INTRAMOLECULAR ENE REACTIONS OF FUNCTIONALISED NITROSO COMPOUNDS

A Thesis Presented by

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In Partial Fulfilment of the Requirements
for the Award of the Degree of

DOCTOR OF PHILOSOPHY OF

UNIVERSITY COLLEGE LONDON

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July 2010

DECLARATION

I Sandra Luengo Arratta, confirm that the work presented in this thesis is my own. Where work has been derived from other sources, I confirm that this has been indicated in the thesis.

ABSTRACT

This thesis concerns the generation of geminally functionalised nitroso compounds and their subsequent use in intramolecular ene reactions of types I and II, in order to generate hydroxylamine derivatives which can evolve to the corresponding nitrones. The product nitrones can then be trapped in the inter- or intramolecular mode by a variety of reactions, including 1,3-dipolar cycloadditions, thereby leading to diversity oriented synthesis.

The first section comprises the chemistry of the nitroso group with a brief discussion of the current methods for their generation together with the scope and limitations of these methods for carrying out nitroso ene reactions, with different examples of its potential as a powerful synthetic method to generate target drugs.

The second chapter describes the results of the research programme and opens with the development of methods for the generation of functionalised nitroso compounds from different precursors including oximes and nitro compounds, using a range of reactants and conditions. The application of these methods in intramolecular nitroso ene reactions is then discussed.

Chapter three presents the conclusions which have been drawn from the work presented in chapter two, and provides suggestions for possible directions of this research in the future.

This work concludes with a formal account of the experimental procedures.

With all my heart
To Inacio Alonso Martínez (Tacho)

ACKNOWLEDGEMENTS

Firstly I would like to thank my supervisor, Professor William Motherwell, for offering me the opportunity to work in his group, for his guidance, help, patience, inspiration and encouragements over the past years. I am also very grateful to Dr. Robyn Motherwell for taking care of me and for her help dealing with everything.

I am also very grateful to all the 'technical' staff at UCL Chemistry Department, John Hill and Lisa for their help with mass spectra, which on occasions was a real challenge. Moreover, I would like to express my acknowledgment to NMR boys, Denis and Dr. Abil Aliev for all their time spent on me, without their help and friendship all this work would have been more difficult.

I have been most fortunate to be surrounded by two excellent postdoctoral research workers, Dr. Tom Sheppard and Dr. Steve Hilton, to whom I would like to thank for all their efforts, advices and help provided during my PhD, including their hard work understanding my spoken and written English. They are not just great chemists but they are also quality people who have guided me from the light to the dark side and *vice versa*. Gracias for everything guapos, I really enjoyed working by your side.

I would also like to thank the old and current members of the WBM family, particularly to; Yuka; I do not know how I would have done without your faxes; Alex; I loved discussing with you especially about ales; Lorna, thank you for your pronunciation and English grammar classes; Yumi, thank you for everything including showing me the best sushi around, I hope you know how important and good working with you has been. Moussa do not ever change, I loved chatting and arguing with you, you are priceless!!!. Josie (Fernanda), dear, you are lovely and it is so funny partying with you; Matt; thanks for your calmness and stability and Shiva you have so such great energy…thank you all for your support and the very good times we spent together. Laure, I cannot think of having done all this hard work without you, sharing all the good and bad moments, you were always there. It was a pleasure to teach you how to climb.

During my walks around the building I established new friendships with Sandra and big Matthew, who always were there to chat with me. Thank you!!! In addition, I would like

to thank my little French community that always has been (and is) by my side, and never left me by myself: Romain and Syl20…….Merçi beaucoup. Je vous adore!!!!

During my years in London there were many people who visited me, making me to miss less the heat of the sun. Thank you very much for all the energy you carried with you: Alf, Jacki, Carolina, Gloria, Vargas, Flor, Ato, Sara, Alain, Dani, Tibo, Ben, Aidine, Julie, Zohra, Fred, Marie, Urko, Ester, Rapon, Belen, Ana, Fernando, Alberto (Karton), Alberto (Santos), Rosa, Mama Pilar, Sandra, Fabi, Hernan… and many others.

Within the Londoner community there were many people who made things easier for me: especially Dr. Johan Gold and Fanny and Tasos who have helped me to stay grounded. Muchas gracias!!!!

I would also like to thank my family, my parents: Marisa and Armando for their love, encouragement and motivation. I am as well so grateful to my beautiful little sister Iciar, who visited me on many occasions and always took care of me, thank you for all your love and support even though many times you were too little to understand me.

Finally, I would like to declare my biggest and special thank you to the person who was unconditionally there for me, Tacho, I cannot imagine to have passed through all that without you. I can not believe how many times you were there listening me carefully and trying to help me with the ene reaction. This entire job would not have been possible without you, thank you for both; this thesis and the last years together.

ABBREVIATIONS

Å	Ångström
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
ANO	aziridine *N*-oxide
aq	aqueous
Ar	aromatic
br	broad
Bu	*n*-butyl
BuLi	*n*-butyllithium
b.p.	boiling point
CAN	ceric ammonium nitrate
Cat	catalyst
CI	chemical ionisation
Cod	cycloocta-1,5-diene
Cp	η^5-cyclopentadienyl
CTABr	cetyltrimethylammonium bromide
CTAOH	cetyltrimethylammonium hydroxide
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBMP	2,6-*tert*-butyl-4-methylpyridine
DBU	diaza(1,3)bicyclo[5.4.0]undecane
9,10-DMA	9,10-dimethylanthracene
DIEA	*N,N*-diisopropylethylamine
DIPA	diisopropylamine
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
ECPI	atmospheric pressure chemical ionisation
ee	enantiomeric excess
EI^+	electron impact
eq	equivalent
g	gram(s)
h	hour(s)

HOMO	higher occupied molecular orbital
HPMA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
i	*iso*
IR	infra red
J	coupling constant
KIE	kinetic isotope effect
L	unspecified ligand
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LICA	lithium isopropylcyclohexylamide
LRMS	low resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital
M	unspecified metal
M+	mass to charge ratio
Me	methyl
MHz	megahertz
min	minute(s)
mL	millilitres
m.p.	melting point
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
NMO	*N*-methylmorpholine-*N*-oxide
n.O.e.	nuclear Overhauser effect
[O]	oxidation
p	*para*
Pc	phthalocyamide
PCC	pyridinium chlorochromate
PE	petroleum ether
Ph	phenyl
pr	propyl
ppm	parts per million
Py	pyridine
R	unidentified alkyl group

R_f	retention factor
rt	room temperature
s	singlet
SET	single electron transfer
t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
p-TsOH	*para*-toluenesulfonic acid
w	weak
X	leaving group
Y	functionalised group
δ	chemical shift

CONTENTS

CHAPTER 1 - INTRODUCTION

Introduction.

The direct allylic amination of unsaturated hydrocarbons is an attractive but underdeveloped synthetic methodology. It is in this context that the ene reaction between alkenes and aza enophiles can be considered as a useful functionalisation protocol. Examples using azo enophiles, such as diethyl azodicarboxylate and triazolinediones, with alkenes have been extensively employed and constitute a mild and convenient method of generating a new nitrogen-carbon bond.[1] Another class of potentially useful nitrogen enophiles are nitroso compounds, but in view of their labile nature they have, by comparison, been scarcely used for this purpose.

The present thesis is accordingly concerned with an exploration of the use of geminally functionalised nitroso compounds in the Alder ene reaction as a vehicle for diversity oriented synthesis.[2] In order to place the work in perspective, the following introduction has been divided into two distinct parts. The first of these focuses on the nature and reactivity of the nitroso group in general including methods available for their preparation, whilst the second part emphasises the behaviour of the nitroso group in pericyclic reactions with a particular reference to the ene reaction. Since, to some extent, our research has been influenced by the idea that the nitroso group can be compared to an aldehyde functional group, relevant parallels and differences will be noted.

1.0 The Nitroso Group.

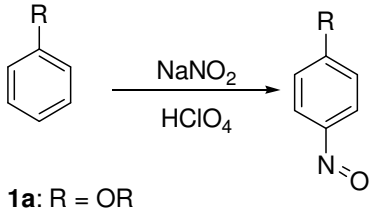
1.1 Preparative Methods.

Despite the high reactivity of the nitroso group and the constraints which this places upon methods employed for their preparation,[3] there is a significant number of synthetic routes available to prepare *C*-nitroso compounds (nitroso compounds), some of which have been used regularly for over a century. It is not our intention to provide a full description of all the different methods or reagents used to generate this functional group *in situ*; the information being available in different early reviews by Touster,[4] Boyer,[5] Metzger and Meier,[6] and in other more recent ones by Gowenlock and Richter-Addo.[7] A general

introduction of how the nitroso group can be generated for use in ene cycloaddition reactions however is discussed below.

In general terms, formation of the nitroso group can be achieved either by creation of a new carbon-nitrogen bond, or through careful oxido-reductive manipulation of amines, hydroxylamines, or nitro compounds respectively.

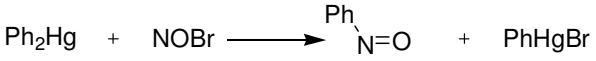
Thus, direct nitrosation of substituted aromatic compounds such as aromatic ethers **1a** and tertiary amines **1b** can be obtained by using sodium nitrite in acid media (Scheme 1).[8]



1a: R = OR
1b: R = NR_2 **2**

Scheme 1

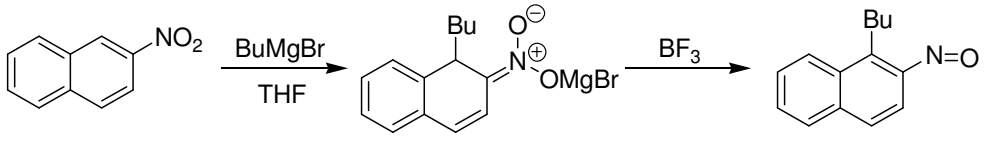
Baeyer has shown that the preparation of nitrosobenzene **5** with metallic reagents can be used to obtain nitroso derivatives as demostrated by the reaction of nitrosyl bromide **4** with diphenylmercury **3** (Scheme 2).[9]



3 **4** **5** **6**

Scheme 2

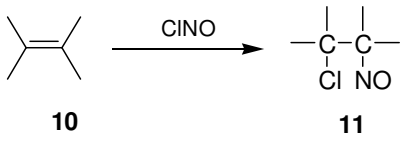
Other organometallic reagents including magnesium,[10] lithium,[11] tin,[12] and thallium can be employed.[13] Nucleophilic addition of butylmagnesium bromide to 2-nitronaphthalene **7** gave the nitronate **8**, which by action of boron trifluoride generated 1-butyl-2-nitrosonaphthalene **9** in good yield (Scheme 3).[14]



7 **8** **9:** 52-63%[a]

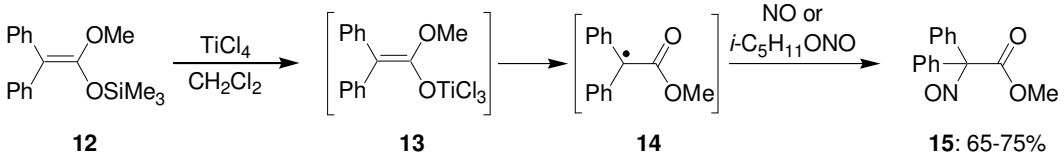
Scheme 3. [a] Yield ranges for three separate reactions.

The electrophilic addition of nitrosyl halides to a carbon-carbon double bond is a well known option for the synthesis of α-chloro nitroso compounds and examples include diverse studies of their reactivity towards a number of terpenes (Scheme 4).[15,16]



Scheme 4

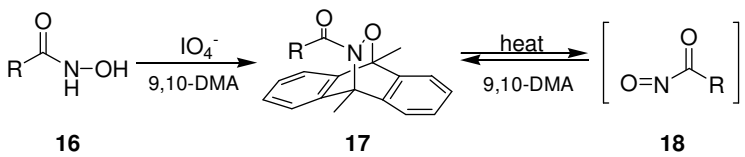
Although addition reactions of oxides of nitrogen (nitric oxide, dinitrogen trioxide or dinitrogen tetraoxide) are less commonly used, a particularly attractive method is the reaction of ketene *O*-alkyl-*O´*-silyl acetals **12** with either nitric oxide or isoamyl nitrite in the presence of titanium (IV) chloride to give good yields of α-nitroso esters **15** (Scheme 5).[17] When titanium (IV) chloride was added to the starting substrate prior to the nitric oxide, the dimer product of **14** was obtained, indicating the presence of radical intermediate **14** during the reaction.



Scheme 5

One of the most useful classes of nitroso compounds are the acylnitroso derivatives **18**. Their extraordinarily high reactivity makes them very attractive intermediates for a number of synthetic operations, but they are virtually impossible to isolate in pure form as a consequence of their rapid dimerisation and decomposition to the corresponding anhydrides with the evolution of dinitrogen oxide gas (*vide infra* Scheme 12).

In consequence, several preparative routes have been developed for the *in situ* generation of acylnitroso derivatives. A traditional method under mild conditions involves the thermal dissociation of their Diels-Alder cycloadducts **17**, which can be prepared by oxidation of a hydroxamic acid **16** with sodium or tetrabutylammonium periodate in the presence of 9,10-dimethylanthracene (9,10-DMA) (Scheme 6).[3,18]

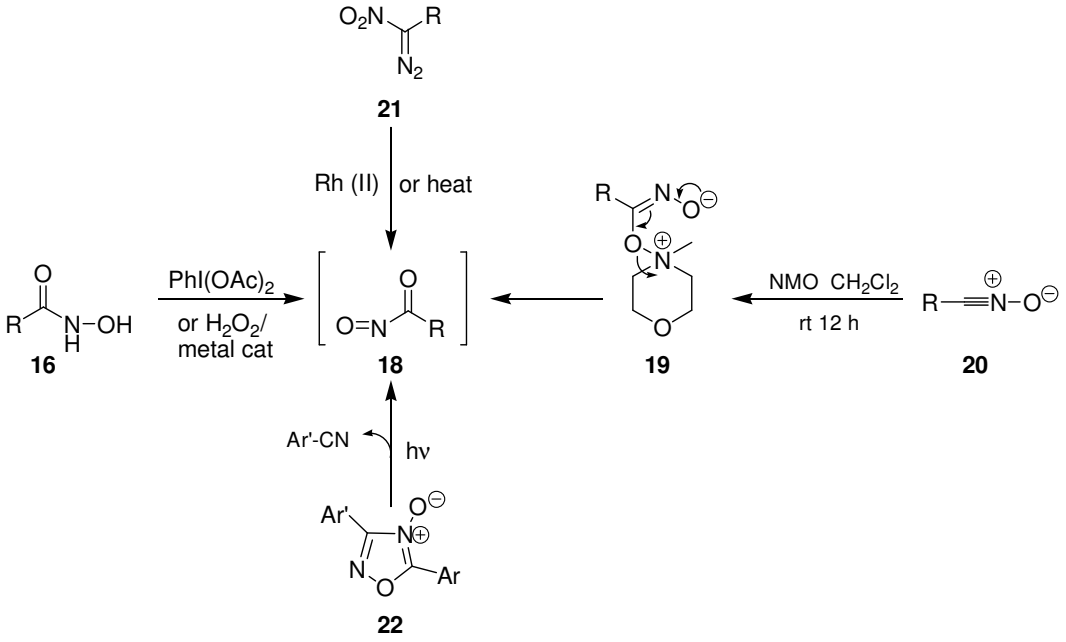


Scheme 6

Results reported on the oxidation of hydroxamic acids **16** without trapping of the acyl nitroso product with 9,10-DMA demonstrated that, whilst generation of the acylnitroso derivatives **18** occurred under these conditions, the subsequent reaction with alkenes

produced only intractable mixtures of products with very poor yields of the expected ene products.[19]

It was not long before studies were carried out to solve this problem through replacement of periodate. Thus, Adam *et al.* described a new mild selective oxidation method starting from hydroxamic acids **16** where the oxidising agents employed were iodosobenzene or iodosobenzene diacetate (Scheme 7).[20] Later, Iwasa *et al.* reported a simple one pot procedure for the ene reaction with alkenes involving ruthenium (II), or iridium (I) or copper (I)-catalysed oxidation of hydroxamic acids **16** with aqueous hydrogen peroxide.[21]

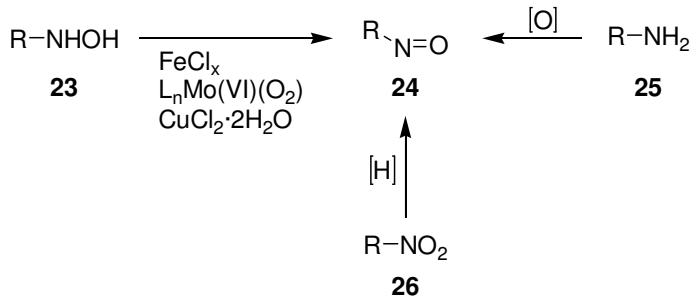


Scheme 7

Other ingeneous solutions include the mild oxidation of nitrile *N*-oxides **20** with *N*-methymorpholine-*N*-oxide (NMO) which was employed by Caramella *et al.*,[22] or use of nitrocarbenoid precursors **21** which undergo a facile [1,2] oxygen atom shift under rhodium diacetate catalysis or upon gentle heating.[23] A further method is the photolysis of 1,2,4-oxadiazole-4-oxides **22** producing nitriles and nitroso carbonyl derivatives **18**.[24]

A wide variety of oxidising agents is available for the oxidation of aromatic and aliphatic primary amines **25** to nitroso derivatives **24** in high yield. These include Caro's acid (H_2SO_5),[25] peracetic acid,[26] potassium permanganate,[27] and peroxybenzoic acid (Scheme 8).[28,29] More recently, oxidation with hydrogen peroxide in the presence of a catalyst such as $MoO_2(acac)_2$ has been reported.[30]

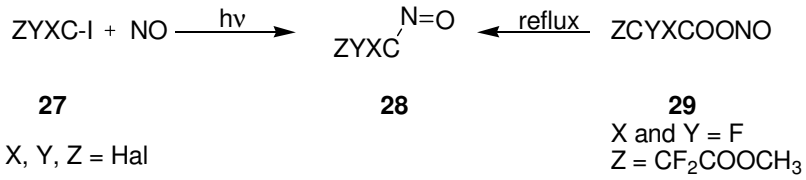
Several approaches to alkyl and aryl nitroso derivatives are based on oxidation of the corresponding hydroxylamines **23** under mild conditions.[31] Common oxidising agents are Mo(VI), Fe(II/III) and Cu(I/II).[32,33,34,35]



Scheme 8

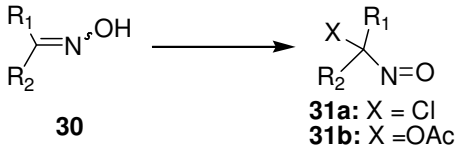
The direct reduction of nitrobenzene **26** (R = Ph) with amalgams of magnesium, zinc, or aluminium amongst others is widely used.[36] Nitroarenes can also be reduced to nitroso derivatives using carbon monoxide and $Ru(CO)_{12}$ or $[CpFe(CO)_2]_2$ as a catalyst. [37,38] Nevertheless, the use of Fe with aromatic hydroxylamines requires conditions of high temperature and pressure and smoother reactions can proceed when a photo-assisted iron catalyst reduction is employed.[39]

Perhaloalkyl nitroso derivatives **28** including perfluoroalkylnitro compounds were synthesised by both photolysis of iodides **27** in the presence of nitric oxide or by pyrolysis of nitrites such as **29** to give the corresponding blue liquid nitroso ester **28** (Scheme 9).[40]



Scheme 9

Several methods have been developed to prepare α-halogen nitroso derivatives **31a** from their corresponding oximes **30** using various halogenating agents such as elemental chlorine,[41] aqueous hypochlorous acids,[42] and *N*-bromo- or *N*-chlorosuccinimide.[43,44] The related geminal nitrosoacetates **31b** can also be prepared from oximes by oxidation with lead tetraacetate or lead tetrabenzoate (Scheme 10).[45]

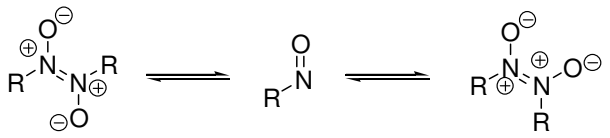


30 **31a:** X = Cl **31b:** X =OAc

Scheme 10

1.2 Factors Influencing the Reactivity of Nitroso Compounds.

Two important physical characteristics of tertiary nitroso compounds were identified at a early stage in the history of this functional group; the intense blue or green colouration as a result of absorption in the visible region at $\lambda_{max} \approx$ 700 nm, and the disappearance of this colour due to their dimerisation (Scheme 11).[46,47] This colourless dimer may exist as *trans*- **32** or *cis*- forms **33** and reversal to the monomer **24** is usually possible in solution.



32 **24** Blue **33**

Scheme 11

Two remarkable features of the nitroso group are its high reactivity as an electrophile, from the polarization of the nitrogen-oxygen bond, and the specific structures formed via equilibration between the monomer and the azodioxy dimers (Scheme 11).[48] However, the position of the equilibrium, which critically depends upon the nature of the group (R), frequently causes various difficulties in the development of selective reactions using nitroso compounds, and has thus hindered their application in organic synthesis.

Nitroso compounds are well known to be very reactive and undergo a variety of reactions. The explanation for this reactivity is related to their low LUMO energy making them powerful electrophiles. However, the high energy of the HOMO, orthogonal to the LUMO, generates a lone pair at nitrogen so they can also act as a nucleophiles,[49] a property shared with carbenes but not with aldehydes. Nevertheless, the dominant behaviour of the nitroso group is its strong tendency to act as an electrophile.

Following on from Baeyer's preparation of nitrosobenzene at the end of the nineteenth century,[9] the nitroso group has been widely recognized as a useful source for the

introduction of heteroatomic functionality. It is very important to recognise however that both the reactivity and the relative stability of nitroso compounds are strongly influenced by the nature of other functional groups attached to the carbon atom bearing the nitroso functionality. Thus, a wide range of nitroso compounds is available including arylnitroso **34**, perhaloalkylnitroso compounds **35** and the parent trifluoronitrosomethane **36**, reagents such as nitrosyl cyanide **37,** and geminally functionalised derivatives such as α-chloronitroso compounds **31a** or their α-acyloxy congeners **38** (Figure 1).[50]

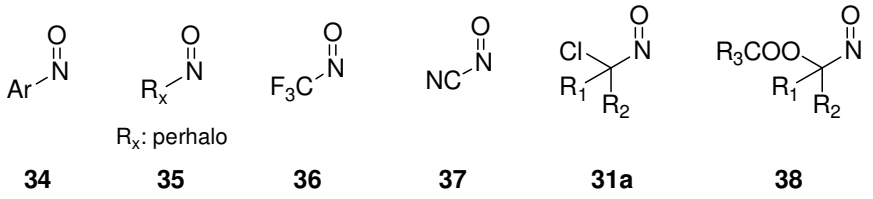


Figure 1

Thus, arylnitroso compounds **34** are relatively stable compounds and hence much less reactive in transformations such as the hetero Diels-Alder reactions than acylnitroso dienophiles **18**. However, these arylnitroso compounds are often employed since they are easy to prepare, as previously explained. Alkylnitroso compounds, by contrast**,** are well known for rapid dimerisation.[51]

Electron withdrawing groups adjacent to the nitroso functionality increase electrophilic reactivity. Examples of this property are the α-chloronitroso compounds **31a**, acylnitroso compounds **18**, nitrosyl cyanide **37** and haloalkyl nitroso derivatives such as **35** and **36**. In particular, the distinguishing property of acylnitroso intermediates **18** is their extremely high reactivity which is a consequence of a low activation energy due to a very small HOMO-LUMO energy gap, when compared to the rest other of nitroso derivatives.[22a]

To the best of our knowledge, although no systematic kinetic study on the relative reactivity of this family has been carried out, it is generally accepted that the stability of nitroso compounds increases as shown in Figure 2.

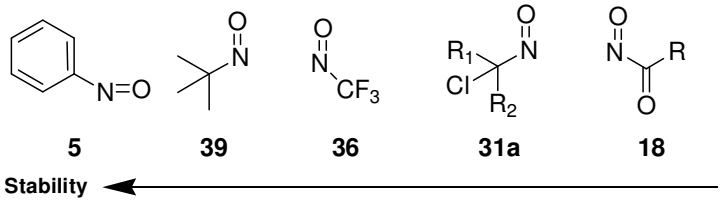
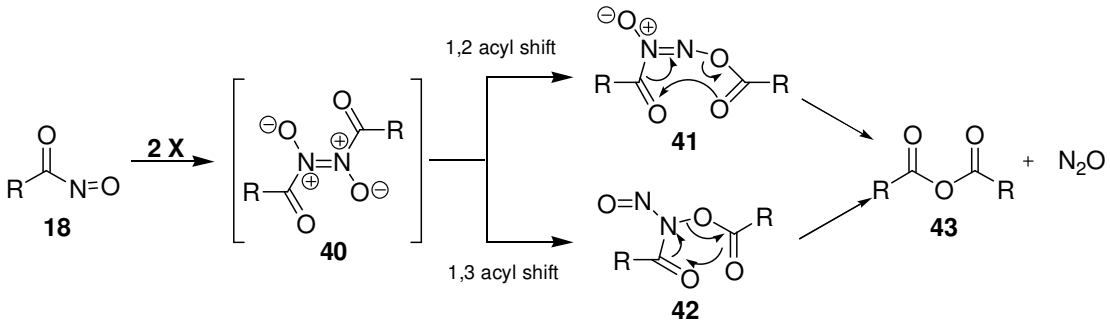


Figure 2

Thus, as shown in Scheme 12 acylnitroso compounds **18** tend to dimerise and disproportionate much faster than α-halonitroso compounds **31a** whilst some aromatic nitroso compounds are commercially available.[19]



Scheme 12

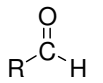
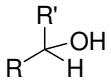
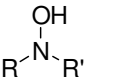
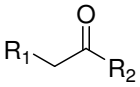
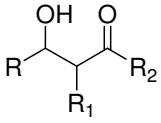
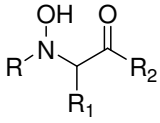
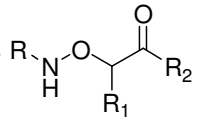
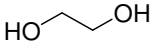
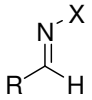
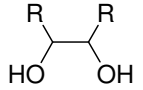
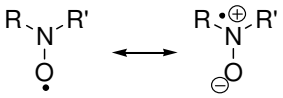
1.3 Representative Reactions of the Nitroso Group.

Within this overview of reactivity, and in the following section which further examplifies the reactions of nitroso compounds, it is of interest to draw a brief comparison with the much more well known chemistry of the aldehyde carbonyl group.

Thus, as emphasised in Scheme 13, whilst both functional groups must be considerd as electrophiles in terms of their susceptibility to attack by Grignard reagents, hydride reducing agents and enols, other classic reactions of the carbonyl group such as formation of, *inter alia*, acetals, oximes or hydrazones, which involve attack of a neutral nucleophilile and loss of water, are not observed with the nitroso group.[52,53] This observation would seem to indicate that formation of aza analogue ($R\text{-}N{=}O^{+}\text{-}R'$) of an oxocarbenium ion ($R_2C{=}O^{+}\text{-}R''$) is not favoured. Futhermore, in terms of redox potential, it should be noted that reduction of the nitroso group can be accomplished under much milder conditions (eg. Zn) than in the case of pinacol (Mg) reactions.[54] Finally, in terms of their radicophilicity, the remarkable capture of alkyl radicals by aromatic or *tert* nitroso compounds to give stable nitroxides stands in sharp contrast to the relatively rare formation of high energy alkoxyls from aldehydes.[55]

In summary, whilst some parallels may be drawn, the chemistry of nitroso group is much richer, more diverse and often challenging, especially in view of the fact that products

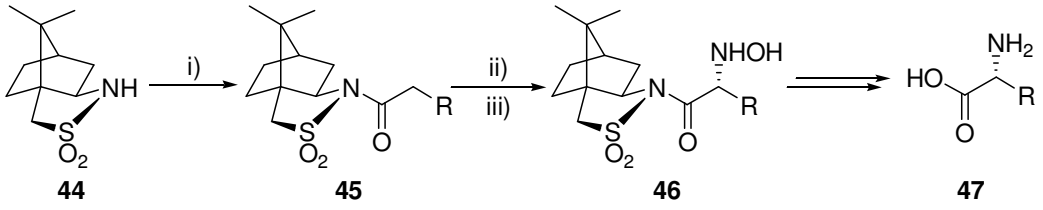
such as hydroxylamines or nitroxide radicals are prone to further redox reactions and disproportionation.

Reaction or **Reagent Type**	**Product(s)**	
	Aldehyde 	**Nitroso Compound** 
Grignard Reaction R'MgX		
Metal Hydride Reduction $M^+M'^-H_n$		 and/or RNH_2
"Aldol" Reaction 		 or 
Acetal Formation 		-
Aza Derivatives NH_2X (X=OH, NHR)		-
Metal Reduction	 Pinacol (Mg)	 and/or RNH_2 (Zn, H^+)
Radicophilicity R'·	 (rare)	 Stable nitroxide

Scheme 13

Within the above basic set it should be noted that the nitroso aldol reaction in particular is very instructive and has proven to be especially useful in recent years, in particular the asymmetric variants.[1a,56] Thus, for example, α-amino acids **47** can be obtained with excellent enantioselectivity using 1-chloro-1-nitrosocyclohexane as the electophilic nitrogen source and the enolate anion generated from the camphor based *N*-acyl sultam chiral auxiliary **45** (Scheme 14). Subsequent hydrolysis of the resultant nitrone hydrochloride under acidic conditions then furnished the hydroxylamine **46** in 87% yield

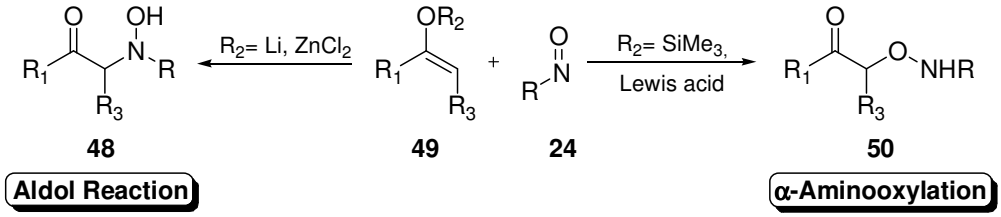
as a single diastereoisomer and transformation of the latter to the corresponding α-amino acids **47** was easily accomplished.



i) NaH, RCH_2COCl. ii) $NaN(SiMe_3)_2$, ii) 1-chloro-1-nitrosocyclohexane. iii) 1N aq HCl, rt

Scheme 14

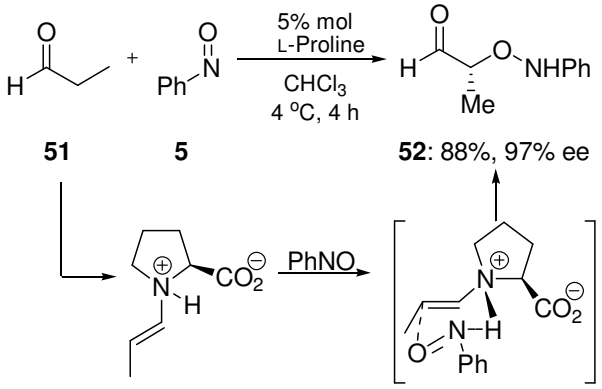
In complete contrast to the aldehydic carbonyl group and to the classical aldol type described above is the α-aminooxylation reaction (Scheme 15), wherein the electrophilic atom of the nitroso group is the oxygen atom rather than the nitrogen atom.[57]



Scheme 15

Early studies using nitrosobenzene with either a silyl or a metal enolate indicated that selectivity for the oxygen or for the nitrogen atom was dependent on the nature of the enolate and on the presence or absence of a Lewis acid.

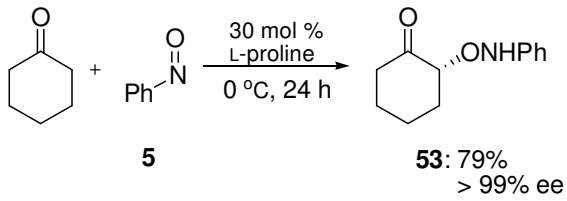
In more recent times, with the progress of organocatalysis, several groups showed that the use of proline leads to α-oxidation of aldehydes.[57,58] Direct α-oxyamination of a variety of aldehydes such as **51** using nitrosobenzene **5** as the oxidant was archived in good yield in the presence of an L-proline catalyst with high levels of asymmetric induction and (Scheme 16).[58d]



Scheme 16

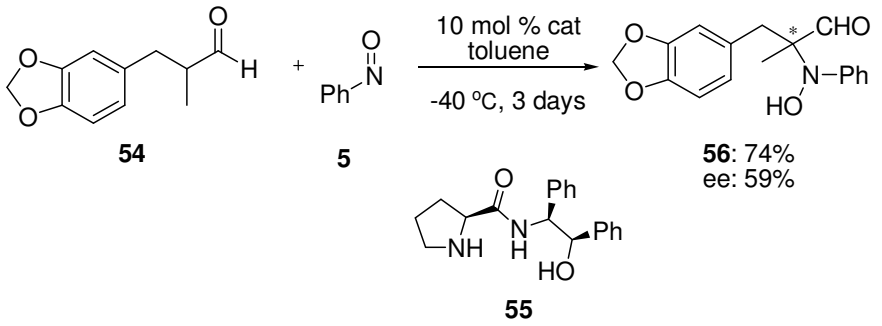
The observed enantioselectivitiy for this reaction can be rationalised by a chair transition state where the *Si* face of an *E* enamine formed from the aldehyde and proline approaches the less-hindered oxygen atom of nitrosobenzene **5** to provide a chiral α-aminoxyaldehyde **52**. This mechanism is completely in accordance with the previously proposed models for proline-catalysed aldol reactions.[59]

A considerable broadening of the reaction scope has recently been achieved by extension to ketones. Reaction between cyclohexanone and nitrosobenzene **5** in the presence of L-proline gave the desired product **53** in good yield and excellent enantioselectivity (Scheme 17).[58b]



Scheme 17

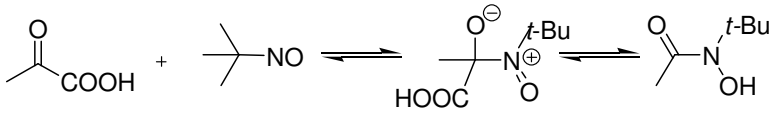
Futhermore, recent studies have demostrated that the *N*-nitroso aldol reaction between aldehyde **54** and nitrosobenzene **5** can be carried out when L-prolinamide derivatives such as **55** were employed as catalysts instead of proline. The α-hydroxyaminocarbonyl derivative **56** was obtained in good yield and moderate ee. Moreover, under these conditions, no *O*-selective product was observed (Scheme 18).[57]



54 **5** **56**: 74% ee: 59% **55**

Scheme 18

Thus far, with the exception of the trapping of neutral radicals to give nitroxides, the above reactions have essentially featured the electrophilic character of the nitroso group. As noted earlier however, the nitroso group possesses a lone pair on the nitrogen atom and can, therefore, in principle, also function as a nucleophile. Such reactions are much rarer but have been observed when the electrophilic partner is very electron deficient. Thus, nitrosobenzene **5** has been shown to react with formaldehyde, glyoxylate, pyruvic acid and acetaldehyde to give *N*-phenylhydroxamic acids, *N*-hydroxyformanilides and *N*-phenylacetohydroxamic acids respectively.[60] A recent example using 2-methyl-2-nitrosopropane **58** with pyruvic acid **57** has also been described (Scheme 19).[61] In this reaction, 2-methyl-2-nitrosopropane **58** has acted as a nucleophile to give intermediate **59** which after proton transfer, decarboxylation and tautomerisation leads to *N-tert*-butyl hydroxamic acid **60**.



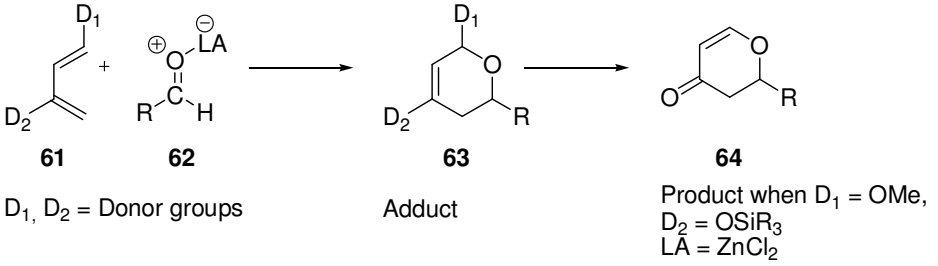
57 **58** **59** **60**

Scheme 19

The final class of reactions in which the nitroso group plays a pivotal role is of course as a source of two π electrons in frontier orbital controlled pericyclic processes. Such behaviour is of direct relevance to the present thesis and, for ease of discussion ene reactions involving the nitroso group have been treated in the subsequent section (*vide infra*).

The Diels-Alder reaction as always has been of paramount importance in this respect and once again it is of interest to provide a comparison with the aldehydic carbonyl group. In general terms, for an aldehyde to function as a dienophile, both Lewis acid complexation

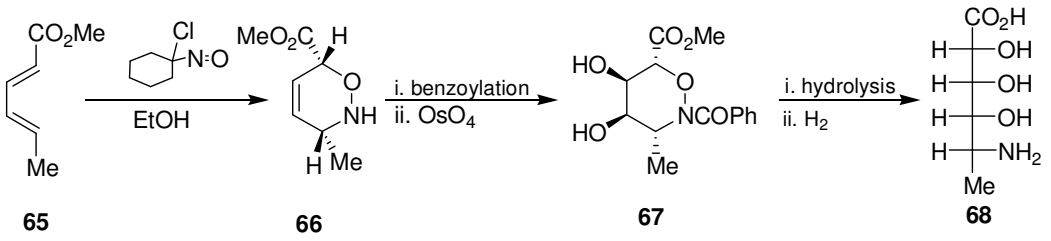
to lower the energy of the LUMO of the π system and selection of an electron rich diene partner are required.[62] This generally favoured combination is shown in Scheme 20.



Scheme 20

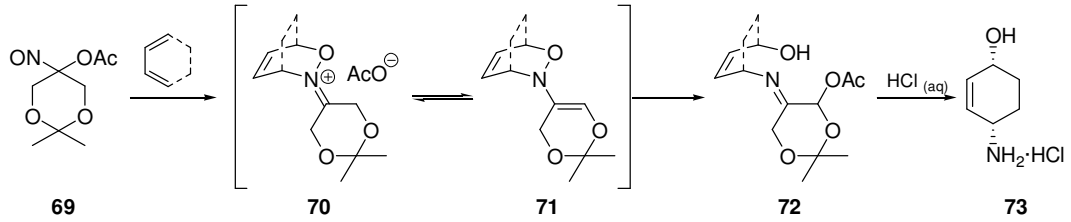
In contrast, a wide range of nitroso compounds has been used as heterodienophiles for both electron rich and electron poor dienes.[63] These include simple aryl as well as geminally functionalysed α-chloro, acyl cyano and sulfoxyl derivatives all of which have proven to be of considerable value for organic synthesis.[50] In mechanistic terms, depending on the exact nature of the nitroso derivative selected, the pathway can vary from a concerted process to stepwise one involving dipolar intermediates. The value of the adducts lies in the good stereocontrol archieved in the cycloaddition and in the fact that hydrogenolysis of the nitrogen-oxygen bond provides a route to 1,4 hydroxy amines.

An elegant example featuring the use of an α-chloronitroso heterodienophile can be seen in a 1963 five step synthesis of (±)-5-amino-5,6-dideoxyallonic acid **68** in which the key step involved the Diels-Alder cycloaddition of (2E,4E)-methyl hexa-2,4-dienoate **65** with 1-chloro-1-nitrosocyclohexane (Scheme 21).[64]



Scheme 21

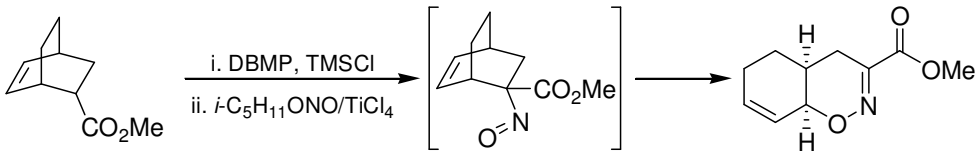
Recent studies by the Kouklovsky group in Orsay have further emphasised the value of the nitroso Diels-Alder reaction through use of the rare α-acetoxy nitroso dienophile **69**,[65] which undergoes efficient nitrogen-oxygen bond cleavage of 3,6-dihydro-1,2-oxazine adducts **71** under very mild conditions to afford *cis* 1,4 amino alcohol **73** (Scheme 22).



69 **70** **71** **72** **73**

Scheme 22

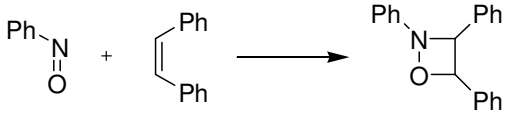
Further examples of pericyclic reactions include the first example of an oxaza-Cope rearrangement**, t**his [3,3]-sigmatropic process involved a direct stereoselective preparation under mild conditions of oxazines **76**.[66] Nitrosonium hexafluoroantimonate was employed both as the nitrosating agent and the Lewis acid to promote the hetero-Cope rearrangement to afford **76** in 71% yield (Scheme 23).



74 **75** **76:** 71%

Scheme 23

The photochemical [2+2] cycloaddition has also been reported to occur smoothly between nitrosobenzene **5** and disubstituted alkenes such as 1,2-diphenyl-ethylene **77** to produce oxazetidine **78** as illustrated in Scheme 24.[67]



5 **77** **78**

Scheme 24

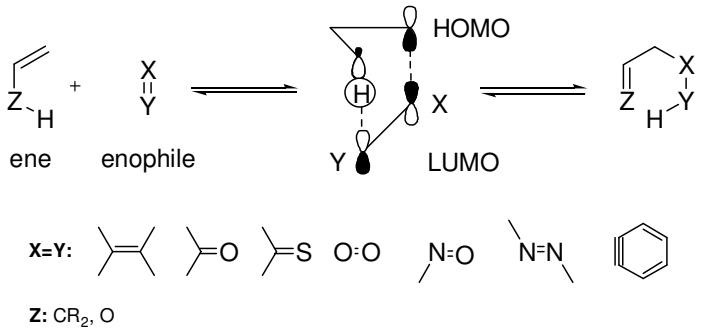
2.0 The Ene Reaction.

As previously outlined, the second section of this introduction will be concerned with the reactivity of different nitroso compounds in both the inter- and intramolecular variants of the ene reaction. It will start with a definition of the ene reaction, particularly when the nitroso group is involved, and then move on to a study of the mechanism, common side reactions encountered during this transformation and issues of regioselectivity and diastereoselectivity. The final section will go on to describe in detail, the discovery, generation and reactivity of those particular types of nitroso compounds participating in

the ene reaction, a topic of particular relevance because of its direct link with the evolution of the work carried out in the present thesis.

2.1 Introduction.

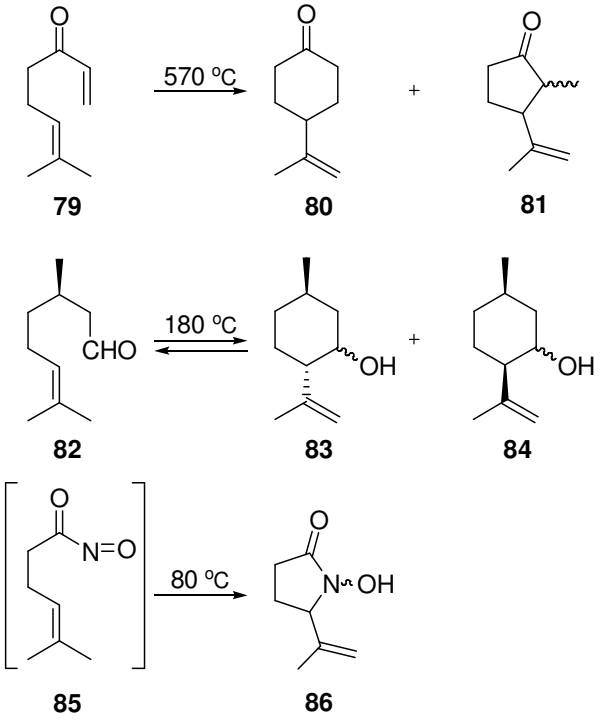
The ene reaction involves the thermal reaction of an olefin containing an allylic hydrogen atom (ene) with an electron deficient double or triple bond (enophile) to form a new bond with migration of the ene double bond and a [1,5]-hydrogen shift (Scheme 25).[68] In terms of pericyclic reactions it is considered to be a $\pi_{2s}+\pi_{2s}+\sigma_{2s}$ reaction.



Scheme 25

The ene reaction is one of the most simple and potentially versatile reactions in organic chemistry, but remains surprisingly underexploited. Isolated examples such as the reaction of olefins with formaldehyde,[69] retro ene reactions including the decarboxylation of β-ketoacids and the formation of olefins by ester pyrolysis have been known since at least the beginning of the 20th century.[70] However, the scope of the ene reaction only began to be recognised following a publication by Alder in 1943.[68] The nitroso ene reaction which was only formally discovered in 1965,[51b] has not been studied to the extent that it merits especially since it constitutes a mild and valuable methodology for the direct regioselective and stereoselective nitrogen atom functionalisation of alkenes.[71]

In the case of the thermal ene reaction with alkenes as enophiles, high temperatures are generally required which render them less useful from a synthetic point of view. However, when the enophile contains one or more heteroatoms, as in a carbonyl or a nitroso group, the ene reaction is faster in both its intra- and intermolecular versions (Scheme 26).



Scheme 26: The acyl nitroso intermediate **85** was thermally released from its Diels-Alder adduct at 80 °C, followed by intramolecular ene reaction.

As illustrated above, the temperature required for the thermal ene reaction decreases considerably when a carbonyl **82**,[72] or a nitroso group **85** is incorporated as the enophile,[73,74] instead of a simple alkene **79**.[75] Although the starting materials are not directly comparable, both substrates **79** and **85** contain an electron-withdrawing group on the internal carbon of the enophile. Nevertheless, these examples clearly illustrate that the ene process is substantially facilitated by increased reactivity of the enophile component.

The enophile reacts as the electrophilic partner, which means that the lower the LUMO energy of the enophile, the higher its reactivity. Since the orbitals of the more electronegative heteroatoms such as oxygen and nitrogen are lower than those of the carbon, the LUMO energies of such enophiles are lower in energy than the LUMO energy of an alkene and thus such heteroenophiles are more reactive in the normal electronic demanding ene reaction, as well as in the Diels-Alder reaction (Figure 3). For the same reason, substitution at either end of the enophile with an electron-withdrawing group enhances reactivity even further.

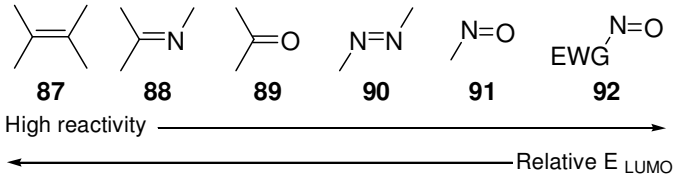


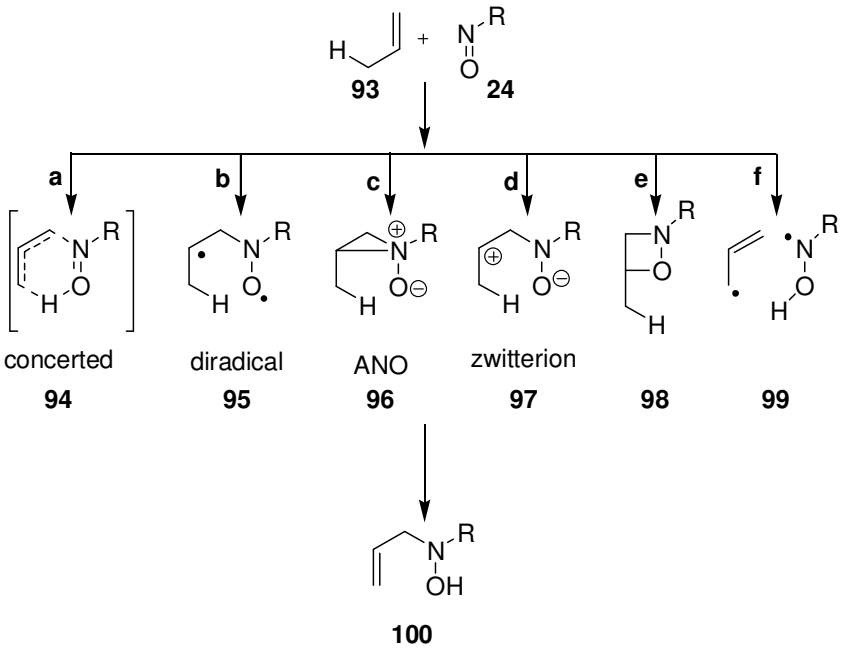
Figure 3

2.2 Mechanism of the Ene Reaction.

While the ene reaction itself can routinely be considered as being concerted but perhaps asynchronous, the mechanism of hetero ene reactions is still the subject of controversial discussion.

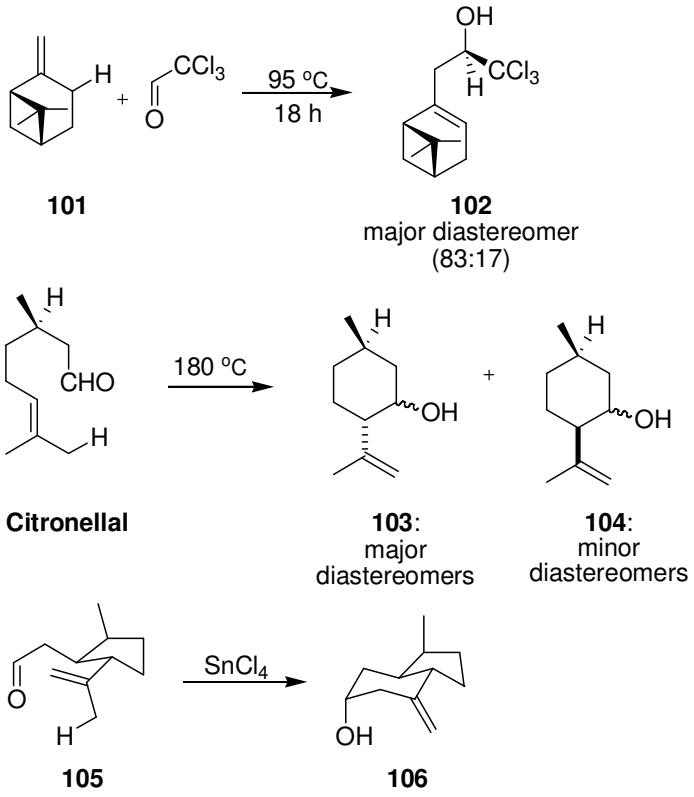
In the thermal ene reactions with alkenes, experimental evidence,[76] and orbital considerations,[77] are consistent with a concerted pathway involving a *supra-supra*facial *endo*- or *exo*-orientation. It thus resembles the Diels-Alder reaction,[78] and [1,5]-sigmatropic shifts,[79] which are considered to involve a cyclic six electron transition state.

By way of contrast, although is generally believed that the hetero Diels-Alder reaction using nitroso compounds is concerted, the mechanism of the nitroso ene reaction is complicated by the high and diverse reactivity of nitroso compounds and hence, is a subject of ongoing debate.[3,80] A total of no less than six distinct mechanisms has been proposed based on observed data (Scheme 27), including a pericyclic transition state **94**, which is allowed by the Woodward-Hoffman selection rules as a [$\pi_{2s}+\pi_{2s}+\sigma_{2s}$] process (path a),[81] and five stepwise paths. Those involving intermediate diradicals **95** (path b),[82,83] aziridine *N*-oxides (ANO) **96** (path c), or zwitterion **97** have all been proposed as plausible intermediates in the ene reaction of nitroso species. The last two pathways proposed (e and f), involve a highly strained oxazetidine **98** or two radical species **99**,[67] and are believed to be the most unlikely.



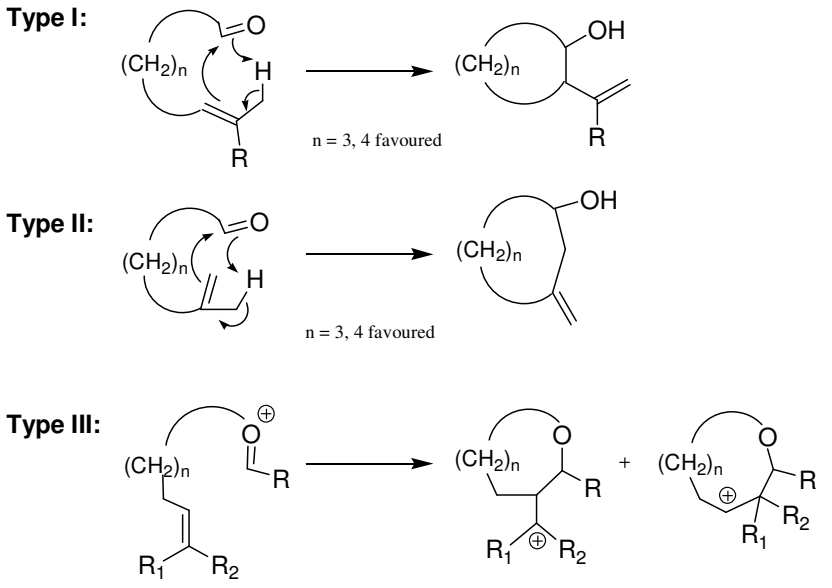
Scheme 27

Such mechanistic controversy is not encountered in the carbonyl ene reaction which has been used extensively in organic synthesis.[84] These reactions are believed to be concerted, except in some cases when, as in the foregoing Diels-Alder reactions, Lewis acids are employed. Some representative carbonyl ene examples, shown in Scheme 28, illustrate that the reaction can be employed in both the inter- and in the intramolecular mode, and as expected, the presence of additional electron withdrawing groups, as in choral or methyl glyoxalate, enhance the reactivity of such enophiles. Both the electronic nature of the carbonyl group as an enophile and the different connectivity patterns in the intramolecular mode are of interest to compare and contrast with those encountered for the nitroso ene reaction (*vide infra*).



Scheme 28

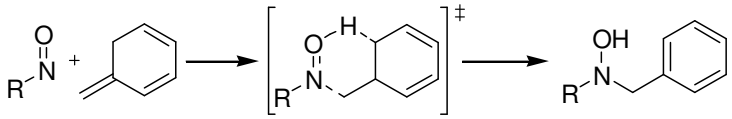
In particular, at this stage, since an intramolecular variant of the nitroso ene reaction is of direct relevance to the work carried out in this thesis, it is appropriate to discuss the three different classes of reaction which have been identified by Oppolzer as a function of the internal connectivity between the alkene and the enophile.[85] These are shown below for the intramolecular carbonyl ene reaction, and were influential in the selection of substrates for our own nitroso ene studies (Scheme 29).



Scheme 29

Type I reactions are defined when the carbon atom of the carbonyl group forms a carbon-carbon bond to the internal carbon atom of the alkene and are restricted to the formation of five and six membered rings. In Type II reactions, the carbon atom of the carbonyl group forms a bond to the terminal carbon atom of the alkene and the observed preference is for formation of six or seven membered rings. For Type III reactions, formation of an oxonium cation from a mixed acetal is required and a stepwise process is followed. Although it is interesting to speculate there is, as yet, no equivalent of this type for an "alkylated" nitroso group.

In general, the nitroso ene reaction is calculated to be stepwise, although Lu reported the first concerted nitroso ene reaction between *o*-isotoluene **107** (or its naphthalenic analogues) and nitroso compounds **24** such as nitrosomethane or 4-nitrosobenzene (Scheme 30).[80] Density functional calculations gave exclusively the pericyclic pathway, with a small activation enthalpy of 2.3 kcal mol^{-1} and so it is the case that a concerted pathway is both thermodynamically and kinetically favoured over the stepwise.



24 **107** **108** **109**

Scheme 30

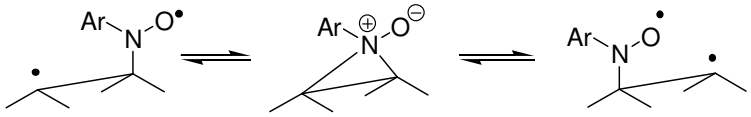
An early PM3 computational study effectuated by Davies and Schiesser of the reaction between propene and nitrosyl hydride allowed the possibility of locating several transition

states on the potentional energy surfaces. According to their calculations, if the ANO intermediate was the pathway, it would cost 8 kcal mol^{-1} less than for the concerted reaction.[86]

More sophisticated calculations (B2LYP/6-31g*) for the same ene reaction between propene and nitrosyl hydride elaborated by Leach and Houk led them to propose the involvement of polarised diradical intermediates during the transformation, and indicated that moreover this is the rate limiting step, in agreement with kinetic isotope effect (KIE) data.[49,82,83,87]

Thus, initial approach of nitrosyl hydride to a propene molecule results in formation of a polarized diradical, characterized by a relatively high rotation barrier for the carbon-nitrogen and carbon-carbon bonds (4-5 kcal mol^{-1}), which are higher than the barriers to formation of the product. This diradical species can then abstract an allylic hydrogen atom to form the corresponding hydroxylamine or equilibrate to the aziridine *N*-oxide.

As a consequence of an exhaustive study to elucidate the mechanism of the ene reaction between pentafluoro-nitrosobenzene and deuterium labelled tetramethylethylenes, Adams and Krebs have alternatively suggested the three-membered ring intermediate as a direct precursor to subsequent ene products.[88] In contrast to the results obtained with 4-nitro-nitrosobenzene as the enophile, the formation of the ANO **111** is reversible when pentafluoro-nitrosobenzene is employed (Scheme 31).



PD **110** ANO **111** PD' **112**

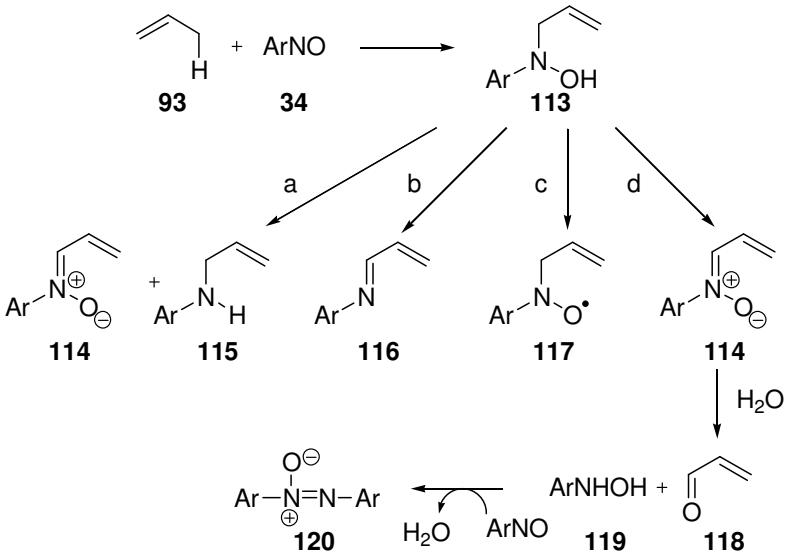
Scheme 31

The observed KIE values were rationalised in terms of hindered rotation around the carbon-nitrogen and carbon-carbon bonds in the polarised diradical **110**, whereas the three membered ring intermediate **111** was necessary for the isomerization between the PD and PD´.

