Novel Methodology for the Synthesis of Isoindole Derived Heterocycles

Peacock, Lucy

Award date:
2014

Awarding institution:
University of Bath

Novel Methodology for the Synthesis of Isoindole Derived Heterocycles

Lucy R. Peacock

A thesis submitted for the degree of Doctor of Philosophy

Department of Chemistry

June 2014

Abstract

This thesis presents research into the development of a novel conjugate-addition/cyclisation methodology for the synthesis of isoindole derived nitrones. To begin, a review of the principle methods for synthesising nitrones is reported, followed by a discussion of the current uses of nitrones and the requirement for straightforward syntheses of nitrones contained within an isoindole scaffold.

The synthesis of an aryl cyclisation substrate possessing the key *ortho*- relationship between an α,β-unsaturated ester and formyl group is then described. The planned conjugate-addition/cyclisation reaction using hydroxylamine was carried to afford a different nitrone structure to that expected, which was later confirmed by X-ray crystallography. A full discussion of the work undertaken to elucidate the compound structure and to probe the reaction mechanism is reported.

A monocyclic nitrone reported in the literature was thought to have been synthesised according to a 1,3-azaprotio cyclotransfer mechanism. Application of the newly discovered conjugate-addition/cyclisation protocol to a linear substrate successfully afforded this monocyclic nitrone, leading us to propose our mechanism as a plausible alternative.

Exploration of the scope and limitation of the nitrone forming reaction afforded total of fourteen isoindole derived nitrones. Applying the protocol to modified cyclisation substrates afforded five dihydroisoquinoline derived nitrones and a bicyclic hydroxamic acid also.

Research into the reactivity of isoindole derived nitrones is then presented. Varying degrees of success were obtained, largely due to the fact that the substrate does not react as a nitrone, but as its isoindole tautomer. An attempted 1,3-dipolar cycloaddition reaction with *tert*-butyl acrylate instead afforded a bridged hydroxylamine product, synthesised by a [4+2] Diels-Alder cycloaddition reaction.

The final part of this thesis reports the application of the [4+2] cycloaddition reaction between nitrone and an alkyne as a novel route for the synthesis of substituted naphthalenes.

Acknowledgements

I would firstly like to thank Steve Bull who has provided great advice and ideas throughout my PhD. I am grateful to him for giving me this opportunity and also for his patience.

The work presented in this thesis was financially supported by GlaxoSmithKline. The experience gained during my CASE placement and the recommendations from my supervisor there, Dominique Amans, were greatly appreciated.

A special mention should go to John Lowe for all of his NMR help throughout my PhD. I am thankful to him for his knowledge and expertise which have been invaluable. I would also like to acknowledge Katie Overington, a fantastic project student who began the work discussed in Chapter 5, and Robert Chapman who has carried on some of the research begun in this thesis.

Thanks must go to past and present members of the Bull group, especially to Dr Paul Fordred and Richard Blackburn for their crude and outrageously offensive sense of humour, to Dr James Taylor for the Gavin & Stacey and pasty days of yore, and to Dr Robert Archer for his advice and infectious spirit. I also have to say a huge thank you to two great friends from the department: Dr Liana Allen and Ruth Lawrence. Their friendship and encouragement have been immeasurable and between the two of them they always helped me to keep going.

I would like to take this opportunity to say thank you to my parents whose guidance and confidence in my abilities has helped me achieve far more than I thought I could. Lastly, I wish to thank Dr James Lightfoot. He has helped me overcome the times that I was ready to walk away from this PhD and without his continued support I would not have got to this point. Thank you.

Abbreviations

AcOH	Acetic acid
Ac	Acetyl
α	Alpha
Ar	Aryl
5-ASA	5-Aminosalicylic acid
Bn	Benzyl
β	Beta
***n*Bu**	*n*-Butyl
***n*BuLi**	*n*-Butyllithium
^{t}**Bu**	*tert*-Butyl
TBDMSCl	*tert*-Butyldimethylsilyl chloride
AMPO	5-Carbamoyl-5-methyl-1-pyrroline-*N*-oxide
δ	Chemical shift
***m*CPBA**	*meta*-Chloroperoxybenzoic acid
COSY	Correlation spectroscopy
J	Coupling constant
CD	Cyclodextrin
°C	Degrees celsius
δ	Delta
DNA	Deoxyribonucleic acid
DMP	Dess-Martin periodinane
$CDCl_3$	Deuterated chloroform
D_2O	Deuterium oxide

DABCO	1,4-Diazabicyclo[2.2.2]octane
DCC	*N,N*-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DECPO	5,5-Diethoxycarbonyl-1-pyrroline-*N*-oxide
DEPMPO	5-(Diethoxyphosphoryl)-5-methyl-1-pyrroline-*N*-oxide
Et_2O	Diethyl ether
DEAD	Diethyl azodicarboxylate
DIC	*N,N*-Diisopropylcarbodiimide
3-TF-TMINO	1,1-Dimethyl-3-(trifluoromethyl)-1*H*-isoindole-*N*-oxide
DMAP	Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMAD	Dimethyl acetylenedicarboxylate
DMPO	5,5-Dimethyl-pyrroline *N*-oxide
DMSO	Dimethyl sulfoxide
d	Doublet
ddd	Doublet of doublet of doublets
dt	Doublet of triplets
EPR	Electron Paramagnetic Resonance
EMPO	5-Ethoxycarbonyl-5-methyl-1-pyrroline-*N*-oxide
Et	Ethyl
EtOAc	Ethyl acetate
Eq.	Equivalents
FVP	Flash Vacuum Pyrrolysis
ν	Frequency
g	Grams
Hex	Hexane
Hz	Hertz
HMBC	Heteronuclear multiple bond coherence
HMQC	Heteronuclear multiple quantum coherence
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry

H_2O_2	Hydrogen peroxide
I.R	Infra Red
LCMS	Liquid chromatography mass spectrometry
mL	Millilitre
m	Multiplet
MeCN	Acetonitrile
MeOH	Methanol
Me	Methyl
TMFD	Methyl(trifluoro-methyl)dioxirane
MTO	Methyltrioxorhenium
mg	Milligrams
mol	Mole
NOE	Nuclear Overhauser effect
NMR	Nuclear magnetic resonance
ppm	Parts per million
Petrol	Petroleum ether
PBN	Phenyl butyl nitrone
PS	Polystyrene
PVP	Polyvinyl pyridine
q	Quartet
rt	Room temperature
s	Singlet
TBAB	Tetrabutylammonium bromide
THF	Tetrahydrofuran
TMIO	1,1,3,3- Tetramethylisoindolin-2-yloxyl
MTSL	(*S*)-(2,2,5,5-Tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)methyl methanesulfonothioate
TLC	Thin layer chromatography
***p*TSA**	*para*-Toluenesulfonic acid
TEA/Et_3N	Triethylamine
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride

TMINO	1,1,3-Trimethylisoindole-*N*-oxide
M_3PO	Trimethyl-pyrroline-*N*-oxide
t	Triplet
td	Triplet of doublets
UHP	Urea hydrogen peroxide

Contents

Chapter 1

Literature Review

1.1 Introduction

Nitrones were first reported by Migrdichian *et al.* in the mid 1950's.[1] Since this time, there has been a huge amount of research into the chemistry of nitrones and they have found widespread use in a number of areas. The nitrone functional group can be formally described as the *N*-oxide of an imine (Figure 1.1).

Figure 1.1: **Formal representation of a nitrone functional group**

Traditionally, nitrones are well known as radical spin traps for probing chemical reactions. They react with free radical intermediates to form more stable nitroxide free radicals, as shown in Figure 1.2. These are more easily characterised and can be used to provide information about radical reaction mechanisms.

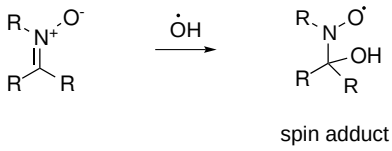


Figure 1.2: **Reaction between a nitrone and a hydroxyl radical to afford a spin adduct**

This area of research has been widely used in biochemistry and pharmacology and has contributed significantly to the understanding of free radical reactions taking place in the body. As a result, the therapeutic effect of nitrones has received much interest, particularly in ageing diseases such as stroke, Parkinson's disease and cancer development.[2–8] Nitrones react with the enhanced levels of free radicals associated with these diseases and have shown potent biological activity in many experimental animal models. Most

recently, the nitrone containing neuroprotectant drug Cerovive (Figure 1.3), originating from AstraZeneca, was discontinued after Phase III trials as it "failed to demonstrate a treatment benefit in acute ischemic stroke", although this was a serious progression towards demonstrating that nitrones could be used as drugs.[7,9,10]

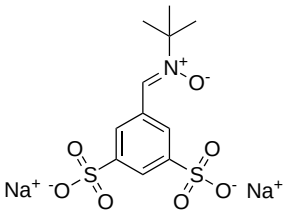


Figure 1.3: **Structure of Cerovive, a drug candidate for the treatment of acute ischemic stroke**

1.2 Synthesis of nitrones

The methods of synthesising nitrones can be broadly categorised as either oxidative or non-oxidative, as highlighted in Figure 1.4. The literature review that follows will briefly discuss the major recent developments for their synthesis.

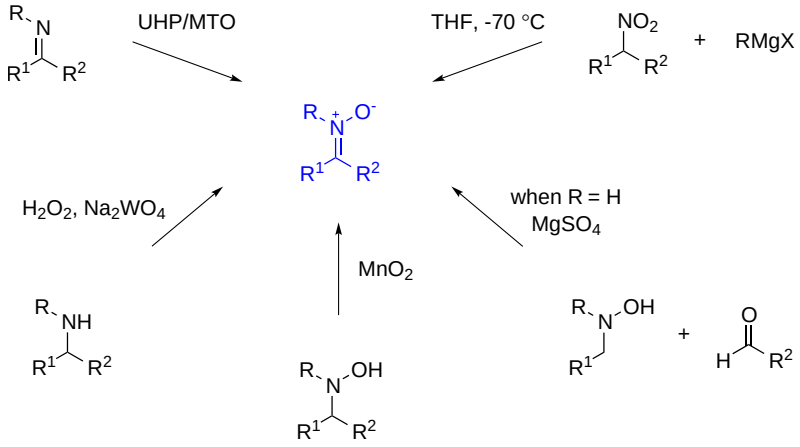


Figure 1.4: **Commonly employed methods for the synthesis of nitrones**

UHP: urea hydrogen peroxide, MTO: methyl rhenium trioxide.

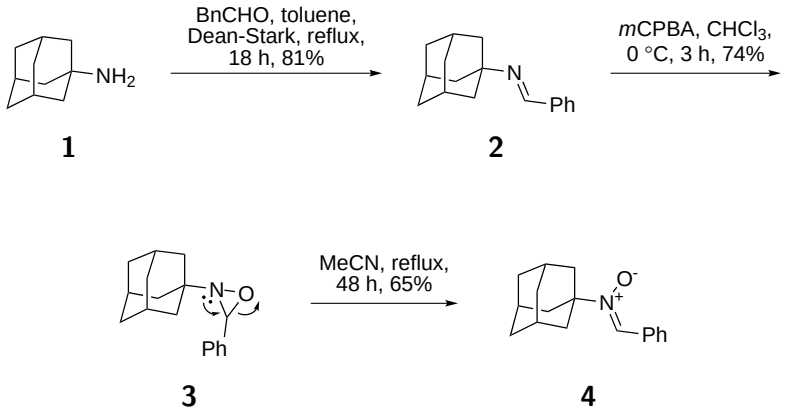
1.3 Oxidative methods

1.3.1 Oxidation of imines

Numerous oxidants can be employed to transform imines into nitrones. Typically, an imine is oxidised to an oxaziridine that then rearranges to the nitrone under the reaction conditions. However, in certain cases the oxaziridine can be isolated and subjected to a

subsequent rearrangement step.

A representative example of this type of chemistry is the oxidation of imine **2** using *meta*-chloroperoxy benzoic acid (*m*CPBA), as shown in Scheme 1.1.[11] As part of their research into novel nitroxides for use in nitroxide mediated radical polymerisation reactions, Braslau *et al.* synthesised the adamantyl based nitrone **4**. In this example, rearrangement of the oxaziridine **3** did not take place spontaneously, and so the rearrangement was induced thermally by refluxing the oxaziridine in acetonitrile. The mechanism for formation of an oxaziridine using *m*CPBA mirrors the mechanism for epoxide synthesis, while the oxaziridine ring opening reaction is though to proceed *via* a concerted mechanism.



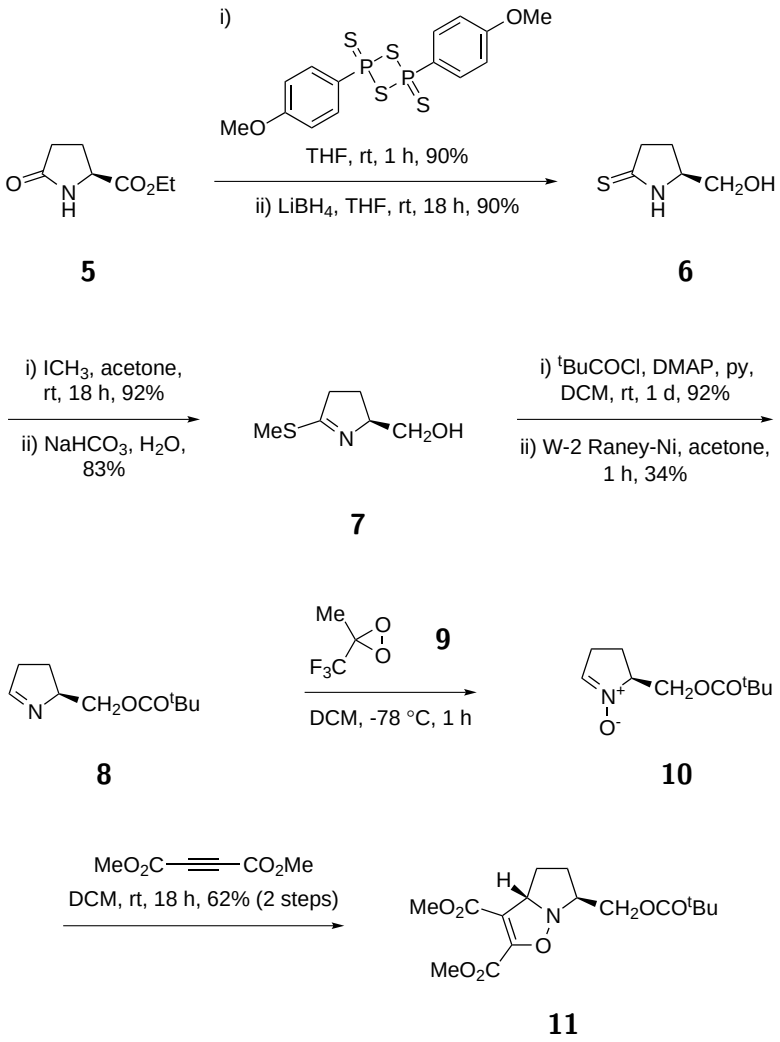
Scheme 1.1: **Braslau's synthesis of an adamantyl nitrone**

Busque *et al.* used a trifluoromethyl dioxirane to carry out a direct imine to nitrone oxidation in their synthesis of the protected (*S*)-3,4-dihydro-2-pivaloyloxymethyl-2*H*-pyrrole 1-oxide **10**, which was the first reported synthesis of an enantiopure C(5) monosubstituted aldonitrone (Scheme 1.2).[12] Starting from ethyl L-glutamate **5**, the group synthesised thiolactam **6** by treatment with Lawesson's reagent followed by ester reduction with lithium borohydride. This thiolactam was subsequently reacted with iodomethane and base to afford the imidothiolate **7**. The primary alcohol group of **7** was protected as the pivaloyl ester and the carbon-sulfur bond cleaved using Raney-Ni which gave the imine **8** in low yield.

At this point, the group attempted to oxidise the imine using *m*CPBA, however a diastereomeric mixture of oxaziridines was obtained, and all attempts to isomerise this mixture of oxaziridines to the nitrone either proved ineffective or gave decomposition products. Using methyltrifluoro(methyl) dioxirane **9** as the oxidant however, afforded the pivaloyl protected nitrone **10** directly from the imine. Nitrone **10** was obtained in 12% overall yield from L-pyroglutamate.

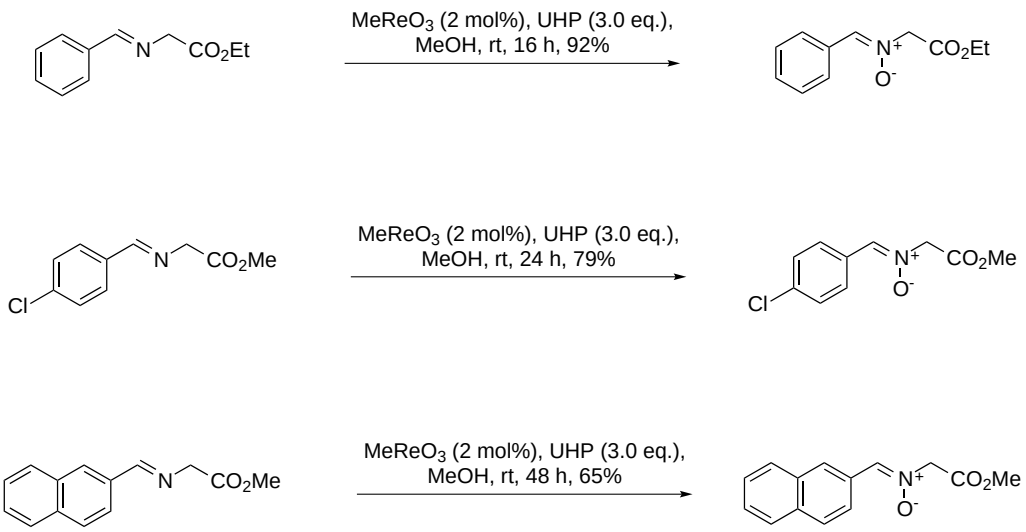
A 1,3 dipolar cycloaddition reaction with dimethyl acetylene dicarboxylate (DMAD) was then carried out with analysis by NOE NMR experiments confirming that a single cy-

cloadduct **11** had been synthesised.



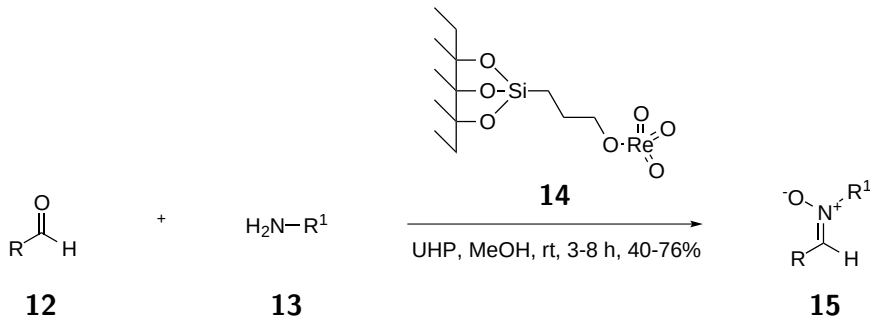
Scheme 1.2: **Busque's synthesis of a 2*H*-pyrrole-*N*-oxide**

Transition metal catalysts have also been employed for the oxidation of imines to nitrones. For example, Soldaini *et al.* first reported the use of a catalytic amount of methyl trioxorhenium (MTO) in the presence of a urea hydrogen peroxide (UHP) complex, to chemo- and regioselectively oxidise imines directly to nitrones.[13] Diez-Martinez *et al.* found success using this methodology more recently to synthesise nitrones containing oxygenated functionality at their β- positions as shown in Scheme 1.3.[14] Fifteen *C*-aryl nitrones were synthesised in 65-92% yields.



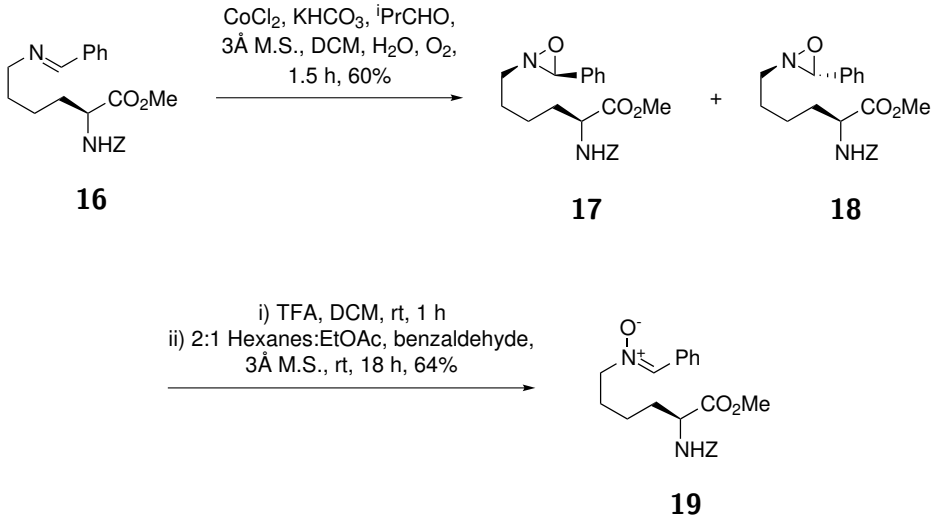
Scheme 1.3: **Diez-Martinez oxidative synthesis of nitrones**

In recent years, the use of the MTO/UHP oxidation system for imine oxidation has advanced significantly. Singh *et al.* developed a silica supported oxo-rhenium catalyst, which allowed for nitrones **15** to be synthesised in a one-pot procedure from an aldehyde **12** and primary amine **13**, rather than synthesising and isolating the imine separately (Scheme 1.4).[15] The two major advantages of their system were the ease of recyclability of their immobilised catalyst, with none of the catalyst leaching seen previously using other types of heterogeneous MTO catalysts.



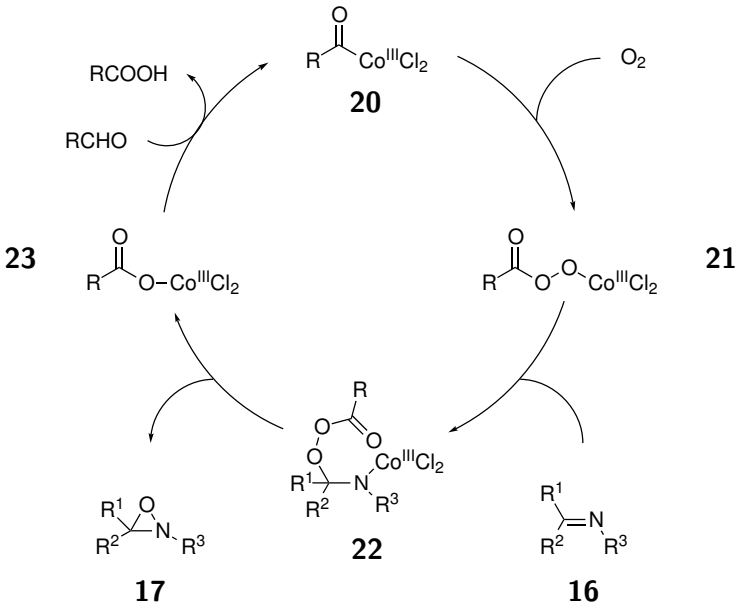
Scheme 1.4: **Singh's immobilised rhenium catalyst for nitrone formation**

Lin *et al.* have developed an improved biphasic procedure for the oxidation of nitrones from imines using molecular oxygen and a cobalt catalyst, that employs isobutryaldehyde as a co-reductant (Scheme 1.5). Oxidation of imine **16** affords a mixture of diastereomeric oxaziridine intermediates **17** and **18**, which upon treatment with acid results in nitrone product **19**.[16]



Scheme 1.5: **Lin's oxidative synthesis of nitrones**

Martiny and Jorgensen first reported this oxidation system, however they only obtained high yielding results from imines that contained tertiary alkyl groups.[17] The mechanism, shown below in Scheme 1.6, is thought to proceed *via* an acyl-cobalt(III) species **20** (which is obtained from a sequence of radical steps initiated by the abstraction of the formyl proton of isobutyraldehyde by cobalt chloride). In the presence of oxygen, the acyl-cobalt(III) species **20** is oxidised to the acyl-peroxo-cobalt species **21**. Reaction of this species with the imine **16** affords complex **22** which rearranges to the oxaziridine **17** and the cobalt carboxylate **23**. It is thought that the catalytic cycle is then completed by reaction of the carboxylate with the aldehyde co-reductant.



Scheme 1.6: **Proposed cobalt chloride/molecular oxygen catalytic cycle for the oxidation of imines to oxaziridines**

Lin *et al.* discovered that water was necessary for active catalyst formation, a fact which

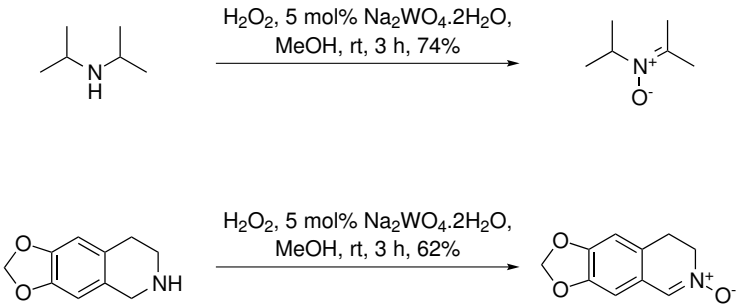
was alluded to in their earlier research due to the observation that the reaction gave a higher yield of oxaziridine, "if rigorously dry conditions are avoided." It is now thought that the small addition of water at the catalyst formation stage serves to increase the solubility of cobalt chloride in the reaction solvent (DCM).

1.3.2 Oxidation of amines

Only secondary amines can be used as substrates for the direct oxidative synthesis of nitrones. Primary amines can undergo imine formation and then oxidation, as discussed above, or they can be oxidized to hydroxylamines, from which nitrones may then be synthesised (Section 1.3.3).

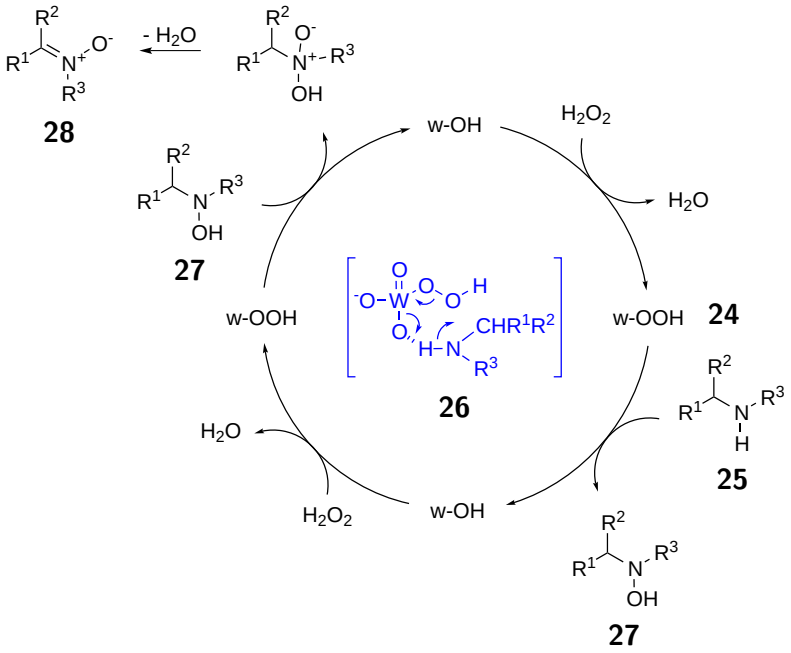
Hydrogen peroxide (H_2O_2) has been used extensively for the oxidation of secondary amines to nitrones. Typically this reaction also employs a catalyst; sodium tungstate has proven to be the most efficient catalyst for this purpose.

For example, Murahashi *et al.* developed a successful tungstate-catalysed oxidation protocol, shown in Scheme 1.7. Their research focused on simulating the action of naturally occurring enzyme-catalysed oxidation reactions of secondary amines, to afford a range of cyclic and acyclic nitrones in moderate to high yields.[18]



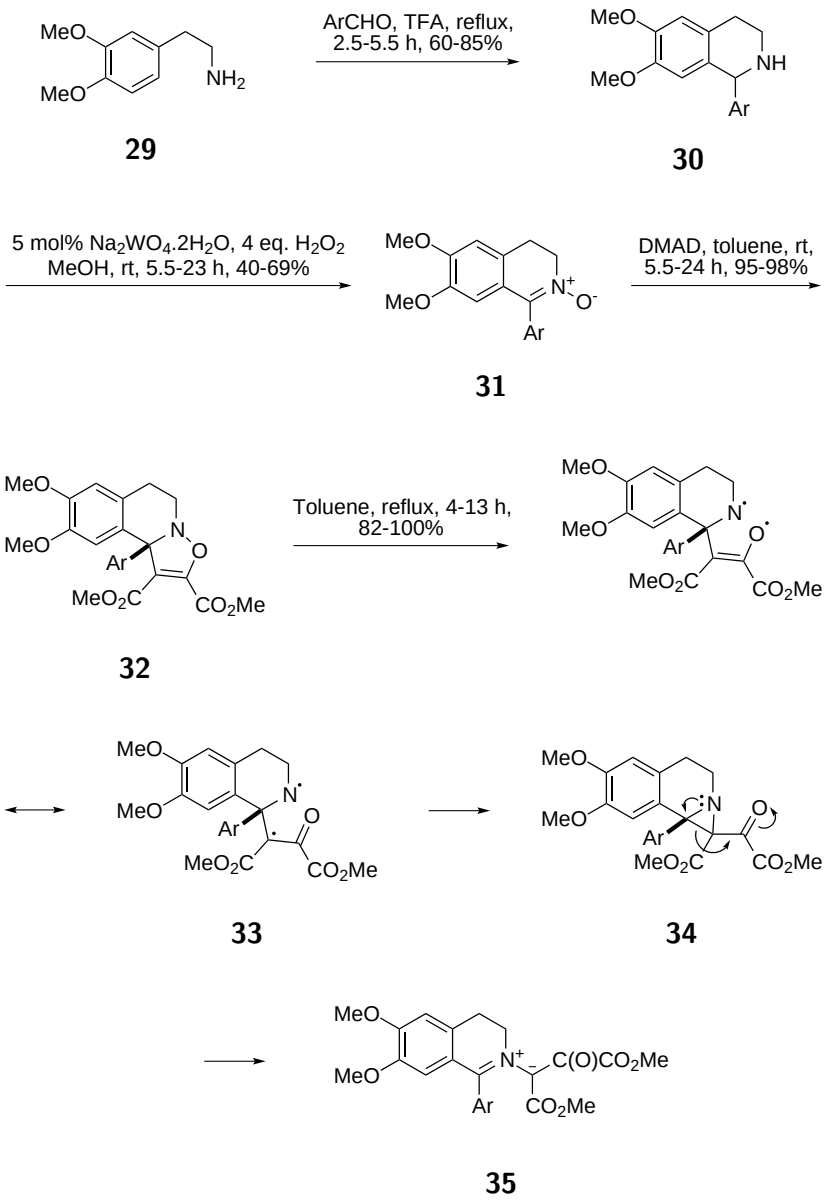
Scheme 1.7: **Murahashi's tungstate catalysed oxidation of amines to nitrones**[18]

Mechanistically, Murahashi *et al.* have shown that the active species in the oxidation is derived from a complex of tungstate and hydrogen peroxide shown in Scheme 1.8. This is supported by oxidation experiments on dibutylamine, which showed that oxidation does not take place in the presence of H_2O_2 or Na_2WO_4 alone. Murahashi's results showed the active species to be peroxytungstates, $HOOWO_3^-$ and $HOOWO_6^-$ (abbreviated to w-OOH, where w = WO_3^- or WO_6^-). The peroxytungstate (w-OOH) **24** attacks the secondary amine **25**, which undergoes rearrangement to hydroxylamine **27** (*via* intermediate **26**). Further oxidation of hydroxylamine **27** with peroxytungstate followed by dehydration, then affords nitrone **28**.



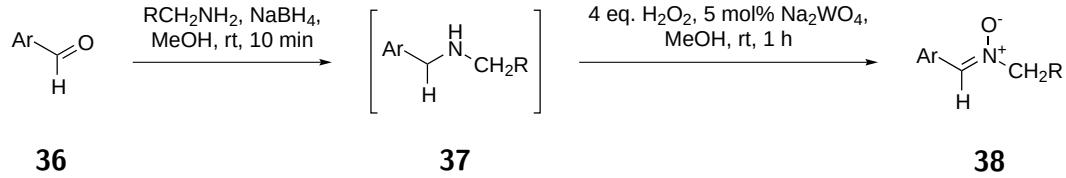
Scheme 1.8: **Proposed tungstate/H_2O_2 catalytic cycle for the oxidation of amines to nitrones**

More recently, Coşkun and Parlar applied this oxidation method to the synthesis of novel, stable 3,4-dihydroisoquinolinium *N*-ylides (Scheme 1.9). The primary amines **29** were reacted with benzaldehydes in the presence of acid to form bicyclic secondary amines **30**, which were oxidised using a catalytic amount of tungstate and four equivalents of hydrogen peroxide to afford the isoquinoline derived nitrones **31** in up to 69% yield. The group then carried out one of the most common reactions of nitrones, a 1,3-dipolar cycloaddition, using DMAD as the dipolarophile. Carrying out the reaction at room temperature afforded the isoxazolidine **32**, which rearranged on refluxing in toluene to afford the 3,4-dihydroisoquinolinium *N*-ylide **35**. The group suggested that this new structure is obtained by homolysis of the N-O bond of the isoxazolidine **32**, followed by cyclisation of the resulting radical species **33** to afford an aziridine **34** which ring opens to afford the ylide products.[19]



Scheme 1.9: **Coskun's tungstate/H_2O_2 mediated oxidative synthesis of nitrones**

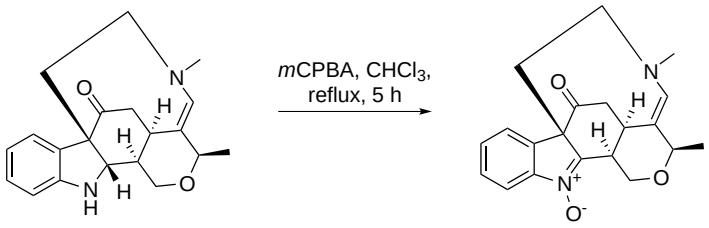
Coşkun *et al.* also developed a one-pot synthesis of acyclic nitrones starting from aromatic aldehydes **36** using related peroxide/tungstate methodology (Scheme 1.10). Firstly, secondary amines **37** were formed by reductive amination using an amine and sodium borohydride, which were then oxidised *in-situ* to afford nitrones **38**.[20]



Scheme 1.10: **Coskun's one-pot synthesis of nitrones**

Alternative oxidants, such as *m*CPBA and Davis oxaziridines have also proved highly

effective for secondary amine oxidation. The Trigalo group selectively used *m*CPBA in their synthesis of the *seco*-curane type indoline alkaloid **39** (Scheme 1.11).[21] The perbenzoic acid selectively oxidised the secondary amine over the enamine double bond and the *N*-CH_3 bond at room temperature, due to the higher reactivity of the indolinic nitrogen.



39

Scheme 1.11: ***m*CPBA mediated oxidation of an amine to nitrone 39**

Davis *N*-sulfonyl oxaziridines, such as the camphor derivative shown in Figure 1.5, are well-known oxidising reagents that have been applied to the synthesis of cyclic nitrones (often from oxidation of substituted piperidines and pyrrolidines). The general mechanism of the reagent is thought to proceed *via* nucleophilic attack of an amino group on the electrophilic oxaziridine oxygen, with simultaneous *N*-*O* bond cleavage. The resultant hemiaminal intermediate then collapses to provide the oxygenated product and an imine by-product (Scheme 1.12).

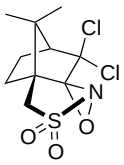
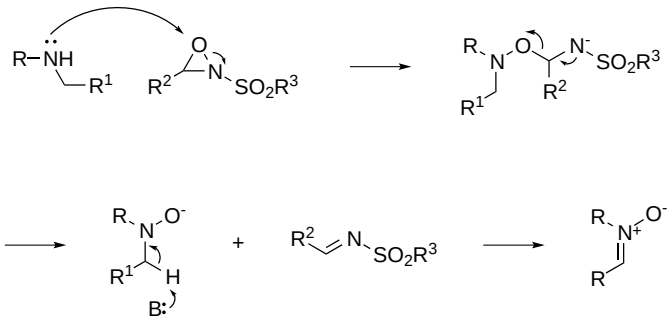


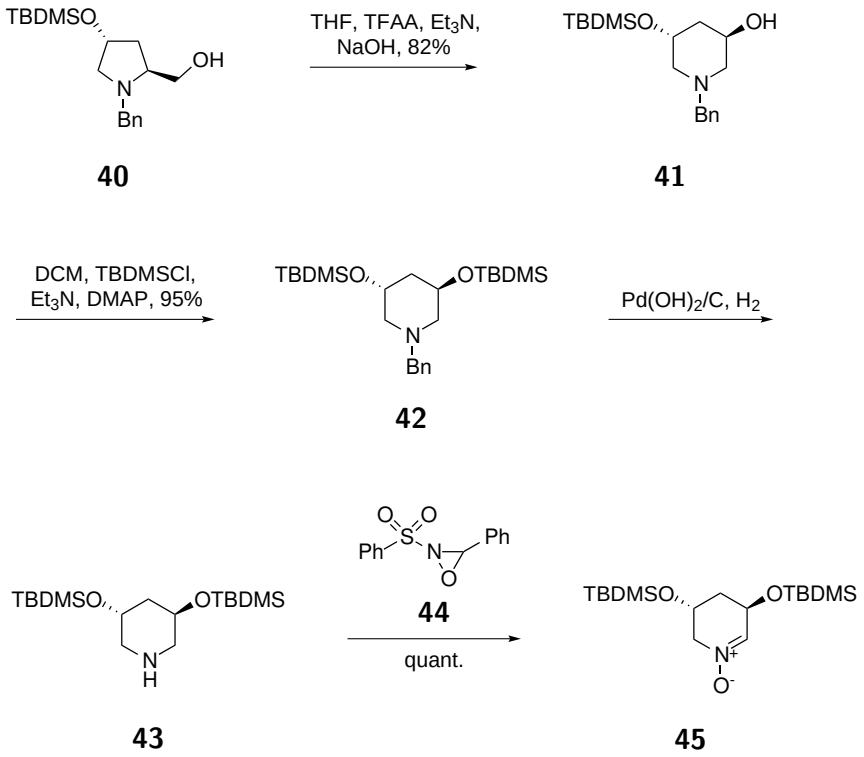
Figure 1.5: **Camphor derived example of a Davis oxaziridine**



Scheme 1.12: **Proposed mechanism for the oxidation of amines to nitrones using a Davis oxaziridine**

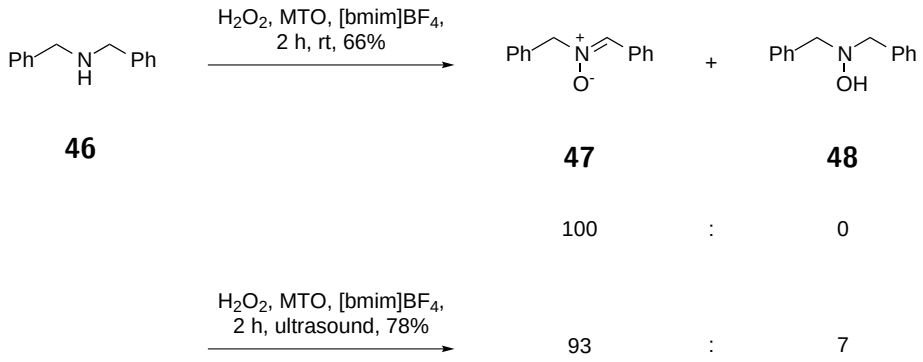
Oxidation using this camphor derived oxaziridine reagent was employed in Brandi's synthesis of a protected dihydroxyindolizidinone (Scheme 1.13).[22] The starting material **40**, derived from commercially available (4*R*)-hydroxy-(2*S*)-hydroxymethylpyrrolidine, was treated with trifluoroacetic anhydride, triethylamine and sodium hydroxide to provide

the ring expanded substituted piperidine **41** using methodology first developed by Cossy *et al.*[23] The free hydroxyl group of piperidine **41** was protected as a silyl ether using *tert*-butyldimethylsilyl chloride (TBDMSCl) to provide the symmetric piperidine **42**. Reductive debenzylation afforded the amine precursor **43**, which was oxidised with Davis oxaziridine **44** to provide the nitrone **45** in quantitative yield.



Scheme 1.13: **Brandi's synthesis of protected dihydroxyindolizidinone 45**

Methyltrioxorhenium (MTO) is an oxidation catalyst that can also be used to oxidise secondary amines to nitrones. The Sebesta group have recently progressed this oxidative method further using ionic liquids as the reaction solvent, in the presence of ultrasound to faciliate the reaction (Scheme 1.14).[24] Using 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) as the solvent, dibenzylamine nitrone **47** was afforded in 66% yield as the sole reaction product. When the oxidation reaction was repeated in an ultrasound bath, the reaction yield was increased significantly, however hydroxylamine **48** was also formed as an unwanted minor reaction product.



Scheme 1.14: **Synthesis of nitrones in ionic solvent**

After carrying out the H_2O_2-MTO oxidation of dibenzylamine in various ionic liquids, the group then selected the best performing reaction to investigate the recyclability of the catalyst. In general, it was found that the combined yield of nitrone and hydroxylamine decreased as subsequent runs were carried out, as did the selectivity for the nitrone product. However, the group reported some inconsistencies within their data set (see Table 1.1) which they attribute to possible leaching of the MTO, as well as decomposition of MTO catalysed by proton donors and hydrogen peroxide.

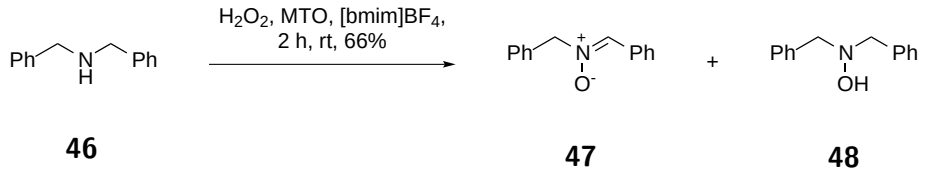


Table 1.1: **Sebesta's catalyst recycling data for the synthesis of nitrones in ionic solvent**

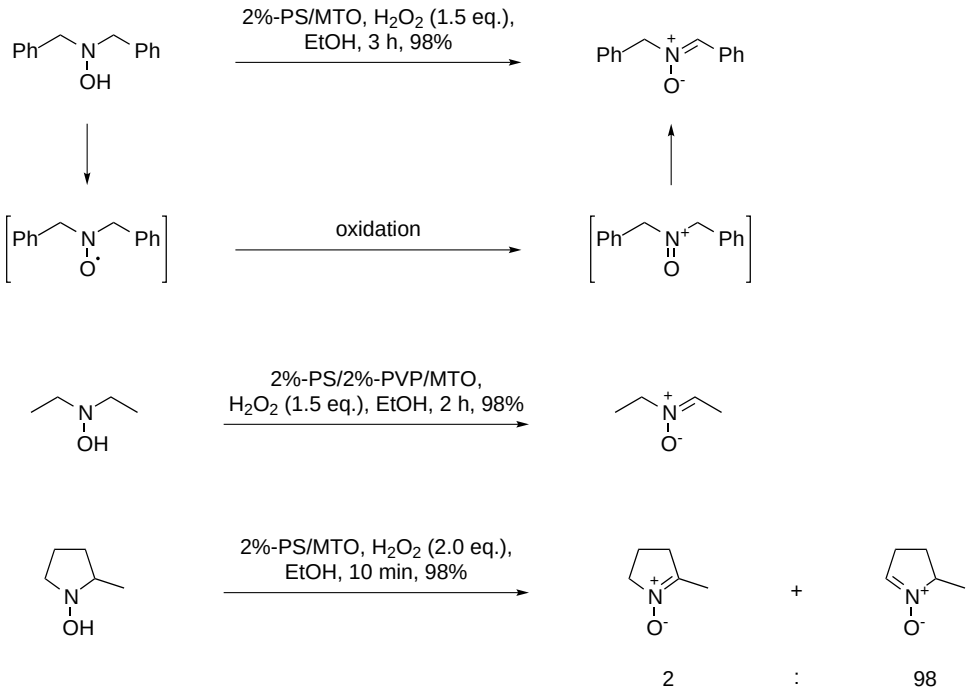
Entry / run	Yield of 47 & 48	Ratio of 47:48
1	66	100:0
2	44	90:10
3	57	94:6
4	50	100:0

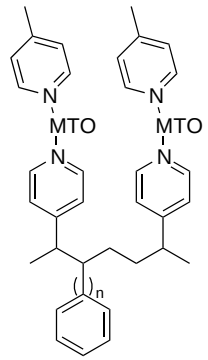
1.3.3 Oxidation of hydroxylamines

Oxidation of hydroxylamines is the third and final general oxidative method for synthesising nitrones. It often employs mild conditions for the oxidation of hydroxylamines that contain at least one proton at their α- carbon position. During the reaction, hydroxylamines are oxidised to nitroxyl radicals, and these radical species then undergo disproportionation to afford the product nitrones. Many of the oxidants used in this transformation are the same as those discussed above for the direct oxidation of imines

and amines.

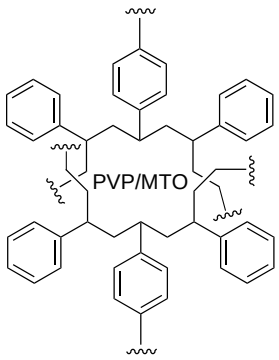
Methyl trioxorhenium in the presence of hydrogen peroxide is just one combination of reagents that can be applied to the oxidation of hydroxylamines. Saladino *et al.* employed polymer supported heterogeneous MTO catalysts, **49** and **50**, to oxidise a range of secondary hydroxylamines to their corresponding nitrones in high percentage conversions and isolated yields. The group applied six different polystyrene (PS) and polyvinyl pyridine (PVP) supported MTO catalysts to the oxidation of symmetrically substituted hydroxylamines and non-symmetrical 3-substituted and 2-substituted hydroxypyrrolidines (Scheme 1.15). All of their experiments afforded higher yields and/or greater conversion to product nitrones than a standard H_2O_2-MTO peroxide procedure, and the catalysts could be recycled up to five times without loss of efficiency.[25]





2%-PS/MTO

49



2%-PS/2%-PVP/MTO

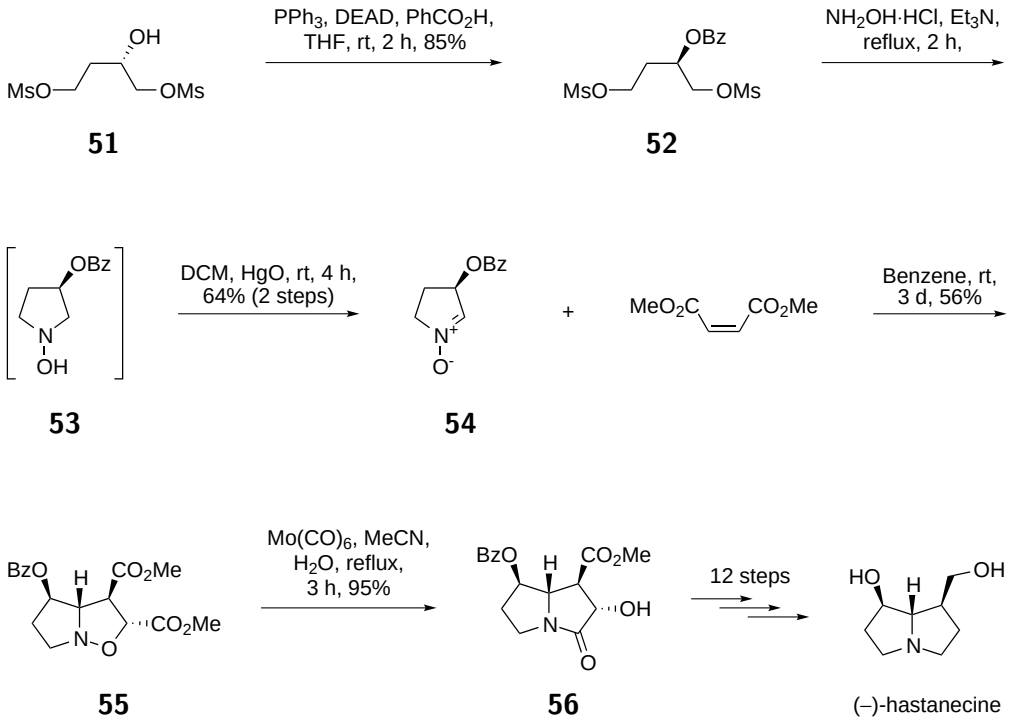
50

Scheme 1.15: **Nitrone synthesis using polymer supported MTO catalysts**

Cicchi *et al.* have long used mercury oxide to oxidise cyclic hydroxylamines to nitrones. Using this methodology they have synthesised functionalised racemic and enantiopure five membered cyclic nitrones from tartaric,[26] malic,[27] aspartic[28] and citramalic[29] acids. The focucs of their research is to employ enantiopure nitrones as building blocks in the synthesis of natural products, and they have recently reported two reviews on this subject.[30,31] Scheme 1.16 shows a representative synthesis of a necine base (–)-hastanecine.[32]

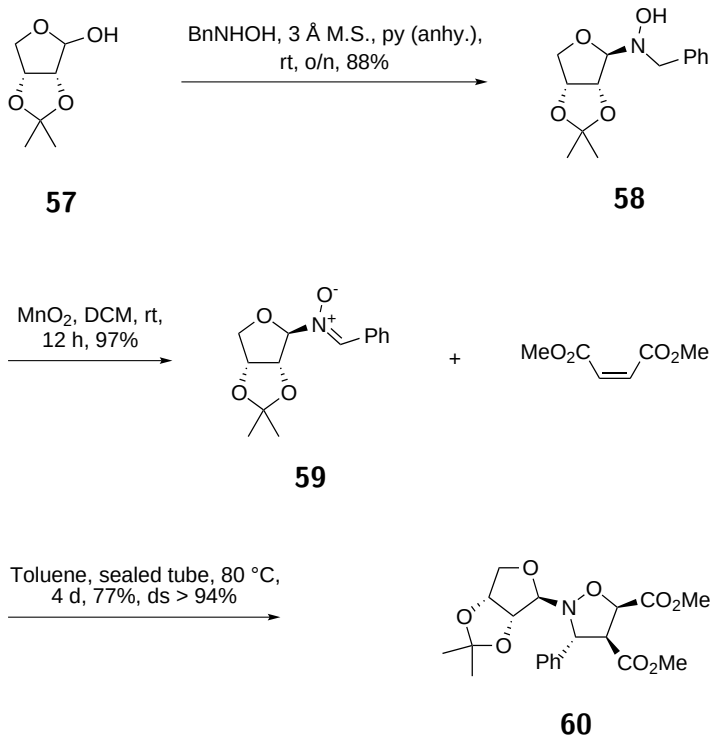
In this case the benzyloxy-dimesylate **52** was synthesised in high yield from the primary alcohol **51** using a Mitsunobu reaction. The dimesylate **52** was then reacted with hydroxylamine in a double nucleophilic displacement/cyclisation reaction to afford the cyclic hydroxylamine intermediate **53**. Nitrone **54** was synthesised in the second stage of this one-pot procedure through oxidation of **53** using mercury oxide. A 1,3-dipolar cy-

cloaddition reaction of nitrone **54** with dimethylmaleate gave the major adduct **55** which was isolated in a moderate 56% yield and then refluxed in acetonitrile in the presence of $Mo(CO)_6$. This induced a *N-O* cleavage/lactamisation reaction to afford intermediate **56** in 95% yield. Following a procedure by Denmark *et al.*, the total synthesis of (–)-hastanecine was then completed in twelve steps in an 8.7% overall yield. The group have employed related pyrroline based hydroxylamine oxidation methodology for the total syntheses of both (+) and (–)-lentiginosine,[33] 7-*epi*-croalbinecine and (–)-croalbinecine.[32]



Scheme 1.16: **Oxidation of hydroxylamine 53 to nitrone 54 for the synthesis of (−)-hastanecine 321**

In a separate report, the Cicchi group have described the enantioselective synthesis of tri-substituted isoxazolidines (Scheme 1.17). For this work, they used another transition metal based oxidant, manganese dioxide, to synthesise the required nitrone precursors.[34] The group began by synthesising the requisite hydroxylamine **58** through the reaction of *N*-benzyl hydroxylamine with the free -OH group at the anomeric carbon of a protected pentose **57**. Hydroxylamine **58** was then oxidised using manganese dioxide to yield the *N*-glycosyl aldonitrone **59**. Cycloaddition of **59** with dimethyl maleate afforded the isoxazolidine **60** in 77% yield with high diastereoselectivity, due to the sugar moiety acting as a chiral auxiliary for control of facial selectivity.



Scheme 1.17: **Oxidative formation of *N*-glycosyl aldonitrone 59 for the synthesis of tri-substituted isoxazolidine 60**

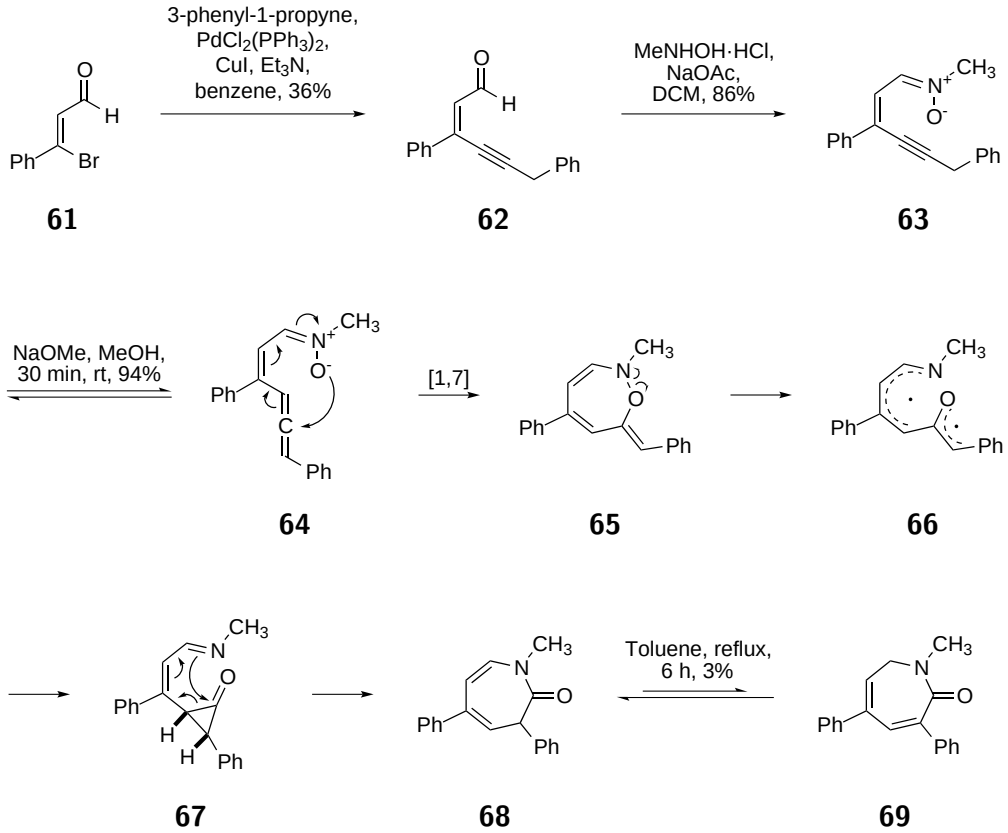
1.4 Non-oxidative methods

1.4.1 Condensation of mono substituted hydroxylamines with carbonyl compounds

The condensation of mono substituted hydroxylamines with carbonyl compounds is the first of two key non-oxidative methods for directly synthesising nitrones. Condensation can be carried out with mild reagents, allowing the presence of a wide range of functional groups within the two reaction components.[35]

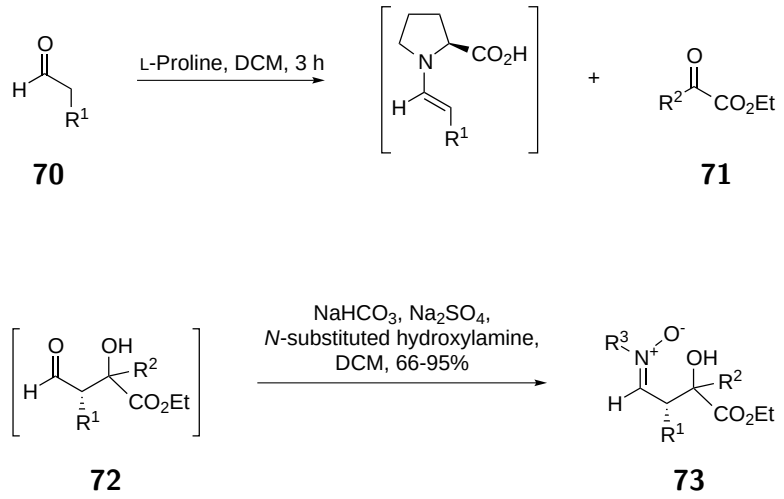
Knobloch *et al.* synthesised conjugated acyclic nitrones in 57-88% yield using condensation methodology for the synthesis of azepin-3-one derivatives (Scheme 1.18).[36] The synthesis began with a Sonogashira alkynylation reaction of 3-bromo aldehyde **61** with 3-phenyl-1-propyne to afford propargyl compound **62** in 36% yield. Treatment of **62** with *N*-methylhydroxylamine hydrochloride and sodium acetate provided the conjugated nitrone **63**, which was subsequently dissolved in methanol and treated with sodium methoxide to yield dihydroazepinone **68**. This transformation was thought to proceed *via* an allene intermediate **64** which underwent a 1,7-dipolar cyclisation reaction to afford the methyleneoxazepine **65**. Cleavage of the *N*-*O* bond of **65** gave the diradical **66** which recombined to afford the azadienylcyclopropanone **67**. Cyclisation of this unstable intermediate then yielded the dihydroazepinone **68**. Heating dihydroazepinone **68** in toluene at reflux set up an equilibrium that furnished the desired conjugated cyclic azepinone **69**, albeit in a

very low 3% yield.



Scheme 1.18: **Condensation methodology used in Knobloch's synthesis of azepin-3-ones**

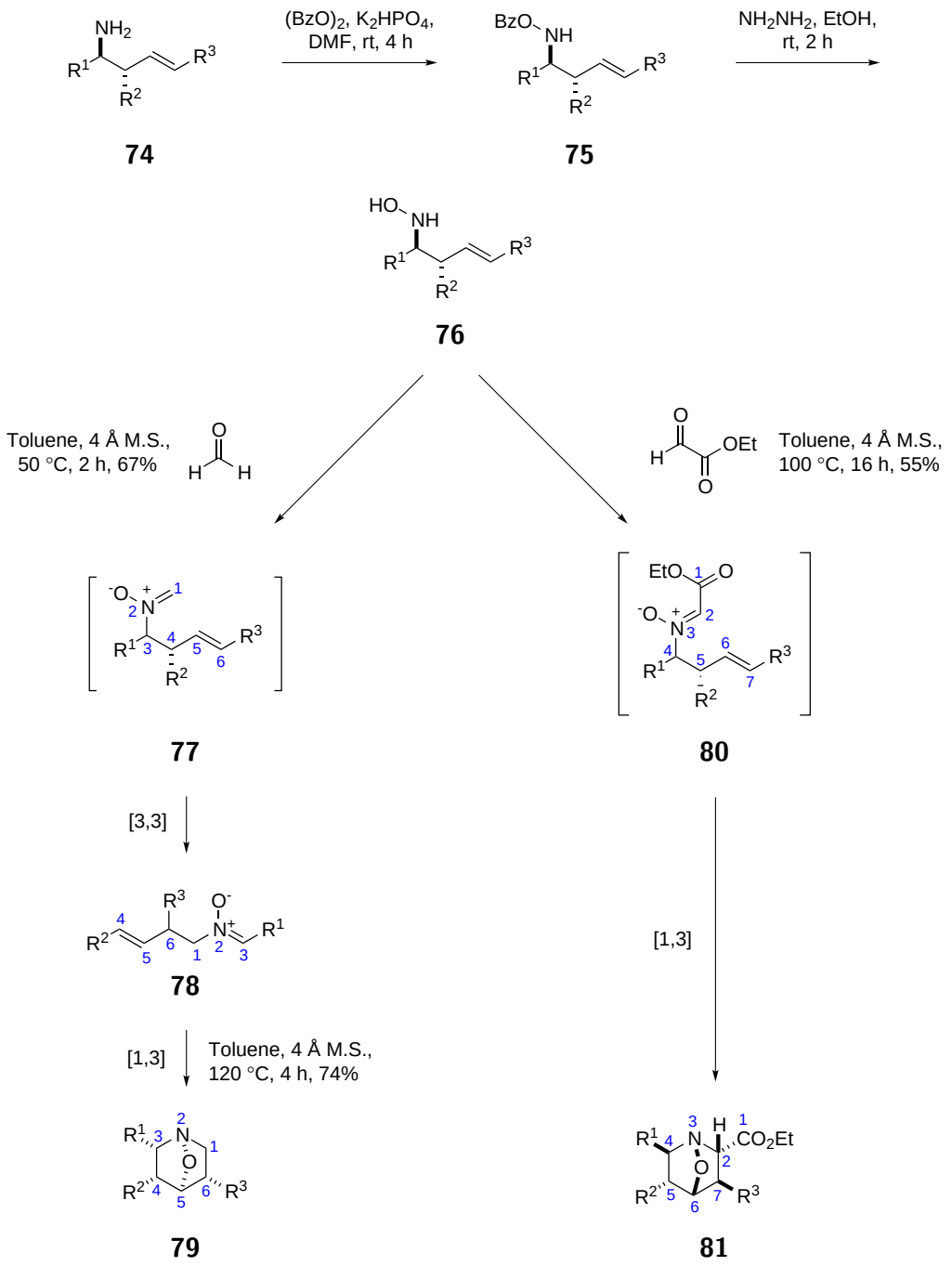
A range of optically active β-hydroxy-nitrones were synthesised by Bøgevig *et al.* through the condensation of aldol products with *N*-substituted hydroxylamines (Scheme 1.19). An L-proline catalysed aldol reaction between aldehydes **70** and activated carbonyl compounds, such as α-keto acid **71**, provided intermediate aldol products **72**. This step was followed by an *in-situ* reaction with *N*-alkyhydroxylamines,[37] to afford nitrones **73** in high yield and enantiomeric excess (up to 96% ee).



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

Scheme 1.19: **Bøgevig's use of condensation methology for the synthesis of optically active β-hydroxy-nitrones 73**

Yang *et al.* used condensation methodology for their stereodivergent syntheses of highly substituted 1-aza-7-oxabicyclo[2.2.1]heptanes.[38] Stereodefined homoallylic amines **74** were reacted with benzoyl peroxide to afford the *O*-benzoyl hydroxylamines **75**, which were subsequently deprotected with hydrazine to afford the homoallylic hydroxylamines **76** (Scheme 1.20). Condensation with formaldehyde initially led to formation of nitrones **77**, followed by a [3,3]-sigmatropic rearrangement to yield the isolable nitrones **78**. Refluxing these nitrones in toluene induced an intramolecular 1,3-dipolar cycloaddition reaction that led to the synthesis of a range of 1-aza-7-oxabicyclo[2.2.1]heptanes **79**, all with >20:1 diastereoselectivity. Alternatively, reacting the homoallylic hydroxylamines **76** with ethyl glyoxolate afforded nitrones **80**, which were stable to sigmatropic rearrangement. They subsequently underwent an intramolecular 1,3-dipolar cycloaddition leading to heptanes **81**, again with >20:1 diastereoselectivity.



Scheme 1.20: **Yang's synthesis of 1-aza-7-oxabicyclo[2.2.1]heptanes**

1.4.2 Syntheses from oximes

The method of synthesising nitrones from oximes is considered to be a facile route, particularly when using electron poor alkenes as the alkylating reagent.[35] Grigg and co-workers developed this field significantly, with their synthetic methods normally incorporating a subsequent 1,3-dipolar cycloaddition reaction, due to the instability of the resultant nitrones.[39–42]

Nitrones formed *via* 1,2-prototropy of oximes

The less frequently used method for synthesising nitrones from oximes employs a 1,2-prototropic reaction, which involves heating an oxime to set up an equilibrium with its nitrone form, as shown in Figure 1.6. The small concentration of nitrone present can then take part in a 1,3-dipolar cycloaddition reaction (Scheme 1.21).[40]

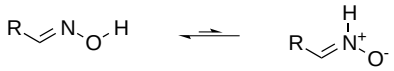
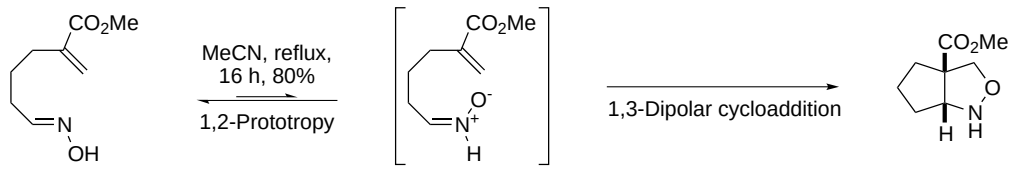


Figure 1.6: **Oxime-nitrone equilibrium**



82 **83** **84**

Scheme 1.21: **1,2-prototropic reaction of oxime 82**

Nitrones formed *via* oxime *N*-alkylation

The more common methods to synthesise nitrones from oximes are *via* Michael addition and 1,3-azaprotio cyclotransfer reactions, (shown in Figure 1.7), which can be conveniently classified into four different reaction types.

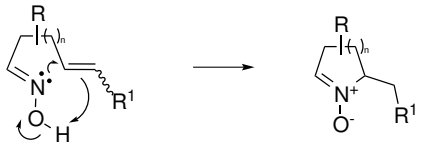


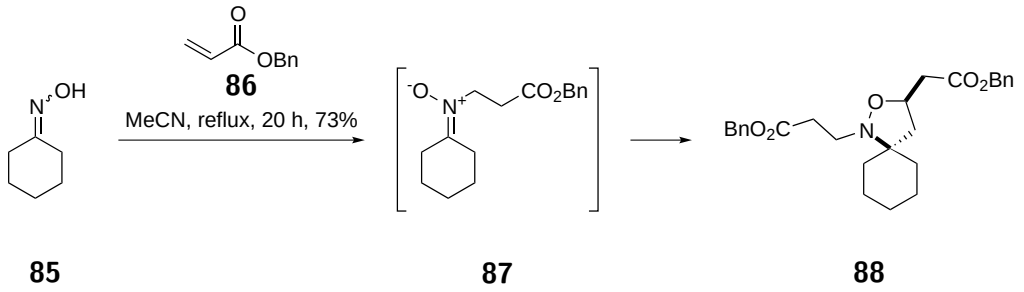
Figure 1.7: **Example of a 1,3-azaprotio cyclotransfer reaction**

Classes I & II:

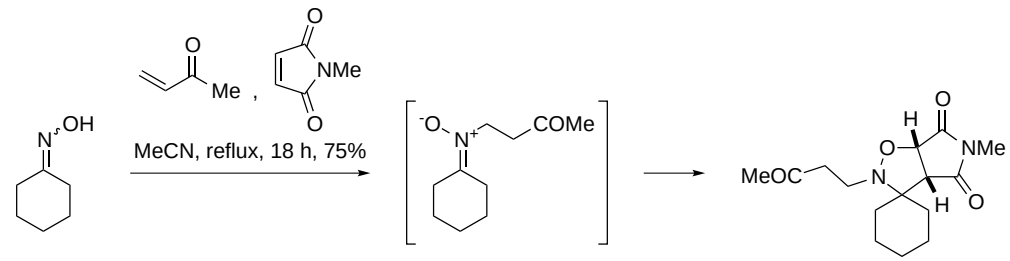
Both Class I and II reactions are based on a nitrone being synthesised from *N*-alkylation of an oxime with an electron deficient alkene, with the resultant nitrones then participating in subsequent dipolar cycloaddition reactions. Classes I and II refer to inter- and intramolecular dipolar cycloadditions reactions, respectively.

Scheme 1.22 shows an example of a class I nitrone synthesis/cycloaddition reaction, where the alkylating reagent and the dipolarophile are the same (in this case benzyl acrylate **86**). Conjugate *N*-alkylation of the oxime with benzyl acrylate **86** affords a nitrone that then undergoes an intermolecular 1,3-dipolar cycloaddition with excess benzyl acrylate.

Scheme 1.23 provides an example where the alkylating reagent and dipolarophile are different, to create the alternative tricyclic isoxazolidine cycloaddition product **90**.

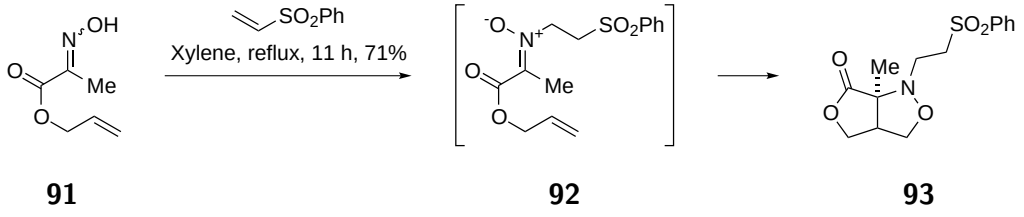


Scheme 1.22: **A Grigg class I reaction where the alkylating reagent and dipolarophile are the same**



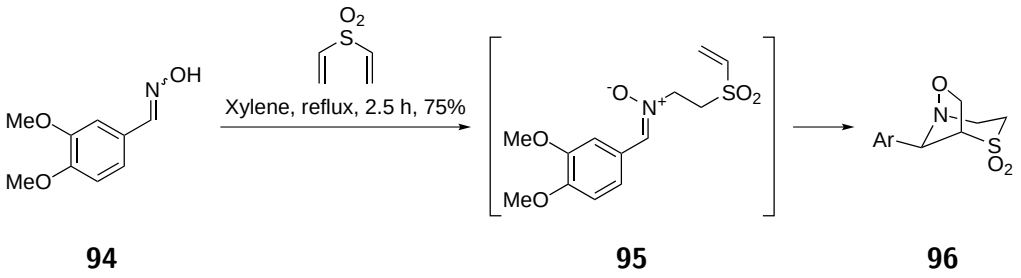
Scheme 1.23: **A Grigg class I reaction where the alkylating reagent and dipolarophile are different**

Examples of Class II reactions are shown in Scheme 1.24 and Scheme 1.25. In the first example, the dipolarophile fragment is derived from the oxime **91**, and so the intramolecular 1,3-dipolar cycloaddition reaction proceeds *via* *C*-alkyl nitrone **92** (Scheme 1.24).



Scheme 1.24: **A Grigg class II reaction proceeding *via* a *C*-alkyl nitrone intermediate**

In Scheme 1.25, the dipolarophile fragment is generated by alkylation of divinyl sulfone by the oxime **94**, to afford an *N*-alkyl nitrone **95** that undergoes an intramolecular 1,3-dipolar cycloaddition reaction *in-situ*.



94 **95** **96**

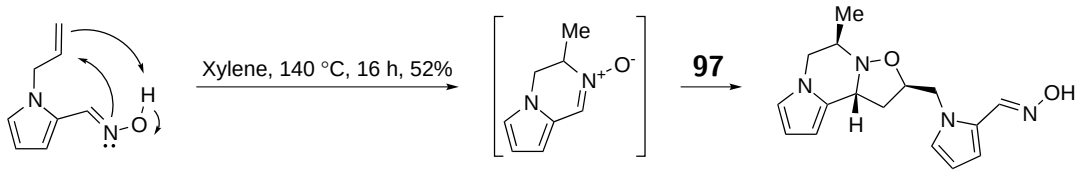
Scheme 1.25: **A Grigg class II reaction proceeding *via* a *N*-alkyl nitrone intermediate**

In the first instance, it was assumed that the *N*-alkylation reaction of oximes with the electronegatively substituted alkenes proceeded *via* conjugate addition reactions. However, during the course of their research into class III and class IV reactions, the Grigg group began to propose an alternative 1,3-azaprotio cyclotransfer mechanism (Figure 1.7).

Classes III & IV:

For Class III and IV nitrone syntheses, oxime substrates underwent intramolecular cyclisation onto alkenes to afford nitrones that could undergo further 1,3-dipolar cycloaddition reactions, allowing a wider range of acyclic scaffolds to be accessed. During this part of the research programme it was also possible to isolate and confirm the structure of some of the proposed nitrone intermediates.

Scheme 1.26 shows a Class III intramolecular reaction of a pyrrole derived oxime **97** on to an unactivated alkene bond to form the nitrone intermediate **98**. This subsequently underwent an intermolecular 1,3-dipolar cycloaddition reaction with the alkene fragment of another molecule of the oxime **97**, to afford the cycloadduct **99**. This study revealed the existence of an alternative "ene" like mechanism which the group concluded to be the dominating mechanism for these type of cyclisation reactions. The mechanistic arrows that they proposed are shown for the pyrrole based reaction drawn in Scheme 1.26, with the reactions being described as 1,3-azaprotio cyclotransfer reactions.

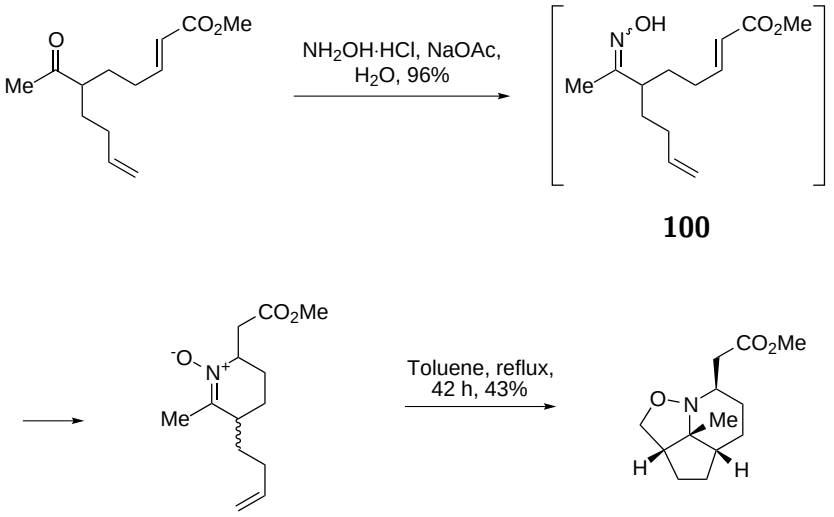


97 **98** **99**

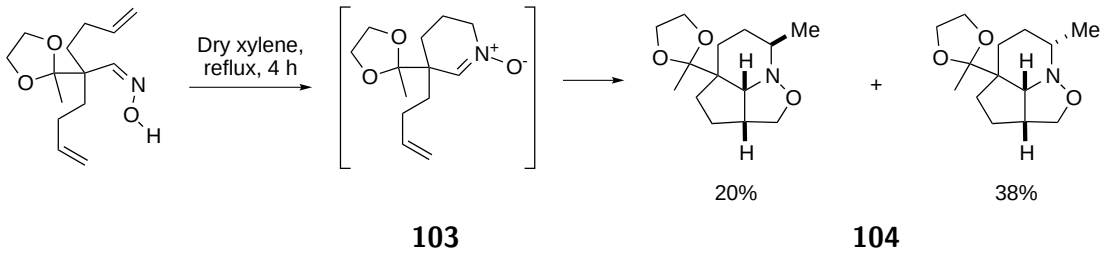
Scheme 1.26: **A Grigg Class III reaction; intramolecular nitrone synthesis followed by intermolecular cycloaddition**

Both Scheme 1.27 and Scheme 1.28 demonstrate intramolecular Class IV reactions. In the first example, oxime **100** cyclised to afford nitrone **101** that underwent a thermal

1,3-dipolar cycloaddition reaction with its alkene fragment to afford tricycle **102**. In the second example, the cyclisation substrate contained two terminal unactivated alkene groups, with initial oxime cyclisation occuring to afford the six membered ring of nitrone **103**. This then underwent a second cyclisation reaction to afford tricycle **104**.

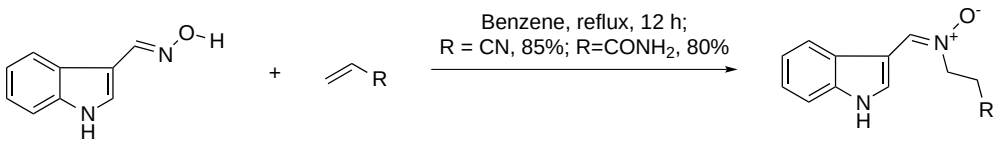


Scheme 1.27: **A Grigg class IV reaction where both the alkylating agent and the dipolarophile are part of the oxime starting material**



Scheme 1.28: **A Grigg Class IV reaction where both the alkylating agent and dipolarophile are terminal alkenes**

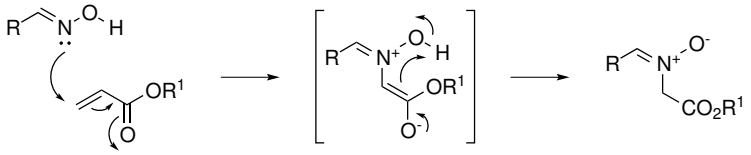
Chakrabarty *et al.* serendipitously incorporated 1,3-azaprotio cyclotransfer methodology into their intermolecular synthesis of indole-nitrones from oximes. Having had previous success with a [4+2] cycloaddition reaction of furfuraldoxime and *N,N*-dimethylhydrazone, the group initially attempted to form the hetero Diels-Alder product from indole-oxime **105** and substituted alkenes. However, as shown in Scheme 1.29, reaction of indol-oxime **105** with methyl acrylate, methyl vinyl ketone and *N*-methylmaleimide yielded the corresponding indole-nitrones **106**.[43]



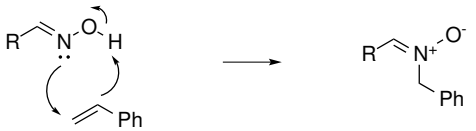
105 **106**

Scheme 1.29: **Chakrabarty's synthesis of indole-nitrones**

In summary, whilst it is apparent that the addition of nitrones to unactivated alkenes must proceed *via* an "ene" type 1,3-azaprotio cyclotransfer reaction, it is possible that the corresponding reactions of alkenes containing electron withdrawing groups may proceed *via* an alternative conjugate addition manifold (Figure 1.8).



