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Novel methods for allylic amination by an intramolecular nitroso ene reaction

by

Duncan Atkinson

Doctoral Thesis

Submitted in partial fulfilment of the requirements for the award of Doctor of Philosophy of

Loughborough University

2nd Aug 2013

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I, Duncan Atkinson, confirm that the work presented in this thesis is my own, and has not been submitted as part of the conditions for the award of any previous degree. Where work has been derived from other sources, I confirm that this has been indicated in the thesis.
Abstract.

C-H functionalisation reactions aim for the selective cleavage of C-H bonds, and formation of a new carbon or heteroatom bond, often with the use of a transition metal catalyst. These reactions offer potential for functionalisation of hydrocarbons in fewer steps than conventional methods, and with high atom efficiency. They are therefore a subject of intense research in organic synthesis. Carbon-heteroatom bond forming reactions are particularly sought after, and useful in the efficient synthesis of many biologically significant groups such as oxazolidinone rings, 1,2 or 1,3 amino alcohols and amino acid analogues. An efficient, cheap and robust method for C-H amination would also be adaptable to varied syntheses of important large molecules. The necessity for complex and efficient transformations with a minimal number of steps means that heteroatom ring closures are also attractive and widely used reactions in such large molecule syntheses.

The nitroso group is a highly reactive species which is normally generated in situ by oxidation of a hydroxylamine, for carbon-nitrogen bond forming reactions including the nitroso Heteroatomic Diels Alder reaction, nitroso ene reaction, and nitroso aldol reaction. Nitroso group reactions often show high stereo- and regioselectivity, and have formed key components of the syntheses of important biological molecules. Enantioselective protocols for the nitroso-ene reaction and, to a lesser extent, the nitroso HDA reaction, are poorly developed, however, and the range of available intramolecular nitroso reactions is limited.

We aimed to establish efficient single-step intermolecular C-H amination reactions, to give 1,2 and 1,3 heteroatom functionalised molecules, and to develop the capacity for enantioselective induction in this reaction, if possible. Having synthesised a model set of unsaturated hydroxycarbamates, we identified a suitable system for nitroso generation, using a catalytic metal and stoichiometric oxidant. This resulted in in situ generation of cyclised product, with the olefin functionality intact. This cyclisation was then optimised and used to obtain a range of new heterocycles. The possibility of enantioselective induction via chiral catalysts was explored, as well as catalytic systems to increase the stereoselectivity of the reaction.

In summary, a cheap, novel and reliable method was developed for formation of oxazolidinone rings from unsaturated hydroxycarbamates using an original intramolecular nitroso ene reaction, and a range of unsaturated heterocycles were synthesised in fairly good yields. Diastereoselectivity of the nitroso ene cyclisations was optimised. However, to-date, we were unable to develop an enantioselective variant of the reaction. Several related aminations, as well as transformations of N-hydroxyoxazolidinone products, were also attempted during the project.
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Abbreviations.

Acac = acetylacetone

AIBN = azobisisobutyronitrile

Alk = generalised non-aromatic organic group

Ar = generalised aromatic group

B3LYP = Becke, three-parameter, Lee-Yang-Parr

Bnp = (R)-[1,1’-bi(naphthalene)]-2,2’-diyl hydrogen phosphate

BIAN = bis(imino)-acenaphthene

BINAP = 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl

BINOL = 1,1’-Bi-2,2’-naphthol

BIPHEP = (S)-(−)-2,2′-bis(diphenylphosphino)-6,6’-dimethoxy-1,1’-biphenyl

BOC = tertiarybutoxycarbonyl

BuOH = butanol

_C. Antarctica B._ = Candida Antarctica lipase B

CAN = ceric ammonium nitrate

CASPT2 = Complete Active Space with second-order Perturbation Theory

Cat. = catalyst

CBS = Corey-Bakshi-Shibata

Cbz = carboxybenzyl

CDI = 1,1’-carbonyldiimidazole

Chloroamine-T = tosylchloramide

Cp = cyclopentadienyl

Cod = 1,5-cyclooctadiene
Coe = cyclooctene

d = doublet

DCE = dichloroethane

dd = double doublet

ddd = double double doublet

ddq = double double quartet

DDQ = 2,3'-dichloro-5,6'-dicyanobenzoquinone

de = diastereomeric excess

DEAD = diethyl azodicarboxylate

DEPT = Distortionless Enhancement by Polarisation Transfer

DFT = density functional theory

DIBAL = diisobutylaluminium hydride

Difluorophos = 5,5'-bis(diphenylphosphanyl)-2,2,2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole

Dipic = pyridine-2,6-dicarboxylate

DMAP = 4-dimethylaminopyridine

DMF = N,N-dimethylformamide

DNA = dioxyribosenucleic acid

DPPH = 2,2-diphenyl-1-picrylhydrazyl

dq = double quartet

dqd = double quadruple doublet

d.r. = diastereomeric ratio

dt = double triplet

dtt = double triple triplet
ee = enantiomeric excess
ESI = electrospray ionisation
EtOAc = ethyl acetate
equiv = equivalent
FID = Free Induction Decay
g = grams
GC = gas chromatography
h = hours
Hagemann’s ester = ethyl-2-methyl-4-oxo-2-cyclohexenecarboxylate
H-bond = hydrogen bond
HDA = hetero Diels-Alder
HDAC = Histone Deacetylase
HMPA = hexamethylphosphoamide
HOMO = highest occupied molecular orbital
HRMS = high resolution mass spectroscopy
HWE = Horner-Wadsworth-Emmons
i-PrOH = iso-propanol
iso-Pr-BOX = (S,S)-isopropylbioxazoline
IR = infra-red
J = coupling constant
KIE = kinetic isotope effect
LDA = lithium diisopropylamide
LUMO = lowest unoccupied molecular orbital
$m = \text{meta}$

m = multiplet

MDF = Multiple Descriptors Family

MeCN = acetonitrile

MeOH = methanol

min = minutes

MLEV = Malcolm Levitt’s CPD sequence

m.p. = melting point

MP2/6-311G = Møller–Plesset2/6-311Gaussian

4Å MS = 4Å molecular sieves

MS = Mass Spectroscopy

m/z = mass/charge ratio

NA = nitroso aldol

NBS = N-bromosuccinimide

NMO = N-methyl morpholine N-oxide

NMR = Nuclear Magnetic Resonance

N-NA = hydroxyamino selective nitroso aldol

NOESY = Nuclear Overhouser Enhancement Spectroscopy

$\sigma = \text{ortho}$

O-NA = $\alpha$-aminooxy selective nitroso aldol

OTIPS = triisopropylsilyl

$p = \text{para}$

PCM = polarizable continuum model
PEI = Polyethyleneimine

PE = petroleum ether (Fraction boiling at 40-60°C)

Ph = phenyl

PhBQ = phenylbenzoquinone

Phen = phenanthroline

Phth = phthalimide

PM3 = parameterised model 3

Py = pyridine

Pybox = 2,6-bis-(4R)-4-phenyl-2-oxazoliny]pyridine

q = quartet

R = variable alkyl group

Rf = retardation factor

RB3LYP/6-31G = Restricted Becke, three-parameter, Lee-Yang-Parr/6-31Gaussian

RT = Room Temperature

s = singlet

Sec = secondary

S-SEGPHOS = 4,4′-bi-1,3-benzodioxole-5,5′-diylbis(diphenylphosphane)

t = triplet

TADDOL = α,α,α,α-tetraaryl-1,3-dioxolan-4,5-dimethanol

TBAF = tetra-n-butylammonium fluoride

TBDPSCI = chloro-tertiary-butyldiphenyilsilane

TBDMS = tertiary-butyldimethylsilane

t-Bu/ t-butyl = tertiary butyl group
Tf = triflate
TFA = trifluoroacetic acid
THF = tetrahydrofuran
TLC = Thin Layer Chromatography
TMS = Trimethylsilyl
TOCSY = Total Correlation Spectroscopy
tpa = triphenylacetate
TS = transition state
UV = Ultra-violet
Walphos = (S)-1-((S)-2-[2-\{Bis(4-methoxy-3,5-dimethylphenyl)phosphino\}phenyl] ferrocenyl)ethylbis [3,5-bis(trifluoromethyl)phenyl]phosphine
δ = chemical shift
1. Background

1.1 Introduction

This background to the thesis will give a description of the nitroso functional group, the methods by which it is synthesised or generated in situ, and a comprehensive summary of reactions which make use of its distinctive properties. Subsets of nitroso group reactions, their mechanisms, and their specific applications, will be discussed to illustrate the role of the nitroso group in organic synthesis.

The nitroso group was first discovered in the form of nitrosobenzene, in 1874. Another synthesis of nitrosochlorides from olefins was published by Tilden the following year. The first notable reaction of nitroso groups to be identified was a base-activated C-H functionalisation of activated methylene protons on phenylacetonitrile to give azomethines, the Ehrlich-Sachs reaction. This set the trend for identification of many useful reactions involving nitroso compounds. Some good reviews on nitroso group generation in situ and the general reactions of nitroso groups have been published.

Nitroso groups make for very versatile and reactive synthetic building blocks, due to their high-energy HOMO occupied by the nitrogen lone pairs, and low energy LUMO positioned orthogonally to the HOMO. Their small HOMO-LUMO gap gives nitroso groups a very low activation energy and high reactivity as both electrophiles and nucleophiles. Side reactions, such as dimerisation and anhydride formation, are consequently a frequent obstacle to the development of practical synthetic methods involving nitroso groups. Electronic effects of other functional groups on the same carbon as a nitroso group will often strongly influence its stability and reactivity. Most nitroso species are generated and reacted in situ to prevent unwanted side reactions, or stored as a crystalline dimer, since the reversible dimerisation of primary or secondary nitroso groups in solution allows for an irreversible tautomerisation to an oxime. This side reaction is often avoided by the use of tertiary or aryl nitroso compounds as reactants, as opposed to the much less stable and highly nucleophilic acyl nitroso compounds. The need to minimise unwanted side reactions and provide conditions conductive to the desired reaction mean that nitroso generation systems are often reaction-specific, and will be listed in the relevant sections. Despite these drawbacks, the varied reactivity of nitroso groups, extending to additions, isomerisations, oxidations and reductions, make them useful and important reactive groups.
A range of common transformations for the generalised nitroso compound 1.1 (reactions A-I) is shown in Scheme 1.1. The dual functionality of nitroso groups makes them highly favourable dienophiles in Hetero-Diels-Alder (HDA) reactions (reaction A on Scheme 1.1), which generate two heteroatom-carbon bonds to give products such as 1.2. Several enantioselective nitroso HDA reactions have been developed.\textsuperscript{12,25} Nitroso groups can also be used in an ene reaction to give 1.3, (reaction B) in a useful method for allylic C-H functionalisation.\textsuperscript{10} However, due to lower reaction rate and increased side reactions, fewer usable nitroso ene methods have been developed, compared to the nitroso HDA reaction. Aldol reactions with aryl nitroso species (reaction C) conveniently give α-aminooxy or hydroxyamino products, depending on the acidity of the conditions, and the catalysts used. Although the necessary reactants are highly functionalised, enantioselective nitroso aldol protocols are highly developed compared to the other two major nitroso reactions, with a range of generally applicable organocatalysts and organometallic catalysts suitable for enantioselective reactions.\textsuperscript{26,27}

\textbf{Scheme 1.1:} Transformations of nitroso compounds used in organic synthesis\textsuperscript{10,12}
Less commonly used reactions readily undergone by nitroso groups include deoxygenation with phosphines to give isocyanates, and formation of azo compounds by dimerization or reaction with amines (reaction D). [2+2] addition (reaction E) is a rarer reaction for nitroso compounds, which trichloronitrosomethane has been known to undergo with electron rich olefins. A nitroso group may serve as an electrophile in a Grignard reaction, giving a secondary hydroxylamine (reaction F). Nitroso groups are also known radical scavengers (reaction G), and react with diazomethane to give nitrone zwitterions (reaction H). Nucleophilic substitution of very electron deficient electrophiles can be carried out using electron rich nitroso compounds, such as 2-methyl-2-propylnitroso, due to the lone pair on the nitrogen atom (reaction I). Aryl nitroso species deoxygenated with phosphines and heated with amines will give an azepine product. A reaction between N,N-disilyl amines and an acyl nitroso gave azoacetylenes, a generally inaccessible set of molecules used to synthesise photoswitches and anti-cancer functionalities. Acyl nitroso species are also susceptible to substitution by nucleophiles, including water, amine, or hydroxamic acid, giving carboxylic acids, amides, and acyhydroxamates.

A useful rearrangement of bicyclic or spirocyclic N-nitrosodihydropyrazoles operates by thermolysis under reduced pressure (the nitroso functionality is added to the secondary amine using NaNO₂), giving a range of dihydroisoxazoles in good yield via cyclopropane and diradical intermediates.

1.2 The nitroso Diels-Alder reaction.

The Diels-Alder reaction is a facile, widely used and versatile reaction, forming 2 new bonds in a pericyclic addition between a diene and dienophile. The hetero-Diels-Alder reaction of nitroso compounds with 1,3-dienes, by involving two non-carbon atoms, dramatically increases the potential of this reaction for further transformations. The excellent regio- and stereoselectivity of this reaction also make it ideal for the synthesis of important biological molecules and natural products. The nitroso HDA reaction proceeds by a commonly observed [4+2] cycloaddition of the nitroso dienophile to the diene, giving products such as 1.2 (This reaction mechanism is shown in Scheme 1.2). Nitroso groups with a directly attached electron withdrawing group such as acyl nitroso, cyanonitroso or C- iminonitroso species, as well as nitrosoformate esters, are some of the most reactive dienophiles of the wide range used in HDA reactions. Trifluoronitrosomethane also readily undergoes a HDA reaction at -78°C. Aryl nitroso groups are usually stable and relatively slow to react, though electron-withdrawing substituents on the aromatic ring greatly increase reactivity.

The least reactive nitroso groups usable in the HDA reaction are those stabilised by direct bonds with electron-
donating heteroatoms, such as phosphine\textsuperscript{42} or sulfonyl compounds.\textsuperscript{43} Resonance stabilisation of nitroso groups by heteroatoms with free lone pairs normally makes them unreactive with dienes, which is the case for \textit{N}-nitroso groups (even those with an adjacent sulphonyl group).\textsuperscript{44} The excellent selectivity of acyl nitroso HDA reactions makes them very important in the synthesis of 3,6-dihydro-1,2-oxazines and 1,4 amino alcohols.\textsuperscript{12,24}

\begin{center}
\textbf{Scheme 1.2: Nitroso Hetero Diels-Alder reaction mechanism}\textsuperscript{12,24}
\end{center}

B3LYP/6-31G* calculations show that a standard Diels-Alder reaction between isoprene and maleic anhydride proceeds concertedly, with a slightly asynchronous transition state and \textit{endo} route of approach.\textsuperscript{45} The mechanism of the acylnitroso HDA reaction, according to a computational study by Leach and Houk,\textsuperscript{24} also normally proceeds concertedly and asynchronously. The \textit{n}-\pi repulsion of the nitrogen’s electron lone pair creates a strong energetic preference for the \textit{endo} transition state\textsuperscript{1.4} (8.6 kcal mol\textsuperscript{-1} lower), referred to as the \textit{exo}-lone pair effect due to the strong repulsion between the diene and the lone pairs on nitrogen in the \textit{exo} configured transition state\textsuperscript{1.5}. This mechanism was confirmed by RB3LYP/6-31G*/RB3LYP/6-31G theory and the observed selectivity of the reaction (The transition states and their calculated energies are shown in Figure 1.1). It is notable that the C-N bond is shorter than the C-O bond in the calculated transition state, since the reverse is the case for the reaction product. Under certain conditions (a small nitroso species R-group, radical stabilising groups on diene, and a protic solvent), a stepwise radical mechanism may be adopted, but this is not usually the lowest energy pathway. Compounds that cannot easily adopt the correct \textit{s-cis} conformation for a concerted nitroso HDA reaction will frequently undergo side reactions such as dimerisation more favorably than a HDA reaction by a stepwise radical mechanism.\textsuperscript{12,24,46}
ΔH‡ = +5.5 (endo)  ΔH‡ = +14.1 (exo)

**Figure 1.1**: The nitroso HDA reaction *endo* and *exo* transition states, and their relative calculated energies.\(^{12,24}\)

Acyl nitroso HDA reactions with unsymmetrical dienes display a proximal regioselectivity, which increases significantly for reactions of dienes with strongly electron withdrawing/donating substituents, as well as for 1-substituted dienes, as in Scheme 1.2. 2-substituted dienes undergo nitroso HDA reactions with a moderate distal regioselectivity. *Cis*-substituents at the 1-position have a variable effect depending on their attractive or repulsive relationship with the nitroso oxygen. Both linear and cyclic dienes give similar selectivity. The selectivity of arylnitroso and acylnitroso compounds is also normally the same, with few exceptions.\(^{57}\) This regioselectivity is determined by frontier molecular orbital theory, mainly between the diene-HOMO and nitroso group LUMO, although electronic interactions of substituents on both reactants can exert a minor influence. The diene-LUMO and nitroso group-HOMO orbitals may also play a secondary appreciable role in determining the selectivity of reactions between an electron poor diene and electron rich nitroso group. Solvent polarity increases the diastereoselectivity of intramolecular nitroso HDA reactions, but has no effect on selectivity of the intermolecular reaction (see section 1.2.3 for applications of this effect in synthesis). Charge transfer between the diene and nitroso group predicted by B3LYP theory indicates that polar solvents may accelerate the nitroso HDA reaction.\(^{12, 48, 49, 50}\)

A Diels-Alder reaction assisted by complexation between aryl or acyl nitroso groups and anthracene was mechanistically studied to determine whether nitroso HDA reaction with butadiene followed thermal dissociation of a nitroso group from anthracene 1.6, or whether the bound nitroso acted as an electrophile in an exchange reaction. A higher enthalpy cost was shown for the latter reaction, even when the more reactive acyl nitroso compound was used; the longer bond lengths for the anthracene adduct 1.7, compared to the butadiene adduct 1.2 created by the Diels-Alder reaction, also argued for the favourability of the former retro-nitroso HDA mechanism. Adduct formation with
anthracene is necessary for this acyl nitroso HDA reaction to occur, since dienes under thermolysis conditions predominantly adopt a cisoid state suitable for the nitroso HDA reaction. Conventional generation of the highly reactive acyl nitroso groups without stabilising anthracene complexation requires low temperature conditions, and primarily gives the diene in an unreactive transoid state. (see Scheme 1.3 for the full reaction).\textsuperscript{51,52}

1.2.1 Generation of nitroso compounds for HDA reactions

The high reactivity of nitroso compounds (particularly acylnitroso groups, which have only been observed via product analysis and time-resolved infrared spectroscopy)\textsuperscript{53} often necessitates that these reactants should be prepared in situ, normally by oxidation of hydroxamic acids (Reaction A on Scheme 1.4). NMR monitoring shows that nitroso generation and appearance of the product are virtually simultaneous.\textsuperscript{54} Periodates such as \( \text{Et}_4\text{NIO}_4 \) are commonly used at low temperatures to
oxidise hydroxamic acids such as 1.8 to acyl nitroso group such as 1.9. Other oxidation systems used to generate acyl nitroso groups from hydroxamic acids include Swern oxidation conditions, lead or silver oxide and Dess-Martin periodinane.\textsuperscript{12, 55, 56, 57}

Some of the most convenient methods of acyl nitroso generation from hydroxamic acids use metal catalysts in combination with a stoichiometric oxidant.\textsuperscript{12} Fe(III) species combined with H\textsubscript{2}O\textsubscript{2} have been used in this way to prepare nitroso compounds from hydroxamic acids for HDA reactions. An iron complex was also notably used to convert a pyridinyl sulfilimine to the corresponding nitroso group for a nitroso HDA reaction.\textsuperscript{54} Other metal/H\textsubscript{2}O\textsubscript{2} systems used to generate nitroso groups from hydroxamic acids include a Ru-pybox complex, a comparatively more soluble and convenient RuCl\textsubscript{3}/NE\textsubscript{t}\textsubscript{3} system, [Ir(cod)Cl\textsubscript{2}] or [Ir(coe)\textsubscript{2}Cl\textsubscript{2}], CuCl and NiCl\textsubscript{2}. Amines were used as activating ligands for these catalysts, as well as with FeCl\textsubscript{3}, but excellent >90% yields were also obtained without amines in THF; in this case the solvent acted as a ligand.\textsuperscript{19, 58, 59} Catalytic CuCl\textsubscript{2} in an O\textsubscript{2} atmosphere, combined with a 2-ethyl-2-oxazoline ligand, also proved an excellent catalyst of inter- and intramolecular nitroso HDA reactions.\textsuperscript{60} t-BuOOH has also been used as an oxidant in these reactions, using Ru-salen complexes or ruthenium (II) phosphine oxide; these reaction are significant for their potential enantioselectivity (see section 1.2.2).\textsuperscript{51, 62} As well as being generated from hydroxamic acids, acyl nitroso groups can be generated for HDA reactions from oxidation of nitrile oxide groups (reaction B), through rearrangement of nitrocarbenes generated from diazo compounds using a rhodium catalyst or heating (reaction C), or photochemical cleavage of 1,2,4-oxadiazole-4-oxides (Reaction D). These reactions leading to acyl nitroso groups are shown in Scheme 1.4.\textsuperscript{55, 63, 64, 65}

\begin{equation}
\begin{align*}
R-\text{C}=\text{N}^+\text{O}^- & \quad \text{R}_3\text{N}^+\text{O}^- \quad \text{(B)} \\
\text{R} & \quad \text{N}^+\text{O}^- \quad \text{(A)} \\
\text{[O]} & \quad \text{(C)} \\
\text{R} & \quad \text{N}^+\text{O}^- \quad \text{(D)} \\
\end{align*}
\end{equation}

\textbf{Scheme 1.4:} The reactions used to synthesise acyl nitroso groups from various starting materials.\textsuperscript{12, 55, 63-65}
Aryl nitroso compounds are relative stable, due to conjugation between the nitroso group and aromatic ring, and are frequently used to explore nitroso reactivity or give a simple N-O bond. They can be readily isolated as nitroso HDA reactants through the oxidation of amines or sulpimines. Direct nitrosation of several electron-rich methylated aromatic rings has also been carried out using nitrosonium trifluoroacetic acid under a nitric oxide atmosphere; aromatic ethers and amines can also be directly nitrosated using sodium nitrite in acid.\textsuperscript{17,20,66} α-Chloronitroso reagents are less commonly used but also stable, and can be synthesised from oximes or sec-nitro alkenes using oxalyl chloride.\textsuperscript{67} Nitrosocyanide compounds are also occasionally used in HDA reactions, and can be generated by reacting nitrosyl chloride with silver cyanide. These nitroso species are stable, but more reactive than α-chloronitroso compounds, and usable in HDA reactions for which the latter compounds are insufficiently reactive.\textsuperscript{12,68}

1.2.2 Stereo- and enantioselective nitroso HDA reactions

Asymmetric induction is most commonly obtained for acylnitroso HDA reactions using chiral auxiliaries temporarily bound to an acylnitroso species. Various auxiliaries have been used to give up to 98% distereoisomeric excess, including pyrrolidine derived hydroxamic acids (\textsuperscript{1.10,1.11} and \textsuperscript{1.12}) and camphor derivatives (\textsuperscript{1.13} and \textsuperscript{1.14}). Easily synthesised α-amino protected amino acid and mandelic acid α-nitroso derivatives (\textsuperscript{1.15} and \textsuperscript{1.16}) have also been used in enantioselective reactions (see Figure 1.2 for structures of chiral auxiliaries).\textsuperscript{12,55,69,70,71,72} Chiral dienes have been used in acylnitroso HDA reactions, but proved less efficient than auxiliaries bonded to nitroso groups. This is explained by the asynchronous transition state of a nitroso HDA reaction with an acyclic diene. In this transition state, the nitroso nitrogen substituant is much nearer to the diene than the oxygen lone pair, placing a chiral group on the diene further away from the nitroso dienophile and reducing its effects. However, some chiral acyclic dienes such as chiral N-dienyllactams and chiral 1-sulpinyl dienes have been used to give excellent diastereoselectivities in acylnitroso HDA reactions.\textsuperscript{12,73,74}
Figure 1.2: Chiral auxiliaries used in stereo- and enantioselective nitroso HDA synthesis, and amino acid/mandelic acid derived chiral nitroso carbonyl species.

Chiral chloronitroso derivatives can also be used in enantioselective nitroso HDA reactions. For example, an \( \alpha \)-chloronitroso D-xylofuranose derivative 1.17 was reacted with cyclohexadienes and cycloheptadienes. The HDA adduct initially produced eliminates the sugar group as ketone 1.18 via solvolysis, giving a nitrone salt 1.19 (see section 1.4.3 for a similar mechanism). The chiral sugar group ensures good stereoselectivity, and \( \text{CHCl}_3/\text{i-PrOH} \) with \( \text{H}_2\text{O} \) was found to be the most favourable solvent for the solvolysis step (Scheme 1.5 shows the full reaction). When cyclopentadiene was reacted with \( \alpha \)-chloronitrosoglucufuranose derivatives, a zwitterionic sugar adduct was formed, which was then reduced using borohydride to a secondary hydroxylamine. These nitroso HDA reactions can be followed by N-O cleavage to give disubstituted rings such as 1.20. \( \alpha \)-Chloronitroso sugar reagents have also been used for stereospecific synthesis of the tropane alkaloid natural products (+)-calystegine B2, (-)-physoperuvine (via a nitroso HDA reaction with a cycloheptadiene compound) and (+)-epibatidine.25, 75, 76
The difficulty of identifying a chiral catalyst to bind with such a facile species as the nitroso group precluded discovery of a significant catalytic asymmetric nitroso HDA reaction, until 2004. Chiral metal complexes dissociated from the nitroso group before completion of the HDA reaction, giving low-to-zero enantioselectivity. It was also shown that Lewis acidic catalysts would form strong complexes with the nitroso dimers formed reversibly in aryl nitroso reactions, and that this complex has no effect on the rate or enantioselectivity of nitroso HDA reactions. The first notable catalytic asymmetric nitroso HDA reaction used cyclohexa-1,3-dienylmethanol as a diene, with stochiometric \((R,R)-t\)-butyl tartrate and zinc salts. Asymmetric induction relied on coordination via zinc between the nitrosobenzene dieneophile and the hydroxyl group on the diene, holding the reactants in a complex with the chiral ligand. This reaction achieved 63% ee.

Several later enantioselective reactions used pyridinyl nitroso 1.21 as a HDA reactant, with secondary coordination between the pyridinyl nitrogen and the metal centre of a chiral ligand anchoring both reactants together throughout the reaction and ensuring enantioselectivity. For example, a chiral binaphthal phosphate 1.24 (R-SEGPHOS) combined with a Cu(II) complex was used to catalyse a HDA reaction between pyridinyl nitroso and cyclohexadiene, giving product 1.22 with 92% ee. A similar enantioselective reaction was achieved with copper-complexes of a Difluorophos ligand 1.23, R-MeO-BIPHEP 1.25 (which gave 90% ee) a copper(II)Triflate BINAP complex 1.26 and several other chiral ligands, including Walphos (93% ee). (Scheme 1.6 shows the reaction scheme and a range of the chiral ligands used). Alkynitrosopyridine was also reacted with 2-silyoxy-1,3-dienes, extending the enantioselective nitroso HDA protocol to linear dienes. Larger silyl protecting groups on the diene were shown to increase enantioselectivity by forcing the diene into an \(s\)-cis conformation. The use of a TIPS protecting group and copper(I) complexes with (S)-difluorophos and (R)-Segphos ligand opened up a >99% enantioselective and highly regioselective path to a range of protected amino alcohols.
A nitroso HDA reaction which gave enantiomerically enriched product from racemic dienes also used a pyridinyl nitroso dienophile, with a copper (I) Walphos complex as catalyst. Two of eight possible diastereoisomers were formed exclusively, in good enantiomeric excess.\(^{81}\) Another stereoselective nitroso HDA method reacted nitrosobenzene (1.28) with a diene substituted with a bulky, stereodirecting phthalimide group, 1.27. The ene group of the resulting nitroso HDA adduct 1.29 was dihydroxylated (giving 1.30) and the N-O bond cleaved, giving a highly substituted ring 1.31 in a single diastereoisomer (Full synthesis shown in Scheme 1.7).\(^{82}\) An efficient enzymatic resolution of the aminocyclopentenols derived from nitroso HDA adducts (see section 1.2.3) has also been developed, using \textit{C. Antarctica B} enzyme to give an enantiopure acetate and alcohol.\(^{83}\)
Scheme 1.7 A stereoselective nitroso HDA reaction with N-(cyclohexa-2,4-dienyl)phthalimide, and further synthesis of a highly substituted hexane ring

A notable asymmetric intramolecular HDA reaction was also developed with a precise $7.2 \times 10^{-2}$ M concentration of diene acyl hydroxycarbamate 1.32, catalysed by a salen-ruthenium oxide chiral catalyst, 1.33. An optimised ee of 75% was achieved for 1.34 at 15°C, with t-BuOOH used as a stoichiometric oxidant. An acceleration of nitroso reactions by Lewis acids was noted in the development of this reaction, suggesting that an H-bonded complex between a Ru(II)-H$_2$O species and the nitroso group, as well as direct nitroso-ruthenium bonding, give rise to the cyclised product (The full reaction is shown in Scheme 1.8). However, an intermolecular HDA acyl nitroso reaction at -78°C, catalysed with a similar salen-ruthenium complex, achieved only 0-9% enantioselectivity. This may have been due to competition between the bimolecular regeneration of Ru(II) by t-BuOOH and the bimolecular HDA reaction. An alternative explanation is that the metal catalyst dissociates from the nitroso group before the slower intermolecular reaction can be completed. This research by Whiting also suggested a concerted, stepwise mechanism involving a Ru(II)-hydroxy complex for this nitroso HDA reaction, but concluded that the ruthenium catalyst dissociates from the nitroso group before the HDA reaction could be completed.
Scheme 1.8: An enantioselective intramolecular nitroso HDA reaction catalysed by a ruthenium-salen complex\textsuperscript{61}

1.2.3 Synthetic applications of the nitroso HDA reaction

Numerous useful molecules can be readily derived from nitroso HDA adducts with simple reactions. Hydrolysis of a chiral auxiliary following a nitroso HDA reaction normally gives an amine ester. Cleavage of the C-O bond of simple nitroso HDA adducts using Lewis acids such as FeCl\textsubscript{3} gives a range of hydroxamate substituted cyclopentene products. In another useful reaction, Pd(0) was used to generate a π-allyl hydroxamate species, which was trapped with a nucleophile to produce additional functionality.\textsuperscript{64} Use of Brønsted acids to cleave the C-O bond of nitroso HDA adducts (1.35 or 1.37) generates new ranges of hydroxylamine substituted rings 1.36 or 1.38 via an intramolecular cyclisation (see Scheme 1.9 for both reaction schemes).\textsuperscript{85,86,87} Treatment of the nitroso HDA adduct with a Grignard reagent, rather than leading to an attack on the carbonyl, causes regioselective C-O cleavage and synthesis of a substituted hydroxamate. An important lipoxygenase inhibitor is synthesised in this way, using a catalytic amount of CuCl\textsubscript{2} to attain a high yield of product at low temperature.\textsuperscript{12,86,88}
Scheme 1.9: Synthesis of a hydroxylamine substituted ring and a bicyclic hydroxamate, via Brønsted acid cleavage of the C-O bond on nitroso HDA adducts\(^{86,87}\).

Cleavage of N-O bonds on nitroso HDA adducts\(^{1.39}\) readily gives 1,4 amino alcohols\(^{1.40}\) (This can be carried out using Zinc/acetic acid, molybdenumhexacarbonyl, hydrogenation, samarium diiodide, or photochemical reactions). These molecules can be usefully transformed into pyrroles\(^{1.41}\) using manganese dioxide. Dihydroxylation of 3,6-dihydro-1,2-oxazines\(^{1.42}\) to give the cyclic product\(^{1.43}\), followed by Pd-C reduction of the N-O bond and cyclisation, gives rise to the aza sugars\(^{1.44}\), which are ideal for derivatisation to pyrrolidine and piperidine sugar analogues (Scheme 1.10 shows both of these reactions\(^{12,89,90,91}\)). The important tropane alkaloids, which form the basis for several anticholinergic drugs, can be synthesised from the nitroso HDA adduct \(N\)-Benzoyl-8-oxa-9-azabicyclo[2.2]-non-6-ene, with N-O cleavage and mercury acetate based cyclisation\(^ {92}\).

Scheme 1.10: Generalised pyrrole and pyrrolidine synthesis via the nitroso HDA reaction\(^{12,89-91}\).
In the synthesis of the natural product dihydronarciclasine 1.45, asymmetric addition of pyridylnitroso in the presence of a Walphos catalyst was employed to introduce alcohol and amine groups on either side of a six-membered ring after N-O bond cleavage and removal of the pyridinyl group, for further onwards synthesis. The same method was used in the synthesis of (-)-peracetylated conduramine 1.49. A highly substituted ring on the natural insecticide (+)-trehazolin 1.46 was similarly synthesised using nitroso HDA, N-O reductive cleavage, and subsequent dihydroxylation of the remaining double bond, while the synthesis of (+)-6-epitrehazolin 1.47 took the same methodology further with a final cyclisation, to give an allosamizoline bicyclic system (A stereopure substituted acyl nitroso was used as the electrophile, to give a stereoselective total synthesis). A simple nitroso HDA reaction was also used in a nucleoside synthesis, with N-O cleavage, addition of a chloropyrimidine to the amine, and condensation with an orthoformate to give a purine group on a benzisoazole framework, 1.50. A synthesis of the piperidine alkaloid (+)-Streptazolin 1.48 also used a nitroso HDA adduct as an early intermediate (The structures of these products are shown in Figure 1.3). 25, 79, 93, 94, 95, 96

![Structures of natural compounds synthesised with the nitroso HDA reaction](image-url)

**Figure 1.3:** Structure of natural compounds synthesised with the nitroso HDA reaction. 25, 76, 93-96
Nitrosocarbonyl HDA reactions with substituted 1,3-cyclohexadienes have been used in the synthesis of Amaryllidacea alkaloids, important anti-cancer natural products.\textsuperscript{97, 98} Therapeutic amino acid derivatives have also been synthesised using HDA adducts, often following an oxidative cleavage.\textsuperscript{12, 99} Original derivatives of various natural products can also be synthesised using the acyl nitroso HDA reaction. A range of cycloadduct derivatives can be synthesised by addition of acyl nitroso compounds (generated using Et$_4$NIO$_4$) to the steroid thebaine. The analogues were derivatised further by samarium dioxo cleavage of N-O and C-O bonds in a one-pot method, giving a new thebaine analogue.\textsuperscript{20, 100, 101}

An unusual ‘reverse’ nitroso HDA reaction for the synthesis of oxime ethers such as 1.53 uses a conjugated nitrosoalkene 1.52, generated \textit{in situ} from $\alpha$-haloaxime 1.51 using sodium carbonate, to react as a diene with an alkene group. A rare [3+2] cyclisation mechanism was observed for this reaction. (The full reaction is shown in Scheme 1.11).\textsuperscript{102} Another similar reaction used furoquinolines with external methylene bonds. Hetero-Diels-Alder reaction with $\alpha$-haloaxime and dibromoformaldehyde acting as dienes gave a range of products with respectively 5- and 6-membered ring spiro substitution.\textsuperscript{103}

\begin{center}
\[
\begin{array}{c}
\text{Ph} \\
\equiv \quad \equiv \\
N \quad N \\
\text{N} \\
\equiv \quad \equiv \\
\text{N} \\
\text{Br} \\
\text{CH}_2\text{Cl}_2 \\
\text{Na}_2\text{CO}_3 \\
1.51 \\
\rightarrow \\
\rightarrow \\
\rightarrow \\
\text{Ph} \\
\equiv \quad \equiv \\
N \quad N \\
\text{N} \\
\equiv \quad \equiv \\
\text{N} \\
1.52 \\
\rightarrow \\
1.53, 64\% \text{ yield}
\end{array}
\]
\end{center}

\textbf{Scheme 1.11}: Diels-Alder reaction of 3-\{(1H-tetrazol-5-yl)-nitrosoalkenes to give oxime ethers\textsuperscript{102}

Synthetic development of acyl nitroso HDA bicyclic [2.2.1] products such as 1.54 into a range of advanced intermediates using Grubbs metathesis is shown in Scheme 1.12. A sequence of ring opening, ring closing and cross metathesis reactions employing 1.54 and an alcohol-functionality-containing terminal alkene led to a wide range of tetrahydrooxazino[2,3-$\alpha$]pyridin-7-one natural products such as 1.55. Similarly, bicyclic [2.2.2] nitroso HDA adducts were subjected to metathesis with simple olefins to give a range of hexahydrooxazino [2,3-$\alpha$]pyridin-8-ones.\textsuperscript{104}
Scheme 1.12: A synthesis of pyridinones from acyl nitroso HDA products via Grubbs metathesis\textsuperscript{104}

Intramolecular nitroso HDA cyclisations are less versatile than intermolecular reactions, but usable and efficient, often able to produce a bicyclic system in a single reaction. Such reactions constitute key steps in the total syntheses of monocyclic alkaloids such as (+)-azimine \textbf{1.56} and (+)-carpaine \textbf{1.57}, where the N-O bond in the bicyclic adducts is cleaved to give advanced intermediates \textit{en route} to the natural product.\textsuperscript{105} Bicyclic systems such (-)-swainsonine, and (-)-lepadin A, B, and C can also be readily synthesised using such intramolecular reactions (Structures are given in Figure 1.4).\textsuperscript{12,106,107,108}

Diastereoselectivity for several of these reactions was improved by increasing solvent polarity, a distinctive property of the intramolecular nitroso HDA reaction (see Section 1.2). In DMF/H\textsubscript{2}O the selectivity of the key bicyclic system formation for lepadins increased almost fourfold, compared to the reaction in non-aqueous solvent; a MeOH/H\textsubscript{2}O solvent exhibited a similar beneficial effect on the \textit{trans}-selective key cyclisation in the synthesis of (-)-pumiliotoxin C \textbf{1.58}.\textsuperscript{109} A hydridane bicyclic system needed for the synthesis of the alkaloid (+)-loline \textbf{1.59} was synthesised \textit{via} an intramolecular periodate mediated nitroso HDA reaction.\textsuperscript{110} A stereoselective intramolecular nitroso HDA reaction of the intermediate \textbf{1.60} was used in the synthesis of lepadiformine \textbf{1.61}. The bromine substituent on \textbf{1.60} determines the stereoselectivity by creating prohibitive 1,3-allylic strain for the \textit{anti}-facial transition state (see Figure 1.4). Although the nitroso HDA selectivity was entirely \textit{syn}, the initial yield for this step was poor due to a sluggish reaction with the electron-poor halogenated diene. This was overcome by trapping the nitroso with anthracene to prevent decomposition during the reaction, followed by thermolytic retro-DA under reflux, regenerating the nitroso species to react with the diene.\textsuperscript{111}
Figure 1.4: Structures of natural compounds synthesised using the intramolecular nitroso HDA reaction, and a key intermediate, 1.60, in the synthesis of lepadiformine 1.61.\textsuperscript{12,105,109-111}

Intramolecular acylnitroso HDA reactions with dienes tethered at 2-C rather than 1-C provide a route to bridged oxazinolactam compounds such as 1.63; complex alkaloids such as stenine can also be synthesised using these reactions.\textsuperscript{112} An intramolecular nitroso HDA reaction with hydroxycarbamate 1.62 was used by Shea et al to give oxazinolactam 1.63, overcoming the poor regioselectivity associated with acyl nitroso HDA reactions involving unsymmetrical 2-substituted dienes as referred to in section 1.2.1.\textsuperscript{12} The acyl group provide a ‘cleavable carbamate tether’ which could be easily lysed to give a new 6-membered oxazinolactam 1.64, though with only moderate selective between the hydroxylated and acetylated forms. Alternatively, when 1.65 was used in the same reaction to give 1.66, cleavage of the N-O bond gave a hydroxyl substituted lactam 1.67 (Both nitroso HDA reactions are given in Scheme 1.13). Shea’s group also synthesised a range of bicyclic 1,2-diazine systems using this reaction. They reported that cyclisations giving ten membered rings showed poor selectivity, and that cyclisation to give eight membered rings yielded a single diastereoisomer.\textsuperscript{113,114}
One of the main hinderances to widespread application of the nitroso HDA reaction in synthesis, apart from limited enantioselectivity, is low robustness, demanding careful thermal and stoichiometric control to avoid dimerisation and other side-reactions. Other techniques have been used to overcome this problem. Solid phase acyl nitroso HDA reactions have been carried out using reactants bound to a Wang resin, protecting acid-sensitive or carbocation forming acyl nitroso groups from side reactions. The acid-sensitive products were removed from the resin using reagents such as DQQ and TBAF. A high yielding nitroso HDA reaction with an acetylloxynitroso dienophile, was carried out in anhydrous toluene with Zn(OTf)$_2$ Lewis acid. Amino alcohol produced by a one-pot N-O bond cleavage of the HDA adduct was obtained as the main product. Under hydrated conditions and without Lewis acid, only the HDA adduct was formed. This one pot HDA reaction and N-O cleavage reduced the potential for degradation of the direct nitroso HDA products (reaction given in Scheme 1.14). A more sophisticated effort to improve robustness for the nitroso HDA reaction used a microreactor to precisely set the optimum temperature and pressure of continuous flow reactions for a range of diene substrates. Very high hydroxamic acid concentrations and short reaction times were used, with a supported NaIO$_4$ cartridge acting as oxidative catalyst. These reactions gave poor results. When NaIO$_4$ oxidant was injected through the reactor in solution with the hydroxamic acid, excellent yields (>90%) of the HAD product were obtained, without generating harmful metal waste or giving unwanted products through side reactions.
Scheme 1.14: An acetyloxynitroso HDA reaction with a combined N-O cleavage reaction in one-pot, under anhydrous conditions with Zn(OTf)$_2$\textsuperscript{116}

![Scheme 1.14](image)

1.3 The nitroso ene reaction.

The nitroso ene reaction is a versatile and facile protocol first described in 1965,\textsuperscript{118} analogous to the O$_2$ ene reaction, in which molecular oxygen reacts directly with an alkene to give an unsaturated peroxide.\textsuperscript{24} Despite clear potential for allylic amination, it has only recently seen intensive research. The reaction normally occurs by oxidation of a hydroxylamine or hydroxamic acid, such as 1.8, to a nitroso 1.9 \textit{in situ}. Hydrogen abstraction, double bond migration, and formation of a new C–N bond give a secondary hydroxylamine product 1.71 (The reaction is shown in Scheme 1.15). The retention of the double bond, maximising functionality and allowing further transformation, is a major advantage of this protocol, as is the atom-efficient C-H amination mechanism. Drawbacks of the reaction include the large excess of olefin required for a typical intermolecular nitroso ene reaction, and the susceptibility of highly reactive acyl nitroso reactants to side reactions, meaning that aryl nitroso groups are more commonly used for this reaction.\textsuperscript{10,119}

![Scheme 1.15](image)

Scheme 1.15: A generalised intermolecular nitroso ene reaction\textsuperscript{119}
The high reactivity of acyl nitroso groups makes disproportionation, dimerisation, and similar side reactions very likely, although the structural versatility of acyl nitroso groups makes them valuable reactants (for example, the carbonyl group can be removed or derivatised easily). In earlier work to alleviate these problems, Keck intercepted unstable acyl nitroso species as a stable Diels-Alder adduct with 9,10-dimethylanthracene. Thermolytic adduct cleavage then restored the nitroso group for the ene reaction with olefin; a similar method using a nitroso Diels-Alder adduct formed with 1,3-pentadiene was also developed by Kirby. Most recent work on the nitroso ene reaction has used electron-poor nitroso species such as acyl nitroso compounds and α-chloronitroso species, to give relatively stable hydroxylamine product. At present, the use of acyl nitroso groups in the nitroso ene reaction is largely limited to reactions with electron-rich and unfunctionalised olefins, as in Scheme 1.15.²⁰,¹¹⁹,¹²⁰,¹²¹

Removal of an aryl group from the product is often necessary for aryl nitroso ene reactions, especially if the reaction forms part of a multi-step synthesis (see Section 1.3.1). The electron-rich 4-methoxyphenyl group is quite easily removed by oxidative dearylation, but the corresponding nitroso compound does not undergo a clean ene reaction. This illustrates the conclusion of an early study into the aryl nitroso ene reaction by Knight and Pepper. The study showed that aryl nitroso species with neutral or electron-withdrawing aromatic ring substituents gave secondary hydroxylamine products which rapidly decayed to nitrones or azoxyarenes, while aryl nitroso reactants with electron donating groups predominantly gave amine products, through reduction of the initial secondary hydroxamic acid product.²³ This problem of aryl group removal makes α-chloronitroso compounds (and possibly heteroatom-substituted nitroso compounds in the future) valuable for use in nitroso ene based syntheses.¹⁰,¹²²,¹²³

α-Chloronitroso compounds are stable nitroso species which provide access to primary amines, since the elimination of HCl gives a nitrone hydrochloride salt, which can be hydrolysed to a ketone and primary hydroxamic acid. These nitroso species are insufficiently reactive to attack unfunctionalised olefins, unless bound to a sugar moiety, which increased their electrophilicity through an inductive α-ether effect (see also Sections 1.2.1 and 1.3.3).¹²⁴,¹²⁵

1.3.1 Generation of nitroso compounds for the ene reaction

The slower rate of the ene reaction compared to the acyl nitroso HDA reaction, and corresponding increase in possible nitroso group side reactions, reduces the number of oxidation systems suitable
for the nitroso ene reaction. Until milder oxidation conditions were developed, this discouraged the use of acyl nitroso groups for an ene reaction. The harshness of the older periodate based system used for nitroso HDA reactions precludes it from direct use in nitroso-ene reactions, due to the degradation of products and starting material. A number of metal catalysts, accompanied by a stoichiometric amount of oxidant, such as H$_2$O$_2$, t-BuOOH or benzoquinone, have been used to oxidise hydroxylamines to aryl and acyl nitroso groups, for in situ ene reaction. Examples include Cu(I) and molybdenum complexes (as well as stoichiometric MoO$_2$(dedtc)$_2$ or molybdooxaziridines). Iron-based catalysts, attractive for their low cost and toxicity, have produced good yields of product in a number of nitroso ene and nitroso HDA reactions. Stochiometric iodosobenzene and iodosobenzene diacetate have also been used as mild and clean oxidants for acyl and aryl nitroso ene reactions. Bottke et al used a range of aryl nitroso compounds generated with PhI(OAc)$_2$ to synthesise a range of secondary amines. The results of this study clearly showed that reactions with electron rich alkenes gave higher yields of product. Reactions with electron-poor olefins were often shown to be prevented by the nitroso reactant decomposing to a p-nitrosobenzene anhydride before the desired ene reaction occurs (an example of this common side reaction for acyl nitroso compounds used in nitroso HDA and nitroso ene reactions is shown in Scheme 1.16). This side reaction also occurs for acyl nitroso groups in the presence of metal catalysts; dimerisation and disproportionation of hydroxyamic acid products under oxidizing reaction conditions are also frequent obstacles to acyl nitroso ene use in synthesis.