Overall, in spite of the considerable number of publications concerning the mechanism of nitroso ene reactions, the nature of the intermediates and the structures of the transition states are still not well resolved.

2.3 Side Reactions.

In spite of the high reactivity of certain nitroso compounds towards the ene reaction, secondary products are frequently generated and only in exceptional cases has it been possible to isolate the hydroxylamine.[71] Under normal conditions, it reacts via further different possible pathways such as thermal decomposition, rearrangement, dehydration, or redox and condensation processes with another molecule of nitroso compound.[89] The more common *in situ* products generated from the initial ene adducts **113** are illustrated in Scheme 32 and comprise nitrones **114,** amines **115**, imines **116**, nitroxides **117**, and azoxy compounds **120**.[90]

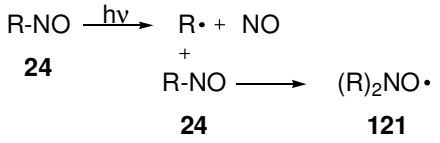


Scheme 32

Ene products derived from electron-rich nitroso compounds such as 4-nitrosophenol are readily oxidised via path a.[90a,90b,91] On treatment with acids and bases or on heating, the product hydroxylamine **113** can also dehydrate to the corresponding imine **116**, path b.[92] The oxidation of the ene products from nitrosoarenes **34** and tetramethyethylene by adventitious oxygen or by an "excess" of nitroso compound leads to relatively persistent nitroxyl radicals **117,** path c, which can undergo disproportionation.[92]

Hydroxylamines **113** which bear a hydrogen atom at the *N*-substituted carbon (e.g., the ene products from di- or trisubstituted alkenes) may be further oxidised to nitrones **114**, path d, which are often labile species and readily undergo polymerisation,[93] 1,3-cycloadditions,[94] or solvolysis.[95]

Spontaneous formation of free radicals has often been observed when nitroso compounds **24** are mixed with other organic compounds at room temperature.[96] It is believed that light assisted carbon-nitrogen bond homolysis occurs causing nitroxide formation **121** (Scheme 33).



Scheme 33

Knight and Pepper have reached some conclusions about aspects of these side reactions which are described in *vide infra* Scheme 43. As a result of the range of potential pathways which can occur subsequent to the ene reaction, more reactive electron deficient nitroso enophiles should be used to gain control of the synthetic outcome, and thus render them more useful as intermediates in organic synthesis.

2.4 Factors Influencing the Regioselectivity and Diastereoselectivity of the Ene Reaction.

In terms of preparative utility, several factors must be taken into account in understanding and controlling the regio- and diastereoselective outcome of the ene reactions.

Hydrogen Abstraction.

In the case of monosubstituted olefins the hydrogen atom must be transferred from the only available allylic position. However, with di-, tri- and tetrasubstituted olefins, several allylic hydrogen atoms from different substituents are available for transfer, and the regioselectivity issue becomes apparent. Unfortunately, no systematic study to determine the regioselectivity of the nitroso ene reaction of disubstituted alkenes has yet been reported. Whereas cyclic alkenes react at approximately equal rates, unsymmetrical (*Z*)-alkenes are react much faster compared to their (*E*)-isomers.[97]

Investigations into the regioselectivity of trisubstituted alkenes were carried out by Adam and Bottke using a CD_3 group to differentiate geminal substituted olefins.[88] As described

in Figure 4, there is a remarkable preference for allylic hydrogen atom abstraction from the *cis* alkyl group.

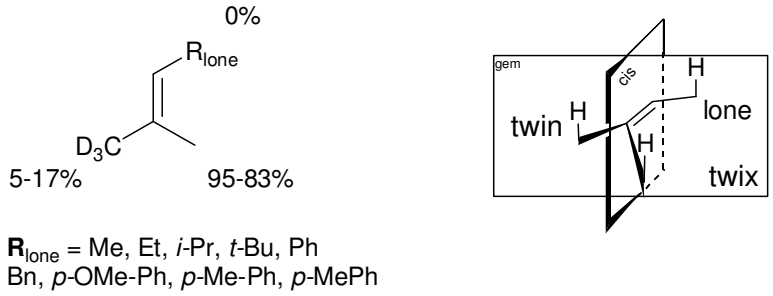
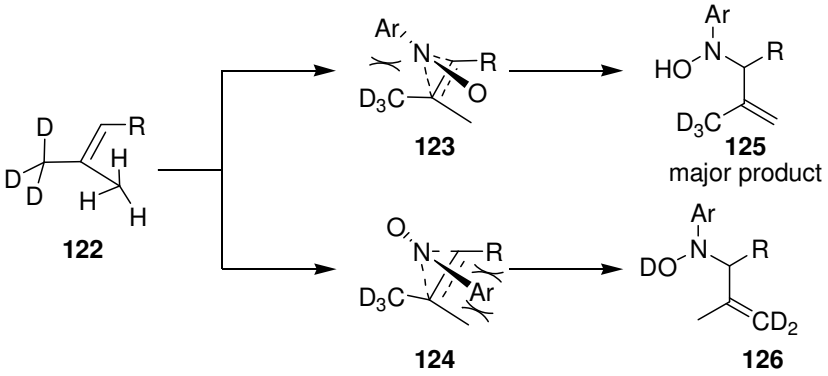


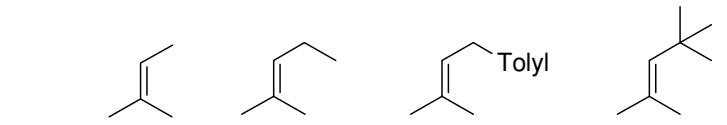
Figure 4

The difference in the regioselectivity has been rationalised in terms of steric hindrance during attack.[98] Such circumstances force the nitroso enophile to follow what has been named as the skew trajectory in the favoured twix arrangement of the enophile **123**, where the aryl group points to the free corner of the alkene and steric repulsions are reduced (Scheme 34). Hydrogen atom abstraction at the twin position is minimal and no ene product is observed from lone hydrogen atom abstraction. The skew effect is therefore defined as the combined features of the abstraction at the more crowded geminally substituted end and the more substituted *cis* side of the double bond known as the twix position.[99]



Scheme 34

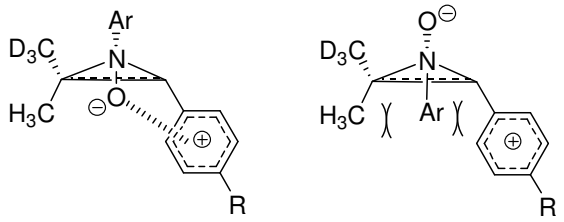
The influence of substitution at the lone position on the reactivity of the double bond has also been determined (Figure 5). An ethyl group **128** accelerates the reaction rate whilst bulky substituents **130** decrease the reactivity. However, as steric obstruction of the lone group increased, higher twix regioselectivity was observed.



K_{rel} **127:** 1.00 **128:** 1.41 **129:** 0.53 **130:** 0.32

Figure 5

When enophiles with nitrosoarenes are employed, twin regioselectivity was proven to be sterically prohibitive as shown in **132** but was nevertheless considered to be insufficient to explain the exclusive twix regioisomer **131** (Figure 6).



131: twix **132:** twin

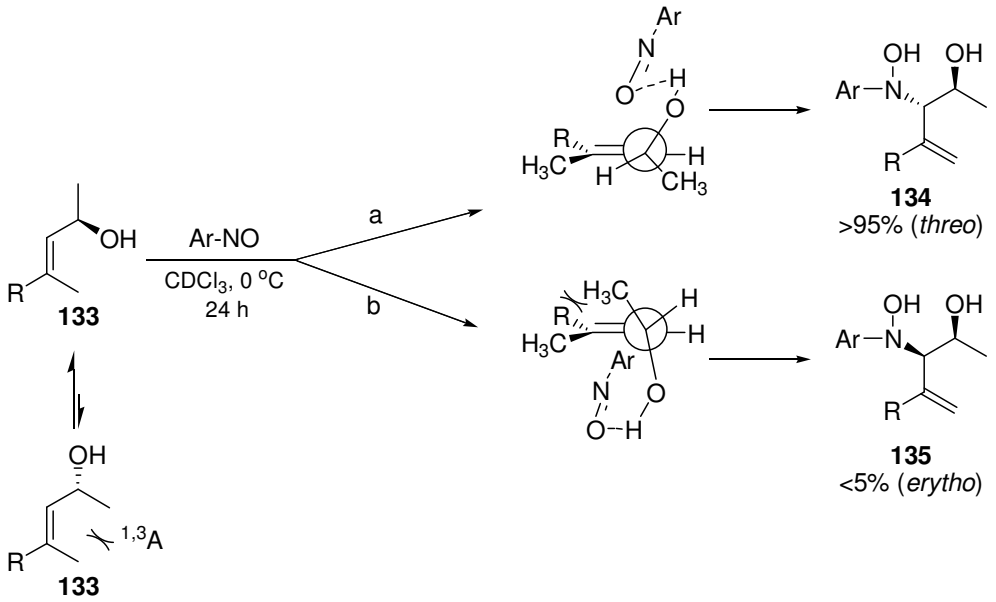
Figure 6

It has been postulated that during the enophilic attack on the conjugated double bond, the aryl group acquires a partial positive charge which can somehow be stabilised by coordination with the developing negative charge on the oxygen atom of the nitroso enophile (Figure 6).[99]

Hydroxy-Directive Effect.

A second intriguing observation relating to diastereoselectivity lies in the ability of the hydroxyl group of an allylic alcohol to act as an "anchor" for the nitroso ene reaction. Such behaviour has of course been long established in such reactions as the Simmons Smith cyclopropanation.[100]

Thus, investigations of the nitroso ene reaction using secondary chiral allylic alcohol **133** with 4-nitrosobenzene were shown to lead to formation of the *threo* isomer **134** with high diastereoselectivity as a consequence of the directing effect of the hydroxyl group (Scheme 35).[95]



R: CH_3 or H

Scheme 35

The abstraction of the hydrogen from the "*cis*" position of chiral alcohols **133** occurred as was expected from the results obtained from the regioselectivity of trisubstituted alkenes. Although two diastereomers can be formed, excellent diastereoselectivity was achieved for the reaction of alcohols **133** with *p*-nitronitrosobenzene (*threo : erythro* >95%). The observed preference was attributed to a combination of various effects. Thus, the determination of a facial orientation was fixed by the conformation of the hydroxyl group avoiding allylic strain ($A^{1,3}$), hence leading to approach of the incoming enophile from less congested side. Additional stabilisation by hydrogen bonding between the enophile with the hydroxyl group was also proposed as shown in Scheme 35.

Solvent effects are consistent with this hypothesis, and when protic solvents were employed, a decrease in diastereoselectivity was observed. Similar results were obtained when the hydroxyl group was replaced by an ether or ester functionality.

2.5 Examples of the Nitroso Ene Reaction.

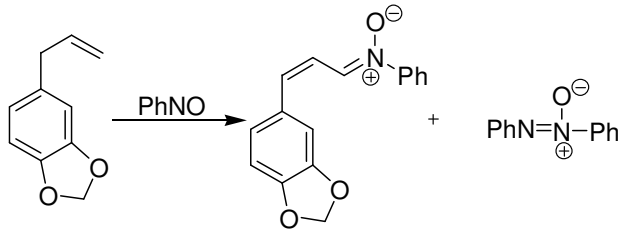
Although, the ability of nitroso compounds to undergo the ene reaction was first reported in 1910 by Alessandri,[101] Considerable time elapsed before Banks clarified relevant aspects of this transformation in 1965.[51b]

In this section, a review of all examples found to the best of our knowledge, is provided. Although represented in chronological order, they are grouped as a function of the enophile used, starting with the first reactions discovered, those of arylnitroso compounds, followed by alkylnitroso-, halonitroso-, α-nitroso- and acylnitroso compounds. Finally, an overview of metal catalysed nitroso ene reactions is described.

2.5.1 Arylnitroso Compounds as Enophiles.

A rationalisation of the reaction of nitrosoarenes with olefins has been carried out by Knight and Pepper by compiling the work previously undertaken by others, along with their own studies.[102]

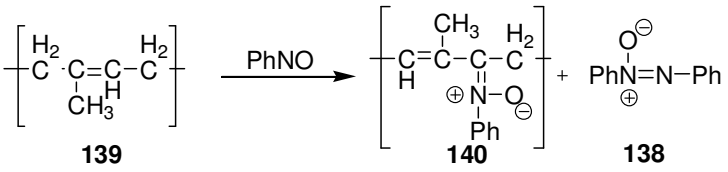
The first example, given by Alessandri *et al.* reported the reaction of nitrosobenzene with safrole **136**, to afford the nitrone **137** and azoxybenzene **138** (Scheme 36).[101]



136 **137** **138**

Scheme 36

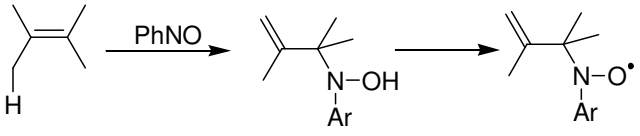
The reaction between nitrosobenzene and natural rubber **139**, *cis*-1,4-polyisoprene, was performed both by both Bruni and Gieger[103] and also by Pummerer and Gündel.[104] When three molar equivalents of nitrosobenzene were placed in a solution of rubber in benzene, azoxybenzene **138** and an "*iso*-rubber nitrone" **140** were obtained (Scheme 37).



139 **140** **138**

Scheme 37

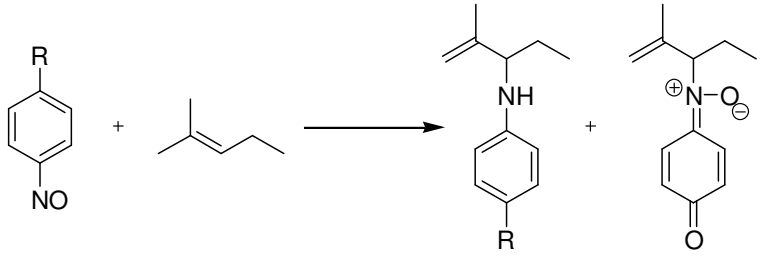
Sullivan proposed the existence of the intermediate *t*-alkenyl-arylhydroxylamine **142** formed by an ene reaction between nitrosobenzene and 2,3-dimethyl-2-butene **141**,[105] and further suggested that subsequent oxidation by air or unreacted nitrosobenzene led to the alkenyl aryl nitroxide **143** which was detected by e.s.r. spectroscopy (Scheme 38).



141 **142** **143**

Scheme 38

The reaction between *p*-nitrosophenol **144a** with 2-methyl-2-pentene, as studied by Pepper, is shown in Scheme 39, wherein *N*-alkenyl *p*-benzoquinoneimine-*N*-oxide **146a** was isolated and identified.[106]



144a R: OH
144b R: NMe_2

145a R: OH
145b R: NMe_2

146a

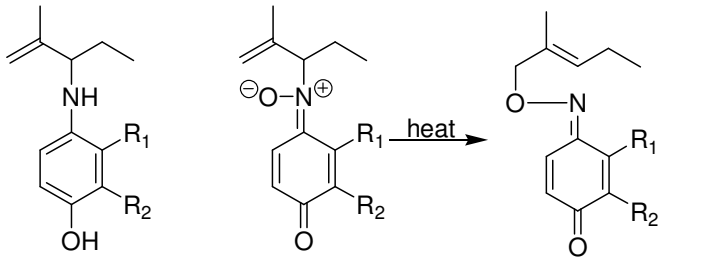
Scheme 39

The ene nature of these reactions was then later confirmed by Knight in 1968, who examined the reaction between nitrosobenzene with 2,3-dimethyl-2-butene and managed to isolate *N*-alkenyl-*N*-phenylhydroxylamine.[107] Subsequently, he repeated the reaction between *p*-nitrosophenol **144a** and *N,N*-dimethyl-*p*-nitrosoaniline **144b** with 2-methyl-2-pentene as described in Scheme 39.

Under moderate temperatures (20-140 ºC), anilines **145a** and **145b** were isolated in 36% and 31% yield respectively when an excess of olefin and nitroso compounds **144a** or **144b** were used. Some of the by-products obtained from this reaction including *p*-substituted

primary anilines, azoxybenzenes and azobenzenes were also identified, but it was the isolation of the *p*-azoquinone-*N*-oxide **146a** from the reaction of *p*-nitrosophenol **144a** with 2-methyl-2-pentene that led him to believe that this transformation had followed an ene pathway.

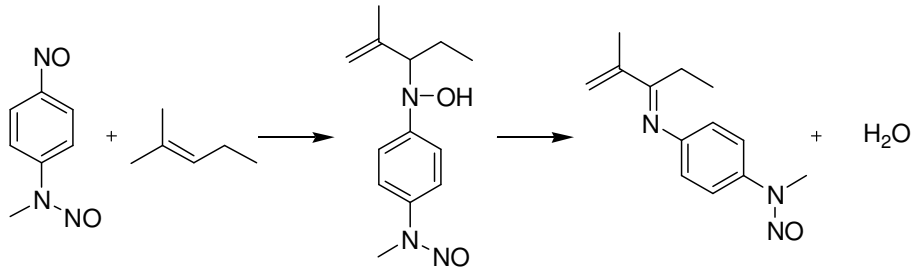
Pepper continued his work with this type of substrate. 2-Methyl-4-nitrosophenol and 3-methyl-4-nitrosophenol were allowed to react with 2-methyl-2-pentene at 100-120 ºC.[107b] In each case, the principal products were amine **147a** or amine **147b** (Scheme 40).



Scheme 40

Nitrone **148a** was also isolated however no nitrone **148b** was observed. Isolation of *O*-alkenyl oxime ether **149a** was explained as the result of thermal rearrangement of the corresponding nitrone **148a**.

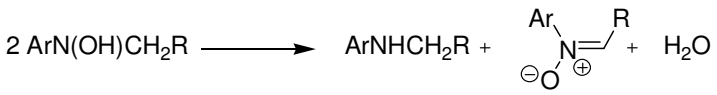
Further work on this class of ene reaction was reported by Zherebkova *et al.* between *N*,4-dinitroso-*N*-methylaniline **150** with 2-methyl-2-pentene to give the unsaturated hydroxylamine **151**, which on dehydration, yielded the anil product **152** (Scheme 41).[108]



Scheme 41

With the above results in hand, Knight and Pepper tried to clarify some aspects of this reaction.[102] At that time, little about the chemistry of alkenyl aryl hydroxylamines was known. As a result of their studies, these authors concluded that there were two main causes responsible for the final products of the ene reaction;

(i) The thermal decomposition of various *N*-phenyl-substituted *N*-benzylhydroxylamines **153** into **154** and **155** confirmed the oxido-reductive type of mechanism shown in Scheme 42.[91a,b]

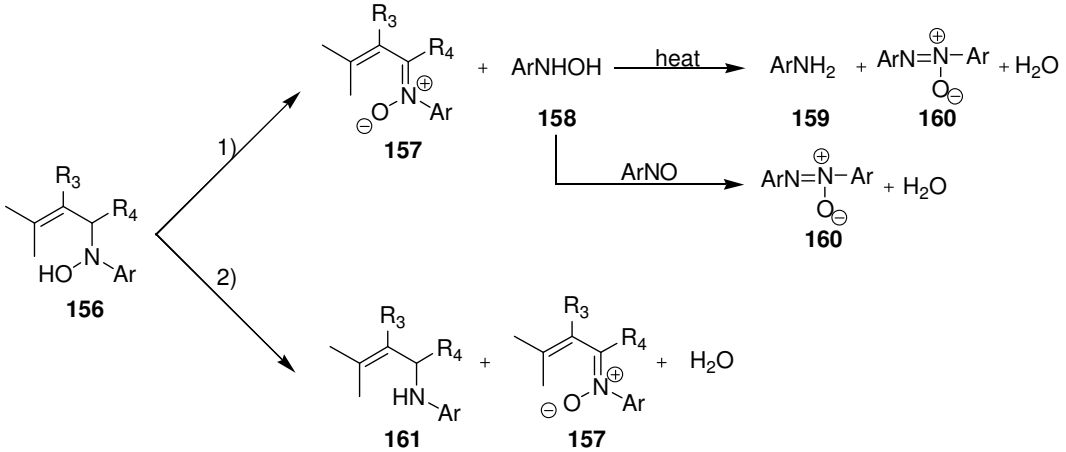


153 **154** **155**

Scheme 42

(ii) Secondary products frequently found in such reactions, nitrones or amines, were obtained by oxidation of the hydroxylamine intermediates with an excess of nitrosobenzene.[109]

Two routes finally emerged for the evolution of alkenyl aryl hydroxylamine products **156** of an ene reaction with an arylnitroso enophiles as illustrated in Scheme 43.

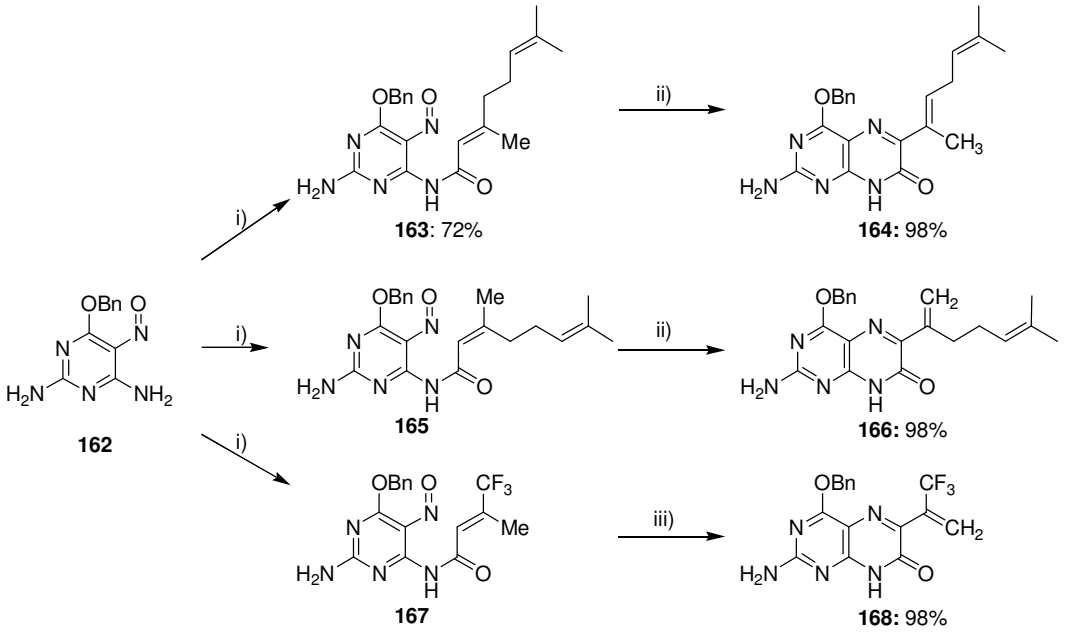


Scheme 43

In summary, when neutral or electron withdrawing substituents are present in the aromatic ring, pathway 1) is mainly followed to provide nitrones **157** and azoxyarenes **160** as observed by Alessandri, Bruni, Pummere and Sullivan. In the presence of an electron-donating aromatic substituent, the main effect is to markedly slow the rate of pathway 1)

whilst reciprocally enhancing the rates of thermal decomposition via pathway 2) so that the major products observed are the alkenyl arylamines **161** as well as nitrones **157**.[107c,110]

One of the most recent examples of an ene reaction using an arylnitroso compound has been reported by Vasella *et al.* and is illustrated in Scheme 44.[111]



i) 1.3 eq RCOCl, K_2CO_3, -18 ^oC, THF. ii) sol in CH_2Cl_2. 4 days. iii) suspension in toluene, 150 ^oC, 8 h in sealed vial.

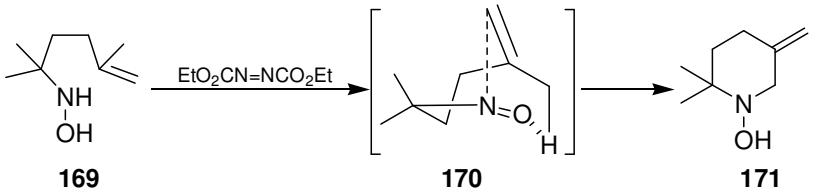
Scheme 44

Acylation of 2,4-diamino-5-nitrosopyrimidine **162** with different acid chlorides gave 4-(alkenoylamino)-5-nitrosopyrimidines **163**, **165** and **167**. These reacted at room temperature with subsequent colour change from blue to yellow to give the final compound C(6)-substituted pteridinones **164**, **166** and **168**. As usual the allylic transposition of hydrogen occurred from the less substituted substituent on the olefinic carbon, and as expected the presence of the strongly electron withdrawing CF_3 group slowed the reaction.

2.5.2 Alkylnitroso Compounds as Enophiles.

In 1972, the first example of the intramolecular ene reaction of a nitroso alkene was described by Motherwell and Roberts (Scheme 45).[112] Oxidation of the hydroxylamino olefin **169** with diethylazodicarboxylate or silver carbonate on Celite® yielded the expected nitroso olefin **170**, which underwent an intramolecular ene reaction of Type II

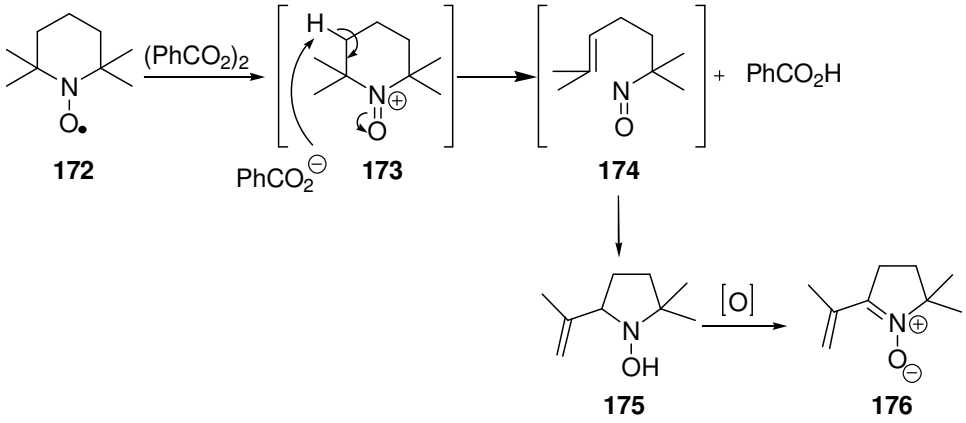
(*vide infra*) to give the new hydroxylamine **171** via the bicyclo [3,3,1] transition state shown (Scheme 45).



169 **170** **171**

Scheme 45

Unexpected results were observed during the investigations of radical polymerisation between vinyl monomers and acyloxy radicals.[113] The use of nitroxides such as 2,2,6,6-tetramethylpiperidinyl-1-oxy **172** with benzoyl or lauroyl peroxides in degassed styrene at 60 ºC gave instead an intramolecular ene reaction, forming nitrone **176** (Scheme 46).



172 **173** **174** **175** **176**

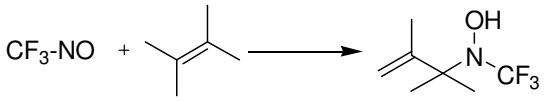
Scheme 46

The mechanism proposed for this process involved a single electron transfer oxidation to give benzoyloxy radicals and intermediate **173**, which directly underwent elimination to benzoic acid and compound **174**. The nitroso derivative **174** can then undergo an intramolecular ene reaction of Type I to give the hydroxylamine **175**, which by further oxidation afforded the nitrone **176**. To the best of our knowledge, these are the only two reported variants using tertiary nitroso alkyl compounds.

2.5.3 Haloalkyl and Haloarylnitroso Compounds as Enophiles.

The success of the ene reaction with nitroso compounds is proportional to the reactivity of the enophile, which increases when electron withdrawing groups are attached to the nitrogen, thus making trifluoronitrosomethane **177** one of the most reactive enophiles. An early e.s.r. study presented by Ginsberg using trifluoronitrosomethane aroused the interest

of Banks and Haszeldine and prompted them to rationalise the behaviour of trifluoronitrosomethane **177** with various olefins as shown in Table 1 (Scheme 47).[114]



177 **178** **179**

Scheme 47

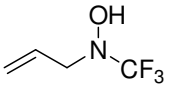
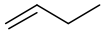
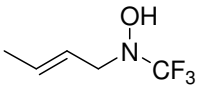
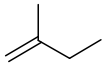
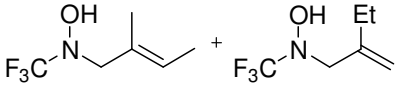
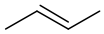
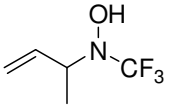
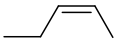
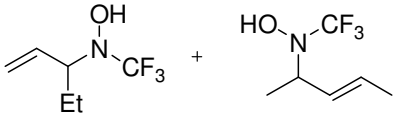
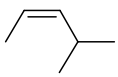
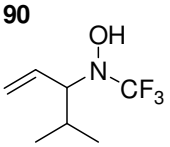
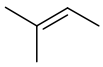
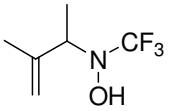
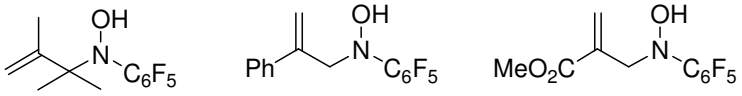
Entry	Substrate		Product		Yield (%)
1		**180**		**181**	90
2		**182**		**183**	83
3		**184**	 **185** **186**		97
4		**187**		**188**	87
5		**189**	 **190** **191**		96
6		**192**		**193**	93
7		**194**		**195**	95

Table 1

Some interesting aspects of the regioselectivity in this transformation can be elucidated. When the transfer of hydrogen can occur from either a methyl or from a methylene group as in the case of 2-methyl-1-butene **184** or *cis*-2-pentene **189** (entries 3 and 5), equal amounts of both products were produced. When competition is between a methyl or a methine group as in **192**, only the former substituent is involved and the major product, **193,** is obtained in 93% yield (entry 6).

In the aromatic series, pentafluoro-nitrosobenzene has been used as an enophile with various olefins: 2,3-dimethyl-2-butene, α-methylstyrene and methyl methacrylate,

producing *N*-alkenyl-*N*-1,2,3,4,5-pentafluorohydroxylamines **196**, **197** and **198** in moderate to good yields. (Scheme 48)



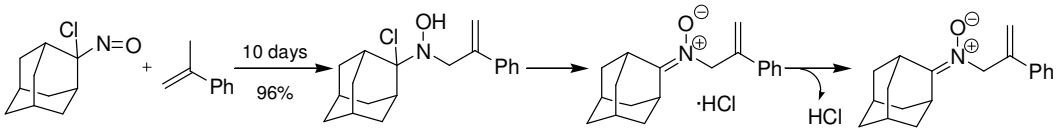
196: 96% **197**: 82% **198**: 41%

Scheme 48

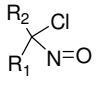
2.5.4 α-Functionalised Nitroso Compounds as Enophiles.

The enhancement of reactivity in the nitroso ene reactions through selection of substrates possessing an electron withdrawing group in the α position has been the subject of considerable discussion. Subsequently, although a number of examples of this type of transformation would be expected to be found in the literature, just two classes have been encountered.

De Boer and Schenk investigated the reaction between chloronitrosoadamantane **199a** and α-methylstyrene (Scheme 49).[115] The gradual disappearance of the initial blue colouration indicated the formation of *N*-α-chloroalkyl-*N*-alkenylhydroxyl-amine **201a** which, due to the lability of the chlorine atom in the α-position to the nitrogen lone pair, evolved via the nitrone hydrochloride **202a** to the nitrone **203a**. This was a fortunate way to safeguard the ene product from complex secondary reactions, because of the efficient formation of the insoluble nitrone **203a** as a white precipitate. Different examples were investigated in order to understand the scope of this transformation. Reaction of 2-chloro-2-nitrosopropane **199b** with α-methylstyrene was faster with completion taking only 12 h as opposed to the 10 days of the chloronitrosoadamantane **199a**.



199a **200** **201a-e** **202a-e** **203a**: 96%



199b-e

203b: $R_1 = R_2 = CH_3$ 91%
203c: $R_1 = CH_3$; $R_2 = C_2H_5$ 79%
203d: $R_1 = CH_3$; $R_2 = C_6H_5CH_2$ 73%
203e: R_1-C-R_2 = c-C_6H_{10} 76%

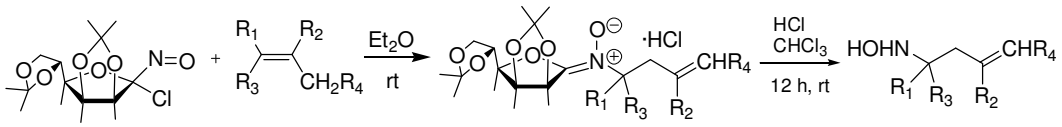
Scheme 49

Alkenes that contain only aliphatic substituents such as 2-methyl-2-butene or 2-methylpropene are not sufficiently reactive towards α-chloronitrosoadamantane **199a**. Investigations showed that the reactivity of such nitroso derivatives is relatively low and α-chloronitrosocyclohexane **199e** or even α,α-dichloronitrosoethane do not react with 2-methyl-2-butene within 10 days at 20 ºC.

However, the work undertaken by De Boer and Schenk had already determined that the rate of the ene reaction of nitroso compounds depends upon the electron density of the nitroso group which is diminished in derivatives containing electron withdrawing substituents such as fluorine or chlorine.

The higher reactivity of an α-chloronitroso sugar derivative **204**, when compared to either 2-chloro-2-nitrosopropane **199b** or α-chloronitrosoadamantane **199a** was first proved in a beautiful study by Vasella and co-workers.[116] They observed an enhancement in reactivity of these sugar derivatives with the reaction occurring even with alkenes containing only alkyl substituents. This was explained by the authors to be a consequence of the $^{-}$I inductive effect of the α-ether functionality.

From a practical standpoint, the use of the carbohydrate template as a chiral auxiliary provides a highly regio- and diastereoselective route from prochiral olefins **205 a-d** to the nitrone hydrochlorides **206 a-d**, which, after hydrolytic cleavage, can furnish chiral unsaturated hydroxylamines **207a-d** of defined geometry (Scheme 50).



204 **205 a-d** **206 a-d** **207 a-d**

a: $\mathbf{R}_1$=$\mathbf{R}_2$=Me, $\mathbf{R}_3$=$\mathbf{R}_4$=H
b: $\mathbf{R}_1$=$\mathbf{R}_2$=$\mathbf{R}_3$=Me, $\mathbf{R}_4$=H
c: $\mathbf{R}_1$=$\mathbf{R}_2$=H, $\mathbf{R}_3$ and $\mathbf{R}_4$-$(CH_2)_3$-
d: $\mathbf{R}_1$=H, $\mathbf{R}_2$=Ph, $\mathbf{R}_3$=$\mathbf{R}_4$=H

a: 98%
b: 94%
c: 99%
d: 96%

Scheme 50

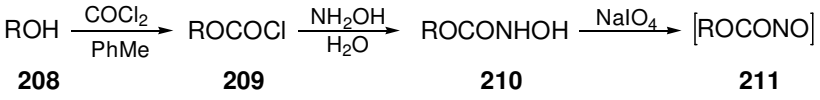
Further studies carried out by Schmidtchen *et al.* demonstrated that the mannose derivatived chiral reagent seems to perform slightly better in this respect than the corresponding chloronitroso ribose derivatives, perhaps due to increased steric crowding at the reactive hemisphere of the former reagent.[97] As expected for the case of 2-methyl-

2-butene, the carbon-nitrogen bond is formed exclusively at the less substituted end of the olefinic double bond.

2.5.5 Acylnitroso Compounds as Enophiles.

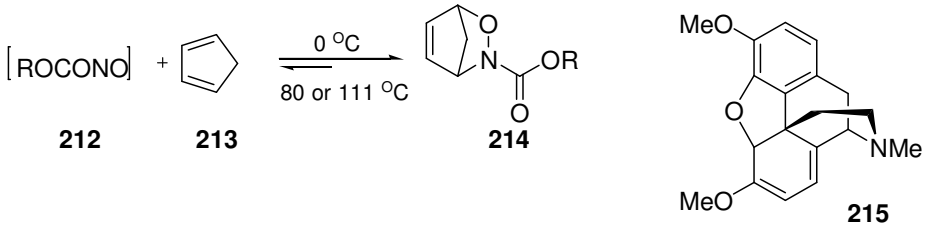
In the course of their investigations into the hetero Diels-Alder reaction using nitroso groups Kirby *et al*. showed that the presence of the electron-withdrawing cyano group enhances the dienophilic character.[3] Based on this result, they considered that compounds of the general class XC(=Y)NO, where Y can be an electronegative element O, N or S, should also be reactive, electron deficient dienophiles.

Hydroxamic acids (RCONHOH) or *N*-hydroxycarbamates **210** (ROCONHOH) were accordingly transformed into their corresponding acylnitroso derivatives **211** (Scheme 51).



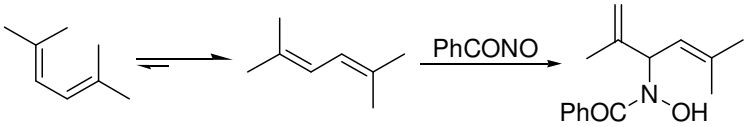
Scheme 51

Thus, alcohols **208** were reacted with phosgene to give a solution containing the chloroformates **209**, which on treatment with aqueous hydroxylamine solution gave the *N*-hydroxycarbamates **210**. Oxidation of **210** with sodium periodate gave the nitroso intermediates **211** which were trapped *in situ* as the Diels-Alder cycloadducts **214** with cyclopentadiene **213** as is shown in Scheme 52. Other dienes commonly used for this purpose are the aforementioned 9,10-DMA and thebaine **215**.[3,18,19,117]



Scheme 52

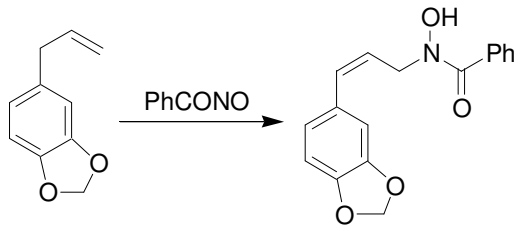
The thermal release of intermediates **212** from cycloadduct **214** in the presence of different dienes gave the corresponding Diels-Alder adducts except in the case of 2,5-dimethylhexa-2,4-diene **216,** which led to hydroxamic acid **217**. In these instances, steric constraints are presumably responsible for the predominance of the s-trans form **216b**, thus making the ene reaction more likely to occur (Scheme 53).[19]



216a **216b** **217**

Scheme 53

Safrole **218** is known to undergo the ene reaction and in the presence of nitrosocarbonyl benzene gave the unsaturated hydroxamic acid **219** (Scheme 54).[102]



218 **219**: 65%

Scheme 54

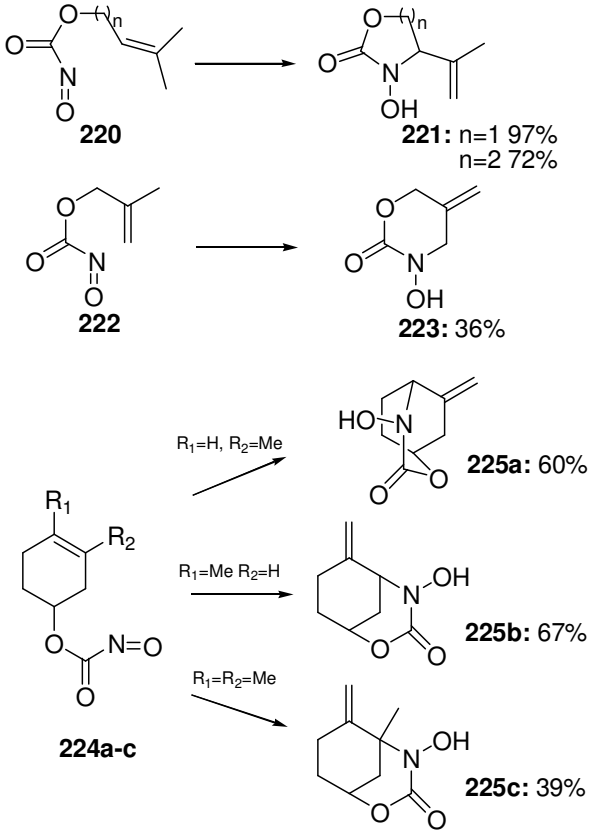
The formation of product **219** was favoured by movement of the double bond into conjugation with the benzene ring and it was obtained in a satisfactory 65% yield.

Further investigations into the intramolecular variant, including the selectivity of nitrosoformates esters **220**, **222** and **224** containing an allylic or homoallylic moiety have also been carried out (Scheme 55).[18] The 9,10-DMA Diels-Alder adducts were generated by the method described in Scheme 52 and their thermal dissociation generated the reactive substrates **220**, **222** and **224** available for the ene reaction.

The allylic **221** (n = 1) and homoallylic **221a** (n = 2) nitrosoformate esters cyclise by a Type I mechanism (*vide infra*), prefering a fused rather than a bridged bicyclic transition state as a consequence of the relative strain for a concerned cyclisation. An example of a Type II mechanism is represented in substrate **222**. In this case a bicyclo [3.3.1] transition state is required, but clearly this process is less favourable than for the Type I case, and thus, product **223** is formed in only 36% yield.

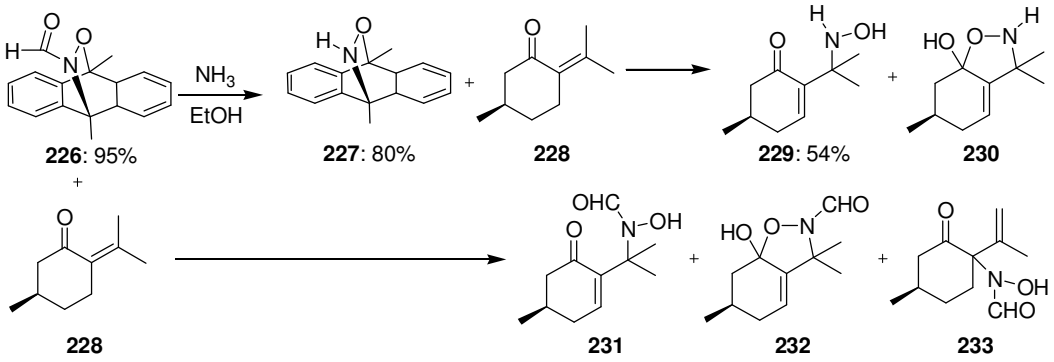
The intramolecular ene reactions of substrates **224 a-c** gave; oxazepinone **225a** in 60% yield, the six-membered ring hydroxamic acid **225b** in 67% yield, and oxazinone **225c** in 39% yield. For these substrates, although more than one proton can participate, only exocyclic olefins **225 a-c** were isolated in all cases. However, these results cannot be

explained by a similar factor, and several effects need to be taken into account, amongst others ring size, steric and electronic effects.



Scheme 55

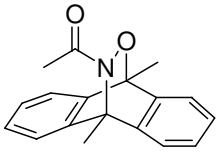
The reactivity of the parent intermediates, nitrosyl hydride and nitrosoformaldehyde, towards further transformations other than dimerisation, was also subject of interest.[118] As usual, the generation of such labile species requires *in situ* generation. Oxidation of formylhydroxamic acid in the presence of 9,10-DMA gave the formylnitroso Diels-Alder adduct **226** in 95% yield. Treatment of an ethanolic solution of **226** with anhydrous ammonia followed by evaporation of the solvent afforded an 80% yield of product **227**. Thermal decomposition liberated nitrosyl hydride which can be trapped with R (+) pulegone **228** (Scheme 56).



Scheme 56

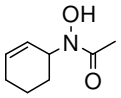
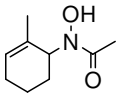
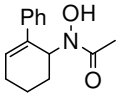
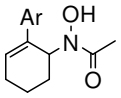
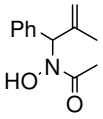
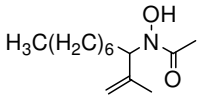
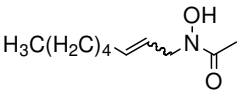
The ene product **229** was obtained in 54% yield and was formed as an equilibrium mixture with its hemiacetal form **230**. However, when the reaction was carried out using **226** as the nitroso source, more complex results were obtained with at least five different compounds being formed, including the ene product **231**, its hemiacetal derivative **232** and compound **233** as a mixture of two diastereomers.

Keck and Webb have published an extensive body of work on both the inter- and intramolecular ene processes in which the acylnitroso group acts as the enophile.[19] They have performed bimolecular ene reactions via thermal transfer of nitrosocarbonylmethane from its Diels- Alder adduct with different olefins and the associated results are summarised in Table 2.



234

+ olefin **heat** → 9.10-DMA + hydroxamic acid

Substrate	Method	Ene Product	Yield (%)
cyclohexene	A	 **235**	85
1-methylcyclohexene	C	 **236**	92
1-phenylcyclohexene	C	 **237**	95
1-*p*-methoxyphenylcyclohexene	B	 **238**	89
2-methyl-1-phenylpropene	C	 **239**	88
2-methyl-2-decene	C	 **240**	83
1-octene	A	 **241**	89

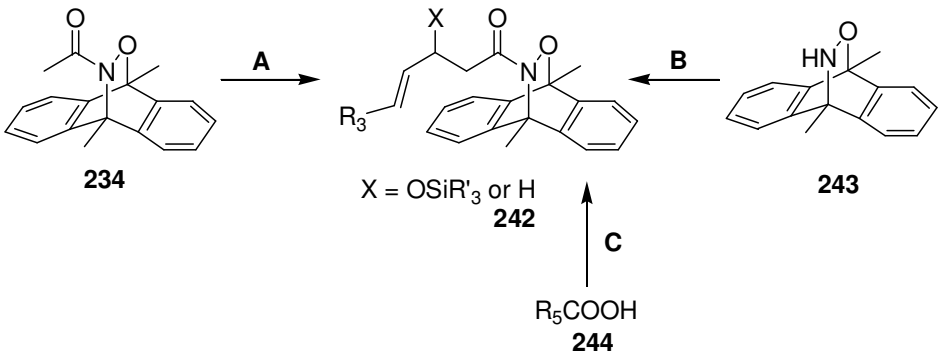
Method **A**: inexpensive olefins with appropiate boiling points are used as solvents. Method **B**: 1.1-1.2 eq of olefin, refluxing in benzene. Method **C**: Small sealed tubes heated at 80 ^{o}C.

Table 2

High yields were obtained for this transformation (83-95%) although restrictions were found when 1,1-diphenylpropene was employed as the enophile when no reaction was observed. This result was explained as a consequence of the olefinic conjugation with the two phenyl groups. However, if only one phenyl group is present in the α position to the double bond, as in 2-methyl-1-phenylpropene, the ene reaction proceeded in high yield.

In order to study the intramolecular nitroso ene version, construction of appropriate substrates was necessary (Scheme 57). Simple substrates can be prepared by alkylation of

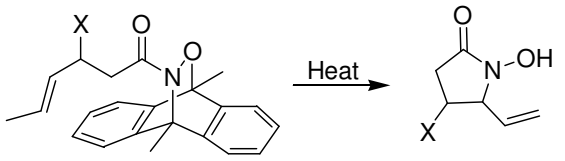
the lithium enolate derivative of Diels-Alder adduct **234** with α,β-unsaturated aldehydes or highly reactive bromides such as 1-bromo-3-methyl-2-butene (path A). Whilst two alternative strategies for the elaboration of more complex substrates exist: either by condensation of a carboxylic acid chloride derivative with **243** (path B) (though this approach suffers from the low thermal stability of hydroxylamine **243**),[119] or by an equivalent procedure using the approach developed by Kirby (path C).[120]



A: i. LDA, -78 ^{O}C, THF-HMPA, ii. $R_1CH=CHCHO$ or $R_2CH=CHBr$. **B:** R_4COCl.
C: i. $SOCl_2$. ii. $NH_2OH{\cdot}HCl$ iii. *n*-Pr_4NIO_4, $CHCl_3$, 9,10-DMA

Scheme 57

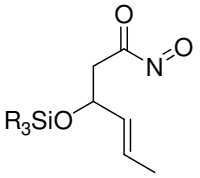
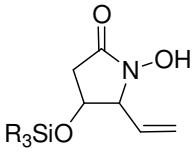
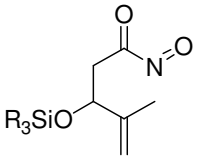
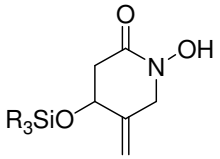
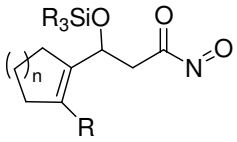
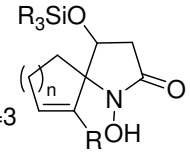
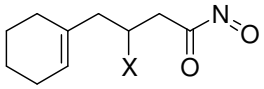
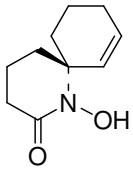
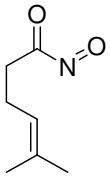
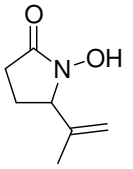
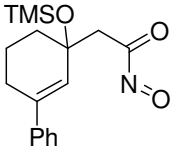
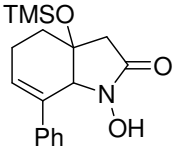
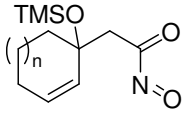
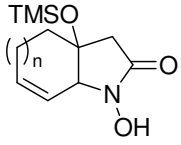
The intramolecular ene process was carried out by pyrolysis of benzene or toluene solutions containing substrates **242** (Scheme 58 and Table 3). It was noted that reaction times were shorter than for bimolecular processes (30-40 min at 110 ºC) with excellent yields obtained for product **245** in all cases, with carbon nitrogen bond formation occurring at the more substituted olefinic carbon.



X = $OSiR_3$, H
242

245

Scheme 58

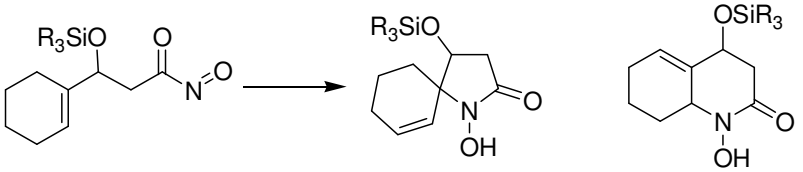
Entry	Acyl Nitroso Intermediate	Yield	Ene Product	Yield
1		**246:** 67%		**247:** 100%
2		**248:** 79%		**249:** 100%
3		**250a:** 80% R=H, n=1 **250 b:** 77% R=H, n=2 **250 c:** 81% R=CH_3, n=3		**251a:** 95% **251b**: 92% **251c**: 100%
4		**252a:** 85% X=$OSiR_3$ **252 b:** 72% X=H		**253a:** 85% **253b:** 100%
5		**85:** 74%		**86:** 100%
6		**254:** 76%		**255:** 96%
7		**256:** 75% n=1,2		**257:** 85-100%

T

able 3

In entries 3 and 4, two possible ene products can be obtained, either the spirocyclic hydroxamic acid **251b** corresponding to a Type I intramolecular ene reaction, and/or the fused azadecalin derivative **251b´** corresponding to a Type II reaction (Scheme 59). In the

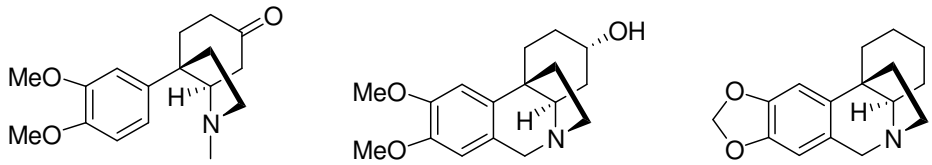
event, only the spiroannulated compound **251b** was formed, presumably since a much less strained conformation was required.



250b **251b** *via* path A **251b'** *via* path B

Scheme 59

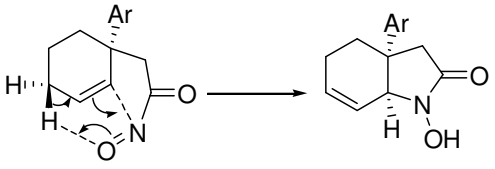
These studies also inspired Keck to investigate alternative connectivity patterns for intramolecular nitroso ene reactions and, in consequence to develop an elegant synthetic route to *dl*-mesembrine **258**,[121] a member of the Amaryllidaceae family of alkaloids which also include dl-dihydromaritidine **259**,[122] and (±)-crinine **260**,[123] amongst others (Figure 7).[124]



258 ***dl*-Mesembrine** **259** ***dl*-Dihydromaritidine** **260** **(±)-Crinane**

Figure 7

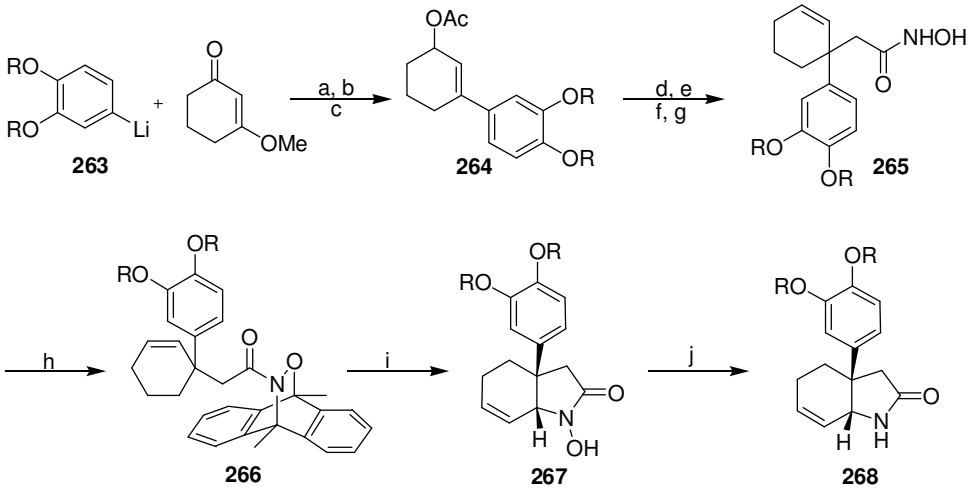
The significant antitumor and analgesic activity of this class has stimulated intense synthetic interest and the major challenge lies in construction of the *cis* fused-1-aza-9-arylbicyclo [4,3,0] nonane core which is the common structural motif.[125] The key element of the strategy lay in the selection of a 3,3´-geminally functionalised cyclohexene unit which can only give rise to a single intramolecular ene product (Scheme 60).



261 **262**

Scheme 60

The required unsaturated lactam **268** was obtained via the route outlined in Scheme 61. Thus, 1,2 addition of lithioveratrole **263** to 3-methoxy-2-cyclohexen-1-one, followed by work up with aqueous acid, afforded the enone which was reduced and acylated with acetic anhydride to yield the acetate **264** in 67% yield.



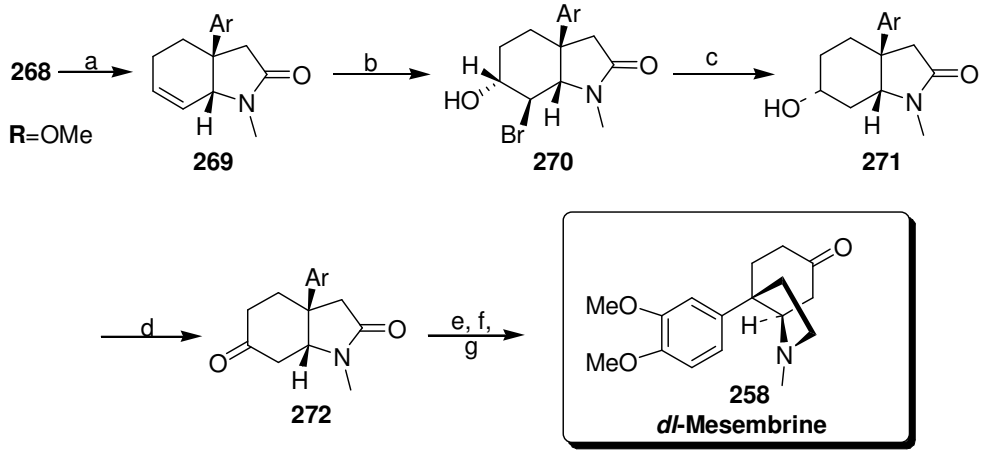
a) H_3O^+; b) $NaBH_4$, EtOH, 0 ^{O}C; c) Ac_2O, Py; d) LICA, THF, HMPA, -78 ^{O}C; e) *t*-$BuMe_2SiCl$, THF, then reflux; f) $SOCl_2$, benzene, DMF, reflux; g) $NH_2OH{\cdot}HCl$, $NaCO_3$, Et_2O/H_2O; h) $(CH_3CH_2CH_2)_4NIO_4$, $CHCl_3$, DMF, 9,10-DMA; i) toluene, reflux; j) $TiCl_3$, H_2O, MeOH, Na_2CO_3.

Scheme 61

Claisen rearrangement of **264** via Ireland's method furnished the crystalline acid, which was then converted via reaction of the corresponding acid chloride with hydroxylamine to the desired hydroxamic acid **265**.