(a) *Activated alkene: conjugate addition mechanism*



(b) *Unactivated alkene: 1,3-azaprotio cyclotransfer reaction mechanism*

Figure 1.8: **The different methods for nitrone synthesis from the reactions of oximes with activated and unactivated alkenes**

1.5 Conclusion

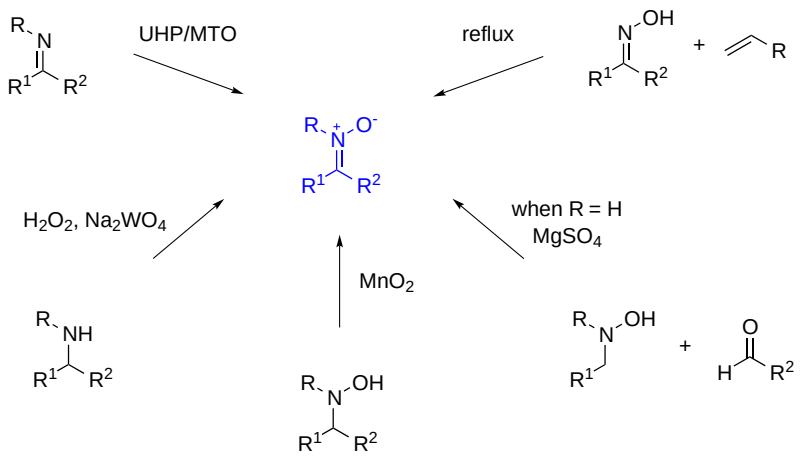
This review has presented relevant literature regarding the five most widely used methods for synthesising nitrones. Imines, amines and hydroxylamines can all be oxidised, using a variety of oxidants and catalysts, to their corresponding nitrones. Condensation of *N*-mono substituted hydroxylamines with carbonyl compounds, and the alkylation of oximes are the two most popular non-oxidative routes for the synthesis of nitrones. This review has highlighted, in many cases, the origins of different methods combined with progress made in recent years to improve reaction scope, efficiencies, and efforts to develop sustainable methodologies. In the following chapters, we will discuss the relevance of this research to my results, regarding the synthesis and reactions of novel isoindole and isoquinoline nitrones.

Chapter 2

Discovery & Mechanism of Cyclisation Reaction for Formation of Isoindole Derived Nitrones

2.1 Introduction

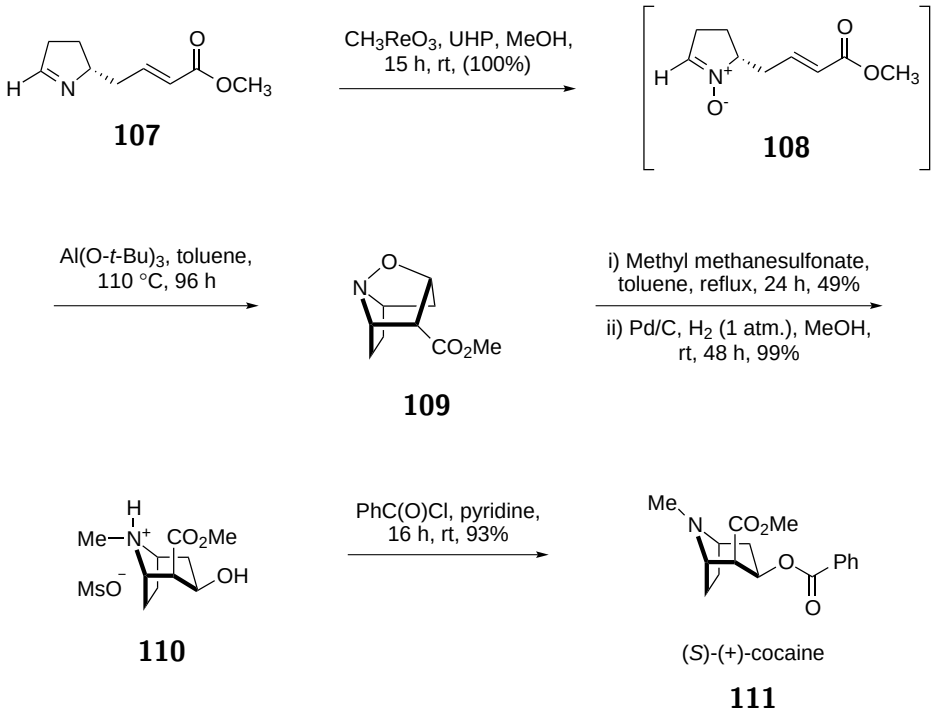
As discussed in Chapter 1, nitrones are commonly synthesised *via* metal catalysed per-acid oxidation of secondary amines and imines (Scheme 2.1). Non-oxidative methods include condensation of *N*-substituted hydroxylamines onto carbonyls, and alkylation of oximes.[35]



Scheme 2.1: **Common methods of nitrone synthesis**

These methods typically require preparation of the nitrone precursors e.g. imine, hydroxylamine, oxime etc., and as many nitrones are unstable, they are often synthesised and reacted *in-situ*. An example of this is illustrated by the synthesis of (*S*)-(+)-cocaine by Theddu *et al*. As shown in Scheme 2.2, imine **107** was oxidised, using standard conditions, to afford the pyrroline nitrone **108**. The group reported that attempted purification of this nitrone resulted in decomposition. Instead, they carried out a highly stereoselective

Lewis acid catalysed intramolecular 1,3-dipolar cycloaddition reaction on the crude material to provide the bicyclic cycloadduct **109**. After reacting cycloadduct **109** with methyl methanesulfonate, the resultant salt underwent *N*-*O* bond cleavage using palladium catalysed hydrogenation to yield alcohol **110**. (*S*)-(+)-cocaine **111** was finally afforded after *O*-acylation of the alcohol **110** with benzoyl chloride in 93% yield.[44]



Scheme 2.2: ***In-situ* cycloaddition reaction of nitrone 108 for the synthesis of (*S*)-(+)-cocaine 111**

In other fields however, stable nitrones have been isolated and employed as spin trap probes in electron paramagnetic resonance (EPR) spectroscopy research, which is a technique used to analyse materials possessing unpaired electrons.

Using nitrone spin traps, such as *N*-tertiary-butyl nitrone (PBN) and 5,5-dimethyl-pyrroline *N*-oxide (DMPO) (Figure 2.1), short lived free radical species can be trapped. The resultant spin-adducts have an increased half life relative to the parent free radical, meaning they are stable enough to be analysed by EPR, with each spin-adduct affording a unique EPR spectrum.

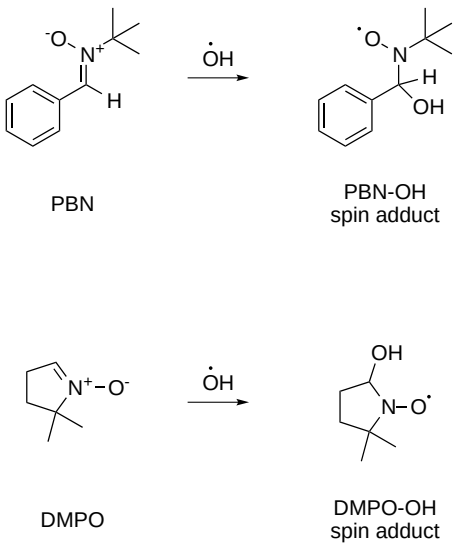


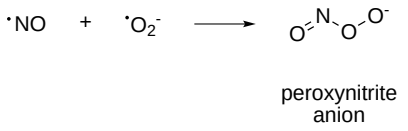
Figure 2.1: **Nitrone derived radical spin traps and adducts**

2.1.1 Electron Paramagnetic Resonance research using 5,5-dimethyl-pyrroline *N*-oxide

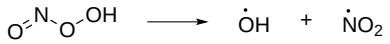
EPR spectroscopy has been employed as a research tool in many scientific fields, with the pyrroline based nitrone trap, DMPO, and its derivatives,[45,46] having become standard radical spin traps over the last few decades (Figure 2.6).[47,48]

In recent years, the application of spin traps and EPR spectroscopy in biological and pharmacological environments has gained increasing interest. Certain diseases, such as Parkinson's, are associated with high levels of free radicals. EPR studies therefore continue to be used to help understand disease cause and mechanism.[48–50]

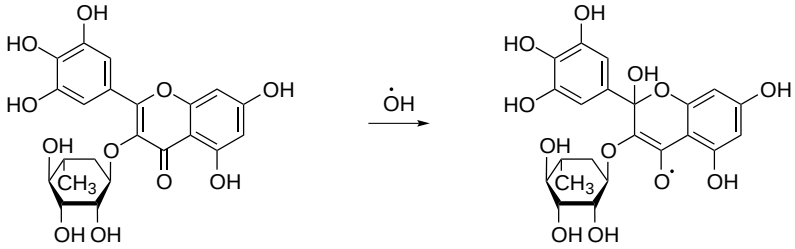
For example, peroxynitrite, a potent oxidising and nitrating anion formed *in vivo* from the reaction of superoxide free radicals with nitric oxide free radicals, is cytotoxic and causes oxidative DNA strand breakage.[51] It is also implicated in neurodegenerative diseases[52] as it decomposes to form reactive oxygen species, such as hydroxyl and superoxide radicals. Using EPR analysis and DMPO as the spin trap, peroxynitrite can be detected *via* formation of its DMPO-hydroxyl (DMPO-OH) spin adduct, which gives diagnostic signals in the EPR spectrum. For example, a recent report by Chen *et al.* employed EPR to prove that myricitrin (a naturally occuring flavonoid) acts as a hydroxyl radical scavenger to reduce the amount of DMPO-OH adduct produced (Figure 2.2c). Thus, myricitrin can potentially protect against both the DNA damage and cytotoxicity of peroxynitrite decomposition, opening up the field for further neuroprotection research.[53]



(a) **Synthesis of peroxynitrite anion**



(b) **Decomposition of peroxynitrite to afford hydroxide and nitrogen dioxide radicals**



(c) **Scavenging of hydroxide radical by myricitrin**

Figure 2.2: **Chemistry of peroxynitrite**

Peroxynitrite is also known to contribute to cancer progression, and research into cancer treatments includes the use of scavengers to inhibit the damaging effect of peroxynitrite. Sufferers of ulcerative colitis are at a higher risk of developing colorectal carcinoma, and it was found that patients taking mesalamine (5-aminosalicylic acid, 5-ASA, Figure 2.3) as a colitis treatment were less likely to develop the cancer.

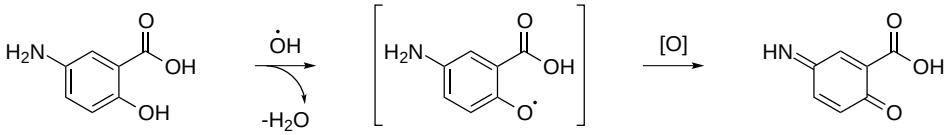


Figure 2.3: **Mesalamine - a peroxynitrite scavenger**

In EPR studies of peroxynitrite-mediated generation of hydroxyl radicals, the Graham group reported that use of a 1 mM concentration of mesalamine resulted in significant inhibition of the formation of the DMPO-OH spin adduct signal.[54] Using other techniques, they also proved 5-ASA's ability to prevent DNA strand breakage in the presence of peroxynitrite, thus potentially affording a dual action medication for the sufferers of ulcerative colitis.

EPR has also found use in the structural and conformational elucidation of proteins,[55–57] nucleic acids,[58] and other biological macromolecules.[59,60] An example of this is the work by Yang *et al.*, whose combination of EPR techniques and NMR analysis allowed for the global 3D structure of the protein homodimer Dsy0195 to be resolved (Figure 2.4).[55] To obtain EPR data (1-oxyl-2,2,5,5-tetramethylpyrroline-3-methyl)methanethiosulfonate (MTSL) was used to spin label the thiol unit of a free cysteine that had been introduced into the protein *via* site directed mutagenesis.

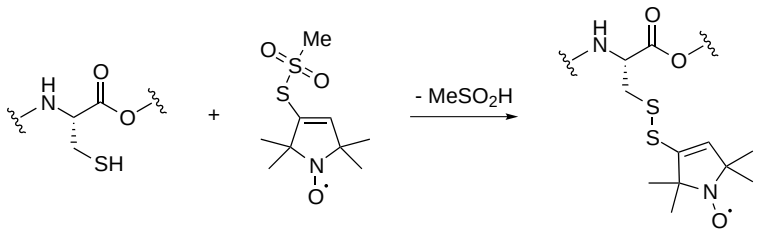


Figure 2.4: **Spin labelling of cysteine within the Dsy0915 protein**

The experimental results were processed by an automatic NMR-based structure determination programme, to produce a network of interchain nuclear Overhauser effect (NOE) constraints. It is these constraints that enabled both the homodimer interface and the global homodimer structure to be mapped.

2.1.2 5,5-dimethyl-pyrroline *N*-oxide limitations

However, there are several problems associated with the use of pyrroline-based spin traps such as DMPO. For example, the -OH adduct has a relatively short lifetime, and issues with DMPO-OH detection in biological studies arise, as •OH radicals are also formed from the decomposition of superoxide radicals that may also be present.[61] DMPO is also particularly slow to react with superoxide and alkylperoxide radicals.[62] Non-radical reactions such as hydrolysis of DMPO based spin-adducts can take place, and for DMPO itself, the presence of a hydrogen on the α carbon makes it and it's spin adducts more susceptible to disproportionation.[63] It has also been demonstrated that •NO radicals can form from degradation of DMPO.[64]

All of these factors add complexity to the interpretation of experimental results, in particular the detection and identification of •OH and superoxide radicals in biological systems. Many of the undesired side reactions can produce new free radical species which can complicate interpretation of the EPR spectrum and inhibit DMPO from trapping the species of interest. Therefore, in order to obtain reliable and accurate EPR data, there is a balance to strike with spin traps between specificity for a free radical species and the stability of the resulting spin-adduct.

Several approaches have been carried out to address the issues that can complicate studies on DMPO-adducts. For example, substitution at the α-carbon of trimethyl-pyrroline-*N*-oxide, M_3PO (Figure 2.5), helps prevent disproportionation of its hydroxyl radical adduct. The resultant M_3PO-OH adduct has been shown to be significantly more persistent than the corresponding DMPO-OH adduct.[65]

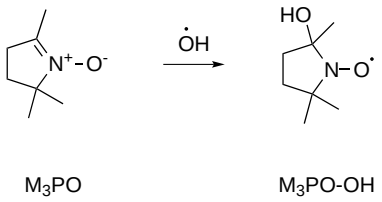


Figure 2.5: **M_3PO spin trap**

Numerous analogues of DMPO have been synthesised (Figure 2.6) and it has been reported that replacement of one of the gem-dimethyl groups with an electron withdrawing substituent, [e.g. ester (EMPO), phospho (DEPMPO)] resulted in a significant increase of the half life of their superoxide radical adducts.[62]

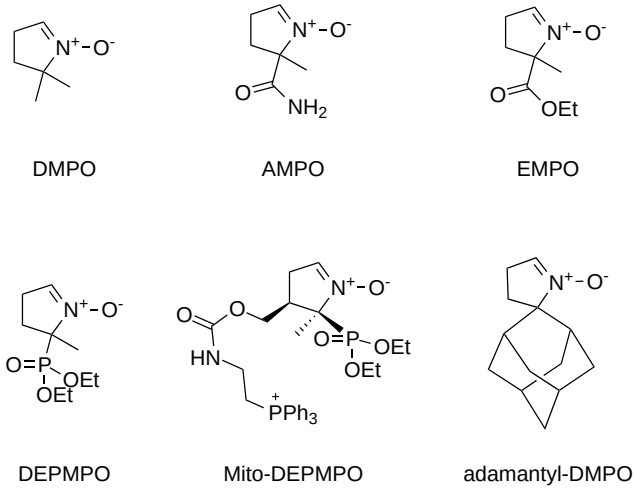


Figure 2.6: **DMPO analogues**

Villamena *et al.* reported that the amide analogue (AMPO, Figure 2.7) is also more reactive with superoxide, as the amide group increases the electrophilicity of the nitrone carbon. Computer modelling has shown that intramolecular hydrogen bonding between the amide proton and the nitrone oxygen atom occurs in the transition state.[66]

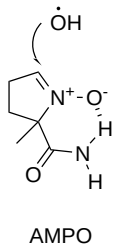
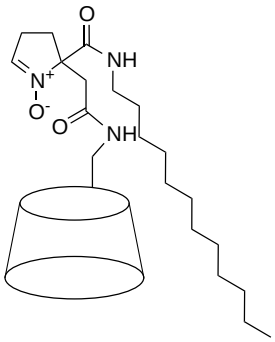


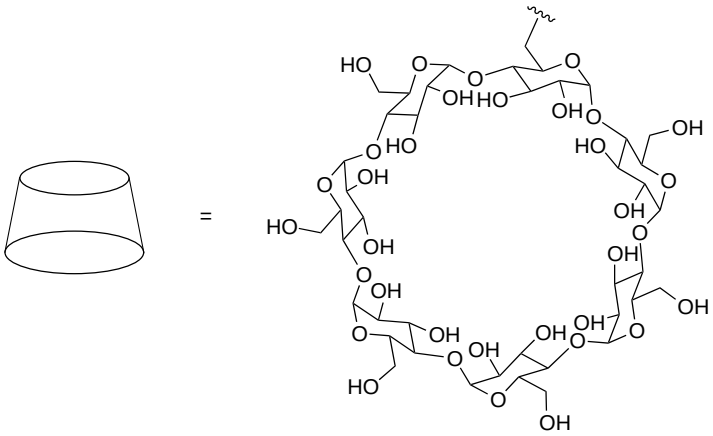
Figure 2.7: **Intramolecular hydrogen bonding of AMPO spin trap increases the electrophilicity of the nitrone carbon**

Cyclodextrins (CDs) have previously been incorporated into spin traps due to their ability to stabilise and protect the corresponding spin adducts. Han *et al.* synthesised a bifunctionalised AMPO derived nitrone spin trap, containing a hydrophilic cyclodextrin-amide

arm and a second amide group bonded to a lipophilic dodecyl chain (Figure 2.8). This probe was designed to ensure that: a) the amide functionality would create a reactive superoxide radical trap, b) the cyclodextrin would give a stable adduct for analysis by EPR, and c) that the dodecyl side chain would enable the probe to insert into the membranes of cells.[45]



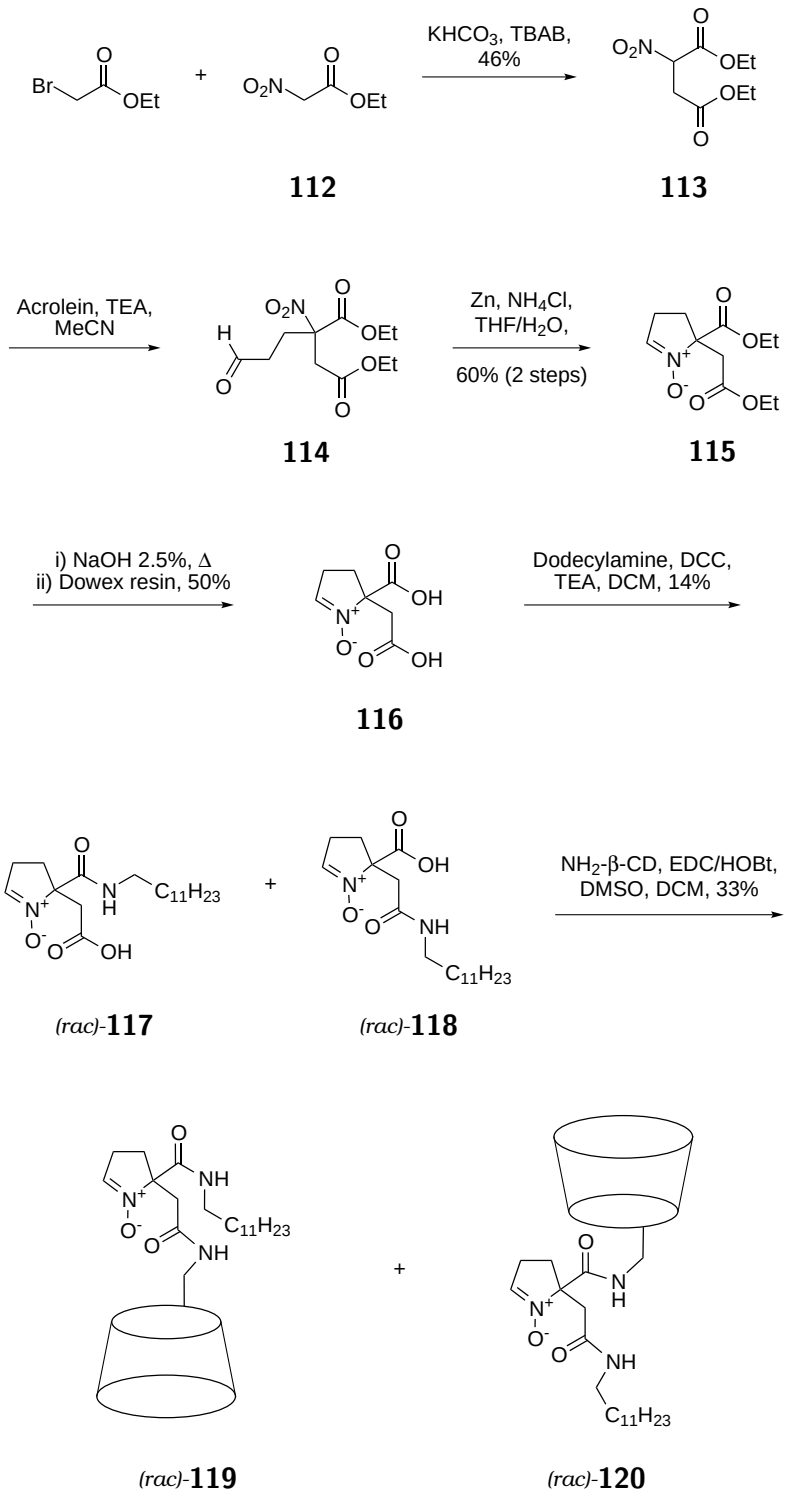
Amphiphilic nitrone spin trap



β-cyclodextrin

Figure 2.8: **Amphiphilic cyclodextrin derived pyrroline based spin trap**

In order to synthesise this nitrone spin trap, the enolate of nitroester **112** was alkylated with ethyl bromoacetate to yield the nitro-*bis*-ester **113** (Scheme 2.3). Conjugate addition of the enolate of *bis*-ester **113** onto acrolein then afforded aldehyde intermediate **114** which was used in the subsequent zinc mediated reductive cyclisation step to give the known diester nitrone spin trap, 5,5-diethoxycarbonyl-1-pyrroline *N*-oxide (DECPO) **115**. Base-catalysed hydrolysis of DECPO to the diacid **116** occurred in a moderate 50% yield. Coupling of diacid **116** with dodecylamine afforded the two structural isomers of monosubstituted nitrone, **117** and **118**, that they were unable to separate.



Scheme 2.3: **Synthesis of bifunctional nitrone spin trap**

The spin trap synthesis was completed by coupling the mixture of nitrones **117** and **118** with amino-β-cyclodextrin. The two constitutional racemic isomers of the product spin traps, **119** and **120**, were then separated by preparative HPLC. **119** was subjected to EPR studies and was found to be highly specific for superoxide radical. The resultant superoxide spin adduct also took longer to decay than the spin adducts of common pyrroline based spin traps, as well as other classes of spin trap containing cyclodextrins.

2.1.3 Isoindole spin traps

As an alternative means to overcome the issues faced with using pyrroline based traps, bicyclic nitrone compounds began to be investigated. In 2003, Bottle *et al.* reported the first bicyclic nitrone spin trap, 1,1,3-trimethylisoindole-*N*-oxide (TMINO), which was synthesised in low yield by carrying out flash vacuum pyrolysis (FVP) of 1,1,3,3-tetramethylisoindolin-2-yloxyl (TMIO, Figure 2.9).[63] This new isoindole based species proved to be less problematic than the more commonly used pyrroline-based spin traps. This was due to increased stability, and therefore half lives, of it's spin adducts and it's selectivity for the •OH radical with respect to superoxide. The group carried out research into the use of TMINO in trapping biologically important radicals, such as the hydroxyl radical, the superoxide radical anion ($\bullet O_2^-$) and nitric oxide radicals (•NO).[61]

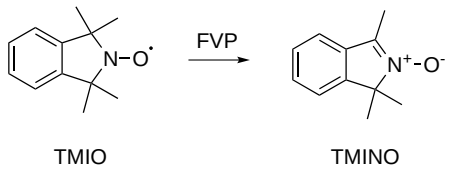
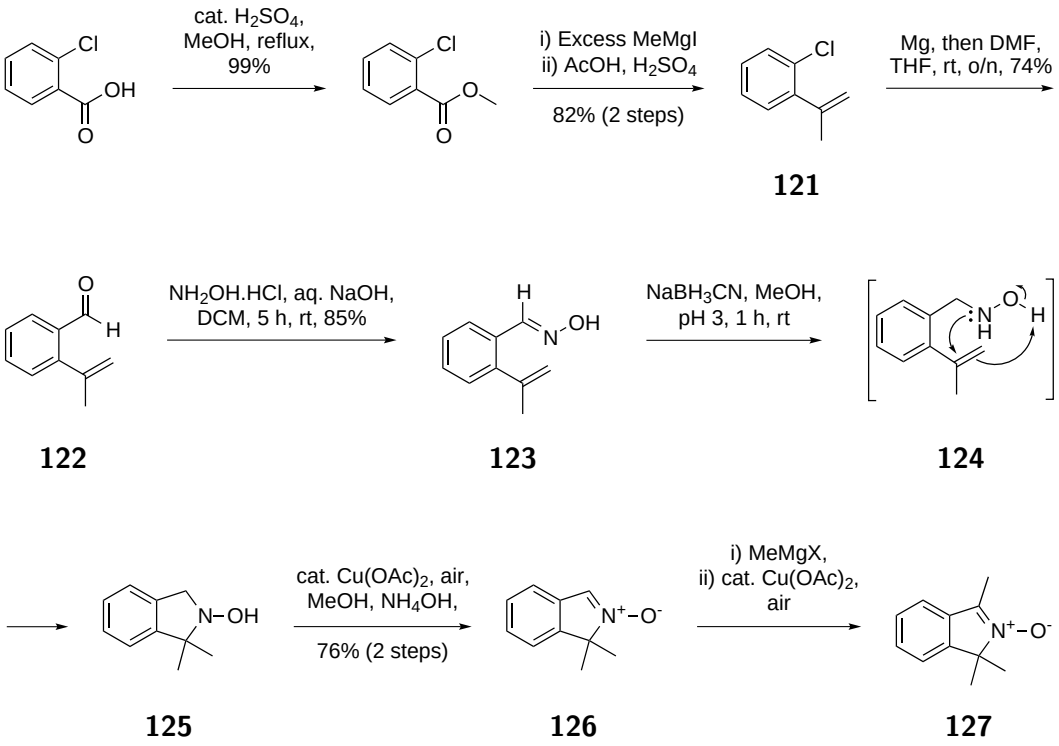


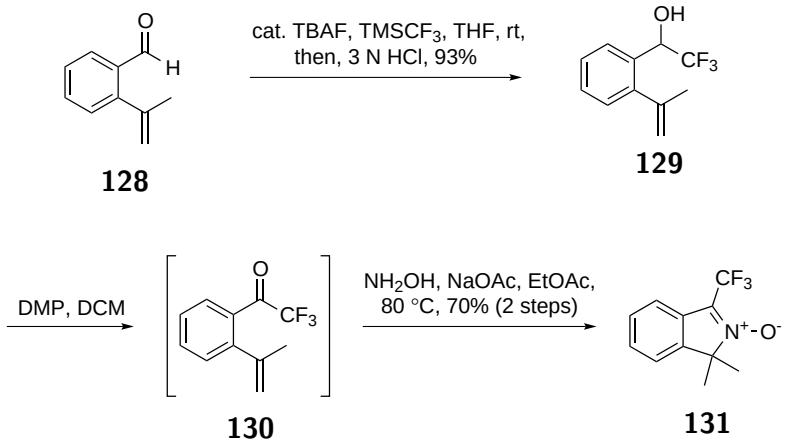
Figure 2.9: **First synthesis of 1,1,3-trimethylisoindole-*N*-oxide - TMINO**

In 2007, Hatano *et al.* published the first synthetic route to TMINO, shown in Scheme 2.4.[67] Beginning with 2-chlorobenzoic acid, they carried out an acid catalysed esterification reaction with methanol, followed by double Grignard addition and dehydration of the resultant alcohol to afford the chloro-styrene derivative **121**. Treatment with magnesium and *N,N*-dimethylformamide (DMF) resulted in formylation to give an aryl aldehyde functionality, which was then reacted with hydroxylamine to give the oxime **123**. Reduction to the hydroxylamine using sodium cyanoborohydride under acidic conditions resulted in a formal reverse Cope cyclisation reaction to afford the cyclic hydroxylamine **125**.[68] Copper catalysed oxidation in air then yielded 1,1-dimethyl nitrone **126**, which upon Grignard addition and a further oxidation step ($Cu(OAc)_2$, air) gave the desired nitrone: 1,1,3-trimethylisoindole *N*-oxide **127**.



Scheme 2.4: **First synthetic route to the spin trap TMINO 127**

Employing the same first four steps, Hatano later synthesised the 3-trifluoromethyl derivative of TMINO (3-TF-TMINO), and subjected this novel compound to a set of EPR studies to demonstrate its efficiency at forming stable radical adducts (Scheme 2.5).[69] Taking aldehyde **128**, addition of the trifluoromethyl nucleophile gave alcohol **129**, which, upon Dess-Martin periodinane (DMP) mediated oxidation, gave ketone **130** that proved to be unstable and decomposed quickly. To overcome this issue, the group synthesised the ketone using the same procedure, but reacted the crude material with hydroxylamine to yield 3-TF-TMINO **131** in 70% yield.

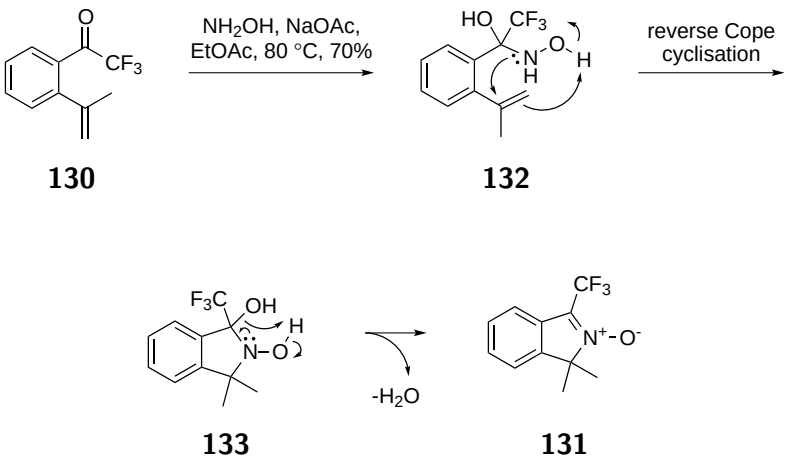


Scheme 2.5: **Synthesis of 3-TF-TMINO 131**

This last step in the synthesis was a surprising result. In their original TMINO synthesis (Scheme 2.4), treatment of the parent aldehyde with hydroxylamine yielded an oxime **123**.

Cyclisation to form the nitrone spin trap only occurred upon reduction of this oxime to the hydroxylamine. With the latter 3-CF_3 example shown in Scheme 2.5 however, oxime forming reaction conditions yielded a cyclised nitrone directly from the ketone.

Condensation of mono substituted hydroxylamines with carbonyl groups is a well known method to form nitrones.[35] However, here an intramolecular cyclisation has occurred, therefore a different pathway must be operating. The group proposed that attack of the hydroxylamine forms the *N,O*-acetal **132**, which undergoes a formal reverse Cope cyclisation reaction at 80 °C to give cyclic hydroxylamine **133** (Scheme 2.6). Proton transfer and dehydration then affords nitrone **131** in good yield.



Scheme 2.6: **Proposed mechanism for formation of 3-TF-TMINO 131 from ketone 130**

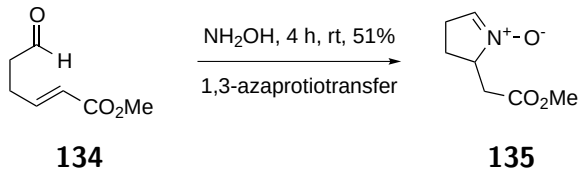
Encouraged by this spontaneous reaction of a γ,δ-unsaturated carbonyl compound with hydroxylamine to afford a cyclic nitrone (without the need to isolate an intermediate oxime or hydroxylamine), we carried out a literature review which revealed that this methodology seemed little utilised. The only evidence of a related reaction was reported by Grigg *et al.* in the early 1990s, which will be discussed in the following section.

2.1.4 1,3-Azaprotiotransfer reactions for the synthesis of nitrones

As discussed in the introduction, the Grigg group have reported a lengthy discussion of their research into the synthesis of nitrones from oximes, and the subsequent 1,3-dipolar cycloaddition of these nitrones on to alkene acceptors in an intra- and intermolecular manner. In doing so, they also proposed a new ene like mechanism, dubbed a "1,3-azaprotio cyclotransfer", for the synthesis of a variety of nitrone cycloadducts derived from oximes.[39–42,70,71]

Interestingly, in a few examples of the Class III reaction (intramolecular nitrone formation - intermolecular cycloaddition),[70] the reaction to form the oxime starting material

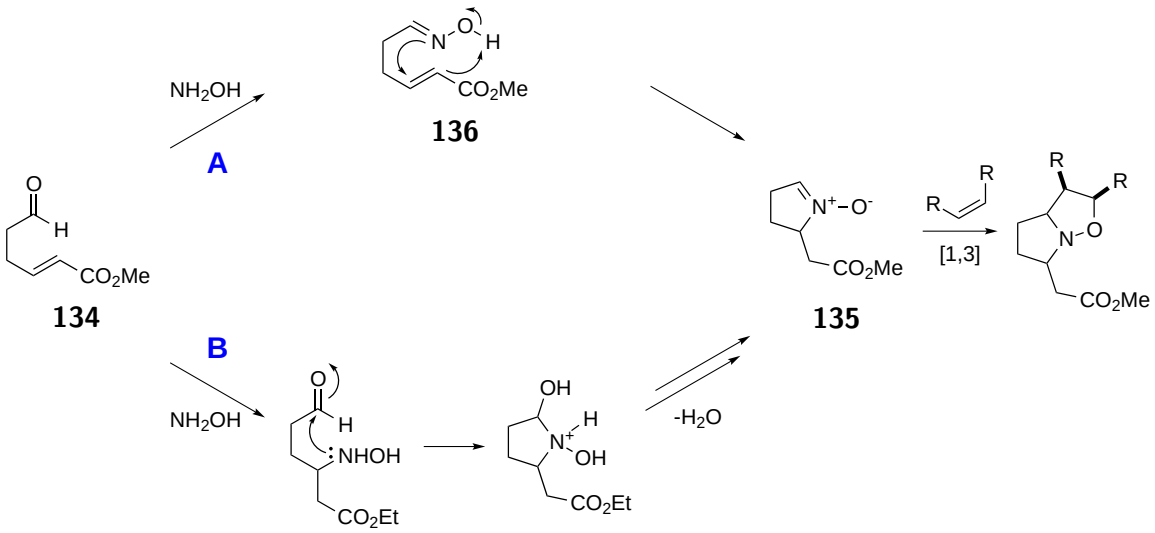
was reported to yield a nitrone product directly. An example of this type of reaction is shown in Scheme 2.7, whereby aldehyde **134** cyclises to afford the pyrroline based nitrone **135**. However, unlike the terminal alkene of Hatano's work, this set of results from Grigg possessed an activated alkene, containing an electron withdrawing ester group.



134 **135**

Scheme 2.7: **Grigg's synthesis of nitrone 135**

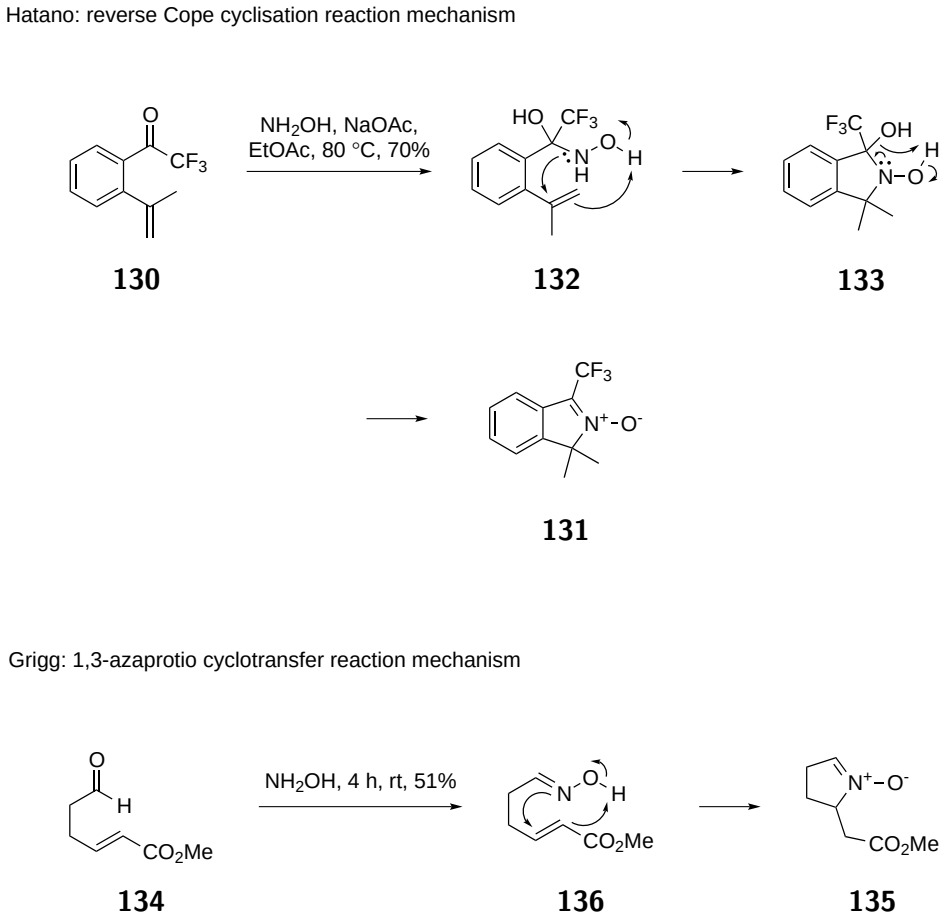
To recap, the group proposed that these reactions proceeded through unisolated oxime intermediates **136**, which underwent 1,3-azaprotiotransfer reactions to give the product nitrones (Scheme 2.8, pathway A). They also presented the possibility in these tranformations that a conjugate addition/condensation strategy might also have occurred (pathway B). The group subsequently explored the synthetic chemistry of the resultant nitrones by using them as substrates for intermolecular 1,3 dipolar cycloaddition reaction.



Scheme 2.8: **Grigg's proposed mechanisms for formation of nitrone 135**

2.1.5 Methodology for the synthesis of isoindole derived nitrones

We were interested in the fact that two groups had separately synthesised cyclic nitrones by subjecting γ,δ-unsaturated aldehydes or ketones to "classic" oxime forming conditions. Hatano *et al.* had proposed that their bicyclic nitrone **131** was formed by a reverse Cope cyclisation reaction of an intermediate hydroxylamine **132**. Grigg *et al.* reported a 1,3-azaprotiotransfer mechanism of an intermediate oxime **136**, to form pyrroline based nitrone **135** (Scheme 2.9).



Scheme 2.9: **Summary of reaction mechanisms to afford cyclic nitrones**

We envisaged combining both of these methodologies into a single protocol to devise a short synthetic route to novel, functionalised, stable isoindole derived nitrones, which could potentially find use in synthesis and as spin traps in EPR studies (Figure 2.10). Whilst isoindole scaffolds are useful for their readiness to undergo [4+2] cycloaddition reactions, their fluorescent and electroluminescent properties [72] and their incorporation into biologically active compounds, [73] the synthetic chemistry of the corresponding nitrones had been much less explored.

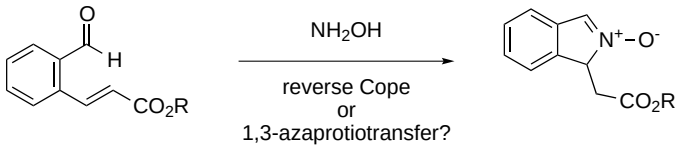


Figure 2.10: **Proposed methodology for the synthesis of novel isoindole nitrones**

The following sections and chapters describe my investigations and discoveries in this area.

2.2 Synthesis of a suitable cyclisation substrate

To begin investigating the proposed chemistry, we needed to prepare an appropriate starting material. Inspired by the previous examples described by Grigg *et al.* shown in Scheme 2.7, it was proposed that my research would commence with investigation of the cyclisation reaction of hydroxylamine with an aromatic aldehyde containing an α,β-unsaturated ester fragment in its *ortho* position (Figure 2.11).

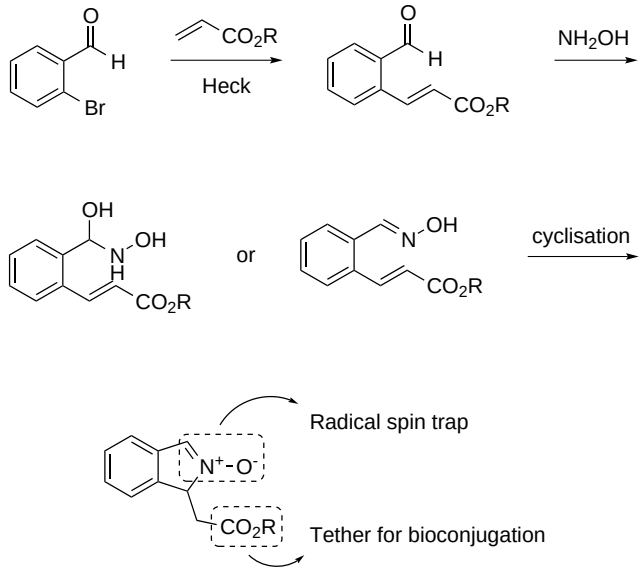


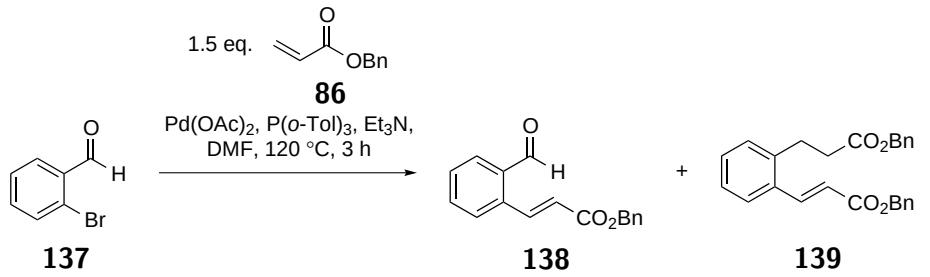
Figure 2.11: **Proposed new syntheses of nitrone products**

Due to the presence of the activated alkene, we tentatively proposed that upon reaction with hydroxylamine, an oxime would be generated from the aldehyde fragment. This fragment would then undergo a formal intramolecular 5-*exo*-trig cyclisation reaction onto the activated alkene group of the α,β-unsaturated ester fragment to provide an isoindole derived nitrone. The presence of the aromatic ring, as well as providing the desired isoindole scaffold, would also faciliate the reaction by restricting the conformational freedom of the cyclisation transition state. This starting material could be readily synthesised by a coupling reaction between commercially available 2-bromobenzaldehyde and an acrylate.

2.2.1 Acetal protection

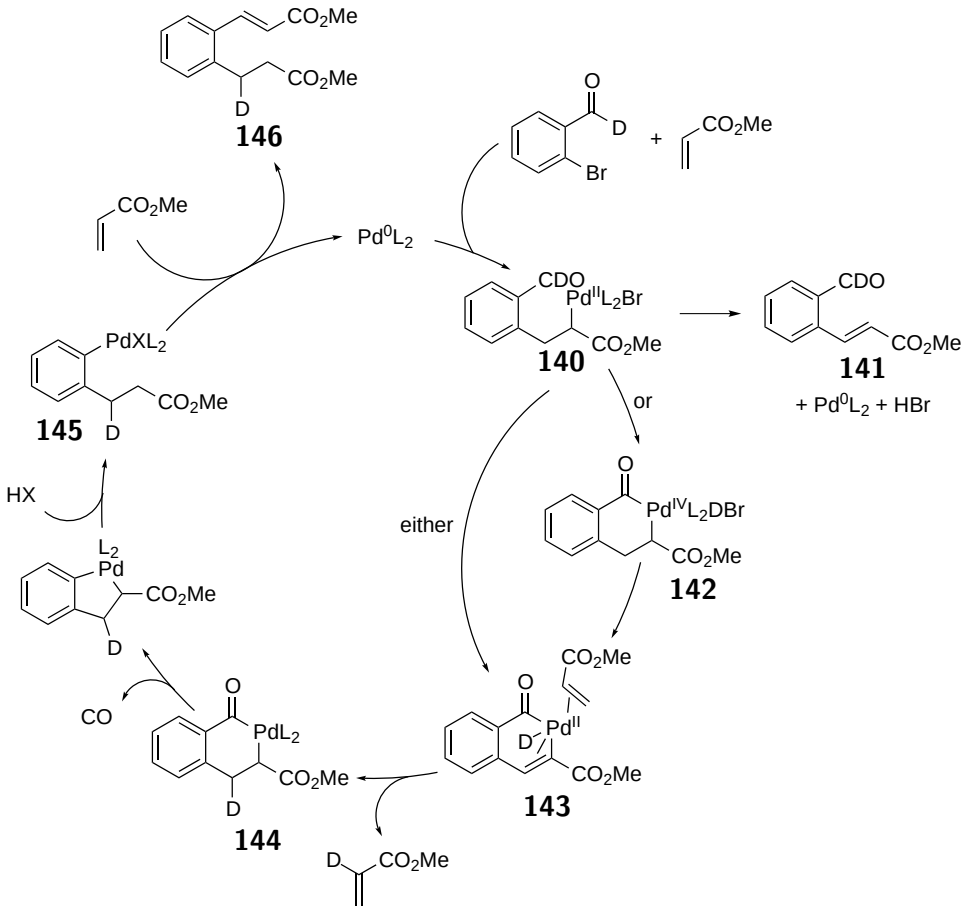
Key to the synthesis of the envisaged nitrones was the *ortho* arrangement of the alkene bond relative to the aldehyde functionality on the aromatic ring, which we intended to set up using a Heck reaction. The Heck reaction is a key carbon-carbon bond formation reaction in organic synthesis.[74] The reaction involves the coupling of an aryl halide to an olefin using a palladium catalyst and a phosphine ligand. Unlike in many other cross-coupling reactions, a base is necessary for the Heck reaction to proceed.

It was quickly discovered that the Heck reaction using 2-bromobenzaldehyde **137** and benzyl acrylate led to the desired ester product **138**, and significant amounts of a by-product (Scheme 2.10). The ^{1}H NMR spectrum of the crude material indicated that the by-product was the doubly substituted deformylated product **139**.



Scheme 2.10: **Heck reaction of unprotected 2-bromobenzaldehyde 137**

Meegalla *et al.* have reported formation of the same type of by-product in their phase-transfer catalysed Heck process.[75] They carried out extensive labelling studies and showed that the hydrogen atom of the formyl group is transferred intramolecularly and regiospecifically to the benzylic carbon of the unsaturated ester (Scheme 2.11).



Scheme 2.11: **Meegalla mechanism for formation of biester 146**

The Heck reaction between the aldehyde and the acrylate proceeds *via* the known catalytic cycle to produce palladated intermediate **140**, which can undergo reductive elimination to give the desired α,β-unsaturated ester **141**. Once formed, this product is unable to re-enter the catalytic cycle. This is thought to be due to the excess base present in the reaction.

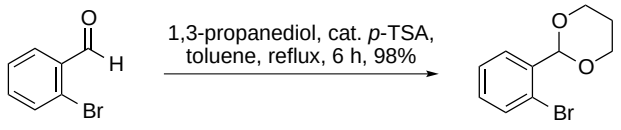
Formation of the bis-ester **146** from palladated intermediate **140** can proceed *via* two possible pathways:

1. Oxidative addition of Pd^{II} to the C-D bond of **140** gives the Pd^{IV} complex **142**, followed by β-hydride elimination to afford compound **143**.

2. The $Pd^{0}L_2$ species generated in the formation of **141** can oxidatively insert into the C-D bond of the formyl group, to form **143**.

Deuteration of the double bond of **143** to give compound **144** is formally a hydropalladation reaction, and compound **144** then decarbonylates to provide the deuterated intermediate **145**. This is because there is no aromatic deuteration the deuterium transfer step must take place before the decarbonylation step. Compound **145** then undergoes a second Heck reaction to couple with the acrylate and produces the doubly substituted by-product **146**.

As the by-product **139** was forming in a significant 31% yield, it was decided to protect the aldehyde functional group before carrying out the Heck reaction. We opted to convert the aldehyde **137** into the six-membered acetal **147**, which would be stable under the basic conditions of the Heck reaction. 2-bromobenzaldehyde **137** was reacted with an excess of 1,3-propanediol and a catalytic amount of *para*-toluenesulfonic acid (*p*-TSA) in toluene, under Dean-Stark conditions. After several hours, the reaction was quenched with sodium hydrogen carbonate and water. Recrystallisation of the crude product from petrol and ether yielded the protected acetal, 2-(2-bromophenyl)-1,3-dioxane **147** in 98% yield as white needles (Scheme 2.12).



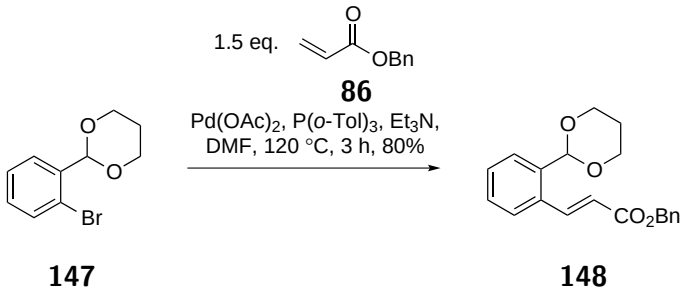
137 **147**

Scheme 2.12: **Acetal protection reaction**

2.2.2 Heck reaction

To carry out the desired cross coupling between 2-(2-bromophenyl)-1,3-dioxane **147** with benzyl acrylate **86**, a procedure by Zhang *et al.* was used (Scheme 2.13).[76] This method

is carried out under air rather than inertly, and uses DMF as the solvent allowing the reaction to be heated to 120 °C. Using this procedure, the reaction reached 100% conversion in three hours, as shown by thin layer chromatography (TLC).

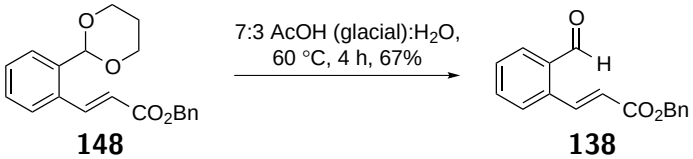


Scheme 2.13: **Heck cross coupling reaction**

The work up procedure involved adding diethyl ether to the cooled reaction mixture to precipitate out the palladium and ligand, which was then filtered off. The combined organic solution was washed three times with water and then concentrated to low volume under reduced pressure. After column chromatography, the purified Heck product **148** was obtained as a yellow oil in 55% yield. The yield could be increased by using a 1:1 mixture of diethyl ether:hexane for extraction, or by filtering the reaction and then removing the solvent under a stream of nitrogen overnight. After optimisation of these purification steps, the product could be obtained in yields of up to 80%.

2.2.3 Acetal deprotection

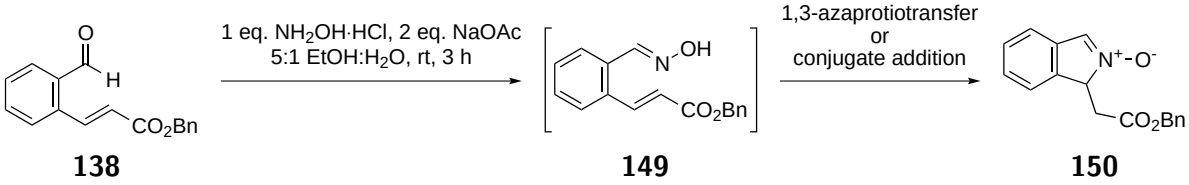
The acetal protecting group of α,β-unsaturated ester **148** was then removed *via* treatment with 7:3 glacial acetic acid:water to afford aldehyde **138**, with the reaction being monitored by TLC to determine when all of the starting material had been consumed (Scheme 2.14). To decrease the reaction time, experiments at different temperatures were carried out to drive the hydrolysis equilibrium towards the product **138**. Acetal **148** was fully deprotected to aldehyde **138**, without hydrolysis of the ester in 67% yield, after four hours at 60 °C.



Scheme 2.14: **Acetal deprotection of ester 148**

2.3 Synthesis of an isoindole nitrone

Our overall goal was to develop a one-pot procedure whereby our aldehyde starting material **138** would react with hydroxylamine to form a bicyclic nitrone. This involved oxime formation followed by intramolecular cyclisation (Scheme 2.15).



138 **149** **150**

Scheme 2.15: **Planned nitrone formation**

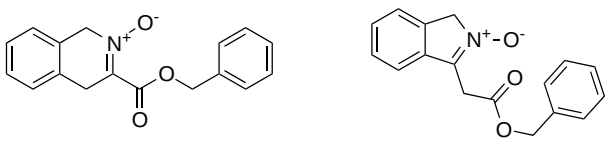
Having successfully synthesised the formyl acrylate **138**, we turned our attention to the nitrone synthesis. Using standard oxime forming conditions, hydroxylamine hydrochloride and sodium acetate were reacted with **138** in a 5:1 mixture of ethanol and water for three hours at room temperature.[77] Two equivalents of base were required, one equivalent releasing the hydroxylamine from its hydrochloride salt, and the second equivalent required to facilitate the oxime formation/cyclisation reaction.

The reaction was worked up by removing the ethanol solvent under reduced pressure. The crude reaction product was dissolved in dichloromethane (DCM), extracted with water, and the DCM removed under reduced pressure to yield a red oil. On obtaining the ^{1}H NMR spectrum of the crude product, it was obvious that the reaction had not formed the expected nitrone **150**. The ^{1}H NMR spectrum also showed no sign of oxime intermediate **149** or the acrylate starting material **138**; instead, the reaction had cleanly formed a different and unexpected product. The following section details elucidation of the structure of this new product.

2.4 Structural determination of unidentified product

2.4.1 Analysis

After completing full spectroscopic analysis of the unidentified product of the nitrone reaction, it was determined that the red oil was indeed a nitrone, whose structure could potentially correspond to either nitrone **151** or nitrone **152** (Figure 2.12).



151 **152**

Figure 2.12: **Possible structures of unidentified product**

High resolution mass spectroscopy confirmed that the product had the same molecular formula as the expected oxime; $C_{17}H_{15}NO_3$, therefore suggesting that the reaction had formed an oxime which had reacted further to give a nitrone containing eleven double bond equivalents.

The ^{1}H NMR spectrum (displayed in the HMQC spectrum shown in Figure 2.13) showed three singlets, each integrating to two protons, and a multiplet at δ 7.30-7.17 ppm integrating to nine aromatic protons. The multiplet confirmed that both aryl rings were still present, with no further substitution having occurred. An infra red spectrum of the compound showed a peak at 1725 cm^{-1}, and the ^{13}C NMR spectrum showed a peak at δ 167.49 ppm, confirming the presence of the carbonyl (**D**) of the ester functional group.

The first singlet in the ^{1}H NMR spectrum at δ 5.12 ppm corresponded to a CH_2 group of a benzyl ester (**E**), and was confirmed by the HMQC spectrum *via* a cross peak with a carbon peak at δ 67.34 ppm.

The second singlet peak at δ 4.94 ppm resonated at a frequency downfield compared to where a benzylic CH_2 group would resonate. Due to its chemical shift and the structure of the expected oxime, this CH_2 group was assigned as being bonded to a heteroatom; in this case the nitrogen atom of the nitrone functionality. The singlet at δ 4.94 ppm was therefore potentially assigned to protons at the (**A**) position of nitrones **151** and **152**, respectively.

The protons from the third singlet peak in the ^{1}H NMR spectrum appeared at δ 3.89 ppm. Using the structure of the expected oxime intermediate, this CH_2 group (**B**) was assigned as either the benzylic position of nitrone **151**, or α- to the ester group of nitrone **152**. NOE spectroscopic analysis showed that both the singlets at δ 4.94 and 3.89 ppm had through-space interactions with protons of their corresponding aromatic rings.

Long range HMBC spectroscopic analysis showed that the methylene group (**A**) at δ 4.94 ppm interacts with the carbonyl carbon (**D**). This would represent a four-bond interaction in the six-membered structure **151**, but a five-bond interaction for the five-membered structure **152**. Unfortunately, this piece of data was not substantial enough to distinguish which nitrone structure was obtained; further evidence was required to assign its structure.

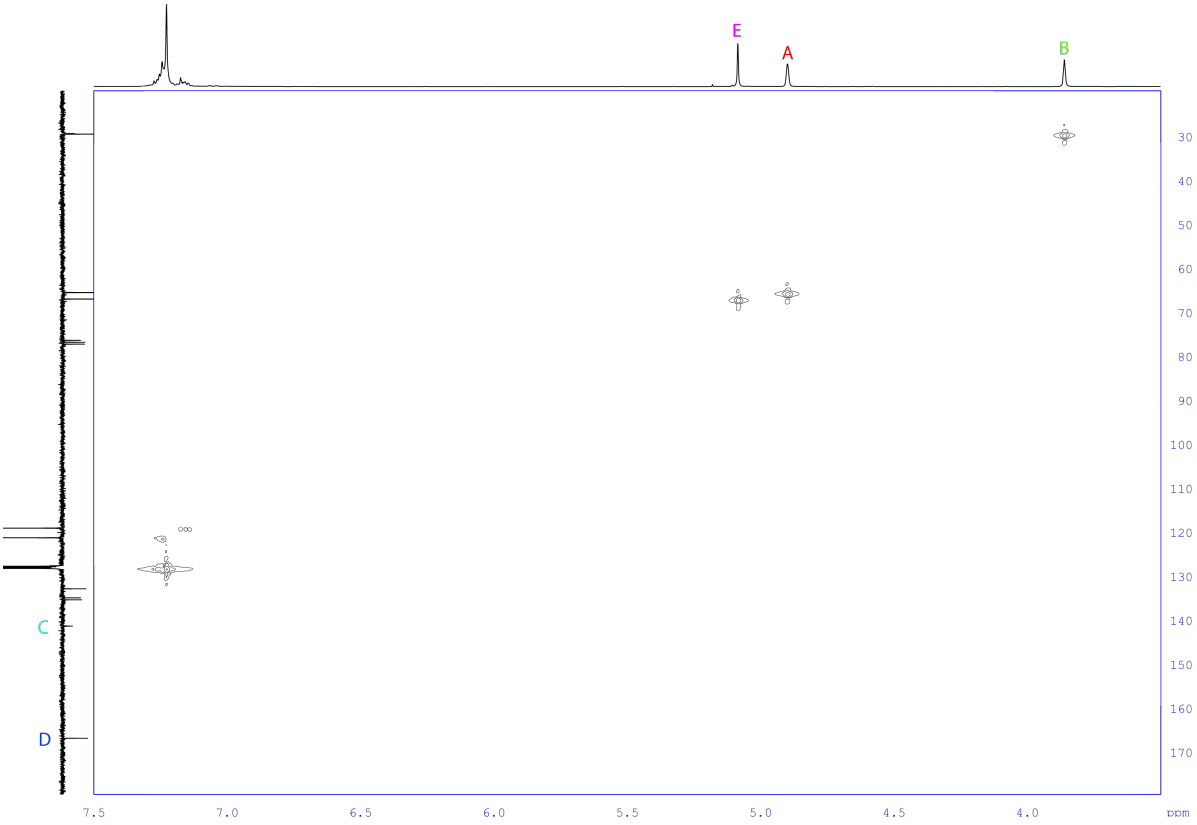
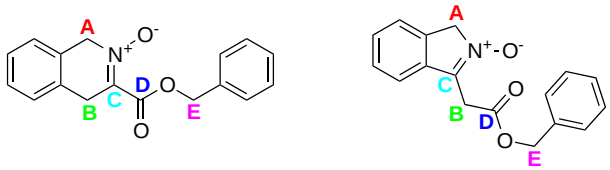


Figure 2.13: **HMQC analysis of unknown nitrone product**

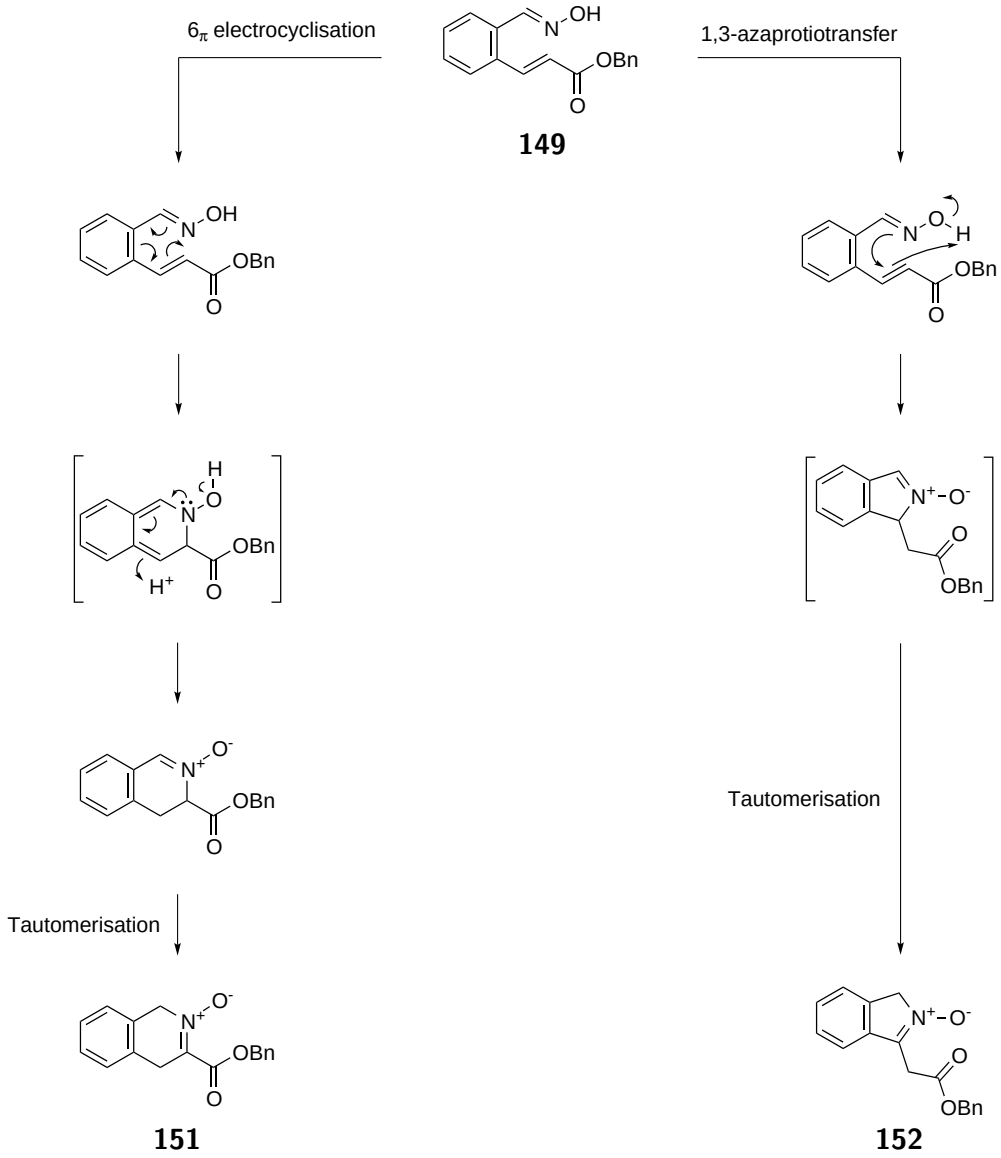


151 **152**

Figure 2.14: **Possible structures of unidentified nitrone product - labelled**

2.4.2 Literature precedence for formation of cyclic nitrones

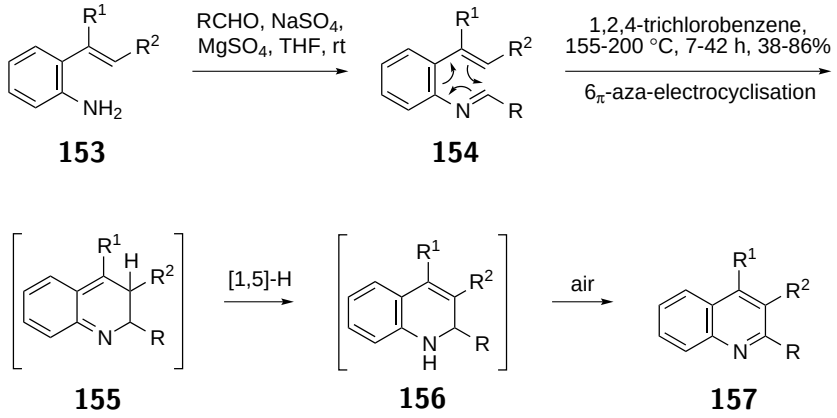
Due to the inconclusiveness over the exact structure of the nitrone product from spectroscopic analysis, we conducted a review of the literature to help determine which of the two structures (nitrone **151** and nitrone **152**) formation was most plausible. Given the similarity between our starting material and that of Grigg *et al.*, we proposed that an oxime intermediate could have undergone a formal 1,3-azaprotiotransfer reaction (or conjugate addition reaction) to afford the five membered structure **152**. However, assuming an oxime intermediate, it was proposed that an alternative electrocylisation reaction of this oxime might also have occurred to form the six-membered nitrone **151** (Scheme 2.16).



Scheme 2.16: **Possible pathways for nitrone formation**

Possible precedent for formation of nitrone 151

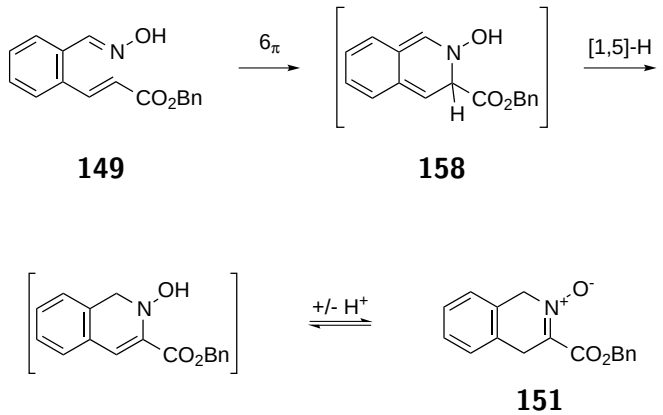
The occurence of 6_π-aza-hexatriene electrocyclisation reactions are well known in synthesis. For example, Qiang *et al.* employed electrocyclic methodology of *o*-vinyl imines for the synthesis of substituted quinolines **157** (Scheme 2.17).[78] The starting anilines **153** were reacted with substituted benzaldehydes to provide the corresponding imines **154** in high yields. These imines underwent 6_π-electrocyclisation reactions to afford quinolines **157** in yields varying from 38% to 86%.



Scheme 2.17: **Qiang 6_π-aza electrocyclisation synthesis of quinolines 157**

The group proposed that, subsequent to the 6_π-electrocyclisation reaction, the intermediates **155** undergo a [1,5]-hydride shift to afford dihydroquinolines **156** that were then oxidised in air to afford the final quinoline products **157**. This mechanism was substantiated by the isolation of a number of the dihydroisoquinolines when the electrocyclisation reactions were carried out in degassed solvent under an inert atmosphere.

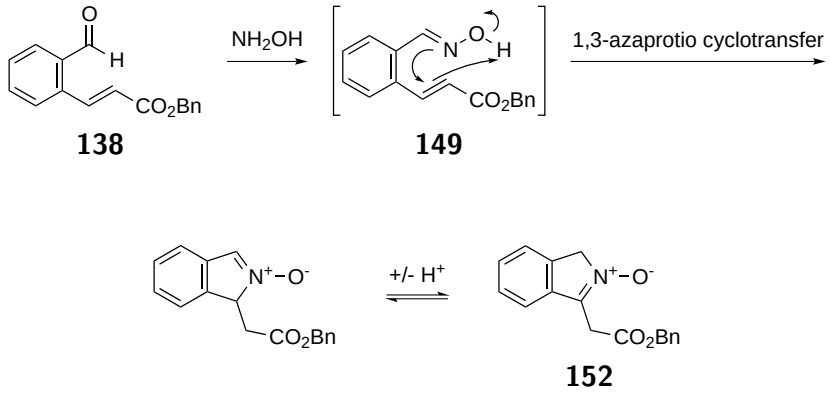
In this respect it was possible that oxime **166** had undergone a 6_π-aza-hexatriene electrocyclisation reaction to afford intermediate **158**, which then rearranged to its corresponding nitrone *via* a [1,5]-hydride shift, followed by a tautomerisation event (Scheme 2.18).



Scheme 2.18: **Suggested mechanism for formation of six-membered nitrone 151**

Precedent for formation of nitrone 152

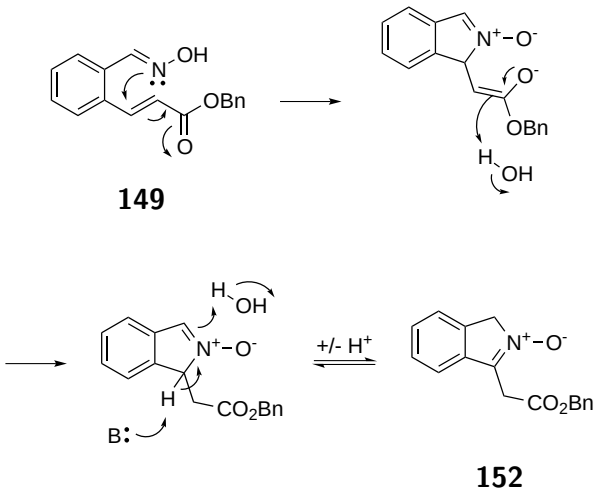
However, there was also significant literature evidence to suggest that the five membered nitrone **152** could have been formed. As discussed in Chapter 1, reaction of the aldehyde with hydroxylamine would afford an oxime intermediate which, following on from Grigg's precedent, would undergo a 1,3-azaprotiotransfer reaction followed by a tautomerisation event to yield nitrone **152**.



Scheme 2.19: **Proposed 1,3-azaprotio cyclisation mechanism for formation of five-membered nitrone 152**

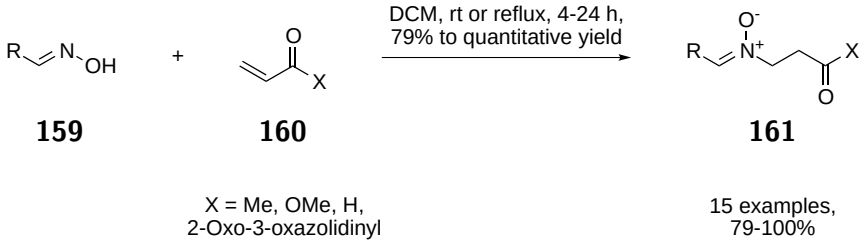
—

However, nitrone **152** could also be synthesised by the direct intramolecular conjugate addition of the nitrogen atom of oxime **149** to its activated alkene functionality (Scheme 2.20). This would represent a formal 5-*exo*-trig ring closure reaction, which would be allowed according to Baldwin's rules. Rearrangement by tautomerisation would then afford the more substituted nitrone **152**.



Scheme 2.20: **Potential conjugate-addition mechanism for formation of nitrone 152**

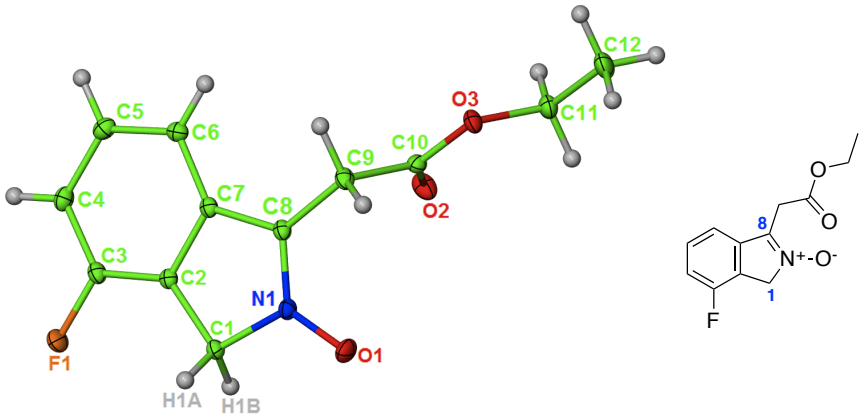
Precedent for this type of conjugate addition reaction has been reported by Nakama *et al.* who showed that Lewis-acid catalysed conjugate addition of aldoximes **159** to α,β-unsaturated carbonyl acceptors **160** could be used to afford *N*-alkylated nitrones **161** (Scheme 2.21).[79] In this case, the carbonyl group of the α,β-unsaturated carbonyl compound **160** coordinates to a Lewis acid (50:50 mix of zinc(II) iodide and boron trifluoride etherate), resulting in conjugate addition of the aldoxime **159** to yield the nitrone product **161**. An array of *N*-alkylated nitrones were formed in high yield, with aliphatic oximes (*E*)-crotonaldoxime and 2-furan carboxaldehyde oxime showing good reactivity.



Scheme 2.21: **Intermolecular conjugate addition reaction of oximes to form nitrones 161**

2.4.3 X-Ray crystal structure of unknown nitrone

As will be described in the following chapter, this cyclisation/nitrone formation methodology was applied to a range of substituted 2-bromobenzaldehydes. The ^{1}H NMR spectra for all of these nitrone analogues showed the same pattern of three singlet peaks integrating to two protons each, as the parent nitrone **152** (peaks A, B and E; see Figure 2.13). During the course of my research, the nitrone derived from 2-bromo-6-fluoro-benzaldehyde was isolated as a solid. After recrystallisation from dichloromethane (DCM) and hexane to provide colourless needles, a crystal structure of this nitrone was obtained (Figure 2.15a). The crystallographic data confirmed that a new five-membered ring had been formed in the reaction. It also confirmed the presence of the nitrone functionality with the C_1-N bond length, at 1.4894 Å, being greater than the C_8-N bond length of 1.3142 Å. Full crystallographic data for this compound is available in the appendix.

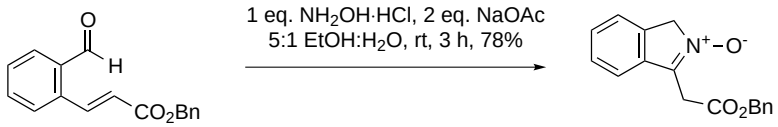


(a) **X-Ray crystal structure of the 6-fluoro-analogue**

Figure 2.15: **Confirmation of the isoindole nitrone structure by X-ray crystallography**

Redissolving the solid six-fluoro nitrone in $CDCl_3$ resulted in a ^{1}H NMR spectrum that matched that of the parent nitrone **152**, suggesting that the same structure exists in the liquid form as it does in the solid state. Thus, we conclude that reaction of aldehyde with hydroxylamine afforded nitrone **152** (Scheme 2.22), and all of the chemistry discussed from this point onwards, is based on the assumption that an isoindole skeleton is formed

in all of these cyclisation reactions.



138 **152**

Scheme 2.22: **Product of nitrone formation reaction**

2.5 Mechanistic investigations

As we had synthesised a novel isoindole based nitrone **152**, we wanted to investigate the mechanism of its formation. Up until now, it appeared reasonable to make two assumptions. Firstly, that an oxime could form *in-situ* which underwent cyclisation, and secondly, that it could do so either *via* a 1,3-azaprotiotransfer or *via* a conjugate addition mechanism. However, in order to establish a mechanism, we thought it informative to ignore these assumptions, and start with a "blank canvas" for our investigations. We felt that there were three key questions that needed to be explored:

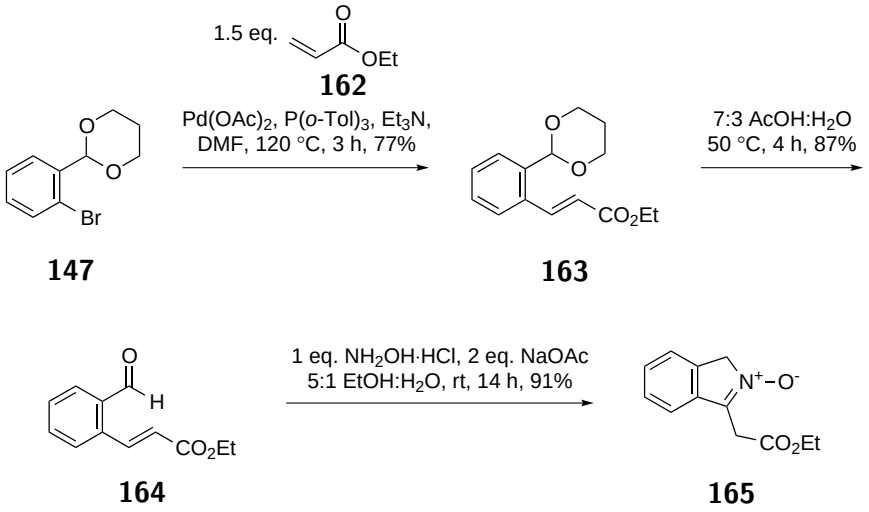
1. What is the structure of the compound/reaction intermediate that undergoes cyclisation?