Scheme 1.16: Mechanism for acyl nitroso decomposition to a corresponding anhydride

The Diels-Alder protected acyl nitroso adducts used by Kirby, as well as being obtained by nitroso HDA reaction with a hydroxamic acid such as 1.75, can also be generated by acylation of a Diels-Alder adduct such as 1.73. A simple acyl nitroso Diels-Alder adduct such as 1.74 can also be converted to a lithium enolate and substituted with a bromide or α,β unsaturated aldehyde. The Diels-Alder adduct
1.76 can then be used in an intramolecular nitroso ene reaction, following thermolytic cleavage to release the nitroso group. A range of heterocyclic products (1.77) were synthesised by Kirby using this method (Synthesis and options for starting material preparation shown in Scheme 1.17). The reactions required pyrolysis at 110°C in toluene or benzene, to release the nitroso group from the Diels-Alder adduct, were completed in 30-40 mins, and gave a range of heterocyclic products in excellent yield, including several spiro-substituted heterocyclic rings.120,131,132

Scheme 1.17: Preperation of nitroso 9,10-dimethylanthracene adducts, for use in a range of intramolecular nitroso ene cyclisations120, 131, 132

As well as hydroxamic acids, nitrile oxides have been oxidised to nitroso groups for nitroso ene reactions, using N-morpholine-N-oxide. Photolysis of 1,2,4-oxadiazole-4-oxides gives a nitrile and an acylnitroso compound which can be used in high yielding nitroso ene reactions with alkenes (both these nitroso generation methods are shown in Scheme 1.4).63,133 Oxidation of nitroaniline with potassium monosulphate gives 4-nitronitrosobenzene, a useful, relatively unreactive nitroso species compatible with many functional groups.10,134 Two recent nitroso ene protocols made use of nitroarenes as a nitroso source, Ru3(CO)12/Ar-BIAN or [CpFe(CO)2]2 as a catalyst, and carbon monoxide as a reducing agent, to give a secondary amine product. Despite the harsh conditions, nitroso ene type regioselectivity (see Section 1.3.2) was preserved. The [CpFe(CO)2]2 catalysed arylation reaction uses 160°C and 800 psi pressure in a CO atmosphere. A photoassisted protocol for this reaction conducted at reduced temperature and pressure also exists, for which [CpFe(CO)2]2
catalyst gave the best yields.\textsuperscript{135, 136} The one-pot reduction of nitroso ene products to amines seen for these aryl nitroso ene reactions increases step efficiency and avoids side reactions of the hydroxylamine ene product that would reduce overall yields.\textsuperscript{123, 137} It is also noteable that 1-methoxy-4-nitrobenzene, when reduced to a nitroso compound, gives a nitroso ene product in good yield, which can easily be dearylated using CAN. Stoichiometric 1-methoxy-4-nitrosobenzene, as mentioned in Section 1.3, does not give a clean reaction.\textsuperscript{10, 138}

The domino reduction of the aromatic nitro group on 1.78 to a nitroso group was also used to give the saturated heterocycle 1.79 in an as yet substrate-specific, but interesting reaction (The full reaction is shown in Scheme 1.18). A sixfold excess of P(OEt)\textsubscript{3} was originally used to maximise yield for the nitro group reduction. However, the yield of the subsequent nitroso ene cyclisation step was reduced by N-ethylated side products. A new system using 2.4 equiv of Ph\textsubscript{3}P oxidant and a catalytic amount of MoO\textsubscript{2}Cl\textsubscript{2}(dmf)\textsubscript{2} at 185°C, gave 1.79 in 60-80% yield. Microwave conditions were also employed, giving fairly similar yields. Ph\textsubscript{3}P does not form an oxide in the same way as P(OEt)\textsubscript{3}, and so did not give any major side products. After the reaction was shown not to proceed in protic polar solvents, toluene was selected as the solvent of choice. The lack of reaction for a substrate with a terminal double bond confirmed an Alder-ene substitution mechanism.\textsuperscript{139}

\[
\begin{align*}
\text{NO}_2 & \quad \text{R} \\
\text{1.78} & \quad \text{R} = \text{H or Me} \\
\text{cat. MoO}_2\text{Cl}_2(\text{dmf})_2 & \quad \text{Ph}_3\text{P (2.4 equiv) C}_7\text{H}_8 \\
\rightarrow & \quad \text{N} \\
\text{1.79} & \quad \text{R}
\end{align*}
\]

\textit{Scheme 1.18}: A nitroso ene intramolecular cyclisation of an aryl nitroso alkene to give a benzothiazine product.\textsuperscript{139}

\subsection*{1.3.2 The mechanism of the nitroso ene reaction.}

An early proposal for the nitroso ene reaction mechanism involved formation of a three membered aziridine ring as a key intermediate. Initial computational studies supported the reversible formation of an aziridine N-oxide.\textsuperscript{10, 140} Later work has suggested equilibrium between formation of the three-membered ring 1.80 and a polarised diradical 1.81 with an electronic structure midway between a true diradical and a closed shell polar species, as shown by CASPT2 calculations. The polarised
Diradical intermediate was shown to give rise to the nitroso ene product, 1.82, whilst the reversibly formed aziridine acts as an onlooker (Mechanism shown in Scheme 1.19). Both ab initio\textsuperscript{141} and DFT\textsuperscript{142} calculations suggested the likelihood that the polarised diradical, rather than the aziridine, was an active intermediate en route to the final product. A B3LYP/6-31G* computational energy profile study showed clearly that the aziridine could not be directly produced from reactants or lead directly to the product, while product-formation via the polarised diradical was found to be energetically favourable.\textsuperscript{24} A significant kinetic isotope effect found by Krebs confirmed that the aziridine intermediate was formed reversibly.\textsuperscript{140} Single-bond rotation in the polarised diradical is limited by weak bonding between the nitroso nitrogen and trigonal carbon, as well as weak O-H bonding between the oxygen and methyl groups (The full reaction mechanism is shown in reaction (a) of Scheme 1.17), explaining the strong stereoselectivity of the nitroso ene reaction without involving an unrotating aziridine intermediate.\textsuperscript{143} The energy of the transition states involved in bond rotation for the diradical has been calculated, and shows a prohibitively high energy barrier to rotation even for less substituted reactants.\textsuperscript{10, 141}

\begin{center}
\includegraphics[width=\textwidth]{scheme19.png}
\end{center}

\textbf{Scheme 1.19:} The stepwise (a) and concerted (b) reaction pathways proposed for simple and aromatic nitroso ene products, respectively.\textsuperscript{10, 144}

A computational study of the reaction between a simple nitrosobenzene and o-isotoluene 1.83 to give 1.84 showed that, in this case, a concerted mechanism was followed, with no intermediates, due
to the lower reaction enthalpy given by the formation of an aromatic product. Simple alkenes were suggested to follow the stepwise reaction path already described (This reaction is also shown in Scheme 1.19, reaction (b)).

A PCM solvent model was used to show that polar solvents promoted the formation of the polarised diradical, encouraging the nitroso ene reaction. Rate of intermolecular nitroso ene reaction using 4-nitronitrosobenzene was shown to be increased by electron donating substituents on the olefin, or by an alcohol group able to coordinate to the enophile. Reaction rate was reduced by electron withdrawing substituents on the olefin, or sterically hindering bulky substituents.

A ‘Skew’ effect is observed for the aryl and acyl nitroso reactions, giving strong cis stereoselectivity and Markovnikov regioselectivity. The nitroso group most favourably lies diagonally across the olefin, with the aryl or acyl substituent placed in the least substituted region of the olefin. This maximises two favourable C-O interactions, minimises steric hinderance and favours abstraction of the twix hydrogen from the olefin’s most crowded end and most substituted side. Free rotation of the polarised diradical intermediate is limited by weak O-H bonding, and a weak bond between the nitrogen and trigonal carbon (see Figure 1.5). By contrast, both the O₂ ene reaction (in which O₂ reacts directly with an olefin to give a peroxide, via a concerted mechanism) and the nitroso ene reaction of HNO, without bulky substituents on the enophile in either case, simply display cis selective proton abstraction, with oxygen coordinating to protons on the more substituted side of the double bond (see Figure 1.5).

The nitroso ene reaction of 4-nitronitrosobenzene with dueterated 2-methylbut-2-ene showed a 85:15 ratio between the products of twix and twin proton abstraction, and no lone abstraction (see Figure 1.4, for the relative positions of these protons). Diradicals favouring twix, twin or lone proton abstraction may be initially formed in the ene reaction, with the twix diradical most favoured. However, while the twin or twix diradicals are favourably converted to the respective products, the energy barrier for hydrogen abstraction from the lone diradical is substantially higher than the energy required for cyclisation to the aziridine N-oxide and reopening as a twix diradical. Consequently, the lone diradical initially formed is converted to twix diradical via reversible aziridine cyclisation, and only twix and twin nitroso ene products are given. This was supported by the nitroso ene reaction of MeNO, with a 76:24 twix:twin product ratio.

A study into acyl nitroso ene reaction regioselectivity found that benzoyl-substituted acyl nitroso groups reacted with trimethylethene mainly yielded the Markovnikov product. However the ene reaction of bulkier mesitoyl substituted nitroso groups yielded only a slight excess of Markovnikov product. Both acyl nitroso reactions were 100% selective for cis proton abstraction. The selectivity
difference is explained by unfavourable steric interactions between methyl groups on the olefin and mesitoyl ring, hindering *twix* or *twin* proton abstraction.\textsuperscript{10, 143}

![Figure 1.5](image)

**Figure 1.5:** (a) The ‘Cis’ effect in the O\textsubscript{2} ene reactions, with Cis protons in bold favourably abstracted (b) The ‘Skew’ effect in the aryl nitroso ene reaction, with the *twix* proton in bold favourably abstracted (c) Bonds hindering rotation of the polarised diradical (d) proton descriptions in olefin amination selectivity\textsuperscript{10, 24, 143}

The regioselectivity of an intramolecular nitroso ene reaction would likely be governed by the favourability of the product ring size, as well as the location of a free allylic hydrogen for abstraction in the ene reaction. The theoretical ring formation would be an *exo*-tet cyclisation, which is normally favoured; a 5 or 6 membered ring would have more acceptable ring strain than any smaller ring that might be formed.\textsuperscript{145}

4-Nitronitrosobenzene was used in an aryl nitroso ene reaction with geraniol derivatives and nerol. The reaction showed a strong locoselectivity favouring 6,7 alkene substitution. Deactivation of the 2,3 double bond by electron withdrawing functional groups, and unfavourable ring strain associated with hydrogen abstraction around the 2,3 bond meant that 6,7 alkene selectivity predominated in all cases. When geraniol and nerol were used as substrates, locoselectivity was slightly reduced, presumably by the free hydroxyl group coordinating with the enophile.\textsuperscript{10, 146, 147}

The mechanism of the metal catalysed nitroso ene reaction has also been studied. The metal binds to the arylhydroxylamines by coordination to the nitrogen lone pair. An intermolecular ene reaction carried out in the presence of a diene gave the ene products only, and no Diels-Alder product, suggesting that free nitroso compound, required for the latter reaction, was not involved in the ene reaction. A tris adduct between copper and nitrosobenzene was reacted with an olefin, and gave similar products to the reaction between hydroxylamine and olefin under the same conditions. The tris adduct was also shown to catalyse the reaction of hydroxylamine to the same extent as copper, suggesting that this complex plays an important role in the reaction. Other results from this study
showed reversible alkene coordination to copper catalysts, dependant on concentration during or before the rate-determining step. A reaction mechanism was proposed in which the alkene and active aryl nitroso complex form a bond via the copper, with movement from a high energy pyramidal form to a lower energy square planar configured intermediate.\textsuperscript{148}

The catalytic cycle shown in Scheme 1.20 was proposed by Srivastava for a copper-catalysed nitroso ene reaction with subsequent reduction from hydroxylamine \textbf{1.87} to amine \textbf{1.91} by Cu(I). Cu(II) oxidises the hydroxylamine to nitroso groups, forming a copper-nitroso complex \textbf{1.87}, which coordinates to an olefin to form complex \textbf{1.88}. This is followed by Cu(I) dissociation from the metal-olefin intermediate \textbf{1.89}, giving the hydroxamic acid, \textbf{1.90}, which is reduced to an amine by Cu(I), thus regenerating the Cu(II) catalyst.\textsuperscript{148}

\begin{center}
\textbf{Scheme 1.20}: A reaction pathway for a copper catalysed aryl nitroso ene reaction\textsuperscript{148}
\end{center}
Srivastava later developed the concept of a Cu(I)/Cu(II) redox pair into a system with 1:1 mixture of CuCl/CuCl₂, under reflux in DCE. Use of a redox pair minimised the reduction of the hydroxylamine to amine by Cu(I), leading to unprecedentedly good yields of aminated product for a range of substrates. It was noted in this work that reactions with electron rich disubstituted and trisubstituted olefins gave the highest yield of aminated product.¹⁴⁹

Acyl nitroso ene reactions can also proceed by oxidation of hydroxamic acids to nitroso groups using catalysts such as NaPr₄IO₄, CuBr.Me₂S, CuCl, [Ir(cod)Cl]₂, and a Ru(pybox) complex. The reduced form of metal catalysts can be regenerated by a stoichiometric oxidant, or by the hydroxamic acid starting material, as in aryl nitroso ene reactions. (The reaction cycle is shown in Scheme 1.21). However, the metal catalyst does not appear to form a strong complex with the nitroso group throughout the reaction, contrary to the mechanism of aryl nitroso ene reactions. Diels-Alder trapping experiments by Whiting indicated dissociation of metal catalyst from an acyl nitroso group before completion of a nitroso HDA reaction, and therefore before completion of the slower nitroso ene reaction as well. Due to the facile and transient nature of acyl nitroso groups, any complex formed with a metal catalyst is short lived; the reaction proceeds by direct allylic proton abstraction and C-N bond formation. In another departure from aryl nitroso reactions, reduction of the hydroxylamine product to an amine does not normally occur. The copper catalysed nitroso ene reaction using BOC-NHOH shown in Scheme 1.21 did give amine product 1.93 when P(OEt)₃ was used in the reaction, due to hydroxylamine reduction by the copper phosphite complex. Only the unreduced hydroxamic acid product 1.92 was given when no phosphite was added.⁵⁴, ¹¹⁹, ¹²⁰, ¹⁴⁸, ¹⁵⁰

(Scheme 1.21): A catalytic cycle for the copper catalysed acyl nitroso ene reaction (Reactions without P(OEt)₃, or with another acyl nitroso compound, give the hydroxylamine product)¹⁵⁰
**Table 1.1:** Aryl nitroso ene reactions carried out with iron and molybdenum catalysts.  

Iron(III) and molybdenum(VI) catalysed aryl nitroso ene reactions with various substrates were carried out by Jorgensen using catalysts **1.94a-d**. A further range of molybdenum catalysed reactions were also carried out by Nicholas et al. The substrates, reagents and products for these reactions are shown in Table 1.1. The yields for different reactions showed that abstraction of methylene protons...
is much less favourable than for methyl protons, though benzylic proton abstraction is made more favourable by the conjugated product. Amination selectively takes place at the least substituted vinylic carbon. The useful reduction of aryl nitroso ene products to amines in molybdenum and iron catalysed reactions occurs in a catalytic cycle, with the reduction of the catalyst during the ene reaction giving Fe(II)/Mo(IV) species capable of reducing the hydroxylamine product to a secondary amine, simultaneously regenerating the original catalyst.\textsuperscript{9, 153, 155}

A triazodioxide iron-hydroxylamine complex (Shown as X-ray structure (a) in Figure 1.6) was isolated during a nitroso ene reaction catalysed by an iron-hexadentate aryl amine complex 1.94c. The complex exhibited catalytic activity in the nitroso ene reaction when added to an olefin-phenyl hydroxylamine mixture, indicating that iron remains bound to the hydroxylamine group during the nitroso ene reaction. Nicholas et al also isolated a Cu(I)-nitroso complex shown to be active in catalysing the nitroso ene reaction, from a reaction using [Cu(CH\textsubscript{3}CN)\textsubscript{4}]PF\textsubscript{6} catalyst and N,N'-diethyl-4-nitrosoaniline, since any PhNO-Cu(I) complex appeared to be too unstable to isolate (shown as structure (b) in Figure 1.6). Kinetic studies of the iron catalysed ene reaction suggested a rate-determining step neither strongly associative or dissociative, associated with a very negative reaction enthalpy, as well as involvement of alkene coordination in the rate determining step. Cu(I) reduced aryl hydroxylamines to aryl amines in test cases very efficiently. This was taken as evidence that the amine product of the copper-catalysed nitroso ene reaction was generated by reduction of the hydroxylamine initially produced in the reaction, rather than insertion into the olefin of an amine transferred directly from the copper-nitroso complex. Diels-Alder trapping experiments with both iron and copper generated nitroso compounds did not lead to the formation of Diels-Alder adducts, also indicating that the metal catalysts remain bound to the nitroso group throughout the reaction. A ruthenium catalysed amination of cyclohexene by aromatic nitro compounds was also developed by Cenini, and was suggested to proceed by a similar mechanism to the iron catalysed nitroso ene reaction.\textsuperscript{9, 148, 154, 156}

The molybdenum complex 1.94d catalysed the nitroso ene reaction with lowered yields compared to iron. MoO\textsubscript{2}(dedtc)\textsubscript{2} was also used to catalyse an aryl nitroso ene reaction, and formed an isolatable complex with hydroxylamine, though this probably did not have implications for the ene reaction. Atypically high levels of by-products from hydroxylamine oxidative side-reactions were also observed with this catalyst. Sharpless identified the active complex between the nitroso species and metal catalyst in these reactions as a molybdoxyaziridine complex. A catalytic cycle for this complex was also worked out by Nicholas et al, involving reduction of the hydroxylamine product to a secondary amine by the reduced form of the molybdenum catalyst. A Diels-Alder trapping
experiment suggested that the nitroso species dissociates from the molybdoxyaziridine complex during the aryl nitroso ene reaction, in contrast to the behaviour of iron and copper catalysts.\textsuperscript{126,155,157}

![Figure 1.6](image)

**Figure 1.6:** The iron (left) and copper (right) complexes isolated as active complexes in nitroso-ene reactions.\textsuperscript{148,154}

Nitroso ene reactions with trifluoronitromethane \textbf{1.95} have also been carried out, with the enophile obtained by pyrolysis of trifluoroacetyl nitrite. The electron withdrawing trifluoromethane group makes these species more reactive than aryl nitroso groups, forming a range of secondary hydroxylamines \textbf{1.96} with up to 97\% yield (selected syntheses shown in Table 1.2). It was noted that methyl and methylene protons are both abstracted readily in these nitroso ene reactions; for entries 2 and 3, equal amounts of each product are formed by both reactions. Methine protons, however, are not abstracted, as shown by entry 4, where the sole nitroso ene product is given by a methyl proton abstraction.\textsuperscript{42}
Table 1.2 Nitroso ene reactions of Trifluoronitrosomethane\textsuperscript{42}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefin</th>
<th>Hydroxylamine product(s)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[\text{CH}_2=\text{CH}_2]</td>
<td>[\text{CH}_2=\text{CH}_2\text{N}^+\text{CF}_3]</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>[\text{CH}_3\text{CH}=	ext{CH}_2]</td>
<td>[\text{CH}_2=\text{CH}_2\text{N}^+\text{CF}_3\text{Et} + \text{CH}_2=\text{CH}_2\text{N}^+\text{CF}_3] (1:1)</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>[\text{CH}_3\text{CH}=\text{CH}_2]</td>
<td>[\text{CH}_2=\text{CH}_2\text{N}^+\text{CF}_3\text{Et} + \text{CH}_2=\text{CH}_2\text{N}^+\text{CF}_3] (1:1)</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>[\text{CH}_3\text{CH}=\text{CH}_2]</td>
<td>[\text{CH}_2=\text{CH}_2\text{N}^+\text{CF}_3]</td>
<td>93</td>
</tr>
</tbody>
</table>

1.3.3 Enantioselective nitroso ene reactions.

The major obstacle to enantioselective nitroso ene reactions has been the transient nature of the reacting nitroso group, which fails to bind to chiral catalysts for the duration of the reaction. An enantioselective nitroso ene reaction has recently been developed using isolated nitrosopyridine, which has been used in prior enantioselective nitroso HDA reactions (see section 1.2.1). An improved yield was attained for this reaction by adding a bromo group \textit{para} to the nitroso group. 5-Methyl-3-nitrosoisoxazole gave an optimal yield of 94%. Substrates without electron withdrawing groups did not react, and were thought to have decomposed in the reaction. A new technique of reacting these substrates with pyridine hydroxylamines bound to a solid resin was developed, giving excellent yields for the initially unsuccessful reactions. As the pyridinyl nitroso group is stable, the racemic protocol proceeded without the use of metal catalysis for nitroso generation. For the enantioselective
protocol, BINAP and difluorophos ligands were tested with CuPF_{6}(MeCN)_{4} (the same copper complex was successfully employed for asymmetric pyridinyl nitroso HDA reactions, see Section 1.2.2 and Scheme 1.5). Nitroso ene reaction of 3-methylnitrosopyridine 1.97 with 2-methylbut-2-ene gave product 1.98, but in low yield and poor enantioselectivity. To the best of our knowledge, these are the best results for a metal-catalysed nitroso ene reaction with enantioselective induction that have been published (Full reaction shown in Scheme 1.22). \(^{158}\)

\[
\begin{array}{c}
\text{1.97} \quad \text{CuPF}_{6}(\text{MeCN})_{4} \quad \text{-(S)-ligand (10 molar %)} \quad \text{CH}_{2}\text{Cl}_{2}, -78^\circ\text{C} \\
\rightarrow \\
\text{1.98}
\end{array}
\]

**Scheme 1.22**: Enantioselective Nitrosopyridine ene reaction catalyzed with (S)-Difluorophos (40% ee, low yield) \(^{158}\)

An enantioselective intermolecular nitroso ene reaction of nitrosoarenes with tiglic amides featuring a camphor-based sultam chiral auxiliary \(^{159}\) was developed by Krebs. \(^{160}\) More recently, the same chiral auxiliary was employed for an asymmetric acynitroso ene reaction reported by De Alaniz (76% yield and 97% ee). In the latter work, the initial experiments aimed at developing a mild system for the oxidation of unsaturated \(N\)-hydroxyformates to acyl nitroso groups. CuCl was used as a catalytic oxidant, with air as a stoichiometric oxidant and with catalytic pyridine (experimentally confirmed to function as an activator rather than a base). These conditions reduced the product decomposition seen when \(\text{H}_{2}\text{O}_{2}\) was used as an oxidant in the intramolecular reaction, and were adaptable to a range of intra- and inter- molecular reactions with varied substrates (through \(\text{cis}\)-olefins could not be cyclised), including tiglic acid derivatives, which provide ready access to disubstituted \(\beta\)-amino acids. A Cbz protected hydroxamic acid 1.100 was used in an enantioselective nitroso ene reaction with tiglic acid 1.99 derived from Oppolzer’s camphorsultam chiral auxiliary, which was easily removed following the reaction. The auxiliary directed nitroso ene reaction was followed by an \textit{in situ} cyclisation to isoxazolidinone product 1.101, with a predominating \(-\text{trans}\) conformation between the carbonyl group and double bond (Reaction shown in Scheme 1.23). \(^{159, 161}\)

\(\alpha\)-chloronitroso sugar derivatives have also been used in nitroso ene reactions. Following nitroso ene...
reaction with an alkene, the sugar moiety is eliminated via a nitrone hydrochloride salt intermediate on HCl addition, giving the allylic hydroxylamine product in good yield and with >90% ee. Mannose derived chloronitroso reagents have been shown to give greater enantioselectivity than other sugar derivatives, probably due to increased steric crowding at their reactive hemisphere.\textsuperscript{124, 125}

\textbf{Scheme 1.23}: An enantioselective nitroso ene cyclisation, with a camphor chiral auxiliary\textsuperscript{161}

1.3.4 Synthetic applications of the nitroso ene reaction.

A study of aryl nitroso ene reactions with allylic alcohols such as 1.102, by Bottke, revealed a natural \textit{syn} selectivity favouring product 1.103 over 1.104, caused by coordination between the nitroso group and alcohol and minimisation of allylic strain in the intermediate. Use of coordinating solvents reduced \textit{syn} selectivity by competitive H-bond formation. Fair amounts of the enone side-product 1.105 were formed, though this was reduced by addition of excess olefin (Shown in Scheme 1.24).\textsuperscript{162}

\textbf{Scheme 1.24}: Nitroso ene reaction with a 1,3 unsaturated alcohol, showing distinctive selectivity\textsuperscript{162}
The intramolecular aryl nitroso ene reactions towards synthesis of pteridines and pyrimidines developed by Vasella and coworkers demonstrate the potential of stable nitroso groups for ring closures in natural product synthesis. The nitrosopyrimidine 1.106 can undergo an intramolecular nitroso ene reaction with its olefin side chain, followed by dehydroxylation, to give a 6-substituted pteridinone 1.107 (Reaction shown in Scheme 1.25). The ene reaction was best accomplished in MeCN, and proceeded in 91% yield with excellent stereoselectivity. The formation of an extended conjugated system increases the favourability of hydroxylamine dehydroxylation.\(^{163}\)

A methoxy substituted pteridinone 1.108, synthesised using a similar method, was used in syntheses of Ciliapterin 1.109 and Dicytopterin 1.110 by Vasella. This demonstrates how the migrated double bond in the nitroso ene reaction can easily be derivatised to give different products, in this case by Sharpless dihydroxylation.\(^{8}\) Zhang also synthesised a range of pyrimidinones using nitrosopyrimidines with C2, rather than C3, substitution on the olefin side chain such as 1.111, which cyclises to give 1.112. Addition of a diene to the reaction mixture resulted in a nitroso ene/Diels-Alder tandem reaction, in which the migrated olefin on the heptyl ring nitroso ene product 1.113, undergoes a Diels Alder reaction to form one of 3 possible spiro-linked rings, including 1.114, depending on the diene used. When 2 out of the 3 amine groups on the pyrimidine starting material were acetylated, treatment with excess NaBH(OAc)\(_3\) and AcOH caused the formation of a third ring, giving further purine products (These reaction are also shown in Scheme 1.25).\(^{164}\)
Scheme 1.25: Intramolecular nitroso ene based syntheses of pteridiones and pyrimidinones developed by Vasella and coworkers\textsuperscript{8, 163, 164}

A few examples of intramolecular tertiary alkynitroso ene cyclisations exist. An intramolecular cyclisation of 1.115, with an aliphatic nitroso group generated using diethyl azodicarboxylate oxidation was tested by Roberts. The single heterocyclic product 1.116 obtained proved highly unstable, and no yield was recorded.\textsuperscript{165} A study of radical polymerisation between vinyl monomers and acyloxy radicals found that nitroxides such as 1.117 were oxidised by benzoyl peroxide to give a nitroso intermediate which underwent an intramolecular nitroso ene reaction, giving the heterocycle 1.118 (both reactions are shown in Scheme 1.26).\textsuperscript{166}
Scheme 1.26 Intramolecular tertiary alkylnitroso ene reactions\textsuperscript{165, 166}

The synthesis of simple oxazolidinones, which have biological significance as intermediates leading to antibiotics, has been one of the major practical uses for the acyl nitroso ene reaction.\textsuperscript{167} The intermolecular nitroso ene reaction developed by Iwasa to give 1.120 from hydroxamic acid 1.119 was followed by a halocyclisation, taking advantage of the double bond to increase product functionality. Molecular iodine was added to the product in a non-protic solvent, prompting iodolactonisation to give 1.121 (Full reaction shown in Scheme 1.27). However, this reaction required a large excess of an electron rich olefin to proceed in good yield.\textsuperscript{119}

Scheme 1.27: A nitroso ene reaction, with halocyclisation of the product to give an oxizolidone ring\textsuperscript{119}

The synthesis of Amaryllis and Scelectum alkaloid skeletons, giving rise to products such as (+)-crinane and DL-mesembrine, (1.122 and 1.123) was achieved using a nitroso ene reaction, again with
trapping of the unstable nitroso species by a Diels-Alder adduct with anthracene, stabilising the reactive group. In the recent development of a library of novel antibiotic candidates, pyridine, quinoline and isoxazole analogues (1.124-1.126) were synthesised using the nitroso ene reaction (Structures shown in Figure 1.7). Several other small molecules were synthesised during the same project using the nitroso HDA reaction, showing the versatility of nitroso compound reactions.  

![Figure 1.7: Natural products synthesised using the nitroso ene reaction](image)

Studies into the cancer-causing mechanism of nitrosoarenes found in plastics and other products have suggested the involvement of several nitroso ene reactions. Interaction with specific receptors may lead to overexpression of cancer-promoting enzymes, or healthy cells may be killed in greater numbers than resistant hepatocytes by harmful nitroso compounds. Direct nitroso ene attack on DNA is also suggested by the ene reaction of 2-nitrosoadenosine (with the nitroso group experimentally generated using NaIO₄), which is also capable of Diels-Alder and azo group forming reactions. A greater understanding of these reaction mechanisms could be useful in cancer therapy.  

The ene reaction of nitrosocarbonyl methane with diethyl allylphosphonate was used as the key step in the synthesis of the antibiotic FR900098. A diene adduct was formed during the reaction to protect the reactive nitroso group, similarly to Kirby’s nitroso ene reaction (see Section 1.3). A paper on the synthesis of 1,3 cyclic dienes by a tandem enyne metathesis Claisen reaction went on to demonstrate a mode selective nitroso ene reaction using the cyclic reaction product 1.127. Despite three possible allylic hydrogens (on C1, C2 and C3) that could be abstracted in the nitroso ene reaction of BOC-nitroso with the diene product, the reaction was entirely mode selective. Selective C1 proton abstraction yielded a single diene, the correct constitutional isomer for a further spontaneous nitroso HDA reaction which gave 1.128 (Reaction shown in Scheme 1.28). A resin
bound pyridyl nitroso ene reaction, using a commercially available resin, proceeded in excellent yield when electron rich olefins were used.\textsuperscript{172}

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {\textbf{Scheme 1.28}: A mode selective intermolecular nitroso ene reaction, followed by an intramolecular nitroso HDA reaction\textsuperscript{171}};
  \end{tikzpicture}
\end{center}

1.4 The nitroso aldol reaction.

The aldol reaction is a useful C-C bond forming reaction normally involving a nucleophilic attack by an enolate or enolate equivalent, on an aldehyde or ketone (\textbf{1.129}). Enolate equivalents (\textbf{1.130}) include nitroalkanes and suitably derivatised carbonyls (silyl enol ethers, lithium enolates, pyrrolidine/ morpholine enamines and others), and allow for the preparation of stable aldol reactants from a desired carbonyl compound. Nitroso groups can present an electrophillic target for attack by an enolate in this reaction, giving rise to a range of $\alpha$-aminoxy/hydroxyamino substituted carbonyl compounds, including \textbf{1.131} and \textbf{1.132} as shown in Scheme 1.29. Significantly increasing the transformations accessible through this reaction, C-O and C-N bond formation can be easily and exclusively selected for by varying specific reaction conditions. This reaction is also important among nitroso group reactions due to the stable bond formed in the synthesis of the enolate equivalent, giving a reliable opportunity for asymmetric induction by an easily removed organocatalyst. Nitroso aldol reactions are frequently carried out with more stable arylnitroso species, rather than highly reactive acyl nitroso species. While the most common reactant used is commercial nitrosobenzene, relatively stable nitroso species such as $\alpha$-chloronitroso groups have also been used in the nitroso aldol reaction and prepared using the same methods as for nitroso HDA and nitroso ene reactions (see sections 1.2.1 and 1.4.3).\textsuperscript{26, 27}
Scheme 1.29: A generalised nitroso aldol reaction

An early synthesis of α-hydroxyaminoketones with nitrosobenzene as an electrophile was the synthesis of azomethine derivatives via a base-catalysed malonic ester attack on nitrosobenzene derivatives. A similar method was used to access anil derivatives of 1,3-diarylnylmethane and related polyketones. The desired product is reached via a condensation similar to those seen for typical aldol reactions between carbonyl groups to give α,β-unsaturated alcohols. An early nitroso aldol reaction with 1-morpholino-1-cyclohexene enolate showed poor selectivity, with hydroxamic acid, secondary amine and azomethine products given. When the silyl enol ether 1.133 was used as an enolate equivalent, the silyl group transferred to the hydroxylamine in the product, giving a siloxyaminoketone, 1.134, which after elimination afforded an azomethine 1.35. This product was further transformed to a heterocycle 1.136, by diene addition (Reaction pathway shown in Scheme 1.30). Lithium, tin and several other metals can also be used to efficiently generate enolates for N-selective nitroso aldol reactions. Enamines synthesised from aldehydes and ketones using amines such as proline or tetrazole act as particularly important intermediates in enantioselective O-NA aldol reactions, which will be dealt with fully in section 1.4.1.26, 174, 177

Scheme 1.30: An early silyl enol ether nitroso aldol reaction with further conversion to an N-heterocycle 176

1.4.1 Regio- and enantioselectivity of the nitroso aldol reaction

N/O selectivity for a typical nitroso aldol reaction between a cyclohexanone derivative and aryl nitroso species is highly controllable. A morpholine enamine 1.137, reacted at low temperature and
with methanol solvent, gave the N-NA reaction product exclusively. Alternatively, an O-NA reaction is almost exclusively selected for when pyrrolidine enamine 1.138 and acetic acid are used in the reaction. Both reactions proceed with fair yield at -78°C (Full reactions shown in Scheme 1.31). The different enamines used strongly vary in nucleophilicity. Pyrrolidine enamines are much more resistant to hydrolysis under acidic conditions than morpholine enamines; consequently, acidic conditions accelerate the O-NA reaction of the former enamine, while less acidic conditions accelerate the N-NA reaction of the latter. Piperidine enamines have a greater range of stability, and can be used for both O-NA and N-NA reactions, by varying the reaction pH. The useful N/O selectivity change is explained by coordination of Brønsted acids to the nitroso nitrogen, prompting a nucleophilic attack on oxygen by the enamine β-carbon, in an O-NA reaction. Conversely, activation of the nitrosobenzene oxygen by weaker acids prompts an N-NA reaction via the nitrogen.26, 27

![Scheme 1.31: Nitroso aldol reactions of pyrrolidine and morpholine enamines showing selectivity control based on acidity](image)

To develop an enantioselective O-NA reaction based on coordination between a Brønsted acid and nitroso group nitrogen, addition of the strong chiral acid 1-(1-naphthyl)glycolic acid 1.140 to a piperidine-catalysed NA reaction was proposed. The O-NA reaction gave 1.132 from enamine 1.139 with 77% yield and 92% ee, with Et₂O emerging as the optimal solvent. To select for an N-NA reaction by modifying the reaction acidity, a naphthalene substituted TADDOL derivative, 1.142, was used as an enantioselective N-NA reaction catalyst, giving 1.143 from enamine 1.141 with 91% ee. (Reactions shown in Scheme 1.32)26, 27
Scheme 1.32: Enantioselective nitroso aldol reactions making use of chiral acids\textsuperscript{27}

Metal-based enolates can be efficiently generated and used in $N$-NA reactions, especially alkyltin enolates, which gave $>99:1$ N/O selectivity and $>90\%$ yield for a range of ketones. Lithium enolates generated from ketones with LDA, were also used in a range of $N$-NA reactions, reacting within 5 minutes at $-78^\circ$C. Amino Grignard reagents, sodium hexamethyldisilazide and potassium hexamethyldisilazide could also be used to generate metal enolates for this reaction. For the NA reactions of silyl enol ethers, the uncatalysed nitroso aldol reaction gives predominantly an $N$-NA reaction, whereas the reaction is 100\% $O$-NA selective in the presence of a Lewis acid such as alkylsilyltriflate. This is explained by the Lewis acid encouraging the dimerization of the nitroso reactant via an azo bond, prompting nucleophilic attack on the nitroso oxygen by the enolate and giving the $O$-NA product. Metal enolates reacted without a Lewis acid react via the nitroso compound monomer, and attack at the nitroso nitrogen.\textsuperscript{179, 180}

Chiral metal complexes can also be used in an enantioselective NA reaction. A 1:1 (R)-BINAP complex with silver triflate or acetate \textsuperscript{1.146} was used to induce $>90\%$ enantioselectivity in an aldol reaction between trialkyltin enolate \textsuperscript{1.144} and nitrosobenzene; the reaction was also nearly 100\% $O$-selective, giving \textsuperscript{1.145}. An enantioselective $N$-NA reaction was achieved for simple cyclic amino enols or trialkyl tin enolates, using a 2:1 AgOTf BINAP complex \textsuperscript{1.147}, with up to 99\% ee. The N/O
selectivity and enantioselectivity for the $N$-NA reaction proved very susceptible to the solvent used, but ethylene glycol diethyl ether gave an excellent enantio- and regioselectivity. The reversal of selectivity by a change in stoichiometry of the metal catalyst illustrates the malleability of the nitroso aldol reaction. A 1:2 AgOTf-BINAP complex 1.148 gave a good yield of $N$-NA product, but negligible enantioselectivity. The enantioselective $O$-NA reaction of silyl enolates such as 1.149 can be catalysed using a BINAP phosphite 1.150 complexed with AgBF$_4$, with 2 equiv of CsF added over 16 h at -78°C (The catalysts and reactions are shown in Scheme 1.33). For substrates other than 6-membered rings, some $N$-NA product was formed, reducing yields.

Scheme 1.33: Asymmetric nitroso aldol reactions catalysed by silver BINAP complexes, and an $O$-NA selective reaction with a silyl enolate.

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Alkyltin enolates for the nitroso aldol reaction were synthesised from trichloroacetates using catalytic Bu₂Sn(OMe)₂ and the silver complex of a quinoline based phosphite ligand. This highly stereoselective O-NA reaction avoided the use of stoichiometric alkyltin reagents normally used in tin enolate generation. In an improved protocol, tin enolate was generated in situ from trichloroacetyl enolate and catalytic quantities of dibutyl tin methoxide, which in the presence of a silver(I)-t-bu-QuinoxP complex showed only around 9:1 O/N selectivity, but 98% ee. Enantioselectivity is determined by transition state interactions of the bulky tin enolates with the side groups of the silver-quinox complexes. Both the silver atom and the tin enolate were thought to be bonded to the nitroso group in the key transition state.

L-proline 1.152 can be used as an organocatalyst for the nitroso aldol reaction, forming enamines in situ with aldehydes or ketones. The availability of this organocatalyst and the excellent enantioselective of its reactions make it very important to nitroso aldol reactions. Several proline catalysed O-NA reactions were published independently of each other in 2003. Zhong’s procedure used DMSO solvent and 20% catalyst loading at RT, over 10-20 mins, with a typical 99% ee over several substrates. A reaction developed by MacMillan et al used lower catalyst loading, low temperature and a less polar CHCl₃ solvent, to prevent a homo aldol reaction between the aldehyde substrates. Catalyst loading was reduced from 5% to 0.5%, with an increase in reaction time but little effect on the yield and enantioselectivity (76-95% yield and around 98% ee). The O-NA reaction developed by Hayashi et al used CH₃CN with an even lower temperature of -20°C and required 30% catalyst loading, giving O-NA product in around 80% yield and 98% ee. Hayashi et al also used ketones as O-NA substrates. This reaction was carried out at RT in DMF solvent, due to the lower reactivity of ketones compared to aldehydes. The reaction proceeded with up to 86% yield and >99% ee. Slow addition of 2 equiv of ketone over 24 h proved vital for maintaining enantioselectivity and selectivity for the singly substituted product.