Oxidation of **265** in the presence of 9,10-DMA gave the Diels-Alder cycloaddition product **266** after purification by column chromatography in 85% yield. The acylnitroso moiety was then thermally released to liberate the precursor for the intramolecular ene process and the cyclic hydroxamic acid **267** was isolated in quantitative yield. Ene product **267** was then reduced to the corresponding lactam **268** by action of titanium (III) chloride.[126]

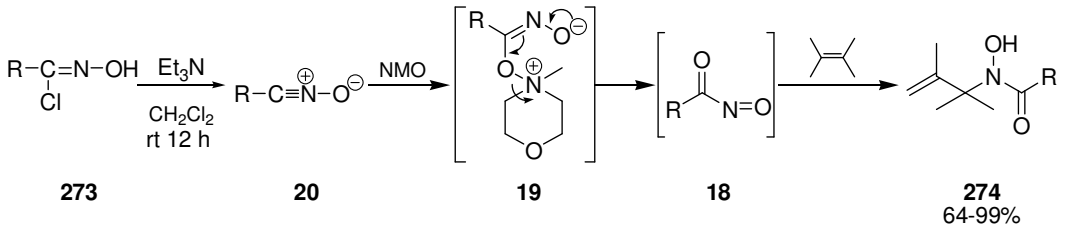
The lactam **268** was then *N*-methylated using NaH and iodomethane to afford lactam **269** which reacted smoothly with NBS yielding bromohydrin **270** as the sole product. Removal of bromide via tin hydride reduction gave lactam alcohol **271** which, after oxidation with PCC, produced keto lactam **272**. Mesembrine **258** was finally obtained after a sequence of transformations including ketone protection with ethylene glycol, reduction with LAH, and hydrolysis with aqueous hydrochloric acid (Scheme 62).



a) NaH, CH_3I, THF; b) NBS, 4:1 DME-H_2O; c) $(CH_3(CH_2)_2CH_2)_3SnH$, AIBN, toluene, reflux; d) PCC, CH_2Cl, 0 °C; e) $HOCH_2CH_2OH$, benzene, reflux, *p*-TsOH; f) LAH, THF, reflux; g) H_2O^+

Scheme 62

As previously discussed in Scheme 7, nitroso carbonyl intermediates are also generated *in situ* by using tertiary amine *N*-oxides to oxidise nitrile oxides under mild conditions (Scheme 63).[22b]

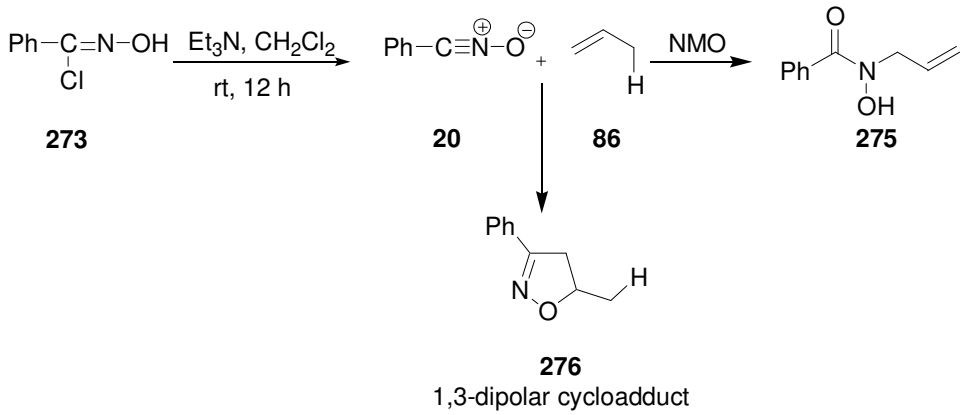


R= Ph-, *p*-ClPh-, 2,4,6-$Me_3C_6H_3$-, *p*-MePh-, *p*-MeOPh-, *p*-NO_2Ph-, Me-, *n*-Pr-, $Me(CH_2)_5$-, $PhCH_2$-, Ph-CH=CH-, PhCO-

Scheme 63

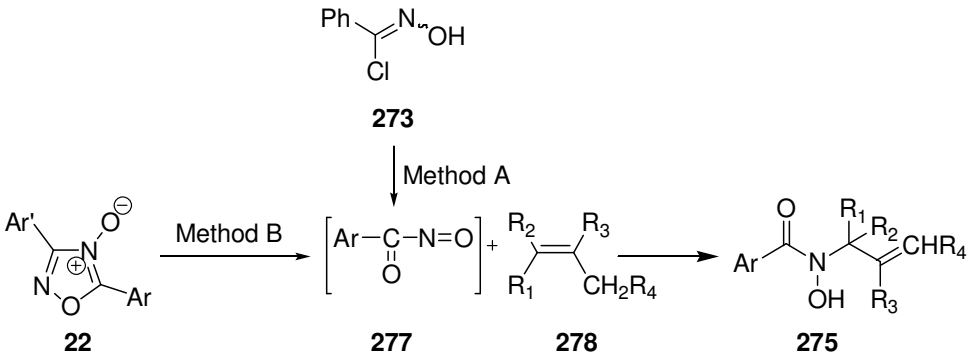
Nitrile *N*-oxides **20** are usually generated *in situ* from chloro oximes **273** by elimination of hydrogen chloride. Mild oxidation of nitrile *N*-oxides **20** with NMO produces intermediate **18** which can be then trapped via an ene reaction in the presence of an excess of tetramethylethylene.

The yields obtained, ranging from 64% for **260** (R = Me) to 99% for **260** (R = Ph), prove that this method is very valuable for carbon-nitrogen bond formation. However, tetramethylethylene is a good olefin in as much as it is fully unreactive in the competitive 1,3-dipolar cycloaddition reactions undergone by nitrile oxides. To observe the behaviour of less substituted double bonds, a number of experiments using the **273** (R = Ph) as a precursor was carried out (Scheme 64).[22b]



Scheme 64

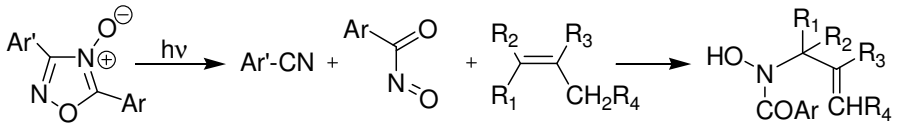
The results obtained are compiled in Table 4 (method A). Whilst highly substituted double bonds (entries 1, 2) and cyclohexene (entry 3) produced excellent yields with no dipolar cycloadduct **276** formed, alkenes such as cyclopentene and 1,2 or 1,1-disubstituted ethylenes (entries 4-7) gave the ene product **275** in much lower yields along with the competing 1,3-dipolar cycloadduct **276** in 10-18% yield.



Entry	Olefin	Yield[A]	Yield[B]
1		99%	99%
2		99%	99%
3		99%	99%
4		49%	99%
5		48%	95%
6		10%	93%
7		61%	-
8	1-octene	-	90%

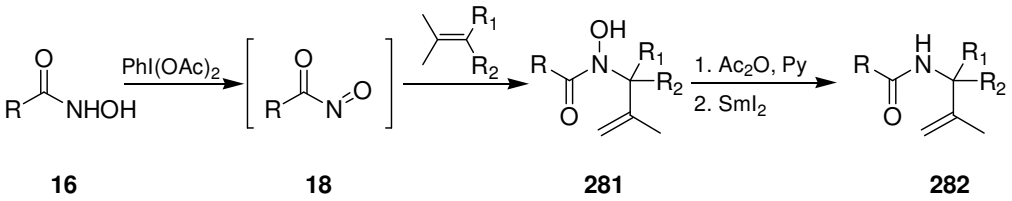
Table 4: [A]Method A: Mild oxidation with NMO of nitrile *N*-oxides[22]. [B]Method B: Photochemical fragmentation of 1,2,4-oxadiazole-4-oxides.[24]

Competition between the ene and 1,3-dipolar cycloaddition reactions with less substituted ethylenes can however be avoided by using a photochemical method for the generation of nitrosocarbonyl intermediate **279** (Scheme 65). Photochemical fragmentation of 1,2,4-oxadiazole-4-oxides **22**, a class of compounds easily available by cycloaddition of nitrile oxides to amidoximes, produced a nitrile and the nitrosocarbonyl compound **279** which can then react with alkenes as shown in Table 4 (method B) to generate the ene product **280** with excellent yields even when 1-octene is selected (entry 8).



Scheme 65

As we have seen, selective *in situ* oxidation of hydroxamic acids generally gives poor yields of ene products. More recently however, iodosobenzene and iodosobenzene diacetate have been demonstrated to be appropiate oxidising agents for a mild and clean preparation of the desired acylnitroso compound *in situ*.[20] Commercially available hydroxamic acids **16** can then be oxidised and trapped as illustrated in Scheme 66.



Scheme 66

N-Allylhydroxamic acids **281** were protected as their *O*-acetylated derivatives to avoid further transformations. Finally selective reduction with samarium diiodide afforded allyl amines **282** in quantitative yield. Table 5 compiles the results obtained when different substituted hydroxamic acids were used with various olefins.

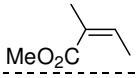
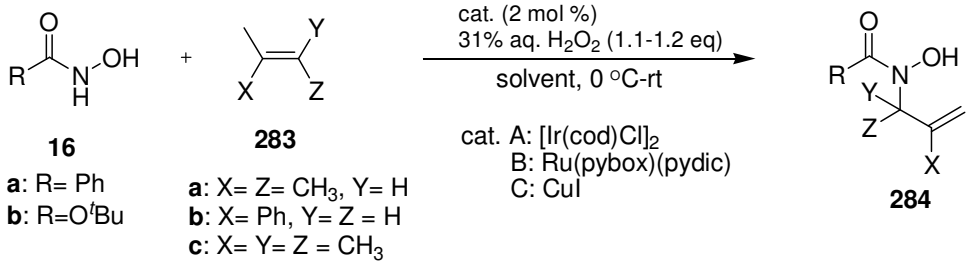
Entry	R	Olefin	Yield[a]
1	-CH_3		62%
2	-$CH_2C_6H_5$		87%
3	*p*-NO_2-C_4H_6-		82%
4	-C_6H_5		70%
5	*p*-NO_2-C_4H_6-		54%
6			10%

Table 5 [a] yield of acetylated ene adduct.

As observed, the more electron rich the olefin is, the greater the yield of the ene product, as in the examples using tetramethylethylene (entries 1-4). For the case of 2-methylbutene, a less electron rich olefin, with *p*-nitro-*N*-hydroxybenzamide only a moderate yield was produced although only one regioisomer was observed (entry 5). An electron poor ene substrate such as methyl tiglate (entry 6) gave only 10% of the acylated ene adduct, even when the most reactive aryl nitroso derivative was employed.

Unfortunately, in all of the methods discussed above, with the exception of oxidation using iodosobenzene or iodosobenzene diacetate, an excess of olefin is required and elaborated precursors such as the 9,10-DMA adduct, require to be prepared. More convenient methods have accordingly been sought.

Further investigations led to a new one pot procedure for the ene reaction with olefins involving ruthenium (II), iridium (I) and copper (I) catalysed oxidation of hydroxamic acids with aqueous hydrogen peroxide (Scheme 67).[21]



16
a: R= Ph
b: R=O^{t}Bu

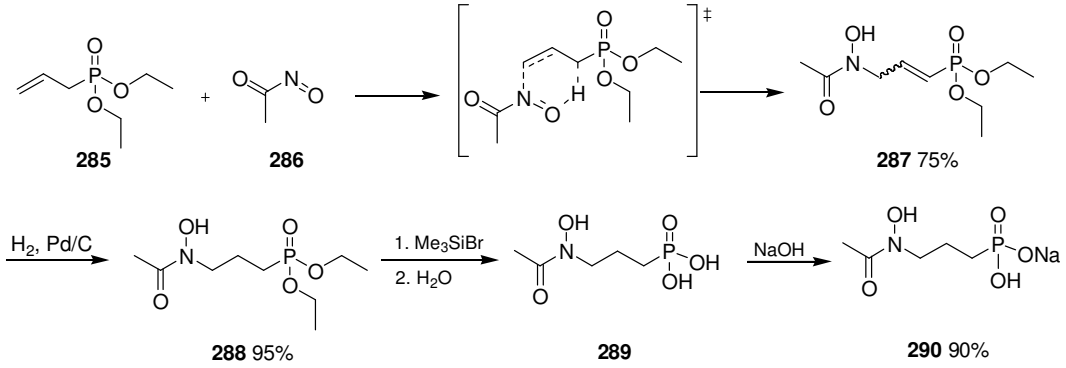
283
a: X= Z= CH_3, Y= H
b: X= Ph, Y= Z = H
c: X= Y= Z = CH_3

284

Scheme 67

Although reactions using phenylhydroxamic acid were generally unsuccessful, important differences were found when *tert*-butoxy hydroxamic acid **16b** was employed. The selection of 2-methyl-2-butene gave good yields (50-86%) regardless of the catalyst used, with good to moderate regioselectivity. However, in the presence of α-methyl styrene to trap the nitroso derivative, only the copper catalyst (C) gave good results.

The first example of an ene reaction between nitrosocarbonyl methane **286** and a functionalised olefin was used in a new approach for the synthesis of FR900098, **290**.[127] Commercially available diethyl allylphosphonate **285** reacted with nitroso carbonyl methane **286**, which was prepared *in situ* via thermolysis of its 9,10-DMA adduct as the key step (Scheme 68). Remarkably, the phosphoryl group remained untouched in the unsaturated adduct **287**, which was isolated as a mixture of E- and Z- isomers in a 1:1 ratio. Further transformation of **287** involved hydrogenation on Pd/C at atmospheric pressure to give diethyl phosphonic ester **288** in 95% yield.



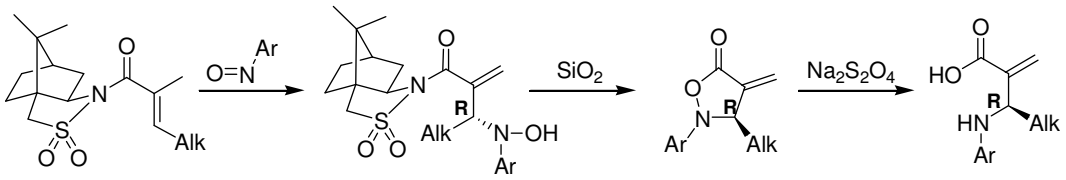
Scheme 68

A mild deprotection reaction based on treatment with bromotrimethylsilane followed by water generated the acid **289** with complete conservation of the acetylhydroxamic functionality. Compound **290** was finally isolated after partial neutralisation of **289** with sodium hydroxide, thus providing the desired drug in only four steps with an overall yield of 64% .

Very few asymmetric variants of the nitroso ene reaction have been reported, as compared to its more famous counterpart, the Diels-Alder reaction using nitroso compounds as dienophiles. The approach based on chiral α–chloro nitroso carbohydrate derivatives mentioned above, is one of only two present examples to date.[116] The second case

involves the synthesis of highly functionalised α-methylene β-aminoacids, and can be achieved, once again, with the help of a chiral auxiliary for stereocontrol.[128]

Thus, optically active tiglic acid derivatives **291** of the camphor-based Oppolzer sultam react with nitrosoarene enophiles to afford the desired ene products **292** in 55-61% yield as single diastereomers (Scheme 69).



291a R = Me
291b R = *i*-Pr

292a 61%
292b 55%

293 >95%

294 75%
294b 84%

Scheme 69

The primary ene products can then be quantitatively converted by treatment with silica gel to highly functionalised α-methylene isoxazolidinones **293**, which, by reductive cleavage of their nitrogen oxygen bond give the β-amino acids **294** in 75-84% yield.

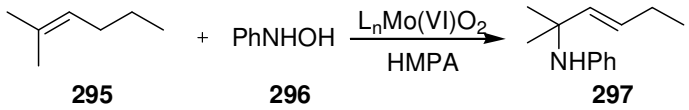
2.5.6 Metal-Catalysed Amination via Nitroso Compounds.

The direct synthesis of nitrogen containing compounds from hydrocarbons remains an attractive but largely elusive goal. New methodologies using metal-catalysed allylic amination of olefins have, in consequence, been investigated by several research groups. Two different approaches have been worked out for such metal catalysed nitroso ene reaction; the first involving oxidative catalytic amination starting from hydroxylamine and the second, a reductive catalytic amination from nitrosoarenes.

Oxidative Catalytic Amination.

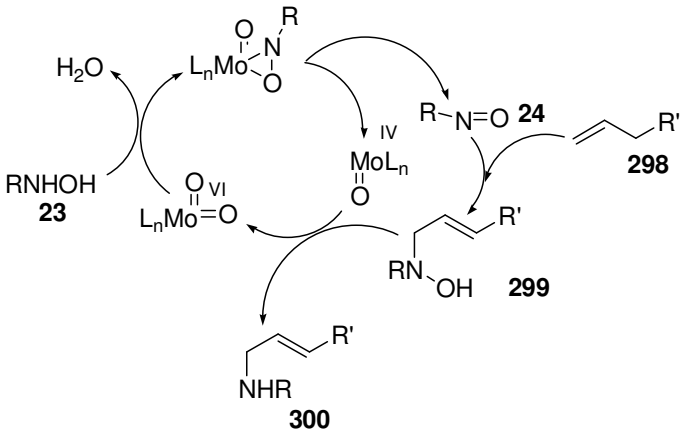
Allylic amination of olefin **295** catalysed by transition metals has been recently studied. Three transition metals; copper, molybdenum and iron, were discovered to be valuable for this purpose. The role of the metal catalysts in these reactions is to serve as a redox agent, by oxidising the starting phenylhydroxylamine **296** to the reactive nitrosobenzene and also by reducing the allylhydroxylamine ene product to the corresponding allylamine **297** with regeneration of the catalytic oxidant.

In typically ingenious fashion, Sharpless has reported the stoichiometric imido-transfer reactions of molybdooxaziridine complex [$MoL_n(\eta^2$-RNO)] with alkenes, producing allylamines **297** (Scheme 70).[32]



Scheme 70

The catalytic cycle for the molybdenum complex is shown in Scheme 71 below. Initially, reaction of $LMo(VI)O_2$ with phenylhydroxylamine **296** to form Mo-oxaziridine and water is then followed by dissociation of this complex forming nitrosobenzene **24** (R=Ph). The ene reaction with olefins **298** then takes place to produce the *N*-allyl hydroxylamine **299**. The final step includes reduction of the latter by oxidation of the reduced form of the catalyst LMo(IV)O regenerating the active species $LMo(VI)O_2$ and the allylamine **300**.

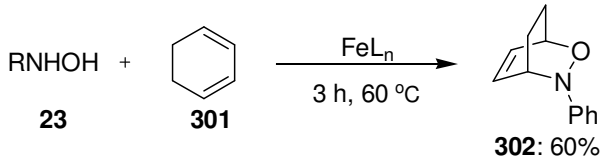


Scheme 71

Studies effectuated by Nicholas *et al.* led to the identification of a novel iron azo dioxide complex $\{Fe[Ph(O)NN(O)Ph]_3\}[FeCl_4]_2$ as another interesting active aminating agent.[33] A combination of iron (II/III) salts ($\{Fe[Ph(O)NN(O)Ph]_3\}[FeCl_4]_2$) as the active species appears to be the active agent for the catalytic cycle according to the authors.

Later, Jørgensen *et al.* reported iron phthalocyamine ($Fe^{II}Pc$) as a superior catalyst for allylic amination with *N*-phenylhydroxylamine **23** as the nitrogen fragment donor.[34] Several mechanisms have been postulated but are still under study. The reactions in which free nitrosobenzene is produced during the cycle in the presence of a catalytic amount of $Fe^{II}Pc$ or other iron complexes are particularly appealing.

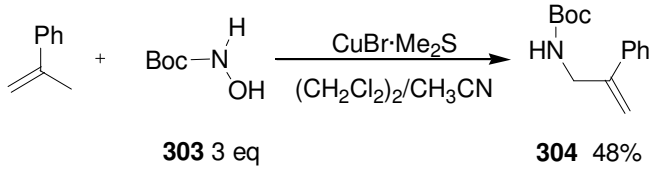
To evaluate if nitrosobenzene was formed during this reaction, a series of trapping experiments has been performed in the presence of 1,3-cyclohexadiene **301**. The high reactivity of nitroso compounds towards dienes is well known and consequently, the presence of free nitrosobenzene can be demonstrated when the hetero Diels-Alder product **302** is obtained (Scheme 72).



Scheme 72

When $Fe^{II}Pc$ was used, the hetero Diels-Alder product was isolated in 60% yield demonstrating that nitrosobenzene was produced.[34] Results were similar when a molybdenum catalyst was employed.[129] However, when a mixture of iron salts (II/III) was chosen for this transformation, no product **302** was recovered.[33] As in the case of the molybdenum catalyst, the last step is thought to involve $Fe^{II}Pc$ reductive cleavage of the allylhydroxylamine to the allylic amine, regenerating the active catalytic species.

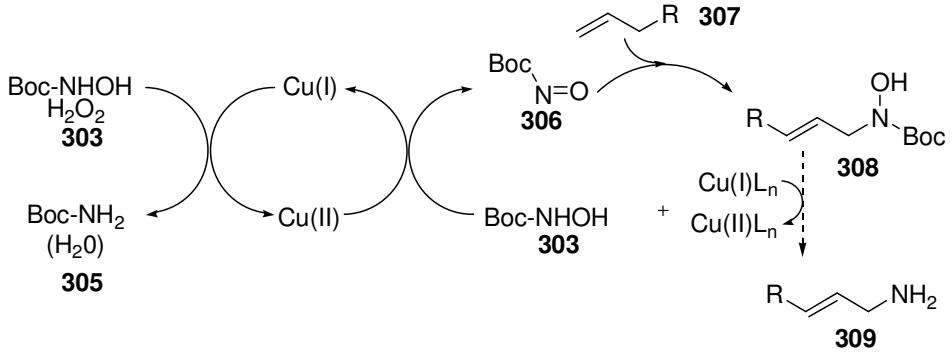
Whilst the Mo(VI) and Fe(II/III) catalysed allylic amination of olefins by aryl hydroxylamines leads to *N*-allylaniline derivatives, the search for a convenient precursor and catalyst for preparation of simple primary allyl amines has also proven to be a worthwhile objective. Copper proved to be a good catalyst for allylic hydroxyamination and amination of alkenes with Boc-hydroxylamine.[35] $CuBr{\cdot}MeS_2$ was shown to be the most effective salt in the reaction between α-methyl styrene and Boc-hydroxylamine **303** producing the allylic amine **304** in 48% yield (Scheme 73).[130] An increase in the yield up to 73% was obtained by using a stoichiometric oxidant, 33% hydrogen peroxide.



Scheme 73

Scheme 74 outlines a possible catalytic pathway which begins with disproportionation of *tert*-butyl hydroxycarbamate **303** induced by $CuBr{\cdot}SMe_2$ or CuCl oxidation if H_2O_2 is present. The resulting nitroso derivative **306** can then undergo an ene reaction with

olefins **307** to give the allyl hydroxylamine **308**. In the presence of ligands, the $Cu(I)L_n$ complex formed reduces the hydroxylamine **308** to the allylamine **309**.



Scheme 74

The results of oxidative catalytic amination employing a hydroxylamine **303** as the nitroso source with various enophiles are summarised in Table 6.

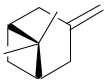
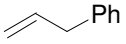
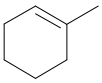
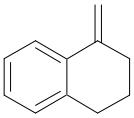
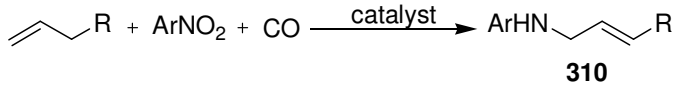
		Yield (%)				
Entry	**Substrate**	**A**	**B**	**C**	**D**	**E**
1		34	76	42	73	52
2		43	-	26	43	12
3		22	80	11	-	-
4		13	22	-	-	13
5		-	62	-	-	72

Table 6: **A**: $FeCl_2{\cdot}4H_2O$-$FeCl_3{\cdot}6H_2O$ (9:1).[33] **B**: Fe(Pc).[33e] **C**: MoO^-_2(dipic) (HMPA).[131] **D**: $CuCl/H_2O_2$.[130] **E**: $CuCl_2{\cdot}H_2O$.[132]

Reductive Catalytic Amination.

Aromatic nitro compounds can be used as aminating reagents under reducing carbon monoxide pressure with olefins in the presence of $[Ru_3(CO)_{12}$ **A**$]$,[37] or $[CpFe(CO)_2]_2$, **B** as catalysts (Scheme 75).[38] Advantages of this method include the absence of further

undesirable reactions of the hydroxylamine product, avoided by reduction *in situ* with carbon monoxide and the straightforward regeneration of the catalyst.



310

A: $[Ru(CO)_{12}]$ 160 ºC, 40 atm CO
B: $[CpFe(CO)_2]_2$ 160 ºC, 50 atm CO
C: $[Cp^*Fe(CO)_2]_2$ hν, 80-120 ºC, 2-6 atm CO

Scheme 75

The first two complexes, $[Ru_3(CO)_{12}]$ and $[CpFe(CO)_2]_2$**,** share the capacity of catalysing allylic amination but extreme conditions of temperature (160 ºC) and pressure (40-50 atm) are required. However, photoassisted nitrosoarene allylic amination proceeds efficiently under milder conditions (80-120 ºC, 2-6 atm) when $[Cp^*Fe(CO)_2]_2$ with near UV irradiation (λ>300 nm) in dioxane solution is employed.[39]

Results obtained for this transformation using the three catalysts **A, B** and **C**, different alkenes and nitroaryl are summarised in Table 7 below.

			Yield of allylic aniline (%)		
Entry	**Alkene**	**Ar-NO_2**	**310^A**	**310^B**	**310^C**
1	cyclohexene	1-methoxy-4-nitrobenzene	78		
2	cyclohexene	1,2-dichloro-4-nitrobenzene	86		
3	α-methylstyrene	$PhNO_2$		92	85
4	α-pinene	$PhNO_2$		64	60
5	1-methylcyclohexene	$PhNO_2$		27	16
6	2-methylhept-2-ene	$PhNO_2$		10	80
7	1-allylbenzene	$PhNO_2$		13	12
8	α-methylstyrene	1,2-dichloro-4-nitrobenzene		54	
9	α-methylstyrene	pentafluoro-nitrobenzene		57	
10	α-methylstyrene	1-nitro-3-(trifluoromethyl)benzene		52	
11	α-methylstyrene	1-methoxy-4-nitrobenzene		2	

Table 7: **A** $[Ru(CO)_{12}]$ 160 ºC, 40 atm CO, **B** $[CpFe(CO)_2]_2$ 160 ºC, 50 atm CO, **C** $[Cp^*Fe(CO)_2]_2$ hν, 80-120 ºC, 2-6 atm CO.

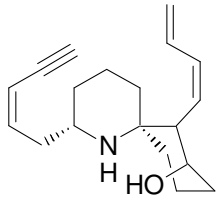
As generally observed in all of the above examples for the ene transformation, unsymmetrical alkenes gave a single regioisomer derived from introduction at the less substituted vinylic carbon with double bond transposition. Further aspects of the mechanism of this new catalytic amination process, including the nature of the active iron species involved are waiting to be clarified. However both the oxidative and the reductive catalytic methods accomplish regioselective catalytic amination in terms of functionalizing simple olefins via the intermediacy of the nitroso ene reaction.

CHAPTER 2 – RESULTS AND DISCUSSION

1.0 Strategic Aims of the Research Programme.

The foregoing introduction has hopefully provided a broad overview of the fascinating and complex chemistry associated with nitroso derivatives, especially when such compounds are employed in the ene reaction as a valuable method for the creation of a new carbon-nitrogen bond.

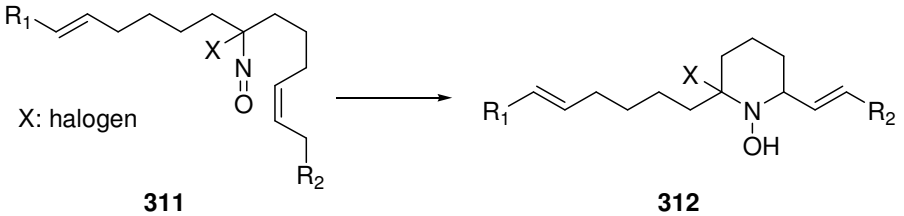
Within this framework, the ultimate objective of the present research programme as originally conceived was to achieve molecular diversity in the construction of alkaloid like scaffolds through a tandem or "one pot" sequence comprising of three steps. An illustrative hypothetical example of the approach is shown in Scheme 76 for the assembly of the azaspiro [5,5] undecane core of the neurophysiologically active alkaloid, histrionicotoxin V Figure 8, a synthetic target which has attracted considerable interest in recent times.[133,134,135]



Histrionicotoxin (V)

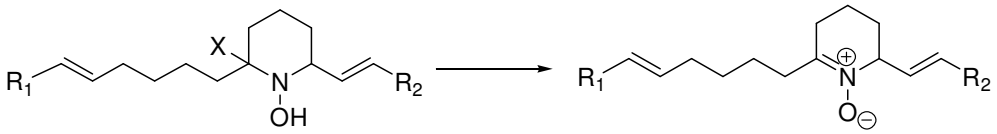
Figure 8

Step 1 The intramolecular ene reaction of an α-halo nitroso compound.



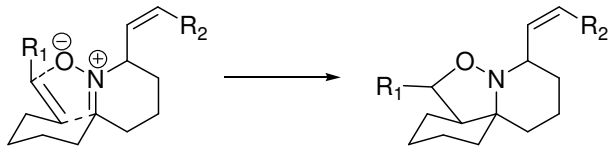
311 **312**

Step 2 Elimination of hydrogen halide to form a nitrone



312 **313**

Step 3 Intramolecular 1,3-dipolar cycloaddition of the nitrone.



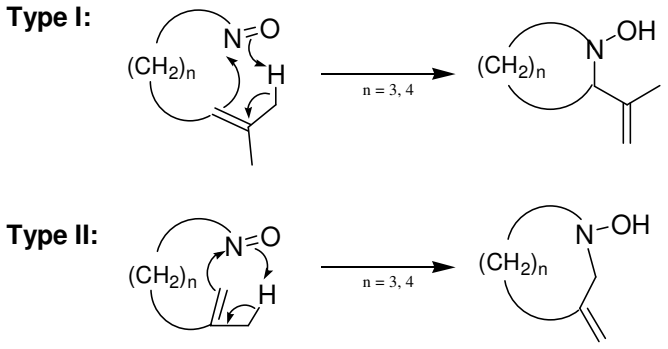
313 **314**

Scheme 76

The first two steps of the sequence form the essence of the research described herein, and it is therefore appropriate to consider them in more detail.

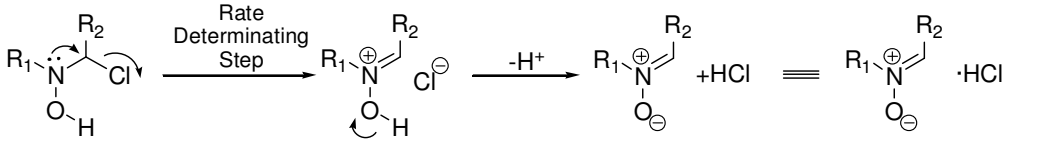
Thus, for step 1, in the first instance, as noted in the preceding introduction, it is important to recognise that, whilst the intramolecular ene reactions of acyl nitroso compounds to give hydroxamic acids have been extensively explored by Keck and others,[18] only two examples using tertiary nitroso alkenes,[112,113] and one using a nitroso arene have been reported in the literature (Chapter 1, Section 2.5).[111] To the best of our knowledge, intramolecular ene reactions of geminally functionalised halo nitroso compounds are unknown, although the intermolecular variant using a carbohydrate chiral auxiliary provides an encouraging indication.[116,97] Moreover, it would be expected that, in analogous fashion to other cycloaddition reactions, intramolecular ene reactions would be favoured over their intermolecular counterparts. This arises from the lower negative entropy of activation ($\Delta S^{\neq}$) that compensates for the high formation enthalpy ($\Delta H^{\neq}$) of unactivated enophiles. Therefore, simple unfunctionalised alkenes and alkynes may be successfully used in the intramolecular but not in the intermolecular ene reaction.

Finally, from the standpoint of molecular diversity, as in the intramolecular variants of the carbonyl ene reaction discussed earlier (Scheme 29), it should be noted that, irrespective of the exact mechanism mechanistic nature of the nitroso ene reaction, type Type I and Type II variants as based on the Oppolzer classification should be possible.[85] These are shown in Scheme 77, differing only in the attachment site of the tether connecting the ene and enophilic components, and if some geometrical analogy can be drawn with the carbonyl ene reaction, Type I reactions should favour formation of five and six membered rings, whereas Type II reactions should be predisposed towards six and seven membered ring formation.



Scheme 77

The second step of the proposed sequence requires elimination of, for example, hydrogen chloride from the initial ene adduct. In this context it was anticipated that such a reaction would be facilitated by the presence of the adjacent nitrogen lone pair and might well, in effect, proceed via an E_1 mechanism as indicated in Scheme 78. When viewed in this way, the evolution of an α-chloro hydroxylamine **315**, for example to a product which is often described as a nitrone hydrochloride **318** is readily appreciated.

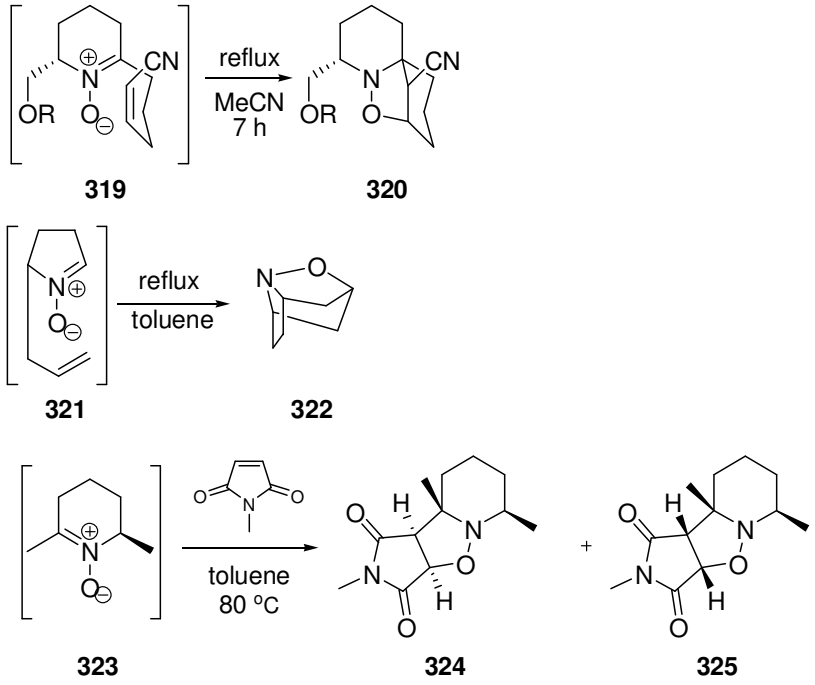


315 **316** **317** **318**
nitrone hydrochloride

Scheme 78

The third and final step of the envisaged tandem or one pot process requires an intramolecular 1,3-dipolar cycloaddition of the nitrone to a second unsaturated linkage. This type of cycloaddition was the earliest and to date has been the most extensively studied.[136,137] The dipolarophile can range from a simple terminal alkene through an E or Z disubstituted alkene to either an acrylate ester or an enol ester and the connectivity

patterns between the nitrone and the unsaturated linkage have been thoroughly established. In view of such literature precedent, this step was not considered to be of high priority in the initial stages, and some representative examples are shown in Scheme 79.[138,139,140,141]



319 **320** **321** **322** **323** **324** **325**

Scheme 79

From the viewpoint of molecular diversity it should also be noted that, since the final product from the first two steps is a nitrone, then advantage can also be taken of the wide variety of intermolecular reactions, including 1,3-dipolar cycloadditions, undergone by this functional group (*vide infra*).

In light of this analysis, the first and most important objective of our research programme was to find a suitable method for the preparation of appropriately substituted unsaturated α-halo nitroso compounds and to examine their subsequent behaviour in prototypical Type I and Type II intramolecular nitroso ene reactions.

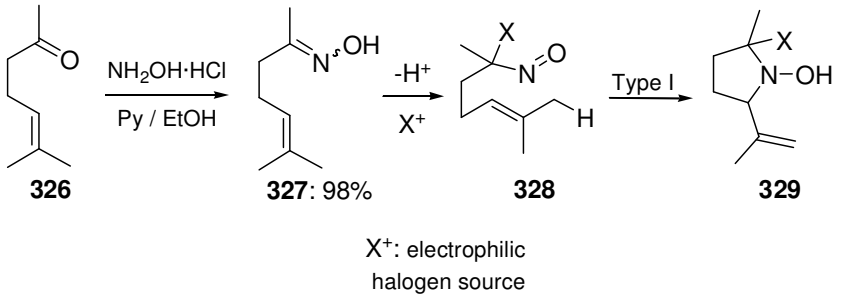
2.0 Intramolecular Ene Reaction.

2.1 *In Situ* Generation of α-halo Nitroso Compounds from Oximes.

From the outset, it was recognised that a major challenge in nitroso chemistry is the high reactivity of these compounds, which necessarily imposes strict constraints upon the methods employed for their preparation. Examples of possible undesired reactions such as oxidations, reductions, radical and nucleophilic attacks have already been provided in Chapter 1. A further consideration to be borne in mind is the possible reactivity of the nitroso compound with the starting materials and/or preparative reagents.

With these constraints in mind, it was initially decided to focus on the use of an oxime as the direct precursor of *in situ* generation of an α–halo nitroso compound. A wide variety of halogenating agents such as chlorine,[41] aqueous hypochlorite acids, alkyl hypochlorites,[42] *N*-bromosuccinimide,[43,44] and *N*-bromoacetamide,[142] are all known to effect this transformation with varying degrees of success. The necessity however that the method be compatible with the presence of alkene functionality led to immediate rejection of the elemental halogens and hypohalous acids, as well as *N*-bromoacetamide which is often used as a precursor for generation of hypobromous acid. Unfortunately kinetic data on the relative rates of halogenation of oximes as opposed to carbon-carbon double bonds do not seem to have been reported in the literature.

The first substrate to be examined was the oxime **327** which was chosen very simply on the basis of the commercial availability of inexpensive 6-methyl-hept-5-ene-2-one **326** and was readily prepared in essentially quantitative yield by reaction with hydroxylamine hydrochloride and pyridine in ethanol.[143] As shown in Scheme 80 this selection predetermined that the first intramolecular ene reaction of an α–halo nitroso compound to be studied would be of Type I.



Scheme 80

In similar fashion, the first halogenating agent to be selected was *N*-bromosuccinimide (NBS) on the basis that, with the exception of free radical allylic bromination, it is not generally considered to react as an electrophilic halogen source towards alkenes.

The addition of oxime **327** to a solution of *N*-bromosuccinimide was accordingly studied in a selection of solvents and the observations noted are summarised in Table 8.

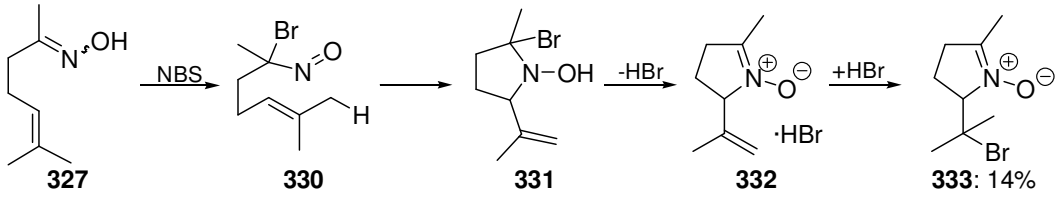
Entry	Solvent	NBS (eq)	T (°C)	Time	Blue colour	Ene product
1	Et_2O	1.0	rt	3 h	√	X
2	Benzene/MeOH	1.0	rt	3 h	√	X
3	$CDCl_3$	1.5	rt	3 h	√	X
4	Benzene d_6	1.5	rt	12 h	√	X
5	Benzene/dioxane	1.5	0	3 h	√	X
6	$NaHCO_3/H_2O$/dioxane	1.5	rt	3 h	√	X
7	$NaHCO_3/H_2O$/dioxane	1.5	0	3 h	√	X

Table 8

Although the blue colouration of the desired α–bromo nitroso intermediates was noted in all cases, examination of the NMR spectra of the crude reaction mixtures provided no evidence for the formation of the desired ene product, whether formulated as α–bromo hydroxylamine **331** or the nitrone hydrobromide, albeit that 50-60% of starting oxime **327** had been consumed.

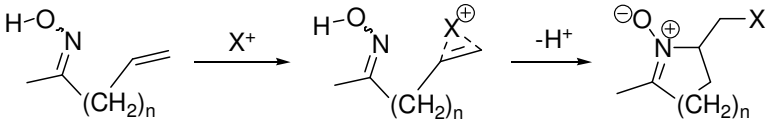
Examination by analytical TLC of entries 1-5 also implied that complex reaction mixtures were produced. At this stage, in spite of the fact that a reaction with NBS should lead to formation of inert succinimide, a literature procedure in which reactions were carried out

in aqueous sodium hydrogen carbonate with a small quantity of methanol or dioxane to help solubilise the oxime **327** was employed.[144] In this instance, the initial blue colouration disappeared after three hours and analytical TLC indicated formation of a new product which was isolated in 14% yield by column chromatography. Examination of the mass spectrum indicated peaks at 219 and 221 consistent with the formation of the α–bromo hydroxylamine (or nitrone hydrobromide) intermediate, but the complete absence of any olefinic protons in the NMR spectrum was more consistent with structure **333** which can be formally derived by loss of hydrogen bromide from the nitrone hydrobromide cycloadduct **332** resulting from the ene reaction and subsequent Markovnikov addition to **332** (Scheme 81).



Scheme 81

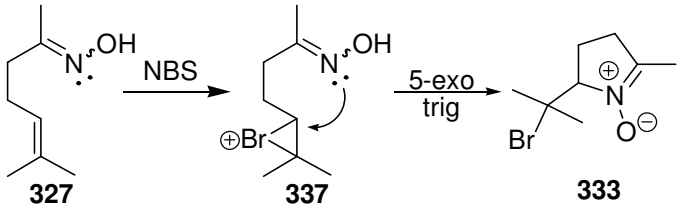
At this stage, a retrospective literature search for halogenated five membered ring nitrones led us to discover the beautiful chemistry of Grigg and co-workers,[144] who had demonstrated that, in the presence of a range of electrophilic agents, suitably constituted unsaturated oximes could undergo cyclisation (Scheme 82).



X^+: Br^+ (NBS)
$AcOHg^+$ ($Hg(OAc)_2$)
I^+ (I_2)
$PhSe^+$ (PhSeBr)

Scheme 82

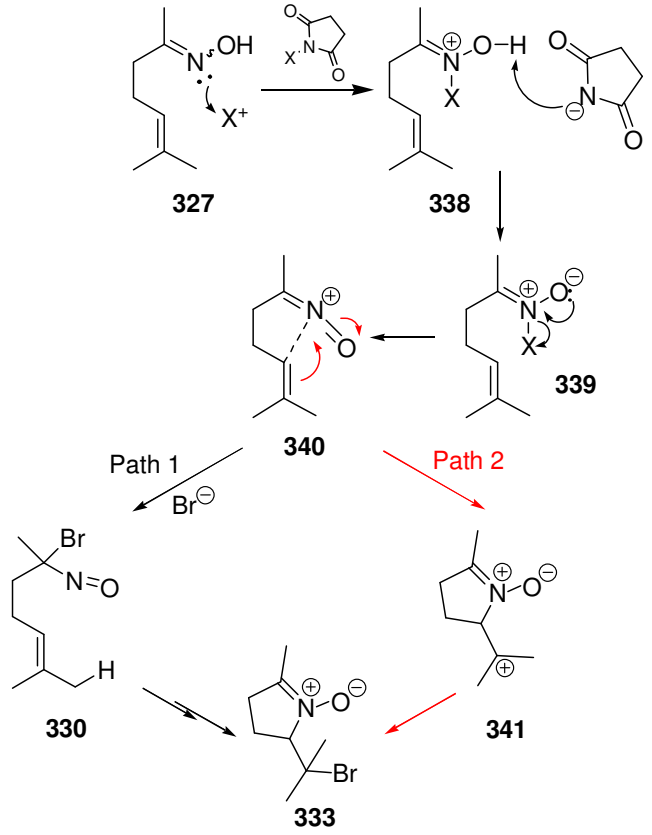
From a mechanistic standpoint, since the substrates chosen by the Grigg group do not possess any suitably located allylic hydrogen atoms, there is no possibility of any intramolecular α–bromo nitroso ene reaction, and hence, the postulated mechanism involving nucleophilic attack by the nitrogen lone pair of the oxime on a bromonium (or iodonium, selenonium or mercurinium) cation is perfectly acceptable. It was therefore possible that, in the case of oxime **327**, cyclisation could have occurred in similar fashion (Scheme 83).



Scheme 83

This example provides clear evidence that, all too often, a scientific investigator is predisposed towards a mechanistic conception or misconception! The Grigg group, curiously, make no mention whatsoever of any blue colouration which developed during their reactions with *N*-bromosuccinimide!

In a similar vein, it is tempting to speculate on the mechanism of formation of an α–halo nitroso compound from an oxime and an electrophilic halogen source. To the best of our knowledge, this has not been investigated in the literature. Thus, as shown in Scheme 84, if it is assumed that the lone pair on the nitrogen atom of the oxime is the best nucleophilic centre, then reaction could proceed via a high energy nitrosonium cation **340**. This, in turn, can capture the liberated halide anion (X^-) (path 1) to form the α–halo nitroso compound **330**, or alternatively, in the presence of a suitably disposed alkene side chain, undergo cyclisation to a carbocation **341** (path 2) which can then capture the halide.



Scheme 84

Whilst such a path via **340** and **341** may be possible for the formation of **333** from **327**, it does however seem less likely for the terminal alkenes studied by the Grigg group since formation of a higher energy primary carbocation on cyclisation would be necessary.

In light of this possible mechanistic controversy, attention then turned to *N*-chlorosuccinimide (NCS), a known reagent for the preparation of α–chloro nitroso compounds,[43,44] but which is not known for its ability to react with isolated double bonds.

Once again, a series of solvents and conditions was investigated and these are summarised in Table 9.

Entry	Solvent	NCS (eq)	T (ºC)	Time	Blue colour	Ene product
1	Et_2O	1.00	rt	3 h	√	traces
2	Benzene/MeOH	1.00	rt	3 h	√	X
3	$CDCl_3$	1.05	rt	3 h	√	traces
4	Benzene d_6	1.05	rt	12 h	√	traces
5	$NaHCO_3/H_2O$/dioxane	1.50	0	3 h	√	X
6	CH_2Cl_2	1.50	0	12 h	X	X
7	Benzene/dioxane	1.50	0	4 h	√	X

Table 9

In all cases, save for dichloromethane (Entry 6) addition of the oxime **327** to the solution containing NCS led to the development of the slightly blue reaction mixture, which was indicative of the presence of the α–chloro nitroso intermediate **342**.[52,116,145] NMR analyses of those reactions carried out in organic solvents revealed a complex mixture of products, although possible traces of the desired ene product could be detected in reactions performed in diethyl ether, benzene d^6 and $CDCl_3$ (entries 1, 3 and 4).

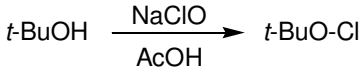
To improve the solubility of NCS the reaction was then carried out in an aqueous solution in the presence of sodium hydrogen carbonate and after addition of the oxime, the blue colouration indicative of the nitroso compound appeared and then rapidly faded (Entry 5). After 3 h, the mixture was extracted to give a complex mixture of products. The use of an aqueous solution has been used by several groups in the literature,[146] but in our hands, the range of products was even more complex than when an organic solvent was used, either because of the propensity of the resulting nitrone to react with nucleophiles, or through formation of hypochlorous acid which could attack the double bond.

Given the complexity of the reaction mixtures, and the fact that some 20-30% of the starting oxime **327** was also recovered, no further efforts were made to use NCS.

Accordingly, it was decided to explore the use of *tert*-butyl hypochlorite, another reagent which is known to be capable of converting an oxime into an α–chloro nitroso

compound,[147] and which also possesses the potential advantages of high solubility in organic solvents and the low nucleophilicity of the resulting *tert*-butanol.[148]

The reagent was simply prepared by a standard literature procedure from an aqueous solution of sodium hypochlorite and *tert*-butanol in the presence of glacial acetic acid (Scheme 85).

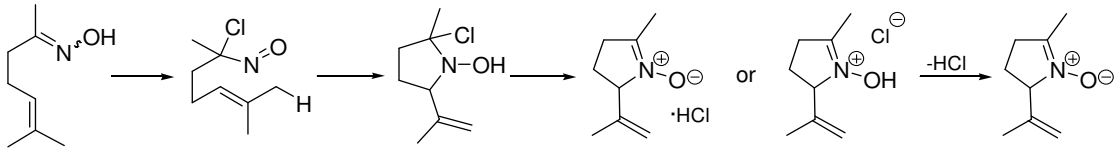


Scheme 85

Purification by distillation is known to be hazardous and proved not to improve the purity. Nevertheless, it can be stored below 4 ºC in the dark over calcium chloride.[148]

Initially, some small scale trial reactions were carried out by adding 1.1 eq of *tert*-butyl hypochlorite to a solution of the oxime **327** in a range of solvents (CH_2Cl_2, toluene, benzene and CCl_4) at room temperature. The blue colour appeared instantly, fading gradually and soon the reaction mixture became dark, and only traces of the expected products could be found by proton NMR spectroscopy. Nevertheless, the complete disappearance of the starting material and the much more intense blue colouration when compared with the halo-succinimide reagents used previously provided a qualitative indication that there had been a better conversion to 6-chloro-2-methyl-6-nitrosohept-2-ene **342** and therefore that this reagent might prove to be a more useful method of obtaining the α-chloro nitroso intermediates.

The trial experiments also demonstrated that the blue solution, whose durability depended on the temperature and rate of addition of the chlorinating agent, eventually became black, and both analytical TLC and NMR spectra were indicative of very complex mixtures. These observations implied that the highly reactive series of intermediates involved in the reaction, *viz*, the α–halo nitroso intermediate **342**, the putative α-chloro hydroxylamine product **343** and/or its derived nitrone hydrochloride **344** as well as the desired product nitrone **332** and even the starting oxime **327** (Scheme 86) were, in all probability, incompatible with the hydrogen chloride liberated during the sequence.

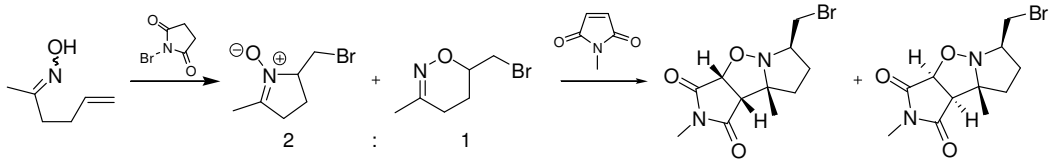


327 **342** **343** **344** **345** **332**

Scheme 86

In light of the fact that the facile elimination of hydrogen chloride from adducts **344** and/or **345** would be favoured by a base, which also neutralises hydrogen chloride, a method involving the use of potassium carbonate was once again selected.

Furthermore, at this juncture, it was of particular interest to compare our own observations with those of Grigg,[144] and specifically the one-pot experiment summarised in Scheme 87.



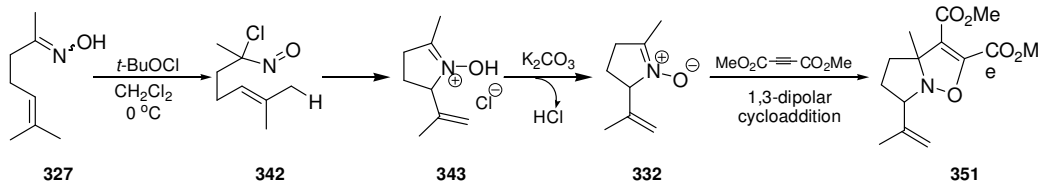
346 **347** **348** **349** **350**

2 : 1 *anti* : *syn*

Scheme 87

Whilst the essential difference is that the intramolecular ene adduct retains problematic olefinic functionality whilst the halonium ion induced cyclisation does not, two other aspects of this reaction were noteworthy. The first of these is that the 2 : 1 *anti* : *syn* ratio of the starting oximes **346** was reflected in the ratio of the nitrone **347** to the six membered ring oxazine **348**, a skeleton which was not observed in own chemistry. The second feature was that the nitrone **347** reacted very efficiently with *N*-methylmaleimide (78% overall based on the percentage of the *anti* oxime **346** in the starting material) in an intermolecular 1,3-dipolar cycloaddition. As mentioned at the outset of this chapter, this class of pericyclic reaction was one of the earliest and most extensively studied.[136-141]

With the above considerations in mind, an adventurous decision was taken to incorporate an additional step into the sequence and hence to develop the cascade sequence summarised in Scheme 88.



Scheme 88

Diethyl acetylenedicarboxylate was initially selected as a simple dipolarophile which would simplify any stereochemical considerations and a series of solvent and base screening experiments were carried out as summarised in Table 10.

Entry	Solvent	Base	Method	Observations
1	Benzene	2 eq K_2CO_3	A	Complex mixture
2	Benzene	2 eq K_2CO_3	B	Complex mixture
3	Toluene	2 eq K_2CO_3	A	Complex mixture
4	Toluene	2 eq K_2CO_3	B	Complex mixture
5	Toluene	2 eq DIPEA	A	SM
6	Toluene	2 eq DIPEA	B	SM
7	CH_3CN	2 eq K_2CO_3	A	traces
8	CH_3CN	2 eq K_2CO_3	B	Complex mixture

Table 10: Method A: Dipolarophile was present before addition of *tert*-butyl hypochlorite. Method B: Dipolarophile was added 80 min after addition of *tert*-butyl hypochlorite.

Experiments were performed by the addition of *tert*-butyl hypochlorite (1.1 eq) to a solution of the oxime **327** and the base (2.0 eq) at -5 ºC, either in the presence of diethyl acetylenedicarboxylate (2.0 eq) (method A) or with a subsequent addition after 80 min (method B) prior to reflux. Unfortunately, with the exception of these reactions using Hünig's base which appeared to totally inhibit the reaction (Entries 5 and 6), only complex reaction mixtures were produced, with the possible exception of an experiment performed in acetonitrile (Entry 7) where traces of the desired product may have been produced.

Following on from these observations, a range of dipolarophiles was also screened using an increased quantity of potassium carbonate as base, dichloromethane as solvent, and an extended reaction time of four days (Table 11).

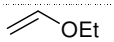
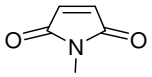
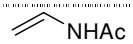
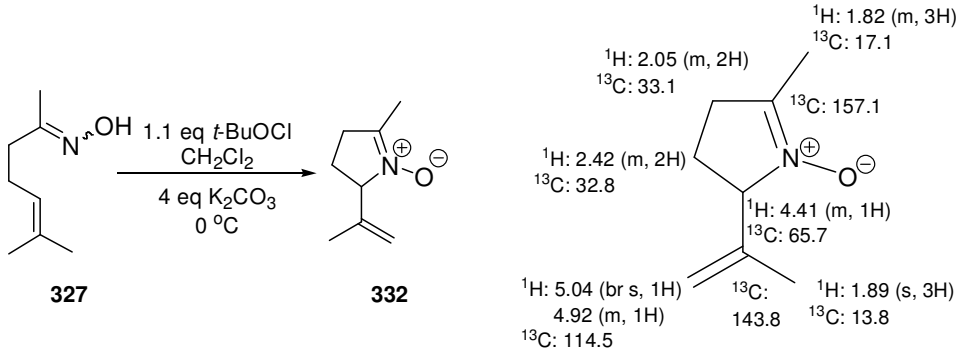
Entry	Dipolarophiles	Blue	Result
1	5.2 eq EtO_2C—≡—CO_2Et	√	Nitrone (8%)
2	20 eq 	X	Nitrone (12%)
3	8.6 eq 	√	Nitrone (21%)
4	20 eq 	X	Insoluble material
5	4 eq 	X	X

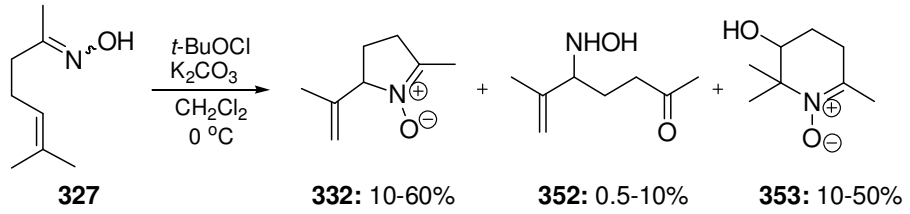
Table 11**:** Conditions: 1.1 eq of *t*-BuOCl, 4.0 eq K_2CO_3 in CH_2Cl_2. After 1 h, the dipolarophile was added, and the mixture was heated at reflux for 4 days.

Whilst the use of *N*-vinylacetamide (Entry 4) led to an insoluble residue and maleic anhydride (Entry 5) furnished a complex mixture of products, the reactions with diethyl acetylenedicarboxylate (Entry 1), ethyl vinyl ether (Entry 2) and *N*-methylmaleimide (Entry 3) all provided an enormous surprise, not in terms of yielding the anticipated 1,3-dipolar cyclic adducts, but in furnishing the long sought after fugitive nitrone **332** (Scheme 89).



Scheme 89

The successful isolation of the nitrone **332** during efforts to achieve an *in situ* cascade sequence immediately prompted experiments using a four fold excess of potassium carbonate as base, but in the absence of any dipolarophile. The results of a large number of experiments are encapsulated in Scheme 90, and in spite of very considerable effort, proved to be frustratingly irreproducible in terms of the relative proportions of the three products **332**, **352** and **353** which were isolated and identified. It was noted however that addition of *tert*-butyl hypochlorite to a solution of the oxime **327** in dichloromethane containing potassium carbonate led to higher yields of the desired nitrone **332** than an inverse addition of the oxime **327** to the hypochlorite solution (Table 12).



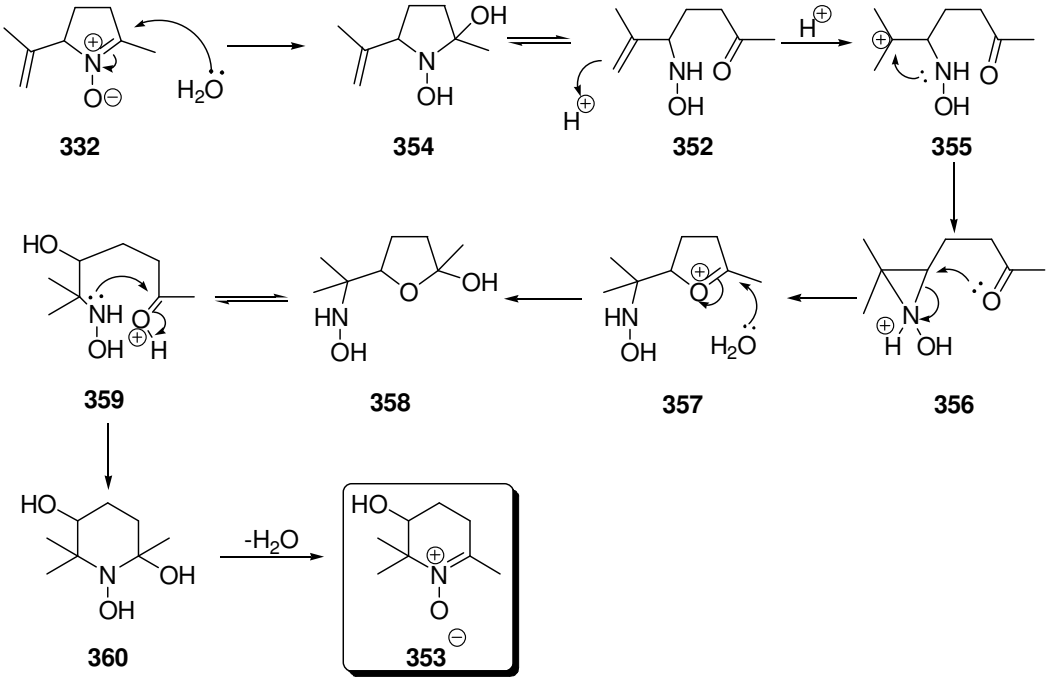
Scheme 90

Method	332	352	353
Normal addition	54%	13%	8%
Inverse addition	28%	30%	6%

Table 12: 500 mg oxime **327**, 1.1 eq *t*-BuOCl, 5.0 eq K_2CO_3, CH_2Cl_2, 0 °C.