2. What is the mechanism of cyclisation?

3. How is the substituted nitrone functionality formed post cyclisation?

2.5.1 Identity of cyclisation precursor

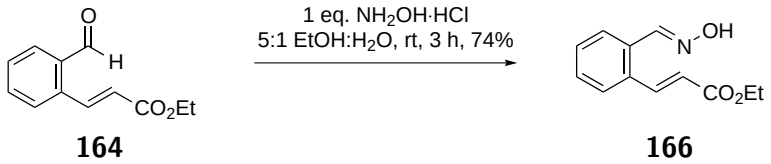
It seemed reasonable to assume that an oxime had been formed as a reaction intermediate, so this was the first postulate to be investigated. At this point, the key aldehyde substrate was re-synthesised using ethyl acrylate **162** instead of benzyl acrylate **86** (Scheme 2.23). Therefore, aldehyde **164** was prepared in 87% yield using our previously optimised 3 step procedure, employing ethyl acrylate **162** as a coupling partner. The aldehyde **164** was reacted with hydroxylamine hydrochloride and sodium acetate for twelve hours, to afford the corresponding nitrone **165** in 75% yield.



Scheme 2.23: **Identity of nitrone 165**

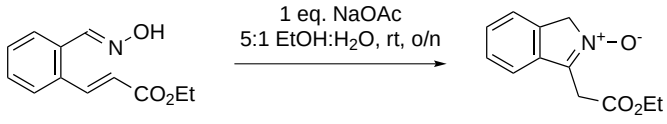
Importantly, it was found that working the reaction up at three hours, as we had with the previous example, gave a ^{1}H NMR spectrum that revealed peaks corresponding to the presence of an oxime intermediate, as well as the expected nitrone product **165**.

Noting that this oxime was likely to be a potential reaction intermediate, we wanted to determine exactly what role the second equivalent of base was playing in the cyclisation reaction. To investigate this, we initially carried out the reaction in the absence of base to see whether any cyclisation would occur (Scheme 2.24). The only product of the reaction was oxime **166**, which was isolated as a pale brown solid in 74% yield. Diagnostic peaks in the ^{1}H NMR spectrum included a singlet peak at δ 8.53 ppm corresponding to the proton α to the C=N functionality, and two doublets at δ 8.13 and 6.34 (J = 15.9 Hz) corresponding to the *trans* alkene protons of the α,β-unsaturated ester.



Scheme 2.24: **Synthesis of oxime 166**

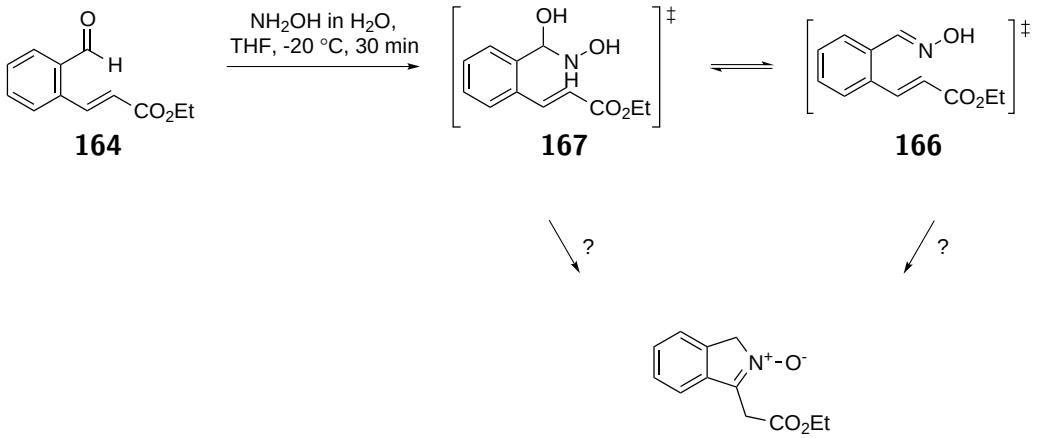
To ascertain whether cyclisation of this oxime could be induced, it was dissolved in ethanol and water and one equivalent of base was added, with the reaction then being stirred overnight. After working up the reaction in DCM and water, nitrone **165** was isolated as a single reaction product, as shown in Scheme 2.25. These experiments provided evidence that oxime **166** was likely to be an intermediate in the cyclisation reaction, that its formation was relatively fast, and that the base was functioning to facilitate nitrone formation in a rate determining step.



166 **165**

Scheme 2.25: **Cyclisation of oxime 166**

At this point, we considered the mechanism of oxime formation, which highlighted hydroxyamino alcohol **167** as a potential intermediate responsible for ring-closure (Scheme 2.26). This intermediate **167** is similar to the structure **129** that Hatano had proposed previously for the synthesis of 3-TF-TMINO (see Scheme 2.5). Due to the presence of water in the reaction, an equilibrium will be present between the hydroxyamino alcohol **167** and the oxime **166**, and as a consequence, either intermediate could potentially be considered as the cyclisation precursor.



164 **167** **166**

Scheme 2.26: **Mechanism of cyclisation to afford nitrone 165**

The sp^3 atom of hydroxyamino alcohol **167** is likely to be more nucleophilic than the corresponding sp^2 nitrogen of oxime **166**, and thus, in accordance with the work of Hatano *et al.*, we propose that the hydroxyamino alcohol species is most likely to initiate the cyclisation reaction. Further work discussed below in section 2.5.3 provides evidence to support this theory.

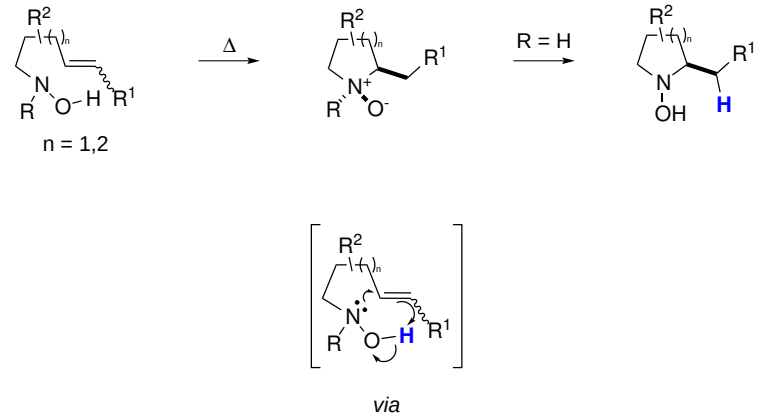
2.5.2 Literature precedent and evidence for cyclisation mechanism

The second question to be investigated was the mechanism of cyclisation. From the structure of the aldehyde starting material and the reagents, we assumed that cyclisation must be initiated by nucleophilic attack of the nitrogen atom on the double bond of the α,β-unsaturated ester group. There were two potential pathways by which this could occur:

1. Reverse Cope cyclisation

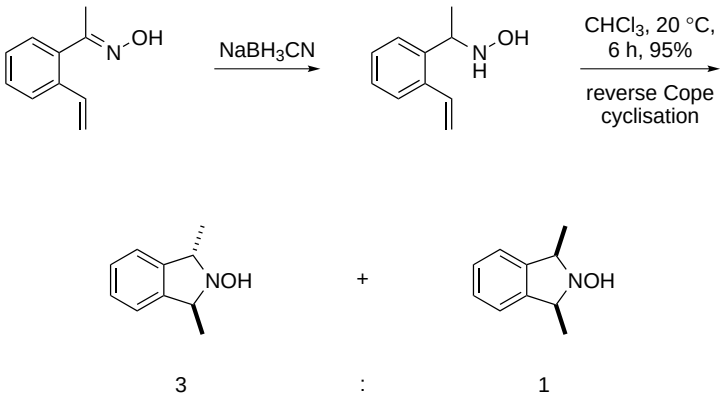
2. Conjugate addition

First reported simultaneously by House and Oppolzer,[80–82] the reverse Cope cyclisation reaction is a type of 1,3-azaprotio cyclotransfer reaction. It is a concerted reaction in which an unsaturated hydroxylamine undergoes an intramolecular thermal 5-*exo*-trig cyclisation to give pyrrolidine-*N*-oxides, or the corresponding *N*-hydroxy derivatives (Scheme 2.27). Formally a $2\sigma + 2\pi + 2n$ ene like cyclisation, the reaction proceeds *via* a planar five-membered transition state.[83–85] The labile hydroxyl proton (in blue) ends up in the β position relative to the nitrogen atom.

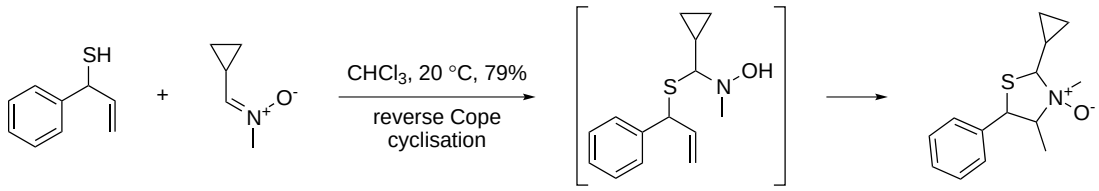


Scheme 2.27: **Reverse Cope cyclisation mechanism**

More recently, Knight *et al.* have carried out considerable research into the scope and limitation of the reverse Cope cyclisation reaction,[86,87] extending the methodology to the synthesis of *N*-hydroxyisoindolines[68] (Scheme 2.28) and 1,3-thiazolidine-*N*-oxides[88] (Scheme 2.29) for example. Nitrones are often used as precursors to the reverse Cope hydroxylamine starting materials, with nucleophilic addition to a nitrone, or reduction, affording its corresponding hydroxylamine.



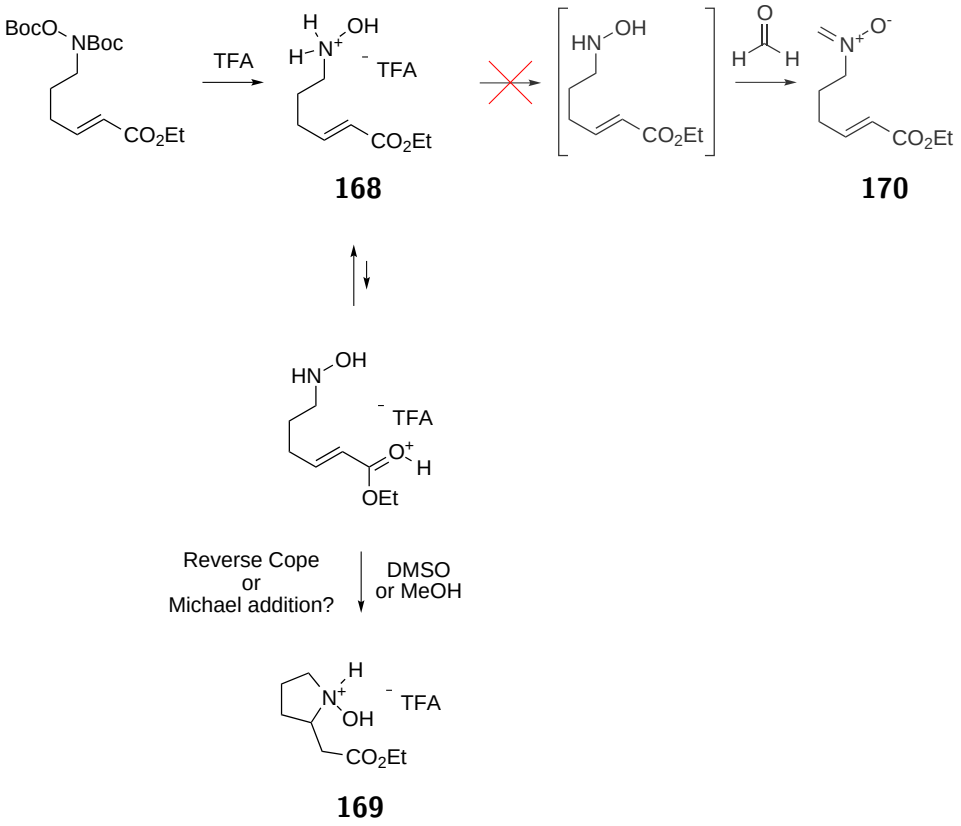
Scheme 2.28: **Reverse Cope cyclisations for the synthesis of *N*-hydroxyisoindolines**



Scheme 2.29: **Reverse Cope cyclisations for the synthesis of 1,3-thiazolidine-*N*-oxides**

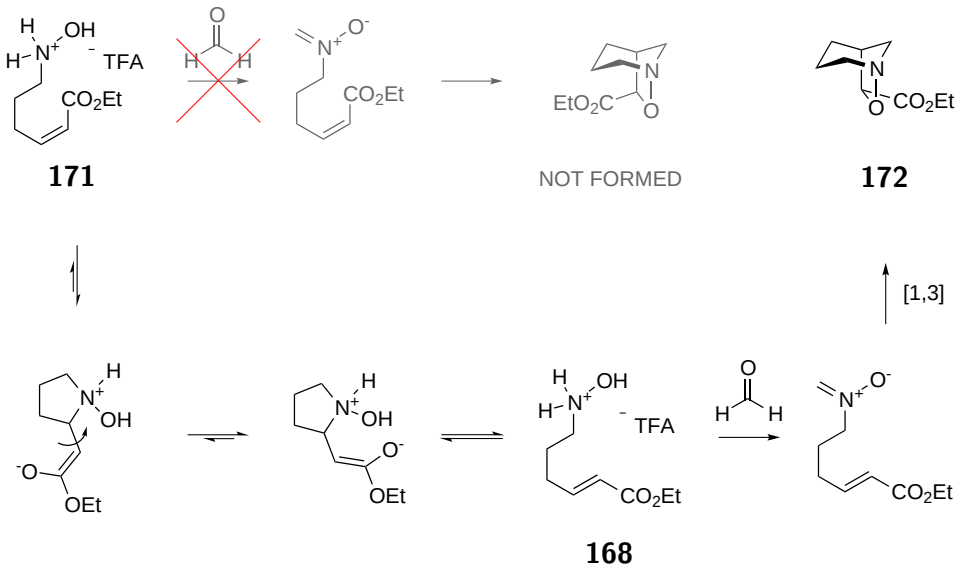
Generally, the reverse Cope cyclisation reaction rate is significantly enhanced by the Thorpe-Ingold effect, when the R group is a methyl group, and by internal alkene substituents (see Scheme 2.27). However, distal alkene substituents retard the reaction rate, and it is unusual to encounter facile cyclisation at ambient temperatures.[86] Importantly, there are few examples of reverse Cope cyclisation reactions where the alkene substituent contains an electron withdrawing group such as an ester.

It is also possible that the five membered ring of these nitrones have been formed through conjugate addition of a nitrogen species to the alkene bond of the α,β-unsaturated ester. This conjugate addition/reverse Cope cyclisation mechanistic query was encountered by the Liu group, in their report on the synthesis of 2,3-disubstituted piperidines from γ-butyrolactone.[89] When attempting to synthesise *N*-4-alkenyl nitrones **170** through condensation with formaldehyde, the group found that the *N*-4-alkenyl hydroxylamine precursor **168** spontaneously cyclised to afford pyrrolidinol **169** (Scheme 2.30). This cyclisation event was speeded up by the presence of base.



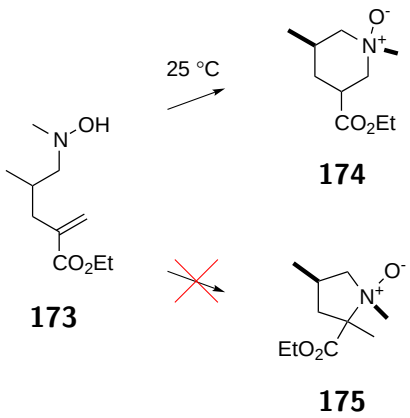
Scheme 2.30: **Liu synthesis of pyrrolidinol ester by-products 169**

This group identified reverse Cope cyclisation and conjugate addition reactions as possible mechanisms for formation of the pyrrolidinols **169**. Having observed the facile nature of the cyclisation, the group then made several other observations that led them to propose the latter mechanism. One of which was the presence of an ester in the distal position, which should retard a reverse Cope cyclisation. The second observation was the fact that *Z*-alkene **171** gave the same product piperidine isoxazoline, **172**, (after an intramolecular 1,3-dipolar cycloaddition reaction) as its corresponding *E*-alkene **168** (Scheme 2.31). This was explained by proposing a reversible cyclisation/elimination reaction to equilibrate the *Z*-alkene geometry into its thermodynamically more stable *E*-isomer.



Scheme 2.31: **Reaction of *Z*-alkene 171 with formaldehyde affords the same piperidine isoxazoline 172 as the *E*-alkene 168**

The Liu group also reported an example from Ciganek *et al.*, whereby *N*-4-alkenyl hydroxylamine **173** did not undergo a reverse Cope cyclisation reaction to produce the pyrroline **175**, but instead gave the piperidine *N*-oxide **174** instead (Scheme 2.32). The Ciganek group presumed that this was the result of an allowed 6-*endo*-trig conjugate addition cyclisation reaction.[84]



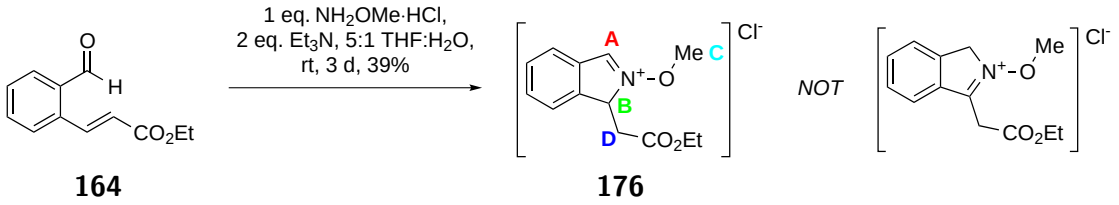
Scheme 2.32: **Intramolecular conjugate addition of hydroxylamine 173 occurs to afford the six-membered piperidine 174**

Comparisons can be drawn between the structures of the *N*-4-alkenyl hydroxylamine **168** of the Liu group and our proposed amino alcohol intermediate **167**, and as a consequence we decided to investigate which reaction pathway was operating in *our* reaction.

Therefore, our reaction conditions were applied to two key substrates. Firstly, *O*-methylhydroxylamine was used as a nucleophile, instead of free hydroxylamine, which we reasoned should prevent a reverse Cope cyclisation reaction from occuring, but still afford a cyclised

product if a conjugate addition mechanism was operating.

Treatment of aldehyde **164** with *O*-methylhydroxylamine in the presence of excess base was monitored by TLC analysis, which after three hours showed complete disappearance of starting material and the presence of two new spots. The ^{1}H NMR spectroscopic analysis of an aliquot showed the *O*-methyl oxime as the major product, with peaks for a minor product that contained a cyclic structure also present. Consequently, the reaction was allowed to continue, and TLC analysis ultimately showed complete disappearance of the oxime after three days. The major reaction product **176**, a dark purple oil, was assigned the cyclic structure shown in Scheme 2.33 after running NMR and HRMS analyses (HMQC data shown in Figure 2.16). Purification proved difficult, as the crude mixture contained other degradation products, and the salt compound proved to be not particularly stable.



Scheme 2.33: **Reaction of aldehyde 164 with *O*-methylhydroxylamine**

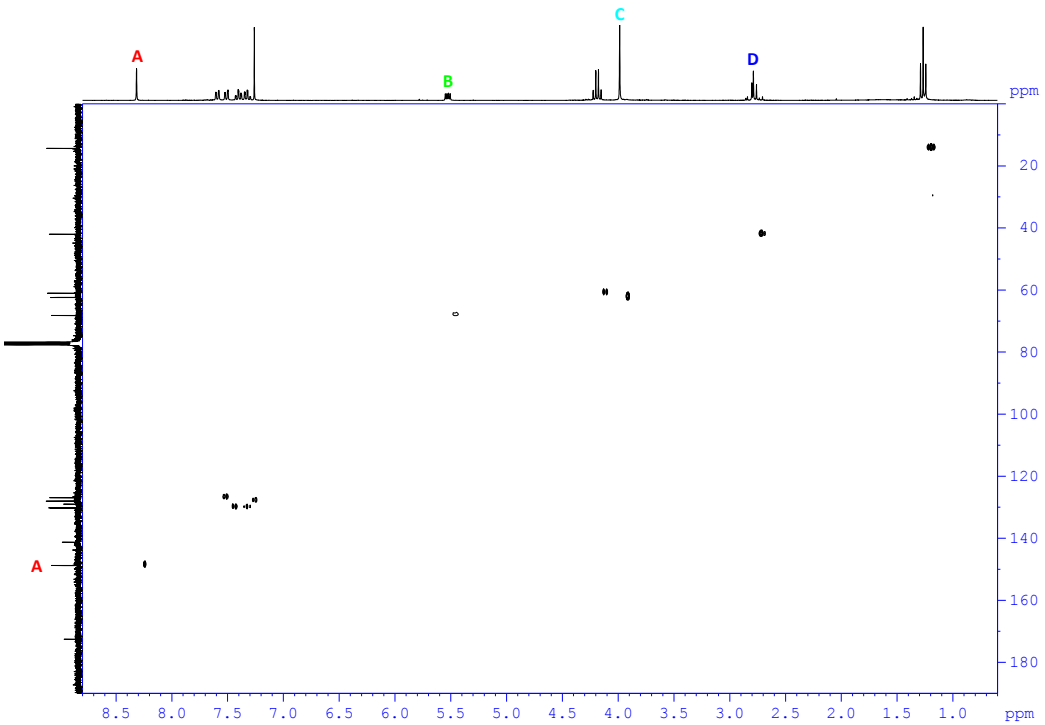
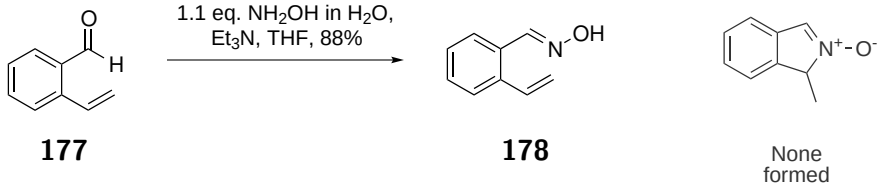


Figure 2.16: **HMQC data of cyclised salt 176**

The HMQC data showed that a different regioisomer of nitrone had been formed, compared to the more substituted nitrone isomer **165** observed when hydroxylamine was employed as a nucleophile. The distinctive nitrone carbon at δ 141 ppm was no longer a quarternary carbon, but was bonded to a proton that presents as a singlet peak at δ 8.32 ppm in the ^{1}H NMR (**A**). The presence of a 1H multiplet at δ 5.52 ppm (**B**), was shown by COSY interactions to be adjacent to a CH_2 group multiplet at δ 2.75 ppm (**D**), also supporting relocation of the double bond.

The second substrate investigated for the cyclisation mechanism was the commercially available aldehyde **177**. This compound should not cyclise if the reaction proceeds *via* conjugate addition. However, we would expect to see rapid cyclisation if a reverse Cope mechanism takes place under these conditions. Therefore, 2-vinylbenzaldehyde **177** was treated with hydroxylamine and base in THF/H_2O, which only resulted in formation of oxime **178** (Scheme 2.34). No other products were isolated, despite varying the temperature and length of these reactions.

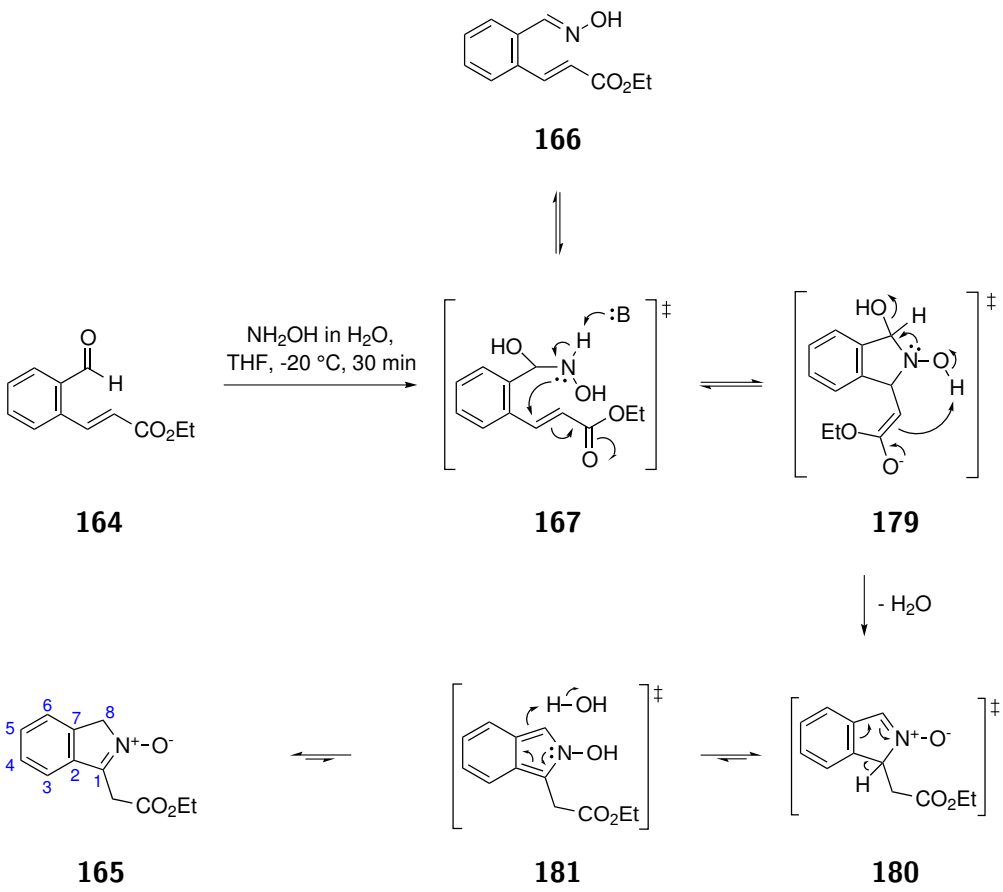


Scheme 2.34: **Failed cyclisation reaction of 2-vinylbenzaldehyde**

Both results presented above provide clear evidence to support a 5-*exo*-trig cyclisation mechanism, in which a hydroxyamino alcohol intermediate attacks the α,β-unsaturated ester in a 1,4 conjugate addition manner, to afford the five membered ring. The next mechanistic step to be investigated was how the more substituted nitrone functional group was formed post-cyclisation, which is discussed in the following section.

2.5.3 Investigating the reaction mechanism

A full reaction mechanism is proposed in Scheme 2.35. Thus far, we had deduced that a hydroxyamino alcohol intermediate **167** was likely to undergo a conjugate addition cyclisation step to afford enolate **179**. Post cyclisation, a dehydration step to form a nitrone was proposed, positioning a carbon-nitrogen double bond in the alternative N-C_8 position as seen for the *O*-methyl salt example (Scheme 2.33). Tautomerisation would then occur to afford a more thermodynamically stable nitrone **165**, with its nitrogen-carbon double bond in the N-C_1 position.

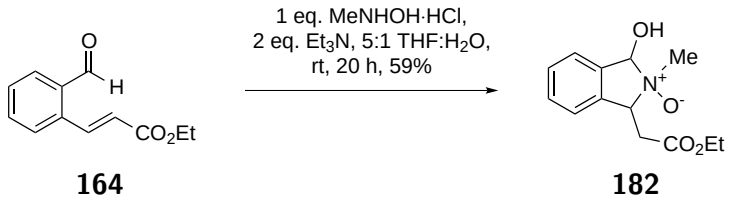


Scheme 2.35: **Proposed reaction mechanism for formation of nitrone 165**

In order to try and confirm that the hydroxyamino alcohol intermediate **167** was the key cyclisation precursor, we decided to employ an *N*-substituted hydroxylamine as a nucleophile in the reaction (Scheme 2.36). If our mechanistic hypothesis was correct, cyclisation should occur, as the cyclised structure would be more stable than the initially formed hydroxyamino alcohol, however, the subsequent dehydration step would not be possible.

N-Methyl hydroxylamine hydrochloride was added to a solution of aldehyde **164** and base affording the cyclised product **182** as a mixture of diastereomers. NMR and HRMS analyses fully support this structure; the proton adjacent to the -OH group in the major diastereomer appears as a singlet at δ 5.71 ppm, in contrast to the singlet observed at δ 8.32 ppm for the nitrone proton of the *O*-methyl cyclised salt **176**. Similarly, the presence of a 1H multiplet at δ 4.26 ppm corresponding to the other benzylic proton, and diastereotopic AB quartets (J_{AB} = 16.0, 5.8 Hz) at δ 3.09 and δ 2.45 support this structure. NOE analysis revealed a correlation between the proton adjacent to the -OH group and the protons of the methyl group.

This result supports our proposition, that the conjugate addition cyclisation reaction is initiated by the sp^3 nitrogen of the more nucleophilic hydroxyamino alcohol intermediate **167**, rather than the sp^2 nitrogen of the corresponding oxime **166**.

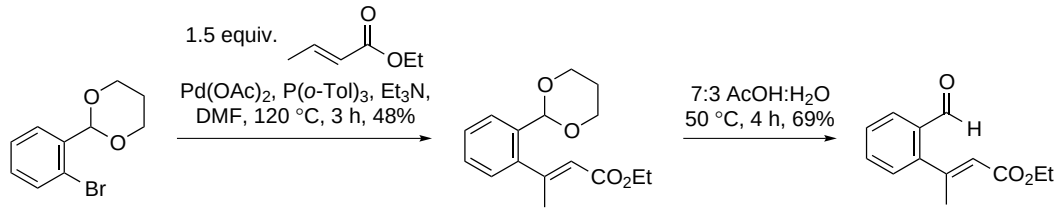


164 **182**

Scheme 2.36: **Reaction of aldehyde 164 with *N*-Methylhydroxylamine**

In the next step of the reaction mechanism, a dehydration reaction is proposed to afford a kinetic nitrone product **180**. Previously, when using *O*-methyl hydroxylamine hydrochloride in the reaction, the salt isolated had the carbon-nitrogen double bond at the upper N-C_8 position of the five membered ring. We wanted to determine whether it would be possible to form a stable nitrone with the double bond in this position, and so the structure of the aldehyde starting material was redesigned to incorporate a β-substituted alkene, since this would prevent isomerisation of the nitrone from the N-C_8 position into its N-C_1 position.

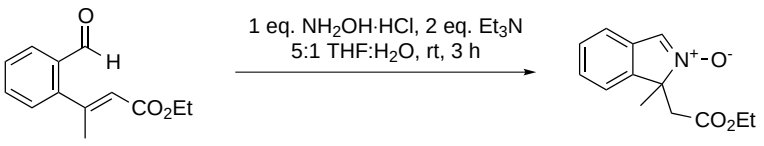
Therefore, acetal **147** was Heck cross-coupled with ethyl crotonate to afford acetal **184**, which was then deprotected under acidic conditions to furnish the corresponding aldehyde **185** in 69% yield (Scheme 2.37).



147 **184** **185**

Scheme 2.37: **Synthesis of β,β-di-substituted ester 185**

This β,β-di substituted ester was then subjected to the cyclisation reaction conditions and afforded the predicted nitrone product **186**, which contained a N-C_8 double bond, as a single product (Scheme 2.38).

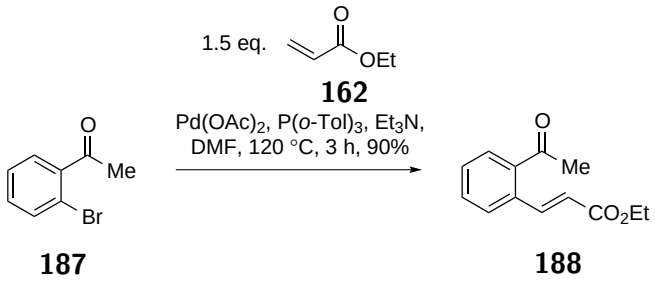


185 **186**

Scheme 2.38: **Cyclisation reaction of β,β-di-substituted ester**

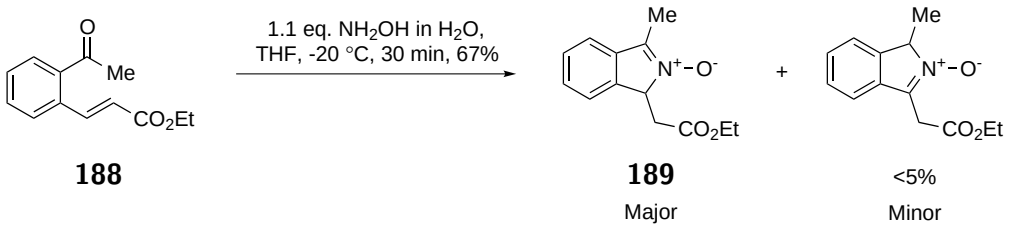
This result proved that cyclisation could occur to afford a N-C_8 nitrone when the N-C_1 double bond position was blocked. The next logical step, therefore, was to explore the reaction outcome when a substrate with carbon substitution at the C_8 position was present.

Therefore, ethyl acrylate **162** was directly coupled to 2-bromoacetophenone using a Heck cross coupling reaction (Scheme 2.39) to afford ketone **188** in 90% yield as a yellow oil. No acetal protecting group step was required in this reaction because the C-H insertion reaction observed for aldehydes could not occur.



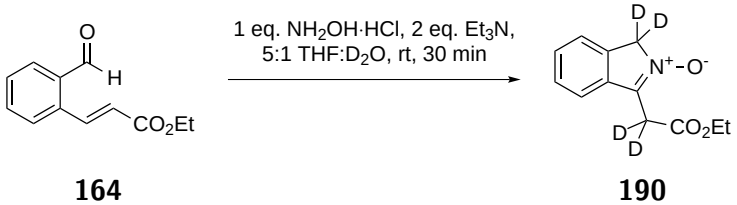
Scheme 2.39: **Synthesis of ketone 188**

After subjecting ketone **188** to the standard cyclisation reaction conditions, nitrone **189** was isolated as a major product containing an N-C_8 nitrone double bond (Scheme 3.13). Analysis of the ^{1}H spectrum of the crude reaction product revealed peaks for a minor product, which corresponded to a nitrone whereby the double bond was present in the alternative N-C_1 position β- to the ester functionality. Leaving the reaction to stir overnight gave no change in the proton NMR spectrum, implying that this was the thermodynamic ratio of the two positional nitrones.



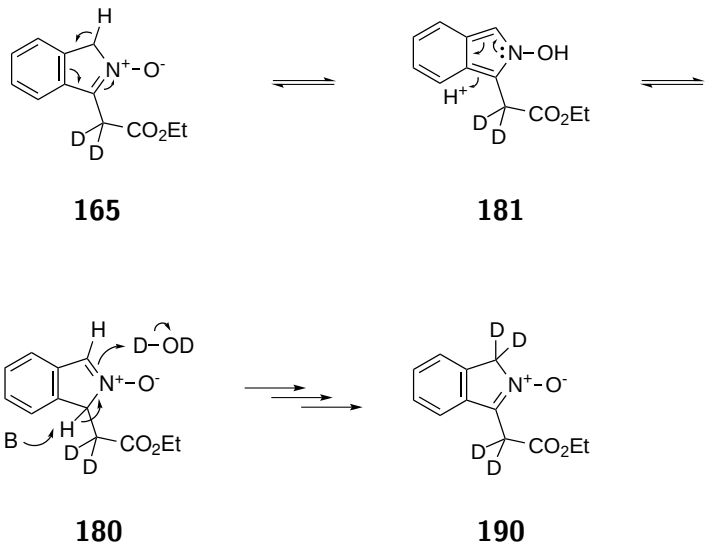
Scheme 2.40: **Cyclisation reaction of ketone 188**

These results confirmed our theory that the N-C_8 tautomers of nitrones are formed initially from aldehyde substrates, and we suggest these undergo a fast tautomerisation step to the thermodynamically more stable structure **165**. To confirm this, we carried out a deuterium incorporation experiment as shown in Scheme 2.41, which involved dissolving aldehyde **164** in a 5:1 mix of THF and D_2O, and reacting under the standard cyclisation conditions for thirty minutes at room temperature, to afford deuterated nitrone **190** as a red oil.



Scheme 2.41: **Deuteration experiment for exploring mechanism of cyclisation of ester 164**

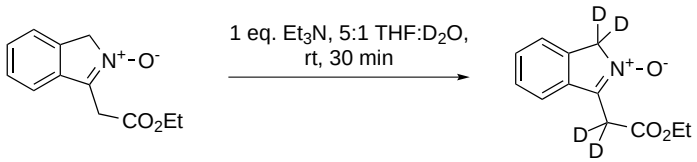
^{1}H NMR spectroscopic analysis showed that the resonances for both the benzylic CH_2 group and the CH_2 group α- to the ester were no longer present with the correct integration. Singlet peaks corresponding to these groups were observed in the corresponding ^{2}H NMR spectrum, however. After a reaction time of 30 minutes, the acidic position adjacent to the ester group showed 77% deuterium incorporation, whilst the benzylic CH_2 position showed 60% deuterium incorporation. Incorporation of deuterium at the CH_2 group α- to the ester can be explained by a series of fast enolate formation/deuteration steps. Deuterium incorporation at the benzylic CH_2 is less simple to explain. We propose that an equilibrium exists between three tautomeric forms in solution (**165**, **181** and **180**), thus allowing deuteration at the benzylic position (Scheme 2.42).



165 **181** **180** **190**

Scheme 2.42: **Nitrone tautomerisation leading to deuterated nitrone 190**

To test this proposal, nitrone **165** was synthesised under optimised conditions and then added to a solution of base in a 5:1 mixture of THF:D_2O. The solution was stirred for thirty minutes at room temperature before being worked up and evaporated to yield a red oil (Scheme 2.43). Both ^{1}H and ^{2}H NMR spectra were obtained and both CH_2 positions showed an increase in deuterium incorporation ($> 90\%$ in both cases). This demonstrates the ease with which the tautomeric forms of the nitrone must interconvert in solution.

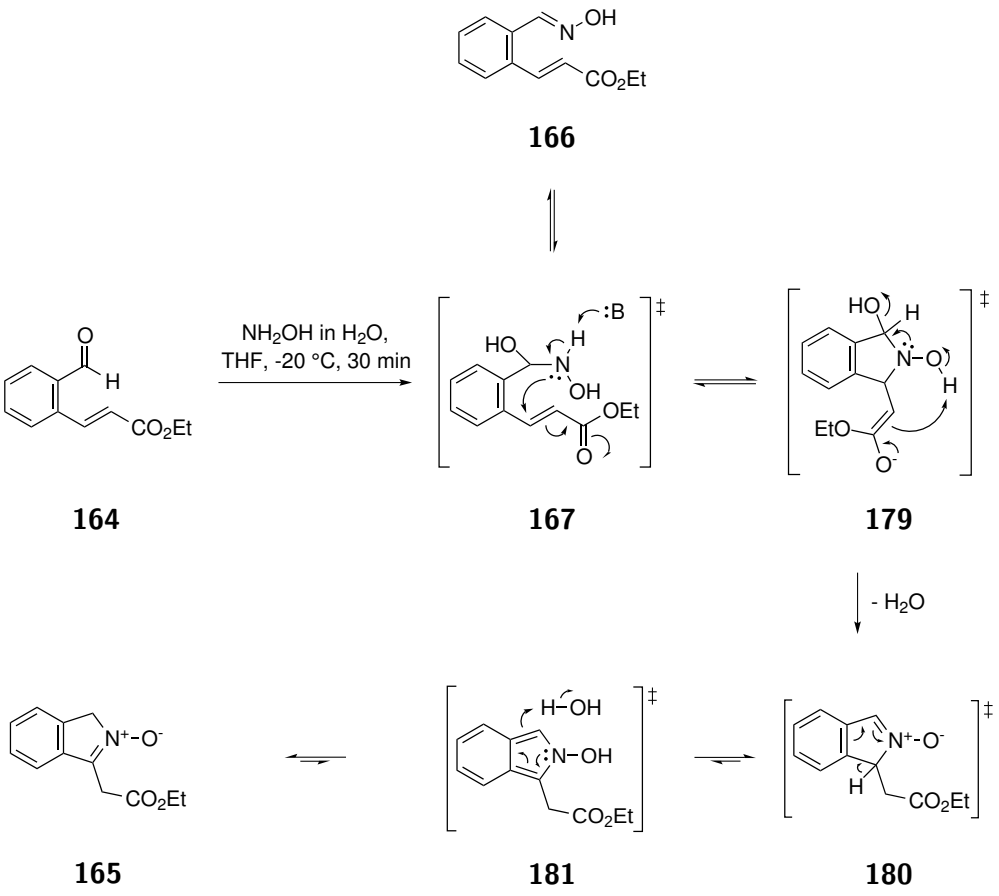


165 **190**

Scheme 2.43: **Deuteration experiment of nitrone 165**

2.6 Proposed reaction mechanism for nitrone formation

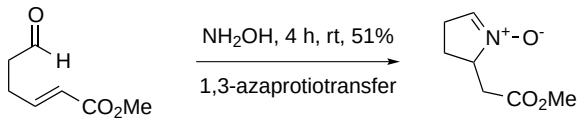
Using the evidence gained from the key mechanistic experiments above, we conclude a mechanism for nitrone formation, shown in Scheme 2.44. We believe that reaction of aldehyde **164** with hydroxylamine forms a hydroxyamino alcohol intermediate **167**, which undergoes a 5-*exo*-trig cyclisation reaction *via* conjugate addition to the α,β-unsaturated ester, to yield enolate **179**. Subsequent to this cyclisation event, loss of a molecule of water yields nitrone **180**, which undergoes an extremely facile tautomerisation step to the isolated, thermodynamic product, nitrone **165**.



Scheme 2.44: **Proposed reaction mechanism for reaction of ester 164 with hydroxylamine**

2.7 Synthesis of monocyclic nitrone

Based on the extensive mechanistic work discussed in section 2.5, we wanted to determine whether the few examples of aldehydes reacting with hydroxylamine to form cyclic nitrones reported by Grigg, were also proceeding *via* a conjugate addition mechanism (Scheme 2.45).



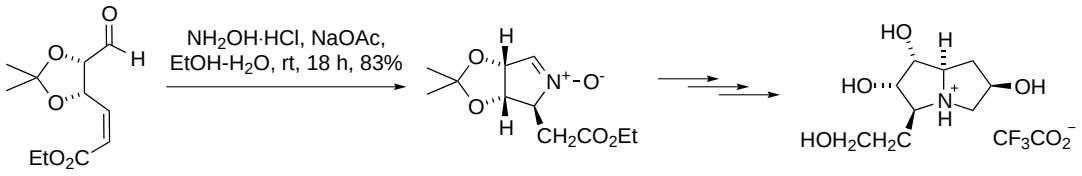
134 **135**

Scheme 2.45: **Grigg's synthesis of monocylic nitrone**

A number of other literature examples have been reported where a hydroxylamine and an aldehyde are reacted together to give a cyclic nitrone. In these cases either:

1. A mechanism is not disclosed
2. A 1,3-azaprotiotransfer mechanism of an intermediate oxime is suggested, or
3. The authors state that the reaction proceeds *via* a non-isolable oxime intermediate, which undergoes a conjugate addition/cyclisation reaction

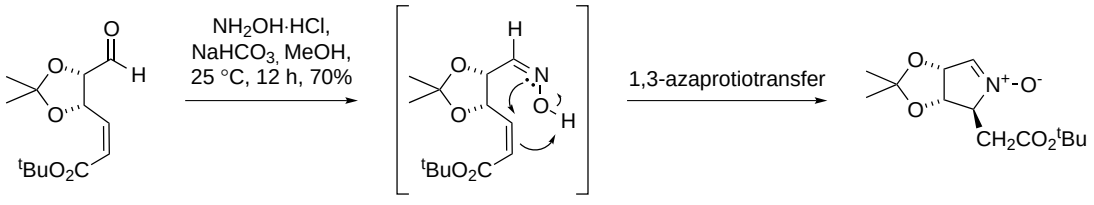
For example, in their synthesis of hydroxylated pyrrolizidines, Hall *et al.* reacted *cis*-alkene **191** with hydroxylamine and base to form nitrone **192**, but did not discuss any mechanism to explain this transformation (Scheme 2.46).[90]



191 **192**

Scheme 2.46: **Hall's synthesis of 192**

Interestingly, the Argyropoulos group reacted an almost identical starting material, aldehyde **193**, with hydroxylamine and base to afford nitrone **195**, as part of their synthesis of hydroxylated pyrroline-*N*-oxides derived from D-ribose (Scheme 2.47).[91] This group proposed that the reaction took place *via* formation of an oxime intermediate **194**, which underwent a 1,3-azaprotio cyclotransfer.

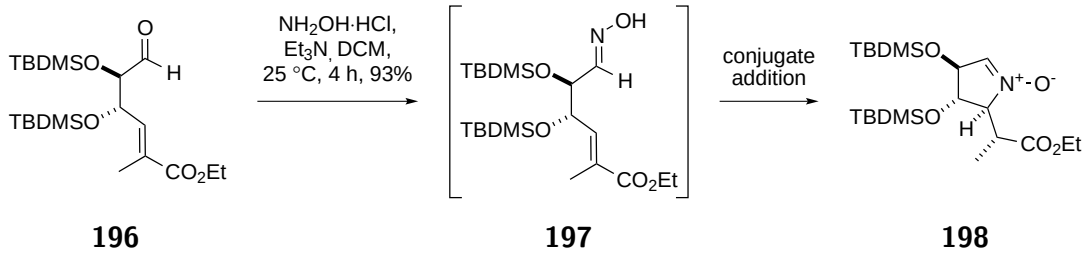


193 **194** **195**

Scheme 2.47: **Argyropoulos' synthesis of nitrone 195**

In their research on asymmetric cycloaddition reactions of nitrones, Ishikawa *et al.* reacted aldehyde **196**, under similar conditions, to yield nitrone **198** (Scheme 2.48). It

was proposed that the nitrogen of an unisolable intermediate oxime, **197**, added to the unsaturated ester in a 1,4 conjugate addition manner to yield the product.[92]



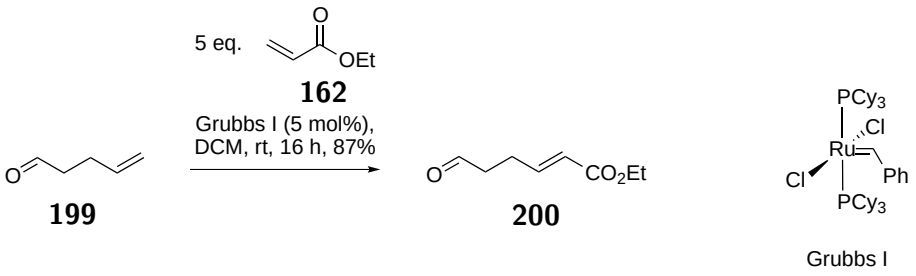
196 **197** **198**

Scheme 2.48: **Ishikawa's synthesis of nitrone 198**

Given the almost identical nature of all three starting materials and products to each other and to Grigg's monocyclic example, it was logical to assume that the mechanism of formation for all four nitrones was the same. In order to determine whether they followed one of the literature mechanisms discussed or our proposed hydroxyamino alcohol mechanism, it was decided to repeat Grigg's cyclisation chemistry under our reaction conditions.

2.7.1 Synthesis of a suitable acyclic substrate

To begin this piece of work, the aldehyde starting material had to be synthesised. Several literature methods were available; either multi step syntheses,[93,89] one step methods affording low yields,[94,95] or methods requiring the use of ozone.[96] We chose to employ a direct method involving cross metathesis of aldehyde 4-pentenal **199** with ethyl acrylate **162**, using Grubbs I catalyst under standard conditions (Scheme 2.49).[97] Aldehyde **200** was obtained as a colourless oil in 87% yield, after purification by column chromatography.

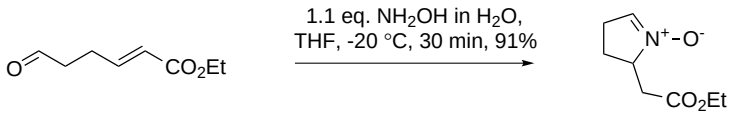


199 **200** Grubbs I

Scheme 2.49: **Cross metathesis reaction of 4-pentenal with ethyl acrylate**

2.7.2 Cyclisation efforts to afford a monocyclic product

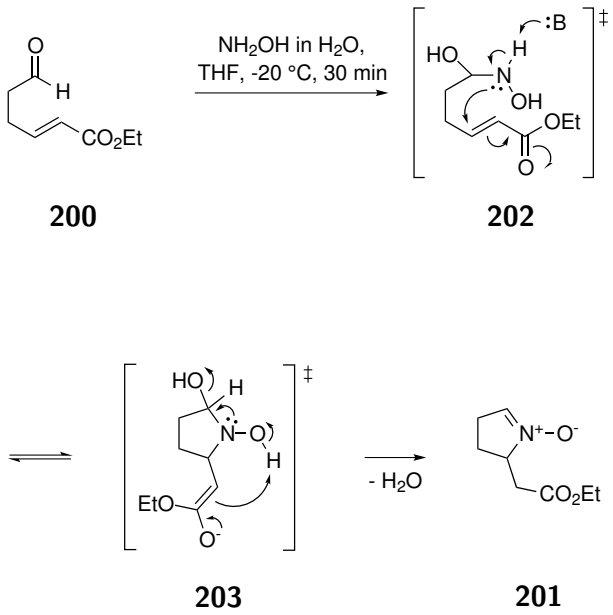
We then subjected aldehyde **200** to our optimised reaction conditions, to afford a white solid which was confirmed to be nitrone **201** by comparison of the NMR spectra with that reported in the literature (Scheme 2.50). Nitrone **201** was isolated as a yellow oil.



200 **201**

Scheme 2.50: **Synthesis of monocylic nitrone 201**

Therefore, we propose that the hydroxyaminoalcohol intermediate **202**, formed after initial attack of hydroxylamine on the formyl group, adds in a 1,4 fashion to the α,β unsaturated ester to give cyclised pyrrolidine **203**, with loss of water affording nitrone **201** (Scheme 2.51). Using our optimised conditions the nitrone is produced in a highly promising 91% yield.

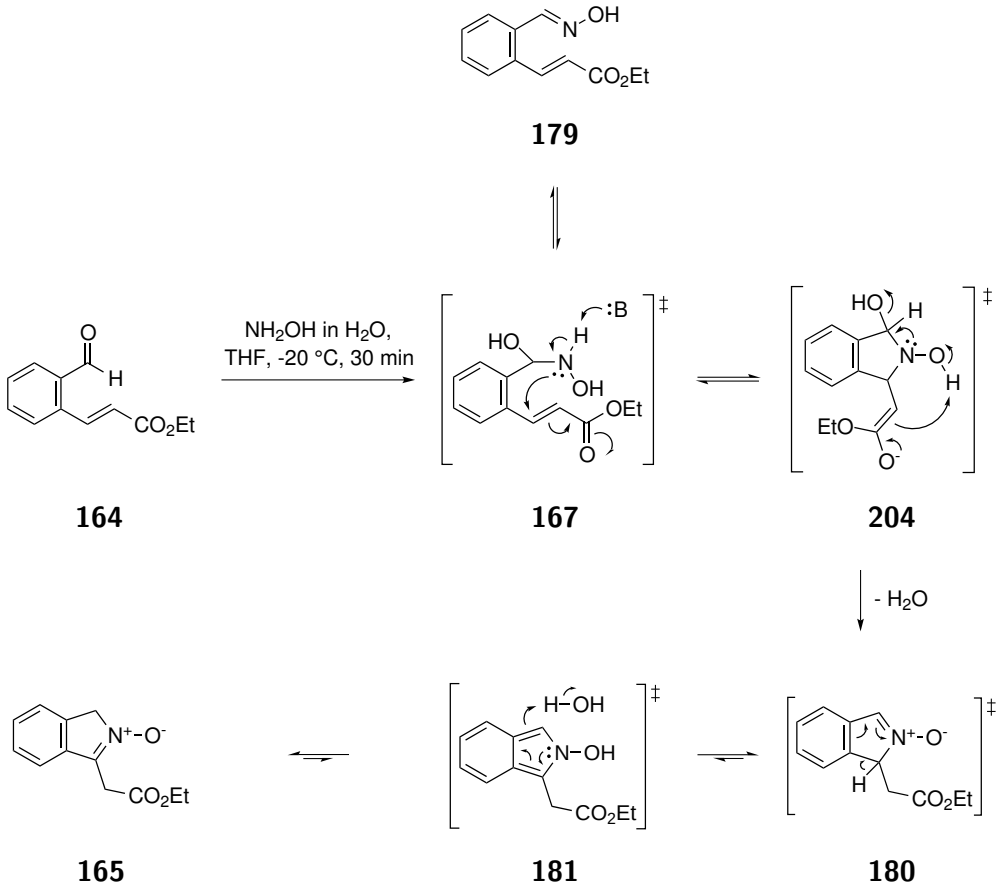


200 **202** **203** **201**

Scheme 2.51: **Proposed mechanism for formation of nitrone 201**

2.8 Conclusion

In this chapter we have presented a new method for the synthesis of isoindole derived nitrones whose mechanism has been elucidated as the conjugate addition cyclisation/tautomerisation pathway shown in Scheme 2.52.



Scheme 2.52: **Proposed reaction mechanism for the synthesis of novel isoindole *N*-oxide 165**

Previous literature reports by on related cyclisations by Hall, Argyropoulos and Ishikawa are likely to proceed *via* this mechanism, and not by 1,3-azaprotio cyclotransfers of oxime intermediates as previously proposed.

The following chapter describes optimisation of this nitrone forming conjugate addition/cyclisation reaction, its scope and limitation, and application of these optimal conditions to other classes of cyclisation substrate.

Chapter 3

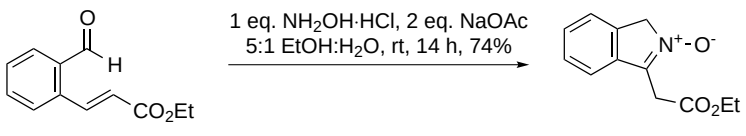
Reaction Optimisation & Exploration of Scope & Limitation of Nitrone Cyclisation Reaction

3.1 Introduction

In the previous chapter a novel route for the synthesis of bicyclic, isoindole based nitrones was presented. This chapter discusses optimisation of this reaction and its application for the synthesis of a wide range of isoindole nitrones.

3.2 Reaction optimisation

The nitrone forming methodology described in the previous chapter involved the reaction of aldehyde **164** with hydroxylamine and sodium acetate in EtOH/H_2O, which required fourteen hours to go to completion (Scheme 3.1). We wanted to shorten this time, and began our optimisation work by picking an arbitrary time of 30 minutes for the screening experiments. Using the same reagents and solvents, the original reaction was carried out for this length of time, and after work up the ^{1}H NMR spectrum showed that there was a 100% conversion from aldehyde to oxime and that 47% of this oxime had rearranged to nitrone (Table 3.1, entry 1). This result confirmed our earlier theory that the synthesis of the oxime cyclisation precursor was a fast step, whilst the cyclisation of the oxime intermediate to form the nitrone was the rate determining step.

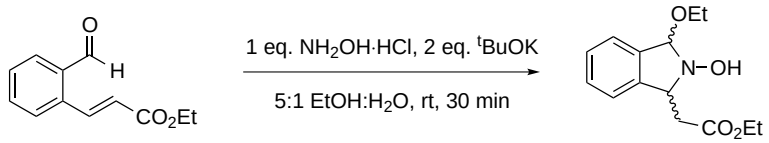


164 **165**

Scheme 3.1: **Synthesis of nitrone 165 using original conditions**

3.2.1 Base screen

It was rationalised that using a stronger base might increase the rate of the reaction, and so a small base screen was performed, with all other reaction conditions remaining the same. Using a strong base such as potassium *tert*-butoxide (Scheme 3.2, Table 3.1, entry 2) gave an unexpected result. All of the starting material was consumed, however there was neither oxime nor nitrone present. The product of the reaction had formed cleanly and in 100% conversion. After carrying out NMR analyses, we determined that the product of the reaction was the cyclised hydroxylamine **205**, whose diastereomers were present in a 1:1.4 ratio.



164 **205**

Scheme 3.2: **Reaction using ^{t}BuOK base**

We continued the screen, using bases with an intermediate strength between sodium acetate and potassium *tert*-butoxide. Caesium carbonate gave a mixture of compounds, not all of which could be identified. Triethylamine and potassium carbonate both gave high conversions to nitrone however, and the reaction using triethylamine was carried forward as it gave the highest yield of nitrone product (entry 4).

Table 3.1: **Base screen for nitrone cyclisation reaction**

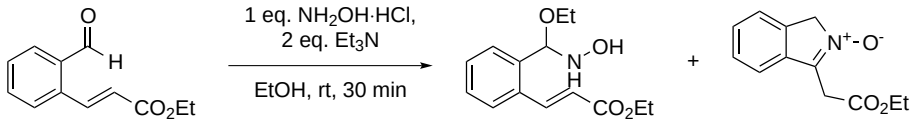
Entry	Base	% Conversion to nitrone product
1	NaOAc	47
2	^{t}BuOK	0
3	K_2CO_3	96
4	Et_3N	98
5	Cs_2CO_3	0

*Conditions: Aldehyde **164** (1 mmol), 1 eq. $NH_2OH{\cdot}HCl$, 2 eq. base, 5:1 EtOH:H_2O (10 mL/g), 30 min. All entries showed 100% consumption of aldehyde starting material. % product determined from ^1H NMR spectra.*

3.2.2 Solvent screen

The second variable investigated was the choice of reaction solvent. Whilst changing the base had given us a system that proceeded to completion within half an hour, the current solvent system was from the original oxime preparation.[77] We wanted to investigate whether the polar protic nature of the solvent was required for our reaction, and to find out if a mixed solvent system was required. At the time we also wanted to identify conditions that would enable us to investigate deuterium incorporation as part of the mechanistic investigation described in Chapter 2, Section 2.5. Therefore, a short solvent screen was carried out using the aldehyde substrate **164** (Table 3.2).

Initially, the reaction was carried out in ethanol and water separately to determine whether both solvents were required for the reaction to proceed (entries 1 and 2). Although both reactions went to 100% conversion (i.e no aldehyde starting material was remaining), neither gave 100% nitrone **165**. Interestingly, the reaction with solely ethanol showed nitrone **165** and also hydroxyamino alcohol **206**, in a 1:2 ratio (Scheme 3.3). The reaction in water alone gave a mixture of products, not all of which could be identified.



164 **206** **165**

Scheme 3.3: **Reaction of aldehyde 164 and hydroxylamine in ethanol**

These results suggested that a dual solvent system was indeed necessary for the nitrone to form cleanly as the sole product. We then wanted to determine whether both solvents had to be polar and protic. We began by investigating aprotic polar solvents that are also miscible with water.

Table 3.2: **Solvent screen for nitrone cyclisation reaction**

Entry	Solvent	% Product
1	5:1 EtOH:H_2O	98
2	EtOH	33
3	H_2O	–[a]
4	5:1 Et_2O:H_2O	–[a]
5	5:1 THF:H_2O	**100**
6	THF	–[a]

*Conditions: Aldehyde **164** (1 mmol), 1 eq. NH_2OH·HCl, 2 eq. Et_3N, solvent (10 mL/g), 30 min. All entries showed 100% consumption of the aldehyde starting material. % product determined from ^{1}H NMR spectra. [a] % product could not be determined due to presence of an unidentifiable mixture of compounds in the ^{1}H NMR spectra.*

A mixture of diethyl ether and water gave an unidentifiable mixture of compounds by ^{1}H NMR spectroscopic analysis (entry 4). However, the last solvent system we screened gave optimal results, with a 5:1 THF:H_2O solvent system giving a 100% conversion to nitrone **165** within the 30 minute screening time frame. For completeness, and to confirm our earlier results that water plays a key part in the reaction, we carried out the reaction solely in THF (Table 3.2, entry 6), which gave a complex ^{1}H NMR spectrum. We chose to continue using THF:H_2O as the reaction solvent rather than revert back to ethanol:water, as it was easier to remove after the reaction work-up.

3.2.3 Hydroxylamine source

The existing procedure employed the hydrochloride salt of hydroxylamine, and required two equivalents of base (see Table 3.3, entry 1). From the results gained above, it seemed

logical to repeat the reaction using a commercially available solution of hydroxylamine in water (50 wt.%), which would simplify the protocol significantly.

We initially carried out the cyclisation reaction by substituting the hydroxylamine salt with the aqueous solution using only one equivalent of base as there was no HCl to liberate, and using only THF as solvent (Table 3.3). The reaction gave 100% conversion to nitrone within the screening time, demonstrating that the lower percentage of water was sufficient for the cyclisation reaction to proceed. We next investigated using one equivalent of the hydroxylamine solution without added base. This reaction gave an encouraging result of 92% and when the amount of hydroxylamine was increased slightly to 1.1 equivalents, 100% conversion to nitrone was achieved in thirty minutes.

Table 3.3: **Hydroxylamine screen for nitrone cyclisation reaction**

Entry	**NH_2OH source**	**Eq. NH_2OH**	**Eq. Et_3N**	**% Product**
1	NH_2OH·HCl	1.0	2.0	100
2	NH_2OH aq.	1.0	1.0	100
3	NH_2OH aq.	1.0	–	92
4	NH_2OH aq.	1.5	–	100
5	NH_2OH aq.	1.1	–	***100***

*Conditions: Aldehyde **164** (1 mmol), entry 1: 5:1 THF:H_2O (10 mL/g), 30 mins; entries 2-4: THF (10 mL/g), 30 mins. All entries showed 100% consumption of the aldehyde starting material **164**. % product determined by ^1H NMR spectra.*

3.2.4 Temperature

Up until this point, the original reaction conditions and all subsequent screening work had afforded nitrone **165** as a dark red thick oil, which hardened into a dark red solid on standing. At the beginning of the reaction, the solution was a pale yellow colour, and over time it darkened, particularly during removal of the solvent post work-up. Now that we had optimised conversion conditions in hand, we sought to improve the yield of nitrone obtained after isolation.

Attempts to recrystallise the dark red solid were fruitless, so we investigated whether another change of conditions could afford the nitrone as a crystalline solid at an earlier stage. The cyclisation reaction was re-run using the newly optimised solvent/reagent system at a range of temperatures (Table 3.4). At 10 °C the reaction remained a solution which darkened over time, whilst at 0 °C the reaction solution remained yellow. At -10 °C a

cloudy suspension formed, which when filtered gave 5 mg of a cream solid identified as the desired nitrone product. A work up of the mother liquors revealed that the majority of product was still present in the liquid phase. Interestingly, even at this reduced temperature, nitrone **165** was the only compound present in the NMR spectrum. At -20 °C, more of this cream solid precipitated out of solution, and, upon filtering after 30 minutes, nitrone was obtained as a solid in 76% yield.

Table 3.4: **Temperature screen for nitrone cyclisation reaction**

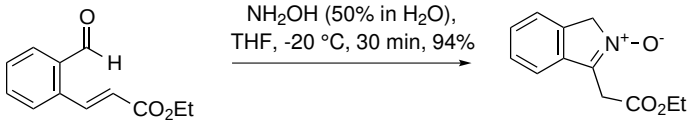
Entry	Temperature (°C)	Reaction Observation	% Product
1	18 (rt)	liquid	–[a]
2	10	liquid	–[a]
3	0	liquid	–[a]
4	-10	cloudy suspension	100
5	-20	cream precipitate	100

Conditions: ***164*** *1 mmol, 1.1 eq. NH_2OH (aq.), THF (10 mL/g), 30 mins. All entries showed 100% consumption of the aldehyde starting material. % product determined from ^{1}H NMR spectra. [a]Reactions not worked up, no NMR data obtained.*

After a few days at room temperature, the solid began to discolour. The ^{1}H NMR spectrum of a sample revealed that the nitrone was no longer clean, with the baseline having become "grassy". Whilst no specific alternative structures could be explicitly identified, this degradation was assigned to its gradual polymerisation, a process that has been reported previously for other reactive nitrone species. However, this instability could be resolved by storing the solid nitrone in the freezer, where it could be stored indefinitely without signs of degradation/polymerisation.

3.2.5 Reaction scale up

Having developed reaction conditions to afford an easy to handle solid nitrone in a short time, we scaled up the reaction to assess the yield. To a solution of aldehyde (10 mmol) in THF at -20 °C hydroxylamine was added as a 50% solution in water (Scheme 3.4). After thirty minutes at -20 °C, the suspension was vacuum filtered, the reaction flask was rinsed with cold THF three times and added to the filter cake, and nitrone **165** isolated in 94% yield with no need for further purification.



164 **165**

Scheme 3.4: **Optimised synthesis of nitrone 165**

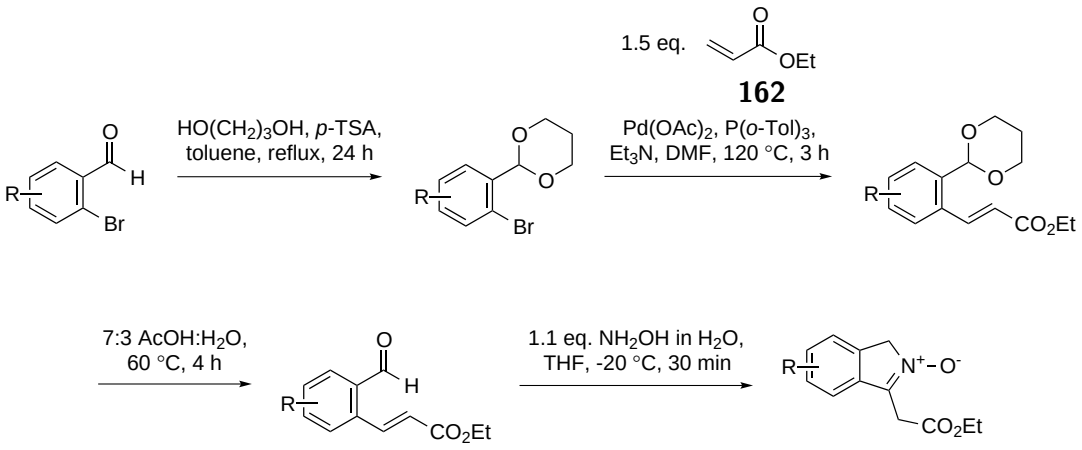
3.2.6 Conclusion

We had successfully optimised the conditions for converting formyl acrylate **164** into the novel bicyclic nitrone **165**, resulting in:

1. The reaction time being cut from 14 hours to 30 minutes.
2. Only 3 reactants being required, instead of the 5 reactants employed in the original procedure.
3. Isolation of the nitrone product as a solid in high yield, by lowering the temperature.

3.3 Reaction scope

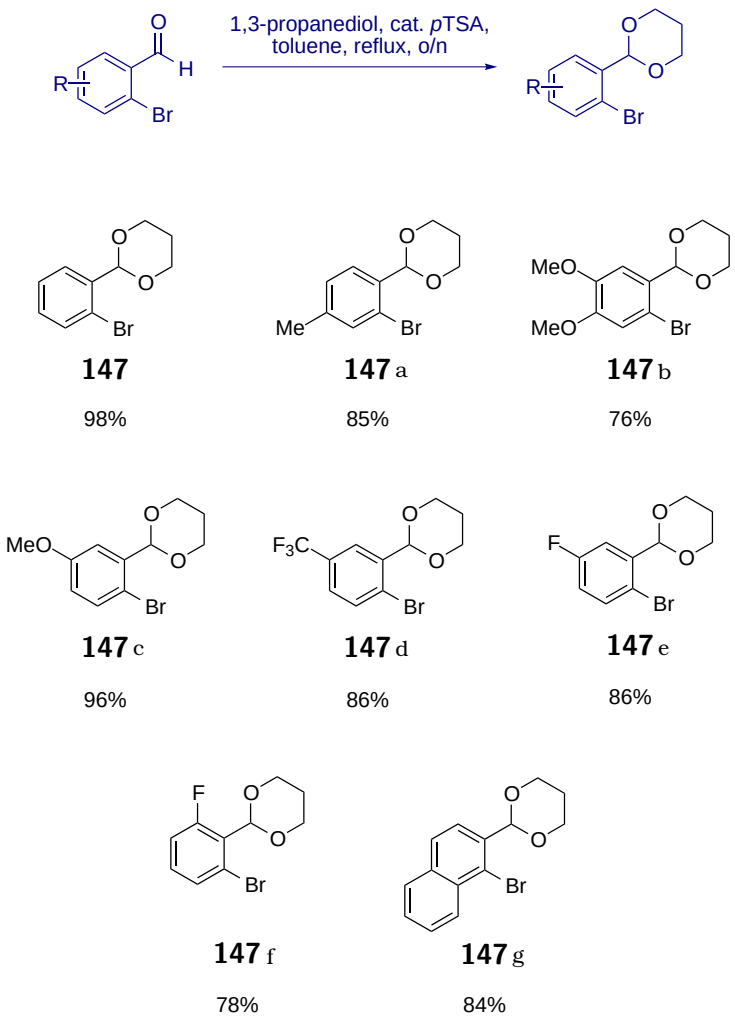
With the reaction optimisation complete, we next wanted to address the scope and limitation of this reaction by synthesising a library of nitrones. Starting from a variety of substituted 2-bromobenzaldehydes, each aldehyde was subjected to a four step synthesis to afford their corresponding nitrone (Scheme 3.5). The following sections describe the full results for these four reactions.



Scheme 3.5: **Four step synthesis of nitrones**

3.3.1 Step 1: Acetal protection reactions

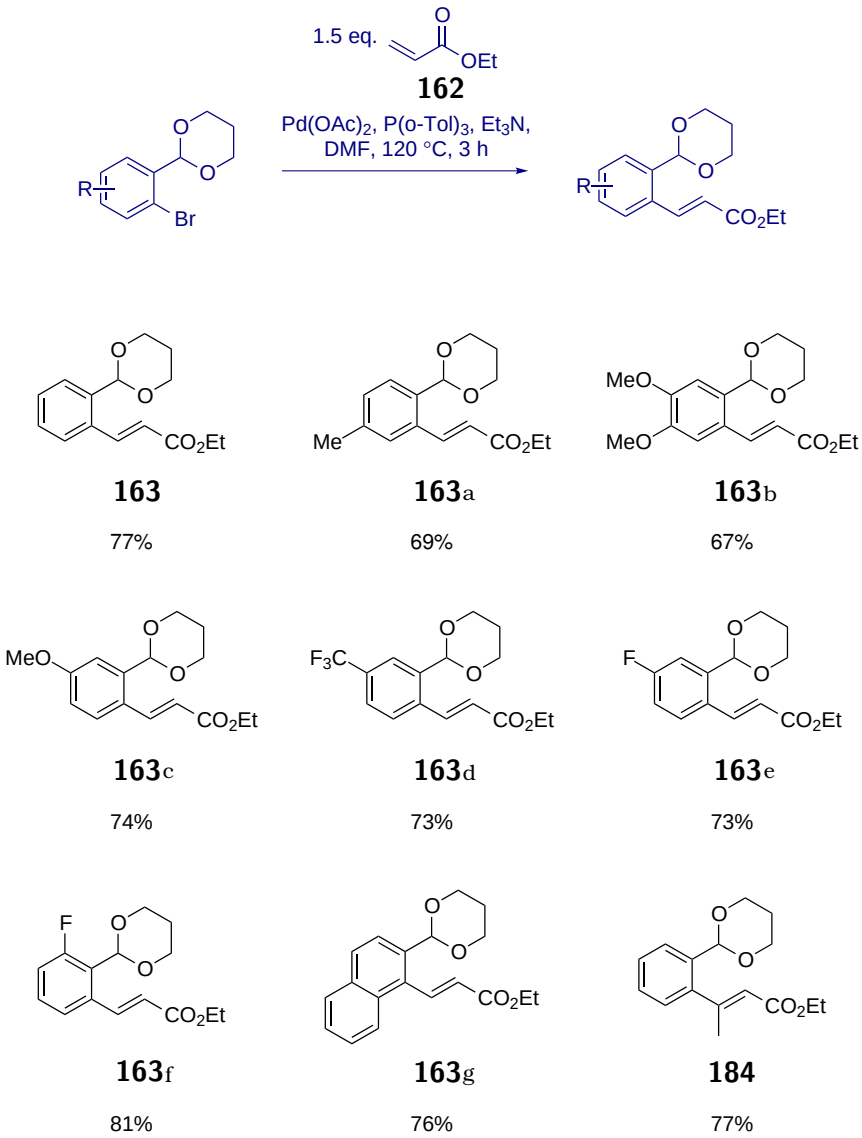
Our standard acetal forming conditions were used to prepare a range of substituted aryl acetals **147** to **147**g. Therefore, each aldehyde was heated with 1,3-propanediol and a catalytic amount of *p*TSA in toluene using a Dean-Stark apparatus, to afford a range of acetals in 76-98% yield.



Scheme 3.6: **Synthesis of eight aryl acetal analogues 147 to 147g**

3.3.2 Step 2: Heck cross-coupling reactions

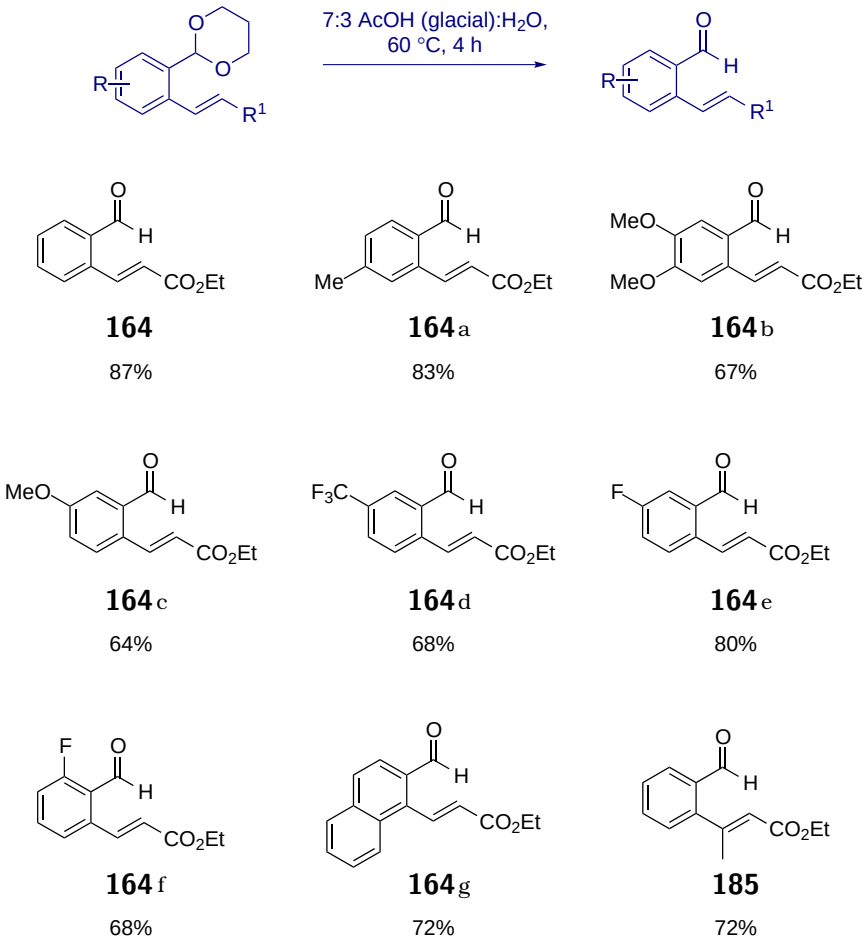
Heck cross-coupling of a range of acetal protected aryl aldehydes with ethyl acrylate **162** was carried out by heating eaching aldehyde with a catalytic amount of palladium acetate, tri-*o*-tolyl phosphine ligand and triethylamine in DMF at 120 °C for three hours. This gave a series of nine α,β-unsaturated esters **163** to **163**h in 67-81% yield. This methodology afforded α,β-unsaturated esters with both electron donating and electron withdrawing substituents around the aromatic ring, as well as substitution at the β- position, achieved by carrying out a Heck cross coupling reaction with ethyl crotonate.



Scheme 3.7: **Heck reaction to afford a range of nine α,β-unsaturated esters 163 to 184**

3.3.3 Step 3: Acetal deprotection reactions

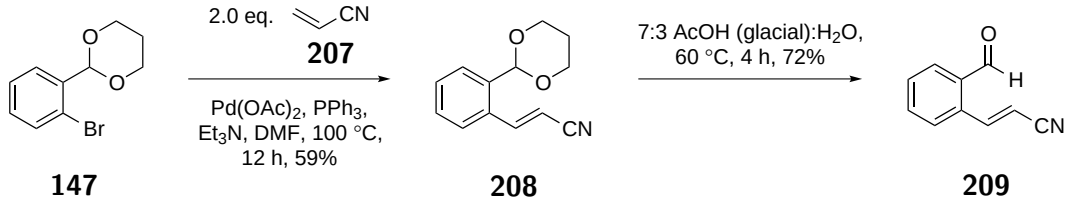
The nine acetals were deprotected using aqueous acetic acid at 60 °C over four hours to give their corresponding aldehydes in 67-87% yield.