Proline and proline derivatives, especially tetrazoles such as 1.153, which can be used at lower catalyst loading than proline, act as important chiral-pool organocatalysts, readily inducing enantioselectivity up to 99% ee without the use of expensive metal catalysts such as silver. Polymer-supported proline catalysts have been developed to facilitate product isolation for this NA reaction. Other organocatalysts used in nitroso aldol reactions include a proline based triflamine 1.154, acidic sulphonylimide derivatives such as 1.155 and a TBDMs substituted hydroxyl proline 1.156 (Structures shown in Figure 1.8). This last catalyst gave a single product from ketone in 1 min, and could be used with NA reactions proline was unable to catalyse; for example with cycloheptanone it gave a good yield of product with 99% ee.
Some non-proline based organocatalysts have also been used successfully in the nitroso aldol reaction, including a axially chiral secondary aminoalcohol, with a BINAP framework and sterically congested tert-alcohol moieties, which has been used to catalyse 99:1 selective O-NA reactions with a range of α-unbranched aldehydes, showing over 97% ee. The suggested transition state involved obstruction of one enamine face by a hydroxy moiety, while another hydroxy group activates the nitrosobenzene by H-bonding and directs selectivity. 2 structurally related BINAP-based secondary amines with more acidic 3,4,5-trifluorophenyl and 3,5-bis(trifluoromethyl) substituants, as well as a BINAP secondary amine with a single amino triflate sulphonamide side group, were also used to catalyse enantioselective O-NA reactions. The two trifluoro-substituted BINAP catalysts selected for opposite enantiomers, despite having the same axial chirality. The carboxylic acids or amine side chains on these organocatalysts coordinate to the nitroso nitrogen atom to ensure O-NA selectivity and >97% stereoselectivity. Toluene was identified as the most favourable solvent for these reactions.

Addition of nitrosobenzene to α-branched aldehyde showed that a 1-1.5:1 mixture of O- and N-substituted products was obtained with various proline derived catalysts, with the best yield and enantioselectivities shown by tetrazole catalysts. Wider studies of proline catalysed NA reactions in linear, branched and cyclic systems found that 2-methyl propanal and other α-branched aldehydes gave a mixture of O- and N-substituted product under L-proline catalysis, possibly due to steric interactions between the enamine substituents and the aryl group on the nitroso in the transition
state. Only 2-arylpropanal derivatives gave a synthetically useful $N$-selectivity for $\alpha$-branched aldehydes (10-20:1), with tetraazole catalysts giving ~60% ee.\textsuperscript{195}

An enantioselective organocatalysed $N$-NA reaction proved less accessible than the enantioselective $O$-NA reactions already discussed. However, prolinamide \textsuperscript{1.157}, shown in Figure 1.8, was shown to catalyse the $N$-NA reaction of aldehydes with up to 59% ee. As a weak acid the prolinamide protonates the nitroso oxygen and renders the nitroso nitrogen more nucleophilic (see section 1.4.1 for description of NA selectivity).\textsuperscript{26,196} Since proline catalysts are assumed to facilitate $O$-alkylation by protonating the more basic nitroso nitrogen, Houk proposed that a non-protonating catalyst would select for the $N$-NA reaction. Diphenylprolinol TMS ether was duly used to catalyse almost entirely $N$-selective NA reactions, with yields up to 75% and >90% ee (see section 1.4.2 for reaction mechanism).\textsuperscript{197} A range of Cinchona alkaloids were also used to catalyse the $N$-NA reaction of oxindoles in good yield and enantioselectivity, with a single cinchona alkaloid catalysing an $O$-NA reaction with 85% yield and 50% ee, possibly due to a difference in acidity, and resultant coordination to the nitroso group.\textsuperscript{198,199}

1.4.2 The mechanism of the nitroso aldol reaction

Studies of the proline catalysed $O$-NA reaction with aldehydes showed the reaction to be autocatalytic, reaching a rate equivalent to that normally observed at the end of the reaction, if the product was added at the start. Enantioselectivity also increases throughout the reaction, contrary to the kinetics of nearly all other proline catalysed reactions. It was suggested that proline can attack the oxyamine product, which forms a new enamine \textsuperscript{1.158} with the aldehyde which then reacts with nitrosobenzene. This reaction regenerates the proline adduct, along with another molecule of oxyamine product \textsuperscript{1.159}, as the most efficient catalyst of the reaction. Another study suggested a straightforward catalytic cycle, with chiral enamine formation, ene reaction, and a reverse condensation yielding the proline catalyst and final oxyamine product. It is probable that both these pathways operate in the reaction (Both theorised catalytic cycles are shown in Scheme 1.30). The $O$-NA reaction of ketones did not display a similar non-linear effect, suggesting this reaction proceeds by a single direct proline catalysis mechanism.\textsuperscript{200,201,202}
Scheme 1.34: L-Proline catalysed nitroso aldol reaction cycles (A) Autocatalytic model; (B) Simple catalytic cycle.200-202
Studies into the proline catalysed aldol reaction of acetone and aldehydes show that enamine formation occurs via an iminium ion. Formation of this ion occurs by C-N bonding between the carbonyl carbon and proline nitrogen, aided by coordination of the acidic carboxylic acid hydrogen on proline with the aldehyde oxygen. An alternative 4-coordinate C-N bond forming transition state, where the amine also protonates the carbonyl, was found to be prohibitively high in energy. A range of more probable transition states (1.160-1.164) for pyrrolidine catalysed nitroso aldol reactions have been proposed, including ene-type zwitterions 1.162, carboxylic acid activated proton transfer 1.161 and amine nitroso complexes 1.163-1.164 (The structures are shown in Figure 1.9). A dimerised nitroso intermediate, initially thought to be responsible for O-selectivity, was shown by computational and NMR studies to not be formed in any abundance. The most stable of the nitroso aldol reactive transition states 1.65-1.67 was found to be an E-anti proline enamine 1.165 adopting a pseudo-axial position for the nitrosobenzene phenyl group, anti with respect to the proline carbonyl. A reaction with 99% ee was predicted from this transition state (confirmed by a typical experimental 97%ee for L-proline catalysed aldehyde NA reactions). It was reasoned that the higher basicity of the nitrogen atom made its protonation by the catalyst unfavourably high, ensuring O-NA selectivity for proline catalysed reactions (The transition states and their energy levels are shown in Figure 1.10).

![Figure 1.9: Theorised transition states of pyrrolidine catalysed nitroso aldol reactions](image-url)
The previously mentioned diphenylprolinol TMS ether organocatalyst 1.171 (see section 1.4.1) was shown by Gibbs free energy calculations to catalyse the $N$-$N$A reaction of aldehydes via an enol intermediate rather than an enamine. MP2/6-311G**/B3LYP/6-31G* (solvation) theoretical calculations identified the most favourable transition state between the aldehyde and organocatalyst, in which the catalyst amine group coordinates with the aldehyde $\alpha$-proton and the amine proton attacks the aldehyde carbonyl, leading to the enol intermediate 1.168. The reaction pathway is determined by the high acidity of the aldehyde $\alpha$-proton, and the lack of an H-bonding carbonyl on the catalyst, which would promote enamine formation. It was then shown that the energy barrier for C-O bond formation via the enol-catalyst-nitrosobenzene complex 1.169 was higher than that for C-N bond formation. This may be due to the electrostatic attraction between the enol $\alpha$-carbon and nitrosobenzene nitrogen. The complex formed between the enol, catalyst and nitrosobenzene controls the stereoselectivity of product 1.170 (The full reaction is shown in Scheme 1.35).

Scheme 1.35: A TMS proline-derivative catalysed nitroso aldol reaction, including the reactive transition state

Figure 1.10: Reactive transition states of the proline catalysed nitroso aldol
1.4.3 Synthetic applications of the nitroso aldol reaction.

One of the first useful nitroso compound reactions took advantage of the greater stability of α-chloronitroso groups by reacting α-chloro-α-nitrosocyclohexane with enamines derived from bornansultam chiral auxillaries in an $N$-$NA$ reaction. As with the nitroso ene reaction, the auxiliary could be easily eliminated via a nitron hydrochloride salt, and the bornansultam easily removed using LiOH.$^{126}$ Similarly, an α-chloronitroso bornansultam 1.173 was used in an $N$-$NA$ reaction with Zinc enolates 1.172 (formed with LiN(SiMe$_3$)$_3$), giving moderate yields but excellent diastereoselectivities (this was one of the earliest nitroso aldol reactions successfully carried out). The zwitterion 1.174 formed in the reaction was hydrolysed with HCl to give ketone 1.175, which was reduced with NaBH$_4$ and zinc powder to give a 1,2-amino alcohol 1.176. X-ray crystallography of the chloronitroso derivative confirmed that the auxiliary sulphonamide blocks one face of the nitroso group to give a reaction with $>$90% anti selectivity (The reaction is shown in Scheme 1.36).$^{208}$

![Scheme 1.36: Nitroso aldol reaction of zinc enolates, catalysed by a bornansultam chiral auxillary.$^{208}$](image)

The α-aminoxy aldehyde products of proline catalysed enantioselective $O$-$NA$ reactions were used as versatile reactants by Zhong, who used allylation or reduction to generate enantiopure aminooxyalcohols, with 1.177 as the major isomer, or 1,2-diols (Reaction shown in Scheme 1.37). A HWE olefination was also used to give enantiopure alcohols from the same substrates.$^{209}$
Scheme 1.37: Synthesis of enantiopure alcohols by allylation of nitroso aldol products\textsuperscript{209}

Reduction of aldehyde N-NA reaction products with LiAlH\textsubscript{4} offers convenient access to 1,2 amino alcohols; these can also be derivatised to diamines without loss of enantiopurity in a simple three step pathway.\textsuperscript{193} An interesting rearrangement of an α-aminoxyketone obtained by an O-NA reaction, gave an α-amino enone \textbf{1.178}, using EuCl\textsubscript{3} and high temperature (Reaction shown in Scheme 1.38).\textsuperscript{210}

Scheme 1.38: Synthesis of α-amino enones from nitroso aldol products using EuCl\textsubscript{3}\textsuperscript{210}

CuSO\textsubscript{4} is commonly used as a reducing agent to give alcohols from α-aminoxy O-NA products such as \textbf{1.179}. NaBH\textsubscript{4} can also be used with H\textsubscript{2}/Pd hydrogenation to give a diol \textbf{1.180} from aldehyde O-NA products, without loss of optical purity. To obtain diol \textbf{1.182} from ketone O-NA products, PtO\textsubscript{2} hydrogenation can be used with NaBH\textsubscript{4}. Na(OAc)\textsubscript{3}BH and Bn\textsubscript{2}NH have also been used to give a 1,2-amino oxyamino molecule \textbf{1.181} from O-NA products (Shown in Scheme 1.39).\textsuperscript{186, 205, 211, 212}
Scheme 1.39: Further derivations of ketone or aldehyde nitroso aldol α-nitroso products

Proline catalysed nitroso aldol reactions have been used in the synthesis of natural products, often with reduction of the added hydroxylamine moiety to an amine or alcohol group. The synthesis of tarchonanthuslactone 1.183 is a representative example, where D-proline catalyses the addition of phenylnitroso to an aldehyde, followed by NaBH₄ reduction to give an α-hydroxyl substituent vital to the forward ring synthesis. Similar techniques were used in the synthesis of (+)-neosymbioimine 1.184 and other natural products.²¹³,²¹⁴,²¹⁵ A key step in the synthesis of the lactone core for the natural product (-)-brasoside 1.185 is a D-proline catalysed nitrosobenzene aldol reaction, followed by a HWE reaction leading to an aldehyde and a Michael cyclisation catalyzed by L-proline.²¹⁶ A tetrazole catalysed nitroso aldol reaction with unsaturated triphenylphosphines was used to synthesise 1,2-oxazines.²¹⁷ Yamaguchi developed a procedure for synthesis of angiogenesis inhibitors such as fumagillin 1.186 based around the nitroso aldol reaction, which can also be used for synthesis of the immune-suppressant FR65814 1.187. The added oxyamine group is reduced to an alcohol to allow further functionalisation of the key side chain (Product structures are shown in Figure 1.11).²¹⁸ Another creative use of the O-NA reaction employed nitrosophenyl, L-proline/tetraazole type catalysts and a series of substituted cyclobutanones, giving a range of α-hydroxy-γ-lactams by a
spontaneous ring-expansion rearrangement. The reaction proceeded in modest 30-65% yield, but with good enantioselectivity.\textsuperscript{219}

![Figure 1.11: Natural products synthesized using the nitroso aldol reaction\textsuperscript{213-218}](image)

The nitroso aldol reaction was also used in a cascade synthesis of \(\alpha\)-hydroxydiarylamines from enones, producing highly functionalized molecules by a convenient one-pot synthesis. A piperidine catalyzed nitroso aldol reaction between Hagemann’s ester 1.188, (synthesised \textit{in situ} from aldehyde and acetoacetate) and a range of aryl nitroso compounds gave a range of aminophenols 1.189. When pyrrolidine was used as an enolate organocatalyst, it withstood hydrolysis, and a range of \(\alpha\)-pyrrolidin-1-yl-diarylamines 1.190 were formed. When \(\text{Cs}_2\text{CO}_3\) and alkylhalides were added to this reaction, \(\alpha\)-alkylation was incorporated into the cascade, giving 1.191 (Shown in Scheme 1.40).\textsuperscript{220}
Scheme 1.40: Cascade reactions from nitroso aldol reaction of Hagemann’s ester giving aminophenols and o-pyrrolidin-1-yl diarylamines\textsuperscript{220}

Useful tandem \textit{O}-nitroso aldol/Michael reactions have been studied by several groups. Their products (1.195) are similar to those of the nitroso HDA reaction, and formed more conveniently with greater selectivity. The product is also usefully formed with opposite regioselectivity to the nitroso HDA reaction, by a two-step reaction (The reaction mechanism is shown in Scheme 1.41).\textsuperscript{221}

An enamine derived from an \textit{\textalpha}-unsaturated ketone 1.192 (tetrazole can be used, giving \textgreater98\% enantioselectivity), or \textit{\textalpha},\textit{\textbeta} unsaturated enolate 1.193, is first attacked by an aryl nitroso species in an \textit{O}-NA reaction, in MeCN at slightly elevated temperature. This forms an unsaturated iminium
intermediate 1.194 which is then attacked by the aminoxyl anion in an intramolecular Michael addition, giving the desired product 1.195 after protonation. Cycloheptenyl ketone gave poor yields with tetrazole derived catalysts, but L-proline was shown to produce acceptable yields. The nitroso aldol/Michael reaction is compatible with varied substitution of the aryl nitroso compounds and can also be used with linear alkenes and nitroalkenals to give tetrahydro-1,2-oxazines.222 An unusual Si(xylyl) substituted BINOL derivative was used to catalyse a similar aldol/Michael reaction from a morpholine enamine, with complete reversal of regioselectivity from the L-proline catalysed aldol/Michael reaction (That is, the same selectivity as a nitroso HDA reaction).223

A nitroso aldol/Michael reaction catalysed with silver-BINAP was attempted, but only the nitroso aldol reaction occurred, without any Michael addition. This is explained by addition of nitrosobenzene to the dienylamine from the same side as the tetrazole moiety, giving an iminium salt in boat form with the aminoxyl group in an axial position. The counterion effect of the enamine and the favourable boat conformation allow the aminoxyl anion to cyclise under tetrazole catalysis. Under silver-ion catalysis, both these factors are absent, so no Michael reaction takes place.221 A computational DFT investigation was also conducted into the mechanism of the nitroso aldol-Michael reaction between cyclohexanone and nitrosobenzene, catalysed by tetrazole. It showed that aldol reaction from the syn-enamine was less energetically favourable than from the anti enamine, that the O-selective NA reaction was more thermodynamically favourable than the N-selective reaction, and that the Michael reaction was the rate limiting step.224

Scheme 1.41: Generalised tandem nitroso aldol/Michael reaction221
The nitroso aldol reaction between nitrosobenzene and a range of α-aromatic cyanoacetate esters (1.196) was found to be an N-NA selective reaction, with good yield and moderate enantioselectivity. The facile reduction of two cyano and hydroxylamino groups on product 1.197 gave access to a range of synthetically useful 1,2-diamines 1.198. Experiments using several cinchona alkaloid organocatalysts (1.199a-e) showed that the 6’-hydroxyl and 9’-methoxy groups (Table 1.3) were vital for appreciable enantioselectivity, and that the use of coordinating solvents reduced enantioselectivity. This may indicate that the hydroxyl group activates the electrophile by H-bonding, which can be blocked by solvent. Thus MeOH solvent gave excellent yield, indicating electrophile activation, but little enantioselectivity.225

It was also found that higher concentrations of chiral catalyst reduced enantioselectivity for this reaction or even reversed it. This was thought to be caused by formation of a product/catalyst/substrate complex at low catalyst loadings, with higher enantioselectivity than the simple substrate/catalyst complex formed at higher catalyst loadings. The reaction was extended to a range of different aryl groups, in which electron deficient and meta/para substituted derivatives reacted very well, but ortho-substituted and electron-rich substrates respectively failed to react and reacted with lowered selectivity. A racemic reaction catalysed with Et₃N was also tested, with excellent yield and regioselectivity (see Table 1.3).225
Table 1.3: Enantioselective nitroso aldol reactions with cyanoacetate esters using cinchona alkaloid organocatalysts, selected entries.\(^{225}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R group</th>
<th>Catalyst</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
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<td>1.199a</td>
<td>90</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
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<td>1.199a</td>
<td>80</td>
<td>(+)-59</td>
</tr>
<tr>
<td>4</td>
<td>t-Bu</td>
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<td>85</td>
<td>(-)-42</td>
</tr>
<tr>
<td>5</td>
<td>t-Bu</td>
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<td>82</td>
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<td>11</td>
<td>t-Bu</td>
<td>Et(_3)N</td>
<td>79</td>
<td>N/A</td>
</tr>
</tbody>
</table>

An unusual nitroso aldol-type reaction was used in the dehydrogenation of an indole aminoester \(1.200\) (Synthesis shown in Scheme 1.42). The unique enophilic reactivity of the indole group caused it to form an adduct with phenylnitroso which was susceptible to elimination by the Lewis acid ZnCl\(_4\). This gave an \(\alpha,\beta\)-unsaturated product \(1.201\) in good yield as a single diastereoisomer, used in the forward synthesis of the alkaloid natural products Stephacidin and Avrainvillamide.\(^{226}\)
Scheme 1.42: Dehydrogenation of tryptophan derivatives with use of nitrosobenzene, giving a bicyclic product (R = silyl group)\textsuperscript{226}
2. Results and Discussion.

2.1 Aims and objectives.

The aim of the project was to establish a method for stereoselective intramolecular allylic C-H amination. Background research indicated that similar previously developed reactions were not without significant drawbacks, as well as indicating the potential of nitroso group reactions for use in efficient C-H amination methods. Our objective was to develop intramolecular nitroso ene reactions to give access to biologically significant 1,2 and 1,3 amino alcohol derivatives.

2.2 Starting Material Synthesis.

2.2.1 Introduction.

Hydroxamic acids (2.1, R = Alk, Ar) are compounds bearing N-acylated hydroxylamine as a functional group. Hydroxycarbamates (2.2, R = OAlk, OAr) are related, functionally similar, compounds derived from haloformates. Due to the strong iron binding properties of these groups, hydroxamic acid-functionalised siderophore molecules have important roles in several bacterial metal ion acquisition pathways. Iron chloride treatment is used as a standard test for hydroxamic acids, as an iron(III)-hydroxamic acid complex gives a distinctive deep purple stain. Hydroxamic acids are often used in nitroso HDA and nitroso ene reactions, as starting materials for the generation of reactive acyl nitroso groups in situ (see section 1.2 and section 1.3).

Apart from nitroso group reactions, hydroxamic acids are used in several other aminations. An aza-Michael reaction between hydroxamic acids and unsaturated carbonyl compounds, followed by an intramolecular aldol reaction, gives 5-hydroxyisoxazolidines or an amino ketone, depending on substitution of the enone. This reaction can be carried out with good enantioselectivity using a primary amine salt chiral catalyst. Hydroxamic acids can be used in the synthesis of isocyanates, ureas and amines via the Lossen rearrangement, where an O-acyl, sulphonyl or phosphonyl hydroxamic acid derivative is reduced to its conjugate base. N-(2-hydroxyalkoxy)-tert-butyl carbamates or N-tosyl carbamates can be derived from hydroxamic acids by base catalysed substitution of epoxides, or sulphonyl chlorides respectively. Hydroxamic acids have also been used in a heterocycle synthesis with thiokeiones, giving a dioxazole ring.

Hydroxamic acid esters are used to prevent the undesirable formation of urea linkages by highly reactive isocyanates in stored coatings and paints. Specific hydroxamic acids are used in industrial reprocessing of irradiated fuel, due to their strong metal chelation properties.
hydroxamic acids have been used as HDAC inhibitors, which show significant anti-cancer properties,\textsuperscript{237} and as ligands used in the synthesis of metallacrowns.\textsuperscript{238}

Numerous methods for hydroxamic acid synthesis have been reported in the literature. Hydroxylamine hydrochloride can be used with cyanates,\textsuperscript{239} esters,\textsuperscript{108} or carboxylic acids\textsuperscript{240} to give varied hydroxamic acids (2.1). Hydroxamic acids can also be readily synthesised from aldehydes using N-hydroxybenzenesulfonamide in the Angeli-Rimini reaction. This reaction is used as a standard test for the presence of aldehyde, when combined with an iron(III) chloride test for hydroxamic acids.\textsuperscript{241} Carboxylic acid derivatives, some carboxylic acid amides, long chain fatty acids and esters have also been converted to hydroxamic acids using an alkaline solution of hydroxylamine hydrochloride, in order to determine their concentration using the iron(III) chloride test, via colorimetry.\textsuperscript{242} Aryl chlorobenzimidazoles,\textsuperscript{243} acid chlorides\textsuperscript{244} and chloroformates\textsuperscript{245} can be used in a base catalysed acylation of hydroxylamine, giving hydroxamic acids (2.1) or hydroxycarbamates (2.2). N-alkylated hydroxamic acids can be synthesised readily by chloroformate acylation of oximes (Selected syntheses of hydroxycarbamates and hydroxamic acids are shown in Scheme 2.1).\textsuperscript{246}

![Scheme 2.1: Diagram of reaction paths used to prepare hydroxycarbamates and hydroxamic acids\textsuperscript{108, 240, 241, 244, 245}]

Alcohols or carboxylic acids can also be reacted with carbonyldiimidazole followed by addition of hydroxylamine hydrochloride. Some one-pot protocols have been developed for this reaction, as well as a two-step method, with variably severe conditions.\textsuperscript{231, 247, 248, 249} Pyridine or imidazole are normally used as basic activators. N,O-bis(trimethylsilyl)hydroxylamine can be used in place of hydroxylamine in a substitution reaction for the least reactive carboxylic acids and chloroformates.\textsuperscript{250} Based on this background research, our initial project strategy was to develop an efficient method for synthesis of variously substituted hydroxycarbamates from a range of allylic alcohols (as detailed in sections 2.2.2
to 2.2.4). Using these unsaturated hydroxycarbamates as substrates, we then aimed to develop an efficient one-step intramolecular allylic amination with convenient conditions, based on the intermolecular nitroso ene reactions described in earlier literature (as detailed in section 2.3.1-2.3.2).¹⁰,¹²

2.2.2 Synthesis of alcohol starting materials.

The preparation of a number of non-commercial primary and secondary substituted allylic and homoallylic alcohols was carried out during the project, for use as starting materials in the synthesis of unsaturated hydroxycarbamates (alcohols shown in Figure 2.1). A wide range of alcohols were selected to show the effect of varied secondary and allylic substitution, as well as stereochemistry, on ease of cyclisation for the corresponding hydroxamic acids (for further justification of substrate selection, see sections 2.3.2-2.3.4). The initial alcohol substrates 2.3a-b, 2.4a-b, 2.5a-b, 2.7 and 2.12 were selected from commercial allylic alcohols for ease of acquisition (as well as a means of conveniently analysing stereochemical effects on a hydroxycarbamate cyclisation, using the stereoisomers 2.5a-b). A range of further noteworthy allylic alcohols, especially secondary and cyclic derivatives, were also synthesised. A variety of synthetic methods selected for reliability, simplicity and availability of necessary reagents were used to obtain a wide range of unsaturated alcohols. To clearly show the effects of alkene group stereochemistry on subsequent reactions, all alcohols were synthesised, or acquired from commercial sources, as an overwhelming excess (90-97%) of a single isomer, with the exception of 2.15, synthesised as a 3:1 trans:cis mixture, due to the limitations of the synthesis method used. Based on the different reactivities of cis and trans hydroxycarbamates in the intramolecular nitroso ene reaction, observed early in the project (see section 2.3.3), most alcohol starting materials were synthesised or acquired as the more reactive trans isomers. The alcohols synthesised as the pure cis isomer, identified in Figure 2.1 as (Z)-2.13, 2.16 and 2.18, were prepared in order to compare the reactivity of unsaturated hydroxycarbamates with either cis or trans stereochemistry. 2.9 has an enforced trans configuration, while 2.16 and 2.18 have enforced cis configurations, due to their ring structure. 2.14 was synthesised from the corresponding commercial diol, E-1,4-dihydroxy-2-butene (2.06 g (7.5 mmol) of tert-butyldiphenylsilylchloride was added dropwise in 5 mL of THF to 1.32 g (15 mmol) of 1,4-dihydroxylbut-2-ene in 50 mL THF with 1.94 g (15 mmol) N,N-diisopropylethylamine. The reaction vessel was sealed and stirred for 12 h before the solvent was removed under reduced pressure. The product was diluted with 20 mL CH₂Cl₂ and washed with NH₄Cl (aq) (2 x 20 mL), before being dried over MgSO₄ and concentrated under reduced pressure). The crude product, protected alcohol 2.14, was used directly in reactions without further purification.
The aryl substituted allyl alcohol $2.3c$ was obtained by a Wittig reaction between a commercial stabilised phosphonium ylide and phenylacetaldehyde under reflux in THF (Shown with the synthesis of further allylic alcohols in Scheme 2.2). A stabilised aryl phosphonium ylide was used to ensure a trans selective synthesis, based on a literature method. The ester product of this Wittig reaction, $2.21$, was subsequently reduced using 2.5 equiv of DIBAL in a THF solution to give the alcohol $2.3c$. Alcohols $2.3d$ and $2.8$ were synthesised from the corresponding commercial esters, $2.22$ and $2.23$, using the same DIBAL reduction method. The use of 2.5 equiv of DIBAL ensured that the esters were completely reduced to the allylic alcohol, with no other reduction products given, eliminating the need for a subsequent purification step. Alcohols $2.9$ and $2.10$ were synthesised from corresponding
carboxylic acids 2.24 and 2.25 by reduction with 1.1 equiv of LiAlH₄. Literature research indicated that the conditions used for carboxylic acid reduction would give the desired allylic alcohol product exclusively; the products were indeed obtained selectively in good yield.²⁵²,²⁵³ A range of cyclic allylic alcohols and one secondary substituted alcohol, (2.16-2.19) were also synthesised from corresponding unsaturated ketones 2.26-2.29 using NaBH₄ in MeOH with CeCl₃•7 H₂O added to preserve the double bond (a Luche reduction). This method gave excellent conversion.

Scheme 2.2: Synthesis of allylic alcohols.
Z-2-Butenol, \((Z)-2.13\), was synthesised by hydrogenation of 2-butynol over Lindlar catalyst (Pd on BaSO₄ support), suitable for selective hydrogenation of alkynes to cis alkenes. The stereochemistry of all allylic alcohol products in Figure 2.1 was confirmed by comparison of product H¹ NMR spectrum with literature spectra, examination of alkene peak coupling constants, whenever possible, as well as manufacturers’ information regarding stereochemistry of the commercial esters and carboxylic acids that we used.

The secondary substituted alcohols 2.4c-e were synthesised by a Grignard addition. A set of Grignard reagents were synthesised from the corresponding bromides \(\textit{in situ}\) using magnesium turnings under reflux, in THF. Predominantly trans crotonaldehyde was added to the mixture at low temperature, upon the formation of the Grignard reagent (shown by colour change of solution from brown to clear, and consumption of the solid magnesium), to afford trans secondary alcohols. The corresponding chlorides were initially used in a Grignard reaction, but found to be insufficiently reactive with magnesium to form the Grignard reagent (Synthesis of secondary alcohols by this method is shown in Scheme 2.3).

\[
\begin{align*}
\text{R}^- \quad \text{Br} & \quad \text{1. Mg\(_\text{\textit{aq}}\), I}_2\text{ (trace), THF, } \Delta \\
\quad \text{R} & \quad \text{2. Crotonaldehyde, 4°C} \\
\text{2.4c, } R & = \text{i-Pr} \\
\text{2.4d, } R & = \text{c-Hex} \\
\text{2.4e, } R & = \text{Ph}
\end{align*}
\]

\textbf{Scheme 2.3:} Synthesis of secondary substituted alcohol starting materials used in hydroxycarbamate synthesis

Asymmetric Grignard additions can be carried out using chiral catalysts and deactivated Grignard reagents (A representative paper used bis[2-(N,N-dimethylamino)ethyl] ether as a deactivating ligand in such a reaction. Chiral diamine and dialcohol ligands have also been used in reactions with multiple equivalents of the Grignard reagent). Allyltrichlorosilanes are known to react with aldehyde under Lewis base catalysis using a chiral controller to give highly enantioenriched homoallylic alcohols in good yield. These reactions use fewer components, or fewer equivalents of nucleophile, than many asymmetric magnesium Grignard reactions. Enantioenriched alcohols from these reactions could be used to synthesise chiral secondary substituted hydroxycarbamates.
We also hoped to develop a double-bond isomerisation reaction, to convert homoallylic alcohols with a terminal double bond to allylic alcohols with an internal double bond suitable for ene cyclisation. The terminal homoallylic alcohol 2.20 was synthesised in order to obtain a secondary aryl-substituted internal alkene hydroxamic acid via a double bond isomerisation reaction. Compound 2.20 was synthesised using a simple allylation reaction, in which allyl trichlorosilane was reacted with benzaldehyde in dry MeCN, with HMPA used as an activating reagent (DMF was tested as a solvent, but HMPA gave better yields). Some existing terminal double-bond isomerisation techniques use a ruthenium catalyst, which also catalyses nitroso group generation in nitroso ene and HDA reactions. In order to isomerise the terminal double bond, 2.20 was protected with TMS-Cl, using a literature method, giving 2.30. In a model experiment, the TMS protected alcohol 2.30 was reacted in MeOH with RuCl₂(PPh₃)₃ as a catalyst, a simple and easily available substitute for Grubbs catalyst II, a catalyst which had been used in a terminal double bond isomerisation. However, this method was unsuccessful. After testing several palladium reagents, isomerisation to 2.31 was achieved in modest yield using Pd(dba)₂ and P(OEt)₃ (Table 2.1, entry 5). The product, after TMS group removal, was compared with the authentic sample of 2.4e which we had already synthesised, to confirm its structure (Reaction methods shown in Table 2.1). Due to inadequate yields, the terminal double bond isomerisation was abandoned.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Reagents (mol %)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Product, yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RuCl₂(PPh₃)₃ (10)</td>
<td>MeOH</td>
<td>60</td>
<td>No conversion</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)₂ (2), i-BuNBH₃ (4), i-PrCOCl (10)</td>
<td>DMF</td>
<td>50</td>
<td>No conversion</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂ (2), i-BuNBH₃ (4), i-PrCOCl (10)</td>
<td>toluene</td>
<td>100</td>
<td>No conversion</td>
</tr>
<tr>
<td>4</td>
<td>[(Allyl)PdCl₂] (5), Ph₃P (10), AgOTf (5)</td>
<td>CH₂Cl₂</td>
<td>RT</td>
<td>No conversion</td>
</tr>
<tr>
<td>5</td>
<td>Pd(dba)₂(1), P(OEt)₃ (1), i-PrCOCl (1)</td>
<td>toluene</td>
<td>80</td>
<td>2.31, 46% yield</td>
</tr>
</tbody>
</table>

Reactions were carried out on a 0.5 mmol scale. The reagents were added to the substrate together, in 4 mL of solvent, and reacted for up to 24 h. 3 mL of solvent used.
Synthesis of homoallylic alcohols such as **2.15** can be carried out using organometallic allylation of aldehydes. Metal mediated Barbier-type reactions can attractively be carried out at room temperature, in green solvents such as H₂O. Tin allylations of this type, in which an allyltin reagent can be formed from an allyl halide and metal species, show good regio- and stereoselectivity. Selective allylation at the more electronegative γ-carbon, rather the α-carbon, to give a non-linear homallylic product **2.32** has been a historic drawback of metal-catalysed Barbier reactions. However, addition of small quantities of H₂O to these reactions leads to selective α-adduct formation. H¹ NMR monitoring of the reaction mixture during the course of an indium catalysed Barbier reaction, with 6 equiv of H₂O added, shows that a γ-carbon adduct is initially formed, giving a branched product. The γ-adduct is then converted to the linear α-adduct via an 2-oxonia-[3,3]-sigmatropic allyl transfer rearrangement with unreacted aldehyde (Shown in Scheme 2.4.)²⁶⁵

![Scheme 2.4: Synthesis of homoallylic secondary alcohol and full mechanism of rearrangement reaction.](image-url)
The rearrangement shown in Scheme 2.4 is catalysed by residual metal species, and H₂O is directly involved in quenching the adduct 2.35 to give 2.36, and in formation of the key oxonium intermediate 2.34. The use of 12 equiv of H₂O rather than 6 equiv appeared to prevent the formation of intermediate 2.34, so that rearrangement to give 2.15 did not occur.²⁶⁵

The stereoselectivity of γ-adduct formation is largely determined by the transition state associated with the metal catalyst used. Two major classes of transition states have been observed for allylations of aldehydes using allylmetal reagents; the closed, chair-like type 1 transition state and the open type 2 transition state. The type 1 TS gives a syn/anti diastereoisomeric mixture of the γ-adduct, 2.37, in proportion to the E/Z ratio of the allylic reactant, due to the chair-like transition state. The type 2 TS selectively gives (predominantly) the syn diastereoisomer of the γ-adduct, 2.38, due to the antiperiplanar relationship between the aldehyde and double bond (see Scheme 2.5).²⁶⁶

²⁶⁷ A metal catalysed allyl transfer reaction for γ-adducts of homoallylic alcohols such as 2.32 has also been developed by Nokami et al, in which a hemiacetyl is formed between an aldehyde and the homoallylic alcohol, and the allylic functionality is transferred to an aldehyde by a 2-oxonia-[3,3]-sigmatropic rearrangement similar to the rearrangement undergone by 2.34 in Scheme 2.4. The α-adduct of the corresponding homoallylic alcohol (2.15) is given with excellent E-selectivity by this reaction, due to the cyclic chair-like transition state of the rearrangement, in which equatorial conformation of the bulkiest groups is enforced to minimise 1,3-diaxial repulsion. It was decided that this allyl transfer reaction could be used by us to increase the stereochemical purity of an alcohol product from a less selective allylation reaction.²⁵⁹, ²⁶⁸

Scheme 2.5: Mechanism of nucleophilic allylation reaction.²⁶⁶, ²⁶⁸

We chose to synthesise the homoallylic secondary alcohol 2.15 using a tin(II) catalysed Barbier reaction between benzaldehyde and crotyl bromide in H₂O, with 0.25 equiv NaBF₄ added as a Lewis
acid activator.269 This reaction yielded a mixture of syn and anti distereoisomers of the γ-adduct, and E/Z isomers of the α-adduct (approximately a 1:4:16:32 mixture of Z-2.15, E-2.15, (anti)-2.32 and (syn)-2.32). The configuration of all four products was confirmed by comparison of product H1 NMR spectra with pure H1 NMR spectra of all four possible isomers. While the α-adduct was produced via the allylation complex with NaBF4 shown in Scheme 2.4, the γ-adduct was likely to have been produced via the type 1 transition state for metal-mediated aldehyde allylations from Scheme 2.5, since a mixture of diastereoisomers was observed rather than selective formation of the syn isomer (reaction shown in Scheme 2.6).

By reacting the mixture of regioisomers from the allylation reaction with benzaldehyde and catalytic Sn(OTf)2 in the allyl transfer reaction used by Nokami et al, (thought to proceed by the pericyclic allyl transfer rearrangement mechanism undergone by 2.34 in Scheme 2.4) we obtained the α-adduct 2.15 as a 3:1 mixture of E/Z stereoisomers (also shown in Scheme 2.6), which proved to be inseparable by silica chromatography. Configuration of the products was confirmed by comparison of their H1 NMR spectra with the H1 NMR spectra of authentic samples, and the alcohol was used in further reactions as a mixture of stereoisomers. The literature spectra used to identify the stereochemistry of 2.15 and 2.32 are shown in Appendix B.259,268

**Scheme 2.6: Synthesis of 1-Phenylbut-3-enol, 2.15** 259,268,269

The synthesis of dihydrogeraniol (E)-2.6a and dihydronerol (Z)-2.6b involved a series of reactions from both geraniol and nerol. The alcohols (E)-2.5a and (Z)-2.5b were acetylated to give (E)-2.39a and (Z)-2.39b using a standard acetylation method (which used acetic anhydride and 5 equiv of Et3N) in order to protect the hydroxyl group during the hydrochlorination. The C-9 double bond in (E)-2.39a and (Z)-2.39b was converted to a chloride with TiCl4 at -78°C. The products of these reactions, (E)-2.40a and (Z)-2.40b, were then further reduced by a radical reaction with n-Bu3SnH and AIBN, giving dihydroacetates (E)-2.41a and (Z)-2.41b in 87% and 92% from their acetates, respectively (with 20% and 35% respective overall yield), after silica chromatography. The acetate group was then
removed using K₂CO₃ and the alcohols used in the appropriate hydroxycarbamate synthesis (The reaction sequence used is shown in Scheme 2.7). 270, 271, 272, 273, 274

\[
\begin{align*}
(E)-2.5a, (Z)-2.5b & \quad \xrightarrow{1.1 \text{ equiv } \text{Ac}_2\text{O} \quad 2 \text{ equiv Et}_3\text{N}} \quad (E)-2.39a, (Z)-2.39b \quad (91\%) \\
& \quad \xrightarrow{\text{TiCl}_4, -78^\circ\text{C}} \\
& \quad \xrightarrow{\text{K}_2\text{CO}_3 \text{ (deprot.) } \quad \text{MeOH}} \quad (E)-2.6a, (Z)-2.6b \quad (87\% \quad 92\%) \\
& \quad \xrightarrow{\text{Bu}_3\text{SnH, AIBN}} \quad (E)-2.40a, (Z)-2.40b \quad (77\% \quad 71\%) \\
& \quad \xrightarrow{\text{Bu}_3\text{SnH, AIBN}} \quad (E)-2.41a, (Z)-2.41b \quad (55\% \quad 59\%)
\end{align*}
\]

Scheme 2.7: Synthetic route from geraniol/nerol ((E)-2.5/(Z)-2.5) to dihydrogeraniol/dihydronerol ((E)-2.6/(Z)-2.6) 270-274

2.14 was synthesised from a commercial diol, acquired as its E-stereoisomer. All other allylic alcohols used in the project (2.3a-b, 2.4a-b, 2.5a-b, 2.7, 2.11, 2.12) were commercial reagents acquired as predominantly the E stereoisomer, and used as recieved. With the exception of 2.15, all alcohols were used as an overwhelming excess of the Z- or E- stereoisomer.

2.2.3 Hydroxycarbamate synthesis from chloroformates.

Synthesis of hydroxycarbamates from chloroformates by coupling with hydroxylamine hydrochloride (see Scheme 2.8) was initially explored as a method for starting material synthesis. Several unsaturated chloroformates synthesised from alcohols, were used to gauge the suitability of chloroformates as starting materials for hydroxycarbamate synthesis. Alcohols can be converted to chloroformates using phosgene or triphosgene, under basic amine activation. 275, 276 Due to the ready availability of alcohol substrates, as well as the comparative safety of using triphosgene as a reagent,
compared to phosgene, we chose to synthesise chloroformates from alcohols (2.42a-b) using triphosgene. A chloroformate synthesis based on two published procedures was developed, using low temperature and pyridine activation (Planned reaction pathway shown in Scheme 2.8).\(^{275,277}\)

While both model products (2.43a; \(R = -\text{CH}=\text{CH}_2\)) and 2.43b; \(R = -\text{CH}_2\text{Ph}\)) were purified in fair yields, the synthesis lacked robustness, with particular vulnerability to variation in rate and time for dropwise addition of pyridine. This reagent was also harmful and noxious; in addition, the dropwise addition was time consuming. For these reasons, an alternative method for synthesising unsaturated hydroxycarbamates from commercial alcohols was sought.

\[\begin{align*}
\text{R-CH}_2\text{OH} & \xrightarrow{0.4 \text{ equiv triphosgene}} \text{Py, } 0^\circ\text{C} \rightarrow \\
\text{R-O-Cl} & \xrightarrow{\text{NH}_2\text{OH-HCl, Base}} \rightarrow \\
\text{R-O-NHOH} &
\end{align*}\]

**Scheme 2.8:** A planned 2-stage synthesis of hydroxamic acid from alcohol via chloroformate (2.42a/2.42a; \(R = -\text{CH}=\text{CH}_2\)), 2.43b/2.43b; \(R = -\text{CH}_2\text{Ph}\)). The second hydroxycarbamate synthesis reaction was planned, but not carried out.\(^{275,277}\)

Hydroxycarbamate synthesis from chloroformates was also tested using commercial benzoyl chloroformate, 2.44, as a starting material. Initial experiments, based on published methods, made use of \(N,O\)-bis(trimethylsilyl)hydroxylamine, \(\text{Et}_3\text{N}\) and DMAP, which gave a fair yield of hydroxylamine 2.45.\(^{245}\) A more cheap, convenient and robust method was quickly discovered. Coupling of hydroxylamine hydrochloride with benzoyl chloroformate in the presence of sodium carbonate (Reaction shown in Scheme 2.9) gave a good yield of hydroxycarbamate 2.45. However, this method was superceded by the more robust carbonyldiimidazole based synthesis discussed in section 2.2.4.

\[\begin{align*}
\text{O-Cl} & \xrightarrow{1. \text{Na}_2\text{CO}_3, \text{CH}_2\text{Cl}_2} \\
\text{O-NHOH} & \xrightarrow{2. \text{NH}_2\text{OH-HCl}} \rightarrow \\
\text{O-NHOH} & \xrightarrow{80\% \text{ yield}} \\
\end{align*}\]

**Scheme 2.9:** Direct synthesis of hydroxamic acid from chloroformate\(^{245}\)
### 2.2.4 Hydroxycarbamate synthesis from Carbonyldiimidazole adducts.

The synthesis of hydroxycarbamates from alcohols using 1,1-carbonyldiimidazole (CDI) was quickly found to be the most suitable protocol for synthesis of unsaturated hydroxycarbamates, compared to chloroformate hydroxyamination or reduction of nitro groups. The reaction proceeds with a nucleophilic attack by the unsaturated alcohol (2.3a-d, 2.4a-d, (E)-2.5a, (Z)-2.5b, (E)-2.6, (Z)-2.6, 2.7-2.17) on carbonyldiimidazole, with imidazole acting as a stable leaving group. The carbonyl-imidazole adduct produced undergoes a base-catalysed substitution by hydroxylamine (added after 1-2 h on confirmation of complete CDI-adduct formation) to give the hydroxycarbamate (Mechanism shown in Scheme 2.10). Several hydroxycarbamate syntheses with these common features have already been reported in the literature. A series of method development experiments were carried out based on these literature experiments, to develop the most suitable general method for synthesis of hydroxycarbamates from a range of alcohols.