From a mechanistic standpoint the formation of "nitrone hydrate" **352** is easily understood and could be formed during the reaction by the water liberated from potassium carbonate during the neutralization of the nitrone hydrochloride precursor to the expected product **332**.

The formation of the six membered nitrone **353** whose structure was deduced from NMR and mass spectroscopy is however of greater interest and a speculative mechanism is shown in Scheme 91.



Scheme 91

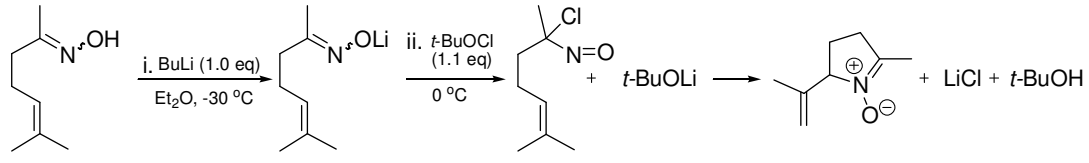
Thus, following on from formation of the ring opened form of the nitrone hydrate **352**, protonation to give a tertiary carbocation **355** followed by neighbouring group participation from the hydroxylamine leads to a protonated *N*-hydroxy aziridinium cation **356** which can then undergo ring opening with relief of strain to generate a cyclic oxonium cation **357** which, after lactol formation can reequilibrate as shown to the more stable six membered ring nitrone **353**.

The mechanistic scenario depicted above does of course require both water (and or carbonate) as well as a proton source and can occur either during the reaction or on subsequent work up and chromatographic separation on silica gel.

From a purely practical viewpoint, some effort was therefore made to screen other inorganic bases including silver carbonate, caesium carbonate and sodium bicarbonate, all of which failed to yield no more than trace quantities of the desired nitrone **332**. The only competitor to potassium carbonate proved to be sodium carbonate, which generally afforded only 25% yield of the ene product. Efforts to scavenge hydrogen chloride using sodium hydride (1.5 eq) in diethyl ether led to recovery of starting material.

Concern over the presence of hydrogen chloride, whether initially present or liberated from the nitrone hydrochloride product of the ene reaction, prompted some additional experiments designed to avoid this potential problem.

Thus, as shown in Scheme 92 it was considered, that prior formation of the lithium alkoxide of the oxime **327** might make it even more reactive to an electrophilic chlorine atom source, and also have the added benefit that the lithium *tert*-butoxide released in this step would scavenge hydrogen chloride from the nitrone hydrochloride product of the ene reaction.

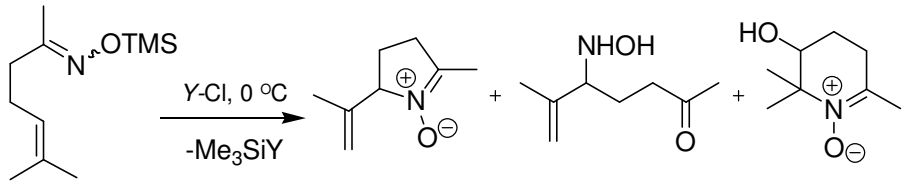


Scheme 92

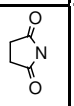
To our surprise, after a deep blue colouration appeared and remained for several seconds, the reaction mixture turned black, and after aqueous work up, only traces of the nitrone

were formed in a very complex mixture. A substoichiometric experiment using 0.9 eq of butyllithium afforded the same result.

Reactions of the *O*-trimethylsilyl derivative **362** of oxime **327** were also investigated, both with *tert*-butyl hypochorite and with NCS, as a method for generation of the α-chloro nitroso species under neutral conditions, but with the intention of forming the nitrone hydrochloride products. The results, summarised in Scheme 93, once again proved to be fruitless.



362 **332** **352** **353**

Method	332	352	353
Y= *t*-BuO	16%	12%	6%
Y= 	-	-	-

Scheme 93

Finally, in an optimistic effort to generate α-chloro nitroso intermediates from oximes at a faster rate than other undesirable reactions such as addition to the carbon-carbon double bond or over oxidation, several additional sources of an electrophilic chlorine atom were investigated.[149] The results, all of which offered no improvement, are shown in Table 13 for the standard reaction of oxime **327** to nitrone **332**.

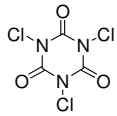
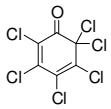
Entry	Chlorinating Agent	Conditions	Yield of 332
1		0 ºC, CCl_4	25%
2		0 ºC, K_2CO_3 (5 eq) CH_2Cl_2	complex mixture
3		0 ºC, K_2CO_3 (5 eq) CH_2Cl_2	16% + traces of hydroxylamine
4	HClO / *n*-Bu_4NHSO_4	CH_2Cl_2	32 %

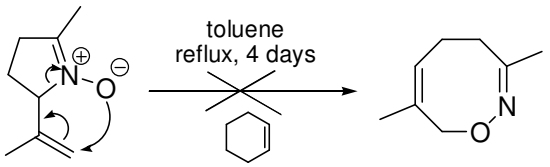
Table 13: Entry 1: *N*-*tert*-butyl-*N*-chlorocyanamide.[150,151] Entry 2: Trichloroisocyanuric acid.[152] Entry 3: 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dienone.[153] Entry 4: hypochlorous acid / tetra-*n*-butylammonium hydrogen sulfate, benzene-water mixture, pH 5.5.[154]

In summary, the best results for obtaining the Type I intramolecular ene reaction of an α-chloro nitroso compound were realised when the reaction of the oxime **327** with *tert*-butyl hypochlorite was carried out via addition of the latter in dichloromethane at 0 ºC in the presence of 4.0-5.0 eq of solid potassium carbonate. The blue colouration appeared instantaneously and lasted for between 2 to 4 hours, thus indicating when the ene reaction was complete. After work up and purification the nitrone **332** could be obtained as a colourless oil in high purity and in moderate to good yield, with a maximum of 60% on a 1.50 g scale albeit that perfectly reproductive reaction conditions could not be found.

With the possibility of preparing pure samples of nitrone **332**, the opportunity of carrying out a brief study of its chemical reactivity was taken, and, of course, a return to the 1,3-dipolar cycloaddition was considered.

In the event, results were disappointing. Intermolecular reactions of the nitrone with a 4 to 5 total excess of dipolarophiles such as ethyl vinyl ether, vinyl acetate, *N*-vinyl acetamide, cyclohexene, and diethyl acetylenedicarboxylate in solvents ranging from benzene through acetonitrile to toluene at reflux for up to four days were all to no avail and led to complex mixtures with varying recovery of starting material. The recovery of the nitrone **332** in an attempted reaction with cyclohexene in toluene at reflux for four

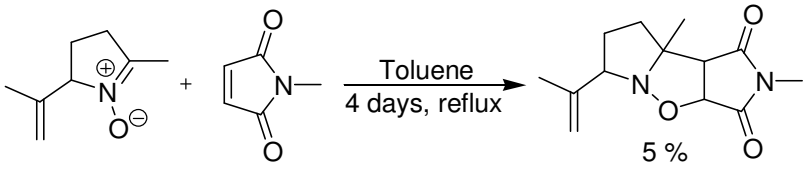
days did however convince us of its thermal stability and indicated that an alternative competing [2,3]-sigmatropic shift was not occurring (Scheme 94).



332 **363**

Scheme 94

A minor success was nevertheless achieved in the reaction with *N*-methylmaleimide which afforded three of the possible diastereomers of the cycloaddition product **364** albeit in an abysmal yield of 5% (Scheme 95).



332 **364**

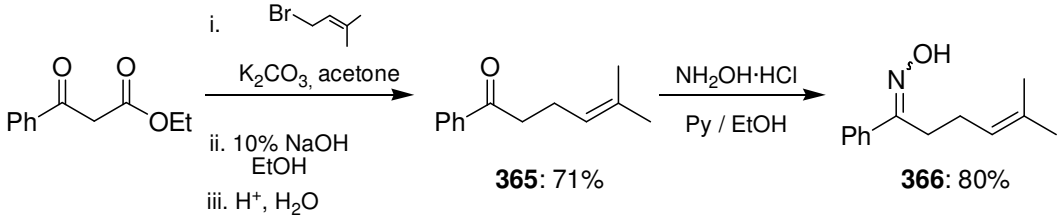
Scheme 95

As noted earlier, the group of Grigg had achieved a very respectable 78% yield in their intermolecular 1,3-dipolar cycloaddition of *N*-methylmalemide to a nitrone of similar structure (Scheme 79) and so,[155] considerable efforts were made to improve the yield of this transformation. These included the use of higher boiling solvents such as 1,2-dichloroethane or 1,2,4-trichlorobenzene, microwave irradiation,[156] differing concentrations and the use of hydroquinone as a radical scavenger but unfortunately no improvement was noted.[157]

At this point in time, having explored a wide range of bases and electrophilic halogen sources for *in situ* generation of the α–halo nitroso compound and subsequent capture of hydrogen chloride from the product nitrone hydrochloride, it was decided to capitalise on the reaction conditions developed thus far in order to examine a range of different substrates.

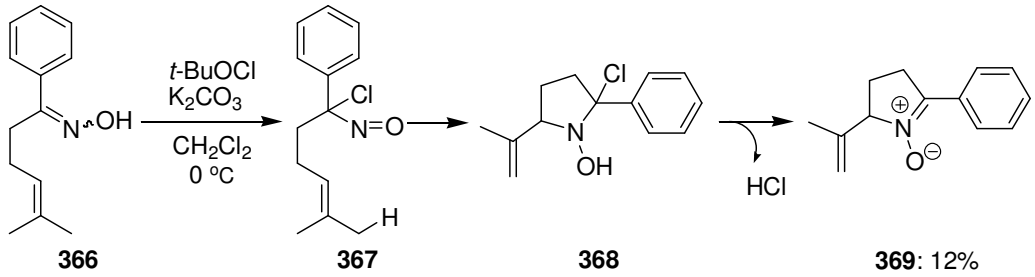
The first compound to be studied was the aryl congener **366** which was simply prepared as shown in Scheme 96. Thus, alkylation of ethyl benzoacetate with 1-bromo-3-methylbut-2-ene followed by hydrolysis and decarboxylation furnished the required ketone **365** in

71% yield.[158] Conversion to the oxime **366** under standard conditions then completed the sequence.



Scheme 96

Treatment of the oxime **366** with *tert*-butyl hypochlorite in the presence of potassium carbonate led to a blue reaction mixture whose colour faded after six hours, and after work up, examination of the crude reaction mixture by proton NMR spectroscopy indicated the presence of the product nitrone **369** (Scheme 97).



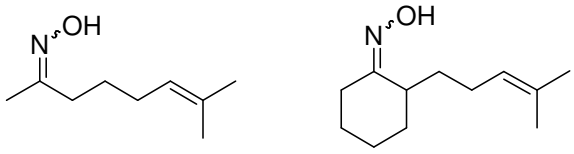
Scheme 97

Unfortunately however, problems of degradation during purification were encountered, irrespective of whether chromatography was performed over silica gel or alumina, and a disappointing 12% yield of product **369** was isolated. The isolated nitrone **369** was however sufficiently stable to be characterised.

In the first instance, although it was anticipated that the reactivity of the initial α–chloro nitroso intermediate **367** as a "benzylic chloride" might make it more susceptible to competing elimination and displacement reactions, it was not expected that the aromatic ring would influence the outcome of the Type I intramolecular nitroso ene reaction. The final loss of hydrogen chloride from the α–chloro hydroxylamine **368** was also anticipated to be more favourable, especially if argued as an E_1 type elimination. In retrospect, it may however be possible that the electron withdrawing effect (-I) of the aromatic ring also renders the product nitrone **369** much more susceptible to reactions such as hydrolytic cleavage.

Nevertheless, having successfully demonstrated that five membered rings could be constructed by a formal Type I intramolecular nitroso ene reaction, it was of interest to examine the potential of this approach for six membered rings. As noted earlier (Chapter 1, Section 2.2) for other reactions such as the carbonyl ene reaction, five and six membered rings are favoured in Type I processes. Two substrates were therefore selected for study.

The first of these was the simple methylene homologue **370** of the acyclic system, whilst the second was the alkylated cyclohexanone oxime **371** (Figure 9)**.**

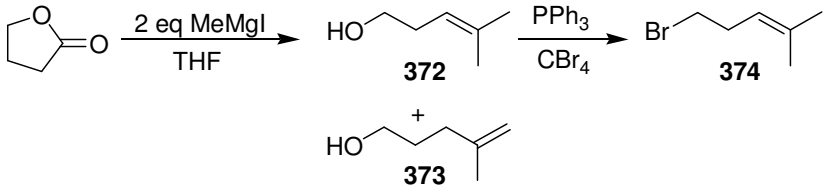


370 **371**

Figure 9

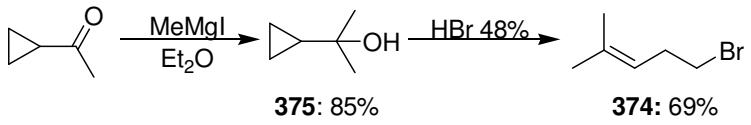
For both of these substrates, it was necessary to prepare 5-bromo-2-methylpent-2-ene **374** as an electrophilic reagent and two routes were investigated.

Thus, following a literature procedure,[159] γ-butyrolactone was treated with methyl magnesium iodide followed by distillation of the hydrolysed aqueous reaction mixture to give alcohol **372**. Reaction of **372** with triphenylphosphine and carbon tetrabromide then yielded the bromide **374** (Scheme 98).



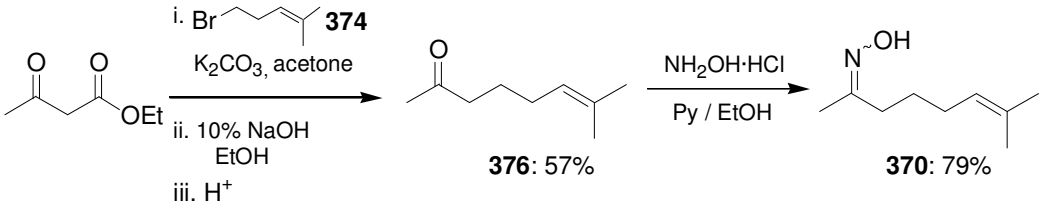
Scheme 98

Unfortunately however, this method gave a 60:40 mixture of both alcohols **372** and **373**, which rendered isolation of the desired bromide difficult. An alternative route was thus investigated involving treatment of commercially available cyclopropyl methyl ketone with methyl magnesium iodide to give 2-cyclopropyl-propan-2-ol **375**.[160] The required 5-bromo-2-methylpent-2-ene **374** was subsequently obtained by treatment of the alcohol **375** with aqueous hydrobromic acid in good yield (Scheme 99).



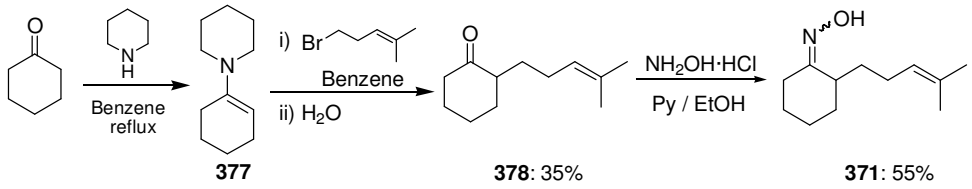
Scheme 99

With a simple route to substantial quantities of bromide **374**, oxime **370** was then prepared as shown in Scheme 100 by an efficient literature procedure which once again involved alkylation of the β-keto ester with bromide **374** in the presence of potassium carbonate followed by decarboxylation under basic conditions to give ketone **376** in 57% yield.[158] 7-Methyloct-6-en-2-one oxime **370** was then obtained in high yield (79%) by treatment of ketone **376** with hydroxylamine.



Scheme 100

For oxime **371**, a short and practical sequence was used which only required alkylation of the piperidine enamine **377** of cyclohexanone with bromide **374** as summarised in Scheme 101.[161]

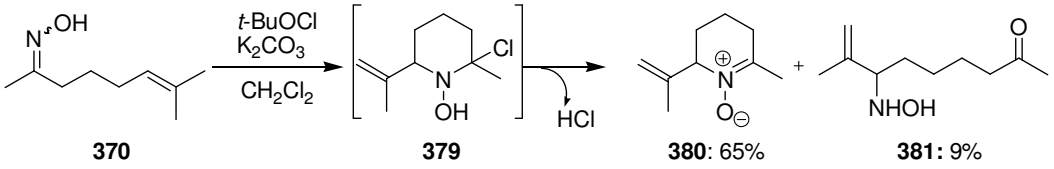


Scheme 101

With the required oximes **370** and **371** in hand, it was then possible to investigate the potential for six membered ring formation via a Type I intramolecular ene reaction of the derived α–chloro nitroso intermediates. The optimum conditions developed for the parent oxime **327** of the series using potassium carbonate and *tert*-butyl hypochlorite were employed.

Thus, as shown in Scheme 102, when *tert*-butyl hypochlorite was added portionwise to a stirred mixture of the oxime **370** and potassium carbonate in dichloromethane, a blue colouration appeared after several seconds and remained for 14 h. To our delight, after aqueous work up, the desired six membered ring nitrone **380** was isolated in very good

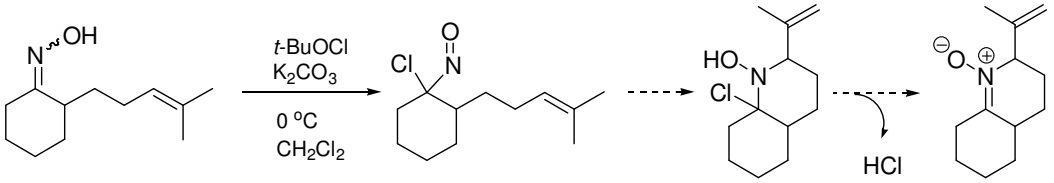
yield (65%), accompanied by a small amount of the hydroxylamine **381** (9%) formed by hydrolysis of the nitrone **380**.



370 **379** **380**: 65% **381:** 9%

Scheme 102

In stark contrast however, when oxime **371** was treated under the same conditions (Scheme 103), even although a pale blue colouration which persisted for 14 h was observed, the desired bicyclic nitrone **384** was not isolated and only starting oxime **371** was recovered in low yield (34%).



371 **382** **383** **384**

Scheme 103

In this instance, in spite of the fact that analysis of the crude reaction mixture after extraction by proton NMR spectroscopy provided some indication for traces of the required olefinic protons of the isopropenyl group, attempted purification using either silica gel or alumina chromatography appeared once again, to lead to further decomposition.

From a stereochemical standpoint, substrate **371** can in principle lead to two different diastereoisomeric α-chloro nitroso intermediates as shown in Figure 10 and, it may be possible that, in any subsequent ene reaction, the geometrical requirements are more difficult to meet for one of the two cases, thus providing opportunities for alternative reactions and severely limiting the yield. Alternatively, the location of the nitrone double bond in the desired bicyclic product **384** may render it more prone to hydrolysis than in the simpler monocyclic six membered ring **380**.

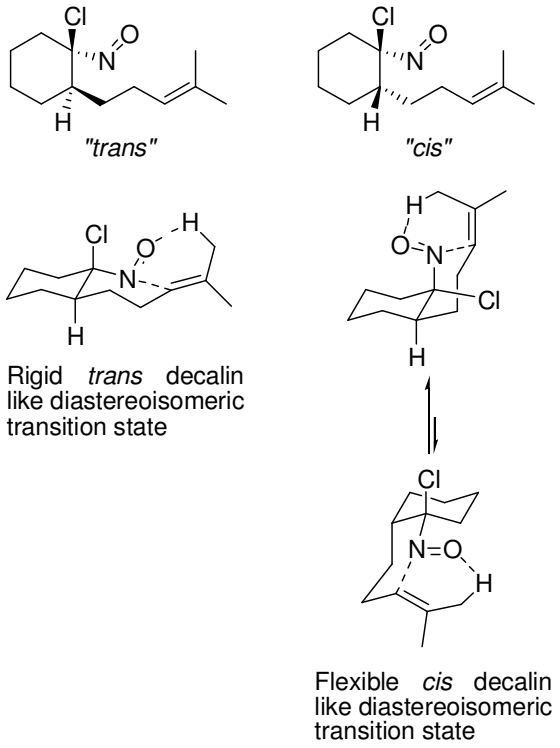
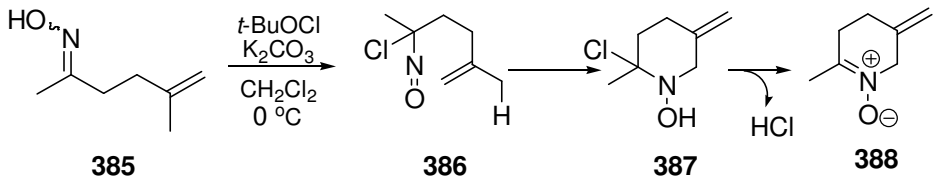


Figure 10

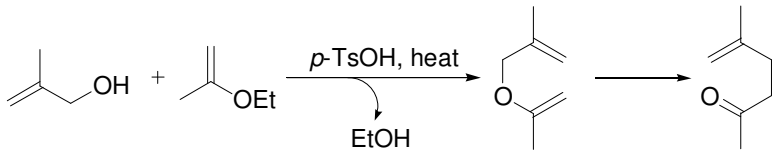
2.1.1 Intramolecular Nitroso Ene Reaction of Type II.

With some firm evidence that the desired intramolecular ene reaction of Type I could lead to formation of 5 and 6 membered nitrones, attention was then directed towards the Type II variant for which six and seven membered rings are favoured. Given the extremely facile reaction of the tertiary alkyl nitroso derivative **170** observed by Motherwell and Roberts,[112] it was anticipated that a similar geometry would exist for the α–chloro nitroso compound **386** as shown in Scheme 104.



Scheme 104

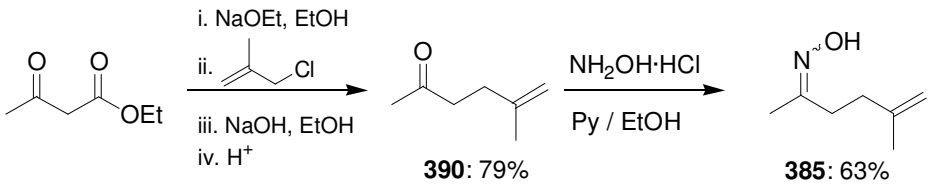
Thus, the acyclic ketone **390** was selected as an appropriate precursor. Two routes were examined. The first of these involved the Claisen allyl ether rearrangement of **389** which could in principle be prepared *in situ* by reaction of readily available methallyl alcohol and ethyl isopropenyl ether as shown in Scheme 105.[162]



Scheme 105

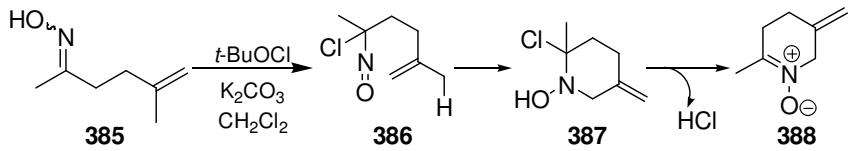
However, when this reaction was attempted by heating the two reagents in toluene under reflux in a Dean and Stark apparatus only traces of product were observed by TLC and proton NMR spectroscopy.

The alternative route shown in Scheme 106 involving alkylation of ethyl acetoacetate with 3-chloro-2-methyl-1-propene in the presence of sodium methoxide was therefore adopted.[163] Hydrolysis followed by decarboxylation furnished the required ketone, 5-methylhex-5-en-2-one **390** in high purity and good yield (63%), and this in turn was converted in the usual way to the precursor oxime **385.**



Scheme 106

When oxime **385** was treated with *tert*-butyl hypochlorite in dichloromethane in the presence of a base at 0 ºC, the characteristically pale blue colouration appeared and remained for two days. After work up, proton NMR spectroscopy of the crude revealed a complex mixture with some interesting signals in the form of two doublets at 4.47 and 4.05 ppm each integrating for one proton. All attempts to purify by column chromatography using silica or alumina proved unproductive. The reaction was then repeated using a scaled-up procedure with the intention of carrying out the purification by distillation. Surprisingly, the proton NMR spectrum of the crude reaction mixture was sufficiently clean to allow for characterisation of a product which was different from the expected nitrone **388** (Scheme 107).



Scheme 107

The assignments made on the basis of the proton and carbon NMR spectra are shown in Figure 11 and consistent with the formation of nitrone **391**, which was further supported by the mass spectrum.

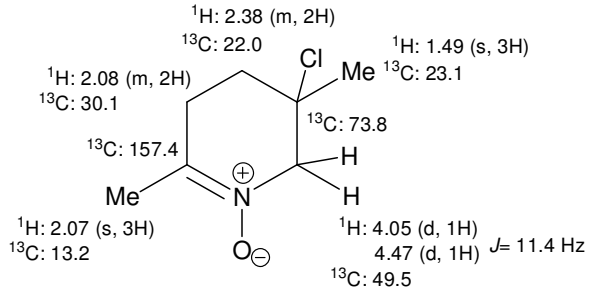
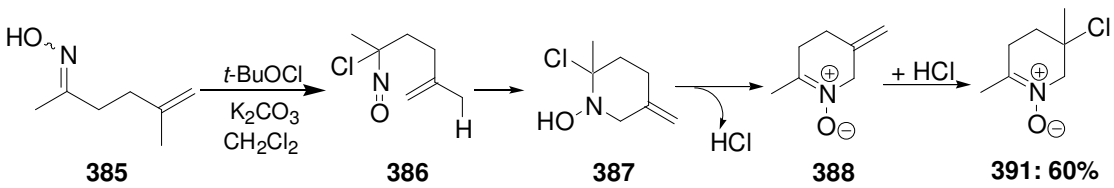


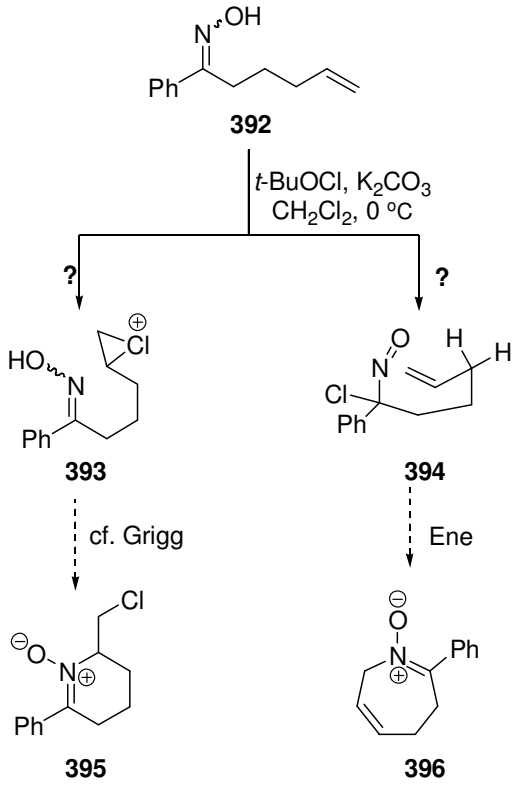
Figure 11

Although, in formal terms, this product could be derived by Markovnikov addition of hydrogen chloride to the exomethylene group of the desired nitrone **388** this was a surprising result, especially since it had not been encountered in the successful Type I reactions leading to the unsaturated five and six membered nitrones (Scheme 108).



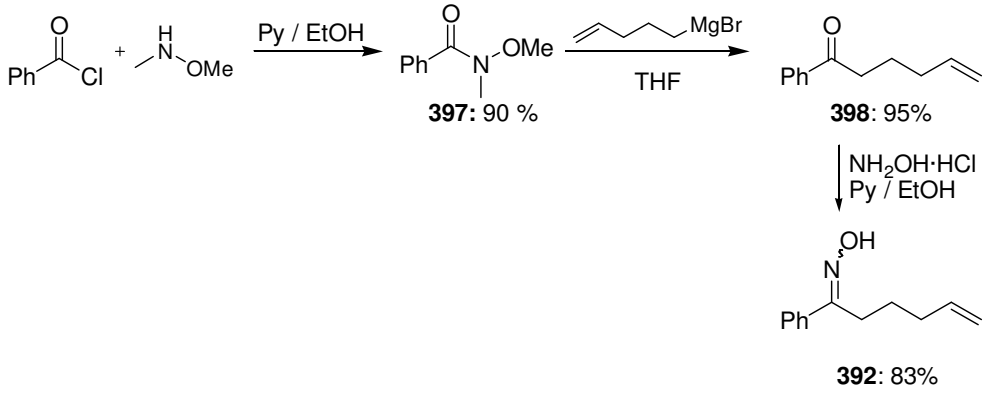
Scheme 108

Finally, within the area of examining potential intramolecular ene reactions of α–chloro nitroso compounds by *in situ* generation from oximes it was decided to examine the unsaturated oxime **392**. As illustrated in the Scheme 109, it must be admitted that the transition state for the ene reaction seems more difficult to achieve. Moreover, since the substrate possesses a terminal alkene as in the chemistry reported by Grigg for five six and seven membered ring nitrone formation,[144] if *tert*-butyl hypochlorite were to induce chloronium cation formation **393**, an alternative outcome might be formation of the six membered nitrone **395**.



Scheme 109

Thus, the required oxime **392** was readily prepared in excellent overall yield using Weinreb amide **397** as outlined in Scheme 110.[164]

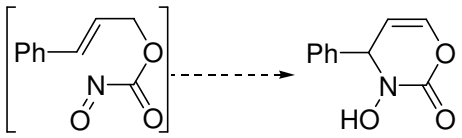


Scheme 110

Unfortunately however, neither the desired nor the undesired nitrone product was isolated from reaction of oxime **392** with *tert*-butyl hypochlorite in the presence of potassium carbonate at 0 ºC, even although an intense blue colouration appeared and lasted for thirty six hours, possibly as consequence of the presence of the aryl ring. The only compound to be isolated from attempted chromatography was the starting oxime **392** (34% recovery)

and proton NMR spectroscopy and TLC of the crude reaction product indicated a complex mixture.

In terms of a literature analogy, the only related instance of an intramolecular ene reaction of such a type can be found in the work of Kirby,[19a] who investigated the cyclisation of (*E*)-cinnamyl nitrosoformate **399** and reported that an intractable mixture of products was formed (Scheme 111).

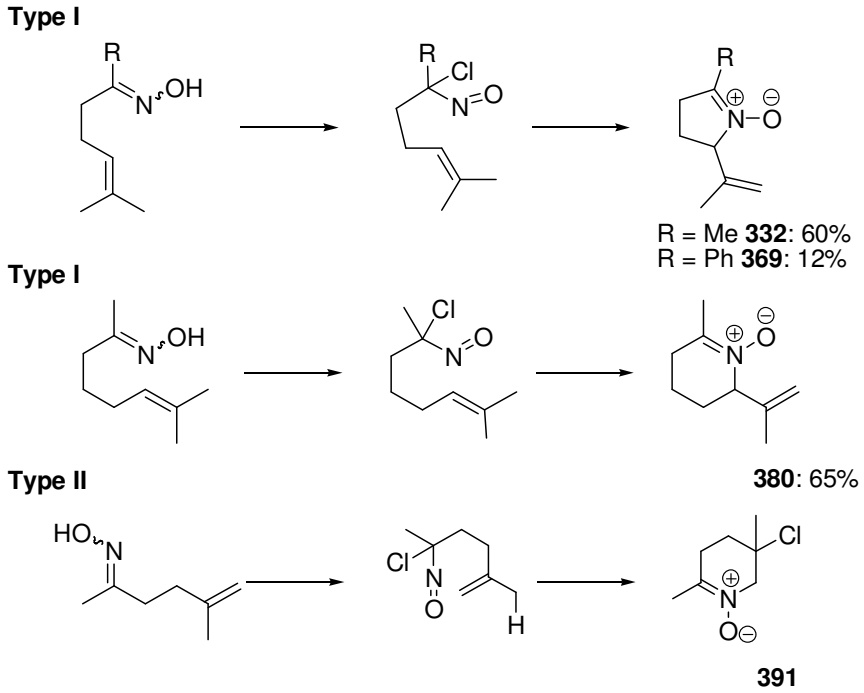


399 **400**

Scheme 111

2.1.2 Intermediate Conclusions and Overview of Intramolecular Ene Reactions of α–Chloro Nitroso Compounds Derived from Oximes.

At this first stage, the overall situation with respect to intramolecular ene reactions of chloro nitroso compounds derived from oximes was somewhat perplexing. As emphasised in Scheme 112, it was very gratifying to note that, for the Type I reaction, good yields of the expected products had been obtained for both five and six membered ring formation. For the Type II reaction however, the isolation of product **391** which could formally be derived by addition of hydrogen chloride to the desired nitrone **388** seemed to be inconsistent with the conditions developed for the Type I reaction. Moreover, efforts to find other examples of Type I reactions had led, either to very low yields or to highly complex mixtures.



Scheme 112

At first sight, it was tempting to speculate that the scavenging of hydrogen chloride by potassium carbonate from the initial ene product or nitrone hydrochloride was inefficient, and that for some reason, in the attempted Type II reaction, addition of hydrogen chloride to the exomethylene group of the desired nitrone product was faster than to the isopropenyl group formed in the Type I adducts. This however seemed to be unlikely. Our attention then turned to possible transition states for the two different types of intramolecular reaction, and in particular to ``ene´´ reactions proceeding via an aziridine-*N*-oxide intermediate. These are shown in Figure 12 below.

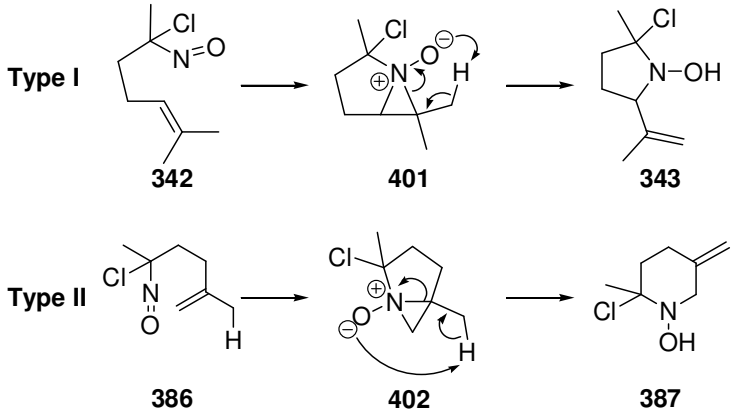


Figure 12

Both in terms of the orbital overlap and strain, it might be argued that the cyclic elimination step from intermediate **402** is more demanding than from **401**, or that bond (a) in the aziridine *N*-oxide intermediate **402** is much weaker and hence, in the presence of hydrogen chloride, could be much more susceptible to Markovnikov type ring opening by chloride anion as shown in Figure 13.

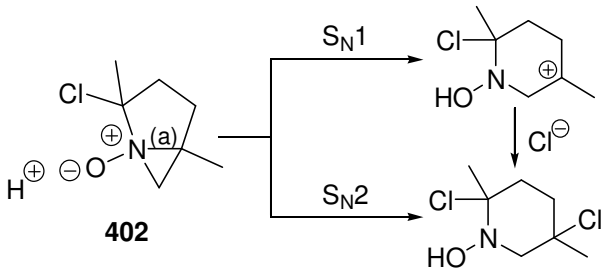
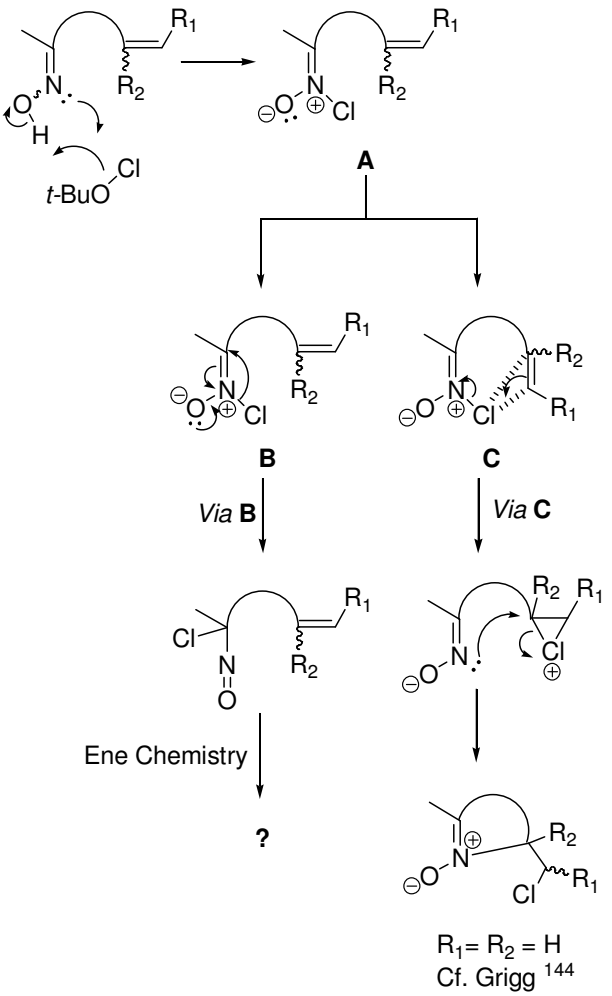


Figure 13

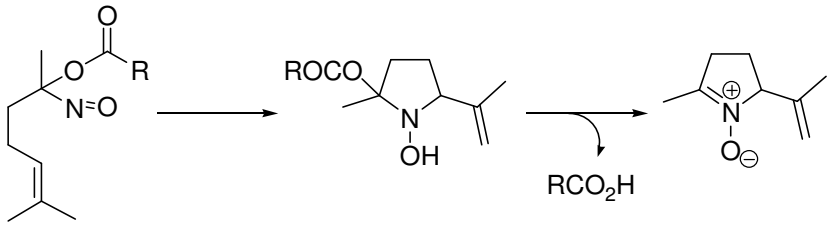
Finally, throughout our study involving the formation of nitroso chlorides from oximes, even although the studies of Grigg were restricted to five membered ring formation involving a monosubstituted alkene,[144] the possible dangers of chloronium ion formation as an unwanted reaction were always present in our considerations. Given that the mechanism for formation of an α–chloro nitroso compound from an oxime is unknown, it is even possible to write intermediates which can either evolve to an α–chloro nitroso compound or function to as an electrophilic halogen source. A possible divergence of mechanistic pathway is shown in Scheme 113.



Scheme 113

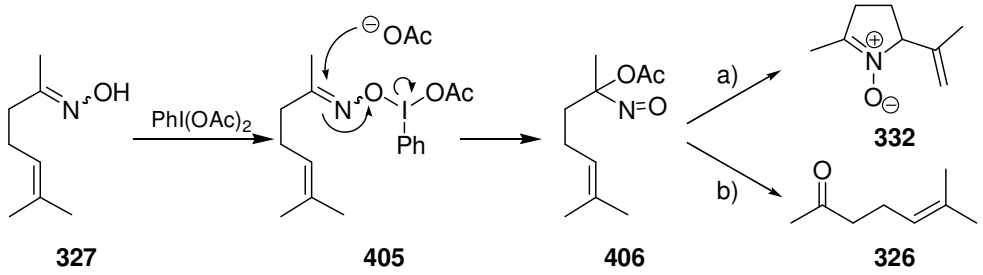
With all of the above uncertainties in mind, the pragmatic solution seemed to be to avoid the use of *tert*-butyl hypochlorite, not only because it was a potential source of chloronium ions, but also because of the dangers of any liberated hydrogen chloride.

The replacement of the chloride atom by an acyloxy group was therefore considered as a potential solution to this issue, since, as implied in Scheme 114, formation of an α–acyloxy hydroxylamine **404** or nitrone carboxylate should not pose problems for an isolated double bond.



Scheme 114

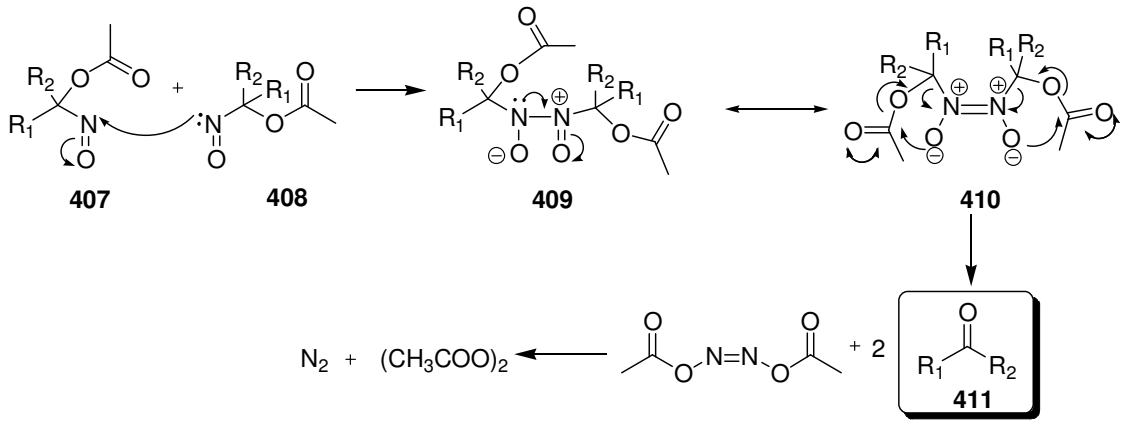
Examination of the literature revealed that the high yielding oxidative cleavage of oximes to ketones with iodosobenzene diacetate was reported to proceed via an α–acetoxy nitroso compound.[45c] The reactivity of oxime **327** was therefore investigated to determine whether the intermediate **406** would react via a Type I intramolecular ene reaction (path a) or evolve, as in the literature examples, to afford a ketone **326** (path b) (Scheme 115).



Scheme 115

Thus, to a stirred solution of iodosobenzene diacetate in glacial acetic acid at -15 ºC was added the ketoxime **327**. The pale blue-green colouration appeared and remained for 3 h before the reaction mixture became orange.[165] Monitoring of the reaction indicated complete disappearance of the starting oxime **327**, and subsequent work up afforded the 6-methylhept-5-en-2-one **326** in 55% yield. No trace of the expected ene product could be observed under those conditions and several attempts to prevent the formation of ketone **326** were carried out at a range of lower temperatures (-15 ºC to -40 ºC), and also in a variety of solvents (CH_2Cl_2, Et_2O) at different concentrations (0.05 to 0.01 M). The ketone **326** was obtained in similar yield in all cases.

Scheme 116 illustrates a possible pathway for the competitive deoximation process involving formation and decomposition of the nitroso dimer **407** followed by acyl migration with liberation of the ketone **411**.



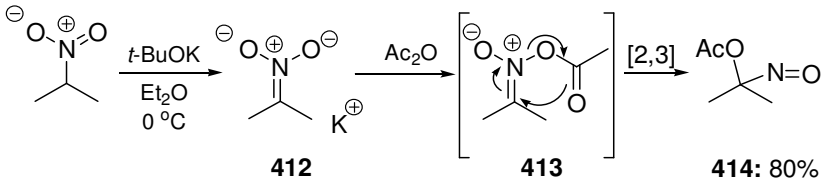
Scheme 116

In spite of this failure, the idea of using α–acyloxy nitroso compounds was an attractive one, especially since, in principle, the leaving group ability of the acid eliminated from the initial product of the ene reaction could be tuned to achieve the desired nitrone formation without any undesired consequences for an isolated double bond. The following section describes efforts made in this direction.

2.2 The Generation and Reactivity of α-Acyloxy Nitroso Compounds in the Ene Reaction.

2.2.1 The Generation of α-Acyloxy Nitroso Compounds.

Even although conversion of oxime **327** to the α-acetoxy nitroso intermediate **406** was apparently unsuccessful because of an alternative decomposition pathway possibly involving dimerisation, a detailed examination of the literature revealed that this class of compound had been prepared from nitro compounds in a beautiful pioneering study by the Russian chemist, Zefirov.[166] Thus, as exemplified in Scheme 117, deprotonation with potassium *tert*-butoxide to give the nitronate anion followed by reaction with an acid chloride or anhydride led, presumably via a sequence involving *O*-acylation followed by a [2,3]-sigmatropic rearrangement, to a very versatile route for this class of compounds.



Scheme 117

Attention was accordingly centred on the chemistry of the nitro group, and, in the first instance, in order to assess the efficiency of the Zefirov method,[166] and also the stability of α-acyloxy nitroso compounds, a preliminary study was carried out on the preparation of 2-acetoxy-2-nitrosopropane **414** from 2-nitropropane (Scheme 117).

In general terms, as described in the literature,[166] the selection of potassium *tert*-butoxide (1 eq) in diethyl ether at 0 ºC followed by addition of either acetyl chloride or acetic anhydride (1 eq) always led to a deep blue mixture in which the desired compound was the major product (Table 14, Entries 1 and 2).

However, as some fluctuations in yield were noted, particularly when reactions were carried out on a small scale, it was decided to carry out a screen of several other bases which might prove easier to handle and purify than potassium *tert*-butoxide. The results of this semi-quantitative exercise are summarised in Table 14.

Entry	Base	Acetylating Agent	Solvent	Conditions	Product
1	*t*-BuOK	AcCl	Et_2O	0 ºC	76%
2	*t*-BuOK	Ac_2O	Et_2O	0 ºC	80%
3	*n*-BuLi	AcCl	Et_2O or THF	-78 ºC to 0 ºC	68%
4	*n*-BuLi	Ac_2O	Et_2O or THF	-78 ºC to 0 ºC	74%
5	NaH	AcCl	Et_2O	rt	X
6	NaH/imidazole	AcCl	Et_2O	rt	X
7	NaH/10% mol *t*-BuOH	AcCl	Et_2O	rt	Traces
8	NaOH	AcCl	Et_2O	0 ºC	X
9	DBU	AcCl	Et_2O	rt	Traces
10	DBU	Ac_2O	Et_2O	rt	Traces
11	Et_3N	AcCl	Et_2O	rt	Traces
12	Et_3N	Ac_2O	Et_2O	rt	Traces
13	5 eq K_2CO_3	Ac_2O	Et_2O	rt	X

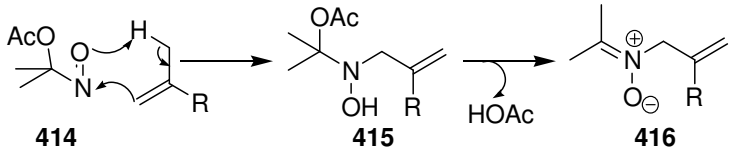
Table 14

In the event, in addition to the literature conditions (Entries 1 and 2) only *n*-butyl lithium (Entries 3 and 4) proved to be competitive in terms of giving a similar conversion. All efforts to use sodium hydride (Entries 5, 6 and 7) including *in situ* generation of sodium *tert*-butoxide were unsuccessful as was sodium hydroxide itself (Entry 8) and potassium carbonate (Entry 13). Organic bases such as DBU or triethylamine gave poor conversion with over 90% of 2-nitropropane being recovered (Entries 9, 10, 11 and 12).

Despite further investigations into a range of conditions, it was not possible to obtain better results than those reported in the literature. From a preparative standpoint, there was no significant difference in distillation of the product when either acetyl chloride or acetic anhydride was used as the acetylating agent, although purification by fractional distillation of acetic anhydride is known to be more effective. Finally, the reaction was carried out using a fresh batch of potassium *tert*-butoxide which was stored in a desiccator.

2.2.2 Intermolecular Ene Reactions of 2-Acetoxy-2-nitrosopropane.

To the best of our knowledge, even although the α-acetoxy nitroso compound developed by Kouklovsky has been used in Diels-Alder reactions (Scheme 22) there are no reports in the literature of either inter- or intramolecular ene reactions of geminal α-acyloxy nitroso compounds.[65] It was therefore of interest, in the first instance to explore the reactivity of 2-acetoxy-2-nitrosopropane **414** with different enophiles since, as indicated in Scheme 117, this would provide an opportunity to assess if the initial α-acetoxy hydroxylamine product **415** would undergo facile elimination of acetic acid to give the nitrone **416**, and hence avoid the problems encountered with α-chloro nitroso compounds.



Scheme 118

Three enophiles were selected for study (Figure 14), two of which were known to be of proven utility in the ene reaction.

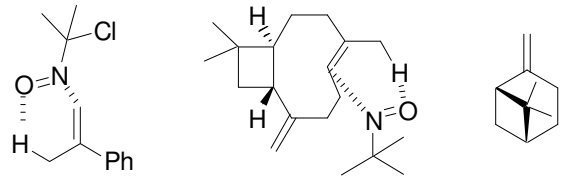


Figure 14

Thus, α-methylstyrene had been shown to react with 2-chloro-2-nitrosopropane **412** to produce the α-chlorohydroxylamine and finally the nitrone after elimination of hydrogen chloride,[115] whilst the strained *trans* double bond in the nine membered ring of caryophyllene had been demonstrated to react successfully with the simplest tertiary alkyl nitroso compound, *tert*-nitrosobutane by Motherwell and Roberts.[112]

Accordingly 2-acetoxy-2-nitrosopropane **414** was generated *in situ* under Zefirov conditions (1.0 eq potassium *tert*-butoxide followed by 1.0 eq of acetic anhydride in diethyl ether at 0 ºC) in the presence of 3.0 molar equivalents of the three enophiles.

To our extreme disappointment, only the unsaturated compound was recovered after aqueous work up in all three cases, and it was presumed 2-acetoxy-2-nitrosopropane **414**

underwent disproportionation to acetone which was removed under vacuum (Scheme 116). In order to avoid this problem and favour the ene reaction, the reactions were carried out again in the presence of a selection of Lewis acids yttrium triflate, zinc triflate and diethylaluminium chloride as Lewis acid and proton scavenger which had proven to be very effective for the analogous ene reactions when aldehydes were used as enophiles (Table 15).[167]

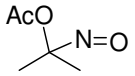
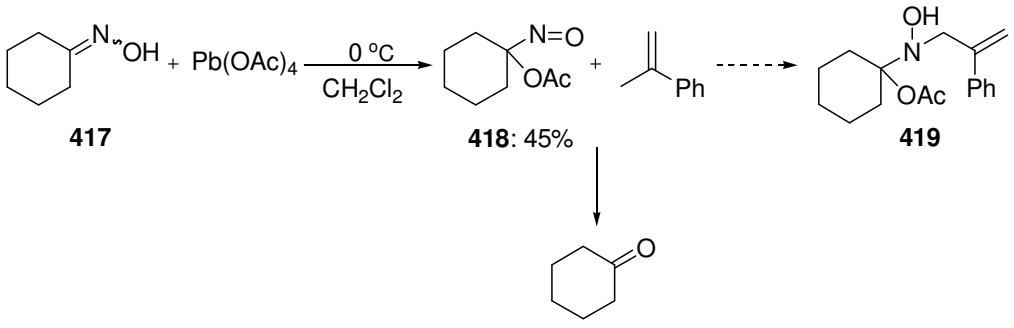
Entry	Substrate	Ene	Lewis acid
1		α-methylstyrene	A, B, C
2		β-pinene	A, B
3		caryophyllene	A, B

Table 15: 2-acetoxy-2-nitrosopropane **412** (1 eq) was mixed with an excess of enophile (3 eq) and catalyst (**A** and **B**: 10% mol and **C**: 1.5 eq). Reaction mixture was stirred at rt until disappearance of blue colouration. **A**: $(CF_3SO_3)_3Y$, **B**: $(CF_3SO_3)_2Zn$, **C**: Et_2AlCl.

Once again however no signals of ene reaction were observed and the enophiles were recovered as the only product. Thwarted by these results we decided to test the theory of the competitive disproportionation reaction previously outlined in Scheme 116.[65] The synthesis of 1-nitrosocyclohexyl **418** was therefore accomplished by Irreland's method by reaction of cyclohexanone oxime **417** with lead tetraacetate to generate the desired nitroso derivative in good yield.[45,168] The deep green solution of **418** was then mixed with α-methylstyrene (3 eq) and stirred at room temperature until the disappearance of the green colouration. As suspected, compound **418** did not react to give the desired adduct **419** but instead cyclohexanone was recovered (Scheme 119).

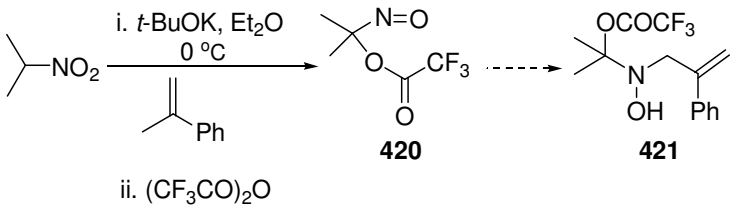


417 **418**: 45% **419**

Scheme 119

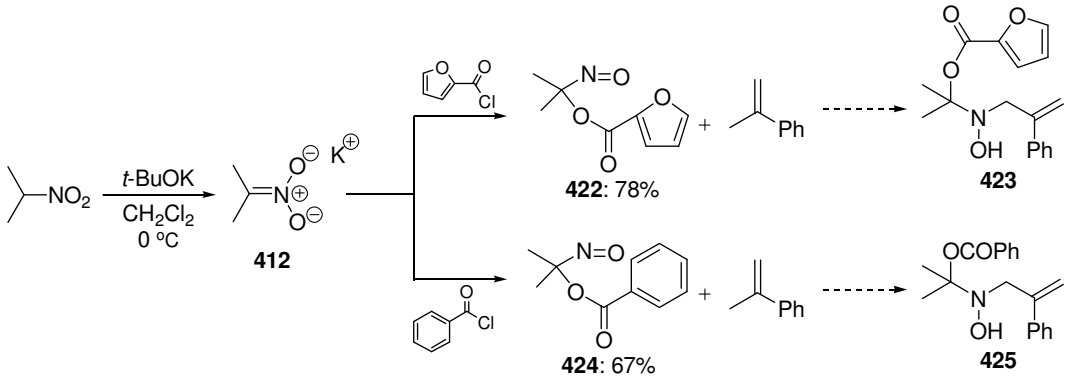
It would therefore appear that disproportionation of the α-acetoxy nitroso compound to ketone is faster than the ene reaction, regardless of concentrations, temperature ranges and the presence of Lewis acid. Although Diels-Alder addition has been described to occur with this kind of nitroso derivative,[65] they seem to be much less reactive towards the ene reaction.

Given that 2-chloro-2-nitrosopropane did react with α-methyl styrene,[115] the first variation from an α-acetoxy nitroso derivative which was considered was to increase the leaving group ability of the geminal substituent by replacing the acetate group by trifluoroacetate. 2-Nitroso-2-trifluoroacetoxy propane **420** was therefore prepared as described by Zefirov but proved to be considerably less stable than the acetate congener **414**.[166] Irrespective of whether this nitroso compound was preformed or generated *in situ* as shown in Scheme 120, the blue colouration was much less intense and the NMR spectrum of the crude reaction mixture which was considerably more complex than for 2-acetoxy-2-nitrosopropane **414** provided no evidence for formation of the desired ene product **421.**



Scheme 120

In a recent study involving the hydrolysis of acyloxy nitroso compounds to yield nitroxyl (HNO) the biologically important reduced form of the nitric oxide, it was noted that the rate of hydrolysis was in general very fast, but depended on the structure of the acyloxy group.[169] Efforts were therefore made to prepare more hydrolytically resistant acyloxy nitroso compounds from the potassium salt of 2-nitropropane **412** (Scheme 121).



Scheme 121

These included the known benzoate **424** which was produced cleanly and in high yield as a deep blue oil,[170] and proved to be considerably more stable than derivatives used previously. Unfortunately however, when **424** was mixed with an excess of α-methylstyrene and the reaction mixture was stirred for 24 h until disappearance of the blue colour, no evidence was obtained for the desired hydroxylamine **425** and only benzoic acid was recovered. We note parenthetically that the 2-furanoyl congener **422** was also prepared at this time as a deep green oil which required one week before hydrolysis to the acid was complete. Furthermore, this compound did not display any tendency to undergo either an inter- or intramolecular Diels-Alder reaction.

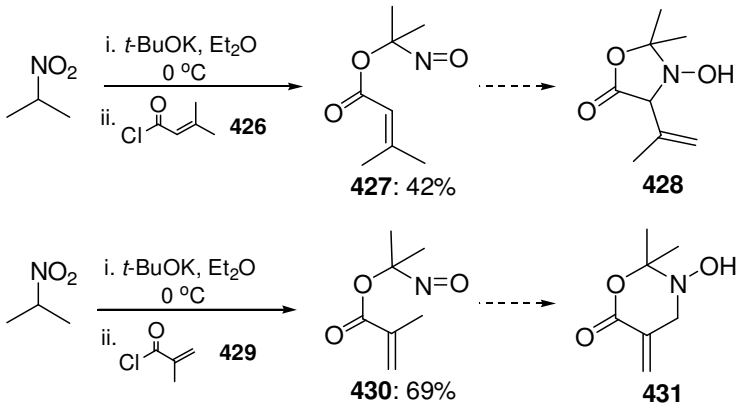
2.2.3 Intramolecular Ene Reactions of α-Acyloxy Nitroso Compounds.

The above studies had indicated that the preparation of α-acyloxy nitroso compounds by the Zefirov route was a viable proposition albeit that their stability was very much a function of the detailed substrate structure.[166] The failure to detect any intermolecular ene reactions, even with the most favoured enophiles, also highlighted, once again, that the ene reaction, in general, is more energetically demanding than its Diels-Alder counterpart. The successful studies by Kouklousky emphasise this statement in the present context.[65]

Nevertheless, as previously noted (Scheme 45) the particularly facile Type II intramolecular ene reaction of simple tertiary alkyl nitroso compounds possessing a relatively unreactive terminal alkene had been discovered by Motherwell and Roberts,[112] and argued that the combined benefits of the Thorpe-Ingold effect induced by geminal substitution and selection of the intramolecular mode might combine to favour the desired process.[171] With these thoughts in mind, and also with the objective of preparing suitable

precursors for testing by the shortest possible route, a variety of preliminary studies were conducted.

