.3 (t), 28.3 (q), 25.2 (t), 18.3 (t), (1 x C missing); MS (EI) *m/z* 323.2 $[M+H]^{+}$; HRMS (EI) found 323.1731 $[M]^{+}$; calculated for $C_{17}H_{25}NO_5$ 323.1733.

***N*-Boc-*N*-(4-Cyanophenyl)-*O*-tetrahydropyranyl hydroxylamine 326**



Following the general coupling procedure to give **324** (242 mg, 76%) as a colourless viscous oil; IR (neat) 2227.3, 1728.0 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62–7.56 (m, 4H), 5.08–5.07 (m, 1H), 3.72–3.70 (m, 1H), 3.46–3.43 (m, 1H), 1.86–1.55 (m, 6H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1 (s), 145.9 (s), 132.3 (d), 122.2 (d), 118.8 (s), 108.2 (s), 102.9 (d), 83.6 (s), 62.9 (t), 28.2 (t), 28.2 (q), 24.9 (t), 18.6 (t); MS (EI) *m/z* 318.2 $[M]^{\cdot+}$; HRMS (EI) found 318.1577 $[M+H]^{\cdot+}$; calculated for $C_{17}H_{22}N_2O_4$ 318.1580.

***N*-Boc-*N*-Phenyl-*O*-THP hydroxylamine 327**[101]



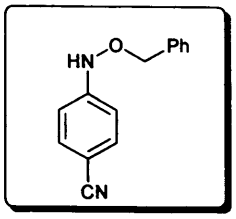
Following the general coupling procedure to give **324** (234 mg, 80%) as a colourless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.40 (m, 2H), 7.36–7.31 (m, 2H), 7.20–7.16 (m, 1H), 5.14–5.13 (m, 1H), 3.72–3.69 (m, 1H), 3.44–3.41 (m, 1H), 1.87–1.62 (m, 6H), 1.49 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 154.4 (s), 142.0 (s), 128.3 (d), 126.0 (d), 124.1 (d), 101.7 (d), 82.2 (s), 62.1 (t), 28.3 (q), 28.3 (t), 25.1 (t), 18.3 (t); HRMS (ES) found 332.1268 $[M + {}^{39}K]^{\cdot+}$; calculated for $C_{16}H_{23}NO_4K$ 332.1264.

Typical experimental procedure for *N*-Boc removal

A solution of *N*-Boc-*O*-benzyl hydroxylamine analogues (0.31 mmol) in CH_2Cl_2 (9 mL) was cooled to 0 °C and trifluroacetic acid (1 mL) was added dropwise. The solution was allowed to stir for 3 hours at 0 °C and then warmed to room temperature. The organic phase was washed with water (2 x 20 mL), brine (20 mL), dried over sodium sulfate and the solvent evaporated. The crude reaction mixture was purified by flash column chromatography on

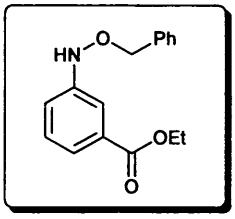
silica eluting with 10% ethyl acetate in hexane to give the Boc deprotected *O*-benzyl hydroxylamine product.

_N_-(4-Cyanophenyl)-_O_-benzyl hydroxylamine 330



Following the general reaction procedure to give *N*-(4-cyanophenyl)-*O*-benzyl hydroxylamine **330** (53 mg, 76%) as a colourless viscous oil; IR (neat) 3424.9, 2219.0 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 6.9 Hz, 2H), 7.43–7.39 (m, 5H), 6.91 (d, J = 6.9 Hz, 2H), 4.90 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1 (s), 136.0 (s), 133.4 (d), 129.0 (d), 128.7 (d), 128.7 (d), 119.5 (s), 113.5 (d), 104.1 (s), 77.6 (t); MS (APCI) *m/z* 225.1 $[M+H]^{+}$; HRMS (EI) found 225.1026 $[M+H]^{+}$; calculated for $C_{14}H_{13}N_2O$ 225.1028.