![Scheme 2.10: Mechanism of hydroxycarbamate synthesis using carbonyldiimidazole](image)

In our initial hydroxycarbamate synthesis (Method A), based on a procedure by Donohoe et al, the allylic alcohol was reacted with 1.5 equiv of CDI in pyridine heated to 40°C. 5 equiv of hydroxylamine hydrochloride were added after formation of the CDI adduct within 2 h, to give the product, with pyridine acting as the base for this step. A method based on a procedure by Lebel et al was also tested (Method B). The only changes from the initial method for this procedure were use of room
temperature, and the use of CH$_2$Cl$_2$ as solvent for the CDI adduct formation step. This solvent was evaporated *in vacuo* after complete CDI-adduct formation had been confirmed by TLC, and replaced with pyridine for the hydroxylamine addition step. Both methods gave good yields of hydroxycarbamate from simple primary substituted allylic alcohols. However, it was decided that the noxious and toxic properties of pyridine made it undesirable as a solvent. The pyridine used was also difficult to completely remove from reaction mixtures, often requiring repeated azeotropic evaporation with toluene and flash column chromatography on silica for complete removal.

A third hydroxycarbamate synthesis (Method C) was tested, based on a procedure used by Fleming, which used MeCN as a solvent. 1.5 equiv of CDI were added to the allylic alcohol as before, and then 5 equiv of hydroxylamine hydrochloride added after 2 h with 4 equiv imidazole to act as a base for the hydroxylamine addition.\(^{278}\) This method gave good yields of hydroxycarbamate from simple allylic alcohols, but lower yields from secondary substituted or cyclic alcohols. Furthermore, these reactions were complete in 2-4 h, as opposed to the 24 h required for completion of the reaction in Method A, (based on times given for literature methods,\(^ {247,278}\) and TLC analysis of our own reactions). To increase the yields of secondary substituted hydroxycarbamates given by Method C, the reaction temperature, reaction time for both steps, and excess of carbonyldiimidazole were all increased in separate experiments. No reproducible increase in hydroxylamine yield was observed over 2-3 repetitions of all conditions with both 2.3a and 2.4a.

A private communication from Donohoe’s group described an optimised protocol, based on an experiment they had conducted, in which a reaction between the isolated CDI adduct and the hydroxycarbamate reaction product gave alcohol starting material. This showed that a side reaction between the product and CDI-adduct intermediate during the reaction was reducing the yield of hydroxycarbamate. The communication described an improved procedure based on Method A which used 10 equiv NH$_2$OH, in a concentrated pyridine solution (2 mL/mmol instead of 5 mL/mmol). This was intended to increase the rate of the hydroxylamine substitution step, reducing the time-period in which the CDI-adduct intermediate was present and able to undergo a destructive side reaction with the hydroxycarbamate product. Based on this communication, we developed Method D for hydroxycarbamate synthesis. 1.5 equiv CDI were reacted with the allylic alcohol in 2 mL/mmol MeCN solvent for 2 h, after which 10 equiv NH$_2$OH were added, with 4 equiv imidazole. This method gave good yields for a wide range of hydroxycarbamates within 2 h, including good yields of hydroxycarbamates from secondary substituted and cyclic alcohols, without the use of pyridine solvent. Scheme 2.11 shows the synthesis of hydroxycarbamates (2.46a-d, 2.47a-d, (E)-2.48a, (Z)-
2.48b, (E)-2.49, (Z)-2.49, 2.50-2.59), by this method (2.46c-d, 2.49a-b, and 2.52-2.59 were synthesised 2-8 times, and all other hydroxycarbamates synthesised over 15 times, using Method D).

Scheme 2.11: Optimised hydroxycarbamate synthesis used to produce the hydroxycarbamate starting materials shown, from the corresponding alcohols.
Solid products shown in Scheme 2.11 (see experimental section 4.1) were recrystallised in PE/EtOAc after silica column purification, to afford high-purity crystalline compounds. Analysis of H1 NMR spectra coupling constants, as well as comparison with alcohol starting material NMR spectra and literature spectra showed that the stereochemistry of unsaturated hydroxycarbamates remained unchanged from the alcohol starting materials. Where it is not shown in Scheme 2.11 that molecules were used as the pure Z-isomer, all hydroxycarbamates were used as an overwhelming excess of the the E-isomer (90->97%), except for 2.58, used as a 3:1 E/Z mixture, reflecting the stereochemistry of the alcohol starting material 2.15. All hydroxamic acids described as (Z)- were used as a single isomer. Some cyclic alcohols (2.17-2.19) continued to give poor yields of hydroxycarbamates even when Method D was used, and could not be used in nitroso ene cyclisations. However the yield of 2.59 given by Method D was improved from earlier methods, to 55%. Synthesis of a hydroxycarbamate from 2.4e by Method D was persistently unsuccessful. Since four examples of secondary substituted hydroxycarbamates had already been synthesised, synthesis from 2.4e was abandoned.

2.3 Intramolecular nitroso ene cyclisation

2.3.1 Introduction

Numerous methods have been developed for allylic C-H amination, although the high C-H bond enthalpy often leads to low selectivity, and transition metal catalysts are often required. Nonetheless, the atom and step efficiency of this method is excellent, and additional methods are being intensively researched to complement existing ones. Intramolecular reactions are a particularly appealing method for exercising some control over the regioselectivity of C-H aminations. These cyclisations have been particularly useful as pathways to amino acids, 1,2 or 1,3 diols and diamines.

Benzylic hydrogens are a possible target for selective amination. A useful protocol for benzylic aminations was developed by Powell using sulfonamides (2.60), giving 2.61 (Full reaction shown in Scheme 2.12). A copper catalyst was used, as well as indanedione; this was assumed to act as a ligand for copper. Based on the mechanism of the related Kharash-Sosnovsky reaction, a radical mechanism was proposed for this reaction.
Scheme 2.12: Benzylic amination by a sulfonamide, under copper catalysis\textsuperscript{282}

Cyclisation of the unsaturated \textit{N}-tosylcarbamate 2.65 proceeded by generation of a nitrene species \textit{via} rhodium catalysis, giving 2.66 by a selective intramolecular C-H amination. In allylic systems with more electron rich double bonds, however, a mixture of aziridine (2.63) and oxazolidinone (2.64) was produced from 2.62 as a result of competing allylic C-H insertion and aziridination reactions (The full reaction is shown in Scheme 2.13). The aziridine was synthesised as a single diastereoisomer, while the C-H amination reaction gave a mixture of stereoisomers.\textsuperscript{231}

Scheme 2.13: Aziridine synthesis from tosylated hydroxycarbamate.\textsuperscript{231}

A useful amination, suitable for intramolecular amination of homoallylic \textit{N}-tosyl carbamates 2.67, was developed by White et al, giving oxazolidinone rings such as 2.68. A sulphoxide/Pd(II) catalyst was used to generate a \( \pi \)-allyl-Pd(II) intermediate, prompting cyclisation \textit{via} nucleophilic attack by the \textit{N}-tosyl group, involving reductive elimination of Pd(0). This species was regenerated to the Pd(II)(OAc)\(_2\) catalyst using PhBQ (stereochemistry of the sulphoxide was not given). For the synthesis of 6-membered ring 2.70 from a homohomoallylic carbamate 2.69 it was found necessary to replace
the tosyl protecting group with a more acidic nosyl group. This group combined good nucleophilicity with the high acidity necessary to promote formation of the active amide anion without metal complexation. \( \rho \)-Nitrobenzoic acid and oxygenated DCE solvent (replacing THF) were also used to promote Pd(II) regeneration, increasing the yield obtained for 6-membered rings to >65% (Reaction shown in Scheme 2.14). Both five and six membered rings were synthesised with fair yield and good diastereoselectivity, although tertiary carbamates could not be cyclised and good diastereoselectivity for 5-membered ring cyclisation was dependant on the presence of a bulky substituent on the substrate secondary carbon. The same amination conditions were also used for an intramolecular lactam cyclisation to give a range of dipeptide rings with anti-inflammatory and cytotoxic properties. No olefin isomerisation was seen, although this is a known problem with other base-activated lactamisation methods. The good distereoselectivity of cyclisation (3:1) was thought to be determined by remote chiral centres. The major drawback of this protocol is the requirement for a terminal double bond; homohomoallylic starting materials are particularly difficult to synthesise.\(^{283, 284, 285}\)

\[
\begin{align*}
\text{O} & \text{NHR} \\
\begin{array}{c}
2.67 \\
R = \text{Ts or Ns} \\
R_1 = \text{Alkyl}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \text{NR} \\
\begin{array}{c}
2.68 \\
\text{Pd(OAc)}_2 (10 \text{ molar %}) \\
1.05 \text{ equiv PhBQ} \\
\text{THF, 45°C}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \text{NHNS} \\
\begin{array}{c}
2.69 \\
R_1 = \text{alkyl/aryl}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \text{NNs} \\
\begin{array}{c}
2.70 \\
\text{Pd(OAc)}_2 (10 \text{ molar %}) \\
1.05 \text{ equiv PhBQ} \\
p-\text{nitrobenzoic acid} (10 \text{ molar %}) , \\
\text{DCE (0.66 M), 45°C}
\end{array}
\end{align*}
\]

\textbf{Scheme 2.14:} Summary of ozazolidinone and oxazolidinone syntheses from N-sulphonyl carbamates by Pd catalysed allylic C-H activation.\(^{283, 285}\)

A range of \( N \)-heterocyclic rings, 2.72 and 2.74, can also be synthesised from an unsaturated alkenylsulphonamides such as 2.71 and 2.73 using chloramine-T and iodine. These reactants give an \( N \)-iodated sulphonylamines, which reacts with the starting material in turn, to give an \( N \)-ido-\( N \)-alkenylsulfonamide suitable for cyclisation. The complete stereoselectivity of the reaction indicates
cyclisation via an iodonium ion (Full reactions shown in Scheme 2.15). The same protocol was also used to cyclise an N-(2-propenyl)benzamide, giving an iodinated oxazolidinone in good yield.286

\[
\begin{align*}
\text{Scheme 2.15: Synthesis of iodated } N\text{-heterocyclic rings from alkenylsulphonamides}^{286}
\end{align*}
\]

An amination method based on Sharpless’ protocol for an oxidative ene reaction used the protected sulphur and selenimide diimido reagents, 2.75a-d. The reaction, as with selenium dioxide oxidation, has a two-step mechanism, with a highly selective 2,3-sigmatropic rearrangement, distinct from the single pericyclic step involved in the nitroso ene reaction. Easier deprotection methods have facilitated the use of the diimido amination, which favours CH₂ substitution over CH₃, and gives an exclusively trans product. Distereoselective amination using N,N-bis [N-(p-tolylsulfonyl)benzenesulfonylimidoyl] selenium diimide gave fairly poor selectivity. N-sulfinylcarbamate, with trans-phenylcyclohexenol as a chiral auxiliary, was used in an amination with good yield and 90% distereoselectivity (The alkenes, reagents and products are shown in Table 2.2). 9

287, 288, 289 The regioselectivity of these reactions generally, though not always, favours preservation of the double bond position. This complements the selectivity of intermolecular aryl nitroso ene reactions, which normally give the products of double bond transposition selectively.127
Table 2.2: Allylic aminations using sulphur and selenium diimides\(^9\)

\[
\text{Olefin} \quad \text{Protected amine} \quad 2.75\text{a-d} \quad \text{NHR} \quad \text{KOH, RT} \quad \text{NHR}
\]

<table>
<thead>
<tr>
<th>Olefin</th>
<th>Protected amine</th>
<th>2.75a, % yield</th>
<th>2.75b, % yield</th>
<th>2.75c, % yield</th>
<th>2.75d, % yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>45</td>
<td>No reaction</td>
<td>54</td>
<td>51</td>
</tr>
<tr>
<td>n-alkyl</td>
<td></td>
<td>56/3 (a/b)</td>
<td>53 (a)</td>
<td>51/11 (a/b)</td>
<td>No reaction</td>
</tr>
<tr>
<td>Ph</td>
<td></td>
<td>56</td>
<td>58</td>
<td>40</td>
<td>No reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38/33 (a/b)</td>
<td>No reaction</td>
<td>35/20 (a/b)</td>
<td>No reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84</td>
<td>No reaction</td>
<td>74</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70</td>
<td>51</td>
<td>45</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Another Pd based pyrimidin-4-one synthesis used *cis* and *trans* allyl-2-aminocyclohexanecarboxamides, 2.76, as starting materials, which were cyclised using Pd(OAc)\(_2\) and NaOAc. Use of the additional phase transfer catalyst n-Bu\(_4\)NCl, under an O\(_2\) atmosphere gave the cyclized product in 69% yield, further increased to 84% by use of reflux at 110°C in toluene solvent. For *cis* substrates where R = allyl group, 1:1 diastereoselectivity of cyclisation was observed; when R = Me, 2.77 (R =Me) was given with complete stereoselectivity. When *trans* carboxamides were cyclized using this method, an unusual 8-endo trig cyclisation, giving a mixture of 2.77 and the 8-...
membered trans-cyclohexane-fused 1,5-diazocin-6-one 2.78, took place. Use of acetonitrile solvent maximized the yield of this new product at 72%, with a 13% yield of the pyrimidin-4-one minor product 2.77 (yield relative to starting material). Control experiments confirmed the product ratio as dependent on solvent rather than temperature. Based on the greater affinity of the protected cyclohexyl nitrogen for the palladium catalyst, the six membered ring cyclisation was suggested to proceed via cis-aminopalladation of the isomerized double bond (via upper-face attack to give 2.77 selectively), and a further hydride elimination, to give 2.77 (Full reaction shown in Scheme 2.16).290

\[
\begin{align*}
\text{O} & \quad \text{Pd(OAc)}_2, \text{NaOAc} \\
\text{O}_2, \text{nBu}_4\text{NCl} & \quad 110^\circ\text{C}, \text{solvent} \\
\text{2.76} & \quad \text{2.77, 6%} \quad \text{2.78, 72%} \\
& \quad \text{R = allyl, Sol. = MeCN, 2.77, 6%, 2.78, 72%} \\
& \quad \text{R = Me, Sol = DMSO, 2.77, 52%, 2.78, 21%} \\
& \quad \text{R = Me, Sol = MeCN, 2.77, 12%, 2.78, 61%}
\end{align*}
\]

Scheme 2.16: A trans-carboxamide cyclisation reaction (product ratio depends on solvent and starting configuration)290

Until recently, the most practical method for carrying out acyl nitroso ene reactions, due to the excessive reactivity of the nitroso group, was based on protection of the nitroso group as a Diels-Alder adduct formed from from nitroso compounds such as 2.79 generated \textit{in situ}, followed by thermolysis and the desired nitroso ene reaction, to give an \textit{N}-hydroxyoxazolidinone product 2.80 (Mechanism shown in Scheme 2.17). In particular, this was the only way to acheive an intramolecular acyl nitroso ene reaction. Without Diels-Alder adduct formation, side-reactions prevent the formation of intramolecular nitroso ene products.120, 291
Scheme 2.17: Intramolecular nitroso ene reaction with Diels-Alder adduct protection

The reactions discussed here offer a wide range of complementary synthetic options for C-H amination. However, it remains desirable to develop a reliable, practical and selective C-H amination which does not use expensive and toxic transition metal catalysts.

2.3.2 Development of the nitroso ene cyclisation.

Having developed a protocol for hydroxycarbamate synthesis suitable for producing a variety of allylic hydroxycarbamates in reasonable yield, we aimed to develop a new intramolecular nitroso ene reaction for synthesis of 5- and 6-membered saturated heterocycles. We also planned to explore the reactivity and mechanism of a developed nitroso ene cyclisation in detail. A number of procedures for generating acyl nitroso species from hydroxamic acids have been published. A simplified pericyclic proton transfer involving double bond formation and C-N bond formation, based on the mechanism proposed by Keck, is shown in Scheme 2.18. The initial research question was to find conditions that were compatible with both generation of unstable nitroso species and the nitroso ene cyclisation. Literature data on oxazolidinone rings indicated that the products of our planned reaction in Scheme 2.18 would be stable enough to isolate (see section 2.3.6 for a stability test on our oxazolidinone products).
Hydroxycarbamates 2.46a and 2.46b, derived from (E)-crotyl alcohol and (E)-hex-2-enol respectively, were selected as model hydroxycarbamates substrates with a simple, straightforward structural variation, and used to establish an initial method. Several oxidation systems were initially tested without giving any cyclised product from 2.46a, including Et₄NIO₄ and n-Bu₄NIO₄, (both used as 1.0 equiv, reacted for 16 h in THF solvent at 0°C), oxalyl chloride with DMSO, and CuI (5 molar% of each catalyst was used with 1.2 equiv H₂O₂ as a stoichiometric oxidant, in THF. The reactions were carried out for 16 h). ³⁵, ¹²⁰, ²⁹² None of these reaction gave any identifiable cyclised product. These were based on established methods for acyl nitroso group generation originally used for Diels-Alder reactions, which occur more rapidly than the ene reactions. The low temperature used with the periodate catalysts was intended to discourage side reactions by the highly reactive acyl nitroso groups, but may have prevented the nitroso ene reaction. It was speculated that any nitroso species generated had either been destroyed by harsh oxidative conditions or consumed in an unwanted side reaction before the nitroso ene cyclisation took place, which would leave the alkyl chain of 2.46a unaltered. This was supported by H¹ NMR of reaction products, in which the allyl chain protons were unaltered from the starting material, despite no starting material being recovered after silica chromatography. This suggests the consumption of starting material by a side reaction was faster than the nitroso ene cyclisation, and only involved the hydroxycarbamate functional group. No definite new product could be identified from NMR spectra of reactions, but reduction of hydroxamic acid, or a dimerisation reaction between nitroso groups, were possible side reactions. ¹⁰

The most promising protocols for generating nitroso groups were based on combining a metal catalyst with a stoichiometric peroxide oxidant. It was predicted that oxidation of the hydroxamic acid to an acyl nitroso group would reduce the metal catalyst from Cu(II) to Cu(I), which would be reoxidised to Cu(II) by the stoichiometric oxidant, completing a full catalytic cycle. A key study by Iwasa¹²⁰ into this intermolecular nitroso ene reaction of t-butyl-N-hydroxycarbamate with 5 equiv of electron rich olefins used Ru(III) or Cu(II) catalyst in the presence of hydrogen peroxide (A catalytic
cycle for this reaction using Cu(II) or Fe(III), based on the cycle developed by Kalita et al shown in Scheme 1.21 is shown in Scheme 2.19). We selected this efficient reaction, requiring simple reagents, as a basis for our intramolecular nitroso ene reaction. Despite the inherent 1:1 stoichochemistry of an intramolecular reaction, we hoped that the increased entropic favourability compared to an intermolecular reaction would give an efficient reaction without the requirement of a 5-fold excess of the olefin).

Scheme 2.19: Catalytic cycle for oxidation of hydroxycarbamates to acyl nitroso compounds by Cu(II) or Fe (III)\textsuperscript{150}

Having already tested CuI as a catalyst for the intramolecular nitroso ene reaction without success, we used Cu(OTf)\textsubscript{2} as a catalyst, with 1.2 equiv of 50% aqueous H\textsubscript{2}O\textsubscript{2}, in THF, for the nitroso ene cyclisation of both 2.46a and 2.46b (The results of the following series of reactions are shown in Table 2.3). Cyclisation of 2.46a (R = Me) was successful at RT, giving the unsaturated N-hydroxyoxazolidinone, 2.81a in 70% yield. For 2.46b (R = n-Pr), the same conditions failed to give any cyclised product at room temperature. It was thought that the abstraction of a methylene proton necessary for nitroso ene cyclisation of 2.46b was less favourable than abstraction of a methyl proton during cyclisation of 2.46a, due to increased double-bond substitution, hindering proton abstraction. Replacing the stoichiometric oxidant H\textsubscript{2}O\textsubscript{2} with t-BuOOH for both reactions did not give any change in the results (Table 2.3, entry 2). Reacting 2.46b at the increased temperature of 60°C under Cu(OTf)\textsubscript{2} catalysis also gave no reaction (Table 2.3, entry 3). Literature reports indicated that molybdenum and iron catalysts had both been employed for oxidation of aryl hydroxylamines to the respective nitrosoarenes, with good associated yields.\textsuperscript{151-155} We decided to apply these catalysts to our own system. We found that 2.46b could be cyclised to give 2.81b in 45% yield using MoO\textsubscript{3}PyHMPA (2 mol %) as catalyst, with 6 equiv H\textsubscript{2}O\textsubscript{2}, and at 60°C (Table 2.3, entry 8). However, the best results for the intramolecular nitroso ene cyclisation were obtained using FeCl\textsubscript{3}•6 H\textsubscript{2}O as a catalyst. This cheap and environmentally friendly metal salt was used to cyclise 2.46a at RT, with H\textsubscript{2}O\textsubscript{2} as a stoichiometric oxidant and in MeOH solvent, giving a 60% yield of 2.81a (Table 2.3, entry...
9). 2.46b only gave a 10% yield of 2.81b under the same conditions, but raising the temperature to 65°C increased the yield of 2.81b to 56%, in a 4:1 E/Z mixture, which appeared to be inseperable (Table 2.3, entry 11).

Table 2.3: Comparison of the reactivity of 2.46a and 2.46b in the nitroso ene cyclisation reaction, by conditions used.\textsuperscript{i}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Yield of 2.81a</th>
<th>Yield of 2.81b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)\textsubscript{2} (2 mol %), 1.2 equiv H\textsubscript{2}O\textsubscript{2}, THF, RT</td>
<td>70%</td>
<td>No conversion</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)\textsubscript{2} (2 mol %), 1.2 equiv t-BuOOH, THF, RT</td>
<td>69%</td>
<td>No conversion</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OTf)\textsubscript{2} (2 mol %), 1.2 equiv H\textsubscript{2}O\textsubscript{2}, THF, 60°C</td>
<td>N/A</td>
<td>No conversion</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OTf)\textsubscript{2} (2 mol %), 1.2 equiv H\textsubscript{2}O\textsubscript{2}, BuOH, 100°C</td>
<td>N/A</td>
<td>No conversion</td>
</tr>
<tr>
<td>5</td>
<td>RuCl\textsubscript{3} (5 mol %), 1.2 equiv H\textsubscript{2}O\textsubscript{2}, THF, RT</td>
<td>20%</td>
<td>No conversion</td>
</tr>
<tr>
<td>6</td>
<td>VO(acac)\textsubscript{2} (4 mol %), 1.2 equiv t-BuOOH, THF, RT</td>
<td>45%</td>
<td>No conversion</td>
</tr>
<tr>
<td>7</td>
<td>Mo(dipic)\textsubscript{2} (2 mol%), 6 equiv H\textsubscript{2}O\textsubscript{2}, EtOH, 75°C</td>
<td>N/A</td>
<td>No conversion</td>
</tr>
<tr>
<td>8</td>
<td>MoO\textsubscript{5} (HMPA) (2 mol %), 6 equiv H\textsubscript{2}O\textsubscript{2}, MeOH, 60°C</td>
<td>N/A</td>
<td>45%</td>
</tr>
<tr>
<td>9</td>
<td>Fe(acac)\textsubscript{3} (5 mol %), 6 equiv H\textsubscript{2}O\textsubscript{2}, EtOH, 75°C</td>
<td>N/A</td>
<td>10%</td>
</tr>
<tr>
<td>10</td>
<td>FeCl\textsubscript{3} (4 mol %), 1.2 equiv H\textsubscript{2}O\textsubscript{2}, i-PrOH, RT</td>
<td>60%</td>
<td>10%</td>
</tr>
<tr>
<td>11</td>
<td>FeCl\textsubscript{3} (4 mol %), 1.2 equiv H\textsubscript{2}O\textsubscript{2}, MeOH, 65°C</td>
<td>N/A</td>
<td>56% (E/Z 4:1)</td>
</tr>
<tr>
<td>12</td>
<td>FeCl\textsubscript{3} (4 mol %), 6 equiv H\textsubscript{2}O\textsubscript{2}, i-PrOH, 100°C</td>
<td>N/A</td>
<td>64% (E/Z 6:1)</td>
</tr>
</tbody>
</table>

\textsuperscript{i}Reactions were carried out on a 0.5 mmol scale. The metal catalyst was mixed with the hydroxycarbamate in 4 mL of solvent, before addition of H\textsubscript{2}O\textsubscript{2}. The mixture was reacted for 18 h.
The product 2.81b given by our cyclisations was assumed to be a mixture of stereoisomers due to the presence of two similar sets of peaks on H\textsuperscript{1} NMR spectra. The stereoselectivity of the cyclisation was deduced from the coupling constants for the alkene peaks of the major isomer, and the relative areas of both sets of NMR peaks. Increasing the temperature further to 100°C (with i-PrOH as solvent, and with a sealed reaction vial used to prevent solvent evaporation) improved the E/Z ratio of 2.81b from a 4:1 mixture to a 6:1 mixture, and the yield to 64% (Table 2.3, entry 12). Increasing the catalyst loading of FeCl\textsubscript{3} to 10 mol % under the same conditions did not increase the yield of the reaction above 64%. The increase in stereoselectivity with reaction temperature is most likely to be explained by the E stereoisomer of 2.81b having higher thermodynamic stability than the Z isomer, increasing the proportion of E isomer in the product given by higher temperature reactions.

The slight drop in yield of 2.81a between Cu(OTf)\textsubscript{2} and FeCl\textsubscript{3} catalysts was probably due to formation of a soluble complex between the iron catalyst and a small amount of product, which was retained in the aqueous phase during workup. 1M HCl\textsubscript{(aq)} was adopted as an aqueous phase to work up the reaction, in order to discourage iron complexation by protonation of the oxazolidinone product. This measure improved the consistency of the yields obtained, allowing the yields given in Table 2.3 to be established as typical for the reactions described. The intramolecular nitroso ene cyclisation was shown to occur in various solvents and with several different catalysts (low yields of, 2.81a, but no yield of 2.81b, were obtained with the metal/oxidant systems RuCl\textsubscript{3}/H\textsubscript{2}O\textsubscript{2} and VO(acac)\textsubscript{2}/t-BuOOH, entries 5 and 6 in Table 2.3). All cyclisation methods were tested 2-5 times; entries 1 (2.81a), 10 (2.81a) and 12 (2.81b) were repeated 10-15 times. The oxazolidinones synthesized did not give a purple stain in the presence of aqueous iron(III) chloride (giving us a useful test for conversion of hydroxycarbamate to oxazolidinone), or a blue stain in the presence of iron chloride in ethanol.

In the literature nitroso ene reactions that used arylhydroxylamines as precursors to the nitroso species, and Fe(III) as a catalyst, the initially formed N-hydroxy-derivatives were normally reduced \textit{in situ} to the respective amines. HRMS of 2.81a, 2.81b and further intramolecular nitroso ene products showed a mass consistent with an N-hydroxy substituted oxazolidinone product in every case. Although H\textsubscript{2}O\textsubscript{2} is often used as a reagent for double bond expoxidation, no epoxides, or epoxide derived products such as diols, were observed in any H\textsuperscript{1} NMR spectra of a cyclised product or unsuccessful reaction. At this point, we had established a practical protocol for nitroso ene cyclisation employing FeCl\textsubscript{3} as a catalyst, H\textsubscript{2}O\textsubscript{2} as a stoichometric oxidant and i-PrOH as a solvent, with the option of increased temperature to encourage the reaction of more substituted
hydroxycarbamates. With this set of conditions in hand, the reaction scope was next investigated over a range of substrates with a different substitution pattern.

2.3.3 Reactivity study of the nitroso ene cyclisation.

During the work described in the previous section, we observed that increased substitution on the olefin group of an allylic hydroxycarbamate reduced substrate reactivity, necessitating harsher conditions for the reaction to achieve good yield. The apparent difference in reactivity between 2.46a and 2.46b prompted us to investigate the effect of steric factors on the favourability of the intramolecular nitroso ene reaction. In the series of substrates 2.46a-d, selected for increasing substitution of the δ-carbon, without other structural variations, the reactivity drops dramatically in the order Me>n-Pr>Bn>i-Pr (Reactivity order shown in Scheme 2.20). As was related in section 2.2.3, cyclisation of 2.46b (cyclised here with 4:1 E:Z selectivity) requires harsher conditions than for 2.46a. Hydroxycarbamate 2.46c gave no cyclised product under the same cyclisation conditions as 2.46b; under the conditions of 15 mol % FeCl$_3$ catalyst with 6 equiv of H$_2$O$_2$ at 100°C only a 10% yield of cyclised product 2.81c was obtained (the amount of product is too low for stereoselectivity to be accurately stated, but only a single stereoisomer was observed). Oxazolidinone 2.81d, under the same cyclisation conditions of 15 mol % catalyst loading, was not formed from 2.46d at all, reflecting the increased steric congestion around the allylic C-H bond. Both reactions were carried out in sealed vials. Reacting 2.46d in the aprotic solvent dioxane, at 100°C, failed to give any yield of product, as did a reaction with microwave heating at 120°C. These results clearly show that steric factors predominately determine the reactivity for intramolecular nitroso ene reactions, above even formation of thermodynamically stable fragments such as styrene (2.81c) or trisubstituted alkene (2.81d). We assumed that the slow cyclisation rate of the nitroso species derived from 2.46d allowed side reactions, including hydrolysis, to consume the nitroso intermediate before completion of the cyclisation reaction. In an attempt to prevent such side reactions in a new experiment, 2.46d was reacted under strictly anhydrous conditions, with stoichiometric anhydrous FeCl$_3$ used in place of FeCl$_3$ and H$_2$O$_2$ (use of a stoichiometric metal catalyst made an additional peroixide oxidant unnecessary). This reaction was left at 100°C for 72 h, however, no cyclisation to give 2.81d was observed. Abstraction of the methylene proton for these substrates appears to be highly unfavourable due to the steric congestion. This reactivity sequence guided subsequent selection of substrates for nitroso ene cyclisation, as shown in section 2.3.5. Cyclisation of 2.46c and 2.46d by the
method shown in Scheme 2.20 was repeated 4-8 times. For both substrates, test cyclisations at room temperature gave no cyclised product.

Scheme 2.20: Steric effects in the intramolecular nitroso ene cyclisation

Nitroso ene substrates with electron rich double bonds were expected to be highly reactive. The cyclisation of 2.51 gave excellent yields of 2.80 at RT, with both FeCl₃/ H₂O₂ (60% yield) and Cu(OTf)₂/ H₂O₂ (83% yield) catalytic systems, with the same methods as for cyclisation of 2.46a. (Conditions and results shown in Table 2.4). The high reactivity of this substrate was useful in later stages of the project for exploring an enantioselective nitroso ene reaction, as 2.51 could be cyclised at low temperature without unnecessary sacrifice of yield (shown in Table 2.5, entry 3 and 5).
Table 2.4: Reactivity of methyl substituted unsaturated hydroxcarbamates. Cyclisation of 2.51 and (Z)-2.52

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Catalyst (mol %)</th>
<th>Oxidant (equiv)</th>
<th>Solvent</th>
<th>Product, yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.51</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>H$_2$O$_2$ (1.2)</td>
<td>THF</td>
<td>2.80, 60%</td>
</tr>
<tr>
<td>2</td>
<td>2.51</td>
<td>FeCl$_3$ (4)</td>
<td>H$_2$O$_2$ (1.2)</td>
<td>CH$_2$Cl$_2$</td>
<td>2.80, 83%</td>
</tr>
<tr>
<td>3&quot;</td>
<td>2.51</td>
<td>-</td>
<td>PhiO (0.75)</td>
<td>CH$_2$Cl$_2$</td>
<td>2.80, 30%</td>
</tr>
<tr>
<td>4</td>
<td>2.51</td>
<td>-</td>
<td>Phi(OAc)$_2$ (0.75)</td>
<td>CH$_2$Cl$_2$</td>
<td>2.80, 59%</td>
</tr>
<tr>
<td>5iii</td>
<td>2.51</td>
<td>-</td>
<td>n-BuNiO$_2$ (1)</td>
<td>CH$_2$Cl$_2$</td>
<td>2.80, 51%</td>
</tr>
<tr>
<td>6</td>
<td>2.51</td>
<td>Cu(I)Cl (5)</td>
<td>O$_2$ atmos</td>
<td>THF</td>
<td>2.80, 53%</td>
</tr>
<tr>
<td>7</td>
<td>(Z)-2.52</td>
<td>FeCl$_3$ (15)</td>
<td>H$_2$O$_2$ (1.2)</td>
<td>i-PrOH</td>
<td>No cyclised product</td>
</tr>
<tr>
<td>8iv</td>
<td>(Z)-2.52</td>
<td>FeCl$_3$ (15)</td>
<td>H$_2$O$_2$ (6)</td>
<td>i-PrOH</td>
<td>No cyclised product</td>
</tr>
</tbody>
</table>

1Reactions were carried out on a 0.5 mmol scale. The metal catalyst (where applicable) was mixed with the hydroxycarbamate in 4 mL of solvent, before addition of oxidant. The mixture was reacted for 18 h. II Reacted at 0°C. oxidant added dropwise in 4 mL reaction solvent III Reacted at -20°C. oxidant added dropwise in 4 mL reaction solvent IV Reacted at 100°C

Other stoichiometric oxidants such as Phi(OAc)$_2$ and PhiO were found to be able to cyclise 2.51 in the absence of metal catalysts, though in moderate yields. CuCl catalyst in an O$_2$ atmosphere (the catalytic system used by De Alaniz$^{161}$ for intramolecular nitroso ene reactions) was also shown to give a fair yield of cyclised product. Cyclisation of a Z-crotyl hydroxycarbamate, (Z)-2.52, attempted under the same conditions as the cyclisation of 2.46a, yielded no cyclised product. Higher reaction temperature and greater H$_2$O$_2$ excess failed to bring any improvement (conditions shown in Table 2.5, entries 7 and 8). This can be explained by the configuration of the terminal methyl protons, which places them too far from the nitroso group for abstraction in the nitroso ene reaction (also see Scheme 2.28). Scheme 2.21 illustrates a mechanistic explanation of nitroso ene reactivity reduction from 2.46c to 2.46d. The allylic hydrogen with is abstracted in the reaction of 2.46c with some
hinderence from the benzene group (the ethyl group of 2.46b would give less hinderence). The on 2.46b is directly obstructed from reacting with the methine allylic hydrogen by the iso-propyl group arms, rendering the cyclisation reaction too energetically unfavourable to take place.

![Scheme 2.21](image)

**Scheme 2.21**: The theorised mechanism of nitroso ene reactivity reduction from 2.46c to 2.46d.

### 2.3.4 Diastereoselectivity of the nitroso ene cyclisation.

In order to assess the diastereoselectivity of the nitroso ene reaction, a series of secondary allylic hydroxycarbamates 2.47a-d with side chains of varying steric bulk were investigated. It was anticipated that larger secondary substituants on allylic hydroxycarbamates would progressively increase the diastereoselectivity of the nitroso ene cyclisation. By using substrates with methyl substituted double bond we ensured reactivity similar to 2.46a. By employing the reaction conditions developed for the cyclisation of 2.46a (FeCl₃•6H₂O (4 mol %) and H₂O₂ (1.2 equiv) in i-PrOH at RT), compounds 2.82a-d were obtained in good yields, but with a 2:1 syn/anti selectivity for all products (yields and diastereoselectivity shown in Scheme 2.22). This poor selectivity was quite surprising. Cyclisation of 2.47a-d using this method were repeated 4-12 times for all 4 substrates. Two sets of alkene region H¹ NMR signals, which were assigned to the major and minor diastereoisomers, could be seen clearly and consistently in the spectra of crude samples for 2.82a-b and 2.82d (Based on these results it was decided that the three alkene NMR peaks seen for 2.82c were caused by overlapping NMR signals from two diastereoisomers). The relative intensity of these NMR peaks in
NMR spectra for the crude products gave the diastereoselectivity of the cyclisations. The syn/anti diastereoisomers for 2.82b were isolated using silica chromatography, and compared with NMRs of the crude mixture to confirm the presence of two stereoisomers. The assignment of the major and minor diastereoisomers as syn and anti respectively was based on supporting evidence given by NOESY and TOCSY NMR analysis of a stereoisomeric mixture of 2.82c. The similarity of all product structures and NMR spectra, with similar relations between NMR signals for syn and anti diastereoisomers allowed 2.82c to be used as a representative compound for TOCSY analysis, indicating the stereochemistry of the major isomer produced in all cyclisations.

It must be noted that the relative configuration of the cyclisation products could also be determined by comparison of reaction product H\textsuperscript{1} NMR spectra with authentic samples of the pure oxazolidinone stereoisomers; however a suitable method to synthesise these isomers could not be found. X-ray crystallography could also be used to determine the stereochemistry of reaction products, but requires highly pure crystals, while oxazolidinones 2.82a-d are oils and waxes. With additional research time and resources, these products could be converted to solid derivatives for crystallisation and X-ray analysis. Reduction of the hydroxyl functionality followed by acetylation of the oxazolidinone\textsuperscript{120,293} is a derivation that could be used to achieve this (for NMR spectra showing the purified minor anti isomer for 2.82b, and all NOESY and TOCSY spectra, see the Experimental part, section 4, Appendix B). It is not clear why the syn isomer is formed predominantly; a detailed computational analysis of the transition state would need to be carried out to give an answer. However, the TS B (Scheme 2.22), leading to the syn isomer, appears to be less sterically encumbered due to the perpendicular arrangement of the R group and the double bond. For TS A, leading to the anti isomer, the R group and double bond are in the same plane, possibility leading to a slight interaction and reducing favourability. This small steric effect may cause the correspondingly slight preference for syn isomer formation seen in our nitroso ene cyclisations.
Scheme 2.22: Yields and distereomeric ratio for cyclisation of secondary hydroxycarbamates. The relative configuration of the major syn isomer of the reaction products is shown. All compounds were synthesised as a racemic mixture.

A large range of conditions were tested to improve the diastereoselectivity of the nitroso ene reaction; the catalyst, oxidant, solvent and temperature were all varied (Reaction conditions and results are given in Table 2.5). This set of nitroso ene reactions, following on from the initial method development in section 2.3.2, showed the compatibility of the nitroso ene reaction with a wide range of organic solvents (alcohols, THF, benzene, CH₂Cl₂). All reactions in Table 2.6 were conducted 1-2 times, except entry 1, which was conducted 5 times. Use of phenanthroline (phen) as a ligand did not effect diastereoselectivity (entries 3 and 4, Table 2.5). Lowering reaction temperature met with partial success. While there was no change in syn/anti ratio at -20°C (cooled using a cold probe) over 72 h for the cyclisation of 2.47a, in the case of 2.47d FeCl₃/H₂O₂ the ratio improved to 5:1 (entry 23, Table 2.6). Unfortunately, this protocol could not be reliably extended to those reactants with smaller substituents on the secondary carbon. In a move away from metal catalysts, Phl(OAc)₂ was used as a stoichiometric oxidant, following literature precedents. This reagent, in the reaction of 2.47d at -20°C produced 2.82d in good yield and with a 5:1 syn/anti ratio (entry 24, Table 2.5).
### Table 2.5: Diastereoselectivity in the intramolecular nitroso ene cyclisation

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Solvent</th>
<th>Catalyst (mol %) /ligand</th>
<th>Oxidant (equiv)</th>
<th>Temp (°C)</th>
<th>Product, conversion, d.r. (syn:anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.47a, Me</td>
<td>THF</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>H$_2$O$_2$ (1.2)</td>
<td>RT</td>
<td>2.82a, 80%, 2:1</td>
</tr>
<tr>
<td>2</td>
<td>2.47a, Me</td>
<td>i-Pr-OH</td>
<td>FeCl$_3$ (4)</td>
<td>H$_2$O$_2$ (1.2)</td>
<td>RT</td>
<td>2.82a, 80% 2:1</td>
</tr>
<tr>
<td>3</td>
<td>2.47a, Me</td>
<td>THF</td>
<td>Cu(OTf)$_2$ (2)/ phen (1.2 eq)</td>
<td>H$_2$O$_2$ (1.2)</td>
<td>RT</td>
<td>2.82a, 85% 2:1</td>
</tr>
<tr>
<td>4</td>
<td>2.47a, Me</td>
<td>i-Pr-OH</td>
<td>FeCl$_3$ (4)/ phen (1.2 eq)</td>
<td>H$_2$O$_2$ (1.2)</td>
<td>RT</td>
<td>2.82a, 80% 2:1</td>
</tr>
<tr>
<td>5</td>
<td>2.47a, Me</td>
<td>THF</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>H$_2$O$_2$ (1.2)</td>
<td>4°C</td>
<td>2.82a, 20% 2:1</td>
</tr>
<tr>
<td>6</td>
<td>2.47a, Me</td>
<td>THF</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>Urea.H$_2$O$_2$ (1.2)</td>
<td>RT</td>
<td>2.82a, 20% 2:1</td>
</tr>
<tr>
<td>7</td>
<td>2.47a, Me</td>
<td>i-Pr-OH</td>
<td>FeCl$_3$ (4)</td>
<td>Urea.H$_2$O$_2$ (1.2)</td>
<td>RT</td>
<td>2.82a, 30% 2:1</td>
</tr>
<tr>
<td>8</td>
<td>2.47a, Me</td>
<td>Chloroform</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>H$_2$O$_2$ (1.2)</td>
<td>RT</td>
<td>2.82a, 40% 2:1</td>
</tr>
<tr>
<td>9</td>
<td>2.47a, Me</td>
<td>C$_6$H$_6$</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>H$_2$O$_2$ (1.2)</td>
<td>RT</td>
<td>2.82a, 60% 2:1</td>
</tr>
<tr>
<td>10</td>
<td>2.47a, Me</td>
<td>CH$_2$Cl$_2$</td>
<td>FeCl$_3$ (4)</td>
<td>H$_2$O$_2$ (1.2)</td>
<td>-20°C</td>
<td>2.82a, 55% 2:1</td>
</tr>
<tr>
<td>11</td>
<td>2.47a, Me</td>
<td>CH$_2$Cl$_2$</td>
<td>-</td>
<td>Phl(OAc)$_2$ (0.75)</td>
<td>-20°C</td>
<td>2.82a, 65% 2:1</td>
</tr>
<tr>
<td>12$^1$</td>
<td>2.47a, Me</td>
<td>CH$_2$Cl$_2$</td>
<td>-</td>
<td>PhlO (0.75)</td>
<td>-20°C</td>
<td>2.82a, 25% 2:1</td>
</tr>
<tr>
<td>13</td>
<td>2.47a, Me</td>
<td>THF</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>H$_2$O$_2$ (1.2)</td>
<td>-20°C</td>
<td>2.82a, 35% 2:1</td>
</tr>
<tr>
<td>14</td>
<td>2.47a, Me</td>
<td>THF</td>
<td>FeCl$_3$ (4)</td>
<td>H$_2$O$_2$ (1.2)</td>
<td>-20°C</td>
<td>2.82a, 50% 2:1</td>
</tr>
<tr>
<td>15</td>
<td>2.47a, Me</td>
<td>i-Pr-OH</td>
<td>FeCl$_3$ (4)</td>
<td>H$_2$O$_2$ (1.2)</td>
<td>80°C</td>
<td>2.82a, 60% 2:1</td>
</tr>
<tr>
<td>16</td>
<td>2.47b, n-Pr</td>
<td>CH$_2$Cl$_2$</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>H$_2$O$_2$ (1.2)</td>
<td>-20°C</td>
<td>2.82b, 35%</td>
</tr>
</tbody>
</table>
17. **2.47b, n-Pr**  
   i-PrOH  
   FeCl₃ (4)  
   H₂O₂ (1.2)  
   -20°C  
   2:1  
   **2.82b**, 37%  
   2:1

18. **2.47b, n-Pr**  
   CH₂Cl₂  
   -  
   Phl(OAc)₂ (0.75)  
   -20°C  
   **2.82b**, 60%  
   2:1

19. **2.47c, i-Pr**  
   CH₂Cl₂  
   FeCl₃ (4)  
   H₂O₂ (1.2)  
   -20°C  
   **2.82c**, 55%  
   2:1

20. **2.47c, i-Pr**  
   CH₂Cl₂  
   Cu(OTf)₂ (2)  
   H₂O₂ (1.2)  
   -20°C  
   **2.82c**, 55%  
   2:1

21. **2.47c, i-Pr**  
   CH₂Cl₂  
   -  
   Phl(OAc)₂ (0.75)  
   -20°C  
   **2.82c**, 65%  
   2:1

22. **2.47d, c-Hex**  
   CH₂Cl₂  
   Cu(OTf)₂ (2)  
   H₂O₂ (1.2)  
   RT  
   **2.82d**, 62%  
   2:1

23. **2.47d, c-Hex**  
   CH₂Cl₂  
   FeCl₃ (4)  
   H₂O₂ (1.2)  
   -20°C  
   **2.82d**, 51%  
   5:1

24. **2.47d, c-Hex**  
   CH₂Cl₂  
   -  
   Phl(OAc)₂ (0.75)  
   -20°C  
   **2.82d**, 55%  
   5:1

*Reactions were carried out on a 0.5 mmol scale. The metal catalyst was added to the hydroxycarbamate in 4 mL of solvent, before addition of H₂O₂. The mixture was reacted for 18 h. **PhIO added dropwise in 4 mL of reaction solvent.***Yield for these reactions is given, rather than the conversion.