Thus, the first two intermediates to be considered were **427** and **430** (Scheme 122), in which the unsaturation is incorporated into the acyl moiety. These arose almost by accident in the initial studies on the preparation and stability of α–acyloxy nitroso compounds. In this instance, the double bond of the ene component is electron deficient by virtue of the carboxylate tether and could therefore be considered as a poor nucleophilic component in a highly asynchronous ene reaction. Both **427** and **430** were readily prepared in good yields by treatment of 2-nitropropane with potassium *tert*-butoxide then followed by addition of the requisite acid chlorides **426** and **429**, with the former being prepared from 3-methylbut-2-enoic acid by a literature method.[172]

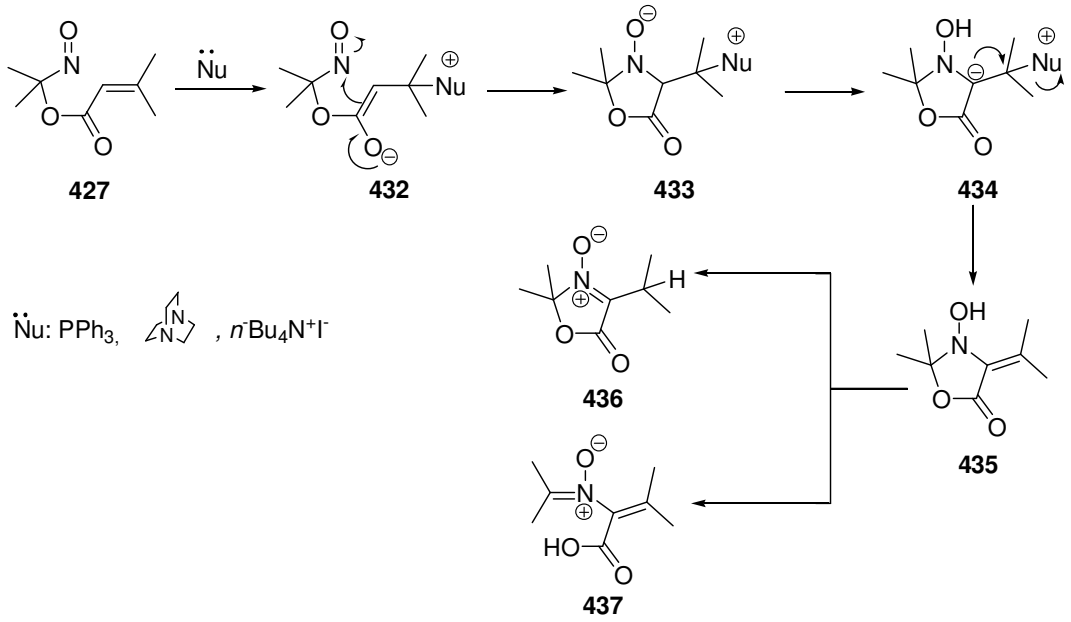


Scheme 122

In the event however, when substrates **427** and **430** were stirred at room temperature, the intense blue colouration remained for three days, and, after this time only 3-methylbut-2-enoic acid or methacrylic acid was isolated. Activation of the reaction was also attempted by employing different Lewis acids such as $AlCl_3$, $SnCl_4$, BF_3, $FeCl_3$, $ZnCl_2$ and $GaCl_3$ (10% mol) and using the isolated nitroso compound in diethyl ether. In these cases, the blue colouration dissipated after only 12 h, but, once again, only the two carboxylic acids were isolated.

Before moving on to prepare more electronically appropriate substrates however, the opportunity of studying the behaviour of **427** under Bayliss-Hillman conditions was taken.[173] Thus, as outlined in Scheme 122 it was envisaged that the use of 1,4-diazabicyclo[2.2.2]octane (DABCO), triphenylphosphine, or tetra-*n*-butylammonium

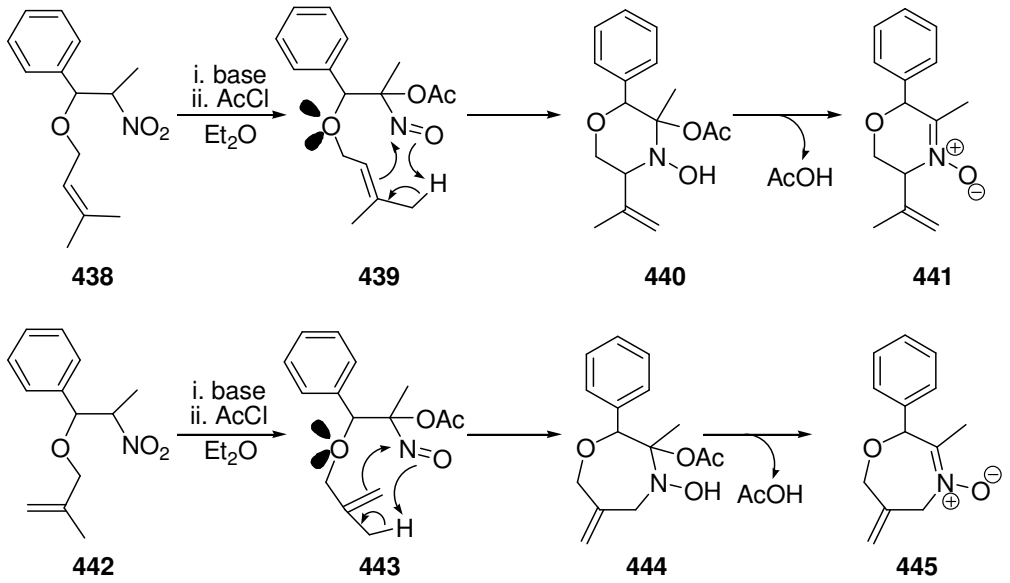
iodide as nucleophilic catalysts might proceed via the traditional mechanism to the unsaturated hydroxylamine **435**. This compound, in turn, could either undergo ring opening to the nitrone **437** or tautomerisation to **436**.



Scheme 123

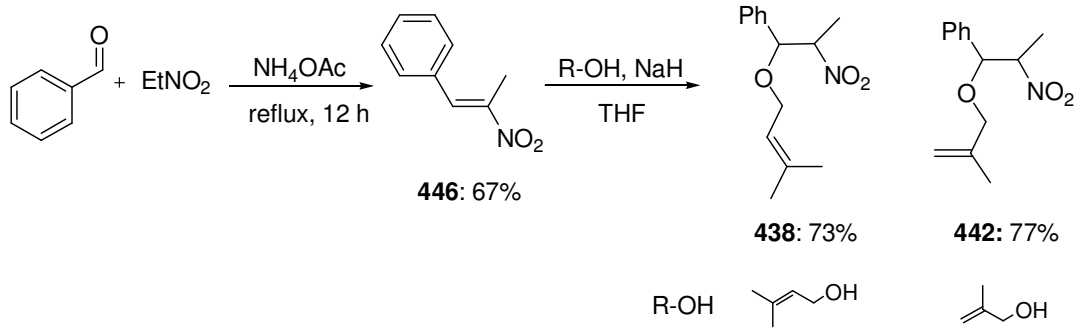
However, as evidenced by analytical TLC and aliquot monitoring of the reactions by proton NMR spectroscopy all of the aforementioned catalysts as well as sodium benzenethiolate failed to yield any detectable products other than starting material **427** together with the corresponding acid obtained after hydrolysis.[155]

Following on from this "divertissement", attention was then redirected towards the synthesis of nitro compounds which contained a more reactive ene component for participation in a Type I or type Type II reaction. The two precursors selected for study are shown in Scheme 124 together with the projected outcomes of the Type I reaction of the gem nitroso acetate **439** generated from **438** and the Type II reaction of **443** from **442**. The incorporation of the oxygen atom in the linking chain between the nitro group and the alkene unit was primarily dictated by the idea that such compounds could be easily prepared and also benefit from the Thorpe-Ingold effect of the oxygen lone pair in subsequent intramolecular ene reactions.



Scheme 124

As expected, substrates **438** and **442** were readily prepared using a modified literature method (Scheme 125).[174] Thus, reaction of benzaldehyde with nitroethane furnished the β-nitrostyrene **446** and subsequent Michael addition of the appropriate allylic alkoxide anion gave the required nitro compounds **438** or **442** as diastereoisomeric mixtures with all steps proceeding in good yield.



Scheme 125

The results for an extensive series of experiments using both β-allyloxy nitro compounds are gathered in Table 16 and proved to be extremely disappointing in as much as no ene product was detected, either in the proposed Type I reaction of **439** (Entries 1-7) or in the Type II reaction from **443** (Entries 8-10).

To our dismay, irrespective of whether efforts were made to generate the potassium nitronate salts (Entries 1-4) for **438** and Entries 8, 9 and 10 for **442** or, to a lesser extent, the lithium nitronate salts (Entries 5-7) for **438** the major products to be isolated were

benzaldehyde and the corresponding allylic alcohol. In essence, the attempted ene reactions had "disassembled" the substrates in an entirely unexpected retrosynthetic manner.

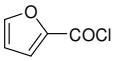
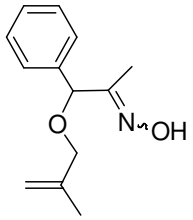
Entry	Substrate	Base	Acylating Agent	Conditions	Product (yield)		
					PhCHO	allylic alcohol	others
1	**436**	1 eq *t*-BuOK	1 eq Ac_2O	0 ºC / Et_2O	32% [A]	19%	-
2	**436**	1 eq *t*-BuOK	2 eq Ac_2O	0 ºC / Et_2O	35% [A]	22%	-
3	**436**	2 eq *t*-BuOK	1 eq Ac_2O	0 ºC / Et_2O	13% [B]	8%	-
4	**436**	1.1 eq *t*-BuOK	1 eq Ac_2O	0 ºC / CD_3CN	36%	23%	-
5	**436**	1 eq *n*-BuLi	1 eq Ac_2O	-50 ºC / THF	10% [B]		-
6	**436**	1 eq *n*-BuLi	1 eq Ac_2O	-78 ºC / THF	15%	-	**SM**: 18% [C] **X:** 35%
7	**436**	1 eq *n*-BuLi	1 eq 	-50 ºC / THF	10% [B,D]	10%	**SM**: 27%
8	**440**	1 eq *t*-BuOK	1 eq Ac_2O	0 ºC / Et_2O	40% [A]	31%	-
9	**440**	1.1 eq *t*-BuOK	1.1 eq Ac_2O	0 ºC / CD_3CN	33% [A]	12%	-
10	**440**	1 eq *t*-BuOK	1 eq Ac_2O	-78 ºC / THF	20%	20%	**447** :14%

Table 16: **A**: traces of starting nitro derivative **438** and **442**. **B**: complex mixture. **C**: only one diastereomer of starting nitro derivative **438.** **D:** furan-2-carboxylic acid was recovered in 18%.

In efforts to understand at what stage formation of benzaldehyde and the allylic alcohols occurred, two reactions were carried out in deuterated acetonitrile (Entries 4 and 9). Examination of the proton NMR spectra indicated clean nitronate formation in both cases

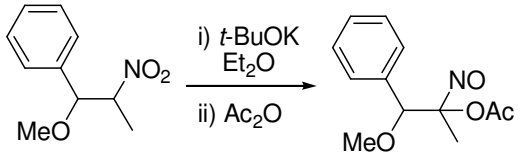
with no apparent decomposition until addition of acetic anhydride as the acylating agent. Following on from our earlier observation that the geminal nitroso acyloxy derivative obtained using 2-furoyl chloride was much more stable, this reagent was also used (Entry 7), but, once again, similar results were obtained. Finally, when efforts were made to conduct the reaction at lower temperatures, initially at -50 °C (Entry 5) and then -78 °C (Entries 6 to 10) it was noted that the NMR spectra of the crude reaction mixtures were more complex, indicating the possibility of isolating other products. In the latter reactions, since the [2,3]-sigmatropic rearrangement of acyloxy nitronic acids only occurs at temperatures above -55 °C,[170] these reactions (Entries 6 and 10) were allowed to warm slowly to 0 °C after 30 min. Unfortunately, even although a new product was formed from substrate **438** under these conditions (Entry 6) a structural assigment could not be made. However, from substrate **442** the data are consistent with the formation of the oxime **447** in 14% yield (Entry 10) (Figure 15).



447

Figure 15

The above reactions clearly raised many unanticipated mechanistic questions, especially in relation to the formation of benzaldehyde and the allylic alcohols; and since β-alkoxy geminal acetoxy nitroso derivatives were unknown, it was therefore decided to probe the behaviour of an even simpler model compound. Towards this end, the methoxy derivative **448** was prepared by conjugate addition of methanol to the nitrostyrene **449** in moderate yield (Scheme 126).



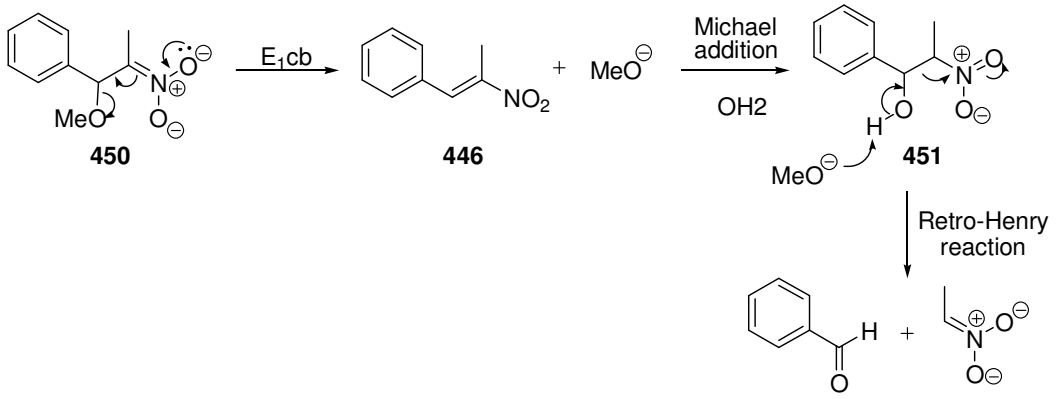
448 **449**

Scheme 126

When the β-methoxy derivative **448** was treated under standard Zefirov conditions, a pale blue solution was obtained, but all efforts to isolate the geminal nitroso acetate **449** were unsuccessful, and when reactions were left stirring until the blue colour had disappeared,

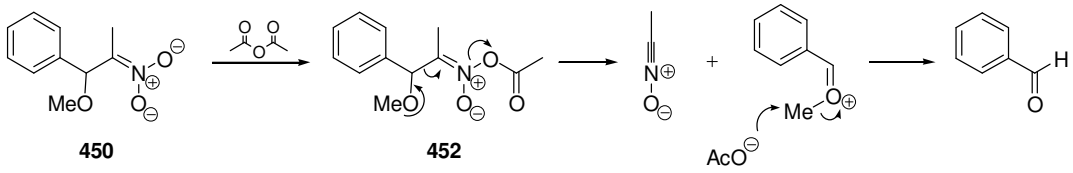
over different temperatures, ranging from -78 ºC to 0 ºC, only benzaldehyde was recovered in all cases in yields ranging from 46% to 24%. These observations clearly indicated that the formation of benzaldehyde was not occurring after formation of any ene adduct, and also that the β-oxygen atom was the inherent source of the unstable nature of this class of compound.

From a mechanistic standpoint, since carbon-carbon bond cleavage must occur in these reactions, the immediate temptation was to consider that E_1cb elimination of alkoxide **450** followed by Michael addition of unwanted hydroxide anion and a subsequent retro Henry reaction might be occurring (Scheme 127).



Scheme 127

Given however that efforts were made to exclude adventitious water, an alternative postulate is shown in Scheme 128.



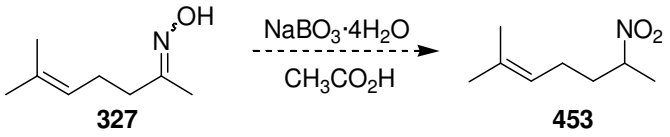
Scheme 128

In light of the results obtained from those substrates which had been selected merely for reasons of rapid assembly, it was then appropriate to design routes to nitro compounds with an all carbon linkage in the tethering chain to the ene component, and hence to provide a better opportunity for direct comparison with the geminal chloro nitroso precursors studied earlier. In essence, this required formal replacement of the oxime functional group by the nitro group, and, as in the preceding study, the incorporation of appropriately substituted alkenes which would permit a study of both Type I and Type II ene reactions for both five and six membered ring formation.

2.2.3.1 Acyclic Substrates for Type I Ene Reactions.

In the first instance, the most direct routes to the desired nitro compounds appeared to be by simple functional group manipulation using the ketonic substrates already prepared.

Towards this end, the oxidation of oxime **327** using a literature method involving sodium perborate in glacial acetic acid at 55-60 ºC was attempted in the hope that the peracid generated *in situ* would react faster with the oxime group than the trisubstituted alkene (Scheme 129).[175]

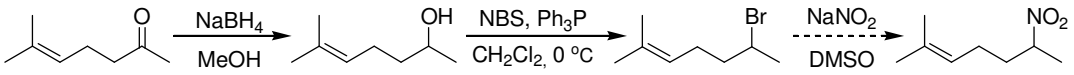


327 **453**

Scheme 129

Unfortunately, no nitro compound **453** could be detected and even repetition of a literature example using cyclohexanone oxime led to a very low yield (10%) of nitrocyclohexane. In light of the probable competitive epoxidation of the alkene and possible subsequent reactions, this approach was abandoned.

An alternative based on the traditional approach of reacting an alkyl halide with sodium or silver nitrate was then considered, albeit that it is most useful for primary nitroparaffins and yields dramatically decrease to around 15% when simple secondary halides are employed.[176] The results of the attempted sequence are shown in Scheme 130.

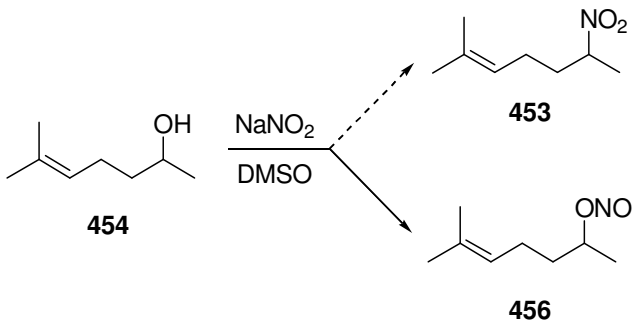


326 **454:** 93% **455:** 65% **453**

Scheme 130

Thus, commercially available ketone **326** was reduced using sodium borohydride in excellent yield to the secondary alcohol **454** which, after treatment with NBS in the presence of triphenylphosphine gave the bromide **455** (Scheme 130). When the latter was subsequently reacted with sodium nitrite in DMSO a complex mixture was produced with only traces of the expected nitro derivative **453**. A blank experiment using bromocyclohexane was similarly unsuccessful.

The final attempt to effect a functional group transformation was based on a literature method published in 2000 which claimed that saturated nitro compounds could be obtained directly from alcohols using sodium nitrite and both hydrochloric acid and acetic acid in DMSO (Scheme 131).[177]

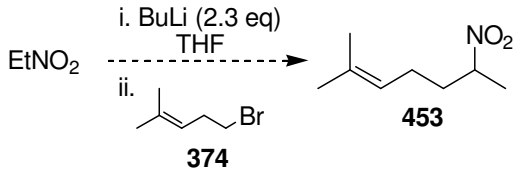


Scheme 131

In our hands however, using alcohol **454**, only the nitrite ester **456** was formed (Scheme 132) and a similar result was obtained using 1-phenylethanol which had been reported as a successful substrate by these authors. It was however of some comfort to note that a subsequent paper by Makosza proved that this method was erroneous for the direct displacement of alcohols by the nitro group.[178]

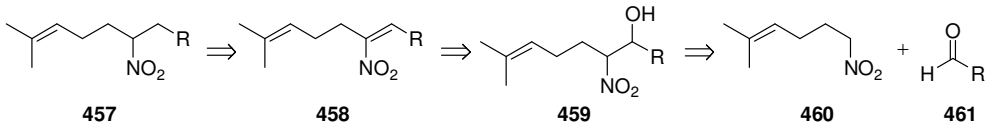
Since "simple" functional group manipulation was proving to be problematic, it was then decided to rely on synthetic methods which featured carbon-carbon formation.

The first of these was based on the seminal studies of Seebach who demonstrated that the strong tendency of aliphatic nitronate anions to undergo *O*-alkylation as opposed to *C*-alkylation could be overcome by double deprotonation of nitroalkanes.[179] However, when such reaction conditions were followed using nitroethane and 5-bromo-2-methylpent-2-ene **374** only starting materials were recovered (Scheme 132). It should be noted that this reaction tends to be limited to reactive allylic and benzylic electrophilic agents, and also that some groups have reported difficulties when attempting to reproduce this class of reaction.[180]



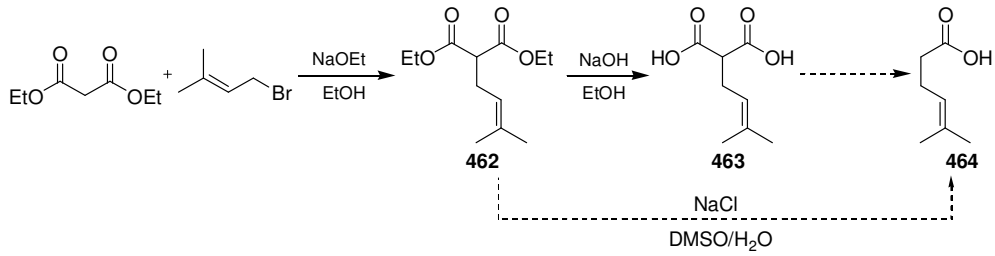
Scheme 132

At this stage, there was little alternative but to follow a well established but relatively lengthy and moderate yielding literature strategy which involved the nitro aldol reaction of a primary nitroalkene with an aldehyde, followed, if necessary, by acylation, elimination and finally conjugate reduction of the nitroalkene. The retrosynthetic scheme for a Type I ene precursor to give a five membered ring is shown by way of example in Scheme 133.



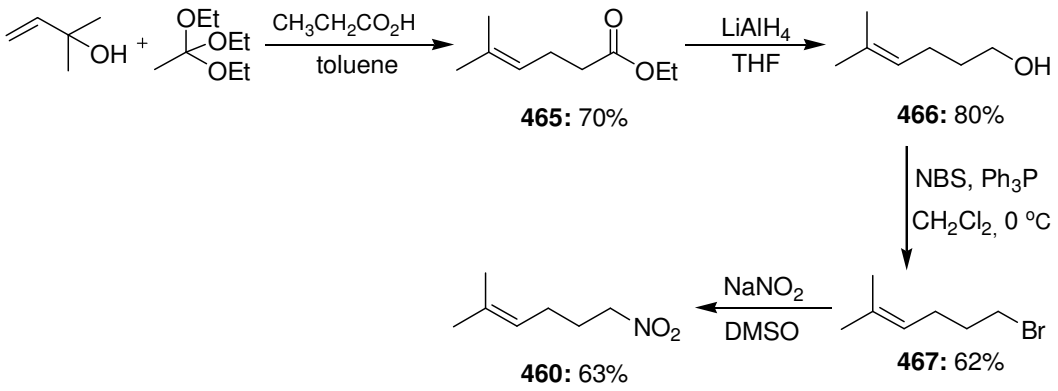
Scheme 133

Since primary nitroalkanes can be prepared efficiently by nitration of the corresponding bromo derivatives which can in turn be obtained from the alcohol, the synthetic route outlined in Scheme 134 was attempted and started with alkylation of diethyl malonate to give ester **462** in excellent yield.[181,182] To our surprise however, decarboxylation of the latter under basic conditions did not produce the expected acid **464** but the malonic acid derivative **463** whilst decarboxylation via the Krapcho method proved ineffective.[183]



Scheme 134

In the event, the desired nitroparaffin **460** was prepared by the effective route outlined in Scheme 135 which featured condensation of the tertiary allylic alcohol with triethylorthoacetate and *in situ* Claisen rearrangement to give the ester **465** in a single step.[184] Subsequent reduction to the alcohol **466** and conversion to the bromide **467** also proceeded smoothly and in high yield. Although the final step is well established as a method for the preparation of primary nitro compounds,[185] the ambident anion character of the nitrite anion can also lead to substantial quantities of nitrite ester. It should be noted that optimisation of the reaction conditions required the use of anhydrous sodium nitrate prepared by heating *in vacuo* at 130 ºC for 2 h in order to isolate the nitro derivative **460** in good yield (63%).[186]



465: 70%

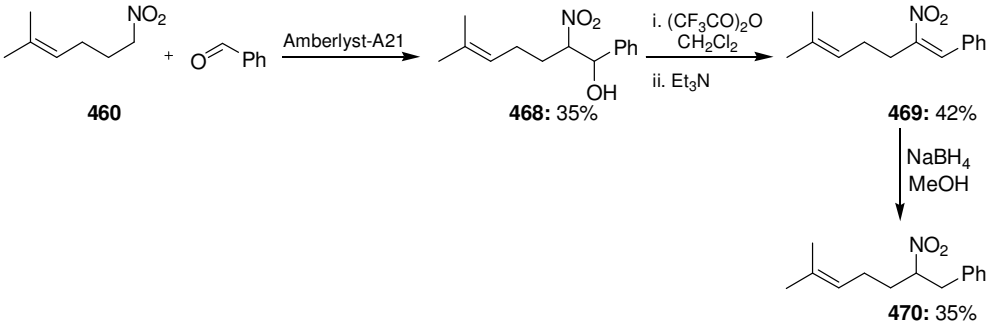
466: 80%

467: 62%

460: 63%

Scheme 135

With the appropriately functionalised primary nitroalkane **460** in hand, conversion to the desired Type I precursor then required a nitro aldol reaction and benzaldehyde was selected as an appropriate electrophile. A very wide variety of conditions has been reported for the Henry reaction including the use of organic or inorganic bases, protic or aprotic solvents and reactions without solvent.[187] The final reaction sequence is set out in Scheme 136.



460

468: 35%

469: 42%

470: 35%

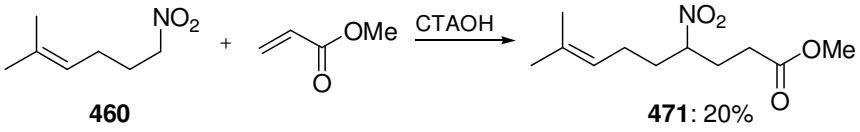
Scheme 136

For the case in hand, condensation in the presence of potassium *tert*-butoxide led to low yields of the β-nitroalcohol **468** and required 3.0 molar equivalents of the precious nitro derivative **460** whilst reactions using substrates adsorbed on basic alumina led to incomplete reactions and formation of both the nitro alcohol **468** and the nitroalkene **469**.[188] The use of Amberlyst A-21 resin in the absence of solvent,[189] eventually proved to be the most convenient method to produce the nitro alcohol **468** albeit in moderate yield.

Dehydration of the alcohol to the nitroalkene **469** was then achieved via a standard protocol involving acylation with trifluoroacetic anhydride and elimination using triethylamine,[190] and subsequent reduction of **469** using a large excess of sodium borohydride led to the target **470**.

Examination of the yields for the last four steps in the sequence highlights the fact that, although this classical strategy is often used, it is far from ideal, in terms of time, side reactions and overall efficiency. The formation of dimeric products derived from Michael addition of nitronates to nitroalkenes during the elimination and reduction steps has, for example, been noted.[191]

Advantage was also taken of a second classical reaction of nitronate anions, *viz*., the Michael addition of methyl acrylate, to produce a second substrate **471** containing additional ester functionality for a potential intramolecular Type I ene reaction to form a five membered ring (Scheme 137).

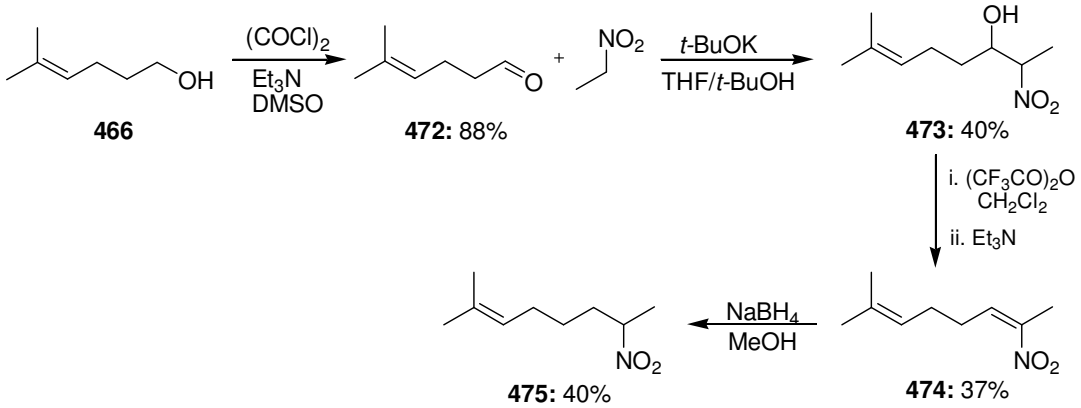


460 **471**: 20%

Scheme 137

The above conditions using sodium hydroxide (0.025 M) in the presence of cetyltrimethylammonium bromide (CTABr) as a cationic surfactant were selected following on from several attempts to use organic bases or alumina.[192] Since such conjugate additions usually employ a large excess of the nitro compound, an advantage of the chosen method was that it was possible to recover the precious starting nitro compound **460**.

A conceptually similar nitro aldol approach was also used for the assembly of a potential six membered ring Type I precursor **475** as shown in Scheme 138.



466 **472:** 88% **473:** 40%

474: 37% **475:** 40%

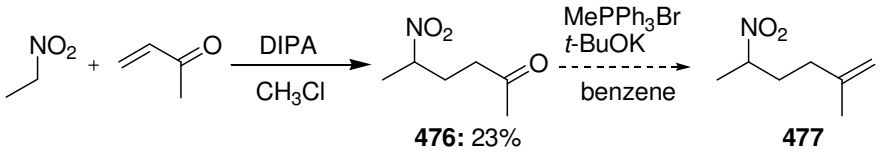
Scheme 138

In this instance, following on from Swern oxidation of the previously prepared alcohol **466** it was possible to use as excess of nitroethane in the subsequent Henry reaction,[190]

and the three remaining steps then furnished the nitro olefin **475** in comparable yields to the earlier sequence.

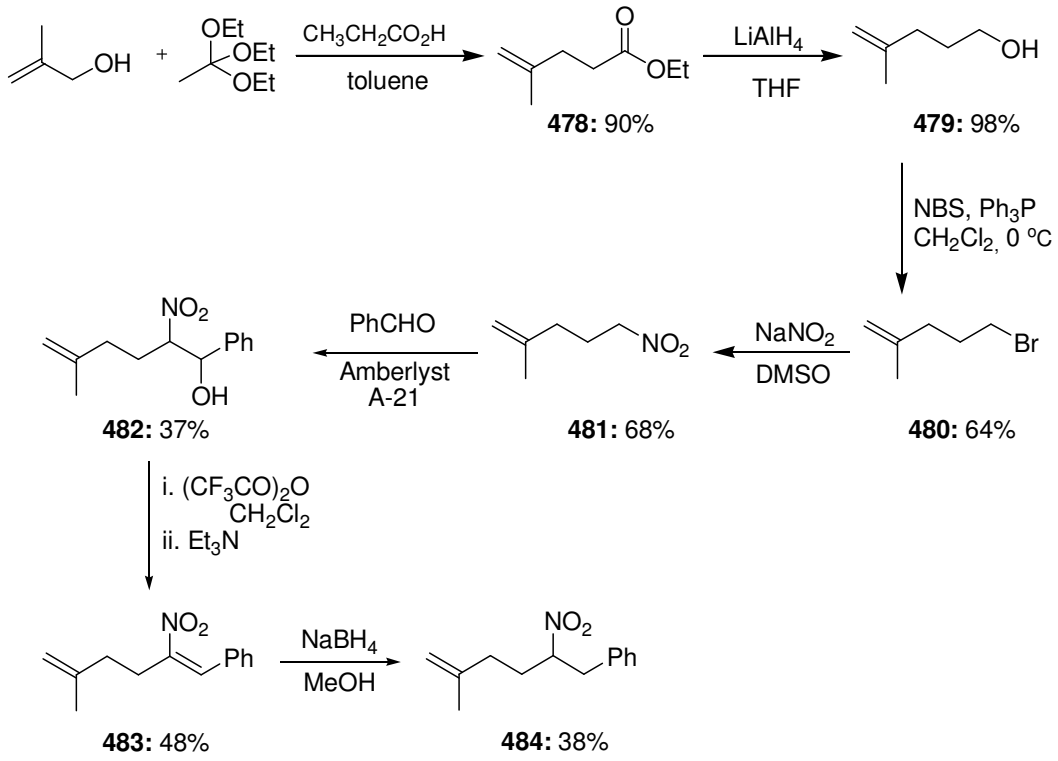
2.2.3.2 Acyclic Substrates for Type II Intramolecular Ene Reactions.

It was, of course, relevant to prepare the corresponding nitro alkenes for examination of the Type II ene reaction, and as in the earlier work on Type I substrates, initial efforts focussed on potentially short routes. An example of this approach is shown in Scheme 139, in which the Michael adduct **476** of 2-nitroethane with methyl vinyl ketone was treated with a greater than two molar excess of methylene triphenylphosphorane in the hope that "protection" via the nitronate anion would allow the Wittig reaction to succeed.



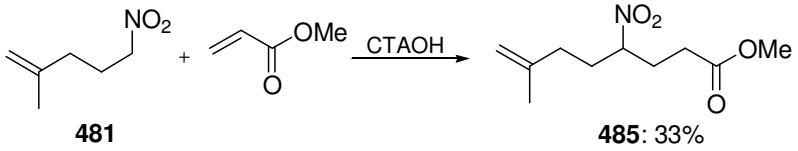
Scheme 139

In the event, only starting material was recovered from this reaction, and, in light of the progress being made in the synthesis of the Type I substrates at the time, a similar classical approach was taken. The entire route is set out in Scheme 140 and requires no further comment.



Scheme 140

Additionally, as in the earlier series, the intermediate nitro alkene **481** was used to advantage in a conjugate addition reaction with methyl acrylate (Scheme 141),



Scheme 141

As emphasised in Table 17, the five nitro alkene precursors were prepared in order to explore the relative efficiencies of the derived geminal acyloxy nitroso compounds as intermediates in both Type I intramolecular ene reactions for formation of five and six membered rings and in Type II six membered ring formation.

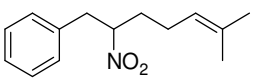
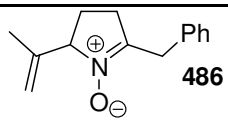
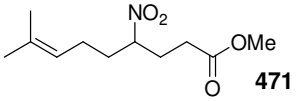
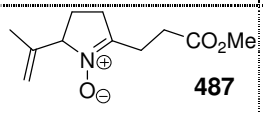
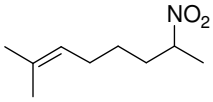
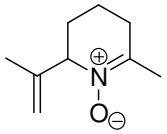
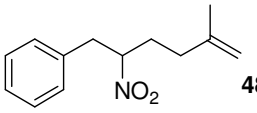
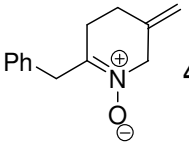
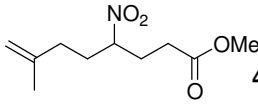
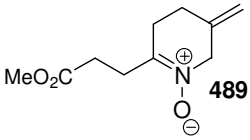
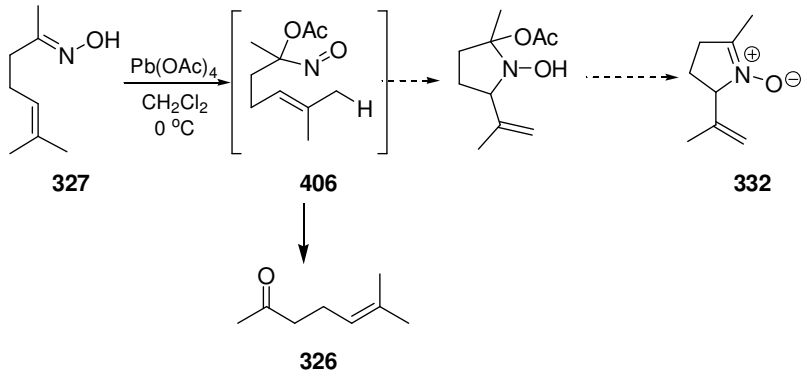
Entry	Substrate	Type		Desired Product	Results (Yield)	
		Class	Ring Size		Ketone	SM
1	 **470**	I	5	 **486**	40%	11%
2	 **471**	I	5	 **487**	0%	68%
3	 **475**	I	6	 **380**	53%	0%
4	 **484**	II	6	 **488**	59%	23%
5	 **485**	II	6	 **489**	0%	73%

Table 17

A series of parallel experiments was therefore conducted under the aforementioned Zefirov conditions using potassium *tert*-butoxide and acetic anhydride and the very disappointing results for each substrate are shown in Table 17. In essence, no hydroxylamines or nitrones were detected in any of those reactions and the results can be grouped into two categories, *viz.*, Entries 1, 3 and 4 in which the transformation of the nitro group to ketone functionality represents a very mild method for the classical Nef reaction, and Entries 2 and 5 in which unreacted starting material was largely recovered. Given the relative acidities for a proton adjacent to a nitro group (pKa~ 8-9 in H_2O) and to an ester ((pKa~ 11-13 in H_2O), the lack of reactivity for Entries 2 and 5 is very surprising and there seems to be no obvious mechanistic rationale involving participation of the ester in terms of deactivating any nitronate formed.

At this stage, in order to gain additional insight, it was also decided to use a classical method for generation of the geminal acetoxy nitroso congener of the chloro nitroso intermediate which had undergone a successful Type I intramolecular reaction. The oxime **327** was accordingly added to a solution of lead tetraacetate in dichloromethane and led to the appearance of a pale blue colouration. After 12 h of stirring however, the only product to be isolated once again, was the ketone **326** (Scheme 142).



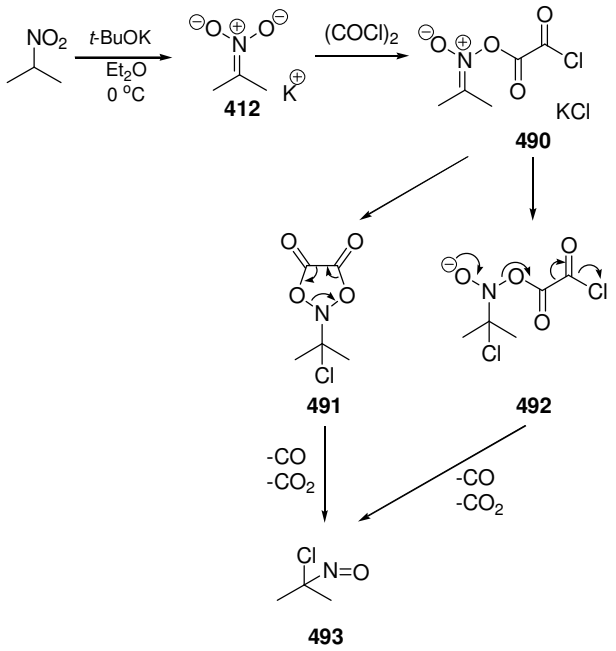
Scheme 142

The generation of carbonyl compounds from geminal acetoxy nitroso intermediates, either by their dimerisation and disproportionation (Scheme 116),[45c] or via hydrolysis with release of nitroxyl (HNO) has already been discussed.[168] In our earlier studies on the intermolecular ene reaction of geminal acyloxy nitroso compounds, reactions had been carried out on a relatively large scale and hence, these compounds appeared to been both isolable and relatively stable. In the work on the intramolecular variant however, reactions were, of necessity, carried out on a much smaller scale, and, with the benefit of hindsight, hydrolysis by water is the most probable explanation for the results in Table 17. Unfortunately, time constraints and the limited availability of substrates prevented further detailed studies in this area, especially since a parallel programme on the generation of an α-chloro nitroso compound from a nitro group was also underway at the same time.

2.3 A New Method for the Preparation of Geminal α-Chloro Nitroso Compounds from Nitro Derivatives.

As outlined in the first section of the present chapter, it was possible to demonstrate that Type I intramolecular ene reactions of α-chloro nitroso compounds generated *in situ* from oximes were possible. Nevertheless, the nagging possibility remained that the use of *tert*-butyl hypochlorite as an electrophilic halogenating agent could lead to competitive

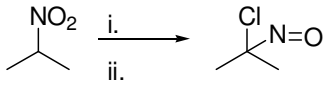
chloronium ion formation and hence to the chemistry observed by Grigg and co-workers.[146] With this thought in mind, and based on the facile *O*-acylation of the nitronate anions, we elected to attempt the hitherto unknown conversion of a nitro compound into the corresponding α-chloro nitroso derivative as outlined in Scheme 143.



Scheme 143

Thus, as illustrated for 2-nitropropane, initial monoacylation of the derived nitronate can lead to an intermediate **490** which can capture chloride anion to give **492** and then break down with evolution of carbon dioxide and carbon monoxide into 2-chloro-2-nitrosopropane **493** Alternatively, a second acylation step to form the cyclic intermediate **491** might then be followed by cycloreversion.

Irrespective of the mechanistic pathway, it was gratifying to note in a preliminary qualitative experiment that addition of oxalyl chloride to a solution of the potassium nitronate of 2-nitropropane was accompanied by gas evolution and appearance of a blue colouration, which did not however remain for very long. Further preliminary observations (Scheme 144) using a range of bases, as in the study of the acylation reaction, demonstrated that *n*-butyllithium and potassium *tert*-butoxide gave comparable results, whilst sodium hydride in the presence of a catalytic amount of imidazole produced a more complex mixture with a worse conversion.

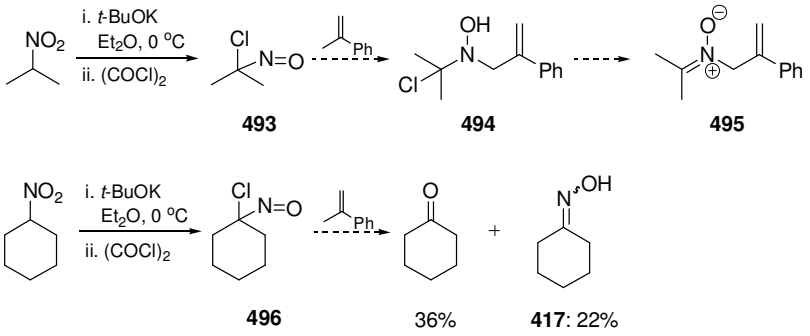


493

Entry	Reagents and Conditions
1	i. *t*-*B*uOK, Et_2O. ii. $(ClCO)_2$, 0 ^oC
2	i. BuLi, Et_2O. ii. $(ClCO)_2$, -78 to 0 ^oC
3	i. NaH, imidazole (10 mol %), Et_2O. ii. $(ClCO)_2$, rt

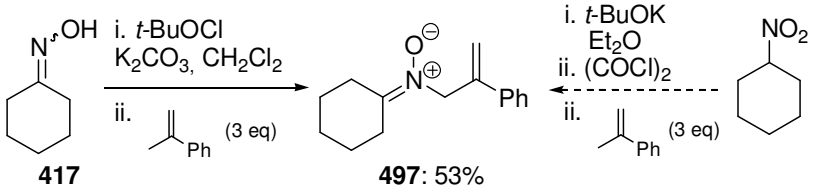
Scheme 144

Once again, however, as measured by the intensity and duration of the blue colour, the α-chloro nitroso compound seemed to be less stable than the geminal acyloxy congener, and decolouration appeared to occur above 0 ºC. An *in situ* intermolecular ene reaction was also attempted at this stage when the sequence was carried out in the presence of α-methylstyrene (Scheme 145).



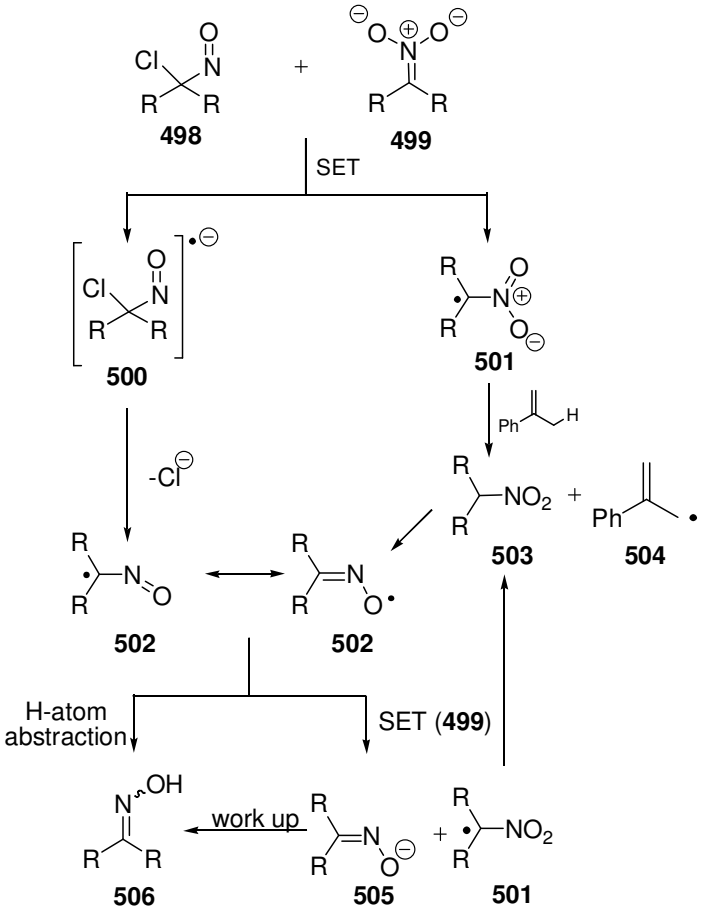
Scheme 145

To our surprise, these reactions did not afford the nitrone hydrochloride or the derived nitrone with 2-nitropropane leading to an intractable mixture and nitrocyclohexane furnishing a combination of the corresponding oxime and ketone. Similar results were obtained when α-methylstyrene was added to the crude oil of the α-chloro nitroso compounds. These observations were even more perplexing since, as noted earlier, we had confirmed the observations of de Boer and Schenk in our own laboratory (Scheme 146).[115]



Scheme 146

From a mechanistic standpoint, it was of interest to rationalise both the appearance of the typical blue colour of the geminal chloro nitroso compound as well as its apparent instability under the reaction conditions and the subsequent isolation of the oxime and the ketone. A possible explanation is set out in Scheme 147.



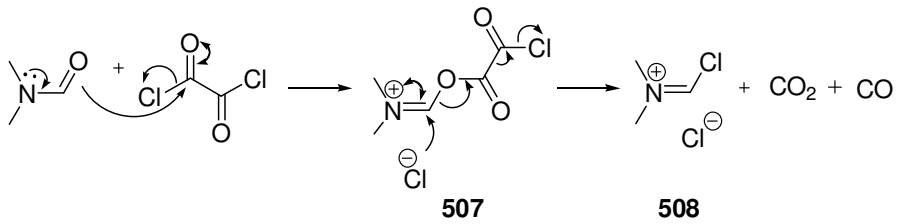
Scheme 147

Thus, if single electron transfer (SET) between the product α-chloro nitroso compound **498** and the substrate nitronate **499** was to occur, the resultant radical anion **500**, on loss of the chloride anion, would generate the low energy iminoxyl radical **502** which can either undergo hydrogen atom abstraction from α-methylstyrene or a second electron transfer from nitronate anion **499** followed by protic work up to give the observed oxime **506**.

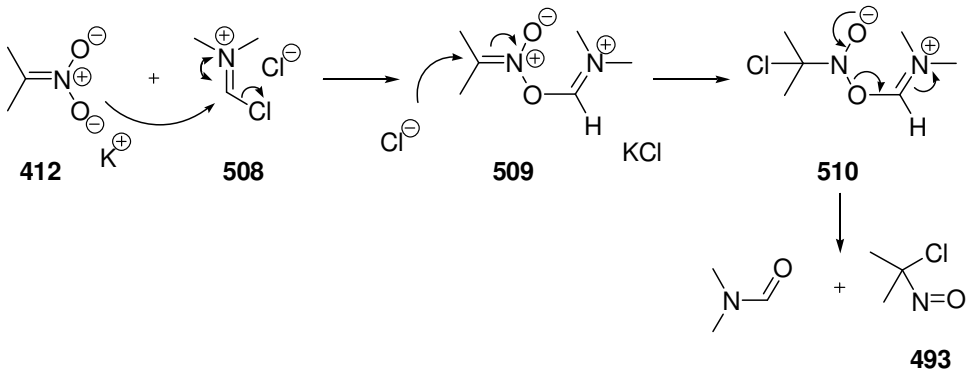
A logical consequence of the above hypothesis is that the contact time between the nitronate salt and the product chloro nitroso compound should be minimised, and, towards this end, an experimental protocol involving a rapid single addition of oxalyl chloride to the nitronate was proposed. In addition, as in the conversion of acids to acid chlorides, a

catalytic quantity of dimethylformamide was added to the nitronate. This may function through the standard formation of the Vilsmeier salt **508** as shown in Scheme 148.

Step 1: Formation of Vilsmeier salt **508**

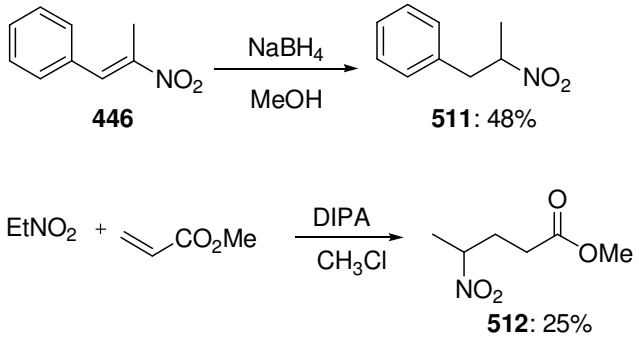


Step 2: Reduction with nitronate anion



Scheme 148

It was accordingly of interest to examine the scope of this reaction, and, towards this end, a set of simple nitroso compounds was investigated. These included 2-nitropropane, nitrocyclopentane and nitrocyclohexane all of which were commercially available together with (1-methoxy-2-nitro-propyl)benzene **448** and 5-nitro-hexan-2-one **476** both of which had been prepared earlier. Two additional substrates **511** and **512** were also prepared using routine methods as summarised in Scheme 149.



Scheme 149

The results for these seven substrates are shown in Table 18. It should be noted that the yields reported are based on the use of 1,3,5-trimethoxybenzene as an NMR standard,

since it is generally accepted that attempted purification of geminal chloro nitroso compounds by chromatography leads to decomposition whilst larger scale work involving distillation can be hazardous.

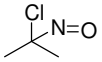
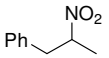
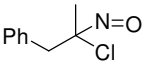
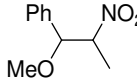
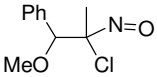
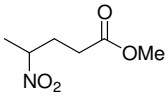
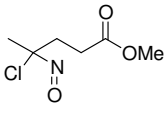
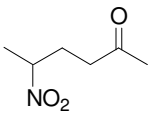
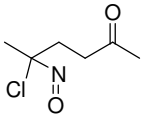
Entry	Substrate	Product	Yield	Starting material
1		 **493**	16%	8%
2		 **513**	24%	8%
3		 **496**	40%	20%
4	 **511**	 **514**	26%	0%
5	 **448**	 **515**	0%[A,B]	33%
6	 **512**	 **516**	28%	19%[A]
7	 **476**	 **517**	0% [A, B C]	21%

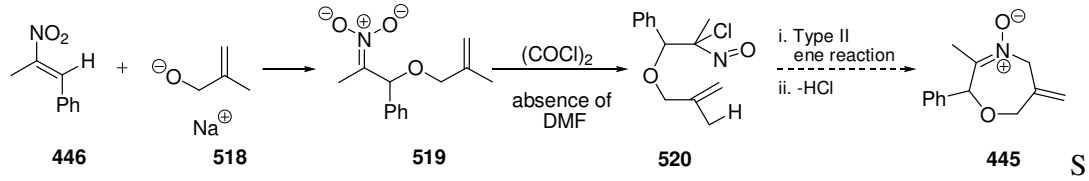
Table 18: Reaction Conditions: i. *t*-BuOK (1 eq), DMF cat, Et_2O, 0 ºC, ii. $(COCl)_2$ (1 eq). Due to the difficulty of the purification of these products, yields were measured by proton NMR spectra using an internal reference (1,3,5-trimethoxybenzene, 10 mol %). **A**: Very pale blue colouration was initially observed. **B:** complex mixture. Substrate **448** gave more than 6 products by proton NMR spectroscopy. **C:** 5-(Hydroxyimino)hexan-2-one was recovered in 64% yield. When reaction was attempted without the presence of DMF, products **493**, **513** and **496** were obtained in 8%, 10% and 2% yields respectively.

In the first instance, for the commercial substrates (Entries 1-3) it was encouraging to note that qualitative comparative studies with and without the addition of dimethylformamide as a catalyst indicated that addition of the latter led to a higher overall conversion, improved yields and avoidance of the troublesome oxime formation in most cases. The relative instability of the products was clearly demonstrated by the gradual disappearance of the blue colour during work up and characterisation, particularly in the cases of 2-chloro-2-nitrosopropane **493** (Entry 1) and **515** (Entry 5). Overall, for these simple cyclic and acylic substrates (Entries 1-4), albeit that the estimated yields were poor to moderate, a proof of concept had been achieved. It was also pleasing to note that ester functionality

was tolerated (Entry 6). Surprisingly however for 5-nitrohexan-2-one **476**, oxime formation (64%) was the dominant reaction (Entry 7), whilst, once again (1-methoxy-2-nitropropyl)benzene **448** (Entry 5) afforded no detectable nitroso product, even although a pale blue colouration was observed in both cases.

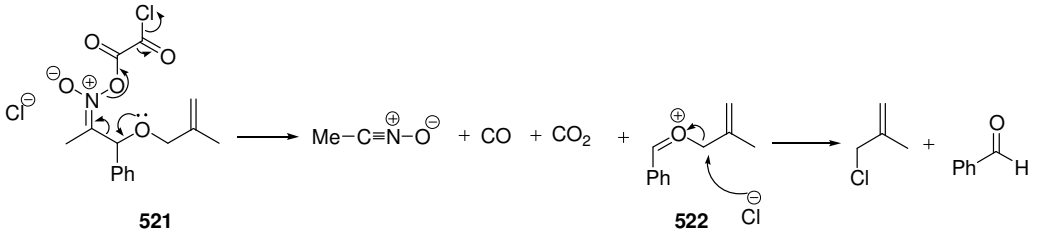
In spite of the fact that further optimisation of this new reaction is clearly required, time constraints coupled with the desire to demonstrate intramolecular ene reactions emanating from acyclic nitro compounds led us to make a final effort in this area.

The first set of reactions involved the simple idea that conjugate addition of the sodium alkoxide of methallyl alcohol would lead directly to the nitronate for subsequent reaction with oxalyl chloride in a one pot sequence (Scheme 150). By "analogy" with the carbonyl ene reaction, formation of a seven membered ring in a Type II intramolecular ene reaction was considered to be favourable.



Scheme 150

Unfortunately, the α-alkoxy nitronate intermediate **519** on treatment with oxalyl chloride (in the absence of DMF) produced a complex mixture from which, once again, benzaldehyde was the only isolable component (18%). This observation reinforces the idea that fragmentation to liberate a nitrile oxide may be occurring (Scheme 151).

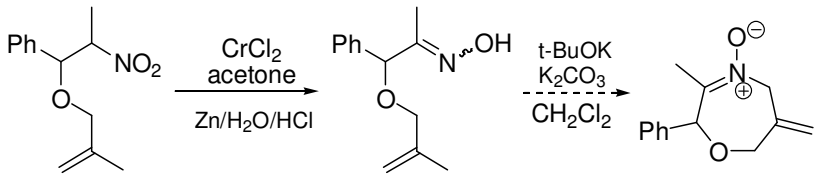


Scheme 151

Advantage was also taken of the α-allyloxy nitro compound **442** to establish correlations and to attempt a further ene reaction.

Thus, as shown in Scheme 152, chromous chloride reduction proceeded in very good yield to afford the oxime **523**.[193] Comparison of the proton NMR spectrum with the oxime

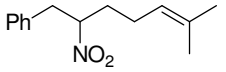
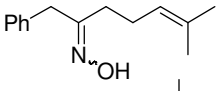
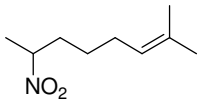
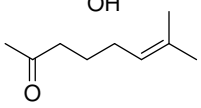
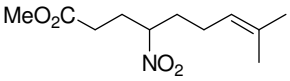
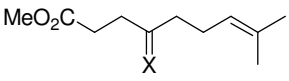
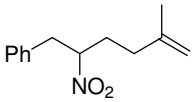
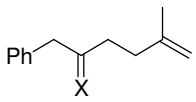
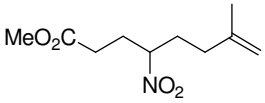
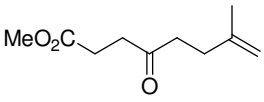
which had been isolated from the attempted α-acetoxy niroso ene reaction using the same nitronate (Figure 15) indicated that the alternative geometrical isomer had probably been formed. The opportunity of examining this substrate in an intramolecular Type II reaction under the conditions developed earlier was, of course, taken. Unfortunately, however, even although some potentially interesting signals were observed in the proton NMR spectrum of the crude reaction mixture, problems of irreproducibility and degradation during chromatography precluded further work (Scheme 152).



442 **523**: 73% **445**

Scheme 152

Finally, albeit that only very limited quantities of material were available, a last effort was made to establish the validity of the use of the nitronate anion as a precursor for the geminal chloro nitroso group in intramolecular ene reactions. The reactions, which were screened on a very small scale are summarised in Table 19, together with the disappointing outcomes.

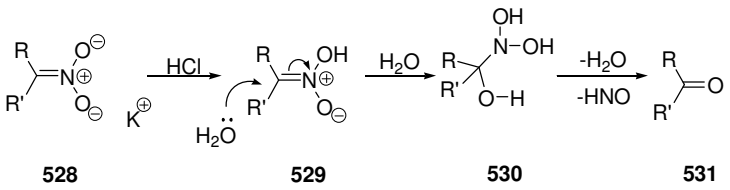
Entry	Substrate		Product		
1		**470**		**524**	40%
2		**475**		**376**	69%
3		**471**		**525**	X= O 22% X= NOH 16% (40% recovered SM)
4		**484**		**526**	X= O 10% X= NOH 20% (40% recovered SM)
5		**485**		**527**	22%

Reagents and conditions: i. *t*-BuOK (1.0 eq), Et_2O ii. $(COCl)_2$ (1.0 eq), DMF_{cat}

Table 19

The formation of the oxime in Entries 1, 3 and 4 can be rationalised by the previously outlined electron transfer mechanism (Scheme 147). The formation of ketonic products in Entries 2, 3, 4 and 5 most probably derives, unfortunately, from the presence of

adventitious water which, on reaction with oxalyl chloride could lead to generation of hydrogen chloride. As shown in Scheme 153 protonation of the nitronate anion **528** on oxygen followed by attack of water would then lead to the ketonic product **531** in a classical Nef reaction.