Scheme 3.8: **Synthesis of aldehyde analogues 164 to 185**

Additional α,β-unsaturated cross-coupled substrates

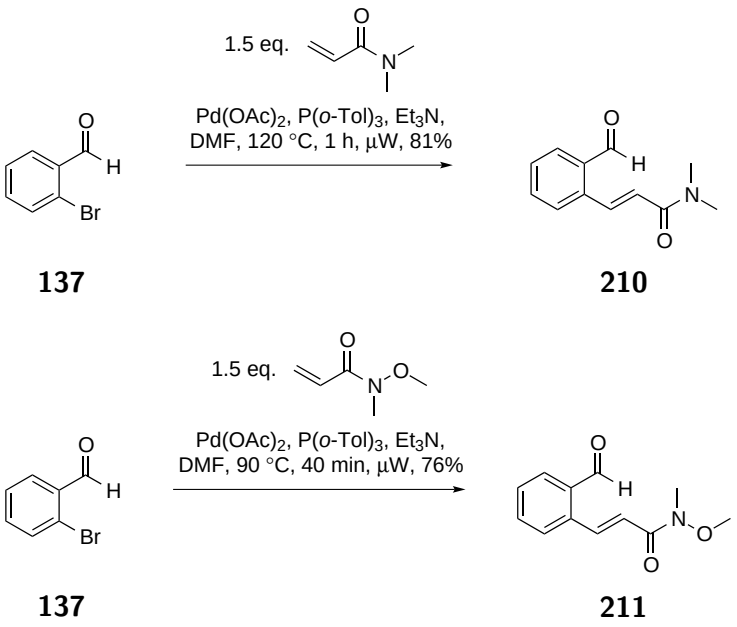
We also wanted to explore whether this methodology could be applied to the synthesis of other isoindole nitrone analogues containing different types of carboxylic acid derivatives. Therefore, a nitrile containing analogue was synthesised in a similar manner, using a slightly different coupling protocol (Scheme 3.9).[98] Carrying out the Pd(0)-catalysed cross coupling of acetal **147** with acrylonitrile **207** at a lower temperature, and for a longer period of time, afforded the protected α,β-unsaturated nitrile **208** in a moderate 59% yield. Acidic deprotection with aqueous acetic acid then gave the aldehyde product **209** in 72% yield.



147 **208** **209**

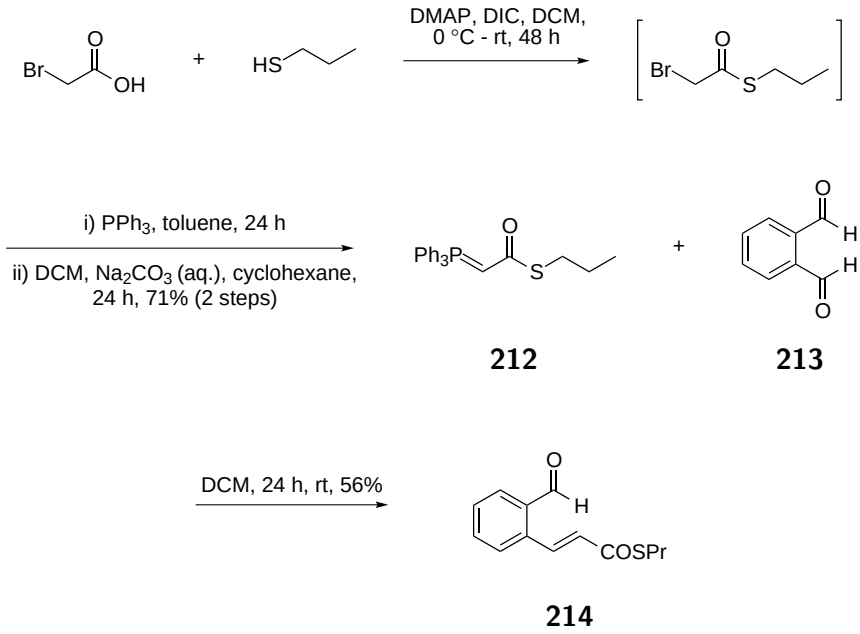
Scheme 3.9: **Synthesis of α,β-unsaturated nitrile 209**

Amide and Weinreb amide containing analogues **210** and **211** were synthesised by Heck reactions of the appropriate acrylamides with 2-bromobenzaldehyde (Scheme 3.10). These reactions were carried out under microwave conditions, and used the same catalyst, ligand, base and solvent as the original procedure. Whilst some doubly substituted deformylated products were seen in the crude ^{1}H NMR spectra (see Chapter 2, Section 2.2.1), these were minor products, and both the desired cross-coupled aldehydes could be obtained in good 76-81% yields after purification.



Scheme 3.10: **Synthesis of amide containing aldehyde analogues**

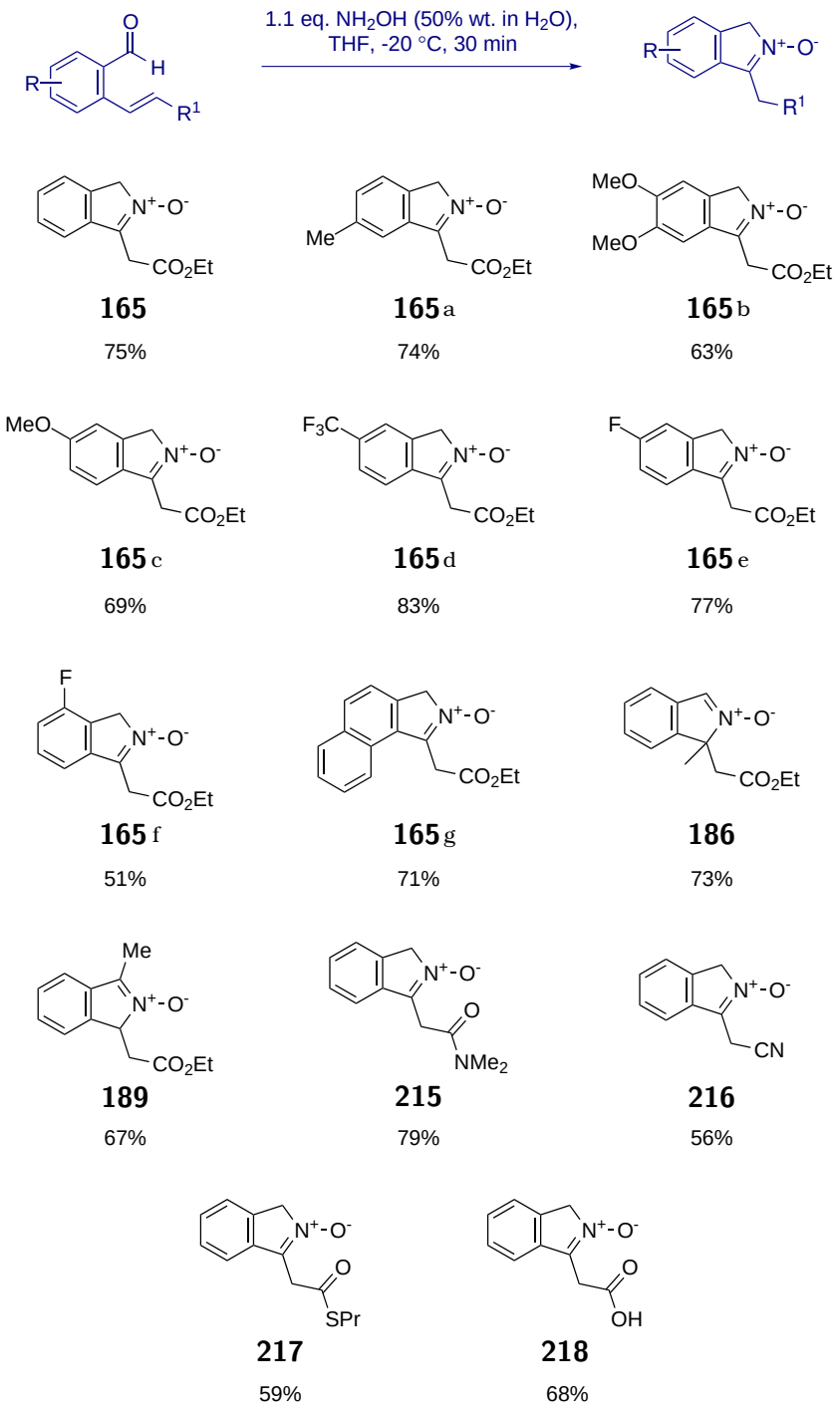
A thioester example was also synthesised *via* Wittig reaction of phosphorane **212** with phthaldialdehyde **213**.[99] The phosphorane was prepared in two steps from bromoacetic acid following a literature method,[100] involving DIC mediated thioester formation, followed by reaction with triphenylphosphine and base (Scheme 3.11). It was then added to a dilute solution of excess phthaldialdehyde in DCM and stirred for one day at room temperature. The solvent was removed under reduced pressure and the crude mixture purified by column chromatography to afford the thioester aldehyde **214** in 56% yield.



Scheme 3.11: **Synthesis of thioester containing aldehyde analogue 214**

3.3.4 Step 4: Nitrone synthesis reactions

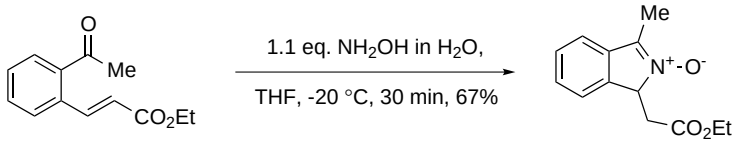
A series of fourteen carboxylic acid derivatives were treated with hydroxylamine (50% wt. in water) in THF at -20 °C for thirty minutes. This resulted in a series of smooth cyclisation reactions occuring to afford their corresponding isoindole derived nitrones as crystalline solids in 51-83% isolated yield.



Scheme 3.12: **Synthesis of isoindole nitrone analogues**

Fourteen nitrones, **165-218**, were successfully synthesised in acceptable to good yields. An array of electron donating and electron withdrawing groups were tolerated around the aromatic ring without significant detrimental affect to the yield. The 4-methyl nitrone **165**a was not formed as a solid under the reaction conditions, so the reaction was worked up in DCM and water to afford this nitrone as a yellow oil.

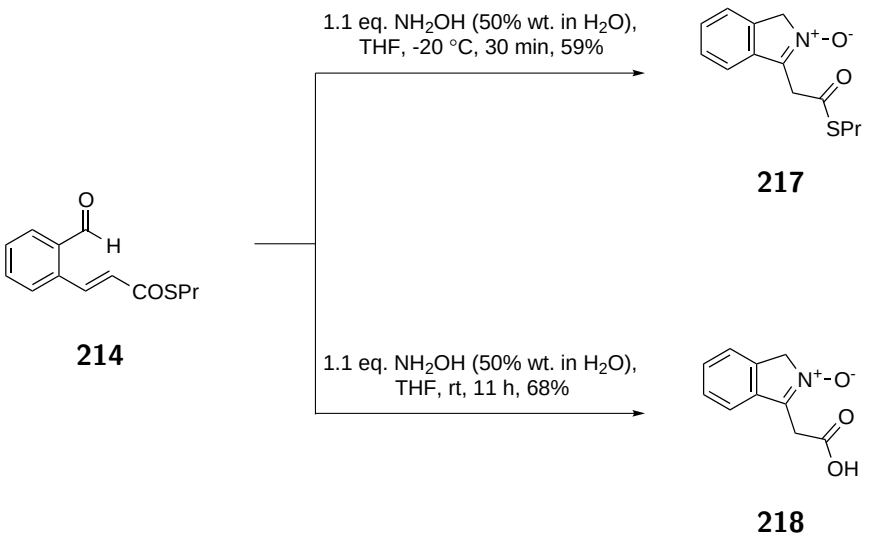
As discussed in the previous chapter, using a ketone starting material for acceptor synthesis yielded a different tautomer of the nitrone.



188 **189**

Scheme 3.13: **Cyclisation of ketone nitrone analogue 188**

The nitrone cyclisation reaction tolerates the presence of other α,β-unsaturated electron withdrawing functional groups with the amide and nitrile analogues, **210** and **209**, both giving the desired nitrone products. Upon carrying out the reaction of the thioester analogue, we noticed that the temperature had to be very tightly controlled due to a faint smell of thiol indicating that competitive hydrolysis was occuring, upon warming.[101] We decided to investigate this hydrolysis reaction further and so reacted the thioester aldehyde with hydroxylamine at room temperature and allowed the crude reaction mixture to stir overnight (Scheme 3.14). The reaction was then taken up in DCM and water, separated, and the aqueous layer neutralised by 1M HCl and extracted with DCM. After removing the solvent under reduced pressure, nitrone acid **218** was afforded as a red oil in 68% yield. This observation is useful since it affords the potential for coupling with amines under neutral DCC coupling conditions, thus enabling bioconjugation reactions to be carried out.



Scheme 3.14: **Nitrones synthesised from reactions of thioester 214 with hydroxylamine**

The Weinreb substrate example did not yield the desired product. The reaction did not produce a solid, and so the solvent and hydroxylamine were removed under reduced pressure. The ^{1}H NMR spectrum of the crude material was very complicated, with none of the desired nitrone peaks being present, which was disappointing as access to a Weinreb amide product would potentially have allowed access to a nitrone aldehyde as a substrate for reductive amination reactions.

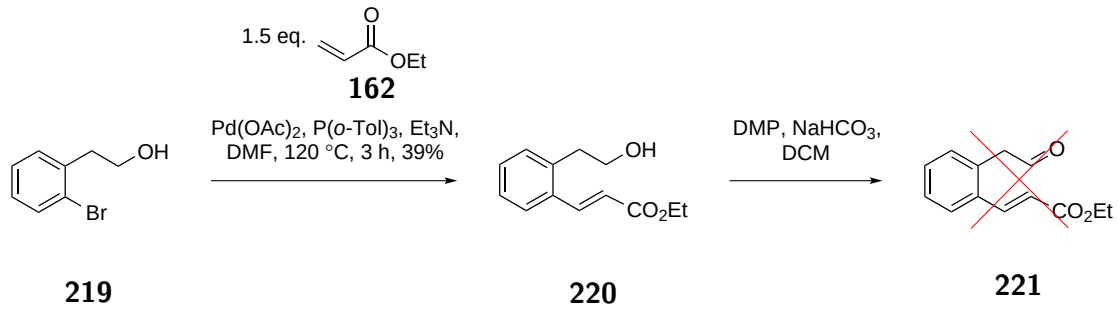
3.4 Synthesis of dihydroisoquinoline nitrones

After completing the synthesis of a library of isoindole based nitrones, we decided to use our novel methodology to prepare dihydroisoquinoline based nitrones, containing a six membered nitrone ring. In order to begin this work we initially had to synthesise the required aldehyde starting materials.

3.4.1 Synthesis of cyclisation precursor - Strategy 1

With our aim now being the synthesis of six membered cyclic nitrones, the structure of our aldehyde starting material had to be adapted to include an extra methylene carbon. We began by exploring the possibility of inserting this requisite carbon between the aldehyde group and the benzene ring. Taking the commercially available 2-bromophenethyl alcohol **219**, we carried out a Heck cross coupling reaction using our previously established conditions (Scheme 3.15). After purification, the coupled alcohol **220** was obtained in a low 39% yield as a yellow oil. This was then oxidised, using Dess-Martin Periodinane, in an attempt to afford the aldehyde **221**, however, despite column chromatography and

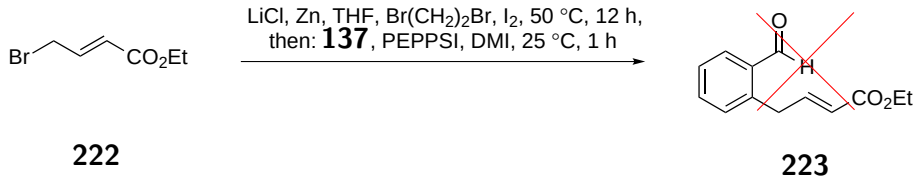
recrystallisation, efforts to obtain clean aldehyde product were unsuccessful.



Scheme 3.15: **Unsuccessful Heck synthesis of ester 221**

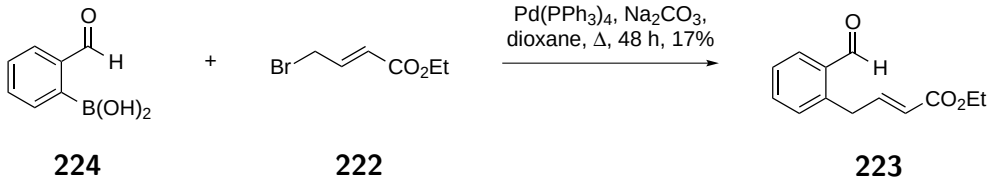
3.4.2 Synthesis of cyclisation precursor - Strategy 2

After carrying out a further search of potential synthetic routes, we attempted the synthesis of aldehyde **223**, which would incorporate the extra methylene carbon adjacent to the α,β-unsaturated ester. An adapted Negishi cross coupling of 2-bromobenzaldehyde **137** and bromocrotonate **222** was attempted,[102] as shown in scheme Scheme 3.16. However, the ^{1}H NMR spectrum of the reaction was complicated, and peaks for the desired cross-coupled product were not observed.



Scheme 3.16: **Unsuccessful Negishi synthesis of ester 223**

We then carried out a Suzuki cross coupling reaction, where after a few attempts with varying conditions,[103 104 105] we found that refluxing in dioxane for two days gave some of the desired product peaks in the crude ^{1}H NMR spectrum.[106] (Scheme 3.17). However, the NMR spectra also showed a number of other products were present, and after chromatography, the desired aldehdye **223** could only be obtained in a low 17% yield.

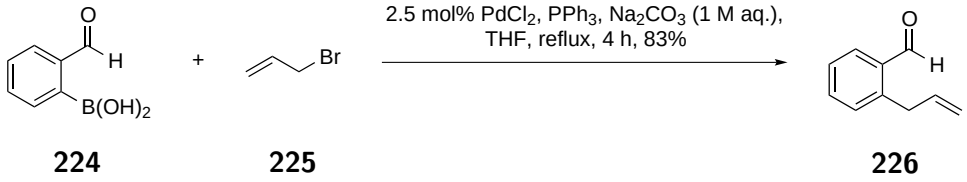


Scheme 3.17: **Suzuki synthesis of ester 223**

3.4.3 Synthesis of cyclisation precursor - Strategy 3

Since our attempts to synthesise aldehyde **223** in one step had only afforded low yields of product at best, it was decided to synthesise it in two steps using a cross metathe-

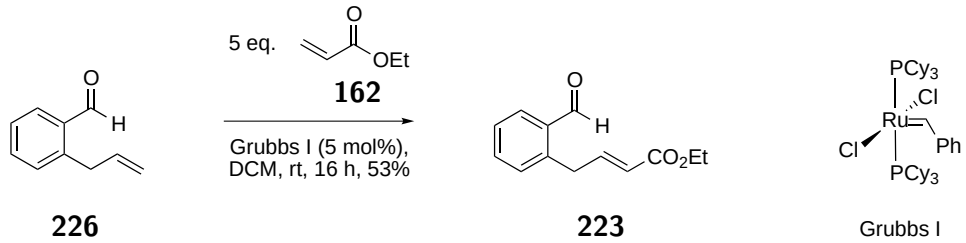
sis protocol. Hence, a Suzuki cross coupling reaction between 2-formylphenylboronic acid **224** and allyl bromide **225** was carried out, following a procedure by Jagdale *et al.* (Scheme 3.18).[103] Treatment of boronic acid **224** with allyl bromide **225**, 2.5 mol% palladium chloride catalyst, triphenyl phosphine ligand and sodium carbonate base in THF at reflux for four hours afforded the desired 2-allylbenzaldehyde **226** in 83% yield.



224 **225** **226**

Scheme 3.18: **Suzuki cross coupling reaction to afford 2-allylbenzaldehyde 226**

The second step of the synthesis involved carrying out a cross metathesis reaction of allylbenzaldehyde **226** with ethyl acrylate.[107,108] The allylbenzaldehyde maybe classified as a type I olefin, and the acrylate as a type II olefin, which was predicted to provide a highly selective cross methathesis reaction for the synthesis of aldehdye **223**.[97] Therefore, the reaction was carried out in DCM at reflux, with an excess of acrylate, and a low loading (0.5 mol%) of Grubbs I catalyst, as shown in Scheme 3.19. After leaving the reaction to stir overnight, the reaction solvent was evaporated, and the crude mixture purified by column chromatography to yield the desired cyclisation substrate **223** in a moderate 53% yield.



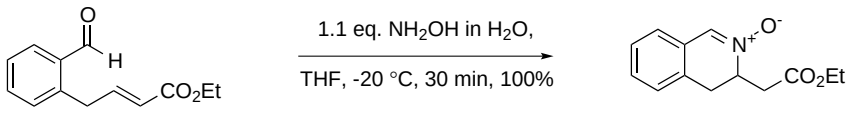
226 **223** Grubbs I

Scheme 3.19: **Cross metathesis reaction of 2-allylbenzaldehyde 226 with ethyl acrylate 162**

3.4.4 Cyclisation reaction

After successfully synthesising the aldehyde precursor **223**, we turned our attention to its use as a substrate for nitrone formation. Using the optimised conditions obtained previously, we added a slight excess of aqueous hydroxylamine solution to aldehyde **223** in THF at -20 °C. The yellow solution became cloudy over time. After filtering, a small amount of cream solid was obtained, however this quickly melted and as a consequence was re-dissolved in extra THF. The combined THF extracts were dried and the solvent removed under vacuum to yield a yellow oil. ^{1}H NMR spectrascopic analysis revealed that a single, clean product had formed. A singlet peak at δ 8 ppm, as well as the presence

of three resonances with multiplicities corresponding to a $CH_2-CH-CH_2$ fragment indicated formation of a dihydroisoquinoline based nitrone **227** (Scheme 3.20) with HRMS and COSY and HSQC NMR analyses confirming that nitrone **227** was the product.

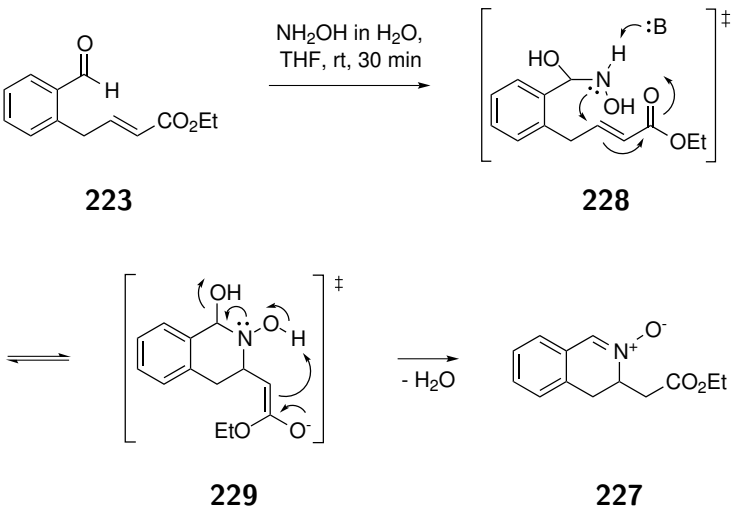


223 **227**

Scheme 3.20: **Cyclisation reaction of aldehyde 223**

3.4.5 Reaction mechanism

It is proposed that this six membered cyclic nitrone had been formed in an identical manner to the isoindole based nitrones described previously (Scheme 3.21). Therefore, reaction of hydroxylamine with the formyl group affords the hydroxyamino alcohol intermediate **228**, with the nitrogen atom of this intermediate then undergoing nucleophilic attack at the α,β-unsaturated ester to form the enolate intermediate **229**. Enolate protonation followed by dehydration affords the dihydroisoquinoline nitrone **227**. In this case, the presence of the extra methylene group in the six membered ring means that nitrone formation takes place and remains at the monosubstituted position conjugated to the aromatic ring.



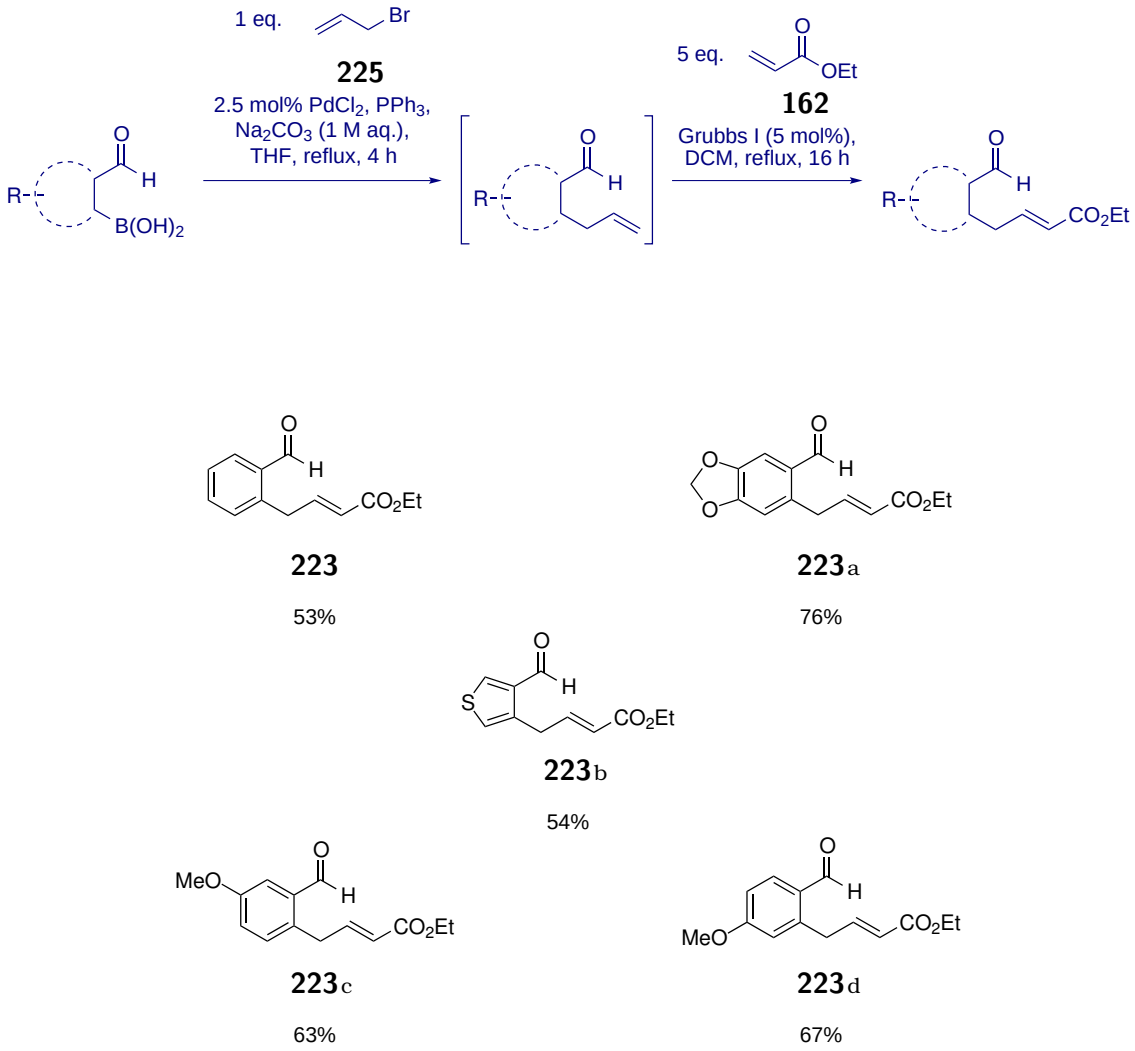
223 **228**

229 **227**

Scheme 3.21: **Proposed reaction mechanism for the synthesis of dihydroisoquinoline based nitrones**

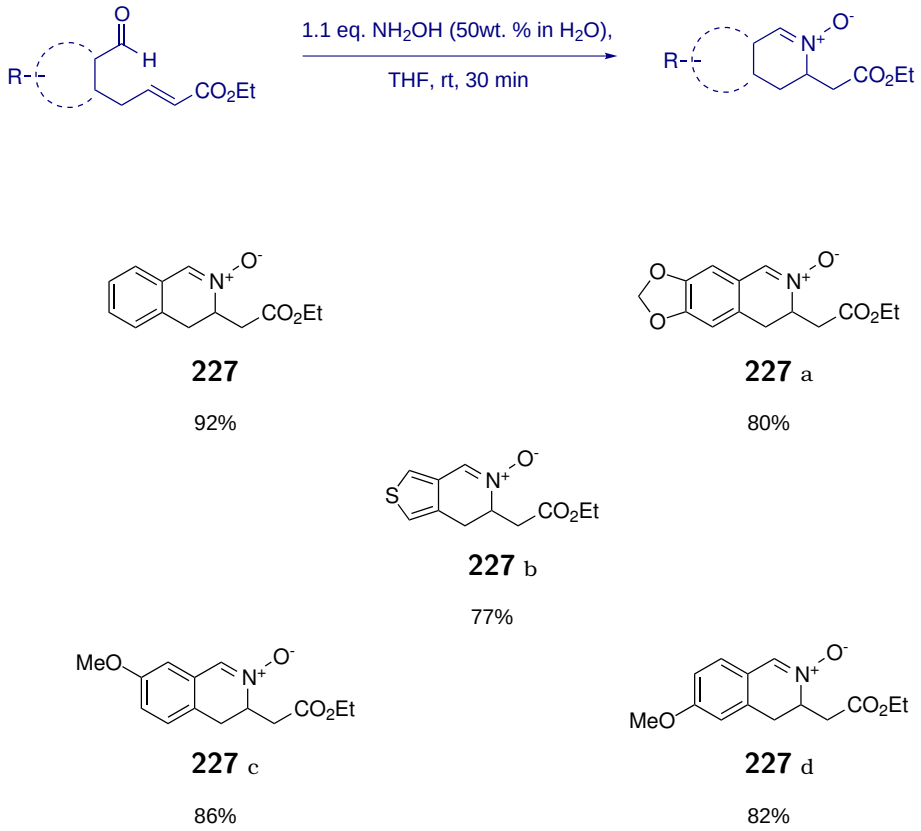
3.4.6 Reaction scope

We then carried out a screen of a range of *ortho*-formyl phenyl boronic acid substrates to assess the scope and limitation of this six membered cyclic nitrone forming reaction. The relatively limited size of the screen was due to the limited number of commercially available formyl aryl boronic acids, that had the key *ortho*- substitution pattern of their formyl and boronic acid groups. During the course of the synthesis of aldehyde **223**, we found it was possible to carry out the cross metathesis reaction on the crude Suzuki cross-coupled material without any observable detrimental affect on the overall yield.



Scheme 3.22: **Synthesis of ester substrates for dihydroisoquinoline synthesis**

In total, five aldehydes **223**-**223**d were successfully synthesised in 53-76% yields. A sixth boronic acid containing a furan backbone did not undergo any cross coupling with allyl bromide using our conditions, and so was abandoned. The five aldehydes were then reacted with hydroxylamine using our standard conditions at room temperature to form the desired cyclic nitrones **227**-**227**d in 80-92% yield.



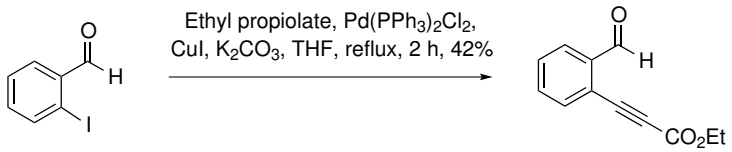
Scheme 3.23: **Synthesis of dihydroisoquinoline nitrones**

3.5 Synthesis of a cyclic hydroxamic acid derivative

Having explored the potential to create six-membered nitrones, we next wanted to investigate what would happen if a starting material containing an extra degree of unsaturation was subjected to our cyclisation reaction conditions, i.e. if an alkyne was present in the acceptor fragment rather than an alkene.

3.5.1 Synthesis of aldehyde precursor

To synthesise the desired starting material, we needed to couple ethyl propiolate with a 2-halobenzaldehyde. Only two procedures were available in the literature, and attempts at carrying out the first ($Pd^{(0)}$ coupling of ethyl propiolate with 2-bromobenzaldehyde **137**) by Zhou *et al.*,[109] consistently gave a complex mixture of compounds, none of which were the desired product. The same results were observed when these reaction conditions were applied to acetal protected bromo-benzaldehyde **147**. Attempts at a second procedure, coupling 2-iodobenzaldehyde with the propiolate, were slightly more successful,[110] however this reaction was still proving to be inconsistent. Following the reaction by LCMS analysis revealed that after two hours the reaction mixture became extremely complex. Working up the reaction at two hours however, enabled a 42% yield of the cross coupled product **231** to be obtained after purification (Scheme 3.24).

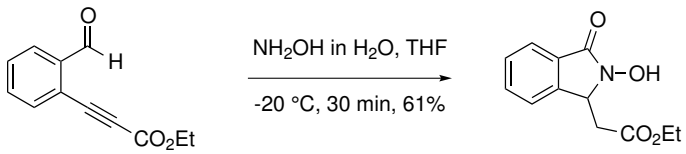


230 **231**

Scheme 3.24: **Sonogashira cross coupling reaction to afford alkyne 231**

3.5.2 Cyclisation reaction

With the starting material in hand, we then reacted it with hydroxylamine using the optimised conditions developed previously. During the course of the reaction, no solid was formed, and so the reaction was worked up by extracting into DCM and water, before drying and removing the solvent under vacuum. The crude ^{1}H NMR spectrum showed a single, clean product, however none of the peaks corresponded to those seen previously in the spectra of previous cyclisation reactions, so full analysis was carried out to determine the structure. HRMS analysis revealed the compound had the formula: $C_{12}H_{13}NO_4$, thus had seven double bond equivalents. Along with four aromatic protons, and the presence of an ethyl ester group, the ^{1}H NMR spectrum also revealed two resonances with diastereotopic multiplicities corresponding to a $CH-CH_2$ fragment. Both the IR and ^{13}C spectra showed the compound contained two carbonyl groups; one of which was part of the ester group, and one of which was unidentified. We assumed that the reaction had taken place *via* 1,4-addition of an intermediate hydroxyamino alcohol to the alkyne fragment of **231**, to afford a five membered ring, which in comparison with the data from the spectroscopic analysis, led us to conclude that the product of the reaction was the cyclic hydroxamic acid **232**.

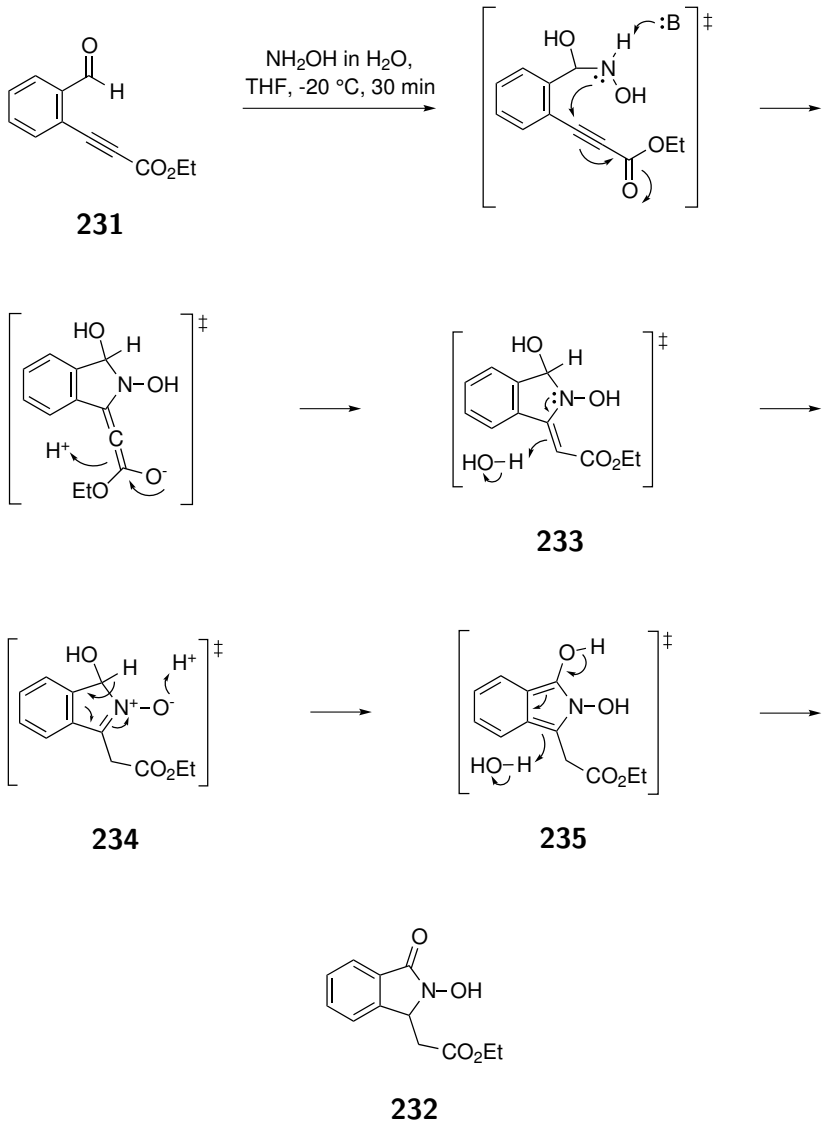


231 **232**

Scheme 3.25: **Synthesis of cyclic hydroxamic acid 232**

3.5.3 Reaction mechanism

For the reaction mechanism to form the cyclic hydroxamic acid **232** from the alkynyl aldehyde **231**, we propose that a 5-*exo*-trig cyclisation reaction of the intermediate hydroxyamino alcohol occurs to afford an enolate that is protonated to give *N*-hydroxy enamine **233** (Scheme 3.26). This is in accordance with the first half of the mechanisms proposed previously for the isoindole and dihydroisoquinoline nitrone syntheses. However, for this reaction we propose that enamine **233** then rearranges to the nitrone compound **234**, which tautomerises to afford cyclic hydroxamic acid **232**.



Scheme 3.26: **Proposed reaction mechanism for the synthesis of cyclic hydroxamic acid 232**

Interestingly, when this cyclisation reaction was later performed at -20 °C, a solid precipitate was formed which was filtered off and analysed by NMR spectroscopy. It was found to correspond to the nitrone intermediate **234**, shown in Figure 3.1. Therefore, the ^{1}H NMR

spectrum revealed the presence of diagnostic peaks at δ 8.76 ppm for an OH resonance, δ 6.15 for the C*H*OH proton and an apparent AB doublet at δ 3.92 corresponding to the CH_2 group. As expected, the resonance corresponding to the OH peak of **234** disappeared when the ^{1}H NMR spectrum was run in methanol. During attempts to recrystallise the solid for X-ray crystal structure analysis, the kinetic intermediate **234** was shown to be transformed (by NMR analysis) into the cyclic hydroxamic acid product **232** over time.

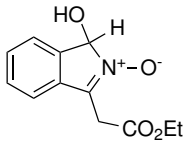
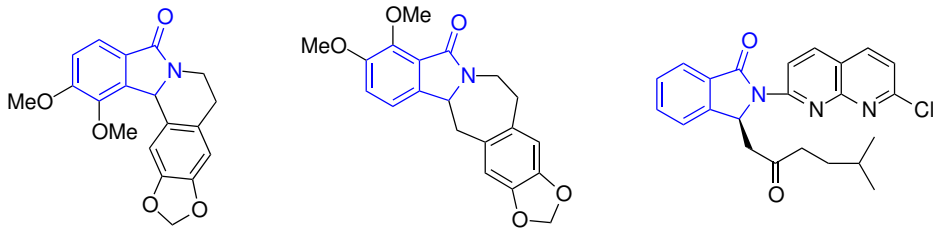


Figure 3.1: **Intermediate nitrone 234**

3.5.4 Conclusion

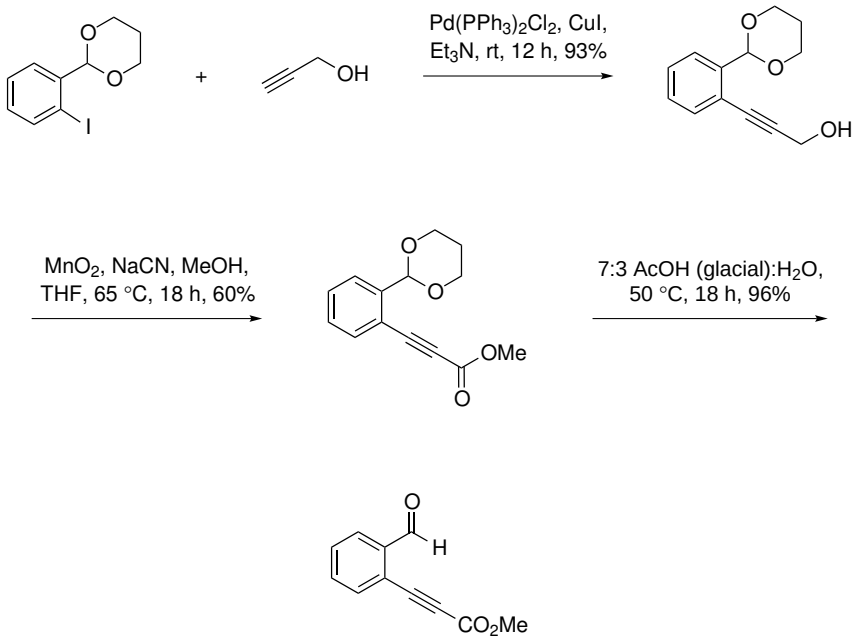
Extending the methodology to include alkyne containing starting materials led to the synthesis of an unexpected class of products: cyclic hydroxamic acids. This result is synthetically very interesting, due to the fact that the bicyclic backbone of this structure is present in numerous natural products and biologically active compounds, such as those shown in Figure 3.2.



Nuevamine Lennoxamine Pagoclone

Figure 3.2: **Potential natural products that could be synthesised using our cyclic hydroxamic acid synthesis**

Difficulties with the Sonogashira reaction used to prepare the starting alkyne substrate for this cyclisation reaction prevented further exploration of the scope and limitation of this methodology. However, recent work by another student within the SDB group has identified a facile route (Scheme 3.27) to these alkyne substrates **236** and a range of cyclisation reactions are currently under exploration.

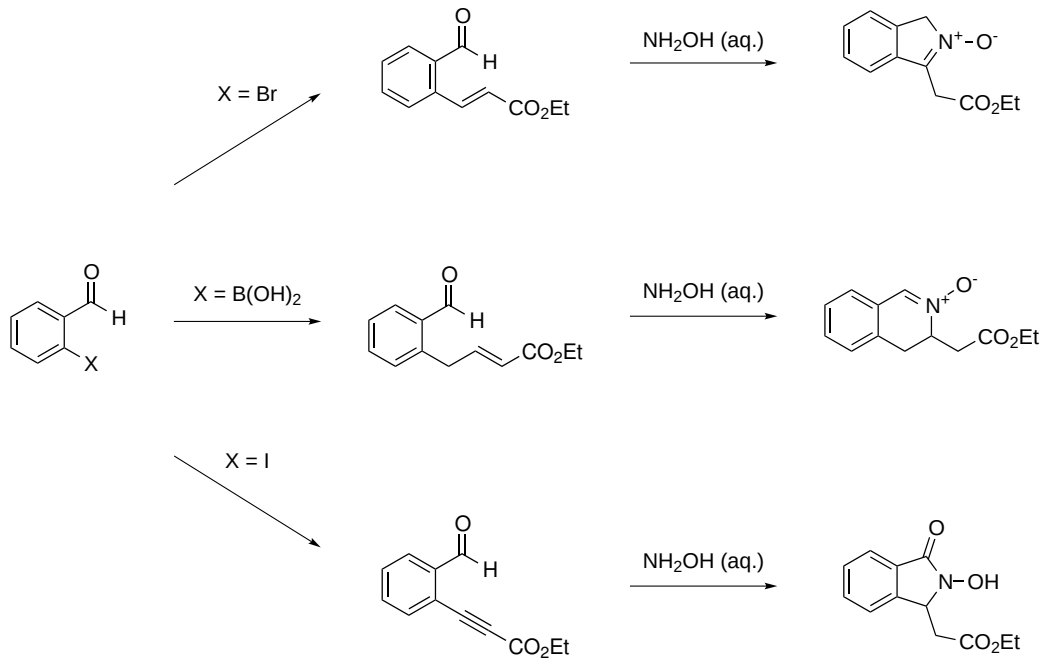


236

Scheme 3.27: **New protocol for the synthesis of alkyne containing cyclisation substrates**

3.6 Conclusion

In this chapter we have identified optimum conditions for carrying out novel cyclisation reactions between aryl aldehydes and hydroxylamine to afford a range of isoindole based nitrones. We then adapted the starting material structure to successfully synthesise a small library of dihydroisoquinoline based nitrones. Lastly, we looked at the reaction of an alkynyl containing cyclisation substrate, which yielded a completely different and synthetically valuable hydroxamic acid scaffold. All of the final products described in this chapter have been synthesised using short routes, in moderate to high yields (Scheme 6.1). This highlights how our cyclisation methodology can be used to prepare a diverse library of bicyclic heterocyclic compounds that can be accessed from small, commercially available starting materials, using uncomplicated reagents and procedures that are amenable to scale-up.



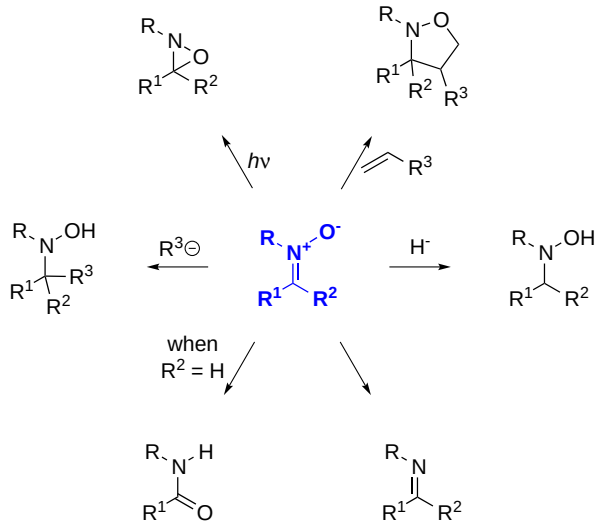
Scheme 3.28: **Range of bicyclic heterocycles synthesised from 2-halo benzaldehydes**

Chapter 4

Nitrone Reactions

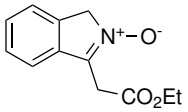
4.1 Introduction

In the previous two chapters we discussed the discovery, mechanism, and optimisation of a novel nitrone forming reaction, and explored the scope of this methodology. In the literature review (Chapter 1) we highlighted the fact that nitrones can partake in a wide variety of reactions, a short selection of which are shown in Scheme 4.1.[35] Due to this precedent, we wished to explore the reactivity of our isoindole nitrones towards a number of those transformations, thus showing the potential utility of our methodology for synthesis.



Scheme 4.1: **A summary of commonly employed nitrone reactions**

All of the reactions investigated were carried out using the parent nitrone (Figure 4.1) as a representative substrate.

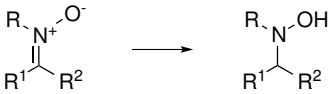


165

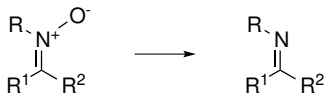
Figure 4.1: **Standard substrate for investigating nitrone reactions**

4.2 Reduction

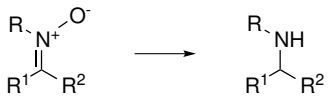
A key source for an overview of nitrone reactions is a book by Henry Feuer.[35] According to this, there are two key reaction pathways available when reducing nitrones: a) reduction to the hydroxylamine, and b) reduction to the imine *via* deoxygenation. We attempted to carry out both of these transformations as well as a third, the reduction of the nitrone functionality to an amine (see Figure 4.2).



(a) *Reduction to hydroxylamine*



(b) *Reduction to imine*



(c) *Reduction to amine*

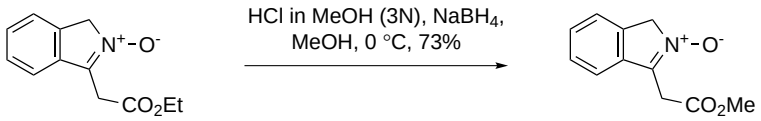
Figure 4.2: **Planned nitrone reductions**

4.2.1 Reduction to a hydroxylamine

To investigate the reduction of nitrone **165** to the hydroxylamine, we carried out a screen of four literature procedures. As shown in Table 4.1, the nitrone (2.00 mmol) was reacted, in turn, with sodium borohydride,[111] sodium borohydride and methanolic hydrogen chloride,[112] sodium cyanoborohydride,[112] and L-selectride.[113] The reactions with sodium borohydride and L-selectride returned solely starting material (entries 1 and 2). The reaction containing methanolic hydrogen chloride and sodium borohydride afforded the transesterified product, nitrone **237** (entry 3, Scheme 4.2).

Table 4.1: **Screen of nitrone reduction reactions to afford hydroxylamine**

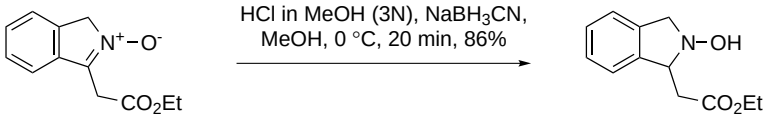
Entry	Reducing agent	Result
1	$NaBH_4$	no reaction
2	L-selectride	no reaction
3	$NaBH_4$, HCl	transesterification to methyl ester
4	$NaBH_3CN$, HCl	reduction to hydroxylamine



165 **237**

Scheme 4.2: **Transesterification of nitrone 165**

Fortunately, the reaction with sodium cyanoborohydride, following the procedure of Maeda *et al.*,[112] was successful and afforded the desired hydroxylamine product (Scheme 4.3). Sodium cyanoborohydride was added portionwise to a cooled solution of nitrone and methanolic hydrogen chloride in methanol. After twenty minutes the reaction was judged to be complete by TLC analysis, and the product, isoindolinol **238**, was afforded as a yellow oil in 86% yield after work up and purification. The compound structure was confirmed by NMR, IR and HRMS analysis, with the diagnostic data being the CH-CH_2 connectivity revealed by the ^{1}H COSY NMR spectrum, and a broad O-H stretch in the IR spectrum at 3343 cm^{-1}.



165 **238**

Scheme 4.3: **Reduction of nitrone 165 to hydroxylamine 238**

4.2.2 Reduction to an imine

The second nitrone reduction investigated was reduction to the imine - a transformation also referred to as a deoxygenation reaction. Generally, the reaction involves a Lewis acid coordinating to the negatively charged nitrone oxygen atom, which increases its reactivity towards the reducing reagent.

In order to reduce nitrone **165** to the imine, several literature procedures were attempted as outlined in Table 4.2. Metal mediated deoxygenations using indium trichloride[114] and titanium trichloride[115] returned only starting material, while mixed metal systems

such as copper iodide and zinc, and a radical based system using lithium and 4,4'-di-*tert*-butylbiphenyl (DTBB),[116] all showed no reaction (entries 1-4). The use of tributyl phosphine afforded a complex mixture of compounds in the ^{1}H NMR spectrum of the crude product (entry 5).

165 **239**

Scheme 4.4: **Attempts to deoxygenate nitrone 165 to afford imine 239**

Table 4.2: **Reduction to imine screen**

Entry	Reagents	Result
1	$InCl_3$	no reaction
2	$TiCl_3$	no reaction
3	CuI, Zn	no reaction
4	Li, DTBB	no reaction
5	PBu_3	unable to interpret
6	$TiCl_4$, $LiAlH_4$, Et_3N	starting material and unidentified product
7	Zn, $AlCl_3 \cdot 6\,H_2O$	starting material and unidentified product
8	Sm, $CoCl_2 \cdot 6\,H_2O$	starting material and unidentified product

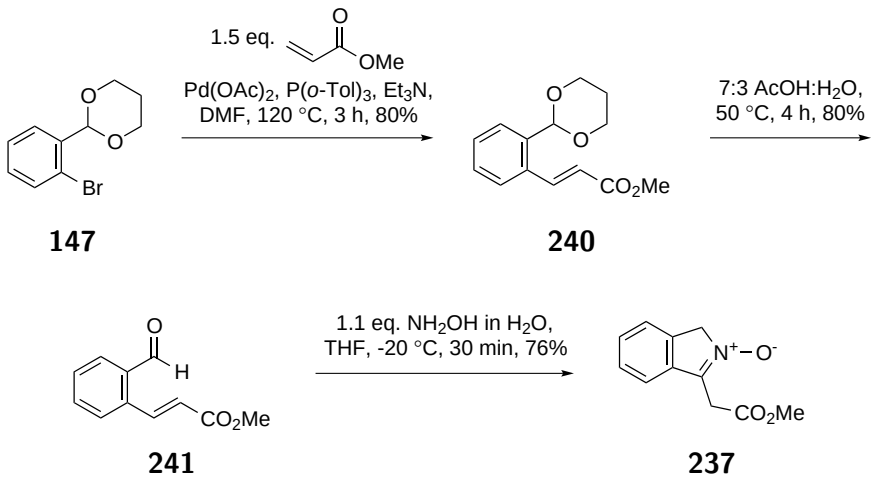
There were three systems, however, that gave interesting results. These were: titanium trichloride with lithium aluminium hydride and triethylamine,[117] aluminium trichloride and zinc,[118] and cobalt choride and samarium (entries 6-8).[119] All three of these experiments showed starting material **165** in their crude ^{1}H NMR spectra, however they also revealed peaks corresponding to a single, unidentified compound. Analysis of the peaks of this new product in the crude ^{1}H NMR spectra did not correspond to the expected imine. Attempts to purify the combined crude materials by column chromatography resulted in degradation, so we decided to try and increase the conversion in each of the three procedures in an effort to determine the structure of the unexpected reaction product.

The procedure employed by Taniguchi *et al.*, which used titanium tetrachloride with lithium aluminium hydride and triethylamine,[117] showed the highest percentage of this unidentified product by ^{1}H NMR spectroscopic analysis. The procedure for this reaction involved the addition of titanium tetrachloride to THF at 0 °C, followed by slow addition of lithium aluminium hydride to create a black reaction mixture. This reaction was stirred

at room temperature for fifteen minutes, then triethylamine was added and the combined mixture added to a solution of nitrone **165** in THF. After thirty minutes the reaction was worked up by the addition of water, filtering the reaction mixture, extracting the liquors with DCM and removing the solvent under reduced pressure to afford crude material. Our efforts to increase the conversion of nitrone **165** to the unidentified product began by increasing the reaction time from the documented thirty minutes. No improvement was seen in the reaction conversion after twenty four hours at room temperature. Experiments in heating the reaction and the addition of extra aliquots of the titanium/hydride/base mixture all resulted in complex ^{1}H NMR spectra which could not be interpreted.

We then attempted to increase the conversion in the zinc and aluminium hexahydrate mediated reduction reaction that followed the procedure by Dutta.[118] This reaction involved the addition of a solution of nitrone **165** in THF to a vigorously stirred solution of zinc and aluminium trichloride hexahydrate at room temperature, followed by working the reaction up in the same manner as the Taniguchi procedure. Initially, the zinc and aluminium reaction was repeated and left for longer, however this yielded the same result as previously. Heating the reaction to reflux for one hour pushed the conversion to 50%, but the reaction stalled and no improvement was seen after 3 hours. Leaving the reaction for longer, and increasing the equivalents of zinc and aluminium resulted in decomposition.

To investigate the cobalt based deoxygenation reaction by Zhang *et al.*,[119] we opted to synthesise the methyl ester containing nitrone, in an effort to simplify the crude ^{1}H NMR spectra. Therefore, acetal **147** was reacted with methyl acrylate in a Heck cross coupling reaction (Scheme 4.5) to produce the coupled product **240**. After an acid catalysed deprotection, aldehyde **241** was afforded in 80% yield. This was then reacted with hydroxylamine to form nitrone **237** in 76% yield.



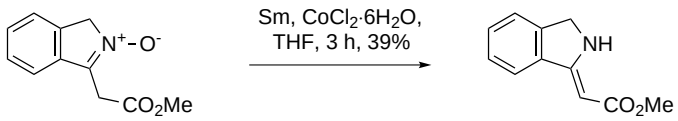
Scheme 4.5: **Synthesis of methyl ester nitrone 237**

Nitrone **237** was added to a solution of samarium and cobalt chloride in THF at room temperature, and the reaction monitored by TLC analysis. After three hours the TLC

plate showed that all of the nitrone starting material had been consumed and only one spot was visible, so the reaction was worked up. The ^{1}H NMR spectrum showed the as yet unidentified product to be the sole compound present, and it required no further purification.

Structural determination

HRMS analysis showed that the unidentified product had the same molecular formula as the expected imine product, $C_{11}H_{11}NO_2$, thus having seven double bond equivalents. Alongside peaks corresponding to resonances from the four aromatic protons and the three protons of the methyl group, ^{1}H NMR spectroscopic analysis showed a broad peak at δ 8.24 ppm, a singlet peak at δ 5.21 ppm integrating to one proton, and a singlet peak at δ 4.69 ppm integrating to two protons. We therefore proposed that the samarium/cobalt reduction protocol had yielded enamine **242** as the reaction product (Scheme 4.6). This is supported by the presence of a peak at 3422 cm^{-1} and a sharp peak at 1653 cm^{-1} in the IR spectrum, as well as an indicative peak at δ 161.23 in the ^{13}C pendant NMR spectrum corresponding to a quarternary carbon. Analysis by NOE spectroscopy showed an interaction between the enamine proton and the aromatic proton shown in Figure 4.3. Therefore, the enamine was assigned as having a *Z*-configuration at its double bond. Ultimately the enamine compound **242** proved to be unstable, and rapid degradation was observed in the ^{1}H NMR spectrum when a sample was left at room temperature overnight.



237 **242**

Scheme 4.6: **Reduction of nitrone 237 to enamine 242**

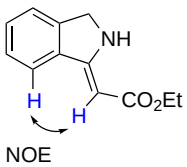
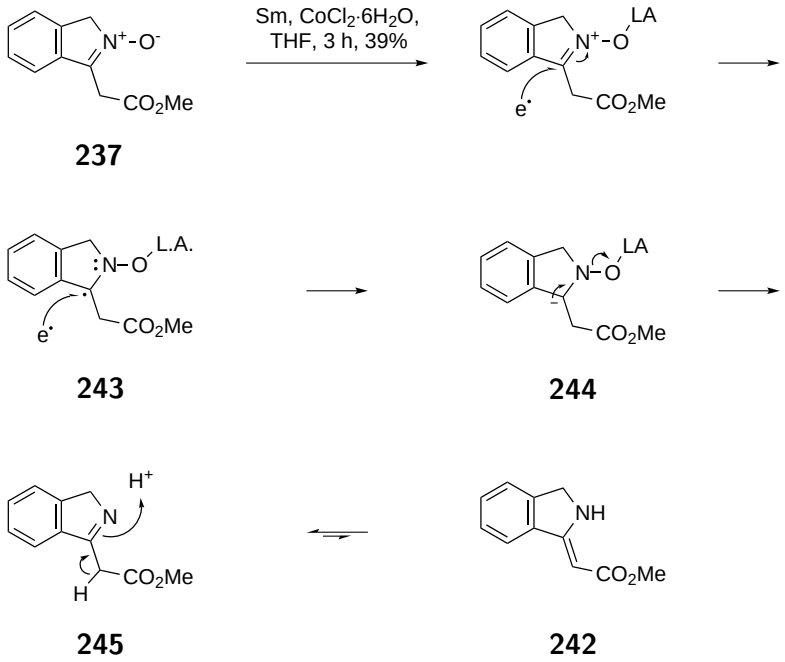


Figure 4.3: **NOE analysis of enamine 242 revealing its *Z*-configuration**

Mechanistic investigation

To gain an insight into how this enamine forming reaction worked, it was carried out with solely samarium and cobalt chloride in turn. Both afforded clean starting material, proving that the two reagents work in tandem. We propose that the cobalt acts as a Lewis acid to coordinate the negatively charged nitrone oxygen atom, whilst reduction of Sm^{3+} to Sm^{2+} provides an electron which attacks at the nitrone carbon atom to provide a radical species **243**. A second electron attacks the radical species to afford the anion **244**

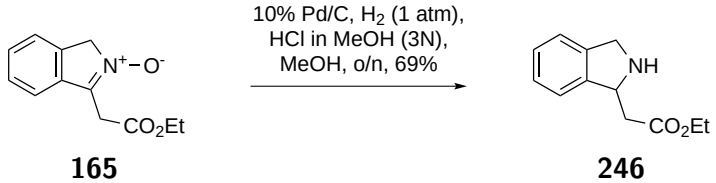
which stabilises by forming the C=N double bond, cleaving the N-O bond in the process, to give the iminium ion **245**, which tautomerises to the enamine **242** (Scheme 4.7).



Scheme 4.7: **Proposed mechanism for the synthesis of enamine 242 from nitrone 237**

4.2.3 Reduction to an amine

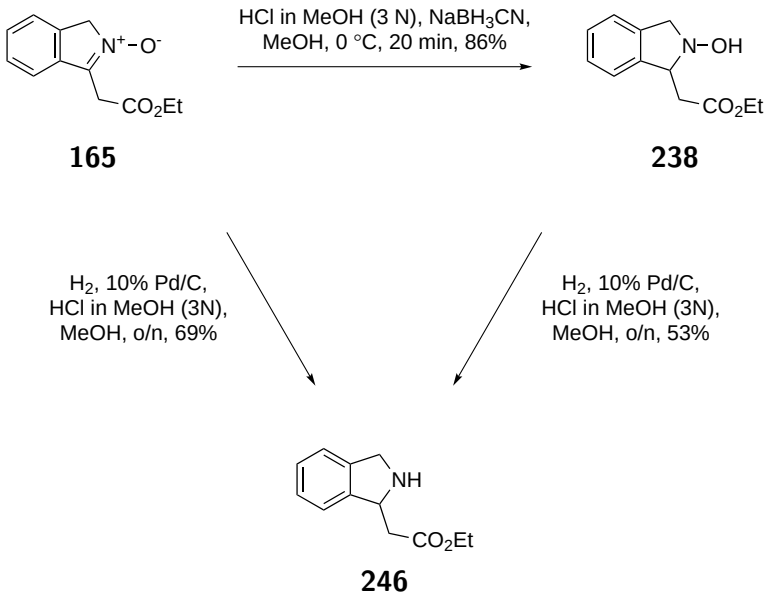
Finally, we attempted a third reduction reaction, to reduce nitrone **165** to the amine. A palladium catalysed hydrogenation procedure by Racine *et al.* was followed as shown in Scheme 4.8.[120] A solution of nitrone **165** in methanol was added to a solution of palladium on carbon catalyst in methanolic hydrogen chloride. The reaction was placed under a hydrogen atmostphere (1 atm) and left to stir overnight. After filtering through Celite, the crude reaction material was evaporated and purified by column chromatography to afford amine **246** as a yellow oil in a moderate 69% yield.



Scheme 4.8: **Reduction of nitrone 165 to amine 246**

Upon working up an initial attempt at the hydrogenation reaction after six hours, the ^{1}H NMR spectrum showed peaks corresponding to hydroxylamine **238** and amine **246**, suggesting that the hydroxylamine was an intermediate in the nitrone-to-amine transformation. To investigate this result, we took nitrone **165** and the previously synthesised hydroxylamine separately, and subjected them both to the hydrogenation conditions

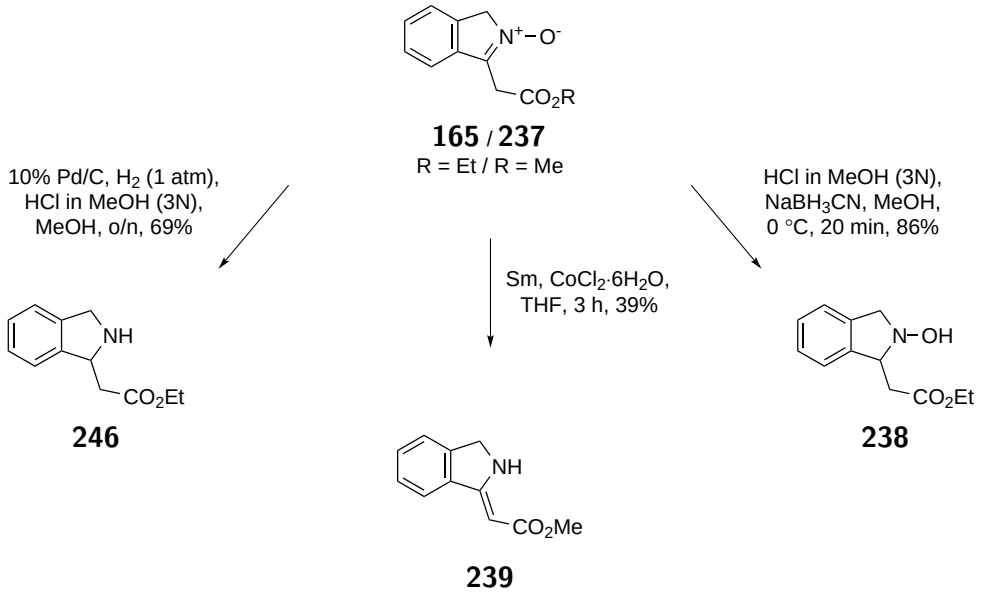
(Scheme 4.9). Amine **246** was the sole product from both of these reactions. We conclude, therefore, that under the palladium catalysed reaction conditions, the nitrone was first reduced to the hydroxylamine by addition of hydrogen across the nitrone moiety. A second molecule of hydrogen then added across the nitrogen-oxygen bond, cleaving it in the process, to afford the amine **246**.



Scheme 4.9: **Reduction of nitrone 165 to amine 246 *via* hydroxylamine 238**

4.2.4 Conclusion

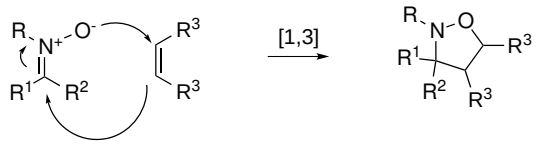
Scheme 4.10 summarises the three transformations described in this section. Nitrones **165** and **237** can be selectively reduced to the hydroxylamine **238** using methanolic hydrogen chloride and sodium cyanoborohydride, to the enamine **242** using samarium and cobalt chloride, and to the amine **246** using a palladium catalysed hydrogenation reaction.



Scheme 4.10: **Summary of the reductive transformations of nitrones 165 and 237**

4.3 1,3-Dipolar cycloaddition

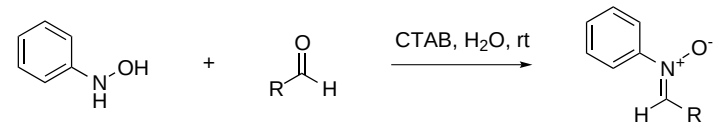
1,3-dipolar cycloaddition reactions are the most widely used reactions of nitrones, whereby a dipolarophile is reacted with a nitrone to form an isoxazolidine product, as shown below in Scheme 4.11.



Scheme 4.11: **Generic 1,3-dipolar cycloaddition reaction with an alkene dipolarophile**

An example of this chemistry is neatly demonstrated by Chatterjee *et al.*, whose methodology involved reaction of a hydroxylamine with an aldehyde to afford a nitrone that then reacts *in-situ* with an electron deficient alkene.[121] For example, nitrones **247** were reacted with ethyl acrylate **162** in 1,3-dipolar cycloaddition reactions to yield isoxazolidine products **248** and **249**. Generally, formation of the five-substituted isoxazolidines **249** was favoured over the four-substituted product **248**, and in some cases the *trans* isomer of

249 was formed as an exclusive product (Scheme 4.12).

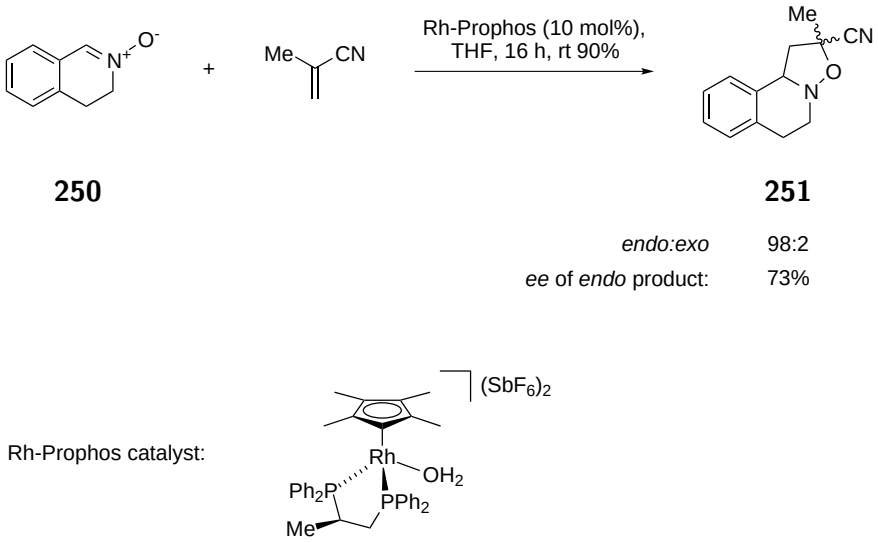


	248 *exo:endo*	:	**249** *cis:trans*
R = *p*-$OMeC_6H_4$	39 (100:0)	:	63 (100:0)
R = *o*-$NO_2C_6H_4$	0	:	100 (32:68)
R = 2,5-diOMe-C_6H_3	0	:	100 (0:100)

Scheme 4.12: **Chatterjee's one-pot synthesis of isoxazolidines 248 and 249**

CTAB: cetyl trimethylammonium bromide, a cationic surfactant.

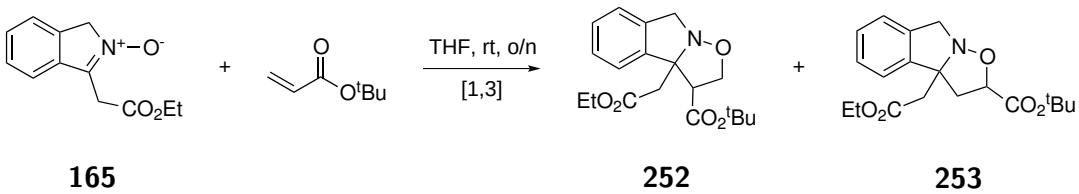
Advances in asymmetric versions of the reaction means that isoxazolidines can now be synthesised with good regio-, stereo- and enantioselectivity. Carmona *et al.* in particular, have focussed their research in this area, employing rhodium and iridium chiral catalysts for stereocontrol. One such example is their 1,3-dipolar cycloaddition reaction of nitrone **250** and methacrylonitrile in the presence of Rh-Prophos catalyst, which regioselectively synthesised the five-substituted isoxazolidine **251** with a 98:2 *endo*:*exo* selectivity and with 73% *ee* for the endo isomer (Scheme 4.13).[122]



Scheme 4.13: **Carmona's regioselective synthesis of five-substituted isoxazolidine 251**

4.3.1 Reaction of nitrone with *tert*-butyl acrylate

For our work, we decided to react nitrone **165** with *tert*-butyl acrylate. It was expected that the nitrone would undergo a 1,3-dipolar cycloaddition reaction to afford the 4- and 5-substituted isoxazolidine regioisomers **252** and **253** (Scheme 4.14).



Scheme 4.14: **Expected 1,3-dipolar cycloaddition reaction of nitrone 165 with *tert*-butyl acrylate**

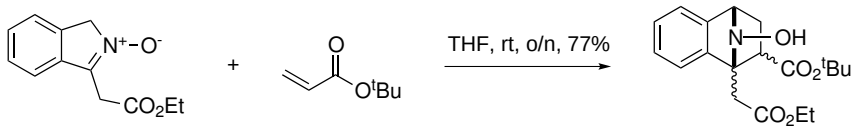
An excess of *tert*-butyl acrylate was added to a solution of nitrone **165** in THF, and the reaction stirred overnight at room temperature. The complex crude ^{1}H NMR spectrum showed that all of the starting material **165** had been consumed and that more than one product was present. Similar patterns of peaks in the ^{1}H NMR spectrum were observed, indicating that the products were similar in structure. HRMS analysis revealed that the molecular formula corresponding to regiosomers **252** and **253** was present ($C_{19}H_{25}NO_5$), so purification of the crude mixture by column chromatography was attempted. Fractions were collected that were one spot by TLC analysis and one peak according to the LCMS chromatogram, yet they showed several compounds to be present in the ^{1}H NMR spectra. It was noted by ^{1}H spectroscopic analysis that the ratio of these compounds changed over time. This led us to initially conclude that we had purified one regioisomer of the expected cycloadducts, but had been unable to separate its configurational isomers.

4.3.2 Structural determination of unknown product

Full spectroscopic analysis was carried out on a sample that had been left to stand for a day, and which, by ^{1}H NMR spectroscopy, consistently showed the same ratio of compounds over time. Due to the complexity of the number of peaks with similar patterns and chemical shifts, we focussed our structural elucidation on the analysis of the peaks corresponding to the major product.

All four protons of the aromatic ring were identified, as were both of the expected ester groups, in the ^{1}H NMR spectrum. The remaining peaks in the ^{1}H NMR spectrum integrated to six protons, all of which were attached to carbon atoms as verified by HSQC analysis. We had expected to integrate peaks corresponding to seven protons for the expected isoxazolidine cycloadducts **252** and **253** (Scheme 4.14), thus we concluded that an -OH or -NH group must be present. Also, a CH$-$CH$_2-$CH connectivity was discovered by COSY and ^{13}C DEPT analysis which did not match with either of the expected isoxazolidine structures.

Thus, we were surprised to discover that the expected tricyclic core of cycloadducts **252** and **253** had not been synthesised. However, knowing that the reaction product had the same molecular formula as the expected isoxazolidine products, we knew that an alternative tricylic compound must have been synthesised. Eventually, we deduced that the the major product of the attempted 1,3-dipolar cycloaddition reaction was an isomer of the bridged hydroxylamine product **254**, shown in Scheme 4.15.



165 **254**

Scheme 4.15: **Major product formed from reaction of nitrone 165 with *tert*-butyl acrylate**

This conclusion was later verified by the NMR analysis suite at GlaxoSmithKline, which also confirmed that the minor peaks in the NMR spectra correspond to the same structure, due to the bridged hydroxylamine heterocycle **254** existing as several conformers at room temperature. The angle with which the nitrogen-oxygen bond sits over the molecule also affects the NMR spectra. A ^{1}H NMR spectrum of a five day old $CDCl_3$ sample shows the average ratio of the different conformers present to be 9:3:2 (Figure 4.4).

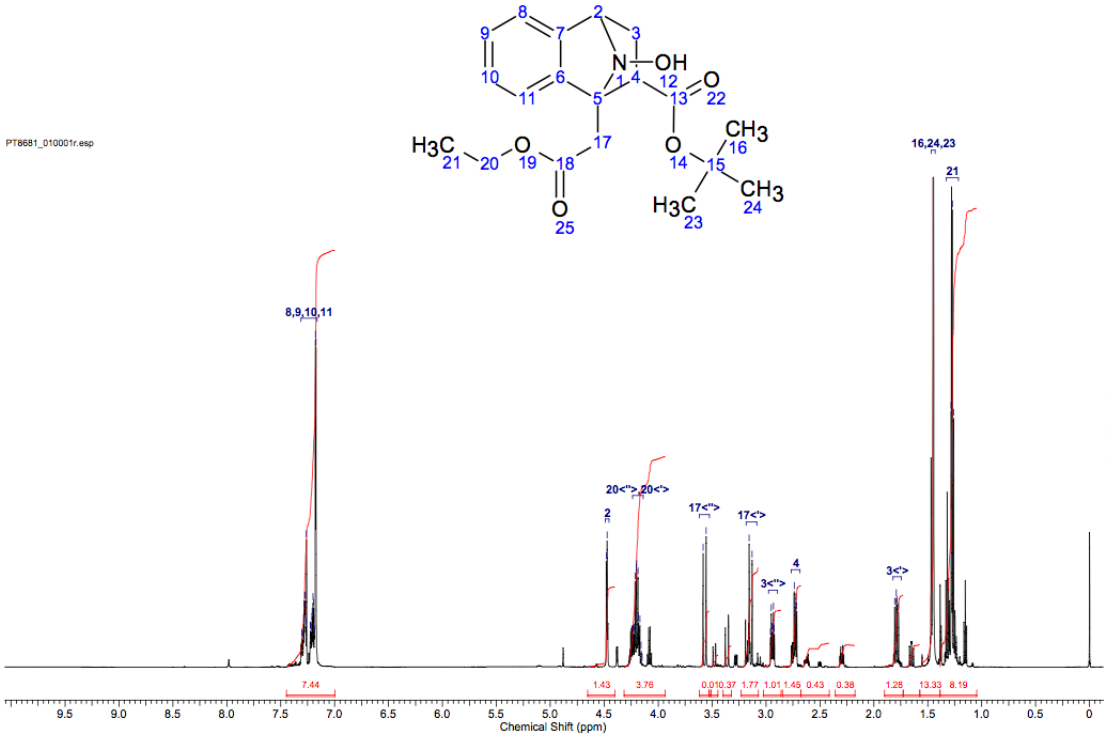
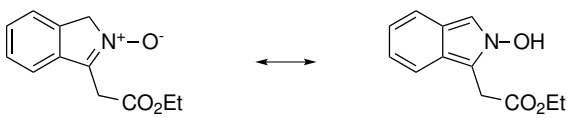


Figure 4.4: **^{1}H NMR spectrum of the bridged hydroxylamine 254 product**

4.3.3 Investigating the reaction mechanism for formation of bridged hydroxylamine

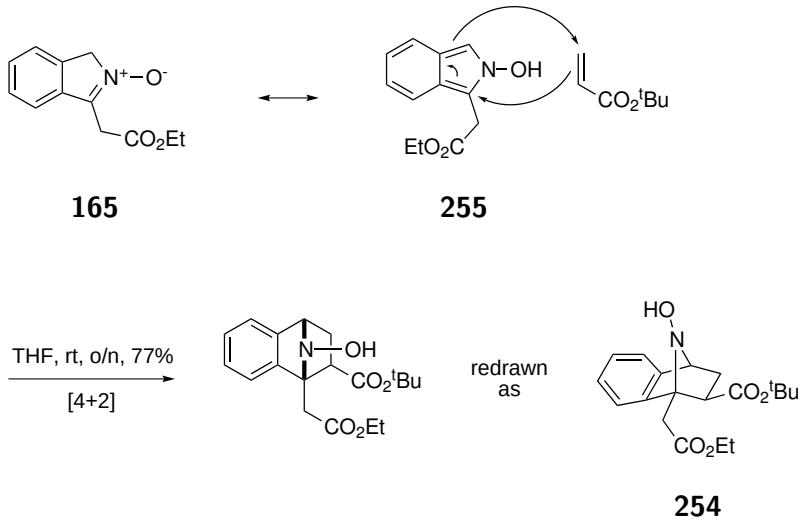
In the reaction of nitrone **165** with *tert*-butyl acrylate, we predicted that a 1,3-dipolar cycloaddition reaction would take place to form isoxazolidine products, however, a bridged hydroxylamine scaffold **254** was formed instead. We propose that the six membered ring of this scaffold must have been formed through a [4+2] Diels-Alder cycloaddition reaction. This could only be possible if the nitrone was reacting *via* its isoindole tautomer (Scheme 4.16), which we had previously proposed as a transient intermediate in the mechanism for the formation of nitrone **165** (Chapter 2, Section 2.6).