### 2.3.5 Full scope of nitroso ene cyclisation.

To show the potential of the intramolecular nitroso ene reaction to give varied products, several highly substituted hydroxycarbamates were synthesised and cyclised. Substrates with bulky alkene substitution were avoided, based on the reactivity study described in section 2.3.2. The FeCl₃ catalysed cyclisation of the cyclic-substituted hydroxycarbamates **2.53** and **2.54** were attempted at 100°C, in sealed vials and with 6 equiv H₂O₂. Both these substrates produced good yields of the cyclohexenyl substituted and spiro substituted N-hydroxyxazolidinone **2.84** and **2.83**, respectively. To show that the intramolecular nitroso ene reaction could give a 6-membered ring, the cyclisation of homoallylic hydroxycarbamate **2.55** to give **2.85** was attempted using both Cu(OTf)₂, which gave no conversion, and FeCl₃, which gave a good yield of **2.85** when reacted at RT, over 72 h. To decrease the reaction time, the cyclisation was carried out at 100°C in a sealed vial, and 3 equiv of H₂O₂ were used, giving a good yield of **2.85** overnight. Purification of **2.85** by silica chromatography proved difficult. To alleviate the problem, the crude product was acetylated to give **2.86** (Shown with other intramolecular nitroso ene reactions in Scheme 2.23), which was purified easily. (A similar derivatisation was used by Bottke et al. for isolation of unstable nitroso ene products).
The secondary hydroxycarbamate with a tri-substituted double bond 2.56 was also cyclised under the same conditions as 2.53 and 2.54, affording the quaternary centre bearing, highly substituted 2.87, in excellent yield (90%) and effectively as a single syn diastereoisomer (d.r. > 25:1). A single set of alkene signals for a trans double bond was seen on the H1 NMR spectra (the configuration was shown by peak coupling constants). The relative configuration for 2.87 was determined by NOESY NMR analysis. Scheme 2.24 illustrates the cross coupling between the ring proton (O-CH-C) and the ring methyl group (C-CH3) shown by the NOESY spectrum, indicating that these protons are close together in space; that is, arranged syn to each other. There is also no cross coupling visible on the NOESY spectrum between the ring proton and the vinyl proton (C-CH=CH-CH3); irradiation of the vinyl proton also showing no cross-coupling with the ring proton, confirming that their arrangement is anti. The relevant NOESY spectra are shown in Appendix B.
Scheme 2.24: Illustration of cross coupling interactions shown by NOESY NMR of 2.87, indicating the syn configuration of the primary stereoisomer

This synthesis, along with the cyclisations of 2.53 and 2.54, also demonstrate that, in contrast to the high sensitivity of the cyclisation to the surroundings of the allylic C-H bond, steric factors do not play any significant role in the formation of the C-N bond. Cyclisation of 2.54 was attempted at RT, with 4 mol % FeCl$_3$ and 6 equiv H$_2$O$_2$, giving the product 2.83 in a 62% yield over 72h; however cyclisation of 2.56 and 2.53 at RT gave <20% conversion over a similar time period. All molecules in Scheme 2.23 were synthesised 5-10 times using the conditions stated in the scheme. The room temperature syntheses of 2.83 and 2.85 were repeated 1-2 times. Cyclisation of the molecules in Scheme 2.23 with catalyst loading increased to 15% did not increase the yield for these reactions above the average yields reported in Scheme 2.23.

The cyclisation of geraniol and nerol derived hydroxycarbamates (E)-2.48a and (Z)-2.48b was attempted in order to determine the regioselectivity of the intramolecular nitroso ene reaction, and the effect of substrate configuration on reactivity. The citronellol-derived hydroxycarbamate 2.50 was also tested to explore the potential formation of a nine-membered ring. Taking into account that only trans alkenes have displayed reactivity in the intramolecular nitroso ene cyclisation, the stereochemistry of (Z)-2.48b suggested that abstraction of the 3-methyl proton would be favourable, due to low steric hindrance and favourable conformation, allowing the hydroxycarbamate cyclisation to proceed favourably at RT. Conversely, the conformation of (E)-2.48a would place the nitroso group away from 3-Me, necessitating less favourable proton abstraction from C-4, and reducing reactivity or preventing the reaction. Reactions at RT, progressively higher temperature, increasing levels of FeCl$_3$/H$_2$O$_2$ and with a number of additives were tested for all three substrates (Reaction conditions and results are shown in Scheme 2.23). No clear cyclised product was identified by NMR analysis of any reaction after 72 h. For (E)-2.48a and (Z)-2.48b a mixture of decomposition and side products was given, none of which could be identified as any of the predicted cyclised products.
For cyclisation of 2.50, a major product was observed by H NMR, which was consistent with the proposed structure 2.93, but could not be purified by column chromatography or confirmed as the cyclised product 2.93. Since it was thought that the presence of two double bonds interfered with the cyclisation of (E)-2.48a and (Z)-2.48b, the terminal double bond for both alcohols was reduced (see section 2.2.4) to give two new hydroxycarbamates, (E)-2.49a and (Z)-2.49b. The cyclisation of both substrates was attempted using conditions D once each (Reactions shown in Scheme 2.25), however only intractable mixtures were produced. Cyclisation of 2.48a-b and 2.50 were all carried out 5-8 times under conditions B, as shown in Scheme 2.25; (E)-2.48a and (Z)-2.48b were each reacted once under conditions C and B respectively. None of these reactions gave any identifiable cyclised product.

Scheme 2.25: Attempted cyclisation of geranyl, neryl and citronellol hydroxycarbamates
Following the publication on the acyl nitroso ene cyclisation by Read De Alaniz, in which O\textsubscript{2} was used as a stoichiometric oxidant, we decided to test their conditions with compounds (E)-2.49a, (Z)-2.249b and 2.50, some of the notable substrates which could not be efficiently cyclised by the metal/H\textsubscript{2}O\textsubscript{2} system. We employed both Cu(I)Cl and FeCl\textsubscript{3} in the presence of pure O\textsubscript{2} as an oxidant (conditions E and F in Scheme 2.25). In the case of (E)-2.49a, a low yield of product was given under CuCl/O\textsubscript{2} catalysis that showed some resemblance to the intended cyclised product 2.91, with clear alkene, CH\textsubscript{2}-O, and CH-N\textsuperscript{1}H NMR signals, shifted when compared to the starting material spectra, but an untidy alkane region. An unidentified product with two sets of alkene proton \textsuperscript{1}H NMR signals was also produced by FeCl\textsubscript{3}/O\textsubscript{2} cyclisation of (Z)-2.49b. However, no definite cyclised product was isolated from any of these reactions. These cyclisations were each carried out 1-2 times. In general, the O\textsubscript{2} oxidation system was no more effective than the metal/peroxide catalytic system.

Other unsaturated hydroxycarbamates that failed to give cyclisation products were compounds 2.57, 2.58 and 2.59 (shown in Scheme 2.26). The parent alcohol of 2.57 was obtained from but-2-ene diol using a literature hydroxyl group protection with 1 equiv of TBDPSCI in THF solvent, with N,N-diisopropylethylamine as a base, giving the monosilated alcohol as an exclusive product. It was hoped that the cyclisation of 2.57 to yield 2.94 would give an aldehyde-substituted hydroxyoxazolidinone ring, after hydrolysis of the resulting enol ether 2.94, as the enolate given by deprotonation of the hydroxyl group would tautomerise to the more stable keto aldehyde tautomer. However, no cyclised product was given under the conditions of 100°C temperature and 6 equiv of H\textsubscript{2}O\textsubscript{2}. Cyclisation of the secondary homoallylic hydroxycarbamate 2.58, to give the disubstituted hydroxyoxazinanone 2.95, was also attempted, but failed under the same conditions as those used for the synthesis of the 6-membered ring 2.85. The non-reaction of 2.58 discouraged us from attempting to synthesise a range of variably substituted 6-membered rings. Cyclisation of 2.59 failed to give 2.96, even at the higher temperature of 100°C, presumably as a result of the fixed cis geometry of the double bond, supported by the unreactivity of (Z)-2.52 (see section 2.3.3). All cyclisations in Scheme 2.26 were carried out 2-5 times, not including control cyclisations at RT (other conditions as given in Scheme 2.26) for each hydroxycarbamate.
Scheme 2.26: Structures of hydroxycarbamates that failed to cyclise

Despite some setbacks the overall results show that the FeCl₃/H₂O₂ catalytic system, with i-PrOH as solvent, is adaptable to the cyclisation of a variety of substrates. While substitution of the allylic C–H bond appears to have a large effect on reactivity, the ready cyclisation of highly substituted hydroxycarbamates such as 2.53 and 2.54 indicates that the C–N bond formation is insensitive to steric factors. Taken together with the ready cyclisation of the secondary hydroxycarbamates 2.47a-d, these results indicate that the intramolecular nitroso ene reaction represents a practical tool for allylic C–H amination (see Schemes 2.20 and 2.21).

2.3.6 Probe into the mechanism of the nitroso ene cyclisation.

The poor reactivity of several unsaturated hydroxycarbamate substrates was thought to arise from lower reaction rates due to unfavourable steric congestion around the olefin C–H bond. A sufficiently slow nitroso ene reaction would be unable to compete with more rapid side reactions of the starting material. Bottke et al.,¹³⁰ investigating intermolecular nitroso ene reactions, noted that electron-withdrawing substituents on olefin substrates reduced reaction rate, resulting in decomposition of the acylnitroso reactants to the parent acid derivatives, although no clear side product was identified from NMR spectra of crude reaction mixtures from our own successful or unsuccessful attempts at cyclisations of 2.46b, 2.46c and 2.46d (see Scheme 2.19).
The increase in yield for 2.46b under increased temperature may be viewed as a result of increased ene reaction rate. As an alternative reason, it was considered that slow formation of the reactive acyl nitroso species from the hydroxycarbamates could be the cause of the failed reactions. To test this latter hypothesis, nitroso ene cyclisation of 2.46a and 2.46d (the most and least reactive primary substituted hydroxycarbamates of the tested range) was attempted in the presence of 2 equiv of 2,3-dimethylbutene. Both were reacted at RT, using Cu(OTf)₂/H₂O₂ and FeCl₃/H₂O₂ catalytic systems. All four reactions gave a nitroso HDA adduct (2.97a or 2.97b) cleanly, with excellent yield and conversion; no ene cyclised product was observed. This result suggested that generation of the transient nitroso species does occur for all substrates within the range tested, and steric hindrance around the alkene primarily determines substrate reactivity. For these reactions, the experiments in entry 3 and 5 in Table 2.6 were carried out 5-6 times; those in entry 4 and 6 were carried out 1-2 times. A cyclisation of 2.46a was also tested using 25 mol % FeCl₃ and no peroxide, to confirm that peroxide was necessary for complete cyclisation. A 30% yield of cyclised product for this reaction confirmed the role of the peroxide in reoxidising the metal catalyst, necessary for full oxidisation of the hydroxycarbamate starting material to an acyl nitroso compound. Similar results were obtained when 25% Cu(OTf)₂ was used to cyclise 2.46a without peroxide (results shown in Table 2.6, entries 1 and 2).

A stability test was conducted with 2.81a to investigate whether the presence of peroxide in the reaction mixture led to degradation of the cyclised product, reducing the yield of product obtained. A pure sample of 2.81a was heated at 65°C for 24 h, in i-PrOH with FeCl₃/H₂O₂, and in THF with Cu(OTf)₂/H₂O₂ (Reagents and conditions, excepting temperature and time, were identical to entries 1 and 10, Table 2.3, section 2.3.2). Afterwards, NMR analysis showed a small amount of decomposition product, but the quantity of 2.81a present had not been significantly reduced from the starting material. This assessment was based on product weight, which showed negligible change, and the area of product H¹ NMR peaks relative to the area of peaks representing decomposition products (approximately 85% of the startingsample of 2.81a remained for the Cu(OTf)₂ stability test and 80% for the FeCl₃ test).
**Table 2.6: Competition experiments between intramolecular nitroso ene reaction and intermolecular cycloaddition**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Metal Catalyst (mol %)</th>
<th>Conditions</th>
<th>Product, yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1¹</td>
<td>2.46a</td>
<td>FeCl₃ (25)</td>
<td>No H₂O₂ used</td>
<td>2.81a, 30%</td>
</tr>
<tr>
<td>2</td>
<td>2.46a</td>
<td>Cu(OTf)₂ (25)</td>
<td>No H₂O₂ used</td>
<td>2.81a, 35%</td>
</tr>
<tr>
<td>3</td>
<td>2.46a</td>
<td>FeCl₃ (4)</td>
<td>2 equiv dimethylbutadiene added</td>
<td>2.97a 48%, 2.81a not formed</td>
</tr>
<tr>
<td>4</td>
<td>2.46a</td>
<td>Cu(OTf)₂ (2)</td>
<td>2 equiv dimethylbutadiene added</td>
<td>2.97a 54%, 2.81a not formed</td>
</tr>
<tr>
<td>5</td>
<td>2.46d</td>
<td>FeCl₃ (4)</td>
<td>2 equiv dimethylbutadiene added</td>
<td>2.97b 50%, 2.81d not formed</td>
</tr>
<tr>
<td>6</td>
<td>2.46d</td>
<td>Cu(OTf)₂ (2)</td>
<td>2 equiv dimethylbutadiene added</td>
<td>2.97b 55%, 2.81d not formed</td>
</tr>
<tr>
<td>7</td>
<td>2.46a</td>
<td>-</td>
<td>Phil(OAc)₂ (0.75 equiv), 1.5 equiv Et₃N, RT</td>
<td>No cyclised product</td>
</tr>
</tbody>
</table>

¹Reactions were carried out on a 1.0 mmol scale. The metal catalyst was added to the hydroxycarbamate in 4 mL of solvent, before addition of H₂O₂. The mixture was reacted for 18 h.

In order to explore whether the acetic acid generated in the Phil(OAc)₂ catalysed cyclisation of 2.46a had a role in the reaction as a Brønsted acid catalyst, 2.46a was cyclised with 0.75 equiv Phil(OAc)₂ in the presence of 1.5 equiv Et₃N, which would neutralise any free acetic acid formed (entry 7, Table 2.6). No cyclisation took place under these basic conditions, suggesting that acetic acid does play some role in the cyclisation reaction. However, a PhilO catalyst also gave a reduced yield of nitroso.
ene cyclisation product (see Table 2.4) without involvement of acetic acid. This can be explained by PhIO being a more efficient oxidant than Phl(OAc)$_2$, or by Et$_3$N preventing the nitroso ene reaction by another mechanism. All experiments in Table 2.6 not already mentioned were carried out once.

A computational study of the intermolecular nitroso ene reaction was carried out by Houk (Intermediates and calculated energies shown in Scheme 2.27). The results pointed towards a stepwise mechanism proceeding via a polarised diradical transition state 2.98 on the reaction path to 2.100, and a reversible parasite equilibrium between the diradical 2.98 and an aziridine N-oxide 2.99.

Scheme 2.27: Mechanism of the intermolecular nitroso ene reaction, according to calculations by Houk (all values in Kcal mol$^{-1}$).

The preliminary DFT calculation study of the intramolecular acyl nitroso ene reaction mechanism performed by Dr Mikhail Kabeshov (work carried out in our research group) suggested a pericyclic 6-membered transition state 2.101 (As shown in Scheme 2.28) as a possible key point of the reaction mechanism. The calculations also identified formation of aziridine-N-oxide 2.101, but its overall contribution to the reaction mechanism is not presently clear. At the same time, we were unable to find a polarised biradical intermediate similar to the intermediate that played an important role in the ene reactions of aryl and acyl nitroso compounds described by Houk. Absence of biradical species is indirectly supported by the different reactivities of (E)-2.46a and (Z)-2.52, since they would otherwise converge to the same biradical intermediate, 2.103, due to rapid rotation about single bonds.
Scheme 2.28: (a) Mechanism of the intramolecular nitroso ene reaction (calculations were carried out by Dr Kabeshov in the group). (b and c) Hypothetical non-radical and radical mechanisms for the nitroso ene cyclisations of (E)-2.46a and (Z)-2.52, in which (Z)-2.52 fails to cyclise under a non-radical mechanism.

The high relative energy of TS 2.102 (25 kcal mol\(^{-1}\)) may explain the relatively slow rate of cyclisation in the absence of catalysts that was observed. In the presence of CuCl\(_2\), the activation energy of H-transfer was found to be 10 kcal\(\cdot\)mol\(^{-1}\) lower (15 kcal\(\cdot\)mol\(^{-1}\) compared to 25 kcal mol\(^{-1}\)). This indicates that the metal catalyst may act as a Lewis acid as well as an oxidant in the intramolecular nitroso ene reaction. Although the reaction also took place without metal catalysis in the presence of either PhIO or Phl(OAc)\(_2\), the latter oxidant would generate acetic acid, which may act as a Brønsted acid catalyst for the reaction.

2.3.7 Further reactions of oxazolidinones.

A number of methods were tested for reduction of N-hydroxyamide groups to amides, in order to give a range of oxazolidinone rings, such as 2.104, from the hydroxyoxazolidinone rings synthesised
using the intramolecular nitroso ene reaction. Hydroxyl group removal would facilitate synthesis of oxazolidinone antibiotics and amino alcohols from the intramolecular nitroso ene reaction products. The major difficulty was in preserving the double bond on the reduced oxazolidinone. A TFA reduction was tested (0.065 g (0.5 mmol) of \(2.81a\) was reacted in \(\text{CH}_2\text{Cl}_2\) with 0.14 g (1 mmol) TFA for 4 hours), but gave no reduced product. A Raney-nickel catalysed hydrogenation of the \(N\)-hydroxyoxazolidinone to an oxazolidinone was also explored in a set of experiments. Two sets of conditions were found under which the \(N\)-hydroxyamide group was reduced to an amide, and the double bond also reduced to a saturated alkane, giving \(2.105\). Since retention of the double bond is a key advantage of the nitroso ene reaction, this reduction is not very useful (Table 2.7 shows the conditions used for the Raney-nickel hydrogenation, and the results. \(2.105\) was not isolated).

**Table 2.7: \(N\)-hydroxyoxazolidinone reduction by hydrogenation\(^i\)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pressure (barr)</th>
<th>Temp(°C)</th>
<th>Product, (conversion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>RT</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>30</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>40</td>
<td>(2.105) (55%)</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>RT</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>RT</td>
<td>(2.105) (45%)</td>
</tr>
</tbody>
</table>

\(^i\)Reactions were carried out on a 1.0 mmol scale.

A cyclisation of \(2.46a\) was also carried out in the presence of stoichiometric \(\text{P(OEt)}_3\), (reaction as described in Table 2.3 entry 1, with \(\text{THF}\) replaced by dry \(\text{CH}_2\text{Cl}_2\) as a solvent, and 0.083 g \(\text{P(OEt)}_3\) (0.5 mmol) added with the metal catalyst) based on a literature intermolecular nitroso ene reaction which afforded secondary amide in a single step.\(^{150}\) However, no reduction of hydroxyamide took place.

### 2.4 Enantio and stereoselective nitroso ene reaction

Although several methods for enantioselective nitroso aldol reactions have been published (see section 1.2.1), an enantioselective nitroso ene reaction has yet to be developed. Catalytic
asymmetric induction, which requires \textit{in situ} interaction between the substrates and a chiral complex to induce enantioselectivity, offers an opportunity of creating a new chiral centre in a single step. Compared to substrate control (which would be applicable if the reaction were used with substrates with an existing chiral centre, or if a chiral auxiliary were attached and removed over multiple steps) catalytic asymmetric induction is a more challenging, but generally more desirable and widely applicable protocol. Such a method might rely on the formation of a complex between the nitroso group, a metal catalyst and chiral ligand, inducing enantioselectivity in the cyclisation.

In the previously mentioned Diels–Alder trapping study on nitrosoarenes by Nicholas (see section 1.3.2), a diene was added to a copper-catalysed intermolecular nitroso ene reaction, and no nitroso HDA product, 2.106, was observed. This suggests possible complexation between the metal and nitroso group during the reaction, and raises the possibility of asymmetric induction by an appropriate metal-ligand complex. Similar results were obtained in an aryl nitroso Diels-Alder trapping experiment with iron. The formation of a metal-nitrosoarene complex was also supported by the isolation of stable iron and copper nitroso complexes from intermolecular nitroso ene reactions. Subsequent nitroso ene reactions on addition of the complex to an alkene confirmed the nitroso-metal complex as a reactive species.\textsuperscript{148,154}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_2.29.png}
\end{center}

\textit{Scheme 2.29:} Diels-Alder trapping experiments with the nitroso ene reaction\textsuperscript{148}

However, all these experiments were carried out with aryl nitroso groups; the comparatively transient nature of complexes between acyl nitroso groups and metals has already been discussed (see section 1.2.2). Our own trapping experiment, in which a diene was added to an intramolecular
aryl nitroso ene reaction, showed complete Diels-Alder adduct formation, and an absence of nitroso ene product, suggesting dissociation of the metal from the nitroso group at a stage of the reaction before cyclisation (The Diels-Alder trapping studies are shown in Scheme 2.29). Computational studies by Dr Kabeshov in our own group described in the previous section indicated the energetic favourability of metal complexation during the key cyclisation transition state (see section 2.3.6).

2.4.1 Attempted asymmetric intramolecular nitroso ene cyclisations using chiral metal catalysts.

After successful nitroso ene cyclisation of 2.46a with a Cu(OTf)_2-phenanthroline complex, confirming that the presence of a ligand does not prevent catalysis of the nitroso ene cyclisation by metals, a number of copper complexes were tested as catalysts for an asymmetric nitroso ene reaction (Figure 2.2 shows the ligands and complexes used in these attempted enantioselective reactions, while Table 2.8 shows the reactions carried out, and their results). Entiopurity of the products was assessed by chiral GC, calibrated by reference to racemic 2.81a. *iso*-Pr-BOX (2.107) was initially selected as a well established chiral ligand, but after repeated attempts, only a racemic product was formed. Four readily available chiral ligands (2.108-2.111) were tested (shown in Table 2.8, entries 2 to 13), but did not produce any chiral induction. These results did show that the presence of a ligand was reducing the rate of the reaction, implying the formation of chiral complexes. Several different solvents were tested with the ligands already used. Cyclisations were also carried out in the presence of a drop of hydrazine in addition to a chiral ligand, in order to determine whether reduction of the Cu(II) catalyst to a Cu(I) species would affect the outcome of the reaction. None of these methods produced any level of enantioselectivity, with yields of racemic 2.80a ranging from low to negligible. For diamine ligand 2.109 a low yield of a racemic oxazolidinone, 2.103, was given (shown in Table 2.8, entry 8). This combined cyclisation and dehydroxylation reaction was intriguing, but gave a low yield of product.

A report of an asymmetric nitroso HDA reaction catalysed by a ruthenium-salen complex encouraged synthesis of both nitro and *t*-butyl substituted salen ligands, which were used to form complexes with ruthenium(II) (2.114 and 2.115), that could be be used as catalysts for nitroso ene reactions (shown in Table 2.8, entries 20 and 21). Again, no enantioselectivity was observed. A copper salt complex with a bulky phosphoric acid counterion, 2.112 was finally used, in order to maximise any chiral environment for asymmetric induction that had failed to have a discernible effect on previously attempted cyclisations. A copper complex was synthesised in MeCN under N₂ with Cu₂O, and used to catalyse the nitroso ene cyclisation of 2.46a, but racemic product was
formed. A BINOL-derived phosphoramidite ligand (2.113) was also used in conjunction with Cu(OTf)$_2$ to catalyse the reaction, based on the use of a similar ligand in the asymmetric rearrangement of amine N-oxides$^{295}$ but this reaction also gave a racemic cyclised product. Adopting a new strategy, we used PhI(OAc)$_2$ as an oxidant in the cyclisation of 2.51 at -20°C. The (S)-Ti-BINOL complex 2.116, a chiral Lewis acid used to catalyse asymmetric carbonyl ene reactions$^{296,297}$ was added to directly bind with the hydroxycarbamate and act as a chiral controller (entry 22, Table 2.9). 2.112 was also used as a directly H-bonding chiral controller for cyclisations of 2.51 at -20°C, with BuNIO$_4$, PhI(OAc)$_2$ and PhIO used as oxidants for the cyclisation (shown in Table 2.8, entries 16, 17 and 18). Although these reactions gave racemic products, a similar strategy towards asymmetric induction was pursued, using H-bonding ligands, as detailed in section 2.4.2. The cyclisation of 2.51 at -20°C also raised the possibility of carrying out nitroso ene cyclisations at lower temperatures, to encourage enantioselectivity. All reactions were continued for 72-96 h, or until significant conversion of starting material to product was observed by TLC. All reactions in Table 2.8 were carried out 1-3 times (For chiral GC data and further discussion of GC conditions, see Appendix A).
Figure 2.2: The chiral ligands and complexes used in the project
Table 2.8: Attempts at asymmetric version of nitroso ene cyclisation.\textsuperscript{1}

\[
\text{O} \quad \text{O} \\
\text{N=O} \quad \text{HO} \\
\text{metal cat., 1.2 equiv H}_2\text{O}_2 \\
solvent, 0^\circ\text{C-RT, Ligand} \\
\rightarrow \quad \text{O} \quad \text{O} \\
\text{N=O} \\
\text{2.81a, X = OH} \\
\text{2.104, X = H}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal (mol %), additive</th>
<th>Ligand, (mol %)</th>
<th>Solvent</th>
<th>Product, (yield), ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>2.107 (2.6)</td>
<td>CH$_2$Cl$_2$</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>2.108 (2.6)</td>
<td>CH$_2$Cl$_2$</td>
<td>No reaction</td>
</tr>
<tr>
<td>3$^i$</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>2.108 (2.6)</td>
<td>CH$_2$Cl$_2$</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>2.108 (2.6)</td>
<td>THF</td>
<td>2.81a (20%), racemic</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>2.109 (2.6)</td>
<td>CH$_2$Cl$_2$</td>
<td>No reaction</td>
</tr>
<tr>
<td>6$^i$</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>2.109 (2.6)</td>
<td>CH$_2$Cl$_2$</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>FeCl$_3$ (4)</td>
<td>2.109 (5.2)</td>
<td>CH$_2$Cl$_2$</td>
<td>2.81a (25%), racemic</td>
</tr>
<tr>
<td>8$^ii$</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>2.110 (2.6)</td>
<td>CH$_2$Cl$_2$</td>
<td>2.104 (22%)</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>2.110 (2.6)</td>
<td>CH$_2$Cl$_2$</td>
<td>2.81a (31%), racemic</td>
</tr>
<tr>
<td>10$^i$</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>2.110 (2.6)</td>
<td>CH$_2$Cl$_2$</td>
<td>No reaction</td>
</tr>
<tr>
<td>11</td>
<td>VO(acac)$_2$ (2)</td>
<td>2.110 (2.6)</td>
<td>CH$_2$Cl$_2$</td>
<td>No reaction</td>
</tr>
<tr>
<td>12</td>
<td>Cu(OTf)$_2$ (5)</td>
<td>2.111 (6.5)</td>
<td>THF</td>
<td>2.81a (19%), racemic</td>
</tr>
<tr>
<td>13</td>
<td>Cu(OTf)$_2$ (0.2)</td>
<td>2.111 (0.2)</td>
<td>toluene</td>
<td>2.81a, (30%) racemic</td>
</tr>
<tr>
<td>14</td>
<td>Cu$_2$(I)O (0.2)</td>
<td>2.112 (0.22)</td>
<td>benzene</td>
<td>2.81a, (10%),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>racemic,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>2.112, (0.22)</td>
<td>THF</td>
<td>2.81, (60%) racemic</td>
</tr>
<tr>
<td>16$^iv$</td>
<td>-</td>
<td>2.112, (0.22)</td>
<td>THF</td>
<td>No reaction</td>
</tr>
<tr>
<td>17$^v$</td>
<td>-</td>
<td>2.112, (0.22)</td>
<td>CH$_2$Cl$_2$</td>
<td>2.80, (15%), racemic</td>
</tr>
<tr>
<td>18$^vi$</td>
<td>-</td>
<td>2.112, (0.22)</td>
<td>CH$_2$Cl$_2$</td>
<td>2.80, (10%), racemic</td>
</tr>
<tr>
<td>19</td>
<td>Cu(OTf)$_2$ (2)</td>
<td>2.113, (10)</td>
<td>CH$_2$Cl$_2$</td>
<td>2.81a, (40%), racemic</td>
</tr>
<tr>
<td>20</td>
<td>2.114</td>
<td>n/a</td>
<td>CH$_2$Cl$_2$</td>
<td>2.81a, (25%), racemic</td>
</tr>
<tr>
<td>21</td>
<td>2.115</td>
<td>n/a</td>
<td>CH$_2$Cl$_2$</td>
<td>No reaction</td>
</tr>
<tr>
<td>22$^v$</td>
<td>-</td>
<td>2.116 (4)</td>
<td>CH$_2$Cl$_2$</td>
<td>2.80, (10%), racemic</td>
</tr>
</tbody>
</table>

$^i$Reactions were carried out on a 0.5 mmol scale. The metal catalyst and ligand were mixed in 4 mL of solvent for 5 mins, before addition of the hydroxycarbamate, followed by addition of H$_2$O$_2$. The mixture was reacted for up to 72 h. $^ii$A drop of phenylhydrazine (PhNHNH$_2$) was added to the catalyst in the reaction solvent, giving Cu(I) from Cu(II), before addition of the substrate and oxidant. $^iii$Reacted at 4°C. $^iv$ Reacted at -20°C. $^v$ Reacted at -20°C. $^vi$Reacted at -20°C. $^vii$ 1.2 equiv H$_2$O$_2$ not used, replaced with 0.025 mol % n-BuNIO$_4$ added dropwise in 2 mL reaction solvent. $^viii$ Reacted at -20°C. $^ix$ 1.2 equiv H$_2$O$_2$ not used, replaced with 0.75 equiv PhI(OAc)$_2$. $^{x}$ Reacted at -20°C. $^{xi}$ 1.2 equiv H$_2$O$_2$ not used, replaced with 0.75 equiv PhIO, added dropwise in 4 mL reaction solvent.

2.4.2 Attempted asymmetric intramolecular nitroso ene cyclisations using chiral ligands capable of hydrogen bonding.

With the apparent failure of the metal binding ligands to induce enantioselectivity, a different approach had to be adopted. Asymmetric induction via a chiral controller H-bonded directly to the
reacting group without an intermediate metal is an established method.\textsuperscript{298, 299} Hydrogen bonding chiral ligands were initially selected to work in conjunction with the metal catalyst, while bypassing the problem of metal dissociation from the substrate by direct bonding to the nitroso group (Shown in Figure 2.3 and Table 2.9). Low yield for the cyclisation of 2.46\textsubscript{a} at low temperature also prompted the use of the more reactive 2.51 as a model substrate in further experiments towards asymmetric cyclisation. 2.51 could be cyclised in reasonable yield at much lower temperatures than 2.46\textsubscript{a}, allowing us to test nitroso ene cyclisations under these conditions for enantioselectivity. The simple enantiopure ligands R-mandelic acid (2.117) and R-tartaric acid (2.118), were initially tested. The ligands were used with both FeCl\textsubscript{3} and Cu(OTf)\textsubscript{2} catalysed ene cyclisations at -20°C (entries 1-2, 4-5, Table 2.9). Subsequently, two commercial Jacobsen’s thioureas 2.119, and 2.120 and Yamamoto’s bis-hydroxycarbamate 2.121\textsuperscript{100} were also used in a FeCl\textsubscript{3} catalysed cyclisations (shown in Table 2.09, entries 7 to 11), with all three experiments carried out at -20°C. A reduced yield of racemic product was isolated in all cases. To eliminate the possibility of a short-lived bond between the metal catalyst and the nitroso group disrupting formation of an H-bond with the chiral ligand, the non-coordinating oxidants n-BuNIO\textsubscript{4} and PhI(OAc)\textsubscript{2} were used with a number of organocatalysts such as mandelic and tartaric acid and TADDOL 2.122 at -20°C. However, all cyclisations returned a racemic product (entries 3, 6, 12-14, Table 2.9).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{ligands_catalysts.png}
\caption{Chiral ligands and catalysts}
\end{figure}
The Lewis acidic CBS reagent 2.123 was also used in a cyclisation of 2.46a, in the hope that a direct bond with the acyl nitroso carbonyl would develop, inducing enantioselectivity, but the cyclisation gave a racemic product. It seems that acyl nitroso group activation, if it happens at all, takes place away from the bond-forming site. A new strategy for development of an asymmetric intramolecular nitroso ene reaction is apparently required.

**Table 2.9:** Chiral ligands capable of H-bonding used with the nitroso ene cyclisation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst, (mol %)</th>
<th>Oxidant, (equiv)</th>
<th>Chiral controller, (mol %)</th>
<th>solvent</th>
<th>Product, (yield), ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)₂ (2)</td>
<td>H₂O₂ (1.2)</td>
<td>2.117, (10)</td>
<td>THF</td>
<td>2.80, (51%), racemic</td>
</tr>
<tr>
<td>2</td>
<td>FeCl₃ (4)</td>
<td>H₂O₂ (1.2)</td>
<td>2.117, (10)</td>
<td>CH₂Cl₂</td>
<td>2.80, (56%), racemic</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>n-BuNiO₄ (1)</td>
<td>2.117, (10)</td>
<td>CH₂Cl₂</td>
<td>2.80, (40%), racemic</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OTf)₂ (2)</td>
<td>H₂O₂ (1.2)</td>
<td>2.118, (10)</td>
<td>THF</td>
<td>2.80, (56%), racemic</td>
</tr>
<tr>
<td>5</td>
<td>FeCl₃ (4)</td>
<td>H₂O₂ (1.2)</td>
<td>2.118, (10)</td>
<td>THF</td>
<td>2.80, (67%), racemic</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>Phl(OAc)₂ (0.75)</td>
<td>2.118, (10)</td>
<td>CH₂Cl₂</td>
<td>2.80, (56%), racemic</td>
</tr>
<tr>
<td>7</td>
<td>FeCl₃ (4)</td>
<td>H₂O₂ (1.2)</td>
<td>2.119, (10)</td>
<td>CH₂Cl₂</td>
<td>2.80, (48%), racemic</td>
</tr>
<tr>
<td></td>
<td>Metal Catalyst</td>
<td>Oxidant</td>
<td>Solvent</td>
<td>Product</td>
<td>Conversion</td>
</tr>
<tr>
<td>---</td>
<td>----------------</td>
<td>---------</td>
<td>---------</td>
<td>----------</td>
<td>-------------</td>
</tr>
<tr>
<td>8</td>
<td>FeCl₃ (4)</td>
<td>H₂O₂ (1.2)</td>
<td>CH₂Cl₂</td>
<td>2.120, (10)</td>
<td>2.80, (49%)</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OTf)₂ (2)</td>
<td>H₂O₂ (1.2)</td>
<td>THF</td>
<td>2.120, (10)</td>
<td>2.80, (36%)</td>
</tr>
<tr>
<td>10</td>
<td>FeCl₃ (4)</td>
<td>H₂O₂ (1.2)</td>
<td>CH₂Cl₂</td>
<td>2.121, (10)</td>
<td>2.80, (44%)</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>n-BuNiO₄ (1)</td>
<td>CH₂Cl₂</td>
<td>2.122, (10)</td>
<td>2.80, (30%)</td>
</tr>
<tr>
<td>12</td>
<td>-</td>
<td>n-BuNiO₄ (1)</td>
<td>CH₂Cl₂</td>
<td>2.122, (10)</td>
<td>2.80, (26%)</td>
</tr>
<tr>
<td>13</td>
<td>-</td>
<td>n-BuNiO₄ (1)</td>
<td>THF</td>
<td>2.122, (10)</td>
<td>2.80, (30%)</td>
</tr>
<tr>
<td>14</td>
<td>-</td>
<td>Phl(OAc)₂ (0.75)</td>
<td>CH₂Cl₂</td>
<td>2.122, (10)</td>
<td>2.80, (28%)</td>
</tr>
</tbody>
</table>

Reactions were carried out on a 0.5 mmol scale. The metal catalyst and hydroxycarbamate were mixed in 4 mL of solvent for 5 mins, before addition of the metal catalyst (where applicable), followed by the oxidant. The mixture was reacted for up to 72 h.
3. Conclusions and Future Outlook

Following the discovery of a mild and efficient catalytic system, a novel intramolecular C-H nitroso ene amination has been developed and optimised to accomplish the cyclisation of a variety of substrates. A range of 5-membered N-hydroxoxazolidinones and a related 6-membered analogue have been synthesised in good yield by nitroso ene cyclisation of unsaturated hydroxycarbamates. The FeCl₃ catalyst is both cheap and safe to use compared to toxic transition metals used previously to synthesise similar compounds. Importantly, the new catalytic system employing FeCl₃ as a catalyst and H₂O₂ as a stoichiometric oxidant for converting hydroxamic acids to the transient acylnitroso species was found to be compatible with an intramolecular carbonyl nitroso ene reaction. The hydroxycarbamate substrates are readily synthesised from allylic and homoallylic alcohols, and the resulting 1,2 and 1,3 amino alcohol derivatives can serve as precursors to a range of biologically active natural products. The cyclisation was highly sensitive to steric congestion around the allylic C-H bond, and the configuration of the double bond. However the facile formation of the spiro substituted and quaternary centre bearing rings 2.84 and 2.87 indicated that steric factors did not effect formation of the C-N bond. The main results of the method development and scope of the reaction have been published in Advanced Synthesis and Catalysis (Appendix C).

According to preliminary computational analysis of the reaction, mechanistically the intramolecular nitroso ene reaction appears to proceed via a 6-membered pericyclic transition state. An N-aziridine intermediate may also be formed reversibly, and react further to give the product. Enthalpy of formation for the 6-membered transition state is significantly reduced by metal complexation, but Diels-Alder trapping experiments carried out in the course of the project indicate dissociation of metal catalysts from the reactive nitroso group before the completion of the nitroso ene reaction. Nitroso ene cyclisation of the secondary substituted hydroxycarbamates favours formation of syn products with diastereoselectivity around 2:1, regardless of the steric size of the substituent on the secondary carbon. For 2.82d, with a bulky cyclohexyl group, d.r. was improved to 5:1 by carrying out the reaction at low temperature. On the other hand, a substrate with a trisubstituted double bond afforded product 2.87 as virtually a single syn diastereoisomer (d.r. > 25:1).

Nitroso ene cyclisations carried out with numerous chiral catalysts failed to produce any enantioselectivity. In combination with the Diels-Alder trapping experiments, this suggests the dissociation of the metal catalyst from the nitroso group prior to cyclisation. A number of cyclisations were also carried out in the presence of H-bonding chiral catalysts and Brønsted acids designed to bond directly to the nitroso group and induce enantioselectivity. These reactions also uniformly gave
a racemic product, indicating the difficulty in forming any temporary bond with the short lived nitroso group, an obstacle which makes development of a chiral version of this reaction a formidable challenge.

To build on the success of the new nitroso ene reaction and to advance this work further, the synthesis and cyclisation of enantioenriched chiral secondary substituted allylic hydroxycarbamates would create a new stereogenic centre and give an enantioselective cyclisation via substrate control.

In conclusion, a useful, novel and versatile reaction for allylic C-H amination has been developed, with some potential for diastereoselective protocols, and offering access to a wide range of biologically significant small molecules.
4. Experimental

4.1 General protocols.

**General Methods:** NMR spectra were recorded in DMSO-d6, acetone-d6 or CDCl$_3$, at 400 MHz for $^1$H spectra and 100.6 MHz for $^{13}$C spectra. TMS was used as an internal standard, unless otherwise indicated (δ 7.26, $^1$H; δ 77.0, $^{13}$C). DEPT $^{13}$C spectra were used to establish the structure of several compounds. IR spectra were recorded for a thin film or CHCl$_3$ solution, between KBr plates. ESI Mass spectra were measured using an LTQ Orbitrap XL mass spectrometer. Chiral gas chromatography was conducted with a Supelco gamma-DEX 120 column. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized by exposure to UV-light (254 nm) or stained with potassium permanganate. All glassware was oven dried before use, unless otherwise stated. Yields are given for pure isolated products that show one spot on a TLC plate and an NMR spectrum without impurities. Where more than one method was used to synthesise a certain product, NMR, IR and TLC results were compared to confirm the product’s identity. All washing and extraction during product workup was followed by drying of the solvent with MgSO$_4$ powder, which was removed by gravity filtration. The yields throughout the experimental section (and yields for new experiments reported throughout this thesis, excluding directly referenced literature examples) are averaged over all repetitions of each experimental method, excluding obviously anomalous results, which were rare for all experiments (the number of repetitions carried out for key methods are given throughout section 2). No identifiable side-products not described in section 2 were observed by NMR analysis to be produced in any repetition of the methods described here (other than a negligible amount of over-reduced side product lacking an alkene group in several repetitions of the syntheses of 2.3c, 2.3d, 2.8-2.10 and 2.13).

**Materials:** Solvents for the reactions listed were reagent grade and dried using the solvent purification system, unless otherwise stated. Petroleum ether refers to the fraction of petrol that boils in the range of 40°C to 60°C. All other compounds used were either acquired from commercial sources or synthesised according to the procedures that follow.
4.2 Experimental data for section 2.2.