Scheme 153

These observations were particularly frustrating since, in the case of Entry 2, generation of the chloro nitroso intermediate from the oxime (Section 2.1) had already led in very good yield to the desired nitrone product. Furthermore, with the benefit of hindsight, the use of two molar equivalents of potassium *tert*-butoxide could have been advantageous in terms of scavenging the hydrogen chloride liberated from any nitrone hydrochloride formed.

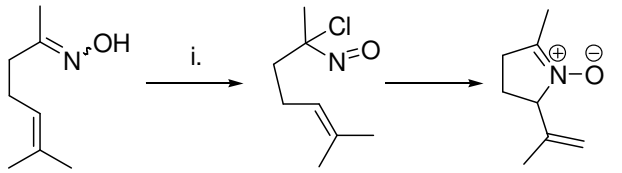
At this stage, even although many encouraging indications were present and the desired tandem sequence appeared to be tantalisingly close, time constraints effectively precluded further study.

CHAPTER 3 – SUMMARY, CONCLUSIONS AND PERSPECTIVE

The ultimate objective of the present thesis was to demonstrate the power of a novel tandem sequence which featured the use of a geminally functionalised nitroso compound in an intramolecular ene reaction to yield an adduct which, on elimination, would reveal a nitrone for subsequent participation in an intramolecular 1,3-dipolar cycloaddition step. Since ene reactions of this type were completely unknown, this key reaction became the primary focus of our studies.

In the first instance, α-chloro nitroso compounds were selected for examination, and, since this class of compounds is most often generated from oximes, a range of suitably constituted oximes with appropriately functionalised unsaturated side chains was prepared. After considerable experimentation, *tert*-butyl hypochlorite was found to be an electrophilic halogen atom source which preferred to react with the oxime functionality rather than the π cloud of the alkene, and conditions using anhydrous potassium carbonate as heterogeneous base were developed. These allowed the first examples of the Type I intramolecular ene reaction for the construction of both five and six membered rings to be achieved, with the added bonus that the potassium carbonate acted as a proton scavenger to yield the desired nitrones in a single operation (Scheme 154). However, efforts to extend the number of examples of this class indicated that the reaction could be both capricious at times and also substrate dependent.

Type I



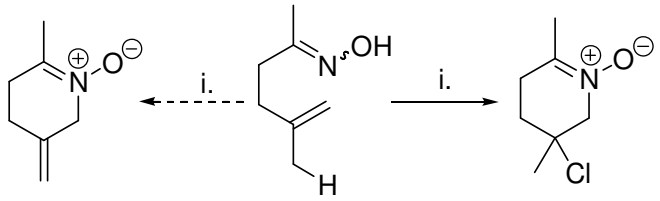
327 **342** **332**: 60%

370 **380**: 65%

i. *t*-BuOCl (1.1 eq), K_2CO_3 (5.0 eq), 0 °C, CH_2Cl_2

Scheme 154

The attempted demonstration of a Type II intramolecular ene reaction using the same method however produced a completely unexpected result inasmuch as the product was not the anticipated alkene **388** but the tertiary chloride **391** (Scheme 155).



388 **385** **391**: 60%

i. *t*-BuOCl (1.1 eq), K_2CO_3 (5.0 eq), 0 °C, CH_2Cl_2

Scheme 155

This observation called into question both the mechanism of the ene reaction itself as well as the mechanism of the formation of the germinal chloro nitroso intermediate, and for these reasons it was decided to investigate the generation of α-acyloxy nitroso compounds from nitronates.

In the first instance, a series of simple α-acyloxy nitroso compounds was prepared using the Zefirov method in order to assess their relative stabilities,[166] and, since the intermolecular variant of the ene reaction with the class of compound was unknown, several reactions were attempted with α-methylstyrene as an ene component which had already been demonstrated to be very successful with α-chloro nitroso compounds.[115] These however were uniformly unsuccessful.

Given however that the intramolecular variant of a simple unfunctionalised tertiary nitroso compound had been demonstrated for Type II reactions by Motherwell and Roberts,[112] a series of appropriate nitro precursors were prepared, albeit using relatively long and inefficient traditional methods. Once again however, in spite of the fact that substrates were prepared for both Type I and Type II reactions leading to both five and six membered rings, no detectable ene products were formed. With the benefit of hindsight, and given that the intramolecular reactions were carried out on a relatively small scale, it is possible that the hydrolytic sensitivity of these intermediates towards release of nitroxyl (HNO) was not sufficiently appreciated.[168]

As a consequence of these misadventures, efforts were then made to discover a new reaction for the conversion of nitronate anions into α-chloro nitroso compounds since the work on oximes as precursors had been very encouraging.

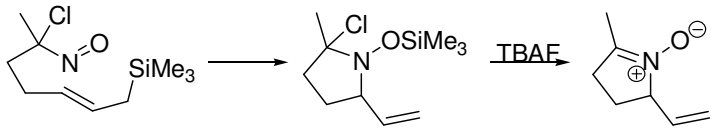
At this stage, in spite of some secondary reactions possibly involving single electron transfer, the reactions using oxalyl chloride in the presence of DMF looked promising and proof of concept has been established. Unfortunately, once again small scale, trial experiments at late stage involving the intramolecular ene precursors were compromised both by unwanted side reactions and possibly by the presence of adventitious water.

Overall, throughout the programme of research, our overall objective of finding a generally applicable approach for the key nitroso ene reactions always appeared to be just within reach, but always elusive. Nevertheless progress has been made, and, in the hope that further work will lead to success, some suggestions for future study are indicated below.

Thus, in contrast to the simplistic analogy drawn with the aldehyde carbonyl group, it is clear, from a practical standpoint, that formation of even a catalytic amount of hydrogen chloride or adventitious water can be deleterious, and that the "rich" chemistry of the nitroso group can intervene. For this reason very rigorously anhydrous conditions must be used, particularly in relation to nitronate anion chemistry.

With respect to α-acyloxy nitroso compounds, the selection of an appropriate acyl group which conserves the balance between stability towards hydrolysis with sufficient reactivity still remains to be found, and in all of the ene reactions studied opportunities exist for the addition of a Lewis acid after formation of the geminal nitroso intermediate which may allow for faster reactions at lower temperature.

Another ene variant which could be attempted is based on the Sakurai reaction,[194] and could well avoid problematic issues with protic acid formation. Thus, as shown in Scheme 156 for a simple example the selection of an allyl silane as the ene component would lead to a protected form of the α-chloro hydroxylamine **533** and this could then be released to the nitrone **534** in a more controlled fashion.

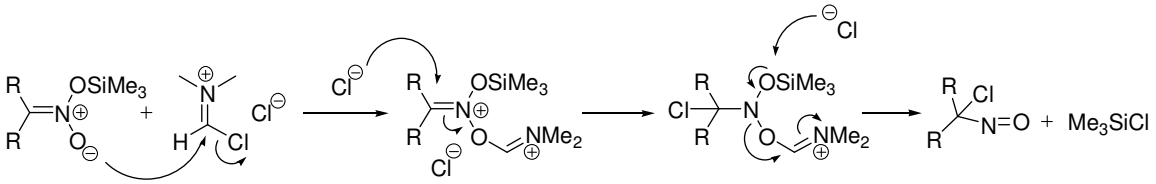


532 **533** **534**

Scheme 156

For the new reaction leading to α-chloro nitroso compounds from nitronates, further optimisation work might include addition of a soluble lithium nitronate to a solution of oxalyl chloride containing DMF. This inverse addition might hopefully avoid electron transfer. The use of the preformed Vilsmeier reagent ($ClCH=N^+(CH_3)_2\ Cl^-$) might also prove beneficial.

Silicon chemistry may also prove advantegous through the use of silyl nitronates as indicated in Scheme 157.[178C]



Scheme 157

As always in any research programme, understanding the problems leads to new suggestions for overcoming them.

CHAPTER 4 – GENERAL EXPERIMENTAL PROCEDURES

1. Solvents and Reagents.

All reactions in non-aqueous solution were performed under a nitrogen atmosphere, using dried glassware, which was cooled under a flow of nitrogen before use. Anhydrous acetone was distilled prior to use while DMSO was distilled and stored over 4Å molecular sieves. Et_2O, THF, CH_2Cl_2, MeCN and toluene were purified from Anhydrous Engineering ® apparatus using double alumina or alumina/copper catalyst columns. MeOH was distilled from calcium hydride. Triethylamine and diisopropylamine were distilled from potassium hydroxide. 2-Methyl-2-aminopropane was distilled prior to use. Petroleum ether (PE) was the fraction of light petroleum ether boiling between 40-60 ºC.

N-Bromosuccinimide (30 g) was dissolved rapidly in boiling water (300 mL) and filtered through a fluted filter paper into a pre-cooled flask immersed and left for 2 h at 0 ºC. The crystals were filtered, washed thoroughly with ice-cold water (100 mL) before drying under high vacuum. Acetic anhydride was purified by fractional distillation (b.p. 138 ºC). Sodium nitrite was dried for 2 h at 130 ºC under high vacuum.[195].

2. Data Collection

Infrared spectra (IR) were carried out on a Perkin-Elmer 1605 FT-IR spectrometer as thin films with a ZnSe crystal or on a Perkin Elmer Spectrum 100 FT-IR spectrometer. Absorption maxima are reported in wave numbers (cm^{-1}). Only selected absorbances are reported and the abbreviations used to denote peak intensity are as follows: w = weak, s = strong.

Proton magnetic resonance (^1H NMR) spectra were recorded at 300 MHz on a Bruker AMX300 spectrometer, at 400 MHz on a Bruker AMX400 spectrometer, at 500 MHz on a Bruker Avance 500 spectrometer or at 600 MHz on a Bruker Avance 600 spectrometer and reported as follows: chemical shifts δ (ppm) (multiplicity, number of protons, coupling constant in J (Hz), assignment). The coupling constants are quoted to the nearest 0.1 Hz using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad or a combination of these. The residual protic solvent $CHCl_3$ (δ =7.26 ppm, s) was used as an internal reference.

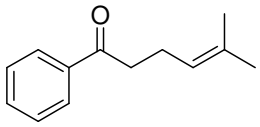
Carbon magnetic resonance (^{13}C NMR) spectra were recorded at 75 MHz on a Bruker AMX300 spectrometer, at 100 MHz on a Bruker AMX400, at 125 MHz on a Bruker Avance 500 spectrometer or at 150 MHz on a Bruker Avance 600 spectrometer, and reported as follows: chemical shifts δ (ppm) (type of carbon; C, CH, CH_2, CH_3). The central line of $CHCl_3$ (δ = 77.0 ppm, t) was used as internal reference and chemical shifts are reported to the nearest 0.1 ppm.

Mass spectra and accurate mass measurements were recorded on a Micromass 70-SE Magnetic Sector spectrometer (VG ZAB) at the University College London's Chemistry Department by electron impact (EI), chemical ionization (CI) or atmospheric pressure chemical ionisation [ECPI (negative mode)].

Melting points were performed on a Reichert hot-stage apparatus and are uncorrected.

Purification was carried out either by distillation or by column chromatography using silica gel BDH (40-60 μm). Analytical thin layer chromatography (TLC) was carried out using Merk Kieselgel aluminium-backed plates coated with silica gel 60 F_{254}. Visualisation was afforded by using ultraviolet light (254 nm) and basic potassium permanganate or acidic ammonium molybdate (IV) dips.

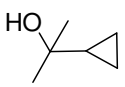
5-Methyl-1-phenylhex-4-en-1-one 365.[196]



$C_{13}H_{16}O$
Mol. Wt.: 188.26

A solution of ethyl benzoacetate (3.87 g, 26.0 mmol), freshly distilled acetone (65 mL) and 1-bromo-3-methylbut-2-ene (4.17 g, 28.0 mmol) was heated at reflux for 10 h in the presence of anhydrous potassium carbonate (4.35 g, 31.5 mmol). After cooling, the solids were removed by filtration and the residue was washed with acetone (2 × 30 mL). The combined filtrates were evaporated under reduced pressure to give 2-benzoacetyl-5-methylhex-4-enoic acid ethyl ester as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, 2H, *J*=7.2 Hz, H_{Ar}), 7.57 (t, 1H, *J*=7.2 Hz, H_{Ar}), 7.47 (t, 2H, *J*=7.2 Hz, H_{Ar}), 5.11-5.09 (m, 1H, CH_2CHC), 4.29 (t, 1H, *J*=7.2 Hz, OCC*H*), 4.13 (q, 2H, *J*=7.1 Hz, CH_2CO), 2.72-2.65 (m, 2H, $CHCH_2CH$), 1.65 (s, 3H, CCH_3), 1.62 (s, 3H, CCH_3), 1.16 (t, 3H, *J*=7.1 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.0 (C), 169.8 (C), 136.3 (C), 134.6 (C), 133.4 (CH), 128.7 (2 CH), 128.6 (2 CH), 120.1 (CH), 61.3 (CH_2), 54.5 (CH), 27.7 (CH_2), 25.7 (CH_3), 17.8 (CH_3), 14.0 (CH_3). The orange oil was then dissolved in a mixture of ethanol (50 mL) and 10% aqueous sodium hydroxide solution (80 mL), and heated at reflux for 3 h. After cooling, the mixture was extracted with Et_2O (2 × 30 mL) and the combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by distillation under reduced pressure (b.p. 143-147 ºC / 15 mmHg) gave a pale yellow oil (3.47 g, 71%). R_f 0.53 in CH_2Cl_2, IR (film): ν_{max} 3062, 2968, 2914, 1684 (s), 1598, 1448, 1265 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98-7.94 (m, 2H, H_{Ar}), 7.56-7.52 (m, 1H, H_{Ar}), 7.48-7.43 (m, 2H, H_{Ar}), 5.17 (tt, 1H, *J*=7.2 and 1.3 Hz, C*H*), 3.00 (t, *J*=7.5 Hz, 2H, $OCCH_2$), 2.42 (q, 2H, *J*=7.5 Hz, CH_2CH), 1.69 (s, 3H, CCH_3), 1.63 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.2 (C), 137.1 (C), 133.0 (CH), 132.9 (C), 128.6 (2 CH), 128.1 (2 CH), 123.0 (CH), 38.8 (CH_2), 25.8 (CH_3), 23.0 (CH_2), 17.8 (CH_3).

2-Cyclopropylpropan-2-ol 375.[160]

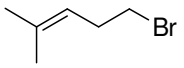


$C_6H_{12}O$
Mol. Wt.: 100.16

A solution of methyl iodide (21.0 g, 0.25 mol) in Et_2O (10.0 mL) was added dropwise to a stirred mixture of magnesium turnings (2.4 g, 0.25 mol) and Et_2O (28.5 mL) at 0 ºC. When addition was complete, the reaction mixture was allowed to warm up to room temperature and stirred for a further 1 h. The freshly prepared Grignard solution was

cooled in an ice bath and a solution of cyclopropyl methyl ketone (9.5 g, 0.11 mol) in Et_2O (47.5 mL) was added dropwise over 20 min. The ice bath was removed and the mixture stirred overnight at room temperature. After re-cooling to 0 ºC, a saturated aqueous solution of ammonium chloride (40 mL) was gradually added and the resulting mixture stirred for a further 15 min. The almost colourless organic phase was separated, and the aqueous phase extracted with Et_2O (3 × 30 mL). The organic phases were combined, washed with water (30 mL), brine (30 mL) and then dried over $MgSO_4$. After filtration, volatiles were removed under reduced pressure to give a pale yellow oil (9.3 g, 85%), which was used without further purification. IR (film): ν_{max} 3955, 3400, 1648, 1465, 1380, 1155, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.87 (s, 6H, 2 C*H*$_3$), 0.98-0.93 (m, 1H, C*H*), 0.39-0.30 (m, 4H, 2 C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 69.8 (C), 28.5 (2 CH_3), 22.4 (CH), 0.9 (2 CH_2); MS (CI) m/z (%): 99 (10, $(M-H)^+$).

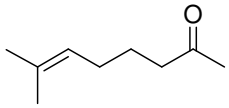
5-Bromo-2-methylpent-2-ene 374.[159]



$C_6H_{11}Br$
Mol. Wt.: 163.05

An aqueous solution of hydrobromic acid, 48% (22 mL, 0.18 mol), was added dropwise over 40 min to 2-cyclopropylpropan-2-ol **375** (11 g, 0.11 mol) with vigorous stirring. The resulting mixture was stirred for an additional 2 h to give a clear organic layer and an turbid aqueous phase. The reaction was monitored by TLC until completion (R_f 0.82 CH_2Cl_2). Water (20 mL) and Et_2O (20 mL) were added and the mixture was stirred until it clarified. The pale yellow organic phase was separated, and the aqueous phase extracted with Et_2O (3 × 30 mL). The organic phases were combined, washed sequentially with water (20 mL), aqueous solution of sodium sulfite (20 mL of a 2% solution), water (20 mL), and brine (20 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated under vacuum. Distillation at reduced pressure (b.p. 52 ºC / 18 mmHg) gave the bromide as a pale yellow oil (12.4 g, 69%). IR (film): ν_{max} 2967, 2920, 1673, 1442, 1377, 1265 (s), 1205, 1096 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.15-5.13 (m, 1H, C*H*), 3.35 (t, 2H, *J*=7.4 Hz, C*H*$_2$Br), 2.57 (pseudo q, 2H, *J*=7.3 Hz, CHC*H*$_2$), 1.73 (s, 3H, C*H*$_3$), 1.64 (s, 3H, C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ 135.0 (C), 120.9 (CH), 22.0 (CH_2), 31.8 (CH_2), 25.7 (CH_3), 17.9 (CH_3); Ms (EI) m/z (%): 163 (10, M^+); HRMS: M^+, obtained 160.99599 $C_6H_{11}Br$ requires 160.99658.

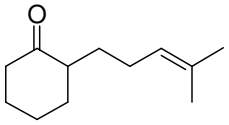
7-Methyloct-6-en-2-one 376.[158]



$C_9H_{16}O$
Mol. Wt.: 140.22

A mixture of ethyl acetoacetate (2.00 g, 16.0 mmol), 5-bromo-2-methylpent-2-ene **374** (2.38 g, 14.6 mmol), dry acetone (40 mL) and anhydrous potassium carbonate (2.42 g, 17.5 mmol) was heated at reflux for 10 h. After cooling, the volatiles were removed under reduced pressure. An aqueous solution of 10% sodium hydroxide (35 mL) and ethanol (30 mL) were added to the residue, which was then heated at reflux for 3 h. After cooling, the mixture was extracted with Et_2O (2 × 30 mL). The combined ethereal extracts were dried over $MgSO_4$, filtered and volatiles were removed under vacuum. The ketone **376** was obtained as a pale yellow oil (1.15 g, 57%) after purification by flash chromatography (PE/Et_2O 2:1, R_f 0.42). IR (film): ν_{max} 2988, 1700, 1650, 1420, 1360, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.08-5.03 (m, 1H, C*H*), 2,39 (t, 2H, *J*=7.5 Hz, CH_2CO), 2.10 (s, 3H, OCCH_3), 1.96 (q, 2H, *J*=7.2 Hz, CHCH_2), 1.66 (s, 3H, CCH_3), 1.60-1.54 (m, 2H, $CH_2CH_2CH_2$), 1.56 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.2 (C), 132.3 (C), 123.7 (CH), 43.1 (CH_2), 29.8 (CH_3), 27.3 (CH_2), 25.7 (CH_3), 23.9 (CH_2), 17.6 (CH_3).

2-(4-Methylpent-3-enyl)cyclohexanone 378.

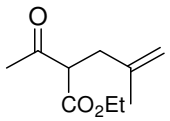


$C_{12}H_{20}O$
Mol. Wt.: 180.28

A mixture of cyclohexanone (5.0 g, 51 mol), pyrrolidine (8.5 mL, 102 mol) and *p*-toluenesulfonic acid monohydrate (15 mg, 0.8 mmol) in benzene (50 mL) was heated at reflux for 24 h using a Dean-Stark water removal apparatus.[161] After evaporation of the volatiles under vacuum, the residue was taken up in a small amount of dry benzene (10 mL) and added to a solution of 5-bromo-2-methylpent-2-ene **374** (5.4 g, 32 mmol) in *tert*-butanol (25 mL), and heated at reflux for 12 h. After cooling, water (20 mL) was added, and the resulting mixture heated to reflux for 3 h. After cooling, the product was extracted with ether (3 × 25 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and the volatiles were removed under vacuum to give a residue which was purified by flash chromatography (PE/Et_2O 2:1, R_f 0.57 in CH_2Cl_2) to give a colourless oil (2.02 g, 35%). IR (film): ν_{max} 2937, 2862, 2253, 1705, 1448, 1377, 906 (s), 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.10-5.01 (m, 1H, C*H*C(CH_3)$_2$), 2,41-2.26 (m, 3H, C*H*COCH_2),

2.01-1.96 (m, 4H, CHCH_2CH_2CH), 1.86-1.81 (m, 2H, CH_2), 1.68 (s, 3H, CCH_3), 1.58 (s, 3H, CCH_3), 1.23-1.19 (m, 4H, 2 CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.5 (C), 131.9 (C), 124.2 (CH), 50.0 (CH), 42.0 (CH_2) 33.9 (CH_2), 28.0 (CH_2), 25.7 (CH_3), 25.6 (CH_2), 25.5 (CH_2), 24.8 (CH_2), 17.6 (CH_3); Ms (EI) m/z (%): 180 (79, M^+); HRMS: M^+, obtained 180.15103 $C_{12}H_{20}O$ requires 180.15087.

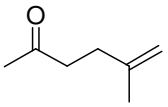
2-Acetyl-4-methylpent-4-enoic acid ethyl ester.[197]



$C_{10}H_{16}O_3$
Mol. Wt.: 184.23

Ethyl acetoacetate (5.00 g, 38.5 mmol) was added to a stirred solution of sodium ethoxide (prepared from metallic sodium (0.88 g, 38.5 mmol, cut into pieces and added to ethanol (24 mL)), at room temperature. After stirring for 1 h 3-chloro-2-methyl-1-propene (3.80 mL, 38.5 mmol) was added over a period of 30 min. The mixture was stirred overnight and heated at reflux for an additional 1 h. After cooling, water (25 mL) was added and the mixture was extracted with Et_2O (3 × 15 mL). The combined ether extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give an orange oil, which was used without further purification (5.67 g, 80%). IR (film): ν_{max} 3080, 2982, 2938, 1739, 1715 (s), 1650, 1243, 1147 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.69 (s, 1H, C*H*H), 4.60 (s, 1H, CH*H*), 4.18 (q, 2H, *J*=7.2 Hz, OCH_2CH$_3$) 3.66 (t, 1H, *J*=7.6 Hz, C*H*), 2.56 (d, 2H, *J*=7.6 Hz, CH_2), 2.23 (s, 3H, OCCH_3), 1.73 (s, 3H, CCH_3), 1.28 (t, 3H, *J*=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6 (C), 169.4 (C), 141.8 (C), 112.2 (CH_2), 61.3 (CH_2), 58.2 (CH) 35.8 (CH_2), 28.8 (CH_3), 22.3 (CH_3), 14.0 (CH_3).

5-Methylhex-5-en-2-one 390.[163]

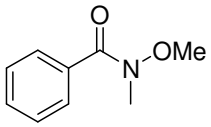


$C_7H_{12}O$
Mol. Wt.: 112.17

2-Acetyl-4-methylpent-4-enoic acid ethyl ester (5.67 g, 30.8 mmol) was heated in aqueous sodium hydroxide (3.60 g sodium hydroxide in 40 mL of deionised water) for 2 h at reflux. When the reaction was complete by TLC (R_f 0.46 in CH_2Cl_2), the cooled mixture was extracted with Et_2O (3 × 30 mL). The combined ether extracts were dried over $MgSO_4$, filtered and concentrated to give a residue that was distilled under reduced

pressure (b.p. 62-65 ºC / 18 mmHg) to give the desired ketone as a pale yellow oil (2.73 g, 79%). IR (film): ν_{max} 3354, 2945, 1708, 1647, 1363, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.73 (s, 1H, C*H*H), 4.65 (s, 1H, CH*H*), 2.58 (t, *J*=7.6 Hz, 2H, COCH_2), 2.28 (t, *J*=7.6 Hz, 2H, CH_2CCH$_3$), 2.16 (s, 3H, OCCH_3), 1.73 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.5 (C), 144.5 (C), 110.2 (CH_2), 41.9 (CH_2), 31.5 (CH_2), 29.9 (CH_3), 22.6 (CH_3); MS (EI) m/z (%): 112 (38, M^+).

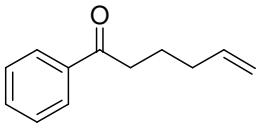
_N_-Methoxy-_N_-methylbenzamide 397.[164]



$C_9H_{11}NO_2$
Mol. Wt.: 165.19

Pyridine (6.40 mL, 80 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (1.55 g, 16 mmol) were added to a stirred solution of benzoyl chloride (2.00 g, 16 mmol) in CH_2Cl_2 (40 mL). After stirring overnight at room temperature, the reaction mixture was diluted with CH_2Cl_2 (60 mL), washed sequentially with 1N aqueous hydrochloric acid (60 mL), saturated aqueous sodium bicarbonate solution (60 mL) and brine (60 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the desired product as a colourless oil (2.36 g, 90%), which was used without further purification. IR (film): ν_{max} 3064, 3009, 2973, 2958, 1638 (s), 1601, 1574, 1447, 1377, 976 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.68-7.65 (m, 2H, H_{Ar}), 7.48-7.37 (m, 3H, H_{Ar}), 3.55 (s, 3H, OCH_3), 3.36 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.7 (C), 133.9 (C), 130.4 (2 CH), 127.9 (CH), 127.8 (2 CH), 60.8 (CH_3), 33.6 (CH_3); MS (EI) m/z (%): 165 (20); HRMS: M^+, obtained 165.07914 $C_9H_{11}NO_2$ requires 165.07897.

1-Phenylhex-5-en-1-one 398.[198]



$C_{12}H_{14}O$
Mol. Wt.: 174.24

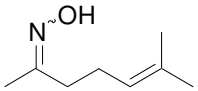
A solution of 5-bromopent-1-ene (1.01 g, 6.6 mmol) in THF (2 mL) was added dropwise over 30 min to a stirred suspension of magnesium turnings (204 mg, 8.4 mmol) in THF (3.5 mL) at room temperature. The mixture was stirred for a further 1 h and transferred via cannula to a solution of *N*-methoxy-*N*-methylbenzamide **397** (1.00 g, 6 mmol) in THF (60 mL). The reaction mixture was heated at 60 ºC for 1 h, cooled and poured onto ice (10 g) followed by addition of 20% aqueous phosphoric acid solution (30 mL). After

separation, the aqueous phase was extracted with ether (2 × 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the volatiles removed under vacuum. After rapid filtration through a pad of silica (R_f 0.53 in CH_2Cl_2) the product **398** was obtained as a colourless oil (1.00 g, 95%). IR (film): ν_{max} 3060, 1680, 1640, 1600, 1450, 910, 755, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.97-7.94 (m, 2H, H_{Ar}), 7.58-7.53 (m, 1H, H_{Ar}), 7.48-7.43 (m, 2H, H_{Ar}), 5.87-5.78 (m, 1H, C*H*), 5.08-4.98 (m, 2H, C*HH*), 2.98 (t, 2H, *J*=7.3 Hz, OCCH_2), 2.19-2.12 (m, 2H, CH_2CH), 1.90-1.80 (m, 2H, CH_2CH$_2$CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.2 (C), 138.1 (C), 137.1 (CH), 132.9 (CH), 128.6 (2 CH), 128.0 (2 CH), 115.3 (CH_2), 37.7 (CH_2), 33.2 (CH_2), 23.1 (CH_2).

General Procedure for Oxime Formation.[143]

Hydroxylamine hydrochloride (159 mmol) was added to a stirred solution of the corresponding ketone (79.3 mmol) in pyridine (46 mL) and ethanol (46 mL) at 20 ºC. After the reaction was complete (by TLC) 0.75 to 2h, the mixture was poured into 2N aqueous hydrochloric acid (350 mL). The product was extracted with CH_2Cl_2 (3 × 250 mL), and the organic extracts were combined, dried over $MgSO_4$, filtered and the volatiles were removed under reduced pressure to give the corresponding crude oxime which was purified by flash chromatography. The data provided in the following examples are for the mixture of *E*- and *Z*- isomers of the corresponding oxime, except in the proton NMR spectra, where values of the major isomer are given.

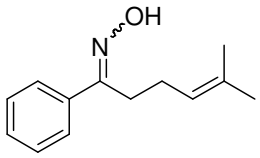
6-Methylhept-5-en-2-one oxime 327.[199]



$C_8H_{15}NO$
Mol. Wt.: 141.11

The product was obtained as a pale yellow oil (8.21 g, 98%). R_f 0.27 in PE/Et_2O (2:1); IR (film): ν_{max} 3245, 2968, 2915, 1441, 1376, 1368, 952 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.24 (br s, 1H, O*H*), 5.14-5.08 (m, 1H, C*H*), 2.41-2.19 (m, 4H, CH_2CH_2), 1.88 (s, 3H, NCCH_3), 1.68 (s, 3H, CCH_3), 1.61 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5 (C), 132.7 (C), 122.8 (CH), 35.8 (CH_2), 24.9 (CH_2), 25.7 (CH_3), 17.7 (CH_3), 13.4 (CH_3); MS (EI) m/z (%): 141 (10, M^+); HRMS: M^+, obtained 141.11439 $C_8H_{15}NO$ requires 141.11482.

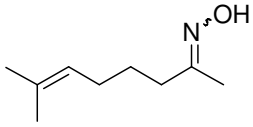
5-Methyl-1-phenylhex-4-en-1-one oxime 366.[200]



$C_{13}H_{17}NO$
Mol. Wt.: 203.28

The product was obtained as a pale yellow oil (12.4 g, 80%) after purification (PE/Et_2O 2:1, R_f 0.35 in CH_2Cl_2). IR (film): ν_{max} 3235, 3058, 2913, 1444, 929, 913, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.22 (br s, 1H, O*H*), 7.62-7.59 (m, 2H, H_{Ar}), 7.39-7.37 (m, 3H, H_{Ar}), 5.18 (tt, 2H, *J*=7.2 and 1.4 Hz, C*H*), 2.82 (t, 2H, *J*=8.0 Hz NCCH_2), 2.29-2.24 (m, 2H, CH_2CH), 1.67 (s, 3H, CCH_3), 1.57 (s, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8 (C), 135.9 (C), 132.8 (C), 129.3 and 129.2 (CH), 128.6 and 128.3 (2 CH), 126.4 and 126.1 (2 CH), 123.3 (CH), 26.4 (CH_2), 25.7 (CH_3), 25.2 and 25.0 (CH_2), 17.7 (CH_3).

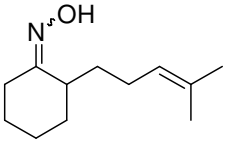
7-Methyloct-6-en-2-one oxime 370.



$C_9H_{17}NO$
Mol. Wt.: 155.24

A pale yellow oil (1.9 g, 79%) was obtained after purification (PE/Et_2O 2:1, R_f 0.27). IR (film): ν_{max} 3232, 2924, 2860, 1665, 1449, 1376, 943 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (br s, 1H, O*H*), 5.12-5.07 (m, 1H, C*H*), 2.19 (t, 2H, *J*=7.7 Hz, CH_3CCH_2), 2.03-1.96 (m, 2H, CHCH_2), 1.89 (s, 3H, NCCH_3), 1.69 (s, 3H, CH_3CCH), 1.59 (s, 3H; CH_3CCH), 1.57-1.49 (m, 2H, CH_2CCH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.7 and 158.6 (C), 132.2 (C), 123.9 (CH), 35.7 and 35.5 (CH_2), 27.6 and 27.1 (CH_2), 26.5 (CH_2), 25.9 and 25.8 (CH_3), 17.8 (CH_3), 13.4 (CH_3); MS (EI) m/z (%): 155 (10, M^+); HRMS: M^+, obtained 155.13018 $C_9H_{15}NO$ requires 155.13046.

2-(4-Methylpent-3-enyl)cyclohexanone oxime 371.

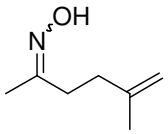


$C_{12}H_{21}NO$
Mol. Wt.: 195.30

The oxime **371** was obtained as a colourless oil (1.13 g, 55%) after flash chromatography (PE/Et_2O 2:1, R_f 0.57 in CH_2Cl_2). IR (film): ν_{max} 2937, 2862, 2253, 1705, 1448, 1377, 906 (s), 733, 652 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.70 (br s, 1H, O*H*), 5.11-5.08 (m, 1H, C*H*C$(CH_3)_2$), 2,39-2.26 (m, 1H, NCC*H*), 2.03-1.92 (m, 3H), 1.84-1.56 (m, 8H), 1.69

(s, 3H, CC*H*$_3$), 1.60 (s, 3H, CC*H*$_3$), 1.50-1.44 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3 and 165.8 (C), 132.5 and 132.2 (C), 123.6 and 123.4 (CH), 40.3 (CH), 33.1 (CH_2) 32.0 (CH_2), 31.3 (CH_2), 29.7 (CH_2), 26.1 (CH_3), 22.7 (CH_2), 20.2 (CH_2), 17.8 and 17.7 (CH_3); MS (EI) m/z (%): 195 (11, M^+); HRMS: M^+, measured mass 195.16223 $C_{12}H_{21}NO$ obtained 195.16177.

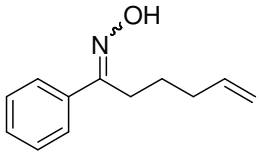
5-Methylhex-5-en-2-one oxime 385.[201]



$C_7H_{13}NO$
Mol. Wt.: 127.18

This product was obtained as a pale yellow oil (8.43 g, 63%). R_f 0.26 in CH_2Cl_2; IR (film): ν_{max} 3229, 3075, 2915, 1650, 1445, 1375, 951, 886 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (br s, 1H, O*H*), 4.70 (br s, 1H, C*H*H), 4.65 (br s, 1H, C*H*H), 2.54-2.30 (m, 2H, NCC*H*$_2$), 2.25-2.19 (m, 2H, C*H*$_2$CCH$_3$) 1.89 (s, 3H, NCC*H*$_3$), 1.76 (s, 3H, CC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.1 (C), 144.6 (C), 110.6 (CH_2), 34.2 (CH_2), 34.2 (CH_2), 22.3 (CH_3), 13.4 (CH_3); MS (EI) m/z (%): 127(15, M^+); HRMS: M^+, obtained 127.18980 $C_8H_{13}NO$ requires 127.18422.

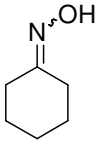
1-Phenylhex-5-en-1-one oxime 392.



$C_{12}H_{15}NO$
Mol. Wt.: 189.25

The oxime **392** was obtained as a colourless oil (1.2 g, 83%) after purification (PE/Et_2O 2:1, R_f 0.33). IR (film): ν_{max} 3228, 3065, 2930, 2865, 1641, 1460, 1303, 940 (s), 915 (s), 762 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.24 (br s, 1H, OH), 7.62-7.61 (m, 2H, H_{Ar}), 7.41-7.39 (m, 3H, H_{Ar}), 5.87-5.79 (m, 1H, C*H*CHH), 5.06-4.98 (m, 2H, CHC*HH*), 2.97-2.79 (m, 2H, PhC(O)C*H*$_2$), 2.18-2.13 (m, 2H, CH_2CH_2CH), 1.73-1.66 (m, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8 (C), 138.1 (CH), 135.7 (C), 129.3 (CH), 128.7 (2 CH), 126.4 (2 CH), 115.2 (CH_2), 33.9 (CH_2), 25.9 (CH_2), 25.6 (CH_2).

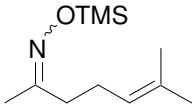
Cyclohexanone oxime 417.[202]



$C_6H_{11}NO$
Mol. Wt.: 113.16

The title oxime was obtained as a white solid (5.2 g, 89%); m.p. 91 ºC (lit m.p.86-89 ºC), IR (film): ν_{max} 3170, 3109, 2930, 1663, 1448, 1252, 1225, 1106, 992 (s), 960 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.50 (br s, 1H, O*H*), 2,54-2.48 (m, 2H, CH_2), 2.22-2.19 (m, 2H, CH_2), 1.66-1.58 (m, 6H, -(CH_2)$_6$-); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.7 (C), 32.3 and 32.2 (CH_2), 26.9 and 26.8 (CH_2), 25.9 (CH_2), 25.6 (CH_2), 24.6 (CH_2).

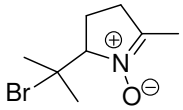
6-Methylhept-5-en-2-one O-trimethylsilyl oxime 362.



$C_{11}H_{23}NOSi$
Mol. Wt.: 213.39

To a stirred solution of oxime **327** (1 g, 7.0 mmol) and trimethylsilyl chloride (1 mL, 8.4 mmol) in THF (8.5 mL), triethylamine (1.7 mL, 11.9 mmol) was added dropwise at 0 ºC.[203] The reaction mixture was stirred for 3 h at this temperature, quickly filtered, and the volatiles were removed under reduced pressure to give a pale yellow oil which was used without further purification due to its hydrolytic instability. IR (film): ν_{max} 3258, 2967, 2916, 1664, 1444, 1376, 1250, 943, 890, 845 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.11-5.09 (m, 1H, C*H*), 2.23-2.21 (m, 4H, CH_2CH_2), 1.87-1.84 (m, 3H, NCCH_3), 1.67 (br s, 3H, CCH_3), 1.61-1.60 (m, 3H, CCH_3), 0.20-0.18 (m, 9H, Si(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.0 and 162.7 (C), 132.3 and 132.6 (C), 123.4 and 123.6 (CH), 36.0 (CH_2), 25.8 (CH_2), 25.1 and 24.1 (CH_3), 17.8 and 17.7 (CH_3), 14.2 (CH_3), -0.55 (3 CH_3).

2-Methyl-5-(2-bromopropan-2-yl)-1 Δ^1-pyrroline *N*-oxide 333

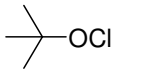


$C_8H_{14}BrNO$
Mol. Wt.: 220.11

6-Methylhept-5-en-2-one oxime **327** (200 mg, 1.42 mmol) was added dropwise in the dark to a stirred mixture of NBS (380 mg, 2.13 mmol), sodium hydrogen carbonate (238 mg, 2.84 mmol), water (6 mL) and 1 drop of methanol. When addition was complete, the reaction mixture turned blue in 10 min, stirring was continued for three hours. Et_2O (6 mL) was added, the light yellow organic phase was separated, and the aqueous phase was

extracted with Et_2O (2 × 6 mL). The organic phases were combined, washed sequentially with water (10 mL), and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated under vacuum. This nitrone **333** was obtained as a pale yellow oil (0.43 mg, 14%) after two successive purifications by flash chromatography (PE/EtOAc 2:1 and PE/CH_2Cl_2 1:1, R_f 0.33 in CH_2Cl_2); IR (film): ν_{max} 3250, 2901, 1456 (s), 1323 (s), 812 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.98-3.93 (m, 1H, CC*H*N), 2.50-2.44 (m, 2H, C*H*$_2$CCH$_3$), 2.11-2.05 (m, 2H, CHC*H*$_2$), 1.80 (s, 3H C*H*$_3$CN), 1.37 (m, 6H, 2 C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.8 (C), 68.0 (CH), 43.3 (C), 30.3 (CH_2), 30.9 (CH_2), 26.3 ($2CH_3$), 13.1 (CH_3); MS (EI) m/z (%): 219 (45, M^+).

***tert*-Butyl hypochlorite.**[148]



C_4H_9ClO
Mol. Wt.: 108.57

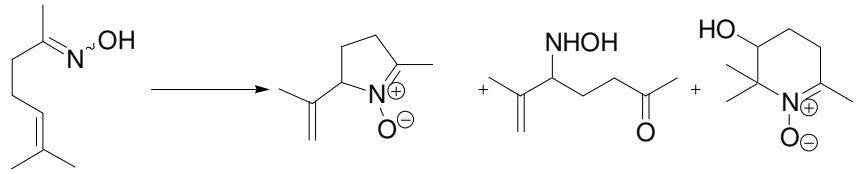
A solution of glacial acetic acid (12 mL) and *tert*-butanol (18 mL) at 0 °C in the dark was added in one portion to an aqueous solution of sodium hypochlorite [sodium hypochlorite (86 mL, 14% available chlorine) and distilled water (150 mL)] and the resulting mixture was stirred for 5 min. The organic phase was separated, and washed successively with aqueous sodium carbonate (10% v/v), water (25 mL) and dried over calcium chloride. Filtration gave the desired product as a yellow liquid. CAUTION: **PURIFICATION BY DISTILLATION WAS PROVED TO NOT IMPROVE THE PURITY AND CAN BE HAZARDOUS**. The product was stored below 4 ºC in the dark over calcium chloride.

General Method for Intramolecular Ene Reactions of α-Chloro Nitroso Compounds generated from Oximes using *tert*-butyl hypochlorite.

tert-Butyl hypochlorite (10.6 mmol) was added in one portion to a stirred solution containing the corresponding oxime (10.5 mmol), potassium carbonate (52 mmol) and CH_2Cl_2 (100 mL) at 0 ºC in the dark. The reaction mixture often turned blue in less than 10 min, but the duration and intensity of the colouration varied. When the solution became colourless (often taking longer than 6 h), stirring was continued for an additional hour (no starting material by TLC), filtered, and the volatiles were removed under reduced pressure. When the crude product contained more than three products (by TLC) two successive purifications by flash chromatography were required (CH_2Cl_2 and Et_2O/PE

1:6). The desired nitrone was recovered with its hydrolysed product and an unexpected nitrone containing a six membered ring.

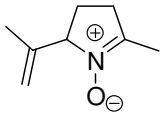
Intramolecular Type I Ene Reaction using 6-Methylhept-5-en-2-one Oxime 327



327 **332** **352** **353**

This reaction was carried out according to the general method on a 10.6 mmol scale to give nitrone **332** as a colourless oil (886 mg, 60%) together with allylic hydroxylamine **352** which was isolated as a colourless (132 mg, 8%) and a six membered ring nitrone **353** as a clear oil (495 mg, 30%).

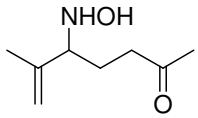
2-Methyl-5-isopropenyl-1 Δ^1-pyrroline *N*-oxide 332.



$C_8H_{13}NO$
Mol. Wt.: 139.19

R_f 0.26 in CH_2Cl_2; IR (film): ν_{max} 3250, 3082, 2922, 1437 (s), 1375 (s), 912 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.04 (br s, 1H, C*H*H), 4.93-4.92 (m, 1H, CH*H*), 4.48-4.35 (m, 1H, CC*H*N), 2.44-2.39 (m, 2H, CH_2CCH$_3$), 2.08-2.02 (m, 2H, CHCH_2), 1.89 (s, 3H CH_3CN), 1.83-1.81 (m, 3H, CH_3CCH$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.1 (C), 143.8 (C), 114.5 (CH_2), 65.7 (CH), 33.1 (CH_2), 32.8 (CH_2), 17.1 (CH_3), 13.8 (CH_3); MS (EI) m/z (%): 140 (98, M^+); HRMS: M^+, obtained 139.09989 $C_8H_{13}NO$ requires 139.09971.

5-(Hydroxyamino)-6-methylhept-6-en-2-one 352.

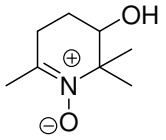


$C_8H_{15}NO_2$
Mol. Wt.: 157.21

R_f 0.31 in CH_2Cl_2; IR (film): ν_{max} 2924, 1716, 1647, 1437, 1367, 1161, 908 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.82 (br s, 1H, NHOH), 5.01 (ddq, 1H, *J*=1.4, 0.9 and 0.7 Hz, C*H*H), 4.89 (dq, 1H, *J*=1.4 and 1.1 Hz, C*H*H), 4.38 (t, 1H, *J*=7.4 Hz, C*H*NHOH), 2.60-2.54 (m, 2H, CH_2CO), 2.14 (s, 3H, CH_3CO), 2.07 (apparent q, 2H, *J*=7.4 Hz, CHCH_2), 1.79 (dd, 3H, *J*=1.4 and 0.7 Hz, CH_3CCH$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.4 (C), 144.0 (C), 114.3 (CH_2), 65.8 (CH), 40.9 (CH_2), 30.2 (CH_2), 30.1 (CH_3), 17.2 (CH_3); MS (CI)

m/z (%): 158 (10, M+H); HRMS: M+H, obtained 158.11835 $C_8H_{16}NO_2$ requires 158.11810.

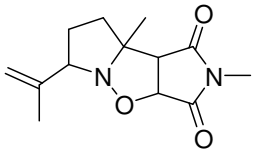
2,2,6-Trimethyl-1-oxy-2,3,4,5-tetrahydropyridin-3-ol 353.



$C_8H_{15}NO_2$
Mol. Wt.: 157.21

R_f 0.17 in CH_2Cl_2; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.89 (dd, 1H, *J*=11.0 and 4.2 Hz, C*H*OH), 2.63-2.58 (ddd, 1H. *J*=14.0, 10.6 and 3.7 Hz, CH_{ax}HCCH$_3$), 2.63-2.58 (ddd, 1H. *J*=14.0, 7.3 and 3.4 Hz, CH_{eq}HCCH$_3$), 2.14-2.08 (m, 1H, CH_{eq}HCHOH), 1.88-1.82 (m, 1H, CH_{ax}HCHOH), 2.02 (s, 3H, CCH_3), 1.47 (s, 3H, CH_{3eq}), 1.30 (s, 3H, CH_{3ax}), 1.23 (br s, 1H, O*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.8 (C), 80.9 (C), 66.4 (CH), 29.3 (CH_2), 28.1 (CH_2), 27.4 (CH_3), 21.5 (CH_3), 18.6 (CH_3); MS (EI) m/z (%): 158 (10, M+H); HRMS: M+H, obtained 158.11875 $C_8H_{16}NO_2$ requires 158.11810.

6-Isopropenyl-2,8a-dimethylhexahydrodipyrrolo[1,2-b;3',4'-d]isoxazole-1,2-dione 364.



$C_{13}H_{18}N_2O_3$
Mol. Wt.: 250.29

A mixture containing the freshly purified nitrone **332** (500 mg, 3.60 mmol), and *N*-methylmaleimide (1.6 g, 14.39 mmol) in toluene (25 mL) was heated at reflux for four days (R_f 0.22 in CH_2Cl_2). After cooling, the reaction mixture was filtered, and concentrated under vacuum to give an orange oil. The crude residue was purified by flash chromatography (Et_2O/PE 2:1) to give an oil containing a mixture of three diastereomers (45 mg, 5%) as observed by ^{13}C NMR spectra.

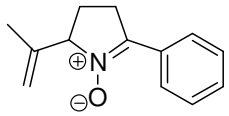
IR (film): ν_{max} 3053, 2985, 2305, 1716, 1421, 1265 (s), 734, 704.cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.96-4.74 (m, 3H, OC*H* and CC*HH*), 3.80-3.77 (m, 1H, NCC*H*), 3.46 (d, 1H, *J*=7.7 Hz, C*H*C(O)), 2.97 (br s, 3H, NCH_3), 2.20-2.12 (m, 2H, $CH_2CH_2CH_3$), 1.96-1.81 (m, 2H, $CH_2CH_2CCH_3$), 1.74 (br s, 3H, CH_3CCH), 1.16 (br s, 3H, NCCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.3, 175.0 and 174.4 (C), 174.6, 174.3and 174.1 (C), 144.5, 144.3 and 144.0 (C), 112.6, 111.9 and 111.1 (CH_2), 79.6, 77.6 and 77.4 (C), 74.7, 74.4 and

74.2 (CH), 71.6, 70.5 and 69.8 (CH), 57.5 and 57.3 (CH), 38.0, 39.6 and 36.2 (CH_2), 27.8, 26.1 and 26.9 (CH_2), 25.0, 24.7 and 23.5 (CH_3), 21.0 (CH_3), 20.0, 18.1 and 14.1 (CH_3). MS (EI) m/z (%): 250 (100, M^+); HRMS: M^+, measured mass 250.13033 $C_{13}H_{18}N_2O_3$ requires 250.13119.

Intramolecular Type I Ene Reaction using 5-Methyl-1-phenylhex-4-en-1-one oxime 366.

The reaction was carried out according to the general method above using oxime **366** (345 mg, 1.7 mmol) and after purification gave aromatic nitrone **369** as an unstable colourless oil (40.8 mg, 12% yield).

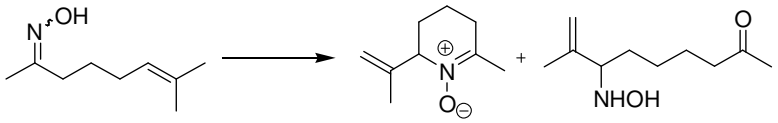
2-Isopropenyl-5-phenylpyrrolidine-1-oxide 369.



$C_{13}H_{15}NO$
Mol. Wt.: 201.26

IR (film): ν_{max} 3335, 2986, 2933, 1605, 1445 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.71-7.69 (m, 2H, H_{Ar}), 7.38-7.36 (m, 3H, H_{Ar}), 5.10 (br s, 1H, C*H*H), 5.01 (m, 1H, CH*H*), 4.24 (dd, 1H, *J*=10.6 and 1.9 Hz, NC*H*), 2.74-2.61 (m, 2H, CH_2CN), 2.15-1.97 (m, 2H, CHCH_2), 1.85 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.2 (C), 142.9 (C), 135.8 (C), 129.4 (CH), 128.4 (2 CH) 125.3 (2 CH), 113.2 (CH_2), 30.9 (CH), 23.0 (CH_2), 21.8 (CH_2), 18.6 (CH_3).

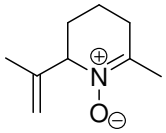
Intramolecular Type I Ene Reaction of the α-chloro nitroso compound generated from 7-Methyloct-6-en-2-one oxime 370.



370 **380** **381**

This reaction was carried out according to the above general method using oxime **370** (497 mg, 3.2 mmol) to give after purification by flash chromatography (PE/Et_2O 5:1, R_f 0.34) nitrone **380** as a colourless oil (318 mg, 65%) together with allylic hydroxylamine **381** as a colourless oil (49 mg, 9%).

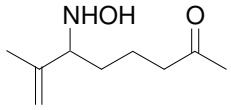
2-Isopropenyl-6-methyl-2,3,4,5-tetrahydropyridine 1-oxide 380.



$C_9H_{15}NO$
Mol. Wt.: 153.22

IR (film): ν_{max} 3225, 2951 (s), 1647, 1451 (s), 1370 (s), 945, 909 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.03 (t, 1H, *J*=0.6 Hz, C*H*H), 4.92-4.90 (m, 1H, CH*H*), 4.40 (t, 1H, *J*=7.3 Hz, CC*H*N), 2.21 (t, 2H, *J*=7.4 Hz, CH_2CNCH$_3$), 1.89-1.83 (m, 2H, CHCH_2), 1.87 (s, 3H, NCCH_3), 1.79 (s, 3H, CH_2CCH_3), 1.71-1.67 (m, 1H, CH_2C*H*HCH_2), 1.60-1.55 (m, 1H, CH_2CH*H*CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.2 (C), 144.2 (C), 114.3 (CH_2), 66.4 (CH), 35.8 (CH_2), 35.0 (CH_2), 23.4 (CH_2), 17.0 (CH_3), 13.3 (CH_3); MS (CI) m/z (%): 154 (33, M+H); HRMS: M+H, obtained 154.12272 $C_9H_{16}NO$ requires154.12318.

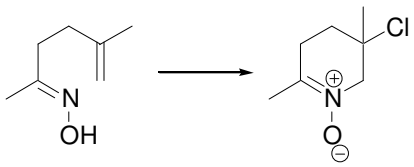
6-(Hydroxyamino)-7-methyloct-7-en-2-one 381.



$C_9H_{17}NO_2$
Mol. Wt.: 171.24

R_f 0.39 in PE/Et_2O 5:1; IR (film): ν_{max} 3417, 2921, 1716, 1646, 1446, 1367, 907 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.02 (br s, 1H, CH*H*), 4.91 (t, 1H, *J*=1.5 Hz, C*H*H), 4.38 (t, 1H, *J*=7.3 Hz, C*H*NHOH), 2.46 (t, 2H, *J*=7.2 Hz, CH_2CO), 2.14 (s, 3H, CH_3CO), 1.83-1.80 (m, 2H, CHCH_2), 1.79 (s, 3H, CH_3CCH$_2$), 1.69-1.56 (m, 2H, CH_2CH_2CH$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.1 (C), 144.1 (C), 114.4 (CH_2), 66.4 (CH), 42.7 (CH_2), 35.7 (CH_2), 30.9 (CH_3), 22.5 (CH_2) 16.9 (CH_3); MS (CI) m/z (%): 154 (32, M-OH); HRMS: M-OH, obtained 154.12272 $C_9H_{16}NO$ requires 154.12318.

Attempted Type II Intramolecular Ene Reaction of the α-chloro nitroso compound generated from 5-Methylhex-5-en-2-one oxime 385.



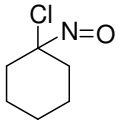
385 **391**

$C_7H_{12}ClNO$
Mol. Wt.: 161,62928

The reaction was carried out according to the general method outline above using oxime **385** (1.15 g, 9.0 mmol) to give 4-chloro-2,4-dimethyl-2,3,5-tetrahydropyridine 1-oxide **391** as a colourless oil (0.88 mg, 60%). (R_f 0.26 in CH_2Cl_2); IR (film): ν_{max} 3250, 3079, 2897, 1443 (s), 1364 (s), 900 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.47 (d, 1H, *J*=11.4

Hz, C*H*HNO), 4.05 (d, 1H, *J*=11.4 Hz, CH*H*NO), 2.41-2.35 (m, 2H, CH_2CCl), 2.11-2.07 (m, 2H, NCCH_2), 2.07 (s, 3H, CH_3CN), 1.49 (s, 3H, CH_3CCl); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.4 (C), 73.8 (C), 49.5 (CH_2), 30.1 (CH_2), 23.1 (CH_3), 22.0 (CH_2), 13.2 (CH_3); MS (EI) m/z (%): 161 (36, M^+).

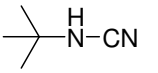
1-Chloro-1-nitrosocyclohexane 496.[204]



$C_6H_{10}ClNO$
Mol. Wt.: 147.60

tert-Butyl hypochlorite (1.05 g, 9.7 mmol) was added in one portion to a stirred mixture of cyclohexanone oxime **417** (1.00 g, 8.8 mmol) and potassium carbonate (6.00 g, 44 mol, 5 eq) in CH_2Cl_2 (100 mL) at 0 ºC in the dark . The deep blue reaction mixture was stirred for 1 h before being quenched with water (100 mL). The aqueous layer was separated and the organic phase was washed with water (50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the chloro nitroso compound as a deep blue oil (1.08 g, 83%). IR (film): ν_{max} 2942, 1714, 1573 (s), 1449, 1252, 1143, 1021, 926, 872 (s), 800, 665 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.67-2.57 (m, 2H, CH_2), 1.92-1.42 (m, 8H, -(CH_2)$_4$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 117.6 (C), 33.2 (2 CH_2), 24.6 (CH_2), 21.7 (2 CH_2).

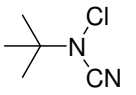
***tert*-Butylcyanamide.**[205]



$C_5H_{10}N_2$
Mol. Wt.: 98.15

A solution of 2-methylpropan-2-amine (10 mL, 100 mmol) and anhydrous triethylamine (21 mL, 200 mmol) in CH_2Cl_2 (300 mL) was cooled to 0 ºC. A solution of cyanogen bromide (11.00 g, 105 mmol) in CH_2Cl_2 (35 mL) was added, and after vigorous stirring for 10 h at room temperature, the mixture was filtered through a short column of silica, and concentrated under reduced pressure. The crude product was purified by distillation under reduced pressure (b.p. 62-64 ºC / 0.3 mmHg) to give a colourless oil (5.58 g, 60%). IR (film): ν_{max} 3200, 2882, 2875, 1443, 1382, 1209 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (br s, 1H, N*H*), 1.38 (s, 9H, 3 CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 114.9 (C), 52.1 (C), 29.6 (3 CH_3).

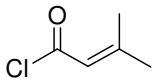
tert-Butylchlorocyanamide.[150,151]



$C_5H_9ClN_2$
Mol. Wt.: 132.59

A solution of tert-butylcyanamide (2.00 g, 24 mmol) in CCl_4 (30 mL) was treated with *tert*-butyl hypochlorite (2.74 g, 25 mmol) and potassium carbonate (60 mg) at room temperature in the dark. The reaction was stirred for 3 h, and the resulting yellow solution was filtered and concentrated under vacuum. The product was obtained as a yellow oil (1.27 g, 40%) after distillation (b.p. 60 ºC / 10 mmHg). IR (film): ν_{max} 3219, 2976, 2210 (s), 1625, 1370, 1206 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 9H, 3 CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 114.5 (C), 66.4 (C), 26.5 (3 CH_3).

3-Methylbut-2-enoyl chloride 424.[172]



C_5H_7ClO
Mol. Wt.: 118.56

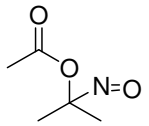
A mixture of 3-methylbut-2-enoic acid (2.00 g, 19.98 mmol), thionyl chloride (1.45 mL, 19.98 mmol) and toluene (10 mL) was heated at reflux for 3 h. After the reaction mixture was cooled to room temperature, the volatiles were removed under vacuum to give the crude product, which was distilled at atmospheric pressure to yield 3-methylbut-2-enoyl chloride **424** (1,83 g, 77%) as a pale yellow oil (b.p. 147-148 ºC / 760 mmHg). IR (film): ν_{max} 2941, 2660, 1687 (s), 1640 (s), 1254 (s), 1144, 855 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.05-6.04 (m, 1H, C*H*), 2.15 (d, 3H, *J*=1.2 Hz, CCH_3), 1.95 (d, 3H, *J*=1.2 Hz, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.2 (C), 163.4 (C), 122.6 (CH), 27.4 (CH_3), 21.6 (CH_3).

General Method of the Preparation of Geminal Acyloxy Nitroso Derivates.[166]

2-Nitropropane (1.00 g, 11 mmol) was added dropwise to a suspension of potassium *tert*-butoxide (1.32 g, 11 mmol) in Et_2O (10 mL) at 0 ºC. When the addition was complete, the reaction mixture was stirred for 45 min before the acylating agent (11 mmol) was added dropwise. After 2-3 minutes, the mixture became deep blue, indicating the presence of the nitroso derivative. After stirring for a further 1 h, the mixture was quickly washed with water (10 mL). The organic layer was dried over $MgSO_4$, filtered and the remaining solids washed with Et_2O until the blue colouration disappeared from the residue. The volatiles were removed under reduced pressure without heating and in the dark to give the

corresponding geminal acyloxy nitroso derivative as a blue or green oil.