165 **255**

Scheme 4.16: **Tautomerisation between nitrone 165 and isoindole *N*-oxide 255**

In this [4+2] cycloaddition reaction we propose that the nitrone **165** tautomerises to the isoindole-*N*-oxide **255**, which then undergoes a [4+2] Diels-Alder cycloaddition reaction with *tert*-butyl acrylate to afford a bicyclic adduct (Scheme 4.17).

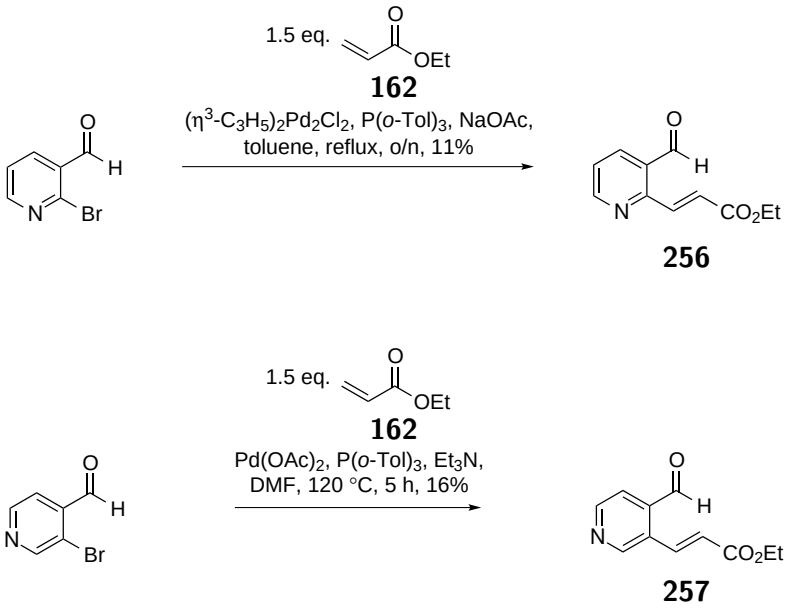


Scheme 4.17: **Proposed [4+2] cycloaddition reaction between isoindole 255 and *tert*-butyl acrylate**

4.3.4 Heteroatom containing analogues

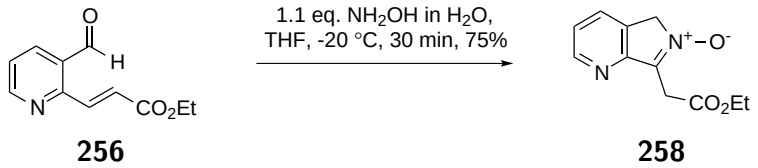
To probe our theory that bridged hydroxylamine **254** was synthesised by a [4+2] cycloaddition reaction of an isoindole-*N*-oxide with the dipolarophile, we decided to synthesise analogues of α,β-unsaturated ester **164** containing a heteroatom in the aromatic ring, and then subject these analogues to our optimised cyclisation reaction conditions. It was hoped that introducing a heteroatom into the pendant aromatic ring would create a substrate that was electron deficient (compared to analogue featuring a benzenoid ring), and would result in it existing preferentially as its isoindole-*N*-oxide tautomer.

To begin this work, we took commercially available 2-bromo-3- and 3-bromo-4-pyridinecarboxaldehydes and attempted to couple them with ethyl acrylate **162** using our standard Heck conditions.[76] The 2-bromo example gave no reaction under these conditions, however, we were able to isolate a small amount of the desired coupled product **256** using the modified conditions of Song *et al.*[123] Thus, a slurry of 2-bromo-3-pyridinecarboxaldehyde, sodium acetate, tri(*o*-tolyl)phosphine, allylpalladium chloride dimer and ethyl acrylate **162** in toluene was heated to reflux under nitrogen for one day. After cooling, filtering, working up the reaction and purifying by column chromatography, the cross-coupled product **256** was synthesised as a yellow oil in a poor 11% yield (Scheme 4.18). The Heck reaction of 3-bromo-4-pyridinecarboxaldehyde afforded a low 16% yield of cross coupled product **257** using our standard conditions.[76]



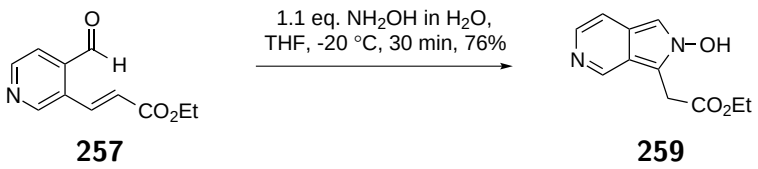
Scheme 4.18: **Heck cross coupling reactions to afford pyridyl α,β-unsaturated ester analogues 256 and 257**

We then took each of these aldehyde analogues in turn and reacted them with aqueous hydroxylamine using our previously optimised cyclisation reaction conditions. The reaction of aldehyde **256** afforded nitrone product **258** as a clean cream solid in 75% yield.



Scheme 4.19: **Reaction of pyridyl analogue 256 with hydroxylamine to afford nitrone 258**

The reaction of aldehyde **257** with hydroxylamine gave a cream solid, the major product of which was shown to be 4-aza-isoindol-*N*-oxide **259** by 2D NMR spectroscopic analysis (Scheme 4.19 and Figure 4.5). This structure was further confirmed by HRMS and IR analyses.



Scheme 4.20: **Reaction of pyridyl analogue 257 with hydroxylamine to afford 4-aza-isoindol-*N*-oxide 259**

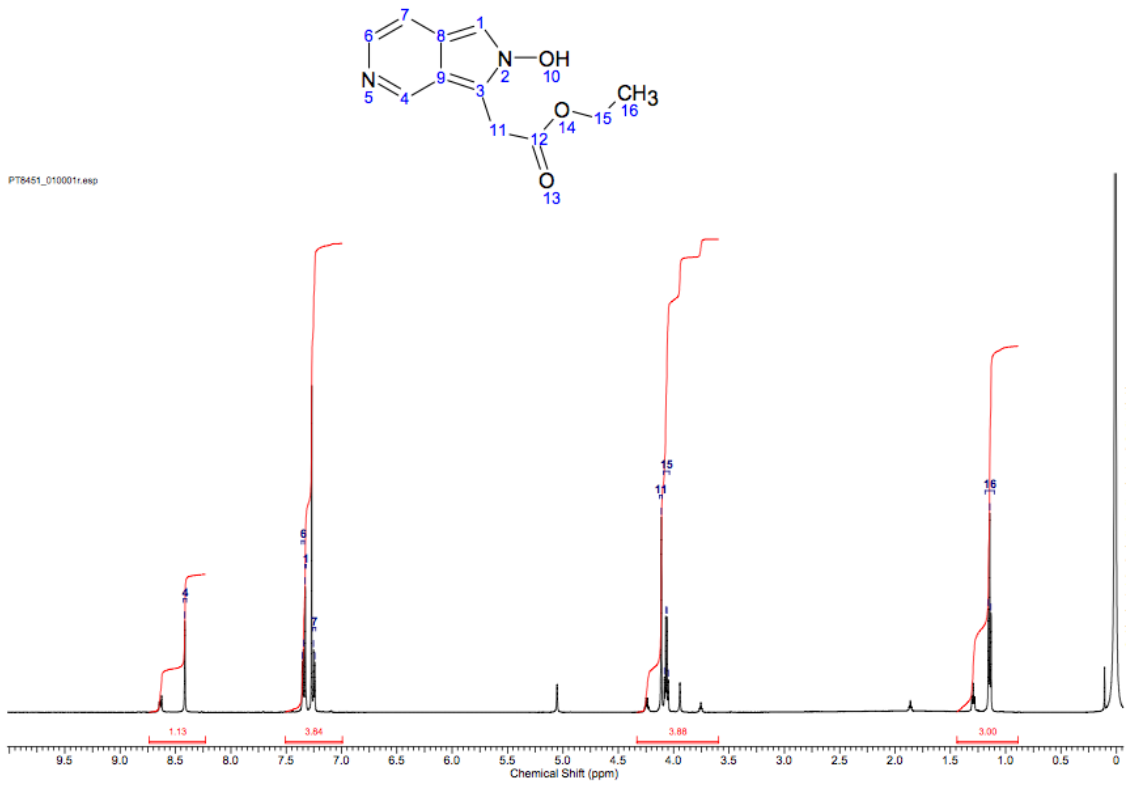


Figure 4.5: **^{1}H NMR spectrum of pyridin-2-ol 259 in $CDCl_3$**

In the ^{1}H NMR spectrum of 4-aza-isoindol-*N*-oxide **259** in $CDCl_3$ shown above it can be seen that there are a series of small peaks corresponding to a minor product present; which we assigned to the nitrone tautomer **260** (Figure 4.6).

260

Figure 4.6: **Nitrone tautomer 260 of the 4-aza-isoindol-*N*-oxide 259**

We decided to see if it was possible to drive this tautomerisation reaction towards one tautomer by changing the polarity of the deuterated solvent used. Analysis of a ^{1}H NMR spectrum run in deuterated methanol straight after the sample was made revealed that the alternative tautomer of nitrone **322** could be observed alongside the 4-aza-isoindol-*N*-oxide structure **259** (Figure 4.7 and Figure 4.8).

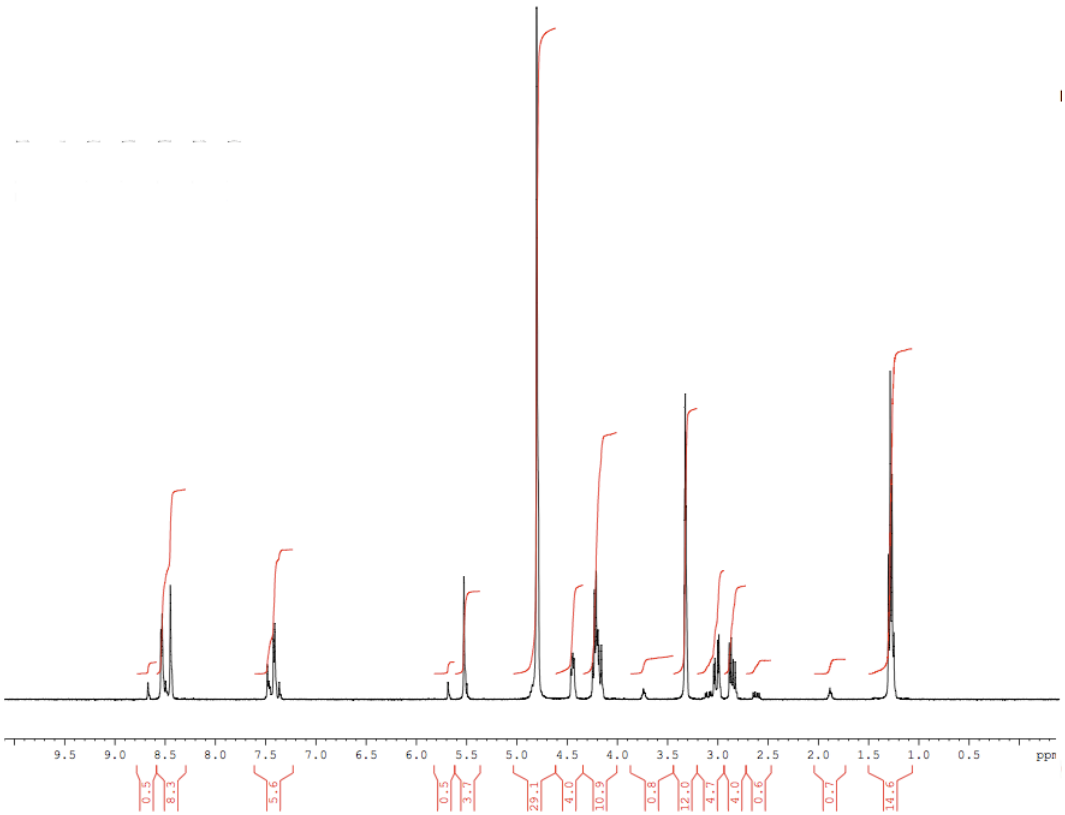
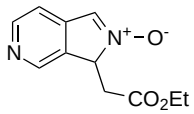


Figure 4.7: **^{1}H NMR spectrum of pyridin-2-ol 259 in methanol-d$_4$**

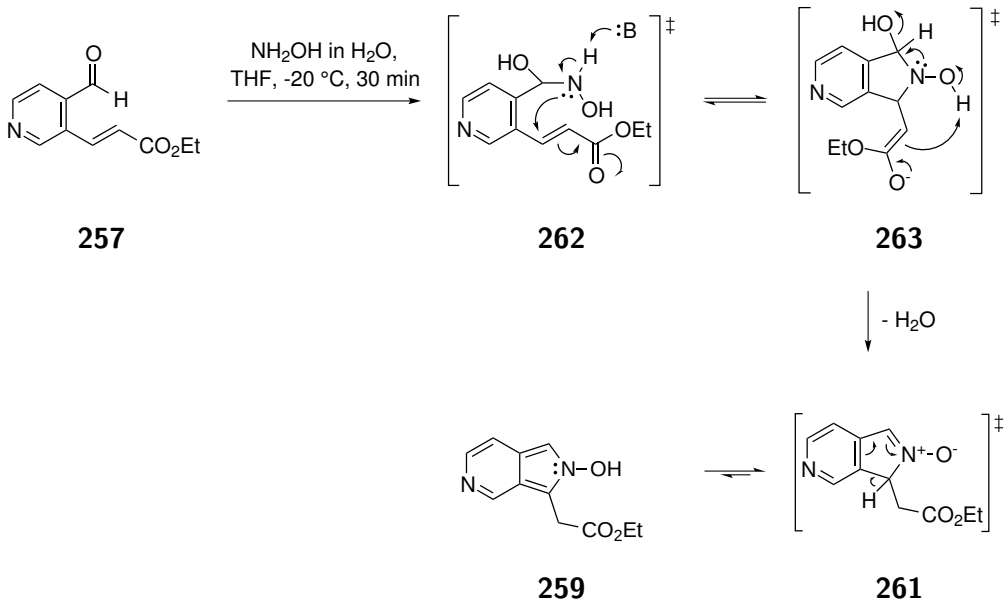


261

Figure 4.8: **Alternative nitrone tautomer 261 of the pyridin-2-ol 259**

4-aza-isoindol-*N*-oxide forming reaction mechanism

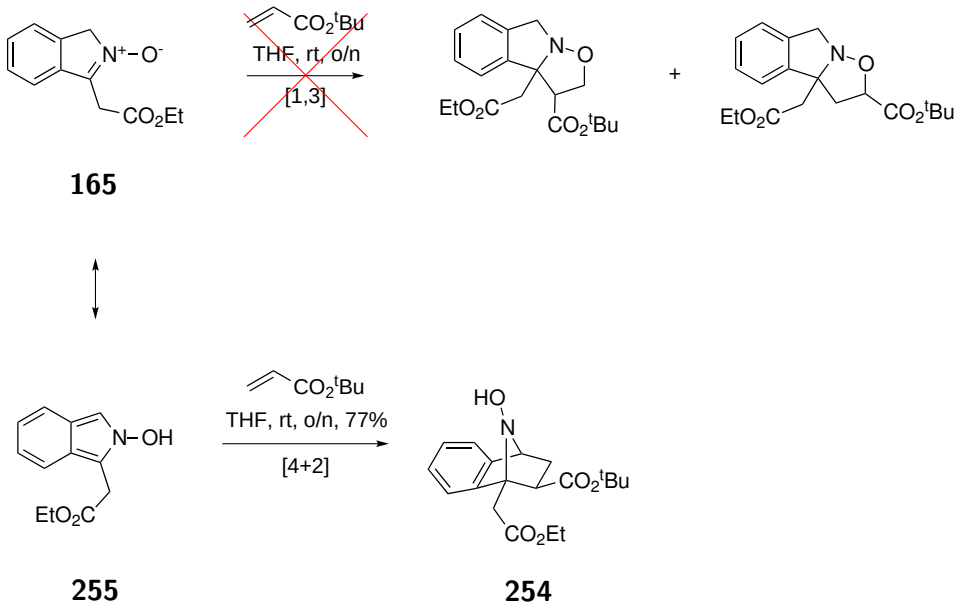
We propose that the mechanism for formation of the pyridin-2-ol **259** is the same as the formation of nitrone **165** and its analogues, with the exception that the final tautomerisation event of isoindole-*N*-oxide to nitrone does not occur (Scheme 4.21). Therefore, aldehyde **257** reacts with hydroxylamine to afford the hydroxyamino alcohol intermediate **262**, which nucleophilically attacks the α,β-unsaturated ester in a 1,4 manner resulting in the enolate intermediate **263**. The enolate extrudes water to form the lesser substituted nitrone **261** which undergoes a final tautomerisation event to afford the pyridin-2-ol product, **259**.



Scheme 4.21: **Proposed mechanism for the formation of pyridin-2-ol 259**

4.3.5 Conclusion

Our attempt to carry out a 1,3-dipolar cycloaddition reaction between nitrone **165** and a dipolarophile to afford an isoxazolidine was prevented by the the fact that a [4+2] Diels-Alder cycloaddition reaction took place instead to afford a bridged hydroxylamine **254** (Scheme 6.1). We proposed that the nitrone **165** tautomerises to the isoindole **255**, that had then taken part in the reaction. Our proposal was supported by the fact that, when using heteroatom containing analogues in our cyclisation reaction, the 4-pyridine analogue **257** afforded the 4-aza-isoindol-*N*-oxide **259** as the major product of the reaction. Running ^{1}H NMR spectroscopic analysis showed the presence of both its nitrone tautomers in deuterated chloroform and deuterated methanol respectively.

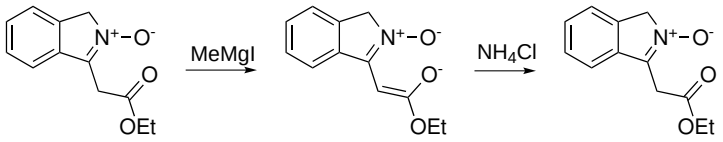


Scheme 4.22: **[4+2] Diels-Alder cycloaddition reaction between isoindole 255 and *tert*-butyl acrylate**

4.4 Other reactions attempted

We then decided to investigate nucleophilic addition reactions to the nitrone **165**, due to the huge amount of literature precedent available for this type of reaction, as covered in reviews by Lombardo[124] and Merino[125] *et al.*

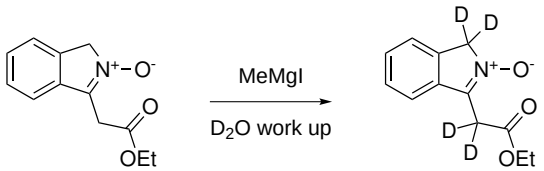
We began by investigating a Grignard reaction. Five equivalents of the Grignard reagent (methyl magnesium iodide) were synthesised *in-situ*, by the addition of iodomethane to a cooled solution of magnesium turnings and ground glass in THF. A solution of nitrone **165** was then added dropwise and reaction progress monitored by TLC.[113] The reaction only ever showed starting material by TLC, even when the reaction was heated to reflux and left overnight. In accordance, the ^{1}H NMR spectra of three separate reactions attempted showed only the presence of starting nitrone **165**. We reasoned that the Grignard reagent must have acted as a base to deprotonate α to the ethyl ester to afford an enolate **264**, which inhibited any further addition from taking place (Scheme 4.23).



165 **264** **165**

Scheme 4.23: **Attempted Grignard reactions afforded solely starting material 165**

To double check this theory, a Grignard reaction was carried out using commercially available ketone, acetophenone, which yielded the expected alcohol product in 100% conversion. We then carried out the reaction of nitrone **165** with the same Grignard reagent for a fourth time, but used D_2O instead of water in the reaction work up. ^{1}H and ^{2}D NMR analysis revealed deuterium incorporation at the α- position, thus confirming our theory of competing enolate formation.

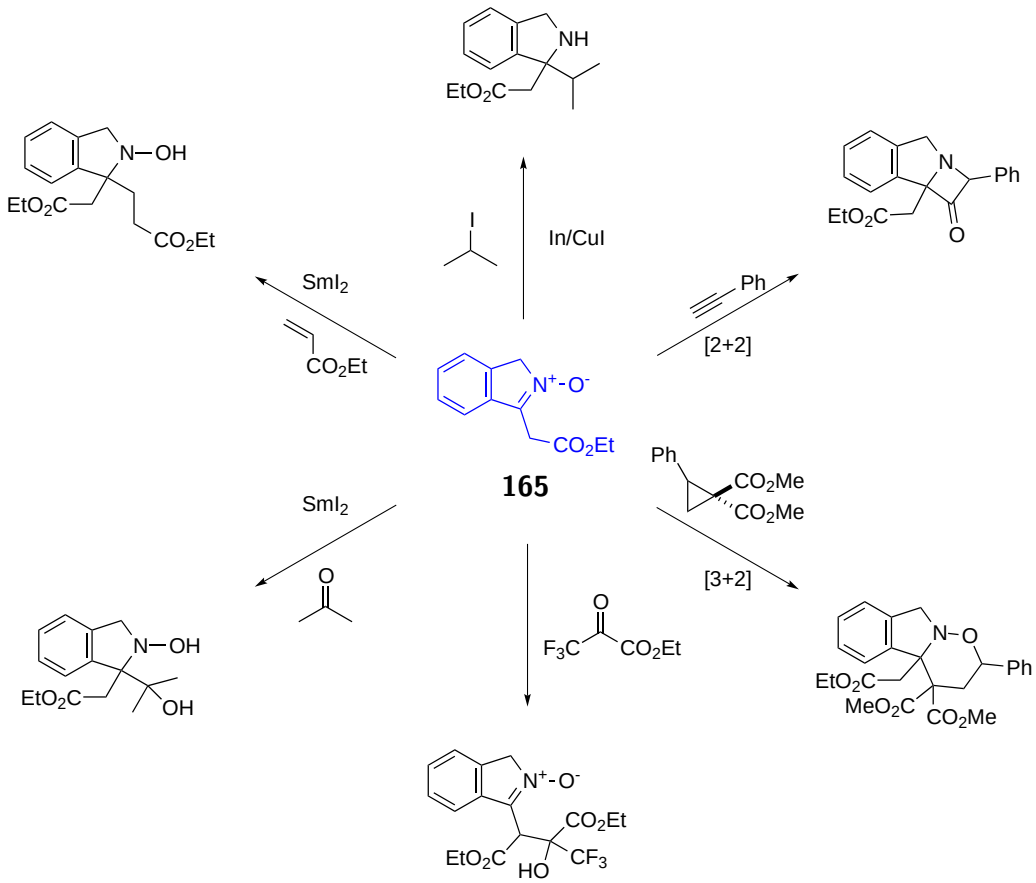


165

Scheme 4.24: **Working up an attempted Grignard reaction in D_2O showed deuterium incorporation at the α- position**

Nucleophilic addition reactions using other nucleophiles such as methyl lithium also returned nitrone starting material. Many other reactions of nitrone **165** were attempted which invariably gave black crude products and were uninterpretable by NMR spectroscopic analysis. These included some common nitrone reactions as well as some lesser known reactions (Scheme 4.25).

- Kinugasa [2+2] cycloaddition reactions[126]
- A [3+2] cycloaddition reaction with a cyclopropane diester[127]
- Reductive coupling reactions with aldehydes and ketones[128] and ethyl acrylate[129]
- Barbier type alkylation reactions with alkyl halides[130]
- Friedel-Crafts alkylations with electron rich aromatic compounds[131]
- A nitrone-aldol reaction with an α-ketoester[132]



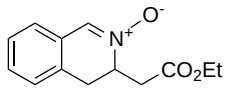
Scheme 4.25: **Attempted reactions of nitrone 165 all afforded uninterpretable crude products**

With the knowledge and experience gained from the cycloaddition experiments, it became apparent that nitrone **165** does not react as one might expect it to react based on literature precedent. Realising that each of the reactions listed above would require significant

work to understand how the substrate is reacting, and optimisation of each set of reactions conditions, we therefore decided to end our investigations into the above reactions and focus on the Diels-Alder cycloaddition between nitrone **165** and alkynes as a method to synthesise substituted naphthalenes (Chapter 5).

4.5 Tricyclic pyrrole synthesis

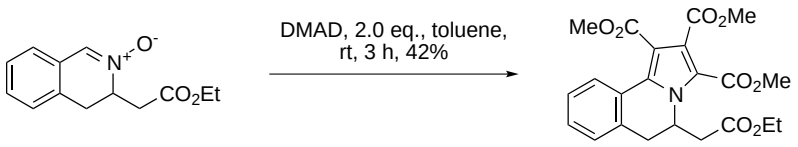
After carrying out [4+2] Diels-Alder cycloadditions between nitrone **165** and alkenes (this chapter) and alkynes (Chapter 5), it was then decided to investigate the cycloaddition reaction of the tetrahydropyridine nitrone **227** (Figure 4.9) with an alkyne. We theorised that the nitrone moeity of this compound might react with an alkyne in a 1,3-dipolar cycloaddition reaction to afford an isoxazole.



227

Figure 4.9: **Tetrahydropyridine nitrone 227**

Therefore, an excess of dimethylacetylenedicarboxylate (DMAD) was added to a solution of nitrone **227** in toluene, and the reaction heated to reflux. Monitoring the reaction by TLC revealed the reaction to be complete at three hours. After removing the solvent under reduced pressure and purifying the crude material by column chromatography, NMR spectroscopic analysis revealed that the sole product of the reaction was not the desired isoxazole. Instead, it was found that pyrrole **265** had been synthesised as the major reaction product (Scheme 4.26). Key details of this structural assignment were the $C_{22}H_{23}NO_8$ formula revealed by HRMS analysis, the presence of three methyl ester singlets in the ^{1}H NMR spectrum, and the absence of a carbon-carbon double bond in the IR spectrum.

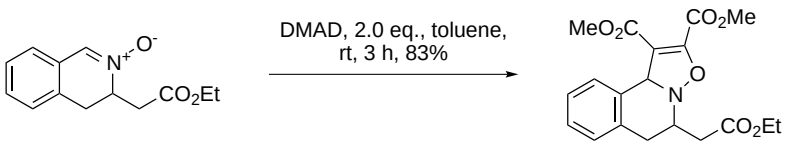


227 **265**

Scheme 4.26: **Unexpected reaction of nitrone 227 with DMAD**

This unexpected result prompted a search of the literature, which revealed several examples of pyrroles having been synthesised from nitrones. Grigg *et al.* were the first group to publish the synthesis of a pyrrole by the reaction of a nitrone and an alkyne.[133] In this first paper, and all subsequent literature examples, the first step in the pyrrole forming mechanism is proposed to be a 1,3-dipolar cycloaddition reaction to afford an isoxazole.

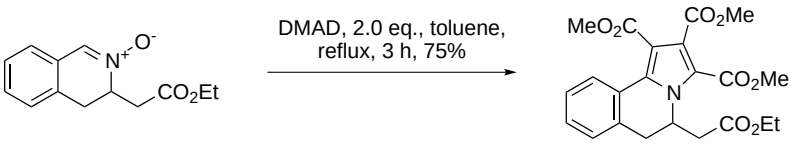
To check that this mechanism for the synthesis of pyrrole **265** was operating, the reaction between nitrone **227** and DMAD was repeated at room temperature. After three hours the reaction showed full consumption of the nitrone starting material by TLC analysis, so the reaction solvent was removed under reduced pressure, and the crude material purified by column chromatography to afford isoxazole **266** as a yellow oil in 83% (Scheme 4.27).



227 **266**

Scheme 4.27: **1,3-dipolar cycloaddition of nitrone 227 with DMAD to afford isoxazole 266**

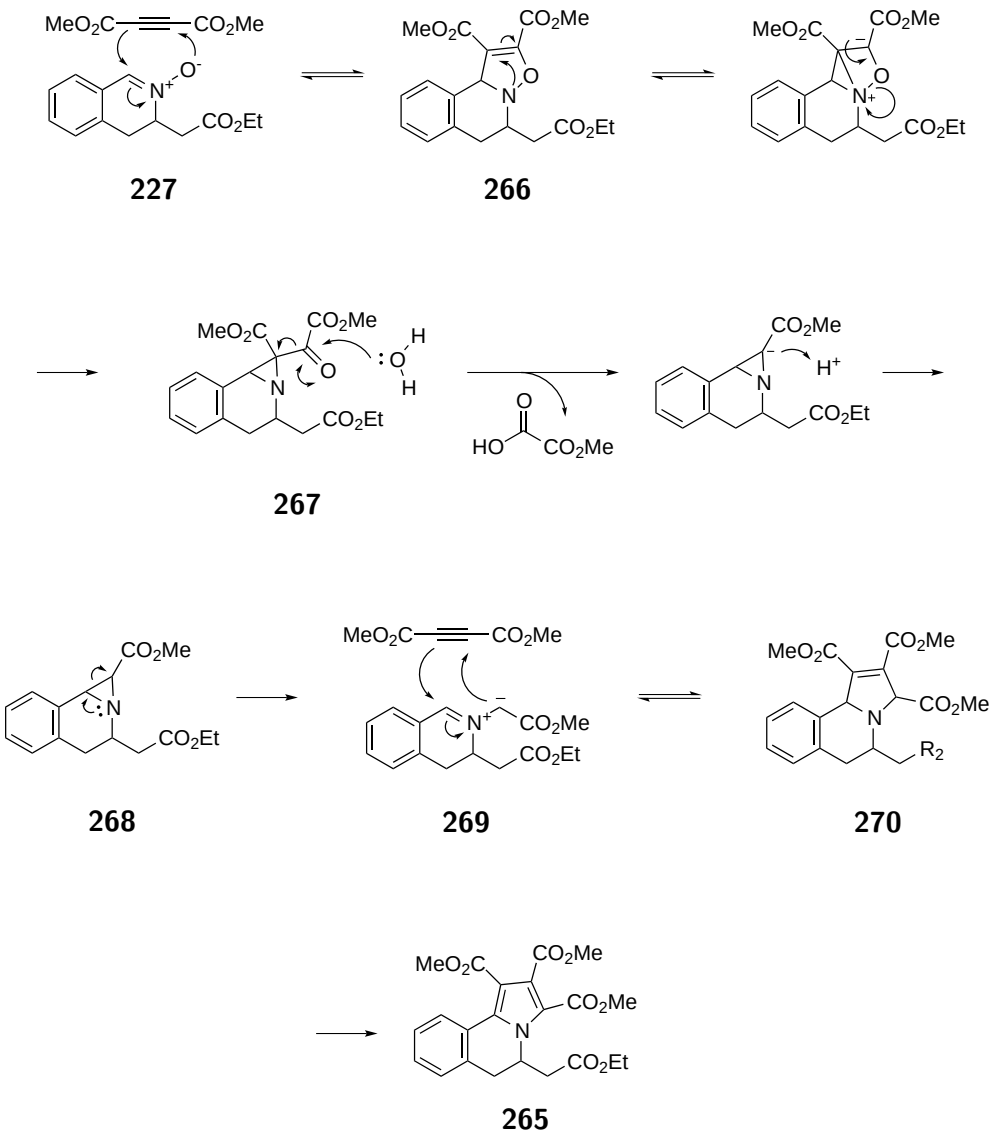
To confirm that isoxazole **266** was an intermediate in the synthesis of pyrrole **265** from nitrone **227**, it was then dissolved in toluene and stirred with an excess of DMAD at reflux for three hours. Pyrrole **265** was afforded as the sole reaction product.



266 **265**

Scheme 4.28: **Synthesis of pyrrole 265 from isoxazole 266**

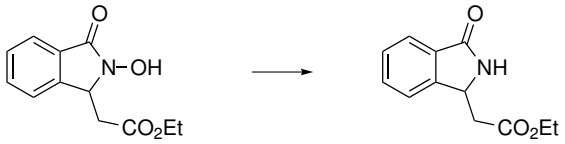
Based on literature precedent, we propose the following mechanism for pyrrole formation from nitrone **227** *via* isoxazole **266** (Scheme 4.29). The isoxazole **266** rearranges to aziridine **267**, an intermediate that Baldwin *et al.* had previously isolated in their synthesis of 4-oxazolines.[134] The aziridine then undergoes a retro Claisen condensation to afford the singly substituted aziridine **268**. This rearranges to azomethine ylide **269** in a step first postulated by Padwa in 1986,[135] and later confirmed by Lopez-Calle *et al.*, who showed that stable azomethine ylides were formed during the irradiation of isoxazoles (*via* acyl aziridine intermediates).[136] In accordance with a later paper published by Lopez-Calle *et al.*,[137] we propose that, following the formation of the azomethine ylide **269**, this intermediate undergoes a second 1,3-dipolar cycloaddition reaction with the excess DMAD to afford the dihydropyrrole **270**. This intermediate subsequently oxidises in air to afford the reaction product, tricyclic pyrrole **265**.



Scheme 4.29: **Proposed mechanism for the synthesis of pyrrole 265**

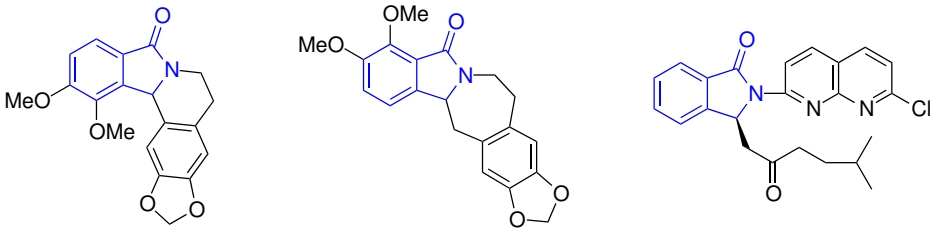
4.6 Isoindolin-2-one synthesis

We next wanted to carry out initial investigations into the cleavage of the N-O bond of hydroxamic acid **232**, the product from the cyclisation reaction of alkyne **231** with hydroxylamine. We wanted to investigate this cleavage reaction because the isoindolin-2-one backbone of the resultant lactam product (Scheme 4.30) is prevalent in a range of natural products and biologically active compounds (Figure 4.10), and would therefore be more a more valuable synthon for natural product synthesis.



232 **271**

Scheme 4.30: **Desired N-O bond cleavage of hydroxamic acid 232**



Nuevamine Lennoxamine Pagoclone

Figure 4.10: **Examples of natural products that contain the same bicyclic carbonyl containing backbone as desired isoindolin-2-one 271**

We began by employing a common method of N-O bond cleavage using acetic acid and zinc (Table 4.3 entry 1).[89,138,139] The acid is supposed to act as a Lewis acid, coordinating with the oxygen lone pair of the OH group, with the zinc then acting as a reductant to cleave the activated N-O bond by single electron transfer. Initial attempts at this reaction showed no conversion, with more forcing conditions showing multiple products in the crude ^{1}H NMR spectra.

Table 4.3: **N-O bond cleavage screen**

Entry	Reagents	Result
1	AcOH, Zn	no reaction
2	Li, DTBB	no reaction
3	SmI_2	no reaction
4	$RuCl_3.3\,H_2O$, Zn-Cu	lactam product

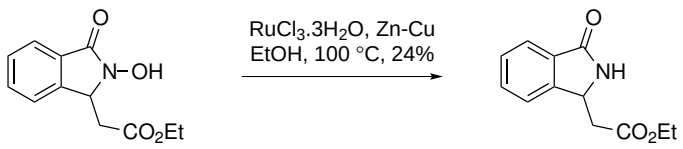
Secondly, we attempted bond cleavage using lithium and a catalytic amount of DTBB, the same system as employed previously when we attempted to cleave the N-O bond of nitrone **165** (entry 2).[140] A solution of hydroxamic acid in anhydrous THF was added to a mixture of lithium and DTBB, and left to stir overnight. However, upon reaction work up, the crude ^{1}H NMR spectrum revealed that no reaction had taken place.

The third attempt at the bond cleavage involved the use of samarium iodide, an excess of which was added dropwise to a solution of hydroxamic acid **232** in anhydrous THF, according to the procedure by Keck *et al.* (entry 3).[141] This reaction, however, once again

returned solely starting material.

Fortunately, a more recently published methodology offered promising results. In 2011, Fukuzawa *et al.* published work concerning the ruthenium catalysed reduction of *N*-alkoxy- and *N*-hydroxyamides.[142] Whilst no cyclic analogues were presented, moderate to good yields were afforded for both secondary and tertiary amides, and as a consequence we decided to employ their metholodogy (entry 4).

A solution of cyclic hydroxamic acid **232** in dehydrated EtOH was added to catalytic amounts of $RuCl_3.3\,H_2O$ and Zn-Cu couple, and the reaction refluxed at 100 °C for three hours (Scheme 4.31). After filtration and purification by column chromatography the bicyclic lactam product, isoindolin-2-one **271**, was afforded in 24% yield as a pale brown oil.

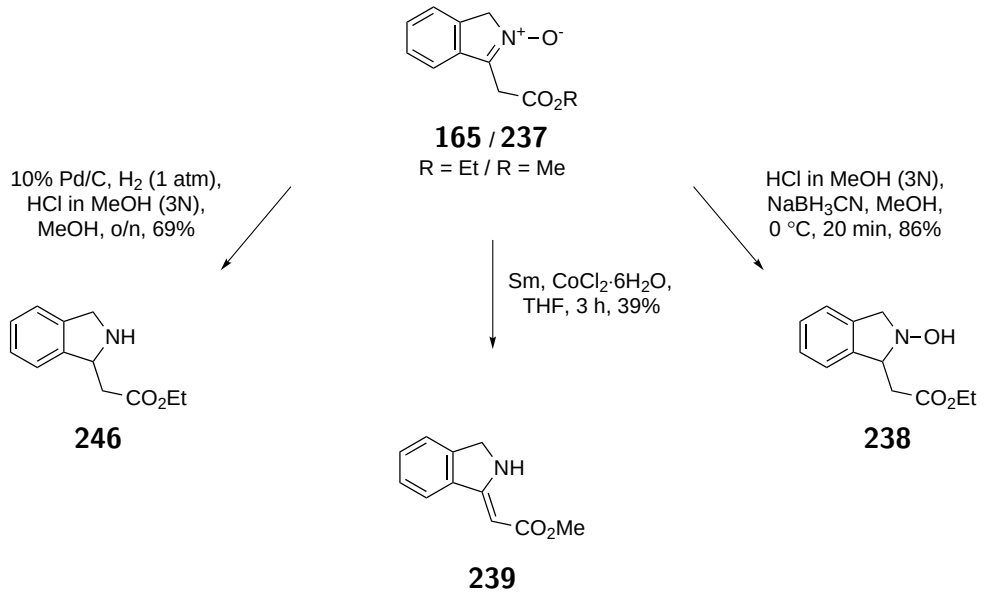


232 **271**

Scheme 4.31: **Synthesis of cyclic lactam 271**

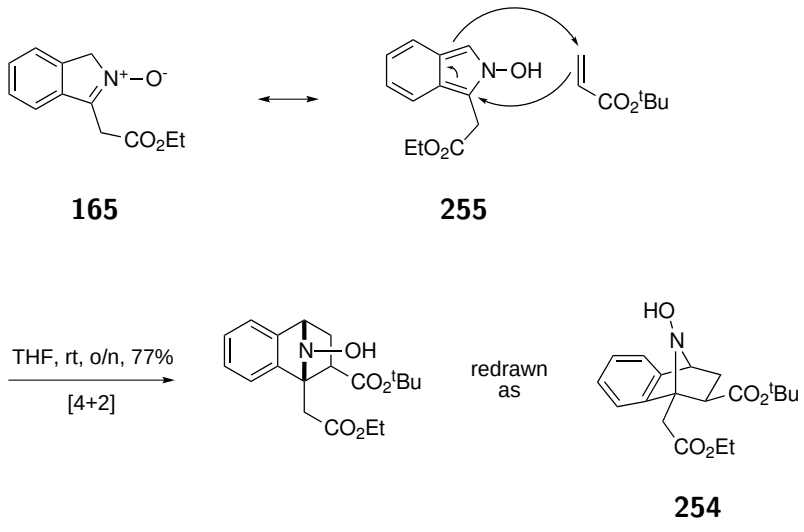
4.7 Conclusion

In this chapter we had set out to explore precedented nitrone reactions using our standard nitrone substrate **165**. Whilst reductions of nitrone **165** to the amine **246** and hydroxylamine **238** proceeded relatively smoothly, our attempts to reduce the nitrone functionality to an imine proved more challenging. After several unsuccessful efforts, three separate sets of conditions all resulted in the formation the enamine **242** in 39% yield (Scheme 4.32).



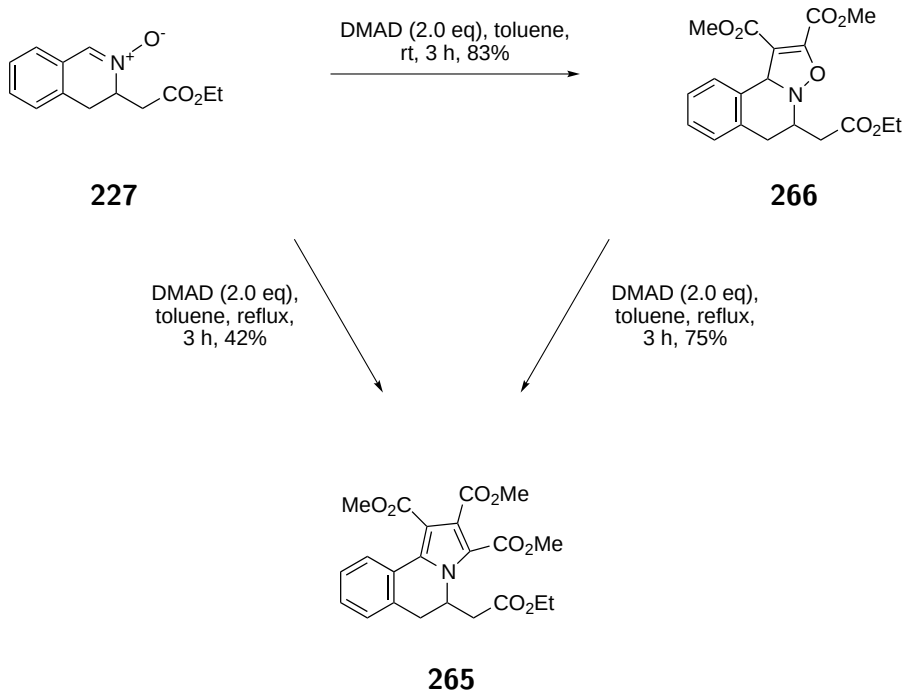
Scheme 4.32: **Summary of the reductive transformations of nitrones 165 and 237**

The attempted 1,3-dipolar cycloaddition reaction of nitrone **165** also proceeded in an unexpected manner (Scheme 4.33). We discovered that, instead of reacting in a 1,3-dipolar cycloaddition reaction, the nitrone tautomerised to its isoindole form **255** and underwent a [4+2] Diels-Alder reaction, to afford the tricyclic hydroxylamine **254**.



Scheme 4.33: **[4+2] cycloaddition reaction between isoindole 255 and *tert*-butyl acrylate**

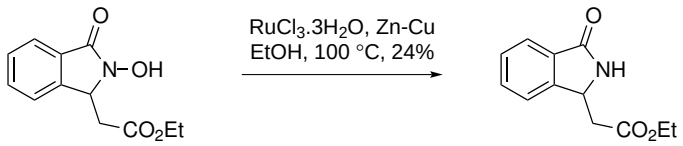
Whilst nitrone **165** proved to react as an isoindole in the cycloaddition reaction, the tetrahydropyridine nitrone **227** proved to react with an alkyne dipolarophile (DMAD) *via* the expected 1,3-dipolar manifold to afford the isoxazole **266** at room temperature. Heating the nitrone **227** or isoxazole **266** with excess alkyne under reflux conditions led to the formation of the tricyclic pyrrole **265**, as shown in Scheme 4.34.



227 **266** **265**

Scheme 4.34: **Synthesis of isoxazole 266 and pyrrole 265 from nitrone 227**

Lastly we carried out a ruthenium trichloride and zinc-copper couple mediated *N*-*O* bond cleavage reaction on the cyclic hydroxamic acid substrate **232**, to afford the bicyclic lactam **271**, as shown below in Scheme 4.35.



232 **271**

Scheme 4.35: **Synthesis of cyclic lactam 271**

Chapter 5

Exploring Methodology for the Synthesis of Naphthalenes

5.1 Naphthalene literature review

5.1.1 Uses of naphthalenes

There has been much scientific interest in recent years regarding efficient ways to synthesise naphthalenes and their derivatives. The reason behind this interest is due to the prevalence of highly substituted naphthalene rings in the structures of many natural products and pharmaceuticals.[143–146]

For example the pharmaceutical drug propranolol (Figure 5.1), whose starting material is naphthol,[147] is a widely used beta blocking drug and its applications include the treatment of angina and hypertension (Figure 5.1).[148] In contrast to propranolol, naphthalenediimide (NDI) components are a common substituent in much larger molecules which are used as anticancer drugs.[149] They act as intercalators, which insert into the DNA helix and alter the DNA structure.

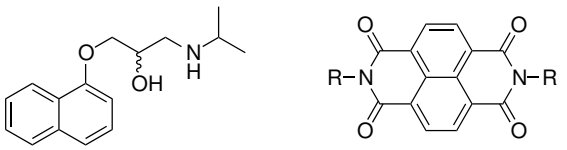


Figure 5.1: **Propanolol and naphthalenediimide**

As well as synthetically made drugs, pharmaceutically promising naphthalene containing compounds also occur in Nature. Both Michellamines A and B and Korupensamines A-D are produced by a plant called *Ancistrocladus korupensis* found in Africa (Figure 5.2). Michellamines A and B exhibit anti-HIV activity,[150] whereas Korupensamines A-D show antimalarial activity.[151]

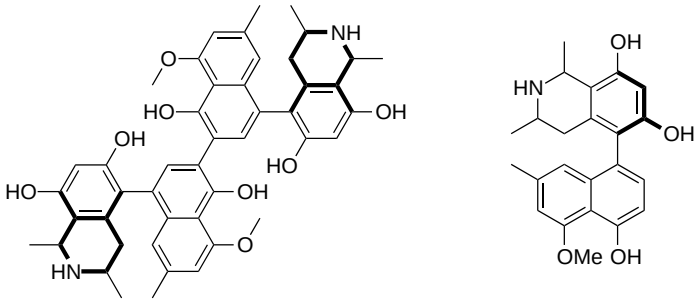


Figure 5.2: **Generic structures of michellamines and korupensamines**

Another naturally occurring naphthalene containing drug is Gossypol, shown in Figure 5.3, which is found in cotton seeds from plants belonging to the *Gossypium* species.[152] The (–) isomer exerts contraceptive affects, whereas the (+) isomer can cause toxic symptoms.

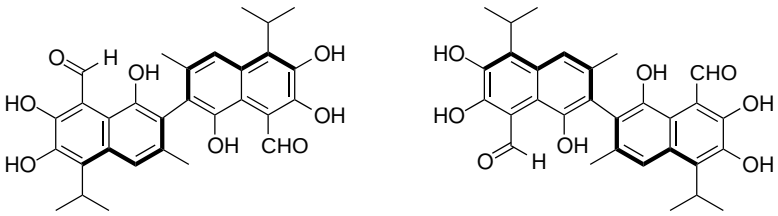
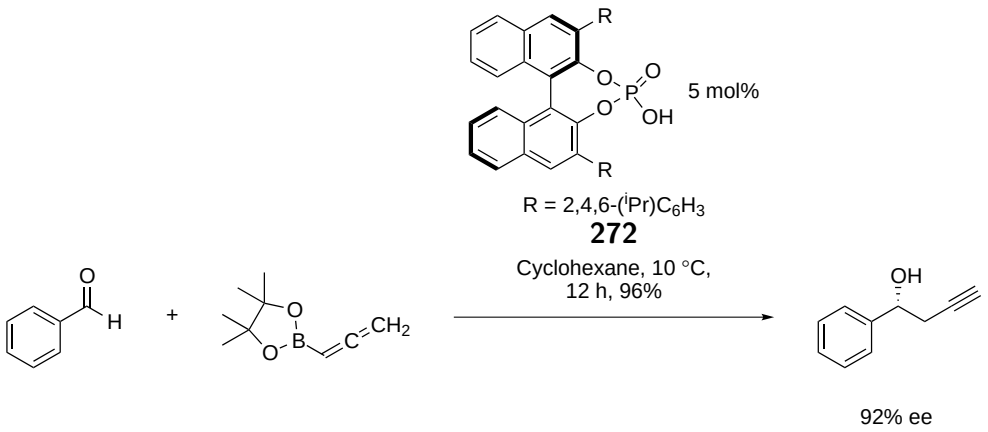


Figure 5.3: **Gossypol stereoisomers**

Naphthalene molecules containing binary linkage bonds are also utilised as chiral reagents to induce stereocontrol into reactions.[153] Well known examples of this type of naphthalene molecules are 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) and 1,1'-bi-2-naphthol (BINOL), which have been used as ligands in many asymmetric reactions.[154,155] A recent example of this research is the asymmetric propargylation of aldehydes reported by Reddy using allenyl boronate ester donors.[156] They screened a range of substituted BINOL derived phosphoric acid catalysts and found that 3,3'-*bis*(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate **272** gave full conversion and greater than 90% ee in all of the aldehyde substrates screened (Scheme 5.1).



Scheme 5.1: **Asymmetric propargylation of benzaldehyde using a BINOL derived phosphoric acid catalyst**

The Bull and James groups have employed (*S*)-BINOL in their chiral derivatization protocols. For example, 2-formylphenylboronic acid has been used to coordinate with (*S*)-BINOL and chiral amines, to afford two diastereomeric imino-boronate ester products shown in Figure 5.4. Resolution of the diastereomers in the ^{1}H NMR spectra allowed the diastereomeric excess to be measured, and therefore the enantiopurity of the parent amines to be calculated.[157]

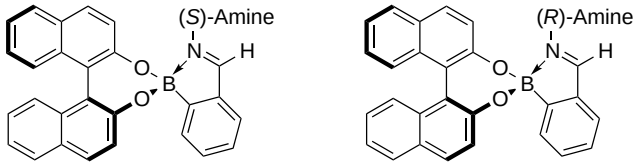


Figure 5.4: **Use of BINOL for determining the enantiomeric excess of amines**

Naphthalenes are also used in inorganic chemistry as they form the backbone of "proton sponges",[158] which are very basic molecules that slowly coordinate to individual protons. Figure 5.5 shows the first known proton sponge,1,8-bis(dimethylamino)naphthalene (DMAN) reported by Alder *et al.* in 1968,[159] and a more recent example is 1,8-bis(tetramethylguanidino)naphthalene (TMGN).[160] Proton sponges coordinate to individual protons due to formation of intramolecular hydrogen bonds between the two nitrogen atoms on the amine groups and the proton. This is possible due to the orientation of the nitrogen atoms providing the correct angle for coordination.[161]

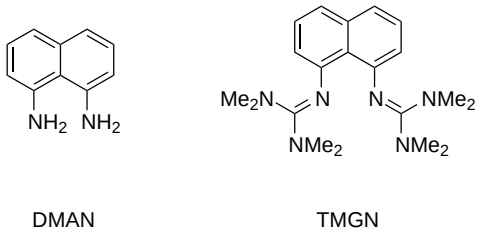


Figure 5.5: **Examples of naphthalene based proton sponges**

In addition, naphthalenes substituted with group thirteen elements have been utilised as Lewis acids to bind halides.[162] Naphthalene based boranes, for example, bind strongly to fluorides due to a combination of the chelate effect and the lack of rotation exhibited by the molecule.[163,164] They can also bind to small organic compounds, such as dimethylpyranone (Figure 5.6).[165]

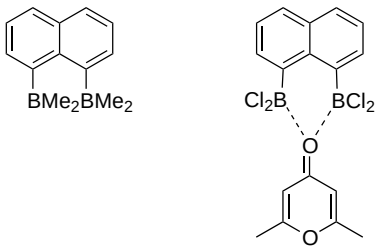


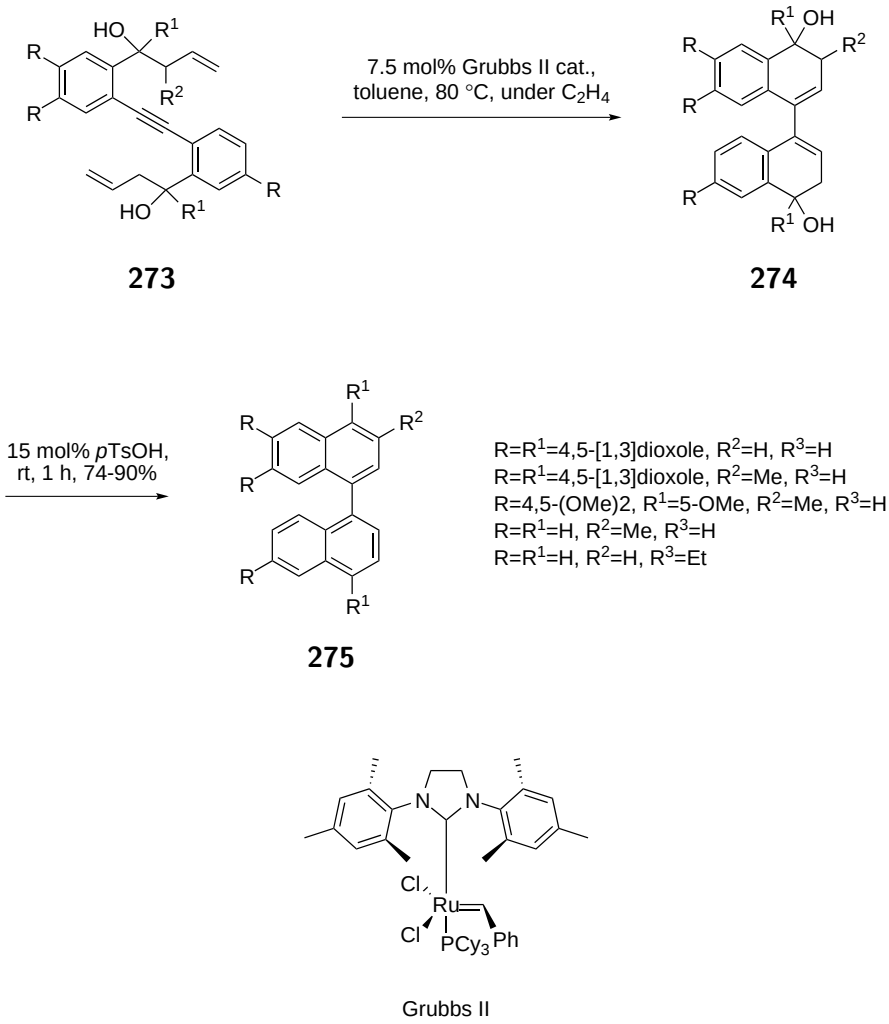
Figure 5.6: **Examples of naphthalene based borane derived Lewis acids and their coordination to dimethylpyranone**

5.1.2 Synthesis of naphthalenes

The examples described in Section 5.1 outline the importance of substituted naphthalenes and explain the interest in their synthesis. Over the past few decades, advances have been made in the synthesis of naphthalenes, and many different synthetic pathways have been developed. The two most widely employed methods will be described briefly in the following sections, based on transition metal mediated syntheses and cycloaddition based syntheses. There are, however, numerous other methods available, such as phthalide annulations, the rearrangement of strained rings and thermal cyclisation reactions. Two extensive reviews on the subject of naphthalene synthesis are those by de Koning and van Otterlo *et al.*[139,166]

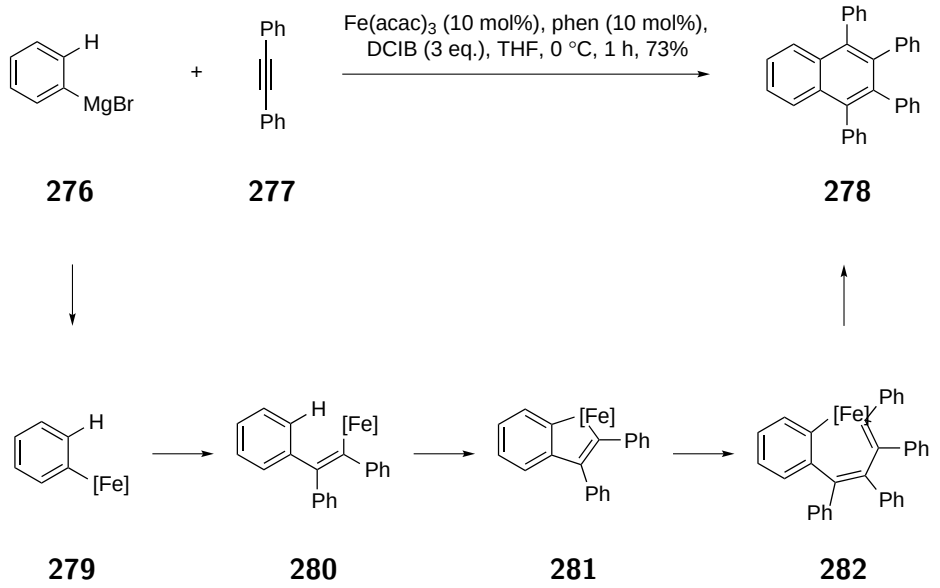
5.1.3 Metal catalysed syntheses

A large number of transition metal catalysed protocols have been employed for the synthesis of naphthalene rings, including chromium, manganese, palladium, cobalt, nickel, copper, zinc, tin, rhodium and ruthenium. Both ene-ene and ene-yne cyclisation reactions mediated by ruthenium have been reported.[139] Yoshida *et al.* used Grubbs second generation catalyst in the Ring Closing Enyne Metathesis (RCEM) of alkynes **273** to form the bicyclic intermediates **274** (Scheme 5.2). Following dehydration, a range of biaryl naphthalene compounds **275** were afforded in 74-90% yields.[167]



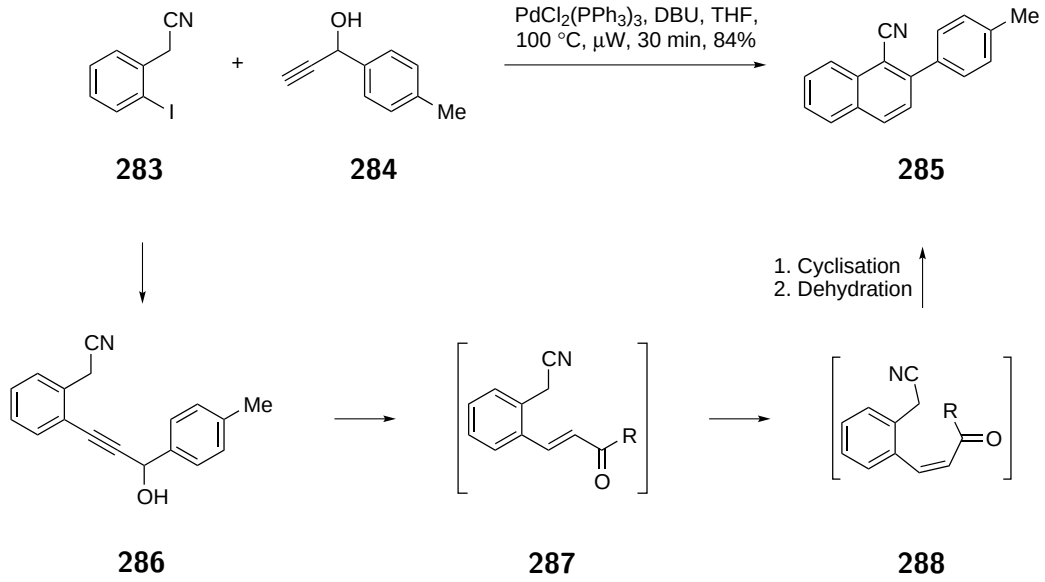
Scheme 5.2: **Ring closing enyne metathesis reaction for the synthesis of biaryl naphthalenes 275**

Recently, work has been undertaken to research the affect iron has on catalysing aryl annulation reactions to afford substituted naphthalenes. Both Adak and Yoshikai,[168] and Ilies *et al.*[169] have reported results in this area concerning the reaction between phenylmagnesium bromide **276** and diphenylacetylene **277**, to afford the substituted naphthalene **278** in 73% yield (Scheme 5.3). It was proposed that reaction of the iron catalyst $Fe(acac)_3$ with phenyl magnesium bromide **276** generated iron intermediate **279**. After insertion of the alkyne **277**, the vinyl iron intermediate **280** subsequently underwent an intramolecular C-H bond activation reaction to form metallacycle **281**, which then reacted with a second equivalent of diphenylacetylene **277** to form the seven membered complex **282**. Oxidatively induced elimination of iron from **282** then afforded the tetra-substituted naphthalene **278**.



Scheme 5.3: **Iron catalysed synthesis of tetra-substituted naphthalene 278**

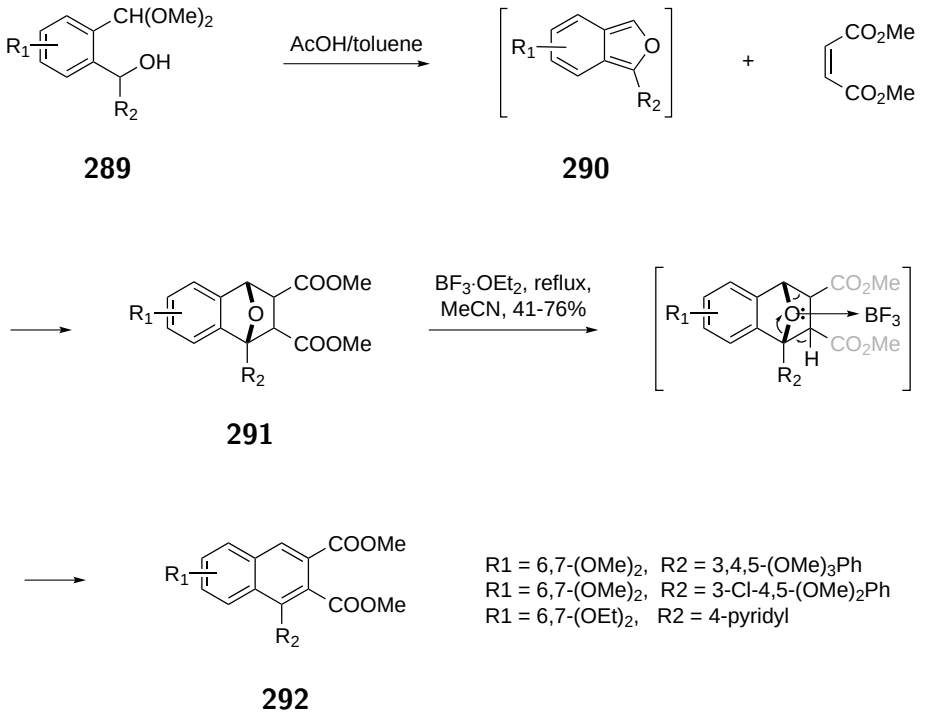
Palladium has often been used as a catalyst in naphthalene synthesis (Scheme 5.4). Wang *et al.*[170] reacted arylhalide **283** and propargyl alcohol **284** together under microwave conditions to afford bi-substituted naphthalene **285**. Their synthesis proceeds *via* a Sonogashira coupling reaction to yield alkyne **286**, which underwent a thermally induced isomerisation reaction to the α,β-unsaturated ketone **287**. Geometric isomerisation to afford the *Z*-alkene **288** resulted in cyclisation followed by a subsequent dehydration step to afford the final naphthalene product **285**.



Scheme 5.4: **Wang's palladium catalysed synthesis of bi-substituted naphthalene 285**

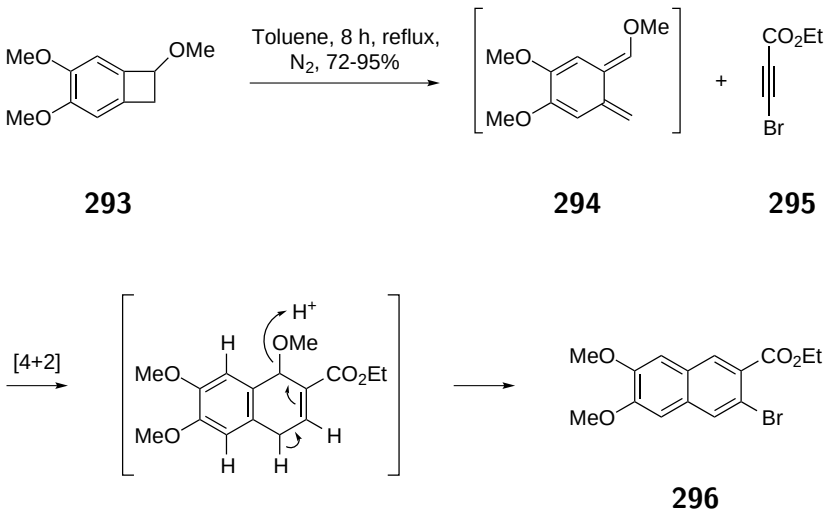
5.1.4 Diels-Alder syntheses of napthalenes

In the late 1990s, Sugahara *et al.* and Ukita *et al.* developed methodology for the synthesis of substituted naphthalenes **292** using a Diels-Alder reaction between hydroxyl acetals **289** and dimethyl fumarate, which proceeded *via* isobenzofuran intermediates **290** (Scheme 5.5).[171,172] In these reactions, hydroxyl acetals **289** underwent acid catalysed ring-closure/dehydration reactions to afford an isobenzofuran **290** that took part in a Diels-Alder reaction with dimethyl fumarate to give the bridged compound **291**. This was then refluxed with boron trifluoride diethyl etherate Lewis acid to induce ring opening and dehydration. This afforded the aromatised naphthalene **292** product.[172]



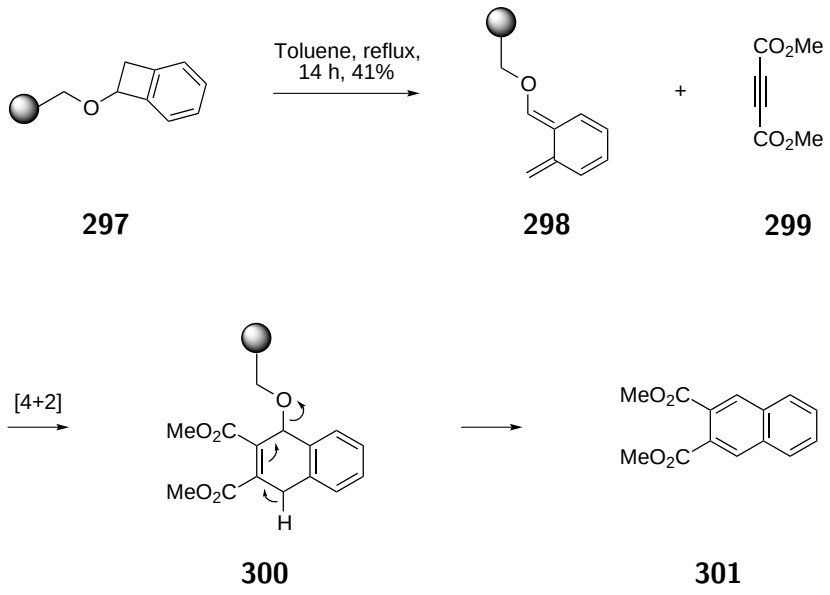
Scheme 5.5: **Diels-Alder reaction between isobenzofuran 290 and dimethyl fumarate to afford penta-substituted naphthalene 292**

In 1987 Charlton and Alaludini published a paper concerning *o*-quinodimethanes, where they reported their use in organic synthesis and as intermediates in naphthalene formation.[173] Following this work, Andersen *et al.* synthesised substituted naphthalene rings *via* *o*-quinodimethane intermediates.[143] Refluxing methoxybenzocyclobutene **293** in toluene afforded the *o*-quinodimethane intermediate **294**, which subsequently reacted with ethyl 3-bromopropiolate **295** in a Diels-Alder reaction (Scheme 5.6), with the resultant cycloaddition product undergoing aromatisation by elimination of methanol to yield naphthalene **296**.



Scheme 5.6: **Andersen synthesis of tetra-substituted naphthalene 296 from *o*-quinodimethane 294**

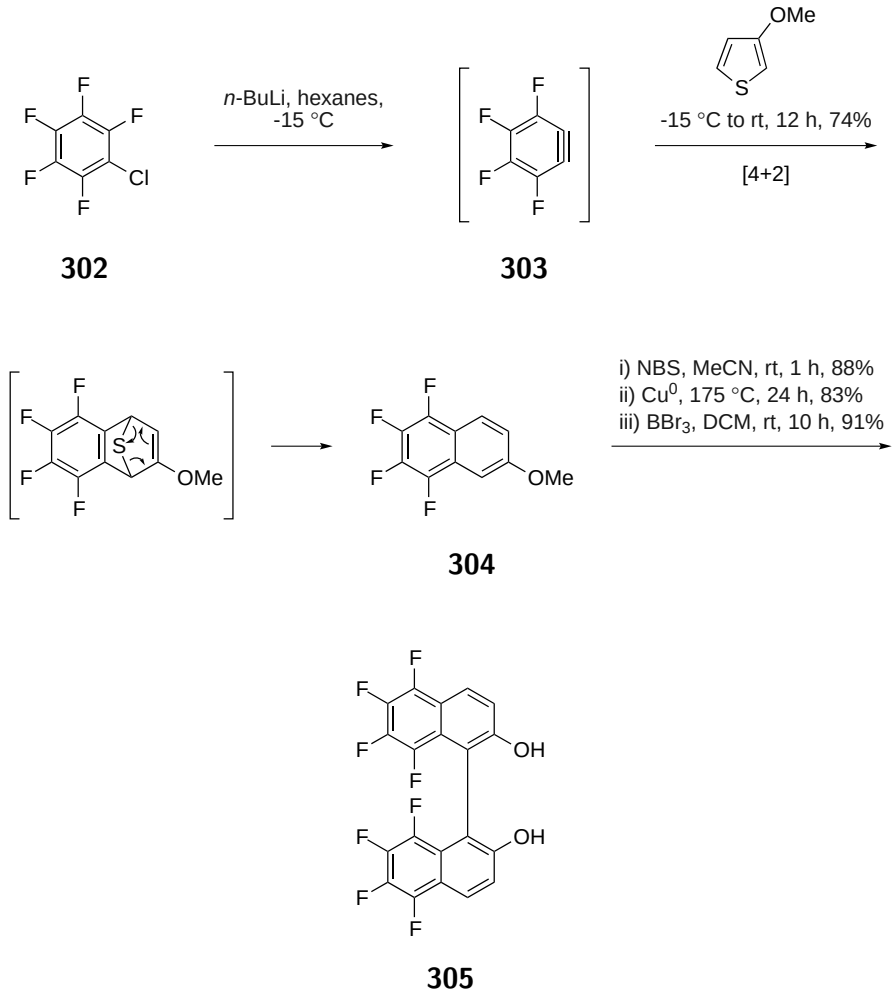
Craig *et al.* also reported on a related synthesis of substituted naphthalenes through a Diels-Alder reaction of polymer supported *o*-quinodimethanes,.[174] This involved refluxing polymer supported cyclobutene **297** to afford the *o*-quinodimethane **298**, which underwent a Diels-Alder reaction with dimethyl acetylenedicarboxylate (DMAD) **299** to give the bicyclic product **300** (Scheme 5.7). After aromatisation and self-cleavage, naphthalene **301** was isolated in 41% yield.



Scheme 5.7: **Craig synthesis of naphthalene 301 from *o*-quinodimethanes**

Diels-Alder reactions of benzynes is another potential route for the synthesis of naphthalenes. One example of this work is the synthesis of fluorinated BINOL precursors by Yudin *et al.*[175] Treatment of the pentafluoro aryl chloride **302** with butyl lithium afforded a benzyne intermediate **303** that underwent a Diels-Alder reaction with thiophene,

as shown in Scheme 5.8. The resulting cycloadduct then extracted sulfur *in-situ* to yield the fluorinated naphthalene **304**. Subsequent arene bromination, Ullman coupling and *O*-demethylation steps then resulted in the desired fluorinated BINOL **305**.



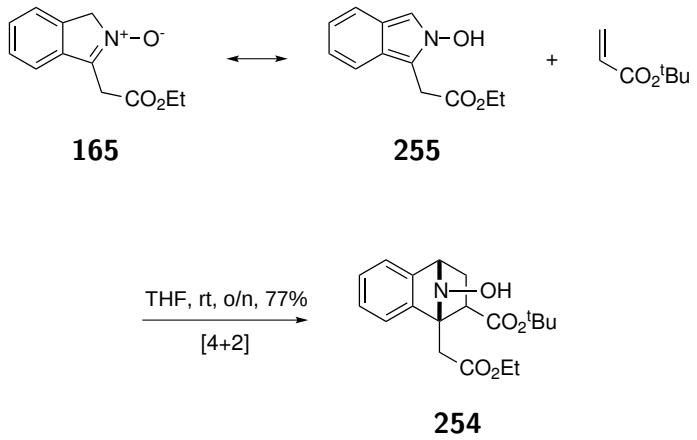
Scheme 5.8: **Diels-Alder reaction of benzyne 303 with thiophene for the synthesis of fluorinated BINOL precursors**

5.1.5 Conclusion

In summary, examples of the two most researched methods for naphthalene synthesis have been discussed. Numerous metals can be employed in metal catalysed strategies to provide a wide variety of naphthalene products. The advantages of the Diels-Alder approaches are that they do not have the issues regarding catalyst recyclability or cost. Both the dipole and the dipolarophile can be changed to provide a greater number of substituted naphthalene scaffolds. I will now describe how the synthetic methodology described in Chapters 2, 3 and 4 enabled us to develop a promising Diels-Alder methodology for the synthesis of naphthalenes.

5.2 Introduction

In Chapter 4 we reported that nitrone **165** undergoes [4+2] cycloaddition reactions with alkene dienophiles, rather than the expected 1,3-dipolar cycloaddition reaction. We proposed that the nitrone **165** tautomerised to its isoindole-*N*-oxide form **255**, and underwent a [4+2] Diels-Alder cycloaddition with *tert*-butyl acrylate to form the bridged hydroxylamine product **254**, as shown in Scheme 5.9.



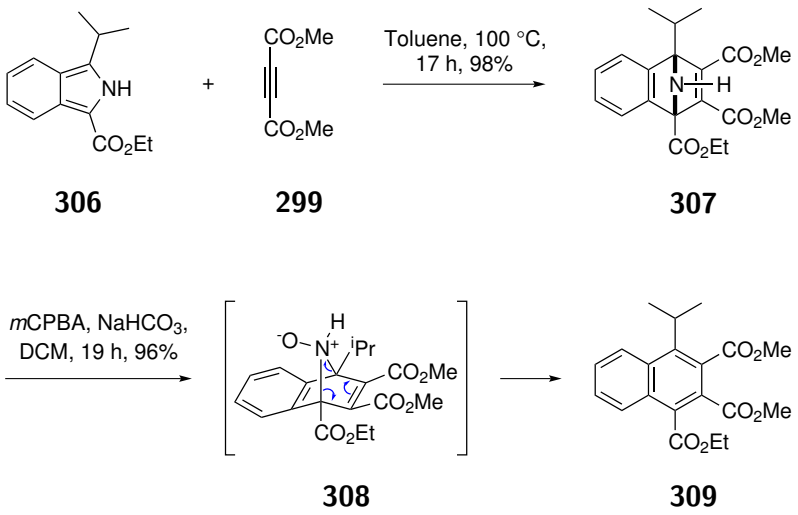
165 **255** **254**

Scheme 5.9: **[4+2] cycloaddition of nitrone 165 with *tert*-butyl acrylate**

5.2.1 Aim

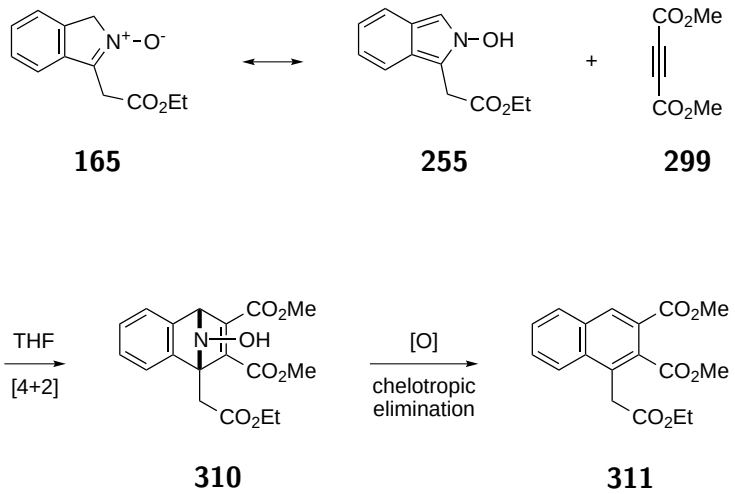
We wanted to explore whether this [4+2] Diels-Alder cycloaddition reaction could be further developed for the synthesis of substituted naphthalenes. An investigation of the literature determined that the precedent for Diels-Alder cycloaddition reactions of isoindole-*N*-oxides was unknown, as was their use as substrates for the direct synthesis of naphthalenes. However, there was precedent for the cycloaddition reactions of the parent isoindoles, and indeed this method has been applied for the synthesis of substituted naphthalenes.