Ethyl-4-phenyl-2-butenoate (2.21): (Ethoxycarbonylmethyl)triphenylphosphonium bromide (6.44 g, 15.0 mmol) was added to a mixture of phenylacetaldehyde (1.80 g, 15.0 mmols) and anhydrous sodium acetate (1.48 g, 18.0 mmols), and left stirring under reflux for 6 h in THF (50 mL). Subsequently, the solvent was removed in vacuo and the product purified by silica column with 15:1 petrol: ethyl acetate eluent to remove residual triphenyl phosphate (yellow oil, 2.45 g, 86% yield).

\[ \text{Ph} = \] \[ \text{O} \]

\[ \text{OEt} \]

\[ 2.21 \]

\[ \text{H NMR (400 MHz, CDCl}_3 \text{)} \delta 7.36-7.21 \text{ (m, 5H, 5 x Ar), 5.84 \text{ (dt, J = 15.6, 6.8 Hz, 1H, CH}_2\text{-CH=CH-CO), 4.21 \text{ (q, J = 7.2 Hz, 2H, O-CH}_2\text{-CH}_3\text{), 3.55 \text{ (dd, J = 6.8, 1.1 Hz, 2H, C-CH}_2\text{-CH=CH), 1.29 \text{ (t, J = 7.2 Hz, 3H, O-CH}_2\text{-CH}_3\text{); in agreement with literature data.} \text{}}\text{}}\text{301} \text{]}

General method for allylic alcohol synthesis by ester reduction (2.22-2.24): DIBAL (37.25 mL, 37.5 mmols), as a 1M solution in THF, was added at 0°C to the appropriate methyl or ethyl ester (15.0 mmols) in THF (50 mL), under nitrogen, using a syringe and a Buchner seal. The mixture was allowed to warm to RT and reacted overnight. A small amount of Na\text{2}CO\text{3(aq)} was then added, and the aqueous phase extracted with ethyl acetate (3 x 30 mL), before solvent removal in vacuo to give the product, which was then used without further purification in all cases.

\[ \text{Ph} = \] \[ \text{OH} \]

\[ 2.3c \]

4-Phenyl-2-butenol (2.3c): yellow oil, 1.73 g, 78% yield. \[ \text{H NMR (400 MHz, CDCl}_3 \text{)} \delta 7.34-7.20 \text{ (m, 5H, 5 x Ar), 5.89 \text{ (dtt, J = 16.0, 6.6 Hz, 1.2 Hz, 1H, CH=CH-CH}_2\text{-O), 5.73 \text{ (dtt, J = 16.0, 6.6, 1.2 Hz, 1H, C-CH}_2\text{-CH=CH), 4.17-4.14 \text{ (m, 2H, CH-CH}_2\text{-O), 3.41 \text{ (d, J = 6.6 Hz, 2H, C-CH}_2\text{-CH), 1.34 \text{ (br s, 1H, OH); in agreement with literature data.} \text{}}\text{302} \text{]}

\[ 128 \]
1,1-Dimethyl-2-butenol (2.3d): synthesised using the general method for ester reduction using 0.99 g (7.0 mmols) of 2.23, with 25 mL THF solvent, and 17.5 mL (17.5 mmols) of DIBAL (colourless oil, 0.62 g, 88% yield).

$^1$H NMR (400 MHz, CDCl$_3$) δ 5.63-5.50 (m, 2H, CH=C=CH$_2$), 4.02 (d, $J = 5.6$ Hz, 2H, CH-CH$_2$-OH), 2.25-2.21 (m, 1H, CH$_3$-CH-CH$_2$), 1.19 (br s, 1H, OH), 0.92 (d, $J = 6.8$ Hz, 6H, CH$_3$-CH-CH$_3$); in agreement with literature data.$^{303,304}$

2-Cyclohexylideneethanol (2.8): colourless oil, 1.21 g, 64% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.39 (t, $J = 7.2$ Hz, 1H, C=CH-CH$_2$), 4.16 (d, $J = 7.2$ Hz, 2H, CH-CH$_2$-OH), 2.20-2.18 (m, 2H, CH-CH$_2$-CH$_2$), 2.14 (br s, 2H, CH-CH$_2$-CH$_3$), 1.57 (br s, 6H, CH$_2$-CH$_2$-CH$_2$), 1.17 (br s, 1H, OH); in agreement with literature data.$^{305}$

General method for allylic/homoallylic alcohol synthesis by carboxylic acid reduction (2.25-2.26): The unsaturated carboxylic acid (10.0 mmol) was added dropwise in THF (12 mL), to LiAlH$_4$ (0.408 g, 11.0 mmols) in a solution of THF (50 mL) at 0°C. The reaction was left overnight at room temperature and under nitrogen, after which a small amount of NaSO$_4$•10 H$_2$O was added and aluminium precipitate filtered off using celite. The solvent was then evaporated to give the product, which was used without further purification.

Cyclohexen-1-methanol (2.9): yellow oil, 0.60 g, 60% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.69 (br s, 1H, CH$_2$-C=CH-CH$_2$), 3.75 (s, 2H, C-CH$_2$-OH), 2.25 (br s, 1H, CH$_2$-CH-H-C-CH$_2$), 2.18 (br s, 1H, CH$_2$-CH-H-C-
CH$_2$), 2.18-1.99 (m, 4H, CH$_2$-CH$_2$-CH=CH), 1.59-1.51 (m, 4H, CH$_2$-CH$_2$-CH$_2$-CH$_2$), 1.85 (br s, 1H, OH); in agreement with literature data.$^{252}$

\[ \text{OH} \]

2.10

3-Penten-1-ol (2.10): yellow oil, 0.43 g, 51% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.53-5.48 (m, 1H, CH$_3$-CH=CH-CH$_2$), 5.37-5.30 (m, 1H, CH$_3$-CH=CH-CH$_2$), 3.60 (t, $J$ = 6.3 Hz, 2H, CH$_2$-CH$_2$-OH), 2.18 (q, $J$ = 6.3 Hz, 2H, CH-CH$_2$-CH$_3$), 1.79 (br s, 1H, OH), 1.62 (d, $J$ = 6.3 Hz, 3H, CH=CH-CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 128.7 (CH, CH$_2$-CH=CH), 127.1 (CH, CH=CH-CH$_3$), 62.0 (CH$_2$, CH$_2$-CH$_2$-OH), 36.0 (CH$_2$, CH-CH$_2$-CH$_3$), 18.1 (CH$_3$, CH-CH$_3$); in agreement with literature data.$^{306}$

\[ \text{OH} \]

(Z)-2-Butenol ((Z)-2.13): 2-butynol (1.40 g, 20.0 mmols) in methanol (30 mL) was passed through a H-cube apparatus at RT and atmospheric pressure, with continuous circulation over a Lindlar catalyst (5% Palladium on a BaSO$_4$ support, poisoned with lead acetate). After about 16 h, the product was flushed from the apparatus with pure methanol, and purified using atmospheric pressure distillation with a Lebig condenser and hotplate heated progressively to a final temperature of 65°C. After the methanol solvent had been entirely distilled off into the receiving flask, the alkene product was isolated in the boiling pot, and used without further purification. The hydrogenation was monitored by periodic aliquots taken from the replenished container of methanol/reactant. (brown oil, 0.88 g, 61% yield).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.60-5.51 (m, 2H, CH$_3$-CH=CH-CH$_3$), 4.15-4.11 (m, 1H, HO-CH$_2$-CH), 1.65 (d, $J$ = 5.2 Hz, 3H, CH-CH$_3$); in agreement with literature data.$^{307}$

General method for conversion of unsaturated ketones to allylic alcohols (2.27-2.30): NaBH$_4$ (0.37 g, 10.0 mmol) was added in small portions over 15 mins to the appropriate ketone (10.0 mmol), in a suspension of cerium trichloride•7 H$_2$O$_{aq}$ (3.72 g, 10.0 mmol) in methanol (50 mL). After 2 h stirring, under a balloon to equalise pressure, the reaction was quenched with a few drops of HCl$_{aq}$, diluted with 50 mL water, and extracted with CH$_2$Cl$_2$ (3 x 30 mL). This was concentrated in vacuo (in all cases
except for 2.18, which was distilled under atmospheric pressure, with the combined eluent factions being heated using a hotplate to a maximum of 35°C, and the solvent collected using a Lebig condenser and collection flask, to give a single product.

![2.16](image)

**2-Cyclohexenol (2.16):** brown oil, 0.80 g, 82% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ: 5.88-5.84 (m, 1H, CH-CH=CH-CH$_3$), 5.79-5.76 (m, 1H, CH-CH=CH-CH$_2$), 4.22 (br s, 1H, CH-OH), 2.07-2.03 (m, 2H, CH$_2$-CH$_2$-CH-OH), 1.91-1.75 (m, 1H, CH=CH-CH$_2$-CH$_2$), 1.66-1.61 (m, 2H, CH$_2$-CH$_2$-CH$_2$), 1.28 (br s, 1H, OH); in agreement with literature data.

![2.17](image)

**3-Methyl-2-cyclohexenol (2.17):** brown oil, 0.81g, 74% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.52 (br s, 1H, CH-CH=C), 4.19 (br s, 1H, CH-OH), 2.01-1.81 (m, 2H, CH=C-CH$_2$), 1.80-1.74 (m, 2H, CH$_2$-CH-OH), 1.69 (s, 3H, CH=CH-CH$_3$), 1.59-1.56 (m, 2H, CH$_2$-CH$_2$-CH$_2$), 1.35 (br s, 1H, OH); in agreement with literature data.

![2.18](image)

**2-Cyclopentenol (2.18):** brown oil, 0.34 g, 40% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 6.00-5.98 (m, 1H, CH-CH=CH), 5.85-5.83 (m, 1H, CH=CH-CH$_2$), 4.87-4.86 (m, 1H, CH-OH), 4.32 (br s, 1H, OH), 2.60-2.40 (m, 1H, O-CH-CH-H-CH$_3$), 2.29-2.25 (m, 2H, CH$_2$-CH$_2$-CH=CH), 1.70-1.67 (m, 1H, O-CH-CH-H-CH$_2$); in agreement with literature data.
4-Methyl-3-penten-2-ol (2.19): brown oil, 0.60 g, 60% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.20 (dq, J = 8.6, 1.2 Hz, 1H, CH-CH=CH), 4.56 (dq, J = 8.6, 6.4 Hz, 1H, CH$_3$-CH-OH), 1.71 (d, J = 1.2 Hz, 3H, CH$_3$-C-CH$_3$), 1.69 (d, J = 1.2 Hz, 3H, CH$_3$-C-CH$_3$), 1.40 (br s, 1H, OH), 1.23 (d, J = 6.4 Hz, 3H, CH$_3$-CH-OH); in agreement with literature data.$^{312}$

**General method for Grignard synthesis of allylic alcohols (2.4c-e):** The relevant aryl or alkyl bromide (20 mmol) was added dropwise to a suspension of magnesium powder (0.58 g, 24.0 mmol) in THF (50 mL) under reflux. An iodine crystal was added to the reaction mixture in advance, and a mild reflux maintained. Afterward the reaction was left for 5 mins to cool, put over an ice-bath, and crotonaldehyde (1.44 g, 20.0 mmols) added dropwise. This was reacted overnight, then worked up with addition of a small amount of water and dilute HCl$_{(aq)}$, before evaporation of THF, and extraction with CH$_2$Cl$_2$ (3 x 30 mL). The solvent was then removed under vacuum, to give an oil product, which required no further purification.

1-iso-Propyl-2-butenol (2.4c): yellow oil, 1.5g, 65% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.61-5.56 (m, 1H, CH-CH=CH), 5.45-5.38 (m, 1H, CH=CH-CH$_3$), 3.71 (t, J = 6.8 Hz, 1H, CH$_3$-CH-CH-OH), 2.04 (br s, 1H, OH), 1.65 (d, J = 6.8 Hz, 3H, CH=CH-CH$_3$), 1.65-1.52 (m, 1H, CH$_3$-CH-CH$_3$), 0.88 (d, J = 6.8 Hz, 3H, CH$_3$-CH-CH$_3$), 0.82 (d, J = 6.8 Hz, 3H, CH$_3$-CH-CH$_3$); in agreement with literature data.$^{313}$

1-Cyclohexyl-2-butenol (2.4d): yellow oil, 2.46g, 80% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.88-5.66 (m, 1H, CH-CH=CH), 5.55-5.32 (m, 1H, CH=CH-CH$_3$), 3.96 (dd, J = 9.6, 4.0 Hz, 1H, CH-CH-OH), 2.00 (d, J =
6.0 Hz, 3H, CH-CH₃), 1.83-1.55 (5H, m, CH₂-CH₂-CH₃), 1.47-0.83 (m, 6H, CH₂-CH₂-CH₂); in agreement with literature data.³¹⁴

\[
\text{2.4e}
\]

\[
\text{1-phenyl-2-butenol (2.4e)}: \text{yellow oil, 1.3 g, 45% yield.} \quad \text{¹H NMR (400 MHz, CDCl₃) δ 7.44-7.36 (m, 4H, 4 x Ar), 7.36-7.28 (m, 1H, Ar), 5.83-5.69 (m, 2H, CH-CH=CH-CH₃), 5.18 (d, J = 6.4 Hz, 1H, CH-CH-OH), 2.03 (br s, 1H, CH-OH), 1.79 (d, J = 5.6 Hz, 3H, CH-CH₃); in agreement with literature data.³¹⁵}
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\[
\text{2.15}
\]

\[
\text{1-Phenyl-3-pentenol (2.15): Sn(II) powder (0.71 g, 6.0 mmols) was added to benzaldehyde (0.53 g, 5.0 mmols), with crotyl bromide (1.35 g, 10.0 mmols), in a aqueous 0.25 mol/L solution of NaBF₄ salt (4.0 mL, 1 mmol). This mixture was stirred at RT for 12 h, after which ethyl acetate was added, and the reaction extracted with ethyl acetate (3 x 30 mL). The combined solvent factions were then filtered through celite to remove any traces of metal powder. The solvent was removed under vacuum to give a complex mixture of the regioisomers Z-2.15, E-2.15, anti-2.32, syn-2.32 in the approximate ratio of 1:4:16:32 (yellow oil, 0.95 g, 65% yield). Without intermediate purification, this mixture was then treated, in dry CH₂Cl₂, with Sn(OTf)₂ (0.135 g, 10 mol %), and benzaldehyde (0.017 g, 5 mol %), in the presence of 4Å MS, and under nitrogen. The reaction mixture was left 2 h, before it was quenched with water and extracted with dichloromethane (3 x 30 mL). This reaction gave 2.15 as a 3:1 mixture of E/Z isomers, with a small remaining proportion of 2.32 which was removed using silica column chromatography with 50:1 → 10:1 petrol/ethyl acetate eluent. 2.15 was isolated as a 3:1 mixture of E/Z isomers (yellow oil, 0.24 g, 30% yield)
\]

¹H NMR (400 MHz, CDCl₃) δ (Taken as a 3:1 E/Z mixture) 7.41-7.28 (m, 5H, 5 x Ar), 5.70-5.65 (m, 1H, CH₂-CH=CH) 5.47-5.43 (m, 1H, CH=CH-CH₃), 4.73 (dd, J = 7.6, 5.2 Hz, 1H, HO-CH-CH (Z-isomer)), 4.71 (dd, J = 7.6, 5.2 Hz, 1H, HO-CH-CH (E-isomer)), 2.61-2.48 (m, 2H, CH-CH₂-CH), 2.01 (br s, 1H, CH-OH), 1.73-1.62 (m, 3H, CH-CH₃); in agreement with literature data.²⁶⁴-²⁶⁸
**1-Phenylbut-3-enol (2.20):** Method 1: Allyltrichlorosilane (2.0 mL, 14.0 mmols) was added to benzaldehyde (1.06 g, 10.0 mmols), in acetonitrile (20 mL), with HMPA (3.07 g, 17.14 mmols), kept at 0°C using a cold probe. The reaction was heated to room temperature and left for 3 h, after which a few drops of H$_2$CO$_3$(aq) were added to quench the reaction, and the mixture extracted with CH$_2$Cl$_2$ or diethyl ether (3 x 30 mL). The combined factions were then washed with brine, and the solvent removed under vacuum to give product 2.20. The product was passed through a small layer of silica gel with 1:15 PE:EtAc eluent to remove excess HMPA, and required no further purification (yellow oil, 0.98 g; 66% yield).

Method 2: Sn(II) powder (0.708 g, 6.0 mmols) was added to benzaldehyde (0.53 g, 5.0 mmols), with allyl bromide (1.21 g, 10.0 mmols), in a aqueous solution of NaBF$_4$ salt (4.0 mL, 0.25 mol/L). This mixture was stirred at RT for 12 h, after which ethyl acetate was added, and the reaction extracted from water with ethyl acetate, which was filtered through celite to remove any traces of metal powder. Solvent was removed under vacuum to give 2.20, which required no further purification (yellow oil, 0.48 g, 65% yield).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.29-7.19 (m, 5H, 5 x Ar), 5.76-5.74 (m, 1H, CH$_2$-CH=CH$_2$), 5.13-5.07 (m, 2H, CH=CH$_2$), 4.68 (dd, J = 7.7, 5.1 Hz, 1H, CH$_2$-CH-OH) 2.49-2.39 (m, 2H, CH-CH$_2$-CH), 1.85 (br s, 1H, CH-OH); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 143.8 (CH, CH$_2$-CH=CH$_2$), 134.4 (CH$_2$, CH=CH$_2$), 128.4 (CH, Ar), 127.6 (CH, 2 x Ar), 125.8 (CH, 2 x Ar) 118.4 (CH, Ar), 73.3 (CH, CH-CH-OH), 43.6 (CH$_2$, CH-CH$_2$-CH); in agreement with literature data.$^{258,260,316}$

**1-phenylbut-3-trimethylsilylether (2.30):** 6.5mmols of product 2.20 was dissolved in 35 mL of CH$_2$Cl$_2$ to which triethylamine (0.21 g, 2.1 mmols), and TMS-Cl (1.40 g, 13.0 mmols) were added; the mixture was then reacted for 5 h. The reaction was quenched with aqueous NaHCO$_3$ and extracted with
CH₂Cl₂ (3 x 30 mL) and ethyl acetate (35 mL). The organic layers were washed in brine, and concentrated by rotary evaporation to give the TMS protected product (0.97 g, 68% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.27-7.18 (m, 5H, 5 x Ar), 5.76-5.70 (m, 1H, CH₂-CH=CH₂), 5.02-4.97 (m, 2H, CH=CH₂), 4.62 (dd, J = 7.6, 5.6 Hz, 1H, CH₂-CH-O) 2.46-2.36 (m, 2H, CH-CH₂-CH), 0.01 (s, 9H, 3 x Si-CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 144.7 (CH, CH₂-CH=CH₂), 135.2 (CH₂, CH=CH₂), 127.9 (CH, Ar), 126.9 (CH, 2 x Ar), 125.7 (CH, 2 x Ar), 116.7 (CH, Ar), 74.7 (CH, CH-CH-OH), 45.0 (CH₂, CH-CH₂-CH) 0.0 (CH₃, 3 x Si-CH₃); in agreement with literature data.²⁷¹

**General procedure for synthesis of acetates from alcohols (2.5a-b):**²⁷¹,²⁷²,²⁷³ Acetic anhydride (1.12 g, 11.0 mmols) and triethylamine (2.02 g, 20.0 mmols) are added to the relevant alcohol (10.0 mmols), in dry CH₂Cl₂ (50 mL), at 0°C. The reaction is stirred for 2 h, and then quenched with 20 mL H₂O. The aqueous layer was extracted with CH₂Cl₂ (3 x 30 mL), the solvent evaporated in vacuo, and the product used without further purification.

Geranyl acetate ((E)-2.39a): colourless oil, 0.18 g, 91% yield. Rf = 0.53 (silica, petroleum ether/ethyl acetate 4:1); ¹H NMR (400 MHz, CDCl₃) δ 5.29-5.25 (m, 1H, C=CH-CH₂-OAc), 5.03-5.00 (m, 1H, C=CH-CH₂-CH₃), 4.52 (d, J = 7.2 Hz, 2H, CH-CH₂-OAc), 2.03-2.01 (m, 4H, CH-CH₂-CH₂-C), 1.98 (s, 3H, O=C-CH₃), 1.63 (s, 3H, CH₃-C=CH-CH₂-OAc), 1.61 (s, 3H, CH₃-C-CH₃), 1.53 (s, 3H, CH₃-C-CH₃); in agreement with literature data.²⁷¹

Neryl acetate ((Z)-2.39b): colourless oil, 0.18 g, 91% yield. Rf = 0.53 (silica, petroleum ether/ethyl acetate 4:1); ¹H NMR (400 MHz, CDCl₃) δ 5.38 (t, J = 7.2 Hz, 1H, C=CH-CH₂-OAc), 5.11-5.10 (m, 1H, C=CH-CH₂-CH₃), 4.51 (d, J = 7.2 Hz, 2H, CH-CH₂-OAc), 2.13-2.07 (m, 4H, CH-CH₂-CH₂-C), 2.06 (s, 3H,
General procedure for selective chlorination of unsaturated acetates (2.39a-b): The acetate (9.0 mmols) was cooled to -78°C in CH₂Cl₂ (10 mL), by means of a bath of acetone and dry ice, with an N₂ balloon. TiCl₄ (1.70 g, 9.0 mmols) was added dropwise to the reaction mixture over 1 min, and the reaction stirred for no more than 2 mins, before it was cautiously quenched with water and warmed to 0°C. The aqueous layer was extracted with CH₂Cl₂ (3 x 30 mL), and the combined extracts washed once each with water and brine. The solvent was evaporated in vacuo, and the product used without further purification.

7-Chloro-3,7-dimethyl-2-E-Octen-1-yl acetate ((E)-2.40a): yellow oil, 1.61 g, 77% yield. ¹H NMR (400 MHz, CDCl₃) δ 5.38 (t, J = 7.2 Hz, 1H, C=CH-CH₂-OAc), 4.62 (d, J = 7.2 Hz, 2H, CH-CH₂-OAc), 2.20 (s, 3H, O=C-CH₃), 2.08 (t, J = 6.0 Hz, 2H, Cl-CH₂-CH₂), 1.73 (s, 3H, CH₃-C=CH-CH₂-OAc), 1.68-1.63 (m, 4H, CH₂-CH₂-CH₂-C), 1.60 (s, 6H, CH₂-C-CH₃); in agreement with literature data.²⁷¹

7-Chloro-3,7-dimethyl-2-Z-Octen-1-yl acetate ((Z)-2.40b): yellow oil, 1.48 g, 71% yield. ¹H NMR (400 MHz, CDCl₃) δ 5.33 (t, J = 7.2 Hz, 1H, C=CH-CH₂-OAc), 4.49 (d, J = 7.2 Hz, 2H, CH-CH₂-OAc), 2.06 (t, J = 7.2 Hz, 2H, Cl-CH₂-CH₂), 1.98 (s, 3H, O=C-CH₃), 1.70 (s, 3H, CH₃-C=CH-CH₂-OAc), 1.65-1.57 (m, 4H, CH₂-CH₂-CH₂-C) 1.56 (s, 6H, CH₂-C-CH₃); in agreement with literature data.²⁷¹

General method for reduction of chlorinated acetates: (2.40a-b) n-Bu₃SnH, (1.89 g, 6.5 mmols) along with the radical initiator AIBN (0.11 g, 0.65 mmols), was mixed in toluene (50 mL) with the chlorinated acetate (6.5 mmols). The reaction was heated to reflux and stirred overnight, then
quenched with water and worked up using CH₂Cl₂ (3 x 30 mL). The tin hydride residues were eliminated by washing the combined fractions with saturated KF(aq). The fractions were dried with MgSO₄(s), concentrated in vacuo, and the product purified by silica column chromatography, using 30:1 → 10:1 petroleum ether: ethyl acetate eluent, giving a usable product.

Dihydrogeranyl acetate ((E)-2.41a): colourless oil, 0.70 g, 55% yield. ¹H NMR (400 MHz, CDCl₃) δ 5.34 (dt, J = 7.2 Hz, 1H, C=CH-CH₂-OAc) 4.60 (d, J = 7.2 Hz, 2H, CH-CH₂-OAc) 2.11 (s, 3H, O=C-CH₃), 2.09-2.01 (m, 2H, CH₂-CH₂-C), 1.71 (s, 3H, CH₃-C=CH-CH₂-OAc), 1.59-1.54 (m, 1H, CH₃-CH-CH₂), 1.47-1.39 (m, 2H, CH₂-CH₂-CH₂), 1.19 (m, 2H, CH₃-CH-CH₂-CH₂), 0.89 (d, J = 6.0 Hz, 6H, CH₃-CH-CH₂); in agreement with literature data.

Dihydrorneryl acetate ((Z)-2.41b): colourless oil, 0.75 g, 59% yield. ¹H NMR (400 MHz, CDCl₃) δ 5.27 (t, J = 7.2 Hz, 1H, C=CH-CH₂-OAc), 4.49 (d, J = 7.2 Hz, 2H, CH-CH₂-OAc), 1.99 (t, J = 7.2 Hz, 2H, CH₂-CH₂-C), 1.96 (s, 3H, O=C-CH₃), 1.62 (s, 3H, CH₃-C=CH-CH₂), 1.53-1.48 (m, 1H, CH₃-CH-CH₂), 1.35-1.31 (m, 2H, CH₂-CH₂-CH₂), 1.15-1.09 (m, 2H, CH₃-CH-CH₂-CH₂), 0.85 (d, J = 6.8 Hz, 6H, CH₃-CH-CH₂); in agreement with literature data.

General method for deacetylation of acetates (2.41a-b): K₂CO₃ (0.41 g, 0.3 mmols) was added to the acetate (3.0 mmols) in a solution of MeOH (20 mL). The mixture was stirred for 1 h, after which the reaction was quenched with water, the methanol evaporated, and the aqueous layer extracted with CH₂Cl₂ (3 x 30 mL). The product was concentrated in vacuo and used without further purification.
Dihydrogeraniol ((E)-2.6a): colourless oil, 0.40 g, 87% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.34 (t, $J$ = 7.0 Hz, 1H, C=CH-CH$_2$-O), 4.05 (d, $J$ = 7.0 Hz, 2H, CH-CH$_2$-O), 1.94 (t, $J$ = 7.6 Hz, 2H, CH$_2$-CH$_2$-C), 1.79 (br s, 1H, OH), 1.66 (s, 3H, CH$_3$-C=CH), 1.50-1.41 (m, 2H, CH$_2$-CH$_2$-CH$_2$), 1.22, (s, 1H, CH$_3$-CH-CH$_2$-O) 0.83 (d, $J$ = 6.6 Hz, 6H, CH$_3$-CH-CH$_3$); in agreement with literature data.\(^{271}\)

Dihydrornerol ((Z)-2.6b): colourless oil, 0.42 g, 92% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.08 (t, $J$ = 7.2 Hz, 1H, C=CH-CH$_2$-O), 4.28 (d, $J$ = 7.2 Hz, 2H, CH-CH$_2$-O), 1.78 (t, $J$ = 7.6 Hz, 2H, CH$_2$-CH$_2$-C), 1.69 (s, 3H, CH$_3$-C=CH), 1.29 (s, 1H, CH$_3$-CH-CH$_3$), 1.16-1.09 (m, 2H, CH$_2$-CH$_2$-CH$_2$), 0.98-0.81 (m, 2H, CH$_3$-CH-CH$_2$-CH$_2$), 0.79 (d, $J$ = 6.6 Hz, 6H, CH$_3$-CH-CH$_3$); in agreement with literature data.\(^{271}\)

**General method for chloroformate synthesis (2.43a-b):** Pyridine (0.05 g, 0.625 mmol) was added dropwise over 2h to triphosgene (0.59 g, 2.0 mmol) in toluene (10 mL), under nitrogen atmosphere, as the reaction was cooled with an ice bath. The relevant alcohol (5.0 mmols) was then added dropwise over half an hour, after a 2 h waiting period. The solid was filtered off, after TLC showed complete conversion to the chloroformate (within 16-17 h), and the solvent evaporated under reduced pressure to give the desired product.

3-Butenylchloroformate (2.43a): yellow oil, 0.42 g, 62% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.80-5.76 (m, 1H, CH$_2$=CH-CH$_2$), 5.16-5.09 (m, 2H, CH=CH$_2$), 4.28 (t, $J$ = 6.8 Hz, 2H, CH$_2$-CH$_2$-O) 2.45-2.35 (m, 2H, CH-CH$_2$-CH$_2$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 155.2 (C, O-C-Cl), 133.5 (CH, CH$_2$=CH-CH$_2$), 117.6 (CH$_3$-CH-CH$_3$).
CH=CH₂, 66.9 (CH₂, CH₂-CH₂-O), 33.1 (CH₂, CH-CH₂-CH₂); IR (KBr) 3079 (C-H), 1642 (C=O), 1246; in agreement with literature data.²⁷⁷

Phenylethyl chloroformate (2.43b): yellow oil, 0.64 g, 70% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.32 (m, 4H, 4 x Ar), 7.28-7.21 (m, 1H, Ar), 4.36 (t, J = 7.2 Hz, 2H, CH₂-CH₂-O), 2.98 (t, J = 7.2 Hz, 2H, C-CH₂-CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.1 (C, O=C-Cl), 137.2 (C, Ar), 129.8 (CH, 2 x Ar), 128.6 (CH, 2 x Ar), 128.7 (CH, Ar), 68.3 (CH₂, CH₂-CH₂-O), 35.2 (CH₂, C-CH₂-CH₂); IR (KBr) 2949 (C-H), 1749 (C=O), 1460; in agreement with literature data.²⁷⁵

Benzyl hydroxycarbamate (2.45): CH₂Cl₂ (20 mL) was used to make up a solution containing Na₂CO₃ (0.63 g, 6.0 mmols) and NH₂OH·HCl (0.35 g, 5.0 mmols). After 15 mins freebasing of these components, benzyl chloroformate (1.02 g, 6.0 mmols) was added, and the reaction mixture left for 25 h. The solution was then filtered to remove solid components, and the solvent evaporated to give the product as a white solid (0.80 g; 80% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.24-7.18 (m, 5H, 5 x Ar), 7.10 (s, 1H, OH), 5.10 (s, 2H, CH-CH₂-O); IR (KBr) 3340 (O-H), 1715 (N=C-O), 1475 (Ar C=C), 1243 (C-O); in agreement with literature data.²⁴⁵

General method for hydroxycarbamate synthesis, Method A (2.3a-b, 2.4a-b, 2.16):²⁴⁷ Carbonyldiimidazole (3.16 g, 19.5 mmols) was added to a solution of the unsaturated alcohol (13.0 mmol) in pyridine (65 mL). The mixture was reacted under nitrogen, at 40°C, for 2 h. NH₂OH·HCl (4.5 g, 65.0 mmols) was then added to the reaction mixture, which was left to react for 24 h. After evaporation of solvent, the product was extracted from 1 M HCl (aq) (20 mL) with ethyl acetate (3 x 30 mL), and washed with brine (20 mL). The solvent was then removed under vacuum to give the
corresponding hydroxycarbamate to the alcohol used. All hydroxycarbamates produced using this method were purified, in those experiments where contamination with unreacted starting material or \( \text{NH}_2\text{OH}\cdot\text{HCl} \) was noted, using a silica column with 3:1 \( \rightarrow \) 1:1 petroleum ether/EtOAc as an eluent (yields for this synthesis were slightly lower than those given for Method D).

**General method for hydroxycarbamate synthesis, Method B (2.3a-b, 2.4a-b, 2.16).**

Carbonyldiimidazole (3.16 g, 19.5 mmols) was added to a solution of the unsaturated alcohol (13.0 mmol) in \( \text{CH}_2\text{Cl}_2 \) (65 mL). The mixture was reacted under nitrogen, for 2 h. After disappearance of starting material was confirmed by TLC, the \( \text{CH}_2\text{Cl}_2 \) solvent was evaporated *in vacuo* and replaced with ptryidine (65 mL). \( \text{NH}_2\text{OH}\cdot\text{HCl} \) (4.5 g, 65.0 mmols) was then added to the reaction mixture, which was left overnight. After evaporation of solvent, the product was extracted from 1 M \( \text{HCl}_{(aq)} \) (20 mL) with ethyl acetate (3 x 30 mL), and washed with brine (20 mL). The solvent was then removed under vacuum to give the corresponding hydroxycarbamate to the alcohol used. All hydroxycarbamates produced using this method were purified, in those experiments where contamination with unreacted starting material or \( \text{NH}_2\text{OH}\cdot\text{HCl} \) was noted, using a silica column with 3:1 \( \rightarrow \) 1:1 petroleum ether/EtOAc as an eluent (yields for this synthesis were slightly lower than those obtained with Method A, C or D).

**General method for hydroxycarbamate synthesis, Method C (2.3a-d, 2.4a-d, 2.16).**

Carbonyldiimidazole (3.16 g, 19.5 mmols) was added to a solution of the unsaturated alcohol (13.0 mmol) in acetonitrile (65 mL). The mixture was reacted under nitrogen, for 3 h. Imidazole (3.54 g, 52.0 mmols) and \( \text{NH}_2\text{OH}\cdot\text{HCl} \) (4.5 g, 65.0 mmols) were then added to the reaction mixture, which was left overnight. After evaporation of solvent, the product was extracted from 1 M \( \text{HCl}_{(aq)} \) (20 mL) with ethyl acetate (3 x 30 mL), and washed with brine (20 mL). The solvent was then removed under vacuum to give the corresponding hydroxycarbamate to the alcohol used. All hydroxycarbamates produced using this method were purified, in those experiments where contamination with unreacted starting material or \( \text{NH}_2\text{OH}\cdot\text{HCl} \) was noted, using a silica column with 3:1 \( \rightarrow \) 1:1 petroleum ether/EtOAc as an eluent (yields for this synthesis were slightly lower than those given for Method D, and significantly lowered for 2.16).
General method for hydroxycarbamate synthesis, Method D (2.3a-d, 2.4a-d, (E)-2.5a, (Z)-2.5b, (E)-2.6a, (Z)-2.6b, 2.7-2.17):\(^{278}\) Carbonyldiimidazole (3.16 g, 19.5 mmols) was added to a solution of the unsaturated alcohol (13.0 mmol) in acetonitrile (26 mL). The mixture was reacted under nitrogen, for 3 h. Imidazole (3.54 g, 52.0 mmols) and NH\(_2\)OH•HCl (9.0 g, 130.0 mmols) were then added to the reaction mixture, which was left overnight. After evaporation of solvent, the product was extracted from 1 M HCl\(_{(aq)}\) (20 mL) with ethyl acetate (3 x 30 mL), and washed with brine (20 mL). The solvent was then removed under vacuum to give the corresponding hydroxycarbamate to the alcohol used. All hydroxycarbamates produced using this method were purified, for experiments where contamination with unreacted starting material or NH\(_2\)OH•HCl was noted, using a silica column with 3:1 → 1:1 petroleum ether/EtOAc as an eluent.

(E)-2-butenyl hydroxycarbamate (2.46a): (obtained by Method D) colourless oil, 1.02 g, 60% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.22\) (br s, 1H, OH), 5.84 (dq, \(J = 15.2, 6.6\) Hz, 1H, CH\(_3\)-CH=CH-CH\(_2\)), 5.60 (dt, \(J = 15.2, 6.6\) Hz, 1H, CH\(_3\)-CH=CH-CH\(_2\)), 4.61 (d, \(J = 6.6\) Hz, 2H, CH-CH\(_2\)-O), 1.75 (d, \(J = 6.6\) Hz, 3H, CH-CH\(_3\)); \(^1^3\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta 159.0\) (C, O-C-N), 132.3 (CH, CH=CH-CH\(_2\)), 124.7 (CH, CH\(_3\)-CH=CH), 66.9 (CH\(_2\), CH-CH\(_2\)-O), 17.8 (CH\(_3\), CH-CH\(_3\)); IR (NaCl) v 3292 (O-H), 2942 (C-H), 1734 (C=O), 1506, 1267 (C-O), 1116; MS (ESI) m/z % 132 (M+H\(^{+}\) 90), 154.1 (100); HRMS (ESI) 132.0652 (C\(_6\)H\(_{10}\)O\(_3\)N (M+H)\(^{+}\) requires 132.0655).

Hex-2-enyl hydroxycarbamate (2.46b): (obtained by Method D) colourless oil, 1.07 g, 52% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.21\) (br s, 1H, OH), 5.65-5.61 (m, 1H, CH=CH-CH\(_2\)-O), 5.49-5.44 (m, 1H, CH=CH-CH\(_2\)-CH), 4.64 (d, \(J = 6.8\) Hz, 2H, CH-CH\(_2\)-O), 2.02 (q, \(J = 7.2\) Hz, 2H, CH\(_2\)-CH\(_2\)-CH), 1.33 (Sextuplet, \(J = 7.2\) Hz, 2H, CH\(_2\)-CH\(_2\)-CH\(_2\)), 0.84 (t, \(J = 7.2\) Hz, 3H, CH\(_3\)-CH\(_2\)); \(^1^3\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta 159.4\) (C, O-C-N), 136.0 (CH, CH=CH-CH\(_2\)), 123.0 (CH, CH-CH=CH), 62.0 (CH\(_3\), CH-CH\(_2\)-O), 29.5 (CH\(_3\), CH\(_2\)-CH\(_2\)-CH), 22.3 (CH\(_2\), CH\(_3\)-CH\(_2\)-CH\(_2\)), 13.5 (CH\(_3\), CH\(_3\)-CH\(_3\)); in agreement with literature data.\(^{231,278}\)
Phenyl-2-butenyl hydroxcarbamate (2.46c): obtained by Method D, using 2.07 g (10.0 mmols) of 2.3c, 20 mL MeCN solvent, 2.43 g (15.0 mmols) of CDI, 6.90 g (100.0 mmols) of NH₂OH•HCl, and 2.72 g (40.0 mmols) of imidazole (White wax, 1.78 g, 66% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.32-7.12 (m, 5 H, Ar), 6.65 (br s, 1 H, OH), 5.98 (dtt, J = 15.3, 6.8, 1.2 Hz, 1H, CH₂-CH=CH₂), 5.66 (dtt, J = 15.3, 6.4, 1.5 Hz, 1H, CH=CH-CH₂-O), 4.55 (dd, J = 6.4, 1.5 Hz, 2H, CH-CH₂-O), 3.32 (d, J = 6.8 Hz, 2H, C-CH₂-CH₂), ¹³C NMR (100.6 MHz, CDCl₃) δ 159.0 (C, O-C-N), 139.4 (CH, CH=CH-CH₂), 135.4 (CH, CH₂-CH₂-CH₂), 128.5 (C, Ar) 128.4 (CH, 2 x Ar), 126.3 (CH, 2 x Ar), 124.8 (CH, Ar), 66.6 (CH₃, CH-CH₂-O), 38.6 (CH₃, CH-CH₂-CH₂) IR (NaCl) ν 3250 (O-H), 2926 (C-H), 1700 (C=O), 1350 (C-H), 1200 (C-O); HRMS (ESI) 230.0285 (C₁₁H₁₃O₃NNa (M+Na⁺) requires 230.0288).

4,4-Dimethylbutenyl hydroxycarbamate (2.46d): obtained by Method D, using 0.80 g (5.0 mmols) of 2.3d, 10 mL MeCN solvent, 1.21 g (7.5 mmols) of CDI, 3.45 g (50.0 mmols) of NH₂OH•HCl, and 1.36 g (20.0 mmols) of imidazole (white crystalline solid, 0.95 g, 46% yield. Rf = 0.1 (silica, petroleum ether/ethyl acetate 2:1); m.p. 58-61°C).

¹H NMR (400 MHz, CDCl₃) δ 7.52 (br s, 1H, OH), 5.68 (dd, J = 15.4, 6.5 Hz, 1H, CH-CH=CH₂), 5.44 (dtt, J = 15.4, 6.5, 1.2 Hz, 1H, CH-CH=CH₂), 4.51 (d, J = 6.5 Hz, 2H, CH-CH₂-O), 2.26-2.21 (m, 1H, CH₂-CH₂), 0.92 (d, J = 6.5 Hz, 6H, CH₃-CH₂-CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 159.5 (C, O-C-N), 144.0 (CH, CH=CH₂), 120.5 (CH, CH-CH=CH₂), 67.1 (CH₃, CH-CH₂-O), 30.7 (CH, CH₂-CH₂), 22.0 (CH₃ x 2, CH₃-CH₂-CH₂); IR (NaCl) ν 3310 (O-H), 2872 (C-H), 1719 (C=O), 1465, 1273 (C-O), 1120; HRMS (ESI) 182.0788 (C₇H₁₃NO₃Na (M+Na⁺) requires 182.0788).
1-Methyl-2-pentenyl hydroxycarbamate (2.47a): (obtained by Method D) colourless oil, 1.02 g, 54% yield; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.35 (br s, 1H, OH), 5.74 (dq, $J = 15.2$, 6.4 Hz, 1H, CH=CH-CH$_3$), 5.48 (dq, $J = 15.2$, 6.4 Hz, 1H, CH-C=CH-CH$_2$), 5.28 (quintet, $J = 6.4$ Hz, 1H, CH$_3$-CH-O), 1.70 (d, $J = 6.4$ Hz, 3H, CH=CH-CH$_3$), 1.33 (d, $J = 6.4$ Hz, 3H, CH$_3$, CH$_3$-CH-O); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 158.8 (C, O-C-N), 130.2 (CH, CH=C=CH$_2$), 129.1 (CH, CH-C=CH$_3$), 73.7 (CH, CH$_3$-CH-O), 20.4 (CH$_3$, CH=CH-CH$_3$), 17.7 (CH$_3$, CH$_2$-CH-O); IR (NaCl) $\nu$ 3287 (O-H), 2950 (C-H), 1712 (C=O), 1267 (C-O); MS (ESI) m/z % 144 (50), 158 (90), HRMS (ESI) 144.0645 (C$_6$H$_{10}$O$_3$N (M-H, neg) requires 144.0644).

1-Propanyl-2-butenyl hydroxycarbamate (2.47b): (obtained by Method D) colourless oil, 1.26 g, 56% yield; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50 (br s, 1H, OH), 5.74 (dq, $J = 15.3$, 6.5 Hz, 1H, CH=CH=CH-CH$_3$), 5.39 (ddq, $J = 15.3$, 7.6, 1.4 Hz, 1H, CH=CH=CH-CH$_3$), 5.15-5.10 (m, 1H, CH$_2$-CH-O), 1.69 (dd, $J = 6.5$, 1.4 Hz, 3H, CH=CH-CH$_3$), 1.64-1.58 (m, 1H, CH$_2$-CH-H-CH), 1.55-1.46 (m, 1H, CH$_2$-CH-H-CH), 1.38-1.30 (m, 2H, CH$_2$-CH$_2$-CH$_3$), 0.89 (t, $J = 7.3$ Hz, 3H, CH$_3$-CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 159.1 (C, O-C-N), 129.9 (CH, CH=CH=CH), 129.2 (CH, CH=CH-CH$_3$), 36.6 (CH, CH$_2$-CH-O), 18.4 (CH$_3$, CH$_2$-CH$_2$-CH), 17.7 (CH$_2$, CH$_2$-CH$_2$-CH$_3$), 13.8 (CH$_3$, CH$_2$-CH$_3$); IR (NaCl) v 3299 (O-H), 2934 (C-H), 1716 (C-O), 1264 (C-O); HRMS (ESI) 196.0940 (C$_8$H$_{15}$O$_3$NNa (M+Na$^+$) requires 196.0944).