_N_-(3-Carboethoxyphenyl)-_O_-benzyl hydroxylamine 331



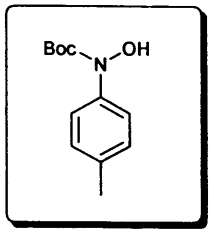
Following the general reaction proceure to give the title product **331** (61 mg, 73%) as a colourless oil; IR (neat) 3285.4, 1716.8 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) δ 7.65–7.60 (m, 2H,), 7.46–7.26 (m, 6H), 7.14–7.12 (m, 2H), 4.93 (s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 166.8 (s), 148.4 (s), 136.5 (s), 131.2 (s), 129.1 (d), 128.9 (d), 128.6 (d), 128.4 (d), 123.3 (d), 118.9 (d), 115.4 (d), 77.3 (t), 61.2 (t), 14.3 (q); MS (ES) *m/z* 272.1 $[M+H]^{+}$; HRMS (EI) found 272.1283 $[M+H]^{+}$; calculated for $C_{16}H_{18}NO_3$ 272.1287.

Typical experimental procedure for _O_-THP removal

A solution of *N*-Boc-*O*-THP hydroxylamine derivative (0.23 mmol) in ethanol (1.8 mL) with 10 mol% of pyridinium *p*-toluene sulfonate (7 mg) was heated at 55 °C for 3 hours. The solvent was evaporated to give a pale yellow oil. The crude reaction mixture was purified by

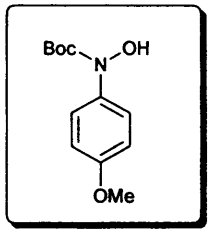
flash chromatography on silica eluting with 15% ethyl acetate in hexane to give the deprotected product.

_N_-Boc-_N_-(4-Tolyl) hydroxylamine 335[101]



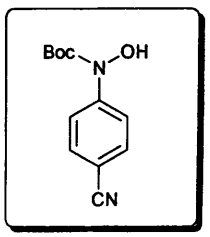
Following the general procedure to yield the title compound **335** (41 mg, 81%) as a colourless oil; IR (neat) 3209.9, 1666.8 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 2.33 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3 (s), 138.1 (s), 135.1 (s), 129.0 (d), 121.7 (d), 83.2 (s), 28.3 (q), 20.9 (q); MS (EI) *m/z* 223.1 $[M]^{+}$; HRMS (EI) found 223.1203 $[M]^{+}$; calculated for $C_{12}H_{17}NO_3$ 223.1208.

_N_-Boc-_N_-(4-Methoxyphenyl) hydroxylamine 336



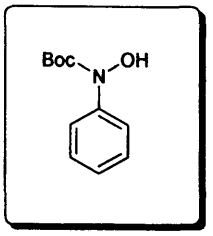
Following the general procedure to yield the title compound **336** (37 mg, 67%) as a white solid; Mpt 114–116 °C; IR (neat) 3202.7, 1669.8 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (bs, 1H), 7.32 (d, J = 7.0 Hz, 2H), 6.86 (d, J = 7.0 Hz, 2H), 3.80 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6 (s), 155.0 (s), 134.2 (s), 124.5 (d), 113.7 (d), 82.8 (s), 55.5 (q), 28.3 (q); MS (EI) *m/z* 239.1 $[M]^{+}$; HRMS (EI) found 239.1158 $[M]^{+}$; calculated for $C_{12}H_{17}NO_4$ 239.1158.

_N_-Boc-_N_-(4-Cyanophenyl) hydroxylamine 337



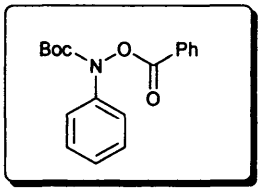
Following the general reaction procedure to give *N*-Boc-*N*-(4-cyanophenyl) hydroxylamine **337** (45 mg, 84%) as a white solid; Mpt 118–120 °C; IR (neat) 3198.3, 2226.3, 162.8 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.57 (m, 4H), 1.54 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6 (s), 143.8 (s), 132.6 (d), 119.0 (d), 106.9 (s), 85.2 (s), 28.2 (q); MS (EI) *m/z* 234.1 $[M+H]^+$; HRMS (EI) found 234.1010 $[M+H]^+$; calculated for $C_{12}H_{14}N_2O_3$ 234.1004.