Tong *et al.* recently published their synthesis of naphthalenes starting from disubstituted isoindoles **306**, as shown in Scheme 5.10.[72] These isoindoles were synthesised in five steps and then reacted with dimethyl acetylenedicarboxylate (DMAD) **299** in a [4+2] cycloaddition reaction to afford the bridged heterocycles **307**. The group reported that oxidation of the amine functionality with *m*CPBA resulted in the formation of naphthalene **309**, which was proposed to proceed *via* chelotropic elimination of an *N*-oxide intermediate **308**.



Scheme 5.10: **Tong's synthesis of tetra-substituted naphthalenes 309 from isoindoles 306**

Using this precedent as inspiration, we envisaged that our nitrone/isoindole-*N*-oxide cycloaddition methodology could potentially be developed for the synthesis of naphthalenes. As outlined in Scheme 5.11, we theorised that nitrone **165** would tautomerise to the isoindole-*N*-oxide **255** and then undergo a [4+2] cycloaddition reaction with DMAD **299** to form the bridged intermediate **310**. Upon heating, this intermediate would undergo a chelotropic elimination of its NOH bridge, to form the stable, trisubstituted naphthalene **311**.

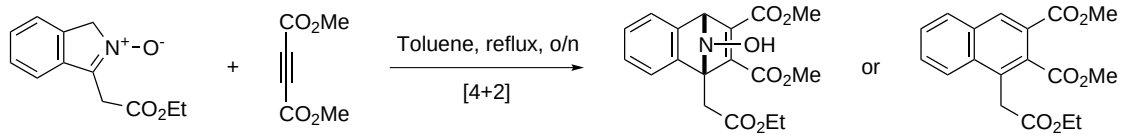


Scheme 5.11: **Proposed synthesis of a tri-substituted naphthalene from nitrone 165**

5.3 Synthesis of naphthalenes from nitrones

We began our work in this area by subjecting nitrone **165** to the same conditions used by Tong *et al*. As shown in Scheme 5.12, DMAD **299** was added to a solution of nitrone

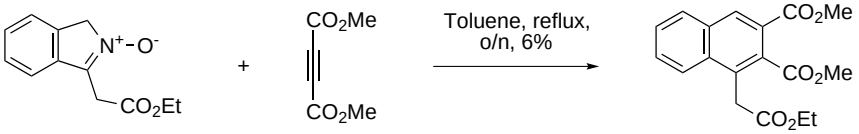
165 in toluene, and the reaction stirred at reflux overnight. It was hypothesised that the reaction would initially proceed *via* a [4+2] cycloaddition reaction, to afford the bridged intermediate **310**, that might then undergo chelotropic elimiation to afford the desired naphthalene **311**.



165 **299** **310** **311**

Scheme 5.12: **Attempted [4+2] cycloaddition reaction of nitrone 165 with DMAD 299**

The resultant ^{1}H NMR spectrum was very complex yet the starting materials, and bridged intermediate **310** could be discerned. Of the multitide of other peaks present, we identified a minor product we believed might correspond to the expected naphthalene product. After two purification attempts using column chromatography, we isolated a product that we identified as the naphthalene product **311** in 6% yield (Scheme 5.13). As well as evidence from the IR and HRMS spectra, the ^{1}H NMR spectrum of **311** showed diagnostic aromatic protons between δ 8.5 and 7.6 ppm, including a singlet at δ 8.50 ppm corresponding to the aromatic proton β to the methyl ester. ^{13}C DEPT NMR analysis was also consistent with the structure, confirming the expected number of CH/CH_3 and CH_2/quarternary carbon environments.



165 **299** **311**

Scheme 5.13: **Initial low yielding naphthalene synthesis**

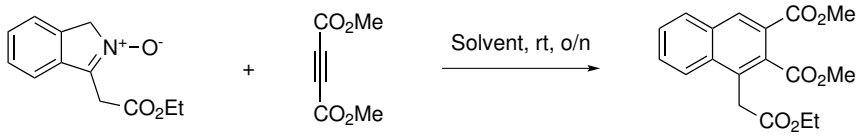
Despite the low 6% yield of naphthalene **311** obtained, this result was a significant breakthrough as we had previously imagined that the bridged hydroxylamine **310** might need to be subjected to further reaction conditions in order to synthesise the naphthalene. This result, however, provided evidence that the bridged hydroxylamine **310** had undergone a chelotropic elimination *in-situ*.

5.4 Reaction optimisation

5.4.1 Solvent screen

Although toluene was the most commonly used solvent for carrying out Diels-Alder reactions in the literature,[72,143] we decided to investigate what solvent system was optimal for running our naphthalene forming reaction. During our previous work synthesising nitrones, we had demonstrated that the reaction solvent played a large role in the reaction outcome. We therefore decided to carry out a solvent screen for the naphthalene forming reaction, with the aim of establishing whether a different solvent would facilitate both the [4+2] cycloaddition reaction *and* the subsequent cheletropic elimination step, to afford naphthalene **311** in higher yield.

The solvent screen was undertaken at room temperature (not reflux) due to the differing boiling temperatures of the solvents. Protic and aprotic solvents with an array of polarities were screened, as shown in Table 5.1. All reactions, bar the one in DMSO, were evaporated to produce a crude product which was analysed by NMR spectroscopy. The DMSO reaction was taken up in water and extracted five times with ether, before drying and evaporating to provide material for analysis.



165 **299** **311**

Scheme 5.14: **Reaction carried out for the solvent screen**

Table 5.1: **Solvent screen**

Entry	Solvent	Observation
1	Toluene (ref)	afforded same ^{1}H NMR spectra as previously[a]
2	Cyclohexane	-[a]
3	THF	naphthalene **311** = major product
4	$CHCl_3$	-[a]
5	DCM	-[a]
6	DMSO	naphthalene **311** = major product
7	IPA	-[a]
8	Methanol	-[a]

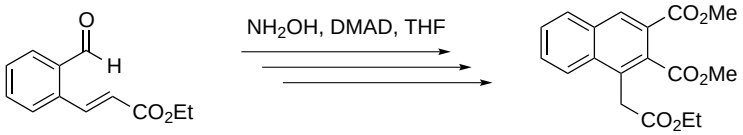
*Conditions: nitrone **165** (1.00 mmol), DMAD **299** (1.00 mmol), solvent (2 mL), rt,*

o/n. Yields not recorded. [a]% naphthalene product could not be determined due to presence of a complex mixture of compounds in the ^1H NMR spectra.

The ^{1}H NMR spectra from this set of experiments gave unexpected results which did not corroborate with the solvent polarity or protic/aprotic nature of the solvent. Whilst some conversion of nitrone and evidence for formation of naphthalene was observed in all solvents, it was not possible to integrate the NMRs and obtain quantifiable data due to the majority of the ^{1}H NMR spectra showing a complex mixture of compounds. The reactions in DMSO and THF, however, were clearly identified as the best results, due to the fact that both spectra showed naphthalene **311** as the major reaction product, with no starting material **165** remaining, and no complex mixture of products as observed in the spectra of the other solvents.

We then repeated the reaction in both DMSO and THF for just thirty minutes in an effort to observe possible reaction intermediates. However, the ^{1}H NMR spectra from these reactions were identical to those run overnight. This demonstrated the facile nature of not only the cycloaddition step, but also the subsequent chelotropic elimination step, which we had previously anticipated might require more forcing conditions to proceed.

We decided to carry out the remaining investigations using THF as this solvent was easier to work with and remove than DMSO. Due to previous work identifying THF as the optimum solvent in which to synthesise nitrones **165**, this result opened up the intriguing possibility of developing a one-pot reaction, involving the synthesis of naphthalenes **311** directly from the treatment of α,β-unsaturated ester **164** with hydroxylamine and DMAD **299**.

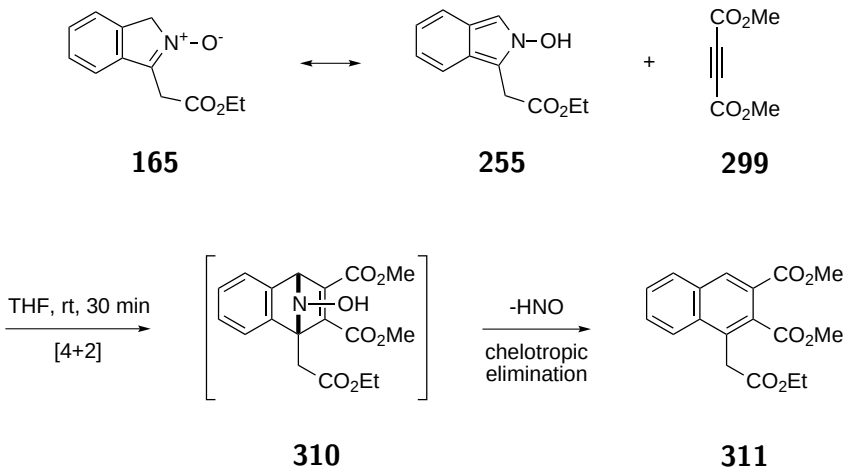


164 **165**

Scheme 5.15: **Could the use of THF solvent open up a one-pot pathway?**

5.4.2 Mechanistic study

In the reaction of nitrone **165** with an alkyne, we had suggested a mechanism whereby a bridged hydroxylamine was formed from a [4+2] cycloaddition reaction of its isoindol-*N*-oxide tautomer **255** with DMAD **299**, which then underwent a chelotropic elimination to afford naphthalene **311**, as shown in Scheme 5.16. To better understand the mechanism of the transformation of nitrone to naphthalene, we decided to carry out a ^{1}H NMR experiment to monitor the time course of the reaction.



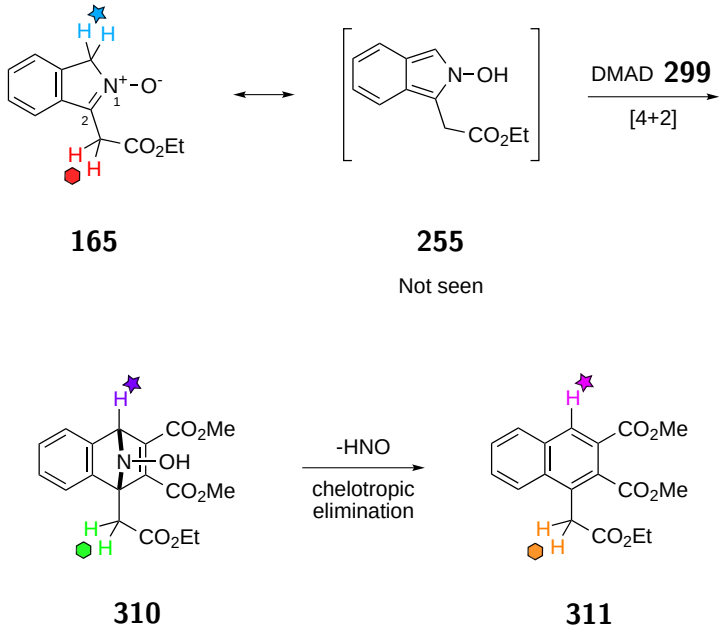
Scheme 5.16: **Proposed reaction mechanism for the synthesis of naphthalene 311 from nitrone 165**

The NMR experiment was run in deuterated THF, at room temperature, using a 500 MHz NMR spectrometer. ^{1}H NMR spectra were recorded every five minutes over a two hour period. Highlighted results from this experiment are shown below in both Scheme 5.17 and Figure 5.7, with key peaks colour coded for clarity.

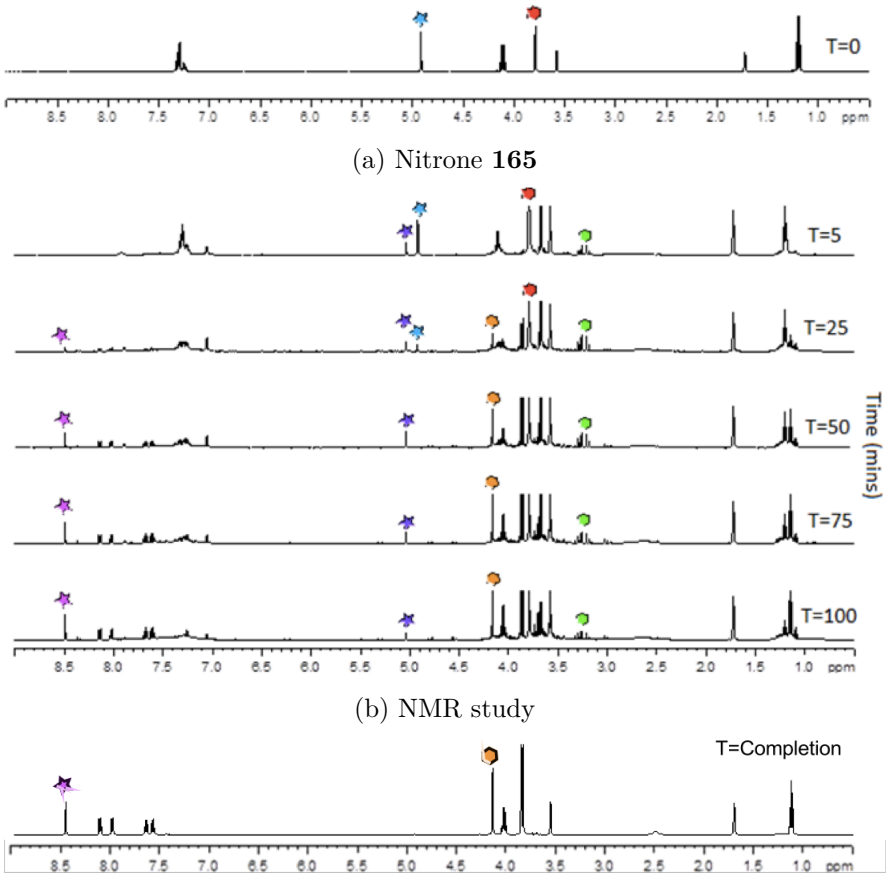
All of the starting nitrone material **165** (red and blue peaks) was consumed around the thirty minute mark. During this time, peaks for another compound emerged which we assigned as the bridged hydroxylamine **310**. The sp^2 hybridised C_2 carbon of the nitrone became the sp^3 hybridised carbon of the bridged hydroxylamine during this reaction, and the nitrogen atom also lost its charge. The CH_2 group (in green) of the hydroxylamine intermediate is therefore shifted upfield from δ 3.8 ppm to $\sim \delta$ 3.2 ppm, where it appears as a multiplet peak with a diastereotopic splitting pattern rather than as a singlet peak. The singlet peak corresponding to the CH group bonded to the nitrogen atom (in purple) is shifted downfield slightly to δ 5.0 ppm compared to the blue CH_2 group of the nitrone at δ 4.9 ppm.

From the thirty minute mark, peaks corresponding to the naphthalene product **311** began to emerge, with its CH_2 group corresponding to a singlet peak at δ 4.1 ppm (orange). A diagnostic singlet peak at δ 8.5 ppm (in pink) corresponding to the aromatic proton β- to the methyl ester group was also observed. Importantly, this NMR study showed that the emergence of naphthalene **311** occured as the hydroxylamine intermediate **310** disappeared.

The reaction did not reach completion within the two hour time frame, despite previously reaching completion within thirty minutes in a preparative reaction in the laboratory. This was thought to be due to a lack of stirring mechanism in the NMR tube.



Scheme 5.17: **^{1}H NMR mechanistic study of naphthalene synthesis**



(a) Nitrone **165**

(b) NMR study

(c) Naphthalene **311**

Figure 5.7: **^{1}H NMR mechanistic study of naphthalene synthesis**

This study provided a valuable insight into the reaction mechanism as it provided evidence that naphthalene formation occurred *via* the bicyclic intermediate **310**, which was stable enough to be observed in the NMR spectrum. Peaks corresponding to the isoindol-*N*-oxide tautomer were not observed in the mechanistic study. We propose that the tautomerisation event and subsequent [4+2] cycloaddition of the isoindol-*N*-oxide with DMAD **299** occur more quickly than the timeframe of the NMR spectrometer can observe.

5.4.3 Reaction scale up

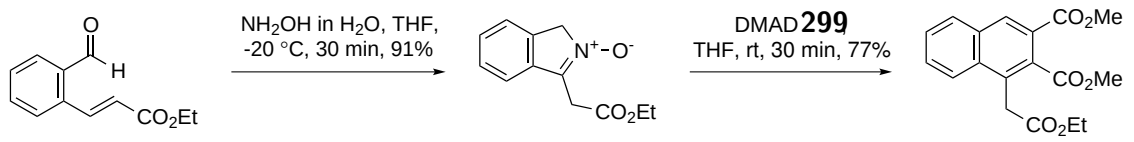
Having successfully synthesised naphthalene **311** from nitrone **165** and identified optimum reaction conditions, the reaction was run at a larger scale to obtain an accurate yield. DMAD **299** was added to a solution of the nitrone **165** (10 mmol) in THF at room temperature. The reaction was stirred for thirty minutes, and the solvent removed under reduced pressure. The crude product was purified using column chromatography to afford naphthalene **311** as a yellow oil in 87% yield.

165 **311**

Scheme 5.18: **Synthesis of naphthalene 311 from nitrone 165**

5.5 A “one-pot” synthesis of naphthalenes from aldehydes

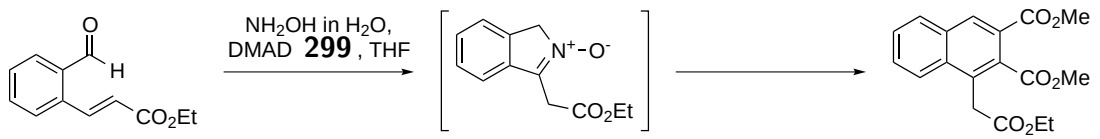
Our research up until this point was based on a stepwise synthesis from aldehyde to nitrone to naphthalene as shown in Scheme 5.19.



164 **165** **311**

Scheme 5.19: **Stepwise synthesis of naphthalene 311**

We now wanted to establish whether conditions could be developed that would allow for naphthalene formation directly from aldehyde **164** in an efficient one-pot procedure, involving *in-situ* nitrone/isoindol-*N*-oxide generation, as shown in Scheme 5.20.



164 **165** **311**

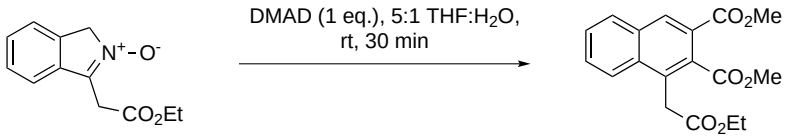
Scheme 5.20: **Proposed one-pot synthesis of naphthalene 311**

To begin investigating this one-pot reaction, we had to determine whether the reagents used in synthesising the nitrone would be compatible with the subsequent naphthalene formation. It was decided to study the effect of both water and hydroxylamine on the subsequent nitrone to naphthalene transformation.

5.6 Reaction investigation

5.6.1 Effect of water on the Diels-Alder cycloaddition reaction

Water was present in the nitrone forming reaction as part of the hydroxylamine solution. However, water was not present in the naphthalene forming Diels-Alder reaction discussed above in Section 5.4.3. Therefore, our first step was to determine whether the presence of water in the naphthalene forming reaction would negatively affect its outcome. We added water as a co-solvent to the reaction of nitrone **165** (after tautomerisation) and DMAD **299** to investigate, and ran a reaction using our standard screening conditions alongside.



165 **311**

Scheme 5.21: **Investigating whether water affects naphthalene synthesis form nitrone**

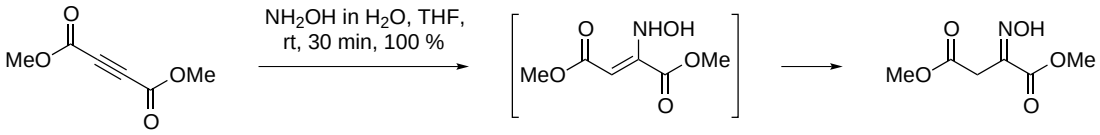
Both reactions resulted in naphthalene **311** in essentially the same yield, and therefore, it was concluded that water would not inhibit the production of naphthalene in a one-pot reaction directly from aldehyde **164**.

5.6.2 Effect of hydroxylamine on the Diels-Alder cycloaddition reaction

With this new one-pot reaction aim another variable, hydroxylamine, needed to be investigated. We knew that an excess of hydroxylamine was used in the nitrone forming reaction, and that this excess did not affect the nitrone once it had been formed. However, it was thought that a reaction between hydroxylamine and the alkyne (DMAD **299**)

might cause issues for the synthesis of naphthalene from nitrone.

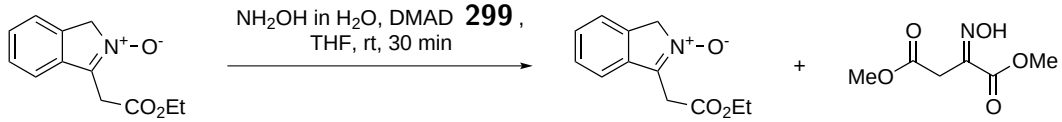
It had been reported in the literature that reaction of DMAD with hydroxylamine would form an oxime.[176] Indeed, on repeating this reaction, oxime **312** was obtained in 100% yield (Scheme 5.22). This oxime is formed *via* conjugate addition of hydroxylamine to the alkyne, followed by isomerisation of the resultant *N*-hydroxy enamine to the oxime, whose structure was confirmed by comparison with literature NMR values.[176]



299 **312**

Scheme 5.22: **Reaction of DMAD with hydroxylamine**

We needed to investigate whether this competing reaction would hamper the development of our one-pot reaction. Initially we decided to determine whether hydroxylamine would affect the reaction of nitrone **165** with the alkyne, DMAD **299**, and so we added one equivalent of each of these reagents to THF and stirred for thirty minutes, as shown in Scheme 5.23.



165 **165** **312**

Scheme 5.23: **Reaction of nitrone 165, hydroxylamine and DMAD 299**

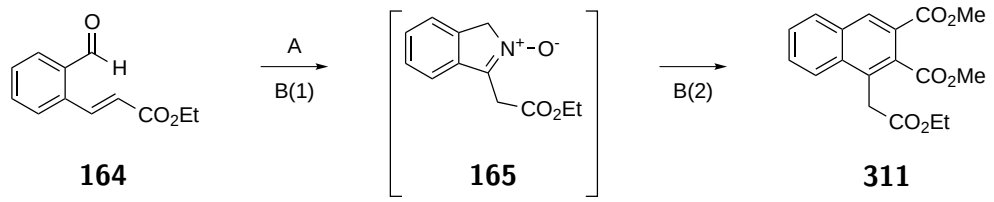
The ^{1}H NMR spectrum of the reaction showed unreacted nitrone **165** and the oxime **312** in an almost 1:1 ratio, with virtually none of the desired naphthalene being present. Thus, hydroxylamine severely inhibits the [4+2] cycloaddition reaction and therefore the production of naphthalene **311**, as DMAD **299** reacts almost exclusively with it rather than with the nitrone **165**. This significant result would suggest that for the one-pot efforts, the hydroxylamine used to synthesise the nitrone would have to be completely consumed in order for the subsequent [4+2] cycloaddition reaction to be viable.

5.6.3 Effect of hydroxylamine on initial "one-pot" efforts

The results described in sections 5.6.1 and 5.6.2 showed that any unreacted hydroxylamine from the nitrone synthesis would impact the subsequent [4+2] cycloaddition reaction, whilst the presence of water would have no effect. So to begin investigating a one-pot

synthesis, we chose to use one equivalent of all of the reagents. Originally when synthesising the reactive nitrone, we ran the reaction at -20 °C to isolate it as a solid, however, as we were now looking to consume the reactive nitrone *in-situ*, the low temperature was no longer required.

At this point, we knew that reaction of hydroxylamine with aldehyde **164**, and the separate reaction of hydroxylamine with alkyne **299**, both took place within thirty minutes. We did not know, however, whether the hydroxylamine had a preference to react with the aldehyde **164** or the alkyne **299**, if both were present. This was the reason for attempting two different one-pot procedures. The first reaction involved hydroxylamine and DMAD **299** being added to the aldehyde **164** simultaneously, as shown in Scheme 5.24 (Method A). Whereas, in the second procedure, there was a stepwise thirty minute delay between the hydroxylamine and alkyne **299** being added (Method B). This method was analysed by TLC to ensure complete formation of the intermediate nitrone **165**, before the alkyne was added, which we hoped would ensure good yields of the desired naphthalene **311**.

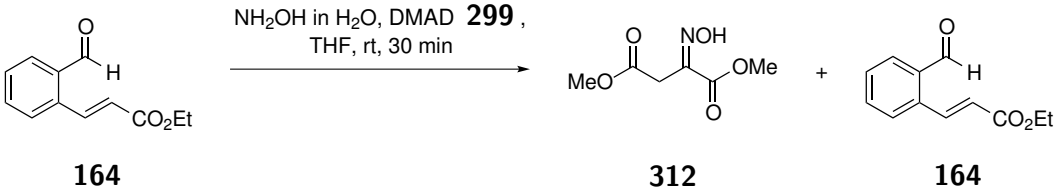


164 **165** **311**

Scheme 5.24: **Proposed methods for the one-pot the synthesis of naphthalene 311**

*Conditions: aldehyde **164** (1.00 mmol), NH_2OH aq. (1.00 mmol), DMAD **299** (1.00 mmol), solvent (2 mL), rt, 30 min. Yields not recorded.*

The ^{1}H NMR spectrum from method A showed oxime **312** and the aldehyde **164** starting material present in an almost 1:1 ratio. Nitrone **165**, naphthalene **311** and DMAD **299** were all present as minor products. This result showed that hydroxylamine preferentially reacts with DMAD over the aldehyde **164**. This meant that a one-pot stepwise approach was the only option to synthesise naphthalene **311** directly from aldehyde **164**.

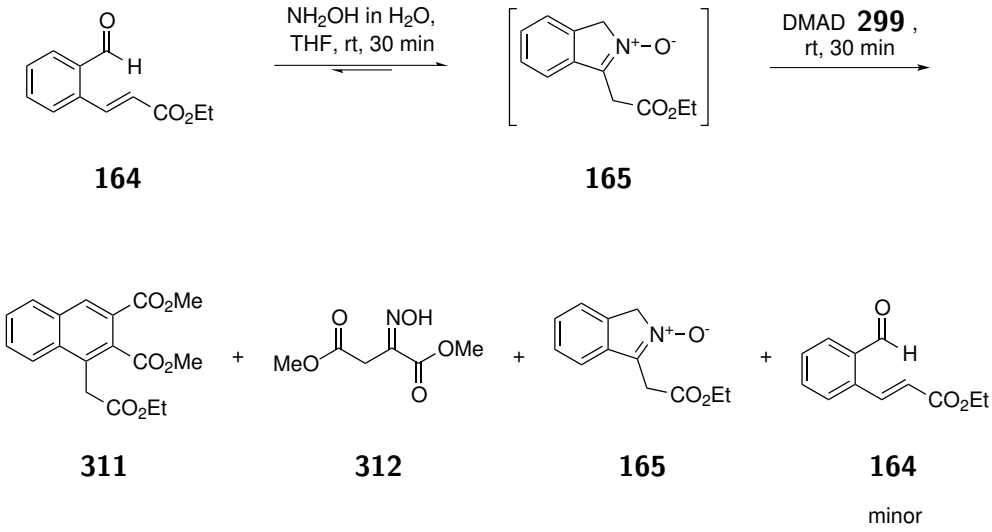


164 **312** **164**

major reaction products

Scheme 5.25: **Method A - simultaneous addition**

The ^{1}H NMR spectrum from method B, the sequential method, did not match our expectations. Although naphthalene **311** was present as a major product, nitrone **165** and oxime **312** were also present, as was the aldehyde starting material **164** as a minor product (Scheme 5.26). This suggested that the nitrone forming reaction was potentially reversible, generating small amounts of aldehyde and hydroxylamine. The hydroxylamine was then able to react with DMAD to form the observed oxime **312**

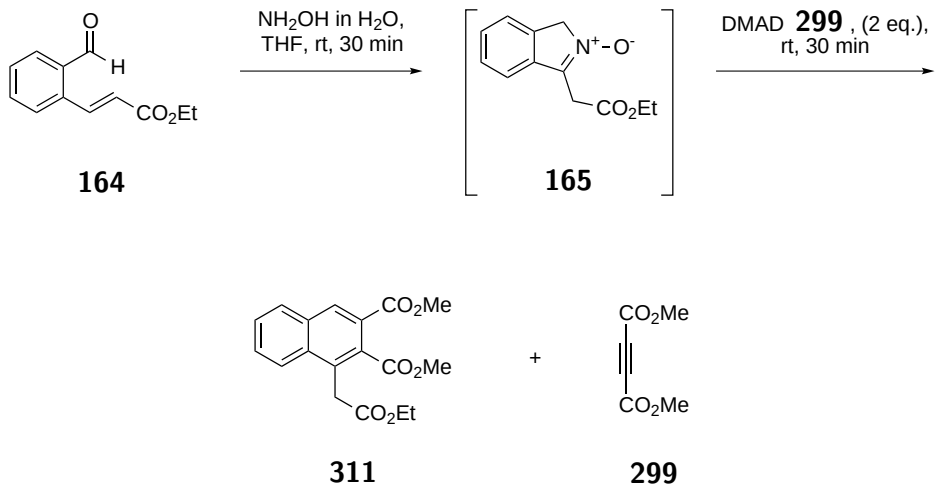


Scheme 5.26: **Method B - sequential addition**

5.6.4 Effect of alkyne

As DMAD could be consumed by both the hydroxylamine and the nitrone, we next investigated increasing the amount of DMAD **299** in the reaction. It was hoped that this would increase the rate of consumption of nitrone to afford a better yield of naphthalene product.

On this basis the sequential one-pot procedure (method B) was repeated using two equivalents of alkyne. The reaction using one equivalent of DMAD **299** as previously was also carried out alongside for reference.

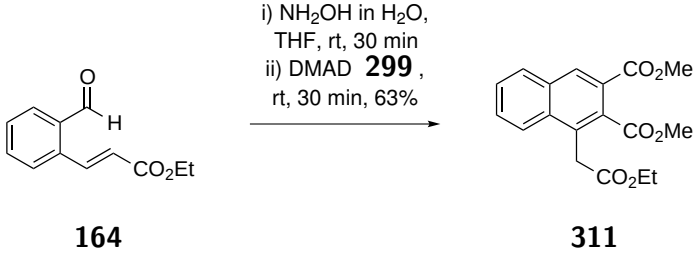


Scheme 5.27: **Sequential one-pot reaction using excess alkyne 299**

The reference experiment gave the same crude ^{1}H NMR spectrum as we had seen previously. The reaction using an excess of DMAD **299** afforded an ^{1}H NMR spectrum that showed naphthalene **311** and unreacted DMAD as the major products and oxime **312** as a minor product. When the methyl ester singlet of DMAD was integrated relative to the aromatic singlet peak of the naphthalene, we were pleased to observe that the two compounds were present in a 0.74:1.00 ratio (naphthalene:alkyne).

5.6.5 Reaction scale up

Due to time constraints our development work ended at this point. Although further research is needed to fine tune the reaction, we took our optimised one-pot reaction conditions from the screening work and applied them on a larger scale to determine whether we had created a viable synthetic route from α,β-unsaturated ester **164** to naphthalene **311**. Therefore, hydroxylamine (1 eq.) was added to a solution of **164** (10.00 mmol) in THF (20 mL) at room temperature, and the reaction mixture left to stir for thirty minutes. DMAD **299** (2 eq.) was then added, and the reaction left for a further thirty minutes. After removal of THF under reduced pressure and purification by column chromatography, naphthalene **311** was afforded as a yellow oil in 63% yield.



Scheme 5.28: **Optimised one-pot synthesis of naphthalene 311**

5.7 Conclusion

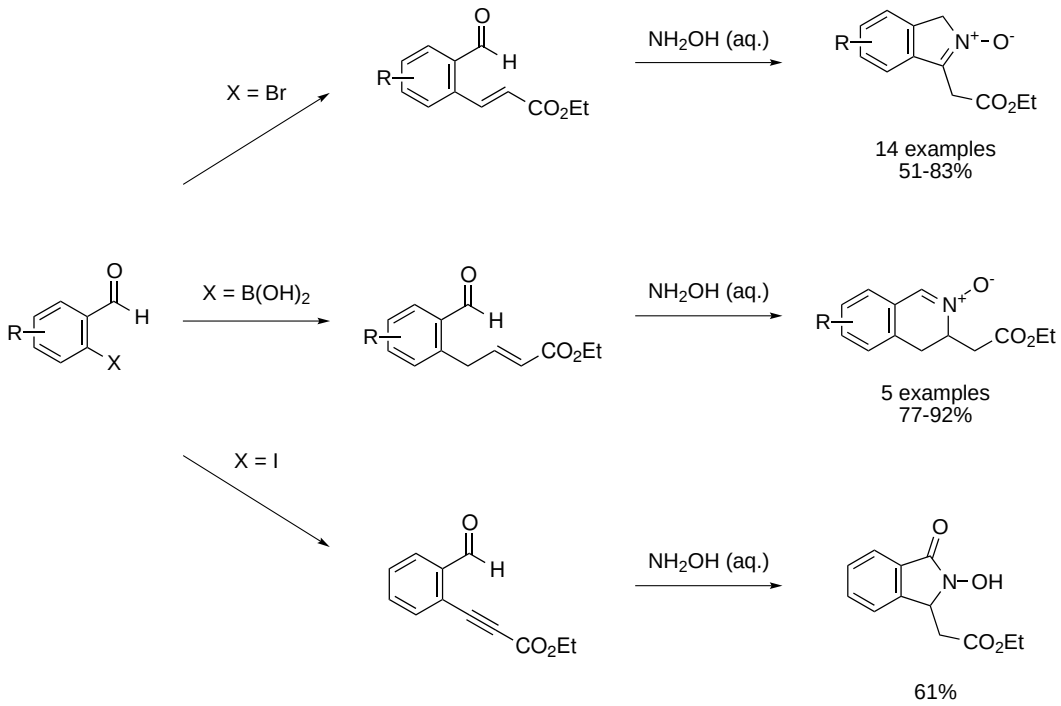
Promising preliminary work has been undertaken to establish a novel method to directly synthesise substituted naphthalenes from both nitrones **165** and α,β-unsaturated esters **164**. The reported procedure possesses many advantages when compared to current literature methods. For example; it negates the need for a metal catalyst or oxidant and does not require high temperatures, inert conditions, or reaction work-up. In addition, the sequential "one-pot" procedure reaches completion in a 1 hour time period, unlike many of the syntheses in the literature which require multiple steps or longer total reaction times. Further work is needed to fully develop the one-pot reaction conditions in order to explore the substrate scope of the reaction. The α,β unsaturated substrates synthesised in Chapter 3 could all be taken through the reaction to produce tri- and tetra- substituted naphthalenes, and changing the alkyne from DMAD **299** opens up the possibility to add further functionality to the right hand side of the naphthalene scaffold. This novel research, whilst still in its early stages, is a very promising methodology for the direct synthesis of naphthalenes.

Chapter 6

Conclusions & Future Work

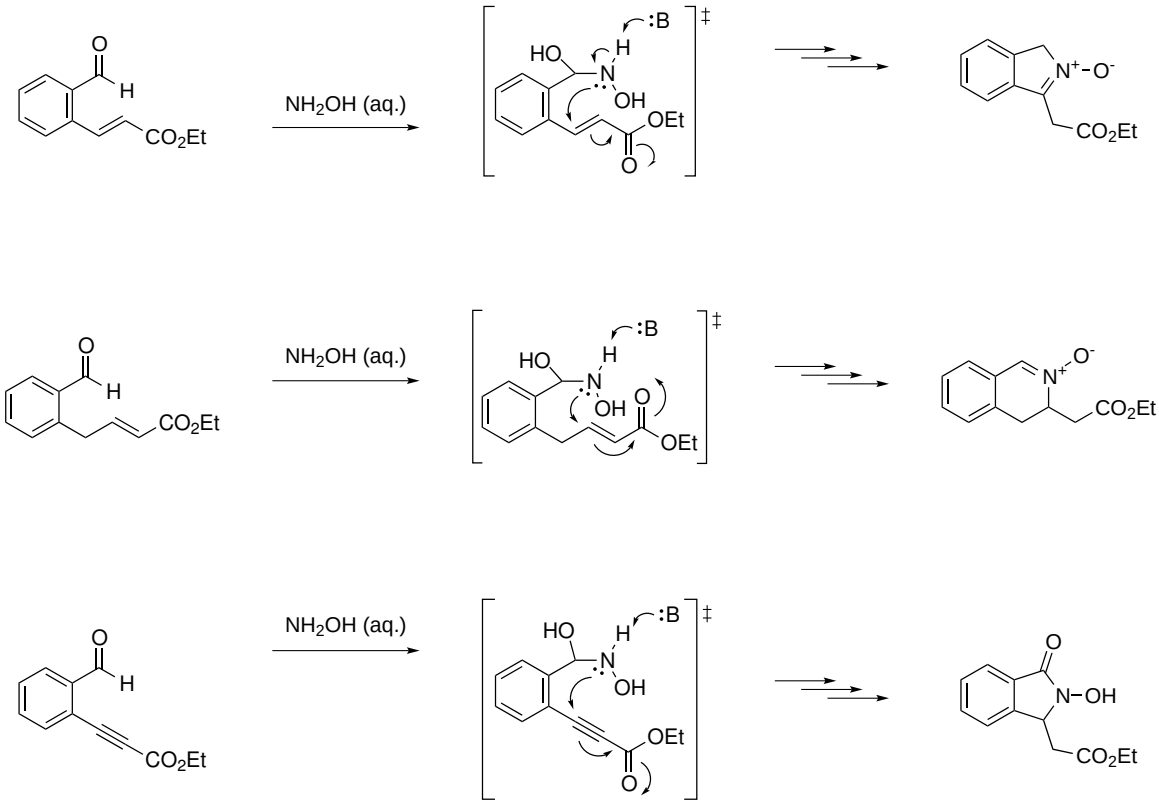
6.1 Conclusions

The development and application of a novel conjugate addition/cyclisation methodology for the synthesis of isoindole derived nitrones has been demonstrated. Extending the methodology to modified cyclisation substrates has also afforded dihydroisoquinoline derived nitrones and a cyclic hydroxamic acid (Scheme 6.1). Each of these three end products have ultimately been obtained through the employment of readily available 2-substituted benzaldehydes.



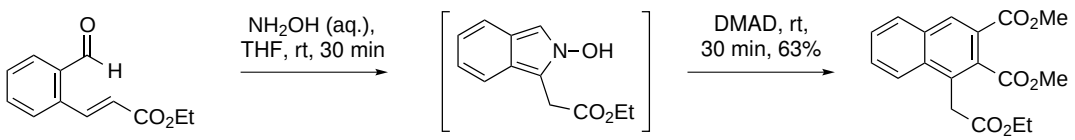
Scheme 6.1: **Synthesis of isoindole nitrones, dihydroisoquinoline nitrones and a cyclic hydroxamic acid from 2-substituted benzaldehydes**

Mechanistically it has been shown that the reaction of cyclisation substrates with hydroxylamine proceeds *via* hydroxyamino alcohol intermediates which nucleophilically attack the α,β-unsaturated ester in a 1,4 manner, and not *via* oxime intermediates nor any type of 1,3-azaprotio cyclotransfer reaction.



Scheme 6.2: **The conjugate addition/cyclisation reaction proceeds *via* common hydroxyamino alcohol intermediates**

Research into the reactivity of nitrone **165** gave a mixture of results, whilst reactions of the dihydroisoquinoline nitrone **227** and cyclic hydroxamic acid **232** successfully afforded isoxazolidine, pyrrole and lactam scaffolds. Preliminary results regarding the synthesis of naphthalenes from cyclisation substrate **323**, *via* a [4+2] Diels-Alder cycloaddition/chelotropic elimination reaction of the isoindole tautomer of nitrone **165**, have also been described.

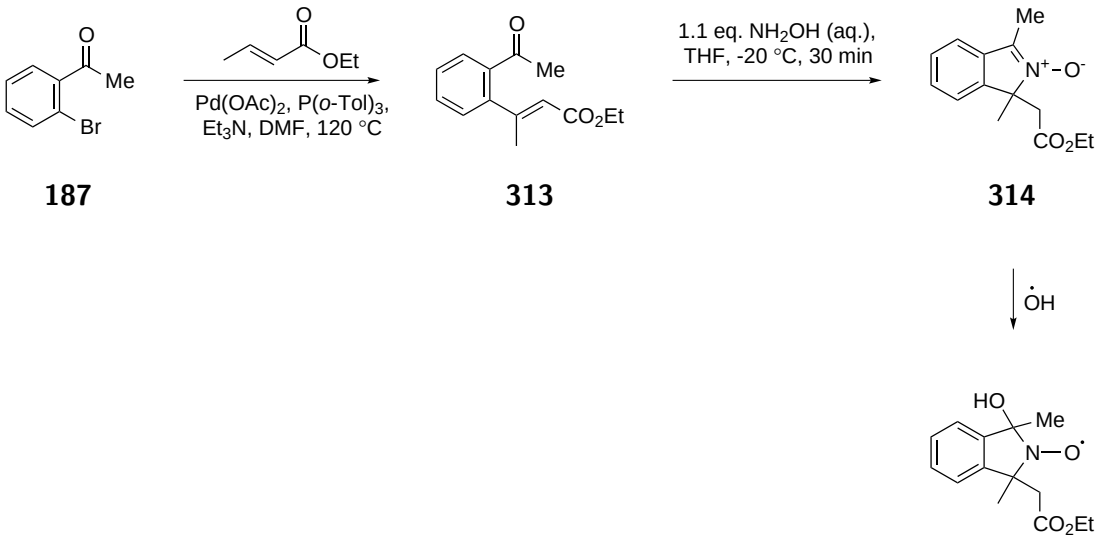


164 **181** **311**

Scheme 6.3: **Naphthalene synthesis from aldehyde 164**

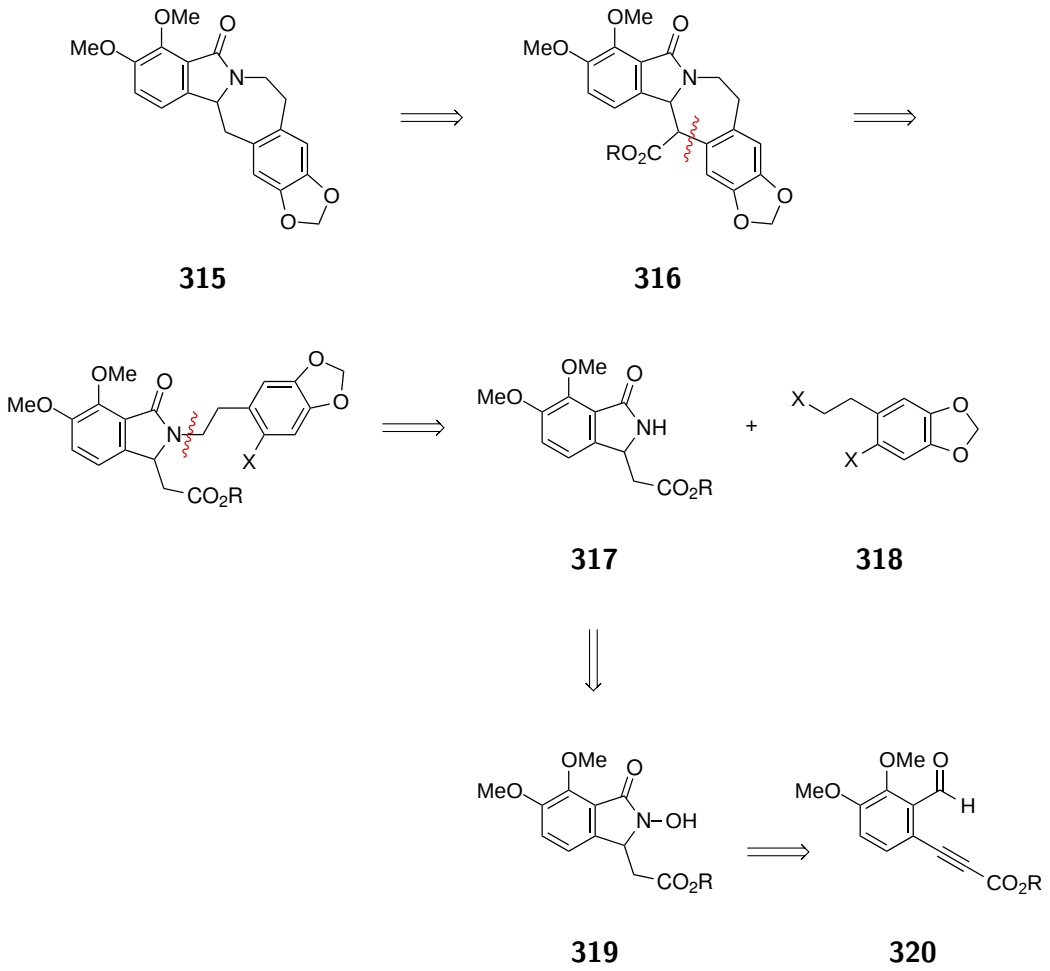
6.2 Future work

At the beginning of this thesis the use of nitrones as spin traps, and the development of isoindole derived spin traps, was discussed. We expressed an interest in analysing a suitable isoindole derived nitrone for its spin trapping properties. Inevitably we focussed on the synthetic utility of the first nitrone we synthesised, nitrone **165**. Hence, the first target for any future work would be to synthesise an appropriate analogue of nitrone **165** and submit it for EPR studies to determine its potential to act as a selective spin trap. A nitrone with increased substitution around the five membered ring would reduce the susceptibility of its spin adducts to disproportionation. A Heck cross-coupling reaction between 2-bromoacetophenone **187** and ethyl crotonate could afford the cyclisation substrate **313**, which upon reaction with hydroxylamine using our conjugate addition/cyclisation protocol, may potentially yield the suitable nitrone for EPR analysis **314**.



Scheme 6.4: **Suggested synthesis of a suitable nitrone spin trap and formation of its -OH spin adduct**

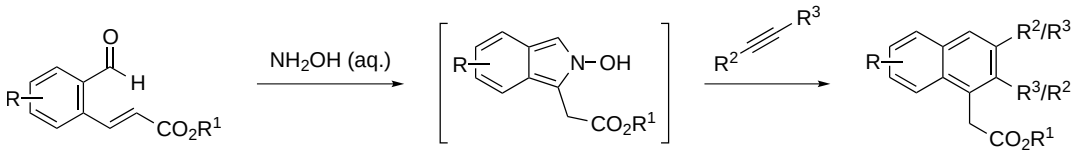
It would also be interesting to utilise the conjugate addition/cyclisation methodology in the synthesis of a natural product. In Chapter 3 we highlighted a few natural products containing the bicyclic lactam structure that is set up in the reaction of an alkyne containing cyclisation substrate with hydroxylamine. Scheme 6.5 shows the retrosynthetic analysis of Lennoxamine, an isoindolobenzazepine alkaloid, which we have used to demonstrate the potential incorporation of our novel methodology for natural product synthesis. The conjugate addition/cyclisation of alkyne **320** would afford the cyclic hydroxamic acid **319**, which would yield the lactam **317** upon reaction with ruthenium trichloride and zinc-copper couple to cleave the N-O bond. *N*-alkylation with the benzodioxole fragment **318** followed by an intramolecular palladium catalysed cross-coupling of the aryl halide portion with the ester enolate would afford the pentacyclic lactam **316**. Reductive decarboxylation would provide Lennoxamine **315**.



Scheme 6.5: **Retrosynthetic analysis of Lennoxamine 315**

Finally, perhaps the most promising area for further investigation is the novel [4+2] Diels-Alder cycloaddition/chelotropic elimination methodology for the synthesis of naphthalenes. Further experiments to explore the robustness and scope of this methodology are required. A key method to determine this would be to run a screen reacting nitrone **165** with different alkyne dipolarophiles, to potentially afford naphthalenes with a variety of substitution patterns around the scaffold. Results from Chapter 3 already show the range of substituents around the aromatic ring, and the variety of α,β-unsaturated electron withdrawing groups, that can be successfully incorporated in the nitrone starting material.

After determining the limitations of the cycloaddition step, naphthalene synthesis from aldehyde starting materials could then be rolled out (Scheme 6.6).



Scheme 6.6: **Potential synthesis of a library of substituted naphthalenes**

Chapter 7

Experimental

7.1 General conditions

Infrared spectra (4000 cm^{-1} to 0 cm^{-1}) were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer using a Universal ATR accessory for sampling. The machine has internal calibration and only selected peaks are quoted in ν (wavenumbers, cm^{-1}).

Proton magnetic resonance spectra were recorded at 300.22 MHz on a Bruker Avance 300 spectrometer unless otherwise stated. Chemical shifts (δH) are quoted in parts per million and are referenced to the residual solvent peak. The multiplicities and general assignments of spectroscopic data are denoted as: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), triplet of doublets (td), quartet of doublets (qd), triplet of triplets (tt), multiplet (m), aromatic (Ar), and apparent (app.). Coupling constants (J) are quoted to the nearest 0.1 Hz. Carbon magnetic resonance spectra were recorded at 75.5 MHz on a Bruker Avance 300 spectrometer unless otherwise stated. Chemical shifts (δC) are quoted in parts per million and are referenced to the residual solvent peak. Coupling constants (J) are quoted to the nearest 0.1 Hz.

Mass spectra were recorded on a Bruker Daltonics micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer. Samples were introduced either by syringe pump or flow injection using an auto-sampler. Samples were diluted in either methanol or acetonitrile.

All capillary melting point determinations were carried out using Büchi 535 melting point apparatus and reported to the nearest degree Celsius.

Analytical thin layer chromatography was carried out using commercially available polyethylene backed plates coated with Merck Kieselgel 60 GF254. Plates were visualised under UV light (at 254 nm) or by staining with potassium permanganate, *p*-anisaldehyde or phosphomolybdic acid followed by heating. Flash chromatography was performed under medium pressure using Merck 60 H silica gel (35-75 μm). Samples were loaded as satu-

rated solutions in an appropriate solvent.

Reactions requiring anhydrous conditions were performed under nitrogen in oven-dried apparatus, which was allowed to cool under nitrogen prior to use. Anhydrous solvents were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. Petrol refers to the fraction of petroleum ether boiling at 40-60 °C. Ether refers to diethyl ether. Hexanes refer to the hexane fraction of petroleum. Solvents were evaporated on a Büchi Rotorvapor.

All commercially available compounds were used as obtained from the chemical suppliers. All temperatures quoted are external.

7.2 General procedures

7.2.1 General procedure A: Synthesis of acetal protected aldehydes

To a solution of aldehyde (5.0 mmol, 1.0 eq.) in toluene, was added 1,3-propanediol (1.5 eq.) and *p*TSA (0.1 eq.). The reaction was heated to reflux and left to stir for 7 hours. After cooling to room temperature, the reaction was extracted with three portions of H_2O, dried over $MgSO_4$ and the solvent removed under reduced pressure to afford the crude acetal protected product.

7.2.2 General procedure B: Synthesis of Heck cross-coupled products

To a solution of acetal protected aldehyde (4.0 mmol, 1.0 eq.), $Pd(OAc)_2$ (1.0 mol%) and (*o*-Tol)$_3$P (2.0 mol%) in DMF, were added Et_3N (1.5 eq.) and ethyl acrylate **162** (1.5 eq.). The reaction was heated to 120 °C and monitored by TLC analysis (DCM, UV visualisation). Upon reaction completion, a 1:1 mixture of ether:Hexanes was added and the solution cooled to 0 °C for 30 minutes. Following filtration of the precipitate using a plug of Celite®, the combined organic solution was extracted with H_2O and brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. This afforded the crude Heck cross-coupled product.[76]

7.2.3 General procedure C: Synthesis of (*E*)-ethyl-formylacrylates

To the Heck cross-coupled product (3.0 mmol, 1.0 eq.) was added a 7:3 mixture of glacial acetic acid:H_2O. The mixture was heated to 50 °C and monitored by TLC. After deprotection, the reaction mixture was separated between Et_2O and H_2O. The H_2O layer was extracted with Et_2O twice and the combined organic layers were neutralised *via* addition of sodium hydrogencarbonate ($NaHCO_3$) until the gas production stopped. After separation, the organic layer was washed with H_2O and brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to afford the crude ((*E*)-ethyl-formylacrylate).

7.2.4 General procedure D: Synthesis of (*E*)-ethyl-formylbutenoates

To a solution of the boronic acid (3.0 mmol) and allyl bromide (1.2 eq.) in THF (0.2 M), were added $PdCl_2(PPh_3)_2$ (2.5 mol%) and aqueous Na_2CO_3 (1.0 M, 2.0 eq.) solution. The reaction mixture was heated to reflux and stirred for 4 hours. The reaction was quenched with H_2O and extracted with DCM (x3). The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent removed under reduced pressure, to afford the crude Suzuki cross-coupled product.[103]

To a solution of the crude cross-coupled product in DCM was added Grubbs I catalyst (5.0 mol%) and ethyl acrylate **162** (5.0 eq.). The reaction was heated to 40 °C and stirred overnight. The solvent was removed under vacuum to afford the crude cross metathesis product - (*E*)-ethyl-formylbutenoate.[107,108]

7.2.5 General procedure E: Synthesis of isoindole nitrones

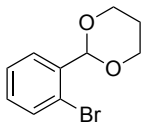
To a solution of aldehyde (2.0 mmol, 1.0 eq.) in THF at -20 °C was added hydroxylamine (50 wt. % in H_2O) (1.1 eq.). The reaction was stirred for 30 minutes. Solids were filtered using a Sinter funnel and dried under vacuum to afford the crude nitrone product. For reactions where no solid was observed, the crude mixture was separated between DCM and H_2O. The H_2O layer was extracted with two portions of DCM, the combined organic layer dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford the nitrone product.

7.2.6 General procedure F: Synthesis of dihydroisoquinoline nitrones

To a solution of aldehyde (2.0 mmol, 1.0 eq.) in THF at room temperature was added hydroxylamine (50 wt. % in H_2O) (1.1 eq.). The reaction was stirred for 30 minutes. Solids were filtered using a Sinter funnel and dried under vacuum to afford the crude nitrone product. For reactions where no solid was observed, the crude mixture was separated between DCM and H_2O. The H_2O layer was extracted with two portions of DCM, the combined organic layer dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to afford the nitrone product.

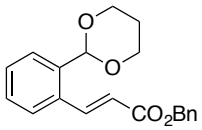
7.3 Compound data

2-(2-bromophenyl)-1,3-dioxane 147



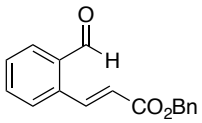
General procedure A was followed using 2-bromobenzaldehyde **137** (925 mg, 5.00 mmol), followed by recrystallisation from petrol:ether, to provide the title compound as white needles in 88% yield (1.07 g, 4.40 mmol). m.p. 83-84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.69 (1H, dd, J = 7.8, 1.7 Hz, ArH), 7.52 (1H, dd, J = 8.0, 1.3 Hz, ArH), 7.33 (1H, td, J = 7.6, 1.2 Hz, ArH), 7.19 (1H, td, J = 7.7, 1.7 Hz, ArH), 5.76 (1H, s, CH), 4.29 (1H, dd, J = 5.1, 1.3 Hz, OCH_AH$_B$), 4.25 (1H, dd, J = 5.1, 1.3 Hz, OCH$_A$$H_B$), 4.03 (2H, td, J = 12.2, 2.4 Hz, OCH_2), 2.32-2.16 (1H, m, CH$_2$CH_AH$_B$CH$_2$), 1.48-1.41 (1H, m, CH$_2$CH$_A$$H_BCH_2$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 137.47, 132.57, 130.27, 128.04, 127.51, 122.27, 100.88, 67.56, 25.67; IR (thinfilm) ν_{max} (cm^{-1}): 1594 (ArC=C), 1570 (ArC=C); HRMS (ESI): m/z calculated for $C_{10}H_{11}BrO_2$: requires: 264.9840 for [M+Na]$^+$; found: 264.9839.

Benzyl (*E*)-3-(2-(1,3-dioxan-2-yl)phenyl)acrylate 148



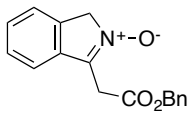
General procedure B was followed using 2-(2-bromophenyl)-1,3-dioxane **147** (972 mg, 4.00 mmol). After 3 hours, the reaction was worked up and purified by column chromatography (eluent: 90:10 petrol:EtOAc) to yield the title compound as a yellow oil in 80% yield (1.04 g, 3.20 mmol). R_f (90:10 petrol:EtOAc) = 0.29; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.25 (1H, d, J = 15.9 Hz, ArCH=CH), 7.73 (2H, td, J = 7.0, 1.7 Hz, ArH), 7.51-7.40 (3H, m, ArH), 7.33-7.28 (4H, m, ArH), 6.37 (1H, d, J = 15.9 Hz, ArCH=CH), 5.62 (1H, s, CH), 5.25 (2H, s, CH_2Ar), 4.30 (1H, dd, J = 5.0, 1.3 Hz, OCH_AH$_B$), 4.24 (1H, dd, J = 5.0, 1.3 Hz, OCH$_A$$H_B$), 3.95 (2H, td, J = 12.2, 2.4 Hz, OCH_2), 2.35-2.18 (1H, m, CH$_2$CH_AH$_B$CH$_2$), 1.49-1.42 (1H, m, CH$_2$CH$_A$$H_BCH_2$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 166.12, 142.11, 137.51, 136.43, 135.61, 133.24, 132.78, 129.99, 128.78, 128.41, 127.32, 126.48, 120.22, 100.43, 67.59, 66.45, 25.75; IR (thinfilm) ν_{max} (cm^{-1}): 1709 (C=O), 1634 (C=C); HRMS (ESI): m/z calculated for $C_{20}H_{20}O_4$: requires: 325.1475 for [M+H]$^+$; found: 325.1261.

Benzyl (*E*)-3-(2-formylphenyl)acrylate 138



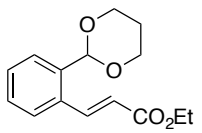
General procedure C was followed using benzyl (*E*)-3-(2-(1,3-dioxan-2-yl)phenyl)acrylate **148** (973 mg, 3.00 mmol). After 4 hours, the reaction was worked up and purified by column chromatography (eluent: 80:20 petrol:EtOAc) to provide the title compound as a yellow oil in 67% yield (535 mg, 2.01 mmol). R_f (80:20 petrol:EtOAc) = 0.50; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 10.29 (1H, s, C*H*O), 8.50 (1H, d, J = 15.9 Hz, ArC*H*=CH), 7.87 (1H, d, J = 6.7, 1.4 Hz, Ar*H*), 7.62-7.52 (3H, m, Ar*H*), 7.45-7.38 (5H, m, Ar*H*), 6.42 (1H, d, J = 15.9 Hz, ArCH=C*H*), 5.28 (2H, s, C*H*$_2$Ar); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 191.69, 165.97, 141.55, 136.50, 135.89, 133.88, 132.26, 129.96, 128.60, 128.28, 127.96, 122.79, 66.55; IR (thinfilm) ν_{max} (cm^{-1}): 1709 (O-C=O), 1693 (H-C=O), 1632 (C=C); HRMS (ESI): m/z calculated for $C_{17}H_{14}O_3$: requires: 267.1021 for $[M+H]^+$; found: 267.1016; requires: 289.0840 for $[M+Na]^+$; found: 289.0828.

3-(2-(benzyloxy)-2-oxoethyl)-1*H*-isoindole 2-oxide 152



General procedure E was followed at room temperature using benzyl (*E*)-3-(2-formylphenyl) acrylate **138** (533 mg, 2.00 mmol). The title compound was formed as a brown oil in 78% yield (439 mg, 1.56 mmol) and required no further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.30-7.17 (9H, m, Ar*H*), 5.12 (2H, s, OC*H*$_2$Ar), 4.94 (2H, s, ArC*H*$_2$N), 3.89 (2H, s, C*H*$_2$C=O); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 167.22, 141.69, 135.74, 135.29, 133.22, 128.57, 128.41, 128.32, 128.09, 121.62, 119.43, 67.34, 65.86, 29.92; IR (thinfilm) ν_{max} (cm^{-1}): 1725 (C=O); HRMS (ESI): m/z calculated for $C_{17}H_{15}NO_3$: requires: 282.1130 for $[M+H]^+$; found: 282.1118; requires: 304.0949 for $[M+Na]^+$; found: 304.0938.

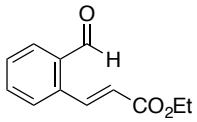
Ethyl (*E*)-3-(2-(1,3-dioxan-2-yl)phenyl)acrylate 163



General procedure B was followed using 2-(2-bromophenyl)-1,3-dioxane **147** (972 mg, 4.00 mmol). After 3 hours, the reaction was worked up and purified by column chromatography (eluent: 90:10 petrol:EtOAc) to yield the title compound as a yellow oil in 77% yield (808

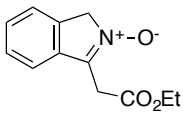
mg, 3.08 mmol). R_f (90:10 petrol:EtOAc) = 0.31; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.23 (1H, d, J = 15.9 Hz, ArC*H*=CH), 7.60 (2H, td, J = 7.8, 2.0 Hz, Ar*H*), 7.41-7.31 (2H, m, Ar*H*), 6.35 (1H, d, J = 15.9 Hz, ArCH=C*H*), 5.70 (1H, s, C*H*), 4.31-4.23 (4H, m, OC*H*$_2$, C*H*$_2$CH$_3$), 4.02 (2H, td, J = 12.2, 2.5 Hz, OC*H*$_2$), 2.37-2.20 (1H, m, $CH_2CH_AH_BCH_2$), 1.50-1.43 (1H, m, $CH_2CH_AH_BCH_2$), 1.34 (3H, t, J = 7.1 Hz, CH_2CH_3); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 167.01, 142.23, 137.17, 132.90, 129.85, 129.16, 127.04, 126.78, 119.95, 100.35, 67.60, 60.49, 25.75, 14.38; IR (thinfilm) ν_{max} (cm^{-1}): 1708 (C=O), 1635 (C=C); HRMS (ESI): m/z calculated for $C_{15}H_{18}O_4$: requires: 263.1283 for $[M+H]^+$; found: 263.1258; requires: 285.1102 for $[M+Na]^+$; found: 285.1086.

(*E*)-ethyl 3-(2-formylphenyl)acrylate 164



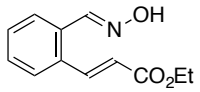
General procedure C was followed using ethyl (*E*)-3-(2-(1,3-dioxan-2-yl)phenyl)acrylate **163** (787 mg, 3.00 mmol). After 6 hours the reaction was worked up and purified by column chromatography (eluent: 90:10 petrol:EtOAc), to yield the title compound as a yellow oil in 87% (533 mg, 2.61 mmol). R_f (90:10 petrol:EtOAc) = 0.43; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 10.20 (1H, s, C*H*O), 8.43 (1H, d, J = 15.8 Hz, ArC*H*=CH), 7.78 (1H, d, J = 7.5 Hz, Ar*H*), 7.56-7.44 (3H, m, Ar*H*), 6.29 (1H, d, J = 15.8 Hz, ArCH=C*H*), 4.20 (2H, q, J = 7.2 Hz, C*H*$_2$CH$_3$), 1.26 (3H, t, J = 7.2 Hz, CH_2CH_3); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 191.67, 166.05, 140.82, 136.44, 133.80, 133.74, 132.21, 129.81, 127.85, 123.05, 60.63, 14.20; IR (thinfilm) ν_{max} (cm^{-1}): 1705 (C=O), 1695 (C=O), 1635 (C=C); HRMS (ESI): m/z calculated for $C_{12}H_{12}O_3$: requires: 227.0684 for $[M+Na]^+$; found: 227.0675.

3-(2-ethoxy-2-oxoethyl)-1*H*-isoindole 2-oxide 165



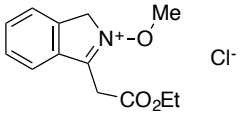
General procedure E was followed using ethyl (*E*)-3-(2-formylphenyl)acrylate **164** (408 mg, 2.00 mmol). The title compound was formed as a white solid in 91% yield (399 mg, 1.82 mmol) and required no further purification. m.p. 130-132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.41-7.28 (4H, m, Ar*H*), 4.99 (2H, s, ArC*H*$_2$N), 4.19 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 3.89 (2H, s, C*H*$_2$C=O), 1.24 (3H, t, J = 7.1 Hz, CH_2CH_3); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 167.49, 141.99, 136.02, 133.30, 128.71, 128.18, 121.72, 119.53, 65.98, 61.83, 30.01, 14.25; IR (thinfilm) ν_{max} (cm^{-1}): 1732 (C=O); HRMS (ESI): m/z calculated for $C_{12}H_{13}NO_3$: requires: 220.0973 for $[M+H]^+$; found: 220.0955; requires: 242.0793 for $[M+Na]^+$; found: 242.0786.

(*E*)-ethyl 3-(2-((*E*)-(hydroxyimino)methyl)phenyl)acrylate 166



To a solution of ethyl (*E*)-3-(2-formylphenyl)acrylate **164** (408 mg, 2.00 mmol) in 5:1 EtOH:H_2O, was added $NH_2OH{\cdot}HCl$ (278 mg, 4.00 mmol), and the reaction stirred for 3 hours at room temperature. After removal of the solvent under reduced pressure, the crude material was taken up in DCM and H_2O, separated, and the organic layer washed with H_2O twice. The organic layer was dried ($MgSO_4$), and the solvent removed under reduced pressure to yield the title compound as a pale brown solid in 74% yield (47.00 mg, 0.21 mmol). No further purification was necessary.[77] m.p. 77-78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.53 (1H, s, *H*C=N-OH), 8.13 (1H, d, J = 15.9 Hz, ArC*H*=CH), 7.69 (1H, dd, J = 5.5, 3.5 Hz, Ar*H*), 7.56 (1H, dd, J = 5.5, 3.5 Hz, Ar*H*), 7.37 (2H, dd, J = 5.8, 3.5 Hz, Ar*H*), 6.34 (1H, d, J = 15.8 Hz, ArCH=C*H*), 4.27 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 1.33 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 167.0, 148.42, 141.89, 133.75, 131.13, 130.04, 129.98, 127.92, 127.45, 121.31, 60.96, 14.40; IR (thinfilm) ν_{max} (cm^{-1}): 3357 (O-H), 1694 (C=O), 1685 (C=N), 1631 (C=C); HRMS (ESI): m/z calculated for $C_{12}H_{13}NO_3$: requires: 242.0793 for $[M+Na]^+$; found: 242.0795.

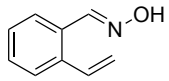
1-(2-ethoxy-2-oxoethyl)-2-methoxy-1*H*-isoindol-2-ium chloride 176



To a solution of ethyl (*E*)-3-(2-formylphenyl)acrylate **164** (613 mg, 3.00 mmol) in 5:1 THF:H_2O was added *O*-methylhydroxylamine hydrochloride (251 mg, 3.00 mmol) and Et_3N (0.84 mL, 6.00 mmol). The reaction was left to stir at room temperature for 14 hours. The crude mixture was then taken up in DCM and H_2O and separated. The aqueous layer was washed with DCM (3 x 20 mL), the combined organics were dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield a yellow oil. Purification by column chromatography (eluent: 70:30 Petrol:EtOAc) afforded the title compound as a red oil in 39% yield. R_f (70:30 Petrol:EtOAc) = 0.28; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.32 (1H, s, *H*-C=N$^+$), 7.59 (1H, dd, J = 7.7, 1.0 Hz, Ar*H*), 7.51 (1H, dd, J = 7.5, 1.4 Hz, Ar*H*), 7.40 (1H, td, J = 7.5, 1.5 Hz, Ar*H*), 7.32 (1H, td, J = 7.4, 1.4 Hz, Ar*H*), 5.52 (1H, dd, J = 8.5, 4.4 Hz, C*H*), 4.19 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 3.99 (3H, s, OC*H*$_3$), 2.86-2.71 (2H, m, CHC*H*$_2$), 1.27 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 172.49, 148.72, 141.22, 130.15, 130.07, 128.96, 127.98, 126.87, 68.13, 62.32, 60.96, 42.00, 14.33; IR (thinfilm) ν_{max} (cm^{-1}): 1732 (C=O); HRMS (ESI): m/z calculated for $C_{13}H_{16}NO_3$: requires: 234.1130 for $[M+H]^+$; found: 234.1118; requires: 256.0949 for

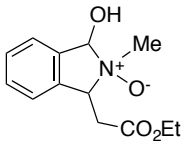
$[M+Na]^+$; found: 256.0956.

(*E*)-2-vinylbenzaldehyde oxime 178



To a solution of 2-vinylbenzaldehyde **177** (397 mg, 3.00 mmol) in THF was added NH_2OH (50 wt% in H_2O) (0.21 mL, 3.30 mmol), and the reaction stirred for 30 minutes at room temperature. The solvent was removed under vacuum and the crude material purified by column chromatography (eluent: DCM) to yield the title compound as a colourless oil in 88% yield (389 mg, 2.67 mmol). R_f (DCM) = 0.27; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 9.44 (1H, br. s, NO*H*), 8.51 (1H, s, *H*-C=N), 7.69 (1H, d, J = 8.7 Hz, Ar*H*), 7.50 (1H, dd, J = 7.6, 0.7 Hz, Ar*H*), 7.38 (1H, td, J = 7.5, 1.2 Hz, Ar*H*), 7.30 (1H, td, J = 7.4, 1.0 Hz, Ar*H*), 7.08 (1H, dd, J = 17.3, 11.0 Hz, C*H*=CH_2), 5.65 (1H, dd, J = 17.3, 1.1 = Hz, CH=CH_AH$_B$), 5.42 (1H, dd, J = 10.9, 1.1 = Hz, CH=CH$_A$$H_B$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 149.02, 137.53, 134.08, 129.99, 129.18, 127.94, 127.14, 127.02, 118.05; IR (thinfilm) ν_{max} (cm^{-1}): 3345 (O-H), 1685 (C=N) 1651 (C=C); HRMS (ESI): m/z calculated for C_9H_9NO: requires: 170.0581 for $[M+Na]^+$; found: 170.0578.

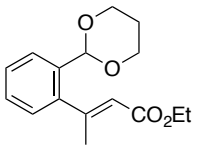
1-(2-ethoxy-2-oxoethyl)-3-hydroxy-2-methylisoindoline 2-oxide 182



To a solution of ethyl (*E*)-3-(2-formylphenyl)acrylate **164** (613 mg, 3.00 mmol) in 5:1 THF:H_2O was added *N*-methylhydroxylamine hydrochloride (251 mg, 3.00 mmol) and Et_3N (0.84 mL, 6.00 mmol). The reaction was left to stir at room temperature for 24 hours. The crude mixture was then taken up in DCM and water and separated. The aqueous layer was washed with DCM (3 x 20 mL), the combined organics were dried ($MgSO_4$), and the solvent was removed under vacuum to yield a yellow oil which solidified on standing. Recrystallisation from DCM:hexane afforded the title compound as a mixture of diasteromers (1:0.2 ratio) as white needles in 59% yield. m.p. = 54-55 °C; **major diastereomer** ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.34-7.26 (3H, m, Ar*H*), 7.12-7.09 (1H, m, Ar*H*), 5.71 (1H, s, C*H*OH), 4.26 (1H, t, J = 5.8 Hz, C*H*CH_2), 4.16 (2H, q, J = 7.3 Hz, C*H*$_2$$CH_3$), 4.04 (1H, br. s, O*H*), 3.09 (1H, dd, J = 16.0, 6.3 Hz, CHCH_AH$_B$), 2.73 (3H, s, NC*H*$_3$), 2.45 (1H, dd, J = 16.0, 5.4, CHCH$_A$$H_B$), 1.24 (3H, t, J = 7.1 Hz, CH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 172.60, 137.61, 134.43, 128.30, 127.52, 127.39, 126.33, 93.89, 60.94, 60.00, 42.06, 33.84, 14.24; **minor diastereomer** ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.34-7.26 (3H, m, Ar*H*), 7.19-7.16 (1H, m, Ar*H*), 5.81 (1H, s, C*H*OH), 4.23-4.08 (3H, m, C*H*CH_2, C*H*$_2$$CH_3$), 4.04 (1H, br. s, O*H*), 2.89 (1H, dd, J

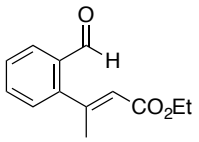
= 16.6, 5.0 Hz, CHCH_AH$_B$), 2.83- 2.76 (4H, m, CHCH$_A$$H_B$, NC$H_3$), 1.27-1.19 (3H, m, CH$_2CH_3$); ^{13}C{^{1}H} NMR (75.5 MHz CDCl$_3$) δ_C: 172.60, 135.65, 132.56, 128.47, 127.14, 126.67, 125.19, 94.19, 62.24, 60.99, 43.28, 33.84, 14.24; IR (thinfilm) ν_{max} (cm^{-1}): 1729 (C=O); HRMS (ESI): m/z calculated for $C_{13}H_{17}NO_4$: requires: 252.1235 for [M+H]$^+$; found: 252.1276.

(*E*)-ethyl 3-(2-(1,3-dioxan-2-yl)phenyl)but-2-enoate 184



General procedure B was followed under inert conditions using 2-(2-bromophenyl)-1,3-dioxane **147** (972 mg, 4.00 mmol) and ethyl crotonate **183**. After 8 hours, the reaction was worked up and purified by column chromatography (eluent: 90:10 petrol:EtOAc) to yield the title compound as a pale yellow oil in 48% yield (531 mg, 1.92 mmol). R$_f$ (90:10 petrol:EtOAc) = 0.47; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 7.70 (1H, dd, J = 7.1, 2.2 Hz, ArH), 7.37-7.27 (2H, m, ArH), 7.10 (1H, dd, J = 7.0, 2.2 Hz, ArH), 5.84 (1H, q, J = 1.4 Hz, HC=CCH$_3$), 5.50 (1H, s, CH), 4.25-4.18 (4H, m, OCH_2, CH_2CH$_3$), 3.90 (2H, td, J = 12.3, 2.4 Hz, OCH_2), 2.48 (3H, d, J = 1.4 Hz, CH=CCH_3), 2.36-2.14 (1H, m, CH$_2$CH_AH$_B$CH$_2$), 1.43-1.37 (1H, m, CH$_2$CH$_A$$H_BCH_2$), 1.31 (3H, t, J = 7.2 Hz, CH$_2$CH_3); ^{13}C{^{1}H} NMR (75.5 MHz CDCl$_3$) δ_C: 166.60, 156.37, 142.47, 134.98, 128.83, 128.16, 127.07, 126.62, 120.07, 99.61, 67.42, 59.91, 25.72, 21.48, 14.39; IR (thinfilm) ν_{max} (cm^{-1}): 1711 (C=O), 1638 (C=C); HRMS (ESI): m/z calculated for $C_{16}H_{20}O_4$:requires: 277.1439 for [M+H]$^+$; found: 277.1416; requires: 299.1259 for [M+Na]$^+$; found: 299.1242.

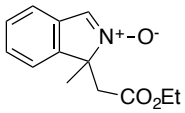
(*E*)-ethyl 3-(2-formylphenyl)but-2-enoate 185



General procedure C was followed using (*E*)-ethyl 3-(2-(1,3-dioxan-2-yl)phenyl)but-2-enoate **184** (829 mg, 3.00 mmol). After 6 hours, the reaction was worked up and purified by column chromatography (eluent: 90:10 petrol:EtOAc) to yield the title compound as a white solid in 69% yield (452 mg, 2.07 mmol). R$_f$ (90:10 petrol:EtOAc) = 0.58; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 10.09 (1H, s, CHO), 7.91 (1H, dd, J = 7.8, 1.2 Hz, ArH), 7.57 (1H, td, J = 7.6, 1.5 Hz, ArH), 7.48-7.42 (1H, m, ArH), 7.27 (1H, dd, J = 7.6, 1.0 Hz, ArH), 5.77 (1H, q, J = 1.4 Hz, HC=CCH$_3$), 4.20 (2H, q, J = 7.1 Hz, CH_2CH$_3$), 2.53 (3H, d, J = 1.4 Hz, CH=CCH_3), 1.28 (3H, t, J = 7.1 Hz, CH$_2$CH_3); ^{13}C{^{1}H} NMR (75.5 MHz CDCl$_3$) δ_C: 191.31, 165.89, 154.34, 147.18, 133.92, 133.04, 129.02, 128.49, 128.41, 122.01, 60.27, 21.83, 14.37; IR (thinfilm) ν_{max} (cm^{-1}): 1710 (C=O), 1692 (C=O), 1638

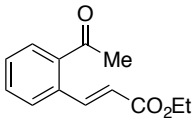
(C=C); HRMS (ESI): m/z calculated for $C_{13}H_{14}O_3$: requires: 241.0840 for $[M+Na]^+$; found: 241.0843.