1-iso-Propyl-2-butenyl hydroxycarbamate (2.47c): (obtained by Method D) colourless oil, 1.17 g, 52% yield. Rf = 0.1 (silica, petroleum ether/ethyl acetate 2:1); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.02 (br s,
1H, OH), 5.69-5.62 (dq, J = 15.2, 6.8 Hz, 1H, CH-CH=CH-CH3), 5.34-5.28 (ddq, J = 15.2, 7.6, 1.6 Hz, 1H, CH-CH=CH-CH3), 4.84 (dd, J = 6.8, 6.8 Hz, 1H, CH-CH-O), 1.76 (m, 1H, CH3-CH-CH3), 1.61 (dd, J = 6.8, 1.6 Hz, 3H, CH=CH-CH3), 0.82 (d, J = 6.8 Hz, 3H, CH3-CH-CH3), 0.80 (d, J = 6.8 Hz, 3H, CH3-CH-CH3); 13C NMR (100.6 MHz, CDCl3) δ 159.3 (C, N-C-O), 130.8 (CH, CH-CH=CH), 127.3 (CH, CH=CH-CH3), 82.0 (CH, CH2-CH-O), 32.1 (CH, CH3-CH-CH3), 18.1 (CH3, CH=CH-CH3), 18.0 (CH3, CH3-CH-CH3), 18.0 (CH3, CH3-CH-CH3); IR (NaCl) ν 3368 (O-H), 2971 (C-H), 1723 (C=O); HRMS (ESI) 196.0944 (C8H15O3Na (M+Na+) requires 196.0955).

1-Cyclohexyl-2-butenyl hydroxycarbamate (2.47d): (obtained by Method D) pale yellow wax, 1.44 g, 52% yield. Rf = 0.1 (silica, petroleum ether/ethyl acetate 2:1); 1H NMR (400 MHz, CDCl3) δ 7.20 (br s, 1H, O), 5.65 (ddq, J = 15.3, 7.2, 1.6 Hz, 1H, CH-CH=CH-CH3), 5.30 (ddq, J = 15.3, 7.2, 1.6 Hz, 1H, CH-CH=CH-CH3), 4.85 (t, J = 7.2 Hz, 1H, CH2-CH-O), 1.65-1.56 (m, 8H, 2x CH2-CH2-CH2), 1.49-1.40 (m, 1H, CH2-CH-CH3), 1.19-1.00 (m, 3H, CH=CH-CH3), 0.93-0.82 (m, 2H, CH2-CH2-CH2); 13C NMR (100.6 MHz, CDCl3) δ 159.2 (C, N-C-O), 130.7 (CH, CH-CH=CH), 127.7 (CH, CH=CH-CH3), 80.5 (CH, CH2-CH-O), 41.7 (CH, CH2-CH-CH3), 28.5 (CH2, CH2-CH2-CH2), 27.9 (CH3, CH-CH2-CH2), 26.3 (CH2, CH2-CH2-CH2), 25.9 (CH2, CH2-CH2-CH2), 25.8 (CH2, CH2-CH2-CH2), 17.8 (CH3, CH=CH-CH3); IR (NaCl) ν 3306 (O-H), 2927 (C-H), 1719 (C=O), 1450, 1377; HRMS (ESI) 236.1252 (C13H19NO3Na (M+Na+) requires 236.1257).

(E)-3,7-Dimethylocta-2,6-dienyl hydroxycarbamate (E)-2.48a): (obtained by Method D) colourless oil, 1.80 g, 65% yield. 1H NMR (400 MHz, CDCl3) δ 5.28 (t, J = 7.2 Hz, 1H, C=CH-CH2-O), 5.00 (t, J = 7.2 Hz, 1H, CH3-C=CH), 4.62 (d, J = 7.2 Hz, 2H, CH-CH2-O), 2.04-1.90 (m, 4H, CH2-CH2-CH2-C), 1.68 (s, 3H, CH2-C-CH3), 1.64 (s, 3H, CH2-C-CH3), 1.57 (s, 3H, CH3-C-CH3); 13C NMR (100.6 MHz, CDCl3) δ 159.3 (C, O-C-N), 143.4 (C, CH2-C-CH2), 132.0 (C, CH3-C-CH3), 123.6 (CH, C=CH-CH2-O), 117.7 (CH, CH3-C=CH), 63.1 (CH2, CH-CH2-O), 39.5 (CH2, CH2-CH2-C), 26.3 (CH2-CH-CH2-O), 25.7 (CH3, CH2-C-CH3), 17.7 (CH3, CH3-C-CH3), 16.5 (CH3, CH3-C-CH3); in agreement with literature data.231
CH₃NMR (100.6 MHz, CDCl₃) δ 7.65 (br s, 1H, OH), 5.34 (t, J = 7.2 Hz, 1H, C=CH-CH₂-O) 5.10-5.06 (m, 1H, CH₂=C=CH), 4.63 (d, J = 7.2 Hz, 2H, CH₂-CH₂-O), 2.14-2.06 (m, 4H, CH₂-CH₂-CH₂-C), 1.76 (s, 3H, CH₃), 1.71 (s, 3H, CH₂-C-CH₃), 1.59 (s, 3H, CH₃-C-CH₂), δ 159.7 (C, O-C-N), 143.4 (C, CH₂-C-CH₂), 132.3 (C, CH₃-C-CH₃), 123.5 (CH, C=CH-CH₂-O), 118.7 (CH, CH₃-C=CH), 62.8 (CH₂, CH-CH₂-O), 31.6 (CH₃, CH₂-CH₂-C), 26.6 (CH₂, CH₂-CH₂-CH₂), 25.7 (CH₃ CH₂-C-CH₃), 23.5 (CH₃, CH₃-C-CH₃), 17.67 (CH₃, CH₃-C-CH₃).

Dihydrogeraniol hydroxycarbatate ([E]-2.49a): (obtained by Method D) Synthesised according to the general method for hydroxycarbatate synthesis, using 0.52 g (2.4 mmols) of (E)-2.6a, 4.8 mL MeCN solvent, 0.58 g (3.6 mmols) of CDI, 1.66g (24.0 mmols) of NH₂OH•HCl, and 0.54 g (9.6 mmols) of imidazole (Colourless oil, 0.20 g, 64% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.15 (br s, 1H, OH), 5.26 (t, J = 7.2 Hz, 1H, C=CH-CH₂), 4.61 (d, J = 7.2 Hz, 2H, CH₂-CH₂-O), 1.93 (t, J = 8.0 Hz, 2H, CH₂-CH₂-C), 1.63 (s, 3H, CH₃-C=CH), 1.49-1.42 (m, 2H, CH₂-CH₂-CH₂), 1.34 (m, 2H, CH₂-CH₂-CH₂), 1.09 (m, 1H, CH₃-C-CH₃), 0.81 (d, J = 6.4 Hz, 6H, CH₃-CH-CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 159.5 (C, N-C-O), 143.8 (C, CH₂-C-CH) 117.5 (CH, C=CH-CH₂-O), 63.1 (CH₂, CH-CH₂-O), 39.8 (CH₃, CH₂-CH₂-C), 38.6 (CH₂, CH₂-CH₂-CH₂), 27.9 (CH, CH₃-C-CH₃), 25.3 (CH₂, CH₂-CH₂-CH₂), 22.6 (CH₃, CH₃-C-CH₃), 16.4 (CH₃, CH₃-C-CH₃); IR (NaCl) ν 3350 (O-H), 2940 (C-H), 1725 (C=O), 1234 (C-O); HRMS (ESI) 238.1409 (C₁₁H₁₂O₃Na (M+Na⁺) requires 238.1414).
Dihydroneerol hydroxycarbamate ([Z]-2.49b): (obtained by Method D) Synthesised according to the general method for hydroxycarbamate synthesis, using 0.52 g (2.4 mmols) of ([Z]-2.6b, 4.8 mL MeCN solvent, 0.58 g (3.6 mmols) of CDI, 1.66g (24.0 mmols) of NH₃OH•HCl, and 0.54 g (9.6 mmols) of imidazole (Colourless oil, 0.18 g, 59% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.09 (br s, 1H, OH), 5.27 (t, J = 7.2 Hz, 1H, C=CH-CH₂), 4.59 (d, J = 7.2 Hz, 2H, CH-CH₂-O), 2.01 (t, J = 8.0 Hz, 2H, CH₂-CH₂-C), 1.69 (s, 3H, CH₃-C=CH), 1.47-1.42 (m, 2H, CH₂-CH₂-CH₂), 1.35-1.27 (m, 2H, CH₂-CH₂-CH₂), 1.11-1.07 (m, 1H, CH₃-CH-CH₃), 0.82 (d, J = 6.4 Hz, 6H, CH₃-CH-CH₂-CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 159.4 (C), 144.2 (C), 118.3 (CH), 77.2 (CH₂), 62.8 (CH₂), 38.7 (CH₃), 32.2 (CH₃), 27.9 (CH), 25.9 (CH₂) 23.5 (CH₃), 22.6 (CH₃); IR (NaCl) v 3369 (O-H), 2937 (O-H), 2917 (C-H), 1718 (C=O), 1267 (C-O); HRMS (ESI) 238.1410 (C₁₁H₂₁O₃NNa (M+Na⁺) requires 238.1414).

Citronel hydroxycarbamate (2.50): (obtained by Method D) colourless oil, 1.73g, 62% yield. Rf = 0.1 (silica, petroleum ether/ethyl acetate 2:1); ¹H NMR (400 MHz, CDCl₃) δ 7.31 (br s, 1H, OH), 5.03-5.01 (m, 1H, C=CH-CH₂), 4.21-4.16 (m, 1H, CH₂-CH₂-O), 2.02-1.93 (m, 2H, C=CH-CH₂-CH₂), 1.68 (s, 3H, CH₃-C-CH₃), 1.60 (s, 3H, CH₃-C-CH₃), 1.55-1.42 (m, 2H, O-CH₂-CH₂-CH), 1.37-1.31 (m, 4H, CH-CH₂-CH₂-CH), 1.22-1.17 (m, 1H, CH₂-CH₂-CH₃), 0.91 (d, J = 6.4 Hz, 3H, CH-CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 159.4 (C, N-C-O), 131.5 (C, CH₃-C=CH), 124.5 (CH, C=CH-CH₂), 64.9 (CH₂, O-CH₂-CH₂), 37.0 (CH₂, C=CH-CH₂-CH₂), 35.6 (CH₂, CH-CH₂-CH₂-O), 29.3 (CH₃, CH₃-C-CH₃), 25.2 (CH₃, CH₃-C-CH₃), 25.4 (CH₂, CH₂-CH₂-CH₃), 19.3 (CH, CH₂-CH₂-CH₃), 12.6 (CH₃, CH-CH₃); IR (NaCl) 3304 (O-H), 2963 (C-H), 1722 (C=O); HRMS (ESI) 238.1412 (C₁₁H₂₁NO₃Na (M+Na⁺) requires 238.1414).
3-methyl-2-butyl hydroxycarbamate (2.51): (obtained by Method D) colourless oil, 1.34 g, 71% yield. Rf = 0.1 (silica, petroleum ether/ethyl acetate 2:1); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.14 (br s, 1H, OH), 5.38-5.32 (m, 1H, C=CH-CH$_3$), 4.59 (d, $J$ = 7.2 Hz, 2H, CH-CH$_2$-O), 1.69 (s, 3H, CH$_3$-C-CH$_3$), 1.65 (s, 3H, CH$_3$-C-CH$_3$), $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 159.1 (C, N-C- O), 140.1 (C, CH$_3$-C=CH), 118.1 (CH, C=CH-CH$_2$), 63.0 (CH$_2$, CH$_3$-C-CH$_2$-O), 25.8 (CH$_3$, CH$_3$-C-CH$_3$), 18.0 (CH$_3$, CH$_3$-C-CH$_3$); in agreement with literature data.$^{278}$

(Z)-2-Butenyl hydroxycarbamate (2.52): (obtained by Method D) colourless oil, 1.12 g, 66% yield; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.20 (br s, 1H, OH), 5.71-5.63 (m, 1H, CH=CH-CH$_2$), 5.51-5.44 (m, 1H, CH$_3$-CH=CH), 4.64 (d, $J$ = 6.8 Hz, 2H, CH-CH$_2$-O), 1.63 (d, $J$ = 6.8 Hz, 3H, CH-CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 159.5 (C, O-C-N), 130.3 (CH, CH=CH-CH$_3$), 123.8 (CH, CH$_3$-CH=CH), 61.7 (CH$_2$, CH-CH$_2$-O), 13.1 (CH$_3$, CH-CH$_3$); IR (NaCl) v 3292 (O-H), 2942 (C-H), 1734 (C=O), 1506, 1262 (C-O); HRMS (ESI) 154.0475 (C$_5$H$_9$NO$_3$Na (M+Na$^+$) requires 154.0474).

Cyclohexenyl-1-ethylene hydroxycarbamate (2.53):$^{231}$ (obtained by Method D) Synthesised according to the general method for hydroxycarbamate synthesis, using 0.99 g (8.0 mmols) of CDI, 5.52 g (80.0 mmols) of NH$_2$OH•HCl, and 2.18 g (32.0 mmols) of imidazole (white solid, 1.25 g, 52% yield)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.71 (br s, 1H, OH), 5.23 (t, $J$ = 7.2 Hz, 1H, C=CH-CH$_2$), 4.62 (d, $J$ = 7.2 Hz, 2H, CH-CH$_2$-O), 2.14 (br s, 2H, CH$_2$-CH$_2$-C), 2.06 (br s, 2H, CH$_2$-CH$_2$-C), 1.49 (br s, 6H, CH$_2$-CH$_2$-CH$_2$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 159.6 (C, N-C-O), 143.0 (C, CH$_2$-C-CH), 114.7 (CH, C=CH-CH$_2$), 62.3 (CH$_2$, CH-CH$_2$-O), 37.0 (CH$_2$, CH$_2$-CH$_2$-C), 29.0 (CH$_2$, CH$_2$-CH$_2$-C), 28.3 (CH$_2$, CH$_2$-CH$_2$-CH$_2$), 27.3 (CH$_2$, CH$_2$-CH$_2$-CH$_2$.-
Cyclohexenylmethyl hydroxycarbamate (2.54): (obtained by Method D) Synthesised according to the general method for hydroxycarbamate synthesis, using 0.55 g (5.0 mmols) of 2.9, 10 mL MeCN solvent, 2.43 g (15.0 mmols) of CDI, 3.45 g (50.0 mmols) of NH₂OH•HCl, and 1.36 g (20.0 mmols) of imidazole (White solid, 1.22 g, 55% yield. Rf = 0.1 (silica, petroleum ether/ethyl acetate 2:1)).

¹H NMR (400 MHz, CDCl₃) δ 5.76 (br s, 1H, CH₂-C=CH), 4.51 (s, 2H, C-CH₂-O), 2.04-2.02 (m, 2H, CH₂-C(CH₂-CH₂-C)), 1.98-1.96 (m, 2H, CH₂-CH₂-CH₂-C), 1.67-1.60 (m, 2H, CH₂-CH₂-CH₂-C), 1.61-1.54 (m, 2H, CH₂-CH₂-CH₂-C); ¹³C NMR (100.6 MHz, CDCl₃) δ 159.3 (C, N-C=O), 128.3 (CH, CH₂-CH=CH), 125.8 (CH, CH=CH-CH₃), 65.9 (CH₃, CH₂-CH₂-O), 32.1 (CH₂, CH₂-CH₂-CH₂-C), 18.0 (CH₃, CH=CH-CH₃); IR (NaCl) ν 3371 (O-H), 2955 (C-H), 1703 (C=O); HRMS (ESI) 208.0940 (C₉H₁₅O₃NNa (M+Na⁺) requires 208.0944).

3-Pentenyl hydroxycarbamate (2.55): obtained by Method D, using 0.43 g (5.0 mmols) of 2.7, 10 mL MeCN solvent, 2.43 g (15.0 mmols) of CDI, 3.45 g (50.0 mmols) of NH₂OH•HCl, and 1.36 g (20.0 mmols) of imidazole (colourless oil, 1.11 g, 59% yield).

¹H NMR (400MHz, CDCl₃) δ 5.54 (dq, J = 14.8, 6.4 Hz, 1H, CH₂-CH=CH-CH₃), 5.37 (dt, J = 14.8, 6.8 Hz, 1H, CH₂-CH=CH-CH₃), 4.17 (t, J = 6.8 Hz, 2H, CH₂-CH₂-O), 2.33 (q, J = 6.8 Hz, 2H, CH₂-CH₂-CH₂-C), 1.79 (br s, 1H, OH), 1.66 (d, J = 6.4 Hz, 3H, CH=CH-CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 159.3 (C, N-C=O), 128.3 (CH, CH₂-CH=CH), 125.8 (CH, CH=CH-CH₃), 65.9 (CH₃, CH₂-CH₂-O), 32.1 (CH₂, CH₂-CH₂-CH₂-C), 18.0 (CH₃, CH=CH-CH₃); IR (NaCl) ν 3237 (O-H), 2955 (C-H), 1703 (C=O); HRMS (ESI) 168.0630 (C₆H₁₁O₃NNa (M+Na⁺) requires 168.0631).
1-Ethyl-2-methyl-2-butenyl hydroxycarbamate (2.56): obtained by Method D, using 0.90 g (7.0 mmols) of 2.10, 14 mL MeCN solvent, 1.13 g (10.5 mmols) of CDI, 4.83 g (70.0 mmols) of NH₂OH•HCl, and 1.90 g (28.0 mmols) of imidazole (colourless oil, 1.22 g, 50% yield. Rf = 0.1 (silica, petroleum ether/ethyl acetate 2:1)).

¹H NMR (400 MHz, CDCl₃) δ 7.41 (br s, 1H, OH), 5.44 (t, J = 7.2 Hz, 1H, C=CH-CH₂), 4.91 (t, J = 7.2 Hz, 1H, C-CH-O), 2.02 (quintet, J = 7.2 Hz, 2H, CH₃-CH₂-CH-O), 1.68-1.64 (m, 1H, C=CH-CH-H), 1.63-1.58 (m, 1H, C=CH-CH₂-H), 1.56 (s, 3H, CH=C-CH₃), 0.96 (t, J = 7.2 Hz, 3H, CH₂-CH₂-CH-O), 0.84 (t, J = 7.2 Hz, 3H, C=CH-CH₂-CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 159.3 (C, N-C-O), 158.4 (C, C=CH-[C-H]), 131.4 (CH, C=CH-CH₂), 83.2 (CH, CH₂-CH₂-CH-O), 25.5 (CH₂, CH₃-CH₂-CH-O), 20.8 (CH₂, C=CH-CH₂-CH₃), 13.8 (CH₃, CH=C-CH₃), 11.3 (CH₃, CH₃-CH₂-CH-O), 9.7 (CH₃, C=CH-CH₂-CH₃); IR (NaCl) v 3302 (O-H), 2966 (C-H), 1716 (C=O), 1462, 1267 (C-O); HRMS 210.1092 (C₉H₁₇O₃NNa (M+Na⁺) requires 210.1101).

Tert-butyldiphenylsiloxy-2-butenyl hydroxycarbamate (2.57): (obtained by Method D) yellow oil, 1.80 g, 43% yield; ¹H NMR (400 MHz, CDCl₃) δ 7.60-7.38 (m, 5H, Ar), 7.35-7.28 (m, 5H, Ar), 7.20 (br s, 1H, OH), 5.79-5.67 (m, 1H, CH=CH-CH₂-O), 5.51-5.36 (m, 1H, CH=CH-CH₂-O), 4.46 (d, J = 6.2 Hz, 2H, CH-CH₂-O-CO), 4.19 (d, J = 6.2 Hz, 2H, Si-O-CH₂-CH), 0.98 (s, 9H, 3 x C-CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 159.0 (C, O-C-N), 135.6 (CH, CH=CH-CH₂-O-C), 133.9 (CH, Si-O-CH₂-CH=CH), 133.4 (C, Ar), 129.8 (CH, 2 x Ar), 127.8 (CH, 2 x Ar), 123.9 (CH, Ar), 62.0 (CH, CH-CH₂-O-C), 60.3 (CH, Si-O-CH₂-CH=CH), 26.8 (CH₃, 3 x C-CH₃), 19.1 (C, Si-C-CH₃); IR (NaCl) 3303-3135 (O-H), 3070-2740 (C-H), 1716 (C=O), 1361; HRMS (ESI) 408.1598 (C₂₁H₂₇O₃SiNa requires 408.1602).
1-phenyl-3-pentenyl hydroxycarbamate (2.58): obtained by Method D, using 0.32 g (2.0 mmols) of 2.15, 4 mL MeCN solvent, 0.49 g (10.5 mmols) of CDI, 1.38 g (20.0 mmols) of NH₂OH•HCl, and 0.54 g (28.0 mmols) of imidazole yellow oil, 1.15 g, 40% yield.

1H NMR (400 MHz, CDCl₃) 3:1 E/Z mixture; δ 8.95 (br s, 1H, OH), 7.48-7.28 (m, 5H, Ar), 5.74-5.68 (m, 1H, CH₂-CH=CH), 5.58-5.52 (m, 1H, CH=CH-CH₃), 5.35-5.29 (m, 1H, CH-CH-O), 2.70-2.55 (m, 1H, O-CH-CH-H), 2.53-2.49 (m, 1H, O-CH-CH-H), 1.63 (dd, J = 6.4, 1.2 Hz, 3H, CH-CH₃ (E-isomer)), 1.63 (dd, J = 6.8, 0.8 Hz, 3H, CH-CH₃ (Z-isomer)); 13C NMR (100.6 MHz, CDCl₃) 3:1 E/Z mixture; δ 159.1 (C, O-C-N), 135.52 (CH, CH₂-CH=CH), 133.8 (CH, CH=CH-CH₃), 129.3 (C, Ar), 127.3 (CH, 2 x Ar), 127.6 (CH, 2 x Ar), 123.9 (CH, Ar), 62.0 (CH, CH-CH-O), 60.3 (CH₂, CH-CH₂-CH=CH), 26.8 (CH₃, CH-CH₃ (major E-isomer)), 19.1 (CH₂, CH-CH₃ (minor Z-isomer)); IR (NaCl), 2968-2872 (C-H), 1655 (C=O), 1452 (Ar C=C).

Cyclohexenylmethyl hydroxycarbamate (2.59) (obtained by Method D) brown oil, 1.23 g, 55% yield. 

1H NMR (400 MHz, CDCl₃) δ 7.06 (br s, 1H, OH), 5.91-5.86, (m, 1H, CH-CH=CH-CH₃), 5.67-5.63 (m, 1H, CH-CH=CH-CH₂), 5.20-5.19 (m, 1H, CH-CH-O), 1.98-1.56 (m, 2H, CH₂-CH₂-CH-O), 1.22-1.18 (m, 4H, CH₂-CH₂-CH₂-CH); 13C NMR (100.6 MHz, CDCl₃) δ 159.6 (C, O-C-N), 132.5 (C, CH-CH=CH), 122.2 (CH, CH=CH-CH₂) 70.7 (CH, CH₂-CH-O), 29.2 (CH₂, CH₂-CH₂-CH-O), 25.0 (CH₂, CH₂-CH₂-CH=CH), 18.0 (CH₂, CH₂-CH₂-CH₂); in agreement with literature data.²⁷⁸

4.3 Experimental data for section 2.3.

General method for hydroxycarbamate nitroso ene cyclization with methyl proton abstraction, Method E (2.46a, 2.47a-d, 2.51): 50% H₂O₂ [aq] (0.041 g, 0.6 mmol) was added to a mixture of the hydroxycarbamate (0.5 mmol), with FeCl₃•6H₂O (0.005 g, 4 mol %) catalyst, in i-PrOH (4 mL), at 0°C.
The reaction mixture was brought to room temperature and left for 18 h. The mixture was then diluted with 1 M HCl\((aq)\) (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were evaporated and the residue was purified by chromatography on silica with 2:1 → 1:1 petroleum ether/EtOAc as an eluent. The oxazolidinones 2.82a-d were formed as a 2:1 mixture of syn and anti diastereoisomers, which were readily separated by column chromatography to give pure isomers. 2.82d was formed as a 5:1 syn:anti mixture when cyclised at -20°C in accordance with the above method.

General method for the above reaction using a copper catalyst, Method F (2.46a, 2.47a-d, 2.51):
50% H\(_2\)O\(_2\)\((aq)\) (0.041 mL, 0.6 mmol) was added, using a 1 mL syringe, to a mixture of the hydroxamic acid (0.5 mmol), with Cu(OTf\(_2\)) (0.004 g, 2 mol %) catalyst, in THF (4 mL), at 0°C. The reaction mixture was brought to room temperature and left for 18 h. The mixture was then diluted with 1M HCl\((aq)\) (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were evaporated and the residue was purified by chromatography on silica with 2:1 → 1:1 petroleum ether/EtOAc as an eluent. The oxazolidinones 2.82a-d were formed as a 2:1 mixture of syn and anti diastereoisomers, which were readily separated by column chromatography to give pure isomers (for the yields given by this method, see Table 2.3, entry 1, Table 2.5 entry 1, and Table 2.6, entries 1, 5, 13 and 21).

General method for hydroxycarbamate cyclization using PhIO or PhI(OAc)\(_2\) oxidants, Method G (2.47a-d, 2.51):
PhI(OAc)\(_2\) (0.12 g, 0.38 mmol) or PhIO (0.08, 0.38 mmols) was added to the appropriate hydroxycarbamate (0.5 mmol) in CH\(_2\)Cl\(_2\) (4 mL), at either room temperature or -20°C, and reacted for 18 h (PhIO was added dropwise in CH\(_2\)Cl\(_2\) (4 mL). The mixture was then diluted with 1 M HCl\((aq)\) (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were evaporated and the residue was purified by chromatography on silica with 2:1 → 1:1 petroleum ether/EtOAc as an eluent. The oxazolidinones 2.82a-c were formed as a 2:1 mixture of syn and anti diastereoisomers, which were readily separated by column chromatography to give pure isomers. 2.82d was formed as a 5:1 syn:anti mixture with PhI(OAc)\(_2\) oxidation at -20°C (see Table 2.5, entry 1, Table 2.5 entry 1, and Table 2.6, entries 11, 12, 17, 20 and 23 for yields and specific methods).

General method for hydroxycarbamate cyclization with a chiral metal catalyst, Method H (2.46a):
The appropriate asymmetric ligand (mol % given in Table 2.10) was added with the metal catalyst
(Cu(OTf)$_2$ (2 mol %), Cu$_2$I (0.2 mol %) or FeCl$_3$ (4 mol %), or VO(acac)$_2$ (2 mol %)) to the appropriate solvent (4 mL) and left for 5 mins. 50% H$_2$O$_2$ (aq) (0.041 g, 0.6 mmol) was then added to the mixture with hydroxycarbamate 2.46a (0.065 g, 0.5 mmol), at 0°C. The reaction mixture was brought to room temperature (unless otherwise stated in Table 2.10) and left until product disappearance was confirmed by TLC. The mixture was then diluted with 1 M HCl (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were evaporated and the enantiopurity of the residue was established using a GC column, as described in Appendix A (see Table 2.10, entries 1-15 and 18-20, for yields and specific methods).

General method for hydroxycarbamate cyclization with (S)-Ti-BINOL (2.116), and PhI(OAc)$_2$ oxidation, Method I (2.51): The appropriate ligand 2.116 (4 mol %) was added to the hydroxycarbamate 2.51 (0.072 g, 0.5 mmol) in CH$_2$Cl$_2$ (4 mL) and left for 5 mins at -20°C. PhI(OAc)$_2$ (0.12 g, 0.38 mmol) was then added to the mixture which was reacted at -20°C until product disappearance was confirmed by TLC. The mixture was then diluted with 1 M HCl (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were evaporated and the enantiopurity of the residue was established using a GC column, as described in Appendix A (10% yield of racemic 2.80, see Table 2.10 entry 22).

General method for hydroxycarbamate cyclization with a H-bonding chiral controller and PhI(OAc)$_2$ oxidation, Method J (2.51): The appropriate ligand (10 mol %, with the exception of 0.22 mol % for 2.112) was added to the hydroxycarbamate 2.51 (0.072 g, 0.5 mmol) in the appropriate solvent (4 mL) and left for 5 mins at -20°C. PhI(OAc)$_2$ (0.12 g, 0.38 mmol) was then added to the mixture which was reacted at -20°C until product disappearance was confirmed by TLC. The mixture was then diluted with 1 M HCl (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were evaporated and the enantiopurity of the residue was established using a GC column, as described in Appendix A (see Table 2.10, entry 16 and Table 2.11, entries 6 and 14, for yields and specific methods).

General method for hydroxycarbamate cyclization with a H-bonding chiral controller and n-BuNIO$_4$ oxidation, Method K (2.51): The appropriate ligand (10 mol %, apart from 2.112, 0.22 mol %) was added to the hydroxycarbamate 2.51 (0.072 g, 0.5 mmol) in the appropriate solvent (4 mL) and left for 5 mins at -20°C. n-BuNIO$_4$ (0.22 g, 0.5 mmol) was then added to the mixture dropwise in 4 mL of
the reaction solvent. The reaction was left until product disappearance was confirmed by TLC. The mixture was then diluted with 1 M HCl (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were evaporated and the enantiopurity of the residue was established using a GC column, as described in Appendix A (see Table 2.10, entry 17, and Table 2.11, entry 3 and 11-13, for yields and specific methods).

General method for hydroxycarbamate cyclization with a H-bonding chiral controller and PhI(OAc)$_2$ oxidation, Method L (2.51): The appropriate ligand (10 mol %) was added to the hydroxycarbamate 2.51 (0.072 g, 0.5 mmol) in the appropriate solvent (4 mL) and left for 5 mins at -20°C. FeCl$_3$•6 H$_2$O (0.005 g, 4 mol %) catalyst was then added to the mixture, followed by 50% H$_2$O$_2$ (aq) (0.03 mL, 0.6 mmol), added using a 1 mL syringe. The mixture was reacted at -20°C until product disappearance was confirmed by TLC. The mixture was then diluted with 1 M HCl (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were evaporated and the enantiopurity of the residue was established using a GC column, as described in Appendix A (see Table 2.11, entries 2, 5, 7, 8 and 10, for yields and specific methods).

General method for hydroxycarbamate cyclization with a H-bonding chiral controller and Cu(OTf)$_2$ catalysis, Method M (2.51): The appropriate ligand (10 mol %) was added to the hydroxycarbamate 2.51 (0.072 g, 0.5 mmol) in the appropriate solvent (4 mL) and left for 5 mins at -20°C. Cu(OTf)$_2$ (0.004 g, 2 mol %) catalyst was then added to the mixture, followed by 50% H$_2$O$_2$ (aq) (0.03 mL, 0.6 mmol), added using a 1 mL syringe. The mixture was reacted at -20°C until product disappearance was confirmed by TLC. The mixture was then diluted with 1 M HCl (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were evaporated and the enantiopurity of the residue was established using a GC column, as described in Appendix A (see Table 2.11, entries 1, 4 and 9 for yields and specific methods).
4-Ethenyl-N-hydroxyoxazoline-2-one (2.81a): (obtained by method E) off-white wax, 0.039 g, yield 60%. Rf = 0.6 (silica, petroleum ether/ethyl acetate 1:1); \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.57 (br s, 1H, O\( \text{-C} \)H), 5.42 (d, \( J = 16.8 \) Hz, 1H, CH=CH\(_2\)), 5.37 (d, \( J = 10.2 \) Hz, 2H, CH=CH\(_{-}\)H (\( cis \))), 4.37 (t, \( J = 8.2 \) Hz, 1H, O-CH-H), 4.28 (q, \( J = 8.2 \) Hz, 1H, N-CH-CH), 3.92 (t, \( J = 8.2 \) Hz, 1H, O-CH-H); \( ^{13} \)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta \) 160.3 (C, O-\( \text{-C} \)H-N), 132.3 (CH, CH=CH\(_2\)), 122.3 (CH\(_2\), CH=CH\(_2\)), 66.2 (CH\(_2\), O-CH\(_2\)-CH), 62.8 (CH, N-CH-CH); IR (NaCl) \( \nu \) 3359 (O\( \text{-H} \)), 2982 (C-H), 1717 (C=O), 1258; MS (ESI) \( m/z \) 130.1 (90, M+H\(^+\)), 152 (100, M+Na\(^+\)); HRMS (ESI) 130.0494 (C\(_5\)H\(_8\)O\(_3\)N (M+H\(^+\)) requires 130.0504).

4-Ethenyl-N-hydroxyazoline-2-one (2.104): (obtained by method H) brown oil, 0.013g, 20% yield. \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 5.85-5.79 (m, 1H, CH-CH=CH\(_2\)), 5.31-5.28 (m, 2H, CH=CH\(_{-}\)H, 4.58-4.52 (m, 1H, O-CH-H), 4.36-4.32 (m, 1H, O-CH-H), 2.52-2.48 (m, 1H, N-CH-CH) (assignment tentative).

4-(1-Methylethenyl)-N-hydroxyoxazoline-2-one (2.80): (obtained by method E) white needles, 0.043, 60% yield. Rf = 0.6 (silica, petroleum ether/ethyl acetate 1:1); m.p. 74.5-75°C; \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.11 (br s, 1H, O\( \text{-C} \)H), 5.06 (br s, 1H, C=CH-H), 5.03 (br s, 1H, C=CH-H), 4.37-4.32 (m, 2H, O-CH\(_2\)-CH), 3.96 (t, \( J = 12.6 \) Hz, 1H, N-CH-CH\(_2\)), 1.76 (s, 3H, C-CH\(_3\)) \( ^{13} \)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta \)
160.7 (C, N-C-O), 139.2 (C, CH=C=CH₂), 116.9 (CH₂, CH=CH₂), 65.7 (CH₂, O-CH-CH), 64.8 (CH, N-CH-CH), 17.6 (CH₃, C-CH₃); in agreement with literature data.¹²⁰

3-Methyl-4-ethenyl-N-hydroxyoxazoline-2-one (2.82a): (obtained by method E) colourless oil, 0.041 g, 58% yield; Rf = 0.6 (silica, petroleum ether/ethyl acetate 1:1); ¹H NMR (400 MHz, CDCl₃) δ major syn isomer 7.66 (br s, 1H, OH), 5.73 (ddd, J = 17.2, 10.1, 8.4 Hz, 1H, CH-CH=CH₂), 5.42 (d, J = 10.1 Hz, 1H, CH=CH-H (cis)), 5.39 (d, 1H, J = 17.2 Hz, CH=CH-H (trans)), 4.67-4.60 (m, 1H, O-CH-CH₃), 4.28-4.24 (m, 1H, N-CH-CH), 1.25 (d, J = 6.8 Hz, 3H, CH₃); minor anti isomer (taken as mixture with major isomer) 7.91 (br s, 1H, OH), 4.19 (dq, J = 9.2, 6.6 Hz, 1H, O-CH-CH₃), 3.85-3.81 (m, 1H, N-CH-CH), 1.38 (d, J = 6.6 Hz, 3H, CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ major syn isomer 160.1 (C, N-C-O), 130.0 (CH, CH-CH=CH₂), 122.9 (CH₂, CH=CH₂), 73.4 (CH, O-CH-CH₃), 65.8 (CH, N-CH-CH) 16.0 (CH₃, CH-CH₃); IR (NaCl) v 3229 (O-H), 2980 (C-H), 1763 (C=O), 1385; MS (ESI) m/z % 144.1 (M+H⁺ 100), 158.1 (20), 180.1 (96) 233 (2); HRMS (ESI) 144.0652 (C₈H₁₀O₃N (M+H⁺) requires 144.0655).

3-Propanyl-1-ethenyl-N-hydroxyoxazoline-2-one (2.82b): (obtained by method E) colourless oil, 0.054 g, 63% yield; Rf = 0.6 (silica, petroleum ether/ethyl acetate 1:1); ¹H NMR (400 MHz, CDCl₃) δ major syn isomer 8.21 (br s, 1H, OH), 5.71 (ddd, J = 16.8, 10.4, 6.8 Hz, 1H, CH-CH=CH₂), 5.41 (d, J = 16.8 Hz, 1H, CH=CH-H (trans)), 5.37 (d, J = 10.4 Hz, 1H, CH=CH-H (cis)), 4.48-4.30 (m, 1H, O-CH-CH₃), 4.26 (apparent t, J = 6.8 Hz, 1H, N-CH-CH), 1.59-1.55 (m, 2H, CH₂-CH₂-CH₂), 1.51-1.21 (m, 2H, CH₂-CH₂-CH₂), 0.83 (t, J = 8.6 Hz, 3H, CH₃); minor anti isomer 7.80 (br s, 1H, OH), 5.73-5.67 (m, 1H, CH-CH=CH₂), 5.48-5.43 (m, 2H, CH=CH₂), 4.05-4.02 (m, 1H, O-CH-CH₂), 3.88-3.86 (m, 1H, N-CH-CH), 1.59-1.55 (m, 2H, CH₂-CH₂-CH₂), 1.51-1.21 (m, 2H, CH₂-CH₂-CH₂), 0.79-0.76 (m, 3H, CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ major syn isomer 160.2 (C, O-C-N), 130.0 (CH, CH-CH=CH₂), 122.8 (CH₂, C-CH₂),
77.0 (CH, O-CH-CH), 65.7 (CH, N-CH-CH), 32.2 (CH₂, CH-CH₂-CH₂), 18.6 (CH₂, CH-CH₂-CH₃), 13.7 (CH₃, CH₂-CH₃); IR (NaCl) ν 3415 (O-H), 2960-2854 (C-H), 1760 (C=O), 1466-1428, 1090; HRMS (ESI) 172.0964 (C₆H₁₂NO₃ (M+H⁺) requires 172.0968).

3-isopropyl-1-ethenyl-N-hydroxyoxazoline-2-one (2.82c): (obtained by method E) colourless oil, 0.053 g, 62% yield (2:1 mixture of syn and anti isomers). Rf = 0.6 (silica, petroleum ether/ethyl acetate 1:1); ¹H NMR (400 MHz, CDCl₃) δ, major syn isomer 7.05 (br s, 1H, OH), 5.73 (ddd, J = 16.8, 9.6, 9.6 Hz, 1H, CH-CH=CH₂), 5.45 (d, J = 9.6 Hz, 1H, CH=CH-H (cis)), 5.42 (d, J = 16.8 Hz, 1H, CH=CH-H (trans)), 4.23 (dd, J = 9.6, 6.8 Hz, 1H, O-CH-CH), 4.03-3.99 (m, 1H, N-CH-CH), 1.98-1.88 (m, 1H, CH₃-CH-CH₃), 0.99 (d, J = 6.4 Hz, 3H, CH₃-CH-CH₃), 0.81 (d, J = 6.4 Hz, 3H, CH₃-CH-CH₃); minor anti isomer (taken from TOCSY spectra of mixture) 7.90 (br s, 1H, OH), 5.81 (ddd, J = 17.0, 10.1, 7.8 Hz, 1H, CH-CH=CH₂), 5.49 (d, J = 17.0 Hz, 1H, CH=CH-H (trans)), 5.43 (d, J = 10.1 Hz, 1H, CH=CH-H (cis)), 4.08-4.04 (m, 1H, O-CH-CH), 3.85 (dd, J = 8.8, 6.0 Hz, 1H, N-CH-CH), 2.02-1.94 (m, 1H, CH₂-CH-CH₃), 1.04 (d, J = 6.8 Hz, 3H, CH₂-CH-CH₃), 1.00 (d, J = 6.8 Hz, 3H, CH₂-CH-CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ major syn isomer 159.9 (C, O-C-N), 128.9 (CH, CH-CH=CH₂), 123.6 (CH₂, CH=CH₂), 81.9 (CH, O-CH-CH), 66.0 (CH, N-CH-CH), 28.1 (CH, CH₂-CH-CH₃), 18.6 (CH₃, CH₃-CH-CH₃), 17.6 (CH₂, CH₃-CH-CH₃), IR (NaCl) ν 3350 (O-H), 2962 (C-H), 1720 (C=O); HRMS (ESI) 170.0826 (C₆H₁₂NO₃ (M+H⁺) requires 170.0812).

Figure 4.1: Syn and anti isomers of 2.82c

NMR analysis of 2.82c. (See Appendix B for all relevant spectra) Syn and anti isomers of 2.82c were clearly displayed in the H¹ NMR spectrum as major and minor components. Jₙ₁H coupling constants derived from the NMR spectrum of the syn/anti mixture are significantly different for each form, and
conformationally distinct. This indicates that these spectra may give diagnostic structural information.

The chemical shifts of the protons in the syn/anti mixture are sufficiently different to allow a 1D TOCSY spectrum to be recorded, which shows coupled multiplets from the CH$_3$ of the methyl group, through to the =CH$_2$ of the alkene for each stereoisomer. The proton NMR signals for the syn and anti forms can be separated and all multiplets extracted and analysed. The multiplet of the isopropyl CH proton is different for each form. Analysis of the multiplets using SpinWorks (Kirk Marat, http://home.cc.umanitoba.ca/~wolowiec/spinworks/index.html) produced a significantly different coupling constant 9.6Hz (syn) and 6.05Hz (anti) to the ring CH, which indicates a different conformation in the two forms (or different weighting of rotamer in an ensemble average). To accommodate the previously determined couplings to the isopropyl proton, the CH-CH multiplets at 3.95–4.15 ppm, which are visually very similar for the two forms, should contain a significantly different coupling in the syn and anti forms. Analysis showed that $^3J_{HA-HB} = 6.3$Hz (syn) and 8.74 Hz (anti). Further geometry information can be gleaned by converting these experimental coupling constants into calculated dihedral angles using the Karplus equation,\(^{320}\) calculating the geometry using Gaussian,\(^{321}\) and then calculating the expected coupling. The expected dihedral angle between C-H$_a$ and C-H$_b$ for an experimentally derived $^3J_{HH}$ coupling of 8.7 Hz is 172 ° (anti). This experimentally measured coupling is much larger than can be expected for the syn derivative. The expected dihedral angle between C-H$_a$ and C-H$_b$ for an experimentally derived $^3J_{HH}$ coupling of 6.3 Hz is 28 ° or 147 ° (syn or anti). This coupling constant supports identification of the major isomer as syn.

Calculated geometries from Gaussian-03 (B3LYP/6-31G(d)), give CH$_2$-CH$_b$ dihedral angles of 156 ° for the anti stereoisomer, and 26 ° for the syn, which match well to the estimated dihedral values from experimental couplings 172 ° and 28 ° respectively.

Selective 1D NOESY spectra were not diagnostic. Complex spectra were produced containing multiple step-wise nOes from near neighbours, which displayed anti-phase signals masking true nOes.

**TOCSY:** Spectra were recorded using the selmlgp.2 pulse program with $\tau_0 = 15.25$ µs covering a sweep width 20.7 ppm (8278 Hz), with 64k time domain data points, giving an acquisition time of 3.95 seconds. Selective shaped-pulses (Gauss 1.1, 40 ms, 70 dB) were used to irradiate individual signals in the NMR spectrum and a MLEV-17 mixing time of 0.06 seconds was used to allow the correlations to propagate. Zero-quantum coherencies were suppressed. FIDs were Fourier transformed using 64k data points and referenced to an internal TMS standard at 0.0 ppm.\(^{322, 323, 324, 325}\)
nOe: Spectra were recorded using the selnogp pulse program with $P_{50} = 15.25 \mu s$ covering a sweep width 20.7 ppm (8278 Hz), with 64k time domain data points giving an acquisition time of 3.95 seconds. Selective shaped-pulses (Gauss 5, 40 ms, 70 dB) were used to irradiate individual signals in the NMR spectrum and a mixing time of 0.6 seconds was used to allow the nOe to propagate. FIDs were Fourier transformed using 64k data points and referenced to an internal TMS standard at 0.0 ppm.