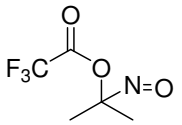
2-Nitrosopropan-2-yl acetate 414.[166]



$C_5H_9NO_3$
Mol. Wt.: 131.13

(1.15 g, 80%). IR (film): ν_{max} 2830, 1880, 1720, 1580, 1560 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.18 (s, 3H, C*H*$_3$), 1.37 (s, 6H, 2 C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2 (C), 120.9 (C), 21.4 (CH_3), 20.8 (2 CH_3).

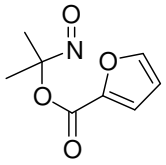
2-Nitroso-2-trifluoroacetoxy propane 421.[166]



$C_5H_6F_3NO_3$
Mol. Wt.: 185,1

2-Nitropropane (1.00 g, 11 mmol) was added dropwise to a suspension of potassium *tert*-butoxide (1.32 g, 11 mmol) in Et_2O (10 mL) at 0 ºC. When the addition was complete, the reaction mixture was stirred for 45 min and trifluoroacetic anhydride (1.54 mL, 11 mmol) was added dropwise. After 2-3 minutes, the mixture became deep blue, indicating the presence of the nitroso derivative; although decomposition was observed, as evidenced by gradual loss of blue colouration after several minutes. The mixture was quickly washed with water (10 mL). The organic layer was dried over $MgSO_4$, filtrated and the remaining solids washed with Et_2O until the blue colouration disappeared from the residue. Volatiles were removed under reduced pressure without heating and in the dark to give the corresponding geminal trifluoroacetoxy nitroso derivative **421** as a blue oil. Different attempts at purification of the crude material led to decomposition of the product. Nevertheless, characterisation of the crude compound was possible. IR (film): ν_{max} 2977, 1785, 1570, 1552 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.19 (s, 6H, 2 C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.2 (C), 124.8 (C), 78.7 (C), 20.3 (2 CH_3).

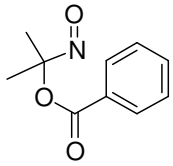
Furan-2-carboxylic acid 1-methyl-1-nitrosoethyl ester 422.



$C_8H_9NO_4$
Mol. Wt.: 183.16

(1.02 g, 78%). IR (film): ν_{max} 2963, 2938, 1799, 1750 (s), 1678, 1551, 1368 (s), 1206 (s), 1185 (s), 1001 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (t, 1H, *J*=0.9 Hz, H_{Ar}), 7.30 (dd, 1H, *J*=3.5 and 0.9 Hz, H_{Ar}), 6.57-6.52 (m, 1H, H_{Ar}), 1.54 (m, 6H, 2 CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.7 (C), 156.4 (C), 146.9 (CH), 121.7 (C), 119.0 (CH), 112.0 (CH), 20.8 (2 CH_3); MS (EI) m/z (%): 153 (100, M-NO); HRMS: M-NO, measured mass 153.05497 $C_8H_9O_3$ requires 153.05462.

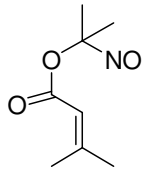
Benzoic acid 1-methyl-1-nitrosoethyl ester 424.[170]



$C_{10}H_{11}NO_3$
Mol. Wt.: 193.20

(1.42 g, 67%). IR (film): ν_{max} 3064 (w), 2991 (w), 1725, 1691, 1564, 1451 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.13-8.12 (m, 2H, H_{Ar}), 7.53-7.48 (m, 3H, H_{Ar}), 1.55 (s, 6H, 2 CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.6 (C), 133.5 (CH), 130.3 (2 CH), 130.0 (C), 129.0 (2 CH), 121.3 (C), 20.9 (2 CH_3).

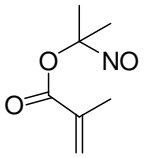
2-Nitrosopropan-2-yl 3-methylbut-2-enoate 427.



$C_8H_{13}NO_3$
Mol. Wt.: 171.19

(4.71 g, 42%). IR (film): ν_{max} 2982, 2941, 1780, 1721, 1692, 1642 (s), 1445, 1132, 1034 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.88-5.87 (m, 1H, C*H*), 1.95 (d, 3H, *J*=1.3 Hz, CHCCH_3), 1.93-1.932 (m, 3H, CHCCH_3), 1.38 (s, 6H, ONC(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3 (C), 159.2 (C), 128.9 (C), 115.1 (CH), 27.4 (CH_3), 20.6 (2 CH_3), 19.7 (CH_3); MS (EI) m/z (%): 141 (26, M-NO); HRMS: M-NO, obtained 141.09128 $C_8H_{13}O_2$ requires 141.09101.

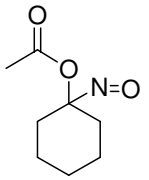
2-Nitrosopropan-2-yl methacrylate 430.



$C_7H_{11}NO_3$
Mol. Wt.: 157.17

(5.96 g, 69%). IR (film): ν_{max} 3413, 2990, 2937, 1743, 1448 (s), 1106 (s), 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.27 (br s, 1H, C*H*H), 5.71-5.70 (m, 1H, CH*H*), 2.00 (s, 3H, CH_2CCH_3), 1.43 (s, 6H, $C(CH_3)_2$; ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2 (C), 136.1 (C), 126.7 (CH_2), 120.8 (C), 20.7 (2 CH_3), 18.2 (CH_3).

1-Nitrosocyclohexyl acetate 418.[206]



$C_8H_{13}NO_3$
Mol. Wt.: 171.19

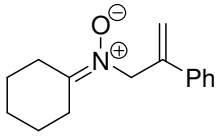
Cyclohexanone oxime **417** (1.0 g, 8.8 mmol) was added portionwise to a suspension of lead tetraacetate (4.3 g, 9.7 mmol) in CH_2Cl_2 (25 mL) at 0 ºC in the dark. The reaction mixture took on a green colouration, and was left under stirring for a further 0.5 h before water (30 mL) was added. After 10 min, the layers were partitioned, and the organic layer was washed sequentially with 1% aqueous sodium bicarbonate solution (30 mL), water (30 mL), dried over $MgSO_4$, filtered and concentrated to give a green oil (0.75 g, 45%). IR (film): ν_{max} 2939, 2864, 2002 (w), 1749, (s), 1714, 1561, 1452, 1367, 1214 (s), 1150 (s), 1016, 916 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.18 (s, 3H, C*H*$_3$), 1.91-1.29 (m, 10H, -(C*H*$_2$)$_5$-); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9 (C), 123.7 (C), 33.8 (CH_2), 29.3 (CH_2), 24.7 (CH_2), 21.9 (2 CH_2), 21.6 (CH_3).

Attempted Intermolecular Ene Reactions of Geminal Acyloxy Nitroso Compounds with α-Methylstyrene. - General Method.

The following method is illustrative: 1-Nitrosocyclohexyl acetate **418** (0.50 mg, 2.9 mmol) was mixed with α-methylstyrene (1.03 mg, 8.7 mmol) and the reaction was stirred for 24 h at room temperature until disappearance of the blue colouration. The yellow organic phase was washed with water (2 × 1 mL), dried over $MgSO_4$, filtered and volatiles were removed under reduced pressure to give a pale yellow oil. Examination of the

proton NMR spectrum of the crude reaction mixture did not provide any evidence of the desired nitrone and the only isolated products were derived from hydrolysis together with α-methylstyrene.

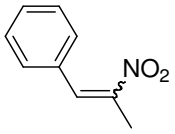
α,α-Cyclohexanyl-*N*-(2-phenyl)prop-1-en-3-yl nitrone hydrochloride 497.[115]



$C_{15}H_{19}NO$
Mol. Wt.: 229,32

1-Chloro-1-nitrosocyclohexane **496** (0.74 g, 5 mmol) was mixed with α-methylstyrene (3.2 mL, 25 mmol) in the dark, and the resulting mixture was stirred at 20 ºC for 2 days. The cyclohexylidene derivative **497** was obtained after removal of the excess of olefin under reduced pressure to give the product as a yellow oil (0.60 g, 53%). IR (film): ν_{max} 3441, 2927, 1756 (s), 1505 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.38-7.24 (m, 5H, H_{arom}), 5.61 (br s, 1H, CH*H*), 5.48 (br s, 1H, C*H*H), 5.33 (br s, 1H, CH_2CPh), 3.00-2.96 (m, 2H, -(CH_2)), 2.62-2.34 (m, 2H, -(CH_2)), 1.67-1.62 (m, 6H, -(CH_2)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.2 (C), 143.2 (C), 135.2 (C), 128.9 (2 CH), 128.2 (CH), 125.3 (2 CH), 113.3 (CH_2), 57.2 (CH_2), 33.6 (CH_2), 32.2 (CH_2), 30.9 (CH_2), 29.2 (CH_2), 27.6 (CH_2).

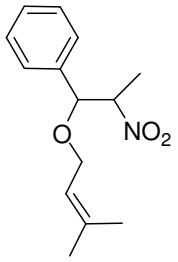
1-(2-Nitropropenyl)benzene 446.[207]



$C_9H_9NO_2$
Mol. Wt.: 163.17

Benzaldehyde (2 mL, 20 mmol) and ammonium acetate (1.54 g, 20 mmol) in nitroethane (40 mL) were heated at reflux for 12 h. Volatiles were then removed under reduced pressure; water (30 mL) and EtOAc (30 mL) were added. After separation of the phases, the organic phase was washed with brine (30 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under vacuum to give a yellow solid (R_f 0.58 in CH_2Cl_2), which was purified by recrystallisation from ethanol (1.82 g, 67%). M.p. 65 ºC (lit m.p. 63-64 ºC); IR (film): ν_{max} 3058, 2974, 2809, 1651, 1514, 1488, 1449, 1429, 1313, 941 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (s, 1H, C*H*), 7.50-7.36 (m, 5H, H_{Ar}), 2.45 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8 (C), 133.5 (CH), 132.4 (C), 130.0 (2 CH), 129.9 (CH), 128.9 (2 CH), 14.0 (CH_3).

[1-(1-(3-Methylbut-2-enyloxy)-2-nitropropyl)]benzene 438.



$C_{14}H_{19}NO_3$
Mol. Wt.: 249,30

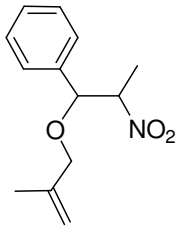
[1-(1-(3-Methylbut-2-enyloxy)-2-nitropropyl)]benzene **438** was prepared by a modification of the literature method.[174] To a stirred suspension of NaH (1.06 g, 22 mmol) in THF (10 mL) at 0ºC was added 3-methylbut-2-en-1-ol (2.2 mL, 22 mmol), and stirring was continued until the evolution of gas ceased. 1-(2-Nitropropenyl)benzene **446** (3.26 g, 20 mmol) was then added at 0 ºC and the resulting mixture was poured into ice-water, acidified with hydrochloric acid solution and extracted with Et_2O (20 mL). The organic extract was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give an orange oil. A pale yellow oil (4.00 g, 73%) containing a mixture of diastereomers (ratio: 1/0.7) was recovered after flash chromatography (Et_2O/PE 3:1, R_f 0.67 in CH_2Cl_2). IR (film): ν_{max} 2976, 2914, 2357 (w), 1676 (w), 1550 (s), 1452, 1388, 1360, 1028, 762, 703 cm^{-1}.

Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.32 (m, 5H, H_{Ar}), 5.29-5.26 (m, 1H, CH_2CH), 4.93 (d, 1H, *J*=5.4 Hz, PhC*H*), 4.63-4.58 (m, 1H, C*H*NO_2), 4.12-3.92 (m, 2H, CH_2CH), 1.73 (s, 3H, CCH_3), 1.54 (d, 3H, *J*=5.4 Hz, $CHCH_3$), 1.52 (s, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2 (C), 137.1 (C), 128.7 (2 CH), 128.6 (CH), 127.0 (2 CH), 120.0 (CH), 87.1 (CH), 80.7 (CH), 65.8 (CH_2), 25.7 (CH_3), 17.9 (CH_3), 13.2 (CH_3).

Minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.32 (m, 5H, H_{Ar}), 5.23-5.20 (m, 1H, CH_2CH), 4.77-4.70 (m, 1H, C*H*NO_2), 4.66 (d, 1H, *J*=9.6 Hz, PhC*H*), 3.75-3.48 (m, 2H, CH_2CH), 1.70 (s, 3H, CCH_3), 1.48 (s, 3H, CH_3), 1.25 (d, 3H, *J*=9.6 Hz, $CHCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2 (C), 136.4 (C), 129.1 (CH), 128.8 (2 CH), 127.8 (2 CH), 120.0 (CH), 87.5 (CH), 82.1 (CH), 65.2 (CH_2), 25.7 (CH_3), 17.9 (CH_3), 16.4 (CH_3).

MS (APCI, negative mode) m/z (%): 163.15 (100, M-OC_5H_9), 216.18 (20, M-O_2), 247.97 (6, M-H).

[1-(1-(2-Methylallyloxy)-2-nitropropyl)]benzene 442.



$C_{13}H_{17}NO_3$
Mol. Wt.: 235.28

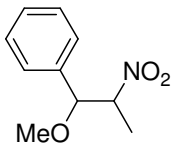
The title product **442** was prepared according to the procedure used for [1-(1-(3-methylbut-2-enyloxy)-2-nitropropyl)]benzene **438**. [1-(1-(2-Methylallyloxy)-2-nitropropyl)]benzene **442** was obtained as a colourless oil (3.13 g, 77%) containing a mixture of diastereomers (ratio 3/2) after purification by flash chromatography (Et_2O/PE 3:1, R_f 0.65 in CH_2Cl_2). IR (film): ν_{max} 3067, 3033, 2978, 1548 (s), 1451, 1070, 903, 762, 701 (s) cm^{-1}.

Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.32 (m, 5H, H_{Ar}), 4.99 (d, 1H, *J*=5.1 Hz, PhC*H*), 4.89-4.61 (m, 3H, C*HH* and C*H*NO_2), 3.91-3.67 (m, 2H, OCH_2), 1.70 (s, 3H, CCH_3), 1.48 (d, 3H, *J*=3.2 Hz, CHCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.2 (C), 136.7 (C), 128.8 (2 CH), 128.7 (CH), 127.0 (2 CH), 113.0 (CH_2), 87.1 (CH), 81.0 (CH), 73.2 (CH_2), 19.4 (CH_3), 12.9 (CH_3).

Minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.32 (m, 5H, H_{Ar}), 5.00-4.61 (m, 4H, C*HH*, PhC*H*O and C*H*NO_2), 3.76-3.59 (m, 2H, OCH_2), 1.64 (s, 3H, CCH_3), 1.25 (d, 3H, *J*=6.7 Hz, CHCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.2 (C), 136.0 (C), 129.2 (CH), 128.9 (2 CH), 127.0 (2 CH), 113.2 (CH_2), 87.5 (CH), 82.3 (CH), 72.7 (CH_2), 19.3 (CH_3), 16.3 (CH_3).

MS (APCI negative) m/z (%): 163.05 (100, M-C_4H_7O), 220.98 (6, M-CH_3), 234.16 (1, M-H).

(1-Methoxy-2-nitropropyl)benzene 448.



$C_{10}H_{13}NO_3$
Mol. Wt.: 195.21

The product was obtained by following the procedure described for the synthesis of [1-(1-(3-methylbut-2-enyloxy)-2-nitropropyl)]benzene **438.** A pale yellow oil (1.92 g, 34%)

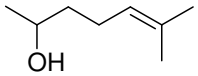
containing a mixture of diastereomers (ratio 3/2) was obtained after purification by flash chromatography (Et_2O/PE 3:1, R_f 0.51 in CH_2Cl_2). IR (film): ν_{max} 2995, 2901, 2830, 1965 (w), 1550 (s), 1454, 1389, 1098 cm^{-1}.

Major diastereomer ; ^1H NMR (300 MHz, $CDCl_3$): δ 7.44-7.31 (m, 5H, H_{Ar}), 4.85 (d, 1H, *J*=4.8 Hz, C*H*OMe), 4.64-4.55 (m, 1H, C*H*NO_2), 3.29 (s, 3H, OCH_3), 1.51 (d, 3H, *J*=6.7 Hz, CHCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.6 (C), 128.9 (CH), 128.8 (2 CH), 127.0 (2 CH), 87.0 (CH), 83.8 (CH), 57.7 (CH_3), 12.8 (CH_3).

Minor diastereomer; ^1H NMR (500 MHz, $CDCl_3$): δ 7.44-7.31 (m, 5H, H_{Ar}), 4.78-4.68 (m, 1H, C*H*NO_2), 4.51 (d, 1H, *J*=9.6 Hz, C*H*OMe), 3.17 (s, 3H, OCH_3), 1.25 (d, 3H, *J*=6.7 Hz, CHCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.9 (C), 129.3 (CH), 129.0 (2 CH), 127.8 (2 CH), 87.6 (CH), 85.2 (CH), 57.0 (CH_3), 16.4 (CH_3).

MS (APCI negative) m/z (%): 163.15 (100, M-H-OMe), 194.06 (10, M-H).

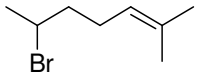
6-Methylhept-5-en-2-ol 454.[208]



$C_8H_{16}O$
Mol. Wt.: 128.21

Sodium borohydride (3.00 g, 79.3 mmol) was added portionwise to a stirred solution of 6-methylhept-5-en-2-one (6 mL, 39.6 mmol) in ethanol (200 mL) at 0 ºC. The reaction mixture was left under stirring for 1 h at room temperature followed by addition of a saturated aqueous solution of ammonium chloride (10 mL) and water (100 mL). The crude product was extracted with Et_2O (3 × 100 mL) and the combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtrated and concentrated under vacuum to give a pale yellow oil (4.72 g, 93%) which was carried through to the next step without further purification. IR (film): ν_{max} 3348, 2967, 2925, 1711 (w), 1449, 1376 (s), 1331, 1128, 1073 (s), 951, 665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.15-5.09 (m, 1H, CC*H*), 3.84-3.76 (m, 1H, C*H*OH), 2.06-2.04 (m, 2H, CH(OH)CH_2), 1.68 (s, 3H, CCH_3), 1.61 (s, 3H, CCH_3), 1.53-1.46 (m, 2H, CH_2CHC), 1.18 (d, 3H, *J*=6.2 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.0 (C), 124.0 (CH), 67.9 (CH), 39.2 (CH_2), 25.7 (CH_3), 23.4 (CH_2), 23.4 (CH_3), 17.6 (CH_3).

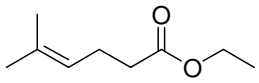
6-Bromo-2-methylhept-2-ene 455.[205]



$C_8H_{15}Br$
Mol. Wt.: 191.11

A solution of 6-methylhept-5-en-2-ol **454** (4.5 g, 35.1 mmol) and triphenylphosphine (10.3 g, 39.3 mmol) in CH_2Cl_2 (50 mL) was cooled at 0 ºC and placed in the dark. *N*-bromosuccinimide (7.7 g, 43.2 mmol) was added in portions of approximately 2 g every 20 m. Once addition was complete, the mixture was left under these conditions for a further 1 h, after which time, TLC analysis showed the reaction to be complete (R_f 0.82 in CH_2Cl_2). The mixture was poured into cold PE (160 mL) and filtered through a pad of silica gel using PE as eluent. The filtrate was concentrated and purification was carried out by flash chromatography (hexane) to give a colourless oil (4.4 g, 65%) IR (film): ν_{max} 2984, 1310 (s), 1287, 890 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.09 (br t, 1H, *J*=7.4 Hz, CC*H*), 4.15 (m, 1H, C*H*Br), 2.15 (m, 2H, CHBrCH_2), 1.90-1.63 (m, 2H, CH_2CHC), 1.72 (d, 3H, *J*=6.3 Hz, CHBrCH_3), 1.69 (s, 3H, CCH_3), 1.64 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.8 (C), 122.8 (CH), 51.3 (CH), 41.2 (CH_2), 26.4 (CH_2), 26.3 (CH_3), 25.7 (CH_3), 17.7 (CH_3).

5-Methylhex-4-enoic acid ethyl ester 465.

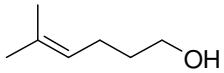


$C_9H_{16}O_2$
Mol. Wt.: 156.22

The title ester **465** was prepared by the standard literature procedure.[184] A solution of 2-methylbut-3-en-2-ol (12.5 mL, 0.12 mol) and catalytic propanoic acid (0.6 mL) in triethyl orthoacetate (150 mL, 0.82 mol) was heated at 90 ºC for 1 h before the ethanol formed was removed by fractional distillation at atmospheric pressure. Heating was continued until ethanol ceased to distil and 1 mL of the alcohol was added to the solution. Distillation of ethanol recommenced maintaining this temperature for a further 30 min more. After cooling to room temperature, the mixture was washed with a solution of water (500 ml) containing camphorsulfonic acid (0.4 g). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 200 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (2 × 300 mL) and brine (300 mL), dried over $MgSO_4$, filtered, and volatiles were removed under reduced pressure. The residue was purified by column chromatography (PE/Et_2O 2:1, R_f 0.54) to give a colourless oil (13.3 g, 70%). IR (film): ν_{max} 2978, 2918, 2186 (w), 1735 (s). 1374, 1178, 1149 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.11-5.05 (m, 1H, C*H*), 4.12 (q, *J*=7.1 Hz, 2H,

OCH_2), 2.303-2.30 (m, 4H, CH_2-CH_2), 1.68 (s, 3H, CCH_3), 1.61 (s, 3H, CCH_3), 1.25 (t, 3H, *J*=7.1 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3 (C), 132.8 (C), 122.3 (CH), 60.0 (CH_2), 34.4 (CH_2), 25.5 (CH_3), 23.5 (CH_2), 17.5 (CH_3), 14.1 (CH_3).

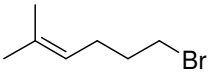
5-Methylhex-4-en-1-ol 466.[181]



$C_7H_{14}O$
Mol. Wt.: 114.18

To a slurry of lithium aluminium hydride (3.19 g, 85.1 mmol) in THF (150 mL) cooled at 0 ºC, was added a solution of 5-methylhex-4-enoic acid ethyl ester **465** (13.30 g, 85.1 mol) in THF (20 mL) under nitrogen. The mixture was stirred overnight at room temperature, cooled again to 0 ºC before water (100 mL) was added very cautiously. The layers were separated, and the aqueous phase was extracted with Et_2O (2 × 80 mL). The combined organic extracts were washed with brine (80 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure, and the resulting oil was used without further purification (13.3 g, 80%). R_f 0.35 in CH_2Cl_2; IR (film): ν_{max} 3326, 2966, 2928 (s), 2861, 1674 (w), 1448, 1377, 1057, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.13 (tt, 1H, *J*=7.2, and 1.3 Hz, C*H*), 3.64 (t, 2H, *J*=6.4 Hz, CH_2OH), 2.07 (q, 2H, *J*=7.2 Hz, CHCH_2), 1.69 (s, 3H, CH_3), 1.66-1.57 (m, 2H, CH_2CH$_2$OH), 1.61 (s, 3H, CH_3), 1.39 (s br, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.3 (C), 123.9 (CH), 62.8 (CH_2), 32.8 (CH_2), 25.8 (CH_3), 24.4 (CH_2), 17.7 (CH_3).

6-Bromo-2-methylhex-2-ene 467. [209]

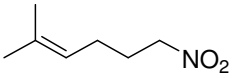


$C_7H_{13}Br$
Mol. Wt.: 177.08

A solution of 5-methylhex-4-en-1-ol **466** (4.32 g, 37.8 mmol) and triphenylphosphine (7.50 g, 42.3 mmol) in CH_2Cl_2 was cooled to 0 ºC and placed in the dark. *N*-bromosuccinimide (10.93 g, 41.6 mmol) was added portionwise (approximatively 2 g every 20 min). When the addition was finished, the mixture was stirred under these conditions for a further 1 h, when TLC analysis showed the reaction was complete (R_f 0.85 in CH_2Cl_2). The mixture was poured into cold PE (180 mL) and filtered through a pad of silica gel using PE as eluent. The filtrate was concentrated and the residue purified by flash chromatography (hexane) to give a colourless oil (4.15 g, 62%). IR (film): ν_{max} 2966, 2929 (s), 2856, 1674 (w), 1435, 1377, 1249 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.07 (tt, 1H, *J*=7.2 and 1.3 Hz, C*H*), 3.40 (t, 2H, *J*=7.0 Hz, CH_2Br), 2.13 (q, 2H, *J*=7.2 Hz,

CHCH_2), 1.93-1.84 (m, 2H, CH_2CH$_2$Br), 1.69 (d, 3H, *J*=1.3 Hz, CH_3), 1.63 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 133.2 (C), 122.5 (CH), 33.6 (CH_2), 32.9 (CH_2), 26.4 (CH_3), 25.7 (CH_2), 17.8 (CH_3).

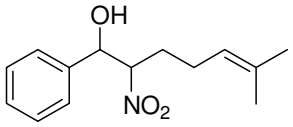
2-Methyl-6-nitrohex-2-ene 460.



$C_7H_{13}NO_2$
Mol. Wt.: 143.18

The title compound was prepared by the standard literature procedure.[210] To a mixture of sodium nitrate (4.95 g, 79.0 mmol) in DMSO (40 mL), a solution of 6-bromo-2-methylhex-2-ene **467** (10.00 g, 56.5 mmol) in DMSO (25 mL) was added dropwise at room temperature, and the resulting reaction mixture was stirred for 4 h until the reaction was complete by TLC (R_f 0.71 in CH_2Cl_2). The reaction was quenched with water (50 mL), and extracted with PE (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and the volatiles were remover under reduced pressure. A pale yellow oil (7.13 g, 63%) was obtained after purification by flash chromatography (PE: Et_2O 2:1). IR (film): ν_{max} 2969, 2920, 1674 (w), 1549 (s), 1434, 1378 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.08-5.04 (m, 1H, C*H*), 4.36 (t, 2H, *J*=6.7 Hz, CH_2NO_2), 2.16-1.09 (m, 4H, CHCH_2CH_2), 1.79 (s, 3H, CH_3), 1.60 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.2 (C), 121.6 (CH), 75.0 (CH_2), 27.5 (CH_2), 25.7 (CH_3), 24.6 (CH_2), 17.7 (CH_3); MS (CI) m/z (%): 144 (21, M+H); HRMS: M+H, obtained 144.10245 $C_7H_{14}NO_2$ requires 144.10211.

6-Methyl-2-nitro-1-phenylhept-5-en-1-ol 468.



$C_{14}H_{19}NO_3$
Mol. Wt.: 249.30

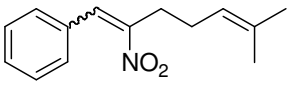
The title compound was prepared by the standard literature procedure.[189] Benzaldehyde (0.71 mL, 7 mmol) was added to 2-methyl-6-nitrohex-2-ene **460** (1.00 g, 7 mmol) at 0 ºC. The mixture was stirred for 15 min before Amberlyst A-21 (1.26 g) was added in one portion and the resulting mixture was stirred for 15 h. Amberlyst A-21 was separated by filtration and washed with ethyl acetate (4 × 25 mL). The combined filtrates were evaporated under vacuum to give the desired product (611 mg, 35%) as a mixture of diastereomers (ratio 83/17), which could be separated by flash chromatography (PE/Et_2O 6:1, R_f 0.48 and 0.37).

Major diastereomer: IR (film): ν_{max} 3532, 3034, 2970, 2857, 1548 (s), 1454, 1437, 1375, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.41-7.35 (m, 5H, H_{Ar}), 5.01 (dd, 1H, *J*=8.8 and 4.1 Hz, C*H*OH), 4.88-4.85 (m, 1H, CH_2CH), 4.73-4.69 (m, 1H, $CHNO_2$), 2.50 (s, 1H, O*H*), 1.95-1.91 (m, 4H, CH_2CH_2), 1.63 (s, 3H, CCH_3), 1.50 (s, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.7 (C), 134.2 (C), 129.3 (CH), 129.1 (2 CH), 127.0 (2 CH), 121.3 (CH), 93.2 (CH), 75.8 (CH), 30.6 (CH_2), 25.7 (CH_3), 24.2 (CH_2), 17.7 (CH_3).

Minor diastereomer: IR (film): ν_{max} 3422, 2967, 2855, 1627 (w), 1549 (s), 1454, 1375, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.41-7.34 (m, 5H, H_{Ar}), 5.19 (d, 1H, *J*=8.8 Hz, C*H*OH), 4.89-4.84 (m, 1H, CH_2CH), 4.75-4.68 (m, 1H, $CHNO_2$), 1.98-1.87 (m, 4H, CH_2CH_2), 1.63 (s, 3H, CCH_3), 1.50 (s, 3H, CCH_3), 1.36 (br s, 1H, O*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.7 (C), 134.2 (C), 129.3 (CH), 129.1 (2 CH), 127.0 (2 CH), 121.3 (CH), 93.2 (CH), 75.8 (CH), 30.6 (CH_2), 25.7 (CH_3), 24.2 (CH_2), 17.7 (CH_3).

MS (APCI, negative mode) m/z (%): 142.39 (52, M-PhCHOH), 201.45 (13, M-H-NO_2), 231.32 (18, M-H_2O), 248.52 (100, M-H).

1-(6-Methyl-2-nitrohepta-1,5-dienyl)benzene 469.

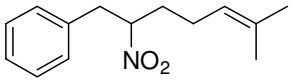


$C_{14}H_{17}NO_2$
Mol. Wt.: 231.29

The title compound was prepared by the standard literature procedure.[190] Trifluoroacetic anhydride (862 μL, 4.2 mmol) was added dropwise to a solution of nitro alcohol **468** (1.00 g, 4 mmol) in CH_2Cl_2 (8 mL) at 0 ºC. After 5 min, triethylamine (1.17 mL, 8.4 mmol) was added dropwise, reaction mixture was monitored by TLC (R_f 0.79 in CH_2Cl_2) and stirring was maintained for 24 h. The reaction was diluted with CH_2Cl_2 (10 mL), then washed sequentially with water (10 mL), a saturated aqueous solution of ammonium chloride (10 mL), and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was purified by flash chromatography (PE/Et_2O 4:1) to give the title nitro alkene **469** (390 mg, 42%). IR (film): ν_{max} 2969, 2927, 2857 (w), 1650 (w), 1520 (s), 1496, 1376, 1322 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (s, 1H, PhC*H*), 7.45-7.42 (m, 5H, H_{Ar}), 5.17-5.11 (m, 1H, CH_2CH), 2.90-2.84 (m, 2H, CH_2CNO_2), 2.37-2.29 (m, 2H, CH_2CH), 1.68 (s, 3H, CCH_3), 1.62 (s, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.0 (C), 134.0 (C), 133.8 (CH), 132.5 (C), 130.0 (CH), 129.7 (2 CH), 129.0 (2 CH), 122.1 (CH), 27.4 (CH_2), 26.4 (CH_2),

25.7 (CH_3), 17.7 (CH_3); MS (EI) m/z (%): 231 (44, M^+); HRMS: M^+, measured mass 231.12473 $C_{14}H_{17}NO_2$ requires 231.12537.

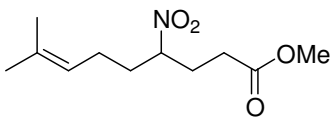
1-(6-Methyl-2-nitrohept-5-enyl)benzene 470.



$C_{14}H_{19}NO_2$
Mol. Wt.: 233.31

The title compound was prepared by the standard literature procedure.[211] A mixture of above nitro olefin **469** (0.50 g, 2.2 mmol) and methanol (40 mL) was cooled to 0 ºC, and under vigorously stirring, slow addition (over 20 min) of sodium borohydride (1.25 g, 33 mmol) was carried out. During addition, hydrogen evolution occurred, and the mixture became quite warm and finally attained a yellow-brown colouration. The mixture was left under stirring for a further 40 min before methanol was removed by concentration under vacuum. The residue obtained was dissolved in water (40 mL) and Et_2O (40 mL), the phases were separated and the organic phase washed sequentially with water (40 mL), a saturated aqueous solution of sodium bicarbonate (40 mL) and brine (40 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated to give the crude product which was purified by flash chromatography (PE/Et_2O 2:1, R_f 0.74 in CH_2Cl_2) to yield a pale yellow oil (770 mg, 35%). IR (film): ν_{max} 3031, 2925, 2857, 1549 (s), 1497, 1455, 1375, 699 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.34-7.31 (m, 2H, H_{Ar}), 7.29-7.26 (m, 1H, H_{Ar}), 7.16 (d, 2H, *J*=7.0 Hz, H_{Ar}), 5.04 (tt, 1H, *J*=7.1 and 1.4 Hz, CH_2CH), 4.75-4.65 (m, 1H, $CHNO_2$), 3.26 (d, 1H, *J*=14.2 and 8.7 Hz, PhC*H*H), 3.04 (d, 1H, *J*=14.2 and 5.7 Hz, PhCH*H*), 2.13-2.00 (m, 2H, CH_2CHNO_2), 1.81-1.76 (m, 2H, CH_2CH_2CH), 1.70 (s, 3H, CCH_3), 1.59 (s, 3H, CCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 135.6 (C), 134.0 (C), 128.8 (2 CH), 128.8 (2 CH), 127.4 (CH), 121.6 (CH), 89.4 (CH), 40.4 (CH_2), 33.5 (CH_2), 25.7 (CH_3), 24.3 (CH_2), 17.7 (CH_3); MS (CI) m/z (%): 234 (13, M+H); HRMS: M+H, measured mass 234.14892 $C_{14}H_{20}NO_2$ requires 234.14940.

8-Methyl-4-nitronon-7-enoic acid methyl ester 471.

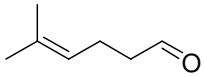


$C_{11}H_{19}NO_4$
Mol. Wt.: 229.27

The title compound **471** was prepared by the standard literature procedure.[192a] 2-Methyl-6-nitrohex-2-ene **460** (2.3 g, 16.2 mmol) and methylacrylate (1 mL, 10.8 mmol) were added to a solution of sodium hydroxide (0.025 M, 25 mL). After 5 min, cetyltrimethyl

ammonium bromide (393 mg) was added at room temperature. The progress of the reaction was monitored by TLC and when complete, the reaction mixture was quenched with brine (30 mL), and the resulting aqueous solution extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under vacuum to afford the crude product, which was purified by flash chromatography (PE/Et_2O 3:1, R_f 0.62 in CH_2Cl_2). The nitro derivative **471** was obtained as a pale yellow oil (496 mg, 20%). IR (film): ν_{max} 2954, 2929, 1738 (s), 1548 (s), 1438, 1176 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.05-5.02 (m, 1H, CC*H*), 4.57-4.52 (m, 1H, C*H*NO_2), 3.69 (s, 3H, OCH_3), 2.42-2.30 (m; 2H, CH_2CO), 2.25-2.18 (m, 1H, NO_2CHC*H*H), 2.13-2.00 (m, 4H CHCH_2CH_2), 1.78-1.71 (m, 1H, NO_2CHC*H*H), 1.69 (s, 3H, CCH_3), 1.58 (s, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4 (C), 134.1 (C), 121.6 (CH), 87.3 (CH), 51.0 (CH_3), 34.0 (CH_2), 30.0 (CH_2), 28.7 (CH_2), 25.8 (CH_3), 24.3 (CH_2), 17.8 (CH_3); MS (CI) m/z (%): 230 (52, M+H); HRMS: M+H, measured mass 230.13872 $C_{11}H_{20}NO_4$ requires 230.13923.

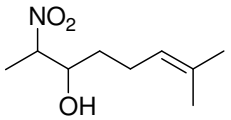
5-Methylhex-4-enal 472.[212]



$C_7H_{12}O$
Mol. Wt.: 112.17

DMSO (12.2 mL, 176 mmol) in CH_2Cl_2 (60 mL) was added to a solution of oxalyl chloride (7.6 mL, 88 mmol) in CH_2Cl_2 (60 mL) at -78 ºC. The solution was stirred for 45 min at the same temperature before a solution of 5-methylhex-4-en-1-ol **466** (5.0 g, 44 mmol) in CH_2Cl_2 (60 mL) was added slowly over 5 min. The mixture was stirred for a further 1 h before triethylamine (67 mL, 485 mmol) was added over 5 min and then allowed to warm slowly to room temperature. The solution was washed successively with an aqueous solution of hydrochloric acid (2N, 120 mL), a solution of saturated aqueous sodium hydrogen carbonate (120 mL), and brine (120 mL) before being dried over $MgSO_4$, filtered and concentrated. The crude product was distilled under reduced pressure to yield the aldehyde **472** (8.69 g, 88%) as a pale yellow oil (b.p. 73-76 ºC / 50 mmHg). IR (film): ν_{max} 2967, 2926, 2725 (w), 1724 (s), 1449, 1377, 808 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.75 (t, 1H, *J*=1.9 Hz, C*H*O), 5.08 (t, 1H, *J*=7.2 Hz, C*H*CH_2), 2.48-2.42 (m, 2H, CH_2CHO), 2.34-2.27 (m, 2H, CHCH_2) 1.68 (s, 3H, CCH_3), 1.62 (s, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.7 (CH), 133.3 (C), 122.2 (CH), 44.0 (CH_2), 25.2 (CH_3), 21.0 (CH_2), 13.1(CH_3).

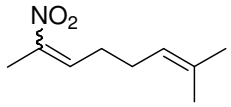
7-Methyl-2-nitrooct-6-en-3-ol 473.[190a]



$C_9H_{17}NO_3$
Mol. Wt.: 187.24

The title nitro alcohol **473** was prepared by the standard literature procedure.[190] A catalytic amount of potassium *tert*-butoxide (0.86 g, 7.6 mmol) and nitroethane (8.3 mL, 114 mmol) were added to a solution of 5-methylhex-4-enal **467** (4.26 g, 38 mmol) in a mixture of THF (34 mL) and *t*-BuOH (25 mL), and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with water (25 mL) and brine (25 mL). The aqueous layer was back extracted with CH_2Cl_2 (25 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash chromatography (PE/CH_2Cl_2 1:1, R_f 0.21 in CH_2Cl_2) to afford the nitro alcohol (2.86 g, 40%) as a clear oil containing a mixture of both possible diastereoisomers (56/44). IR (film): ν_{max} 3067, 2930, 2860, 1725, 1684 (s), 1448, 1259, 911 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.12-5.09 (m, 1H, C*H*), 4.56-4.48 (m, 1H, C*H*NO_2), 4.20-4.16 (m, 0.5H, C*H*OH), 3.94-3.90 (m, 0.5H, C*H*OH), 2.38 (d, 0.5H, *J*=12.3 Hz, CHO*H*), 2.27 (d, 0.5H, *J*=8.1 Hz, CHO*H*), 2.21-2.13 (m, 2H, CHOHCH_2), 1.70 (s, 3H, CCH_3), 1.63 (s, 3H, CCH_3)), 1.55 (d, 1.5H, *J*=6.9 Hz, CHCH_3), 1.55 (d, 1.5H, *J*=6.9 Hz, CHCH_3), 1.63-1.58 (m, 2H, CHCH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.5 (C), 122.9 and 122.8 (CH), 87.9 and 86.5 (CH), 72.6 and 71.7 (CH), 33.0 (CH_2), 25.8 (CH_3), 24.3 and 23.8 (CH_2), 17.8 and 16.3 (CH_3), 12.5 (CH_3).

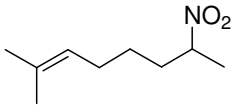
2-Methyl-7-nitroocta-2,6-diene 474.



$C_9H_{15}NO_2$
Mol. Wt.: 169.22

The elimination was carried out in a similar manner as in the synthesis of 1-(6-methyl-2-nitrohepta-1,5-dienyl)benzene **469**, and after purification by flash chromatography (PE/Et_2O 4:1, R_f 0.65 in CH_2Cl_2), the expected nitro alkene **474** was obtained as a yellow oil (836 mg, 37%). IR (film): ν_{max} 3359, 2921, 1790, 1558, 1222, 1148 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.12 (br t, 1H, *J*=7.4 Hz, CH_3CC*H*), 5.13-5.08 (m, 1H, CH_2C*H*C), 2.26-2.15 (m, 2H, CH_2CHCNO_2), 2.17 (s, 3H, CH_3CNO_2), 1.70 (s, 3H, CCH_3), 1.62-1.54 (m, 2H, CH_2CHC$(CH_3)_2$), 1.61 (s, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.3 (C), 136.0 (CH), 122.2 (C), 121.4 (CH), 30.0 (CH_2), 25.7 (CH_3), 23.6 (CH_2), 17.7 (CH_3), 15.7 (CH_3).

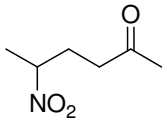
2-Methyl-7-nitrooct-2-ene 475.



$C_9H_{17}NO_2$
Mol. Wt.: 171.24

The title nitro derivative **475** was obtained following the procedure used in the synthesis of 1-(6-methyl-2-nitrohept-5-enyl)benzene **470** giving the product as a colourless oil (323 mg, 40%) after purification by flash chromatography (PE/Et_2O 3:1, R_f 0.72 in CH_2Cl_2). IR (film): ν_{max} 2929, 2862, 1549 (s), 1450, 1390, 1359 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.08-5.03 (m, 1H, C*H*C$(CH_3)_2$), 4.57-4.52 (m, 1H, C*H*NO_2), 2.01-1.98 (m, 2H, CCHC*H*$_2$), 1.73-1.68 (m, 2H, CHNO_2C*H*$_2$), 1.68 (s, 3H, CC*H*$_3$), 1.59 (s, 3H, CC*H*$_3$), 1.57 (d, 3H, *J*=4.3 Hz, CHC*H*$_3$), 1.40-1.33 (m, 2H, CH_2C*H*$_2$$CH_2$); ^{13}C NMR (150 MHz, $CDCl_3$): δ 132.7 (C), 123.4 (CH), 83.7 (CH), 34.8 (CH_2), 27.3 (CH_2), 26.0 (CH_2), 25.9 (CH_3), 19.4 (CH_3), 17.8 (CH_3); MS (ACPI negative) m/z (%): 116.26 (18, M-C_4H_7), 141.04 (100, M-2 Me), 170.34 (6, M-H).

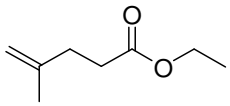
5-Nitrohexan-2-one 476.[213]



$C_6H_{11}NO_3$
Mol. Wt.: 145.16

Nitroethane (7.0 mL, 97.7 mmol) and diisopropylamine (6.8 mL, 48.8 mmol) were successively added to a solution of methylvinyl ketone (7.9 mL, 97.7 mmol) in $CHCl_3$ (50 mL). The reaction was stirred at reflux for 12 h. Water (50 mL) was added to the cooled reaction mixture, phases were separed and the resulting aqueous phase was extracted with Et_2O (3 × 50 mL). Organic phases were combined, dried over $MgSO_4$, filtered and volatiles were removed under reduced pressure. The Michael adduct was obtained as a pale yellow oil (3.25 g, 23%) after purification by flash chromatography (PE/Et_2O 4:1, R_f 0.4 in CH_2Cl_2). IR (film): ν_{max} 2993, 2943, 1718, 1550, 1361, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.66-4.55 (m, 1H, C*H*), 2.51 (t, 2H, *J*=6.7 Hz, OCC*H*$_2$), 2.16 (s, 3H, C*H*$_3$CO), 2.13-2.06 (m, 2H, C*H*$_2$CH), 1.54 (d, 3H, *J*=6.7 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.4 (C), 82.5 (CH), 39.2 (CH_2), 30.0 (CH_3), 28.7 (CH_2), 19.4 (CH_3).

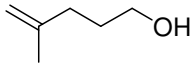
Ethyl 4-methylpent-4-enoate 478.[184]



$C_8H_{14}O_2$
Mol. Wt.: 142.19

The procedure to obtain 5-methylhex-4enoic acid ethyl ester **465** was followed using 2-methylprop-2-en-1-ol (10 mL, 0.12 mol) as the starting allylic alcohol. The ester **478** was obtained as a colourless oil (16.6 g, 90%). IR (film): ν_{max} 3071, 2988, 1730, 1649, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.74 (br s, 1H, C*H*H), 4.68 (br s, 1H, CH*H*), 4.13 (q, 2H, *J*=7.2 Hz, CH_2O), 2.46-2.43 (m, 2H, CH_2C(O)), 2.33-2.30 (m, 2H, CH_3CCH_2), 1.73 (s, 3H, CCH_3), 1.25 (t, 3H, *J*=7.2 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3 (C), 144.1 (C), 110.3 (CH_2), 60.3 (CH_2), 32.7 (CH_2), 32.6 (CH_2), 22.5 (CH_3), 14.2 (CH_3).

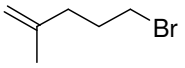
4-Methylpent-4-en-1-ol 479.[214]



$C_6H_{12}O$
Mol. Wt.: 100.16

The reduction of the above ester, ethyl 4-methylpent-4-enoate **478** (13.3 g, 84 mmol) was carried out using a similar procedure as employed for obtaining 5-methylhex-4-en-1-ol **466** , to give a colourless oil (8.2 g, 98%) after purification by flash chromatography (PE/Et_2O 2:1, R_f 0.37 in CH_2Cl_2). IR (film): ν_{max} 3342, 3076 (w), 2938, 1650, 1444, 1052, 885 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.71-4.70 (m, 2H, C*HH*), 3.64 (t, 2H, *J*=6.6 Hz, CH_2OH), 2.08 (t, 2H, *J*=7.6 Hz, CCH_2), 1.77 (br s, 1H, OH), 1.72 (s, 3H, CH_3), 1.72-1.69 (m, 2H, C$H_2$$CH_2$OH); ^{13}C NMR (150 MHz, $CDCl_3$): δ 145.6 (C), 110.2 (CH_2), 62.7 (CH_2), 34.1 (CH_2), 30.5 (CH_2), 19.2 (CH_3).

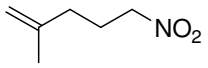
5-Bromo-2-methylpent-1-ene 480.[207]



$C_6H_{11}Br$
Mol. Wt.: 163.05

The product was synthesised by following the bromination procedure described for 6-bromo-2-methylhex-2-ene **467**. 5-Bromo-2-methylpent-1-ene **480** was obtained after purification by flash chromatography (PE/Et_2O 4:1, R_f 0.83 in CH_2Cl_2) as a pale yellow oil (3.65 g, 64%). IR (film): ν_{max} 3053, 2963, 1650 (w), 1478, 1433 1088, 641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.76 (s, 1H, C*H*H), 4.22 (s, 1H, CH*H*), 3.41 (t, 2H, *J*=6.7 Hz, CH_2Br), 2.19-2.14 (m, 2H, CCH_2), 2.04-1.97 (m, 2H C$H_2$$CH_2$Br), 1.72 (s, 3H, C$H_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.0 (C), 111.1 (CH_2), 36.1 (CH_2), 33.4 (CH_2), 30.6 (CH_2), 22.4 (CH_3).

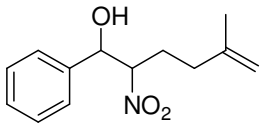
2-Methyl-5-nitropent-1-ene 481.



$C_6H_{11}NO_2$
Mol. Wt.: 129.16

5-Bromo-2-methylpent-1-ene **480** (9.13 g, 56 mmol) was nitrated using a similar method as for the synthesis of 2-methyl-6-nitrohex-2-ene **460**. The reaction was monitored by TLC (R_f 0.75 CH_2Cl_2). The product was obtained as a pale yellow oil (4.92 g, 68%) after purification by flash chromatography (PE/Et_2O, 2:1). IR (film): ν_{max} 2920, 1651 (w), 1549, 1435, 1377, 893 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.80 (d, 1H, *J*=1.0 Hz, C*H*H), 4.72 (d, 1H, *J*=1.0 Hz, CH*H*), 4.38 (t, 2H, *J*=6.9 Hz, CH_2NO_2), 2.22-2.08 (m, 4H, CCH_2CH_2), 1.74 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.0 (C), 111.8 (CH_2), 74.9 (CH_2), 34.1 (CH_2), 25.0 (CH_2), 22.1 (CH_3); MS (CI) m/z (%): 130 (24, M+H); HRMS: M+H, obtained 130.08623 $C_6H_{12}NO_2$ requires 130.08680.

5-Methyl-2-nitro-1-phenylhex-5-en-1-ol 482.



$C_{13}H_{17}NO_3$
Mol. Wt.: 235.28

The condensation was made in an analogous manner as the one carried out for the synthesis of 6-methyl-2-nitro-1-phenylhept-5-en-1-ol **468**, by the use of 2-methyl-5-nitropent-1-ene **481** (0.9 g, 7 mmol). The product contained both diastereomers (3 to 1) which could be separated by column chromatography (PE/Et_2O 4:1, R_f 0.43 and 0.34 in CH_2Cl_2) to give both compounds as pale yellow oils although they were combined for the next step (609 mg, 37%).

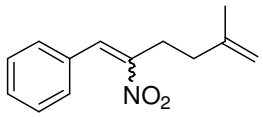
Major diastereomer: IR (film): ν_{max} 3501, 2971, 2935, 1551 (s), 1455, 1373, 766, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.41-7.36 (m, 5H, H_{Ar}), 5.04 (d, 1H, *J*=9.0 Hz, C*H*OH), 4.74-4.70 (m, 2H, CH*H* and C*H*NO_2), 4.56 (br s, 1H, CH*H*), 2.42 (d, 1H, *J*=4.3 Hz, O*H*), 2.30-1.91 (m, 4H, CH_2CH_2), 1.53 (s, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.8 (C), 138.6 (C), 129.4 (2 CH), 126.9 (CH), 126.1 (2 CH), 111.9 (CH_2), 92.9 (CH), 75.7 (CH), 33.4 (CH_2), 28.2 (CH_3), 22.0 (CH_2).

Minor diastereomer: IR (film): ν_{max} 3521, 2972, 2933, 1551 (s), 1454, 1374, 702 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.41-7.36 (m, 5H, H_{Ar}), 5.23 (d, 1H, *J*=4.6 Hz, C*H*OH), 4.74-4.70 (m, 1H, CH*H*), 4.68-4.64 (m, 1H, C*H*NO_2), 4.60 (br s, 1H, CH*H*), 2.63 (d, 1H, *J*=3.1

Hz, O*H*), 2.30-1.91 (m, 4H, CH_2CH_2), 1.56 (s, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.1 (C), 138.4 (C), 129.8 (2 CH), 129.2 (CH), 126.9 (2 CH), 111.8 (CH_2), 92.9 (CH), 74.4 (CH), 33.7 (CH_2), 25.3 (CH_3), 22.2 (CH_2).

MS (APCI negative) m/z (%): 128.11 (36, M-PhCHOH), 179.09 (13, M-C_4H_9), 218.17 (80, M-OH), 234.15 (100, M-H).

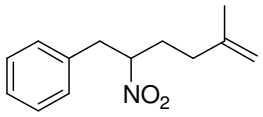
1-(6-Methyl-2-nitrohepta-1,6-dienyl)benzene 483.



$C_{13}H_{15}NO_2$
Mol. Wt.: 217.26

The product was synthesised following the procedure used for the preparation of 1-(6-methyl-2-nitrohepta-1,5-dienyl)benzene **469** (500 mg, 2.1 mmol). After purification by flash chromatography (PE/Et_2O 4:1, R_f 0.79 in CH_2Cl_2), the expected nitro alkene **483** was obtained as an orange oil (222 mg, 48%). IR (film): ν_{max} 3074, 2972, 2937, 1650, 1519 (s), 1449, 1323 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (s, 1H, PhC*H*), 7.49-7.40 (m, 5H, H_{Ar}), 4.79 (s, 1H, C*H*H), 4.75 (s, 1H, CH*H*), 3.01-2.96 (m, 2H, NO_2CCH_2), 2.34 (t, 2H, *J*=8.0 Hz, CH_2CH_3), 1.75 (s, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.8 (C), 143.9 (C), 133.9 (CH), 132.3 (C), 130.1 (CH), 129.7 (2 CH), 129.1 (2 CH), 111.3 (CH_2), 35.7 (CH_2), 25.9 (CH_2), 22.4 (CH_3); MS (CI) m/z (%): 218 (94, M+H); HRMS: M+H, measured mass 218.11835 $C_{13}H_{16}NO_2$ requires 218.11810.

1-(5-Methyl-2-nitrohex-5-enyl)benzene 484.

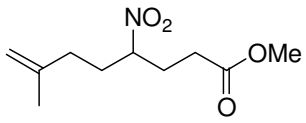


$C_{13}H_{17}NO_2$
Mol. Wt.: 219.28

The condensation was made in a similar manner as the one carried out for the synthesis of 1-(6-methyl-2-nitrohept-5-enyl)benzene **470**. 1-(5-Methyl-2-nitrohex-5-enyl)benzene **484** was obtained as a pale yellow oil (136 mg, 38%) after purification by flash chromatography (PE/Et_2O 4:1, R_f 0.76 in CH_2Cl_2). IR (film): ν_{max} 3031, 2925, 2857, 1549 (s), 1497, 1455, 1375, 699 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34-7.31 (m, 2H, H_{Ar}), 7.29-7.26 (m, 1H, H_{Ar}), 7.17 (d, 2H, *J*=7.4 Hz, H_{Ar}), 4.79 (br s, 1H, CH*H*), 4.74-4.70 (m, 1H, C*H*NO_2), 4.70 (br s, 1H, *CH*H), 3.29 (dd, 1H, *J*=14.2 and 8.5 Hz, PhC*H*H), 3.07 (dd, 1H, *J*=14.2 and 5.9 Hz), 2.22-2.16 (m, 2H, CHCH_2), 1.95-1.90 (m, 2H, CH_2C), 1.69 (s,

3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.2 (C), 135.6 (C), 128.9 (3 CH), 127.5 (2 CH), 111.7 (CH_2), 89.3 (CH), 40.1 (CH_2), 33.7 (CH_2), 30.4 (CH_2), 22.2 (CH_3); MS (EI) m/z (%): 219 (66, M^+); HRMS: M^+, measured mass 219.12588 $C_{13}H_{17}NO_2$ requires 219.12537.

7-Methyl-4-nitrooct-7-enoic acid methyl ester 485.



$C_{10}H_{17}NO_4$
Mol. Wt.: 215.25

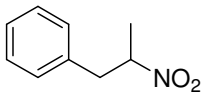
The title Michael adduct was synthesised in a similar manner to the method used for 8-methyl-4-nitronon-7-enoic acid methyl ester **471**, using the appropriate nitro derivative, 2-methyl-5-nitropent-1-ene **481** (2.1 g, 16.2 mmol). After purification by flash chromatography (PE/Et_2O 4:1, R_f 0.59 in CH_2Cl_2), the product was obtained as a pale yellow oil (760 mg, 33%). IR (film): ν_{max} 2936, 2852, 1738 (s), 1651 (w), 1549 (s), 1439, 1371, 1259, 1219, 1176 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.78 (br s, 1H, CH*H*), 4.70 (br s, 1H, C*H*H), 4.60-4.51 (m, 1H, C*H*NO_2), 3.69 (s, 3H, OC*H*$_3$), 2.41-1.82 (m, 8H, 4 C*H*$_2$), 1.71 (s, 3H, CC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4 (C), 143.1 (C), 111.7 (CH_2), 87.2 (CH), 52.0 (CH_3), 33.6 (CH_2), 31.7 (CH_2), 30.0 (CH_2), 28.7 (CH_2), 22.3 (CH_3); MS (CI) m/z (%): 216 (100, M+H); HRMS: M+H, measured mass 216.12372 $C_{10}H_{18}NO_4$ requires 216.13258.

Attempted Intramolecular Ene Reaction of *In situ* Generated α-Acyloxy Nitroso Compounds Using Substrates 470, 471, 475, 484 and 485.- General Method.

To a suspension of potassium *tert*-butoxide (0.35 mg, 0.29 mmol) in Et_2O (1 mL) at 0 ºC was added the appropriately substituted nitro alkene (eg. 2-methyl-7-nitrooct-2-ene **475** (50 mg, 0.29 mmol)). Acetic anhydride (0.29 μL, 0.29 mmol) was added dropwise after stirring for 45 min at the same temperature. The progress of the reaction was monitored by TLC and the characteristical blue colouration appeared in a very low intensity. Water was added (1 mL), phases were separated and the organic phase was dried over $MgSO_4$, filtered and concentrated under vacuum. Examination of the crude reaction mixture by proton NMR spectroscopy did not provide any evidence for the ene adduct or the derived nitrone. As tabulated in the results and discussions section (Table 17) the derived oxime

and/or ketone were obtained. The identity of these products was confirmed either from literature data or by spectral comparison with compounds already prepared in this work.

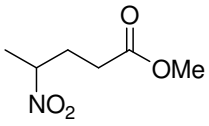
1-(3-Nitrobutan-2-yl)benzene 511. [215]



$C_9H_{11}NO_2$
Mol. Wt.: 165,19

The title nitro derivative **511** was obtained from 1-(2-nitro-propenyl)benzene **446** (2.53 g, 15.5 mmol) following the procedure used for the synthesis of 1-(6-methyl-2-nitrohept-5-enyl)benzene **470** to give the product as a pale yellow oil (1.23 g, 48%) after purification by flash chromatography (PE/Et_2O 2:1, R_f 0.51 in CH_2Cl_2). IR (film): ν_{max} 2938, 1713, 1545 (s), 1454, 1388, 1361, 698 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.33-7.30 (m, 2H, H_{Ar}), 7.28-7.26 (m, 1H, H_{Ar}), 7.17-7.16 (m, 2H, H_{Ar}), 4.81-4.75 (m, 1H, C*H*NO_2), 3.33 (dd, 1H, *J*=14.1 and 7.4 Hz, PhC*H*H), 3.01 (dd, 1H, *J*=14.1 and 6.8 Hz, PhCH*H*), 1.55 (d, 3H, *J*=6.8 Hz, CHCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.5 (C), 129.0 (2 CH), 128.8 (2 CH), 127.4 (CH), 84.4 (CH), 41.1 (CH_2), 18.8 (CH_3).

4-Nitropentanoic acid methyl ester 512. [192a]



$C_6H_{11}NO_4$
Mol. Wt.: 161.16

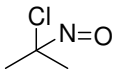
The nitro ester **512** was prepared in the same manner employed in the synthesis of 5-nitrohexan-2-one **476**. Methyl acrylate (10 mL, 110 mmol) was used as the acceptor, and the nitro product **512** was obtained as a pale yellow oil (4.52 g, 25%) after being purified by distillation under reduced pressure (b.p. 110 ºC / 10 mmHg). IR (film): ν_{max} 2993, 2956, 2036 (w), 1733 (s), 1546 (s), 1438, 1359, 1176 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.71-4.60 (m, 1H, C*H*), 3.69 (s, 3H, OCH_3), 2.43-2.03 (m, 4H, CH_2CH_2), 1.56 (d, 3H, *J*=6.7 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4 (C), 82.4 (CH), 51.9 (CH_3), 29.9 (CH_2), 29.8 (CH_2), 19.3 (CH_3).