_N_-Boc-_N_-Phenyl hydroxylamine 338[117]



Following the general THP deprotection procedure to yield the title compound **338** (166 mg. 79%) as a pale yellow solid; Mpt 89–91 °C (Mpt Lit[118] 92 °C); ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (br s, 1H), 7.47–7.45 (m, 2H), 7.34 (*app.* t, J = 7.3 Hz, 2 H), 7.15 (t, J = 7.3 Hz, 1H), 1.50 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 154.4 (s), 140.8 (s), 128.4 (d), 125.2 (d), 121.5 (d), 83.4 (s), 28.3 (q); HRMS (ES) found 210.1132 $[M+H]^+$; calculated for $C_{11}H_{16}NO_3$ 210.1130.

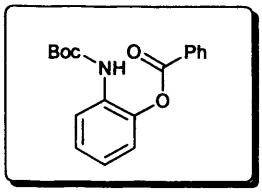
_N_-Boc-_N_-Phenyl-_O_-benzoyl hydroxylamine 339[100]



To a solution of **338** (100 mg, 0.48 mmol) in THF (5 mL) was added NEt_3 (100 mg, 1 mmol) and the reaction mixture was cooled to 0 °C. Benzoyl chloride (70 mg, 0.5 mmol) was added and the resulting solution was stirred for 1 h at 0 °C and 2 h at room temperature. The reaction mixture was diluted with ether (20 mL) and washed with saturated $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL). The organic phase was dried with ($MgSO_4$) and the volatiles removed under reduced pressure. The crude product was purified by column chromatography on silica eluting with petroleum ether/ethyl acetate (3:1) to give the title compound **339** (115 mg, 76%) as colourless oil; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, J = 7.5 Hz, 2H), 7.68–7.65 (m, 1H), 7.55–7.48 (m, 4H), 7.43–7.37 (m, 2H), 7.22–7.17 (m, 1H),

1.52 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 164.5 (s), 152.1 (s), 140.4 (s), 134.3 (s), 130.6 (d), 130.0 (d), 128.9 (d), 128.7 (d), 126.5 (d), 123.3 (d), 83.2 (s), 28.2 (q); HRMS (ES) found 331.1645 $[M+NH_4]^+$; calculated for $C_{18}H_{23}N_2O_4$ 331.1658.

2-*N*-Boc-Aminophenol-1-benzoate 340



The *N*-Boc-*N*-phenyl-*O*-benzoyl hydroxylamine **339** (0.3 mmol) was dissolved in toluene (3 mL) and heated to reflux for 48 hours. After cooling, the crude mixture weas dir ectly subjected to column chromatography (gradient petroleum ether/ethyl acetate 8:1 to 3:1) to obtain the rearrangement product **340** as a white solid (63 mg, 55%); Mpt 67–69 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.24 (m, 2H), 8.10 (br s, 1H), 7.71–7.69 (m, 1H), 7.58–7.54 (m, 2H), 7.28–7.23 (m, 1H), 7.20–7.17 (m, 1H), 7.12–7.08 (m, 1H), 6.54 (br s, 1H), 1.48 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 164.5 (s), 152.4 (s), 140.2 (s), 134.0 (d), 130.7 (s), 130.3 (d), 129.1 (s), 128.8 (d), 126.5 (d), 123.4 (d), 122.2 (d), 121.2 (d), 80.9 (s), 28.3 (q); HRMS (ES) found 331.1645 $[M+NH_4]^+$; calculated for $C_{18}H_{23}N_2O_4$ 331.1658.

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