3-Cyclohexenyl-1-ethenyl-N-hydroxyoxazoline-2-one (2.82d): (obtained by method E) off-white wax, 0.065 g, 62% yield. Rf = 0.6 (silica, petroleum ether/ethyl acetate 1:1); 2.82d was also synthesised according to Method E, except at -20°C, in CH$_2$Cl$_2$ solvent (0.054 g, 51% yield, 5:1 d.r.).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ major syn isomer 7.09 (br s, 1H, OH), 5.82 (ddd, $J = 16.8$, 10.0 Hz, 1H, CH=CH=CH$_2$), 5.45 (d, $J = 10.0$ Hz, 1H, CH=CH-H (cis)), 5.40 (d, $J = 16.8$ Hz, 1H, CH=CH-H (trans)), 4.21 (dd, 10.0, 6.4 Hz, 1H, O-CH-CH), 4.06 (dd, $J = 10.0$, 6.4 Hz, 1H, N-CH-CH), 1.98-1.94 (m, 1H, CH$_2$-CH-CH$_3$), 1.69-1.50 (m, 6H, CH$_2$-CH$_2$-CH$_2$), 1.21-1.09 (m, 2H, CH$_2$-CH$_2$-CH$_2$), 1.01-0.85 (m, 1H, CH$_2$-CH-CH$_2$); minor anti isomer (taken as mixture with major isomer) 7.35 (br s, 1H, OH), 3.99-3.98 (m, 1H, O-CH-CH), 3.87-3.83 (m, 1H, N-CH-CH); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ major syn isomer 160.1 (C, N-C-O), 129.0 (CH, CH-CH=CH$_2$), 123.4 (CH$_2$, CH=CH$_2$), 80.7 (CH, O-CH-CH), 65.8 (CH, N-CH-CH), 37.2 (CH, CH$_2$-CH-CH$_2$), 28.6 (CH$_2$, CH$_2$-CH-CH$_2$), 27.7 (CH$_2$, CH$_2$-CH-CH$_2$), 26.1 (CH$_2$, CH$_2$-CH$_2$-CH$_2$-CH$_2$), 25.3 (CH$_2$, CH-CH$_2$-CH$_2$-CH$_2$-CH$_2$), 25.1 (CH$_2$, CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$); IR (NaCl) v 3399 (O-H), 2927-2853 (C-H), 1760 (C=O), 1220 (C-O); HRMS (ESI) 234.1096 (C$_{11}$H$_{17}$NO$_3$Na (M+Na$^+$) requires 234.1101).

2-Ethenyl-N-hydroxyoxazinan-2-one (2.85): FeCl$_3$$\cdot$6H$_2$O (0.005 g, 4 mol %) was added to the hydroxycarbamate 2.55 (0.073 g, 0.5 mmol), in i-PrOH (4 mL) at 0°C, and, after the addition of 50%
H₂O₂(aq) (0.10 mL, 1.5 mmols) using a 1 mL syringe, heated to reflux for 18 h. The reaction mixture was then diluted with 1M HCl (20 mL) and extracted with ethyl acetate (3 x 30 mL), the organic fractions were combined and evaporated to give a crude product (2.85, 0.043 g, 60% yield). To obtain an analytically pure sample, the product was acetylated. The crude product was dissolved in dry CH₂Cl₂ (5 mL) at 0°C, to which was added triethylamine (0.061, 0.6 mmols), dried overnight with 4Å MS, and acetic anhydride (0.034 g, 0.33 mmols). The reaction was warmed to room temperature, stirred for 4 h, quenched with H₂O, and then extracted from the aqueous layer with CH₂Cl₂ (3 x 30 mL). The combined organic layers were evaporated and the residue was purified by chromatography on silica with 2:1 → 1:1 petroleum ether/EtOAc as an eluent to give the acetylated product as a colourless oil (2.86, 0.047 g, 82% yield).

2.85 was also synthesised at RT, without any other changes to the method already given, except that the reaction time was 72 h (0.042 g, 58% yield).

Rf = 0.6 (silica, petroleum ether/ethyl acetate 1:1); ¹H NMR (400 MHz, CDCl₃) δ 5.73 (ddd, J = 17.2, 10.0, 6.8 Hz, 1H, CH-CH=CH₂), 5.28 (d, J = 17.2 Hz, 1H, C=CH-H (trans)), 5.23 (d, J = 10.0 Hz, 1H, C=CH-H (cis)), 4.27-4.22 (m, 2H, O-CH₂-CH₂), 2.36-2.28 (m, 1H, N-CH-CH), 2.10 (s, 3H, O=C-CH₃), 2.10-1.93 (m, 2H, CH₂-CH₂-CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 168.0 (C, N-C=O), 151.4 (C, O=C-CH₃), 134.8 (CH, CH-CH=CH₂), 119.0 (CH₂, C=CH₂), 64.2 (CH₂, O-CH₂-CH₂), 62.2 (CH, N-CH-CH), 29.2 (CH₂, CH₂-CH₂-CH), 18.2 (CH₃, O=C-CH₃), IR (NaCl) v 2987 (C-H), 1798 (C≡N), 1732 (C=O), 1265 (C-O); HRMS (ESI) 186.0761 (C₈H₁₂O₄N (M+H') requires 186.0761).

General procedure for hydroxycarbamate cyclization with methylene hydrogen abstraction,
Method N (2.46b-c, 2.53, 2.54, 2.56): FeCl₃•6 H₂O (0.005 g, 4 mol %; 0.02 g, 15 mol % for 2.81c) was added to the appropriate hydroxycarbamate (0.5 mmol) in i-PrOH (6 mL), and, after the addition of 50% H₂O₂(aq) (0.20 mL, 3 mmols) using a 1 mL syringe, heated to 100°C in a sealed vial for 6 h. The mixture was then diluted with 1 M HCl (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were evaporated and the residue was purified by chromatography on silica with 1:2 → 1:1 petroleum ether:EtOAc as an eluent.
**E-4-(But-1-enyl)-N-hydroxyoxazoline-2-one (2.81b):** (obtained by Method N) off-white wax, 0.050 g, 64% yield. Rf = 0.5 (silica, petroleum ether/ethyl acetate 1:1); Major E isomer ¹H NMR (400 MHz, CDCl₃) δ 7.74 (br s, 1H, O-H), 5.86 (dt, J = 15.2, 6.4 Hz, 1H, CH=CH=CH-CH₂), 5.35-5.28 (m, 1H, CH-CH=CH-CH₂), 4.32 (t, J = 8.0 Hz, 1H, O-CH-H), 4.25 (q, J = 8.0 Hz, 1H, N-CH-CH), 3.91-3.84 (m, 1H, O-CH-H), 2.09-2.01 (m, 2H, CH-CH₂-CH₃) 0.95 (t, J = 7.2 Hz, 3H, CH₃-CH₂); δ Minor Z isomer (visible peaks from a mixture of E and Z isomers) 5.90-5.85 (m, 1H, CH-CH=CH-CH₂), 4.66-4.64 (m, 1H, O-CH-H); ¹³C NMR (100.6 MHz, CDCl₃) δ 160.5 (C, O-C-N), 141.0 (CH, CH-CH=CH) 123.0 (CH, CH=CH=CH₂), 66.5 (CH₂, O-CH₂-CH₃), 62.6 (CH, N-CH-CH), 25.3 (CH₃, CH-CH₂-CH₃), 13.0 (CH₃, CH₂-CH₃); IR (NaCl) v 3286 (O-H), 1764 (C=O), 1262; MS (ESI) m/z (%) 158.1 (M+H⁺), 153 (5), 125, 180 (29), 301 (10), HRMS (ESI) 158.0809 (C₇H₁₁O₃N (M+H⁺) requires 158.0812).

**Phenylethenyl-N-hydroxyoxazoline-2-one (2.81c):** synthesised according to Method N, with 0.02 g, (15 mol %) of FeCl₃•H₂O used, and all other quantities remaining unchanged (white solid, 0.010 g, 10% yield. Rf = 0.6 (silica, petroleum ether/ethyl acetate 1:1)).

¹H NMR (400 MHz, CDCl₃) δ 7.36-7.19 (m, 5H, 5 x Ar), 6.71 (d, J = 15.8 Hz, 1H, C-CH=CH-CH₂), 6.03 (ddd, J = 15.8, 7.8 Hz, 1H, C-CH=CH-CH), 4.43-4.38 (m, 2H, O-CH₂-CH), 4.04-3.98 (m, 1H, N-CH-CH); HRMS (ESI) 230.0785 (C₁₁H₁₃O₃NNa (M+Na⁺) requires 230.0788).
4-(Cyclohex-2-enyl)-spiro-N-hydroxyoxazoline-2-one (2.83): (obtained by Method N) white wax, 0.057 g, 65% yield. Rf = 0.6 (silica, petroleum ether/ethyl acetate 1:1). This compound was also synthesised at RT, without any other changes to the general method N, except that the reaction time was 72 h (0.055 g, 62% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.61 (br s, 1H, OH), 6.12 (dt, J = 10.0, 4.0 Hz, 1H, CH=CH-CH\(_2\)), 5.59 (d, J = 10.0 Hz, 1H, C-CH=CH), 4.09 (d, J = 8.4 Hz, 1H, O-CH-H), 4.00 (d, J = 8.4 Hz, 1H, O-CH-H), 2.20-1.90 (m, 2H, CH-CH\(_2\)-CH\(_3\)), 1.75-1.68 (m, 2H, C-CH\(_2\)-CH\(_2\)), 1.61-1.56 (m, 2H, CH\(_2\)-CH\(_2\)-CH\(_2\)); \(^13\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 159.3 (C, O=CH), 135.8 (CH, C-CH=CH), 125.9 (CH, CH=CH-CH\(_2\)), 71.6 (CH\(_2\), O-CH\(_2\)-C), 62.8 (C, CH\(_2\)-C-CH), 24.3 (CH\(_2\), C-CH\(_2\)-CH\(_2\)), 22.7 (CH\(_2\), CH-CH\(_2\)-CH\(_2\)), 19.2 (CH\(_2\), CH\(_2\)-CH\(_2\)-CH\(_2\)); IR (NaCl) v 3271 (O-H), 2925 (C-H), 1713 (C=O), 1641 (C=C), 1263 (C-O); MS (ESI) m/z (%) 180 (M+H\(^+\)), 192 (M+Na\(^+\)); HRMS (ESI) 180.0806 (C\(_8\)H\(_{12}\)O\(_3\)N (M+H\(^+\)) requires 180.0812).

1-(Cyclohex-1'-enyl)-N-hydroxyoxazoline-2-one (2.84): (obtained by Method N) white solid, 0.055 g, 60% yield. Rf = 0.6 (silica, petroleum ether/ethyl acetate 1:1); m.p. 73-76°C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.20 (br s, 1H, OH), 5.77 (br s, 1H, C=CH-CH\(_2\)), 4.30-4.23 (m, 2H, O-CH\(_2\)-CH), 3.98-3.92 (m, 1H, N-CH-C), 2.11-1.81 (m, 2H, CH-CH\(_2\)-CH\(_2\)), 1.65-1.52 (m, 2H, C-CH\(_2\)-CH\(_2\)), 1.26-1.11 (m, 2H, CH\(_2\)-CH\(_2\)-CH\(_2\)), 0.91-0.75 (m, 2H, CH\(_2\)-CH\(_2\)-CH\(_2\)); \(^13\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 160.9 (C, O-C-N), 131.6 (C, CH=C=CH), 129.4 (CH, C=CH-CH\(_2\)), 65.6 (CH\(_2\), O-CH\(_2\)-CH), 65.5 (CH, N-CH-C), 25.1 (CH\(_2\), CH-CH\(_2\)-CH\(_2\)), 22.3 (CH\(_2\), C-CH\(_2\)-CH\(_2\)), 22.2 (CH\(_2\), CH\(_2\)-CH\(_2\)-CH\(_2\)), 22.2 (CH\(_2\), CH\(_2\)-CH\(_2\)-CH\(_2\)); IR (NaCl) v, 3269 (O-H), 2928 (C-H), 1765 (C=O); HRMS (ESI) 206.0284 (C\(_8\)H\(_{13}\)O\(_3\)NNa (M+Na\(^+\)) requires 206.0288).
3-Ethyl-4-methyl-4(prop-2'-enyl)-N-hydroxyoxazoline-2-one (2.87): (obtained by Method N) colourless oil, 0.083g, 90% yield. Rf = 0.6 (silica, petroleum ether/ethyl acetate 1:1); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.74 (dq, $J = 15.6, 6.4$ Hz, 1H, C-CH=CH-CH$_3$), 5.33 (dq, $J = 15.6, 1.6$ Hz, 1H, C-CH=CH-CH$_3$), 3.99 (dd, $J = 9.2, 4.0$ Hz, 1H, O-CH-C), 2.01 (br s, 1H, OH), 1.70 (dd, $J = 6.4, 1.6$ Hz, 3H, CH-CH$_3$), 1.68-1.61 (m, 1H, O-CH-CH-H), 1.47-1.41 (m, 1H, O-CH-CH-H), 1.38 (s, 3H, C-CH$_3$), 0.95 (t, $J = 7.2$ Hz, 3H, CH$_2$-CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 159.7 (C, O-C-N), 130.4 (CH, C-CH=CH), 126.4 (CH, CH=CH-CH$_3$), 85.4 (CH, O-CH-C), 66.7 (C, C-CH$_3$), 23.1 (CH$_2$, CH$_2$-CH$_2$-CH$_3$), 20.5 (CH$_3$, C-CH$_3$), 18.1 (CH$_3$, CH$_2$-CH$_3$), 10.1 (CH$_3$, CH$_2$-CH$_3$); IR (NaCl) v 3270 (O-H), 2973 (C-H), 1755 (C=O), 1261 (C-O); HRMS (ESI) 208.0944 (C$_9$H$_{15}$O$_3$NNa (M+Na$^+$) requires 208.0940).

![Image](image-url)

Buten-2-yl oxycarbonyl-4.5-dimethyl-3.6-dihydro-1.2-oxazin (2.97a): 50% H$_2$O$_2$ (aq) (0.068 mL, 1.2 mmol) was added, using a 1 mL syringe, to a mixture of buten-2-yl hydroxcarbamate (1 mmol), FeCl$_3$·6H$_2$O (0.011 g, 4 mol %) catalyst and 2,3-dimethylbutadiene (0.16 g, 2.0 mmol), in i-PrOH (4 mL). The reaction mixture was brought to room temperature and left for 6 h, after which the mixture was worked up from 1M HCl with ethyl acetate (3 x 30 mL). The product was then dried in vacuo, and purified using a silica column with 20:1 → 15:1 PE:EtOAc eluent (yellow oil, 0.10 g, 48% yield).

Rf = 0.6 (silica, petroleum ether/ethyl acetate 1:1); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.85-5.76 (m, 1H, CH=CH-CH$_3$), 5.66-5.58 (m, 1H, CH$_2$-CH=CH), 4.59 (d, $J = 6.4$ Hz, 2H, O-CH$_2$-CH), 4.21 (s, 2H, O-CH$_2$-C), 3.94 (s, 2H, N-CH$_2$-C), 1.73 (d, $J = 9.2$ Hz, 3H, CH=CH-CH$_3$), 1.71 (br s, 3H, O-CH$_2$-C-CH$_3$), 1.70 (br s, 3H, N-CH$_2$-C-CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 155.6 (C, O-C-N), 131.6 (C, O-CH$_2$-C-CH$_3$), 125.3 (C, N-CH$_2$-C-CH$_3$), 123.1 (CH, CH$_2$-CH=CH), 121.8 (CH, CH=CH-CH$_3$), 71.6 (CH$_2$, O-CH$_2$-CH), 66.8 (CH$_2$, O-CH$_2$-C), 48.4 (CH$_2$, N-CH$_2$-C), 17.8 (CH$_3$, O-CH$_2$-C-CH$_3$), 15.2 (CH$_3$, N-CH$_2$-C-CH$_3$), 13.8 (CH$_3$, CH-CH$_3$); IR (NaCl) v 2970 (C-H), 1730 (C=O), 1440, 1225; HRMS (ESI) 234.1096 (C$_{11}$H$_{17}$O$_3$NNa (M+Na$^+$) requires 234.1101).
4',4'-Dimethylbut-2-enyl oxycarbonyl-4,5-dimethyl-3,6-dihydro-1,2-oxazin (2.97b): 50% H₂O₂ (aq) (0.068 mL, 1.2 mmol) was added, using a 1 mL syringe, to a mixture of 4,4-dimethylbut-2-enyl hydroxycarbamate (1.0 mmol), FeCl₃•6H₂O (0.011 g, 4 mol %) and 2,3-dimethylbutadiene (0.164 g, 2 mmols), in i-PrOH (4 mL) at 0°C. The reaction mixture was brought to room temperature and left for 6 h, after which the mixture was diluted with 1M HCl (20 mL) and extracted with ethyl acetate (3 x 30 mL). The product was then dried in vacuo, and purified using a silica column with 20:1 → 15:1 petroleum ether/EtOAc as an eluent (yellow oil, 0.12 g, 50% yield).

Rf = 0.3 (silica, petroleum ether/ethyl acetate 1:1); ¹H NMR (400 MHz, CDCl₃) δ 5.71-5.65 (m, 1H, CH₂=CH); 5.50-5.46 (m, 1H, CH=C(CH₃)₃); 4.54 (d, J = 6.4 Hz, 2H, O-C(CH₃)₂-C); 4.15 (s, 2H, O-C(CH₃)₂-C); 3.88 (s, 2H, N-C(CH₃)₂-C); 2.25-2.24 (m, 1H, CH=CH); 1.60 (br s, 3H, O-CH₂-C(CH₃)₃); 1.52 (br s, 3H, N-CH₂-C(CH₃)₃); 0.94-0.92 (m, 6H, C(CH₃)₃); 13C NMR (100.6 MHz, CDCl₃) δ 155.7 (C, O-C(CH₃)₂-N); 143.4 (C, O-C(CH₃)₂-C); 123.1 (C, N-CH₂-C(CH₃)₃); 121.8 (CH, CH₂-C=CH); 121.1 (CH, CH=CH-C(CH₃)₃); 121.0 (CH, CH=CH-C(CH₃)₃); 71.6 (CH₂, O-CH₂-C(CH₃)₃); 67.0 (CH₂, O-CH₂-C(CH₃)₃); 48.4 (CH₂, N-CH₂-C(CH₃)₃); 30.8 (CH, CH=CH-C(CH₃)₃); 22.0 (CH₃, O-CH₂-C(CH₃)₃); 13.9 (CH₃, N-CH₂-C(CH₃)₃); 13.8 (CH₃, CH₃-C(CH₃)₃); IR (NaCl) ν 2964 (C-H), 1713 (C=O); 1267; HRMS (ESI) 262.1414 (C₁₃H₂₁O₃NNa (M+Na⁺) requires 262.1406).

4.4 Experimental data for section 2.4.

Dichlorotris(triphenylphosphine)ruthenium(II):³²⁶ To ruthenium trichloride trihydrate (1.25 g, 4.8 mmols) in methanol (50 mL) was added a sixfold excess of triphenylphosphine (7.55 g, 28.8 mmols). After heavy stirring for 15 mins, the undissolved powder was filtered off, and the solution stirred at RT for 25 h, under nitrogen. The solution was then heated to reflux, and stirred under nitrogen for a further 6 h. The reddish-brown crystals produced were filtered off, washed with methanol, and dried under vacuum. The product identity was confirmed using elemental analysis (1.71 g, 37% yield).

General procedure for Ruthenium-Salen complex synthesis (2.114-115): Triethylamine (0.24 g, 2.4 mmols) was added to a mixture of the appropriate salen ligand (0.4 mmols) and dichlorotris(triphenylphosphine)ruthenium(II) (0.36 g, 0.38 mmols). The reaction was stirred for 2 h
under reflux, and the precipitate collected by filtration, for recrystallisation in a hexane:CH$_2$Cl$_2$ mixture (6:1). The product precipitated out of solution after being refrigerated overnight.

\[
\text{N,N'-Bis(3,5-dinitro-salicylidene)-1,2-cyclohexanediamine bis (triphenylphosphine) ruthenium(II) (2.114): dark solid, 0.131 g, 39\% yield. } \]

$^1$H NMR (400 MHz, acetone-d$_6$) $\delta$ 8.25 (s, 2H, 2 x Ar), 7.52-7.20 (m, 2H, 2 x Ar), 7.16-7.14 (m, 30H, Ar), 6.28 (d, $J = 7.2$ Hz, 2H, 2 x C-CH=N), 3.35-3.28 (m, 2H, 2 x N-CH-CH$_2$), 2.18-1.43 (m, 8H, CH$_2$-CH$_2$-CH$_2$-CH$_2$); $^{13}$C NMR (100.6 MHz acetone-d$_6$) $\delta$ 173.5 (CH, Ar), 156.9 (CH, Ar), 128.5 (CH, 2 x C-CH=N), 73.9 (CH, 2 x N-CH-CH$_2$), 28.8 (CH$_2$, 2 x CH-CH$_2$-CH$_2$), 24.7 (CH$_2$, CH$_2$-CH$_2$-CH$_2$-CH$_2$); in agreement with literature data.$^{61}$

(Reacted with dichlorotris(triphenylphosphine)ruthenium(II) as above to give 2.115, complex used directly without isolation in cyclisation of 2.46a (see Table 2.8, entry 22))

\[
\text{N,N'-Bis(3,5-tert-butyrsalicylidene)-1,2-cyclohexanediamine (3.1): dark solid } \]

$^1$HNMR (400 MHz, CDCl$_3$) $\delta$ 10.18 (br s, 2H, 2 x OH), 7.36-7.25 (m, 2H, 2 x Ar), 7.18-6.97(m, 2H, 2 x Ar), 3.13-3.08 (m, 2H, 2x C-CH=N), 3.42 (m, 2H, N-CH-CH$_2$), 1.98-1.96 (m, 2H), 1.95-1.91 (m, 2H,), 1.35-1.30 (m, 18H, 6 x C-CH$_3$), 1.15-1.09 (m, 18H, 6 x C-CH$_3$); in agreement with literature data.$^{327}$
(R)-(1,1-binaphthalen-2,2-yl)dioxytitanium dichloride (2.116) \textsuperscript{296,297} \textsuperscript{2} TiCl\textsubscript{2} (0.59 g, 5.0 mmol) was added dropwise to Ti(IV)(i-PrO)\textsubscript{4} (0.54 g, 5.0 mmol), in hexane (5 mL). The mixture was stirred for 10 mins, in which time it was visibly warmed by the reaction, and then left to stand for 6 h without further heating. The solid product was isolated by removing the solvent with a syringe, and washed with dry hexane (2 x 20 mL). The precipitate of diisopropoxytitanium dichloride that was isolated (0.98 g, 82% yield) was added to (R)-BINOL (1.17 g, 4.1 mmols), in CH\textsubscript{2}Cl\textsubscript{2} (4 mL) with 4Å MS and under an N\textsubscript{2} atmosphere. This mixture was stirred for 1 h. Due to the high sensitivity of 2.116 to moisture it was not isolated in a pure state. Aliquots were taken from the CH\textsubscript{2}Cl\textsubscript{2} solution, with concentration of 2.116 estimated at 1 mmol/mL, and added to the nitroso ene cyclisation of 2.51 as described in section 2.4.1.

Oxodiperoxymolybdenum (pyridine) (Hexamethylphosphoric triamide) 3.0 g (21.0 mmol) of molybdenum trioxide was dissolved in 50% H\textsubscript{2}O\textsubscript{2} solution (9.0 mL, 0.265 mol), and heated to 35-40°C over an oil bath for 30 mins, after which the temperature was maintained at 40°C for 3.5 h. After this, the solution was cooled to RT, filtered, and HMPA (3.76 g, 21.0 mol) added dropwise over 5 minutes. The new precipitate was filtered off, recrystallised in neat methanol and then dried in a vacuum desiccator, whilst being sheltered from light, overnight. This yellow powder was then dissolved in 20ml THF, and pyridine 0.8 g added dropwise at RT over 30 mins. The yellow crystalline product was washed with THF (20 mL) and dried under vacuum (2.64 g, 30% yield).

MP 114-15.4°C \textsuperscript{328}
(R)-3,3’-bis(3,5-bis(trifluoromethyl)phenyl)-1,1’-binaphthyl-2,2’-diylcopperphosphate (3.2): Cu₂O (0.001 g, 0.01 mmol) was added to (0.015 g, 0.02 mmol) of (R)-3,3’-bis(3,5-
bis(trifluoromethyl)phenyl)-1,1’-binaphthyl-2,2’-diylhydrogenphosphate, in dry MeCN (2 mL), under
N₂ atmosphere. After 2 h, when the absence of a solid suspension of Cu₂O indicated complete
formation of the complex, the solvent was removed via syringe, and the product (0.016 g, suggesting
approximately 90% crude yield) used directly in a nitroso ene cyclisation of 2.46a or 2.51.
5. References


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Appendix A: GC analysis of attempted enantioselective cyclisations

The enantiopurity of the oxazolidinone products 2.81a and 2.80, as synthesised by the methods described in section 2.4, was analysed using a chiral GC column. The GC column was calibrated using a pure racemic sample of 2.81a. It was determined by testing several separation conditions that chromatography using a Supelco gamma-DEX 120 column, 2 minutes injection time, an initial temperature of 100°C, and +1.5°C/min temperature gradient, gave the best separation of 2 peaks with roughly equal area on the GC trace. In the absence of any other peaks, these were identified as the two enantiomers of racemic 2.81a (a β-CD chiral column was also tested, giving inferior separation). Calibration of the same column with a racemic sample of 2.80 showed that same conditions were also optimal for separating the enantiomers of 2.80. Chiral separation of a racemic sample of 2.81b showed that a β-CD column gave the best separation for this oxazolidinone with 2 mins injection time, 120°C initial temperature and 1.5°C/min temperature gradient. The GC traces (generated using Clarity – Chromatography SW software) for racemic calibration samples are given below, with exemplary traces for the experimental products analysed by GC for enantiopurity. All experimental products tested gave two peaks of equal area, identified as the enantiomers of the oxazolidinone by comparison with traces from racemic samples. This indicated that all nitroso ene cyclisations that were carried out gave racemic products, and that further research would be required to develop an enantioselective intramolecular nitroso ene reaction.
Figure A1: GC trace for racemic sample of 2.81a

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<th>Height [mV]</th>
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<th>Height [%]</th>
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Figure A2: GC trace for 2.81a, product of entry 15, Table 2.9

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</table>
Figure A3: 2 GC traces for racemic samples of 2.81b
Appendix B: determination of oxazolidinone stereochemistry

The oxazolidinones 2.82a-d were synthesised as a 2:1 mixture of stereoisomers (see section 2.3.4). The very similar structure, NMR spectra and stereoisomeric ratios of all these products allowed us to analyse the stereochemistry of the single oxazolidinone 2.82b as representative of the whole series. The H¹ NMR spectrum in Figure B1 shows a crude reaction mixture of 2.82b. Two sets of peaks from 4.45 ppm to 3.85 ppm, in a 2:1 ratio by peak area, were judged to correspond to two different stereoisomers. The spectra of the isolated minor isomer of 2.82b is given in Figure B2, with peaks at 4.05 ppm (CH₂-CH-CH=CH₂) and 3.85 ppm (CH₂-CH), distinct from the spectra of the isolated major product, given in section 4.3. The isolation of these two molecules, with ¹H NMR spectra showing no structural variation, allows them to be identified as two stereoisomers of the target product. Two similar sets of peaks were seen for all spectra of crude reaction mixtures for 2.82a-d, indicating that two stereoisomers are formed for all these compounds. The best resolution of stereoisomeric signals was seen for 2.82b, while the peaks for the two stereoisomers of 2.82c at 4.05-3.95 ppm are distinguishable, but not entirely resolved, as shown in Figure B3.

The relative configuration of the major and minor isomers was determined using NOESY and TOCSY NMR spectroscopy of a 2:1 stereoisomeric mixture of 2.82c (shown in Figure B4 and Figure B5), as described with the NMR data for 2.82c in section 4.3, which supported assignment of the minor stereoisomer as anti and the major as syn. NOEY NMR of 2.87 (results shown in Figure B6-Figure B8) was also undertaken to confirm that the synthesis of this compound had given a single synthesised isomer produced by a stereoselective reaction (This was implied by the single set of ¹H NMR peaks observed for the spectrum of pure 2.87), and determine the relative configuration of the isomer synthesised. The results of NOESY spectroscopy indicated that 2.87 had been synthesised as a syn stereoisomer, with >25:1 stereoselectivity. A clear cross coupling is shown between the ring proton (O-CH-C) and the ring methyl group (C-CH₃), indicating that these protons are close together in space; that is, arranged syn to each other. There is also no cross coupling visible between the ring proton and the vinyl proton (C-CH=CH₂); irradiation of the vinyl proton also showing no cross-coupling with the ring proton, confirming that their arrangement is anti. Literature H¹ NMR spectra for the allylic alcohols Z-2.15, E-2.15, (anti)-2.32 and (syn)-2.32 are also given in Figure B14-Figure B17. These spectra were used to assign the stereochemistry and positional isomerism of the products from the allylic alcohol synthesis and rearrangement to give 2.15 with trans as the major isomer, discussed in section 2.2.2.
Figure B1: $^1$H NMR of 2.82b crude reaction product (shows 2:1 ratio of syn/anti stereoisomers)
Figure B2: H$^1$ NMR of 2.82b purified anti stereoisomer
Figure B3: H$^1$ NMR of 2.82c crude reaction product (shows 2:1 ratio of syn/anti stereoisomers)
Figure B4: TOCSY NMR spectra of crude 2.82c sample
Figure B5: 1D TOCSY NMR spectra of crude 2.82c sample
Figure B6: NOSEY NMR spectra of pure sample of 2.87
Figure B7: 1D NOSEY NMR spectra of pure sample of 2.87
Figure B8: 2D NOSEY NMR spectra of pure sample of 2.87
Figure B9: literature H\textsuperscript{1} NMR spectra of pure sample of (\textit{E})-2.15
Figure B10: literature H$^1$ NMR spectra of pure sample of (Z)-2.15
Figure B11: literature H$^1$ NMR spectra of pure sample of syn-2.32
Figure B12: literature $^1$H NMR spectra of pure sample of anti-2.32
Appendix C – Intramolecular Carbonyl Nitroso Ene Reaction Catalyzed by Iron(III) Chloride/Hydrogen Peroxide as an Efficient Tool for Direct Allylic Amination
Intramolecular Carbonyl Nitroso Ene Reaction Catalyzed by Iron(III) Chloride/Hydrogen Peroxide as an Efficient Tool for Direct Allylic Amination

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Dedicated to Professor Pavel Kočovský on the occasion of his 60th birthday.

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Abstract: A mild, simple oxidation protocol employing iron(III) chloride as a catalyst and hydrogen peroxide as a stoichiometric oxidant was found to be compatible with an intramolecular carbonyl nitroso ene reaction and allowed us to efficiently convert hydroxamic acids into a diverse range of 1,2- and 1,3-amino alcohol derivatives in a single operation.

Keywords: amination; amino alcohols; cyclization; ene reaction; oxidation

Amino alcohols, particularly 1,2- and 1,3-derivatives, are commonly featured in many pharmaceuticals and natural products, and they also find wide use as synthetic building blocks. [1] In recent years, synthetic strategies towards these structural motifs employing C–H functionalization as a key bond-forming event are increasingly gaining momentum. [2]

Intramolecular allylic amination (1→2, Scheme 1) can be accomplished in the presence of Pd(II) [3,4] and Rh(II) [5] catalysts, however, in the latter case allylic C–H insertion of nitrenes competes with aziridination, furnishing a mixture of the respective products 2 and 3 (Scheme 1).

Scheme 1. Transition metal-catalyzed intramolecular amination.

The nitroso ene reaction is another type of allylic amination that can give rise to similar products without using noble metal catalysts. [6] An intramolecular variant of the carbonyl nitroso ene reaction was reported by Kirby [7] more than two decades ago but since then it has remained unexplored (Scheme 2, 4→5→6→7). Due to the instability of nitroso compounds 5, they were prepared in situ by low temperature periodate oxidation of the corresponding hydroxamic acids 4 and intercepted with cyclopentadiene to form adducts 6, which then, after isolation, were thermally converted into 7, presumably through the transition state A. This method represents a complementary alternative to the Pd- and Rh-catalyzed aminations: here the new C–N bond is formed with a concomitant allylic shift of the double bond. However, the synthetic potential of this method is limited by the need to isolate the Diels–Alder adducts. Herein, we report on the development of a catalytic oxidation protocol to effect cyclization of hydroxamic acids 4 into 7 in a single step. While this manuscript was in preparation, a similar single-pot intramolecular acyl nitroso reaction was reported by Read de Alanis. [8]

Scheme 2. Intramolecular carbonyl nitroso ene reaction.
Table 1. Optimization of the intramolecular nitroso ene cyclization.\[a\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Oxidant</th>
<th>Solvent, T [°C]</th>
<th>Yield[^{[b]}] 9a [%]</th>
<th>Yield[^{[b]}] 9b [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)(_2) (_2), (2)</td>
<td>H(_2)O(_2)</td>
<td>THF, r.t.</td>
<td>70</td>
<td>0[^{[e]}]</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)(_2) (_2), (2)</td>
<td>t-BuOOH</td>
<td>THF, r.t.</td>
<td>69</td>
<td>0[^{[e]}]</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OTf)(_2) (_2), (2)</td>
<td>H(_2)O</td>
<td>THF, 60</td>
<td>n/a</td>
<td>0[^{[e]}]</td>
</tr>
<tr>
<td>4</td>
<td>Mo(_2)(HMPA)-py (_2) (2)</td>
<td>H(_2)O[^{[d]}]</td>
<td>MeOH, 60</td>
<td>n/a</td>
<td>45[^{[i]}]</td>
</tr>
<tr>
<td>5</td>
<td>FeCl(_3) (4)</td>
<td>H(_2)O</td>
<td>MeOH, r.t.</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>FeCl(_3) (4)</td>
<td>H(_2)O[^{[d]}]</td>
<td>MeOH, 60</td>
<td>n/a</td>
<td>56[^{[i]}]</td>
</tr>
<tr>
<td>7</td>
<td>FeCl(_3) (4)</td>
<td>H(_2)O[^{[d]}]</td>
<td>i-PrOH, 100</td>
<td>n/a</td>
<td>64[^{[i]}]</td>
</tr>
<tr>
<td>8</td>
<td>FeCl(_3) (25)</td>
<td>–</td>
<td>i-PrOH, r.t.</td>
<td>30</td>
<td>n/a</td>
</tr>
</tbody>
</table>

\[^{[a]}\] The reactions were carried out on a 0.5-mmol scale with 1.2 equiv. of oxidant for 18 h, unless stated otherwise.
\[^{[b]}\] Isolated yield.
\[^{[c]}\] Not formed, starting material decomposed.
\[^{[d]}\] 6 equiv. of oxidant were used.
\[^{[e]}\] E/Z 4:1.
\[^{[f]}\] E/Z 6:1.

In the past, the procedures for the oxidation of hydroxamic acids were tailored for cycloaddition of nitroso derivatives to dienes (e.g., 5→6, Scheme 2).\[^{[9]}\] The ene reaction is substantially slower than cycloaddition. Strong oxidants employed in the cycloaddition methods at prolonged exposures appear to destroy both the carbonyl nitroso intermediates and the ene adducts and therefore, for the successful ene reaction, milder oxidation protocols are required. Following earlier reports on a single-pot intermolecular carbonyl nitroso ene reaction, which usually requires excess alkene,\[^{[10]}\] we set out to investigate a more challenging intramolecular variant with an inherent 1:1 stoichiometry. Preliminary experiments were carried out employing model substrates 8a and 8b derived from (E)-crotyl alcohol and (E)-2-hexenol (Table 1). Cyclization of hydroxamic acid 8a (R=Me) proceeded smoothly in the presence of catalytic Cu(II) triflate (2 mol%) and 50% aqueous H\(_2\)O\(_2\) (1.2 equiv.) to furnish the respective product 9a in 70% yield (Table 1, entry 1). For hexenyl derivative 8b (R=n-Pr), the same Cu(II) system proved inefficient resulting in decomposition of the starting material. Changing the stoichiometric oxidant to t-BuOOH essentially reproduced the results obtained with H\(_2\)O\(_2\) (Table 1, entry 2); raising the reaction temperature to 60°C was not helpful (Table 1, entry 3). A brief screening of catalytic systems\[^{[11]}\] revealed that Mo\(_2\)(HMPA)Py (2 mol%) with 6 equiv. of H\(_2\)O\(_2\) at 60°C did show some activity providing 9b in 45% yield (Table 1, entry 4). However, the best results were obtained with Fe(III) as a catalyst. Crotyl derivative 8a was readily cyclized into 9a in the presence of FeCl\(_3\), 6 H\(_2\)O (4 mol%) and 50% aqueous H\(_2\)O\(_2\) (1.2 equiv.) in MeOH at room temperature. The less reactive 8b under these conditions gave only 10% of 9b (Table 1, entry 5), however raising the temperature to 60°C produced the desired 9b in 56% yield as a 4:1 E/Z mixture (Table 1, entry 6). Interestingly, a further increase of the reaction temperature to 100°C (the solvent was changed to i-PrOH) improved the E/Z ratio of 9b to 6:1 (yield 64%, Table 1, entry 7).

Oxidation of the hydroxamic acids to the respective nitroso intermediates is likely to be carried out by the metal. The role of the stoichiometric oxidant is to regenerate the catalytically active metal species, as without the oxidant no catalytic turnover was observed (Table 1, entry 8). It is worth noting that the catalytic system based on Fe(III)/H\(_2\)O\(_2\), known to promote epoxidation of alkenes,\[^{[12]}\] under the reaction conditions employed here did not produce epoxides.

The apparent difference in reactivity of 8a and 8b prompted us to have a closer look at the steric factors influencing removal of the allylic hydrogen (Scheme 3). In the set of substrates 8a–d, the reactivity drops dramatically in the order Me> n-Pr > Bn > i-Pr, where 9c was isolated in just 10%, whereas 9d was not formed at all,\[^{[13]}\] which reflects increase of the steric congestion around the allylic C–H bond. Even formation of the thermodynamically stable fragments, such as styrene (9e) or trisubstituted alkene (9d), was not able to offset this trend.

Next, we investigated diastereoselectivity of the nitroso ene cyclization. To circumvent the issues of reactivity, secondary crotyl analogues 10a–d were selected (Scheme 4). By employing the reaction conditions...
developed for 8a (4 mol% FeCl$_3$·6 H$_2$O and 1.2 equiv. H$_2$O$_2$ in i-PrOH at room temperature), cyclization proceeded uneventfully to furnish mixtures of syn and anti products 11a–d. Rather surprisingly, a 2:1 syn/anti mixture was formed regardless of the steric size of the substituent. Relative configurations of the stereoiso-
mers were established by analysis of their $^1$HN MR spectra (for details, see Supporting Information). Var-
ation of solvents (CH$_2$Cl$_2$, CHCl$_3$, THF, toluene) and
catalyst [Cu(OTf)$_2$, ligand free and as a complex with
phenanthroline] had no effect on the syn/anti ratio.
However, the diastereoselectivity was improved by
lowering the reaction temperature. The reactivity of
hydroxamic acids 10 proved to be sufficient to attain
good conversion at −20°C in 72 h. Thus, in the case of
11d diastereoselectivity increased to 5:1 (yield
51%). It is worth noting that the diastereoisomers are
readily separable by chromatography.

The scope of the reaction was investigated with the
aid of hydroxamic acids 12, 14, 15, 17, 19 and 21 rep-
resenting diverse substitution patterns (Table 2). Prenyl derivative 12 with a relatively electron-rich
double bond proved to be one of the most reactive
substrates. The reaction was complete in less than 3 h
with both Fe(III) and Cu(II) catalysts furnishing the
respective oxazolidinone 13 in good yields (Table 2,
entry 1). E-Geometry of the alkene appears to be an
important factor affecting the cyclization, as 14, a Z-
isomer of 8a, failed to give any product. Formation of
the 6-membered ring required more forcing condi-
tions than the 5-membered counterpart. At room
temperature, cyclization of hydroxamic acid 15 into
16 took 72 h (58% yield), but at 100°C it was com-
plete overnight (yield 60%, Table 2, entry 3). Cycliza-
tion of the more substituted derivatives 17, 19 and 21
required elevated temperature and was accomplished
in good yields (Table 2, entries 4–6). Importantly, in
contrast to the high sensitivity of the cyclization to
the surroundings of the allylic C–H bond, steric fac-
tors do not play any significant role in the formation of
C–N bond, which is manifested by a facile forma-
tion of spiro derivative 20 and a highly substituted ox-
azolidinone 22 (Table 2, entries 5 and 6, respectively).
Furthermore, 22 was obtained in high diastereoselec-
tivity ($dr > 25:1$).

Preliminary DFT calculations[14] suggest a pericyclic
6-membered transition state D (Scheme 5) as a possi-
ble key point of the reaction mechanism[15,16] We
have also identified formation of aziridine N-oxide C,
however the extent of its contribution to the overall
reaction mechanism is not clear at the moment. At
the same time, we were unable to find a polarized bir-
adical intermediate that played an important role in
the case of aryl and alkyl nitroso compounds.[16] Ab-
sence of biradical species is indirectly supported by
the different reactivities of E-8a and Z-14, since oth-
erwise they would converge to the same biradical in-
termediate due to a rapid rotation about single bonds.
The high relative energy of TS D (25 kcal mol$^{-1}$) may
explain the observed relatively slow rate of cycliza-
tion. In the presence of CuCl$_2$, the activation energy
of H-transfer was found to be 10 kcal mol$^{-1}$ lower
(15 kcal mol$^{-1}$ vs. 25 kcal mol$^{-1}$). This suggests that
in our catalytic system transition metal species may play
the dual role of both oxidant and Lewis acid.
Experimental Section

General Method for Cyclization of Hydroxamic Acids with Methyl Hydrogen Abstraction (9a, 11a–d)

50% aqueous \( H_2O_2 \) (0.041 mL, 0.6 mmol) was added to a mixture of the hydroxamic acid (0.5 mmol) and \( FeCl_3 \cdot 6H_2O \) (5.4 mg, 4 mol%), in \( i-PrOH \) (4 mL), at 0°C. The reaction mixture was brought to room temperature and left for 18 h. The mixture was then diluted with 1M HCl (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic fractions were evaporated at reduced pressure and the crude product was purified by chromatography on a column of silica gel with a mixture of petroleum ether (40–60) and AcOEt (2:1 → 1:1).

General Procedure for Cyclization of Hydroxamic Acids with Methylene Hydrogen Abstraction (9b, 9c, 18, 20, 22)

\( FeCl_3 \cdot 6H_2O \) (5.4 mg, 4 mol%) was added to the appropriate hydroxycarbamate (0.5 mmol) in \( i-PrOH \) (6 mL), and, after the addition of 50% \( H_2O_2 \) (0.20 mL, 3 mmol), heated at 100°C in a sealed vessel for 18 h. The mixture was then diluted with 1M HCl (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were evaporated at reduced pressure and the crude product was purified by chromatography on a column of silica gel with a mixture of petroleum ether (40–60) and AcOEt (2:1 → 1:2).

Acknowledgements

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References


[11] Catalytic systems based on RuCl3/H2O2, RuCl/PhIO, VO(acac)2/t-BuOOH showed low-to-moderate conversions in the case of 8a but all failed in the case of 8b.


[13] Formation of the respective nitroso intermediate does take place, as it can be intercepted with 2,3-dimethylcyclobutadiene as a Diels–Alder adduct in 74% yield. In the absence of diene, due to a very slow nitroso ene reaction the nitroso compounds decompose by alternative routes.

[14] For details, see the Supporting Information.


Intramolecular Carbonyl Nitroso Ene Reaction Catalyzed by Iron(III) Chloride/Hydrogen Peroxide as an Efficient Tool for Direct Allylic Amination


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