1-(2-ethoxy-2-oxoethyl)-1-methyl-1*H*-isoindole 2-oxide 186



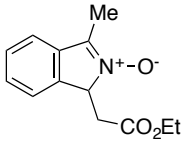
General procedure E was followed using ethyl (*E*)-3-(2-formylphenyl)but-2-enoate **185** (437 mg, 2.00 mmol). The title compound was formed as a yellow oil in 71% yield (331 mg, 1.42 mmol) and required no further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.69 (1H, s, *H*-C=N), 7.37-7.32 (4H, m, Ar*H*), 4.00-3.89 (2H, m, C*H*$_2$CH$_3$), 3.01 (2H, s, C*H*$_2$C=O), 1.61 (3H, s, C*H*$_3$), 1.02 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 168.60, 142.94, 133.29, 132.82, 128.86, 127.82, 121.58, 120.40, 60.74, 40.99, 29.80, 24.43, 13.98; IR (thinfilm) ν_{max} (cm^{-1}): 1730 (C=O); HRMS (ESI): m/z calculated for $C_{13}H_{15}NO_3$: requires: 234.1130 for $[M+H]^+$; found: 234.1130; requires: 256.0949 for $[M+Na]^+$; found: 256.0953.

(*E*)-ethyl 3-(2-acetylphenyl)acrylate 188



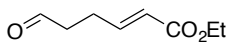
General procedure B was followed using 2-bromoacetophenone **324** (796 mg, 4.00 mmol). After 3 hours, the reaction was worked up and purified by column chromatography (eluent: 90:10 petrol:EtOAc) to provide the title compound as a yellow oil in 90% yield (786 mg, 3.60 mmol). R_f (90:10 petrol:EtOAc) = 0.69; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.07 (1H, d, J = 15.9 Hz, ArC*H*=CH), 7.66 (1H, d, J = 7.6 Hz, Ar*H*), 7.49 (1H, d, J = 7.6 Hz, Ar*H*), 7.44-7.34 (2H, m, Ar*H*), 6.19 (1H, dd, J = 15.9, 1.1 Hz, ArCH=C*H*), 4.17 (2H, qd, J = 7.2, 0.8 Hz, C*H*$_2$CH$_3$), 2.53 (3H, d, J = 3.0 Hz, C*H*$_3$), 1.24 (3H, td, J = 7.2, 0.9 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 200.42, 166.13, 143.60, 137.82, 134.42, 131.64, 129.09, 128.95, 127.98, 120.54, 60.15, 28.87, 13.97; IR (thinfilm) ν_{max} (cm^{-1}): 1708 (CH$_3$-C=O), 1680 (O-C=O), 1633 (C=C); HRMS (ESI): m/z calculated for $C_{13}H_{14}O_3$: requires: 219.1021 for $[M+H]^+$; found: 219.1006; requires: 241.0840 for $[M+Na]^+$; found: 241.0855.

1-(2-ethoxy-2-oxoethyl)-3-methyl-1*H*-isoindole 2-oxide, 189



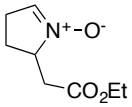
General procedure E was followed using ethyl (*E*)-3-(2-acetylphenyl)acrylate **188** (437 mg, 2.00 mmol). The title compound was formed as the major reaction product as a yellow oil in 87% yield (406 mg, 1.74 mmol) and required no further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.34-7.22 (4H, m, Ar*H*), 5.03-5.00 (1H, m, ArC*H*-N^+), 4.11 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 3.37 (1H, dd, J = 16.7, 4.4 Hz, C*H*$_A$CH$_B$C=O), 2.61 (1H, dd, J = 16.7, 9.0 Hz, CH$_A$*H*$_B$C=O), 2.28 (3H, d, J = 1.6 Hz, C*H*$_3$C=N^+), 1.16 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 170.00, 143.86, 137.51, 135.54, 128.76, 128.04, 121.77, 119.17, 71.14, 61.03, 36.25, 14.02, 9.32; IR (thin-film) ν_{max} (cm^{-1}): 1730 (C=O); HRMS (ESI): m/z calculated for $C_{13}H_{15}NO_3$: requires: 234.1130 for $[M+H]^+$; found: 234.1119; requires: 256.0949 for $[M+Na]^+$; found: 256.0943.

Ethyl (*E*)-6-oxohex-2-enoate 200



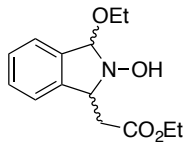
To a solution of 4-pentenal (252 mg, 3.00 mmol) in DCM was added Grubbs I catalyst (5.0 mol%) and ethyl acrylate **162** (1.64 mL, 5.0 eq.). The reaction was heated to reflux and left to stir for 16 hours. The reaction was then cooled and the solvent removed under reduced pressure. Purification of the crude material by column chromatography afforded the title compound as a colourless oil in 87% yield. R_f (DCM) = 0.43; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 9.79 (1H, s, C*H*O), 6.93 (1H, dt, J = 15.6, 6.5 Hz, CH$_2$C*H*=CH), 5.84 (1H, dt, J = 15.6, 1.5 Hz, CH$_2$CH=C*H*), 4.17 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 2.67-2.61 (2H, m, C*H*$_2$CH=CH), 2.56-2.48 (2H, m, CHO-C*H*$_2$), 1.27 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 200.55, 166.42, 146.45, 122.57, 60.49, 41.96, 24.54, 14.37; IR (thinfilm) ν_{max} (cm^{-1}): 1712 (C=O) 1654 (C=C); HRMS (ESI): m/z calculated for $C_8H_{12}O_3$: requires: 179.0684 for $[M+Na]^+$; found: 179.0709.

2-(2-ethoxy-2-oxoethyl)-3,4-dihydro-2*H*-pyrrole 1-oxide 201



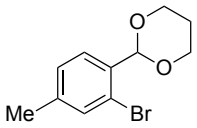
General procedure E was followed using ethyl (*E*)-6-oxohex-2-enoate **325** (312 mg, 2.00 mmol). The title compound was formed as a white solid in 89% yield (305 mg, 1.78 mmol) and required no further purification. m.p. 47-49 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.12 (1H, s, *H*C=N), 4.40 (1H, br. s, CH$_2$C*H*CH$_2$), 4.16, (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 3.02 (1H, dd, J = 16.6, 4.6 Hz, CHC*H*$_A$CH$_B$C=O), 2.78-2.72 (3H, m, CHCH$_A$C*H*$_B$C=O, C*H*$_2$C=N), 2.57-2.50 (1H, m, CH$_2$C*H*$_A$CH$_B$CH), 2.09-2.02 (1H, m, CH$_2$CH$_A$C*H*$_B$CH), 1.26 (3H, t, J = 7.0 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (125 MHz $CDCl_3$) δ_C: 171.19, 141.59, 70.19, 61.92, 37.43, 27.92, 25.94, 14.42 IR (thinfilm) ν_{max} (cm^{-1}): 1729 (C=O); HRMS (ESI): m/z calculated for $C_8H_{13}N_1O_3$: requires: 194.0793 for $[M+Na]^+$; found: 194.0823.

Ethyl 2-(3-ethoxy-2-hydroxyisoindolin-1-yl)acetate 205



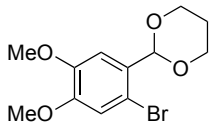
To a solution of ethyl (*E*)-3-(2-formylphenyl)acrylate **164** (204 mg, 1.00 mmol) in ethanol was added hydroxylamine hydrochloride (1.0 eq.) and Et_3N (2.0 eq.). The reaction was stirred at room temperature for 30 minutes. The mixture was taken up in DCM and H_2O and separated. The organic layer was washed twice with H_2O and once with brine. The organic layer was then dried ($MgSO_4$) and the solvent removed under vacuum to afford the title compound as an inseparable mixture of diastereomers in 86% yield (228 mg, 0.86 mmol). **major diastereomer** ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.41-7.34 (3H, m, Ar*H*), 7.28-7.21 (1H, m, Ar*H*), 6.15 (1H, s, OC*H*), 5.55 (1H, dd, J = 7.7, 5.8 Hz, C*H*CH_2), 4.28-4.15 (2H, m, $CO_2CH_2CH_3$), 3.90-3.60 (2H, m, OCH_2CH_3), 2.88-2.68 (2H, m, CHC*H*$_2$), 1.31-1.22 (6H, m, $CO_2CH_2CH_3$, OCH_2CH_3); **minor diastereomer** ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.41-7.34 (3H, m, Ar*H*), 7.28-7.21 (1H, m, Ar*H*), 6.25 (1H, d, J = 2.4 Hz, OC*H*), 5.75 (1H, td, J = 7.1, 1.7 Hz, C*H*CH_2, 4.28-4.15 (2H, m, $CO_2CH_2CH_3$), 3.90-3.60 (2H, m, OCH_2CH_3), 2.88-2.68 (2H, m, CHC*H*$_2$), 1.31-1.22 (6H, m, $CO_2CH_2CH_3$, OCH_2CH_3); IR (thinfilm) ν_{max} (cm^{-1}): 3299 (O-H), 1725 (C=O); HRMS (ESI): m/z calculated for $C_{14}H_{19}NO_4$: requires: 266.1347 for $[M+H]^+$; found: 266.1356.

2-(2-bromo-4-methylphenyl)-1,3-dioxane 147a



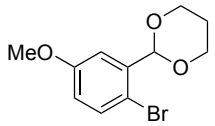
General procedure A was followed using 2-bromo-4-methylbenzaldehyde (995 mg, 5.00 mmol), followed by purification by column chromatography (eluent: DCM), to provide the title compound as a pale yellow oil in 85% yield (1.09 g, 4.25 mmol). R_f (DCM) = 0.50; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.55 (1H, d, J = 8.0 Hz, Ar*H*), 7.35 (1H, s, Ar*H*), 7.13 (1H, d, J = 7.7 Hz, Ar*H*), 5.72 (1H, s, C*H*), 4.27 (1H, dd, J = 5.1, 1.3 Hz, OCH_AH_B), 4.23 (1H, dd, J = 5.1, 1.3 Hz, OCH_AH_B), 4.03 (2H, td, J = 12.2, 2.4 Hz, OC*H*$_2$), 2.30 (3H, s, C*H*$_3$), 2.28-2.15 (1H, m, $CH_2CH_AH_BCH_2$), 1.47-1.40 (1H, m, $CH_2CH_AH_BCH_2$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 140.65, 134.69, 133.05, 128.45, 127.80, 122.09, 101.02, 67.67, 25.79, 20.97; IR (thinfilm) ν_{max} (cm^{-1}): 1610 (ArC=C), 1566 (ArC=C); HRMS (ESI): m/z calculated for $C_{11}H_{13}BrO_2$: requires: 278.9996 for $[M+Na]^+$; found: 279.0002.

2-(2-bromo-4,5-dimethoxyphenyl)-1,3-dioxane 147b



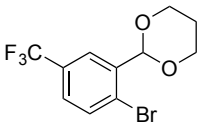
General procedure A was followed using 2-bromo-4,5-dimethoxybenzaldehyde (1.22 g, 5.00 mmol), followed by recrystallisation from petrol:ether, to provide the title compound as cream needles in 76% yield (1.15 g, 3.80 mmol). m.p. 98-99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.19 (1H, s, Ar*H*), 6.97 (1H, s, Ar*H*), 5.69 (1H, s, C*H*), 4.27 (1H, dd, *J* = 5.1, 1.3 Hz, OCH_AH$_B$), 4.23 (1H, dd, *J* = 5.1, 1.3 Hz, OCH$_A$$H_B$), 4.01 (2H, td, *J* = 12.3, 2.4 Hz, OC*H₂*), 3.90 (3H, s, OC*H₃*), 3.85 (3H, s, OC*H₃*), 2.32-2.16 (1H, m, CH_2CH_AH$_B$CH_2), 1.47-1.40 (1H, m, CH_2CH$_A$$H_BCH_2$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 149.86, 148.58, 129.88, 115.10, 112.50, 110.31, 101.04, 67.62, 56.22, 56.05, 25.69; IR (thinfilm) ν_{max} (cm^{-1}): 1602 (ArC=C), 1502 (ArC=C); HRMS (ESI): m/z calculated for $C_{12}H_{15}BrO_4$: requires: 325.0051 for [M+Na]$^+$; found: 325.0049.

2-(2-bromo-5-methoxyphenyl)-1,3-dioxane 147c



General procedure A was followed using 2-bromo-5-methoxybenzaldehyde (1.08 g, 5.00 mmol), to provide the title compound as an orange oil in 96% yield (1.31 g, 4.80 mmol), which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.40 (1H, d, *J* = 8.9 Hz, Ar*H*), 7.24 (1H, d, *J* = 3.1 Hz, Ar*H*), 6.76 (1H, dd, *J* = 8.8, 3.3 Hz, Ar*H*), 5.71 (1H, s, C*H*), 4.28 (1H, dd, *J* = 5.1, 1.3 Hz, OCH_AH$_B$), 4.24 (1H, dd, *J* = 5.1, 1.3 Hz, OCH$_A$$H_B$), 4.02 (2H, td, *J* = 12.2, 2.5 Hz, OC*H₂*), 3.80 (3H, s, OC*H₃*), 2.32-2.16 (1H, m, CH_2CH_AH$_B$CH_2), 1.48-1.41 (1H, m, CH_2CH$_A$$H_BCH_2$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 159.23, 138.34, 133.31, 117.23, 112.79, 112.69, 100.92, 67.66, 55.63, 25.77; IR (thinfilm) ν_{max} (cm^{-1}): 1596 (ArC=C), 1575 (ArC=C); HRMS (ESI): m/z calculated for $C_{11}H_{13}BrO_3$: requires: 273.0126 for [M+H]$^+$; found: 273.0129.

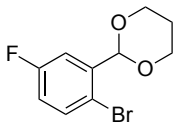
2-(2-bromo-5-(trifluoromethyl)phenyl)-1,3-dioxane 147d



General procedure A was followed using 2-bromo-5-(trifluoromethyl)benzaldehyde (1.27 g, 5.00 mmol), followed by purification by column chromatography (eluent: 80:20 petrol: EtOAc), to provide the title compound as a pale yellow oil in 86% yield (1.34 g, 4.30

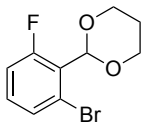
mmol). R_f (80:20 petrol:EtOAc) = 0.80; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.98 (1H, d, J = 2.1 Hz, ArH), 7.65 (1H, d, J = 8.3 Hz, ArH), 7.44 (1H, dd, J = 8.4, 2.3 Hz, ArH), 5.76 (1H, s, CH), 4.30 (1H, dd, J = 5.0, 1.2 Hz, OCH_AH$_B$), 4.26 (1H, dd, J = 5.0, 1.2 Hz, OCH$_A$$H_B$), 4.02 (2H, td, J = 12.5, 2.1 Hz, OCH_2), 2.34-2.18 (1H, m, CH$_2$CH_AH$_B$CH$_2$), 1.49-1.42 (1H, m, CH$_2$CH$_A$$H_BCH_2$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 138.53, 133.17, 130.00 (q, J = 33.1 Hz), 126.77 (q, J = 3.8 Hz), 126.12 (q, J = 1.5 Hz) 125.35 (q, J = 3.8 Hz), 123.72, (q, J = 272.7 Hz), 99.96, 67.53, 25.50; IR (thinfilm) ν_{max} (cm^{-1}): 1609 (ArC=C), 1584 (ArC=C).

2-(2-bromo-5-fluorophenyl)-1,3-dioxane 147e



General procedure A was followed using 2-bromo-5-fluorobenzaldehyde (1.02 g, 5.00 mmol), to provide the title compound as a colourless in 92% yield (1.20 g, 4.60 mmol), which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.48 (1H, dd, J = 8.7, 5.1 Hz, ArH), 7.42 (1H, dd, J = 9.3, 3.1 Hz, ArH), 6.93 (1H, m, ArH), 5.69 (1H, d, J = 0.6 Hz, CH), 4.28 (1H, dd, J = 5.0, 1.0 Hz, OCH_AH$_B$), 4.24 (1H, dd, J = 5.1, 1.2 Hz, OCH$_A$$H_B$), 4.02 (2H, td, J = 12.1, 2.3 Hz, OCH_2), 2.32-2.15 (1H, m, CH$_2$CH_AH$_B$CH$_2$), 1.49-1.43 (1H, m, CH$_2$CH$_A$$H_BCH_2$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 162.19 (d, J = 247.0 Hz), 139.57 (d, J = 7.5 Hz), 133.96 (d, J = 7.7 Hz), 117.64 (d, J = 23.3 Hz), 116.33 (d, J = 3.2 Hz), 115.67 (d, J = 24.4 Hz), 100.31, 67.69, 25.71; IR (thinfilm) ν_{max} (cm^{-1}): 1582 (ArC=C); HRMS (ESI): m/z calculated for $C_{10}H_{10}BrFO_2$: requires: 260.9926 for $[M+H]^+$; found: 260.9930.

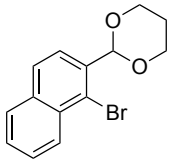
2-(2-bromo-6-fluorophenyl)-1,3-dioxane 147f



General procedure A was followed using 2-bromo-6-fluorobenzaldehyde (1.02 g, 5.00 mmol), followed by recrystallisation from petrol:ether, to provide the title compound as white needles in 83% yield (1.08 g, 4.15 mmol). m.p. 59-60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.35 (1H, dd, J = 8.0, 0.9 Hz, ArH), 7.15 (1H, td, J = 8.5, 5.6 Hz, ArH), 7.04 (1H, td, J = 8.5, 1.2 Hz, ArH), 6.03 (1H, s, CH), 4.30 (1H, dd, J = 5.0, 1.0 Hz, OCH_AH$_B$), 4.26 (1H, dd, J = 5.0, 1.2 Hz, OCH$_A$$H_B$), 3.98 (2H, td, J = 11.8, 1.4 Hz, OCH_2), 2.41-2.25 (1H, m, CH$_2$CH_AH$_B$CH$_2$), 1.46-1.41 (1H, m, CH$_2$CH$_A$$H_BCH_2$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 161.42 (d, J = 251.7 Hz), 130.92 (d, J = 9.7 Hz), 128.86 (d, J = 3.7 Hz), 125.26 (d, J = 13.9 Hz), 122.87 (d, J = 5.3 Hz), 115.88 (d, J = 22.9 Hz), 100.49 (d, J = 1.6 Hz), 67.67, 25.47; IR (thinfilm) ν_{max} (cm^{-1}): 1603 (ArC=C), 1575 (ArC=C);

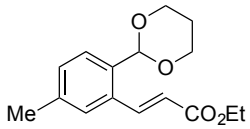
HRMS (ESI): m/z calculated for $C_{10}H_{10}BrO_2F$: requires: 282.9745 for $[M+Na]^+$; found: 282.9738.

2-(naphthalen-2-yl)-1,3-dioxane 147g



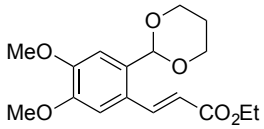
General procedure A was followed using 1-bromo-2-naphthaldehyde (1.18 g, 5.00 mmol), followed by recrystallisation from petrol:ether, to provide the title compound as white plates in 84% yield (1.23 g, 4.20 mmol). m.p. 131-133; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.37 (1H, dd, J = 8.4, 1.3 Hz, ArH), 7.84-7.80 (3H, m, ArH), 7.87-7.50 (2H, m, ArH) 6.11 (1H, s, CH), 4.34 (1H, dd, J = 5.0, 1.2 Hz, OCH_AH$_B$), 4.30 (1H, dd, J = 5.0, 1.2 Hz, OCH$_A$$H_B$), 4.10 (2H, td, J = 12.4, 2.5 Hz, OCH_2), 2.39-2.23 (1H, m, CH$_2$CH_AH$_B$CH$_2$), 1.52-1.45 (1H, m, CH$_2$CH$_A$$H_BCH_2$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 135.60, 134.86, 132.05, 128.21, 128.07, 127.79, 127.42, 127.07, 124.65, 123.00, 102.01, 67.73, 25.85; IR (thinfilm) ν_{max} (cm^{-1}): 1597 (ArC=C), 1557 (ArC=C); HRMS (ESI): m/z calculated for $C_{14}H_{13}BrO_2$: requires: 293.0177 for $[M+H]^+$; found: 293.0164.

Ethyl (*E*)-3-(2-(1,3-dioxan-2-yl)-5-methylphenyl)acrylate 163a



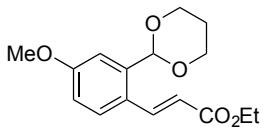
General procedure B was followed using 2-(2-bromo-4-methylphenyl)-1,3-dioxane **147**a (1.03 g, 4.00 mmol). After 4 hours, the reaction was worked up and purified by column chromatography (eluent: 90:10 petrol:EtOAc) to yield the title compound as a yellow oil in 69% yield (763 mg, 2.76 mmol). R_f (90:10 petrol:EtOAc) = 0.20; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.21 (1H, d, J = 15.9 Hz, ArCH=CH), 7.48 (1H, d, J = 7.9 Hz, ArH), 7.39 (1H, s, ArH), 7.19 (1H, d, J = 7.9 Hz, ArH), 6.34 (1H, d, J = 15.9 Hz, ArCH=CH), 5.67 (1H, s, CH), 4.30-4.23 (4H, m, OCH_2, CH_2CH$_3$), 4.00 (2H, td, J = 12.2, 2.1 Hz, OCH_2), 2.34 (3H, s, ArCH_3), 2.34-2.19 (1H, m, CH$_2$CH_AH$_B$CH$_2$), 1.48-1.43 (1H, m, CH$_2$CH$_A$$H_BCH_2$), 1.34 (3H, t, J = 7.1 Hz, CH$_2$CH_3); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 167.13, 142.43, 138.91, 134.59, 132.72, 130.68, 127.37, 127.06, 119.68, 100.43, 67.62, 60.49, 25.80, 21.27, 14.42; IR (thinfilm) ν_{max} (cm^{-1}): 1708 (C=O), 1636 (C=C); HRMS (ESI): m/z calculated for $C_{16}H_{20}O_4$: requires: 277.1439 for $[M+H]^+$; found: 277.1444; requires: 299.1259 for $[M+Na]^+$; found: 299.1258.

Ethyl (*E*)-3-(2-(1,3-dioxan-2-yl)-4,5-dimethoxyphenyl)acrylate 163b



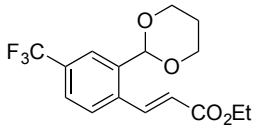
General procedure B was followed using 2-(2-bromo-4,5-dimethoxyphenyl)-1,3-dioxane **147**b (1.21 g, 4.00 mmol). After 4.5 hours, the reaction was worked up and purified by column chromatography (eluent: 70:30 petrol:EtOAc) to yield the title compound as a yellow oil in 67% yield (864 mg, 2.68 mmol). R_f (70:30 petrol:EtOAc) = 0.36; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.07 (1H, d, J = 15.9 Hz, ArC*H*=CH), 7.15 (1H, s, Ar*H*), 7.04 (1H, s, Ar*H*), 6.25 (1H, d, J = 15.8 Hz, ArCH=C*H*), 5.69 (1H, s, C*H*), 4.27-4.20 (4H, m, OC*H*$_2$, C*H*$_2$CH$_3$), 4.00 (2H, td, J = 12.3, 2.5 Hz, OC*H*$_2$), 3.90 (3H, s, OC*H*$_3$), 3.87 (3H, s, OC*H*$_3$), 2.32-2.16 (1H, m, $CH_2CH_AH_BCH_2$), 1.46-1.41 (1H, m, $CH_2CH_AH_BCH_2$), 1.31 (3H, t, J = 7.1 Hz, CH_2CH_3); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 167.05, 150.53, 149.12, 141.25, 131.17, 125.06, 117.64, 109.33, 108.66, 99.30, 67.44, 60.30, 55.88, 25.55, 14.29; IR (thinfilm) ν_{max} (cm^{-1}): 1701 (C=O), 1630 (C=C); HRMS (ESI): m/z calculated for $C_{17}H_{22}O_6$: requires: 323.1494 for $[M+H]^+$; found: 323.1513; requires: 345.1314 for $[M+Na]^+$; found: 345.1322.

Ethyl (*E*)-3-(2-(1,3-dioxan-2-yl)-4-methoxyphenyl)acrylate 163c



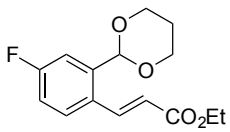
General procedure B was followed using 2-(2-bromo-5-methoxyphenyl)-1,3-dioxane **147**c (1.09 g, 4.00 mmol). After 6 hours, the reaction was worked up and purified by column chromatography (eluent: 80:20 petrol:EtOAc) to yield the title compound as a yellow oil in 74% yield (865 mg, 2.96 mmol). R_f (80:20 petrol:EtOAc) = 0.39; m.p. 43-44 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.09 (1H, d, J = 15.9 Hz, ArC*H*=CH), 7.53 (1H, d, J = 8.7 Hz, Ar*H*), 7.15 (1H, d, J = 2.7 Hz, Ar*H*), 6.84 (1H, dd, J = 8.7, 2.7 Hz, Ar*H*), 6.24 (1H, d, J = 15.9 Hz, ArCH=C*H*), 5.67 (1H, s, C*H*), 4.28-4.19 (4H, m, OC*H*$_2$, C*H*$_2$CH$_3$), 3.99 (2H, td, J = 12.3, 2.4 Hz, OC*H*$_2$), 3.79 (3H, s, OC*H*$_3$), 2.32-2.16 (1H, m, $CH_2CH_AH_BCH_2$), 1.46-1.40 (1H, m, $CH_2CH_AH_BCH_2$), 1.30 (3H, t, J = 7.1 Hz, CH_2CH_3); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 167.25, 161.02, 141.47, 138.94, 128.22, 125.09, 117.42, 115.36, 111.55, 99.65, 67.48, 60.27, 55.38, 25.63, 14.34; IR (thinfilm) ν_{max} (cm^{-1}): 1702 (C=O), 1605 (C=C); HRMS (ESI): m/z calculated for $C_{16}H_{20}O_5$: requires: 293.1388 for $[M+H]^+$; found: 293.1367; requires: 315.1208 for $[M+Na]^+$; found: 315.1195.

Ethyl (*E*)-3-(2-(1,3-dioxan-2-yl)-4-(trifluoromethyl)phenyl)acrylate 163d



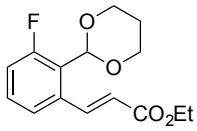
General procedure B was followed using 2-(2-bromo-5-(trifluoromethyl)phenyl)-1,3-dioxane **147**d (1.24 g, 4.00 mmol). After 5 hours, the reaction was worked up and purified by column chromatography (eluent: 90:10 petrol:EtOAc) to yield the title compound in 73% yield (964 mg, 2.92 mmol) as a yellow oil. R_f (90:10 petrol:EtOAc) = 0.46; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.13 (1H, d, J = 16.0 Hz, ArC*H*=CH), 7.91 (1H, t, J = 0.6 Hz, Ar*H*), 7.64 (1H, dd, J = 8.1, 5.5 Hz, Ar*H*), 7.57 (1H, dd, J = 8.4, 1.7 Hz, Ar*H*), 6.38 (1H, d, J = 16.0 Hz, ArCH=C*H*), 5.70 (1H, s, C*H*), 4.30-4.23 (4H, m, OC*H*$_2$, C*H*$_2$CH$_3$), 4.00 (2H, td, J = 12.2, 2.5 Hz, OC*H*$_2$), 2.34-2.18 (1H, m, $CH_2CH_AH_BCH_2$), 1.49-1.43 (1H, m, $CH_2CH_AH_BCH_2$), 1.33 (3H, t, J = 7.1 Hz, CH_2CH_3); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 166.29, 140.47, 137.72, 136.35 (q, J = 1.3 Hz), 131.25 (q, J = 32.8 Hz), 127.10, 125.69 (q, J = 3.8 Hz), 124.07 (q, J = 3.7 Hz), 123.19, (appt. d, J = 272.4 Hz), 122.16, 99.03, 67.44, 60.64, 25.47, 14.17; IR (thinfilm) ν_{max} (cm^{-1}): 1715 (C=O), 1630 (C=C); HRMS (ESI): m/z calculated for $C_{16}H_{17}O_4F_3$: requires: 331.1157 for $[M+H]^+$; found: 331.1147; requires: 353.0976 for $[M+Na]^+$; found: 353.0970.

Ethyl (*E*)-3-(2-(1,3-dioxan-2-yl)-4-fluorophenyl)acrylate 163e



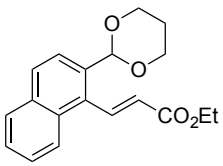
General procedure B was followed using 2-(2-bromo-6-fluorophenyl)-1,3-dioxane **147**e (1.04 g, 4.00 mmol). After 4 hours, the reaction was worked up and purified by column chromatography (eluent: 90:10 petrol:EtOAc) to yield the title compound as a yellow oil in 85% yield (953 mg, 3.40 mmol). R_f (90:10 petrol:EtOAc) = 0.36; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.07 (1H, d, J = 15.8 Hz, ArC*H*=CH), 7.57 (1H, dd, J = 8.6, 5.5 Hz, Ar*H*), 7.37 (1H, dd, J = 9.6, 2.7 Hz, Ar*H*), 7.03 (1H, td, J = 8.1, 2.7 Hz, Ar*H*), 6.30 (1H, d, J = 15.8 Hz, ArCH=C*H*), 5.68 (1H, s, C*H*), 4.30-4.23 (4H, m, OC*H*$_2$, C*H*$_2$CH$_3$), 4.02 (2H, td, J = 12.2, 2.4 Hz, OC*H*$_2$), 2.34-2.18 (1H, m, $CH_2CH_AH_BCH_2$), 1.51-1.45 (1H, m, $CH_2CH_AH_BCH_2$), 1.34 (3H, t, J = 7.1 Hz, CH_2CH_3); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 166.95, 163.66 (d, J = 250.4 Hz), 140.89, 139.69 (d, J = 7.7 Hz), 128.94 (d, J = 3.4 Hz), 128.82 (d, J = 8.3 Hz), 119.84 (d, J = 1.8), 116.29 (d, J = 22.6 Hz), 114.24 (d, J = 22.6 Hz), 98.94 (d, J = 1.5 Hz), 67.61, 60.65, 25.66, 14.43; IR (thinfilm) ν_{max} (cm^{-1}): 1710 (C=O), 1637 (C=O); HRMS (ESI): m/z calculated for $C_{15}H_{17}FO_4$: requires: 281.1189 for $[M+H]^+$; found: 281.1188.

Ethyl (*E*)-3-(2-(1,3-dioxan-2-yl)-3-fluorophenyl)acrylate 163f



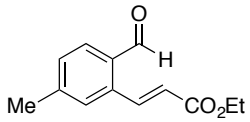
General procedure B was followed using 2-(2-bromo-6-fluorophenyl)-1,3-dioxane **147**f (1.04 g, 4.00 mmol). After 4 hours, the reaction was worked up and purified by column chromatography (eluent: 80:20 petrol:EtOAc) to yield the title compound as a yellow oil in 81% yield (908 mg, 3.24 mmol). R_f (80:20 petrol:EtOAc) = 0.48; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.75 (1H, d, J = 16.1 Hz, ArC*H*=CH), 7.42 (1H, d, J = 8.0 Hz, Ar*H*), 7.30 (1H, td, J = 8.2, 5.5 Hz, Ar*H*), 7.04 (1H, td, J = 8.2, 1.1 Hz, Ar*H*), 6.31 (1H, d, J = 16.1 Hz, ArCH=C*H*), 6.05 (1H, s, C*H*), 4.32-4.23 (4H, m, OC*H*$_2$, C*H*$_2$CH$_3$), 3.97 (2H, td, J = 12.2, 2.3 Hz, OC*H*$_2$), 2.47-2.31 (1H, m, $CH_2CH_AH_BCH_2$), 1.50-1.45 (1H, m, $CH_2CH_AH_BCH_2$), 1.31 (3H, t, J = 7.2 Hz, CH_2CH_3); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 166.89, 160.22 (d, J = 248.3 Hz), 143.29 (d, J = 2.66 Hz), 136.33 (d, J = 2.82 Hz), 130.44 (d, J = 9.5 Hz), 124.33 (d, J = 11.26 Hz), 123.02 (d, J = 3.7 Hz), 119.61, 116.48 (d, J = 23.46 Hz), 96.29 (d, J = 10.17 Hz, CH), 67.96, 60.40, 25.85, 14.34; IR (thinfilm) ν_{max} (cm^{-1}): 1709 (C=O), 1639 (C=C); HRMS (ESI): m/z calculated for $C_{15}H_{17}FO_4$: requires: 281.1189 for $[M+H]^+$; found: 281.1179; requires: 303.1008 for $[M+Na]^+$; found: 303.0993.

Ethyl (*E*)-3-(2-(1,3-dioxan-2-yl)naphthalen-1-yl)acrylate 163g



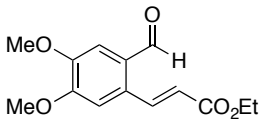
General procedure B was followed using 2-(3-bromonaphthalen-2-yl)-1,3-dioxane **147**g (1.17 g, 4.00 mmol). After 6 hours, the reaction was worked up and purified by column chromatography (eluent: 85:15 petrol:EtOAc) to yield the title compound as a yellow oil in 80% yield (1.00 g, 3.20 mmol). R_f (85:15 petrol:EtOAc) = 0.47; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.31 (1H, d, J = 16.2 Hz, ArC*H*=CH), 8.03 (1H, dd, J = 6.3, 3.4 Hz, Ar*H*), 7.87 (2H, s, Ar*H*), 7.84 (1H, dd, J = 6.2, 3.4 Hz, Ar*H*), 7.54-7.48 (2H, m, Ar*H*), 6.29 (1H, d, J = 16.2 Hz, ArCH=C*H*), 5.74 (1H, s, C*H*), 4.35 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 4.30-4.35 (2H, m, OC*H*$_2$), 4.00 (2H, td, J = 12.2, 2.4 Hz, OC*H*$_2$), 2.38-2.22 (1H, m, $CH_2CH_AH_BCH_2$), 1.49-1.44 (1H, m, $CH_2CH_AH_BCH_2$), 1.39 (3H, t, J = 7.1 Hz, CH_2CH_3); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 165.15, 140.91, 133.77, 133.27, 130.98, 130.77, 128.92, 128.15, 126.47, 126.34, 126.27, 125.06, 123.40, 99.66, 67.11, 60.53, 25.50, 14.15; IR (thinfilm) ν_{max} (cm^{-1}): 1712 (C=O), 1639 (C=C); HRMS (ESI): m/z calculated for $C_{19}H_{20}O_4$: requires: 313.1439 for $[M+H]^+$; found: 313.1429; requires: 335.1259 for $[M+Na]^+$; found: 335.1255.

(*E*)-ethyl 3-(2-formyl-5-methylphenyl)acrylate 164a



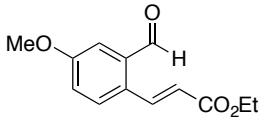
General procedure C was followed using (*E*)-ethyl 3-(2-(1,3-dioxan-2-yl)-5-methylphenyl) acrylate **163**a (829 mg, 3.00 mmol). After 4 hours, the reaction was worked up and purified by column chromatography (eluent: 90:10 petrol:EtOAc) to yield the title compound as a yellow oil in 83% yield (543 mg, 2.49 mmol). R_f (90:10 petrol:EtOAc) = 0.40; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 10.23 (1H, s, C*H*O), 8.49 (1H, d, J = 15.9 Hz, ArC*H*=CH), 7.76 (1H, d, J = 7.8 Hz, Ar*H*), 7.42 (1H, s, Ar*H*), 7.34 (1H, d, J = 7.9 Hz, Ar*H*), 6.35 (1H, d, J = 15.9 Hz, ArCH=C*H*), 4.28 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 2.43 (3H, s, ArC*H*$_3$), 1.34 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 191.46, 166.34, 144.99, 141.19, 136.74, 132.52, 131.72, 130.70, 128.64, 123.04, 60.81, 21.85, 14.36; IR (thinfilm) ν_{max} (cm^{-1}): 1708 (H-C=O), 1690 (O-C=O), 1635 (C=C); HRMS (ESI): m/z calculated for $C_{13}H_{14}O_3$: requires: 241.0840 for $[M+Na]^+$; found: 241.0835.

(*E*)-ethyl 3-(2-formyl-4,5-dimethoxyphenyl)acrylate 164b



General procedure C was followed using (*E*)-ethyl 3-(2-(1,3-dioxan-2-yl)-4,5-dimethoxy phenyl)acrylate **163**b (967 mg, 3.00 mmol). After 14 hours, the reaction was worked up and purified by recrystallisation (petrol:ether) to yield the title compound as cream needles in 71% yield (563 mg, 2.13 mmol). m.p. 121-124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 10.33 (1H, s, C*H*O), 8.46 (1H, d, J = 15.9 Hz, ArC*H*=CH), 7.40 (1H, s, Ar*H*), 7.05 (1H, s, Ar*H*), 6.35 (1H, d, J = 15.9 Hz, ArCH=C*H*), 4.29 (2H, q, J = 15.6 Hz, C*H*$_2$CH$_3$), 3.99 (3H, s, OC*H*$_3$), 3.97 (3H, s, OC*H*$_3$), 1.35 (3H, t, J = 15.6 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 189.07, 166.24, 153.65, 150.59, 139.29, 131.67, 127.75, 121.94, 111.04, 108.99, 60.79, 56.22, 56.18, 14.29; IR (thinfilm) ν_{max} (cm^{-1}): (H-C=O), 1679 (O-C=O), 1636 (C=C); HRMS (ESI): m/z calculated for $C_{14}H_{16}O_5$: requires: 265.1075 for $[M+H]^+$; found: 265.1063; requires: 287.0895 for $[M+Na]^+$; found: 287.0877.

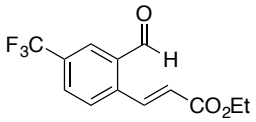
(*E*)-ethyl 3-(2-formyl-4-methoxyphenyl)acrylate 164c



General procedure C was followed using (*E*)-ethyl 3-(2-(1,3-dioxan-2-yl)-4-methoxyphenyl)

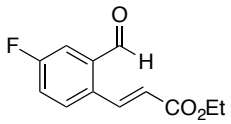
acrylate **163**c (877 m.o.g, 3.00 mmol). After 6 hours, the reaction was worked up and purified by recrystallisation (petrol:ether) to yield the title compound as a yellow solid in 65% yield (457 mg, 1.95 mmol). m.p. 59-60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 10.32 (1H, s, C*H*O), 8.41 (1H, d, J = 15.8 Hz, ArC*H*=CH), 7.58 (1H, d, J = 8.7 Hz, Ar*H*), 7.35 (1H, d, J = 2.8 Hz, Ar*H*), 7.12 (1H, dd, J = 8.6, 2.8 Hz, Ar*H*), 6.29 (1H, d, J = 15.8 Hz, ArCH=C*H*), 4.25 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 3.87 (3H, s, OC*H*$_3$), 1.32 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 190.94, 166.45, 160.95, 139.61, 135.03, 129.33, 121.27, 120.72, 114.48, 60.65, 55.64, 14.26; IR (thinfilm) ν_{max} (cm^{-1}): 1709 (H-C=O), 1674 (O-C=O), 1636 (C=C); HRMS (ESI): m/z calculated for $C_{14}H_{16}O_5$: requires: 257.0789 for $[M+Na]^+$; found: 257.0780.

(*E*)-ethyl 3-(2-formyl-4-(trifluoromethyl)phenyl)acrylate 164d



General procedure C was followed using (*E*)-ethyl 3-(2-(1,3-dioxan-2-yl)-4-(trifluoromethyl) phenyl)acrylate **163**d (991 mg, 3.00 mmol). After 7 hours, the reaction was worked up and purified by recrystallisation (petrol:ether) to yield the title compound as cream needles in 68% yield (555 mg, 2.04 mmol). m.p. 65-67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 10.37 (1H, s, C*H*O), 8.20 (1H, d, J = 15.9 Hz, ArC*H*=CH), 8.14 (1H, s, Ar*H*), 7.84 (1H, d, J = 8.0 Hz, Ar*H*), 7.74 (1H, d, J = 8.0 Hz, Ar*H*), 6.43 (1H, d, J = 15.9 Hz, ArCH=C*H*), 4.30 (2H, q, J = 7.2 Hz, C*H*$_2$CH$_3$), 1.35 (3H, t, J = 7.2 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 190.05, 165.57, 139.95 (q, J = 1.2 Hz), 139.16, 133.93, 131.95 (q, J = 33.8 Hz), 130.16 (q, J = 3.4 Hz), 128.72, 128.51 (q, J = 3.7 Hz), 125.43, 123.19, (appt. d, J = 272.4 Hz), 61.03, 14.19; IR (thinfilm) ν_{max} (cm^{-1}): 1717 (C=O), 1703 (C=O), 1638 (C=C); HRMS (ESI): m/z calculated for $C_{13}H_{11}F_3O_3$: requires: 273.0738 for $[M+H]^+$; found: 273.0725; requires: 295.0557 for $[M+Na]^+$; found: 295.0546.

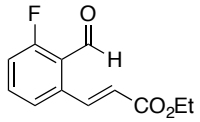
(*E*)-ethyl 3-(3-formylnaphthalen-2-yl)acrylate 164e



General procedure C was followed using ethyl (*E*)-3-(2-(1,3-dioxan-2-yl)-4-fluorophenyl) acrylate **163**e (841 mg, 3.00 mmol). After 14 hours, the reaction was worked up and purified by recrystallisation (petrol:ether) to yield the title compound as cream needles in 73% yield (487 mg, 2.19 mmol). m.p. 92-94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 10.30 (1H, s, C*H*O), 8.41 (1H, d, J = 15.8 Hz, ArC*H*=CH), 7.64 (1H, dd, J = 8.6, 5.1 Hz, Ar*H*), 7.58 (1H, dd, J = 8.5, 2.7 Hz, Ar*H*), 7.32 (1H, td, J = 8.0, 2.7 Hz, Ar*H*), 6.34 (1H, d, J = 15.8 Hz, ArCH=C*H*), 4.29 (2H, q, J = 7.1

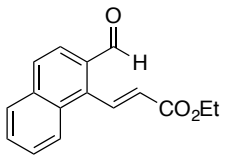
Hz, C*H*$_2$CH$_3$), 1.35 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz CDCl$_3$) δ_C: 190.00, 166.11, 163.51 (d, J = 252.9 Hz), 139.31, 135.64 (d, J = 4.8 Hz), 133.12 (d, J = 4.8 Hz), 130.30 (d, J = 7.6 Hz), 123.57, 121.41 (d, J = 22.2 Hz), 117.53 (d, J = 22.2 Hz), 60.99, 14.38; IR (thinfilm) ν_{max} (cm^{-1}): 1719 (C=O), 1706 (C=O), 1675 (C=C); HRMS (ESI): m/z calculated for $C_{12}H_{11}FO_3$: requires: 245.0589 for [M+Na]$^+$; found: 245.0601.

(*E*)-ethyl 3-(3-fluoro-2-formylphenyl)acrylate 164f



General procedure C was followed using (*E*)-ethyl 3-(2-(1,3-dioxan-2-yl)-3-fluorophenyl) acrylate **163**f (841 mg, 3.00 mmol). After 5 hours the reaction was worked up and purified by recrystallisation (petrol:ether) to yield the title compound in 80% yield (533 mg, 2.40 mmol) as white needles. m.p. 88-91 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 10.53 (1H, s, C*H*O), 8.40 (1H, d, J = 15.9 Hz, ArC*H*=CH), 7.56 (1H, td, J = 8.2, 5.6 Hz, Ar*H*), 7.37 (1H, d, J = 7.7 Hz, Ar*H*), 7.23-7.16 (1H, m, Ar*H*), 6.31 (1H, d, J = 15.9 Hz, ArCH=C*H*), 4.27 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 1.35 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz CDCl$_3$) δ_C: 188.29 (d, J = 10.8 Hz), 166.07, 165.75 (d, J = 258.3 Hz), 141.78 (d, J = 2.8 Hz), 138.15, 135.39 (d, J = 10.4 Hz), 123.95 (d, J = 3.5 Hz), 123.51, 122.03 (d, J = 6.6 Hz), 117.22 (d, J = 21.8 Hz), 60.76, 14.26; IR (thinfilm) ν_{max} (cm^{-1}): 1707 (C=O), 1686 (C=O), 1637 (C=C); HRMS (ESI): m/z calculated for $C_{12}H_{11}FO_3$: requires: 245.0589 for [M+Na]$^+$; found: 245.0579.

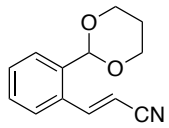
(*E*)-ethyl 3-(3-formylnaphthalen-2-yl)acrylate 164g



General procedure C was followed using (*E*)-ethyl 3-(3-(1,3-dioxan-2-yl)naphthalen-2-yl)acrylate **163**g (937 mg, 3.00 mmol). After 6 hours the reaction was worked up and purified by column chromatography (eluent: DCM) to yield the title compound in 72% yield (549 mg, 2.16 mmol) as a yellow oil. R$_f$ (DCM) = 0.50; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H: 10.39 (1H, s, C*H*O), 8.45 (1H, d, J = 15.9 Hz, ArC*H*=CH), 8.14 (1H, d, J = 8.8 Hz, Ar*H*), 8.01 (1H, d, J = 8.8 Hz, Ar*H*), 7.93 Ð 7.90 (2H, m, Ar*H*), 7.69 Ð 7.58 (2H, m, Ar*H*), 6.20 (1H, d, J = 15.9 Hz, ArCH=C*H*), 4.35 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 1.38 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz CDCl$_3$) δ_C: : 191.58, 165.44, 139.27, 138.98, 135.85, 131.88, 131.25, 130.01, 129.52, 129.29, 128.79, 127.62, 126.05, 123.24, 61.27, 14.42; IR (thinfilm) ν_{max} (cm^{-1}): 1717 (C=O), 1678 (C=O), 1636 (C=C); HRMS (ESI): m/z calculated for $C_{16}H_{14}O_3$: requires: 255.1021 for [M+H]$^+$;

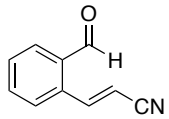
found: 255.1001; requires: 277.0840 for $[M+Na]^+$; found: 277.0827.

(*E*)-3-(2-(1,3-dioxan-2-yl)phenyl)acrylonitrile 208



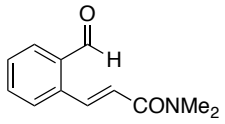
To a solution of 2-(2-bromophenyl)-1,3-dioxane **147** (972 mg, 4.00 mmol), $Pd(OAc)_2$ (1.0 mol%) triphenylphosphine (2.0 mol%) in DMF, was added acrylonitrile **207** (2.0 eq.) and Et_3N (2.0 eq.) The reaction was heated to 100 °C and stirred for 12 hours. After cooling to room temperature, H_2O was added and the solution was extracted with Et_2O (x3). Removal of the solvent under reduced pressure gave an orange oil that was purified by column chromatography (eluent: 85:15 petrol:EtOAc) to afford the title compound as a yellow oil in 59% yield (594 mg, 2.76 mmol).[98] R_f (85:15 petrol:EtOAc) = 0.39; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.04 (1H, d, J = 17.0 Hz, ArC*H*=CH), 7.56 (1H, dd, J = 7.5, 1.6 Hz, Ar*H*), 7.47 (1H, dd, J = 7.5, 1.6 Hz, Ar*H*), 7.43-7.31 (2H, m, Ar*H*), 5.77 (1H, d, J = 17.0 Hz, ArCH=C*H*), 5.58 (1H, s, C*H*), 4.29 (1H, dd, J = 5.0, 1.2 Hz, OCH_AH$_B$), 4.25 (1H, dd, J = 5.0, 1.2 Hz, OCH$_A$$H_B$), 3.97 (2H, td, J = 12.2, 2.4 Hz, OCH_2), 2.33-2.17 (1H, m, $CH_2CH_AH_BCH_2$), 1.50-1.43 (1H, m, $CH_2CH_AH_BCH_2$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 148.73, 136.67, 131.98, 130.57, 129.25, 127.55, 126.02, 118.35, 100.88, 97.47, 67.54, 25.54; IR (thinfilm) ν_{max} (cm^{-1}): 2212 (C≡N); 1617 (C=C); HRMS (ESI): m/z calculated for $C_{13}H_{13}NO_2$: requires: 216.1024 for $[M+H]^+$; found: 216.1006; requires: 238.0843 for $[M+Na]^+$; found: 238.0839.

(*E*)-3-(2-formylphenyl)acrylonitrile 209



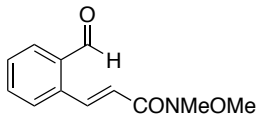
General procedure C was followed using (*E*)-3-(2-(1,3-dioxan-2-yl)phenyl)acrylonitrile **208** (646 mg, 3.00 mmol). After 14 hours the reaction was worked up and purified by column chromatography (eluent: 90:10 petrol:EtOAc) to yield the title compound as a white solid in 66% yield (312.00 mg, 1.98 mmol). R_f (90:10 petrol:EtOAc) = 0.36; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 10.13 (1H, s, C*H*O), 8.40 (1H, d, J = 16.6 Hz, ArC*H*=CH), 7.88-7.82 (1H, m, Ar*H*), 7.64 (2H, dd, J = 5.3, 3.6 Hz, Ar*H*), 7.60-7.55 (1H, m, Ar*H*), 5.85 (1H, d, J = 16.6 Hz, ArCH=C*H*); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 192.39, 148.17, 134.77, 134.58, 134.08, 133.35, 130.92, 127.34, 117.62, 100.62; IR (thinfilm) ν_{max} (cm^{-1}): 2210 (C≡N), 1708 (C=O), 1637 (C=C); HRMS (ESI): m/z calculated for $C_{10}H_7NO$: requires: 180.0417 for $[M+Na]^+$; found: 180.0425.

(*E*)-3-(2-formylphenyl)-*N*,*N*-dimethylacrylamide 210



To a solution of 2-bromobenzaldehyde (0.32 mL, 2.70 mmol), $Pd(OAc)_2$ (1.0 mol%) and (o-Tol)$_3$P (2.0 mol%) in DMF (5 mL) in a 20 mL microwave vial, was added *N,N*-dimethylacrylamide (0.42 mL, 4.05 mmol) and Et_3N (0.57 mL, 4.05 mmol). The reaction vessel was sealed and heated to 120 °C in a Biotage Initiator microwave for 1 hour. After cooling, the reaction was diluted with Et_2O, filtered through Celite® and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield the crude product as a brown oil. The crude material was purified using a Biotage SP4 (eluent: 30:70 cyclohexane:EtOAc; 50 g Biotage SNAP cartridge) and recrystallised from Et_2O:hexane. The yellow solid was filtered and dried under vacuum to yield the title compound in 81% yield (462 mg, 2.18 mmol). R_f (70:30 cyclohexane:EtOAc) = 0.39; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 10.36 (1H, s, C*H*O), 8.34 (1H, d, J = 15.4 Hz, ArC*H*=CH), 7.89 (1H, d, J = 7.6 Hz, Ar*H*), 7.64 - 7.58 (2H, m, Ar*H*), 7.55 - 7.48 (1H, m, Ar*H*), 6.77 (1H, d, J = 15.4 Hz, ArCH=C*H*), 3.18 (3H, s, NC*H*$_3$*A*CH$_3$B), 3.08 (3H, s, NCH$_3$AC*H*$_3$*B*); ^{13}C{^{1}H} NMR (100 MHz $CDCl_3$) δ_C: 191.39, 165.99, 138.28, 138.08, 133.91, 133.77, 130.74, 129.18, 128.03, 123.47, 37.52, 35.87; IR (thinfilm) ν_{max} (cm^{-1}): 1694 (C=O), 1646 (C=O), 1595 (C=C); HRMS (ESI): m/z calculated for $C_{12}H_{14}N_1O_2$: requires: 204.1025 for [M+H]$^+$; found: 204.1017.

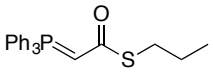
(*E*)-3-(2-formylphenyl)-*N*-methoxy-*N*-methylacrylamide 211



To a solution of 2-bromobenzaldehyde (0.32 mL, 2.70 mmol), $Pd(OAc)_2$ (1.0 mol%) and (o-Tol)$_3$P (2.0 mol%) in DMF (5 mL) in a 20 mL microwave vial, was added *N*-methoxy-*N*-methylacrylamide (467 mg, 4.05 mmol) and Et_3N (0.57 mL, 4.05 mmol). The reaction vessel was sealed and heated to 90 °C in a Biotage Initiator microwave for 40 minutes. After cooling, the reaction was diluted with Et_2O, filtered through Celite® and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield the crude product as a brown oil. The crude material was purified using a Biotage SP4 (eluent: 60:40 cyclohexane:EtOAC, 50 g SNAP cartridge), to yield the title compound as a yellow oil in 76% yield (451 mg, 2.06 mmol). R_f (60:40 cyclohexane:EtOAc) = 0.46; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H: 10.39 (1H, s, C*H*O), 8.48 (1H, d, J = 15.8 Hz, ArC*H*=CH), 7.92 (1H, d, J = 7.7 Hz, Ar*H*), 7.64-7.69 (1H, m, Ar*H*), 7.60-7.64 (1H, m, Ar*H*), 7.51-7.56 (1H, m, Ar*H*), 6.96 (1H, d, J = 15.8 Hz, ArCH=C*H*), 3.77 (3H, s, OC*H*$_3$), 3.34 (3H, s, NC*H*$_3$); ^{13}C{^{1}H} NMR (150 MHz $CDCl_3$) δ_C: 191.29, 166.04, 139.37, 137.97, 134.07, 133.79, 130.77, 129.47, 128.14, 121.48, 61.97, 32.54; IR (thinfilm) ν_{max} (cm^{-1}): 1686 (C=O), 1646 (C=O), 1611

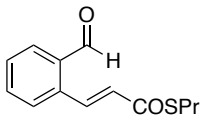
(C=C); HRMS (ESI): m/z calculated for $C_{12}H_{14}NO_3$: requires: 220.0974 for $[M+H]^+$; found: 220.0969.

S-propyl 2-(triphenylphosphoranylidene)ethanethioate 213



To a solution of *S*-propyl 2-bromoethanethioate (1 g, 5.07 mmol), in toluene (10 mL) at room temperature was added triphenylphosphine (1.397 g, 5.33 mmol) in one charge. The reaction mixture was left to stand at room temperature for 3.5 days to yield 2.35 g of white crystals after filtering and washing with toluene (3 x 10 mL). The crystals were dissolved in 10 mL of DCM and stirred with 10 mL of a 10% aqueous Na_2CO_3 solution for 30 minutes. The layers were separated and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were partially concentrated under vacuum, diluted with cyclohexane and allowed to stand to precipitate out colourless plate crystals. The crystals were filtered and a second crop of precipitate acquired from the filtrate. The crystals were dried under vacuum to yield the title compound (1.66 g, 4.39 mmol, 86%), which was used without purification.[100] m.p. 82-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.60-7.67 (6H, m, Ar*H*), 7.54-7.59 (3H, m, Ar*H*), 7.44-7.50 (6H, m, Ar*H*), 3.58-3.75 (1H, m, Ph_3P=C*H*), 2.83 (2H, t, J = 7.2 Hz, C*H*$_2$$CH_2CH_3$), 1.58 - 1.65 (2H, m, CH_2C*H*$_2$$CH_3$), 0.97 (3H, t, J = 7.3 Hz, CH_2CH_2C*H*$_3$); ^{13}C{^{1}H} NMR (100 MHz $CDCl_3$) δ_C: 133.07, 132.97, 132.16, 128.93, 128.80, 127.34, 30.79, 24.52, 13.55; IR (thinfilm) ν_{max} (cm^{-1}): 1579 (C=O), 1566 (P=C); HRMS (ESI): m/z calculated for $C_{23}H_{24}OPS$: requires: 379.1286 for $[M+H]^+$; found: 379.1278.

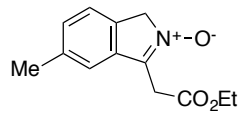
S-propyl (*E*)-3-(2-formylphenyl)prop-2-enethioate 214



To a solution of phthaldialdehyde (1.61 g, 12.00 mmol, 3.0 eq.) in DCM (5 mL) was added *S*-propyl 2-(triphenylphos-phoranylidene)ethanethioate **213** (1.51 g, 4.00 mmol, 1.0 eq.) in one portion. The reaction was left to stir at room temperature for 3 days. The solvent was removed under reduced pressure and the crude material purified by column chromatopgraphy (eluent: 90:10 petrol:EtOAc), and recrystallisation to yield the title compound as colourless plates in 56% yield (525 mg, 2.24 mmol).[99] m.p. 34-35 °C; R_f (90:10 petrol:EtOAc = 0.36); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 10.29 (1H, s, C*H*O), 8.48 (1H, d, J = 15.7 Hz, ArC*H*=CH), 7.88 (1H, dd, J = 6.7, 1.6 Hz, Ar*H*), 7.67-7.54 (3H, m, Ar*H*), 6.63 (1H, d, J = 15.7 Hz, ArCH=C*H*), 3.00 (2H, t, J = 7.2 Hz, C*H*$_2$$CH_2CH_3$), 1.68 (2H, p, J = 7.3 Hz, CH_2C*H*$_2$$CH_3$), 1.01 (3H, t, J = 7.3 Hz, CH_2CH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 191.98, 189.94, 136.91, 136.52, 134.24, 134.04, 132.69, 130.18, 129.87,

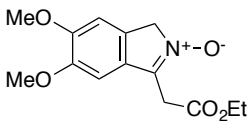
128.06, 31.11, 23.07, 13.56; IR (thinfilm) ν_{max} (cm^{-1}): 1686 (C=O), 1660 (C=O), 1609 (C=C); HRMS (ESI): m/z calculated for $C_{13}H_{14}O_2S$: requires: 235.0787 for $[M+H]^+$; found: 235.0787.

3-(2-ethoxy-2-oxoethyl)-5-methyl-1*H*-isoindole 2-oxide 165a



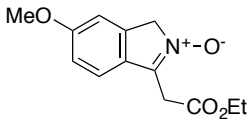
General procedure E was followed using ethyl (*E*)-3-(2-formyl-5-methylphenyl)acrylate **164**a (437 mg, 2.00 mmol). The title compound was formed as a brown oil in 74% yield (345 mg, 1.48 mmol) and required no further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.20 (1H, d, J = 7.6 Hz, Ar*H*), 7.14 (1H, d, J = 7.8 Hz, Ar*H*), 7.10 (1H, s, Ar*H*), 4.93 (2H, s, ArC*H*$_2$N), 4.19 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 3.86 (2H, s, C*H*$_2$C=O), 2.38 (3H, s, ArC*H*$_3$), 1.24 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (125 MHz $CDCl_3$) δ_C: 167.42, 141.73, 138.54, 135.97, 130.28, 128.83, 121.34, 119.94, 65.69, 61.66, 29.83, 21.53, 14.11; IR (thinfilm) ν_{max} (cm^{-1}): 1724 (C=O); HRMS (ESI): m/z calculated for $C_{13}H_{15}NO_3$: requires: 234.1130 for $[M+H]^+$; found: 234.1130; requires: 256.0949 for $[M+Na]^+$; found: 256.0952.

3-(2-ethoxy-2-oxoethyl)-5,6-dimethoxy-1*H*-isoindole 2-oxide 165b



General procedure E was followed using ethyl (*E*)-3-(2-formyl-4,5-dimethoxyphenyl)acrylate **164**b (529 mg, 2.00 mmol). The title compound was formed as a yellow solid in 83% yield (463 mg, 1.66 mmol) and required no further purification. m.p. 152-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.93 (1H, s, Ar*H*), 6.84 (1H, s, Ar*H*), 4.95 (2H, s, ArC*H*$_2$N), 4.19 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 3.91 (6H, s, OC*H*$_3$), 3.89 (2H, s, C*H*$_2$C=O), 1.26 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (100 MHz $CDCl_3$) δ_C: 167.44, 150.30, 149.94, 142.73, 128.18, 126.53, 105.72, 103.01, 65.49, 61.85, 56.43, 56.36, 30.22, 14.22; IR (thinfilm) ν_{max} (cm^{-1}): 1730 (C=O); HRMS (ESI): m/z calculated for $C_{14}H_{17}NO_5$: requires: 280.1184 for $[M+H]^+$; found: 280.1185; requires: 302.1004 for $[M+Na]^+$; found: 302.1011.

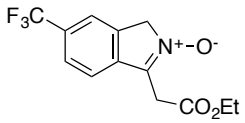
3-(2-ethoxy-2-oxoethyl)-6-methoxy-1*H*-isoindole 2-oxide 165c



General procedure E was followed using ethyl (*E*)-3-(2-formyl-4-methoxyphenyl)acrylate

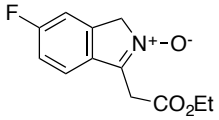
164c (469 mg, 2.00 mmol). The title compound was formed as a white solid in 79% yield (394 mg, 1.58 mmol) and required no further purification. m.p. 143-145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.20 (1H, d, J = 8.3 Hz, ArH), 6.92 (2H, dd, J = 11.5, 2.9 Hz, ArH), 4.97 (2H, s, ArCH_2N), 4.19 (2H, q, J = 7.1 Hz, CH_2CH$_3$), 3.88 (2H, s, CH_2C=O), 3.83 (3H, s, OCH_3), 1.25 (3H, t, J = 7.2 Hz, CH$_2$CH_3); ^{13}C{^{1}H} NMR (125 MHz $CDCl_3$) δ_C: 167.39, 160.63, 140.13, 135.51, 128.43, 120.72, 114.14, 108.57, 65.45, 61.77, 55.74, 30.09, 14.18; IR (thinfilm) ν_{max} (cm^{-1}): 1732 (C=O); HRMS (ESI): m/z calculated for $C_{13}H_{15}NO_4$: requires: 250.1079 for $[M+H]^+$; found: 250.1075; requires: 272.0898 for $[M+Na]^+$; found: 272.0891.

3-(2-ethoxy-2-oxoethyl)-6-(trifluoromethyl)-1*H*-isoindole 2-oxide 165d



General procedure E was followed using ethyl (*E*)-3-(2-formyl-4-(trifluoromethyl)phenyl) acrylate **164**d (544 mg, 2.00 mmol). The title compound was formed as a pale green solid in 83% yield (477 mg, 1.66 mmol) and required no further purification. m.p. 148-149 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.63 (1H, d, J = 7.5 Hz, ArH), 7.56 (1H, s, ArH), 7.38 (1H, d, J = 8.0 Hz, ArH), 5.03 (2H, s, ArCH_2N), 4.17 (2H, q, J = 7.1 Hz, CH_2CH$_3$), 3.87 (2H, s, CH_2C=O), 1.23 (3H, t, J = 7.1 Hz, CH$_2$CH_3); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 167.16, 140.92, 139.42, 133.27, 129.87, 126.03 (q, J = 2.7 Hz), 124.10 (q, J = 272.3 Hz), 119.41, 118.67 (q, J = 3.9 Hz), 66.03, 61.92, 29.81, 14.14; IR (thinfilm) ν_{max} (cm^{-1}): 1732 (C=O); HRMS (ESI): m/z calculated for $C_{13}H_{12}NO_3F_3$: requires: 288.0847 for $[M+H]^+$; found: 288.0827; requires: 310.0666 for $[M+Na]^+$; found: 310.0652.

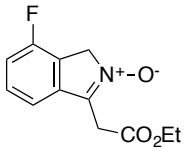
3-(2-ethoxy-2-oxoethyl)-6-fluoro-1*H*-isoindole 2-oxide 165e



General procedure E was followed using ethyl (*E*)-3-(4-fluoro-2-formylphenyl)acrylate **164**e (444 mg, 2.00 mmol). The crude product, a green solid, was recrystallised from DCM:hexane to yield white needles in 85% yield (403 mg, 1.70 mmol) and required no further purification. m.p. 134-136; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.29-7.25 (1H, m, ArH), 7.14-7.08 (2H, m, ArH), 4.99 (2H, s, ArCH_2N), 4.21 (2H, q, J = 7.1 Hz, CH_2CH$_3$), 3.90 (2H, s, CH_2C=O), 1.26 (3H, t, J = 7.1 Hz, CH$_2$CH_3); ^{13}C{^{1}H} NMR (125 MHz $CDCl_3$) δ_C: 167.38, 163.19 (d, J = 249.1 Hz), 141.12, 135.16 (d, J = 9.1 Hz), 132.16 (d, J = 2.5 Hz), 120.82 (d, J = 8.6 Hz), 115.97 (d, J = 23.4 Hz), 110.24 (d, J = 25.2 Hz), 65.76, 61.92, 30.00, 14.25; IR (thinfilm) ν_{max} (cm^{-1}): 1724 (C=O); HRMS (ESI): m/z calculated for $C_{12}H_{12}FNO_3$: requires: 238.0879 for $[M+H]^+$; found: 238.0906; requires:

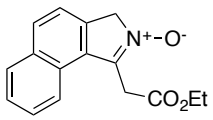
260.0698 for $[M+Na]^+$; found: 260.0719.

3-(2-ethoxy-2-oxoethyl)-7-fluoro-1*H*-isoindole 2-oxide 165f



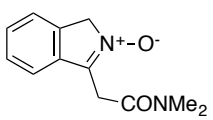
General procedure E was followed using ethyl (*E*)-3-(3-fluoro-2-formylphenyl)acrylate **164**f (444 mg, 2.00 mmol). The crude product, a purple solid, was recrystallised from DCM:hexane to yield colourless needles in 72% yield (342 mg, 1.44 mmol). m.p. 141-144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.35 (1H, td, J = 8.0, 5.0 Hz, Ar*H*), 7.08 (1H, d, J = 7.6 Hz, Ar*H*), 7.01 (1H, t, J = 8.6 Hz, Ar*H*), 5.00 (2H, s, ArC*H*$_2$N), 4.16 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 3.83 (2H, s, C*H*$_2$C=O), 1.21 (3H, t, J = 7.2 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (125 MHz $CDCl_3$) δ_C: 167.15, 156.29 (d, J = 249.1 Hz), 141.09, 138.61 (d, J = 5.6 Hz), 130.97 (d, J = 7.2 Hz), 118.35 (d, J = 18.93), 115.52 (d, J = 3.1 Hz), 115.26 (d, J = 20.14 Hz), 63.42, 61.77, 29.95, 14.09; IR (thinfilm) ν_{max} (cm^{-1}): 1720 (C=O); HRMS (ESI): m/z calculated for $C_{12}H_{12}NO_3F$: requires: 260.0698 for $[M+Na]^+$; found: 260.0697. For crystallographic data see Appendix 1.

1-(2-ethoxy-2-oxoethyl)-3*H*-benzo[*e*]isoindole 2-oxide 165g



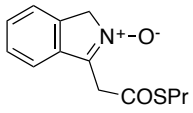
General procedure E was followed using ethyl (*E*)-3-(2-formylnaphthalen-1-yl)acrylate **164**g (509 mg, 2.00 mmol). The crude product, a purple solid, was recrystallised from DCM:hexane to yield purple needles in 74% yield (399 mg, 1.48 mmol). m.p. 173-175 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.03 (1H, d, J = 8.07 Hz, Ar*H*), 7.93-7.86 (2H, m, Ar*H*), 7.60-7.50 (2H, m, Ar*H*), 7.46 (1H, d, J = 8.28 Hz, Ar*H*), 5.13 (2H, s, ArC*H*$_2$N), 4.39 (2H, s, C*H*$_2$C=O), 4.20 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 1.20 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 167.96, 143.58, 133.90, 132.17, 131.17, 129.58, 129.19, 127.60, 126.47, 126.39, 122.46, 119.10, 65.85, 61.96, 32.38, 14.24; IR (thinfilm) ν_{max} (cm^{-1}): 1731 (C=O); HRMS (ESI): m/z calculated for $C_{16}H_{15}NO_3$: requires: 270.1130 for $[M+H]^+$; found: 270.1133; requires: 292.0949 for $[M+Na]^+$; found: 292.0951.

3-(2-(dimethylamino)-2-oxoethyl)-1*H*-isoindole 2-oxide 215



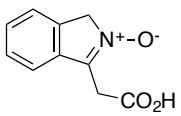
General procedure E was followed using (*E*)-3-(2-formylphenyl)-*N,N*-dimethylacrylamide **210** (406 mg, 2.00 mmol). The title compound was formed as a white solid in 79% yield (345 mg, 1.58 mmol) and required no further purification. m.p. 124-126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.45 (1H, dd, J = 6.03, 2.13 Hz, Ar*H*), 7.32-7.23 (3H, m, Ar*H*), 4.90 (2H, s, ArC*H*$_2$N), 3.88 (2H, s, C*H*$_2$C=O), 3.06 (3H, s, NC*H*$_3$), 2.86 (3H, s, NC*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 166.50, 143.08, 135.95, 133.03, 128.55, 127.96, 121.24, 120.43, 65.61, 37.71, 35.56, 30.26; IR (thinfilm) ν_{max} (cm^{-1}): 1634 (C=O), HRMS (ESI): m/z calculated for $C_{12}H_{14}N_2O_2$: requires: 219.1133 for $[M+H]^+$; found: 219.1119.

3-(2-oxo-2-(propylthio)ethyl)-1*H*-isoindole 2-oxide 217



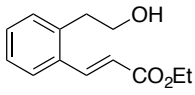
General procedure E was followed using *S*-propyl (*E*)-3-(2-formylphenyl)prop-2-enethioate **214** (469 mg, 2.00 mmol). The title compound was formed as colourless needles in 59% yield (294 mg, 1.18 mmol) and required no further purification. m.p. 119-121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.39-7.25 (4H, m, Ar*H*), 4.98 (2H, s, ArC*H*$_2$N), 3.85 (2H, s, C*H*$_2$C=O), 2.99 (2H, t, J = 7.2 Hz, C*H*$_2$CH$_2$CH$_3$), 1.65 (2H, p, J = 7.3 Hz, CH$_2$C*H*$_2$CH$_3$), 1.00 (3H, t, J = 7.3 Hz, CH$_2$CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 190.20, 142.18, 136.05, 133.43, 128.47, 127.95, 121.61, 119.64, 65.57, 31.09, 30.13, 23.21, 13.55; IR (thinfilm) ν_{max} (cm^{-1}): 1683 (C=O); HRMS (ESI): m/z calculated for $C_{13}H_{15}NO_2S$: requires: 250.0874 for $[M+H]^+$; found: 250.0839.

3-(carboxymethyl)-1*H*-isoindole 2-oxide 218



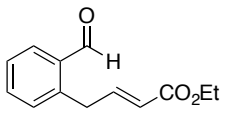
General procedure E was followed using *S*-propyl (*E*)-3-(2-formylphenyl)prop-2-enethioate **214** (469 mg, 2.00 mmol) at room temperature. The title compound was formed as a red oil in 68% yield (260 mg, 1.36 mmol) and required no further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 7.45-7.33 (4H, m, Ar*H*), 5.06 (2H, s, ArC*H*$_2$N), 3.58 (2H, s, C*H*$_2$C=O); ^{13}C{^{1}H} NMR (75.5 MHz DMSO-d_6) δ_C: 163.58, 140.92, 136.35, 133.67, 127.94, 127.22, 121.58, 119.42, 65.77, 28.30; IR (thinfilm) ν_{max} (cm^{-1}): 1722 (C=O); HRMS (ESI): m/z calculated for $C_{10}H_9NO_3$: requires: 192.0679 for $[M+H]^+$; found: 192.0691.

Ethyl (*E*)-3-(2-(2-hydroxyethyl)phenyl)acrylate 220



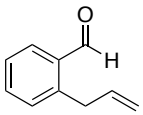
General procedure B was followed using 2-(2-bromophenyl)ethan-1-ol **219** (804 mg, 4.00 mmol). After 4 hours, the reaction was worked up and purified by column chromatography (eluent: 70:30 petrol:EtOAc) to yield the title compound as a pale yellow oil in 39% yield (344 mg, 1.56 mmol). R_f (70:30 Petrol:EtOAc) = 0.25; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.00 (1H, d, J = 15.8 Hz, ArC*H*=CH), 7.58-7.55 (1H, m, Ar*H*), 7.34-7.28 (1H, m, Ar*H*), 7.26-7.21 (2H, m, Ar*H*), 6.35 (1H, d, J = 15.8 Hz, ArCH=C*H*), 4.24 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 3.81-3.76 (2H, m, C*H*$_2$OH), 3.01 (3H, t, J = 4.2 Hz), 2.31 (1H, br. s, O*H*), 1.32 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 167.22, 142.05, 138.26, 133.59, 130.92, 130.19, 127.14, 126.79, 119.84, 63.39, 60.71, 36.54, 14.39; IR (thinfilm) ν_{max} (cm^{-1}): 3383 (O-H), 1707 (C=O), 1630 (C=C); HRMS (ESI): m/z calculated for $C_{13}H_{16}O_3$: requires: 221.1177 for $[M+H]^+$; found: 221.1199.

Ethyl (*E*)-4-(2-formylphenyl)but-2-enoate 223



General procedure D was followed using 2-formylphenyl boronic acid **224** (450 mg, 3.0 mmol), followed by purification by column chromatography (eluent: 95:5 petrol:EtOAc), to yield the title compound as colourless oil in 52% yield (340 mg, 1.56 mmol). R_f (95:5 Petrol:EtOAc) = 0.46; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 10.15 (1H, s, C*H*O), 7.83 (1H, dd, J = 7.5, 1.4 Hz, Ar*H*), 7.54 (1H, td, J = 7.4, 1.5 Hz, Ar*H*), 7.46 (1H, td, J = 7.4, 1.2 Hz, Ar*H*), 7.28-7.26 (1H, m, CH$_2$C*H*=CH), 7.13 (1H, dt, J = 15.6, 6.3 Hz, Ar*H*), 5.71 (1H, dt, J = 15.6, 1.7 Hz, CH$_2$CH=C*H*), 4.15 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 3.98 (2H, dd, J = 6.4, 1.4 Hz, ArC*H*$_2$), 1.26 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 192.62, 166.48, 146.78, 139.90, 134.19, 133.98, 133.81, 131.61, 127.66, 122.82, 60.46, 35.36, 14.36; IR (thinfilm) ν_{max} (cm^{-1}): 1712 (C=O), 1695 (C=O), 1651 (C=C); HRMS (ESI): m/z calculated for $C_{13}H_{14}O_3$: requires: 241.0840 for $[M+Na]^+$; found: 241.0838.

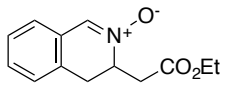
2-allylbenzaldehyde 226



To a solution of 2-formylphenyl boronic acid **224** (450 mg, 3.0 mmol) and allyl bromide (1.2 eq.) in THF (0.2 M), were added $PdCl_2(PPh_3)_2$(2.5 mol%) and aqueous Na_2CO_3 (1 M, 2.0 eq.) solution. The reaction mixture was heated to reflux and stirred for 4 hours. The reaction was quenched with H_2O and extracted with DCM (x3). The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude material was purified by column chromatography (eluent:

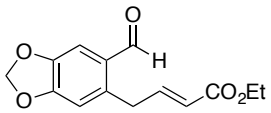
95:5 petrol:EtOAc) to afford the title compound in 83% yield (364 mg, 2.49 mmol).[103] R_f (95:5 Petrol:EtOAc) = 0.49; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 10.24 (1H, s, C*H*O), 7.84 (1H, dd, J = 7.6, 1.3 Hz, Ar*H*), 7.5 (1H, td, J = 7.4, 1.4 Hz, Ar*H*), 7.39 (1H, td, J = 7.5, 1.0 Hz, Ar*H*), 7.29 (1H, d, J = 7.5 Hz, Ar*H*), 6.03 (1H, ddt, J = 16.9, 10.2, 6.1 Hz, C*H*CH_2), 5.08 (1H, dq, 10.1, 1.4 Hz, CH=C$H_A H_B$), 4.98 (1H, dq, J = 17.0, 1.6 Hz, CH=C$H_A H_B$), 3.82 (2H, d, J = 6.1 Hz, CH_2CH=CH_2); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 192.41, 142.34, 137.03, 134.05, 133.96, 131.68, 131.16, 127.00, 116.50, 36.61; IR (thinfilm) ν_{max} (cm^{-1}): 1692 (C=O), 1598 (C=C), 752 (C=C); HRMS (ESI): m/z calculated for $C_{10}H_{10}O$: requires: 167.1752 for $[M+Na]^+$; found: 167.1797.

3-(2-ethoxy-2-oxoethyl)-3,4-dihydroisoquinoline 2-oxide 227



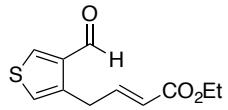
General procedure F was followed using ethyl (*E*)-4-(2-formylphenyl)but-2-enoate **223** (437 mg, 2.00 mmol). The title compound was formed as a colourless oil in 92% yield (429 mg, 1.87 mmol) and required no further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.71 (1H, s, *H*-C=N$^+$), 7.28-7.25 (2H, m, Ar*H*), 7.21-7.18 (1H, m, Ar*H*), 7.12-7.09 (1H, m, Ar*H*), 4.50 (1H, m, C*H*), 4.23-4.08 (2H, m, C$H_2$$CH_3$), 3.36 (1H, dd, J = 16.5, 6.0 Hz, ArC$H_A H_B$), 3.13-3.05 (2H, m, ArC$H_A H_B$, C$H_A$$CH_B CO_2$Et), 2.59 (1H, dd, J = 16.1, 8.7 Hz, $CH_A H_B CO_2$Et), 1.25 (3H, t, J = 7.1 Hz, CH_2CH_3); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 170.36, 133.88, 129.70, 128.90, 127.94, 127.80, 125.35, 64.36, 61.042, 35.37, 32.45, 14.16; IR (thinfilm) ν_{max} (cm^{-1}): 1726 (C=O); HRMS (ESI): m/z calculated for $C_{13}H_{15}NO_3$: requires: 234.1130 for $[M+H]^+$; found: 234.1137.