General procedure for the transformation of nitro compounds into geminal chloro nitroso derivatives.

Potassium *tert*-butoxide (1.0 mmol) was added portionwise to a stirred solution of the appropriate nitro compound (1.0 mmol) in Et_2O (2.2 mL) with one drop of DMF at 0 ºC.

After 0.5 h, reaction mixture was placed in the dark, and oxalyl chloride (1.0 mmol) was added at the same temperature. Vigorous evolution of gases (CO and CO_2) was observed and reaction mixture turned blue. Water was added (3 mL), phases were separated, the organic phase was dried over $MgSO_4$, and volatiles were removed under reduced pressure to give a blue oil. Due to the difficulty of the purification of these products, yields were measured by proton NMR spectra using an internal reference (1,3,5-trimethoxybenzene, 10% mol).

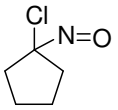
2-Chloro-2-nitrosopropane 493.[216]



C_3H_6ClNO
Mol. Wt.: 107.54

The reaction was carried out according to the above general method on a 12.1 mmol scale to give **493** as a blue oil (191.4 mg, 16%). IR (film): ν_{max} 2944, 2842, 1597, 1552, 1205, 1066, 804 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.52 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 85.7 (C), 27.7 (2 CH_3).

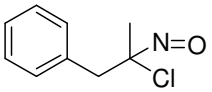
1-Chloro-1-nitrosocyclopentane 513.[41f,204]



C_5H_8ClNO
Mol. Wt.: 133.57

The reaction was carried out according to the above general method on a 0.94 mmol scale to give **513** as a blue oil (30.1 mg, 24%). IR (film): ν_{max} 2966, 1746, 1556, 800 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 2.84-2.76 (m, 2H, CH_2), 2.41-2.35 (m, 2H, CH_2), 1.99-1.88 (m, 4H, 2 CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ 107.0 (C), 44.2 (2 CH_2), 23.3 (2 CH_2).

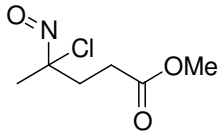
1-(2-chloro-2-nitrosopropyl)benzene 514.



$C_9H_{10}ClNO$
Mol. Wt.: 183.63

The reaction was carried out according to the above general method on a 0.55 mmol scale to give **509** as a blue oil (26.2 mg, 26%). IR (film): ν_{max} 3031, 2962, 1746, 1602, 1559 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.34 (m, 2H, H_{meta}), 7.27 (m, 1H, H_{para}), 7.23 (m, 2H, H_{orto}), 3.65 and 3.59 (AB system, 2H, J=14.2 Hz, CH_2), 2.06 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 132.6 (C), 128.7 (2 CH), 130.5 (2 CH), 128.8 (CH), 104.4 (C), 48.4 (CH_2), 28.4 (CH_3); MS (CI) m/z (%): 150 (51, (M-Cl)+H).

Methyl 4-chloro-4-nitrosopentanoate 516.



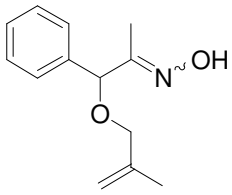
$C_6H_{10}ClNO_3$
Mol. Wt.: 179.60

The reaction was carried out according to the above general method on a 0.46 mmol scale to give **516** as a blue oil (23 mg, 28%). IR (film): ν_{max} 2956, 1734, 1550, 1439, 1370 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 3.70 (s, 3H, OC*H*$_3$), 2.48-2.36 (m, 2H, C*H*$_2$CO), 2.31-2.22 (m, 1H, C*H*HCCl), 2.21 (s, 3H, C*H*$_3$CCl), 2.13-2.07 (m, 1H, CH*H*CCl); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.5 (C), 115.7 (C), 51.9 (CH_3), 29.9 (CH_2), 29.8 (CH_2), 19.3 (CH_3).

Attempted Intramolecular Ene Reaction of *In situ* Generated α-Chloro Nitroso Compounds from Nitro Precursors 470, 471, 475, 484 and 485. - General Method.

The following method for substrate 2-methyl-7-nitrooct-2-ene **475** is representative. To a suspension of potassium *tert*-butoxide (35mg, 0.29 mmol) in Et_2O (1 mL) containing DMF as catalyst (1 drop) at 0 ºC was added the nitro compound (50 mg, 0.29 mmol)). After 45 min of stirring the reaction mixture was cooled to -10 ºC and oxalyl chloride (37 mg, 0.29 mmol) was added rapidly in one portion. Evolution of gas was observed together with blue colouration of the reaction mixture. The progress of the reaction was monitored by TLC. Water was added (1 mL), phases were separated and the organic phase was dried over $MgSO_4$, filtered and concentrated under vacuum. Examination of the crude reaction mixture by proton NMR spectroscopy did not provide any evidence for the ene adduct or the derived nitrone. As tabulated in the results and discussions section (Table 19) the identity of these products was confirmed either from literature data or by spectral comparison with compounds already prepared in this work.

1-(2-methylallyloxy)-1-phenylpropan-2-one oxime 447.



$C_{13}H_{17}NO_2$
Mol. Wt.: 219.28

The title compound **447** was prepared by a standard literature procedure.[193] Chromium (II) chloride was prepared from chromium (III) chloride (1 g) in water (4.7 mL) and

concentrated hydrochloric acid (2 mL) by reduction with an excess of granulated zinc (0.6 g).[217] The blue chromium (II) solution was filtered into a solution of [1-(1-(2-methylallyloxy)-2-nitropropyl)]benzene **442** (185 mg, 0.79 mmol) in acetone (50 mL). In seconds, the blue solution became green, and was stirred for 30 min before brine (50 mL) was added. The crude product was extracted with Et_2O (2 × 50 mL). The organic phases were combined, washed with water (50 mL), dried over $MgSO_4$, filtered and volatiles were removed under reduced pressure. The crude product was filtered through silica with CH_2Cl_2 as eluent giving the product as a colourless oil (126 mg, 73%) IR (film): ν_{max} 3232, 3080, 2916, 1656 (w), 1494, 1450, 1367, 905, 700 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.27 (br s, 1H; NO*H*), 7.43 (d, 2H, *J*=7.6 Hz, H_{Ar}), 7. 36 (t, 2H, *J*=7.6 Hz, H_{Ar}), 7.31-7.28 (m, 1H, H_{Ar}), 5.04 (s, 1H, CH*H*), 5.01 (s, 1H, PhC*H*O), 4.93 (s, 1H, C*H*H), 3.95 (d, 2H, *J*=7.1 Hz, CH_2O), 1.78 (br s, 6H, 2 CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8 (C), 141.8 (C), 138.4 (C), 128.7 (2 CH), 127.7 (CH), 126.3 (2 CH), 112.4 (CH_2), 81.1 (CH), 72.6 (CH_2), 19.6 (CH_3), 9.3 (CH_3); Ms (EI) m/z (%): 219 (10, M^+); HRMS: M^+, measured mass 219.12573 $C_{13}H_{17}NO_2$ requires 219.12538.

CHAPTER 5 – REFERENCES

[1] a) H. Yamamoto and M. Kawasaki, *Bull. Chem. Soc. Jpn.*, **2007**, Vol 80 (4), pp 595-607. b) M. A. Brimble, C. H. Heathcock and G. N. Nobin, *Tetrahedron: Asymmetry,* **1996**, Vol 7 (7), pp 2007-2016. c) M. A. Brimble and C. H. Heathcock, *J. Org. Chem.*, **1993**, Vol 58 (19), pp 5261-5263. d) Y. Leblanc, R. Zamboni and M. A. Bernstein, *J. Org. Chem.*, **1991**, Vol 56 (5), pp 1971-1972. e) C. C. Cheng, C. A. Seymour, M. A. Petti, F. D. Greene and J. F. Blount, *J. Org. Chem.*, **1984**, Vol 49 (16), pp 2910-2916.

[2] W. Adam and O. Krebs, *Chem. Rev.*, **2003**, Vol 103 (10), pp 4131-4146.

[3] G. W. Kirby, *Chem. Soc. Rev.*, **1977**, Vol 6, pp 1-24.

[4] O. Touster, *Org. React*, **1953**, Vol 7, p 327.

[5] J. H. Boyer, *The Chemistry of the Nitro and Nitroso Group,* Part 1, **1969**, Ed.; Interscience, NY., Chapter 5, pp 215-299.

[6] a) H. Metzger and H. Meier, *in Methoden der Organischen Chemie,* **1971**, Ed.; Georg Thieme Verlag: Stuttgart, p 1017 and 1090. b) B. C. Challis and A. J. Lawson, *J. Chem. Soc. B*, **1971**, pp 770-775.

[7] B. G. Gowenlock and G. B. Richter-Addo*, Chem. Rev.*, **2004**, Vol 104 (7), pp 3315-3340.

[8] a) Q. Q. Ridd, *Chem. Soc. Rev.*, **1961**, Vol 15, pp 418-441. b) B. C. Challis and A. J. Lawson, *J. Chem. Soc. B*, **1971**, pp 770-775. c) E. Bosch and J. K. Kochi. *J. Org. Chem.*, **1994**, Vol 59 (19), pp 5573-5586. d) A. Baeyer and H. Caro, *Ber*, **1874**, Vol 7 (2), pp 963-968. e) F. Radner, A. Wall and M. Loncar, *Acta Chem. Scand.,* **1990**, Vol 44, pp 152-153. f) J. H. Atherton, R. B. Moodie and D. R. Noble, *J. Chem. Soc., Perkin Trans. 2*, **2000**, pp 229-234.

[9] A. Baeyer, *Ber.*, **1874**, Vol 7 (2), pp 1638-1640.

[10] B. Oddo, *Gazz. Chim. Ital.,* **1911**, Vol 39, p 659.

[11] J. M. Kauffman, J. Green, M. S. Cohen, M. M. Fein and E. L. Cottrill, *J. Am. Chem. Soc.*, **1964**, Vol 86 (19), pp 4210-4211. b) L. I. Zakharkin and G. G. Zhigareva, *J. Gen. Chem.*, **1975**, Vol 45, pp 1268-1275.

[12] a) J. C. Motte and H. G. Viehe, *Chimia*, **1975**, Vol 29, pp 515-516. b) C. Eaborn, I. D. Jenkinsand and D. R. M. Walton, *J. Chem. Soc., Perkin Trans. 1*, **1974**, pp 870-871.

[13] E. C. Taylor, R. H. Danforth and A. McKillop, *J. Org. Chem.,* **1973**, Vol 38 (11), pp 2088-2089.

[14] G. Bartoli, R. Leardini, A. Medici and G. Rosini, *J. Chem. Soc., Perkin Trans.* 1, **1978**, pp 692-696.

[15] L. J. Beckham, W. A. Fessler and M. A. Kise, *Chem. Rev.*, **1951**, Vol 24 (3), pp 319-396.

[16] a) P. P. Kadzyauskas and N. S. Zefirov, *Russ. Chem. Rev.*, **1968**, Vol 37, pp 543-550. b) O. Wallach, *Terpene und Campher*; 2nd ed.; Veit and Co.: Leipzig, **1914**. c) M. N. Mallya, G. Nagendrappa, J. S. Prasad, M. A Sridhar, N. K. Lokanath and N. S. Begum, *Tetrahedron Lett.*, **2001**, Vol 42 (13), pp 2565-2568.

[17] S. M. Ali, Y. Matsuda and S. Tanimoto, *Synthesis*, **1988**, No 11, pp 805-806.

[18] G. E. Keck, R. R. Webb and J. B. Yates, *Tetrahedron*, **1981**, Vol 37 (23), pp 4007-4016.

[19] a) J. E. T. Corrie, G. W. Kirby and J. W. M. Mackinnon, *J. Chem. Soc., Perkin Trans. 1*, **1985**, pp 883-886. b) G. W. Kirby, H. McGuigan and D. McLean, *J. Chem. Soc., Perkin Trans. 1*, **1985**, pp 1961-1966.

[20] W. Adam, N. Bottke, O. Krebs, C. R. Saha-Möller, *Eur. J. Org. Chem.*, **1999** (8), pp 1963-1965.

[21] A. Fakhruddin, S. Iwasa, H. Nishiyama and K. Tsutsumi, *Tetrahedron Lett*., **2004**, Vol 45 (51), pp 9323-9326.

[22] a) P. Quadrelli, A. G. Invernizzi and P. Caramella, *Tetrahedron Lett.*, **1996**, Vol 37 (11), pp 1909-1912. b) P. Quadrelli, M. Mella and P. Caramella, *Tetrahedron Lett.,* **1998**, Vol 39 (20), pp 3233-3236.

[23] a) P. E. O'Bannon and W. P. Dailey, *Tetrahedron Lett*., **1988**, Vol 29 (45), pp 5719-5722. b) P. E. O'Bannon and W. P. Dailey, *J. Org. Chem*., **1989**, Vol 54 (13), pp 3096-3101.

[24] a) P. Quadrelli, G. Campari, M. Mella and P. Caramella, *Tetrahedron Lett*., **2000**, Vol 41 (12), pp 2019-2022. b) P. Quadrelli, M. Mella and P. Caramella, *Tetrahedron Lett*., **1999**, Vol 40 (4), pp 797-800.

[25] a) H. Z. Caro, *Angew. Chem*., **1898**, Vol 11 (36), pp 845-846. b) R. R. Holmes, R. P. Bayer, L. A. Errede, H. R. Davis, A. W Wiesenfeld, P. M. Bergman and D. L. Nicholas, *J. Org. Chem.*, **1965**, Vol 30 (11), pp 3837-3840. c) R. R. Holmes, *J.*

Org. Chem., **1964**, Vol 29 (10), pp 3076-3078. d) J. K. Crandall and T. Reix , *J. Org. Chem.* **1992**, Vol 57 (25), pp 6759-6764.

[26] a) R. R. Holmes and R. P. Bayer, *J. Am. Chem. Soc.,* **1960**, Vol 82 (13), pp 3454-3456. b) J. W. Gorrod, *Tetrahedron Lett.*, **1968**, Vol 9 (59), pp 6155-6158. c) K. M. Ibne-Rasa and E. Koubek, *J. Org. Chem.*, **1963**, Vol 28 (11), pp 3240-3241. d) E. J. Corey and A. W. Gross, *Tetrahedron Lett.,* **1984**, Vol 25 (5), pp 491-494.

[27] M. Hedayatullah, F. Thevenet and L. Denivelle, *Tetrahedron Lett.*, **1977**, Vol 18 (18), pp 1595-1596.

[28] a) M. J. Corkill, A. P. Cox and J. A. Norris, *J. Chem. Soc., Chem. Commun.*, **1978**, pp 388-389. b) R. Okazaki, T. Hosogai, E. Iwadare, M Hashimoto and N. Inamoto, *Bull. Chem. Soc. Jpn.*, **1969**, Vol 42 (12), pp 3611-3612. c) L. Nunno, S. Florio and P. E. Todesco, *J. Chem. Soc. C*, **1970**, pp 1433-1434. d) K. E. Gilbert and W. T. Borden, *J. Org. Chem.*, **1979**, Vol 44 (4), pp 659-661. e) H. H. Baer and S. H. L. Chiu, *Can. J. Chem.*, **1973**, Vol 51 (11), pp 1812-1818. f) J. E. Baldwin, A. K. Qureshi and B. Sklarz, *J. Chem. Soc., Chem. Commun.* (London), **1968**, pp 373-374 g) A. H. Beckett, G. R. Jones and R. T. Coutts, *Tetrahedron*, **1976**, Vol 32 (11), pp 1267-1276. h) R. J. Holman and M. J. Perkins, *J. Chem. Soc. C*, **1970**, p 2195.

[29] W. R. Thiel and K. Krohn, *Chem. Eur. J.,* **2002**, Vol 8 (5), pp 1049-1058.

[30] A. V. Biradar, T. V. Kotbagi, M. K. Dongare and S. B. Umbarkar, *Tetrahedron Lett.,* **2008**, Vol 49 (22), pp 3616-3619.

[31] a) J. W. Hartgerink, J. B. F. N. Engberts, A. J. W. Wajer and J. de Boer, *Recl. Trav. Chim. Pays-Bas*, **1969**, Vol 88 (5), pp 481-484. b) G. H. Coleman, C. M. McCloskey and F. A. Stuart, *Organic Syntheses*, Collective Volume 3, **1955**, Ed.; Wiley & Sons, N.Y., p 668.

[32] a) S. Liebeskind, K. B. Sharpless, R. D. Wilson and J. A. Ibers, *J. Am. Chem. Soc.*, **1978**, Vol 100 (22), pp 7061-7063. b) Y. Yost, *J. Med. Chem.*, **1969**, Vol 12 (5), p 961.

[33] a) S. Singh and K. M. Nicholas, *Synth. Commun.*, **2001**, Vol 31 (20), pp 3087-3097. b) R. S. Srivastava and K. M. Nicholas, *Tetrahedron Lett.*, **1994**, Vol 35 (47), pp 8739-8742. c) R. S. Srivastava, M. A. Khan and K. M. Nicholas, *J. Am. Chem. Soc.*, **1996**, Vol 118 (13), pp 3311-3312. d) R. S. Srivastava and K. M.

Nicholas, *J. Am. Chem. Soc*,. **1997**, Vol 119 (14), pp 3302-3310. e) M. Johannsen and K. A. Joergensen, *J. Org. Chem*., **1994**, Vol 59 (1), pp 214-216.

[34] M. Johannsen and K. A. Jorgenson, *J. Org. Chem*., **1995**, Vol 60 (18), pp 5979-5982.

[35] a) G. A. Hogan, K. M. Nicholas and R. S. Srivastava, *Tetrahedron Lett*., **2002**, Vol 43 (52), pp 9505-9508. b) A. A. Gallo, K. M. Nicholas and R. S. Srivastava, *Tetrahedron Lett*., **2002**, Vol 43 (52), pp 9505-9508.

[36] a) S. Kobayashi and Y. Aoyama, *Aromatic nitroso, azoxy, azo, and hydrazo compounds*, *Japan Patent 4329*, **1953**. b) F. J. Alway and R. A. Gortner, *Ber.*, **1905**, Vol 38 (2), pp 1899-1901.

[37] a) S. Cenini, F. Ragaini, S. Tollari and D. Paone, *J. Am. Chem. Soc*., **1996**, Vol 118 (47), pp 11964-11965. b) F. Ragaini, S. Cenini, S. Tollari, G. Tummolillo, and R. Beltrami, *Organometallics*, **1999**, Vol 18 (5), pp 928-942. c) R. S. Srivastava and K. M. Nicholas, *J. Chem. Soc., Chem. Commun*., **1998**, pp 2705-2706.

[38] M. K. Kolel-Veetil, M. A. Khan and K. M. Nicholas, *Organometallics*, **2000**, Vol 19 (19), pp 3754-3756.

[39] R. S. Srivastava, M. Kolel-Veetil, K. M. Nicholas, *Tetrahedron Lett*., **2002**, Vol 43 (6), pp 931-934.

[40] a) R. N. Haszeldine, *J. Chem. Soc.*, **1953**, pp 2075-2081. b) J. Banus, *J. Chem. Soc.,* **1953**, pp 3755-3761. c) A. H. Dinwoodie and R. N. Haszeldine, *J. Chem. Soc.,* **1965**, pp 1675-1681. d) J. Mason and J. Dunderdale, *J. Chem. Soc.,* **1956**, pp 754-759. e) W. Pritzkow and H. Nitzer, *J. Prakt. Chem.,* **1964**, Vol *25*, p 69. f) E. C. Stump, W. H. Oliver and C. D. Padgeti, *J. Org. Chem.,* **1968**, Vol 33 (5), pp 2102-2104. g) T. Umemoto and H. Tsutsumi, *Bull. Chem. Soc. Jpn.,* **1983**, Vol 56 (2), pp 631-632.

[41] a) M. Christl and R. Huisgen, *Ber*., **1973**, Vol 106 (10), pp 3345-3367. b) E. Eibler, J. Kasbauer, H. Pohl and J. Sauer, *Tetrahedron Lett*., **1987**, Vol 28 (10), pp 1097-1100. c) D. F. Corbett, *J. Chem. Soc., Perkin Trans. 1*, **1986**, pp 421-428. d) M. Tordeux, K. Boumizane and C. Wakselman, *J. Fluorine Chem.*, **1995**, Vol 70 (2), pp 207-214. e) E. Müller, D. Fries and H. Metzger, *Ber.*, **1955**, Vol 88 (12), pp 1891-1905. f) A. Mackor, Th. J. de Boer, *Recl. Trav. Chim. Pays-Bas*,

1970, Vol 89, pp 151-158. g) D. L. Hammick and M. W. Lister, *J. Chem. Soc.,* **1937**, pp 489-493.

[42] a) G. A. Lee, *Synthesis*, **1982**, No 6, pp 508-509. b) T. G. Archibald, L. G. Garver, K. Baum, M. C. Cohen, *J. Org. Chem*., **1989**, Vol 54 (12), pp 2869-2873. c) H. L. Labaziewicz and F. G. Riddell, *J. Chem. Soc*., *Perkin Trans. 1*, **1979**, pp 2926-2929. d) H. Diekmann and W. Luttke, *Angew. Chem., Int. Ed*., **1968**, Vol 7 (5), p 387-388. e) M. W. Barnes and J. M. Patterson, *J. Org. Chem*., **1976**, Vol 41 (4), pp 733-735.

[43] a) S. K. Amstrong, E. W. Collington, J. G. Knight, A. Naylorb and S. Warren, *J. Chem. Soc*., *Perkin Trans. 1*, **1993**, pp 1433-1447. b) J. R. Bull, E. R. H. Jones and G. D. Meakins, *J. Chem. Soc.,* **1965**, pp 2601-2614.

[44] a) K. C. Liu, B. R. Shelton and R. K. J. Howe, *Org. Chem*., **1980**, Vol 45, pp 3916-3918. b) H. J. Gi, Y. Xiang, R. F. Schinazi and K. J. Zhao, *Org. Chem*., **1997**, Vol 62, pp 88-92.

[45] a) J. W. Lown, *J. Chem. Soc. B*, **1966**, pp 441-446. b) V. H. Kropf and R. Lambeck, *Liebigs Ann. Chem*., **1966**, Vol 700 (1), pp 1-17. c) E. V. Zhutov, Y. V. Skornyakov, M. V. Proskurina and N. S. Zefirov, *Russ. J. Org. Chem.,* **2003**, Vol 39 (11), pp 1672-1673.

[46] A. H. Beckett, G. R. Jones and R. T. Coutts, *Tetrahedron*, **1976**, Vol 32 (11), pp 1267-1276.

[47] J. Lee, L. Chen, A. H. West and G. B. Richter-Addo, *Chem. Rev*., **2002**, Vol 102 (4), pp 1019-1065.

[48] a) R. Glaser, R. K. Murmann and C. L. Barnes, *J. Org. Chem*., **1996**, Vol 61 (3), pp 1047-1058. b) J. C. Stowell, *J. Org. Chem*., **1971**, Vol 36 (20), pp 3055-3056. c) H. Yamamoto and N. Momiyama, *J. Chem. Soc., Chem. Commun*., **2005**, pp 3514-3525.

[49] A. G. Leach and K. N. Houk, *J. Chem. Soc., Chem. Commun*., **2002**, pp 1243-1255.

[50] P. F. Vogt and M. J. Miller, *Tetrahedron,* **1998**, Vol 54 (8), pp 1317-1348.

[51] a) S. K. Quek, I. M. Lyapkalo and H. V. Huynh, *Synthesis*, **2006**, No 9, pp 1423-1426. b) R. E. Banks, M. G. Barlow and R. N. Haszeldine, *J. Chem. Soc*., **1965**, pp 4714-4718.

[52] For Grignard reaction with nitroso compounds: W. Chen, C. S. Day, and S. B. King, *J. Org. Chem.*, **2006**, Vol 71 (24), pp 9221-9224.

[53] For metal hydride reduction with nitroso compounds: a) G. R. Delpierre and M. Lamchen, *J. Chem. Soc.*, **1963**, pp 4693-4701. b) R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland and A. Todd, *J. Chem. Soc.*, **1959**, pp 2094-2102. c) B. K. Matharu, J. R. Sharma and M. R. Manrao, *J. Ind. Chem. Soc.,* **2005**, Vol 82 (10), pp 917-918.

[54] For metal reduction with nitroso compounds: L. M. Mironovich, S. Salistaya and V. K. Promonenkov, *Russ. J. Gen. Chem.*, **2001**, Vol 71 (6), pp 991-992.

[55] a) A. Mackor, Th. A. J. W. Wajer and Th. J. de Boer, *Tetrahedron Lett.*, **1967**, Vol 8 (5), pp 385-390. b) A. Mackor, Th. A. J. W. Wajer, Th. J. de Boer and J. D. W. van Voorst, *Tetrahedron Lett.*, **1966**, Vol 7 (19), pp 2115-2123. c) Y. L. Chow and G. E. Buono-Core, *J. Am.* Chem. *Soc*., **1986**, Vol. 108 (6), pp 1234-1239.

[56] a) W. Oppolzer and O. Tamura, *Tetrahedron Lett*., **1990**, Vol 31 (7), pp 991-994. b) W. Oppolzer, O. Tamura and J. Deerberg, *Helv. Chim. Acta*, **1992**, Vol 75 (6), pp 1965-1978.

[57] H. Guo, L. Cheng, L. F. Cun, L. Z. Gong, A. G. Miac and Y. Z. Jiang, *J. Chem. Soc., Chem. Commun.*, **2006**, pp 429-431.

[58] a) G. Zhong, *Angew. Chem. Int. Ed*., **2003**, Vol 42 (35), pp 4247-4250. b) Y. Hayashi, J. Yamaguchia, K. Hibinoa and M. Shojia, *Tetrahedron Lett*, **2003**, Vol 44 (45), pp 8293-8296. c) Y. Yamamoto, N. Momiyama and H. Yamamoto, *J. Am. Chem. Soc.*, **2004**, Vol 126 (19), pp 5962-5963. d) S. P. Brown, M. P. Brochu, C. J. Sinz and D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2003**, Vol 125 (36), pp 10808-10809. e) P. Merino and T. Tejero, *Angew. Chem. Int. Ed*., **2004**, Vol 43 (23), pp 2995-2997.

[59] a) K. Sakthivel, W. Notz, T. Bui and C. F. Barbas III, *J. Am. Chem. Soc*., **2001**, Vol 123 (22), pp 5260-5267. b) S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, **2001**, Vol 123 (46), pp 11273-11283.

[60] a) O. Kronja, J. Matijević-Sosa and S. Uršić, *J. Chem. Soc., Chem. Commun.*, **1987**, pp 463-464. b) S. Uršić, V. Pilepić, V. Vrček, M. Gabričević and B. Zorc, *J. Chem. Soc., Perkin Trans. 2*, **1993**, pp 509-514. c) S. Uršić, *Helv. Chim. Acta*,

Vol 76 (1), pp 131-138. d) M. D. Corbett and B. R. Corbett, *J. Org. Chem.*, **1980**, Vol 45 (14), pp 2834-2839.

[61] V. Pilepić and S. Urćiš, *Tetrahedron Lett*., **1994**, Vol 35 (40), pp 7425-7428.

[62] B M. Trost and I Flemming, *Comprehensive Organic Synthesis*, Vol 2, **1991**, Ed:, Pergamon Press, pp 661-705.

[63] I. Fleming, L. A. Paquette and B. M. Trost, *Comprehensive Organic Synthesis*, Vol 5, **1992**, Ed.; Pergamon Pr, pp 417-422.

[64] B. Belleau and Y. K. Au-Young, *J. Am. Chem.* Soc., **1963**, Vol 85 (1), pp 64-71**.**

[65] a) G. Calvet, M. Dussaussois, N. Blanchard and C. Kouklovsky, *Org. Lett.*, **2004**, Vol 6 (14), 2449-2451. b) G. Calvet, R. Guillot, N. Blanchard and C. Kouklovsky**,** *Org. Biomol. Chem.*, **2005**, Vol 3, pp 4395-4401**.**

[66] a) A. Zakarian and C. Lu, *J. Am. Chem. Soc*., **2006**, Vol 128 (16), pp 5356-5357. b) A. Jabbari and K. N. Houk, *Org. Lett*., **2006**, Vol 8 (26), pp 5975-5978.

[67] J. Hamer and A. Macaluso, *Tetrahedron Lett*., **1963**, Vol 4 (6), pp 381-384.

[68] K. Alder, F. Pascher and A. Schimitz, *Dtsch. Chem. Ges.*, **1943**, Vol 76, p 27.

[69] H. J. Prins, *Chem.Weekblad*, **1919**, Vol 16, p 1510.

[70] J. L. Ripoll and Y. Vallée, *Synthesis,* **1993**, No 7, pp 659-677.

[71] G. T. Knight, *J. Chem. Soc. D*, **1970**, pp 1016-1017.

[72] K. H. Schulte-Elte and G. Ohloff, *Helv. Chim. Acta*, **1967**, Vol 50 (1), p 153.

[73] G. E. Keck and R. R. Webb II, *J. Am. Chem. Soc*., **1981**, Vol 103 (11), pp 3173-3177.

[74] G. E. Keck and R. Webb, *Tetrahedron Lett*., **1979**, Vol 20 (14), pp 1185-1186.

[75] a) C. F. Mayer and J. K. Crandall, *J. Org. Chem.*, **1970**, Vol 35 (8), pp 2688-2690. b) B M. Trost and I Fleming, *Comprehensive Organic Synthesis,* Vol 2, **1991**, Ed:, Pergamon Press, Vol 5, Ch. 4.2.

[76] a) L. M. Stephenson and D. L. Mattern, *J. Org. Chem*.,**1976**, Vol 41 (22), p 3614-3619. b) F. R. Benn, J. Dwyer and I. Chappell, *J. Chem. Soc. Perkin Trans. 2*, **1977**, pp 533-535.

[77] S. Inagaki, H. Fujimoto, K. Fukui, *J. Am. Chem. Soc*., **1976**, Vol 98 (16), pp 4693-4701.

[78] H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **1969**, Vol 8 (11), pp 781-853.

[79] R. C. Bingham and M. J. S. Dewar, *J. Am. Chem. Soc.*, **1972**, Vol 94 (26), pp 9107-9112.

[80] X. Lu, *Org. Lett.*, **2004**, Vol 6 (16), pp 2813-2815.

[81] R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **1969**, Vol 8 (11), pp 781-853.

[82] A. G. Leach and K. N. Houk, *J. Am. Chem. Soc.*, **2002**, Vol 124 (50), pp 14820-14821.

[83] A. G. Leach and K. N. Houk, *Org. Biomol. Chem.*, **2003**, Vol 1, pp 1389-1403.

[84] *Comprehensive Organic Synthesis*, I. Fleming, L. A. Paquette and B. M. Trost, Ed, Ed Pergamon Pr, Vol 2, pp 527-562.

[85] W. Oppolzer and V. Snieckus, *Angew. Chem., Int. Ed.*, **1978**, Vol 17 (7), 476-486.

[86] a) A. G. Davies and C. H. Schiesser, *Tetrahedron*, **1991**, Vol 47 (9), pp 1707-1726. b) J. E. Baldwin, A. K. Bhatnagar, S. C. Choi and T. J. Shortrige, *J. Am. Chem. Soc.*, **1971**, Vol 93 (16), pp 4082-4084.

[87] A. G. Leach and K. N. Houk, *J. Am Chem. Soc.*, **2003**, Vol 125 (45), pp 13825-13830.

[88] a) W. Adam, N. Bottke, B. Engels and O. Krebs, *J. Am. Chem. Soc.* **2001**, Vol 123 (23), pp 5542-5548. b) W. Adam, N. Bottke and O. Krebs, *J. Am. Chem. Soc.*, **2000**, Vol 122 (28), pp 6791-6792.

[89] a) Z. G. Remner, *Anal. Chem.,* **1963***,* Vol 193, p 92. b) G. E. Utzinger and F. A. Regenass, *Helv. Chim. Acta*, **1954**, Vol 37 (6), pp 1892-1901. c) A. Schonberg and R. Michaelis, *J. Chem. Soc.,* **1937**, pp 627-628.

[90] a) G. T. Knight and M. J. R**.** Loadrnan, *J. Chem. Soc. B*, **1971**, pp 2107-2112**.** b) Y. Ogata, M. Tsuchide and J. Takagi, *J. Am. Chem.* Soc., **1957**, Vol 79 (13), pp 3397-3401. c) L. A. Neiman, V. I. Maimind and M. N. Shemyakin, *Tetrahedron Lett.,* **1965**, Vol 6 (85), pp 3157-3162. d) G. A. Russell, E. G. Geels, F. J. Smentowski, K. Y. Chang, J. Reynolds and *G.* Kaup, *J. Am. Chem. Soc.,* **1967**, Vol 89 (15), pp 3821-3828.

[91] J. H. Boyer, *The Chemistry of the Nitro and Nitroso Group,* Part 1, **1969**, Ed.; Interscience, NY., Chapter 5.

[92] a) R. A. Abramovitch, S. R. Challand and Y. Yamada, *J. Org. Chem.,* **1975**, Vol 40 (11), pp 1541-1547. b) D. Mulvey and W. A. Walters, *J. Chem. Soc.*, Perkin. *Trans. 2*, **1978**, pp 1059-1061.

[93] a) D. Braun and W. Neumann, *Angew. Chem., Int. Ed.*, **1965**, VoI. 4 (1), p 969. b) W. Kliegel, *Tetrahedron Lett.*, **1969**, Vol 10 (31), pp 2627-2630.

[94] a) R. Huisgen. *Angew. Chem*., **1963**, Vol 75 (13), pp 604-636. b) R. E. Banks, R. N. Haszeldine and P. J. Miller, *Tetrahedrom Lett*., **1970**, Vol 11 (50), pp 4417-4418.

[95] W. Adam and N. J. Bottke, *J. Am. Chem. Soc*., **2000**, Vol 122 (40), pp 9846-9847.

[96] C. Chatgilialoglu and K. U. Ingold, *J. Am. Chem. Soc*., **1981**,Vol 103 (16), pp 4833-4837.

[97] H. Braun, H. Felber, G. Kreße, A. Ritter, F. P. Schmidtchen and A. Schneider, *Tetrahedron*, **1991**,Vol 47 (20-21), pp 3313-3328.

[98] W. Adam, O. Krebs, M. Orfanopoulos and M. Stratakis, *J. Org. Chem*., **2002**, Vol 67 (24), pp 8395-8399.

[99] For the differentiation of the regioisomeric ene products derived from *twix* and *twin* hydrogen abstraction, deuterium-labeling of one of the positions is necessary, unless the substrate bears different substituents.

[100] T. Sugimura, T. Futagawa, M. Yoshikawa, T. Katagiri, R. Miyashige, M. Mizuguchi, S. Nagano, S. Sugimori, A. Tai, T. Tei and T. Okuyama, *Tetrahedron*, **2001**, Vol 57 (35), pp 7495-7499.

[101] a) L. Alessandri, A. Angeli and R. Pegna, *Atti. accad. Lincei*, **1910**, Vol 19, p 650. b) L. Alessandri, *Atti. accad. Lincei*, **1915**, Vol 24, p 62. c) L. Alessandri, *Gazz. Chim. Ital*. **1921**, Vol 51, p 129.

[102] G. T. Knight and B. Pepper, *Tetrahedron*, **1971**, Vol 27 (24), pp 6201-6208.

[103] G. Bruni and E. Gieger, *Rubber Chem. and Tech*., **1928**, Vol 1, p 177.

[104] R. Pummerer and W. Gündel, *Rubber Chem. and Tech*., **1929**, Vol 2, p 373.

[105] A. B. Sullivan, *J. Org. Chem.*, **1966**, Vol 31 (9), pp 2811-2817.

[106] B. Pepper and M. Porter, *J. Chem. Soc., Chem. Commun*., **1974**, pp 130-131.

[107] a) G. T. Knight and B. Pepper, *J. Chem. Soc. D*, **1971**, pp 1507-1508. b) M. E. Cain, G. T. Knight and P. M. Lewis, *Chem. & Ind*., **1970**, p 126.

[108] L. S. Zherebkova, A. S. Shashkov, T. N. Dyumayeva, E. Ya. Devirts and F. A. Galil-Ogly Vysokomol, *Soedin*, **1969**, Vol 11 (1) Ser. A, p 227.

[109] a) A. Schonberg and R. Michaelis, *J. Chem. Soc*., **1937**, pp 627-628. b) G. T. Knight and M. J. R. Loadman, *J. Chem. Soc. B*, **1971**, pp 2107-2112.

[110] a) M. E. Cain, G. T. Knight, P. M. Lewis and B. Saville, *Rubber J*., **1968**, Vol 150 (11), p 10.

[111] a) F.-L. Zhang and A. Vasella, *Helv. Chim. Acta*, **2007**, Vol 90 (12), pp 2315-2329. b) F.-Li Zhang, W. B. Schweizer, M. Xu and A. Vasella, *Helv. Chim. Acta*, **2007**, Vol 90 (3), pp 521-534.

[112] a) W. B. Motherwell and J. S. Roberts, *J. Chem. Soc., Chem. Commun.,* **1972**, pp 328-329. b) W. B. Motherwell and J. S. Roberts, *J. Chem. Soc., Chem. Commun*., **1972**, pp 329-330.

[113] G. Moad, E. Rizzardo and D. H. Solomon, *Tetrahedron Lett.*, **1981**, Vol 22 (12), pp 1165-1168.

[114] M. G. Barlow, R. N. Haszeldine and K. W. Murria, *J. Chem. Soc., Perkin Trans. 1*, **1980**, pp 1960-1964.

[115] C. Schenk and Th. J. De Boer, *Tetrahedron*, **1979**, Vol 35 (1), pp 147-153.

[116] G. Kreβe, A. Vasella, H. Felber and B. Ascherl, *Recl. Trav. Chim. Pays-Bas*, **1986**, Vol 105, pp 295-298.

[117] G. W. Kirby and J. G. Sweeny, *J. Chem. Soc., Perkin Trans. 1*, **1981**, pp 3250-3254.

[118] H. E. Ensley and S. Mahadevan, *Tetrahedron Lett.*, **1989**, Vol 30 (25), pp 3255-3258.

[119] E. T. Corrie, G. W. Kirby, A. E. Laird, L. W. Mackinnon and J. K. Tyler, *J. Chem. Soc., Chem. Commun.*, **1978**, pp 275-276.

[120] G. W. Kirby and J. W. M. Mackinnon, *J. Chem. Soc., Perkin Trans. 1*, **1985**, pp 887-892.

[121] S. F. Martin, T. A. Puckette and J. A. Colapret, *J. Org. Chem.*, **1979**, Vol 44 (19), pp 3391-3396.

[122] J. B. P. A. Wijnberg and W. N. Speckamp, *Tetrahedron*, **1978**, Vol 34 (16), pp 2579-2586.

[123] a) G. E. Keck and R. R. Webb II, *J. Org. Chem*., **1982**, Vol 47 (7), pp 1302-1309. b) G. E. Keck and R. R. Webb II, *J. Am. Chem. Soc*., **1981**, Vol 103 (11), pp 3173-3177.

[124] S. Goodwin, J. N. Shoolery and E. C. Horning, *J. Am. Chem. Soc.*, **1959**, Vol 81 (14), pp 3736-3738.

[125] a) W. C. Wildman and D. T. Bailey, *J. Org. Chem.*, **1968**, Vol 33 (10), pp 3749-3753. b) W. C. Wildman and D. T. Bailey, *J. Am. Chem. Soc*., **1970**, Vol 92 (18), pp 5538-5539.

[126] P. G. Mattingly and M. J. Miller, *J. Org. Chem.*, **1980**, Vol 45 (3), pp 410-415.

[127] A. A. Fokin, A. G. Yurchenko, V. N. Rodionov, P. A. Gunchenko, R. I. Yurchenko, A. Reichenberg, J. Wiesner, M. Hintz, H. Jomaa and P. R. Schreiner, *Org. Lett.*, **2007**, Vol 9 (21), pp 4379-4382.

[128] W. Adam, H. Degen, O. Krebs and C. R. Saha-Möller, *J. Am. Chem. Soc.*, **2002**, Vol 124 (44), pp 12938-12939.

[129] R. S. Srivastava and K. M. Nicholas, *J. Org. Chem.*, **1994**, Vol 59 (18), pp 5365-5371.

[130] B. Kalita and K. M. Nicholas, *Tetrahedron Lett.*, **2005**, Vol 46 (9), pp 1451-1453.

[131] A. Srivastava, Y. Ma, R. Pankayatselvan, W. Dinges and K. M. Nicholas, *J. Chem. Soc., Chem. Commun.*, **1992**, pp 853-854.

[132] C. M. Ho and T. C. Lau, *New J. Chem.*, **2000**, Vol 24, pp 859-863.

[133] R. A. Stockman, A. Sinclair, L. G. Arini, P. Szeto and D. L. Hughes, *J. Org. Chem.*, **2004**, Vol 69 (5), pp 1598-1602.

[134] C. J. Smith, A. B. Holmes and N. J. Press, *J. Chem. Soc., Chem. Commun.*, **2002**, pp 1214-1215.

[135] J. Liu, J. J. Swidorski, S. D. Peters and R. P. Hsung, *J. Org. Chem.*, **2005**, Vol 70 (10), pp 3898-3902.

[136] M. E. Fox, A. B. Colmes, I. T. Forbes and M. Thompson, *J. Chem. Soc. Perkin Trans. 1*, **1994**, pp 3379-3395.

[137] W. Friebolin and W. Eberbach, *Tetrahedron*, **2001**, Vol 57 (20), pp 4349-4358.

[138] For an introduction to nitrone chemistry see: B M. Trost and I Flemming, *Comprehensive Organic Synthesis*, Vol 4, **1991**, Ed:, Pergamon Press, pp 1113-1124.

[139] R. A. Stockman, A. Sinclair, L. G. Arini, P. Szeto and D. L. Hughes, *J. Org. Chem.*, **2004**, Vol 69 (5), pp 1598-1602.

[140] J. J. Tufariello and E. J. Trybulski, *J. Chem. Soc., Chem. Comm.*, **1973**, p 720.

[141] M. Frederickson, R. Grigg, J. Markandu, M. Thornton-Pett and J. Redpath, *Tetrahedron,* **1997**, Vol 53 (44), pp 15051-15060.

[142] D. C. Iffland and T. Fu-Yen, *J. Am. Chem. Soc.* **1954**, Vol 76 (16), pp 4083-4085.

[143] A. I. Mikhaleva, A. B. Zaitsev and B. A. Trofimov, *Russ. Chem. Rev.*, **2006**, Vol 75 (9), pp 797-823.

144 H. A. Dondas, R. Grigg, M. Hadjisoteriou, J. Markandu, P. Kennewell and M. Thornton-Pett, *Tetrahedron*, **2001**, Vol. 57 (6), pp 1119-1128.

145 S. V. Filip and N. Sewald, *Synthesis*, **2005**, No 20, pp 3565-3570.

146 D. L. Haire and E. Anzen, *Can. J. Chem.*, **1982**, Vol 60 (12), pp 1514-1522.

147 J. Lub, M. L. Beckes and Th. J. de Boer, *Recl. Trav. Chim. Pays-Bas*, **1986**, Vol 105, pp 22-27.

148 M. J. Mintz and C. Walling, *Org. Synth.*, **1973**, Vol 5, pp 184-185.

149 a) O. Wichterle and M. Hudlicky, *Collect. Czech. Chem. Commun.*, **1947**, Vol 12, p 661. b) F. Cuthbertson, W. K. R. Musgrave, *J. Appl. Chem.*, **1957**, Vol 7, pp 99-102. c) W. Doering and W. A. Von. Henderson, *J. Am. Chem. Soc.*, **1958**, Vol 80 (19), pp 5274-5277. d) O. O. Orazi, R. A. Corral and H. Schuttenberg, *J. Chem. Soc.*, Perkin Trans. 1, **1974**, pp 2087-2091. e) D. Seyferth, G. J. Murphy and B. Mauze*, J. Am. Chem. Soc.*, **1977**, Vol 99 (16), pp 5317-5330. f) J. Villieras, P. Perriot and J. F. Normant, *Bull. Soc. Chim. Fr.*, **1977**, pp 765-771. g) N. V. Kruglova and R. K. Freidline, *Bull. Acad. Sci. USSR, Engl. Trans.* **1984**, pp 346-352. h) G. M. Lee and S. M. Weinreb, *J. Org. Chem.*, **1990**, Vol 55 (4), pp 1281-1285.

150 V. Kumar and M. P. Kaushik, *Tetrahedron Lett.*, **2006**, Vol 47 (9), pp 1457-1460.

151 a) R. S. Neale and N. L. Marcus, *J. Org. Chem.*, **1969**, Vol 34 (6), pp 1808-1816. b) V. Kumar and M. P. Kaushik, *Chem. Lett.*, **2005**, Vol 34 (9), pp 1230-1231.

152 R. C. Rodrigues and A. P. de Aguiar, *Synth. Commun.,* **2001**, Vol 31 (20), pp 3075-3080.

153 A. Guy, M. Lemaire and J. P. Guetté, *Synthesis*, **1982**, No 12, pp 1018-1020.

154 E. J. Corey and H. Estreicher, *Tetrahedron Lett.*, **1980**, Vol 21 (12), pp 1117-1120.

155 H. A. Dondas, R. Grigg and C. S. Frampton, *Tetrahedron Lett.,* **1997**, Vol 38 (32), pp. 5719-5722.

156 a) Q. Cheng, W. Zhang, Y. Tagami and T. Oritani, *J. Chem. Soc., Perkin Trans. 1*, **2001**, pp 452-456. b) S. Sing, M. P. S. Ishar, G. Singh and R. Singh, *Can. J. Chem.*, **2005**, Vol 83 (3), pp 260-265.

157 I. D. Cunningham, A. Brownhill, I. Hamerton and B. J. Howlin, *Tetrahedron*, **1997**, Vol 53 (39), pp 13473-13494.

[158] a) M. G. Banwell, D. C. Hochless and M. D. McLeod, *New.*, *J. Chem.*, **2003**, Vol 27, pp 50-59. b) S. Boatman, T. M. Harris and C. R. Hauser, *J. Org. Chem.*, **1965**, Vol 30 (10), pp 3321-3324.

[159] B. K. Sarmah and N. C. Barua, *Tetrahedron*, **1993**, Vol 49 (11), pp 2253-2260.

[160] M. E. Jung, S. Angelica and D. C. D'Amico, *J. Org. Chem.*, **1997**, Vol 62 (26), pp 9182-9187.

[161] G. Zon, L.A. Paquette, *J. Am. Chem. Soc.,* **1974**, Vol 96 (17), pp 5478-5487.

[162] R. E. Ireland, R. H. Mueller and A. K. Willard, *J. Am. Chem. Soc.*, **1976**, Vol 98 (10), pp 2868-2877.

[163] A. J. Bloodworth, J. L. Courtneidge, R. J. Curtis and M. D. Spencer*, J. Chem. Soc. Perkin Trans. 1*, **1990**, pp 2951-2955.

[164] S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, **1981**, Vol 22 (39), pp 3815-3818.

[165] R. M. Moriarty, O. Prakash and P. R. Vavilikolanu, *Synth. Commun.*, **1986,** Vol 16 (10), pp 1247-1254.

[166] V. I. Daineko, M. V. Proskurnina, Y. V. Skornyakov, B. A. Trofimov and N. S. Zefirov, *Russ. J. Org. Chem*, **2002**, Vol. 38 (10), pp. 1431-1433.

[167] a) P. Laszlo and M. Teston-Henry, *Tetrahedrom Lett.*, **1991**, Vol 32 (31), pp 3837-3838. b) M. A. Ciufolini, M. V. Deaton, S. Zhu and M. Chen, *Tetrahedron,* **1997**, Vol 53 (48), pp 16299-16312. c) R. K. Pandey, S. P. Dagade, K. M. Malase, S. B. Songire and P. Kumar, *J. Molec. Cat. A: Chem.,* **2006**, Vol 245, pp 255-259.

[168] a) G. B. Gubelt and J. Warkentin, *Can. J. Chem.,* **1969**, Vol 47, pp 3983-3987. b) D. Shafiullah and H. Ali, *Synthesis,* **1979**, No 4, pp 124-126. c) A. Kotali and V. P. Papageorgiou, . *J. Chem. Soc., Perkin Trans. 1,* **1985**, pp 2083-2086.

[169] a) H. J. Peter de Lijser, F. H. Fardoun, J. R. Sawyer and M. Quant, *Org. Lett.*, **2002**, Vol 4 (14), pp 2325-2328. b) J. W. Bird and D. G. M. Diaper, *Can. J. Chem.*, **1969**, Vol 47, pp 145-150.

[170] E. H. White and W. J. Considine*, J. Am. Chem. Soc.*, **1958**, Vol 80 (3), pp 626-630.

[171] S. M. Bachrach, *J. Org. Chem.,* **2008**, Vol 73 (6), pp 2466-2468.

[172] A. K. Sharma, S. N. Mazumdar and M. P. Maja, *J. Org. Chem.*, **1996**, Vol 61 (16), pp 5506-5509.

[173] a) M. E. Krafft and K. A. Seibert, *Synlett*, **2006**, No 19, pp 3334-3336. b) M. Shi and Y.-H. Liu, *Org. Biomol. Chem.*, **2006**, Vol 4, pp 1468-1470. c) J. Cai, Z. Zhou, G. Zhao and C. Tang, *Org. Lett.*, **2002**, Vol 4 (26), pp 4723-4725. d) K.-S. Park, J. Kim, H. Choo and Y. Chong, *Synlett*, **2007**, No 3, pp 395-398.

[174] N. Ono, H. Miyake, A. Kamimura, I. Hamamoto, R. Tamura and A. Kaki, *Tetrahedron*, **1985**, Vol 41 (19), pp 4013-4023.

[175] a) G. A. Olah, P. Ramarah, C. S. Lee and G. K. S. Prakash, *Synlett*, **1992**, No 4 pp 337-339. b) A. MeKillop and W. R Sanderson, *Tetrahedron*, **1995**, Vol 51 (22), pp 6145-6166.

[176] a) N. Kornblum, B. Taub and H. E. Ungnade, *J. Am. Chem. Soc.*, **1954**, Vol 76 (12), pp 3209-3211. b) N. Kornblum, R. A. Smiley, H. E. Ungnade, A. M. White, B. Taub and S. A. Herbert, *J. Am. Chem. Soc.,* **1955**, Vol 77 (21), pp 5528-5533.

[177] A. Baruah, B. Kalita and N. C. Barva, *Synlett.,* **2000**, No 7, pp 1064-1066.

[178] M. Makosza, M. Barbasiewicz and K. Wojciechowski, *Synlett.*, **2001**, No 7, pp 1121-1122.

[179] a) D. Seebach, R. Henning, F. Lehr and J. Gonnermann, *Tetrahedron Lett.*,**1997**, Vol 38 (7), pp 1161-1164. b) M. Eyer and D. Seebach, *J. Am. Chem. Soc.*, **1985**, Vol 107 (12), pp 3601-3606. c) E. W. Colvin and D. Seebach, *J. Chem. Soc., Chem. Commun*, **1978**, pp 689-691. d) R. Henning, F. Lehr and D. Seebach, *Helv. Chim. Acta*., **1976**, Vol 59 (6), pp 2213-2217. e) D. Seebach and F. Lehr, *Angew. Chem., Int. Ed. Engl.*, **1976**, Vol 15 (8), pp 505-506.

[180] K. Yamada, S. Tanaka, S. Kohmoto and M. Yamamoto, *J. Chem. Soc., Chem. Commun.*, **1989**, pp 110-111.

[181] P. Bird, J. Eames, A. G. Fallis, R. V. H. Jones, M. Roddis, C. F. Sturino, S. O'Sullivan, S. Warren, M. S. Westwell and J. Worrall, *Tetrahedron Lett.*, **1995**, Vol. 36 (11), pp 1909-1912.

[182] T. L. Hutchison and W. J. Brouillette, *Bioorg. & Chem.,* **1998**, Vol 6 (11), pp 2133-2138.

[183] a) A. P. Krapcho, *Synthesis*, **1982**, No 10, pp 805-822. b) A. P. Krapcho, *Synthesis*, **1982**, No 11, pp 893-914. c) A. P. Krapcho and A. J. Lovey, *Tetrahedron Lett.*, **1973,** Vol 14 (12), pp 957-960. d) C. J. Martin, D. J. Rawson and J. M. J. Williams, *Tetrahedron: Assymetry*, **1998**, Vol 9 (15), pp 3723-3730.

[184] a) M. F. Buffet, D. J. Dixon, G. L. Edwards, S. V. Ley and E. W. Tate, *J. Chem. Soc., Perkin Trans. 1*, **2000**, pp 1815-1827. b) M. Freiría, A. J. Whitehead, W. B. Motherwell, *Synlett*, **2003**, No 6, pp 805-808.

[185] N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto and G. E. Greham, *J. Am. Chem. Soc.*, **1956**, Vol 78 (7), pp 1497-1501.

[186] R. Balini and M. Petrini, *Synth. Commun.*, **1986**, pp 849-852.

[187] F. A. Luzzio, *Tetrahedron,* **2001**, Vol 57 (6), pp 915-945.

[188] a) I. Kádas, G. Árvai, L. Tőke, G. Tóth, Á. Szöllősy and M. Bihari, *Tetrahedron*, **1994**, Vol 50 (9), pp 2895-2906. b) R. Ballini, A. Palmiery and P. Righi, *Tetrahedron*, **2007**, Vol 63 (49), pp 12099-12121.

[189] R. Ballini, G. Bosica, P. Forconi, *Tetrahedron*, **1996**, Vol 52 (5), pp 1677-1684.

[190] a) S. E. Denmark and C. B. W. Senanayake, *Tetrahedron,* **1996**, Vol 52 (35), pp 11579-11600. b) L. I. Kruse and M. D. Meyer, *J. Org. Chem.*, **1984**, Vol 49 (24), pp 4761-4768.

[191] G. B. Bachean and R. J. Malaski, J. *Org. Chem.*, **1972**, Vol 37 (18), pp 218-2814.

[192] a) R. Ballini and G. Bosica, *Eur. J. Org. Chem.*, **1998**, pp 355-357. b) R. Ballini, D. Fiorini, M. V. Gil and A. Palmieri, *Tetrahedron*, **2004**, Vol 60 (12), pp 2799-2804.

[193] D. H. R. Barton, W. B. Motherwell and S. Z. Zard, *Bull. Soc. Chim. Fr.*, **1982**, No 3-4, pp II-61-65.

[194] S. Yamasaki, K. Fujii, R. Wada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.*, **2002**, Vol 124, pp 6536-6537.

[195] D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals 3rd Ed.*, ed Pergamon Press.

[196] a) Y. Yu and L. S. Liebeskind, *J. Org. Chem.*, **2004**, Vol 69 (10), pp 3554-3557. b) J. P. Michael and M. M. Nkuwelo, *Tetrahedron*, **1990**, Vol 46 (7), pp 2549-2560.

[197] G. Rosini, E. Marotta, M. Petrini and R. Ballini, *Tetrahedron*, **1985** Vol 41 (20), pp 4633-4638.

[198] a) O. Masahito, U. Tatsuzo, Iwaki, Shigeru, N. Yoshimitsu and F. Eiichi, *J. Org. Chem.*, **1989**, Vol 54 (20), pp 4832-4840. b) A. Eddaif, A. Laurent, P. Mison, N. Pellissier, P-A. Carrupt and P. Vogel, *J. Org. Chem.*, **1987**, Vol 52 (25), pp 5548-5560.

[199] R. E. Gawley and E. J. Termine, *J. Org. Chem.*, **1984**, Vol 49 (11), pp 1946-1951.

[200] X. Chaminade, S. Chiba, K. Narasaka and E. Dunach, *Tetrahedron Lett.,* **2008**, Vol 49 (15), pp 2384-2387.

[201] D. S. C. Black and J. E. Doyle*, Aust. J. Chem.*, **1978**, Vol 31 (10), pp 2247-2257.

[202] V. Šimunić-Mežnarić, Z. Mihalić, H. Vančik, *J. Chem. Soc., Perkin Trans. 2*, **2002**, pp 2154-2158.

[203] M. Ortiz Marciales, M. De Jesús, D. Figueroa, J. Hernández, L. Vázquez, R. Vega, E. M. Morales and J. A. López, *Synth. Commun.,* **2003**, Vol 33 (2), pp 311-323.

[204] a) M. Tordeux, K. Boumizane and C. Wakselman, *J. Fluorine Chem.*, **1995**, Vol 70 (2), pp 207-214. b) I. Sakai, N. Kawabe and M. Ohno, *Bull. Chem. Soc. Jpn*., **1979**, Vol 52 (11), pp 3381-3383. c) E. Muller, H. Metzger and D. Fries, *Ber*., **1954**, Vol 87 (10), pp 1449-1460.

[205] Q. Jia, T. Cai, M. Huang, H. Li, M. Xian, T. L. Polous and P. G. Wang, *J. Med. Chem.*, **2003**, Vol 46 (12), pp 2271-2274.

[206] X. Sha, T. S. Isbell, R. P. Patel, C. S. Day and S. B. King, *J. Am. Chem. Soc.*, **2006**, Vol 128 (30), pp 9687-9692.

[207] Y. Hawai, Y. Inaba and N. Tokitoh, *Tetrahedron: Asymmetry*, **2001**, Vol 12, pp 309-318.

[208] M. C. Marcotullio, V. Campagna, S. Sternatio, F. Constantino and M. Curini, *Synthesis*, **2006**, No 16, pp 2760-2766.

[209] a) J. R. Vyvyan, C. Loitz, R. E. Looper, C. S. Mattingly, E. A. Peterson and S. T. Staben, *J. Org. Chem*., **2004**, Vol 69 (7), pp 2461-2468. b) P. K. Somers, T. J. Wandless and S. L. Schrelber, *J. Am. Chem. Soc*., **1991**, Vol 113 (21), pp 8045-8056.

[210] R. Ballini, *J. Chem. Soc., Perkin Trans. 1*, **1991**, pp 1419-1421.

[211] G. B. Bachman and R J. Maleski, *J. Org. Chem.*, **1972**, Vol 37 (18), pp 2810-2814.

[212] P. A. Clarke, M. Grist, M. Ebden, C. Wilson and A. J. Blake, *Tetrahedron*, **2005**, Vol 61 (2), pp 353-363.

[213] R. Ballini, L. Barboni, F. Fringuelli, A. Palmieri, F. Pizzo and L. Vaccaro, *Green Chem*., **2007**, Vol 9, pp 823-838.

[214] P. Kraft and A. Bruneau, *Eur. J. Org. Chem*., **2007** (14), pp 2257-2267.

[215] Y. Kawai, Y. Inaba and N. Tokitoh, *Tetrahedron: Asymmetry,* **2001**, Vol 12 (2), pp 309-318.

[216] K. M. Evans, S. J. Ireson, M. R. S. McCoustra and J. Pfab, *Spectrochimica Acta*, **1992,** Vol 48A (5), pp. 659-670.

[217] J. R. Hanson and T. D. Organ, *J. Chem. Soc. (C)*, **1970**, pp 1182-1183.