Ethyl (*E*)-4-(6-formylbenzo[*d*][1,3]dioxol-5-yl)but-2-enoate 223a



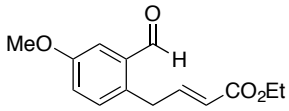
General procedure D was followed using (6-formylbenzo[*d*][1,3]dioxol-5-yl)boronic acid (582 mg, 3.0 mmol), followed by purification by column chromatography (eluent: 95:5 petrol:EtOAc), to yield the title compound as colourless oil in 72% yield (566 mg, 2.16 mmol). R_f (95:5 Petrol:EtOAc) = 0.40; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 10.09 (1H, s, C*H*O), 7.30 (1H, s, Ar*H*), 7.12 (1H, dt, J = 15.6, 6.4 Hz, CH_2C*H*=CH), 6.72 (1H, s, Ar*H*), 5.98 (2H, s, OCH_2), 5.68 (1H, dt, J = 15.6, 1.6 Hz, CH_2CH=C*H*), 4.16 (2H, q, J = 7.1 Hz, C$H_2$$CH_3$), 3.86 (2H, dd, J = 6.4, 1.6 Hz, ArCH_2), 1.27 (3H, t, J = 7.1 Hz, CH_2CH_3); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 189.47, 166.25, 152.59, 147.42, 146.58, 137.15, 128.49, 122.92, 111.07, 110.25, 102.24, 60.45, 34.71, 14.28; IR (thinfilm) ν_{max} (cm^{-1}): 1713 (C=O), 1677 (C=O), 1652 (C=C); HRMS (ESI): m/z calculated for $C_{14}H_{14}O_5$: requires: 285.0738 for $[M+Na]^+$; found: 285.0749.

Ethyl (*E*)-4-(4-formylthiophen-3-yl)but-2-enoate 223b



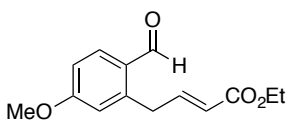
General procedure D was followed using (4-formylthiophen-3-yl)boronic acid (468 mg, 3.0 mmol), followed by purification by column chromatography (eluent: DCM), to yield the title compound as a yellow oil in 54% yield (363 mg, 1.62 mmol). R_f (DCM) = 0.32; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 9.96 (1H, s, C*H*O), 8.12 (1H, d, J = 3.1 Hz, Ar*H*), 7.16-7.05 (2H, m, CH_2C*H*=CH, Ar*H*), 5.80 (1H, dt, J = 15.5, 1.6 Hz, CH_2CH=C*H*), 4.17 (2H, q, J = 7.1 Hz, C*H*$_2$$CH_3$), 3.84 (2H, dt, J = 6.6, 1.2 Hz, ArC*H*$_2$), 1.27 (3H, t, J = 7.1 Hz, CH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 185.65, 166.57, 145.95, 140.68, 140.05, 137.85, 124.96, 122.87, 60.48, 31.95, 14.38; IR (thinfilm) ν_{max} (cm^{-1}): 1716 (C=O), 1684 (C=O), 1655 (C=C); HRMS (ESI): m/z calculated for $C_{11}H_{12}O_3S$: requires: 247.0404 for $[M+Na]^+$; found: 247.0383.

Ethyl (*E*)-4-(2-formyl-4-methoxyphenyl)but-2-enoate 223c



General procedure D was followed using (2-formyl-4-methoxyphenyl)boronic acid (540 mg, 3.0 mmol), followed by purification by column chromatography (eluent: DCM), to yield the title compound as a pale green oil in 63% yield (469 mg, 1.89 mmol). R_f (DCM) = 0.27; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 10.14 (1H, s, C*H*O), 7.36 (1H, d, J = 2.7 Hz, Ar*H*), 7.19-7.07 (3H, m, Ar*H*, CH_2C*H*=CH), 5.67 (1H, dt, J = 15.6, 1.7 Hz, CH_2CH=C*H*), 4.15 (2H, q, J = 7.1 Hz, C*H*$_2$$CH_3$), 3.89 (2H, dd, J = 6.2, 1.7 Hz, ArC*H*$_2$), 3.86 (3H, s, OC*H*$_3$), 1.25 (3H, t, J = 7.1 Hz, CH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 191.85, 166.48, 159.08, 147.30, 134.78, 132.81, 132.11, 122.66, 120.76, 116.38, 60.46, 55.71, 34.32, 14.36; IR (thinfilm) ν_{max} (cm^{-1}): 1708 (C=O), 1693 (C=O), 1651 (C=C); HRMS (ESI): m/z calculated for $C_{14}H_{16}O_4$: requires: 271.0946 for $[M+Na]^+$; found: 271.0930.

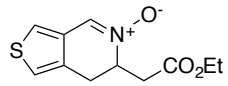
Ethyl (*E*)-4-(2-formyl-5-methoxyphenyl)but-2-enoate 223d



General procedure D was followed using (2-formyl-5-methoxyphenyl)boronic acid (540 mg, 3.0 mmol), followed by purification by column chromatography (eluent: DCM), to yield the title compound as a pale green oil in 67% yield (499 mg, 2.01 mmol). R_f (DCM)

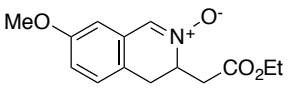
= 0.27; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 10.00 (1H, s, C*H*O), 7.78 (1H, d, J = 8.5 Hz, Ar*H*), 7.11 (1H, dt, J = 15.6, 6.4 Hz, CH_2CH=CH), 6.92 (1H, dd, J = 8.5, 2.5 Hz, Ar*H*), 6.74 (1H, d, J = 2.4 Hz, Ar*H*), 5.73 (1H, dt, J = 15.6, 1.7 Hz, CH_2CH=C*H*), 4.15 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 3.95 (2H, dd, J = 6.4, 1.6 Hz, ArC*H*$_2$), 3.87 (3H, s, OC*H*$_3$), 1.25 (3H, t, J = 7.1 Hz, CH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 191.04, 166.47, 164.03, 146.59, 142.46, 136.61, 127.54, 122.81, 117.31, 112.24, 60.43, 55.69, 35.51, 14.34; IR (thinfilm) ν_{max} (cm^{-1}): 1716 (C=O), 1686 (C=O), 1652 (C=C); HRMS (ESI): m/z calculated for $C_{14}H_{16}O_4$: requires: 271.0946 for $[M+Na]^+$; found: 271.0938.

6-(2-ethoxy-2-oxoethyl)-6,7-dihydrothieno[3,4-*c*]pyridine 5-oxide 227b



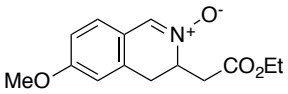
General procedure F was followed using ethyl (*E*)-4-(4-formylthiophen-3-yl)but-2-enoate **223**b (449 mg, 2.00 mmol). The title compound was formed as an orange oil in 77% yield (368 mg, 1.54 mmol) and required no further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.85 (1H, s, *H*-C=N$^+$), 7.30 (1H, s, Ar*H*), 7.04 (1H, s, Ar*H*), 4.60-4.46 (1H, m, C*H*), 4.24-4.10 (2H, m, C*H*$_2$CH$_3$), 3.32 (1H, dd, J = 16.0, 6.2 Hz, ArC*H*$_A$H$_B$), 3.18-3.02 (2H, m, ArCH$_A$*H*$_B$, C*H*$_A$CH$_B$CO$_2$Et), 2.61 (1H, dd, J = 16.0, 8.8 Hz, CH$_A$*H*$_B$CO$_2$Et), 1.26 (3H, t, J = 7.1 Hz, CH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 170.33, 130.62, 129.85, 129.48, 122.73, 121.87, 65.63, 61.22, 36.01, 28.86,14.26; IR (thinfilm) ν_{max} (cm^{-1}): 1719 (C=O); HRMS (ESI): m/z calculated for $C_{11}H_{13}NO_3S$: requires: 239.0672 for $[M+Na]^+$; found: 239.0666.

3-(2-ethoxy-2-oxoethyl)-7-methoxy-3,4-dihydroisoquinoline 2-oxide 227c



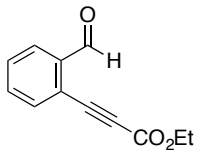
General procedure F was followed using ethyl (*E*)-4-(2-formyl-4-methoxyphenyl)but-2-enoate **223**c (497 mg, 2.00 mmol). The title compound was formed as a pale brown oil in 86% yield (453 mg, 1.72 mmol) and required no further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.66 (1H, s, *H*-C=N$^+$), 7.08 (1H, d, J = 8.2 Hz, Ar*H*), 6.78 (1H, dd, J = 8.2, 2.5 Hz, Ar*H*), 6.61 (1H, d, J = 2.4 Hz, Ar*H*), 4.51-4.44 (1H, m, C*H*), 4.20-4.05 (2H, m, C*H*$_2$CH$_3$), 3.76 (3H, s, OC*H*$_3$), 3.26 (1H, dd, J = 16.4, 6.1 Hz, ArC*H*$_A$H$_B$), 3.07-2.95 (2H, m, ArCH$_A$*H*$_B$, C*H*$_A$CH$_B$CO$_2$Et), 2.56 (1H, dd, J = 16.1, 8.8 Hz, CH$_A$*H*$_B$CO$_2$Et), 1.22 (3H, t, J = 7.1 Hz, CH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 170.39, 159.09, 133.95, 128.93, 128.83, 120.82, 115.23, 110.54, 64.74, 61.01, 55.49, 35.30, 31.60, 14.14; IR (thinfilm) ν_{max} (cm^{-1}): 1726 (C=O); HRMS (ESI): m/z calculated for $C_{14}H_{17}NO_4$: requires: 264.1235 for $[M+H]^+$; found: 264.1218.

3-(2-ethoxy-2-oxoethyl)-6-methoxy-3,4-dihydroisoquinoline 2-oxide 227d



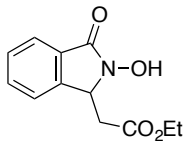
General procedure F was followed using ethyl (*E*)-4-(2-formyl-5-methoxyphenyl)but-2-enoate **223**d (497 mg, 2.00 mmol). The title compound was formed as a pale brown oil in 82% yield (432 mg, 1.64 mmol) and required no further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.79 (1H, s, *H*-C=N$^+$), 7.13 (8.3H, d, J = , Hz, Ar*H*) 6.81 (8.3, 2.7H, dd, J = , Hz, Ar*H*) 6.74 (1H, s, Ar*H*), 4.53-4.41 (1H, m, C*H*), 4.21-4.08 (2H, m, C*H*$_2$CH$_3$), 3.81 (3H, s, OC*H*$_3$), 3.34 (1H, dd, J = 16.5, 6.1 Hz, ArC*H*$_A$H$_B$), 3.12-2.95 (2H, m, ArCH$_A$*H*$_B$, C*H*$_A$CH$_B$CO$_2$Et), 2.57 (1H, dd, J = 16.0, 8.7 Hz, CH$_A$*H*$_B$CO$_2$Et), 1.24 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 170.36, 161.43, 135.35, 131.31, 127.71, 125.59, 120.52, 114.44, 113.00, 63.46, 61.13, 55.61, 35.17, 32.63, 14.22; IR (thinfilm) ν_{max} (cm^{-1}): 1728 (C=O); HRMS (ESI): m/z calculated for $C_{14}H_{17}NO_4$: requires: 264.1235 for [M+H]$^+$; found: 264.1226.

Ethyl 3-(2-formylphenyl)propiolate 231



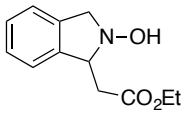
To a solution of 2-iodobenzaldehyde **230** (928 mg, 4.00 mmol) and ethyl propiolate (1.62 mL, 16 mmol) in THF were added $Pd(PPh_3)_2C_{12}$ (2.0 mol%), CuI (4.0 mol%) and K_2C_{03} (1.11 g, 8 mmol). The reaction was stirred at 65 °C for 2 hours. After cooling to room temperature, the solvent was removed under reduced pressure, and the remaining black oil was extracted with Et_2O (x3). The Et_2O solution was dried ($MgSO_4$), and the solvent removed under reduced pressure. The crude material was purified by column chromatography (eluent: DCM) to afford the title compound as a yellow solid in 42% yield (340 mg, 1.68 mmol).[110] R_f (DCM) = 0.67; m.p. 43-45 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 10.46 (1H, s, C*H*O), 7.96-7.93 (1H, m, Ar*H*), 7.70-7.67 (1H, m, Ar*H*), 7.63-7.53 (2H, m, Ar*H*), 4.30 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 1.34 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 190.43, 153.51, 137.25, 134.58, 133.94, 130.99, 127.85, 122.72, 86.57, 81.11, 62.57, 14.14; IR (thinfilm) ν_{max} (cm^{-1}): 2212 (C≡C), 1694 (C=O), 1660 (C=O); HRMS (ESI): m/z calculated for $C_{12}H_{12}O_3$: requires: 225.0527 for [M+Na]$^+$; found: 225.0532.

Ethyl 2-(2-hydroxy-3-oxoisoindolin-1-yl)acetate 232



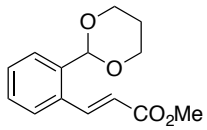
General procedure F was followed using ethyl 3-(2-formylphenyl)propiolate **231** (404 mg, 2.00 mmol). The title compound was afforded as an orange oil in 81% yield (381 mg, 1.62 mmol) and required no further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 11.15 (1H, br. s, O*H*), 7.73 (1H, d, J = 7.2 Hz, Ar*H*), 7.54-7.41 (3H, m, Ar*H*), 5.13 (1H, dd, J = 8.4, 4.4 Hz, C*H*), 4.20 (2H, q, J = 7.1 Hz, CH_2CH$_3$), 3.31 (1H, dd J = 16.3, 4.4 Hz CHCH_AH$_B$, 2.62 (1H, dd J = 16.3, 8.6 Hz, CHCH$_A$$H_B$), 1.25 (3H, t, J = 7.1 Hz, CH$_2$CH_3); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 170.54, 164.87, 141.86, 132.10, 129.80, 128.76, 123.44, 122.77, 61.19, 59.13, 36.12, 14.22; IR (thinfilm) ν_{max} (cm^{-1}): 3311 (O-H), 2969 (C-H), 1732 (O-C=O), 1693 (C=O); HRMS (ESI): m/z calculated for $C_{12}H_{13}NO_4$: requires: 236.0922 for $[M+H]^+$; found: 236.0932.

Ethyl 2-(2-hydroxyisoindolin-1-yl)acetate 238



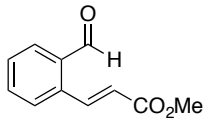
To a solution of 3-(2-ethoxy-2-oxoethyl)-1*H*-isoindole 2-oxide **165** (438 mg, 2.0 mmol) in anhydrous MeOH under nitrogen at 0 °C, was added 3 M HCl in MeOH (1.33 mL, 4.0 mmol, 2.0 eq.) and $NaBH_3CN$ (103 mg, 1.64 mmol, 0.8 eq.). The reaction was stirred at 0 °C for 30 minutes, before quenching with ice and $NaHCO_3$ solution. EtOAc was added, the layers separated, and the aqueous layer extracted with EtOAc. The combined organics were extracted with H_2O and brine, dried ($MgSO_4$), and the solvent removed under reduced pressure. Purification by column chromatography (eluent: 75:25 petrol:EtOAc)afforded the title compound as a yellow oil in 86% yield (381 mg, 1.72 mmol).[112] R_f (75:25 Petrol:EtOAc) = 0.34; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.26-7.18 (3H, m, Ar*H*), 7.16-7.14 (1H, m, Ar*H*), 4.63 (1H, t, J = 6.5 Hz, C*H*CH$_2$), 4.43 (1H, d, J = 13.5 Hz, CH_AH$_B$N), 4.24-4.17 (3H, m, CH$_A$$H_BN, CH_2CH_3$), 2.92-2.77 (2H, m, CHC$H_2$), 1.27 (3H, t, J = 7.1 Hz, CH$_2$CH_3); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 172.14, 139.87, 137.18, 127.98, 127.68, 122.76, 122.43, 69.77, 62.13, 60.92, 38.01, 14.29; IR (thinfilm) ν_{max} (cm^{-1}): 3343 (O-H), 1729 (C=O); HRMS (ESI): m/z calculated for $C_{12}H_{15}NO_3$: requires: 244.0949 for $[M+Na]^+$; found: 244.0939.

Methyl (*E*)-3-(2-(1,3-dioxan-2-yl)phenyl)acrylate 240



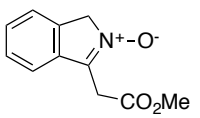
General procedure B was followed using 2-(2-bromophenyl)-1,3-dioxane **147** (972 mg, 4.00 mmol). After 3.5 hours, the reaction was worked up and purified by column chromatography (eluent: 90:10 petrol:EtOAc) to yield the title compound as a yellow oil in 80% yield (794 mg, 3.20 mmol). R_f (90:10 Petrol:EtOAc) = 0.29; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.23 (1H, d, J = 15.9 Hz, Ar*H*), 7.62-7.55 (2H, m, Ar*H*), 7.39-7.29 (2H, m, Ar*H*), 6.35 (1H, d, J = 15.9 Hz, ArC*H*=CH), 5.68 (1H, s, C*H*), 4.27 (1H, dd, J = 4.9, 1.0 Hz, OCH_AH$_B$), 4.23 (1H, dd, J = 5.0, 1.1 Hz, OCH$_A$$H_B$), 3.98 (2H, td, J = 12.2, 2.3 Hz, OC*H₂*), 3.79 (3H, s, C*H₃*), 2.33-2.17 (1H, m, CH$_2$CH_AH$_B$CH$_2$), 1.46-1.39 (1H, m, CH$_2$CH$_A$$H_BCH_2$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 167.31, 142.44, 137.17, 132.74, 129.81, 129.07, 126.99, 126.71, 119.38, 100.22, 67.48, 51.61, 25.65; IR (thinfilm) ν_{max} (cm^{-1}): 1713 (C=O), 1634 (C=C); HRMS (ESI): m/z calculated for $C_{14}H_{16}O_4$: requires: 249.1126 for [M+H]$^+$; found: 249.1110; requires: 271.0946 for [M+Na]$^+$; found: 271.0945.

Methyl (*E*)-3-(2-formylphenyl)acrylate 241



General procedure C was followed using ethyl methyl (*E*)-3-(2-(1,3-dioxan-2-yl)phenyl) acrylate **240** (745 mg, 3.00 mmol). After 14 hours the reaction was worked up and purified by column chromatography (eluent: DCM), to yield the title compound as a yellow oil in 80% (456 mg, 2.40 mmol). R_f (DCM) = 0.61; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 10.26 (1H, s, C*H*O), 8.51 (1H, d, J = 15.9 Hz, ArC*H*=CH), 7.87-7.84 (1H, m, Ar*H*), 7.62-7.53 (3H, m, Ar*H*), 6.36 (1H, d, J = 15.9 Hz, ArCH=C*H*), 3.81 (3H, s, C*H₃*); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 191.91, 166.74, 141.36, 136.59, 133.99, 133.93, 132.51, 130.02, 128.05, 122.79, 51.99; IR (thinfilm) ν_{max} (cm^{-1}): 1705 (C=O), 1632 (C=C); HRMS (ESI): m/z calculated for $C_{11}H_{10}O_3$: requires: 191.0572 for [M+H]$^+$; found: 191.0561.

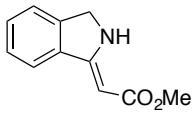
3-(2-methoxy-2-oxoethyl)-1*H*-isoindole 2-oxide 237



General procedure E was followed using methyl (*E*)-3-(2-formylphenyl)acrylate **241** (380 mg, 2.00 mmol). The title compound was formed as a white solid in 76% yield (312 mg, 1.82 mmol) and required no further purification. m.p. 66-67 °C; ^{1}H NMR (300 MHz,

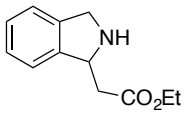
$CDCl_3$) δ_H: 7.43-7.29 (4H, m, Ar*H*), 5.00 (2H, s, ArC*H*$_2$N), 3.91 (2H, s, C*H*$_2$C=O), 3.74 (3H, s, C*H*$_3$); $^{13}C\{^1H\}$ NMR (75.5 MHz $CDCl_3$) δ_C: 167.90, 141.51, 135.92, 133.20, 128.71, 128.15, 121.71, 119.36, 65.95, 52.72, 29.69; IR (thinfilm) ν_{max} (cm^{-1}): 1726 (C=O); HRMS (ESI): m/z calculated for $C_{11}H_{11}NO_3$: requires: 206.0817 for $[M+H]^+$; found: 206.0827; requires: 228.0636 for $[M+Na]^+$; found: 228.0648.

Methyl (*Z*)-2-(isoindolin-1-ylidene)acetate 242



To a mixture of Sm powder (4.0 mmol) and $CoCl_2{\cdot}6H_2O$ (4.0 mmol) under nitrogen, was added anhydrous THF (10 mL) and 3-(2-ethoxy-2-oxoethyl)-1*H*-isoindole 2-oxide **165** (438 mg, 2.0 mmol). The reaction was stirred at room temperature for 3 hours. The reaction mixture was poured into saturated NH_4Cl aqueous solution (50 mL) and extracted with Et_2O (3x20 mL). The combined extracts were washed with saturated aqueous solution of $Na_2S_2O_3$ (20 mL), saturated brine (20 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded the title compound as an orange oil in 39% yield which required no further purification. (148 mg, 0.78 mmol).[119] ^1H NMR (300 MHz, $CDCl_3$) δ_H: 8.24 (1H, br. s, N*H*), 7.64 (1H, d, J = 7.4 Hz, Ar*H*), 7.47-7.46 (2H, m, Ar*H*), 7.44-7.38 (1H, m, Ar*H*), 5.21 (1H, s, C=C*H*), 4.69 (2H, s, C*H*$_2$), 3.72 (3H, s, C*H*$_3$); $^{13}C\{^1H\}$ NMR (75.5 MHz $CDCl_3$) δ_C: 171.74, 161.23, 141.51, 135.34, 130.40, 127.70, 122.85, 121.78, 74.72, 51.40, 50.45; IR (thinfilm) ν_{max} (cm^{-1}): 3299 (N-H), 1692 (C=O); HRMS (ESI): m/z calculated for $C_{11}H_{11}NO_2$: requires: 212.0743 for $[M+Na]^+$; found: 212.0745.

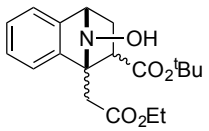
Ethyl 2-(isoindolin-1-yl)acetate 246



A solution of 3-(2-ethoxy-2-oxoethyl)-1*H*-isoindole 2-oxide **165** (438 mg, 2.0 mmol) in MeOH (10 mL) was added to a suspension of 10% Pd/C (22 mg) in a 3 M solution of HCl in MeOH (20 mL). The suspension was stirred under a hydrogen atmosphere (1 atm) overnight, and then filtered under Celite®. The Celite® was rinsed with MeOH and the filtrate concentrated under reduced pressure to afford a red oil. This was dissolved in methanol:DMSO (1:1) (2 x 1 mL) and purified using a Mass Directed Autopreparation (MDAP) apparatus (column: Sunfire C18, eluent: acetonitrile:H_2O with a formic acid modifier). After removal of the solvent under a stream of nitrogen, the title compound was afforded as a mixture of diastereomers an orange oil in 69% yield (283 mg, 1.38 mmol).[120] **major diastereomer** ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.29-7.16 (4H, m, Ar*H*), 4.86 (1H,

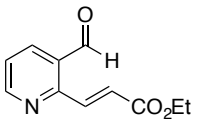
dt, J = 9.2, 1.9 Hz, CH), 4.26 (2H, s, CH_2N), 4.19 (2H, q, J = 7.1 Hz, CH_2CH$_3$), 2.85 (1H, dd, J = 15.8, 3.9 Hz, CH_AH$_B$), 2.61 (1H, dd, J = 15.8, 9.2 Hz, CH$_A$$H_B$), 2.26 (1H, br. s, N$H$), 1.27 (3H, t, J = 7.1 Hz, CH$_2$CH_3); ^{13}C{^{1}H} NMR (75.5 MHz CDCl$_3$) δ_C: 172.25, 142.81, 141.37, 127.42, 126.98, 122.74, 122.11, 60.70, 59.97, 51.58, 41.67, 14.34; IR (thinfilm) ν_{max} (cm^{-1}): 3364 br. (N-H), 1733 (C=O); HRMS (ESI): m/z calculated for $C_{12}H_{15}NO_2$: requires: 206.1181 for [M+H]$^+$; found: 206.1171; requires: 228.1000 for [M+Na]$^+$; found: 228.0991.

Tert-butyl 1-(2-ethoxy-2-oxoethyl)-9-hydroxy-1,2,3,4-tetrahydro-1,4-epimino naphthalene-2-carboxylate 254



To a solution of 3-(2-ethoxy-2-oxoethyl)-1H-isoindole 2-oxide **165** (110 mg, 0.5 mmol) in THF (2 mL), was added tert-butyl acrylate (0.15 mL, 1.0 mmol). The reaction was stirred overnight at room temperature. After removal of the solvent under reduced pressure, the crude product was dissolved in 1:1 MeOH:DMSO 1 mL and purified using an MDAP apparatus (column: Sunfire C18, eluent: acetonitrile:H_2O with a formic acid modifier). The solvent was dried under a stream of nitrogen using a Radleys blowdown apparatus, to give the title compound as a yellow oil in 51% yield (177 mg, 0.26 mmol), as a mixture of inseparable conformers. Analysis of the major product is as follows: ^{1}H NMR (600 MHz, CDCl$_3$) δ_H: 7.31-7.16 (4H, m, ArH), 4.48 (1H, d, J = 4.4 Hz, NCHCH$_2$), 4.24-4.14 (2H, m, CH_2CH$_3$), 3.57 (1H, d, J = 16.7 Hz, CH_AH$_B$CO$_2$Et), 3.14 (1H, d, J = 16.7 Hz, CH$_A$$H_BCO_2$Et), 2.94 (1H, dt, J = 12.3, 5.0 Hz, NCHCH_AH$_B$), 2.73 (1H, dd, J = 9.3, 5.2 Hz, NCHCH$_2$CH), 1.79 (1H, dd, J = 12.3, 9.4 Hz, NCHCH$_A$$H_B$CH), 1.45 (9H, s, C(C$H_3$)$_3$), 1.27 (3H, t, J = 7.2 Hz, CH$_2$CH_3); ^{13}C{^{1}H} NMR (150 MHz CDCl$_3$) δ_C: 172.77, 171.16, 143.42 141.19, 127.47, 127.04, 120.76, 120.12, 81.16, 76.27, 68.42, 60.57, 46.53, 34.02, 30.82, 28.00, 14.20; IR (thinfilm) ν_{max} (cm^{-1}): 3231 br. (O-H), 1732 (C=O), 1728 (C=O); HRMS (ESI): m/z calculated for $C_{19}H_{25}NO_5$: requires: 348.1810 for [M+H]$^+$; found: 348.1812; requires: 370.1630 for [M+Na]$^+$; found: 370.1635.

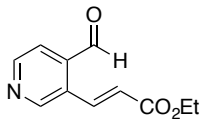
Ethyl (*E*)-3-(3-formylpyridin-2-yl)acrylate 256



To a solution of 2-bromonicotinaldehyde (0.32 mL, 2.69 mmol), (μ_3-C$_3$H$_5$)$_2$Pd$_2$Cl$_2$ (98 mg, 0.27 mmol) and (o-Tol)$_3$P (164 mg, 0.54 mmol) in toluene (3.5 mL), was added ethyl acrylate **162** (0.44 mL, 4.03 mmol) and sodium acetate (662 mg, 8.06 mmol). The reaction mixture (a slurry) was stirred at 110 °C overnight. The reaction mixture was cooled

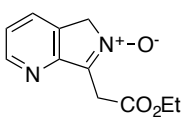
to room temperature and the precipitates filtered. The filtrate was washed with water (10 mL), $NaHCO_3$ solution (10 mL) and 10% citric acid solution (10 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure to give the crude product as a brown oil. The crude product was purified using a Biotage SP4 (eluent: 70:30 cyclohexane:EtOAc; 50 g Biotage SNAP cartridge) to yield the title compound as an orange solid in 11% yield (60 mg, 0.29 mmol).[123] R_f (70:30 cyclohexane:EtOAc) = 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 10.45 (1H, s, C*H*O), 8.81 (1H, dd, J = 4.7, 1.6 Hz, NAr*H*), 8.46 (1H, d, J = 15.4 Hz, ArC*H*=CH), 8.18 (1H, dd, J = 7.8, 1.8 Hz, Ar*H*), 7.46 (1H, dd, J = 7.8, 4.8 Hz, Ar*H*), 7.18 (1H, d, J = 15.4 Hz, ArCH=C*H*), 4.31 (2H, q, J = 7.2 Hz, C*H*$_2$CH$_3$), 1.36 (3H, t, J = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (100 MHz $CDCl_3$) δ_C: 190.07, 166.22, 153.64, 153.38, 138.20, 137.39, 129.30, 127.12, 124.30, 60.84, 14.21; IR (thinfilm) ν_{max} (cm^{-1}): 1708 (H-C=O), 1683 (O-C=O), 1630 (C=C); HRMS (ESI): m/z calculated for $C_{11}H_{11}N_1O_3$: requires: 220.0952 for $[M+H]^+$; found: 220.0940.

Ethyl (*E*)-3-(4-formylpyridin-3-yl)acrylate 257



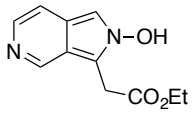
To a solution of 3-bromoisonicotinaldehyde (1.00 g, 5.38 mmol), $Pd(OAc)_2$ (121 mg, 0.54 mmol, 10.0 mol%) and (o-Tol)$_3$P (327 mg, 1.08 mmol, 20.0 mol%) in DMF, was added ethyl acrylate **162** (0.88 mL, 8.06 mmol) and Et_3N (1.14 mL, 8.06 mmol). The reaction was heated to 120 °C and stirred for 5 hours. The reaction mixture was cooled to room temperature and diluted with diethyl ether (25 mL). The resulting slurry was filtered through Celite®, dried ($MgSO_4$), and the solvent removed under vacuum to give the crude product as a brown oil. The crude product was purified by column chromatography (eluent: cyclohexane/EtOAc (80:20)) and recrystallisation from Et_2O:cyclohexane. The title compound was isolated as a cream solid in 16% yield (187 mg, 0.88 mmol). m.p. 55-56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 10.37 (1H, s, C*H*O), 8.96 (1H, s, Ar*H*), 8.87 (1H, d, J = 5.1 Hz, Ar*H*), 8.36 (1H, d, J = 15.9 Hz, ArC*H*=CH), 7.70 (1H, d, J = 5.1 Hz, Ar*H*), 6.48 (1H, d, J = 15.9 Hz, ArCH=C*H*), 4.32 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 1.37 (3H, t, J = 7.2 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (100 MHz $CDCl_3$) δ_C: 190.78, 165.55, 151.54, 149.75, 138.53, 137.37, 130.02, 125.07, 123.00, 61.06, 14.25; IR (thinfilm) ν_{max} (cm^{-1}): 1703 (C=O), 1637 (C=C); HRMS (ESI): m/z calculated for $C_{11}H_{12}NO_3$: requires: 206.0817 for $[M+H]^+$; found: 206.0811.

7-(2-ethoxy-2-oxoethyl)-5*H*-pyrrolo[3,4-*b*]pyridine 6-oxide 258



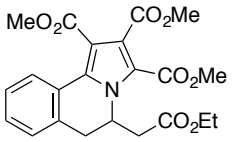
General procedure E was followed using ethyl (*E*)-3-(3-formylpyridin-2-yl)acrylate **256** (410 mg, 2.00 mmol). The title compound was formed as a red oil in 89% yield (392 mg, 1.78 mmol) and required no further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ_H: 8.56 (1H, d, J = 5.1 Hz, NAr*H*), 7.62 (1H, d, J = 7.3 Hz, Ar*H*), 7.23 (1H, dd, J = 7.7, 5.1 Hz, Ar*H*), 5.03 (2H, s, ArC*H*$_2$N), 4.22 (2H, q, J = 7.3 Hz, C*H*$_2$CH$_3$), 3.96 (2H, s, C*H*$_2$C=O), 1.27 (3H, t, J = 7.3 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (150 MHz $CDCl_3$) δ_C: 167.15, 155.12, 150.03, 142.15, 128.47, 127.99, 121.88, 64.66, 61.62, 28.76, 14.09; IR (thin-film) ν_{max} (cm^{-1}): 1728 (C=O); HRMS (ESI): m/z calculated for $C_{11}H_{12}N_2O_3$: requires: 243.0789 for [M+Na]$^+$; found: 243.0770.

Ethyl 2-(2-hydroxy-2*H*-pyrrolo[3,4-*c*] pyridin-3-yl)acetate, 259



General procedure E was followed using ethyl (*E*)-3-(4-formylpyridin-3-yl)acrylate **257** (410 mg, 2.00 mmol). The title compound was isolated as a cream solid in 76% yield (335 mg, 1.52 mmol) and required no further purification. m.p. 123-125 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H: 8.41 (1 H, s, *H*-C=N), 7.35 (2H, d, J = 6.6 Hz, N-C*H*=CH), 7.33 (1H, s, *H*CN-OH), 7.25 (1H, d, J = 7.0 Hz, N-CH=C*H*), 4.11 (2H, s, C*H*$_2$C=O), 4.07 (2H, q, J = 7.3 Hz, C*H*$_2$CH$_3$), 1.14 (3H, t, J = 7.2 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (150 MHz $CDCl_3$) δ_C: 169.84, 132.33, 123.31, 121.20, 118.50, 114.88, 111.55, 110.76, 61.20, 29.74, 14.08; IR (thinfilm) ν_{max} (cm^{-1}): 3306 (O-H), 1727 (C=O); HRMS (ESI): m/z calculated for $C_{11}H_{13}N_2O_3$: requires: 221.0926 for [M+H]$^+$; found: 221.0916.

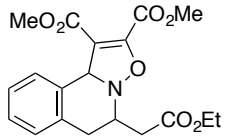
Trimethyl 5-(2-ethoxy-2-oxoethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarbox-ylate 326



To a solution of 3-(2-ethoxy-2-oxoethyl)-3,4-dihydroisoquinoline 2-oxide **227** (467 mg, 2.0 mmol) in toluene was added DMAD (0.49 mL, 4.0 mmol) in one portion. The reaction was stirred at reflux for 3 hours, dried ($MgSO_4$) and the solvent removed under reduced pressure to afford a yellow oil. Purification by column chromatography (eluent: DCM) afforded the title compound as a yellow oil in 42% yield (360 mg, 0.84 mmol). R_f (DCM) = 0.30; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.10-8.05 (1H, m, Ar*H*), 7.31-7.27 (2H, m, Ar*H*), 7.23-7.18 (1H, m, Ar*H*), 5.74-5.67 (1H, m, C*H*), 4.07 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 3.89 (3H, s, OC*H*$_3$), 3.82 (3H, s, OC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 3.26 (1H, dd, J = 16.0, 5.7 Hz, ArC*H*$_A$CH$_B$), 3.03 (1H, dd, J = 16.0, 1.3 Hz, ArCH$_A$C*H*$_B$), 2.56 (1H, dd, J = 16.0, 3.5, C*H*$_A$CH$_B$CO$_2$Et), 2.32 (1H, dd, J = 16.0, 10 2 Hz, CH$_A$C*H*$_B$CO$_2$Et), 1.18 (3H, t, J =

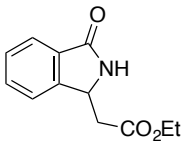
7.1 Hz, CH_2CH_3); $^{13}C\{^1H\}$ NMR (75.5 MHz $CDCl_3$) δ_C: 170.07, 166.34, 163.71, 159.81, 135.76, 131.34, 129.69, 128.73, 128.03, 127.23, 126.90, 125.70, 118.48, 110.77, 60.79, 52.64, 52.22, 51.88, 48.98, 36.11, 32.88, 14.04; IR (thinfilm) ν_{max} (cm^{-1}): 1708 br. (C=O); HRMS (ESI): m/z calculated for $C_{22}H_{23}NO_8$: requires: 452.1316 for $[M+Na]^+$; found: 452.1365.

Dimethyl 5-(2-ethoxy-2-oxoethyl)-6,10b-dihydro-5*H*-isoxazolo[3,2-*a*]isoquinoline-1,2-di-carboxylate 327



To a solution of 3-(2-ethoxy-2-oxoethyl)-3,4-dihydroisoquinoline 2-oxide **227** (467 mg, 2.00 mmol) in toluene was added DMAD (0.49 mL, 4.0 mmol) in one portion. The reaction was stirred at room temperature for 3 hours, dried ($MgSO_4$) and the solvent removed under reduced pressure to afford an orange oil. Purification by column chromatography (eluent: DCM) afforded the title compound as an inseparable mixture of diastereomers (1:0.15 ratio) in 83% yield (623 mg, 1.66 mmol). R_f (DCM) = 0.33; **major diastereomer** ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.42-7.39 (1H, m, Ar*H*), 7.23-7.20 (2H, m, Ar*H*), 7.10-7.07 (1H, m, Ar*H*), 5.83 (1H, s, *H*C-N), 4.21-4.11 (3H, CH_2CHCH_2, CH_2CH_3), 3.85 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.22 (1H, dd, J = 16.1, 4.2 Hz, $ArCH_ACH_B$), 2.66 (1H, dd, J = 16.3, 5.0 Hz, $ArCH_ACH_B$), 2.50 (1H, dd, J = 15.7, 6.8 Hz, $CH_ACH_BCO_2Et$), 2.26 (1H, dd, J = 15.7, 7.3 Hz, $CH_ACH_BCO_2Et$), 1.24 (3H, t, J = 7.3 Hz, CH_2CH_3); $^{13}C\{^1H\}$ NMR (75.5 MHz $CDCl_3$) δ_C: 170.94, 162.91, 159.15, 150.80, 132.57, 131.37, 129.04, 128.01, 127.40, 127.06, 112.42, 65.43, 60.90, 56.11, 53.21, 52.07, 37.24, 29.55, 14.27. **minor diastereomer** ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.49-7.46 (1H, m, Ar*H*), 7.42-7.07 (3H, m, Ar*H*), 5.92 (1H, s, *H*C-N), 4.25-4.05 (3H, CH_2CHCH_2, CH_2CH_3), 3.84 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.12-2.95 (2H, m, $ArCH_AH_B$), 2.74-2.57 (2H, m, $CH_AH_BCO_2Et$), 1.30-1.25 (3H, m, CH_2CH_3); $^{13}C\{^1H\}$ NMR (75.5 MHz $CDCl_3$) δ_C: 171.29, 162.77, 159.21, 150.80, 134.62, 133.05, 128.94, 127.47, 127.33, 126.86, 112.42, 66.87, 58.74, 56.12, 53.22, 51.95, 38.56, 27.96, 14.31; IR (thinfilm) ν_{max} (cm^{-1}): 1725 br. (C=O), 1649 (C=C); HRMS (ESI): m/z calculated for $C_{19}H_{21}NO_7$: requires: 376.1396 for $[M+H]^+$; found: 376.1420; requires: 398.1215 for $[M+Na]^+$; found: 398.1234.

Ethyl 2-(3-oxoisoindolin-1-yl)acetate 271

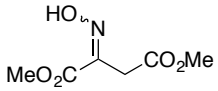


$RuCl_3.3\,H_2O$ (20 mg, 0.08 mmol) and Zn-Cu couple (29 mg, 0.45 mmol) were placed in a glass Schlenk tube which was filled with nitrogen. A solution of ethyl 2-(2-hydroxy-3-

oxoisoindolin-1-yl)acetate **232** (353 mg, 1.50 mmol) in dehydrated EtOH (3.0 mL) was added to the mixture, and the reaction mixture was refluxed at 100 °C for 3 hours.

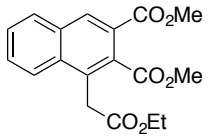
The reaction mixture was cooled to room temperature and filtered to remove insoluble materials. After removal of the solvent under reduced pressure, the residue was taken up in EtOAc, and this solution filtered to remove insoluble materials. After removal of the solvent under reduced pressure, the crude material was purified by column chromatography (eluent: 100% DCM to 2% MeOH in DCM). The title compound was yielded as a pale brown oil in 24% yield (79%, 0.36 mmol).[142] R_f (1% MeOH in DCM) = 0.17; ^{1}H NMR (500 MHz, MeOD) δ_H: 7.77 (1H, dd, J = 7.5 Hz, ArH), 7.64-7.58 (2H, m, ArH), 7.52 (1H, t, J = 7.3 Hz, ArH), 5.01 (1H, dd, J = 8.4, 5.0 Hz, CHCH$_2$), 4.17 (2H, q, J = 7.1 Hz, CH_2CH$_3$), 2.98 (1H, dd, J = 16.4, 5.0 Hz, CHCH_AH$_B$), 2.62 (1H, dd, J = 16.4, 8.1 Hz, CHCH$_A$$H_B$), 1.23 (3H, t, J = 7.1 Hz, CH$_2$CH_3); ^{13}C{^{1}H} NMR (125 MHz MeOD) δ_C: 173.60, 173.05, 149.07, 134.26, 133.78, 130.50, 125.25, 124.96, 62.86, 55.69, 40.83, 15.28; IR (thinfilm) ν_{max} (cm^{-1}): 3533 (N-H), 2967 (C-H), 1734 (O-C=O), 1689 (C=O); HRMS (ESI): m/z calculated for $C_{12}H_{13}NO_3$: requires: 242.0793 for [M+Na]$^+$; found: 242.0782.

Dimethyl 2-(hydroxyimino)succinate 328



To a solution of DMAD (0.12 mL, 1.00 mmol), in THF (2.0 mL) was added hydroxylamine (50 wt% in H$_2$O) (63 μL, 1.10 mmol) and the solution was stirred for 30 minutes at room temperature. The solvent was removed under reduced pressure, to afford the title compound as a yellow oil in 100% yield (175 mg, 1.00 mmol), which required no further purification. ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 3.88 (3H, s, CO$_2$CH_3), 3.71 (3H, s, CH$_2$CO$_2$CH_3), 3.71 (2H,s, CH_2); ^{13}C{^{1}H} NMR (75.5 MHz CDCl$_3$) δ_C: 168.55, 163.41, 146.04, 53.15, 52.60, 30.32; IR (thinfilm) ν_{max} (cm^{-1}): 3349 (O-H), 1725 br. (C=O); HRMS (ESI): m/z calculated for $C_6H_9NO_5$: requires: 176.0558 for [M+H]$^+$; found: 176.0563; requires: 198.0378 for [M+Na]$^+$; found: 198.0390.

Dimethyl 1-(2-ethoxy-2-2oxoethyl)naphthalene-2,3-dicarboxylate 329



Procedure 1: To a solution of the 3-(2-ethoxy-2-oxoethyl)-1H-isoindole 2-oxide **165** (219 mg, 1.0 mmol) in THF (2 mL), was added DMAD (0.12 mL, 1.0 mmol), and the reaction stirred for 30 minutes at 18 °C. The reaction mixture was dried (MgSO$_4$) and

the solvent removed under reduced pressure. The crude product was purified by column chromatography (eluent: 70: 30 petrol:EtOAc), to afford the title compound as a yellow oil in 87% yield (286 mg, 0.87 mmol).

Procedure 2: To a solution of the aldehyde (204.22 mg, 1.0 mmol) in THF (2 mL), was added hydroxylamine (50 wt% in H_2O) (62 μL, 1.0 mmol), and the reaction was stirred for 30 minutes at 18 °C. To the solution was then added DMAD (0.25 mL, 2.0 mmol), and the reaction stirred for a further 30 minutes. The resulting reaction mixture was dried ($MgSO_4$), and the solvent removed under reduced pressure. The crude product was purified by column chromatography (eluent: 90:10 - 70:30 petrol:EtOAc) to afford title compound as a yellow oil in 33% yield (110 mg, 0.33 mmol).

R_f (70:30 Petrol:EtOAc) = 0.29; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.50 (1H, s, Ar*H*), 8.04 (1H, d, J = 8.5 Hz, Ar*H*), 7.94 (1H, d, J = 8.1 Hz, Ar*H*), 7.70-7.65 (1H, m, Ar*H*), 7.62-7.56 (1H, m, Ar*H*), 4.16-4.09 (4H, m, C*H*$_2$CH$_3$, ArC*H*$_2$), 3.97 (3H, s, CO_2C*H*$_3$), 3.94 (3H, s, CO_2C*H*$_3$), 1.18 (3H, t, J = 7.1 Hz, CH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz $CDCl_3$) δ_C: 170. 33, 169.82, 166.46, 133.97, 132.65, 131.85, 131.83, 130.11, 129.60, 129.51, 127.70, 125.20, 124.69, 61.27, 52.81, 52.72, 35.45, 14.18; IR (thinfilm) ν_{max} (cm^{-1}): 1724 (C=O); HRMS (ESI): m/z calculated for $C_{18}H_{18}O_6$: requires: 331.1181 for $[M+H]^+$; found: 331.1201.

Appendix A

Crystallographic data

Table A.1: **Crystal data and structure refinement for Nitrone 165**

Identification code	**k10sdb2**
Empirical formula	$C_{12}H_{12}FNO_3$
Formula weight	237.23
Temperature 150(2)	K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21/c
Unit cell dimensions	a = 14.2610(2)Å a = 90°
-	b = 4.7690(1)Å b = 102.805(1)°
-	c = 16.5160(3)Å g = 90°
Volume	1095.33(3) $Å^3$
Z	4
Density (calculated)	1.439 Mg/m^3
Absorption coefficient	0.115 mm^{-1}
F(000)	496
Crystal size	0.35 x 0.25 x 0.10 mm
Theta range for data collection	4.40 to 27.49°
Index ranges	-18<=h<=18; -6<=k<=6; -21<=l<=21
Reflections collected	20506
Independent reflections	2505 [R(int) = 0.0348]

Crystal data and structure refinement for Nitrone 165 cont.

Identification code	**k10sdb2**
Reflections observed (>2s)	2185
Data Completeness	0.996
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.978 and 0.920
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	2505 / 0 / 156
Goodness-of-fit on F^2	1.020
Final R indices [I>2s(I)]	R1 = 0.0335 wR2 = 0.0841
R indices (all data)	R1 = 0.0403 wR2 = 0.0901
Largest diff. peak and hole	0.240 and -0.163 $eÅ^{-3}$

Table A.2: **Bond lengths [Å] and angles [°] for Nitrone 165**

F(1)-C(3)	1.3526(13)	O(1)-N(1)	1.2866(12)
O(2)-C(10)	1.2045(14)	O(3)-C(10)	1.3368(13)
O(3)-C(11)	1.4567(14)	N(1)-C(8)	1.3142(15)
N(1)-C(1)	1.4894(13)	C(1)-C(2)	1.4945(15)
C(1)-H(1A)	0.9900	C(1)-H(1B)	0.9900
C(2)-C(3)	1.3720(15)	C(2)-C(7)	1.4039(15)
C(3)-C(4)	1.3856(17)	C(4)-C(5)	1.3923(17)
C(4)-H(4)	0.9500	C(5)-C(6)	1.3949(16)
C(5)-H(5)	0.9500	C(6)-C(7)	1.3912(16)
C(6)-H(6)	0.9500	C(7)-C(8)	1.4508(15)
C(8)-C(9)	1.4851(15)	C(9)-C(10)	1.5090(16)
C(9)-H(9A)	0.9900	C(9)-H(9B)	0.9900
C(11)-C(12)	1.5082(17)	C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900	C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800	C(12)-H(12C)	0.9800
-	-	-	-
C(10)-O(3)-C(11)	116.39(9)	O(1)-N(1)-C(8)	126.48(9)
O(1)-N(1)-C(1)	121.03(9)	C(8)-N(1)-C(1)	112.47(9)
N(1)-C(1)-C(2)	101.27(8)	N(1)-C(1)-H(1A)	111.5
C(2)-C(1)-H(1A)	111.5	N(1)-C(1)-H(1B)	111.5
C(2)-C(1)-H(1B)	111.5	H(1A)-C(1)-H(1B)	109.3
C(3)-C(2)-C(7)	118.33(10)	C(3)-C(2)-C(1)	132.29(10)
C(7)-C(2)-C(1)	109.38(9)	F(1)-C(3)-C(2)	119.39(10)
F(1)-C(3)-C(4)	118.89(10)	C(2)-C(3)-C(4)	121.72(10)
C(3)-C(4)-C(5)	119.11(10)	C(3)-C(4)-H(4)	120.4
C(5)-C(4)-H(4)	120.4	C(4)-C(5)-C(6)	121.12(11)
C(4)-C(5)-H(5)	119.4	C(6)-C(5)-H(5)	119.4
C(7)-C(6)-C(5)	117.97(10)	C(7)-C(6)-H(6)	121.0
C(5)-C(6)-H(6)	121.0	C(6)-C(7)-C(2)	121.76(10)
C(6)-C(7)-C(8)	130.89(10)	C(2)-C(7)-C(8)	107.35(9)
N(1)-C(8)-C(7)	109.33(9)	N(1)-C(8)-C(9)	120.84(10)

Bond lengths [Å] and angles [°] for Nitrone 165 cont.

C(7)-C(8)-C(9)	129.81(10)	C(8)-C(9)-C(10)	113.47(9)
C(8)-C(9)-H(9A)	108.9	C(10)-C(9)-H(9A)	108.9
C(8)-C(9)-H(9B)	108.9	C(10)-C(9)-H(9B)	108.9
H(9A)-C(9)-H(9B)	107.7	O(2)-C(10)-O(3)	123.76(10)
O(2)-C(10)-C(9)	125.83(10)	O(3)-C(10)-C(9)	110.41(9)
O(3)-C(11)-C(12)	106.75(11)	O(3)-C(11)-H(11A)	110.4
C(12)-C(11)-H(11A)	110.4	O(3)-C(11)-H(11B)	110.4
C(12)-C(11)-H(11B)	110.4	H(11A)-C(11)-H(11B)	108.6
C(11)-C(12)-H(12A)	109.5	C(11)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5	C(11)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5	H(12B)-C(12)-H(12C)	109.5

Table A.3: **Dihedral angles [°] for Nitrone 165**

Atom1 - Atom2 - Atom3 - Atom4	**Dihedral**
O(1) - N(1) - C(1) - C(2)	-177.16(9)
C(8) - N(1) - C(1) - C(2)	4.51(12)
N(1) - C(1) - C(2) - C(3)	177.76(12)
N(1) - C(1) - C(2) - C(7)	-3.23(11)
C(7) - C(2) - C(3) - F(1)	179.49(9)
C(1) - C(2) - C(3) - F(1)	-1.57(18)
C(7) - C(2) - C(3) - C(4)	-0.71(17)
C(1) - C(2) - C(3) - C(4)	178.23(11)
F(1) - C(3) - C(4) - C(5)	-179.98(10)
C(2) - C(3) - C(4) - C(5)	0.22(18)
C(3) - C(4) - C(5) - C(6)	0.23(18)
C(4) - C(5) - C(6) - C(7)	-0.16(17)
C(5) - C(6) - C(7) - C(2)	-0.36(16)
C(5) - C(6) - C(7) - C(8)	-179.77(11)
C(3) - C(2) - C(7) - C(6)	0.79(16)
C(1) - C(2) - C(7) - C(6)	-178.38(10)
C(3) - C(2) - C(7) - C(8)	-179.68(10)
C(1) - C(2) - C(7) - C(8)	1.16(12)
O(1) - N(1) - C(8) - C(7)	177.71(10)
C(1) - N(1) - C(8) - C(7)	-4.07(13)
O(1) - N(1) - C(8) - C(9)	-3.67(17)
C(1) - N(1) - C(8) - C(9)	174.56(9)
C(6) - C(7) - C(8) - N(1)	-178.74(11)
C(2) - C(7) - C(8) - N(1)	1.78(12)
C(6) - C(7) - C(8) - C(9)	2.8(2)
C(2) - C(7) - C(8) - C(9)	-176.69(11)
N(1) - C(8) - C(9) - C(10)	84.18(14)
C(7) - C(8) - C(9) - C(10)	-97.50(14)
C(11) - O(3) - C(10) - O(2)	-3.43(17)
C(11) - O(3) - C(10) - C(9)	176.45(9)

Dihedral angles [°] for Nitrone 165 cont.

Atom1 - Atom2 - Atom3 - Atom4	**Dihedral**
C(8) - C(9) - C(10) - O(2)	3.80(17)
C(8) - C(9) - C(10) - O(3)	-176.08(9)
C(10) - O(3) - C(11) - C(12)	-174.80(10)

References

[1] Migrdichian, V. *Org. Synth.* **1957**, *2*, 1634–1635.

[2] Dias, A. G.; Santos, C. E. V.; Cyrino, F. Z. G. A.; Bouskela, E.; Costa, P. R. R. *Bioorg. Med. Chem.* **2009**, *17*, 3995–3998.

[3] Fan, L.-W.; Mitchell, H. J.; Tien, L.-T.; Rhodes, P. G.; Cai, Z. *Exp. Neurol.* **2009**, *220*, 143–153.

[4] Fan, L. W.; Tien, L. T.; Zheng, B.; Pang, Y.; Rhodes, P. G.; Cai, Z. *Neuroscience* **2010**, *168*, 240–252.

[5] Floyd, R. A.; Hensley, K.; Forster, M. J.; Kelleher-Andersson, J. A.; Wood, P. L. *Mech. Ageing Dev.* **2002**, *123*, 1021–1031.

[6] Floyd, R.; Kopke, R.; Choi, C.; Foster, S.; Doblas, S.; Towner, R. *Free Radical Bio. Med.* **2008**, *45*, 1361–1374.

[7] Green, A. R.; Ashwood, T.; Odergren, T.; Jackson, D. M. *Pharmacol. Ther.* **2003**, *100*, 195–214.

[8] Shah, I. M.; Macrae, I. M.; Di Napoli, M. *Curr. Mol. Med.* **2009**, *9*, 336–354.

[9] Ginsberg, M. D. *Stroke* **2007**, *38*, 1967–1972.

[10] Jönsson, S.; Cheng, Y.-F.; Edenius, C.; Lees, K.; Odergren, T.; Karlsson, M. *Clin. Pharmacokinet.* **2005**, *44*, 863–878.

[11] Braslau, R.; O'Bryan, G.; Nilsen, A.; Henise, J.; Thongpaisanwong, T.; Murphy, E.; Mueller, L.; Ruehl, J. *Synthesis* **2005**, *2005*, 1496–1506.

[12] Busqué, F.; de March, P.; Figueredo, M.; Font, J.; Gallagher, T.; Milán, S. *Tetrahedron: Asymmetry* **2002**, *13*, 437–445.

[13] Soldaini, G.; Cardona, F.; Goti, A. *Org. Lett.* **2007**, *9*, 473–476.

[14] Diez-Martinez, A.; Gultekin, Z.; Delso, I.; Tejero, T.; Merino, P. *Synthesis* **2010**, 678–688.

[15] Singh, B.; Jain, S. L.; Rana, B. S.; Khatri, P. K. *ChemCatChem* **2010**, *2*, 1260–1264.

[16] Lin, Y. M.; Miller, M. J. *J. Org. Chem.* **2001**, *66*, 8282–8285.

[17] Martiny, L.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 699–704.

[18] Murahashi, S.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736–1744.

[19] Coşkun, N.; Tunçman, S. *Tetrahedron: Asymmetry* **2006**, *62*, 1345–1350.

[20] Coşkun, N.; Parlar, A. *Synth. Commun.* **2005**, *35*, 2445–2451.

[21] Trigalo, F.; Martin, M.-T.; Rasolondratovo, B.; Blond, A.; Youte, J. J.; Rasoanaivo, P.; Frappier, F. *Tetrahedron: Asymmetry* **2002**, *58*, 4555–4558.

[22] Brandi, A.; Cicchi, S.; Paschetta, V.; Gomez Pardo, D.; Cossy, J. *Tetrahedron Lett.* **2002**, *43*, 9357–9359.

[23] Cossy, J.; Dumas, C.; Michel, P.; Pardo, D. *Tetrahedron Lett.* **1995**, *36*, 549–552.

[24] Mečiarová, M.; Mojzesová, M.; Šebesta, R. *Chem. Pap.* **2013**, *67*, 51–58.

[25] Saladino, R.; Neri, V.; Cardona, F.; Goti, A. *Adv. Synth. Catal.* **2004**, *346*, 639–647.

[26] Cicchi, S.; Hold, I.; Brandi, A. *J. Org. Chem.* **1993**, *58*, 5274–5275.

[27] Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743–4748.

[28] Goti, A.; Cicchi, S.; Fedi, V.; Nannelli, L.; Brandi, A. *J. Org. Chem.* **1997**, *62*, 3119–3125.

[29] Merino, P.; Revuelta, J.; Tejero, T.; Cicchi, S.; Goti, A. *Eur. J. Org. Chem.* **2004**, 776–782.

[30] Revuelta, J.; Cicchi, S.; Goti, A.; Brandi, A. *Synthesis* **2007**, 485–504.

[31] Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chemistry* **2009**, *15*, 7808–7821.

[32] Goti, A.; Cicchi, S.; Cacciarini, M.; Cardona, F.; Fedi, V.; Brandi, A. *Eur. J. Org. Chem.* **2000**, 3633–3645.

[33] Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806–6812.

[34] Cicchi, S.; Marradi, M.; Corsi, M.; Faggi, C.; Goti, A. *Eur. J. Org. Chem.* **2003**, 4152–4161.

[35] Feuer, H. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, 2nd ed.; Feuer, H., Ed.; Wiley, 2008.

[36] Knobloch, K.; Koch, J.; Keller, M.; Eberbach, W. *Eur. J. Org. Chem.* **2005**, *13*, 2715–2733.

[37] Bøgevig, A.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *Synlett* **2003**, 1915–1918.

[38] Yang, D.; Micalizio, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 9216–9219.

[39] Armstrong, P.; Grigg, R.; Heaney, F.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron: Asymmetry* **1991**, *47*, 4495–4518.

[40] Grigg, R.; Heaney, F.; Markandu, J.; Surendrakumar, S.; Mark, T.; William Warnock, J. *Tetrahedron: Asymmetry* **1991**, *47*, 4007–4030.

[41] Grigg, R.; Heaney, F.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron: Asymmetry* **1991**, *47*, 4477–4494.

[42] Grigg, R.; Dorrity, M. J.; Heaney, F.; Malone, J. F.; Rajviroongit, S.; Sridharan, V.; Surendrakumar, S. *Tetrahedron: Asymmetry* **1991**, *47*, 8297–8322.

[43] Chakrabarty, M.; Sarkar, S.; Khasnobis, S.; Harigaya, Y.; Sato, N.; Arima, S. *Synth. Commun.* **2002**, *32*, 2295–2306.

[44] Theddu, N.; Edupuganti, R. *Org. Lett.* **2010**, *12*, 4118–4121.

[45] Han, Y.; Liu, Y.; Rockenbauer, A.; Zweier, J. L.; Durand, G.; Villamena, F. A. *J. Org. Chem.* **2009**, *74*, 5369–5380.

[46] Sár, C. P.; Ősz, E.; Jekő, J.; Hideg, K. *Synthesis* **2005**, 255–259.

[47] Janzen, E. G.; Liu, J. I.-P. *J. Magn. Reson.* **1973**, *9*, 510–512.

[48] Janzen, E. G.; Jandrisits, L. T.; Shetty, R. V. *Chem-Biol Interact.* **1989**, *70*, 167–172.

[49] Fevig, T. L.; Bowen, S. M.; Janowick, D. A.; Jones, B. K.; Munson, H. R.; Ohlweiler, D. F.; Thomas, C. E. *J. Med. Chem.* **1996**, *39*, 4988–4996.

[50] Thomas, C. E.; Bernardelli, P.; Bowen, S. M.; Chaney, S. F.; Friedrich, D.; Janowick, D. A.; Jones, B. K.; Keeley, F. J.; Kehne, J. H.; Ketteler, B.; Ohlweiler, D. F.; Paquette, L. A.; Robke, D. J.; Fevig, T. L. *J. Med. Chem.* **1996**, *39*, 4997–5004.

[51] Pacher, P.; Szabo, C. *Am. J. Pathol.* **2008**, *173*, 2–13.

[52] Vauzour, D.; Ravaioli, G.; Vafeiadou, K.; Rodriguez-Mateos, A.; Angeloni, C.; Spencer, J. P. E. *Arch. Biochem. Biophys.* **2008**, *476*, 145–151.

[53] Chen, W.; Zhuang, J.; Li, Y.; Shen, Y.; Zheng, X. *Food Chem.* **2013**, *141*, 927–933.

[54] Graham, P. M.; Li, J. Z.; Dou, X.; Zhu, H.; Misra, H. P.; Jia, Z.; Li, Y. *Mol. Cell. Biochem.* **2013**, *378*, 291–298.

[55] Yang, Y.; Ramelot, T. A.; McCarrick, R. M.; Ni, S.; Feldmann, E. A.; Cort, J. R.; Wang, H.; Ciccosanti, C.; Jiang, M.; Janjua, H.; Acton, T. B.; Xiao, R.; Everett, J. K.; Montelione, G. T.; Kennedy, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 11910–11913.

[56] Möbius, K.; Savitsky, A.; Wegener, C.; Plato, M.; Fuchs, M.; Schnegg, A.; Dubinskii, A. A.; Grishin, Y. A.; Grigor'ev, I. A.; Kühn, M.; Duché, D.; Zimmermann, H.; Steinhoff, H.-J. *Magn. Reson. Chem.* **2005**, *43*, S4–S19.

[57] Klare, J. P. In *Site-Directed Spin Labeling and Electron Paramagnetic Resonance (EPR) Spectroscopy: A Versatile Tool to Study Protein-Protein Interactions*, 1st ed.; Cai, J., Ed.; InTech, 2012.

[58] Biswas, R.; Kühne, H.; Brudvig, G. W.; Gopalan, V. *Sci. Prog.* **2001**, *84*, 45–68.

[59] Klare, J. P.; Steinhoff, H.-J. *Photosyn. Res.* **2009**, *102*, 377–390.

[60] Bedrood, S.; Li, Y.; Isas, J. M.; Hegde, B. G.; Baxa, U.; Haworth, I. S.; Langen, R. *J. Biol. Chem.* **2012**, *287*, 5235–5241.

[61] Bottle, S. E.; Hanson, G. R.; Micallef, A. S. *Org. Biomol. Chem.* **2003**, *1*, 2585–2589.

[62] Clement, J. L.; Tordo, P. In *Advances in Spin Trapping*, 1st ed.; Gilbert, B. C., Davies, M. J., Murphy, D. M., Eds.; RSC Publishing, 2007.

[63] Bottle, S. E.; Micallef, A. S. *Org. Biomol. Chem.* **2003**, *1*, 2581–2584.

[64] Locigno, E. J.; Zweier, J. L.; Villamena, F. A. *Org. Biomol. Chem.* **2005**, *3*, 3220–3227.

[65] Tsai, P.; Pou, S.; Straus, R.; Rosen, G. M. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1759–1764.

[66] Villamena, F. A.; Rockenbauer, A.; Gallucci, J.; Velayutham, M.; Hadad, C. M.; Zweier, J. L. *J. Org. Chem.* **2004**, *69*, 7994–8004.

[67] Hatano, B.; Sato, H.; Ito, T.; Ogata, T. *Synlett* **2007**, 2130–2132.

[68] Knight, D. W.; Leese, M. P.; De Kimpe, N. *Tetrahedron Lett.* **2001**, *42*, 2597–2600.

[69] Hatano, B.; Miyoshi, K.; Sato, H.; Ito, T.; Ogata, T.; Kijima, T. *Tetrahedron Lett.* **2010**, *51*, 5399–5401.

[70] Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. *Tetrahedron: Asymmetry* **1992**, *48*, 6929–6952.

[71] Grigg, R.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. *Tetrahedron: Asymmetry* **1992**, *48*, 10399–10422.

[72] Tong, B.; Hui, B.; Chua, S.; Chiba, S. *Synthesis* **2011**, 3552–3562.

[73] Serrano, O. *J. Org. Chem.* **2010**, *75*, 6267–6270.

[74] Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.

[75] Meegalla, S.; Taylor, N.; Rodrigo, R. *J. Org. Chem.* **1992**, *57*, 2422–2427.

[76] Zhang, H.-X.; Luo, C.-C.; Jin, T.; Luo, X.-P. *Synth. Commun.* **2007**, *37*, 191–197.

[77] Quan, C.; Kurth, M. *J. Org. Chem.* **2004**, *69*, 1470–1474.

[78] Qiang, L. G.; Baine, N. H. *J. Org. Chem.* **1988**, *53*, 4218–4222.

[79] Nakama, K.; Seki, S.; Kanemasa, S. *Tetrahedron Lett.* **2001**, *42*, 6719–6722.

[80] House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855–863.

[81] House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863–869.

[82] Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron Lett.* **1979**, *20*, 4391–4394.

[83] Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007–3009.

[84] Ciganek, E.; Read, J., Jr *J. Org. Chem.* **1995**, *60*, 5795–5802.

[85] Ciganek, E. *J. Org. Chem.* **1995**, *60*, 5803–5807.

[86] Cooper, N.; Knight, D. *Tetrahedron: Asymmetry* **2004**, *60*, 243–269.

[87] Bainbridge, N. P.; Currie, A. C.; Cooper, N. J.; Muir, J. C.; Knight, D. W.; Walton, J. M. *Tetrahedron Lett.* **2007**, *48*, 7782–7787.

[88] Coogan, M. P.; Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *Tetrahedron Lett.* **1997**, *38*, 8549–8552.

[89] Stephens, B. E.; Liu, F. *J. Org. Chem.* **2009**, *74*, 254–263.

[90] Hall, A.; Meldrum, K.; Therond, P.; Wightman, R. *Synlett* **1997**, *1*, 123–125.

[91] Argyropoulos, N. G.; Panagiotidis, T. D.; Gallos, J. K. *Tetrahedron: Asymmetry* **2006**, *17*, 829–836.

[92] Ishikawa, T.; Tajima, Y.; Fukui, M.; Saito, S. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1863–1864.

[93] Cheruku, P.; Keffer, J. L.; Dogo-Isonagie, C.; Bewley, C. A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4108–4111.

[94] FreirÄśÌĄa, M.; Whitehead, A. J.; Tocher, D. A.; Motherwell, W. B. *Tetrahedron: Asymmetry* **2004**, *60*, 2673–2692.

[95] Freiría, M.; Whitehead, A. J.; Motherwell, W. B. *Synlett* **2003**, 805–808.

[96] Richards, E. L.; Murphy, P. J.; Dinon, F.; Fratucello, S.; Brown, P. M.; Gelbrich, T.; Hursthouse, M. B. *Tetrahedron: Asymmetry* **2001**, *57*, 7771–7784.

[97] Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

[98] Xu, X.; Fakha, G.; Sinou, D. *Tetrahedron: Asymmetry* **2002**, *58*, 7539–7544.

[99] Sánchez-Larios, E.; Holmes, J. M.; Daschner, C. L. *Synthesis* **2011**, 1896–1904.

[100] Keck, G. E.; Boden, E. P.; Mabury, S. A. *J. Org. Chem.* **1985**, *50*, 710–712.

[101] Bracher, P. J.; Snyder, P. W.; Bohall, B. R.; Whitesides, G. M. *Origins Life Evol. B.* **2011**, *41*, 399–412.

[102] Sase, S.; Jaric, M.; Metzger, A.; Malakhov, V.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 7380–7382.

[103] Jagdale, A. R.; Park, J. H.; Youn, S. W. *J. Org. Chem.* **2011**, *76*, 7204–7215.

[104] Abreu, A. S.; Ferreira, P. M. T.; Monteiro, L. S.; Queiroz, M.-J. R. P.; Ferreira, I. C. F. R.; Calhelha, R. C.; Estevinho, L. M. *Tetrahedron: Asymmetry* **2004**, *60*, 11821–11828.

[105] Silva, N. O.; Abreu, A. S.; Ferreira, P. M. T.; Monteiro, L. S.; Queiroz, M.-J. R. P. *Eur. J. Org. Chem.* **2002**, 2524–2528.

[106] Bonini, C.; Chiummiento, L.; De Bonis, M.; Funicello, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2919–2924.

[107] Wang, X.-F.; Hua, Q.-L.; Cheng, Y.; An, X.-L.; Yang, Q.-Q.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2010**, *49*, 8379–8383.

[108] Wang, X.-F.; Peng, L.; An, J.; Li, C.; Yang, Q.-Q.; Lu, L.-Q.; Gu, F.-L.; Xiao, W.-J. *Chem. Eur. J.* **2011**, *17*, 6484–6491.

[109] Zhou, F.; Han, X.; Lu, X. *J. Org. Chem.* **2011**, *76*, 1491–1494.

[110] Eckert, T.; Ipaktschi, J. *Synth. Commun.* **1998**, *28*, 327–335.

[111] Zhang, H.-L.; Zhao, G.; Ding, Y.; Wu, B. *J. Org. Chem.* **2005**, *70*, 4954–4961.

[112] Maeda, H.; Kraus, G. A. *J. Org. Chem.* **1997**, *62*, 2314–2315.

[113] Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. J. Org. Chem.* **2008**, 2929–2947.

[114] Ilias, M.; Barman, D. C.; Prajapati, D.; Sandhu, J. S. *Tetrahedron Lett.* **2002**, *43*, 1877–1879.

[115] Murahashi, S.-I.; Kodera, Y. *Tetrahedron Lett.* **1985**, *26*, 4633–4636.

[116] Radivoy, G.; Radivoy, G.; Alonso, F.; Yus, M. *Synthesis* **2001**, 427–430.

[117] Taniguchi, M.; Ra, D.; Mo, G.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem.* **2001**, *66*, 7342–7354.

[118] Dutta, D. K.; Konwar, D. *J. Chem. Research (S)* **1998**, 266–267.

[119] Zhang, J. M.; Zhang, Y. M. *Chinese Chem. Lett.* **2001**, *12*, 945–946.

[120] Racine, E.; Bello, C.; Gerber-Lemaire, S.; Vogel, P.; Py, S. *J. Org. Chem.* **2009**, *74*, 1766–1769.

[121] Chatterjee, A.; Maiti, D. K.; Bhattacharya, P. K. *Org. Lett.* **2003**, *5*, 3967–3969.

[122] Carmona, D.; Lamata, M. P.; Viguri, F.; Rodríguez, R.; Lahoz, F. J.; Oro, L. A. *Chem. Eur. J.* **2007**, *13*, 9746–9756.

[123] Song, Z. J. et al. *J. Org. Chem.* **1999**, *64*, 9658–9667.

[124] Lombardo, M.; Trombini, C. *Synthesis-Stuttgart* **2000**, 759–774.

[125] Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett* **2000**, 442–454.

[126] Miura, M.; Enna, M.; Okuro, K. *J. Org. Chem.* **1995**, *60*, 4999–5004.

[127] Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953–955.

[128] Masson, G.; Py, S.; Vallée, Y. *Angew. Chem.* **2002**, *114*, 1850–1853.

[129] Desvergnes, S.; Py, S.; Vallée, Y. *J. Org. Chem.* **2005**, *70*, 1459–1462.

[130] Yang, Y.; Shen, Z.; Loh, T. *Org. Lett.* **2009**, *11*, 1209–1212.

[131] Su, J.-K.; Jia, Y.-M.; He, R.; Rui, P.-X.; Han, N.; He, X.; Xiang, J.; Chen, X.; Zhu, J.; Yu, C.-Y. *Synlett* **2010**, 1609–1616.

[132] Bøgevig, A.; Gothelf, K. V.; Jørgensen, K. A. *Chem. Eur. J.* **2002**, *8*, 5652–5661.

[133] Grigg, R. *Chem. Commun.* **1966**, 607–608.

[134] Baldwin, J. E.; Pudussery, R. G.; Qureshi, A. K. *J. Am. Chem. Soc.* **1968**, 5325–5326.

[135] Padwa, A.; Wong, G. S. K. *J. Org. Chem.* **1986**, *51*, 3125–3133.

[136] Lopez-Calle, E.; Eberbach, W. *J. Chem. Soc., Chem. Commun.* **1994**, 301–302.

[137] Lopez-Calle, E.; Keller, M.; Eberbach, W. *Eur. J. Org. Chem.* **2003**, 1438–1453.

[138] Rehák, J.; Fišera, L.; Kožíšek, J.; Bellovičová, L. *Tetrahedron: Asymmetry* **2011**, *67*, 5762–5769.

[139] van Otterlo, W. A. L.; de Koning, C. B. *Chem. Rev.* **2009**, *109*, 3743–3782.

[140] Yus, M.; Radivoy, G.; Alonso, F. *Synthesis* **2001**, 0914–0918.

[141] Keck, G. E.; Wager, T. T.; McHardy, S. F. *Tetrahedron: Asymmetry* **1999**, *55*, 11755–11772.

[142] Fukuzawa, H.; Ura, Y.; Kataoka, Y. *J. Organomet. Chem.* **2011**, *696*, 3643–3648.

[143] Andersen, N. G.; Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 2885–2887.

[144] Cho, C. S.; Lim, D. K.; Zhang, J. Q.; Kim, T.-J.; Shim, S. C. *Tetrahedron Lett.* **2004**, *45*, 5653–5656.

[145] Malakar, C. C.; Schmidt, D.; Conrad, J.; Beifuss, U. *Org. Lett.* **2011**, *13*, 1972–1975.

[146] Wang, J.-g.; Wang, M.; Xiang, J.-c.; Zhu, Y.-p.; Xue, W.-j.; Wu, A.-x. *Org. Lett.* **2012**, *14*, 6060–6063.

[147] Huang, K. S.; Wang, E. C. *Tetrahedron Lett.* **2001**, 6155–6157.

[148] Paterson, J. W.; Conolly, M. E.; Dollery, C. T.; Hayes, A. *Pharmacol. Clin.* **1970**, 127–133.

[149] Milelli, A. *Eur. J. Med. Chem.* **2012**, *57*, 417–428.

[150] Boyd, M. R.; Hallock, Y. F.; Cardellina, J. H.; Manfredi, K. P.; Blunt, J. W.; McMahon, J. B.; Buckheit, R. W.; Bringmann, G.; Schäffer, M.; Cragg, G. M. *J. Med. Chem.* **1994**, *37*, 1740–1745.

[151] Hoye, T. R.; Mi, L. *Tetrahedron Lett.* **1996**, *37*, 3097–3098.

[152] Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*, 3rd ed.; Wiley, 2011.

[153] Bringmann, G.; Walter, R. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 977–991.

[154] Akutagawa, S. *Applied Catalysis A: General* **1995**, *128*, 171–207.

[155] Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.* **2002**, *344*, 3.

[156] Reddy, L. R. *Org. Lett.* **2012**, *14*, 1142–1145.

[157] Pérez-Fuertes, Y.; Kelly, A. M.; Johnson, A. L.; Arimori, S.; Bull, S. D.; James, T. D. *Org. Lett.* **2006**, *8*, 609–612.

[158] Wild, U.; Hübner, O.; Maronna, A.; Enders, M.; Kaifer, E.; Wadepohl, H.; Himmel, H.-J. *Eur. J. Inorg. Chem.* **2008**, 4440–4447.

[159] Alder, R. W.; Bowman, P. S.; Steele, W. R. S.; Winterman, D. R. *Chem. Commun.* **1968**, 723–724.

[160] Raab, V.; Kipke, J.; Gschwind, R. M.; Sundermeyer, J. *Chem. Eur. J.* **2002**, *8*, 1682–1693.

[161] Dávalos, J. Z.; Lago, A. F.; Costa, J. C. S.; Santos, L. M. N. B. F.; González, J. *J. Chem. Thermodyn.* **2012**, *54*, 346–351.

[162] Hoefelmeyer, J. D.; Schulte, M.; Tschinkl, M. *Coordin. Chem. Rev.* **2002**, *235*, 93–103.

[163] Katz, H. E. *J. Am. Chem. Soc.* **1985**, *107*, 1421–1423.

[164] Katz, H. E. *J. Org. Chem.* **1985**, *50*, 5027–5032.

[165] Reilly, M.; Oh, T. *Tetrahedron Lett.* **1995**, *36*, 217–220.

[166] de Koning, C. B.; Rousseau, A. L.; van Otterlo, W. A. L. *Tetrahedron: Asymmetry* **2003**, *59*, 7–36.

[167] Yoshida, K.; Shida, H.; Takahashi, H.; Yanagisawa, A. *Chem. Eur. J.* **2011**, *17*, 344–349.

[168] Adak, L.; Yoshikai, N. *Tetrahedron: Asymmetry* **2012**, *68*, 5167–5171.

[169] Ilies, L.; Matsumoto, A.; Kobayashi, M.; Yoshikai, N.; Nakamura, E. *Synlett* **2012**, *23*, 2381–2384.

[170] Wang, Y.; Tan, C.; Zhang, X.; He, Q.; Xie, Y.; Yang, C. *Eur. J. Org. Chem.* **2012**, 6622–6629.

[171] Sugahara, M.; Moritani, Y.; Terakawa, Y.; Ogiku, T.; Ukita, T.; Iwasaki, T. *Tetrahedron Lett.* **1998**, *39*, 1377–1380.

[172] Ukita, T.; Nakamura, Y.; Kubo, A.; Yamamoto, Y.; Takahashi, M.; Kotera, J.; Ikeo, T. *J. Med. Chem.* **1999**, *42*, 1293–1305.

[173] Charlton, J. L.; Alauddin, M. M. *Tetrahedron: Asymmetry* **1987**, *43*, 2873–2889.

[174] Craig, D.; Robson, M. J.; Shaw, S. J. *Synlett* **1998**, 1381–1383.

[175] Yudin, A.; Martyn, L.; Pandiaraju, S.; Zheng, J.; Lough, A. *Org. Lett.* **2000**, *2*, 41–44.

[176] Mitani, M.; Tanaka, Y.; Sawada, A.; Misu, A. *Eur. J. Org. Chem.* **2008**, 1383–1391.